A multinational registry for rhabdoid tumors of any anatomical site

EUROPEAN RHABDOID REGISTRY

EU-RHAB

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EUROPEAN RHABDOID REGISTRY EU-RHAB

1 General information

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1.2 Signature Page

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		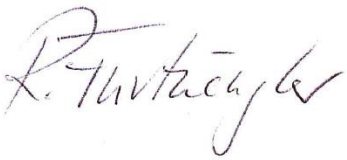
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1.3 Synopsis

Title:	EUROPEAN RHABDOID REGISTRY A multinational registry for rhabdoid tumors of any anatomical site
Short title:	EU-RHAB
Investigators / Germany:	Michael C. Frühwald MD, PhD and Rhoikos Furtwängler, MD
Indication:	Rhabdoid tumors of the brain, kidney and soft tissue
Primary objectives:	• Creation of a comprehensive database for patients with rhabdoid tumors of any anatomical site diagnosed in European countries. • Development of a structured plan for central review of histology (including *SMARCB1* immunhistochemistry) and molecular genetics. To improve (neuro-) pathological, clinical and molecular genetic characterization of rhabdoid tumors. • To render support to existing tumor banks and to perform biological studies, to identify future therapeutic targets. • To cooperate with: Groups specialized in pediatric Soft Tissue Sarcoma (e.g. CWS, EPSSG) and Nephroblastoma, in studying similarities between extra- (RTK and MRT) and intra-CNS (AT/RT) rhabdoid tumors and in defining common treatment elements used in AT/RT and extra-CNS rhabdoid tumors. To communicate with groups in the USA and Australia, to define points of reciprocal interest and potential for cooperation.
Secondary objectives:	• To determine event free and overall survival of patients. • To evaluate the time to progression in patients with rhabdoid tumors treated on a consensus therapeutic regimen. • To assess the importance of surgical technique, particularly the effect of complete surgical resection. • To assess the importance of involved field radiotherapy.
Participating centers and patients:	The registry is available to all centers in participating European countries.
Inclusion criteria:	Patients of any age with histologically proven rhabdoid tumors, verified by central pathology review. Informed consent by legal guardians to contribute data to the registry.
Exclusion criteria:	Absence of informed consent by legal guardians and/or patient to contribute data to the registry.
Financial support:	Deutsche Kinderkrebsstiftung Lichtblicke e.V. / Germany

1.4 Important Note

The prognosis of children with rhabdoid tumors has improved, but remains dismal for patients with certain risk factors and survivors are ridden with severe side effects of therapy. Due to the rarity of the disease, controlled trials are missing.

The focus of the *European Rhaboid Registry* (EU-RHAB) is the institution of a registry for rhabdoid tumors in European countries. The data gained from this registry are novel and unique. The registry shall build the basis for therapeutic trials. The aim of the registry is thus to contribute to improvements in the diagnostic and eventually therapeutic manangement of affected patients.

As mainly very young infants and children (rarely adolescents) are affected by this disease this population defines our target. According to international and EU regulations children may not be excluded from advances in medical research, but should rather be included into specifically designed trials. As no such trial currently exists for children with rhabdoid tumors regardless of origin, the European Rhaboid Registry is the first step in the direction of creating such a trial.

The *European Rhaboid Registry* contains recommendations for standardized therapy, which were generated from data derived from the current literature, the investigators' clinical experience and data derived from the GPOH and SIOP studies for high risk Wilms tumors, soft tissue sarcomas and malignant brain tumors of infants and children.

A common protocol for rhabdoid tumors of any anatomical location is currently not in use anywhere. The recommendations for therapy represent a current "State of the Art" and can thus not be viewed as investigational, but rather as a consensus derived from available data. ***The responsibilty for treatment and potential side effects remains at the discretion of the individual treating physician.*** Adherence to the recommendations for therapy will improve and facilitate the evaluation of the data gained from the registry.

Ultimate aim of the registry is to create a platform onto which clinical phase I/II trials shall be built.

1.5 Abbreviations

ACGT	Advancing clinicogenomic trials on cancer
AE	Adverse Event
AIEOP	Associazione Italiana Ematologia Oncologia Pediatrica
AMG	German Medicines Law (Arzneimittelgesetz)
AR	Adverse Reaction
AT/RT	Atypical teratoid, rhabdoid tumor
BERA	Brain stem evoked response audiometry
BSA	Body Surface Area
BW	Body Weight
CBC	Complete blood count
CNS	Central Nervous System
COG	Children's Oncology Group
CRF	Case Report Form
CSI	Craniospinal irradiation
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
dHPLC	denaturing High Pressure Liquid Chromatography
DNA	Desoxy Ribonucleic Acid
DOX	Doxorubicin
DVH	Dose Volume Histogram
ECG	Electrocardiogram
EEG	Electroencephalogram
EFS	Event Free Survival
EMA	Epithelial membrane antigene
ENT	Ear, Nose and Throat
EpSSG	European Soft Tissue Sarcoma Study Group
ESRT	Extra-cranial stereotactic radiotherapy
EU	European Union
FISH	Fluorescence In Situ Hybridization
FLAIR	Fluid Attenuated Inveres Recovery
FS	Shortening fraction
G-BA	The Federal Joint Committee (Gemeinsamer Bundesausschuss)
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GFAP	Glial fibrillary acidic protein
GFR	Glomerular Filtration Rate
GTV	Gross Tumor Volume
Gy	Gray
HDCT	High-dose Chemotherapy
ICE	Ifosfamide, Carboplatinum, Etoposide
ICH	International Conference on Harmonisation of Technical Requirements or Registration of Pharmaceuticals for Human Use
ICRU	International commission on radiation units
IHC	Immunhistochemistry
IMRT	Intensity-modulated radiotherapy
INN	International non proprietary names
ISHAGE	International Society of Hematotherapy and Graft Engeneering
ISRT	Intracranial Stereotactic Radiotherapy
KPS	Karnofsky Performance Status
LVEF	Left ventricular ejection fraction
MIBG	meta-jodo-benzyl-guanidine
MRI	Magnetic Resonance Imaging
MRT	Malignant rhabdoid tumor of soft tissues

MUGA	Multiple gated acquisition
MV	Mega electron Volt
NFP	Neurofilament protein
NSE	Neuron specific enolase
n.s.	not significant
OAR	Organ at Risk
ObTIMA	Ontology based clinical trial management
OS	Overall Survival
PBL	Peripheral Blood Lymphocytes
PCR	Polymerase Chain Reaction
PD	Progressive disease
PFS	Progression free survival
PI	Principal Investigator
PRV	Planning Organ at Risk Volume
PTV	Planning Target Volume
RT	Radiotherapy
RTK	Rhabdoid tumor of the kidney
RTPS	Rhabdoid tumor predisposition syndrom
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCA	Stem cell apheresis
SD	Stable disease
SFOP	Société Française d'Oncologie Pédiatrique
SIOP	Société Internationale Oncologique Pédiatrique
SMA	Smooth muscle antigen
SMARCB1	SW1/SNF related, matrix associated, actin dependent regulator of chromatin B1
i.ventr.	intraventricular
SUSAR	Suspected Unexpected Serious Adverse Reaktion
TLS	Target Levels of Safety
TV	Target Volume
UKCCSG	United Kingdom children’s cancer study group
VCD	Vincristine, Cyclophosphamide, Doxorubicin
VD	Vincristine, Doxorubicin
vWF	von Willebrand Factor

2 Introduction

The primary objective of the current project is the standardized registration of epidemiologic, molecular and clinical data of patients with rhabdoid tumors of any anatomical localisation.

Secondary objectives are the observation of survival data and therapeutic response to an expert consensus standard therapy.

The document contains recommendations for a consensus therapy, which was generated from data derived from the current literature, the investigators' own experience and data from GPOH and SIOP studies for high risk Wilms tumors, soft tissue sarcomas and malignant brain tumors in infants and children. The recommendations for therapy can thus not be viewed as investigational, but rather as a consented recommendation derived from available data.

It is open to the individual treating physician whether he/she adheres to the therapeutic guidelines within this document. Other studies including a trial by the EpSSG on extracranial rhabdoid tumors and one by the COG group on high risk kidney tumors are actively recruiting patients.

The ultimate goal of EU-RHAB is optimization of the management of affected patients by obtaining epidemiologic and molecular biology data in a cohort of patients, that have been treated on a standard therapeutic schedule. The focus of the current document is therefore the institution of a registry for rhabdoid tumors. The data gained from this registry are novel and unique and will thus contribute to improvements in the diagnostic and eventually therapeutic management of affected patients.

Enrollment into the registry and adherence to the therapeutic recommendations mandates knowledge and experience in the treatment of children and young adults with malignant disease and the dedication to comply with GCP and/or GEP guidelines. Decisions concerning treatment remain at the discretion of the treating physician. The trial centre will provide detailed recommendations.

In Germany for instance this generally requires the accreditation of the treating pediatric oncology centre according to the guidelines of the GBA (2006). Due to the rarity of rhabdoid tumors and their dismal prognosis it is strictly recommended to centralize and restrict the treatment of these patients to selected pediatric oncology centres.

This document was prepared with highest possible care. Mistakes and inaccuracies can not be completely excluded. The individual treating physician carries full responsibility for treatment. The listed investigators can not be held legally responsible for potential harm following the use of the treatment recommendation.

Non-generic names were identified by ®. If this symbol is missing it can not be concluded that the name listed is an INN.

3 Background

3.1 Rationale of a registry for rhabdoid tumors

Rhabdoid tumors are rather rare, highly aggressive malignancies usually taking a dismal clinical course. They were first described in the early `80ies as an individual anatomic entity (Haas et al., 1981). Over the last 25 years rhabdoid tumors have been described in almost any anatomical localisation (Oda & Tsuneyoshi, 2006). Despite a multitude of case series and single reports very little reliable data exist in regard to incidence, molecular basis, a potential rhabdoid stem cell and most importantly promising unified national or international therapeutic approaches (Athale et al., 2009; Corey et al., 1991; Gururangan et al., 1993; Hirose et al., 1996). A recent article demonstrated that CD133+ AT/RT cells exhibit characteristics of cancer stem cells and may be used as potential targets for future therapeutic strategies (Chiou, 2008). Most published reports consist of small case series or compilations of case series. Recent publications describe successful therapeutic approaches even in primarily metastasized or relapsed disease (Chi et al., 2008; Zimmerman et al., 2005). Common to the employed therapeutic regimens is the use of intensive anthracycline based polychemotherapy regimens and aggressive local therapy, in most instances using radiotherapy (Chi et al., 2008; Squire et al., 2007; Wagner et al., 2002; Waldron et al., 1999; Zimmerman et al., 2005). Common therapeutic strategies are in the planning stages in Europe. A common protocol for rhabdoid tumors of any anatomical location is currently not in use anywhere.

3.2 Rhabdoid tumors – Current knowledge

3.2.1 The genetics of rhabdoid tumors

Unifying features of rhabdoid tumors derived from the kidney, CNS and soft tissue are genetic mutations of the tumor suppressor gene candidate *SMARCB1* (*hSNF5/INI1*). Previously mutations had been detected in over 80 % of cases in chromosome band 22q11.2 (Biegel et al., 2002a; Jackson et al., 2009; Versteege et al., 1998). Recent data using different techniques indicate that the genetic mutation rate may be up to 100% with *SMARCB1* being the only mutated locus (Jackson et al., 2009). Whether this mutation may be viewed as an indicator of a common histogenetic origin remains unclear (Parham et al., 1994; Weeks et al., 1989; Wick et al., 1995). While rhabdoid tissue components have been demonstrated especially among soft tissue tumors such as undifferentiated sarcomas and carcinomas rhabdoid tumors in a less broad sense can be characterized by genomic mutation and repression of expression of *SMARCB1* by immunohistochemical and molecular genetic techniques (Judkins, 2007).

Loss of genetic material from chromosome 22q11 has been demonstrated by molecular genetic analyses, fluorescence *in situ* hybridisation and loss of heterozygosity studies (Biegel et al., 1996; Rickert & Paulus, 2004). Versteege *et al.* isolated the gene *SMARCB1 (hSNF5/INI1)* from chromosome 22q11.2 by positional cloning. *SMARCB1* is a member of the SWI/SNF complex (Versteege et al., 1998). The gene contributes to gene transcription through chromatin remodelling (Zhang et al., 2002). Transgenic mice heterozygous for *SMARCB1* develop rhabdoid tumors and T-cell lymphomas (Roberts et al., 2000; Roberts et al., 2002). *SMARCB1* mutations have been detected in all nine exons (Biegel et al., 2002b). These were predominantly nonsense and reading frame mutations. Some authors claim that rhabdoid tumors of the CNS (AT/RT) are characterized by mutations in exons 5 and 9. Newer reports contradict this view and show a broad mutational spectrum of *SMARCB1* across tumors from different anatomical locations (Kordes et al., 2009).

Germ line mutations in *SMARCB1* have been multiply reported. Correspondingly families with more than one affected member, but also patients with synchronous rhabdoid tumors of the CNS and of the kidney have been described (Proust et al., 1999; Sevenet et al., 1999b; Taylor et al., 2000). Familial cases are summarized under the term “rhabdoid tumor predisposition syndrome” – RTPS (Kordes et al., 2009; Louis et al., 2007). A report by Janson *et al.* demonstrated identical germ line mutations in affected children and their non-affected siblings (Janson et al., 2006). While the majority of the patients affected by the rhabdoid tumor predisposition syndrome are characterized by *SMARCB1* mutations, one report describes a family with two affected children without mutation of

SMARCB1 (Frühwald et al., 2006). Furthermore a pedigree containing family members, who carried a germ line mutation without evidence of any tumor has been described (Ammerlaan et al., 2007). A correlation between the mutational status of certain nucleotides and the clinical course of the disease has not been demonstrated. However reports from the literature suggest that patients with germ line mutations commonly affect smaller children and are characterized by an almost inevitably fatal course (Kordes et al., 2009).

An important goal of the current registry is the central review of registered tumors by a panel of dedicated pathologists and molecular biology specialists. These analyses will help in the definition of the entity “rhabdoid tumor” and help understand the differentiation of extra- vs. intracranial and renal vs. extrarenal rhabdoid tumors. The registry seeks to delineate the incidence of *SMARCB1* mutations in rhabdoid tumors. In addition a correlation between the type of mutation and the clinical phenotype is sought (e.g. germline vs. constitutional, exon 5 and 9 vs. other exons and clinical data of the affected patients). Thus it may be possible to delineate whether a common therapeutic strategy makes sense on biological grounds.

3.2.2 The pathology of rhabdoid tumors

Rhabdoid tumors are characterized by heaps of cells with an excentric nucleus and prominent nucleolus, abundant cytoplasm with eosinophilic inclusion bodies and distinct cellular membranes, resembling the rhabdomyoblastic differentiation of rhabdomyosarcomas. Mitoses are frequent, as well as areas of necrosis, hemorrhage and calcification. Rhabdoid differentiation may also be encountered in a variety of other entities such as meningeoma, melanoma, lymphoma and others.

Common to rhabdoid tumors of any anatomical localisation (AT/RT, RTK, MRT) are lesions in chromosome 22. The gene *hSNF5/INI1/SMARCB1* which fulfils the criteria of a tumor suppressor gene resides on the long arm of chromosome 22. In animal models inactivation of this gene leads to rhabdoid tumors (Roberts et al., 2000). Mutations of *SMARCB1* were detected in 51 of 76 RTK and in 25 of 29 extrarenal rhabdoid tumors (AT/RT and MRT) (Biegel, 2006). While previous studies suggested that mutations may differ between tumors of different anatomical localisations, recent evidence suggests that mutations are distributed and non characteristic. The loss of INI1 protein expression resulting from *SMARCB1* mutations can be demonstrated using immunohistochemistry, supporting the diagnosis of rhabdoid tumors (Judkins, 2007).

Rhabdoid tumors have been demonstrated in the context of families as well as metachronous in children suffering from a rhabdoid tumor of kidney and the brain. As children with a so-called rhabdoid tumor predisposition syndrome (RTPS) appear to bear a worse prognosis, genetic counselling appears mandatory. It is suggested that in case of detection of a mutation in *SMARCB1* within the tumor tissue analysis of the blood of the patients is performed. Once a mutation is detected in constitutional DNA (blood of the patient) parents may be counselled about the potential risk in siblings of the affected patient.

Rhabdoid tumors of the CNS (AT/RT)

AT/RT commonly affect infants and small children below the age of three years. Very rarely these tumors can be found in children over six years. The exact incidence of AT/RT is not known, however derived from institutional reviews and from data of institutional cancer registries it is suggested that in children below one year of age AT/RT constitute 50 % of all malignant brain tumors (Packer et al., 2002). The relation between supratentorial and infratentorial tumors is 1.3:1. Supratentorial tumors are mainly located in the hemispheres. Very rarely they can also be found in the ventricular system, the suprasellar region or in the hypophysis. Infratentorial tumors are found in the hemispheres of the cerebellum, cerebellopontine angle and in the brain stem. Very rarely AT/RT may also be found in the spine. Metastases via the CSF are common and can be found in about 20 % of the cases at diagnosis (Tekautz et al., 2005).

Macroscopically, AT/RT resembles medulloblastoma and sPNET. The tumors are soft, pale pink and show areas of hemorrhage as well as necrotic regions. Very commonly rhabdoid cells characterized by eosinophilic cytoplasm, large nuclei with excentric nucleoli and a prominent membrane as well as

cytoplasmic eosinophilic inclusion bodies are seen. These diagnostic cells may be grouped in nests close to areas composed of neuroectodermal, mesenchymal or epithelial tissue types. Only about 10 to 15% of AT/RT consist almost exclusively of rhabdoid cells. AT/RT exhibit a broad spectrum of immunohistochemical reactions corresponding to the different tissue subtypes (Louis et al., 2007). Rhabdoid cells are characterized by expression of vimentin, EMA (epithelial membrane antigen) and cytokeratins, less commonly by SMA (smooth muscle actin). The immunohistochemical demonstration of lost INI1 protein expression in the tumor cells is a strong indicator for AT/RT, however, rare AT/RT with preserved INI1 expression are also on record.

Rhabdoid tumors of the kidney (RTK)

Rhabdoid tumors of the kidney (RTK) constitute 2% of all kidney tumors in infants and children. Microscopically RTK demonstrate extensive infiltration of diffuse round cells with broad eosinophilic cytoplasm (Sotelo-Avila et al., 1986). The nuclei are very commonly excentric, rather large and exhibit a large nucleolus and a prominent nuclear membrane. In the cytoplasm inclusion of intermediary filaments may be seen. The typical configuration of cells is a rather large, non-cohesively growing accumulation of cells, which can also be found in a focal variation. Other areas of the tumor may be sclerosed, but still exhibit the typical cytologic changes of rhabdoid cells. Immunohistochemically coexpression of vimentin and cytokeratines, less commonly positivity for desmin, S-100, NSE as well as other antigens may be found. *SMARCB1* mutations are common (Jackson et al., 2009; Tomlinson et al., 2005).

Rhabdoid tumors of soft tissue (MRT)

Rhabdoid tumors of soft tissue are rare and can be detected in almost any part of the body. They can be regularly found in the liver, the heart and the GI-tract. The neck, the back and the skin are also affected (Bourdeaut et al., 2008). Microscopically these tumors are not surrounded by a capsule and are most commonly less than 5 cm in diameter at diagnosis. The surface of these tumors is soft and pale grey. Necrotic areas and zones of hemorrhage can commonly be found. On histology again the typical rhabdoid tumor cells can be found, characterized by large excentric nuclei, eosinophilic cytoplasm and inclusion bodies. However, tumors can be found which consist mainly of small blue round cells with only interspersed nests and isles of typical rhabdoid cells. This characteristic may cause difficulties in the differetial diagnosis (Gururangan et al., 1993; Madigan et al., 2007).

Localisation / Antigen	AT/RT	MRT	RTK
EMA	**++**	**++**	**+**
Vimentin	**++**	**++**	**+**
SMA	**+**		
GFAP	**+**		
NFP	**+**		
NSE		**+**	**+**
Synaptophysin	**+**	**+**	
Myoglobin		**-**	
CD 34		**-**	
CD 99		**+**	**+**
Keratin	**++**	**++**	**++**
Desmin		**-**	**+**
S100		**+**	**+**
SMARCB1	**--**	**--**	**--**

Table 3.1: Immunohistochemical characteristics of rhabdoid tumors
EMA: epithelial membrane antigen
SMA: smooth muscle antigen
GFAP: glial fibrillary acidic protein
NFP: neurofilament protein
NSE: neuron specific enolase

3.3 Historical overview of the treatment of rhabdoid tumors

3.3.1 Results of a retrospective analysis of rhabdoid tumors in Germany

Between 1984 and 1999 70 children with rhabdoid tumors (any anatomical location) were diagnosed in Germany. 35 children were below 1 year of age, 10 between 1 and 2 years and 9 between 2 and 3 years. Only 10 children were older than 4 years. 32 tumors were localized in the kidneys (RTK), 25 in soft tissue (MRT) and 13 in the CNS (AT/RT). 20% of AT/RT and 40% of RTK patients demonstrated metastases at diagnosis. Treatment was according to the respective available protocols at that time (HIT, SIOP, CWS). 28 patients received radiotherapy (30 to 40 Gy) in addition to surgery and chemotherapy. Of the 70 registered patients 46 died within two years of diagnosis. Two additional patients succumbed to the disease until the fourth year after diagnosis. More follow-up data are currently not available. The prognosis was dismal regardless of localisation of the primary tumor or the protocol used. The only statistically relevant negative prognostic factor was metastatic disease (Reinhard et al., 2008). Clearly the diagnosis of AT/RT was underrepresented in this cohort.

3.3.2 The treatment of intracranial rhabdoid tumors (AT/RT)

In a review of the literature Hilden *et al.* described survival rates of 17% (6/35) in patients suffering from AT/RT (Hilden et al., 1998). Medium follow-up in this report was between 5 and 89 months. The survivors had been treated with a combination of neurosurgery, radiotherapy and chemotherapy regimens. Cytostatic drugs applied were mainly cisplatinum, etoposide, vincristine, ifosfamide, doxorubicin, actinomycin-D, cyclophosphamide and some intraventricular component.

Tekautz *et al.* report on the experience of the St. Jude Center comprising 31 patients with AT/RT. 22 of the patients were younger than three years of age (Tekautz et al., 2005). Most patients diagnosed after the 3rd birthday were treated with chemotherapy and radiotherapy. Following surgery 30 of the 31 patients received chemotherapy. Three of four patients who suffered from progression during therapy could be salvaged by treatment with ICE. The only statistically significant prognostic factor in this study was age. 89 % of the children below three years and thus the majority of patients (n=20) succumbed to the disease.

In the databases of the German HIT studies (1988-2004) 57 patients were diagnosed with AT/RT (reference pathology confirmed). 22 of the patients were female and 29 patients younger than 1.5 years. Anatomically tumors were evenly distributed between the supra- and infratentorial location (each 27). 3 tumors were located supra- and infratentorially. 28 patients had no metastases at the time of diagnosis (M0). 13 patients had suspicious CSF-findings (M0/M1), 5 patients presented with M1 disease and 10 had M2/M3 disease. In 1 patient no data were available. Patients with metastases were younger than those without. A complete neurosurgical resection was possible in 18 cases (31.6%). A subtotal or partial removal was possible in the same number of cases. Two cases were submitted to a biopsy only. 27 patients received radiotherapy, 55 patients received chemotherapy. Medium time of follow-up is now 3.5 years. 3-year-EFS and OS were determined to be 22 and 16% respectively. 12 patients did not show any tumor progression more than one year following therapy (1.1 up 10.7 years). Seven of these patients are in complete remission. Tumor progression was diagnosed in 60% following initial post-operative chemotherapy. Positive and statistically relevant prognostic factors were age above three years, absence of metastases and a complete response to chemotherapy. Intraventricular therapy had no significant impact on survival, but was not formally tested as an endpoint (von Hoff, submitted 2010).

The currently most successful therapeutic strategy has been published by Chi *et al.* (Chi et al., 2008). Following an intensive anthracycline based induction chemotherapy regimen including intraventricular chemotherapy, early radiotherapy (RT) was followed by continuation therapy using temozolomide and actinomycin-D. Intraventricular chemotherapy was given concomitant to RT and afterwards. OS and EFS rates at two years were 70±10% and 53±13% respectively. The protocol exihibted significant toxicity with 1 toxic death and a series of severe adverse events such as transverse myelitis and radiation recall.

3.3.3 The treatment of rhabdoid tumors of the kidney (RTK)

In the United Kingdom patients with rhabdoid tumors of the kidney have been treated according to the Wilms tumor studies UKW2 and UKW3 containing a combination of vincristine, actinomycin-D and doxorubicin. The survival rate of 21 patients was 35% (SD ± 9%). All deaths occurred within 13 months following diagnosis. Two stage I patients survived, three patients with stage III died. Four of nine patients with stage III survived. Of seven patients with stage IV disease there was only one survivor. Two of the stage III patients received radiotherapy. One patient with RTK stage IV disease is allive 10 years from diagnosis (*personal communication*). Following initial nephrectomy the patient was treated with an intensive regimen consisting of vincristine (2 mg/m²), carboplatinum (500 mg/m²), epirubicin (100 mg/m²) and etoposide (300 mg/m²). These courses were switched with a regimen consisting of vincristine (2 mg/m²), ifosfamide (7.5 g/m²) and actinomycin D (1.8 mg/m²). This intensive regimen was followed by a maintenance therapy using oral etoposide.

In the United States patients with RTK were until recently enrolled into the NWTS studies employing compounds such as vincristine, actinomycin-D and doxorubicin with or without cyclophosphamide (D'Angio et al., 1989; Tomlinson et al., 2005). Despite high therapy intensity the survival within these therapeutic strata was unsatisfactory. Similar survival rates have been reported by the SIOP (Vujanic et al., 1996). To improve these results the NWTS5 study employs a strategy using carboplatinum and etoposide with cyclophosphamide (Regimen RTK). Preliminary analyses demonstrate survival around 26 %. Due to no improvement in comparison to the previous study this arm was closed preliminary. The most important conclusion from studies NWTS1-5 was a highly significant correlation between outcome and age at diagnosis. Based on the currently available data, the role of radiotherapy in the treatment of RTK can not be judged conclusively (Tomlinson et al., 2005). A recent window study using topotecan in the induction was prematurely closed due to inneffectivity (COG AREN0321).

3.3.4 The treatment of rhabdoid tumors of soft tissue (MRT)

Clinical data regarding patients with extracranial, extrarenal rhabdoid tumors are rather sparse in the literature. In a retrospective analysis of the IRS III trials only 26 cases among 3.000 were compatible with the diagnosis of a rhabdoid tumor. These 26 cases were located in the extremities, soft tissue of the trunk, retroperitoneum, abdomen and pelvis. Only five of 26 patients survived between two and 13 years (Kodet et al., 1991). Within the same time frame 22 children with extracranial / extrarenal rhabdoid tumors were enrolled into the British UKW2 and 3 studies. Of these only one patient is alive, who was treated with vincristine, etoposide, epirubicin, actinomycin-D, ifosfamide and carboplatinum. Histopathologic evaluation of *SMARCB1* was not yet possible at the time of recording. In an institutional report from the Children's Hospital of Los Angeles nine patients with extracranial/ extrarenal rhabdoid tumors were diagnosed. Of the nine patients three are at 26, 33 and 104 months after diagnosis without evidence of disease. The time to disease progression in the remainder was rapid (mean 3.6 months). No recurrences or deaths were recorded beyond 10 months after diagnosis. All survivors received multimodal therapy, including chemotherapy, surgery and two patients also radiotherapy. One patient received high-dose chemotherapy. There were no survivors after disease recurrence or progression (Madigan et al., 2007). Similar dismal results are reported in an even larger series of extracranial RT by Bourdeaut et al. (Bourdeaut et al., 2008).

3.4 The role of radiotherapy in rhabdoid tumors of the CNS (AT/RT)

Radio-oncology strategies in children with AT/RT are based on retrospective data from the German HIT studies and published trials of larger US centers such as the St. Jude Children's Research Hospital.

HIT AT/RT registry (Dannemann-Stern et al., 2005)

Between 1988 and 2004 65 children with AT/RT were diagnosed. 61/65 children were evaluated by a centralized reference pathology review. 28 of 65 children (mostly infants) were treated with chemotherapy only after initial surgery. 36 patients received radio- and chemotherapy. 44 (68.8 %) were below three years of age, 18 of these were treated with a combination of radiotherapy and chemotherapy. In the group of patients above three years 18 patients received radiotherapy. In 18 cases radiotherapy (RT) was applied to children below three years. In 19 patients RT was part of the primary therapy and in 17 part of relapse therapy.

14 patients (39 %) received local RT (seven in the course of primary and seven in the course of relapse therapy). In 21 patients RT was applied as CSI, followed by RT to the tumor region (58 %). Here therapy was in 11 cases part of the primary therapy and in 10 cases relapse treatment. No information was available for one patient. RT followed the therapeutic recommendations of the HIT 91 protocol respecting the prescription of dose for children below three years (in analogy to HIT SKK). 33 patients received a conventionally fractionated RT. CSI doses were between 23.4 and 36.8 Gy with a median dose of 35.2 Gy. Local doses were between 44.5 and 59.4 Gy with a median of 54.6 Gy. Two patients received hyperfractionated RT (one patient was diagnosed as a medulloblastoma and treated according to HIT 2000). One patient received stereotactic one-time RT (16 Gy).

Hematological toxicity was evaluated in 12 of 33 patients (CTC grade 3/4). Following focal RT in three of 12 patients (25 %), following RT of the CSI in nine of 21 patients (43 %). Neurological toxicity (CTC grade 3/4) was found in only one patient who had hemorrhage to the brain stem close to the tumor region after the end of focal RT. Following primary RT nine of 19 children were free of disease (47.4 %). In five patients local and in another five patients disseminated relapse occurred. In the course of primary chemotherapy three of 44 patients remained free of relapse. 17 of 41 patients who suffered relapse received RT as part of their salvage therapy.

19 of 64 patients survived for more than 24 months with a median survival of 37.5 months (24 to 109 months) of which all received RT either as part of their primary or salvage therapy. A median progression free survival with primary RT was 22 months in comparison to four months following primary chemotherapy. Overall survival following primary RT was 31 months in comparison to nine months following primary chemotherapy. The 2-yrs progression free survival following local RT was 59 % in comparison to 46 % following craniospinal RT (p = n.s.). Accordingly 2-yrs overall survival following local RT was 54 %, following CSI 46 %. No difference was seen between progression free and overall survival comparing primary RT or relapse RT. The corresponding progression free survival after two years following primary RT was 53 %, following salvage RT 58 %. Overall survival was 55 % resp. 52 %.

AT/RT registry Cleveland (Hilden et al., 2004)

This registry reports on 42 patients of which 20 received RT. Nine of the children received local RT, four CSI. Median survival is 48 months (10 to 96 months). Eight of the children (62%) were alive at the time of publication. Local RT appears to have positive influence on survival.

AT/RT registry Memphis (Tekautz et al., 2005)

The registry contains retrospective data on 31 patients of which 21 received RT. 10 of 21 received RT as part of primary therapy. Eight of the children who received RT in their primary therapy were alive at the time of analysis (80 %).

The following conclusions thus apply:

- RT may improve local tumor control.
- Patients undergoing RT can achieve long-term remission.
- Progression-free and overall survival demonstrate no difference between local RT and CSI.
- Progression-free and overall survival show no difference between RT in primary disease or relapse.

3.5 The role of intra-ventricular therapy in rhabdoid tumors of the CNS (AT/RT)

Due to the resistance towards systemic chemotherapy and the negative effects of radiotherapy on the developing brain, intraventricular chemotherapy has been introduced into the treatment of young children with high risk brain tumors.

First reports on intra-ventricular therapy in AT/RT are derived from the '90s. Chou *et al.* reported on a patient who received RT following subtotal resection (Chou & Anderson, 1991). Four months following termination of therapy the patient presented with hydrocephalus which was treated by the implantation of a VP-shunt. The patient received two doses of MTX intraventricularly 12 mg each. Despite this intervention disease progressed and the patient died.

Weinblatt *et al.* published a patient who received multimodal therapy following resection including triple intra-ventricular therapy (Weinblatt & Kochen, 1992). The patient survived for 4 ½ years.

In their paper Satoh *et al.* report on a 3-year old girl with AT/RT which could not be resected despite several surgical attempts. IT therapy consisted of MTX 0.3 mg/kg followed by whole brain RT. The patient succumbed to the disease at 13 months after diagnosis.

In 1993 Olson *et al.* were the first to publish the successful therapy in a patient with AT/RT and persistent disease after radiotherapy (Olson et al., 1995). These authors report three patients with AT/RT who were treated with triple intraventricular therapy. The basis for this therapy consisting of intraventricular MTX, ara-C and hydrocortisone was a recommendation of the IRS III study for parameningeal rhabdomyosarcoma. In two cases only a subtotal resection was possible, in one of the three patients metastatic disease to the CSF was seen. In addition to intraventricular therapy all three patients received anthracycline based polychemotherapy as well as radiotherapy. At the time of publication of this paper the patients were alive five years, two years and nine months after diagnosis. Side-effects of therapy were mild developmental delay and facial paresis.

Hilden *et al.* report four patients who received intraventricular thiotepa following subtotal tumor resection, chemotherapy and high-dose chemotherapy. At the time of publication one of these patients was alive 46 months after diagnosis (Hilden et al., 1998).

In 2004 Ronghe *et al.* published the course of two patients. One received triple intraventricular therapy following subtotal resection and chemotherapy as well as high-dose chemotherapy followed by autologous bone-marrow rescue. This patient is allive 43 months after diagnosis and without any neurological side effects. The second patient received a subtotal resection followed by polychemotherapy and intraventricular therapy as well as RT. This patient is also alive 55 months after diagnosis without any signs of disease (Ronghe et al., 2004).

In 2004 Hilden *et al.* published the results of a registry on 42 patients with AT/RT. 2/3 of these patients were male (Hilden et al., 2004). The median age was 24 months at the time of diagnosis. In 20 patients an initial complete tumor resection was achieved. In all patients therapy consisted of polychemotherapy, RT in 13 patients and high-dose chemotherapy in 13 patients. 16 patients received intraventricular chemotherapy. 27 patients died of disease (median: 12 months from diagnosis). Another patient died after 5.5 months due to toxicity. The remaining 14 patients are without signs of disease, 10 of these patients more than 24 months. Most important prognostic factor in this series was age. Of the 13 patients who received RT eight are without disease. 16 patients received intraventricular therapy, 13 of these patients were given triple therapy (MTX, Ara-C, Hydrocortisone). Seven of these patients are free of relapse, the median survival is 23 months. Looking at the 14 patients who were free of disease at the time of publication, 10 of these had a complete resection, six of ten had received intraventricular therapy. Five of these patients also received radiotherapy. The median age of the surviving patients was 30 months at diagnosis; median event-free survival was 42 months.

In 2005 Zimmerman *et al.* reported on four patients with AT/RT (n=2 new diagnoses, n=2 relapses). All four received polychemotherapy including 11 doses of triple intraventricular therapy (MTX, Ara-C, hydrocortisone). Patients with new diagnosis were irradiated. One of the patients received

stereotactic RT. All four patients were alive without evidence of disease at the time of publication; however significant neurological deficits such as hemiparesis were noted (Zimmerman et al., 2005). A newer follow-up demonstrates that one patient died of disease progression 3 years after diagnosis; a second suffers from an undifferentiated secondary sarcoma (Zimmermann, *personal communication*).

In a conference contribution Lowis reported on a series of 51 patients with AT/RT treated at UKCCSG centers. 40 of these have so far died of disease, 11 are alive and free of disease 2-10 years following diagnosis. Of the 11 surviving patients six had a complete resection, 10 an initial chemotherapy, three i.th. chemotherapy, two high-dose chemotherapy and eight initial radiotherapy.

In 2008 Chi *et al.* published data of 20 patients with AT/RT. All received chemotherapy including intra-ventricular therapy. 12 of the 20 patients are still alive. All of them received additional radiotherapy. 9 of 12 had a total resection.

Yano *et al.* published in 2008 the case of a 21 months old girl with intraspinal AT/RT who received multimodal therapy including total extirpation, five courses of chemotherapy containing vincristine, adriamycin, cyclophosphamide, cisplatin, etoposide and intra-thecal triple therapy, followed by high-dose therapy with thiotepa, carboplatin and etoposide. This therapy lead to a remission of the tumor until radiotherapy could be performed at the age of 33 months. The child is in complete remission at the age of 4 years.

Author	Patients [N=]	Surgery	i.th.	Survivors [N=]	Adjuvant therapy survivors	Adjuvant therapy non-survivors
Chou (1991)	1	subtotal	MTX (2 x 12 mg)	0		RT
Weinblatt (1992)	1	grossly excised	MTX, ARA-C, Hydrocortison	1	CT, RT	
Satoh (1993)	1	subtotal resection	MTX (2 x 0,3 mg/kgKG, 1 x 3 mg/kgKG)	0		CT (ACNU), RT
Olsen (1995)	3	Pat 1: PR Pat 2: PR Pat 3: TR	MTX 6 mg, ARA-C 12 mg, Hydrocortison 6 mg	3	CT, RT	
Hilden (1998)	2	Pat 1: PR Pat 2: PR	Pat 1: 6 x Thiotepa Pat 2: Thiotepa, ITT (ITT 7 x)	Pat 1	CT, RT, HD	CT
Hirth (2003) Abstract	1	TR	11 Doses: ARA-C 12 mg, MTX 6 mg, Methylprednisolon 2 mg	1	CT, Gamma-Knife-Surgery	
Ronghe (2004)	2	Pat 1: PR Pat 2: PR	9 elements ITT	2	Pat 1: CT, HD Pat 2: CT, RT	
Hilden (2004)	16	10 x TR 5 x PR 1 x Biopsy	2 patients: only MTX, 12 patients: ITT 1 patient: only Thiotepa 1 patient: ITT and Thiotepa	7	7 x CT, 6 x RT	7 x CT, 2 x CT+RT
Zimmermann (2005)	4	Pat 1: PR Pat 2: TR Pat 3: TR Pat 4: TR	ITT: MTX 15 mg/m² Ara-C 60 mg/m²,max 60 mg Hydrocortison 30 mg/m², max 30 mg Pat 2 and 3 additional Mafosfamid i.th.	4	4 x CT, 3 x RT (except pat. 3)	
Lowis (2007)	8 (with ITT)	n.i.	n.i.	3	n.i.	
Chi (2008)	20	11 x TR (10 alive, one toxic death) 6 x PR (4 alive, 2 dead) 3 x Biopsy (3 dead)	ITT: M0: MTX, ARA-C, Hydrocortison with every chemo-cycle Pos. CSF-Cytology: weekly until two samples were neg, then scheme as for M0	12	All: CT, RT	8 x CT, 3 x RT 4 x no RT, one off study
Yano (2008)	1	TR	ITT: MTX, Ara-C, hydrocartison (5 elements)	1	CT, RT, HDCT	

CT= Chemotherapy, RT= Radiotherapy, HD= High-dose-therapy, ITT= intraventricular triple-therapy (MTX, ARA-C, Hydrocortison) PR= partial resection, TR= total resection, n.i.= no information

Table 3.2: Published cases of patients with AT/RT treated with intraventricular chemotherapy

3.6 The role of high dose chemotherapy (HDCT) therapy in rhabdoid tumors

The first reports on treatment of rhabdoid tumors using high-dose chemotherapy followed by autologous stem cell rescue are derived from a publication by Hilden *et al.* in 1998. These authors report on two patients who received stem cell transplants in the course of their treatment for AT/RT (Hilden et al., 1998). The first patient was 38 months at the time of therapy. Following a subtotal resection (70%) two courses of cisplatinum, etoposide, vincristine, ifosfamide and doxorubicin were performed. The patient then received weekly vincristine and intraventricular thiotepa for six weeks. 13 months following diagnosis, autologous stem cell transplantation after conditioning with melphalan and cyclophosphamide was performed. At the time of publication the patient was without evidence of disease for 46 months with only minor neurological deficits and deafness. The second patient was an 18 months old boy with AT/RT of the pineal region. The tumor was only subtotally resected. The patient received two courses of cisplatinum and etoposide followed by weekly vincristine and intraventricular thiotepa. Two additional cycles of chemotherapy using ifosfamide and doxorubicin ensued. Six months after diagnosis, the patient presented with meningeal tumor spread. Reinduction chemotherapy consisted of etoposide, cyclophosphamide and seven doses of intraventricular therapy (Ara-C, MTX, Prednisone). High-dose chemotherapy with autologous stem cell rescue was performed using melphalan, busulfan and thiotepa. As the disease progressed, radiotherapy was performed. Despite these efforts the patient died 19 months post diagnosis. At autopsy persistent tumor in the pineal and metastatic spread along the spine was evident.

In 2003 Katzenstein *et al.* reported on a 21 months old patient with a malignant rhabdoid tumor to the liver, local lymph node metastases and distant lung metastases (Katzenstein et al., 2003). As the lesions were deemed inoperable, treatment consisted of chemotherapy using cisplatinum, amifostine, vincristine, 5-FU, ifosfamide, carboplatinum, etoposide, cyclophosphamide and doxorubicin. Subsequent to this induction high-dose chemotherapy employing a tandem approach with etoposide, carboplatinum and cyclophosphamide for the first cycle and melphalan and cyclophosphamide for the second cycle was applied. Despite these aggressive measures the tumor progressed and the patient died nine months following diagnosis.

In 2003 Sahdev *et al.* published a report on identical twins both suffering from rhabdoid tumors of the kidney (Sahdev et al., 2003). The first patient was diagnosed at the age of five months. Following complete resection of the tumor, metastases to the lung and brain were demonstrated. Despite chemotherapy using carboplatinum, etoposide and cyclophosphamide the disease progressed. The patient received two cycles of taxol, but died at the age of 12 months. The second child became symptomatic at the age of two years. He also suffered from metastases to the lung and brain. Following subtotal resection and six cycles of chemotherapy using cisplatinum, doxorubicin, vincristine, cyclophosphamide, actinomycin D, etoposide and ifosfamide the tumor demonstrated a good response. Due to chemosensitivity of the tumor high-dose therapy using etoposide, thiotepa and cyclophosphamide was performed. At the time of publication the patient was alive without evidence of disease at six years.

Ronghe *et al.* (2004) report on the successful treatment of one patient. This 14 months old girl with AT/RT was subjected to a subtotal resection (Ronghe et al., 2004). She then received induction chemotherapy using vincristine, actinomycin-D, ifosfamide, epirubicin, carboplatinum and etoposide. In addition she received nine doses of intraventricular triple chemotherapy. To avoid RT, consolidation was performed by high-dose chemotherapy using busulfan and thiotepa. At the time of publication the patient was without evidence of disease 52 months following diagnosis.

Hilden *et al.* report on a larger series of patients with AT/RT (Hilden et al., 2004). In their series of 42 patients, 13 received consolidation using myeloablative therapy with stem cell rescue in addition to induction chemotherapy. In eight patients single high-dose chemotherapy was performed. Five of these were alive without evidence of disease at the time of publication, three died between 10 and 22 months following diagnosis. In an additional five patients high-dose chemotherapy was performed in the form of three mini-transplants. Of these five only one is allive 48 months following diagnosis. In this series no influence of resection, age or concomitant therapy on survival was seen.

In 2005 Tekautz *et al.* report on a series of 37 patients with AT/RT. Only two patients in their series received high-dose chemotherapy (Tekautz et al., 2005). From the published data the outcome of these patients is not evident.

In their publication Dallorso *et al.* discuss the role of high-dose chemotherapy in brain tumors overall (Dallorso et al., 2005). In a series of 29 AT/RT patients included into the AIEOP trial 13 patients received myeloablative chemotherapy. The event-free survival at five years did not differ between patients who received conventional chemotherapy and those who received high-dose chemotherapy. The authors concluded that the role of high-dose chemotherapy has to be judged as questionable.

In 2005 Fujita *et al.* published the case of a newborn with a tumor of the orbit (Fujita et al., 2005). At the age of 10 months the eye was enucleated and histologically proven to be affected by AT/RT. On imaging a further lesion was found in the fourth ventricle of the CNS. This lesion was completely resected. The patient received induction chemotherapy using cisplatinum, etoposide, ifosfamide, carboplatinum, vincristine and nimustine. Consolidation consisted of thiotepa, melphalan, followed by autologous stem cell rescue. At the time of publication the patient was alive without evidence of disease 24 months following surgery.

In 2006 Watanabe *et al.* report on a 15 months old boy with MRT of the orbit (Watanabe et al., 2006). Following subtotal resection induction chemotherapy was applied, consisting of cisplatinum, etoposide and vincristine. As there was no response, therapy was augmented with doxorubicin and ifosfamide. After two cycles clinical and radiological response was demonstrated. As the parents refused radical surgery, gamma-knife-surgery was applied in addition to high-dose chemotherapy. A first cycle of high-dose chemotherapy consisted of melphalan and cyclophosphamide, the second of ifosfamide and thiotepa. At the time of publication the patient was alive four years following diagnosis.

In 2006 Beschorner *et al.* reported on a 14 months old boy with AT/RT (Beschorner et al., 2006). Following subtotal resection and induction chemotherapy, one year from diagnosis relapse occurred. Reinduction chemotherapy consisted of carboplatinum, etoposide and thiotepa. Following surgery high-dose chemotherapy using carboplatinum, thiotepa, etoposide and MTX was performed. As on neuroradiological imaging complete remission was seen, the patient received 54 Gy of local RT for consolidation. The patient stayed in remission for eight years following diagnosis. He then suffered from relapse to the trigeminal nerve. After relapse surgery the patient was submitted to cyber-knife RT. At the time of publication the patient was alive for three months.

Madigan *et al.* report on a series of 14 patients with extracranial rhabdoid tumors treated between the years 1983 and 2003 (Madigan et al., 2007). Among these 14 patients five long-term survivors are described. All of these had radical surgery and chemotherapy with or without RT. Two of the surviving patients received high-dose chemotherapy followed by stem cell rescue in addition to induction chemotherapy. The first patient is a six months old boy with a rhabdoid tumor of the kidney. Following total resection and chemotherapy with vincristine, adriamycin, cyclophosphamide, cisplatinum and etoposide, high-dose chemotherapy using carbo-platinum, etoposide and melphalan was performed. The patient did not receive RT and was allive 34 months following diagnosis at the time of publication. The second patient was a 30 months old girl with a rhabdoid tumor of the neck. She received a subtotal resection followed by induction chemotherapy using vincristine, actinomycin-D, cyclophosphamide and ifosfamide/adriamycin. She then received carboplatinum, etoposide and melphalan in myeloablative doses as consolidative treatment. She furthermore received 45 Gy of local RT. This patient is without evidence of disease 104 months following diagnosis at the time of publication.

In a conference report Garré *et al.* presented the Italian experience of the AIEOP on infants with AT/RT treated from 1995-2003. All patients had been enrolled on medullolastoma-like protocols. Eleven patients were treated on standard chemotherapy protocols, while 13 received HDCT. 5-year-PFS did not differ between the two groups (18.2% vs. 15.4%).

Yano *et al.* published in 2008 the case of a 21 months old girl with intraspinal AT/RT who received multimodal therapy including total extirpation, five courses of chemotherapy containing vincristine,

adriamycin, cyclophosphamide, cisplatin, etoposide and intra-thecal triple therapy, followed by high-dose therapy with thiotepa, carboplatin and etoposide. This therapy lead to a remission of the tumor until radiotherapy could be performed at the age of 33 months. The child is in complete remission at the age of 4 years.

Very recently a single patient (4 months) with AT/RT was reported, who achieved long-term disease-free survival, despite incomplete resection and without the use of RT, by intensive chemotherapy followed by tandem high-dose chemotherapy (Gidwani et al., 2008).

The SFOP has recently reported their experience using an intensive induction regimen including anthracyclines followed by RT and as a consolidation measure HDCT. Disappointingly survival did not exceed 33% after 2 years (C. Dufour*, personal communication*).

Similar results are reported by the Head Start group (J. Finlay, *personal communication).* Neither Head Start II nor III demonstrated any significant benefit when compared to conventional type chemotherapy.

Author	n =	Age (months)	surgery	HDCT	Survivors [n =]	Adjuvant therapy survivors	Adjuvant therapy non-survivors
Hilden (1998)	2	Pat 1: 38 Pat 2: 18	Pat 1: PR Pat 2: PR	Pat 1: melphalan, cyclo-phosphamide Pat 2: melphalan, busulfan, thiotepa	1 (Pat 1)	CT, IT-Chemo thiotepa, RT	CT, ITT + thiotepa, stereotactic radiosurgery, RT
Katzenstein (2003)	1	21	biopsy	1.: etoposide, carboplatinum, cyclo-phosphamide 2.: melphalan, cyclo-phosphamide	0		CT
Sahdev (2003)	1	24	PR	etoposide, thiotepa, cyclo-phosphamide	1	CT	
Ronghe (2004)	1	14	PR	busulfan, thiotepa	1	CT, ITT	
Hilden (2004)	13	DOD: 7,14,22,31 ,46,52,72 NED: 6,19,22,40 ,44,49	DOD: TR: 4, PR: 3 NED: TR: 3,PR: 3	varying regimen	6	CT: 6 RT: 2 intrath. CT: 2	CT: 7 RT: 3 intrath. CT:2
Tekautz (2005)	2	?	?	?	?	?	?
Dallorso (2005)	13	?	?	?	?	?	?
Fujita (2005)	1	1	TR	thiotepa, melphalan	1	CT	
Watanabe (2006)	1	15	PR	1.: melphalan, cyclo-phosphamide 2.: ifosfamide, thiotepa	1	CT, gamma-knife-surgery	
Beschorner (2006)	1	14	PR	carboplatinum, thiotepa, etoposide, MTX	1	CT, RT, gamma knife surgery	
Madigan (2007)	2	Pat 1: 6 Pat 2: 30	Pat 1: TR Pat 2: PR	Pat 1 und 2: carboplatinum, etoposide, melphalan	2	Pat 1: CT Pat 2: CT, RT	
Yano (2008)	1	21	TR	Thiotepa, carboplatin, etoposide	1	CT, ITT, RT	
Gidwani (2008)	1	4	PR	Tandem: carboplatin, etoposide, thiotepa 2. busulfan, melphalan, thiotepa	1	CT	

CT= Chemotherapy, RT= Radiotherapy, HD= High-dose-therapy, ITT= intraventricular triple-therapy (MTX, ARA-C, Hydrocortison) PR= partial resection, TR= total resection, n.i.= no information

Table 3.3: Published literature on patients with rhabdoid tumor treated by HDCT

Current data suggest that in the treatment of rhabdoid tumors:

- ***Patients with rhabdoid tumors profit from anthracycline based regimens.***
- ***Dose dense regimens appear beneficial.***
- ***Local therapy is an important prognostic indicator.***
- ***Early radiotherapy is beneficial.***
- ***Intraventricular therapy concomitant or following radiotherapy is associated with high toxicity.***
- ***The value of HDCT remains to be determined.***

4 Objectives

4.1 Primary objectives

Primary objectives of the European Rhabdoid Registry are:

- Creation of a comprehensive database for patients with rhabdoid tumors of any anatomical site diagnosed in European countries.
- Development of a structured plan for central review of histology (including *SMARCB1* immunhistochemistry) and molecular genetics. To improve (neuro-) pathological, clinical and molecular genetic characterization of rhabdoid tumors.
- To render support to existing tumor banks and to perform biological studies, to identify future therapeutic targets.
- To cooperate with: Groups specialized in pediatric Soft Tissue Sarcoma (e.g. CWS, EPSSG) and Nephroblastoma, in studying similarities between extra- (RTK and MRT) and intra-CNS (AT/RT) rhabdoid tumors and in defining common treatment elements used in AT/RT and extra-CNS rhabdoid tumours. To communicate with groups in the USA and Australia to define points of reciprocal interest and potential for cooperation.

4.2 Secondary objectives

Secondary objectives of the European Rhabdoid Registry are:

- To determine event free and overall survival of patients.
- To evaluate the time to progression in patients with rhabdoid tumors treated on consensus therapeutic regimen.
- To assess the importance of surgical technique, particularly the effect of complete surgical resection.
- To assess the importance of involved field radiotherapy.

5 Inclusion into the registry

5.1 Inclusion criteria

- Patients with histologically proven rhabdoid tumors, confirmed by central pathology.
- In general absence of nuclear SMARCB1 staining should have been demonstrated. However, as rhabdoid tumor cases without *SMARCB1* mutations have been published, reference pathology may suggest inclusion of tumors with positive SMARCB1 staining, but unequivocal diagnostic criteria for histopathologic diagnosis of a rhabdoid tumor.
- Patients that have been pretreated under the suspicion of a renal tumor (RTK), malignant tumor of the brain (e.g. glioblastoma, sPNET or medulloblastoma) (AT/RT) or soft tissue tumor (MRT).
- Informed consent of the legal guardians concerning data and tumor material transfer.

5.2 Exclusion criteria

- Diagnoses other than rhabdoid tumors.
- Missing consent of the legal guardians.

6 EUROPEAN RHABDOID REGISTRY – Primary Endpoints

6.1 Institution of a comprehensive registry for rhabdoid tumors

Exact incidence rates on rhabdoid tumor are hard to obtain. The target high-risk population comprises newborns and infants up to the age of three years, however rhabdoid tumors may be encountered in school children and as a rarity also in adults. The Cleveland Clinic Registry for rhabdoid tumors has been collecting data on therapy, molecular biology and basic patient data for several years, however no comparable data exist for children diagnosed within Europe or even individual European countries. In many instances children may not ever be reported to national cancer registries, as they do not reach pediatric oncologists and may thus be lost when left to palliative care without any curative option at hand.

Estimates from reported case series, institutional patient cohorts and the Cleveland Clinic Registry suggest that rhabdoid tumors may be much more common than previously reported. Data from the Italian AEIOP suggest that the subgroup of AT/RT may constitute up to 50% of all brain tumors diagnosed in infants up to the age of 6 months and 25-30% of children up to 1 year of age. Data of children with rhabdoid tumors of the kidney (RTK) and soft tissue (MRT) have been mainly collected within the cooperative study group's data bases for Wilms' tumors and rhabdomyosarcomas. However, as within these groups rhabdoid tumors constitute an exceptional diagnosis, no large data sets have been available to calculate true incidence rates.

Within the proposed registry we seek to shed light on these issues in infants and children affected by rhabdoid tumors. In cooperation with the German Cancer Registry in Mainz/Germany and cooperating European registries all clinically relevant data from children affected by rhabdoid tumors will be collected in a prospective fashion. It will thus be possible to review the patients in regard to epidemiologic data such as age at diagnosis, gender, correlation to affected family members etc. The registry is thus the first attempt to comprehensively collect relevant data on all children affected by this disease, regardless of anatomical location. The registry constitutes the basis for future cooperative therapeutic trials but also for accompanying analyses on the molecular biology of rhabdoid tumors and eventually the detection of molecular targets for innovative therapeutic approaches.

6.2 Pathology review of rhabdoid tumors

Rhabdoid tumors regardless of origin share certain features, but do also differ in certain aspects. Unifying features for all rhabdoid tumors are:

- medium to large cells;
- round to oval or polygonal shape;
- large oval, polygonal, reniform or elongated nuclei;
- open or unevenly distributed chromatin pattern;
- small to moderately prominent nucleolus;
- eccentric position of the nuclei;
- fine granular homogeneous cytoplasm;
- poorly defined denser pink bodies resembling cytoplasmatic inclusions;
- distinct cell borders;
- mitotic figures easily seen.

In addition over 80% of tumors lack the expression of the protein SMARCB1. Tumors lacking SMARCB1 immunoreactivity have to be judged as rhabdoid tumors until proven otherwise. Entities with missing SMARCB1 not compatible with rhabdoid tumors are certain schwannomas, medullary renal carcinomas, epithelioid sarcoma, plexus carcinoimas and a novel entity termed CRINET (Bourdeaut et al., 2007; Cheng et al., 2008; Hasselblatt et al., 2009; Mannan et al., 2009).

Diagnosis of a rhabdoid tumor

Please send Material to:

Reference	*AT/RT*	*MRT/RTK*	*Material*
Pathology	Prof. Hasselblatt (Form 9.5.1.1)	Kindertumorregister Sektion Kinderpathologie (Form 9.5.2.1)	1 representative paraffin-block if available additional fresh frozen material
Genetics	Prof. Hasselblatt (Form 9.5.1.1)	Prof. Schneppenheim (Form 9.5.2.2) Prof. Siebert (Form 9.5.2.3)	1 representative paraffin-block if available additional fresh frozen material 2 – 5 ml EDTA Blood 2 – 5 ml heparin Blood alternatively DNA from constitutive tissue (blood, fibroblasts)
CSF Cytology	Prof. Frühwald (Form 9.5.1.3)		at least 5 unstained air-dried cytospins
Radiology	Prof. Warmuth-Metz (Form 9.5.1.4)	Prof. Kröncke (Form 9.5.2.4)	images on CD or via imaging server
Radio Therapy	Prof. Timmermann	Prof. Rübe	summary of the case
Protonbeam Therapy	Prof. Timmermann		summary of the case
Surgery		Prof. v. Schweinitz	summary of the case
Neurosurgery	Prof. Krauß		summary of the case
	Ancillary Studies:	***(see chapter 6.4)***	***Tumor markers in the CSF of patients with AT/RT***
CSF Tumor Marker	Dr. Kerl (Form 9.5.3.1)		2 – 5ml frozen native CSF

Table 6.1 Material shipping list for reference evaluation - GERMANY

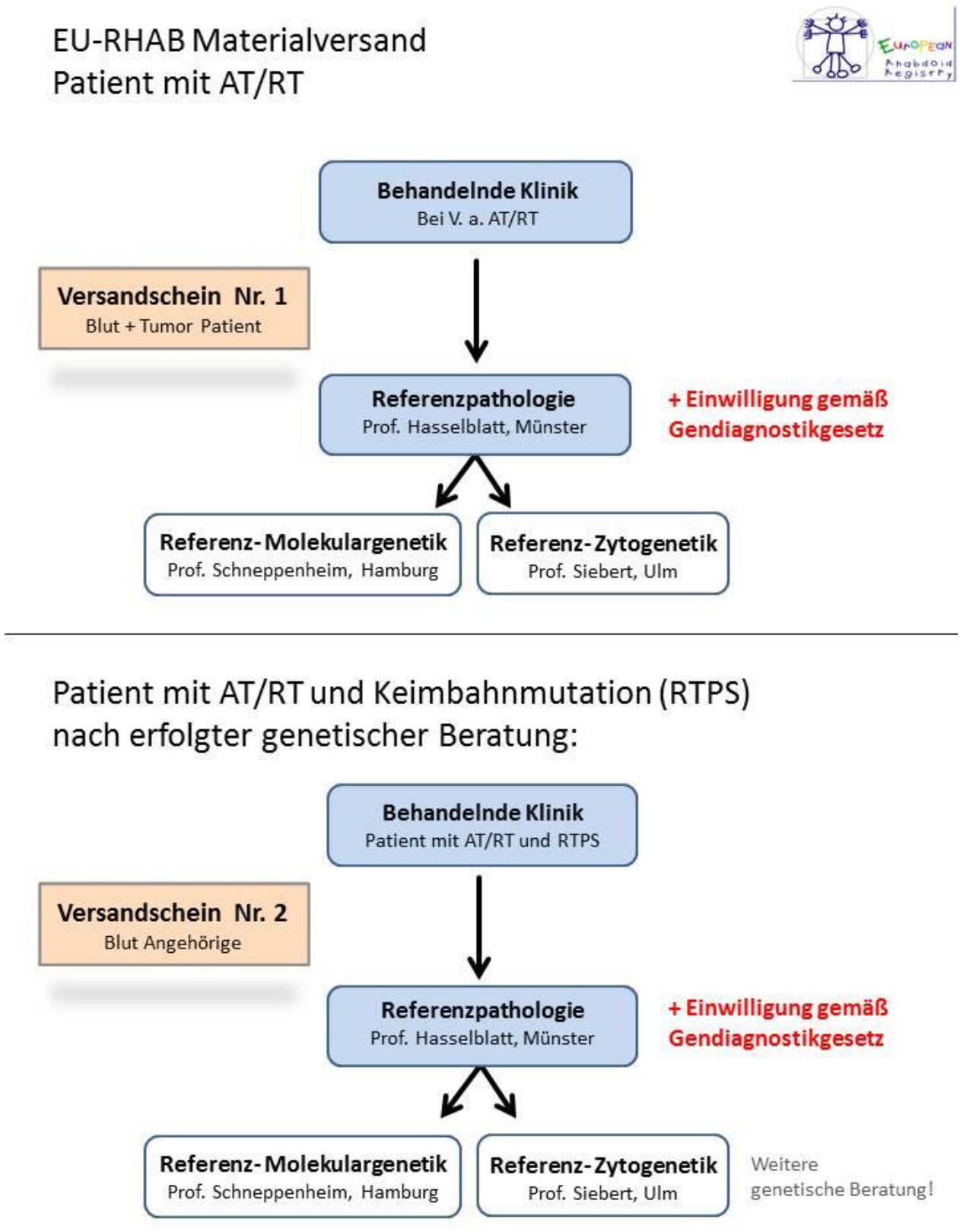

Figure 6.1a: Flow chart for reference pathology AT/RT

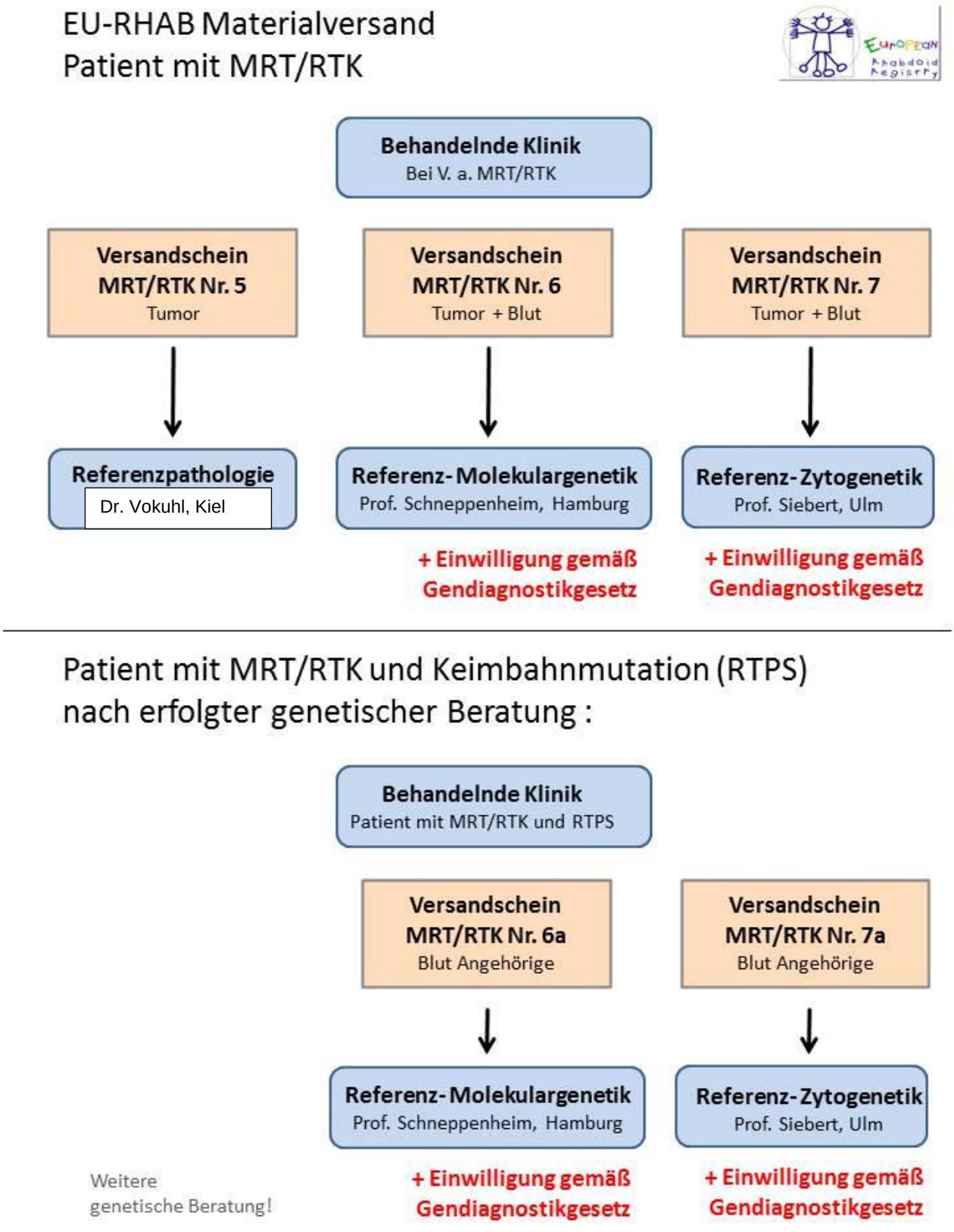

Figure 6.1b: Flow chart for reference pathology MRT/RTK

Common to rhabdoid tumors of any anatomical site are mutations in *SMARCB1*, which can be detected in over 80% of tumors. Whether rhabdoid tumors of e.g. the liver and the CNS share a common tumor stem cell remains speculative. A parallel may be drawn to intra- and extracranial germ cell tumors which are derived from a common ectodermal progenitor cell.

A reference pathology panel shall be convened. Main task of this group will be to define unequivocal criteria for the diagnosis of rhabdoid tumors in the presence and absence of *SMARCB1* mutations. Especially the differentiation against other potentially treatable diagnoses (e.g. CPT, epithelioid sarcoma…) must be based on solid diagnostic criteria.

In Germany histopathologic diagnosis is performed by the local neuro-pathologist and tumor material is then sent to a reference pathologist. Within the German HIT network, brain tumor samples of unknown histology are primarily sent to the HIT neuropathology reference centre in Bonn. Once other tumors such as glioblastoma or medulloblastoma have been excluded the material is sent to the centre in Münster (Professor Dr. M. Hasselblatt) for reference evaluation. If the local pathologist diagnoses an AT/RT, material should directly be sent to Münster.

Within southern European countries the Institute of Neuropathology in Rome headed by Professor F. Giangaspero has demonstrated high expertise and interest in these tumors. Material may thus be sent to either of the two institutions listed below.

Within Germany all extracranial rhabdoid tumors are sent to the pediatric pathology reference centre in Kiel (Dr. C. Vokuhl) for reference evaluation.

As many different pathology reference centres exist within European countries we ask, that if no reference evaluation is performed in the mentioned institutions, that at least a reference pathology report is sent to the centre of competence in Münster/Germany

It is thus suggested, that ***reference*** pathology ***evaluation*** is performed by either of these reference institutions:

Rhabdoid Tumors of the CNS (AT/RT):

1) Professor Dr. M. Hasselblatt, Institute for Neuropathology, Münster, Germany

Rhabdoid Tumors of soft tissue and of the kidney (MRT / RTK):

2) Dr. Vokuhl, Institute of Pathology, Kiel, Germany)

Forms for reference evaluation can be found in appendix 9.6 and IV.8.

6.3 Molecular genetic evaluation of rhabdoid tumors

Rhabdoid tumors regardless of anatomical locus, may occur in the context of a predisposing syndrome transmitted in some instances following an autosomal dominant trait (Biegel et al., 1999; Sevenet et al., 1999a). In the context of a Rhabdoid Tumor Predisposition Syndrome (RTPS), the tumors are more likely to be multifocal, to occur early in infancy and to affect more than one relative.

About 40 germline mutations of the *SMARCB1* gene have been described. They consist of point or splice site mutations within the coding sequence or in splicing sites. Furthermore nucleotide deletions or insertions, whole exon or gene deletions have been found. The mutations may lead to a truncated product and thus to a non-functional protein. Deletions of the entire *SMARCB1* locus, detected by cytogenetics, have also been described (Biegel et al., 1999). Even though *SMARCB1* mutations have been reported in up to 90% of rhabdoid tumors, the mutation has also been described in the entity of epithelioid sarcomas, schwannomas, medullary renal tumors and CRINET (Boyd et al., 2008; Cheng et al., 2008; Hasselblatt et al., 2009; Mannan et al., 2009). Furthermore, one family affected by a rhabdoid tumor presdisposition syndrome (RTPS) without mutation of *SMARCB1* has been observed (Frühwald et al., 2006).

As germline mutations have not been systematically evaluated in patients with RT, their actual incidence is currently unknown. Estimations arise to one third of the patients affected before their second birthday (Bourdeaut et al., 2007). However, some germline mutations have been reported in children with “late” rhabdoid tumor (Sevenet et al., 1999a).

De novo mutations occurring during gametogenesis in one parent or during early embryogenesis (somatic mosaicism) account for most predisposed children. Familial cases are rare. In most cases, two siblings are affected. They carry a common mutation while the parents are non-carriers. Gonadal mosaicism of one parent may account for such families. However recently a family has been published in which several members of a family were carriers of a *SMARCB1* mutation, but did not develop tumors and reached adulthood (Ammerlaan et al., 2007).

There is a definite risk for recurrence in the siblings of an affected child. The risk is low in most cases, but not predictable and different from one case to another. Only two families with a dominant mendelian segregation pattern of RT predisposition have been reported (Janson et al., 2006; Taylor et al., 2000). In general, adults carrying the mutation were not affected in infancy by RT, indicating that, although very high, the penetrance can not be complete. In one additional family, a father and his daughter carried a *SMARCB1* germline heterozygous mutation, but neither was affected by rhabdoid tumors. Surprisingly, both suffered from schwannomatosis. Accordingly, complete inactivation of the *SMARCB1* gene has been observed in sporadic schwannomas (Hulsebos et al., 2007). At the present time, there is no explanation of the exceptional phenotype and concurrent *SMARCB1* mutation in this family.

Much more knowledge is needed to evaluate the actual frequency and significance of germline and somatic mutations in *SMARCB1* and potentially other loci. In particular, information is missing regarding the rate of germline mutations in late infancy or adulthood and thus the risk of late onset RT and/or schwannomas.

No recommendations are currently available on the appropriate surveillance of siblings of affected children or unaffected carriers of germline mutations. More information needs to be collected. This is one of the aims of the current study.

The search for a germline *SMARCB1* mutation needs to consider the following aspects:

- No reliable strategy can be offered to mutation carriers for preventive purposes. The identification of a germline mutation in a healthy sibling will generate considerable anxiety but may ***not*** lead to a change in clinical management.

- The only clinical interest in the detection of a germline mutation is to allow for genetic counselling in families with the desire for additional children.

The search for a germline *SMARCB1* mutation should be considered in case of

- accurate diagnosis of rhabdoid tumor (negative IHC for *SMARCB1*)
- a patient with multifocal tumors or/and younger than 2 years of age at diagnosis or/and associated with other cases in the family.
- whenever possible, analysis of tumor and germline DNA (blood) should be conducted in parallel

It has to be postulated that genetic counselling is added to explain and advise the parents. Informed consent will be collected. It deserves stressing that the parents have the right to deny knowledge about the genetic cause of their child's disease.

The high penetrance and aggressiveness of the disease justify prenatal diagnosis. This can be proposed only to families with at least one documented germline mutation in one first-degree relative. Prenatal diagnosis should rely on biopsy of chorionic villi.

In sporadic rhabdoid tumors the situation may somewhat differ. However we suggest, that in these tumors molecular genetic analyses shall also be obtained whenever possible and acceptable to the parents. The current literature discusses whether extracranial rhabdoid tumors differ from rhabdoid tumors of the CNS (AT/RT). While some studies demonstrate mutation patterns in *SMARCB1* specific for different anatomical sites, other data contradict this view (Kordes et al., 2009).

An important aim of the current study is to clarify this aspect by assessing molecular genetic changes in *SMARCB1* and other potential candidate genes. Molecular genetic data will be put into context with pathologic and clinical data and patterns will be elucidated. These may eventually aide in the stratification of patients and help to uncover molecular structures for targeted therapy.

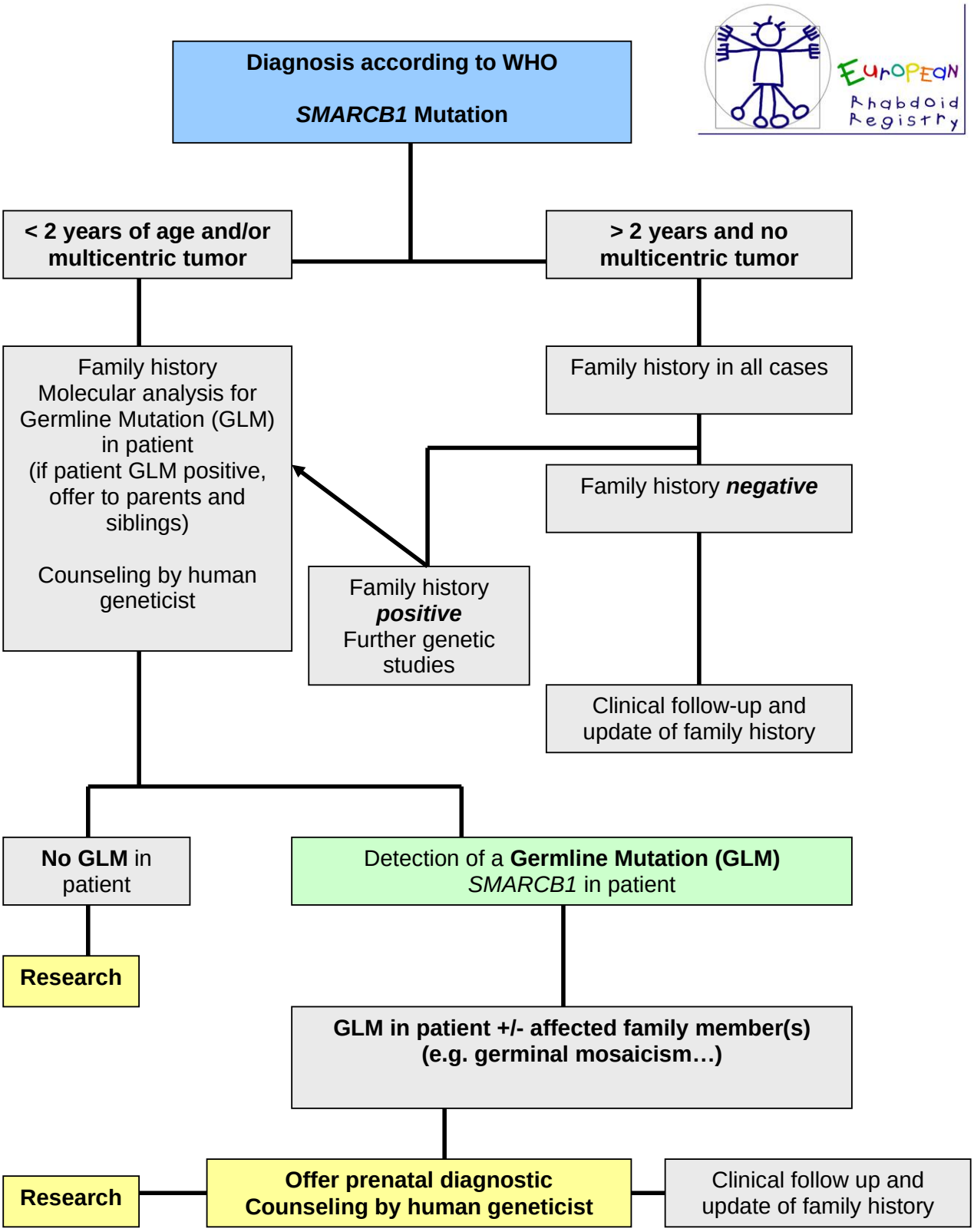

Figure 6.2: Flow chart for genetic counseling of patients with suspected rhabdoid tumor predisposition

Molecular techniques employed to test for chromosomal alterations and mutations in the DNA exist in all varieties. Genetic reference evaluation for the purpose of the European Rhabdoid Registry will rely on the following solid and repeatedly validated techniques (Frühwald et al., PBC 2006):

FISH analyses

Fluorescence *in situ* hybridisation is performed on metaphase cells from peripheral blood samples (if available) as well as on interphase cells from tissue sections of the rhabdoid tumors using 4 probes for the *SMARCB1* locus in 22q11.2 (RPCI11-BAC clones 1112A23, 71G19, 911F12 and 76E8).

Mutational Analysis of *SMARCB1*

Genomic DNA derived from rhabdoid tumors and PBL of affected patients (or parents and siblings in case a germline mutation has been identified in the index patient) is used for sequencing analysis. All nine coding exons and flanking intronic sequences of *SMARCB1* are amplified by PCR using primers chosen from published sequences (Genbank accession No. Y17118 - Y17126). All PCR products are sequenced directly using an ABI 310 automatic sequencer. Gene dosage is determined by quantitative dHPLC subsequent to competitive PCR of *SMARCB1* sequences against a reference target (exon 3 of the vWF gene).

Reference evaluation for molecular genetics and cytogenetics shall be performed in the following laboratories:

Cytogenetics and Molecular Cytogenetics including FISH:

Professor Dr. R. Siebert, Institute of Human Genetics, Ulm, Germany or

Molecular Genetics

Professor Dr. R. Schneppenheim, Pediatric Hematology/Oncology, Hamburg, Germany

Forms for reference evaluation (molecular genetics and cytogenetics) can be found in appendix 9.3 and IV.8.

6.4 Ancillary Studies

Tumor markers in the CSF of patients with atypical teratoid rhabdoid tumors

About 50% of patients with atypical teratoid rhabdoid tumors will relapse despite major advancements and aggressive multimodal therapy. Early detection of relapse may be a contributing factor helping improve relapse therapy.
From a diagnostic point of view rather crude methodologies such as imaging procedures including MRI and CT plus CSF cytology are available. However only macroscopically detectable lesions can be visualized by these methods. A major disadvantage of imaging procedures is that they can not be repeated in a rather short time frame.
In several malignancies of childhood sensitive tumor markers help in the diagnosis, follow up and early relapse detection of embryonal tumors. Among others these include alpha-fetoprotein demonstrated in serum and CSF in the detection of germ cell tumors. Another example are vanillic acid and other catecholamine products in serum and urine of patients with neuroblastoma.

NO corresponding tumor markers exist for patients with AT/RT. These markers are hoped to help better prognosticate the course of the disease, potential response to therapy and detection of relapses.
Patients with AT/RT registered to the European Registry are repeatedly evaluated by CSF and blood analysis for diagnostic purposes. Leftover material of these clinically indicated procedures shall be used for the current research project.
We will use CSF from affected and non-affected children and submit the protein material to 2-dimensional gel electropheresis followed by mass-spectroscopy. We expect significant improvement in the early diagnosis of relapse by identifying selective and hopefully specific tumor markers.

Information and consent forms as well as forms for material shipping (CSF) will be found in appendix 9.5 and IV.5

7 Data management and statistical considerations

It is estimated that within Europe at least 40 patients with ATRT are diagnosed annually. In 2007 14 such patients were reported to the German Childhood Cancer Registry alone. Equal or similar numbers have been reported to registries within France, Italy and the UK. We anticipate that an equal or slightly larger number of RTK and MRT are diagnosed. One of the purposes of the registry is to obtain a more accurate estimate of these figures.

All patient information will be collected using CRF. A remote data entry database is created. This database allows import and export of data for statistical purpose and sponsored by the GPOH (MARVIN). Procedures concerning data base entry and export have been approved by the local data safety officer.

All patients registered in this study will be included in the final analysis. The number of patients who were not evaluable, who died or withdrew before treatment began will be specified. Statistical analysis will be performed according to the study objectives and questions posed.

Primarily this includes:

- epidemiologic characterization of the patient population (demographics, tumor location and dissemination),
- identification of genetic mutations and
- evaluation of the toxicity of therapy.

In general, data will be analyzed applying descriptive and inductive statistical methods. Descriptive analyses comprise preparation of frequency tables, calculation of univariate and bivariate statistics (mean, standard deviation, quantiles, odds ratio), and graphical diagrams (e.g., Box-and-Whisker plots, Kaplan-Meier curves for survival data). Inductive statistical analyses will be performed using significance tests (Student's t-test or nonparametric alternatives, χ^2 test and Log-rank test for survival data). All significance tests will be performed controlling for a maximum (two-sided) type I error α=5%. If applicable, confidence intervals of statistics of interest will be established on 95% significance level. Univariate and multivariate model-based analyses will be performed (e.g., Cox's proportional hazards model for survival data). Analyzing survival data, the distribution of the follow-up times will be described, and the number of patients lost to follow-up will be reported. Response rates will be summarized if available.

8 Ethical and legal considerations

The current document has been reviewed by the ethics committee of the Westfalian Wilhelms University of Münster in Germany.
Approval has been granted on 01.03.2010 and is shown in copy form in the Appendix IV.10.

In case the registry is expanded into or appended with a trial of investigational drugs the ethics committee will be contacted again and all EU and national guidelines for such a trial will be met in due time.

Informed consent

Before accepting patient data into the registry each patient will be counselled about the different parts of the registry and informed consent for data entry. A *pro forma* consent form for the local institution is provided and may be used. Patients will be informed on the right to withdraw from the registry and associated therapeutic interventions at any time. Informed consent forms using lay terms have been created and will be distributed.

Data registration will follow once informed consent has been reviewed by the trial center. All participating patients are informed that their disease related and personal data will be handled with care and whenever possible in pseudonymised form. They consent in written form to the use of these data for scientific evaluations. Informed consent forms will be signed by the patient and legal guardians and the treating physician. Informed consent forms may be found in Appendix 9.4 and IV.5.

Legal aspects

The European registry does not fulfill the criteria of a phase I, II or III trial. Nevertheless it complies with GCP, GEP and EU guidelines regarding patient data safety.

Financial issues

The registry is currently supported by the German Childhood Cancer Foundation (DKKS) and a limited grant of a German parent's association (Lichtblicke e.V.).

Publication rules

Publication will be performed once critical numbers of patients have been enrolled onto the registry. The chairpersons of the individual countries will be coauthors on the manuscript. The order of the coauthors will be according to the patients accrued.

9 Appendix

9.1 References

Ammerlaan, A.C., Ararou, A., Houben, M.P., Baas, F., Tijssen, C.C., Teepen, J.L., Wesseling, P. & Hulsebos, T.J. (2007). Long-term survival and transmission of INI1-mutation via nonpenetrant males in a family with rhabdoid tumour predisposition syndrome. *Br J Cancer*, **18,** 18.

Athale, U.H., Duckworth, J., Odame, I. & Barr, R. (2009). Childhood atypical teratoid rhabdoid tumor of the central nervous system: a meta-analysis of observational studies. *J Pediatr Hematol Oncol.*, **31,** 651-63.

Beschorner, R., Mittelbronn, M., Koerbel, A., Ernemann, U., Thal, D.R., Scheel-Walter, H.G., Meyermann, R. & Tatagiba, M. (2006). Atypical teratoid-rhabdoid tumor spreading along the trigeminal nerve. *Pediatr Neurosurg.*, **42,** 258-63.

Biegel, J.A. (2006). Molecular genetics of atypical teratoid/rhabdoid tumor. *Neurosurg Focus*, **20,** E11.

Biegel, J.A., Allen, C.S., Kawasaki, K., Shimizu, N., Budarf, M.L. & Bell, C.J. (1996). Narrowing the critical region for a rhabdoid tumor locus in 22q11. *Genes Chromosomes Cancer*, **16,** 94-105.

Biegel, J.A., Kalpana, G., Knudsen, E.S., Packer, R.J., Roberts, C.W., Thiele, C.J., Weissman, B. & Smith, M. (2002a). The role of INI1 and the SWI/SNF complex in the development of rhabdoid tumors: meeting summary from the workshop on childhood atypical teratoid/rhabdoid tumors. *Cancer Res*, **62,** 323-8.

Biegel, J.A., Tan, L., Zhang, F., Wainwright, L., Russo, P. & Rorke, L.B. (2002b). Alterations of the hSNF5/INI1 gene in central nervous system atypical teratoid/rhabdoid tumors and renal and extrarenal rhabdoid tumors. *Clin Cancer Res*, **8,** 3461-7.

Biegel, J.A., Zhou, J.Y., Rorke, L.B., Stenstrom, C., Wainwright, L.M. & Fogelgren, B. (1999). Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. *Cancer Res*, **59,** 74-9.

Bourdeaut, F., Freneaux, P., Thuille, B., Bergeron, C., Laurence, V., Brugieres, L., Verite, C., Michon, J., Delattre, O. & Orbach, D. (2008). Extra-renal non-cerebral rhabdoid tumours. *Pediatr Blood Cancer.*, **51,** 363-8.

Bourdeaut, F., Freneaux, P., Thuille, B., Lellouch-Tubiana, A., Nicolas, A., Couturier, J., Pierron, G., Sainte-Rose, C., Bergeron, C., Bouvier, R., Rialland, X., Laurence, V., Michon, J., Sastre-Garau, X. & Delattre, O. (2007). hSNF5/INI1-deficient tumours and rhabdoid tumours are convergent but not fully overlapping entities. *J Pathol.*, **211,** 323-30.

Boyd, C., Smith, M.J., Kluwe, L., Balogh, A., Maccollin, M. & Plotkin, S.R. (2008). Alterations in the SMARCB1 (INI1) tumor suppressor gene in familial schwannomatosis. *Clin Genet.*, **74,** 358-66 Epub 2008 Jul 21.

Cheng, J.X., Tretiakova, M., Gong, C., Mandal, S., Krausz, T. & Taxy, J.B. (2008). Renal medullary carcinoma: rhabdoid features and the absence of INI1 expression as markers of aggressive behavior. *Mod Pathol.*, **21,** 647-52 Epub 2008 Mar 7.

Chi, S.N., Zimmerman, M.A., Yao, X., Cohen, K.J., Burger, P., Biegel, J.A., Rorke-Adams, L.B., Fisher, M.J., Janss, A., Mazewski, C., Goldman, S., Manley, P.E., Bowers, D.C., Bendel, A., Rubin, J., Turner, C.D., Marcus, K.J., Goumnerova, L., Ullrich, N.J. & Kieran, M.W. (2008). Intensive Multimodality Treatment for Children With Newly Diagnosed CNS Atypical Teratoid Rhabdoid Tumor.*J Clin Oncol*, **8,** 8-14.

Chou, S.M. & Anderson, J.S. (1991). Primary CNS malignant rhabdoid tumor (MRT): report of two cases and review of literature. *Clin Neuropathol.*, **10,** 1-10.

Corey, S.J., Andersen, J.W., Vawter, G.F., Lack, E.E. & Sallan, S.E. (1991). Improved survival for children with anaplastic Wilms' tumors. *Cancer*, **68,** 970-4.

D'Angio, G.J., Breslow, N., Beckwith, J.B., Evans, A., Baum, H., deLorimier, A., Fernbach, D., Hrabovsky, E., Jones, B., Kelalis, P. & et al. (1989). Treatment of Wilms' tumor. Results of the Third National Wilms' Tumor Study. *Cancer*, **64,** 349-60.

Dallorso, S., Dini, G., Ladenstein, R., Cama, A., Milanaccio, C., Barra, S., Cappelli, B. & Garre, M.L. (2005). Evolving role of myeloablative chemotherapy in the treatment of childhood brain tumours. *Bone Marrow Transplant.*, **35,** S31-4.

Frühwald, M.C., Hasselblatt, M., Wirth, S., Köhler, G., Schneppenheim, R., Subero, J.I., Siebert, R., Kordes, U., Jürgens, H. & Vormoor, J. (2006). Non-linkage of familial rhabdoid tumors to *SMARCB1* implies a second locus for the rhabdoid tumor predisposition syndrome. *Pediatr Blood Cancer***,** 273-278.

Fujita, M., Sato, M., Nakamura, M., Kudo, K., Nagasaka, T., Mizuno, M., Amano, E., Okamoto, Y., Hotta, Y., Hatano, H., Nakahara, N., Wakabayashi, T. & Yoshida, J. (2005). Multicentric atypical teratoid/rhabdoid tumors occurring in the eye and fourth ventricle of an infant: case report. *J Neurosurg.*, **102,** 299-302.

Gidwani, P., Levy, A., Goodrich, J., Weidenheim, K. & Kolb, E.A. (2008). Successful outcome with tandem myeloablative chemotherapy and autologous peripheral blood stem cell transplants in a patient with atypical teratoid/rhabdoid tumor of the central nervous system. *J Neurooncol***,** 4.

Gururangan, S., Bowman, L.C., Parham, D.M., Wilimas, J.A., Rao, B., Pratt, C.B. & Douglass, E.C. (1993). Primary extracranial rhabdoid tumors. Clinicopathologic features and response to ifosfamide. *Cancer*, **71,** 2653-9.

Haas, J.E., Palmer, N.F., Weinberg, A.G. & Beckwith, J.B. (1981). Ultrastructure of malignant rhabdoid tumor of the kidney. A distinctive renal tumor of children. *Hum Pathol*, **12,** 646-57.

Hasselblatt, M., Oyen, F., Gesk, S., Kordes, U., Wrede, B., Bergmann, M., Schmidt, H., Frühwald, M.C., Schneppenheim, R., Siebert, R. & Paulus, W. (2009). Cribriform neuroepithelial tumor (CRINET): a non-rhabdoid ventricular tumor with INI1 loss and relatively favourable prognosis. *J Neuropathol Ex Neurol*, **in press**.

Hilden, J.M., Meerbaum, S., Burger, P., Finlay, J., Janss, A., Scheithauer, B.W., Walter, A.W., Rorke, L.B. & Biegel, J.A. (2004). Central nervous system atypical teratoid/rhabdoid tumor: results of therapy in children enrolled in a registry. *J Clin Oncol.*, **22,** 2877-84.

Hilden, J.M., Watterson, J., Longee, D.C., Moertel, C.L., Dunn, M.E., Kurtzberg, J. & Scheithauer, B.W. (1998). Central nervous system atypical teratoid tumor/rhabdoid tumor: response to intensive therapy and review of the literature. *J Neurooncol*, **40,** 265-75.

Hirose, M., Yamada, T., Toyosaka, A., Hirose, T., Kagami, S., Abe, T. & Kuroda, Y. (1996). Rhabdoid tumor of the kidney: a report of two cases with respective tumor markers and a specific chromosomal abnormality, del(11p13). *Med Pediatr Oncol*, **27,** 174-8.

Hulsebos, T.J., Plomp, A.S., Wolterman, R.A., Robanus-Maandag, E.C., Baas, F. & Wesseling, P. (2007). Germline mutation of INI1/SMARCB1 in familial schwannomatosis. *Am J Hum Genet.*, **80,** 805-10.

Jackson, E.M., Sievert, A.J., Gai, X., Hakonarson, H., Judkins, A.R., Tooke, L., Perin, J.C., Xie, H., Shaikh, T.H. & Biegel, J.A. (2009). Genomic analysis using high-density single nucleotide polymorphism-based oligonucleotide arrays and multiplex ligation-dependent probe amplification provides a comprehensive analysis of INI1/SMARCB1 in malignant rhabdoid tumors. *Clin Cancer Res.*, **15,** 1923-30 Epub 2009 Mar 10.

Janson, K., Nedzi, L.A., David, O., Schorin, M., Walsh, J.W., Bhattacharjee, M., Pridjian, G., Tan, L., Judkins, A.R. & Biegel, J.A. (2006). Predisposition to atypical teratoid/rhabdoid tumor due to an inherited INI1 mutation. *Pediatr Blood Cancer*, **47,** 279-84.

Judkins, A.R. (2007). Immunohistochemistry of INI1 expression: a new tool for old challenges in CNS and soft tissue pathology. *Adv Anat Pathol.*, **14,** 335-9.

Katzenstein, H.M., Kletzel, M., Reynolds, M., Superina, R. & Gonzalez-Crussi, F. (2003). Metastatic malignant rhabdoid tumor of the liver treated with tandem high-dose therapy and autologous peripheral blood stem cell rescue. *Med Pediatr Oncol.*, **40,** 199-201.

Klingebiel, T., Boos, J., Beske, F., Hallmen, E., Int-Veen, C., Dantonello, T., Treuner, J., Gadner, H., Marky, I., Kazanowska, B. & Koscielniak, E. (2008). Treatment of children with metastatic soft tissue sarcoma with oral maintenance compared to high dose chemotherapy: report of the HD CWS-96 trial. *Pediatr Blood Cancer.*, **50,** 739-45.

Kodet, R., Newton, W.A., Jr., Sachs, N., Hamoudi, A.B., Raney, R.B., Asmar, L. & Gehan, E.A. (1991). Rhabdoid tumors of soft tissues: a clinicopathologic study of 26 cases enrolled on the Intergroup Rhabdomyosarcoma Study. *Hum Pathol*, **22,** 674-84.

Kordes, U., Gesk, S., Frühwald, M.C., Leuschner, I., Hasselblatt, M., Jeibmann, A., Oyen, F., Peters, O., Pietsch, T., Siebert, R. & Schneppenheim, R. (2009). Clinical and molecular features in patients with rhabdoid tumor predisposition syndrome. *Genes Chrom Cancer*, **in press**.

Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavenee, W.K., Burger, P.C., Jouvet, A., Scheithauer, B.W. & Kleihues, P. (2007). The 2007 WHO Classification of Tumours of the Central Nervous System. *Acta Neuropathol (Berl)*, **114,** 97-109.

Madigan, C.E., Armenian, S.H., Malogolowkin, M.H. & Mascarenhas, L. (2007). Extracranial malignant rhabdoid tumors in childhood: the Childrens Hospital Los Angeles experience. *Cancer.*, **110,** 2061-6.

Mannan, A.A., Rifaat, A.A., Kahvic, M., Kapila, K., Mallik, M., Grover, V.K., Bharati, C. & Perry, A. (2009). Proximal-Type Epithelioid Sarcoma in the Groin Presenting as a Diagnostic Dilemma. *Pathol Oncol Res*, **8,** 8.

Oda, Y. & Tsuneyoshi, M. (2006). Extrarenal rhabdoid tumors of soft tissue: clinicopathological and molecular genetic review and distinction from other soft-tissue sarcomas with rhabdoid features. *Pathol Int*, **56,** 287-95.

Olson, T.A., Bayar, E., Kosnik, E., Hamoudi, A.B., Klopfenstein, K.J., Pieters, R.S. & Ruymann, F.B. (1995). Successful treatment of disseminated central nervous system malignant rhabdoid tumor. *J Pediatr Hematol Oncol*, **17,** 71-5.

Packer, R.J., Biegel, J.A., Blaney, S., Finlay, J., Geyer, J.R., Heideman, R., Hilden, J., Janss, A.J., Kun, L., Vezina, G., Rorke, L.B. & Smith, M. (2002). Atypical teratoid/rhabdoid tumor of the central nervous system: report on workshop. *J Pediatr Hematol Oncol*, **24,** 337-42.

Parham, D.M., Weeks, D.A. & Beckwith, J.B. (1994). The clinicopathologic spectrum of putative extrarenal rhabdoid tumors. An analysis of 42 cases studied with immunohistochemistry or electron microscopy. *Am J Surg Pathol*, **18,** 1010-29.

Proust, F., Laquerriere, A., Constantin, B., Ruchoux, M.M., Vannier, J.P. & Freger, P. (1999). Simultaneous presentation of atypical teratoid/rhabdoid tumor in siblings. *J Neurooncol*, **43,** 63-70.

Reinhard, H., Reinert, J., Beier, R., Furtwängler, R., Alkasser, M., Rutkowski, S., Frühwald, M., Koscielniak, E., Leuschner, I., Kaatsch, P. & Graf, N. (2008). Rhabdoid tumors in children: prognostic factors in 70 patients diagnosed in Germany. *Oncol Rep.*, **19,** 819-23.

Rickert, C.H. & Paulus, W. (2004). Chromosomal imbalances detected by comparative genomic hybridisation in atypical teratoid/rhabdoid tumours. *Childs Nerv Syst*, **20,** 221-4. Epub 2004 Feb 4.

Roberts, C.W., Galusha, S.A., McMenamin, M.E., Fletcher, C.D. & Orkin, S.H. (2000). Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice. *Proc Natl Acad Sci U S A*, **97,** 13796-800.

Roberts, C.W., Leroux, M.M., Fleming, M.D. & Orkin, S.H. (2002). Highly penetrant, rapid tumorigenesis through conditional inversion of the tumor suppressor gene Snf5. *Cancer Cell*, **2,** 415-25.

Ronghe, M.D., Moss, T.H. & Lowis, S.P. (2004). Treatment of CNS malignant rhabdoid tumors. *Pediatr Blood Cancer.*, **42,** 254-60.

Sahdev, I., James-Herry, A., Scimeca, P. & Parker, R. (2003). Concordant rhabdoid tumor of the kidney in a set of identical twins with discordant outcomes. *J Pediatr Hematol Oncol.*, **25,** 491-4.

Sevenet, N., Lellouch-Tubiana, A., Schofield, D., Hoang-Xuan, K., Gessler, M., Birnbaum, D., Jeanpierre, C., Jouvet, A. & Delattre, O. (1999a). Spectrum of hSNF5/INI1 somatic mutations in human cancer and genotype-phenotype correlations. *Hum Mol Genet*, **8,** 2359-68.

Sevenet, N., Sheridan, E., Amram, D., Schneider, P., Handgretinger, R. & Delattre, O. (1999b). Constitutional mutations of the hSNF5/INI1 gene predispose to a variety of cancers. *Am J Hum Genet*, **65,** 1342-8.

Sotelo-Avila, C., Gonzalez-Crussi, F., deMello, D., Vogler, C., Gooch, W.M., 3rd, Gale, G. & Pena, R. (1986). Renal and extrarenal rhabdoid tumors in children: a clinicopathologic study of 14 patients. *Semin Diagn Pathol*, **3,** 151-63.

Squire, S.E., Chan, M.D. & Marcus, K.J. (2007). Atypical teratoid/rhabdoid tumor: the controversy behind radiation therapy. *J Neurooncol.*, **81,** 97-111 Epub 2006 Jul 20.

Taylor, M.D., Gokgoz, N., Andrulis, I.L., Mainprize, T.G., Drake, J.M. & Rutka, J.T. (2000). Familial posterior fossa brain tumors of infancy secondary to germline mutation of the hSNF5 gene. *Am J Hum Genet*, **66,** 1403-6. Epub 2000 Mar 14.

Tekautz, T.M., Fuller, C.E., Blaney, S., Fouladi, M., Broniscer, A., Merchant, T.E., Krasin, M., Dalton, J., Hale, G., Kun, L.E., Wallace, D., Gilbertson, R.J. & Gajjar, A. (2005). Atypical teratoid/rhabdoid tumors (ATRT): improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy. *J Clin Oncol*, **23,** 1491-9.

Tomlinson, G.E., Breslow, N.E., Dome, J., Guthrie, K.A., Norkool, P., Li, S., Thomas, P.R., Perlman, E., Beckwith, J.B., D'Angio, G.J. & Green, D.M. (2005). Rhabdoid tumor of the kidney in the National Wilms' Tumor Study: age at diagnosis as a prognostic factor. *J Clin Oncol*, **23,** 7641-5.

Versteege, I., Sevenet, N., Lange, J., Rousseau-Merck, M.F., Ambros, P., Handgretinger, R., Aurias, A. & Delattre, O. (1998). Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. *Nature*, **394,** 203-6.

Vujanic, G.M., Sandstedt, B., Harms, D., Boccon-Gibod, L. & Delemarre, J.F. (1996). Rhabdoid tumour of the kidney: a clinicopathological study of 22 patients from the International Society of Paediatric Oncology (SIOP) nephroblastoma file. *Histopathology*, **28,** 333-40.

Wagner, L., Hill, D.A., Fuller, C., Pedrosa, M., Bhakta, M., Perry, A. & Dome, J.S. (2002). Treatment of metastatic rhabdoid tumor of the kidney. *J Pediatr Hematol Oncol*, **24,** 385-8.

Waldron, P.E., Rodgers, B.M., Kelly, M.D. & Womer, R.B. (1999). Successful treatment of a patient with stage IV rhabdoid tumor of the kidney: case report and review. *J Pediatr Hematol Oncol*, **21,** 53-7.

Watanabe, H., Watanabe, T., Kaneko, M., Suzuya, H., Onishi, T., Okamoto, Y., Miyake, H., Yasuo, K., Hirose, T. & Kagami, S. (2006). Treatment of unresectable malignant rhabdoid tumor of the orbit with tandem high-dose chemotherapy and gamma-knife radiosurgery. *Pediatr Blood Cancer.*, **47,** 846-50.

Weeks, D.A., Beckwith, J.B. & Mierau, G.W. (1989). Rhabdoid tumor. An entity or a phenotype? *Arch Pathol Lab Med*, **113,** 113-4.

Weinblatt, M. & Kochen, J. (1992). Rhabdoid tumor of the central nervous system. *Med Pediatr Oncol.*, **20,** 258.

Wick, M.R., Ritter, J.H. & Dehner, L.P. (1995). Malignant rhabdoid tumors: a clinicopathologic review and conceptual discussion. *Semin Diagn Pathol*, **12,** 233-48.

Zimmerman, M.A., Goumnerova, L.C., Proctor, M., Scott, R.M., Marcus, K., Pomeroy, S.L., Turner, C.D., Chi, S.N., Chordas, C. & Kieran, M.W. (2005). Continuous remission of newly diagnosed and relapsed central nervous system atypical teratoid/rhabdoid tumor. *J Neurooncol*, **72,** 77-84.

9.2 Participating groups

SIOP Brain Tumor Working group on AT/RT

Austria:	**Irene Slavc, Vienna**
France:	**Christelle Dufour and Franck Bourdeaut, Paris**
Italy:	**Maria Luisa Garrè, Genova; Lorenza Gandola, Milan**
Germany	**Michael Frühwald, Augsburg**
Ireland	**Jane Pears, Dublin**
Netherlands:	**Marianne van de Wetering, Amsterdam**
Russia	**Denis Kachanov, Moscow**
Portugal:	**Maria João Gil da Costa, Porto**
Poland:	**Martha Perek-Polnik, Warsaw**
Scandinavia:	**Karsten Nysom, Kobenhavn**
Spain:	**Aurora Navajas, Valencia; Ofelia Cruz, Barcelona**
Switzerland:	**Nicolas Gerber, Zürich**
United Kingdom:	**Stephen Lowis, Bristol**

Expert panel / Germany (Specialists AT/RT, MRT, RTK)

Pediatric Oncology

Prof. Dr. J. Boos	Münster	boosj@uni-muenster.de
Prof. Dr. E. Koscielniak	Stuttgart	E.Koscielniak@klinikum-stuttgart.de
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Prof. Dr. R. Schneppenheim	Hamburg	schneppenheim@uke.uni-hamburg.de

Pediatric Surgery

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Diagnostic Radiology

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Radiotherapy

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Prof. Dr. Ch. Rübe	Homburg	radioonkologie@uks.eu

Pathology

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Molecular Genetics

Prof. Dr. R. Schneppenheim	Hamburg	schneppenheim@uke.uni-hamburg.de

Cytogenetics and Molecular Cytogenetics

Prof. Dr. R. Siebert	Ulm	reiner.siebert@uni-ulm.de

Biometrics – data management

Dr. rer. nat J. Gerß	Münster	Joachim.gerss@ukmuenster.de

Biometrics – data analysis

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PD Dr. R. Furtwängler	Homburg	rhoikos.furtwaengler@uks.eu

Expert panel / Spain (Specialists AT/RT, MRT, RTK)

Pediatric Oncology

Ofelia Cruz	Barcelona	ocruz@hsjdbcn.org
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Eduardo Quiroga	Sevilla	uopvr@supercable.es

Pediatric Surgery

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Radiotherapy

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Pathology

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Molecular Genetics

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Biometrics – data management

Rafael Peris	Valencia	Rafael.peris@uv.es

Biometrics – data analysis

Ofelia Cruz	Barcelona	Ocurz@hsjdbcn.org

The following expert panels will be amended once available:

Expert panel / Austria (Specialists AT/RT, MRT, RTK)

Expert panel / Belgum (Specialists AT/RT, MRT, RTK)

Expert panel / France (Specialists AT/RT, MRT, RTK)

Expert panel / Ireland (Specialistis AT/RT, MRT, RTK)

Expert panel / Italy (Specialists AT/RT, MRT, RTK)

Expert panel / Netherlands (Specialists AT/RT, MRT, RTK)

Expert panel / Scandinavia (Specialists AT/RT, MRT, RTK)

Expert panel /Switzerland (Specialists AT/RT, MRT, RTK)

Expert panel / United Kingdom (Specialists AT/RT, MRT, RTK)

9.3 Important addresses

Important addresses for reference evaluation / Germany
(for further information contact principal investigator)

Radiology:

AT/RT	**MRT/RTK**
Fau. Prof. Dr. Warmuth-Metz Universitätsklinikum Würzburg Abt. f. Neuroradiologie Josef-Schneider-Str. 11 97080 Würzburg Telefon: 0931 201-34799/34624 Telefax: 0931 201-34789 hit@neuroradiologie.uni-wuerzburg.de	Herr Prof. Dr. med. Thomas Kröncke Klinikum Augsburg Abt. f. Diagnostische Radiologie Stenglinstr. 2 86156 Augsburg Telefon: 0821/400-2441 Telefax: 0821/400-3312 radiologie@klinikum-augsburg.de

Pathology:

RTK / MRT	**AT/RT**
Dr. C. Vokuhl Institut für Pathologie der Universität Abt. Paidopathologie Michaelisstr. 11 24105 Kiel Telefon: 0431 500-15603 Telefax: 0431 500-15604 cvokuhl@path.uni-kiel.de	Prof. Dr. M. Hasselblatt Universitätsklinikum Münster Institut für Neuropathologie Pottkamp 2 49149 Münster Telefon: 0251 83-56969 Telefax: 0251 83-56971 martin.hasselblatt.@ukmuenster.de

Molecular Genetics:	**Cytogenetics and Molecular Cytogenetics:**
Prof. Dr. R. Schneppenheim Klinik und Poliklinik für Pädiatr. Hämatologie und Onkologie Universitätsklinikum Hamburg-Eppendorf Martinistr. 52 20246 Hamburg Telefon: 040 7410-54270 Telefax: 040 7410-54601 schneppenheim@uke.uni-hamburg.de	Prof. Dr. med. Reiner Siebert Institut für Humangenetik Institutsdirektor Universitätsklinikum Ulm EU-RHAB Referenzzentrum Albert-Einstein-Allee 11 89081 Ulm Telefax: 0731-500-65402 Telefon: 0731-500-65400 sekretariat.humangenetik@uni-ulm.de

Surgery:

AT/RT	**RTK / MRT**
Dr. J. Krauß Neurochirurgische Klinik und Poliklinik Universitätsklinikum Würzburg Josef-Schneider-Str. 11 Bau B1 97080 Würzburg Telefon: 0931 201-24 587 krauss.j@nch.uni-wuerzburg.de	Prof. Dr. D. von Schweinitz Kinderchirurgische Klinik Dr. von Haunersches Kinderspital Ludwig-Maximilians-Universität München Lindwurmstraße 4 80337 München Telefon: 089 5160-3101 Telefax: 089 5160-4726 dietrich.vonschweinitz@kk-i.med.uni-muenchen.de

Radiotherapy:

AT/RT	**RTK / MRT**
Frau Univ. Prof. Dr. med. Beate Timmermann Direktorin der Klinik für Partikeltherapie Westdeutsches Protonentherapiezentrum Essen Universitätsklinikum Essen Hufelandstr. 55 45147 Essen Telefon: 0201 723 6607 Telefax : 0201 723 5255 beate.timmermann@uk-essen.de	Prof. Dr. med. Ch. Rübe Klinik für Strahlentherapie und Radioonkologie, Gebäude 6.5 Universitätsklinikum des Saarlandes Kirrberger Str. 66421 Homburg/Saar Telefon: 06841 16-24606 Telefax: 06841 16-24699 radioonkologie@uks.eu

Proton therapy:

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9.4 Informed consent forms

9.4.1 Informed consent forms – German

9.4.1.1 Aufklärung zur Registrierung, Weitergabe und Verarbeitung von Patientendaten und Untersuchungsmaterial

9.4.1.2 Einwilligung zur Registrierung, Weitergabe und Verarbeitung von Patientendaten und Untersuchungsmaterial

9.4.1.3 Einwilligung zur Teilnahme an der Konsensus-Therapie des European Rhabdoid Registry

Briefkopf der behandelnden Klinik

9.4.1.1 Aufklärung zur Registrierung, Weitergabe und Verarbeitung von Patientendaten und Untersuchungsmaterial

Patient/-in: _____ _____

Name, Vorname Geburtsdatum

Aufklärungsgespräch am: _____

Datum

Aufklärender Arzt/Ärztin: _____

Name, Funktion

Sehr geehrte Patientin, sehr geehrter Patient!

Sie werden als Patient am Krankenhaus:_____ _____mit der Diagnose eines rhabdoiden Tumors nach den Empfehlungen des EU-RHAB Registers behandelt. Hiermit bitten wir Sie darum Ihre Daten in unserem Register erfassen zu dürfen.
Im Rahmen von EU-RHAB arbeiten viele Kliniken Europas zusammen. Es sollen möglichst viele Patienten mit einem Rhabdoid-Tumor einheitlich behandelt, die Therapie und die Heilungsaussichten verbessert werden.

Verwendung personenbezogener Daten und Biomaterialien
Ein wesentlicher Bestandteil der Teilnahme am EU-RHAB Register ist der Austausch von Bildmaterial (Röntgenbilder, Computertomographie, Magnet-Resonanz-Tomographie) und Biomaterial (Tumor, Blut, Liquor(Hirnwasser)). Der Austausch erlaubt die Mitbeurteilung durch ein Team von Experten (Referenz-Pathologen, Referenz-Radiologen (für AT/RT Patienten erfolgt die Bildübermittlung ggf. über einen elektronischen Bildserver: MDPE Bildserver: Institut für Medizinische Biometrie, Epidemiologie und Informatik (IMBEI); Universitätsmedizin der Johannes Gutenberg-Universität Mainz; Obere Zahlbacher Straße 69; 55131 Mainz (Prof. Ückert), Referenz-Chirurgen, Referenz-Strahlentherapeuten, etc.). Unser Ziel ist es, umfassende diagnostische Daten und ggf. eine zweite Meinung zu jedem Patienten einzuholen. Um Verwechselungen zu vermeiden, ist es sinnvoll, für Expertenmeinungen kein anonymisiertes Untersuchungs- oder Bildmaterial auszutauschen, sondern personenbezogenes Material. Für die Weitergabe der Daten bitten wir Sie, die behandelnden Ärzte von Ihrer Schweigepflicht zu entbinden. Dieses Einverständnis zur Weitergabe der Daten ist freiwillig und kann jederzeit ohne Angaben von Gründen widerrufen werden, ohne dass Ihnen oder Ihrem Kind ein Nachteil daraus entsteht. Alle Personen, die Einblick in die gespeicherten Daten haben, sind zur Wahrung des Datengeheimnisses verpflichtet.

Verwendung anonymisierter Daten

In wissenschaftlichen Veröffentlichungen, die aus den Registerdaten hervorgehen, finden ausschließlich anonymisierte Daten Verwendung. Ein Rückschluss auf die Identität eines betroffenen Patienten oder einer Patientin ist in keinem Fall, auch nicht unter Ausnahmebedingungen möglich. Wir informieren Sie darüber, dass Ihre Daten an das zuständige LKR (Landeskrebsregister) gemeldet werden.

Verwendung von Untersuchungsmaterial für Diagnose und Forschung
Die Untersuchung von menschlichen Körpergeweben und die Analyse der daraus gewonnenen oder zu gewinnenden Daten sind zu einem wichtigen Instrument medizinischer Forschung geworden. Deshalb fragen wir unsere Patienten und daher auch Sie, ob Sie bereit sind, uns bestimmte Körpermaterialien und Daten, psyeudonymisiert, d.h. Angabe von Diagnose und Alter, für die Forschung zur Verfügung zu stellen. Ihre Teilnahme ist völlig freiwillig. Soweit Sie sich nicht beteiligen möchten oder Ihre Zustimmung später widerrufen möchten, erwachsen Ihnen daraus keine Nachteile.
Sollte Ihnen etwas unklar sein, fragen Sie bitte Ihren behandelnden Arzt bzw. Ihren Studienarzt, bevor Sie Ihre Zustimmung erteilen.

Vorteile einer Teilnahme am europäischen Rhabdoidregister
Ihre Teilnahme an unserem Europäischen Rhabdoidregister (EU-RHAB) weist sowohl Vorteile für den einzelnen betroffenen Patienten als auch für zukünftige Patienten und die wissenschaftliche Gemeinschaft auf.
So konnte wiederholt belegt werden, dass die Teilnahme an klinischen Studien oder vergleichbaren Strukturen wie z. B. einem klinischen Register mit einem Überlebensvorteil assoziiert ist. Weiterhin garantiert Ihnen die Teilnahme an unserem Register sowohl eine Referenzevaluation der diagnostischen Schritte (z.B. Bildgebung, Genetik, Pathologie usw.) als auch die Beratung der behandelnden Ärzte durch ein internationales Expertenteam.
Wissenschaftlich gesehen umfasst das Europäische Rhabdoidregister mittlerweile eine der größten Datensammlungen zu rhabdoiden Tumoren. Hierdurch konnte die (neuro-) pathologische Diagnose genauer definiert sowie auch die molekularen Signalwege besser charakterisiert werden.
Durch die internationale Zusammenarbeit profitieren nicht nur deutsche, sondern auch europaweit und weltweit Patienten von den Erfahrungen des Registers.
In der Zusammenschau tragen Sie durch die Teilnahme am Europäischen Rhabdoidregister zu einer Mehrung des Wissens über die grundlegenden Mechanismen, aber auch das praktische Herangehen an die Erkrankung bei gegenwärtigen und zukünftigen Patienten bei.

Welche Risiken sind mit Ihrer Zustimmung verbunden?
Da wir für weiterführende Diagnostik und Forschung lediglich Körpermaterial verwenden wollen, das im Rahmen der bei Ihnen vorgesehenen diagnostischen oder therapeutischen Maßnahmen ohnehin entnommen wird und als Restmaterial normalerweise vernichtet würde, ist die Spende für Sie mit keinem zusätzlichen gesundheitlichen Risiko verbunden.

Zum Zeitpunkt der Diagnose und im Verlauf der Behandlung und Nachsorge werden Blut-, Liquor- und Gewebeproben zur Mitbeurteilung an Referenzinstitutionen gesandt. Außerdem wird Tumorgewebe zur Erforschung der Krankheit in ihren molekularen, genetischen, immunologischen und anderen, mit der Krankheit direkt verbundenen Merkmalen untersucht und gegebenenfalls für die Entwicklung neuer Behandlungsverfahren eingesetzt. Die Entnahme des Tumorgewebes erfolgt schmerzlos im Rahmen der notwendigen chirurgischen Tumorentfernung bzw. während der zur Diagnosestellung erforderlichen Probeentnahme aus dem Tumor. Falls bei der Tumorentfernung aus medizinisch chirurgischen Notwendigkeiten gesundes Gewebe mit entfernt werden muss, kann dieses als Vergleichsgewebe für die Tumoreigenschaften eingesetzt werden. Eine medizinisch nicht notwendige Erweiterung des chirurgischen Eingriffes erfolgt dazu nicht. Zugestimmt wird der Entnahme einer Blutprobe während der Narkose als Vergleichsmaterial für die Eigenschaften des Tumors. Tumor, Vergleichsgewebe und Vergleichsblut werden zentral in einer der unter „Pathologie“ aufgelisteten Tumorbanken bis zum Widerruf Ihres Einverständnisses gelagert.

Ziele der Sammlung von Patientendaten und Untersuchungsmaterialien
Die von Ihnen zur Verfügung gestellten Biomaterialien und Daten werden ausschließlich für die medizinische Forschung bereitgestellt. Sie sollen im Sinne eines breiten Nutzens für die

Allgemeinheit für viele verschiedene medizinische Forschungszwecke verwendet werden. Zum derzeitigen Zeitpunkt können noch nicht alle zukünftigen medizinischen Forschungsziele beschrieben werden. Diese können sich sowohl auf bestimmte Krankheitsgebiete (z.B. Krebsleiden, Herz-Kreislauf-Erkrankungen, Erkrankungen des Gehirns) als auch auf heute zum Teil noch unbekannte Krankheiten und genetische Defekte beziehen. Es kann also sein, dass Ihre Proben und pseudonymisierte Daten auch für medizinische Forschungsfragen verwendet werden, die wir heute noch nicht absehen können. Deshalb werden an Ihren Biomaterialien/ ihres Kindes möglicherweise auch genetische Untersuchungen, also Untersuchungen der Erbsubstanz, durchgeführt, und zwar unter Umständen auch eine Untersuchung Ihres gesamten Genoms. Die Biomaterialien und Daten sollen für unbestimmte Zeit aufbewahrt und für die medizinische Forschung zur Verfügung gestellt werden, um die Vorbeugung, Erkennung und Behandlung von Erkrankungen zu verbessern. Auf diese Weise sollen die Diagnose sicherer gemacht, das biologische Verständnis der Erkrankung verbessert und neue therapeutische Ansätze gefunden werden. Die Proben werden kostenfrei und pseudonymisiert Wissenschaftlern, die in universitären Einrichtungen oder in Krankenhäusern tätig und kooperativ im EU-RHAB Register eingebunden sind für krankheitsbezogene Untersuchungen zur Verfügung gestellt.

Erfolgt eine erneute Kontaktaufnahme mit Ihnen?
Zur Erhebung von weiteren Verlaufsdaten kann es sinnvoll werden, zu einem späteren Zeitpunkt erneut Kontakt mit Ihnen aufzunehmen, um ergänzende Informationen und/oder Biomaterialien von Ihnen zu erbitten. Zudem kann die erneute Kontaktaufnahme genutzt werden, um z. B. Ihre Einwilligung zum Abgleich mit anderen Datenbanken einzuholen oder Ihnen /Ihrem behandelnden Arzt/ Ihrem Hausarzt eine Rückmeldung über für Sie gesundheitlich relevante Ergebnisse zu geben. Falls Sie eine erneute Kontaktaufnahme nicht wünschen, kreuzen Sie bitte das entsprechende Kästchen in der Einwilligungserklärung an.

Was beinhaltet Ihr Widerrufsrecht?
Sie können Ihre Einwilligung zur Verwendung Ihrer Biomaterialien und Daten/ ihres Kindes jederzeit ohne Angabe von Gründen und ohne nachteilige Folgen für Sie widerrufen. Im Falle eines Widerrufs können Sie entscheiden, ob Ihre Biomaterialien vernichtet und die dazu gehörenden Daten gelöscht werden sollen, oder ob sie in anonymisierter Form für weitere Forschungsvorhaben verwendet werden dürfen. Sobald der Bezug der Biomaterialien und der übrigen Daten zu Ihrer Person gelöscht wurde, ist eine Vernichtung jedoch nicht mehr möglich. Zudem können Daten aus bereits durchgeführten Analysen nicht mehr entfernt werden. Trotz Widerrufs kann eine spätere Zuordnung des genetischen Materials zu Ihrer Person über andere Quellen niemals ausgeschlossen werden.

Falls eine der Organisationen keine Informationen erhalten soll, wenden Sie sich für einen Widerruf bitte direkt an u.a. Ansprechpartner (Adressen und Referenzärzte).

Adressen:

- European Rhabdoid Registry EU-RHAB, Prof. Dr. Dr. M. Frühwald, Klinkum Augsburg, Klinik für Kinder und Jugendliche, Stenglinstr. 2, 86156 Augsburg
- European Rhabdoid Registry EU-RHAB, PD Dr. R. Furtwängelr, Klinik für pädiatrische Hämatologie und Onkologie, Universitätsklinikum des Saarlandes, Gebäude 9; 66421 Homburg
- Deutsches Kinderkrebsregister (Leitung: PD Dr. Peter Kaatsch) am Institut für Medizinische Biometrie, Epidemiologie und Informatik (IMBEI) der Universitätsmedizin Mainz, 55101 Mainz
- LESS Spätfolgenerfassungsstudie/Endokrinologische Begleitstudie, PD Dr. Med. Thorsten Langer, Kinder- und Jugendklinik Friedrich-Alexander-Universität Erlangen-Nürnberg, Loschgestraße 15, 91054 Erlangen

- AG Lebensqualität, Dr. Gabriele Calaminus, Universitäts-Klinik Münster, Klinik für Kinder und Jugendmedizin, Pädiatrische Hämatologie und Onkologie, Albert-Schweitzer-Str. 33, 48149 Münster
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- Tumormarkerstudie (Liquor,…..) Dr. Kornelius Kerl, Universitätsklinikum Münster, Klinik für Kinder- und Jugendmedizin Pädiatrische Hämatologie und Onkologie, Albert-Schweitzer-Campus 1, 48149 Münster und Institut für Molekulare Tumorbiologie, Dr. Kornelius Kerl, Robert-Koch-Straße 43, 48149 Münster

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- Institut für Pathologie der Universität Kiel, Abteilung Paidopathologie, Dr. C. Vokuhl,, Michaelisstraße 11, 24105 Kiel

Molekulargenetik und Cytogenetik

- Klinik für pädiatrische Hämatologie und Onkologie, Universitätsklinikum Hamburg-Eppendorf, Prof. Dr. med. Reinhard Schneppenheim, Martinistraße 52, 20246 Hamburg
- Institut für Humangenetik, Universitätsklinikum Ulm, Prof. Dr. med. Reiner Siebert, Albert-Einstein-Allee 11, 89081 Ulm

Chirurgie

- Neurochirurgische Klinik und Poliklinik, Universitätsklinikum Würzburg, Dr. J. Krauß, Josef-Schneider-Straße 11, Bau B1, 97080 Würzburg
- Kinderchirurgische Klinik Dr. von Haunersches Kinderspital, Ludwig-Maximilians-Universität München, Prof. Dr. D. von Schweinitz, Lindwurmstraße 4, 80337 München

Strahlentherapie

- Westdeutsches Protonenzentrum, Prof. Dr. Beate Timmermann, Hufelandstr. 55, 45147 Essen
- Klinik für Strahlentherapie und Radioonkologie, Universitätsklinikum des Saarlandes, Prof. Dr. med. Ch. Rübe, Kirrberger Str., 66421 Homburg/Saar

Radiologie

- Abteilung für Neuroradiologie der Universität Würzburg, Prof. Dr. Monika Warmuth-Metz, Josef-Schneider-Straße 11, 97080 Würzburg.
- Abteilung für Diagnostische Radiologie des Klinikum Augsburg, Prof. Dr. Thomas Kröncke, Stenglinstr. 2, 86156 Augsburg

Liquor (Hirnwasser)

- Prof. Dr. Dr. M. Frühwald, Klinkum Augsburg, Klinik für Kinder und Jugendliche, Stenglinstr. 2, 86156 Augsburg

Briefkopf der behandelnden Klinik

9.4.1.2 Einwilligung zur Registrierung, Weitergabe und Verarbeitung von Patientendaten und Untersuchungsmaterial

Ich erkläre mich damit einverstanden, dass meine personenbezogenen Daten (Name, Geburtsdatum, Wohnort, Diagnose mit Befunderhebung und andere medizinische Daten) bzw. die personenbezogenen Daten meiner Tochter / meines Sohnes

_____ _____

Name, Vorname Geburtsdatum

registriert und verarbeitet werden (Speicherung und Übermittlung).

Ich bin damit einverstanden, dass meine Biomaterialien und Daten/ die meines Kindes, wie in der Aufklärungsschrift beschrieben für medizinische Forschungszwecke verwendet werden. Das Eigentum an den Biomaterialien übertrage ich an:

- Institut für Neuropathologie, Universitätsklinikum Münster, Prof. Dr. M. Hasselblatt, Pottkamp 2, 19, 48129 Münster
- Institut für Pathologie der Universität Kiel, Abteilung Paidopathologie, Dr. C. Vokuhl, Michaelisstraße 11, 24105 Kiel
- Klinik für pädiatrische Hämatologie und Onkologie, Universitätsklinikum Hamburg-Eppendorf, Prof. Dr. med. Reinhard Schneppenheim, Martinistraße 52, 20246 Hamburg
- Institut für Humangenetik, Universitätsklinikum Ulm, Prof. Dr. med. Reiner Siebert, Albert-Einstein-Allee 11, 89081 Ulm
- Prof. Dr. Dr. M. Frühwald, Klinikum Augsburg, Klinik für Kinder und Jugendliche, Stenglinstr. 2, 86156 Augsburg

Ich habe die Informationsschrift gelesen und hatte die Gelegenheit, Fragen zu stellen.

Ich weiß, dass meine Teilnahme freiwillig ist und ich meine Einwilligung jederzeit ohne Angabe von Gründen widerrufen kann, ohne dass mir daraus irgendwelche Nachteile entstehen.

Ich bin damit einverstanden, dass ich evtl. zu einem späteren Zeitpunkt erneut kontaktiert werde

- zum Zweck der Gewinnung weiterer Informationen / Biomaterialien, ☐ **ja** ☐ **nein**
- zum Zweck der Einwilligung in den Abgleich mit anderen Datenbanken, ☐ **ja** ☐ **nein**
- zum Zweck der Rückmeldung für mich gesundheitsrelevanter Ergebnisse ☐ **ja** ☐ **nein**

Diese Rückmeldung soll erfolgen über die Einrichtung, in der meine Biomaterialien / Daten gewonnen wurden oder über folgenden Arzt (falls gewünscht, bitte angeben)

Name und Anschrift des Arztes: .....

Datenschutzerklärung:

Ich erkläre mich damit einverstanden, dass
- personenbezogene Daten von mir/meines Kindes erhoben und gespeichert werden,
- weitere Angaben über meine Gesundheit/über die Gesundheit meines Kindes aus den Krankenunterlagen entnommen werden,
- und die Daten gemeinsam mit meinen bzw. den Biomaterialien meines Kindes pseudonymisiert für medizinische Forschungsvorhaben zur Verfügung gestellt werden.

Die Biomaterialien und Daten dürfen unbefristet für medizinische Forschungsvorhaben verwendet werden.

Sie dürfen pseudonymisiert an Universitäten und Forschungsinstitute zu Zwecken medizinischer Forschung weitergegeben werden.

Ich bin darüber aufgeklärt worden, dass ich meine Einwilligung ohne Angabe von Gründen jederzeit widerrufen kann. Beim Widerruf werden auf mein Verlangen die verbliebenen Biomaterialien und die erhobenen Daten vernichtet bzw. gelöscht oder anonymisiert.

Eine Kopie der Patienten-/Probandeninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt bei der:

(Name Klinik/Ort)_____

_____
Name des Patienten/Probanden in Druckbuchstaben

Patient/in Name, Vorname	Unterschrift	Datum
Sorgeberechtigte/r Name, Vorname	Unterschrift	Datum
Sorgeberechtigte/r Name, Vorname	Unterschrift	Datum
Aufklärende/r Ärztin/Arzt Name, Vorname	Unterschrift	Datum
Zeuge: Name, Vorname	Unterschrift	Datum

Briefkopf der behandelnden Klinik

9.4.1.3 Einwilligung zur Teilnahme an der Konsensus-Therapie des European Rhabdoid Registry

Zur Unterschrift durch die/den Patientin/en bzw. Sorgeberechtigten nach dem Aufklärungsgespräch

Patient/in: _____ _____
Name, Vorname Geburtsdatum

Aufklärung am _____ durch _____
Datum Name, Dienstbezeichnung

Durch meine Unterschrift bestätige ich, dass ich heute durch den/die unten genannte/n Arzt/Ärztin ausführlich über den bei mir/meinem Kind vorliegenden Rhabdoid-Tumor, dessen Aussichten auf Heilung, das Ergebnis der Operation und die mögliche Behandlung aufgeklärt worden bin. Mir ist bewusst, dass es sich bei der vorgeschlagenen Behandlung um eine Empfehlung gemäß dem Einvernehmen einer Gruppe von Experten handelt. Diese fußt sowohl auf Untersuchungen der Studienleiter als auch internationalen Erfahrungen. Die Patienten-/Elterninformation zu rhabdoiden Tumoren wurde mit ausgehändigt und ausführlich erläutert. Mir wurde ausreichend Bedenkzeit eingeräumt und ich fühle mich ausreichend informiert und habe keine weiteren Fragen.

Ich erkläre mich damit einverstanden, dass die Behandlung entsprechend den Empfehlungen der Experten des Registers **EU-RHAB European Rhabdoid Registry** durchgeführt wird.

Ich kann diese Einverständniserklärung jederzeit formlos widerrufen ohne dass mir daraus ein Schaden entsteht oder dass ich Konsequenzen für die Fortführung der Behandlung fürchten muss.

Die Einwilligung zur Weitergabe und Verarbeitung von Patientendaten und Biomaterial sowie die Einverständniserklärungen für eine Bestrahlung oder andere Therapieformen wie Hochdosischemotherapie und/oder weitere Operationen erfolgen gesondert.

Patient/in Name, Vorname	Datum	Unterschrift
Sorgeberechtigte/r Name, Vorname	Datum	Unterschrift
Sorgeberechtigte/r Name, Vorname	Datum	Unterschrift
Aufklärender Arzt/Ärztin Name	Datum	Unterschrift
Zeuge/in Name, Vorname	Datum	Unterschrift

9.4.2 Informed consent forms – English

9.4.2.1 Consent form data registration, exchange, participation in research projects and tumor banking

9.4.2.2 Consent form participation in the consented therapy of the European Rhabdoid Registry

Letter head of the treating facility

9.4.2.1 Consent form data registration, exchange, participation in research projects and tumor banking

Patient: _____ _____

name date of birth

Information: _____

date

Informing physician: _____

physician, name, title

Use of personal data

Within EU-RHAB a large number of specialized European hospitals communicate to cure as many affected children as possible. An integral part is the exchange of imaging files as well as tumor and other biological materials (e.g. CT, MRI, X-Ray, Tumor, blood, CSF).

This exchange allows the involvement of a panel of experts with this rare disease such as reference pathologists, radiologists, surgeons, radiotherapists, geneticists…
To avoid mix-ups, it is reasonable not to use anonymized but rather personal material, as each reference specialist may thus directly impact on the care of each patient. Each expert is obliged to strictly adhere to confidentiality and data secrecy.

Publications concerning patient data will only contain anonymized data. Conclusion as to the name of the individual patient is not possible even under exceptional circumstances.

We ask for your permission to pass on personal data along with the material of interest to guarantee a maximum gain of information. We ask that you acquit your personal doctor from medical confidentiality to pass on the data.

Your consent to this is absolutely voluntary and may be revoked at any time. You or your child will not have any disadvantages if you revoke your consent.

Use of material for diagnostic and research purposes

When routine examinations are performed at the beginning or during treatment, blood- CSF- and tissue-specimens will be send to reference institutions. Furthermore tumor-tissue of me/my child will be examined regarding molecular, genetic, immunologic or other characteristics that are connected to the disease. The tissue may also be used for the development of new treatment strategies. The extraction of tumor-tissue takes place during the necessary surgery for tumor-extraction or biopsy. In case that during surgery healthy tissue has to be removed for medical reasons, this may be used as comparative tissue for special tumor characteristics. An extention of surgery without medical necessity will not be performed. I give my consent to the extraction of blood samples during anaesthesia as comparative tissue for special tumor characteristics. Tumor-tissue, comparative tissue and comparative blood samples will be stored centrally in one of the institutions listed under “Pathology” – until you revoke your consent and will be put without costs and anonymously to the disposal of research scientists of University-Hospitals or hospitals that perform research on these tumours. In this way diagnosis shall be made saver, the biological understanding of the tumor shall be improved and new therapeutic strategies shall be found.

Addresses:

- European Rhabdoid Registry EU-RHAB, Prof. Dr. Dr. M. Frühwald, Klinikum Augsburg, Klinik für Kinder und Jugendliche, Stenglinstr.2, 86156 Augsburg
- European Rhabdoid Registry EU-RHAB, PD Dr. R. Furtwängler, Klinik für pädiatrische Hämatologie und Onkologie, Universitätsklinikum des Saarlandes, Gebäude 9; 66421 Homburg
- Deutsches Kinderkrebsregister (Leitung: Dr. Peter Kaatsch) am Institut für Medizinische Biometrie, Epidemiologie und Informatik (IMBEI) der Universitätsmedizin Mainz, 55101 Mainz
- LESS Spätfolgenerfassungsstudie/Endokrinologische Begleitstudie, PD Dr. Med. Thorsten Langer, Kinder- und Jugendklinik Friedrich-Alexander-Universität Erlangen-Nürnberg, Loschgestraße 15, 91054 Erlangen
- AG Lebensqualität, Dr. Gabriele Calaminus, Universitäts-Klinik Münster, Klinik für Kinder und Jugendmedizin, Pädiatrische Hämatologie und Onkologie, Albert-Schweitzer-Str. 33, 48149 Münster
- Universität Würzburg, Physiologische Chemie I, Prof. Dr. M. Gessler, Universität Würzburg, Biozentrum, Am Hubland, 97074 Würzburg
- University Children's Hospital Münster, Pediatric Hematology and Oncology, Dr. Kornelius Kerl, Albert-Schweitzer-Campus 1, 48149 Münster, Germany and Institute of Molecular Tumorbiology, Dr. Kornelius Kerl, Robert-Koch-Straße 43, 48149 Münster Germany

Reference institutions:

Pathology

- Institut für Neuropathologie, Universitätsklinikum Münster, Prof. Dr. M. Hasselblatt, Pottkamp 2, 48129 Münster
- Institut für Pathologie der Universität Kiel, Abteilung Paidopathologie, Dr. C. Vokuhl, Michaelisstraße 11, 24105 Kiel

Molecular genetics and Cytogenetics

- Klinik für pädiatrische Hämatologie und Onkologie, Universitätsklinikum Hamburg-Eppendorf, Prof. Dr. med. Reinhard Schneppenheim, Martinistraße 52, 20246 Hamburg
- Institut für Humangenetik, Universitätsklinikum Ulm, Prof. Dr. med. Reiner Siebert, Albert-Einstein-Allee 11, 89081 Ulm

Surgery

- Neurochirurgische Klinik und Poliklinik, Universitätsklinikum Würzburg, Dr. J. Krauß, Josef-Schneider-Straße 11, Bau B1, 97080 Würzburg
- Kinderchirurgische Klinik Dr. von Haunersches Kinderspital, Ludwig-Maximilians-Universität München, Prof. Dr. D. von Schweinitz, Lindwurmstraße 4, 80337 München

Radiotherapy

- Westdeutsches Protonenzentrum, Prof. Dr. Beate Timmermann, Hufelandstr. 55, 45147 Essen
- Klinik für Strahlentherapie, Universitätsklinikum des Saarlandes, Prof. Dr. med. Ch. Rübe, Kirrberger Str., 66421 Homburg/Saar

Radiology

- Abteilung für Neuroradiologie der Universität Würzburg, Prof. Dr. Monika Warmuth-Metz, Josef-Schneider-Straße 11, 97080 Würzburg

Liquor

- Prof. Dr. Dr. M. Frühwald, Klinkum Augsburg, Klinik für Kinder und Jugendliche, Stenglinstr. 2, 86156 Augsburg

I agree with the registration and exchange of my personal data or the personal data of my daughter/my son (name, date of birth, residence, diagnosis and other medical data)

_____ _____

Surname, name date of birth

I agree that the biological material may be taken, analysed and stored as described above.

_____ _____

Patient: name signature date

Legal representative: name	signature	date
Legal representative: name	signature	date
Pricipal investigator: name	signature	date
Witness: name	signature	date

Letter head of treating facility

9.4.2.2 Consent form participation in the consented therapy of the European Rhabdoid Registry

To be signed by the patient/the legal representative after information.

Patient: _____ _____
name date of birth

Information _____ by _____
date physician: name, title

With my signature I confirm, that today I have been informed in detail by the physician mentioned above about the rhabdoid tumor of myself/my child, the chances for a cure, the result of surgery and possible therapy. I am aware of the fact, that the recommended therapy is an agreement of a group of experts, which is based on investigations of a panel of experts as well as on international experiences. I received the patient/parent-information, which was explained to me in detail. I was given sufficient time to think and I have discussed this recommendation, the risks and benefits and have no further questions.

I agree, that the therapy will be performed according to the recommendations of the experts of the **European Rhabdoid Registry (EU-RHAB)**.

I can withdraw at any time, for any reason, without penalty or loss of benefit. I will continue to receive medical care.

Informed consent for transmission and evaluation of patient data and material as well as informed consent for radiotherapy or other therapy-elements like stem-cell-harvest and high-dose-therapy or further surgical procedures follow separately.

Patient: name	date	signature
Legal Representative: name	date	signature
Legal Representative: name	date	signature
Principal Investigator: name	date	signature
Witness: name	date	signature

9.5 Forms for Reference Evaluation

9.5.1. Forms for Reference Evaluation AT/RT - German

9.5.1.1 Versandschein Nr. 1 - Referenz-Neuropathologie (Prof. Hasselblatt / Münster)

9.5.1.2 Versandschein Nr. 2
Molekulargenetische Untersuchung Familienangehörige
(Prof. Schneppenheim/Hamburg, Prof. Siebert/Ulm
– über Prof. Hasselblatt/Münster)

9.5.1.3 Versandschein Nr. 3 - Referenz-Liquordiagnostik (Prof. Frühwald / Augsburg)

9.5.1.4 Versandschein Nr. 4 - Referenz-Neuroradiologie
(Prof. Warmuth-Metz / Würzburg)

9.5.1.4.1 Versandschein Nr. 4a - Referenz-Neuroradiologie
Erstuntersuchung (Prof. Warmuth-Metz / Würzburg)

9.5.1.4.2 Versandschein Nr. 4b - Referenz-Neuroradiologie
Früh postoperative Untersuchung (Prof. Warmuth-Metz / Würzburg)

9.5.1.4.3 Versandschein Nr. 4c - Referenz-Neuroradiologie
Verlaufsuntersuchung (Prof. Warmuth-Metz / Würzburg)

9.5.2. Forms for Reference Evaluation MRT/RTK – German

9.5.2.1 Versandschein Nr. - 5 Referenzpathologie
(Dr. C. Vokuhl / Kiel)

9.5.2.2 Versandschein Nr. 6 Referenz Molekulargenetische - Untersuchung
(Prof. Schneppenheim/Hamburg)

9.5.2.2.1 Versandschein Nr. 6a – Referenz Molekulargenetische - Untersuchung
Familienangehörige
(Prof. Schneppenheim/Hamburg)

9.5.2.3. Versandschein Nr. 7 - Referenz Molekularzytogenetische – Untersuchung
(Prof. Siebert, Ulm)

9.5.2.3.1 Versandschein Nr. 7a - Referenz Molekularzytogenetische - Untersuchung
Familienangehörige
(Prof. Siebert, Ulm)

9.5.2.4 Versandschein Nr. 8 - Referenz-Radiologie für MRT/RTK
(Prot. Kröncke / Augsburg)

9.5.2.4.1 Versandschein Nr. 8a – Referenz-Radiologie
Erstuntersuchung (Prof. Kröncke)

9.5.2.4.2 Versandschein Nr. 8b – Referenz-Radiologie
Früh postoperative Untersuchung (Prof. Kröncke)

9.5.2.4.3 Versandschein Nr. 8c – Referenz Radiologie
Verlaufsuntersuchung (Prof. Kröncke)

9.5.3 Ancillary Studies AT/RT (*see chapter 6.4)*

9.5.3.1 Versandschein Nr. 9 – Liquor für Tumormarkerstudie (Dr. Kornelius Kerl/Münster)

9.5.1.1 Versandschein Nr. 1 AT/RT Referenzpathologie und molekulargenetische Diagnostik *– Patient –*

Herrn
Prof. Dr. med. Martin Hasselblatt
Referenzzentrum EU-RHAB
Institut für Neuropathologie
Pottkamp 2
48149 Münster - Germany

E-mail:
hasselblatt@uni-muenster.de

FAX: 0251 83 56971
Tel.: 0251 83 56967

Patientenetikett

Name _____

Vorname _____

Geburtsdatum ____.____.____

Geschlecht □ männlich □ weiblich

OP-Datum ____.____.____

Histologie
(örtl. Pathologe) _____

Lokalisation _____

Benötigtes Material:

Für Referenzpathologie und molekulargenetische Untersuchungen bitten wir zu übersenden:

□ 1 repräsentativer Paraffin-Block (wenn nicht möglich bitten wir um Rücksprache!)

□ 5 ungefärbte Kryo-Schnitte des Tumors (oder Kryo-Block) auf Trockeneis (wenn vorhanden)

□ 2-5 ml EDTA-Blut (oder DNS)

□ 2-5 ml Heparin-Blut des Patienten

Die Eltern wurden über die genetischen Untersuchungen aufgeklärt und haben die entsprechenden Einwilligungserklärungen unterzeichnet (Bitte als Kopie mitschicken - ohne Einwilligung ist eine genetische Untersuchung nicht möglich!):

□ Ja □ Nein

Referenzbegutachtung: Prof. Dr. med. Martin Hasselblatt (Neuropathologie, Uni Münster),
Prof. Dr. med. Reiner Siebert (Humangenetik, Uni Ulm),
Prof. Dr. rer. nat. Reinhard Schneppenheim (Molekulargenetik, Uni Hamburg)

_____
Datum, Unterschrift (Arzt)

Klinik (Stempel)

Bitte lokalen Pathologiebefund beilegen. Für die Referenzpathologie nicht benötigtes Paraffinmaterial wird innerhalb von 10 Tagen an den Einsender zurückgeschickt.

9.5.1.2 Versandschein Nr. 2
AT/RT molekulargenetische Diagnostik
- Familienangehörige -

Herrn
Prof. Dr. med. M. Hasselblatt
Referenzzentrum EU-RHAB
Institut für Neuropathologie
Pottkamp 2
48149 Münster

E-mail:
hasselblatt@uni-muenster.de

FAX: 0251 83 56969
Tel.: 0251 83 56971

Patientenetikett

Name _____

Vorname _____

Geburtsdatum ____.____.____

Geschlecht □ männlich □ weiblich

OP-Datum ____.____.____

Histologie
(Referenzpathologe) _____

Lokalisation _____

Benötigtes Material:

Bei Bestätigung einer Keimbahnmutation bzw. eines Rhabdoidtumor-Prädispositionssyndroms (RTPS) des Patienten bitten wir für molekulargenetische Untersuchungen der Angehörigen zu übersenden:

□ 5 ml EDTA-Blut (oder DNS) + 10 ml Heparin-Blut (Vater des Patienten)

□ 5 ml EDTA-Blut (oder DNS) + 10 ml Heparin-Blut (Mutter des Patienten)

□ 2-5 ml EDTA-Blut (oder DNS) + 2-5 ml Heparin-Blut (Geschwister des Patienten)

Die Familienangehörigen wurden über die genetischen Untersuchungen aufgeklärt und haben die entsprechenden Einwilligungserklärungen unterzeichnet.

(Bitte als Kopie mitschicken - ohne Einverständnis ist eine genetische Untersuchung nicht möglich!)

□ Ja □ Nein

Referenzbegutachtung: Prof. Dr. med. Reiner Siebert, Ulm (Humangenetik),
Prof. Dr. rer. nat. Reinhard Schneppenheim, Hamburg(Molekulargenetik)

Datum, Unterschrift (Arzt)

Klinik (Stempel)

9.5.1.3 Versandschein Nr. 3 Liquorpräparate

Prof. Dr. Dr. Michael Frühwald
I. Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg

E-Mail:
michael.fruehwald@klinikum-augsburg.de

FAX: 0821 400 9201
Tel.: 0821 400 179201

Name des/der Patienten/in _____ **Geburtsdatum** _____

Einsendende/r Arzt/Ärztin: _____

Primärdiagnostik / Staging: _____

		Punktions-Datum
	OP-Datum:	___.___.___
□ lumbal	präoperativ	___.___.___
□ ventrikulär	intraoperativ	___.___.___
□ lumbal	intraoperativ	___.___.___
□ lumbal	postoperativ	___.___.___
□ ventrikulär	postoperativ	___.___.___

einsendende Klinik

(Stempel)

Im Verlauf des European Rhabdoid Registry:_____

□ nach Zyklus Nr. ___ □ nach Bestrahlung □ anderer Zeitpunkt: _____

Liquor (lumbal/ventrikulär)
nicht zutreffendes streichen

Datum der Punktion: ___.___.___

Bitte mindestens 5 (erhöhte diagnostische Sicherheit je mehr Präparate)

ungefärbte luftgetrocknete Zytozentrifugenpräparate einsenden!

Herstellung von Zytospinpräparaten EU-RHAB

1. Objektträger mit Namen des Patienten und Abnahmedatum des Liquors beschriften
2. Auf den Objektträger 2 Papierfilterstreifen geben (mit der glatten Papierseite auf die Glas-fläche des Objektträgers)
3. Austrittsöffnung auf der Rückseite des Objektträgers markieren
4. Küvette auf Papierstreifen aufsetzen (Küvettenöffnung auf Papieröffnung)
5. Küvette in den Clip einklemmen und in die Zentrifuge einsetzen
6. 1 (-2) Tropfen Serum-Albumin (z.B. der Fa. Dade Behring, Spez.-Albumin 22% cat-no. 050111) in die vorbereitete Küvette geben und anschließend 0,5 ml Liquor dazu geben, nachdem zuvor die Zellen durch vorsichtiges Schwenken des Liquorröhrchens aufgeschwemmt wurden (Liquor mit sehr hoher Zellzahl von über 200 Zellen/µl wird mit NaCl verdünnt).
7. Liquor 5 min bei 700 U/min zentrifugieren
8. Liquor gut trocknen lassen und erst dann Färben (panoptische Färbung nach Pappenheim)
9. Auszählung wie beim Differentialblutbild (unter 100 Zellen/µl werden alle Zellen gezählt) sowie Durchsicht des gesamten Präparates nach Tumorzellen und Tumorzellverbänden
10. **Mindestens 2 (wünschenswert sind 5) ungefärbte und luftgetrocknete Präparate an das Referenzlabor schicken für die (immun-) zytochemischen Färbungen !**

9.5.1.4 Versandschein Nr. 4 Neuroradiologie AT/RT

Frau
Prof. Dr. med. Monika Warmuth-Metz
Referenzzentrum EU-RHAB
Abteilung für Neuroradiologie
Universitätskliniken
Josef-Schneider-Str. 11
97080 Würzburg

e-mail: hit@neuroradiologie.uni-wuerzburg.de

FAX: 0931-201-2685
Tel.: 0931-201-2626 / 5791

Name des/der Patienten/ _____ **Geburtsdatum**_____

Einsendende/r Arzt/Ärztin: _____

Datum OP _____

Primärdiagnostik / Staging _____

		Datum
o kraniell	präoperativ	___.___.___
o kraniell	früh-post-OP (24 – 48 Std. nach OP)	___.___.___
o spinal	Staging	___.___.___

einsendende Klinik
(Stempel)

Im Verlauf des European Rhabdoid Registry

o nach Zyklus Nr. ___ o nach Bestrahlung o anderer Zeitpunkt: _____

o kraniell ___.___.___ (Datum) o spinal ___.___.___ (Datum)

Abschlusstaging

o nach Zyklus Nr. ___ o nach Dauerttherapie o anderer Zeitpunkt: _____

o nach HDCT o nach Bestrahlung

o kraniell ___.___.___ (Datum) o spinal ___.___.___ (Datum)

Der lokale schriftliche Befund sollte als Kopie beigelegt werden. Aus diesem sollten die Angaben zur Durchführung der Kontrastmitteldarstellung hervorgehen.

9.5.1.4.1 Versandschein Nr. 4a für MRT/CT - Bilder EU-RHAB

Frau
Prof. Dr. med. Monika Warmuth-Metz
Referenzzentrum EU-RHAB
Abteilung für Neuroradiologie
Universitätskliniken
Josef-Schneider-Str. 11
97080 Würzburg

e-mail: bit@neuroradiologie.uni-wuerzburg.de
FAX: 0931/201-34789
Tel.: 0931/201-34799 oder 34624

Erstuntersuchung

Name		Histologie	
Vorname		Untersuchungsdatum	
Geburtsdatum	☐ männlich ☐ weiblich	Alle Bilder versandt?	☐ Ja ☐ Nein
Bisherige Therapie			

Die schattierten Felder sind vom Einsender auszufüllen!

Kranielles MRT oder CT		☐ nativ	☐ mit Kontrast	☐ ohne und mit Kontrast
Tumorlokalisation				
Ausdehnung				
Ursprung				
Größe a/c/s cm	cm x	cm x	cm²	cm³
Begrenzung	☐ scharf (≥90%)	☐ mäßig scharf (≥50%)	☐ unscharf (<50%)	
Ödem	☐ ipsilateral	☐ kontralateral	Cm	
Zysten	☐ Ja	☐ Nein	☐ wie Liquor	☐ heller als Liquor
Hydrozephalus	☐ nein	☐ leichtgradig	☐ mittelgradig	☐ schwergradig ☐ Shunt
KM-Enhancement	☐ kräftig	☐ mittelstark	☐ leicht	☐ kein
Anreichernder Tumoranteil	☐ homogen	☐ überwiegend homogen	☐ überwiegend inhomogen	☐ inhomogen
	☐ 0-25%	☐ 26-50%	☐ 51-75%	☐ 76-100%
Meningeose	☐ nein	☐ fraglich	☐ M2a	☐ M2b ☐ M3a ☐ M3b
Metastase wo:				
Spinales MRT	☐ ja ☐ nein	Datum	☐ vollständig	☐ insuffizient

Tumorstaging				
☐ T1	☐ T2	☐ T3/T3a	☐ T3b	☐ T4

☐ **MRT**				
T2	☐ nicht	☐ hyperintens	☐ isointens	☐ hypointens
	☐ homogen	☐ überwiegend homogen	☐ überwiegend inhomogen	☐ inhomogen
T1	☐ nicht	☐ hyperintens	☐ isointens	☐ hypointens
	☐ homogen	☐ überwiegend homogen	☐ überwiegend inhomogen	☐ inhomogen

☐ **CT**				
Dichte	☐ hypodens	☐ isodens	☐ hyperdens	☐ Blut
	☐ homogen	☐ überwiegend homogen	☐ überwiegend inhomogen	☐ inhomogen
Verkalkungen	☐ nein	☐ grob	☐ fein	

Stratifizierung möglich anhand des Bildmaterials ja nein

9.5.1.4.2 Versandschein Nr. 4b für MRT/CT - Bilder EU-RHAB

Frau
Prof. Dr. med. Monika Warmuth-Metz
Referenzzentrum EU-RHAB
Abteilung für Neuroradiologie
Universitätskliniken
Josef-Schneider-Str. 11
97080 Würzburg

e-mail: hit@neuroradiologie.uni-wuerzburg.de
FAX: 0931/201-34789
Tel.: 0931/201-34799 oder 34624

Früh postoperative Untersuchung

Name		Histologie	
Vorname		Untersuchungsdatum	
Geburtsdatum	☐ männlich ☐ weiblich	Alle Bilder versandt?	☐ Ja ☐ Nein
Bisherige Therapie			

OP-Datum

Die schattierten Felder sind vom Einsender auszufüllen !

Kranielles MRT oder CT		☐ nativ	☐ mit Kontrast	☐ ohne und mit Kontrast	
Tumorrest	☐ nein	☐ Ring	☐ <1,5 cm	☐ >1,5 cm	☐ Inf. HS ☐ S4
Größe a/c/s cm	cm x	cm x	cm²	cm³	
Hydrozephalus	☐ nein	☐ leichtgradig	☐ mittelgradig	☐ schwergradig	☐ Shunt
KM-Enhancement des Tumorrestes	☐ ja	☐ nein			
Anreichernder Tumoranteil	☐ homogen	☐ überwiegend homogen	☐ überwiegend inhomogen	☐ inhomogen	
	☐ 0-25%	☐ 26-50%	☐ 51-75%	☐ 76-100%	
Meningeose	☐ nein	☐ fraglich	☐ M2a	☐ M2b	☐ M3a ☐ M3b
Metastase wo:					
Spinales MRT	☐ ja ☐ nein	Datum	☐ vollständig	☐ insuffizient	

Resttumor-Staging

☐ S0	☐ S1	☐ S2	☐ S3	☐ S4

Stratifizierung möglich anhand des Bildmaterials ja nein

Freitext :

9.5.1.4.3 Versandschein Nr. 4c für MRT/CT - Bilder EU-RHAB

Frau
Prof. Dr. med. Monika Warmuth-Metz
Referenzzentrum EU-RHAB
Abteilung für Neuroradiologie
Universitätskliniken
Josef-Schneider-Str. 11
97080 Würzburg

e-mail: bit@neuroradiologie.uni-wuerzburg.de
FAX: 0931/201-34789
Tel.: 0931/201-34799 oder 34624

Verlaufsuntersuchung

Name		Histologie	
Vorname		Untersuchungsdatum	
Geburtsdatum	☐ männlich ☐ weiblich	Alle Bilder versandt?	☐ Ja ☐ Nein
Bisherige Therapie			

Die schattierten Felder sind vom Einsender auszufüllen!

Kranielles MRT oder CT		☐ nativ	☐ mit Kontrast	☐ ohne und mit Kontrast		
Tumorlokalisation						
Ausdehnung						
Größe a/c/s cm	cm x cm x		cm²	cm³		
Rest/Rezidivtumor	☐ ja	☐ fraglich	☐ nein			
Begrenzung	☐ scharf (≥90%)	☐ mäßig scharf (≥50%)	☐ unscharf (<50%)			
Ödem	☐ zunehmend	☐ gleich	☐ abnehmend			
Zysten	☐ zunehmend	☐ gleich	☐ abnehmend			
Hydrozephalus	☐ zunehmend	☐ gleich	☐ abnehmend	☐ Shunt		
KM-Enhancement	☐ zunehmend	☐ gleich	☐ abnehmend	☐ kein		
Meningeose	☐ nein	☐ fraglich	☐ M2a	☐ M2b	☐ M3a	☐ M3b
Metastase wo:						
Spinales MRT	☐ ja ☐ nein	Datum	☐ vollständig	☐ insuffizient		

Staging					
☐ CR	☐ PR >50%	☐ IMP 50-25%	☐ SD < 25%	☐ PD >25% oder neu	☐ unbestimmt

Beurteilung möglich anhand des Bildmaterials	ja	nein

Freitext:

9.5.2.1 Versandschein Nr. 5
MRT + RTK Referenzpathologie

Kindertumorregister
Sektion Kinderpathologie
Referenzzentrum EU-RHAB
Dr. C. Vokuhl
Arnold-Heller-Str. 3
Haus 14
24105 Kiel

E-mail:
cvokuhl@path.uni-kiel.de
FAX: 0431-50015603
Tel.: 0431-50015604

Patientenetikett

Name _____

Vorname _____

Geburtsdatum ____.____.____

Geschlecht □ männlich □ weiblich

OP-Datum ____.____.____

Histologie
(örtl. Pathologe) _____

Lokalisation _____

Benötigtes Material:

Für Referenzpathologie und molekulargenetische Untersuchungen bitten wir zu übersenden:

□ 1 repräsentativer Paraffin-Block (wenn nicht möglich bitten wir um Rücksprache!)

□ 5 ungefärbte Kryo-Schnitte des Tumors (oder Kryo-Block) auf Trockeneis (wenn vorhanden)

□ Ja □ Nein

Referenzbegutachtung: Dr. med. C. Vokuhl (Pathologie), Kiel

_____
Datum, Unterschrift (Arzt)

Klinik (Stempel)

Bitte lokalen histopathologischen Befund beilegen. Für die Referenzpathologie nicht benötigtes Paraffinmaterial wird innerhalb von 10 Tagen an den Einsender zurückgeschickt.

9.5.2.2 Versandschein Nr. 6
MRT + RTK
molekulargenetische Diagnostik
- Patient -

Prof. Dr. rer. nat. R. Schneppenheim
Dr. med. U. Kordes
UKE Hamburg
Molekulargenetisches Labor
Pädiatrische Hämatologie und Onkologie
EU-RHAB Referenzzentrum
Martinistraße 52
20246 Hamburg

E-Mail:
f.oyen@uke.de

FAX: 040 7410 58931
Tel.: 040 7410 54742

Patientenetikett

Name _____

Vorname _____

Geburtsdatum ____.____.____

Geschlecht □ männlich □ weiblich

OP-Datum ____.____.____

Histologie
(örtl. Pathologe) _____

Lokalisation _____

Benötigtes Material:

Für Referenzmolekulargenetische Untersuchungen bitten wir zu übersenden:

□ 1 repräsentativer Paraffin-Block (wenn nicht möglich bitten wir um Rücksprache!)

□ 5 ungefärbte Kryo-Schnitte des Tumors (oder Kryo-Block) auf Trockeneis (wenn vorhanden)

□ 2-5 ml EDTA-Blut (oder DNS) des Patienten

□ 2-5 ml Heparin-Blut des Patienten

Die Eltern wurden über die genetischen Untersuchungen aufgeklärt und haben die entsprechenden Einwilligungserklärungen unterzeichnet (Bitte als Kopie mitschicken - *ohne Einwilligung ist eine genetische Untersuchung nicht möglich!):*

□ Ja □ Nein

_____
Datum, Unterschrift (Arzt)

Klinik (Stempel)

9.5.2.2.1 Versandschein Nr. 6a MRT + RTK molekulargenetische Diagnostik *- Familienangehörige-*

Prof. Dr. rer. nat. R. Schneppenheim
Dr. med. U. Kordes
Pädiatrische Hämatologie und Onkologie
Molekulargenetisches Labor
UKE Hamburg
EU-RHAB Referenzzentrum
Martinistraße 52
20246 Hamburg

E-Mail:
f.oyen@uke.de

FAX: 040 7410 58931
Tel.: 040 7410 54742

Patientenetikett

Name _____

Vorname _____

Geburtsdatum ____.____.____

Geschlecht □ männlich □ weiblich

OP-Datum ____.____.____

Histologie (Referenzpathologe) _____

Lokalisation _____

Benötigtes Material:

Bei Bestätigung einer Keimbahnmutation bzw. eines Rhabdoidtumor-Prädispositionssyndroms (RTPS) des Patienten bitten wir für molekulargenetische Untersuchungen der Angehörigen zu übersenden:

□ 5 ml EDTA-Blut (oder DNS) + 10 ml Heparin-Blut (Vater des Patienten)

□ 5 ml EDTA-Blut (oder DNS) + 10 ml Heparin-Blut (Mutter des Patienten)

□ 5 ml EDTA-Blut (oder DNS) + 2-5 ml Heparin-Blut (Geschwister des Patienten)

Die Familienangehörigen wurden über die genetischen Untersuchungen aufgeklärt und haben die entsprechenden Einwilligungserklärungen unterzeichnet.

(Bitte als Kopie mitschicken - *ohne Einverständnis ist eine genetische Untersuchung nicht möglich!)*

□ Ja □ Nein

Datum, Unterschrift (Arzt) Klinik (Stempel)

9.5.2.3 Versandschein Nr. 7
MRT + RTK
molekularzytogenetische Diagnostik
- Patient -

Prof. Dr. med. Reiner Siebert
Institut für Humangenetik
Institutsdirektor
Universitätsklinikum Ulm
EU-RHAB Referenzzentrum
Albert-Einstein-Allee 11
89081 Ulm

Email:
sekretariat.humangenetik@uni-ulm.de

FAX: 0731-500-65402
Tel.: 0731-500-65400

Name _____

Vorname _____

Geburtsdatum ____.____.____

Patientenetikett

Geschlecht □ männlich □ weiblich

OP-Datum ____.____.____

Histologie
(örtl. Pathologe) _____

Lokalisation _____

Benötigtes Material:

Für die molekularzytogenetische Untersuchungen bitten wir zu übersenden:

□ 2 ungefärbte Paraffinschnitte des Tumors (oder 1 repräsentativer Paraffin-Block)

□ 2-5 ml Heparin-Blut des Patienten

□ optional falls möglich: 2-5 ml EDTA-Blut oder DNS des Patienten für etwaige molekulargenetische Analysen

Die Eltern wurden über die genetischen Untersuchungen aufgeklärt und haben die entsprechenden Einwilligungserklärungen unterzeichnet (Bitte als Kopie mitschicken - *ohne Einwilligung ist eine genetische Untersuchung nicht möglich!):*

□ Ja □ Nein

Datum, Unterschrift (Arzt)

Klinik (Stempel)

9.5.2.3.1 Versandschein Nr. 7a
MRT + RTK
molekularzytogenetische Diagnostik
- Familienangehörige-

Prof. Dr. med. Reiner Siebert
Institut für Humangenetik
Institutsdirektor
Facharzt für Humangenetik
Universitätsklinikum Ulm
EU-RHAB Referenzzentrum
Albert-Einstein-Allee 11
89081 Ulm

Email:
sekretariat.humangenetik@uni-ulm.de

FAX: 0731-500-65402
Tel.: 0731-500-65400

BETROFFENES KIND

Name _____

Vorname _____

Geburtsdatum ____.____.____

Patientenetikett

MUTTER

Name _____

Vorname _____

Geburtsdatum ____.____.____

VATER

Name _____

Vorname _____

Geburtsdatum ____.____.____

Benötigtes Material:
Bei Bestätigung einer Keimbahnmutation bzw. eines Rhabdoidtumor-Prädispositionssyndroms (RTPS) des Patienten bitten wir für molekularzytogenetische Untersuchungen der Angehörigen zu übersenden:

□ 5 ml Heparin-Blut (und falls möglich 5 ml EDTA-Blut oder DNS) der Mutter
□ 5 ml Heparin-Blut (und falls möglich 5 ml EDTA-Blut oder DNS) des Vaters
□ 5 ml Heparin-Blut (und falls möglich 5 ml EDTA-Blut oder DNS) des Angehörigen (bei Kindern reichen 2-5 ml) (Verwandtschaftsgrad?)_____

Die Familienangehörigen wurden über die genetischen Untersuchungen aufgeklärt und haben die entsprechenden Einwilligungserklärungen unterzeichnet (Bitte als Kopie mitschicken - *ohne Einverständnis ist eine genetische Untersuchung nicht möglich!):*

□ Ja □ Nein

_____
Datum, Unterschrift (Arzt) Klinik (Stempel)

9.5.2.4 Versandschein Nr. 8
Radiologie MRT/RTK

Herrn
Prof. Dr. med. Thomas Kröncke
Abt. für diagnostische Radiologie
Klinikum Augsburg
Stenglinstr. 2
86316 Augsburg

E-Mail:
radiologie@klinikum-augsburg.de

Tel. 0821/400-2441
Fax: 0821/400-3312

Name des/der Patienten/in _____ **Geburtsdatum** _____

Einsendende/r Arzt/Ärztin: _____

Datum OP_____

Primärdiagnostik / Staging _____

		Datum
o ……..	präoperativ	___.___.___
o ……..	früh-postoperativ	___.___.___
o ……..	Staging	___.___.___

einsendende Klinik
(Stempel)

Im Verlauf des European Rhabdoid Registry

o nach Zyklus Nr. ___ o nach Bestrahlung o anderer Zeitpunkt: _____

o …….. ___.___.___ (Datum) o …… ___.___.___ (Datum)

Abschlusstaging

o nach Zyklus Nr. ___ o nach Dauerttherapie o anderer Zeitpunkt: _____

o nach HDCT o nach Bestrahlung

o …….. ___.___.___ (Datum) o …… ___.___.___ (Datum)

Der lokale schriftliche Befund sollte als Kopie beigelegt werden. Aus diesem sollten die Angaben zur Durchführung der Kontrastmitteldarstellung hervorgehen.

9.5.2.4.1 Versandschein Nr. 8a für MR/CT - Bilder *(MRT/RTK)* **EU-RHAB**

Herrn
Prof. Dr. Thomas Kröncke
Klinikum Augsburg
Abt. Diagnostische Radiologie
Referenzzentrum EU-RHAB
Stenglinstr. 2
86156 Augsburg

E-Mail:
radiologie@klinikum-augsburg.de
Tel.:
0821/400-2441
FAX:
0821/400-3312

Erstuntersuchung

Name		Histologie	
Vorname		Untersuchungsdatum	
Geburtsdatum	☐ männlich ☐ weiblich	Alle Bilder versandt?	☐ Ja ☐ Nein
Bisherige Therapie			

Die schattierten Felder sind vom Einsender auszufüllen!

MRT oder CT ☐ nativ ☐ mit Kontrast ☐ ohne und mit Kontrast

Tumorlokalisation				
Ausdehnung				
Ursprung				
Größe a/c/s cm	cm x	cm x	cm²	cm³
Begrenzung	☐ scharf (≥90%)	☐ mäßig scharf (≥50%)	☐ unscharf (<50%)	
Ödem	☐ ipsilateral	☐ kontralateral	Cm	
Zysten	☐ Ja	☐ Nein	☐ wie Liquor	☐ heller als Liquor
KM-Enhancement	☐ kräftig	☐ mittelstark	☐ leicht	☐ kein
Anreichernder Tumoranteil	☐ homogen	☐ überwiegend homogen	☐ überwiegend inhomogen	☐ inhomogen
	☐ 0-25%	☐ 26-50%	☐ 51-75%	☐ 76-100%
Metastase wo:				
Spinales MRT	☐ ja ☐ nein	Datum	☐ vollständig	☐ insuffizient

Tumorstaging				
☐ T1	☐ T2	☐ T3/T3a	☐ T3b	☐ T4

☐ MRT

T2	☐ nicht	☐ hyperintens	☐ isointens	☐ hypointens
	☐ homogen	☐ überwiegend homogen	☐ überwiegend inhomogen	☐ inhomogen
T1	☐ nicht	☐ hyperintens	☐ isointens	☐ hypointens
	☐ homogen	☐ überwiegend homogen	☐ überwiegend inhomogen	☐ inhomogen

☐ CT

Dichte	☐ hypodens	☐ isodens	☐ hyperdens	☐ Blut
	☐ homogen	☐ überwiegend homogen	☐ überwiegend inhomogen	☐ inhomogen
Verkalkungen	☐ nein	☐ grob	☐ fein	

Stratifizierung möglich anhand des Bildmaterials ja nein

9.5.2.4.2 Versandschein Nr. 8b für MR/CT - Bilder *(MRT/RTK)* **EU-RHAB**

Herrn
Prof. Dr. Thomas Kröncke
Klinikum Augsburg
Abt. Diagnostische Radiologie
Referenzzentrum EU-RHAB
Stenglinstr. 2
86156 Augsburg

E-mail:
radiologie@klinikum-augsburg.de
Tel.:
0821/400-2441
FAX:
0821/400-3312

Früh postoperative Untersuchung

Name		Histologie	
Vorname		Untersuchungsdatum	
Geburtsdatum	☐ männlich ☐ weiblich	Alle Bilder versandt?	☐ Ja ☐ Nein
Bisherige Therapie			

OP-Datum

Die schattierten Felder sind vom Einsender auszufüllen!

MRT oder CT ☐ nativ ☐ mit Kontrast ☐ ohne und mit Kontrast

Tumorrest	☐ nein	☐ Ring	☐ <1,5 cm	☐ >1,5 cm	☐ Inf. HS	☐ S4
Größe a/c/s cm	cm x	cm x	cm²	cm³		
KM-Enhancement des Tumorrestes	☐ ja	☐ nein				
Anreichernder Tumoranteil	☐ homogen	☐ überwiegend homogen	☐ überwiegend inhomogen	☐ inhomogen		
	☐ 0-25%	☐ 26-50%	☐ 51-75%	☐ 76-100%		
Metastase wo:						
Spinales MRT	☐ ja ☐ nein	Datum	☐ vollständig	☐ insuffizient		

Resttumor-Staging

☐ S0	☐ S1	☐ S2	☐ S3	☐ S4

Stratifizierung möglich anhand des Bildmaterials **ja** **nein**

Freitext :

9.5.2.4.3 Versandschein Nr. 8c für MR/CT - Bilder *(MRT/RTK)* **EU-RHAB**

Herrn
Prof. Dr. Thomas Kröncke
Klinikum Augsburg
Abt. Diagnostische Radiologie
Referenzzentrum EU-RHAB
Stenglinstr. 2
86156 Augsburg

E-Mail:
radiologie@klinikum-augsburg.de
Tel.:
0821/400-2441
FAX:
0821/400-3312

Verlaufsuntersuchung Nr.

Name		Histologie	
Vorname		Untersuchungsdatum	
Geburtsdatum	☐ männlich ☐ weiblich	Alle Bilder versandt?	☐ Ja ☐ Nein
Bisherige Therapie			

Die schattierten Felder sind vom Einsender auszufüllen !

MRT oder CT ☐ nativ ☐ mit Kontrast ☐ ohne und mit Kontrast

Tumorlokalisation				
Ausdehnung				
Größe a/c/s cm	cm x	cm x	cm²	cm³
Rest/Rezidivtumor	☐ ja	☐ fraglich	☐ nein	
Begrenzung	☐ scharf (≥90%)	☐ mäßig scharf (≥50%)	☐ unscharf (<50%)	
Ödem	☐ zunehmend	☐ gleich	☐ abnehmend	
Zysten	☐ zunehmend	☐ gleich	☐ abnehmend	
KM-Enhancement	☐ zunehmend	☐ gleich	☐ abnehmend	☐ kein
Metastase wo:				
Spinales MRT	☐ ja ☐ nein	Datum	☐ vollständig	☐ insuffizient

Staging					
☐ CR	☐ PR >50%	☐ IMP 50-25%	☐ SD < 25%	☐ PD >25% oder neu	☐ unbestimmt

Beurteilung möglich anhand des Bildmaterials ja nein

Freitext:

9.5.3.1 Versandschein Nr. 9 „Liquor“ für Tumormarkerstudie

Herrn
Dr. med. Kornelius Kerl
Tumorbiologie EURHAB
Institut für molekulare Tumorbiologie
Robert-Koch-Straße 43
48149 Münster

E-mail:
kornelius.kerl@ukmuenster.de

FAX: 0251 83 55318
Tel.: 0251 83 55303

Patientenetikett

Name _____

Vorname _____

Geburtsdatum ____.____.____

Geschlecht □ männlich □ weiblich

Tag der Entnahme ____.____.____

Behandlungszeitpunkt
□ vor Therapiebeginn

□…während der Therapie *(bitte spezifizieren)*_____

□…nach Therapieende

Tumorstatus
□ makroskopisch sichtbarer Tumor (Bildgebung zuletzt am _____)

□ makroskopisch kein sichtbarer Tumor (Bildgebung zuletzt am _____)

Benötigtes Material:

Für das Forschungsprojekt „Tumormarker“ bitten wir zu übersenden:

□ 2 - 5ml Liquor (bitte nach der Punktion einfrieren und auf Trockeneis einschicken)

Die Eltern wurden über das Forschungsprojekt „Tumormarker“ aufgeklärt und haben die entsprechenden Einwilligungserklärungen unterzeichnet.

□ Ja □ Nein

_____
Datum, Unterschrift Arzt

Klinik (Stempel)

9.5.4 Forms for reference evaluation AT/RT - English

9.5.4.1 Reference evaluation neuropathology and molecular genetics (Prof. Hasselblatt / Münster, Germany)

9.5.4.2 Reference evaluation CSF (Prof. Frühwald / Augsburg, Germany)

9.5.4.3 Reference evaluation Neuroradiology (Prof. Warmuth-Metz / Würzburg, Germany)

9.5.5 Forms for reference evaluation MRT/RTK – English

9.5.5.1 Reference evaluation pathology (Dr. Vokuhl / Kiel, Germany)

9.5.5.2 Reference evaluation molecular genetics – patient – (Prof. Schneppenheim / Hamburg, Germany)

9.5.5.3 Reference evaluation molecular genetics – family members – (Prof. Schneppenheim / Hamburg, Germany)

9.5.5.4 Reference evaluation human genetics – patient – (Prof. Siebert / Ulm, Germany)

9.5.5.5 Reference evaluation human genetics – family members – (Prof. Siebert / Ulm, Germany)

9.5.5.6 Reference evaluation radiology (Prof. Kröncke / Augsburg, Germany)

9.5.4.1 Reference Evaluation Neuropathology and Genetic Analyses AT/RT

Prof. Martin Hasselblatt
Reference evaluation EU-RHAB
Institute of Neuropathology
University Hospital Münster
Pottkamp 2
48149 Münster - GERMANY

E-mail:
hasselblatt@uni-muenster.de

FAX: 0049 251 83 56971
Tel.: 0049 251 83 56967

Surname _____

Name _____

Date of birth ____.____.____

Gender □ male □ female

Date of surgery ____.____.____

Histology
(local pathologist) _____

Localisation _____

patient label

Material:
For reference neuropathology and molecular genetic studies of tumor material (Professoren Hasselblatt, Siebert and Schneppenheim) please mail

□ one representative paraffin-block

□ if available, additional fresh-frozen material would be highly appreciated

□ 2 - 5 ml EDTA Blood of the patient (or DNA)

□ 2 - 5 ml Heparin Blood of the patient

_____
Date, signature

Treatment centre
(stamp)

Please enclose report of local pathologist.

Material not used will be returned within 10 days.

9.5.4.2 Reference evaluation CSF AT/RT

Prof. Dr. Dr. Michael Frühwald
I. Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg – GERMANY

e-mail:
michael.fruehwald@klinikum-augsburg.de

FAX: 0049 821 400-179201
Tel.: 0049 821 400-9201

Patient`s name _____ **Date of birth** _____

Treating physician: _____

Primary diagnostic / staging: _____

		Date of punction
	Date of surgery:	___.___.___
□ Lumbar	Pre-operative	___.___.___
□ Ventricular	Intra-operative	___.___.___
□ Lumbar	Intra-operative	___.___.___
□ Ventricular	Post-operative	___.___.___

Treatment centre (stamp)

Time point within EU-RHAB therapy:_____

□ After course no. ___ □ After radiation □ Other time point: _____

CSF (lumbar/ventricular) Date of tap: ___.___.___

Delete as applicable

Please send at least 5 (more slides for increased diagnostic accuracy)

unstained air-dried cytospins!

9.5.4.3 Reference evaluation neuroradiology AT/RT

Frau
Prof. Dr. med. Monika Warmuth-Metz
Referenzzentrum EU-RHAB
Abteilung für Neuroradiologie
Universitätskliniken
Josef-Schneider-Str. 11
97080 Würzburg-GERMANY

E-mail: hit@neuroradiologie.uni-wuerzburg.de

FAX: 0049 931-201-2685
Tel.: 0049 931-201-2626 / 5791

Name of patient _____ **Date of birth** _____

Treating physician: _____

Primary diagnostic / staging: _____

		Date
o cranial	Pre-operatively	___.___.___
o cranial	Early post-operatively	___.___.___
o spinal	Staging	___.___.___

Treatment centre (stamp)

Time point within EU-RHAB therapy: _____

□ After course no. ___ □ After radiation □ Other time point: _____

o cranial ___.___.___ (Date) o spinal ___.___.___ (Date)

Final staging

□ After course no. ___ □ After radiation □ Other time point: _____

o After HDCT

o cranial ___.___.___ (Date) o spinal ___.___.___ (Date)

Please enclose copy of local report. Please indicate details on contrast enhanced imaging.

9.5.5.1 Reference Histopathology

MRT/RTK

Kindertumorregister
Sektion Kinderpathologie
Referenzzentrum EU-RHAB
Dr. med. C. Vokuhl
Arnold-Heller-Str. 3 – Haus 14
24105 Kiel - GERMANY

e-mail:
cvokuhl@path.uni-kiel.de

FAX: +49 431-500 15603
Tel.: +49 431-500 15604

Patient label

Patient surname _____

First name _____

Date of birth ____.____.____

Gender □ male □ female

Date of surgery ____.____.____

Histology
(local Pathologist) _____

Localisation _____

Material needed for confirmation of diagnosis:

We are kindly asking you to send:

□ 1 representative paraffin block (if not possible please contact us!)

□ if possible additional 5 unstained cryo sections of the tumor on dry ice

Please attach report of local pathologist.

We kindly ask you for allowance to keep the paraffine block

The parents have been informed about investigations and signed informed consent.

_____
Date, signature

Treatmend center (stamp)

9.5.5.2 Reference evaluation
MRT + RTK
molecular genetics
- Patient -

Prof. Dr. rer. nat. R. Schneppenheim
Dr. med. U. Kordes
UKE Hamburg
Molekulargenetisches Labor
Pädiatrische Hämatologie und Onkologie
EU-RHAB Referenzzentrum
Martinistraße 52
20246 Hamburg

E-Mail:
f.oyen@uke.de

FAX: 040 7410 58931
Tel.: 040 7410 54742

Patient Label

Surname _____

First name _____

Date of birth ____.____.____

Gender □ male □ female

Surgery ____.____.____

Histology
(local Pathologist) _____

Localisation _____

Mandatory Material:

For Reference molecular genetics please send:

□ 1 repräsentative paraffin-block

□ 5 unstained cryo sections of the tumor on dry ice

□ 2-5 ml EDTA blood (or DNS) of the patient

□ 2-5 ml Heparin-blood of the patient

The parents have been informed about investigations and have signed informed consent forms

□ yes □ no

_____
Date, signature

Treatment center stamp

9.5.5.3 Reference evaluation MRT + RTK molecular genetics *- Family members -*

Prof. Dr. rer. nat. R. Schneppenheim
Dr. med. U. Kordes
Pädiatrische Hämatologie und Onkologie
Molekulargenetisches Labor
UKE Hamburg
EU-RHAB Referenzzentrum
Martinistraße 52
20246 Hamburg

E-Mail:
f.oyen@uke.de

FAX: 040 7410 58931
Tel.: 040 7410 54742

Patient label

Surname _____

First name _____

Date of birth ____.____.____

Gender □ male □ female

Surgery ____.____.____

Histology (Reference Pathologist _____

Localisation _____

In case of a germline mutation or a rhabdoidtumor predisposition syndrome of the patient, please send blood samples of the family members for molecular cytogenetic diagnosis:

□ 5 ml EDTA-blood (or DNS) + 10 ml Heparin-blood of the father

□ 5 ml EDTA-blood (or DNS) + 10 ml Heparin-blood of the mother

□ 5 ml EDTA-blood (or DNS) + 2-5 ml Heparin-blood of the siblings

The parents have been informed about investigations and have signed informed consent forms

□ yes □ no

Date, signature Treatment center stamp

9.5.5.4 Reference Human Genetics MRT + RTK

- Patient -

Direktor
Prof. Dr. med. Reiner Siebert
Institut für Humangenetik
Universitätsklinikum Ulm
EU-RHAB Referenzzentrum
Albert-Einstein-Allee 11
89081 Ulm -

E-mail:
sekretariat.humangenetik@uni-ulm.de

FAX: 0731-500-65402
Tel.: 0731-500-65400

Patient label

Patient's surname _____

First name _____

Date of birth ____.____.____

Gender □ male □ female

Date of surgery ____.____.____

Histology
(local Pathologist) _____

Localisation _____

Mandatory Material for confirmation of diagnosis:

□ 2 unstained cryo sections of the tumor on dry ice and 1 representative paraffin block

□ 2-5 ml Heparin-blood of the patient

□ optional if possible: 2-5 ml EDTA blood oder DNS of the patient

The parents have been informed about investigations and have signed informed consent forms

□ Yes □ No

Date, signature

Treatment center stamp

9.5.5.5 Reference Human Genetics
MRT + RTK

- Family members -

Direktor
Prof. Dr. med. Reiner Siebert
Institut für Humangenetik
Universitätsklinikum Ulm
EU-RHAB Referenzzentrum
Albert-Einstein-Allee 11
89081 Ulm

E-mail:
sekretariat.humangenetik@uni-ulm.de

FAX: 0731-500-65402
Tel.: 0731-500-65400

PATIENT NAME

Surname _____

First name _____

Date of birth ____.____.____

Patient label

MOTHER

Surname _____

First name _____

Date of birth ____.____.____

FATHER

Surname _____

First name _____

Date of birth ____.____.____

In case of a germline muation or a rhabdoidtumor predisposition syndrome of the patient please send blood samples of the family members for molecular cytogenetic diagnosis:

□ 5 ml Heparin-Blood (and if possible 5 ml EDTA-Blood oder DNS) of the mother
□ 5 ml Heparin-Blood (and if possible 5 ml EDTA-Blood oder DNS) of the father
□ 5 ml Heparin-Blood (and if possible 5 ml EDTA-Blood oder DNS) of siblings (2-5ml for childs)
(relation fo patient?)_____

The parents have been informed about investigations and have signed informed consent forms.

□ Yes □ No

_____
Date, signature

Treatment center stamp

9.5.5.6 Reference evaluation Radiology MRT/RTK

Herrn
Prof. Dr. med. Thomas Kröncke
Abt. für diagnostische Radiologie
Klinikum Augsburg
Stenglinstr. 2
86316 Augsburg - GERMANY

E-Mail:
radiologie@klinikum-augsburg.de

Tel. 0821/400-2441
Fax: 0821/400-3312

Name of patient _____ **Date of birth** _____

Treating physician: _____

Primary diagnostic / staging: _____

		Date
o	Pre-operatively	___.___.___
o	Early post-operatively	___.___.___
o	Staging	___.___.___

Treatment centre (stamp)

Time point within EU-RHAB therapy: _____

□ After course no. ___ □ After radiation □ Other time point: _____

o ___.___.___ Date o ___.___.___ Date

Final staging

□ After course no. ___ □ After radiation □ Other time point: _____

o After HDCT

o ___.___.___ Date o ___.___.___ Date

Please enclose copy of local report. Please indicate details on contrast enhanced imaging

ADDENDUM

PART I:

CONSENSUS THERAPY RECOMMENDATIONS

FOR PATIENTS WITH RHABDOID TUMORS OF THE CNS

(AT/RT – atypical teratoid / rhabdoid tumors)

Responsibility for the use of the therapeutic recommendations in this document and all clinical decisions lie at the discretion of the treating physician.

I.1 Diagnostic evaluation

Basic Assessment

- complete medical history
- physical examination including neuropediatric evaluation
- weight, height, body surface area and pubertal status
- Karnofsky Performance Status (KPS) or Lansky play score
- complete blood count (CBC) and serum chemistries (electrolytes, liver function tests, kidney function tests)
- blood type
- transfusion associated viral status (i.e. hepatitis A, B and C, HIV, CMV, Parvovirus B19)
- calculation of GFR or if possible measurement of GFR
- urine analysis: protein, α1-microglobulin, creatinin, phosphate, calculation of tubular phosphate reabsorption and proteinuria in 24 h

Initial Staging

- Imaging of the primary tumor: ultrasound and MRI scan with measurement of tumor volume (for details see chapter I.2)
- Skeletal system: if available PET-CT, alternatively Tc bone scan, MRI of sites suspicious on bone scan (details see chapter I.2)
- Whole body MRI (see below)
- Cerebro-Spinal-Fluid: local pathology and reference evaluation (competence centre)

It is recommended that imaging is performed fewer than 28 days prior to the start of treatment. Documentation of the dimensions of the tumour is obtained. Data will be reviewed centrally (see below). Detailed guidelines for imaging, especially neuroradiologic imaging, are given below. Early postoperative imaging (24 – 48 hours after neurosurgery) will help delineate postoperative residual tumor from non-specific tissue changes associated with the operative procedure.

Pre-treatment evaluation

The following pre-treatment evaluations are recommended prior initiation (suggested within 14 days) of therapy:

- physical examination including neuropediatric evaluation
- weight, height and body surface area
- Karnofsky Performance Status (KPS) or Lansky play score
- documentation of doses of steroids (if any) and any hormone replacement therapy or antiepileptic or behavioral medication
- complete blood count (CBC) and serum chemistries (electrolytes, liver function tests, kidney function tests)
- ECG, echocardiogram, EEG, audiometry or BERA
- genetic evaluation in children with a potentail rhabdoid tumor predisposition syndrom, in all children below two years with multifocal disease, synchronous rhabdoid tumors and when genetic mutations are known in the pedigree (e.g. Li Fraumeni…)
  (see also chapter 6.3 and figure 6.2)
- Please send Liquor CNS-Reference Evaluation to Professor Frühwald/Augsburg-Germany 14 days after surgery and prior to chemotherapy (AT/RT only)
- a urine pregnancy test for women of childbearing potential should be performed within 7 days prior to administration of chemotherapy

In addition, the patient/parents must be thoroughly informed about all aspects of any therapy, including evaluations and all regulatory requirements for informed consent. Written informed consent must be obtained by both parents (and patient where appropriate) prior to initiation of therapy.

Prior to each scheduled dose of chemotherapy

Performed on Day 1 prior to each cycle or within 72 hours prior to Day 1:

- documentation of concomitant drugs (particularly steroids, dose and duration during and after radiotherapy)
- physical examination including neurologic evaluation, vital signs, height and weight (percentiles)
- Karnofsky Performance Status or Lansky play score
- CBC and serum chemistries
- imaging (see below)
- ECG and echocardiography prior to anthracycline-containing elements
- Severe adverse events will be assessed according to the Common Toxicity Criteria (CTCAE) on an ongoing basis during therapy.

If a cycle of chemotherapy is delayed, only the CBC must be repeated weekly or within 72 hours of that day until treatment is given. The physical examination, including neurologic evaluation, vital signs, weight, neurologic performance grading and Karnofsky Performance Status should be repeated on the actual day of dosing (or within 72 hours prior to this day) if the actual day of dosing is more than 2 weeks delayed.

- **Whole body MRI** is recommended to exclude multifocality in all patients with rhabdoid tumors. If this is not possible imaging studies as listed below are strongly recommended. In AT/RT patients the response and tumor-volume measurement is best performed by MRI. Whole body MRI does however not replace MRI imaging of specific tumor sites (better resolution). In patients with MRT or RTK these controls may be performed by sonographic methods, but MRI is the recommended method.

- **Echocardiographic evaluation** is recommended prior to each anthracycline-containing element.

- In case of **tumor progression** imaging of other loci with potential involvement has to be considered (e.g. kidney in AT/RT) due to the possibility of a rhabdoid tumor predisposition syndrome (see genetics).

Examination during chemotherapy

See figures I.1 – I.4

European Rhabdoid Registry – schedule of examinations

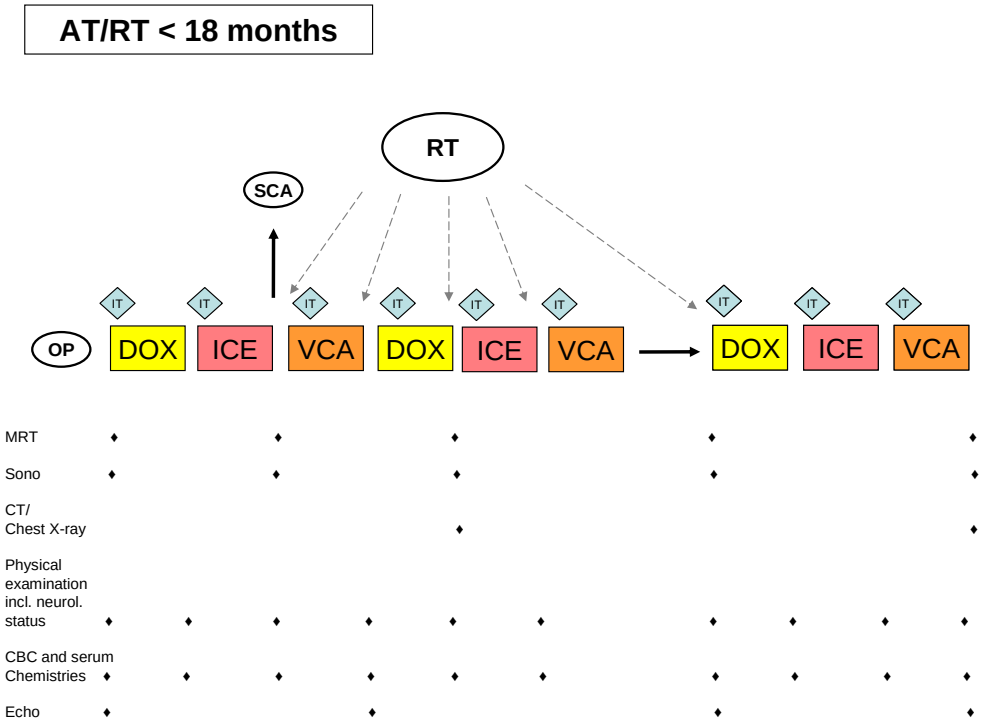

Figure I.1: AT/RT < 18 months, conventional therapy

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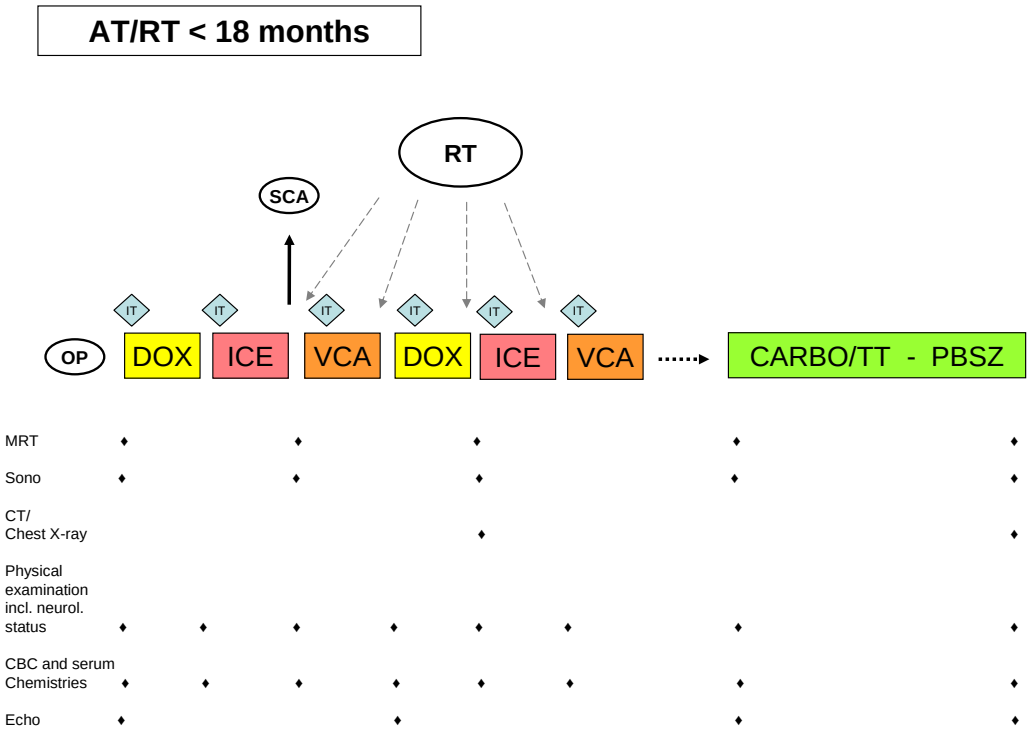


Figure I.2: AT/RT < 18 months HD-chemotherapy

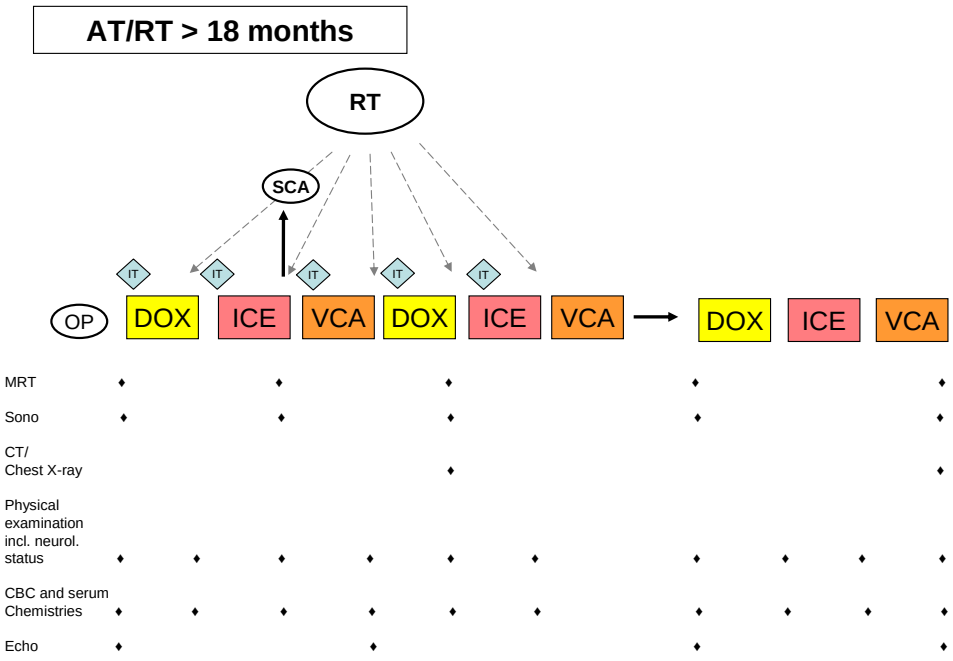


Figure I.3: AT/RT > 18 months, conventional therapy

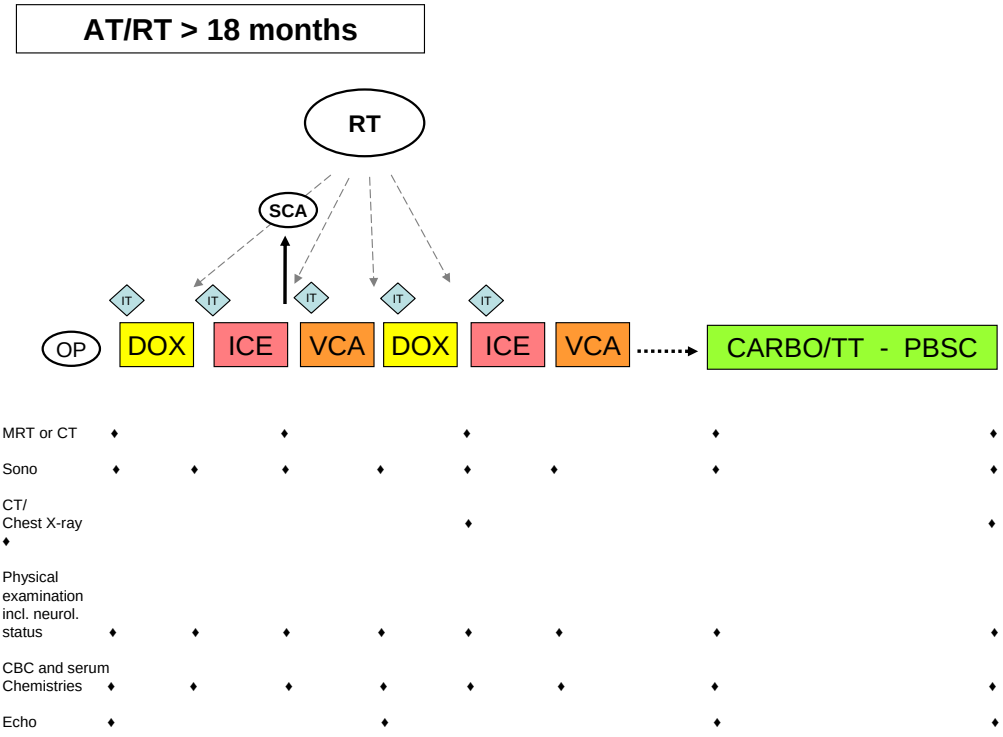


Figure I.4: AT/RT > 18 months HD-chemotherapy

	1. / 2. Year after completion of therapy	3. - 5. Year after completion of therapy	6. - 10. Year after completion of therapy	Second decade after completion of therapy
Physical and neurologic examination	bimonthly	every 6 months	twice yearly or yearly	yearly
MRI cranial	every 3 months	twice to four times yearly	yearly	if symptomatic
MRI spinal	every 6 months	in case of symptoms	in case of symptoms	if symptomatic
Lumbar tap	twice yearly (chemotherapy only)	if symptomatic	if symptomatic	if symptomatic
Height, weight, pubertal status	every 3-4 months	every 6 months	yearly	individually
Bone age	yearly	only if deviations of normal puberty developement		
T3/T4/TSH, IGF1, IGFBP3, Cortisol, DHEAS*	yearly	yearly	yearly	every second year
Sono thyroid gland	twice yearly	yearly	yearly	yearly
CBC	every second month	every 6 months	yearly	yearly
Renal function Serum-chemistry	bimonthly	every 6 months	yearly	yearly
Radiotherapist**	yearly	yearly	yearly	yearly
Ophthalmologist	twice yearly	yearly	if symptomatic	if symptomatic
ENT consult	yearly	if symptomatic	if symptomatic	if symptomatic
Echo/ECG	twice yearly	yearly	yearly	yearly

*with onset of puberty LH/FSH, testosteron, history of menses and contraception; 2 years after completion of therapy function testing; ** initiate 6 months after end of radiotherapy

Table I.1: Follow-up examinations in patients with rhabdoid tumors of the CNS (AT/RT)

I.2 Imaging Studies - Atypical teratoid, rhabdoid tumors (AT/RT)

Initial interpretation of neuroradiologic imaging is performed by the local radiologist. The neuroradiology report should contain all information necessary for evaluation as indicated in the CRF (e.g. pre- and postoperative tumor size).

Central Neuroradiology Review in Germany is performed by the:

Institute of Neuroradiology, University of Würzburg
Prof. Dr. Monika Warmuth-Metz
Josef-Schneider-Straße 11, 97080 Würzburg

It may be submitted through a central imaging server. The reference neuroradiology panel will evaluate the fulfilment of response criteria. Neuroradiological review should be performed until the end of therapy. The modality of imaging depends on the individual patient and the situation of the institution. In general, MRI is preferable over CT imaging. If early postoperative evaluation can only be done by CT, preoperative evaluation should also be done by CT with and without contrast enhancing agents. Evaluation of the spine should always be done by MRI. Pre- and postoperative imaging should be performed with and without contrast and using identical sequences. **Postoperative imaging needs to be performed 24 to 48 hours following surgery.** Following more than 48 up to 72 hours non-specific postoperative disturbances of the blood-brain-barrier may not be distinguishable from enhancement caused by the tumor.

Technical aspects:

Cranial MRI:
The following are minimal requirements for imaging and individual protocols may be added:
T2-SE-double echo sequences in axial direction. TSE-sequences are also admissible, even though not desired. Proton density sequences may be replaced by FLAIR sequences. Maximal slice thickness should be 5-6 mm. T1-SE-sequences with and without contrast in axial direction. If possible no gradient echo sequences (exeption: 3 T scanners). Slice thickness and position should be as in the T2-sequence. Optional is a T1-SE-sequence following contrast application in one or two additional axes. Most importantly imaging should allow an accurate comparison to previous imaging. If axial T2-imaging is not available from previous exams this should be performed in addition. All imaging should contain size markers.

*Spin*al MRI:
T1 sagittal slices following contrast. In general the evaluation should be performed following cranial imaging. Maximum slice thickness should be 3 mm. In case of uncertain findings (i.e. blood vessels can not be distinguished from meningeosis) additional axial sequences of the regions in question have to be performed. Axial slices at the conus and epiconus level are very often necessary. The dural sac (usually ending at the level of S2-3) has to be covered completely.
T2 weighted sequences (gradient echo sequences or TSE-sequences) are of use only under circumstances when metastases do not take up contrast enhancing agents or when there are medullary tumors, which is very rarely the case. If cranial and spinal imaging is performed in the same setting, only spinal T1 with contrast should be performed (sagittal and axial).

In certain situations (synchronous or metasynchronous, multifocal rhabdoid tumors) it is adviseable to follow the imaging recommendations as listed below for extra-cranial RT. Whenever possible whole body MRI may help exclude synchronous and multifocal RT at diagnosis. Alternatively metastases may be excluded by sonography of the abdomen, CT of the thorax and possibly technetium scintigraphy.

For further information see also the imaging protocol for patients in European SIOP Brain Tumour Studies (16.09.09) (chapter IV.4).

I.3 Surgical approach to patients with AT/RT

Primary resection is of highest importance since many patients are threatened by the mass lesion and disturbances in CSF flow which lead to hydrocephalus necessitating emergent surgery.

A radical resection in the sense of a compartment resection is impossible in AT/RT. Primary aim of the neurosurgical procedure is therefore a complete resection according to the operation microscope. This is defined in a way that at the end of surgery there should be no visible residual tumor under the operation microscope.

The topographical relation to cranial nerves and nuclei of the brain and other important structures forbid aggressive neurosurgical interventions to avoid unnecessary neurological deficits post-surgery. If the tumor is in close relation to the rhomboid fossa or infiltrates the rhomboid fossa, tumor tissue should be left *in situ*. Tumors within the cerebellopontine angle need to be approached with alert awareness due to the potential for loss of function in cranial nerves VII, VIII, IX and X.

Microsurgical operation techniques enable the surgeon to remove most of the tumor tissue in over 50% of patients. Clinicians must be cautioned of the phenomenon of the posterior fossa syndrome which is characterized by cerebellar mutism. This phenomenon is most of the time transient in nature, but may cause permanent neurocognitive deficits. Permanent placement of a VP-shunt due to hydrocephalus becomes necessary in about 20 % of patients.

Extent of resection

The extent of resection should be judged by the neurosurgeon applying the SIOP recommendations (Gnekow, 1995):

Due to inherent differences in the method of visualising residual tumor, surgical description and early postoperative neuroimaging may arrive at different judgements as to the extent of the achieved resection. Classification of the extent of resection should therefore be a radiodiagnostic classification supported by the surgical report.

Four categories may be distinguished:

I. Total resection (S1, R1): surgical and radiographic judgements are congruent.

II. Near total resection (S2, R1-2): Leaving a small residual behind can result in rim enhancement at radiologic investigation or may not be visible.

III. Partial resection (S1-3, R3): If postoperative scanning reveals measurable tumor of any size, surgical estimate may or not may be congruent.

IV. Biopsy (S4, R4): The surgical report and radiodiagnostic findings should be identical.

Table I.2: Extent of Resection – Surgical Assessment	
S 1	Total resection, no recognizable residues
S 2	Remaining tumor of less than 1,5 cm in size, possible localized invasion
S 3	Remaining tumor of more than 1,5 cm
S 4	Biopsy

Table I.3: Extent of Resection – Radiological Assessment	
R 1	No visible tumor on early postoperate CT or MR without and with contrast enhancement
R 2	Rim enhancement at the operation site only
R 3	Residual tumor of a measurable size
R 4	No significant change to preoperative tumor size

Table I.4: Categories Defining the extent of Resection		
	Radiographic result	Surgical judgement
I	R 1	S 1
II	R 1 or R 2	S 2
III	R 3	S 1, S 2 or S 3
IV	R 4	S 4

Second-Look-Surgery

The following situations may be indications for second-look-surgery:

- Total or partial resection of primary tumor, post-operative (residual) tumor or recurrent tumor can lead to increased overall survival.
- Total or partial resection prior to radiotherapy may lead to a smaller radiation field.
- Total or partial resection prior to chemotherapy may enhance the effects of post-operative chemotherapy.

In case second look surgery is performed, material should be sent for reference pathology evaluation.

I.4 Chemotherapeutic approach to patients with AT/RT

The protocol of the European Rhabdoid Registry contains the following recommendations for standardized therapy, which were generated from data derived from the current literature, the investigators' own experience and data derived from the GPOH studies for high risk Wilms tumors, soft tissue sarcomas and malignant brain tumors of infants and children.

The therapeutic recommendations have been consented by the SIOP working group on AT/RT of the SIOP Brain tumor committee.

!!! ALL SCHEDULES CAN BE FOUND IN THE APPENDIX !!!

Since it remains unclear whether High Dose Chemotherapy (HDCT) is beneficial to children with AT/RT chemotherapy may be performed either as a sequence of

a) Chemotherapy:

DOX: doxorubicin, intra-ventricular MTX
ICE: ifosfamide, carboplatinum, etoposide, intra-ventricular MTX
VCA: vincristine, cyclophosphamide, actinomycin-D, intra-ventricular MTX

NO intra-ventricular therapy during or after radiation!

or a sequence of conventional chemotherapy with a consolidation using HDCT.

b) High Dose Chemotherapy:

carboplatinum / thiotepa

Radiotherapy (RT):

RT should be performed as soon as possible but not in children below the age of 18 months. **NO** intra-ventricular therapy during or after radiation. For details see chapter radiotherapy.

Second-look-surgery:

Generally a second-look-surgery may be necessary or useful at any time during therapy. In case second look surgery is performed, material should be sent for reference pathology evaluation (see chapter 9.6.1.1 or IV.8.1.2).

Stem-cell-separation:

Collection of stem-cells may be conducted starting after the first ICE-element. If necessary another time point following ICE is also possible.

High Dose Chemotherapy (HDCT):

The use of HDCT is at the discretion of the individual treating physician. The role of HDCT in rhabdoid tumors remains undefined. As individual centers and some countries prefer to employ HDCT, it is suggested to harmonize strategies as much as feasible in order to obtain a maximum of information. This may deliver the necessary preliminary evidence for a randomized trial e.g. comparing HDCT vs. conventional chemotherapy. If high-dose-therapy is planned by the treating physician, it may follow the suggestions in the appendix and may contain the compounds carboplatinum and thiotepa.

Cardiotoxicity:

The application of anthracyclines (e.g. doxorubicin) appears to be essential in the treatment of patients with rhabdoid tumours. Both compounds are cardiotoxic, especially in children below the age of two years, with prior cardio-vascular diseases and radiotherapy of the mediastinum. If side effects occur, dose-modification is necessary. In any case the form "cardiotoxicity" should be filled out and sent to the study coordinator.

Event:

In case an adverse event, a severe adverse event or any other important event (progress during therapy, death etc.) occurs during therapy, the investigators shoul be informed via the attached forms. Adverse drug reactions should be submitted to the respective national agencies (see Appendix IV.2).

G-CSF:

Since treatment intensity and density is essential in the treatment of rhabdoid tumors, G-CSF support is preferable over dose reduction. The recommended dose is 5 µg/kg/d as once daily s.c. injection. According to label GCSF should be paused 24 hours before and after chemotherapy. No data exist whether GCSF can be given concomitant with VCR.

Maintenance therapy:

In cases of residual disease at the end of treatment, the application of a maintenance therapy has to be considered and discussed with the study coordinator.

I.4.1 Schematic diagrams for chemotherapy

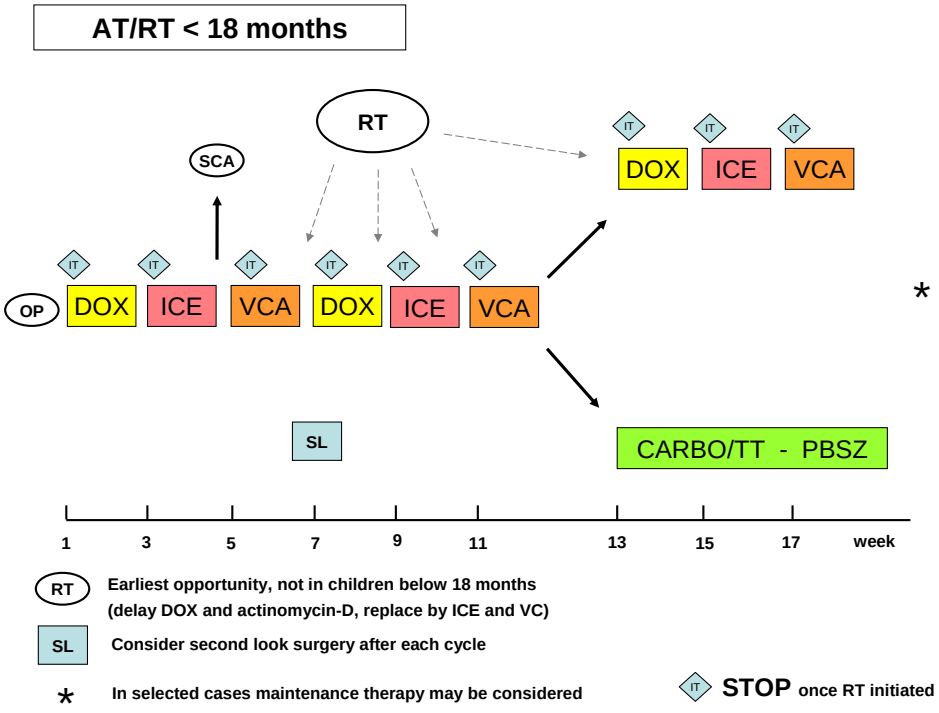


Figure I.5: AT/RT < 18 months

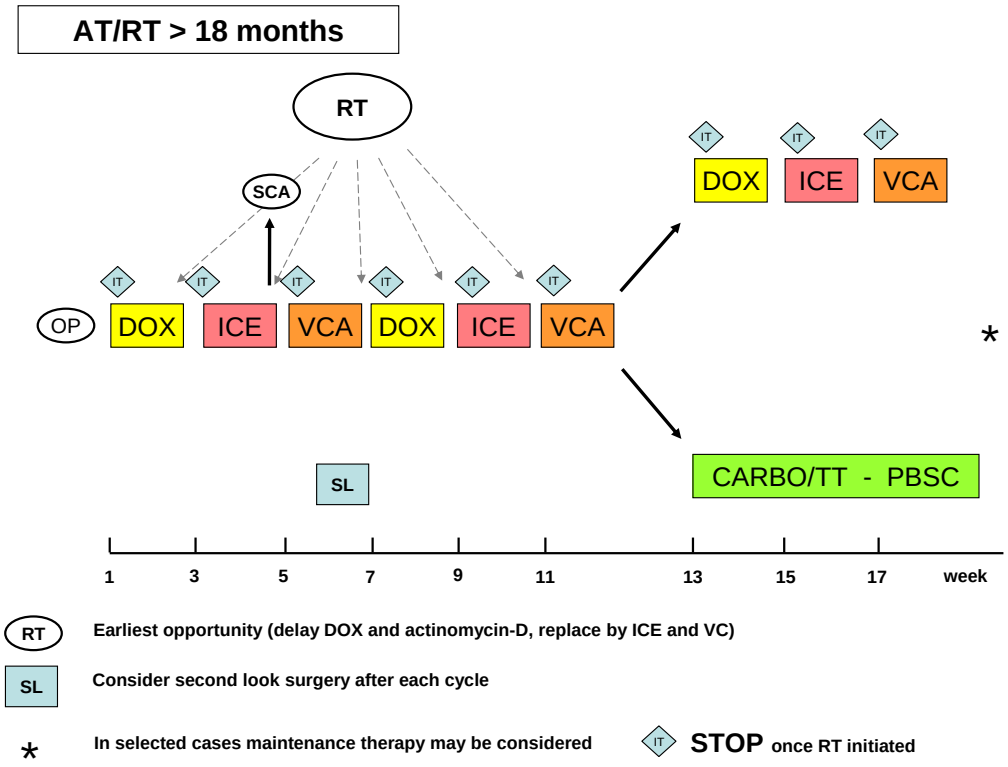


Figure I.6: Standard Therapy > 18 months

Abbreviations:

OP = surgery or initial biopsy, SL= second-look-surgery, DOX= doxorubicin, ICE = ifosfamide, carboplatinum, etoposide, VCA = vincristin, cyclophosphamide, actinomycin-D, SCA = stem cell apheresis, IT= intra-thecal chemotherapy, RT= radiotherapy, Carbo/TT – PBSC= high-dose chemotherapy with caraboplatinum/thiotepa

I.4.2 Chemotherapy

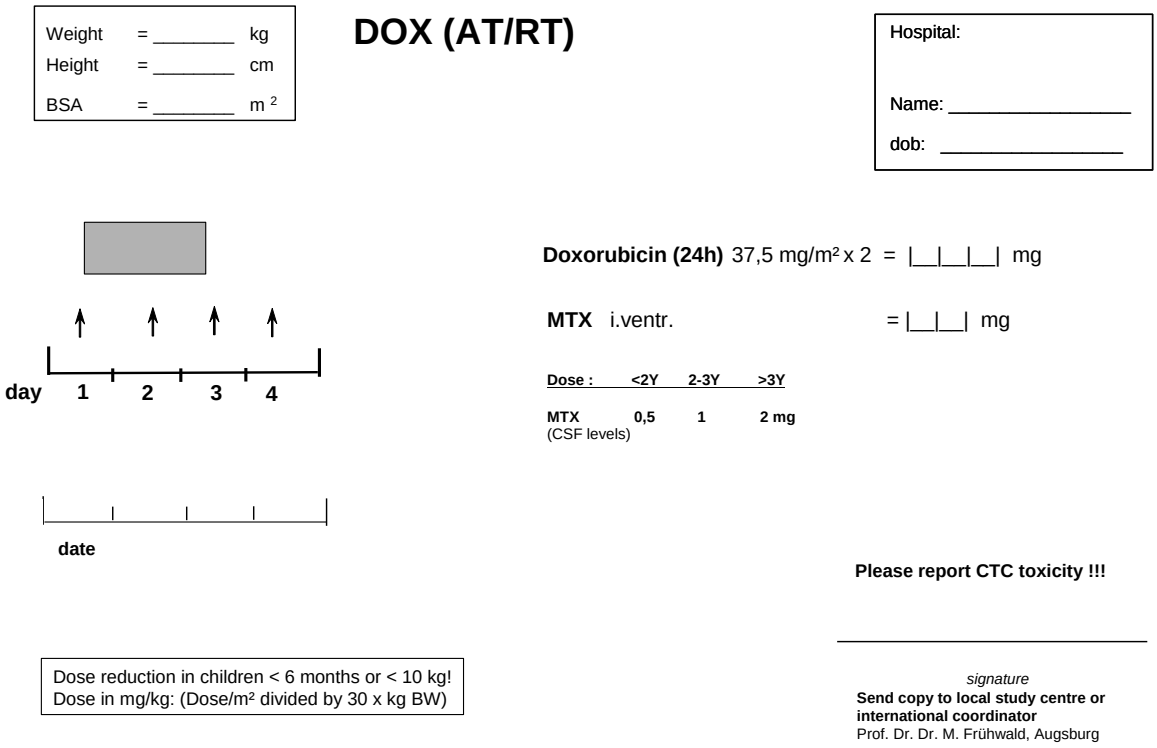


Figure I.7: Doxorubicin schedule

Day	Doxorubicin	Intraventricular Therapy
1	37,5 mg/m²	MTX
2	37,5 mg/m²	MTX
3		MTX
4		MTX
Cum. dose per cycle	75 mg/m²	age-dependent dose

Table I.5: Doxorubicin

I.ventr. therapy will only be applied before radiotherapy and *not* concurrent or following radiotherapy!

Age-dependent dose (applied via rickham reservoir):

Dose in mg	< 2 years	2-3 years	> 3 years
MTX	0,5 mg	1 mg	2 mg

See also MTX-guidelines 1.4.3.

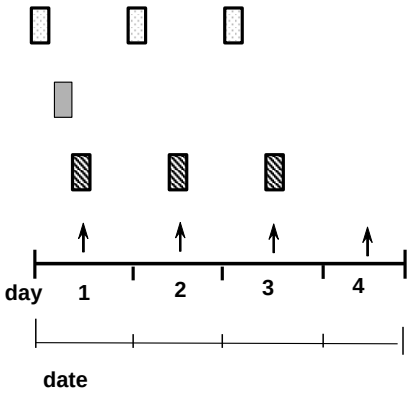
Weight = _____ kg
Height = _____ cm
BSA = _____ m²

ICE (AT/RT)

Hospital:

Name: _____

dob: _____



Ifosfamide p.i. (1h) 2000mg/m² x 3 = |__|__|__|__| mg/D
with MESNA:
2.000mg/m² with hydration 3.000ml/m2/d

Carboplatinum (1h) 500mg/m² = |__|__|__| mg

Etoposide (1h) 100mg/m² x 3 = |__|__|__| mg/D

MTX i.ventr. = |__|__| mg

Dose :	**<2Y**	**2-3Y**	**>3Y**
MTX (CSF levels)	**0,5**	**1**	**2 mg**

Dose reduction in children < 6 months or < 10 kg!
Dose in mg/kg: (Dose/m² divided by 30 x kg BW)

Please report CTC toxicity !!!

_____
signature
Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

Figure I.8: ICE schedule

Day	Ifosfamide	Carboplatinum	Etoposide	Intraventricular Therapy
1	2000 mg/m² over 1 h	500 mg/m² over 1 h	100 mg/m² over 1 h	MTX
2	2000 mg/m² over 1 h		100 mg/m² over 1 h	MTX
3	2000 mg/m² over 1 h		100 mg/m² over 1 h	MTX
4				MTX
Cum. dose per cycle	6000 mg/m²	500 mg/m²	300 mg/m²	age-dependent dose

Table I.6: ICE: Ifosfamide/Carboplatinum/Etoposid

Etoposide may be substituted by etoposidphosphate if available. The dosage used is 114mg/m² of etoposidphosphate for equivalent dose of etoposide (100mg).

I.ventr. therapy will only be applied before radiotherapy and *not* concurrent or following radiotherapy!

Age-dependent dose (applied via rickham reservoir):

Dose in mg	< 2 Year	2-3 Years	> 3 Years
MTX	0,5 mg	1 mg	2 mg

See also MTX-guidelines 1.4.3.

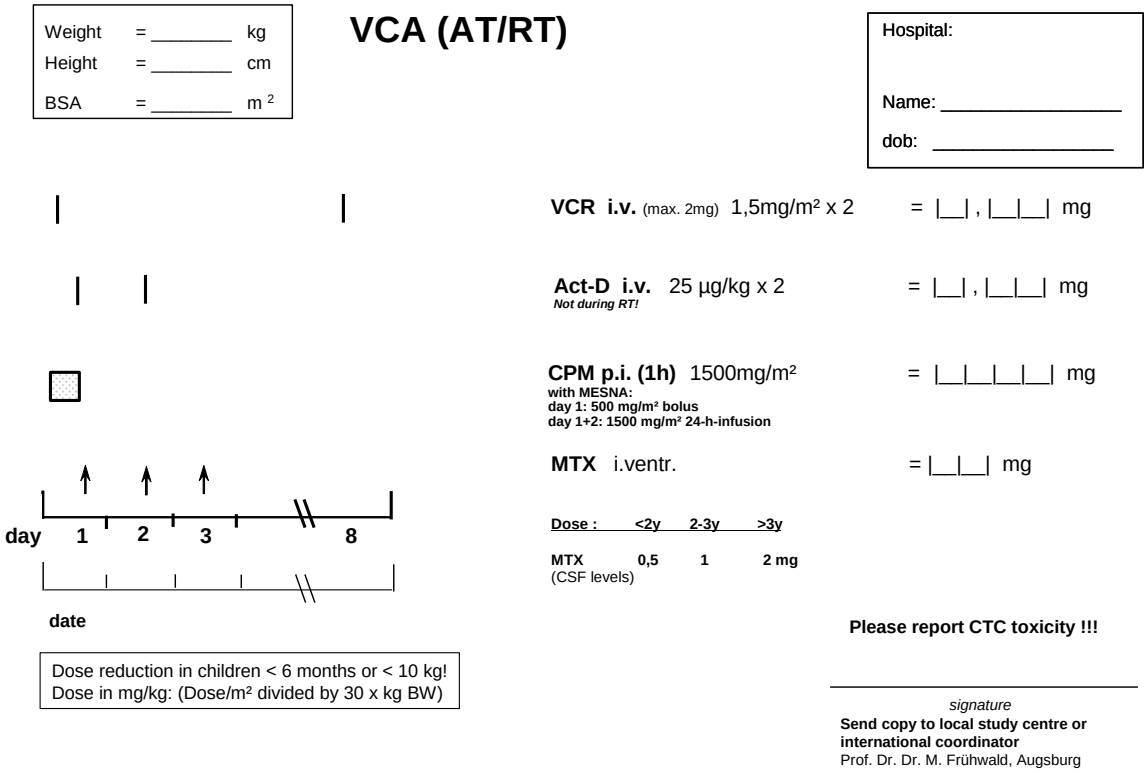


Figure I.9: VCA schedule

Day	Vincristine	Cyclophosphamide	Actinomycin-D	Intraventricular Therapy
1	1,5 mg/m² max 2 mg	1500 mg/m² over 1 h	25µg/kg	MTX
2			25µg/kg	MTX
3				MTX
8	1,5 mg/m² max 2 mg			
Cum. dose per cycle	3,0 mg/m² max 4 mg	1500 mg/m²	50 µg/kg	age-dependent dose

Table I.7: VCA: Vincristine/ Cyclophosphamide/Actinomycin-D

Dose reduction Actinomycin-D:
For infants < 1 year or < 10 kg only 2/3 of the already reduced Actinomycin-D dose should be administered. If tolerated well individual increase of the dose in the next cycle may be considered.

Cyclophosfamide can be increased to 1800mg/m2 if recovery allows after the first application!!!

I.ventr. therapy will only be applied before radiotherapy and *not* concurrent or following radiotherapy!

Age-dependent dose (applied via rickham reservoir):

Dose in mg	< 2 Year	2-3 Years	> 3 Years
MTX	0,5 mg	1 mg	2 mg

See also MTX-guidelines 1.4.3.

Initiation:

The scheduled interval between day 1 of the elements is 14 days.
If it is not possible to adhere to this schedule, the next element should begin as soon as possible after regeneration.

Prerequisites:

- satisfactory general condition
- no signs of infection
- no signs of CSF-circulation-disorders
- cardiac function: Echo (FS>28%) or RNV (LVEF>50%)
- Hb: > 8 g%
- platelets: > 80.000/mm³ (or indication of consistent rise)
- neutrophils: > 1000/µl (or indication of consistent rise)
- GFR: > 70 ml/min/1,73m² or adequate renal function
- urine: no hematuria

Hydration: 3000 ml/m²/d, 24 h-hydration until day 4 (incl.)

Start infusion 6 hours before application of carboplatinum.

Recommendation for composition of 1000 ml solution:

Glucose 5%	480 ml
NaCl 0,9%	480 ml
KCl 7,45%	30 ml
Ca-Gluconat 10%	10 ml

Add Magnesium 3 mmol/l.

Mesna-Application: Day 1: MESNA 500mg/m² i.v. as short-infusion or bolus
Day 1: MESNA 1.500 mg/m² i.v. continuous infusion over 24 hours
Day 2: MESNA 1.500 mg/m² i.v. continuous infusion over 24 hours
(Day 2 may be omitted in children over 3 years of age)

G-CSF: G-CSF is started on day 5
Dose: 5µg/kg/d s.c. injection

Dose adjustment for toxicity

Febrile neutropenia or infection	CTCAE grade 4, possibly grade 3	IFO and ETO dose reduction to 2/3
Mucositis	CTCAE grade 4, possibly repeated grade 3	ETO dose reduction of 50% DOXO dose reduction of 20%
Kidney: glomerular function	Krea > 1,5 x base value or Krea-Clearance <70 ml/min/ 1,73m²	delay element 1 week; if no recovery: no further IFO replace with Cy
Kidney: tubular function	CTCAE grade 2 CTCAE grade 3/4	poss. IFO reduction of 20% no further IFO replace with Cy
Hematuria	Stix positive during IFO 2 x microhematuria during IFO CTCAE > grade 2 CTCAE grade 3/4	double MESNA MESNA Bolus 600 mg/m², then MESNA-Infusion with doubled dosing. If persisting: Stop IFO Stop IFO, double MESNA-Infusion contact study-coordinator
Neurotoxicity	CTCAE > grade 2 CTCAE grade 4	see below NO FURTHER IFO!
Cardiac toxicity	FS < 28% or LVEF < 50% Acute Cardiotoxicity	repeat examination after one week, if no improvement: NO FURTHER DOXORUBICIN. stop Doxo-Infusion

Table I.8: Dose-modifications in case of toxicity

Central Neurotoxicity:

If CTC grade 3 or 4 central neurotoxicity occurs (somnolence >30% of the time, disorientation/hallucination/echolalia/perseveration/coma, or seizures on which consciousness is altered, or which are prolonged, repetitive or difficult to control), consider

- use of methylene blue (methylthionin) 50 mg as i.v. infusion.
- prolong ifosfamide-infusion to 4-8 hours with the next application, and infuse methylene blue 50 mg three times daily.
- in the next course, apply methylene blue one dose of 50 mg 24 hours prior to ifosfamide. During ifosfamide infusion give three times daily methylene blue as described above (refer to Nicolao and Giometto, Oncology 2003, 65[Suppl 12]:11-16 for further information).
- if repeated grade 3 or 4 central neurotoxicity occurs, consider withholding ifosfamide and substitute cyclophosphamide 1500 mg/m² BSA.
- Alternatively piracetam 100mg/kg may be given prophylactically (q 6h) or in therapeutic intention (q 4 h)

I.4.3 Intraventricular chemotherapy (via rickham reservoir) for patients with AT/RT

I.ventr. therapy will only be applied before radiotherapy and *not* concurrent with or following radiotherapy!

Application in courses 1-9: DOX/ICE: day 1 - 4; VCA:day 1 - 3

The MTX-dose is age-dependent:

Dose in mg	< 2 Year	2-3 Years	> 3 Years
MTX	0,5 mg	1 mg	2 mg

Prerequisites:

- *no* CNS-infection
- platelets > 30.000/µl
- no disturbance of CSF-circulation
- MTX-level in CSF < 5µmol/l
- no v.p./v.a.-Shunt (except M+)
- CSF-protein < 80 mg/dl

!!! DO NOT apply any other compound intraventricularly!!!

I.th. injection has to be performed by an experienced physician under sterile conditions. Face mask, sterile gloves and sterile covering are mandatory. Patients should be placed in a half sitting position (45^{o}) and wear a face mask. In general the skin over the site of injection should be cleaned with a sterile e.g. povidon iodine solution at least three times. In case of an Ommaya reservoir CSF should be pumped out of the system by compressing the reservoir six times. This should be repeated after injection and removal of the needle.

Procedure for obtaining CSF for MTX levels and injection:

1. aspirate 2ml CSF for rinsing after MTX-injection (approx. 4 ml in case of Ommaya-Reservoir)
2. aspirate 2 ml CSF for MTX- and protein-level-measurement, on day 1 additional 4 ml CSF for cytology
3. fill 2-ml-syringe containing MTX with CSF
4. inject MTX
5. inject the 2 ml of CSF taken at the beginning (ca. 4 ml in case of Ommaya-Reservoir)

Day 2: no MTX-Injection before MTX-level < 5 µmol/l!!!!
2 punctures of the reservoir in one day (day 2)!!!!

!!! In case of increased MTX-levels contact competence centre !!!

First, laboratory and individual mistakes should be excluded, especially if there is no sign of a stop in CSF circulation and the child is in good clinical condition. Especially when using an Ommaya reservoir, mistakes may be made by not pumping MTX out of the system before obtaining CSF. MTX levels should be repeated after discarding 4 ml of CSF.

If **toxic levels** are observed, which are not due to erroneous measurements (i.e. MTX after 48 h > 5µmol/l) initiate FIRST-AID-measures immediately:

1. Contact competence centre
2. Extraction of at least 20 to 30 ml CSF
3. Further measures in accordance to severity of intoxication:
   - Leukovorin i.v. – ***NOT*** into the ventricular system or the spinal canal because of toxicity
   - dexamethasone i.v./oral
   - ventriculo-lumbar shunting for flushing with NaCl
   - intraventricular application of carboxypeptidase

In case of low CSF-levels an increase of MTX-dose may be considered.

In case of repeated MTX-trough-levels of < 0,25 µmol/l in one course the dose in the ***next course*** may be increased by ***max. 50%*** (e.g. 0.5→ mg 0.75 mg; 1 mg→ 1.5 mg).

The maximum dose of 2 mg should not be exceeded.

If an increased dose is given, the following should only be injected if MTX-level is safe < 5 µmol/l.

If radiotherapy can be performed at an early time point during therapy (e.g. with the first ICE-course) CNS therapy may be performed via the lumbar route and in single doses. Implantation of an Ommaya- or Rickham-Reservoir may be avoided in these cases. For advice please consult the Registry headquarters.

Examples for dosages via the lumbar route are age-dependent:

Dose in mg	1 - 2 years	2-3 years	> 3 years
MTX	8 mg	10 mg	12 mg

I.4.4 High Dose Chemotherapy approach (HDCT)

Stem-cell-harvest:

Stem cell harvest may be performed after the first ICE-element. It can be repeated after the second ICE-element if necessary.

Priming of peripheral blood progenitor cells with G-CSF, e.g. 10µg/kg/d G-CSF is advised from 24 hours after the last dose of chemotherapy until completion of harvest. Apheresis may start after three days.

- A total of at least two units containing $3x10^6$ CD34+ cells/kg each should be collected.
- Stem cell harvest has to be performed according the ISHAGE Guidelines.

One of the aliquots is needed for high-dose-therapy, the other is needed as backup.

Cyclophosphamide for stem-cell-harvest:

This therapy is not generally recommended for all patients, but it may be performed in cases with difficult stem cell mobilization.

- Hydratation: 3000 ml/m²/d for 24 hours
- MESNA 1300 mg/m² as i.v. bolus before application of cyclophosphamide
- Cyclophosphamide 4000 mg/m² over 4 hours as short infusion
- MESNA 4000 mg/m²/d for 24 hours

Prerequisites:

- satisfactory general condition
- no signs of infection
- no signs of CSF-circulation-disorders
- cardiac function: Echo (FS>28%) or RNV (LVEF>50%)
- Hb: > 8 g%
- platelets: > 100.000/mm³
- neutrophils: > 1000/µl
- GFR: > 70 ml/min/1,73m²

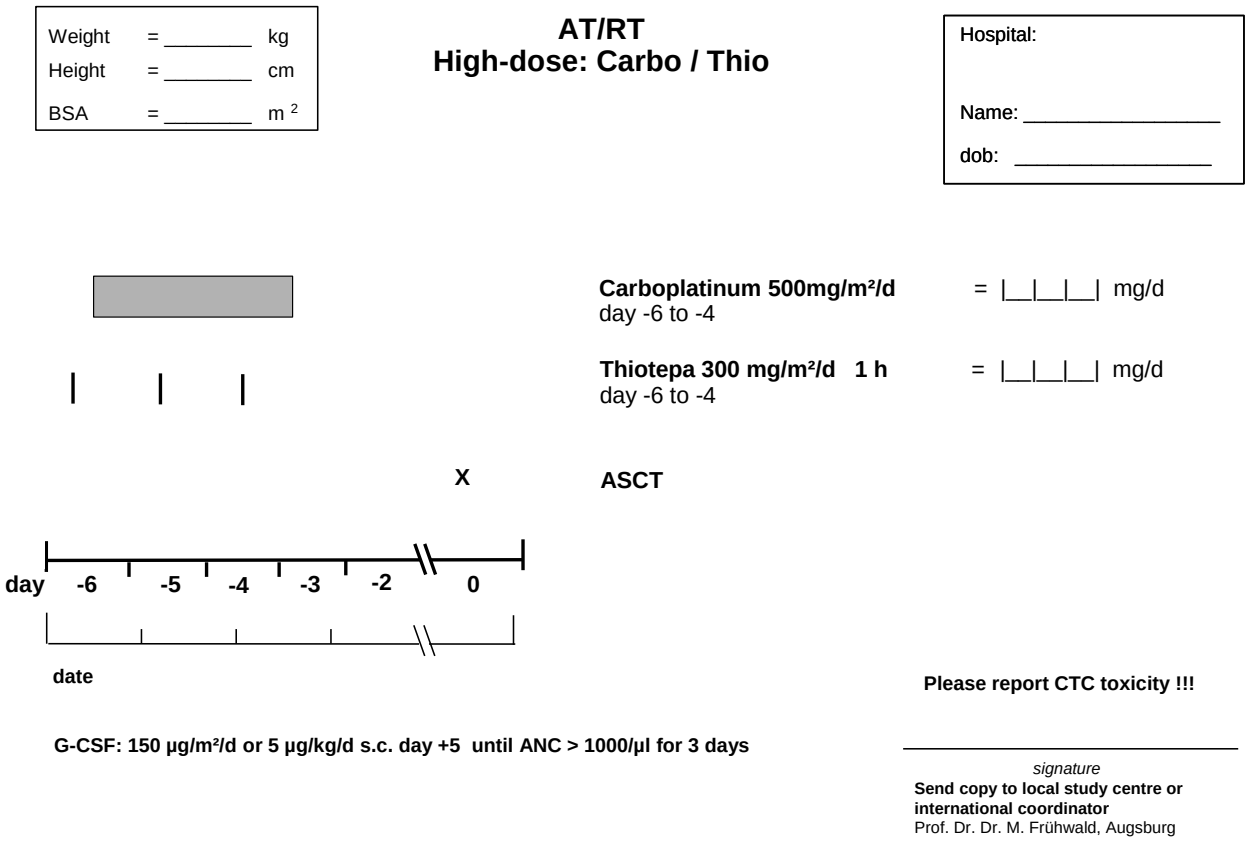


Figure I.10: High-dose-therapy (Carbo/Thiotepa)

Day	carboplatinum	thiotepa	PBSC
-6	500 mg/m²/d	300 mg/m² 1 h	
-5	500 mg/m²/d	300 mg/m² 1 h	
-4	500 mg/m²/d	300 mg/m² 1 h	
-3			
0			X
Cum. dose per cycle	1500 mg/m²	900 mg/m²	

Table I.9: High-dose-therapy Carbo/Thiotepa

Prerequisites:

- satisfactory general condition
- no signs of infection
- no signs of CSF-circulation-disorders
- cardiac function: Echo (FS>28%) or RNV (LVEF>50%)
- Hb: > 8 g%
- platelets: > 100.000/mm³
- neutrophils: > 1000/µl
- GFR: > 70 ml/min/1,73m²
- urine: no hematuria

Hydration: 3 000 ml/m²/d, 24 h, day -6 to -2

G-CSF: 150 µg/m²/d or 5 µg/kg/d s.c. day +5 until ANC > 1000 for 3 days

Supportive Care:

- substitution of blood products
- early analgesia with opioids
- parenteral feeding with substitution of vitamine K
- NG-tube for enteral fluid substitution day -1
- antimicrobial prophylaxis, antimycotics, yotrimoxazol, aciclovir

I.5 Radiotherapy guideline for patients with AT/RT of the CNS

Guidelines for radiation therapy of AT/RT

As the affected children are usually very young, optimization of timing, dosimetry and target volume to be irradiated are important aspects in the therapeutic approach towards children with rhabdoid tumors and however, need further evolution.

According to the available data radiotherapy (RT) is an important component in the therapy of patients with AT/RT (see introduction). In view of the international data bases and the HIT registry a recommendation can be made which essentially corresponds to the recommendations of the HIT 91 or HIT 2000 trials. The international data including the German data reach a level of evidence between 2 and 3 according to Woolf et al., 1990. The following recommendations can thus be made:

(1) Timing of RT

1. Children below the age of 18 months should only be irradiated under particular circumstances (minimal age of </= 8 months, localized tumour, residual disease >1.5cm2, progression, proton beam therapy available,).
2. Children of 18 months or older should be irradiated as soon as possible.
3. In case of primary metastasized disease RT may be delayed until the end of intensive chemotherapy (following element 9). Due to special circumstances such as progressive disease, RT may be performed at any time.
4. For infants and children below 18 months radiotherapy may be delayed until age permits or following element 9.

(2) Dose and Volume Concept

A. Localized disease supratentorial or infratentorial (M_0 according to Chang), age ≥ 18 months

RT to the extended tumor region according to CT planning. Total dose and fractionation 5 x 1.8 Gy per week, 54.0 Gy PTV according to ICRU 50/62.

Target volume

The target volume should include the postoperative or postchemotherapeutic tumour region including potential residual tumour as indicated by CT or T1-T2 MRI following contrast application. MRI fusion with the planning CT is strongly recommended. A safety margin of 1 cm should be added for the clinical target volume (= CTV). Tissue having been in contact with the initial tumour need to be included in the clinical target volume. Anatomical barriers need to be respected. The definition of the PTV needs to regard the precision of the technique used. Usually an additional safety margin of about 3-5 mm has

to be added to the CTV to define the planning target volume (=PTV). It is strongly recommended that this volume should be treated conformally (including non-coplanar beams). The field arrangement should be chosen to provide a high conformity index and to minimise the RT-dose to OARs.

New technologies such as IMRT or protons should be considered and discussed with the national representatives for radiotherapy.

In case of residual disease, a boost to 59.4 Gy has to be considered (see B and C).

B. Patients with metastatic disease (M_1 to M_3 according to Chang, age >18 months to 3 years)

Radiation therapy to the entire craniospinal axis will be given with a conventionally fractionated dose prescription with 1 x 1.6 Gy daily, 5 times per week to a total dose of 24.0 Gy.

Boost to primary tumour site.

The primary tumour site will be boosted up to total dose of 54.6 Gy with a conventional fractionation of 1 x 1.8 Gy daily, 5 times per week. If any residual tumour persists in a control MRI following at about 45.0 Gy an additional Boost to the residual disease only (GTV=PTV) up to 59.4 Gy can be considered. Still, dose constraints have to be respected..

Boost to spinal deposits.

Circumscribed solid spinal lesions should be boosted up to 49.2 Gy cumulative dose (for spinal lesions extension according to prior to chemotherapy), fractionation 1 x 1.8 Gy daily, 5 times per week. Safety margins in longitudinal extension extent for 1 cm but respecting anatomical barriers.

In diffuse spinal spread a total dose up to 35.2 Gy should not be exceeded in this age group (< 3 years).

Boost to intracranial deposits.

Circumscribed solid intracranial lesions should be boosted up to 49.2 Gy cumulative dose (for several lesions extension according to post chemotherapy imaging), fractionation 1 x 1.8 Gy daily, 5 times per week. The safety margin is 1 cm, but again respecting anatomical boarders.

C. Patients with metastatic disease (M_1 to M_3 according to Chang, age > 3 years)

Conventionally fractionated RT of the craniospinal axis with 1 x 1.6 Gy, five times a week, up to a total dose of 35.2 Gy is performed. The tumor region can be boosted up to 55.0 Gy using 1 x 1.8 Gy daily, five times per week. The concepts are as described above.

Total dose in the upper cervical myelon should be blocked after 49.6 Gy prescription dose. If tumor persists in a control MRI following at about 45.0 Gy a boost to the residual disease without a safety margin of up to 59.4 Gy can be considered while respecting the proposed dose constraints.

Documentation of therapy should be done according to the guidelines listed in the HIT 2000 protocol.

D. Boost for residual disease of the primary

If residue is present at time of RT planning without any chance for second surgery, we strongly recommend a control MRI following at about 45.0 Gy. In case of any residual tumour at 45 Gy,

a boost to the residual disease (GTV only) up to 59.4 Gy can be considered. Still, dose constraints of normal tissue has to respected.

E. **Treatment interruptions**

Delays due to machine services and planned holidays should be avoided wherever possible. In general, any prolongation for the total RT course of more than 2 days (i.e. 2 weeks with only 4 fractions instead of 5) will be considered as a major protocol violation.

(3) Radiotherapy technique

The Clinical Target Volume for **craniospinal irradiation** (CSA-RT) comprises the whole brain as well as the spinal cord and thecal sac. In case of megavoltage photon therapy, the cranial (whole brain) fields shall be treated with energies in the range of 4-6 MV. Energies more than 6 MV should be avoided because of under-dosage to the lateral meninges due to dose built up effect. Photons of energy 4-6 MV are advisable for spinal irradiation but electrons of suitable energy can be used as an alternative.

- **Whole Brain Volume**

The whole brain CTV should extend anteriorly to include the entire frontal lobe and cribriform plate region. In order to include the cribriform fossa within the CTV, and allowing an additional appropriate margin for PTV, the edge of the field (i.e. the geometric edge of the shielding block) would in many cases include the lenses. The geometric edge of the shield on the film should extend at least 0.5 cm inferiorly below the cribriform plate and at least 1 cm elsewhere below the base of the skull (paying particular attention to the margin around the inferior aspect of the temporal lobes). The margin between the shielding and the anterior border of the upper cervical vertebrae should be 0.5 cm. The lower border of the cranial fields should form a precise match with the upper border of the spinal field. Junctions of abutting fields should be moved either on a daily rotating basis or weekly (moving junction technique).

- **Cervical Spinal Volume**

As much as possible of the cervical spinal volume is included in the lateral cranial fields with the junction between the cranial and spinal fields kept as inferior as possible. This is advised for avoidance of as much thyroid tissue irradiation as possible, by shielding this within the “cranio-cervical” volume.

The spinal field should extend superiorly to form an accurate match with the lower borders of the cranio-cervical fields.

- **Dorso-Lumbar Spine Volume**

The inferior limit of the spinal CTV must be determined by imaging the lower limit of the thecal sac on a spinal MR and will usually extend inferiorly to at least the lower border of the second sacral vertebra.

Width of the spinal volume: the aim is to include the entire subarachnoid space including the extensions along the nerve roots as far as the intervertebral foramina. The spinal CTV should extend laterally to cover the intervertebral foramina. An additional margin, generally 1.0 cm on either side should be added for PTV, and an appropriate field width chosen to allow for this. The use of a ‘spade’ shaped field to treat the lumbo-sacral spine is not recommended.

(4) Organs at risk (OAR)

The following organs will be outlined:

Whole brain, brain stem (down to kranial boarder of C1), spinal cord (starting at upper boarder of C1), eye lens, optic nerves, chiasm, pituitary, inner ear. Delineation of temporal lobes, hippocampus, hypothamalmus and dentition is encouraged.

Please note:

- Below the level of the first cervical vertebra the myelon should be blocked after about 50 Gy (absolute dose maximum should not exceed 54 Gy).
- If possible, at least one inner ear should be kept below 30 Gy (mean dose*).*

Please recognize dose tolerances of normal tissue according to the following table:

Organ	Mean dose (Gy)	Max dose (D2) (Gy)	Comment/priority
Optic nerve L/R	54	60	high
chiasm	54	60	High
Inner ear L/R	30	45	High ((at least one side)
Cervical spine	50	54	high
Lens L/R	5	7	Medium
Temporal lobe L/R	30% Vol. < 25 Gy, 60% Vol. < 20 Gy		Medium
Hippocampus L/R	30% Vol. < 30 Gy, 60% Vol. < 25 Gy		Medium
Thyroid	36	-	Low
Pituitary	36	-	Low

For organs of high priority even compromises for target coverage are allowed to preserve organ integrity; preferably PTV margin should be compromised first. Compromises of GTV/CTV should be avoided if possible. For organs of medium and low priority, we would recommend to use the most appropriate beam arrangement and RT modality in order to achieve best sparing; however, targets should not be compromised to spare those organs.

(5) Dose specification

- Dose definition

All doses for photon techniques will be specified according to ICRU 50/ICRU 62; At least 95% of the PTV is therefore to be treated with 95-107% of the prescribed dose.

- **Reference point**

Tumour bed: The dose should be defined at the isocentre.
Brain: if the brain is treated by a pair of parallel opposed fields, the dose should be defined at the midpoint of the central axis otherwise at the isocentre.

Spine: The dose to the spine should be prescribed along the central axis at a depth representing the posterior margin of the vertebral bodies.

In the case of electron RT to the spine the anterior border of the target volume (posterior aspect of the vertebral bodies) must be encompassed within the 85% isodose and the dose along the entire spinal axis should be calculated with an appropriate correction for tissue heterogeneity.

- **Dose Uniformity and Reference Points**

Tumour bed: Homogeneity of +7%, -5% relative to the prescription point is required (ICRU 50/62).

Spine: *The maximum dose variation along the longitudinal axis of the spinal cord should be +7% to -5%. Tissue compensations may be required to achieve this degree of dose uniformity. The dose at the level of C5 and L3 should be recorded.*

(6) Documentation and reporting

It is mandatory to document prescribed and applied doses. The following data (copies or electronic data) is requested to be send to the radiation therapy reference center:

- Radiation prescription
- Computer assisted treatment plans including isodoses and DVH's of tumor volumes and OAR's
- Patient data (appendix)
- Radiation forms (appendix)
- Toxicity forms (appendix)
- Treatment delivery forms (appendix)
- Final letter with delivered dose summary and start/end of RT course

Please send the requested complete material at the end of RT to the reference center at the following address:
Prof. Dr. med. B. Timmermann, Am Mühlenbach 1, D-45147 Essen

(7) Equipment

Radiation therapy today offers a variety of modern conformal techniques helping to significantly spare dose to the normal tissue. Particularly when looking on the low age of this patient cohort, any effort should be made to chose the modality offering maximal dose reduction after evaluating each individual case carefully. Treateing clinicians are encouraged to contact the radiation reference board for individual discussions.

- **Modern conformal radiation technique** shall be used for tumour bed and craniospinal fields either by linear accelerator producing adequat photon or electron beam or proton beam treatment.

- The use of **electrons for spinal fields** will be acceptable provided a beam of sufficient energy is available to ensure adequate irradiation of the target volume allowing for tissue heterogeneity and the junction between the photon cranial fields and spinal electron field can be precisely calculated and implemented.

- Treatment with **60Co is not permitted**.

- **Stereotactic radiation therapy**

Stereotactic, rigid immobilization methods might help to reduce safety margins for the planning target volume and are therefore allowed.
However, stereotactic treatments techniques with the meaning of Gamma-Knife, Cyberknife or stereotactic fractionation schedules as hypofrationation or single fraction treatment have no role in the irradiation of ATRT. A stereotactic boost for small volume residue may be of potential benefit but has to be considered on an individual bases.

Newer technologies such as IMRT or protons should be explicitly considered and discussed with the national representatives for radiotherapy (see details below).

- **Intensity Modulated Radiotherapy (IMRT)**

It is likely that during the duration of this study, IMRT planning and delivery techniques will be increasingly employed. However, they should be used with caution considering the low dise bath and potential impact on secondary cancer induction. Long-term data on it´s use for children are still very limited.
IMRT may in principle be used as an option for reducing the radiation dose to the cochlea. IMRT has also been used to improve homogeneity of spinal RT. If centres employ IMRT then it will be essential to observe strict criteria for immobilisation and departmental quality assurance.
It will be important to consider and to define multiple OARs (which were not of any interest when old fashioned techniques were applied) according to all beam entrances and exits present when multiple field-IMRT techniques are used, especially for craniospinal axis, i.e. female breast, heart, thyroid gland etc.
IMRT techniques will be allowed assuming that appropriate departmental QA procedures are available and prospectively approved by the national study co-ordinator. A primary IMRT approach (including arcing techniques e.g. tomotherapy, VMAT, RapidArc) must ensure adequate irradiation of the target volume allowing for tissue heterogeneity and the junction between the cranial fields and spinal field can be precisely calculated and implemented and a sufficient dose gradient is employed over the vertebral bodies to ensure symmetrical bone growth arrest. All patients must be treated on isocentric linear accelerators with a minimum source-to-axis distance (SAD) of 80 cm. Megavoltage photons with a nominal energy ≥ 4 MV must be used.

Proton therapy

Nowadays, innovative treatment techniques are increasingly explored to lower the burden of late toxicity. Proton beam therapy seems to be of particular interest. Early evaluation report promising results of early and late toxicity and comparative planning studies demonstrate lower dose to normal brain and inner ear for posterior fossa irradiation when compared to photon modalities. However, prospective data, quality of life analysis and long term evaluation are needed to prove clinical superiority.
Today, it has to be taken into account, that any access to proton facilities is and will be still limited, especially when considering individual technical restrictions of the present facilities. However, due to the superiority of dose distribution for larger intracranial volumes with proton beams, and the high rate of long term survival in those children and adolescents, proton therapy may be considered for treatment. The decision has to be made with the national coordinator for radiotherapy and adjusted to the national legislation for radioprotection.
For posterior fossa treatment, horizontal beam line does not seem to be optimal to spare inner ears sufficiently, whereas for supratentorial treatment, lateral fields with fixed beam line may be satisfying. As with conventional treatment, organ tolerances as well as target coverage are to be respected.
Any definition of target volumes given in this protocol will also apply for proton beam therapy. Prescription, recording and reporting of proton beam therapy shall be performed according to ICRU 78 report. For proton beam therapy modifications or special needs may need to be addressed like field-specific margins, compensation for range uncertainties or tissue inhomogeneities. Any individual adaptation is at the discretion of the local radiotherapist. As there is some uncertainty about increased RBE at the distal bragg peak, weighthing of spots

and bragg peaks need to be carefully evaluated. The use of at least 2 fields should be preferred especially when high weighted spots cumulate in critical areas.

(8) Simultaneous radio-, chemotherapy in patients with rhabdoid tumors

Radiotherapy may be complicated in some affected patients due to the necessity for deep sedation or even anaesthesia, young age or neurological deficits.
Optimal preparation for radiotherapy always involves assessment of risk factors for anaesthesia which may due to pre-existing conditions such as neurological deficits including difficult swallowing or repeated aspirations. These hint towards much enhanced risk for anaesthesia.

Aims of the following recommendations are thus:

- The planed radiotherapy as a local therapeutic measure should be done without any interruptions due to complications such as febrile neutropenia, documented infections, severe mucositis with the need for analgesics or the need for parenteral nutrition and
- Systematic chemotherapy in parallel to radiotherapy in order to maximize tumour control

Recommendations

Pre- and post-radiotherapy:
Prerequisite for radiotherapy in any patient is complete imaging (e.g. craniospinal MRI) plus complete staging (e.g. CSF analysis) not older than four weeks before sending the patient for radiotherapy.

- Avoidance of Actinomycin D: 2 weeks before and 2 weeks after radiotherapy
- Avoidance of Doxorubicine: 2 weeks before and 4 weeks after radiotherapy
- No intrathecal, intraventricular chemotherapy during or after radiotherapy (AT/RT only)

Simultaneous radio-, chemotherapy

- No Actinomycin D, no Doxorubicin, no intrathecal chemotherapy
- VCA: No Actinomycin D, no intrathecal methotrexate
  Vincristin 100% of the dose,
  Cyclophosphamide 100% to 65% depending on previous tolerance, MESNA dose needs to be adjusted
- ICE: No intrathecal methotrexate reduction of all doses to 50% i.e.
  Ifosfamide day 1 and 2: each 1.500mg per m^2, no Ifosfamide on day 3
  Carboplatinum day 1: each 250mg per m^2 per day
  Etoposide day 1 and 2: each 75mg m^2 per day no day 3 Etoposide
  MESNA Bolus day 1: 500 mg/m^2
  24h dose day 1, 2 (3): 1500 mg/m^2 day
- Consider
  G-CSF 5µg/kg/day starting day +8 to avoid nadir of ANC < 500/µl

Special situation: Craniospinal irradiation in AT/RT
Start only with LK ≥ 2.000/µl, ANC ≥ 1.000/µl, Thrombocytes ≥ 80.000/µl.

No simultaneous chemotherapy during craniospinal radiotherapy.

Under certain circumstances chemotherapy maybe continued during boost radiotherapy. An ANC < 500/µl should be avoided.

Special situation: Patients with severe or life threatening complications during pre-radiotherapy- chemotherapy

Try to avoid simultaneous intensive chemotherapy.

Consider applying well tolerable oral chemotherapy e.g. Trofosfamide 75-100 mg/m²

(9) Related Literature

Radiotherapy for AT/RT in general

Athale, U. H., Duckworth, J., Odame, I., Barr., R. (2009). Childhood Atypical Teratoid Rhabdoid Tumor of the Central Nervous System: A Meta-Analysis of Observational Studies. *J Pediatr Hematol Oncol* 31(9): 651-63.

Bishop, A. J., McDonald, M. W., Chang, A. L., Esiashvili, N. (2012). Infant Brain Tumors: Incidence, Survival, and the Role of Radiation Based on Surveillance, Epidemiology, and End Results (SEER) Data. *Int J Radiat Oncol Biol Phys* 82(1): 341-7.

Biswas, A., Goyal, S., Puri, T., Das, P., Sarkar, C., Julka, P. K., Bakhshi, S., Rath, G. K. (2009). Atypical Teratoid Rhabdoid Tumor of the Brain: Case Series and Review of Literature. *Childs Nerv Syst* 25(11): 1495-500.

Buscariollo, D. L., Park, H. S., Roberts, K. B., Yu, J. B. (2012). Survival Outcomes in Atypical Teratoid Rhabdoid Tumor for Patients Undergoing Radiotherapy in a Surveillance, Epidemiology, and End Results Analysis. *Cancer* 118(17): 4212-9.

Chen, Y. W., Wong, T. T., Ho, D. M., Huang, P. I., Chang, K. P., Shiau, C. Y., Yen, S. H. (2006). Impact of Radiotherapy for Pediatric Cns Atypical Teratoid/Rhabdoid Tumor (Single Institute Experience). *Int J Radiat Oncol Biol Phys* 64(4): 1038-43.

Dufour, C., Beaugrand, A., Le Deley, M. C., Bourdeaut, F., Andre, N., Leblond, P., Bertozzi, A. I., Frappaz, D., Rialland, X., Fouyssac, F., Edan, C., Grill, J., Quidot, M., Varlet, P. (2012). Clinicopathologic Prognostic Factors in Childhood Atypical Teratoid and Rhabdoid Tumor of the Central Nervous System: A Multicenter Study. *Cancer* 118(15): 3812-21.

Fidani, P., De Ioris, M. A., Serra, A., De Sio, L., Ilari, I., Cozza, R., Boldrini, R., Milano, G. M., Garre, M. L., Donfrancesco, A. (2009). A Multimodal Strategy Based on Surgery, Radiotherapy, ICE Regimen and High Dose Chemotherapy in Atypical Teratoid/Rhabdoid Tumours: A Single Institution Experience. *J Neurooncol* 92(2): 177-83.

Geyer, J. R., Sposto, R., Jennings, M., Boyett, J. M., Axtell, R. A., Breiger, D., Broxson, E., Donahue, B., Finlay, J. L., Goldwein, J. W., Heier, L. A., Johnson, D., Mazewski, C., Miller, D. C., Packer, R., Puccetti, D., Radcliffe, J., Tao, M. L., Shiminski-Maher, T. (2005). Multiagent Chemotherapy and Deferred Radiotherapy in Infants with Malignant Brain Tumors: A Report from the Children's Cancer Group. *J Clin Oncol* 23(30): 7621-31.

Hilden, J. M., Meerbaum, S., Burger, P., Finlay, J., Janss, A., Scheithauer, B. W., Walter, A. W., Rorke, L. B., Biegel, J. A. (2004). Central Nervous System Atypical Teratoid/Rhabdoid Tumor: Results of Therapy in Children Enrolled in a Registry. *J Clin Oncol* 22(14): 2877-84.

Hoffman, K. E. and Yock, T. I. (2009). Radiation Therapy for Pediatric Central Nervous System Tumors. *J Child Neurol* 24(11): 1387-96.

Inoue, N., Watanabe, H., Okamura, K., Sakaki, M., Kageji, T., Nagahiro, S., Kagami, S. (2014). Atypical Teratoid Rhabdoid Tumor in the Cavernous Sinus of a Toddler Presenting with Oculomotor Nerve Palsy. *Childs Nerv Syst*.

Kirsch, D. G. and Tarbell, N. J. (2004). Conformal Radiation Therapy for Childhood CNS Tumors. *Oncologist* 9(4): 442-50.

Knipstein, J. A., Birks, D. K., Donson, A. M., Alimova, I., Foreman, N. K., Vibhakar, R. (2012). Histone Deacetylase Inhibition Decreases Proliferation and Potentiates the Effect of

Ionizing Radiation in Atypical Teratoid/Rhabdoid Tumor Cells. *Neuro Oncol* 14(2): 175-83.

Lafay-Cousin, L., Hawkins, C., Carret, A. S., Johnston, D., Zelcer, S., Wilson, B., Jabado, N., Scheinemann, K., Eisenstat, D., Fryer, C., Fleming, A., Mpofu, C., Larouche, V., Strother, D., Bouffet, E., Huang, A. (2012). Central Nervous System Atypical Teratoid Rhabdoid Tumours: The Canadian Paediatric Brain Tumour Consortium Experience. *Eur J Cancer* 48(3): 353-9.

Lee, J. Y., Kim, I. K., Phi, J. H., Wang, K. C., Cho, B. K., Park, S. H., Ahn, H. S., Kim, I. H., Kim, S. K. (2012). Atypical Teratoid/Rhabdoid Tumors: The Need for More Active Therapeutic Measures in Younger Patients. *J Neurooncol* 107(2): 413-9.

Morgenstern, D. A., Gibson, S., Brown, T., Sebire, N. J., Anderson, J. (2010). Clinical and Pathological Features of Paediatric Malignant Rhabdoid Tumours. *Pediatr Blood Cancer* 54(1): 29-34.

Nomura, Y., Yasumoto, S., Yanai, F., Akiyoshi, H., Inoue, T., Nibu, K., Tsugu, H., Fukushima, T., Hirose, S. (2009). Survival and Late Effects on Development of Patients with Infantile Brain Tumor. *Pediatr Int* 51(3): 337-41.

Pai Panandiker, A. S., Merchant, T. E., Beltran, C., Wu, S., Sharma, S., Boop, F. A., Jenkins, J. J., Helton, K. J., Wright, K. D., Broniscer, A., Kun, L. E., Gajjar, A. (2012). Sequencing of Local Therapy Affects the Pattern of Treatment Failure and Survival in Children with Atypical Teratoid Rhabdoid Tumors of the Central Nervous System. *Int J Radiat Oncol Biol Phys* 82(5): 1756-63.

Perreault, S., Lober, R. M., Carret, A. S., Zhang, G., Hershon, L., Decarie, J. C., Yeom, K., Vogel, H., Fisher, P. G., Partap, S. (2013). Relapse Patterns in Pediatric Embryonal Central Nervous System Tumors. *J Neurooncol* 115(2): 209-15.

Slavc, I., Chocholous, M., Leiss, U., Haberler, C., Peyrl, A., Azizi, A. A., Dieckmann, K., Woehrer, A., Peters, C., Widhalm, G., Dorfer, C., Czech, T. (2014). Atypical Teratoid Rhabdoid Tumor: Improved Long-Term Survival with an Intensive Multimodal Therapy and Delayed Radiotherapy. The Medical University of Vienna Experience 1992-2012. *Cancer Med* 3(1): 91-100.

Squire, S. E., Chan, M. D., Marcus, K. J. (2007). Atypical Teratoid/Rhabdoid Tumor: The Controversy Behind Radiation Therapy. *J Neurooncol* 81(1): 97-111.

Stadler, P. and Peters, O. (2006). The Importance of Radiotherapy in at/Rt Patients Less Than 3 Years of Age: In Regards to Chen Et Al. (Int J Radiat Oncol Biol Phys 2006;64:1038-1043). *Int J Radiat Oncol Biol Phys* 65(4): 1273; author reply 1273-4.

Sultan, I., Qaddoumi, I., Rodriguez-Galindo, C., Nassan, A. A., Ghandour, K., Al-Hussaini, M. (2010). Age, Stage, and Radiotherapy, but Not Primary Tumor Site, Affects the Outcome of Patients with Malignant Rhabdoid Tumors. *Pediatr Blood Cancer* 54(1): 35-40.

Tekautz, T. M., Fuller, C. E., Blaney, S., Fouladi, M., Broniscer, A., Merchant, T. E., Krasin, M., Dalton, J., Hale, G., Kun, L. E., Wallace, D., Gilbertson, R. J., Gajjar, A. (2005). Atypical Teratoid/Rhabdoid Tumors (AT/RT): Improved Survival in Children 3 Years of Age and Older with Radiation Therapy and High-Dose Alkylator-Based Chemotherapy. *J Clin Oncol* 23(7): 1491-9.

von Hoff, K., Hinkes, B., Dannenmann-Stern, E., von Bueren, A. O., Warmuth-Metz, M., Soerensen, N., Emser, A., Zwiener, I., Schlegel, P. G., Kuehl, J., Fruhwald, M. C., Kortmann, R. D., Pietsch, T., Rutkowski, S. (2011). Frequency, Risk-Factors and Survival of Children with Atypical Teratoid Rhabdoid Tumors (AT/RT) of the CNS Diagnosed between 1988 and 2004, and Registered to the German Hit Database. *Pediatr Blood Cancer* 57(6): 978-85.

Radiotherapy of pediatric brain tumors with stereotactical techniques

Keshavarzi, S., Meltzer, H., Ben-Haim, S., Newman, C. B., Lawson, J. D., Levy, M. L., Murphy, K. (2009). Initial Clinical Experience with Frameless Optically Guided Stereotactic Radiosurgery/Radiotherapy in Pediatric Patients. *Childs Nerv Syst* 25(7): 837-44.

Krieger, M. D. and McComb, J. G. (2009). The Role of Stereotactic Radiotherapy in the Management of Ependymomas. *Childs Nerv Syst* 25(10): 1269-73.

Peugniez, C., Dewas, S., Coche-Dequeant, B., Leblond, P., Defachelles, A. S., Thebaud, E., Lacornerie, T., Lartigau, E. (2010). Use of Conventional Fractionation with Cyberknife in Children: A Report of 5 Cases. *J Pediatr Hematol Oncol* 32(6): 472-5.

Tamura, N., Hayashi, M., Chernov, M., Tamura, M., Horiba, A., Konishi, Y., Muragaki, Y., Iseki, H., Okada, Y. (2012). Outcome after Gamma Knife Surgery for Intracranial Arteriovenous Malformations in Children. *J Neurosurg* 117(Suppl): 150-7.

Radiotherapy of pediatric brain tumors with IMRT

Beltran, C., Gray, J., Merchant, T. E. (2012). Intensity-Modulated Arc Therapy for Pediatric Posterior Fossa Tumors. *Int J Radiat Oncol Biol Phys* 82(2): e299-304.

Chi, S. N., Zimmerman, M. A., Yao, X., Cohen, K. J., Burger, P., Biegel, J. A., Rorke-Adams, L. B., Fisher, M. J., Janss, A., Mazewski, C., Goldman, S., Manley, P. E., Bowers, D. C., Bendel, A., Rubin, J., Turner, C. D., Marcus, K. J., Goumnerova, L., Ullrich, N. J., Kieran, M. W. (2009). Intensive Multimodality Treatment for Children with Newly Diagnosed Cns Atypical Teratoid Rhabdoid Tumor. *J Clin Oncol* 27(3): 385-9.

Kusters, J. M., Louwe, R. J., van Kollenburg, P. G., Kunze-Busch, M. C., Gidding, C. E., van Lindert, E. J., Kaanders, J. H., Janssens, G. O. (2011). Optimal Normal Tissue Sparing in Craniospinal Axis Irradiation Using Imrt with Daily Intrafractionally Modulated Junction(S). *Int J Radiat Oncol Biol Phys* 81(5): 1405-14.

Merchant, T. E., Kun, L. E., Hua, C. H., Wu, S., Xiong, X., Sanford, R. A., Boop, F. A. (2013). Disease Control after Reduced Volume Conformal and Intensity Modulated Radiation Therapy for Childhood Craniopharyngioma. *Int J Radiat Oncol Biol Phys* 85(4): e187-92.

Paulino, A. C., Mazloom, A., Terashima, K., Su, J., Adesina, A. M., Okcu, M. F., The, B. S., Chintagumpala, M. (2013). Intensity-Modulated Radiotherapy (IMRT) in Pediatric Low-Grade Glioma. *Cancer* 119(14): 2654-9.

Polkinghorn, W. R., Dunkel, I. J., Souweidane, M. M., Khakoo, Y., Lyden, D. C., Gilheeney, S. W., Becher, O. J., Budnick, A. S., Wolden, S. L. (2011). Disease Control and Ototoxicity Using Intensity-Modulated Radiation Therapy Tumor-Bed Boost for Medulloblastoma. *Int J Radiat Oncol Biol Phys* 81(3): e15-20.

Sharma, S. D., Jalali, R., Phurailatpam, R. D., Gupta, T. (2009). Does Intensity-Modulated Stereotactic Radiotherapy Achieve Superior Target Conformity Than Conventional Stereotactic Radiotherapy in Different Intracranial Tumours? *Clin Oncol (R Coll Radiol)* 21(5): 408-16.

Radiotherapy of pediatric brain tumors with Proton beam therapy

Armstrong, F. D. (2012). Proton-Beam Radiation Therapy and Health-Related Quality of Life in Children with CNS Tumors. *J Clin Oncol* 30(17): 2028-9.

Athar, B. S., Bednarz, B., Seco, J., Hancox, C., Paganetti, H. (2010). Comparison of out-of-Field Photon Doses in 6 Mv Imrt and Neutron Doses in Proton Therapy for Adult and Pediatric Patients. *Phys Med Biol* 55(10): 2879-91.

Bjork-Eriksson, T. and Glimelius, B. (2005). The Potential of Proton Beam Therapy in Paediatric Cancer. *Acta Oncol* 44(8): 871-5.

Boehling, N. S., Grosshans, D. R., Bluett, J. B., Palmer, M. T., Song, X., Amos, R. A., Sahoo, N., Meyer, J. J., Mahajan, A., Woo, S. Y. (2012). Dosimetric Comparison of Three-Dimensional Conformal Proton Radiotherapy, Intensity-Modulated Proton Therapy, and Intensity-Modulated Radiotherapy for Treatment of Pediatric Craniopharyngiomas. *Int J Radiat Oncol Biol Phys* 82(2): 643-52.

Brodin, N. P., Munck Af Rosenschold, P., Aznar, M. C., Kiil-Berthelsen, A., Vogelius, I. R., Nilsson, P., Lannering, B., Bjork-Eriksson, T. (2011). Radiobiological Risk Estimates of Adverse Events and Secondary Cancer for Proton and Photon Radiation Therapy of Pediatric Medulloblastoma. *Acta Oncol* 50(6): 806-16.

Cochran, D. M., Yock, T. I., Adams, J. A., Tarbell, N. J. (2008). Radiation Dose to the Lens During Craniospinal Irradiation-an Improvement in Proton Radiotherapy Technique. *Int J Radiat Oncol Biol Phys* 70(5): 1336-42.

De Amorim Bernstein, K., Sethi, R., Trofimov, A., Zeng, C., Fullerton, B., Yeap, B. Y., Ebb, D., Tarbell, N. J., Yock, T. I., MacDonald, S. M. (2013). Early Clinical Outcomes Using Proton Radiation for Children with Central Nervous System Atypical Teratoid Rhabdoid Tumors. *Int J Radiat Oncol Biol Phys* 86(1): 114-20.

Howell, R. M., Giebeler, A., Koontz-Raisig, W., Mahajan, A., Etzel, C. J., D'Amelio, A. M., Homann, K. L., Newhauser, W. D. (2012). Comparison of Therapeutic Dosimetric Data from Passively Scattered Proton and Photon Craniospinal Irradiations for Medulloblastoma. *Radiat Oncol* 7: 116.

Lee, C. T., Bilton, S. D., Famiglietti, R. M., Riley, B. A., Mahajan, A., Chang, E. L., Maor, M. H., Woo, S. Y., Cox, J. D., Smith, A. R. (2005). Treatment Planning with Protons for Pediatric Retinoblastoma, Medulloblastoma, and Pelvic Sarcoma: How Do Protons Compare with Other Conformal Techniques? *Int J Radiat Oncol Biol Phys* 63(2): 362-72.

Lin, R., Hug, E. B., Schaefer, R. A., Miller, D. W., Slater, J. M., Slater, J. D. (2000). Conformal Proton Radiation Therapy of the Posterior Fossa: A Study Comparing Protons with Three-Dimensional Planned Photons in Limiting Dose to Auditory Structures. *Int J Radiat Oncol Biol Phys* 48(4): 1219-26.

MacDonald, S. M., Safai, S., Trofimov, A., Wolfgang, J., Fullerton, B., Yeap, B. Y., Bortfeld, T., Tarbell, N. J., Yock, T. (2008). Proton Radiotherapy for Childhood Ependymoma: Initial Clinical Outcomes and Dose Comparisons. *Int J Radiat Oncol Biol Phys* 71(4): 979-86.

MacDonald, S. M., Trofimov, A., Safai, S., Adams, J., Fullerton, B., Ebb, D., Tarbell, N. J., Yock, T. I. (2011). Proton Radiotherapy for Pediatric Central Nervous System Germ Cell Tumors: Early Clinical Outcomes. *Int J Radiat Oncol Biol Phys* 79(1): 121-9.

Merchant, T. E., Hua, C. H., Shukla, H., Ying, X., Nill, S., Oelfke, U. (2008). Proton Versus Photon Radiotherapy for Common Pediatric Brain Tumors: Comparison of Models of Dose Characteristics and Their Relationship to Cognitive Function. *Pediatr Blood Cancer* 51(1): 110-7.

Moteabbed, M., Yock, T. I., Paganetti, H. (2014). The Risk of Radiation-Induced Second Cancers in the High to Medium Dose Region: A Comparison between Passive and Scanned Proton Therapy, IMRT and Vmat for Pediatric Patients with Brain Tumors. *Phys Med Biol* 59(12): 2883-2899.

Rieken, S., Habermehl, D., Haberer, T., Jaekel, O., Debus, J., Combs, S. E. (2012). Proton and Carbon Ion Radiotherapy for Primary Brain Tumors Delivered with Active Raster Scanning at the Heidelberg Ion Therapy Center (HIT): Early Treatment Results and Study Concepts. *Radiat Oncol* 7: 41.

Semenova, J. (2009). Proton Beam Radiation Therapy in the Treatment of Pediatric Central Nervous System Malignancies: A Review of the Literature. *J Pediatr Oncol Nurs* 26(3): 142-9.

Sethi, R. V., Giantsoudi, D., Raiford, M., Malhi, I., Niemierko, A., Rapalino, O., Caruso, P., Yock, T. I., Tarbell, N. J., Paganetti, H., MacDonald, S. M. (2014). Patterns of Failure after Proton Therapy in Medulloblastoma; Linear Energy Transfer Distributions and Relative Biological Effectiveness Associations for Relapses. *Int J Radiat Oncol Biol Phys* 88(3): 655-63.

Yeung, D., McKenzie, C., Indelicato, D. J. (2014). A Dosimetric Comparison of Intensity-Modulated Proton Therapy Optimization Techniques for Pediatric Craniopharyngiomas: A Clinical Case Study. *Pediatr Blood Cancer* 61(1): 89-94.

Yoon, M., Shin, D. H., Kim, J., Kim, J. W., Kim, D. W., Park, S. Y., Lee, S. B., Kim, J. Y., Park, H. J., Park, B. K., Shin, S. H. (2011). Craniospinal Irradiation Techniques: A Dosimetric Comparison of Proton Beams with Standard and Advanced Photon Radiotherapy. *Int J Radiat Oncol Biol Phys* 81(3): 637-46.

Yuh, G. E., Loredo, L. N., Yonemoto, L. T., Bush, D. A., Shahnazi, K., Preston, W., Slater, J. M., Slater, J. D. (2004). Reducing Toxicity from Craniospinal Irradiation: Using Proton Beams to Treat Medulloblastoma in Young Children. *Cancer J* 10(6): 386-90.

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PART II:

CONSENSUS THERAPY RECOMMENDATIONS

FOR PATIENTS WITH RHABDOID TUMORS OF THE KIDNEY

(RTK – rhabdoid tumor of the kidney)

The treatment of extra CNS rhabdoid tumors has in most instances been based on sarcoma-like protocols. Currently several different study groups recruit patients into trials icluding a trial for extracranial rhabdoid tumors under direction of the EpSSG (directed by B. Brennan) or under the guidance of the COG such as the AREN0321 trial for high risk renal tumors.

The following recommendations represent a synthesis of the published literature and an expert panel's experience. Its main purpose is to give guidance to clinicians not recruiting patients in any of the afore mentioned trials.

Responsibility for the use of the therapeutic recommendations in this document and all clinical decisions lie at the discretion of the treating physician.

II.1 Diagnostic evaluation

Basic Assessment

- complete medical history
- physical examination including neuropediatric evaluation
- weight, height and body surface area and pubertal status
- Karnofsky Performance Status (KPS) or Lansky play score
- complete blood count (CBC) and serum chemistries (electrolytes, liver function tests, kidney function tests)
- blood type
- transfusion associated viral status (i.e. hepatitis A, B and C, HIV, CMV, Parvovirus B19)
- calculation of GFR or if possible measurement of GFR
- urine analysis: protein, α1-microglobulin, creatinine, phosphate, calculation of tubular phosphate reabsorption and proteinuria in 24 h

Initial Staging

- Imaging of the primary tumor: ultrasound and MRI scan with measurement of tumor volume (for details see chapter II.2)
- Whole body MRI (see below)
- Cerebro-Spinal-Fluid: local pathology and reference evaluation (competence centre), only if neurological symptoms or suspicion on cranial imaging

It is recommended that imaging is performed fewer than 28 days prior to the start of treatment. Documentation of the dimensions of the tumour is obtained. Data will be reviewed centrally (see below). Detailed guidelines for imaging, especially neuroradiologic imaging, are given below. Postoperative imaging will help delineate postoperative residual tumor from non-specific tissue changes associated with the operative procedure.

Pre-treatment evaluation

The following pre-treatment evaluations are recommended prior initiation (suggested within 14 days) of therapy:

- physical examination including neuropediatric evaluation
- weight, height and body surface area
- Karnofsky Performance Status (KPS) or Lansky play score
- documentation of doses of steroids (if any) and any hormone replacement therapy, antiepileptic therapy or medication modifying behaviour
- complete blood count (CBC) and serum chemistries (electrolytes, liver function tests, kidney function tests)
- ECG, echocardiogram, audiometry or BERA
- genetic evaluation in children with a potentail rhabdoid tumor predisposition syndrom, in all children below two years with multifocal disease, synchronous rhabdoid tumors and when genetic mutations are known in the pedigree (e.g. Li Fraumeni…)
  (see also chapter 6.3 and figure 6.2)
- a urine pregnancy test for women of childbearing potential should be performed within 7 days prior to administration of chemotherapy

In addition, the patient/parents must be thoroughly informed about all aspects of any therapy, including evaluations and all regulatory requirements for informed consent. Written informed consent must be obtained by both parents (and patient where appropriate) prior to initiation of therapy.

Prior to each scheduled dose of chemotherapy

Performed on Day 1 prior to each cycle or within 72 hours prior to Day 1:

- documentation of concomitant drugs (particularly steroid usage, dose and duration during and after radiotherapy)
- physical examination including neurologic evaluation, vital signs, height and weight (percentiles)
- Karnofsky Performance Status or Lansky play score
- CBC and serum chemistries
- imaging (see below)
- ECG and echocardiography prior to anthracycline-containing elements
- Severe adverse events will be assessed according to the Common Toxicity Criteria (CTCAE) on an ongoing basis during therapy.

If a cycle of chemotherapy is delayed, only the CBC should be repeated weekly or within 72 hours of that day until treatment is given. The physical examination, including neurologic

evaluation, vital signs, weight, neurologic performance grading and Karnofsky Performance Status should be repeated on the actual day of dosing (or within 72 hours prior to this day) if the actual day of dosing is more than 2 weeks delayed.

- **Whole body MRI** is recommended to exclude multifocality in all patients with rhabdoid tumors. If this is not possible imaging studies as listed below are strongly recommended. In AT/RT patients the response and tumor-volume measurement is best performed by MRI. Whole body MRI does however not replace MRI imaging of specific tumor sites (better resolution). In patients with MRT or RTK these controls may be performed by sonographic methods, but MRI is the recommended method.

- **Echocardiographic evaluation** is recommended prior to each anthracycline-containing element.

- In case of **tumor progression** imaging of other loci with potential involvement has to be considered (e.g. kidney in AT/RT) due to the possibility of a rhabdoid tumor predisposition syndrome (see genetics).

Examination during chemotherapy

See figures II.1 – II.4

European Rhabdoid Registry – schedule of examinations

RTK / MRT < 18 months

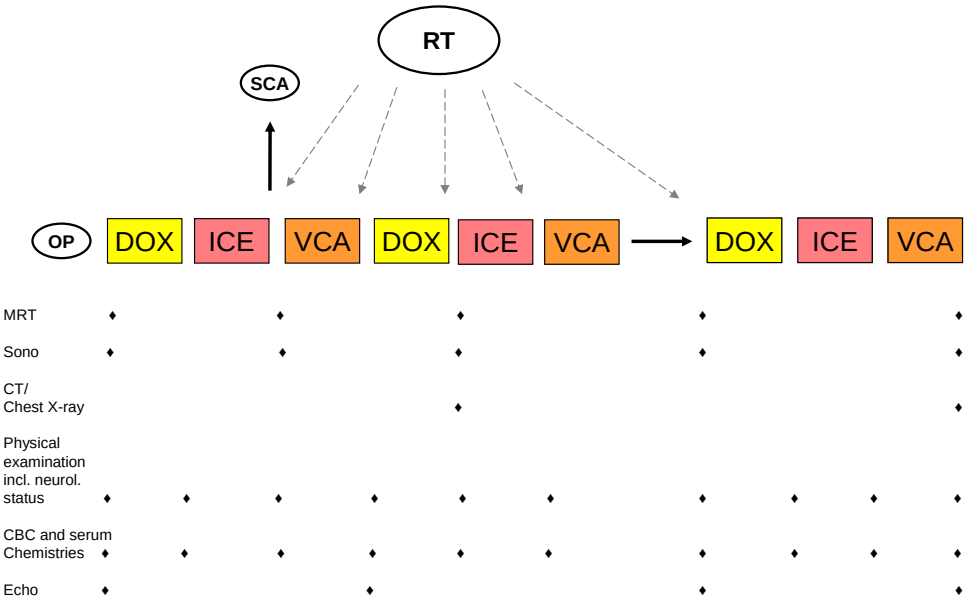


Figure II.1: RTK < 18 months: conventional chemotherapy

RTK / MRT < 18 months

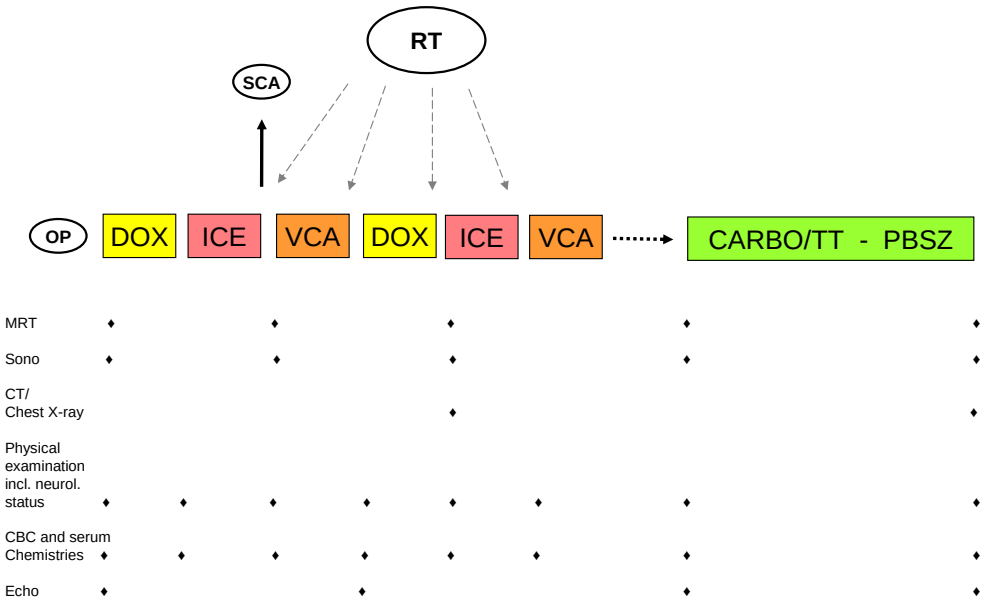


Figure II.2: RTK < 18 months: HD-chemotherapy

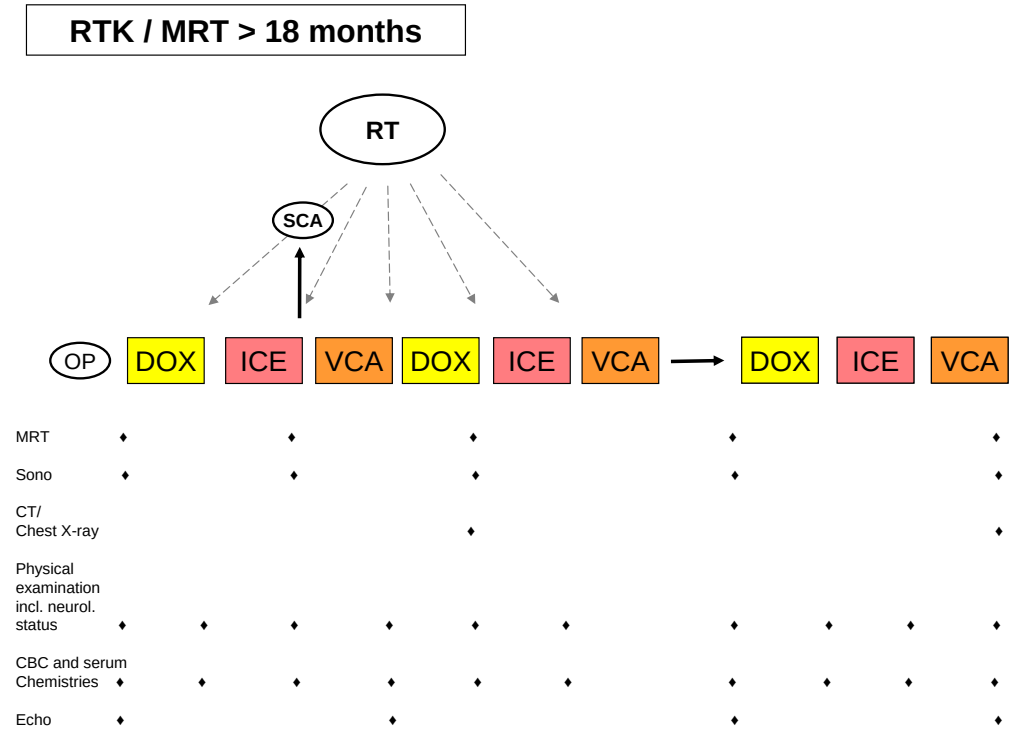


Figure II.3: RTK > 18 months: conventional chemotherapy

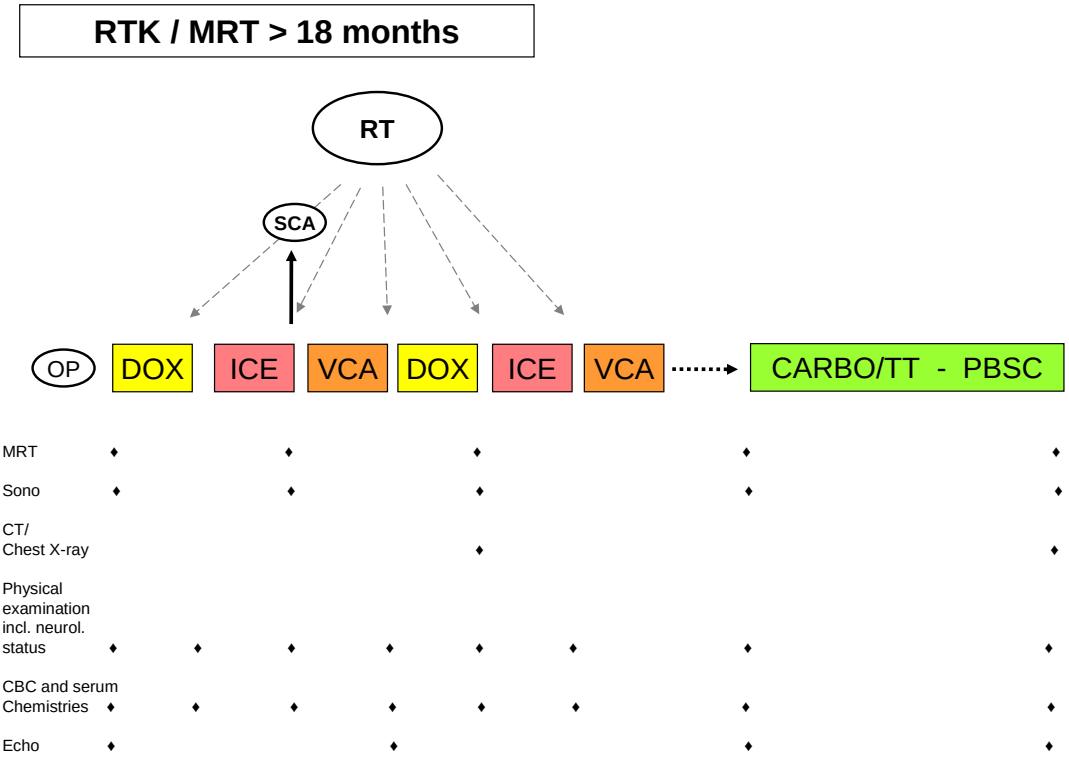


Figure II.4: RTK > 18 months: HD-chemotherapy

Follow-up after completion of therapy

After completion of the chemotherapy it is advised to perform examinations according to the follow-up schedule:

	1. / 2. Year after completion of therapy	3. - 5. Year after completion of therapy	6. - 10. Year after completion of therapy	Second decade after completion of therapy
Physical examination	bimonthly	every 6 months	twice yearly or yearly	yearly
MRI local side	every 3 months	twice to four times yearly	yearly	if symptomatic
Chest CT	every 6 months	in case of symptoms	in case of symptoms	if symptomatic
Cranial MRI	once, at the end of treatment	only, if pathological before	only, if pathological before	only, if pathological before
Sonography	four times yearly	four times yearly	if symptomatic	if symptomatic
Height, weight, pubertal status	every 6 months	every 6 months	yearly	individually
CBC	every second month	every 6 months	yearly	yearly
Renal function Serum-chemistry	bimonthly	every 6 months	yearly	yearly
Radiotherapist**	yearly	yearly	yearly	yearly
ENT consult	yearly	if symptomatic	if symptomatic	if symptomatic
Echo/ECG	twice yearly	yearly	yearly	yearly
Skeletal scintigraphy	once, at the end of treatment	only, if pathological before	only, if pathological before	only, if pathological before
Lung function (if age permitts)	once, at the end of treatment	only, if irradiation to the lung	only, if irradiation to the lung	only, if irradiation to the lung

Table II.1: Follow-up examinations in patients with extracranial rhabdoid tumors

II.2 Imaging Studies

Ultrasound of the abdomen

The physician evaluating the lesion should describe the following aspects of the tumor in detail:

1. localisation within the affected organ, border, relation to blood vessels and lymph node regions
2. evaluation of the contralateral organ for comparison (i.e. contralateral kidney)
3. echogenicity of the lesion
4. description and measurement of cystic areas of the tumor
5. measurement of the lesion in the plain with the largest diameter and in an angle 90° perpendicular to it
6. evaluation of tumor thrombi within blood vessels draining the tumor region (i.e. renal vein or inferior vena cava)
7. evaluation of intra-abdominal or regional lymph node sizes
8. evaluation of metastatic lesions (i.e. liver, spleen, local lymph nodes)

The primary tumor size should be measured at the time of diagnosis in three plains. The type of measurement should be documented. Individual tumor lesions should be measured separate from each other. Tumor volume may be calculated according to the following formula:

V = L x T x B x 0.523 in cm^3 ***L = length, T = depth, B = width***

MRI or CT

Besides sonography an additional imaging technique should be used. Preoperative imaging especially under circumstances when local RT is in planning stages is mandatory. MRI is the method of choice.

MRI is always indicated

1. if large thrombi within the vena cava or other draining vessels are suspected and may even reach the thoracic cavity
2. if there is liver and diaphragm involvement
3. if there is suspected continuous spread into the thoracic cavity or from the thoracic cavity into the abdomen.

Imaging of the thorax

Lung metastases may be imaged by native radiological imaging in two plains. But the gold standard should be a CT scan of the thorax.

MIBG scintigraphy

MIBG scanning should be performed in cases when neuroblastoma can not be differentiated by imaging (MRI) from a potential lesion of the kidney such as Wilms or rhabdoid tumor.

Technetium scintigraphy

Scintigram of the skeletal system has to be discussed in all patients. Currently no data exist in the literature. Therefore it is adviseable to perform an initial technetium scan for all patients.

PET-CT

The value of PET-CT in the imaging of patients with AT/RT, RTK and MRT remains to be defined. In selected cases PET-CT scanning might be a valuable asset in the diagnostic follow-up and the response evaluation of patients.

Cranial imaging

In patients who suffer from metastases of RTK or MRT cranial MRI is the method of choice and should be performed according to the guidelines listed above for AT/RT. In all patients with RTK or MRT a cerebral MRI should be performed according to the guidelines listed above for AT/RT.

Selective angiography of the kidneys

This method of imaging is indicated in patients with horseshoe kidneys and in cases where the surgeon requires this information.

II.3 Surgical approach to patients with renal rhabdoid tumors (RTK)

The surgeon needs to obtain all necessary information about tumor size, exact localisation, and relation to large blood vessels, potential existence of tumor thrombi and involvement of adjacent organs.

Thoracic CT is indicated if native two-dimensional X-ray does not reveal a clear picture. Immediate postoperative sonographic evaluation is recommended.

Choice of surgical approach:
The transperitoneal approach may be viewed as the obligatory standard. The incision itself whether transverse or upper abdomen or subcostal is at the discretion of the individual surgeon.

Inspection of the abdominal cavity:
The abdominal cavity has to be inspected before tumor removal to review all metastatic lesions, e. g. in the liver, lymph nodes and peritoneum. All visible lesions that can easily be resected should be removed. Non-resectable lesions should be biopsied and their location marked. As a complete resection is the most important prognostic factor, it should be the surgeon's primary goal to remove all visible tumor. Inoperable tumor has to be biopsied.

Special considerations:

Nephrectomy:
Due to th aggressive nature of rhabdoid tumors of the kidney a tissue sparing operation can not be recommended. Neprectomy is thus the surgical approach of choice. First the renal artery is ligated to prevent swelling of the tumor and to prevent the danger of tumor rupture. Only in case of a large tumor infiltrating the surrounding, early ligation of the kidney vessels may be difficult and increase the risk of tumor rupture. In these instances the tumor has to be mobilized from the surrounding tissue.

Involvement of renal veins or vena cava:
In those cases with intravascular extension of the tumor into adjacent veins especially into the V. cava (evident from preoperative imaging) intraoperative inspection of these vessels is mandatory. A tumor associated thrombus needs to be removed. Special attention should be paid that no compression of the V. cava is caused by the surgery. In special circumstances with large infiltration of the V. cava advantages and disadvantages of surgery vs. local radiotherapy have to be weighed against each other.

Adrenals and ureter:
The adrenals may be left *in situ* and do not have to be removed if the kidney is affected. The ureter should be resected as close to the bladder as possible.

Lymph nodes:
The operative removal of the lymph nodes is mandatory. Lymph nodes close to the hilium of the kidney and paraaortal lymph nodes have to be removed even if they appear macroscopically normal.

Tumor rupture:
In case of a tumor rupture the anatomical site and potential spread within the operational field have to be documented with highest possible precision. Infiltrations into adjacent tissue, affected lymph nodes, macroscopic residues and microscopic as well as macroscopic tumor ruptures should be described in detail.

II.4 Chemotherapeutic approach to patients with renal rhabdoid tumors (RTK)

The protocol of the European Rhabdoid Registry contains the following recommendations for a standardized therapy, which were generated from data derived from the current literature, the investigators' own experience and data derived from the GPOH studies for high risk Wilms tumors, soft tissue sarcomas and malignant brain tumors of infants and children.

!!! ALL SCHEDULES MAY BE FOUND IN THE APPENDIX !!!

Chemotherapy as suggested for the European Rhabdoid Registry contains the following therapy-elements:

a) Chemotherapy:

DOX: doxorubicin
ICE: ifosfamide, carboplatinum and etoposide
VCA: vincristine, cyclophosphamide and actinomycin-D

b) High Dose Chemotherapy:

carboplatinum / thiotepa

Radiotherapy:

RT should be performed ass soon as possible. RT in children below the age of 18 months has to be considered individually. For details see chapter radiotherapy.

Second-look-surgery:

Generally a second-look-surgery may be necessary or useful at any time during therapy. In case second look surgery is performed, material should be sent for reference pathology evaluation. (see page xy)

High Dose Chemotherapy (HDCT):

The use of HDCT is at the discretion of the individual treating physician. The role of HDCT in rhabdoid tumors remains undefined. In general it has been shown that high-risk sarcomas respond better to maintenance chemotherapy then to HDCT (Klingebiel et al., 2008). As individual centers and some countries prefer to employ HDCT, it is suggested to harmonize strategies as much as feasible in order to obtain a maximum of information. This may deliver the necessary preliminary evidence for a randomized trial e.g. comparing HDCT vs. conventional chemotherapy.

If high-dose-therapy is planned by the treating physician, it may thus follow the suggestions in the appendix.

Stem-cell-separation:

Collection of stem-cells may be conducted after the first ICE-element 3. If necessary another point following ICE is also possible.

Cardiotoxicity:

The application of anthracyclines (e.g. doxorubicin) appears to be essential in the treatment of patients with rhabdoid tumours. Anthracyclines are cardiotoxic, especially in children below the age of two years, prior cardio-vascular diseases and radiotherapy of the mediastinum. If side effects occur, a dose-modification is necessary (see below). In any case the form "cardiotoxicity" should be filled out and sent to the study coordinator.

Event:

In case an adverse event, a severe adverse event or any other important event (progress under therapy, death etc.) occurs during therapy, the corresponding forms should be sent immediately to the registry.

G-CSF:

Since treatment intensity and density is essential in the treatment of Rhabdoid tumors, G-CSF support is preferable to dose reduction. The recommended dose is 5 µg/kg/d as once daily s.c. injection.

Maintenance therapy:

In cases of residual disease at the end of treatment, the application of a maintenance therapy has to be considered and discussed with the study coordinator.

II.4.1 Schematic diagram of chemotherapy

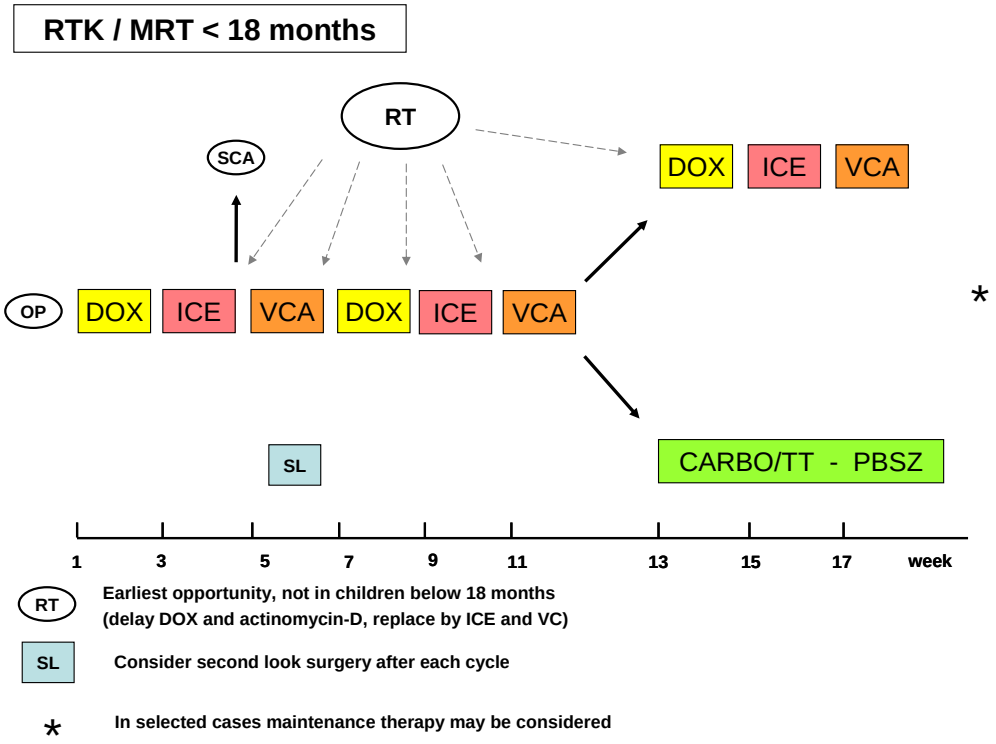


Figure II.5: RTK < 18 months

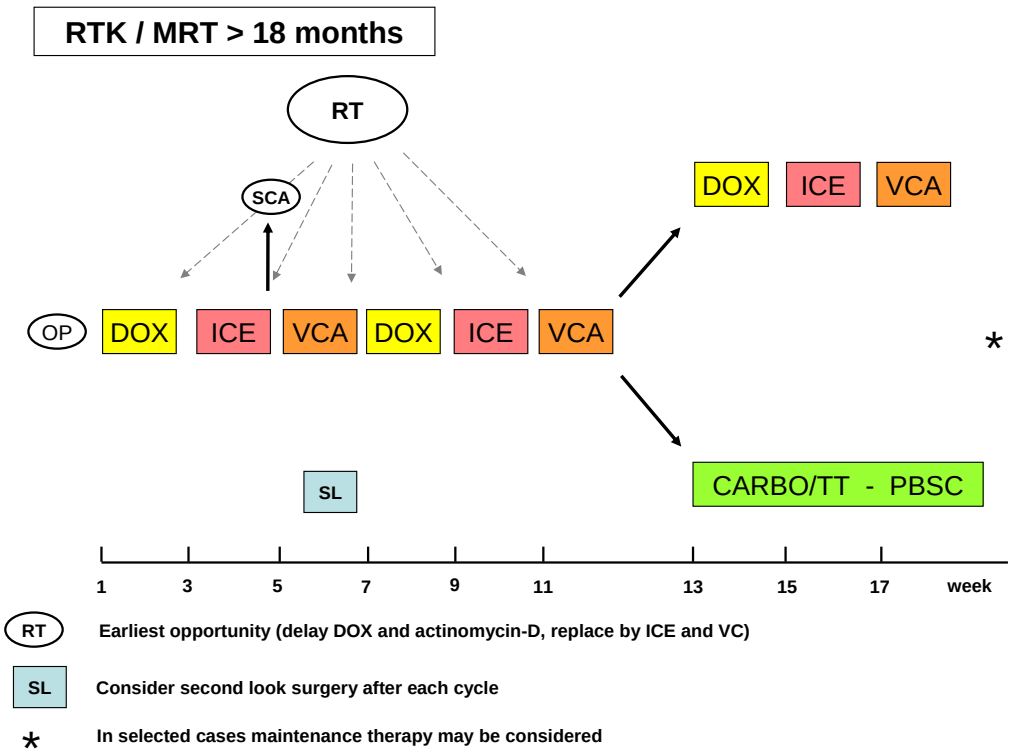


Figure II.6: RTK > 18 months

Abbreviations:

OP = surgery or initial biopsy, SL= second-look-surgery, DOX= doxorubicin, ICE = ifosfamide, carboplatinum, etoposide, VCA = vincristin, cyclophosphamide, actinomycin-D, SCA = stem cell apheresis, IT= intra-thecal chemotherapy, RT= radiotherapy, Carbo/TT – PBSC= high-dose chemotherapy with caraboplatinum/thiotepa

II.4.2 Chemotherapy

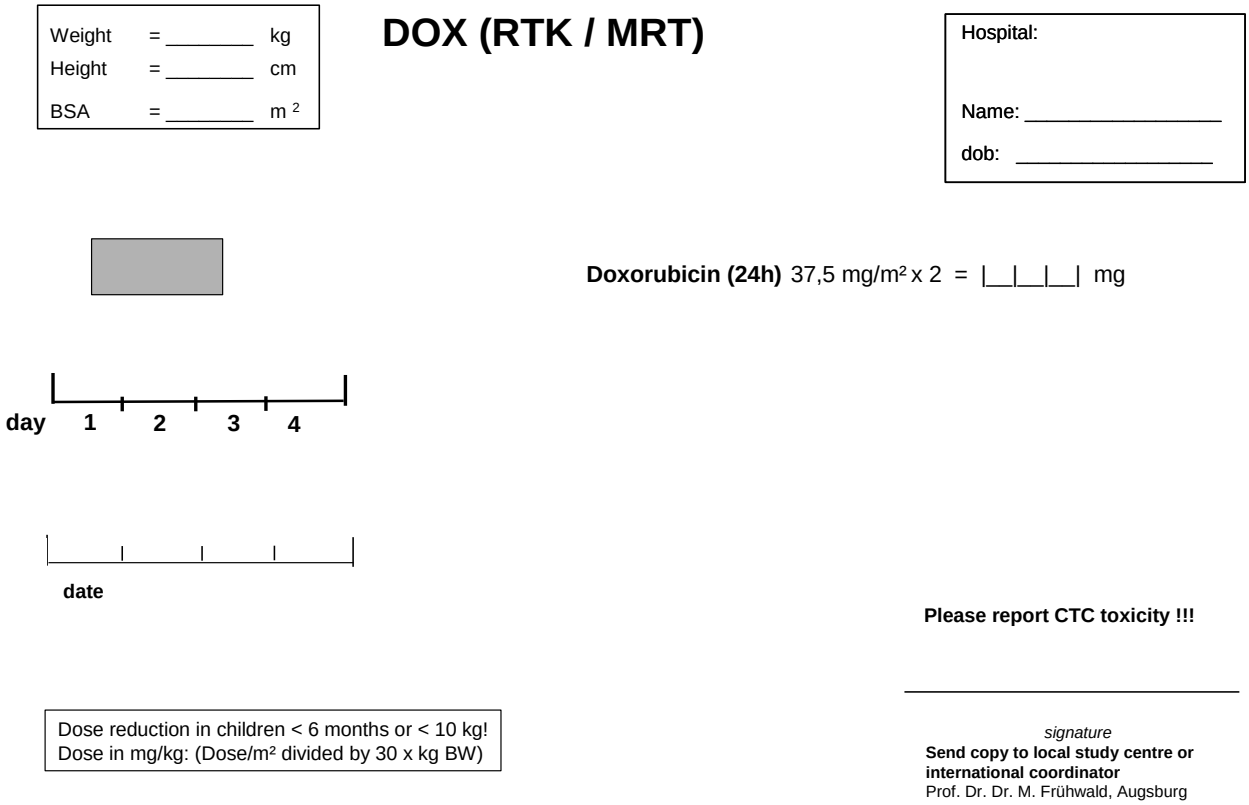


Figure II.7: Doxorubicin schedule

Day	Doxorubicin
1	37,5 mg/m²
2	37,5 mg/m²
3	
4	
Cum. dose per cycle	75 mg/m²

Table II.2: Doxorubicin

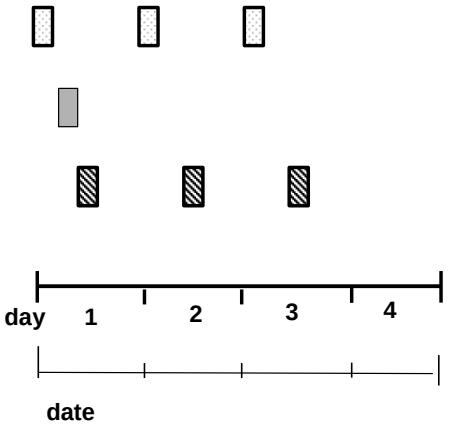
Weight = _____ kg
Height = _____ cm
BSA = _____ m^2

ICE (RTK / MRT)

Hospital:

Name: _____

dob: _____



Ifosfamide p.i. (1h) 2000mg/m^2 x 3 = |__|__|__|__| mg/D
with MESNA:
2.000mg/m^2 with hydration 3.000ml/m2/d

Carboplatinum (1h) 500mg/m^2 = |__|__|__| mg

Etoposide (1h) 100mg/m^2 x 3 = |__|__|__| mg/D

Dose reduction in children < 6 months or < 10 kg!
Dose in mg/kg: (Dose/m^2 divided by 30 x kg BW)

Please report CTC toxicity !!!

signature
Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

Figure II.8: ICE schedule

Day	Ifosfamide	Carboplatinum	Etoposide
1	2000 mg/m² over 1 h	500 mg/m² over 1 h	100 mg/m² over 1 h
2	2000 mg/m² over 1 h		100 mg/m² over 1 h
3	2000 mg/m² over 1 h		100 mg/m² over 1 h
Cum. dose per cycle	6000 mg/m²	500 mg/m²	300 mg/m²

Table II.3: ICE: Ifosfamide/Carboplatinum/Etoposide

Etoposide may be substituted by etoposidphosphate if available. The dosage used is 114mg/m^2 of etoposidphosphate for equivalent dose of etoposide (100mg).

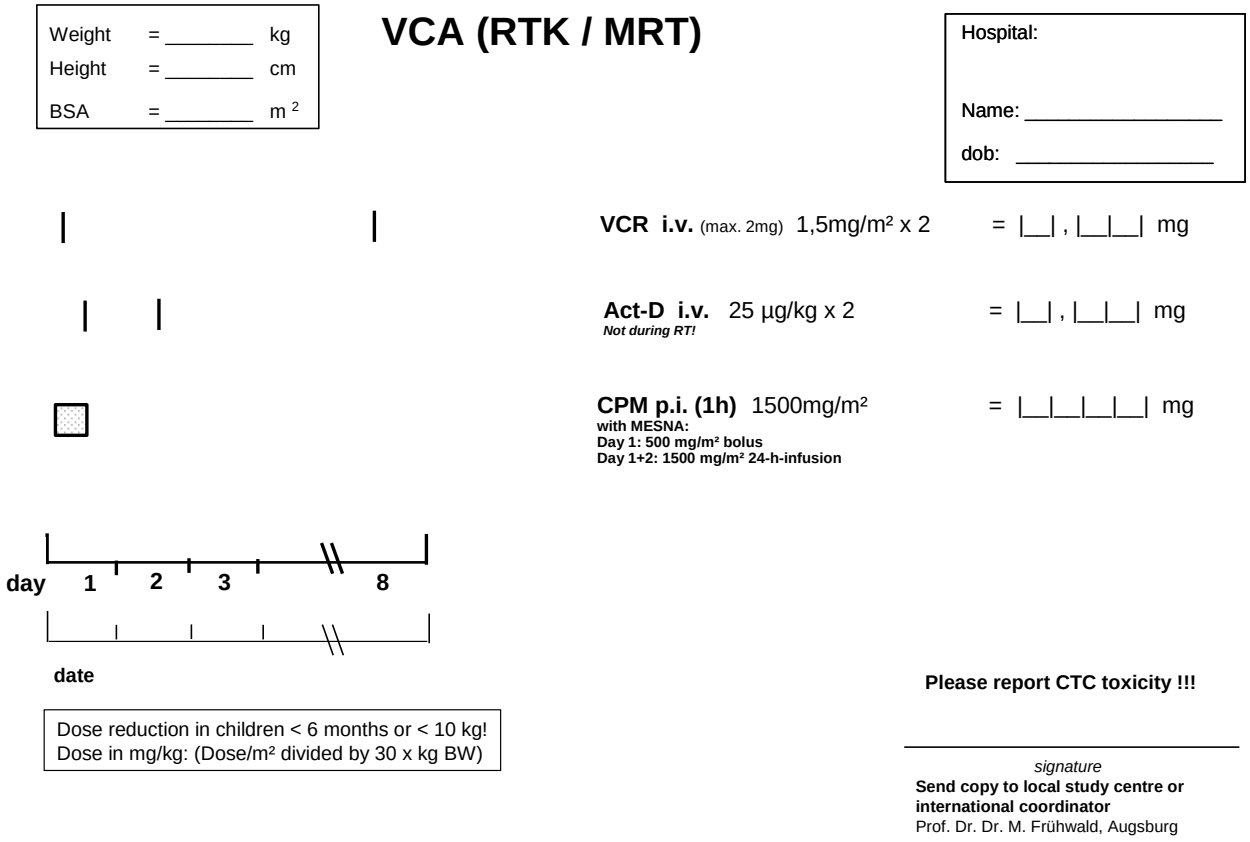


Figure II.9: VCA schedule

Day	Vincristine	Cyclophosphamide	Actinomycin-D
1	1,5 mg/m² max 2 mg	1500 mg/m² over 1 h	25 µg/kg
2			25 µg/kg
8	1,5 mg/m² max 2 mg		
Cum. dose per cycle	3,0 mg/m² max 6 mg	1500 mg/m²	50 µg/kg

Table II.4: VCA: Vincristine/Cyclophosphamide/Actinomycin-D

Dose reduction Actinomycin-D:
For infants < 1 year or < 10 kg only 2/3 of the already reduced Actinomycin-D dose should be administered. If tolerated well individual increase of the dose in the next cycle may be considered.

Initiation:

The scheduled interval between day 1 of the elements is 14 days. If it is not possible to adhere to this schedule, the next element should begin as soon as possible after regeneration and normalisation of hematologic parameters.

Prerequisites:

- satisfactory general condition
- no signs of infection
- no signs of CSF-circulation-disorders
- cardiac function: Echo (FS>28%) or RNV (LVEF>50%)
- Hb: > 8 g%
- platelets: > 100.000/mm³
- neutrophils: > 1000/µl
- GFR: > 70 ml/min/1,73m²
- urine: no hematuria

Hydration: 3000 ml/m²/d, 24 h-hydration until day 4 (incl.)

Start infusion 6 hours before application of carboplatinum.

Recommendation for composition of 1000 ml solution:

Glucose 5%	480 ml
NaCl 0,9%	480 ml
KCl 7,45%	30 ml
Ca-Gluconat 10%	10 ml

Add Magnesium 3 mmol/l.

Mesna-Application: Day 1: MESNA 500mg/m² i.v. as short-infusion or bolus
Day 1: MESNA 1.500 mg/m² i.v. continuous infusion over 24 hours
Day 2: MESNA 1.500 mg/m² i.v. continuous infusion over 24 hours
(Day 2 may be omitted in children over 3 years of age)

G-CSF: G-CSF is started on day 5
Dose: 5µg/kg/d s.c. injection

Febrile neutropenia or infection	CTCAE grade 4, possibly grade 3	IFO and ETO dose reduction to 2/3
Mucositis	CTCAE grade 4, poss. repeated grade 3	ETO dose reduction of 50% DOXO Dose reduction of 20%
Kidney: glomerular function	Krea > 1,5 x base value or Krea-Clearance <70 ml/min/1,73m²	delay element 1 week; if no recovery: no further IFO
Kidney: tubular function	CTCAE grade 2 CTCAE grade 3/4	poss. IFO reduction of 20% no further IFO
Hematuria	Stix positive under IFO 2 x microhematuriea under IFO CTCAE > grade 2 CTCAE grade 3/4	double MESNA MESNA Bolus 600 mg/m², then MESNA-Infusion with doubled dosing. If persisting: Stop IFO stop IFO, double MESNA-Infusion contact study-coordinator
Neurotoxicity	CTCAE > grade 2 CTCAE grade 4	see below NO FURTHER IFO!
Cardiac toxicity	FS < 28% or LVEF < 50% Acute Cardiotoxicity	repeat examination after one week, if no improvement: NO FURTHER DOXORUBICIN. stop Doxo-Infusion

Table II.5: Dose-modifications in case of toxicity

Central Neurotoxicity:

If CTC grade 3 or 4 central neurotoxicity occurs (somnolence >30% of the time, disorientation/hallucination/echolalia/perseveration/coma, or seizures on which conciousness is altered, or which are prolonged, repetitive or difficult to control), consider

- use of methylene blue (methylthionin) 50 mg as i.v. infusion.
- prolong ifosfamide-infusion to 4-8 hours with the next application, and infuse methylene blue 50 mg three times daily.
- in the next course, apply methylene blue one dose of 50 mg 24 hours prior to ifosfamide. During ifosfamide infusion give three times daily methylene blue as described above (refer to Nicolao and Giometto, Oncology 2003, 65[Suppl 12]:11-16 for further information).
- if repeated grade 3 or 4 central neurotoxicity occurs, consider withholding ifosfamide and substitute cyclophosphamide 1500 mg/m² BSA.
- alternatively piracetam 100mg/kg may be given prophylactically (q 6h) or in therapeutic intention (q 4 h)

II.4.3 High Dose Chemotherapy approach (HDCT)

Stem-cell-harvest:

Stem cell harvest may take place after the first ICE-element. It can be repeated after the second ICE-element if necessary.

Priming of peripheral blood progenitor cells with G-CSF, e.g. 10µg/kg/d G-CSF is advised from 24 hours after the last dose of chemotherapy until completion of harvest. Apheresis may start after three days.

- A total of at least two units containing $3x10^6$ CD34+ cells/kg each should be collected.
- Stem cell harvest has to be performed according the ISHAGE Guidelines.

One of the aliquots is needed for high-dose-therapy, the other is needed as backup.

Cyclophosphamide for stem-cell-harvest:

This therapy is not recommended generally for all patients, but it may be performed in cases with difficult stem cell mobilization.

- Hydratation: 3000 ml/m²/d for 24 hours
- MESNA 1300 mg/m² as i.v. bolus before application of cyclophosphamide
- Cyclophosphamide 4000 mg/m² over 4 hours as short infusion
- MESNA 4000 mg/m²/d for 24 hours

Prerequisites:

- satisfactory general condition
- no signs of infection
- no signs of CSF-circulation-disorders
- cardiac function: Echo (FS>28%) or RNV (LVEF>50%)
- Hb: > 8 g%
- platelets: > 100.000/mm³
- neutrophils: > 1000/µl
- GFR: > 70 ml/min/1,73m²

Weight = _____ kg
Height = _____ cm
BSA = _____ m²

RTK / MRT
High-dose: Carbo / Thio

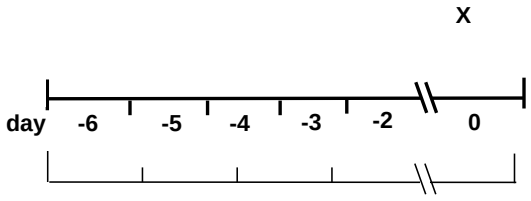
Hospital:

Name: _____

dob: _____

Carboplatinum 500mg/m²/d = |__|__|__| mg/d
day -6 to -4

Thiotepa 300 mg/m²/d 1 h = |__|__|__| mg/d
day -6 to -4



Please report CTC toxicity !!!

G-CSF: 150 µg/m²/d or 5 µg/kg/d s.c. day +5 until ANC > 1000/µl for 3 days

_____
signature
Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

Figure II.10: RTK High-dose-therapy (Carbo/Thiotepa)

Day	Carboplatin	Thiotepa	PBSC
-6	500 mg/m²/d	300 mg/m² 1 h	
-5	500 mg/m²/d	300 mg/m² 1 h	
-4	500 mg/m²/d	300 mg/m² 1 h	
-3			
-2			
0			X
Cum. dose per cycle	1500 mg/m²	900 mg/m²	

Table II.6: High-dose-therapy Carbo/Thiotepa

Prerequisites:

- satisfactory general condition
- no signs of infection
- no signs of CSF-circulation-disorders
- cardiac function: Echo (FS>28%) or RNV (LVEF>50%)
- Hb: > 8 g%
- platelets: > 100.000/mm³
- neutrophils: > 1000/µl
- GFR: > 70 ml/min/1,73m²
- urine: no hematuria

Hydration: 3 000 ml/m²/d, 24 h, day -6 to -2

G-CSF: 150 µg/m²/d or 5 µg/kg/d s.c. day +5 until ANC > 1000 for 3 days

Supportive Care:

- substitution of blood products
- early analgesia with morphins
- parenteral feeding with substitution of vitamine K
- NG-tube for enteral fluid substitution day -1
- antimicrobial prohylaxis with amphotericin B (oral and inhalative), cotrimoxazol, aciclovir

II.5 Radiotherapeutic approach to patients with extracranial rhabdoid tumors

Optimization of timing, dosimetry and target volume to be irradiated are evolving aspects in the therapeutic approach towards children with rhabdoid tumors.

Timing:

1. Children below the age of 18 months should only be irradiated under exceptional circumstances.

2. Children with an age of 18 months or older should be irradiated as soon as feasible. Post-operative RT to the flank is mandatory.

3. In case of primary metastasized disease RT may be delayed until the end of intensive chemotherapy (following element 9). Other special circumstances may apply such as progressive disease, when RT may be performed at any time.

4. For infants and children below 18 months radiotherapy may be delayed until age permits or following element 9.

Children with primarily metastasized rhabdoid tumors may be irradiated at later time points. Current data for AT/RT suggest that in tumors with leptomeningeal dissemination salvage RT may be successful. These instances may be directly discussed with the refernce radiotherapist.

Guidelines for radiation therapy of rhabdoid tumors of the kidneys - RTK

General guidelines

a) Indications for post-operative RT to the flank:
Stage I-III RTK (19.8 Gy for children ≥ 12 months, 10.8 Gy for patients < 12 months)

b) Indications for whole abdominal RT:
a) Stage III – ascites positive for rhabdoid cells
b) Preoperative tumor rupture
c) Diffuse operative spill
d) Peritoneal seeding

c) Indications for RT to the lung:
Lung metastases (15 Gy) (not in children below three years of age)

d) Indications for RT to the liver:
Liver metastases (19.8 Gy)

e) Indications for whole brain RT:
Brain metastases (21.6 Gy) plus boost of 10.6 Gy

f) Indications for bone metastases RT:
Bone metastases (25.2 Gy)

Timing and Equipment

Radiotherapy should be initiated as soon as possible unless there is progressive disease following induction chemotherapy.. Patients should be treated using megavoltage equipment. 3-D-conformal radiotherapy planning using CT guided imaging is recommended when critical structures are close to the target volume (TV). The prescribed dose is in accordance to ICRU 50.

Fractionation

Dosing is applied employing conventional fractionation using 1.8 Gy per day five days per week. Once treatment has been initiated there should be no interruptions unless life-threatening events occur. If white blood cells fall below 300/µl or platelets below 40,000/µl during the course of treatment radiation therapy may be delayed until counts have recovered at the discretion of the treating oncologist.

Treatment interruption: In case of a treatment interruption two fractions with an interval of at least six hours between fractions should be given to enable completion of treatment within the initially scheduled time frame.

Target volume definition

The target volume is chosen according to the initial tumor volume (gross tumor volume - GTV). A pre-therapeutic CT or MRI scan is usually the optimal imaging modality. The clinical target volume (CTV) is defined as the GTV + 1 cm. The planning target volume (PTV) is defined as the CTV + 1 cm. The PTV should also consider special needs of pediatric radiation oncology such as the inclusion of the complete vertebra in the radiation field to avoid scoliosis.

Flank radiotherapy

Preoperative CT planning is performed. The GTV comprises the kidney plus the associated tumor. The medial border of the radiation therapy field is extended across the midline in order to include all of the vertebral bodies at the respective level. The contralateral kidney should not be touched. In patients with tumors that exceed into the contralateral flank without tumor invasion into the contralateral kidney the addition of a 1 cm margin to the medial tumor extension will include significant volumes of the contralateral normal kidney. Therefore not more than 1 cm margin beyond the vertebral body is required. The radiation field should not be extended into the dome of the diaphragm unless there is tumor extension. In the case of positive lymph nodes that have been removed, the entire length of the paraaortic chain of lymph nodes will be included. An AP/PA-parallel-opposed technique is recommended. Daily dose to the prescription points will be 1.8 Gy. The dose to more than 1/3 of the contralateral kidney should not exceed 14.4 Gy. The dose should not be more than 19.8 Gy in 11 fractions of 1.8 Gy over 15 days to 50 % of the uninvolved liver.

Whole abdomen and pelvis radiotherapy

The clinical target volume will be the entire peritoneal cavity. The superior border of the abdominal field will be placed approx. 1 cm above the diaphragm. The inferior border of the field will be placed at the bottom of the foramen obturatorium. The lateral borders will be placed 1 cm beyond the lateral abdominal wall. The femoral heads should be shielded. An AP-PA field technique is recommended for whole abdomen irradiation. Fractionation should be 19.5 Gy in 13 fractions of 1.5 Gy for 17 days in children 12 months and older and 10.5 Gy in infants at 7 fractions of 1.5 Gy over 9 days. When the total dose is 20 Gy, appropriate renal shielding is to be utilized in order to limit the dose to the remaining kidney to not more than 15 Gy.

Boost irradiation

Conformal down boost therapy may be used for patients with gross residual tumor after surgery at a total dose of 10.8 Gy. Three-dimensional CT planning should be used. The GTV will specifically be based on the postoperative CT/MRI scans. The clinical target volume will be anatomically defined surrounding 1 cm of the GTV. A dose to more than 1/3 of the contralateral kidney or to the residual normal kidney should not exceed 14.4 Gy, nor should the dose to more than 50 % of the uninvolved liver exceed 19.8 Gy.

Whole lung irradiation

Both lungs are irradiated regardless of the number and location of the metastases. The inferior extent of the anterior and posterior costodiaphragmatic recesses of the pleural cavity is determined by a lateral radiograph. The inferior border of the lung irradiation field will be approximately at the L1 vertebral body. The shoulder joints should be shielded. If patients require both whole lung and whole abdomen irradiation both fields should be treated simultaneously. The whole lung irradiation dose is 15.0 Gy in 10 fractions of 1.5 Gy over 12-14 days. Dose calculation should be based on a CT scan with the reference point within the lung tissue (doses prescribed according to ICRU 50 report; in case of central beam calculation, which should be avoided, the lung correction factor has to be considered). In infants this may be reduced to 10.5 Gy in 7 fractions of 1.5 Gy over 9 days. Localized foci in the lung persisting two weeks after whole lung irradiation may be submitted to surgery or an additional 7.5 Gy in five fractions.

Liver irradiation

The entire liver should be included in the irradiation field only if the liver is diffusely involved (19.8 Gy, 11 fractions). In infants the dose fractionation should be 15 Gy, 10 fractions of 1.5 Gy. In the case of individual foci these metastastic lesions should be irradiated with a margin of 2 cm. Additional boost irradiation doses of 5.4 Gy to 10.8 Gy may be administered to limited volumes. The dose to the upper pole of the remaining kidney should be monitored.

Brain irradiation

In patients with brain metastases the whole brain is included in the irradiation field to a dose of 21.6 Gy in 12 fractions of 1.8 Gy. A boost of at least 10.8 Gy is required to individual sites of metastases. In patients with less than three lesions a limited volume boost dose of 10.8 Gy in six fractions using MRI or stereotactic radiotherapy may be administered.

Bone irradiation

In patients with bone metastases the GTV is the lesion as shown on appropriate imaging, which may include Tc-scintigraphy, plain radiographic films, MRI or CT. The CTV will usually include a margin of apparently healthy bone up to 2 cm. A narrower margin may be appropriate when the metastasis is close to the edge of the bone. RT to the epiphysis should be avoided where possible. An appropriate margin should be added for the PTV, taking into account the immobilisation technique employed. In case of irradiation of vertebrae the security margin should include the whole upper and lower vertebra. The bone dose is 25.2 Gy in 14 fractions of 1.8 Gy, but may be modified if appropriate.

Lymph node irradiation

Positive lymph nodes that have not been surgically removed should receive radiation therapy to 19.8 Gy in 11 fractions at 1.8 Gy. Lymph node groups that were involved at presentation should be irradiated in their entirety. The GTV will be the nodal area including any residual mass after chemotherapy as defined on the planning CT. The CTV will be a 1 cm margin around the GTV. For mediastinal and abdominal nodes a parallel opposed field arrangement gives best coverage of the PTV. When possible, nodal areas will be treated in continuity with the primary tumor or other metastatic sites requiring irradiation.

Target dose

The daily dose to ICRU prescription points shall be 1.8 Gy, except in younger children (<3 years) or when large volumes (e.g. whole lung or abdomen) are to be treated.

Simultaneous radio-, chemotherapy in patients with rhabdoid tumors

Radiotherapy may be complicated in some affected patients due to the necessity for deep sedation or even anaesthesia, young age or neurological deficits.
Optimal preparation for radiotherapy always involves assessment of risk factors for anaesthesia which may due to pre-existing conditions such as neurological deficits including difficult swallowing or repeated aspirations. These hint towards much enhanced risk for anaesthesia.

Aims of the following recommendations are thus:

- The planed radiotherapy as a local therapeutic measure should be done without any interruptions due to complications such as febrile neutropenia, documented infections, severe mucositis with the need for analgesics or the need for parenteral nutrition and
- Systematic chemotherapy in parallel to radiotherapy in order to maximize tumour control

Recommendations

Pre- and post-radiotherapy:
Prerequisite for radiotherapy in any patient is complete imaging (e.g. craniospinal MRI) plus complete staging (e.g. CSF analysis) not older than four weeks before sending the patient for radiotherapy.

- Avoidance of Actinomycin D: 2 weeks before and 2 weeks after radiotherapy
- Avoidance of Doxorubicine: 2 weeks before and 4 weeks after radiotherapy
- No intrathecal, intraventricular chemotherapy during or after radiotherapy (AT/RT only)

Simultaneous radio-, chemotherapy

- No Actinomycin D, no Doxorubicin, no intrathecal chemotherapy
- VCA: No Actinomycin D, no intrathecal methotrexate
  Vincristin 100% of the dose,
  Cyclophosphamide 100% to 65% depending on previous tolerance, MESNA dose needs to be adjusted
- ICE: No intrathecal methotrexate reduction of all doses to 50% i.e.
  Ifosfamide day 1 and 2: each 1.500mg per m^2, no Ifosfamide on day 3
  Carboplatinum day 1: each 250mg per m^2 per day
  Etoposide day 1 and 2: each 75mg m^2 per day no day 3 Etoposide
  MESNA Bolus day 1: 500 mg/m^2
  24h dose day 1, 2 (3): 1500 mg/m^2 day
- Consider
  G-CSF 5µg/kg/day starting day +8 to avoid nadir of ANC < 500/µl

Special situation: Craniospinal irradiation in AT/RT
Start only with LK ≥ 2.000/µl, ANC ≥ 1.000/µl, Thrombocytes ≥ 80.000/µl.

No simultaneous chemotherapy during craniospinal radiotherapy.

Under certain circumstances chemotherapy maybe continued during boost radiotherapy. An ANC < 500/µl should be avoided.

Special situation: Patients with severe or life threatening complications during pre-radiotherapy- chemotherapy

Try to avoid simultaneous intensive chemotherapy.
Consider applying well tolerable oral chemotherapy e.g. Trofosfamide 75-100 mg/m²

PART III:

CONSENSUS THERAPY RECOMMENDATIONS FOR PATIENTS WITH RHABDOID TUMORS OF SOFT TISSUE

(MRT – malignant rhabdoid tumor of the soft tissue)

The treatment of extra CNS rhabdoid tumors has in most instances been based on sarcoma-like protocols. Currently several different study groups recruit patients into trials icluding a trial for extracranial rhabdoid tumors under direction of the EpSSG (directed by B. Brennan) or under the guidance of the COG such as the AREN0321 trial for high risk renal tumors.

The following recommendations represent a synthesis of the published literature and an expert panel's experience. Its main purpose is to give guidance to clinicians not recruiting patients in any of the afore mentioned trials.

Responsibility for the use of the therapeutic recommendations in this document and all clinical decisions lie at the discretion of the treating physician.

III.1 Diagnostic evaluation

Basic Assessment

- complete medical history
- physical examination including neuropediatric evaluation
- weight, height and body surface area and pubertal status
- Karnofsky Performance Status (KPS) or Lansky play score
- complete blood count (CBC) and serum chemistries (electrolytes, liver function tests, kidney function tests)
- blood type
- transfusion associated viral status (i.e. hepatitis A, B and C, HIV, CMV, Parvovirus B19)
- calculation of GFR or if possible measurement of GFR
- urine analysis: protein, α1-microglobulin, creatinine, phosphate, calculation of tubular phosphate reabsorption and proteinuria in 24 h

Initial Staging

- Imaging of the primary tumor: ultrasound and MRI scan with measurement of tumor volume (for details see chapter II.2)
- Whole body MRI (see below)
- Cerebro-Spinal-Fluid: local pathology and reference evaluation (competence centre) (only if neurologic symptoms or suspicion on cranial imaging).

It is recommended that imaging is performed fewer than 28 days prior to the start of treatment. Documentation of the dimensions of the tumour is obtained. Data will be reviewed centrally (see below). Detailed guidelines for imaging, especially neuroradiologic imaging, are given below. Postoperative imaging will help delineate postoperative residual tumor from non-specific tissue changes associated with the operative procedure.

Pre-treatment evaluation

The following pre-treatment evaluations may be performed prior initiation (suggested within 14 days) of therapy:

- physical examination including neuropediatric evaluation
- weight, height and body surface area
- Karnofsky Performance Status (KPS) or Lansky play score
- documentation of doses of steroids (if any) and any hormone replacement therapy, antiepileptic therapy or medication modifying behaviour
- complete blood count (CBC) and serum chemistries (electrolytes, liver function tests, kidney function tests)
- ECG, echocardiogram, audiometry or BERA
- genetic evaluation in children with a potentail rhabdoid tumor predisposition syndrom, in all children below two years with multifocal disease, synchronous rhabdoid tumors and when genetic mutations are known in the pedigree (e.g. Li Fraumeni…)
  (see also chapter 6.3 and figure 6.2)
- a urine pregnancy test for women of childbearing potential should be performed within 7 days prior to administration of chemotherapy

In addition, the patient/parents must be thoroughly informed about all aspects of any therapy, including evaluations and all regulatory requirements for informed consent. Written informed consent must be obtained by both parents (and patient where appropriate) prior to initiation of therapy.

Prior to each scheduled dose of chemotherapy

Performed on Day 1 prior to each cycle or within 72 hours prior to Day 1:

- documentation of concomitant drugs (particularly steroid usage, dose and duration during and after radiotherapy)
- physical examination including neurologic evaluation, vital signs, height and weight (percentiles)
- Karnofsky Performance Status or Lansky play score
- CBC and serum chemistries
- imaging (see below)
- ECG and echocardiography prior to anthracycline-containing elements
- Severe adverse events will be assessed according to the Common Toxicity Criteria (CTCAE) on an ongoing basis during therapy.

If a cycle of chemotherapy is delayed, only the CBC must be repeated weekly or within 72 hours of that day until treatment is given. The physical examination, including neurologic

evaluation, vital signs, weight, neurologic performance grading and Karnofsky Performance Status should be repeated on the actual day of dosing (or within 72 hours prior to this day) if the actual day of dosing is more than 2 weeks delayed.

- **Whole body MRI** is recommended to exclude multifocality in all patients with rhabdoid tumors. If this is not possible imaging studies as listed below are strongly recommended. In AT/RT patients the response and tumor-volume measurement is best performed by MRI. Whole body MRI dooes however not replace MRI imaging of specific tumor sites (better resolution). In patients with MRT or RTK these controls may be performed by sonographic methods, but MRI is the recommended method.

- **Echocardiographic evaluation** is recommended prior to each anthracycline-containing element.

- In case of **tumor progression** imaging of other loci with potential involvement has to be considered (e.g. kidney in AT/RT) due to the possibility of a rhabdoid tumor predisposition syndrome (see genetics).

Examination during chemotherapy

See figures III.1 – III.4

European Rhabdoid Registry – time table of examinations

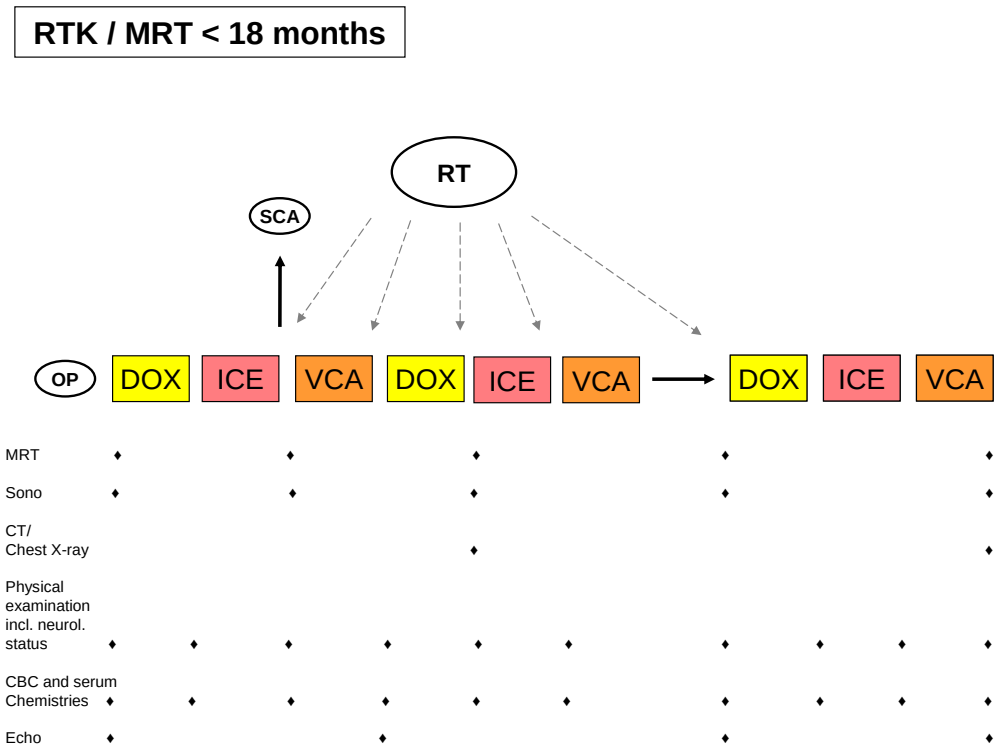


Figure III.1: MRT < 18 months: conventional chemotherapy

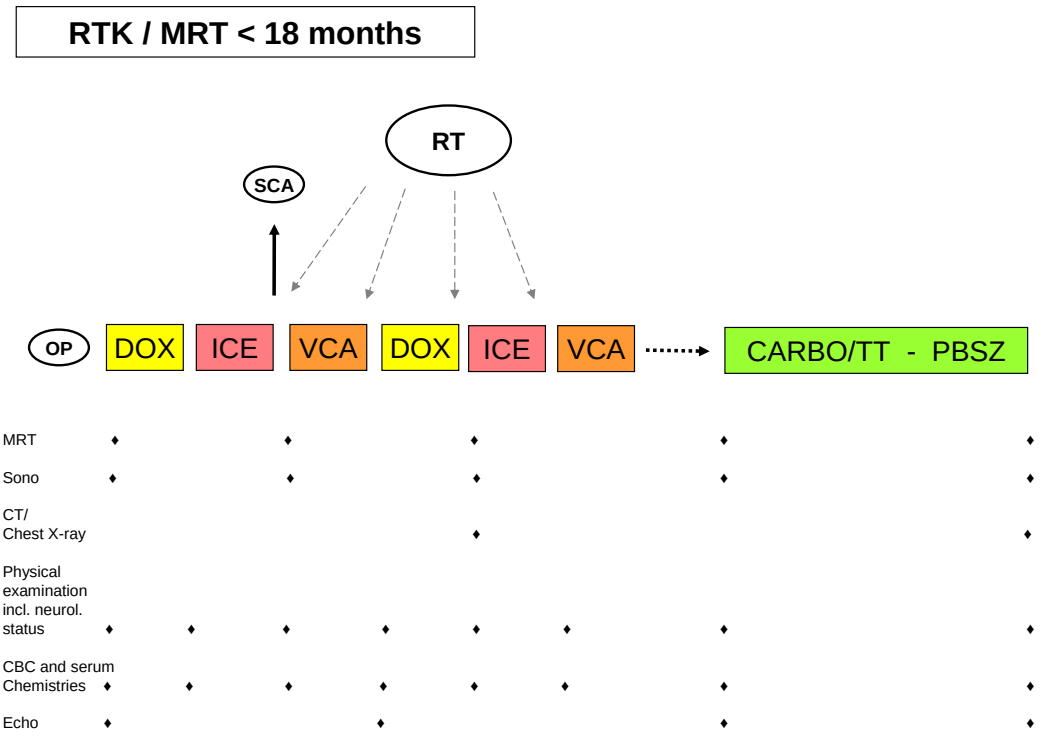


Figure III.2: MRT < 18 months: HD-chemotherapy

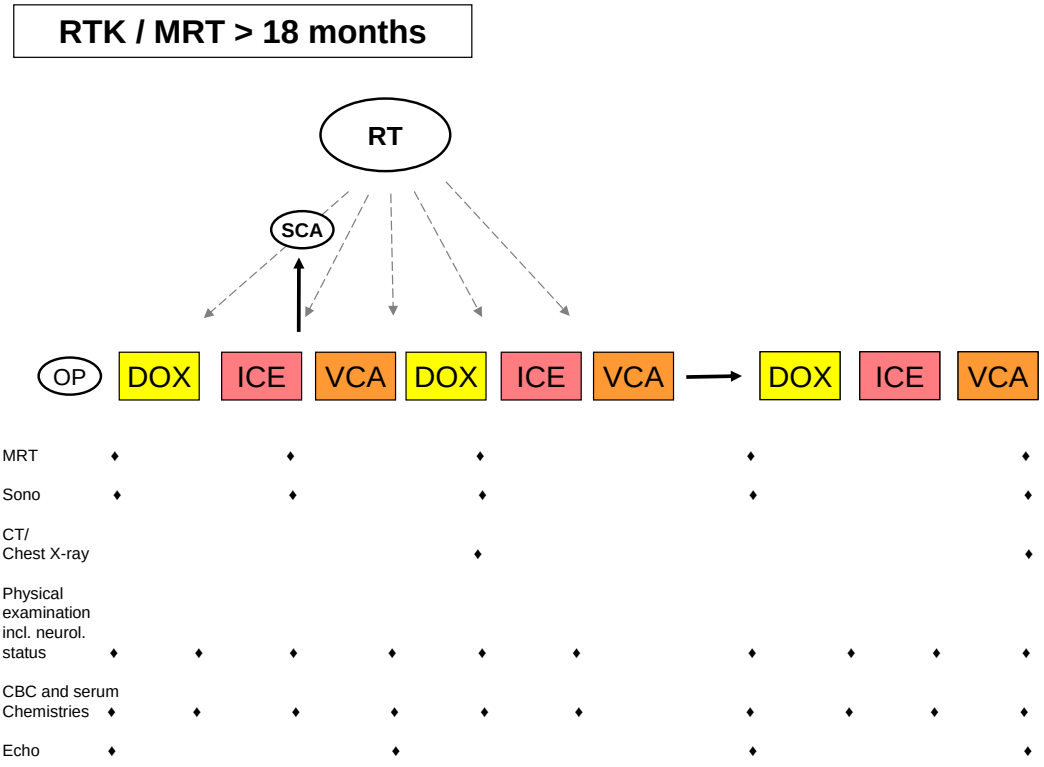


Figure III.3: MRT > 18 months: conventional chemotherapy

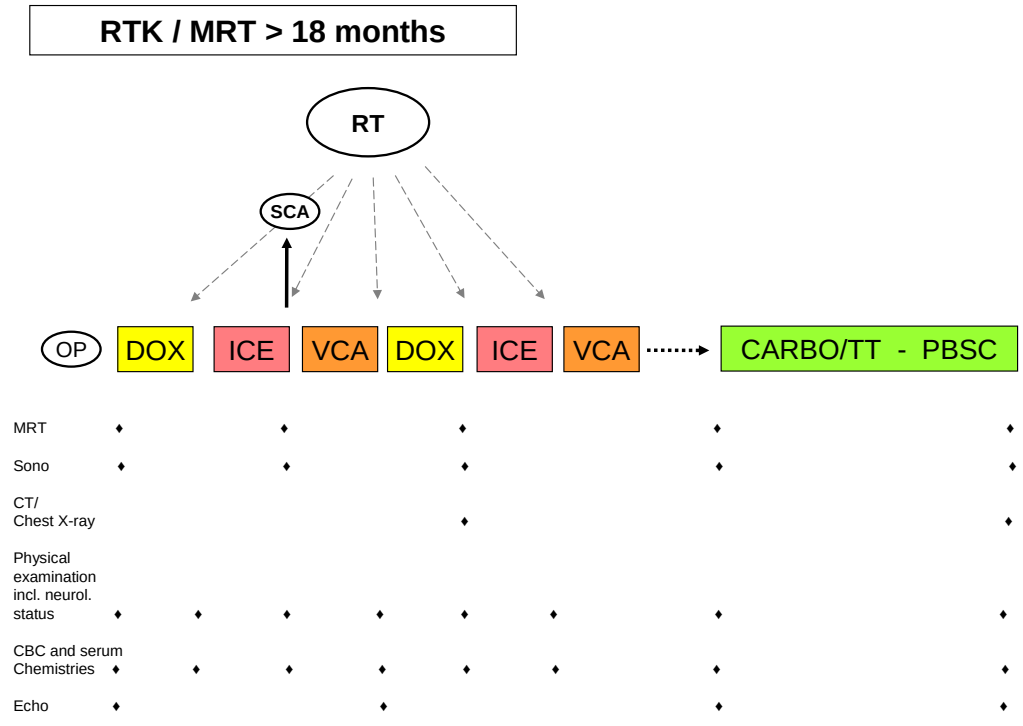


Figure III.4: MRT > 18 months: HD-chemotherapy

Follow-up after completion of therapy

After completion of the chemotherapy it is advised to perform examinations according to the follow-up schedule:

	1. / 2. Year after completion of therapy	3. - 5. Year after completion of therapy	6. - 10. Year after completion of therapy	Second decade after completion of therapy
Physical examination	bimonthly	every 6 months	twice yearly or yearly	yearly
MRI local side	every 3 months	twice to four times yearly	yearly	if symptomatic
Chest CT	every 6 months	in case of symptoms	in case of symptoms	if symptomatic
Cranial MRI	once, at the end of treatment	only, if pathological before	only, if pathological before	only, if pathological before
Sonography	four times yearly	four times yearly	if symptomatic	if symptomatic
Height, weight, pubertal status	every 6 months	every 6 months	yearly	individually
CBC	every second month	every 6 months	yearly	yearly
Renal function Serum-chemistry	bimonthly	every 6 months	yearly	yearly
Radiotherapist**	yearly	yearly	yearly	yearly
ENT consult	yearly	if symptomatic	if symptomatic	if symptomatic
Echo/ECG	twice yearly	yearly	yearly	yearly
Skeletal scintigraphy	once, at the end of treatment	only, if pathological before	only, if pathological before	only, if pathological before
Lung function (if age permitts)	once, at the end of treatment	only, if irradiation to the lung	only, if irradiation to the lung	only, if irradiation to the lung

Table III.1: Follow-up examinations in patients with extracranial rhabdoid tumors

III.2 Imaging Studies

Ultrasound of the abdomen

The physician evaluating the lesion should describe the following aspects of the tumor in detail:

1. localisation within the affected organ, border, relation to blood vessels and lymph node stations
2. echogenicity of the lesion
3. description and measurement of cystic areas of the tumor
4. measurement of the lesion in the plain with the largest diameter and in an angle 90° perpendicular to it
5. evaluation of tumor thrombi within blood vessels draining the tumor region (i.e. renal vein or inferior vena cava)
6. evaluation of intra-abdominal or regional lymph node sizes
7. evaluation of metastatic lesions (i.e. liver, spleen, local lymph nodes)

The primary tumor size should be measured at the time of diagnosis in three plains. The type of measurement should be documented. Individual tumor lesions should be measured separate from each other. Tumor volume may be calculated according to the following formula:

V = L x T x B x 0.523 in cm^3 ***L = length, T = depth, B = width***

MRI or CT

Besides sonography an additional imaging technique should be used. Preoperative imaging especially under circumstances when local RT is in planning stages is mandatory. MRI is the method of choice.

MRI is always indicated

4. if large thrombi within major draining vessels are suspected and may even reach the thoracic cavity
5. if there is liver and diaphragm involvement
6. if there is suspected continuous spread into the thoracic cavity or from the thoracic cavity into the abdomen.

Imaging of the thorax

Lung metastases may be imaged by native radiological imaging in two plains. The gold standard is a CT scan of the thorax.

MIBG scintigraphy

MIBG scanning should be performed in cases when neuroblastoma can not be differentiated by imaging (MRI) from a potential lesion of the kidney such as Wilms tumor or rhabdoid tumor.

Technetium scintigraphy

Scintigram of the skeletal system has to be discussed in all patients.

PET-CT

The value of PET-CT in the imaging of patients with AT/RT, RTK and MRT remains to be defined. In selected cases PET-CT scanning might be a valuable asset in the diagnostic follow-up and the response evaluation of patients.

Cranial imaging

In patients who suffer from metastases of RTK or MRT cranial MRI is the method of choice and should be performed according to the guidelines listed above for AT/RT. In all patients with RTK or MRT a cerebral MRI should be performed according to the guidelines listed above for AT/RT.

III.3 Surgical approach to patients with extracranial rhabdoid tumors

Rhabdoid tumor of the soft tissues (MRT)

The surgeon needs to obtain all necessary information about tumor size, exact localisation, and relation to large blood vessels, potential existence of tumor thrombi and involvement of adjacent organs.

Thoracic CT is indicated if native two-dimensional X-ray does not reveal a clear picture. Immediate postoperative sonographic evaluation is recommended.

According to the site of the primary tumor including those of soft tissue, liver, GI-tract, heart, and other organs, further specific imaging modalities besides MRI may become necessary to depict the extension of the tumor, involvement of vessels, nerves, and other vital structures as well as tumor in the peritoneum, pleura and lymph nodes.

During the operation the surgeon should always attempt a radical resection, if the surgical risk can be calculated and mutilation can be avoided. This means resection with sufficient margins if possible and meticulous dissection of all relevant lymph node stations. For liver tumors anatomical resections (lobectomy, trisegmentectomy) are highly recommended, while enucleations or wedge resections should be avoided. All visible tumor sites should be resected or at least biopsied. In case of non-resectable tumor extension the lesion should also be sufficiently biopsied.

For example of surgical approach see also CWS-guidance.

III.4 Chemotherapeutic approach to patients with MRT

The protocol of the European Rhabdoid Registry contains the following recommendations for a standardized therapy, which were generated from data derived from the current literature, the investigators' own experience and data derived from the GPOH studies for high risk Wilms tumors, soft tissue sarcomas and malignant brain tumors of infants and children.

In a second period the efficacy and tolerability of an induction window chemotherapy using further compounds will be evaluated in classical phase-II studies.

!!! ALL SCHEDULES MAY BE FOUND IN THE APPENDIX !!!

Chemotherapy as suggested for the European Rhabdoid Registry contains the following therapy-elements:

a) Chemotherapy:

DOX: doxorubicin
ICE: ifosfamide, carboplatinum and etoposide
VCA: vincristine, cyclophosphamide and actinomycin-D

b) High Dose Chemotharpy:

carboplatinum / thiotepa

Radiotherapy:

RT should be performed ass soon as possible. RT in children below the age of 18 months has to be considered individually. For details see chapter radiotherapy.

Second-look-surgery:

Generally a second-look-surgery may be necessary or useful at any time during therapy. In case second look surgery is performed, material should be sent for reference pathology evaluation. (see page xy)

High Dose chemotherapy (HDCT):

The use of HDCT is at the discretion of the individual treating physician. The role of HDCT in rhabdoid tumors remains undefined. As individual centers and some countries prefer to employ HDCT, it is suggested to harmonize strategies as much as feasible in order to obtain a maximum of information. This may deliver the necessary preliminary evidence for a randomized trial e.g. comparing HDCT vs. conventional chemotherapy.

If High-dose-therapy is planned by the treating physician, it may thus follow the suggestions in the appendix.

Stem-cell-separation:

Collection of stem-cells may be conducted after the first ICE-element 3. If necessary another point following ICE is also possible.

Cardiotoxicity:

The application of anthracyclines (e.g. doxorubicin) appears to be essential in the treatment of patients with rhabdoid tumours. Anthracyclines are cardiotoxic, especially in children below the age of two years, prior cardio-vascular diseases and radiotherapy of the mediastinum. If side effects occur, a dose-modification is necessary (see below). In any case the form "cardiotoxicity" should be filled out and sent to the study coordinator.

Event:

In case an adverse event, a severe adverse event or any other important event (progress under therapy, death etc.) occurs during therapy, the corresponding forms should be sent immediately to the registry.

G-CSF:

Since treatment intensity and density is essential in the treatment of Rhabdoid tumors, G-CSF support is preferable to dose reduction. The recommended dose is 5 µg/kg/d as once daily s.c. injection.

Maintenance therapy:

In cases of residual disease at the end of treatment, the application of a maintenance therapy has to be considered and discussed with the study coordinator.

III.4.1 Schematic diagram of chemotherapy

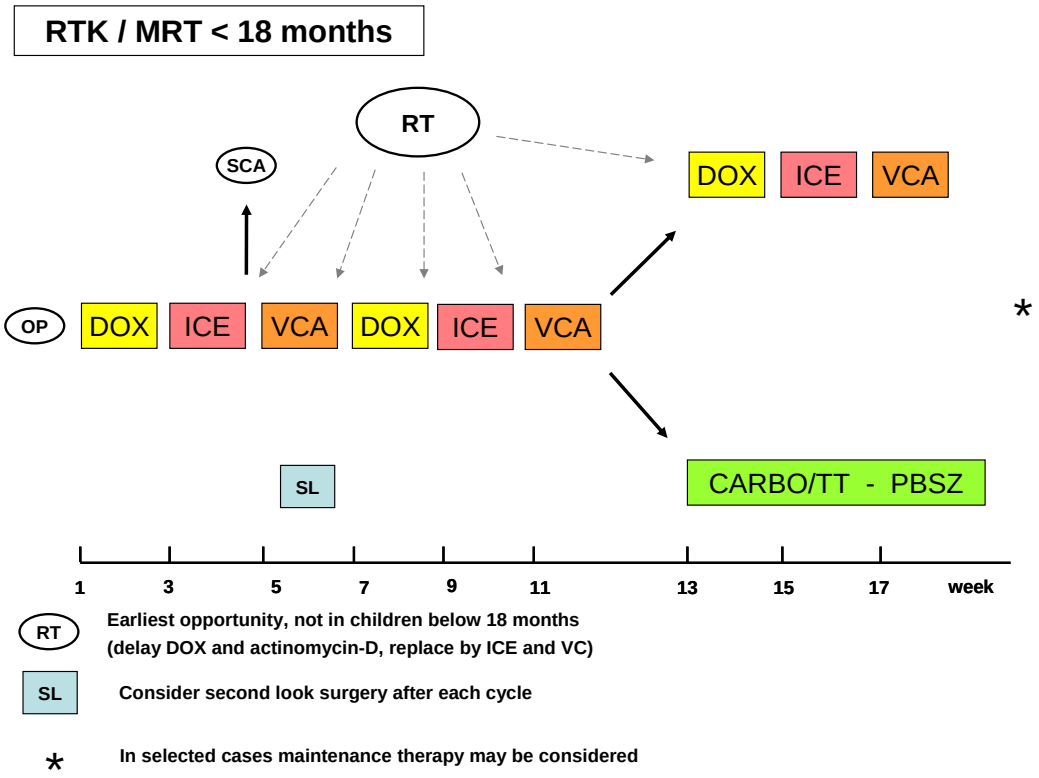


Figure III.5: MRT < 18 months

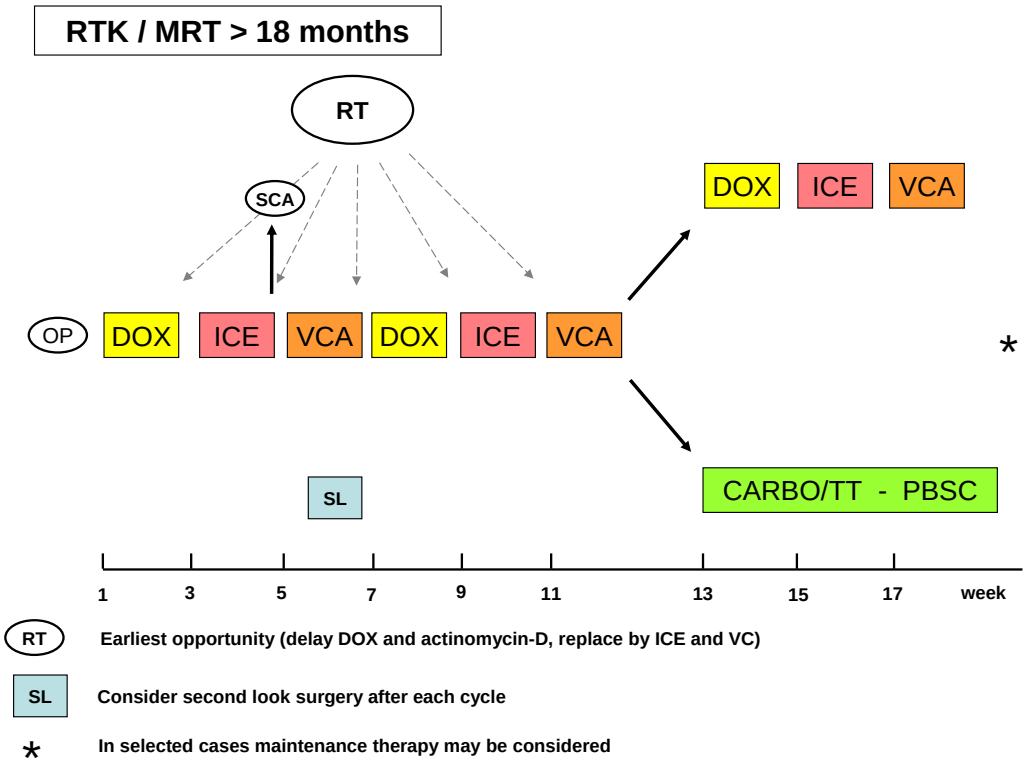


Figure III.6: MRT > 18 months

Abbreviations:

OP = surgery or initial biopsy, SL= second-look-surgery, DOX= doxorubicin, ICE = ifosfamide, carboplatinum, etoposide, VCA = vincristin, cyclophosphamide, actinomycin-D, SCA = stem cell apheresis, IT= intra-thecal chemotherapy, RT= radiotherapy, Carbo/TT – PBSC= high-dose chemotherapy with caraboplatinum/thiotepa

III.4.2 Chemotherapy

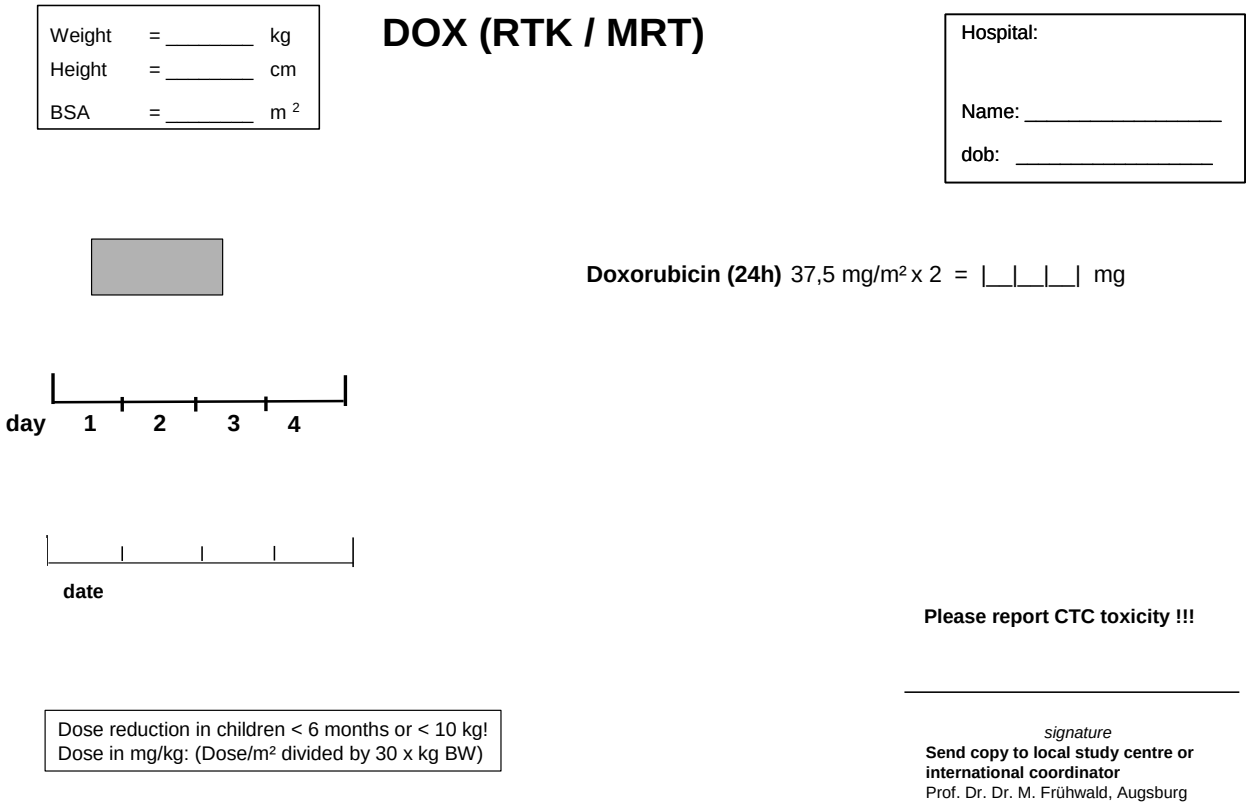


Figure III.7: DOX schedule

Day	Doxorubicin
1	37,5 mg/m²
2	37,5 mg/m²
3	
4	
Cum. dose per cycle	75 mg/m²

Table III.2: Doxorubicin

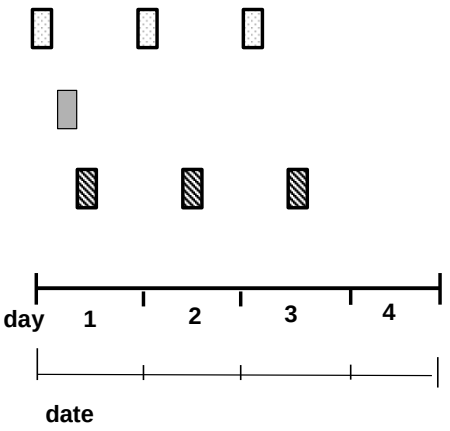
Weight = _____ kg
Height = _____ cm
BSA = _____ m^2

ICE (RTK / MRT)

Hospital:

Name: _____

dob: _____



Ifosfamide p.i. (1h) 2000mg/m^2 x 3 = |__|__|__|__| mg/D
with MESNA:
2.000mg/m^2 with hydration 3.000ml/m2/d

Carboplatinum (1h) 500mg/m^2 = |__|__|__| mg

Etoposide (1h) 100mg/m^2 x 3 = |__|__|__| mg/D

Dose reduction in children < 6 months or < 10 kg!
Dose in mg/kg: (Dose/m^2 divided by 30 x kg BW)

Please report CTC toxicity !!!

signature
Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

Figure III.8: ICE schedule

Day	Ifosfamide	Carboplatinum	Etoposide
1	2000 mg/m² over 1 h	500 mg/m² over 1 h	100 mg/m² over 1 h
2	2000 mg/m² over 1 h		100 mg/m² over 1 h
3	2000 mg/m² over 1 h		100 mg/m² over 1 h
Cum. dose per cycle	6000 mg/m²	500 mg/m²	300 mg/m²

Table III.3: ICE: Ifosfamide/Carboplatinum/Etoposide

Etoposide may be substituted by etoposidphosphate if available. The dosage used is 114mg/m^2 of etoposidphosphate for equivalent dose of etoposide (100 mg).

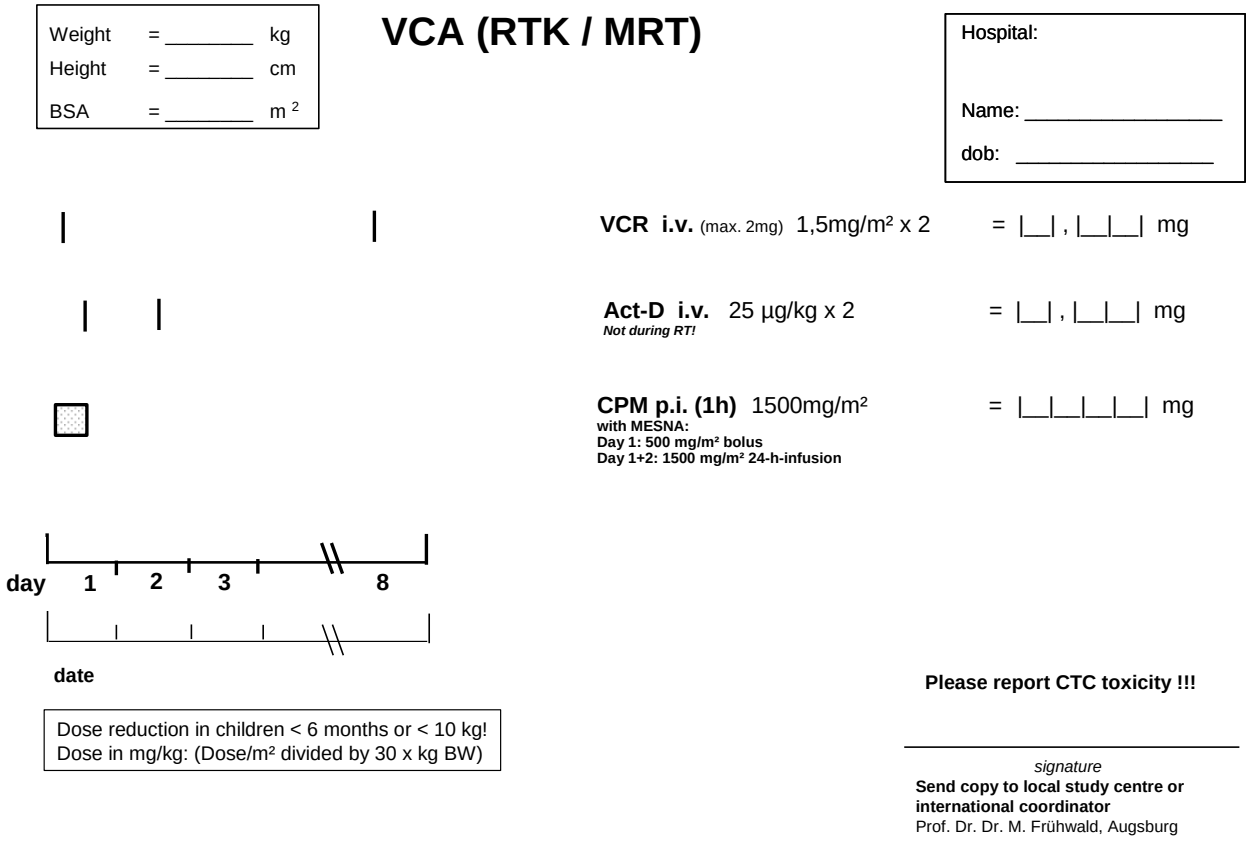


Figure III.9: VCA schedule

Day	Vincristine	Cyclophosphamide	Actinomycin-D
1	1,5 mg/m² max 2 mg	1500 mg/m² over 1 h	25 µg/kg
2			25 µg/kg
3			
4			
8	1,5 mg/m² max 2 mg		
Cum. dose per cycle	3,0 mg/m² max 6 mg	1500 mg/m²	50 µg/kg

Table III.4: VCA: Vincristine/Cyclophosphamide/Actinomycin-D

Dose reduction Actinomycin-D:
For infants < 1 year or < 10 kg only 2/3 of the already reduced Actinomycin-D dose should be administered. If tolerated well individual increase of the dose in the next cycle may be considered.

Initiation:

The scheduled interval between day 1 of the elements is 14 days. If it is not possible to adhere to this schedule, the next element should begin as soon as possible after regeneration and normalisation of hematologic parameters.

Prerequisites:

- satisfactory general condition
- no signs of infection
- no signs of CSF-circulation-disorders
- cardiac function: Echo (FS>28%) or RNV (LVEF>50%)
- Hb: > 8 g%
- platelets: > 100.000/mm³
- neutrophils: > 1000/µl
- GFR: > 70 ml/min/1,73m²
- urine: no hematuria

Hydration: 3000 ml/m²/d, 24 h-hydration until day 4 (incl.)

Start infusion 6 hours before application of carboplatinum.

Recommendation for composition of 1000 ml solution:

Glucose 5%	480 ml
NaCl 0,9%	480 ml
KCl 7,45%	30 ml
Ca-Gluconat 10%	10 ml

Add Magnesium 3 mmol/l.

Mesna-Application: Day 1: MESNA 500mg/m² i.v. as short-infusion or bolus
Day 1: MESNA 1.500 mg/m² i.v. continuous infusion over 24 hours
Day 2: MESNA 1.500 mg/m² i.v. continuous infusion over 24 hours
(Day 2 may be omitted in children over 3 years of age)

G-CSF: G-CSF is started on day 5
Dose: 5µg/kg/d s.c. injection

Febrile neutropenia or infection	CTCAE grade 4, possibly grade 3	IFO and ETO dose reduction to 2/3
Mucositis	CTCAE grade 4, poss. repeated grade 3	ETO dose reduction of 50% DOXO Dose reduction of 20%
Kidney: glomerular function	Krea > 1,5 x base value or Krea-Clearance <70 ml/min/1,73m²	delay element 1 week; if no recovery: no further IFO
Kidney: tubular function	CTCAE grade 2 CTCAE grade 3/4	poss. IFO reduction of 20% no further IFO
Hematuria	Stix positive under IFO 2 x microhematuriea under IFO CTCAE > grade 2 CTCAE grade 3/4	double MESNA MESNA Bolus 600 mg/m², then MESNA-Infusion with doubled dosing. If persisting: Stop IFO stop IFO, double MESNA-Infusion contact study-coordinator
Neurotoxicity	CTCAE > grade 2 CTCAE grade 4	see below NO FURTHER IFO!
Cardiac toxicity	FS < 28% or LVEF < 50% Acute Cardiotoxicity	repeat examination after one week, if no improvement: NO FURTHER DOXORUBICIN. stop Doxo-Infusion

Table III.5: Dose-modifications in case of toxicity

Central Neurotoxicity:

If CTC grade 3 or 4 central neurotoxicity occurs (somnolence >30% of the time, disorientation/hallucination/echolalia/perseveration/coma, or seizures on which conciousness is altered, or which are prolonged, repetitive or difficult to control), consider

- use of methylene blue (methylthionin) 50 mg as i.v. infusion.
- prolong ifosfamide-infusion to 4-8 hours with the next application, and infuse methylene blue 50 mg three times daily.
- in the next course, apply methylene blue one dose of 50 mg 24 hours prior to ifosfamide. During ifosfamide infusion give three times daily methylene blue as described above (refer to Nicolao and Giometto, Oncology 2003, 65[Suppl 12]:11-16 for further information).
- if repeated grade 3 or 4 central neurotoxicity occurs, consider withholding ifosfamide and substitute cyclophosphamide 1500 mg/m² BSA.
- alternatively piracetam 100mg/kg may be given prophylactically (q 6h) or in therapeutic intention (q 4 h)

III.4.3 High Dose Chemotherapy approach (HDCT)

Stem-cell-harvest:

Stem cell harvest may take place after the first ICE-element. It can be repeated after the second ICE-element if necessary.

Priming of peripheral blood progenitor cells with G-CSF, e.g. 10µg/kg/d G-CSF is advised from 24 hours after the last dose of chemotherapy until completion of harvest. Apheresis may start after three days.

- A total of at least two units containing $3x10^6$ CD34+ cells/kg each should be collected.
- Stem cell harvest has to be performed according the ISHAGE Guidelines.

One of the aliquots is needed for high-dose-therapy, the other is needed as backup.

Cyclophosphamide for stem-cell-harvest:

This therapy is not recommended generally for all patients, but it may be performed in cases with difficult stem cell mobilization.

- Hydratation: 3000 ml/m²/d for 24 hours
- MESNA 1300 mg/m² as i.v. bolus before application of cyclophosphamide
- Cyclophosphamide 4000 mg/m² over 4 hours as short infusion
- MESNA 4000 mg/m²/d for 24 hours

Prerequisites:

- satisfactory general condition
- no signs of infection
- no signs of CSF-circulation-disorders
- cardiac function: Echo (FS>28%) or RNV (LVEF>50%)
- Hb: > 8 g%
- platelets: > 100.000/mm³
- neutrophils: > 1000/µl
- GFR: > 70 ml/min/1,73m²

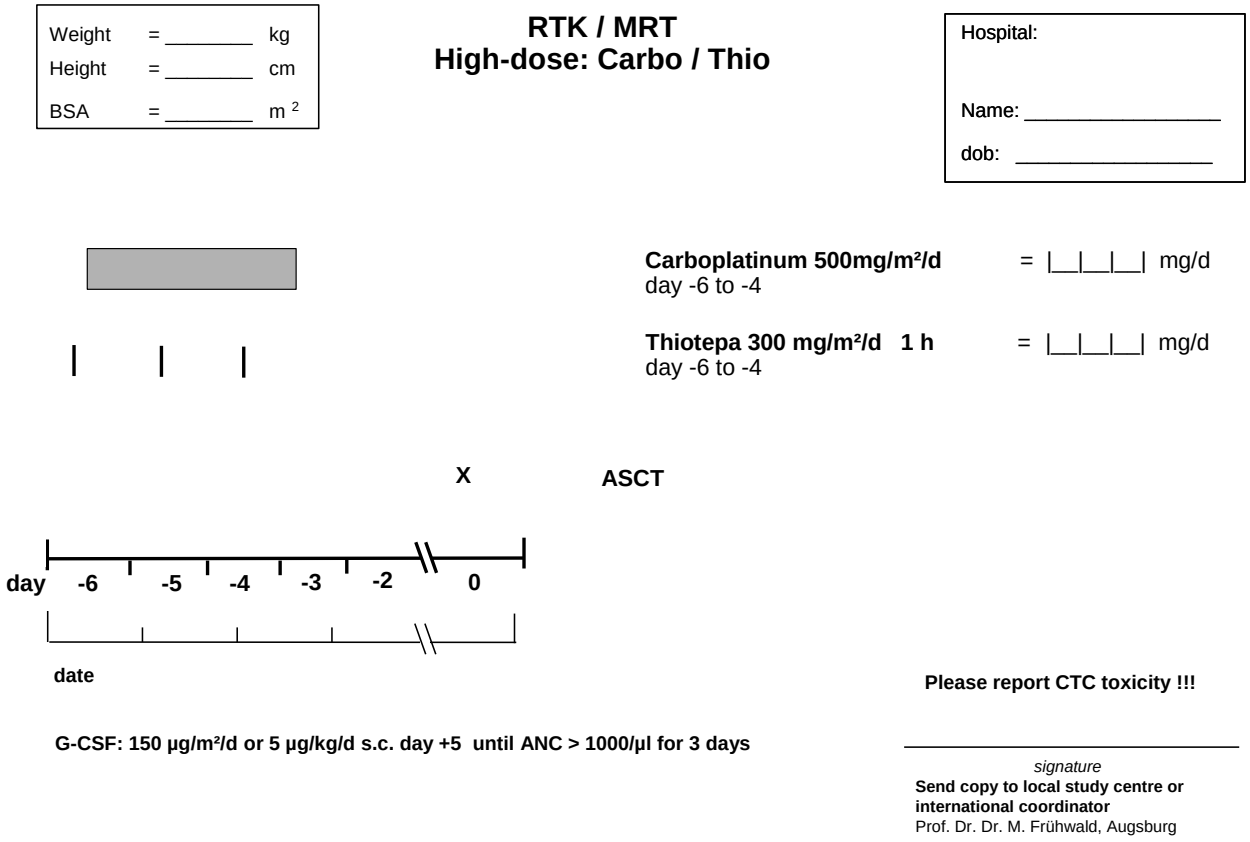


Figure III.10: MRT High-dose-therapy (Carbo/Thiotepa)

Day	Carboplatin	Thiotepa	PBSC
-6	500 mg/m²/d	300 mg/m² 1 h	
-5	500 mg/m²/d	300 mg/m² 1 h	
-4	500 mg/m²/d	300 mg/m² 1 h	
-3			
-2			
0			X
Cum. dose per cycle	1500 mg/m²	900 mg/m²	

Table III.6: High-dose-therapy Carbo/Thiotepa

Prerequisites: satisfactory general condition
no signs of infection
no signs of CSF-circulation-disorders
cardiac function: Echo (FS>28%) or RNV (LVEF>50%)
Hb: > 8 g%
platelets: > 100.000/mm³
neutrophils: > 1000/µl
GFR: > 70 ml/min/1,73m²
urine: no hematuria

Hydration: 3 000 ml/m²/d, 24 h, day -6 to -2

G-CSF: 150 µg/m²/d or 5 µg/kg/d s.c. day +5 until ANC > 1000 for 3 days

Supportive Care:
- substitution of blood products
- early analgesia with morphins
- parenteral feeding with substitution of vitamine K
- NG-tube for enteral fluid substitution day -1
- antimicrobial prohylaxis with amphotericin B (oral and inhalative), cotrimoxazol, aciclovir

III.5 Radiotherapeutic approach to patients with extracranial rhabdoid tumors

Optimization of timing, dosimetry and target volume to be irradiated are evolving aspects in the therapeutic approach towards children with rhabdoid tumors.

Timing:

1. Children below the age of 18 months should only be irradiated under exceptional circumstances.
2. Children of an age of 18 months or older should be irradiated as soon as feasible.
3. In case of primary metastasized disease RT may be delayed until the end of intensive chemotherapy (following element 9). Other special circumstances may apply such as progressive disease, when RT may be performed at any time.
4. For infants and children below 18 months radiotherapy may be delayed until age permits or following element 9.

Children with primarily metastasized rhabdoid tumors may be irradiated at later time points. Current data for AT/RT suggest that in tumors with leptomeningeal dissemination salvage RT may be successful. These instances may be directly discussed with the reference radiotherapist.

Guidelines for radiation therapy of extrarenal, extracranial non-CNS rhabdoid tumors

Patients who received a gross total resection of their primary tumor with no residual disease receive 36 Gy in 20 fractions, 1.8 Gy each.

Patients with gross total resection of the primary but microscopic residual disease receive 45 Gy in 25 fractions, 1.8 Gy each.

Those patients who have received biopsy only or who have gross residual disease receive 50.4 Gy in 28 fractions, 1.8 Gy each.

Equipment

Treatment will usually be with X-ray photons of 4 to 20 MV, linear accelerator. The use of cobalt teletherapy is not acceptable. In selected circumstances the use of electrons may result in a more favourable dose distribution. Similarly interstitial or intracavitary brachytherapy may be preferable in certain circumstances such as with tumors at gynaecological, extremity and some none-parameningeal sites of the head and neck. Brachytherapy should not be used without careful discussion and is only appropriate in specialized centers. Other specialized treatment techniques such as intra- or extracranial stereotactic radiotherapy (ISRT/ESRT) or intensity-modulated radiotherapy (IMRT) should be discussed with the study centre. Proton beam therapy is permitted in specialized treatment centers.

Target volumes

Three-dimensional treatment planning is strongly encouraged for all patients treated in this study. All treatment planning, regardless of whether it is standard or 3D conformal/IMRI, will be based upon the following target definitions.

GTV
The GTV is defined as the pre-treatment visible or palpable disease defined by physical exam, operative surgical findings, CT or MRI. T_1 weighted MRI with contrast constitutes the optimal imaging study. Under special circumstances changes may be made for this definition based upon the post-operative geometry of the target volume. In patients who have undergone primary tumor resection, the entire surgical scar as well as scars of drainages should be included in the GTV. In general, the GTV does not change based on any surgical resection or chemotherapy response.

CTV
The CTV is defined as the GTV plus 1.5 cm. For some sites this may be modified to account for anatomic barriers to tumor spread. The CTV should always include the entire draining lymph node chain if the regional lymph nodes are clinically involved with the tumor. Patients with gross residual disease and primary sites in the head and neck or vulva and uterus who have not undergone second look surgery may have second CTV and PTV defined for a cone down boost. The patients will receive a total dose of 50.4 Gy in 28 fractions, 1.8 Gy each.

PTV
PTV is defined as the CTV plus an institution specific margin to account for day to day setup variations. Classically 0,5 cm are used so that: PTV = GTV + 2cm (1,5 cm + 0,5 cm).

PRV (Planning Organ at Risk Volume)
PRV is defined for each organ-at-risk defined in this protocol and for any other organ that the treating clinical oncologist wishes to limit to a specific dose. The PRV is defined as the volume of the organ-at-risk plus a margin to account for that organ's positional uncertainty.

Modifications for special sites

Orbit:

CTV should not extend outside of the bony orbit, providing there is no bone erosion.

Thorax:

Tumors that have displaced significant amounts of lung parenchyma, which has subsequently returned to normal anatomic position will have the GTV defined as the pre-operative tumor volume excluding the intrathoracic tumor which was debulked. All areas of preoperative involvement of the pleura will be included in the GTV.

Bladder, prostate, perineum, pelvis, biliary tree and abdomen:

Tumors which have displaced a significant amount of bowel which has subsequently returned to normal anatomic position following surgical debulking will have the GTV defined as the preoperative tumor volume excluding the intra-abdominal or intra-pelvic tumor which has been debulked. All areas of preoperative involvement of the peritoneum or mesentery and the site of origin should be included in the GTV.

Timing of Radiotherapy

As noted, radiotherapy may be initiated after four cycles of chemotherapy. Chemotherapy may be given concurrent with radiotherapy. Anthracycline containing chemotherapy should be avoided when concomitant RT is given to the spinal cord or parts of the heart or bowel. In general, Doxorubicin should be avoided during the 6 weeks following RT. Radiotherapy of metastases should be timed after surgery of metastases (if possible) and may be done after the 6^{th} or 7^{th} course of chemotherapy. A combined strategy may be chosen i.e. surgery of metastases may be followed by local RT.

Patients requiring an interruption of radiotherapy will receive a modification in the schedule. In general, to compensate for unavoidable gaps patients will be treated twice per day with an interfraction interval of six hours to keep the overall treatment duration the same as intended. In small children who need general anesthesia for RT the interfraction interval needs to be planned individually.

Normal Tissue sparing

It is important to protect normal vital structures whenever possible. Such shielding must be weighed against the possibility of under-treatment of known tumor bearing tissue. In general, the chiasm and optic nerve should not receive more than 60 Gy, lacrimal gland 40.1 Gy, small bowels 50.0 Gy, spinal cord up to 45.0 Gy, lung when > ⅓ but < ½ of total lung volume 18.0 Gy, lung when > ½ of total lung volume is in the PTV 15.0 Gy, whole kidney 19.8 Gy (if the other kidney is not irradiated at all), whole liver 23.4 Gy.
These dose recommendations have to be weighed against the potential benefit the patient may have (i.e. the case of paraspinal tumor invading intravertebral foramina and compressing the spinal cord).

Whole lung irradiation

Both lungs are irradiated regardless of the number and location of the metastases. The inferior extent of the anterior and posterior costodiaphragmatic recesses of the pleural cavity is determined by a lateral radiograph. The inferior border of the lung irradiation field will be approximately at the L1 vertebral body. The shoulder joints should be shielded. If patients require both whole lung and whole abdomen irradiation both fields should be treated simultaneously. The whole lung irradiation dose is 15.0 Gy in 10 fractions of 1.5 Gy over 12-14 days. Dose calculation should be based on a CT scan with the reference point within the lung tissue (doses prescribed according to ICRU 50 report; in case of central beam calculation, which should be avoided, the lung correction factor has to be considered). In infants this may be reduced to 10.5 Gy in 7 fractions of 1.5 Gy over 9 days. Localized foci in the lung persisting two weeks after whole lung irradiation may be submitted to surgery or an additional 7.5 Gy in five fractions.

Liver irradiation

The entire liver should be included in the irradiation field only if the liver is diffusely involved (19.8 Gy, 11 fractions). In infants the dose fractionation should be 15 Gy, 10 fractions of 1.5 Gy. In the case of individual foci these metastastic lesions should be irradiated with a margin of 2 cm. Additional boost irradiation doses of 5.4 Gy to 10.8 Gy may be administered to limited volumes. The dose to the upper pole of the remaining kidney should be monitored.

Brain irradiation

In patients with brain metastases the whole brain is included in the irradiation field to a dose of 21.6 Gy in 12 fractions of 1.8 Gy. A boost of at least 10.8 Gy is required to individual sites of metastases. In patients with less than three lesions a limited volume boost dose of 10.8 Gy in six fractions using MRI or stereotactic radiotherapy may be administered.

Bone irradiation

In patients with bone metastases the GTV is the lesion as shown on appropriate imaging, which may include Tc-scintigraphy, plain radiographic films, MRI or CT. The CTV will usually include a margin of apparently healthy bone up to 2 cm. A narrower margin may be appropriate when the metastasis is close to the edge of the bone. RT to the epiphysis should be avoided where possible. An appropriate margin should be added for the PTV, taking into account the immobilisation technique employed. In case of irradiation of vertebrae the security margin should include the whole upper and lower vertebra. The bone dose is 25.2 Gy in 14 fractions of 1.8 Gy, but may be modified if appropriate.

Lymph node irradiation

Positive lymph nodes that have not been surgically removed should receive radiation therapy to 19.8 Gy in 11 fractions at 1.8 Gy. Lymph node groups that were involved at presentation should be irradiated in their entirety. The GTV will be the nodal area including any residual mass after chemotherapy as defined on the planning CT. The CTV will be a 1 cm margin around the GTV. For mediastinal and abdominal nodes a parallel opposed field arrangement gives best coverage of the PTV. When possible, nodal areas will be treated in continuity with the primary tumor or other metastatic sites requiring irradiation.

Target dose

The daily dose to ICRU prescription points shall be 1.8 Gy, except in younger children (<3 years) or when large volumes (e.g. whole lung or abdomen) are to be treated.

Simultaneous radio-, chemotherapy in patients with rhabdoid tumors

Radiotherapy may be complicated in some affected patients due to the necessity for deep sedation or even anaesthesia, young age or neurological deficits.
Optimal preparation for radiotherapy always involves assessment of risk factors for anaesthesia which may due to pre-existing conditions such as neurological deficits including difficult swallowing or repeated aspirations. These hint towards much enhanced risk for anaesthesia.

Aims of the following recommendations are thus:

- The planed radiotherapy as a local therapeutic measure should be done without any interruptions due to complications such as febrile neutropenia, documented infections, severe mucositis with the need for analgesics or the need for parenteral nutrition and
- Systematic chemotherapy in parallel to radiotherapy in order to maximize tumour control

Recommendations

Pre- and post-radiotherapy:
Prerequisite for radiotherapy in any patient is complete imaging (e.g. craniospinal MRI) plus complete staging (e.g. CSF analysis) not older than four weeks before sending the patient for radiotherapy.

- Avoidance of Actinomycin D: 2 weeks before and 2 weeks after radiotherapy
- Avoidance of Doxorubicine: 2 weeks before and 4 weeks after radiotherapy
- No intrathecal, intraventricular chemotherapy during or after radiotherapy (AT/RT only)

Simultaneous radio-, chemotherapy

- No Actinomycin D, no Doxorubicin, no intrathecal chemotherapy
- VCA: No Actinomycin D, no intrathecal methotrexate
  Vincristin 100% of the dose,
  Cyclophosphamide 100% to 65% depending on previous tolerance, MESNA dose needs to be adjusted

- ICE: No intrathecal methotrexate reduction of all doses to 50% i.e.
  Ifosfamide day 1 and 2: each 1.500mg per m^2, no Ifosfamide on day 3
  Carboplatinum day 1: each 250mg per m^2 per day
  Etoposide day 1 and 2: each 75mg m^2 per day no day 3 Etoposide
  MESNA Bolus day 1: 500 mg/m^2
  24h dose day 1, 2 (3): 1500 mg/m^2 day
- Consider
  G-CSF 5µg/kg/day starting day +8 to avoid nadir of ANC < 500/µl

Special situation: Craniospinal irradiation in AT/RT

Start only with LK ≥ 2.000/µl, ANC ≥ 1.000/µl, Thrombocytes ≥ 80.000/µl.

No simultaneous chemotherapy during craniospinal radiotherapy.

Under certain circumstances chemotherapy maybe continued during boost radiotherapy. An ANC < 500/µl should be avoided.

Special situation: Patients with severe or life threatening complications during pre-radiotherapy- chemotherapy

Try to avoid simultaneous intensive chemotherapy.

Consider applying well tolerable oral chemotherapy e.g. Trofosfamide 75-100 mg/m²

Part IV:

General Information, Recommendations and Forms

IV.1 Drug Information

In children below the age of six months or with a body weight of less than 10 kg chemotherapy doses should be calculated according to kg body weight.

Actinomycin-D is calculated according to kg body weight in all children.

1 m² body surface area (BSA) is considered equivalent to 30 kg body weight (BW).

	Dose per m²	Dose according to kg body weight
actinomycin-D	-	25 µg/kg BW
carboplatinum	500 mg/m² BSA	17 mg/kg BW
cyclophosphamide	1800 mg/m² BSA	60 mg/kg BW
doxorubicin	37,5 mg/m² BSA	1,25 mg/kg BW
etoposide	100 mg/m² BSA	3,3 mg/kg BW
ifosfamide	2000 mg/m² BSA	66,7 mg/kg BW
vincristin	1,5 mg/m² BSA	0,05 mg/kg BW
etoposide	2 x 25 mg/m²/d	2 x 0,83 mg/kg BW
idarubicin	1 x 5 mg/m²/d	1 x 0,17 mg/kg BW
trofosfamide	2 x 75 mg/m²/d	2 x 2,5 mg/kg BW

Table IV.1: Doses per m² - doses according to kg body weight

Cumulative doses

Cumulative doses in patients with **AT/RT** (conventional chemotherapy)					
Compound [mg/m²]	3 x DOX	3 x ICE	3 x VCA		Total
actinomycin-D			150 µg/kg		
carboplatinum		1.500			1.500
cyclophosphamide			4.500		4.500
doxorubicin	225				225
etoposide		900			900
ifosfamide		18.000			18.000
vincristin			9		9
MTX intraventricular	age dependent	age dependent	age dependent		age dependent

Table IV.2: Cumulative doses in patients with AT/RT (conventional chemotherapy)

Cumulative doses in patients with **AT/RT** (HD-therapy)					
Compound [mg/m²]	2 x DOX	2 x ICE	2 x VCA	HD	Total
actinomycin-D			100 µg/kg		
carboplatinum		1.000		1.500	2.500
cyclophosphamide			3.000		3.000
doxorubicin	150				150
etoposide		600			600
ifosfamide		12.000			12.000
vincristin			6		6
thiotepa				900	900
MTX intraventricular	age dependent	age dependent	age dependent	4 x 2 mg	age dependent

Table IV.3: Cumulative doses in patients with AT/RT (HD-therapy)

Cumulative doses in patients with **RTK / MRT** (conventional chemotherapy)					
Compound [mg/m²]	3 x DOX	3 x ICE	3 x VCA		Total
actinomycin-D			150 µg/kg		
carboplatinum		1.500			1.500
cyclophosphamide			4.500		4.500
doxorubicin	225				225
etoposide		900			900
ifosfamide		18.000			18.000
vincristin			9		9

Table IV.4: Cumulative doses in patients with RTK or MRT (conventional chemotherapy)

Cumulative doses in patients with **RTK / MRT** (HD-therapy)					
Compound [mg/m²]	2 x DOX	2 x ICE	2 x VCA	HD	Total
actinomycin-D			100 µg/kg		
carboplatinum		1.000		1.500	2.500
cyclophosphamide			3.000		3.000
doxorubicin	150				150
etoposide		600			600
ifosfamide		12.000			12.000
vincristin			6		6
thiotepa				900	900

Table IV.5: Cumulative doses in patients with RTK or MRT (HD-therapy)

Drug notes

Block chemotherapy and high-dose therapy

1. Actinomycin-D
(Dactinomycin, Cosmegen)
Formulation: Dry powder vials to dissolve with sterile water, containing 0.5 mg dactinomycin
Application: intravenous infusion, 2 x 25µg/kg (VCA)
Known important incompatibilities: doxorubicin, allopurinol, colchicine, probenecid, sulfinpyrazon
Side effects and main toxicities: Nausea, vomiting, stomatitis, mucositis, diarrhoea, myelosuppression, immunosuppression, fever, alopecia, transient increase of liver function, hyhpocalcaemia, allergic reaction

2. Carboplatinum
(Carbo, Carboplat, Carboplatin-Gry, Carboplatin-Meinel, Carboplatin O.R.C.A)
Formulation: Vials with 5ml, 15ml, 45ml containing carboplatinum 50mg, 150 mg, 450mg. Solution in dextrose 5 %
Application: intravenous infusion over 1 hour, 500 mg/m² (ICE); 500 mg/m²/d over 96 h (high-dose)
Stability: Vial stable for 18 months, preparation with dextrose 5 % is stable 28 days if prepared under sterile conditions, otherwise 8 hours at room temperature and 24 hours refrigerated
Known important incompatibilities: aluminium, amphotericin B, NaBic
Side effects and main toxicities: Nausea, vomiting, painful gastrointestinal sensations, allergic reactions (pruritus, fever, redness, very rarely anaphylactoid reaction with bronchospasm and cardiodepressive effects), transient myelosuppression, change of taste, rarely optic neuritis, auditory and peripheral neuropathy, transient increase of liver function tests.
Dose reduction: In case of kidney insufficiency calculation of the dose according to following formula: % of intended dose = (0.82*GFR) +18

3. Cyclophosphamide
(CPM, Endoxan)
Formulation: Vials of 100mg, 200mg, 500mg, 1,000mg available, dry powder vials plus saline solution vials.
Application: intravenous infusion over one hour, 1500 mg/m² (VCA)
Known important incompatibilities: amphotericin B, benzyl alcohol, induction of microsomal liver enzymes by phenobarbital, phenytoin, benzodiazepines, chloralhydrate or dexamethasone resulting in increased activity of cyclophosphamide, increased cardiotoxicity with simultaneous application of anthracyclines.
Side effects and main toxicities: Transient myelosuppression, reversible hair loss, nausea and vomiting, hemorrhagic cystitis due to accumulation of acrolein in the urine, water retention, cardiotoxicity in high doses, VOD in high dose approaches, secondary malignancy, infertility.

4. Doxorubicin
(DOX, Adriblastin HL)
Formulation: Dry powder and saline solution for dissolving, one vial contains 100mg doxorubicinhydrochlorid
Application: 37.5mg per m^2 x 2 as a 24 hour continuous intravenous infusion (DOX)
Important incompatibilities: allopolinol, aluminium, cephalotin, dexamethasone, gancyclovir, diazepam, fluorouracil, furosemide, heparin, hydrocortisone, methotrexate, natrium-hydrogencarbonat, piperacilin, theophylin, vincristine
Side effects and main toxicities: Transient myelosuppresion, reversible hair loss, cardiotoxicity (acute arrhythmias and late cardiomyopathy), nausea and vomiting, mucositis, transient increase in liver function tests, allergic reactions, paravasation necrosis, in cases of doses excessive of a maximum cumulative dose 400mg/m^2 the risk of cardiomyopathy arises without existing risk factors. In acute cardiomyopathy within 24 to 48 hours arrhythmias, extrasystoles, EKG changes which are in general reversible. A minor side effect is red discoloration of the urine.

5. Etoposide
(VP16, Etopophos, Etoposide main)
Formulation: Dry powder vials to dissolve with sterile water, 5 % dextrose or normal saline.
Application: regular: intravenous infusion of 100mg/m^2 x 3 over one hour (ICE)
Known important incompatibilities: amphotericin B, cefepime, chlorpromazine, imipenem, methylprednisolone, mitomycin. Interaction with coumadin and derivatives.
Side effects and main toxicities: myelosuppression, reversible hair loss, fever, hypotension, anaphylactic reactions, nausea and vomiting, diarrhea, mucositis, hepatic enzyme elevation, secondary malignant disease, rarely myalgias, central nervopus system disturbances, peripheral neuropathy, in isolated cases acute leukemia, cardiac dysrhythmias, heart attacks, Stevens-Johnson-Syndrome

6. Ifosfamide
(Ifo, Holoxan)
Formulation: Dry powder vials to dissolve with sterile water or vials with 4% Ifosfamide solution, vials as dry powder available Ifosfamide 200, 500, 1,000, 2,000, 3,000 mg
Application: 2,000mg/m^2 x 3 over one hour as an intranvenous infusion (ICE)
Known incompatibilities: none
Side effects and main toxicities: transient myelosuppression, reversible hair loss, nausea and vomiting, hemorrhagic cystitis, encephalopathy (10% with agitation, nightmares, loss of consciousness and/or seizures), transient increased liver function tests, Fanconi-syndrome, CNS toxicity in up to 12% in phase II studies, in isolated cases cardiotoxicity.

7. Methotrexat
(MTX, Methotrexat-Dinatrium)
Formulation: Vials with 20 ml, 40 ml containing MTX-Dinatrium 548.37 mg/1096 mg (500 mg/1000 mg)
Application: injection via Rickham/Ommaya-Reservoir (intra-thecal, intra-ventricular), age-dependent dose, patients with AT/RT only (window, ICE, VCD, high-dose therapy)
Known incompatibilities: none
Side effects and main toxicities: rare allergic reactions, central-nervous changes like leukencephalopathy, especially if applicated after radiotherapy of the brain.

8. Thiotepa
(Thiotepa Lederle)
Formulation: Dry powder vials to dissolve with sterile water, isotonic saline solution or 5% dextrose containing 15 mg thiotepa
Application: intravenous infusion over one hour, 300 mg/m²/d x 3 (high-dose)
Known incompatibilities: none
Side effects and main toxicities: Severe myelosuppression (nadir 2-3 weeks after application), mucositis, nausea and vomiting, intestinal ulcerations, hemorrhagic cystitis, neurologic changes (headache, behavioural changes, confusion, somnolence), erythrodermie,chronic discoloration of the skin, allergic reactions, amenorrhoe, disturbance of spermatogenesis, secondary malignancy. Death under thiotepa-therapy has been reported.

9. Vincristin
(VCR, Vincristinesulfat-Gry)
Formulation: Ready-to-use vials, one vial contains vincristinesulfate 1mg (= 0.895 mg Vincristine) plus lactose
Application: intravenous infusion as recommended by the WHO, 1.5 mg/m² (max. 2 mg) x 2 (VCA)
Known incompatibilities: All solutions with a pH other than 3.5 to 5.0
Side effects and main toxicities: **ONLY FOR INTRAVENOUS INFUSION**, peripheral neuropathy, central neurotoxicity, constipation, VOD, poly-, dysuria, inadequate ADH secretion, transient myelosuppression, reversible hair loss, necrosis after paravenous injection, in combination with cyclosporin A potential for severe neurotoxicity. Cross-reactivity with doxorubicin, daunorubicin, actinomycin-D, metramicin and mitomycin.

IV.2 Adverse Reactions

As this is a registry and not an interventional trial, SAE reporting to the registry headquarters is not legally binding. We suggest that adverse reactions are still reported to the competence centre, which will then pass the information (if necessary) on to the spontaneous reporting institutions of the nation (e.g. within Germany to the BfARM or AkdÄ).

Risks and burden of the consensus strategy will be continuously evaluated in order to improve counselling of clinicians caring for affected patients. The registry will thus also summarize the reported events into an annual safety report.

We thus recommend registering and reporting SAE immediately to each countries respective spontaneous reporting system. We would appreciate if SAE were also reported to the competence centre in Muenster for quality control of the recommended therapy.

Definitions:
Unexpected events are defined according to GCP-Guidelines:

Adverse Event (AE)
An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can be any unfavourable and unintended sign including an abnormal laboratory finding, a symptom or a disease temporary associated with the use of an IMP, whether or not considered related to the IMP.
Furthermore, any event which is associated with, or observed in conjunction with:

- product overdose whether accidental or intentional,
- product abuse and/or withdrawal,
- is also considered an adverse event.

Adverse Reaction (AR)
An adverse reaction (AR) is an untoward and unintended response to an IMP which is RELATED to any dose administered. All adverse events judged by the reporting investigator as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The evidence of reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
A serious adverse event or serious adverse reaction constitutes:
Any untoward medical occurrence or effect that at any dose

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing in-patients´ hospitalisation
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect

The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event i.e. required immediate intervention with life-saving intensive care treatment.
Important medical events that may not result in death, be life threatening or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse reaction (UAR)
An unexpected adverse reaction is an AR, the nature or severity of which is not consistent with the applicable Summary of Product Characteristics (Product Information).

Examples of UAR:
An expected / labelled SAR with an unexpected more severe outcome (e.g. a fatal outcome).
An increase in the rate of occurance of an expected, serious AR is considered as unexpected.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
A serious adverse event where a causal relationship to the IMP cannot be excluded is a suspected SAR and when the nature or severity is not consistent with the Product Information it constitutes a serious unexpected adverse reaction (SUSAR).

Documentation:
Patients within the registry exhibiting adverse events should be monitored with relevant clinical assessments and laboratory tests as determined by the treating physician. All adverse events must be followed to satisfactory resolution or stabilization of the event(s).

Grading and Relationship Assessment Guidelines for Adverse Event Evaluations

The CTC v. 3.0 grading system of toxicity (see Appendix) will be used for grading adverse events, where applicable. All other events will be graded for severity according to the definitions in the following tables.

mild	awareness of sign, symptom or event, but easily tolerated.
moderate	discomfort enough to cause interference with usual activity and may warrant intervention.
severe	incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.
life threatening	immediate risk of death.

Table IV.6: Definitions of Adverse Event Severity Categories

IV.3 Supportive care

Prophylaxis for infectious disease

The attending physician is responsible for infection prophylaxis and appropriate treatment. The following remarks have to be viewed as advice rather than generally accepted guidelines.
The most important infection prophylaxis is the appropriate information of the parents about neutropenia and the risks of infection. The application of non-absorbable antibiotics for total or selective decontamination of the intestinuum may increase the selection of resistent pathogens with unproven effectivity. Oral antimycotic chemoprophylaxis with Amphotericin B-suspension or Fluconazol prevents colonisation of most Candida species, but it does not reduce the incidence of systemic Candida or Aspergillus infections.
In cases of highly repetitive and prolonged conditions with neutropenia and mucositis intensified infection prophylaxis is recommended.

Pneumocystis-jiroveci-prophylaxis

Prophylaxis is strongly recommended in all patients during the block-chemotherapy to prevent pneumocystis-jiroveci-pneumonia. If therapy is to be continued (e.g. maintenance therapy) continuation of the prophylaxis is recommended. In case of TMP-SMZ-intolerance Pentamidine-inhalations may be used even in smaller children.

Drug	**Dose**
TMP-SMZ	8 mg TMP/kg/d p.o. in 2 doses on 2 days (tue, fri)
alternatives:	
Dapsone	3 months-12 years 2mg/kg daily
Pentamidin-Aerosol (if tolerated)	< 4 Years: 150 mg/month in 5 ml aqua dest. over 20-30 min. > 4 Years: 300 mg/month in 5 ml aqua dest. over 20-30 min.

Table IV.7: Pneumocystis-jiroveci-prophylaxis

Varicella exposition prophylaxis

The contact of patients with rhabdoid tumors treated with chemotherapy and persons with varicella or varicella zoster disease has to be avoided (parent information!). If an exposition happens, there is the risk to develop the disease for a min. of 28 days, not dependent on serological status, the risk beeing less for sero-positive patients. In each case the immuno-suppression at the time of exposition is relevant for therapeutic action.

In general we recommend the following procedure:

Status of patient	**Procedure**
has had Varicella (anamnestic, skars, titer) currently immunocompetent	Observation
has NOT had Varicella ± immuno-suppression	Aciclovir 10 mg/kg/d p.o. or i.v. 3 times per day for 14-28 days. alternatively Brivudin 125mg for 7 days
manifest disease	see Varicella, Varicella zoster (manifest disease)

Table IV.8: Varicella prophylaxis

Further prophylactic measures:

Duration of the prophylaxis: from initiation of therapy to 4 weeks after completion.

Compounds	Dosing
1. Amphotericin-B p.o.	4 x 1 ml
Ampho-B Aerosol	2 inhalations / week with nebulizer 1 ml Amphothericin-B (1 ampule = 1 ml = 50 mg) in 10 ml Aqua dest. 2 ml = 10 mg used for nebulization
poss. additional:	
Ampho Moronal tabl.	12.5 mg/kg/6h p.o., max. SD 400 mg q 6h (siehe CESS S. 15)
alternative:	
Fluconazol p.o.	4-6 mg/kg/d as SD
2. Routine care of oral mucosa	4 times daily (after meals) rinse mouth with mineral water over 1 min. In toddlers clean oral cavity with cotton swabs moistened with mineral water
Mucositis	*NO* hexidine, in any case rinse with tea (e.g. sage or other herbs)
3. Dental hygiene	Consistent care of oral mucosa, use soft tooth brush,
4. Food	During therapy and all phases of neutropenia only cooked food. No fresh vegetables, fruits or salads.

Table IV.9: Prophylactic measures during chemotherapy

Procedure in case of infection

Mucositis:
Obtain cultures for fungi and bacteria, attempt virus isolation from mouth wash solutions.

With open lesions do not use hexidin (inhibition of fibroblasts!)
* no mouth rinse using Leucovorin, use adstrigents
* mouth rinse with e.g. Maalox-Susp. / Xylocain viscous 2% / Panthenol-sol. 5% 1:1:1
* in case of oral thrush due to candida not resolving with intensive local therapy incl. 6 x daily. Amphotericin-B Suspension p.o.: Amphotericin-B 0,1-0,5 mg/kg/d p.i. (4 h) for 5-7 days alternatively: Fluconazol 4-6 mg/kg/d
* for proven Herpes: Aciclovir 30-50 mg/kg/d in 3 Doses p.i. (1h) 5 d
* for necrosis of periapical gingiva systemic antibiotic treatment for anaerobic infection e.g. Metronidazol

Neutropenic Fever:

Definition: temperature (rectal) > 38,5° C or 4 x > 38,0° C within 24 h with interval of more than 4 hours
Neutrophil count < 500/µl

- blood cultures each central line separately! Stool cultures, urinalysis
- throat, skin and mucosa (incl. anal) cultures
- virus isolation from lesions, stool and urine
- chest X-ray, sonography of abdomen
- if pulmonary symptoms persist despite broad spectrum antibiotic therapy for 72 hours bronchial lavage may be considered
- beside intensive diagnostics it is recommended to start systemic antibiotic therapy immediately. The combination of antibiotics have to be selected according to typical pathogens of the institutionan.

Begin with:

aminoglykoside + cephalosporin of 3rd generation (e.g. Ceftriaxon / Ceftazidim)

In case of ß-Lactam-resistent Staph. aureus / Staph. mitis isolates or suspicion of other virulent gram-positive pathogens (mucositis, catheter, abdominal symptoms):
initial therapy plus additional vancomycin (40 mg/kg/d) or teicoplanin (only >3 J.; 3 x 10 mg/kg, interval 12 h, then 6-10 mg/kg/24 h)

Extension of the antibiotic therapy: - if fever is not declining after 2-3 days
- if fever persists for > 5-7 days after initiation of i.v. antibiotics

add: liposomal Amphothericin-B i.v.

Suspected infection with anaerobic pathogens: additional metronidazol

Application of antibiotics until ANC > 500/µl, even when no infectious-focus may be found.

Systemic (invasive) fungal disease:

In case of suspected or prooven sytemic fungal disease:

liposomal Amphotericin B (Ambisome):	1-3 mg / kg KG

Varizella and Herpes zoster (disease):

Aciclovir i.v.:	1.500 mg/m²/d in 3 doses p.i. (1 h) for at least 5 days (until all efflorescenses have dried) < 10 kg or < 18 months: 30 mg/kg BW in 3 doses (3 x 10 mg/kg BW)

Severe systemic CMV-Infection (CMV-Pneumonitis):

Ganciclovir:	i.v. 10 mg/kg/d p.i. (1h) in 2 doses
Standard 7S-Immunoglobulins with high CMV-Titer (> 25 PEI-Units)	500 mg/kg/d over several days

Pneumocystis jiroveci-pneumonia:

Trimethoprim / Sulfamethoxazol i.v.:	TMP 20 mg / SMZ 100 mg/kg/d p.i. in 4 doses

G-CSF

The recommended dose is 5µg/kg/d G-CSF (Filgrastim, Lenograstim) as once daily s.c. injection according to international recommendation.

Begin day 5.

Blood component therapy

Due to risk of graft versus host reactions in patients under chemotherapy all blood products (not valid for granulocyte and stem cell products) should be irradiated with at least 20 Gy prior to transfusion, according to institutionals policies. The use of leukocyte filters for leukocyte depletion (CMV negativity) is advised.

Erythrocytes
Keep haemoglobin above 6 g/dl (hematocrit above 20%).

Thrombocytes
Platelet substitution is advised when platelets are < 10.000/µl, and/or clinical evidence of bleeding.

Antiemetic therapy

Antiemetic therapy should be administered according to institutional policy. The following compounds should be mentioned:
Vomex®; Zofran®; Navoban® poss. + Dexamethason (Fortecortin®)

Chemotherapy and surgery

In case of extensive initial surgery, chemotherapy should not be started before day 7 after operation.

Chemotherapy and radiotherapy

To use synergistic effects of chemotherapy and radiation, RT and CT are performed in parallel. To minimize toxicity radiotherapy must not be applied together with:
a*nthracyclines, actinomycin-D, intraventricular therapy*

Tumor lysis

Tumor lysis (TLS) is a complex metabolic disorder as a result of fast degradation of tumor cells under inadeqate renal functon. Especially in extensive, fast growing tumors TLS can occur, but it is a rare complication. (exception:disseminated alveolar RMS + RT). The onset lies before or within the first days of chemotherapy.
The main metabolic problems are:

* Hyperuricemia
* Hyperkaliemia
* Hyperphosphatemia

Clinically you often find:

* Secondary renal insufficiency
* Hypocalcemia.

Before starting chemotherapy in patients with extensive disease it has to be assured, that the patients are in stable metabolic condition (check: Na, K, Ca, Ph, CO2, blood gases, BUN, uric acid, creatinine, urinalysis, balanced in and out of fluids). For prophylaxis of renal failure it is important to administer hydration with alkalinization and additional allopurinol, alkalinization has to be stopped with the beginning of chemotherapy.

The following schedule may be adopted:

1. allopurinol 10 mg/kg/d p.o. in 2-3 single doses over 3-8 days
2. hydratation: 3.000 - 5.000 ml/m²/d (5 % glucose in half-isoton NaCl-solution)
3. fluid output = intake - perspiration
4. body weight: measure daily
5. in case of insufficient output: furosemide 1-10 mg/kg/d
6. initially do not add K+ to infusion: a low-grade hypokaliemia is not problematic
7. alkalinization of urine: add NaHCO3 40-80 mmol/L to infusion (or 100 - 200 mmol/m²/d infusion);
Balance Na-Bicarb according to urine-pH (optimum: 7,0); specific gravity in urine £1010
8. laboratory tests: CBC, Na, K, Cl, Ca, phosphate, uric acid, creatinine every 12-24h, if necessary more frequently

Renal dysfunction, non-specific increase of serum-creatinine

Dose modifications due to increasing serum-creatinin-levels may only be performed regarding creatinine-clearance. Generally the following steps are conceivable:

1. application of ifosfamide over 24 hours instead of short infusion
2. dose reduction of ifosfamide of about 1/3
3. give cyclophosphamide in exchange for ifosfamide

Similar strategies are possible in case of ifosfamide induced CNS-toxicity.

IV.4 Imaging protocol for patients in European SIOP Brain Tumour Studies (16.09.09)

Evaluation of primary tumours of the CNS and possible CNS dissemination is core to their management. Patients entering therapeutic trials must therefore meet and adhere to the minimum imaging requirements for recruitment into the various studies. The most important issue is comparability of pre- and post-operative MRI examinations and subsequent follow up studies. Therefore, if the baseline MRI did not conform to these requirements it should either be repeated pre-operatively or the post operative imaging should be performed in a way (e.g. additional sequences to the standard protocol) that will ensure comparability with the preoperative MRI. This is especially important for brain tumours that show little or no enhancement. In these cases the T2, PD, FLAIR and pre-contrast T1 images must be comparable.

In the case of very small primary, residual or recurrent tumours, measurement of such a small structures requires smaller slice thicknesses (3mm or less). In-plane resolution is an essential factor in image quality and therefore a 256 (or preferably 512) matrix is necessary for imaging the brain and a 512 matrix for the spinal canal imaging The FOV should be restricted to about 230 mm for the brain and a maximum of 350 mm for the spinal MRI.

The tumour and any post-operative residue should be measured in all 3 planes for the calculation of tumour volume (a x b x c/2). 3D-volume calculations may be performed additionally. These volume calculations are the basis for follow-up evaluation and every effort should be made to ensure the highest possible accuracy

Cranial MRI:
The standard imaging plane for the brain should be the axial plane (aligned to the AC-PC axis). Slice thickness should not exceed 4mm and must be adapted to the individual problem. As the signal of a tumour depends on the field strength of the MRI scanner the field strength must not be changed during the study.

For 1-1.5 Tesla MR scanners sequences:
For T1 and T2-weighted sequences SE or TSE are recommended
Axial T1, T2 and PD or FLAIR
Coronal FLAIR
Post contrast axial, coronal and sagittal T1

Axial DWI with ADC

Optional: 3D gradient echo T1 post contrast (particularly for computer guided surgical planning); functional imaging (e.g. perfusion, MRS, DTI and any other individual local imaging protocols).

For 3 Tesla MRI scanners:

The T1 imaging should be undertaken using a 3D-gradient echo T1 volume sequence pre- and post-contrast in addition to a T1 SE or gradient echo sequence (e.g. in the axial plane).

Spinal MRI:
Avoid 3T MRI for spinal imaging as the image quality is often inferior to that of 1.5T MR-scanners and more unpredictable. The entire dural sac must be fully visualized.

As only meningeal disease is of interest **only sagittal post-contrast T1-weighted sequences are necessary Slice thickness must not exceed 3 mm**. The physiological veins of the cord can be mistaken for nodules of dissemination and therefore **axial slices** without gaps (slice thickness can be chosen individually) are essential **for all suspicious areas**. As fat suppression often leads to artefacts and is not necessary for the delineation of meningeal disease it should not be used routinely.
Optional:

T2 TSE sequences (particularly when the primary tumour does not enhance or minimally enhances) or fat suppression techniques.

Early postoperative imaging:

As non-specific intracranial enhancement is often seen after 3 days following surgery the postoperative MRI must be obtained within this time. Optimal evaluation is made within the first 48 hours following surgery, and therefore should be undertaken within this period. However, even within this time false positive nodular enhancement can be seen with haemostatic materials and after electrocoagulation and therefore the pre- and post-contrast T1-weighted images need to be carefully evaluated in combination with the signal intensities on the T2-weighted and FLAIR series. Comparability with the preoperative MRI is essential for the detection of residual tumour. The size of a possible residuum has to be measured in all three planes. If the residuum is best visible on T2-weighted images a second plane incorporating a T2-weighted sequence must be employed.
A residuum is considered to be any area of pathological signal and/or enhancement comparable with the appearance of the pre-operative tumour.
For the evaluation of residual tumour seen on imaging the surgical report is often valuable and should be available.

Sequences for cranial and spinal imaging see prescriptions for cranial and spinal MRI (page xx).
Please note if spinal MRI is performed post-operatively:
Non-specific subdural and intradural enhancement and possible intradural blood products may be identified on early post-operative imaging of the spine and must not be mistaken for meningeal dissemination. Where there is ongoing doubt or if intense subdural enhancement is seen, the spinal MRI should be repeated after 2 weeks to clarify the situation.

Follow-up MRIs:

Timing for follow-up MRIs should be planned according to the individual protocol

Tumour measurement: Multiply the largest diameters in the three planes according to the formula axbxc/2. Additionally volume calculations of a 3D-dataset can be calculated if available for comparison. If the tumour enhances uniformly then the post-contrast T1 should be used for the measurement of the diameters. For heterogeneously, poorly or non-enhancing tumours the dimensions on T2/FLAIR or PD and pre-contrast T1 can be relevant and the best sequence cannot be predicted. For follow-up it is useful to choose the same sequence or if you need to change the sequence e.g. due to a change in contrast behaviour, then measure the tumour dimensions using the same sequence as on the previous examination for comparison.

Definitions of residual tumour:

As very subtle residual tumours may not be visible on imaging the results of imaging should be compared with the neurosurgical report. A thin line of enhancement can be physiological on early postoperative MRI in the absence of a residual tumour and must not be considered tumour.
The residual tumour will be defined as follows (applies only for early postoperative MRI):

R0: No residual tumour on post-operative MRI in accordance with the neurosurgical report

R1: No residual tumour on MRI but description of a small tumour residuum by the neurosurgeon or if the neurosurgical result is unkown.

R2: Small residual tumour on MRI with the maximum diameter < 5mm in any direction in ependymomas and/ or thin residual tumour covering the surgical margins like a ring or extending beyond the surgical margins.

R3: Residual tumour measurable in 3 planes.

R4: Size of the residual tumour unchanged or only minimally changed from the pre-operative status (e.g. after biopsy)

For historical reasons, the postoperative classification system according to Chang will be used for medulloblastomas. Previous studies found a worse prognosis for residual tumours that after resection were larger than 1.5 cm^2 in area (in the axial plane to enable comparison to imaging in studies during the CT era).

SO: no residual tumour

S1: residual tumour ≤ to 1.5 cm^2.

S2: residual tumour > 1.5 cm^2.

S3: residual tumour infiltration of the brain stem, irrespective of size

S4: residual tumour extending out of the posterior fossa.

As the Chang classification system is based on the neurosurgical intra-operative impression, the exact identification of infiltration of the brain stem by MRI will not be possible in every case. Additional information about the surgical procedure should be obtained as often as possible.

If imaging is inadequate or the appearance of the surgical cavity is difficult to interpret the term “unclear” should be used. Blood products in the spinal thecal sac can sometimes be differentiated from tumour by a repeat MRI in 1-2 weeks.

The staging of a possible residual tumour follows the guidelines of the PNET IV study:

CR (complete response): no evidence of residual or recurrent tumour or meningeal dissemination.

PR (partial response): Reduction of tumour volume ≥ to greater 50% compared to the previous staging MRI. (The trend of -meningeal dissemination has to be estimated and PR means considerable reduction of meningeal disease)

IMP (improvement or minor response): Reduction of tumour volume between 50% and ≥ 25% (and minor reduction of meningeal dissemination)

SD (stable disease): Tumour volume between +25% and -25% compared to the previous staging MRI (no significant change of meningeal dissemination)

PD (progressive disease): increase of tumour volume of ≥ 25% or new lesion.

IV.5 Informed consent forms German / English

IV.5.1 Information and Consent Forms - German

IV.5.1.1 Patienten- und Elterninformationen

IV.5.1.2 Aufklärungsbogen für Kinder bis 8 Jahre

IV.5.1.3 Aufklärungsbogen für Kinder und Jugendliche von 8 bis 14 Jahren

IV.5.1.4a Aufklärung zur Registrierung, Weitergabe und Verarbeitung von Patientendaten und Untersuchungsmaterial
form see chapter 9.4.1.1 Page 56

IV.5.1.4b Einwilligung zur Registrierung, Weitergabe und Verarbeitung von Patientendaten und Untersuchungsmaterial
form see chapter 9.4.1.2 Page 60

IV.5.1.5 Einwilligung zur Teilnahme an der Registerstudie European Rhabdoid Registry incl. standardisierter Chemotherapie
form under chapter 9.4.1.3 Page 62

IV.5.1.6 Aufklärung autologe Blut-Stammzell-Sammlung

IV.5.1.7 Einwilligung autologe Blut-Stammzell-Sammlung

IV.5.1.8 Aufklärung Hochdosis-Chemotherapie mit autologer Blut-Stammzell-Transplantation

IV.5.1.9 Einwilligung Hochdosis-Chemotherapie mit autologer Blut-Stammzell-Transplantation

IV.5.1.10 Aufklärung vor genetischen Analysen gemäß Gendiagnostikgesetz (GenDG) – Diagnostische oder prädikative Gentests

IV.5.1.11 Einwilligung zur Ausführung genetischer Analysen gemäß Gendiagnostikgesetz (GenDG) – Diagnositsche oder prädikative Gentests

IV.5.1.12 Einwilligungserklärung zur zytogenetischen/molekular-zytogenetischen Untersuchung an Tumorgewebe (Chromosomenanalyse/ FISH-Analyse)

IV.5.1.13 Aufklärung zur Verwendung von Liquorproben – wissenschaftliches Forschungsprojekt zur Etablierung von Tumormarkern für Rhabdoidtumoren des Gehirn (AT/RT)
discription see chapter 6.4

IV.5.1.14 Einwilligung zur Verwendung von Liquorproben - wissenschaftliches Forschungsprojekt zur Etablierung von Tumormarkern für Rhabdoidtumoren des Gehirn (AT/RT)
discription see chapter 6.4

Briefkopf der behandelnden Klinik

IV.5.1.1 Patienten- und Elterninformationen

Liebe Patientin, lieber Patient, liebe Eltern,

bei Ihnen/Ihrem Kind wurde die Diagnose eines Rhabdoid-Tumors gestellt. Für diesen seltenen Tumor wurde zu Forschungszwecken ein europäisches Register namens EU-RHAB gestartet und wir möchten Sie um Ihre/die Teilnahme Ihres Kindes daran bitten. Bevor Sie einwilligen, dass Daten von Ihnen/Ihrem Kind im Register EU-RHAB erfasst werden, lesen Sie bitte aufmerksam die folgenden Informationen über die Grundlagen, Ziele und die Durchführung des Registers. Markieren Sie die Abschnitte, die Sie nicht verstanden haben und die im Aufklärungsgespräch noch einmal besonders erklärt werden müssen.

Was sind rhabdoide Tumoren?

Rhabdoide Tumoren sind seltene, hoch aggressive und häufig ungünstig verlaufende Tumorerkrankungen. Aufgrund der Seltenheit gibt es in der Fachliteratur nur wenig verlässliche Daten zu Häufigkeit, Ursachen und Behandlungsstrategien. Die meisten veröffentlichten Untersuchungen bestehen aus kleineren Fallserien. Vereinheitlichte Behandlungskonzepte befinden sich in verschiedenen Ländern in Europa und in den USA im Aufbau. Das Register EU-RHAB beinhaltet die erste Behandlungsempfehlung für rhabdoide Tumoren jeder anatomischen Lokalisation.

Die Diagnose eines Rhabdoid-Tumors kann bei Tumoren der Niere (RTK), des Gehirns und Rückenmarks (AT/RT) sowie der Leber, Hals-, Oberschenkel-, Brustwand- und anderer Weichgewebe (MRT) gestellt werden.

Rhabdoide Tumoren betreffen fast ausschließlich Säuglinge und Kleinkinder. So findet man z.B. 85% der RTK in den ersten beiden Lebensjahren. Beim AT/RT liegt das Durchschnittsalter in den meisten Fallserien bei 20 bis 25 Monaten. Bei Rhabdoid-Tumoren des Weichgewebes sind immerhin noch 60% der Patienten unter 10 Jahre alt.

Die Symptome, die bei Kindern mit Rhabdoid-Tumoren zur Diagnose führen, unterscheiden sich nicht von denen, die bei anderen bösartigen Erkrankungen auftreten. So präsentieren sich die meist kleinen Kinder mit Nierentumoren durch einen vorgewölbten Bauch, Schmerzen oder Blut im Urin. Bei Tumoren der Weichgewebe fällt als erstes in der Regel eine Schwellung auf. Kleinkinder und Säuglinge mit AT/RT präsentieren sich oftmals mit Müdigkeit, Lethargie, Erbrechen und Gedeihstörungen. Oft findet man eine Kopfschiefhaltung und Lähmungen von Hirnnerven. In den meisten Fällen führen die o.g. Zeichen zu einer Durchführung von Bild gebenden Verfahren wie Ultraschall, Röntgen, Computer-Tomographie (CT) und Kernspintomographie. Diese hat wiederum in der Regel eine Operation mit Gewebeentnahme zur Folge.

Die alleinige feingewebliche Diagnose eines Rhabdoid-Tumors kann Schwierigkeiten bereiten. Durch Fortschritte in der genetischen Diagnostik wurde dies wesentlich erleichtert. Allen drei Gruppen von Rhabdoid-Tumoren ist eine Veränderung am Chromosom 22 in den Tumorzellen gemeinsam. Deshalb wird die feingewebliche Untersuchung regelmäßig durch eine genetische Untersuchung der Tumorzellen auf solche Veränderungen ergänzt. Bei einem Teil der an Rhabdoid-Tumoren erkrankten Personen findet sich aber eine solche Veränderung an Chromosom 22 in allen Körperzellen. Durch eine Blutentnahme kann hier der Nachweis von Veränderungen helfen, die Diagnose zu sichern. Es handelt sich bei einer solchen Blutuntersuchung dann um einen „diagnostischen Gentest nach dem Gendiagnostikgesetz (GenDG)“. Leider scheint es ein erhöhtes Risiko für die Geschwister von betroffenen Patienten zu geben, so dass es bei Nachweis einiger besonderer Chromosomen-Veränderungen beim Patienten ratsam ist, auch Blut beider Elternteile sowie sämtlicher leiblicher Geschwister zu untersuchen. Bei einer solchen Untersuchung gesunder Angehöriger handelt es sich dann um einen “prädiktiven Gentest“ nach dem Gendiagnostikgesetz.
Hinsichtlich dieser Gentests werden Sie entsprechend der Vorgaben des Gendiagnostikgesetzes umfassend von einem Facharzt/einer Fachärztin, der/die sich im Rahmen seines/ihres Fachgebietes qualifiziert hat, über die Untersuchungen und deren Konsequenzen aufgeklärt. Nach einer angemessenen Bedenkzeit entscheiden Sie, ob Sie diesen weiterführenden Untersuchungen zustimmen. Sie bzw. Ihre volljährigen Verwandten, die einen diagnostischen oder prädiktiven Gentest durchführen lassen möchten, müssen dieser Untersuchung separat durch Unterschrift zustimmen. Dafür erhalten Sie einen entsprechenden Aufklärungs- und Einverständnisbogen.

Entnahme von Gewebe, Blut und Liquor im Rahmen des EU-RHAB Registers

Es ist vorgesehen Tumorgewebe, Blut und Liquor (nur AT/RT) im Rahmen der chirurgischen Tumor-Entfernung oder bei ohnehin notwendigen Blutentnahmen und Liquorpunktionen zu entnehmen. Falls bei der Operation aus medizinisch-chirurgischen Gründen gesundes Gewebe mit entfernt werden muss, kann dieses als Vergleichsgewebe für die Tumoreigenschaften verwendet werden. Eine medizinisch nicht notwendige Erweiterung des chirurgischen Eingriffs erfolgt dazu nicht. Tumorgewebe, Vergleichsgewebe und Vergleichsblut werden zentral in einer der in der Einwilligungserklärung gelisteten Tumorbanken bis zum Widerruf Ihrer Einwilligung gelagert. Die Proben werden kostenfrei und anonymisiert Wissenschaftlern, die in universitären Einrichtungen oder in Krankenhäusern tätig und kooperativ eingebunden sind, für krankheitsbezogene Untersuchungen zur Verfügung gestellt. Auf diese Weise sollen die Diagnose sicherer gemacht, das biologische Verständnis der Erkrankung verbessert und neue therapeutische Ansätze gefunden werden.

Bisherige Behandlungsansätze für Patienten mit Rhabdoid-Tumoren

In Deutschland werden über 90% aller Kinder/Jugendlichen mit bösartigen Erkrankungen nach gemeinsam entwickelten Konzepten, sog. „Studien“ behandelt, die von der deutschen Gesellschaft für pädiatrische Hämatologie und Onkologie (GPOH) koordiniert werden. Von Seiten der GPOH wird dazu eine sog. Studienkommission und eine Studienleitung bestimmt, die sich aus bundesweiten Experten in der Behandlung dieses speziellen Tumortyps zusammensetzt.

In diesem sehr erfahrenen Gremium wurden Therapiewege entwickelt und in der Form eines sog. Studienprotokolls niedergelegt. Auch die Experten des EU-RHAB Registers haben eine Standardtherapie entwickelt.

Das Register EU-RHAB hat sich zum Ziel gesetzt, alle Patienten mit einem Rhabdoid-Tumor zu erfassen, um Daten zu Häufigkeit, Alter, Lokalisation und Therapie-Erfolgen zu sammeln. Die Auswertung dieser Daten soll das Verständnis dieser relativ seltenen Erkrankung verbessern und so zu einer verbesserten Therapie mit möglichst guten Ergebnissen beitragen.

Trotz vielfacher aggressiver und experimenteller Therapieansätze sind die Heilungsaussichten v.a. von Kleinkindern und Säuglingen mit Rhabdoid-Tumoren äußerst ungenügend. Das junge

Alter, die oftmals ungünstige und/oder inoperable Lokalisation, sowie das Vorliegen von Metastasen schränken die Behandlungsmöglichkeiten zusätzlich ein. Bis zu 80% der Kinder mit solchen Risikofaktoren versterben innerhalb von zwei Jahren nach Diagnosestellung.

Bislang wurden Patienten mit einem Rhabdoid-Tumor der Niere im Rahmen der Wilmstumor-Studie behandelt. Diese Therapie umfasste bislang eine intensive Block-Chemotherapie, die Operation und eine Bestrahlung. Rhabdoid-Tumoren der Weichteile wurden bislang meistens im Rahmen der Weichteil-Sarkom-Studien als Hochrisiko-Patienten behandelt. Kinder mit einem AT/RT wurden bis vor kurzem international im Rahmen von Hirntumor-Studien für Säuglinge und Kleinkinder behandelt. Die überwiegende Mehrheit dieser Therapieansätze zeigten jedoch unbefriedigende Ergebnisse, so dass Einigkeit darüber besteht, dass alle Rhabdoid-Tumoren einheitlich behandelt werden sollten.

Das europäische Register EU-RHAB wurde von einer Gruppe von Spezialisten gegründet, welche sich in besonderem Maße mit rhabdoiden Tumoren beschäftigen. Diese legten die Grundlage für den aktuellen Status und trugen die noch offenen Fragen zusammen, welche nun durch die Daten der Patienten des EU-RHAB Registers beantwortet werden sollen. Des Weiteren wurde eine Konsensus-Therapie ausgearbeitet, welche auf den Erkenntnissen der aktuellen Literatur und der Erfahrung der Experten beruht.

Nur durch Erfahrungen mit früheren Patienten und deren Familien ist es möglich geworden, diese Erkenntnisse zu gewinnen, die jetzt in die standardisierte Behandlung für Sie/Ihr Kind eingeflossen sind. In diesem Sinne stellt auch Ihre bzw. die Teilnahme Ihres Kindes einen wichtigen Baustein für die stete Weiterentwicklung der Therapie dieser Tumoren dar.

EU-RHAB – Konsensus-Therapie für Patienten mit rhabdoiden Tumoren
(die im Folgenden beschriebenen Therapien stellen keine Neuheiten bei der Behandlung rhabdoider Tumoren dar und wurden bislang auch außerhalb des EU-RHAB Registers angewandt).

Operation

Zunächst einmal muss immer versucht werden einen Rhabdoid-Tumor soweit wie möglich chirurgisch zu entfernen. Dies wird nicht in allen Fällen komplett gelingen, da z.B. im Gehirn nicht immer radikal operiert werden kann ohne die Lebensqualität postoperativ deutlich einzuschränken. Gleichzeitig wird bei Kindern mit AT/RT ein Zugang zu einer Hirnkammer gelegt. Durch dieses so genannte „Ommaya-Reservoir“ bzw. diese „Rickham-Kapsel“ können Medikamente direkt in die Hirn-Rückenmarkflüssigkeit appliziert werden.

Nach der Operation erfolgt eine intensive Blockchemotherapie über 20 Wochen. Während der Blockchemotherapie oder unmittelbar im Anschluss wird weiterhin eine Bestrahlung des Tumors vorgenommen, sofern dies der Zustand und das Alter des Patienten erlauben.

Behandlung mit Zellgiften (Chemotherapie)

Medikamente, die sich bei Rhabdoid-Tumoren als wirksam erwiesen haben und daher von den Experten des EU-RHAB Registers empfohlen werden, sind z.B. Vincristin, Doxorubicin, Ifosfamid, Carboplatin, Etoposid, Cyclophosphamid und Actinomycin-D. Bei rhabdoiden Tumoren des Gehirns wird außerdem die Substanz Methotrexat über den oben erwähnten Zugang direkt in das Hirnkammersystem verabreicht, um zu verhindern, dass sich der Tumor im Nervenwasser ausbreitet. Ihr behandelnder Arzt wird Ihnen eine genaue Übersicht aushändigen, aus der Sie entnehmen können welche Medikamente zu welchem Zeitpunkt verabreicht werden. Es wird empfohlen, dass diese intensive Block-Chemotherapie um eine Bestrahlungsbehandlung erweitert wird, sobald der Patient das hierzu als sicher angesehene Alter erreicht hat.

Zum jetzigen Zeitpunkt ist es nicht eindeutig geklärt ob Patienten, die eine Hochdosistherapie erhalten bessere Ergebnisse erzielen als Patienten, welche eine konventionelle Chemotherapie erhalten. Die Entscheidung zwischen diesen beiden Wegen wird Ihr

behandelnder Arzt mit Ihnen besprechen. Bei einer Hochdosis-Chemotherapie wird die Menge der verabreichten Medikamente angehoben, mit dem Ziel die Tumorzellen zu zerstören. Auch die Blutbildung im Knochenmark wird dabei dauerhaft zerstört, so dass die Patienten anschließend Blutbildungszellen (so genannte Stammzellen) benötigen, die ihnen vor der Chemotherapie aus dem eigenen Blut entnommen wurden.

Die Chemotherapiephase dauert sowohl mit wie auch ohne Hochdosis-Therapie insgesamt ca. 20 Wochen und wird zum großen Teil stationär stattfinden. Zwischen den einzelnen Blöcken können die Patienten für einige Tage entlassen werden, sofern es der Zustand erlaubt. Wichtig bei der Behandlung ist es allerdings, Verzögerungen im Ablauf wenn möglich zu vermeiden, um dem Tumorgewebe keine Chance zu geben sich zu erholen.

Nebenwirkungen der Chemotherapie

Bei der Chemotherapie werden hochwirksame Zellgifte verabreicht, die den ganzen Organismus des Kindes treffen. Außer Haarausfall können folgende Organe in Ihrer Funktion gestört werden: Schleimhäute, Knochenmark (Blutbildung), Infektabwehr, Nieren, Gehör, Gehirn und Nervensystem, Leber, Lunge und Eierstöcke/Hoden. Selten können nach einer solchen Behandlung auch Zweittumoren auftreten. Den möglichen Nebenwirkungen einer Chemotherapie wird durch eine Dosierung, die sich nach dem Alter und der Körperoberfläche richtet, und eine genaue zeitliche Abfolge der Medikamentengabe Rechnung getragen. Vorbeugende Maßnahmen (z.B. gegen Übelkeit und Erbrechen) sollen die Nebenwirkungen in erträglichen Grenzen halten oder teilweise völlig verhindern.

Strahlentherapie

Eine Bestrahlung erfolgt je nach Alter des Patienten so früh wie möglich. Hierüber werden Sie ausführlich durch den Strahlentherapeuten aufgeklärt.

Untersuchungen, Schwangerschaftstest, Kontrazeption

Vor Beginn und während der Therapie erfolgen ausführliche Untersuchungen, um den gesamten Gesundheitszustand und auch die Belastung aller Organe des Körpers durch das Tumorleiden oder durch unerkannte Erkrankungen beurteilen zu können. Bei jugendlichen Patientinnen muss ein Schwangerschaftstest erfolgen. Noch 6 Monate nach Ende der Therapie muss eine Schwangerschaft zuverlässig verhindert werden.

Vertraulichkeit und Weitergabe personenbezogener Daten im Rahmen des EU-RHAB Registers

Im Rahmen von EU-RHAB arbeiten viele Kliniken in Europa zusammen, um möglichst viele Patienten mit einem Rhabdoid-Tumor zu heilen. Ein wesentlicher Bestandteil ist der Austausch von Bild- und Untersuchungsmaterial (Röntgenbilder, Computertomographie, Magnet-Resonanz-Tomographie, Tumor, Blut, Liquor). Der Austausch erlaubt die Mitbeurteilung durch ein Team von Experten (Referenzpathologen, Referenz-Strahlentherapeuten, etc.), um eine zweite Meinung zu jedem Patienten einzuholen. Um Verwechselungen zu vermeiden, ist es sinnvoll, für Expertenmeinungen kein anonymisiertes Untersuchungs- oder Bildmaterial auszutauschen, sondern personenbezogenes Material. Alle Personen, die Einblick in die gespeicherten Daten haben, sind zur Wahrung des Datengeheimnisses verpflichtet.

In Publikationen, die aus Studiendaten hervorgehen, finden ausschließlich anonymisierte Daten Verwendung. Ein Rückschluss auf die Identität eines betroffenen Patienten oder einer Patientin ist in keinem Fall, auch nicht unter Ausnahmebedingungen möglich.

Für die Weitergabe der Daten bitten wir Sie daher, die behandelnden Ärzte von Ihrer Schweigepflicht zu entbinden. Dies schließt explizit auch die genetischen Daten ein, die gemäß den Auflagen des Gendiagnostikgesetzes ansonsten nur dem anfordernden Arzt mitgeteilt werden dürfen.Dieses Einverständnis der Weitergabe der Daten ist freiwillig und kann jederzeit widerrufen werden, ohne dass Ihnen oder Ihrem Kind ein Nachteil daraus entsteht.

Freiwillige Teilnahme am EU-RHAB Register

Sowohl die Registrierung der Daten wie auch die Behandlung mit einer konsentierten Therapie sind freiwillig. Sie können die Teilnahme jederzeit mündlich oder schriftlich widerrufen, ohne dass Ihnen oder Ihrem Kind dadurch Nachteile entstehen. Im Falle des Widerrufs Ihrer Einwilligung können Sie die Vernichtung der von Ihnen/Ihrem Kind gelagerten Gewebe-, Blut- und Liquorproben verlangen.

Alternative Behandlungsmöglichkeiten

Wenn während der Laufzeit dieser Studie neue und bessere Behandlungsmöglichkeiten beschrieben werden, werden wir Sie informieren und gegebenenfalls eine Änderung der Therapie vorschlagen.

Ethikkommission und behördliche Auflagen

Die Studie wurde der zuständigen Ethikkommission (Münster) vorgelegt und in der vorliegenden Fassung akzeptiert.

Kontaktadresse

Falls Sie zusätzliche Informationen wünschen, können Sie mit den Leitern des Registers EU-RHAB Kontakt aufnehmen:

EU-RHAB

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IV.5.1.2 Aufklärungsbogen für Kinder bis 8 Jahren

EUROPEAN Rhabdoid Registry

Aufklärung für Kinder bis 8 Jahre

Patient/in

Name

Vorname

geboren am

Gesprächspartner/in

Sorgeberechtigte/r

Patient/in

Arzt/Ärztin

Zeuge/Zeugin

Hallo liebe Patientin, lieber Patient!

Bei Dir wurde eine Krankheit festgestellt, die **Rhabdoid-Tumor** heißt. Diese Tumoren können im Kopf liegen, dann sagt man dazu AT/RT. Liegen sie in der Niere, so heißen sie RTK. Findet man sie in den Weichteilen oder anderen Organen, nennt man sie MRT.

Ohne eine Behandlung ist diese Krankheit sehr gefährlich. Du bist hier im Krankenhaus, damit Du eine Behandlung bekommst, die Dich hoffentlich wieder ganz gesund macht.

Alle Menschen hier im Krankenhaus helfen Dir dabei.

Egal, wo der Tumor gefunden wurde - die Behandlung ist für alle drei Gruppen ähnlich.

Zuerst wird man versuchen, den Tumor in einer Operation soweit wie möglich zu entfernen. Dabei bekommst Du eine Narkose, so dass Du von der Operation nichts merkst.

Nach der Operation werden wir Dir Medikamente geben. Das nennt man Chemotherapie.
Wenn Du die Medikamente bekommst, musst du für einige Tage zu uns ins Krankenhaus kommen.

Die Chemotherapie wird über eine Blutader gegeben.

Viele Kinder sind in dieser Zeit müde und manchen ist es schlecht. Aber hier im Krankenhaus haben wir Mittel, die Dir helfen.

Allen Kindern fallen während der Behandlung die Haare aus. Aber keine Angst, die kommen hinterher wieder!

Auch zwischendurch zu Hause wirst Du manchmal schlapp und müde sein. Aber dann geht es Dir auch wieder gut.

Die meisten Kinder mit einem **Rhabdoid-Tumor** bekommen auch noch eine Strahlentherapie.

Insgesamt wird es mindestens 20 Wochen dauern, bis die intensive Behandlungszeit vorbei ist.

Hinterher musst Du regelmäßig zu uns kommen, damit wir Dich untersuchen können.

Die Ärzte wollen herausfinden, wie man die Behandlung von **Rhabdoid-Tumoren** noch verbessern kann. Deswegen wollen sie von möglichst vielen Kindern Informationen zusammentragen.

Deshalb fragen wir Dich und Deine Eltern, ob Du dabei mitmachen willst.

Wenn Deine Eltern damit einverstanden sind, dann kannst Du helfen, dass man immer mehr über die Krankheit und die richtige Behandlung lernt und die Patienten mit einem **Rhabdoid-Tumor** immer besser heilen kann.

Hier kannst Du Deinen Namen schreiben:

IV.5.1.3 Aufklärungsbogen für Kinder und Jugendliche von 8 bis 14 Jahren

EUROPEAN Rhabdoid Registry

Aufklärung für Kinder von 8-14 Jahren

Patient/in

Name

Vorname

geboren am

Gesprächspartner/in

Sorgeberechtigte/r

Patient/in

Arzt/Ärztin

Zeuge/Zeugin

Hallo liebe Patientin, lieber Patient!

Bei Dir wurde eine Krebs-Erkrankung festgestellt, die **Rhabdoid-Tumor** heißt. Diese Tumoren können im Kopf liegen, dann sagt man dazu **AT/RT**. Liegen sie in der Niere, so heißen sie **RTK**. Findet man sie in den Weichteilen oder anderen Organen, nennt man sie **MRT**.

Ohne eine Behandlung ist diese Krankheit sehr gefährlich.
Du bist hier im Krankenhaus, damit Du eine Behandlung bekommst, die Dich hoffentlich wieder ganz gesund macht. Alle Menschen hier im Krankenhaus helfen Dir dabei.

Deine Ärzte haben Dir vorgeschlagen, am **Register EU-RHAB** teilzunehmen.
Dieses Register sammelt Daten und Informationen von möglichst vielen Patienten mit einem **Rhabdoid-Tumor**, um immer mehr über diese Tumoren zu lernen und die bestmögliche Therapie zu finden.
Ausgewertet werden all diese Informationen von Spezialisten, die sich besonders mit Deiner Krankheit auskennen.

BEHANDLUNG

Egal, wo der Tumor gefunden wurde - die Behandlung ist für alle drei Gruppen fast gleich.
Zuerst wird man versuchen, den Tumor in einer **Operation** soweit wie möglich zu entfernen. Dabei bekommst Du natürlich eine **Narkose**, so dass Du von dem Eingriff nichts merkst.

Nach der Operation wirst Du Medikamente bekommen.
Das nennt man **Chemotherapie**.
Diese Behandlung sorgt dafür, dass übrig gebliebene Tumor-Zellen abgetötet werden und sich nicht weiter in Deinem Körper ausbreiten können. Wenn Du die Medikamente bekommst, musst Du für einige Tage ins Krankenhaus kommen.
Die Chemotherapie wird über eine Blutader gegeben.

Es gibt zwei verschiedene Therapie-Wege:

In dem einen bekommst Du 9 Blöcke Chemotherapie.
Jeweils dreimal

- **DOX** (Doxorubicin),
- **ICE** (Ifosfamid, Carboplatin, Etoposid) und
- **VCA** (Vincristin, Cyclophosphamid, Actinomycin-D).

In dem anderen bekommst Du 6 Blöcke Chemotherapie.
Jeweils zweimal

- **DOX** (Doxorubicin),
- **ICE** (Ifosfamid, Carboplatin, Etoposid) und
- **VCA** (Vincristin, Cyclophosphamid, Actinomycin-D).

Und im Anschluss daran eine Hochdosis-Chemotherapie mit

- **Carbo/TT** (Carboplatin und Thiotepa)
  und Rückgabe Deiner eigenen Stammzellen, die am Anfang der Therapie aus Deinem Blut heraus gefiltert und gesammelt wurden.

Welchen Therapieweg Du bekommst, werden Deine Ärzte entscheiden.

Patienten mit einem Tumor im Kopf oder Rückenmark bekommen in einer kleinen Operation eine kleine Kapsel in den Kopf eingesetzt, in die noch ein zusätzliches Medikament (MTX, Methotrexat) direkt verabreicht wird. Dieses ist dazu da, Tumorzellen im Nervenwasser direkt abzutöten.

Die meisten Kinder mit einem **Rhabdoid-Tumor** bekommen auch noch eine **Strahlentherapie** der Körperregion, an der der Tumor festgestellt worden ist.

Du erhältst einen eigenen, genauen Behandlungsplan, in dem Du den Ablauf der Therapie ablesen kannst. Außerdem kannst Du dann markieren, welche Abschnitte der Therapie Du schon geschafft hast.

Insgesamt wird es mindestens 20 Wochen dauern, bis die intensive Therapie-Zeit vorbei ist. Hinterher musst Du regelmäßig zu uns kommen, damit wir Dich untersuchen können.

ZENTRALER ZUGANG

Die meisten Medikamente, die Du bekommst, können nicht geschluckt werden, sondern werden über eine Blutader gegeben. Die Medikamente können die Blutadern reizen und schwere Gewebsschäden hervorrufen, wenn sie versehentlich neben die Blutadern laufen.
Daher bekommen alle Patienten für die Therapie einen so genannten **zentralen Zugang**.
Hierfür wird in einer kurzen Operation ein dünner Schlauch in eine große Körperader gelegt, der für die gesamte Therapie dort bleibt und aus dem man auch fast alle notwendigen Blutentnahmen machen kann. Deine Ärzte werden Dir erklären, wie dieser Schlauch genau funktioniert.

NEBENWIRKUNGEN DER CHEMOTHERAPIE

Starke Medikamente haben neben den gewünschten Wirkungen auch unerwünschte Wirkungen, die man Nebenwirkungen nennt.
Manche Nebenwirkungen treten bei allen Patienten auf, andere nur bei wenigen.
Bei allen Patienten treten auf:

- Haarausfall (kommen nach der Therapie wieder)
- zu wenig weiße Blutkörperchen (Infektionsgefahr)
- zu wenig rote Blutkörperchen (schlapp, müde)
- zu wenig Blutplättchen (blaue Flecken, Blutungsgefahr)

Bei vielen Kinder treten auf:

- Übelkeit, Erbrechen, Verstopfung, Durchfall
- Schleimhautentzündung, Schmerzen im Mund und im Hals
- Fieber, Müdigkeit, Muskelschmerzen

Hier im Krankenhaus haben wir Mittel, die Dir bei solchen Nebenwirkungen helfen.
Auch zwischendurch zu Hause wirst Du manchmal schlapp und müde sein, aber dann geht es Dir auch wieder gut.

Manche Medikamente haben noch ganz spezielle Nebenwirkungen:

Doxorubicin kann Dein Herz schädigen. Deshalb wird vor jeder Gabe von Doxorubicin Dein Herz untersucht. Diese Untersuchungen müssen auch noch lange nach der Therapie regelmäßig durchgeführt werden.

Ifosfamid und Cyclophosphamid können der Blase schaden. Deshalb bekommst Du ein Schutzmedikament, das **MESNA** heißt, und viel Flüssigkeit, um die Niere und die Blase gut durch zu spülen. Auch nach der Therapie werden die Ärzte die Funktion Deiner Nieren immer gut untersuchen.

Alle Medikamente können auch Allergien auslösen, wenn sie nicht vertragen werden.

Gegen viele Nebenwirkungen gibt es Gegenmittel. Sind die Nebenwirkungen jedoch zu stark, können die Ärzte das Medikament auch eventuell absetzen und gegen ein anderes austauschen.

SPÄTFOLGEN

Herz- und Nierenschäden können auch erst lange nach der Therapie auftreten. Deshalb ist es besonders wichtig, dass Du auch in den Jahren nach der Therapie regelmäßig zu den Kontroll-Untersuchungen gehst.

Ifosfamid, Cyclophosphamid und die Hochdosistherapie können die Produktion von Geschlechtshormonen stören und dazu führen, dass Du keine eigenen Kinder bekommen kannst.

Ganz selten kann durch die Behandlung eine zweite Krebserkrankung entstehen.

DAS REGISTER EU-RHAB UND DER DATENSCHUTZ

Die Ärzte wollen herausfinden, wie man die Behandlung von Rhabdoid-Tumoren noch verbessern kann. Deswegen wollen sie von möglichst vielen Kindern Informationen und Daten zusammentragen.
Deshalb fragen wir Dich und Deine Eltern, ob Du dabei mitmachen willst.

Dein Alter, ob Du ein Junge oder Mädchen bist, in welcher Klinik Du behandelt wirst, Deine Behandlung, wie es Dir während der Behandlung geht und Dein Heilerfolg werden auf Dokumentationsbögen eingetragen. Diese werden an die Studienzentrale EU-RHAB geschickt, wo die Daten in einen Computer eingegeben werden. Die Daten von vielen Patienten aus verschiedenen Ländern in Europa werden zusammen ausgewertet. Die Menschen, die mit diesen Daten arbeiten, kennen Deinen Namen und Deine Adresse nicht.

Es werden auch Informationen über Deine Erkrankung an andere Ärzte geschickt, die sich besonders gut mit Deiner Krankheit auskennen. Diese Daten werden mit Deinem Namen verschickt, damit es nicht zu Verwechselungen kommt, und Deine Ärzte sich mit diesen Spezialisten über Deine Behandlung austauschen können. Niemand, der etas von Dir und Deiner Erkrankung erfährt, darf es anderen weitersagen.

Während Deiner Therapie werden Gewebe- und Blutproben gesammelt, aber ohne dass zusätzliche Blutabnahmen oder Operationen notwendig werden. Die daraus gewonnenen Informationen werden auch an die EU-RHAB Studienzentrale geschickt und ausgewertet.

EINVERSTÄNDNIS ZUR TEILNAHME AM REGISTER

Du kannst Dir nun überlegen, ob Du am Register EU-RHAB teilnehmen möchtest oder nicht.
Wenn Du und Deine Eltern einverstanden sind, dass Deine Daten ausgewertet werden dürfen, dann machst auch Du bei dieser Untersuchung mit und kannst helfen, dass man immer mehr über die Krankheit und die richtige Therapie lernt und die Patienten mit einem Rhabdoid-Tumor immer besser behandeln kann.

Eine Behandlung Deiner Erkrankung brauchst Du in jedem Fall. Das kann als Patient des Registers oder außerhalb des Registers geschehen.
Auch wenn Du Dein Einverständnis für die Teilnahme am Register wieder rückgängig machst, wird Dir daraus kein Nachteil entstehen.
Alle werden immer dafür sorgen, dass Du die bestmögliche Behandlung bekommst.
Denn alle wollen, dass Du wieder ganz gesund wirst!

Hier kannst Du unterschreiben:

Hier kannst Du alle Fragen aufschreiben, die Du noch hast. Sprich in aller Ruhe mit Deinen Eltern und/oder mit wem Du sonst wichtige Dinge gut besprechen kannst.
Wenn Du noch Fragen hast, sind Deine Ärzte auch immer für ein Gespräch da.

Briefkopf der behandelnden Klinik

IV.5.1.6 Aufklärung Autologe Blut-Stammzell-Sammlung

Was sind „Stammzellen“?

Stammzellen sind die „Mutterzellen“ der Blutbildung. Durch Vermehrung und Ausreifung sorgen sie im Knochenmark für die ständige Neubildung aller drei Zellreihen: weiße Blutkörperchen (Leukozyten), rote Blutkörperchen (Erythrozyten) und Blutplättchen (Thrombozyten). Normalerweise kommen Stammzellen im Blut nur zu einem verschwindend geringen Anteil vor. Wenn man Stammzellen sammeln will, muss man ihr Austreten aus dem Knochenmark in die Blutbahn stimulieren. Dies gelingt durch die Anwendung von so genannten Wachstumsfaktoren (z.B. G-CSF). Teilweise nutzt man vorausgegangene Chemotherapie zur Stimulation aus, weil bekannt ist, dass nach einer Chemotherapie die Stammzellen auch vermehrt im Blut auftreten. Es gibt somit die Möglichkeit zu einem beliebigen Zeitpunkt oder nach verabreichter Chemotherapie die Stammzellen mittels Wachstumsfaktoren zu mobilisieren, um sie dann aus dem Blut zu sammeln.

Warum werden Stammzellen gesammelt?

In einigen Fällen bösartiger Erkrankungen im Kindes, Jugend- und auch Erwachsenenalter besteht nur eine geringe Chance auf langfristige Heilung unter der bisher üblichen Dosierung der zytostatischen Medikamente. Es ist eine allgemein anerkannte Methode, die Medikamentenmenge (Dosis) und damit die Chance auf eine Heilung zu erhöhen. Es können aber nur solche Medikamente in ihrer Dosis gesteigert werden, deren Nebenwirkungen hauptsächlich die Beeinträchtigung der Funktion des Knochenmarks ist, d.h. die die Blutbildung unterdrücken. Bei sehr hoher Dosierung dieser Medikamente würde der Patient wochenlang keine Blutzellen bilden können bzw. würde sich die Blutbildung nie wieder richtig erholen. Das kann durch eine autologe (körpereigene) Stammzelltransplantation abgewendet werden. Zusammengefasst bedeutet das, man kann dem Patienten eine hoch dosierte Chemotherapie vorschlagen, wenn vorher genügend Stammzellen gesammelt wurden. Stammzellen werden bei -170° Celsius in flüssigem Stickstoff gelagert und haben eine unbegrenzte Haltbarkeit.
Wie werden Stammzellen gesammelt?

Die Stammzellen werden durch die Gabe eines Wachstumsfaktors aus dem Knochenmark in das Blut mobilisiert. Man benötigt zwei großlumige Venenzugänge, so dass bei kleinen Armvenen für die Separation und die darauf folgende Hochdosischemotherapie ein doppelläufiger zentraler Venenkatheter (z.B. Sheldon-Katheter) eingelegt wird. Aus dem einen Schenkel wird das Blut (durch Zentrifugieren) heraus gesogen und fließt durch einen Zellseparator, der das Blut in seine Bestandteile auftrennt. Die Stammzellfraktion wird separat gesammelt und anschließend fließt das Blut durch den zweiten Zugang wieder zurück in den Körper.

Es wird dabei das 2 – 3 fache des Blutvolumens separiert. Dazu werden ca. 4 Stunden benötigt. Die Zellseparation tut nicht weh, ist den Kindern jedoch manchmal lästig oder unangenehm, weil sie lange still liegen müssen. Um eine ausreichende Menge an Stammzellen zu sammeln, werden im Schnitt 5 – 6 Separationen (in 2 Zyklen) nötig sein. Vorraussetzung für eine erfolgreiche Stammzellseparation sind ausreichend Blutplättchen und ein genügend hoher Hämoglobinwert. Deshalb müssen vor oder zwischen den Separationen gelegentlich Erythrozyten- oder Thrombozytentransfusionen erfolgen.

An den Tagen der Stammzellseparation werden alle Patienten teil- oder vollstationär aufgenommen.

Nebenwirkungen der Wachstumsfaktorgabe:

1. Gelegentlich grippeartige Beschwerden wie Abgeschlagenheit, Muskel-, Kopf- und Glieder-Schmerzen, erhöhte Temperatur.

2. Der Wachstumsfaktor wird 1 – 2 x täglich unter die Haut gespritzt. An der Einspritzstelle kann es zu Entzündungen kommen.
3. In seltenen Fällen lassen sich trotz Wachstumsfaktor-Gabe keine Stammzellen mobilisieren, dann ist eine Hochdosistherapie ***nicht*** möglich.

Risiken der Stammzellseparation:

1. Durch größere Blutvolumenschwankungen können Kreislaufprobleme auftreten, die neben Lagerungsmaßnahmen mitunter einer medikamentösen Therapie bedürfen.
2. Da das Blut nicht gerinnen darf, fließt kontinuierlich ein Zusatz (Zitrat) in das Separationssystem, der dieses verhindert. Als Nebenwirkung bindet Zitrat Kalzium im Blut. Dadurch kann es zu einem akuten Kalzium-Mangel kommen, der zu Kribbeln und Taubheitsgefühl vor allem im Gesicht und an den Händen führt. Ebenso können Übelkeit, Muskelkrämpfe und Herzrhythmusstörungen auftreten. Um dem vorzubeugen, wird während der Separation regelmäßig Kalzium zugeführt.
3. Weitere beobachtete Elektrolytveränderungen sind ein vorübergehender Kaliummangel, der meistens keiner Therapie bedarf.
4. Das Blut wird zentrifugiert. Dadurch ist theoretisch eine Schädigung der Blutkörperchen möglich. Diese könnte zum Zerfall eines Teiles der roten Blutkörperchen (als Hämolyse bezeichnet) führen und ggf. eine Bluttransfusion erforderlich machen.
5. Da durch die Separation auch rote Blutkörperchen und Blutplättchen entzogen werden, ist eine anschließende Transfusion von roten Blutkörperchen (Erythrozyten) oder Blutplättchen (Thrombozyten) gelegentlich notwendig.
6. Bei langsamem Blutfluss oder häufiger Unterbrechung des Blutflusses kann es zur Gerinnselbildung (Thrombus) im Schlauchsystem kommen. In diesem Fall muss die Separation unterbrochen und alles getan werden, um das System wieder durchgängig zu bekommen, bzw. muss ggf. das gesamte System erneuert werden.

Briefkopf der behandelnden Klinik

IV.5.1.7 Einwilligung Autologe Blut-Stammzell-Sammlung

Patient:

Name: _____

Vorname:_____ geb. am:_____

Gesprächspartner:

□ Sorgeberechtigte/r:_____

□ Patient/in:_____

□ Arzt/Ärztin:_____

□ Zeuge:_____

☐ Die Aufklärung zur autologen Blut-Stammzell-Sammlung wurde mir ausgehändigt und ausführlich erläutert

☐ Mir wurde ausreichend Bedenkzeit eingeräumt und ich fühle mich ausreichend informiertund habe keine weiteren Fragen

☐ Ich bin darüber aufgeklärt worden, dass ich mein Einverständnis jederzeit und ohne Angabe von Gründen und ohne nachteilige Folgen widerrufen kann

☐ Ich habe die Aufklärung über die autologe Stammzell-Sammlung verstanden und habe keine weiteren Fragen mehr

☐ Ich willige hiermit in die autologe Stammzell-Sammlung ein

_____	_____	_____
Patient/in Name, Vorname	Datum	Unterschrift
_____	_____	_____
Sorgeberechtigte/r Name, Vorname	Datum	Unterschrift
_____	_____	_____
Sorgeberechtigte/r Name, Vorname	Datum	Unterschrift
_____	_____	_____
Aufklärender Arzt/Ärztin Name	Datum	Unterschrift
_____	_____	_____
Zeuge/in Name, Vorname	Datum	Unterschrift

Briefkopf der behandelnden Klinik

IV.5.1.8 Aufklärung Hochdosis-Chemotherapie mit Autologer Blut-Stammzell-Transplantation

Die konventionelle, auch als „normal dosiert“ bezeichnete Chemotherapie hat leider bei einigen bösartigen Erkrankungen des Kindes- und Jugendalters nur geringe Chancen auf eine langfristige Heilung des Patienten. Dazu gehören insbesondere Rezidive bösartiger Erkrankungen, primär metastasierende Tumoren und gegen herkömmliche Therapien resistente Tumoren.

In einigen dieser Fälle kann durch eine Therapieintensivierung, d.h. durch die Verabreichung einer hoch dosierten zytostatischen Chemotherapie mit anschließender autologer Stammzelltransplantation, der Patient langfristig geheilt, bzw. eine deutliche Lebensverlängerung erreicht werden. Zum heutigen Zeitpunkt liegen diesbezüglich allerdings erst begrenzte Erfahrungen vor. Es handelt sich bei der Behandlung um einen individuellen Heilversuch.

Voraussetzungen für den Beginn einer Hochdosischemotherapie sind:

1. Erreichen einer deutlichen Tumorverkleinerung bzw. kompletten Tumorbeseitigung durch normal dosierte Chemotherapie.
2. Den qualitativen und quantitativen Anforderungen entsprechende ausreichende Anzahl eigener Stammzellen.
3. Der Patient muss sich im stabilen Allgemein- und Ernährungszustand befinden. Es dürfen keine Hinweise in klinischen, chemischen oder röntgenologischen Untersuchungen auf schwere vor bestehende Organstörungen (z.B. des Herzens, der Lunge, der Leber oder der Nieren, schweres Anfallsleiden) bzw. auf lebensbedrohliche Komplikationen unter der normal dosierten Therapie bestehen.

Die Hochdosis-Chemotherapie ist stets eine dem Krankheitsbild des Patienten angepasste und eine auf den Ergebnissen der normal dosierten Therapie basierende und somit individuell festgelegte Therapie. Die hoch dosierte zytostatische Therapie wird über einen Zeitraum von 4 Tagen verabreicht. Im Anschluss daran erfolgt nach 96 bis 120 Stunden die Rückgabe, der bis zu diesem Zeitpunkt eingefrorenen Stammzellen über den zentralvenösen Katheter oder über eine Armvene.
Während der Verabreichung der Hochdosis-Chemotherapie können folgende Nebenwirkungen bzw. Komplikationen eintreten:

1. Übelkeit, Erbrechen, Schwächegefühl, Inappetenz
2. Herzkreislaufstörungen, Herzrhythmusstörungen, Bluthochdruck, Blutdruckabfall
3. Ausscheidungsstörungen der Niere
4. Allergische Reaktionen
5. Kopfschmerzen

Nach Rückgabe der Stammzellen finden diese den Weg zurück in das Knochenmark und bilden dort erneut ein funktionsfähiges Knochenmark, das in der Lage ist, reife Blutzellen (Erythrozyten, Leukozyten, Thrombozyten) in das Blut abzugeben. Die Neubildung der eigenen Blutzellen beginnt etwa 10-21 Tage nach Stammzellrückgabe. In der Zeit zwischen Stammzellrückgabe und der ausreichenden Neubildung der Blutzellen ist das eigene Knochenmark infolge der Hochdosis-Chemotherapie so geschädigt, dass eine Transfusion von Erythrozyten bei Blutarmut (Anämie) bzw. Thrombozyten (Blutplättchen) zur Vermeidung von Blutungen unumgänglich ist.

Die Veränderung der Leukozyten (weißen Blutzellen) führt zu erheblicher Infektanfälligkeit des Patienten. Fieber, schwere Infektionen der Atemwege, des Magen-Darm-Traktes oder des Blutes können die Folge sein und eine umfangreiche antibiotische, antimykotische bzw. antivirale Therapie erforderlich machen. Aus diesem Grund wird bereits zu Beginn der Hochdosis-Chemotherapie eine medikamentöse Infektionsprophylaxe zur Verminderung krankmachender Keime auf der Schleimhaut und der Haut des Patienten eingeleitet.

Durch die gleichzeitige Gabe eines Wachstumsfaktors (G-CSF) wird versucht, die Neubildung insbesondere der weißen Blutzellen zu beschleunigen.

Infolge der Hochdosis-Chemotherapie kann es zu weiteren kurzfristigen und langfristigen Nebenwirkungen kommen:

Kurzfristige Nebenwirkungen:

1. Haarausfall
2. Hautausschlag
3. geschwürige Schleimhautentzündungen im Mund und gesamten Magen-Darm-Trakt mit der Notwendigkeit einer Schmerzmittelgabe bzw. einer Ernährung über Infusionen wegen drohendem Gewichtsverlust
4. Infektionen der Haut, des Darmes (Durchfall), der Nieren und ableitenden Harnwege, der Lunge (Pneumonien) bzw. im Bereich des zentralvenösen Katheters
5. Schädigung von Nieren, Leber und Herz
6. Unverträglichkeitsreaktionen gegenüber Blutprodukten bei Bluttransfusionen
7. Auftreten von Gerinnungsstörungen mit Blutungsgefahr
8. Schädigung des Nervensystems bzw. Krampfanfälle

Langfristige Nebenwirkungen:

1. Wachstumsstörungen
2. Fertilitätsstörungen
3. erhöhtes Risiko für Zweittumoren
4. chronische Schädigung von Leber, Niere, Herz und Hirn

Bis zur Anhaltenden Erholung des Patienten erfolgt die Behandlung ausschließlich stationär (in der Regel 4 – 6 Wochen). Vor, während und im Anschluss an die Hochdosis-Chemotherapie mit autologer Stammzelltransplantation sind regelmäßige Blutuntersuchungen und mikrobiologische Untersuchungen und manchmal in Abhängigkeit von der Grunderkrankung und möglichen Komplikationen der Therapie auch röntgenologische und Ultraschalluntersuchungen notwendig.

Briefkopf der behandelnden Klinik

IV.5.1.9 Einwilligung Hochdosis-Chemotherapie mit Autologer Blut-Stammzell-Transplantation

Patient:

Name: _____

Vorname:_____ geb. am:_____

Gesprächspartner:

☐ Sorgeberechtigte/r:_____

☐ Patient/in:_____

☐ Arzt/Ärztin:_____

☐ Zeuge:_____

☐ Die Aufklärung zur Hochdosis-Chemotherapie mit autologer Stammzelltransplantation wurde mir ausgehändigt und ausführlich erläutert

☐ Mir wurde ausreichend Bedenkzeit eingeräumt und ich fühle mich ausreichend informiertund habe keine weiteren Fragen

☐ Ich bin darüber aufgeklärt worden, dass ich mein Einverständnis jederzeit und ohne Angabe von Gründen und ohne nachteilige Folgen widerrufen kann

☐ Ich habe die Aufklärung über die Hochdosis-Chemotherapie mit autologer Stammzell-transplantation verstanden und habe keine weiteren Fragen mehr

☐ Ich willige hiermit in die Hochdosis-Chemotherapie mit autologer Stammzelltransplantation ein

_____	_____	_____
Patient/in Name, Vorname	Datum	Unterschrift
_____	_____	_____
Sorgeberechtigte/r Name, Vorname	Datum	Unterschrift
_____	_____	_____
Sorgeberechtigte/r Name, Vorname	Datum	Unterschrift
_____	_____	_____
Aufklärender Arzt/Ärztin Name	Datum	Unterschrift
_____	_____	_____
Zeuge/in Name, Vorname	Datum	Unterschrift

Briefkopf der behandelnden Klinik

IV.5.1.10
Aufklärung vor genetischen Analysen gemäß Gendiagnostikgesetz (GenDG) – Diagnostische oder prädiktive Gentests

Die Deutsche Gesellschaft für Humangenetik (GfH) und der Berufsverband Deutscher Humangenetiker (BVDH) weisen ausdrücklich darauf hin, dass das Gendiagnostik Gesetz (GenDG) für alle genetischen Analysen gemäß GenDG eine ausführliche Aufklärung und eine schriftliche Einwilligung der Patienten voraussetzt. Vor vorgeburtlichen und prädiktiven (vorhersagenden) Analysen ist zusätzlich eine genetische Beratung erforderlich. Bitte lesen Sie diese Patienteninformation zur Aufklärung vor genetischen Analysen sorgfältig durch und sprechen Sie uns gezielt an, wenn Sie Fragen dazu haben.

Ihnen (oder einer Person, für die Sie sorgeberechtigt sind oder die Sie betreuen) wurde die Durchführung einer genetischen Analyse empfohlen, um die Fragestellung eines Prädispositions-Syndroms bei rhabdoiden Tumoren (RTPS) abzuklären. Diese besondere Ausprägung der Tumorerkrankung rhabdoider Tumoren tritt bei ungefähr 20-30% der Betroffenen auf.

Wir möchten Ihnen erläutern, welches Ziel diese Analysen haben, was bei genetischen Analysen geschieht und welche Bedeutung die Ergebnisse für Sie und Ihre Angehörigen erlangen können.

Eine genetische Analyse hat zum Ziel,
- die Chromosomen als Träger der Erbsubstanz mittels Chromosomenanalyse bzw. molekular-zytogenetischer Analyse,
- die Erbsubstanz selbst (DNS/DNA) mittels molekulargenetischer bzw. Array-Analyse oder
- die Produkte der Erbsubstanz (Genproduktanalyse)
- auf genetische Eigenschaften zu untersuchen, die möglicherweise die Ursache der bei Ihnen oder Ihren Angehörigen aufgetretenen oder vermuteten Erkrankung / Störung sind.

Als Untersuchungsmaterial dient eine Blutprobe (2 mal 5-9 ml), bei Kindern ist oft auch weniger ausreichend. Normalerweise bedingt eine Blutentnahme keine gesundheitlichen Risiken. Manchmal kann im Bereich der Einstichstelle eine Blutansammlung (Hämatom) oder extrem selten eine Nervenschädigung auftreten. In seltenen Fällen könnte auch eine Hautstanze als Untersuchungsmaterial verwendet werden.
Ein weiteres, nie völlig auszuschließendes Risiko besteht in der Möglichkeit einer Probenverwechslung. Es werden alle Maßnahmen unternommen, um diese und andere Fehler zu vermeiden.

Bei einer genetischen Analyse werden
- entweder bei einem konkreten Verdacht gezielt einzelne genetische Eigenschaften (z.B.

mittels molekularzytogenetischer, molekulargenetischer oder Genproduktanalyse)
- oder viele genetische Eigenschaften gleichzeitig im Sinne einer Übersichtsmethode (z.B. mittels Chromosomenanalyse, DNA-Array, Genomsequenzierung) untersucht.

In der Regel erfolgt eine sog. direkte Gendiagnostik. Hierbei werden die krankheitsverursachenden Veränderungen (Mutationen) in einer Erbanlage (einem Gen) direkt nachgewiesen bzw. ausgeschlossen. Wenn bei einer direkten Gendiagnostik keine Mutationen gefunden werden, können je nach Erkrankung bzw. Erbanlage trotzdem für die Erkrankung verantwortliche Mutationen in dem untersuchten Gen oder Mutationen in anderen Genen vorliegen.
Für bestimmte Erkrankungen kann eine indirekte Gendiagnostik durchgeführt werden, wenn keine direkte Gendiagnostik möglich ist. Bei der indirekten Gendiagnostik werden nicht die Mutationen selbst, sondern genetische „Marker" innerhalb oder in der Nachbarschaft des jeweiligen krankheitsverursachenden Gens untersucht.

Bedeutung der Ergebnisse
Wird eine krankheitsverursachende Eigenschaft (z.B. eine Mutation) nachgewiesen, hat dieser Befund in der Regel eine hohe Sicherheit. Wird keine krankheitsverursachende Mutation gefunden, können trotzdem für die Erkrankung verantwortliche Mutationen in dem untersuchten Gen oder in anderen Genen vorliegen. Eine genetische Krankheit bzw. Veranlagung für eine Krankheit lässt sich daher meist nicht mit völliger Sicherheit ausschließen. In diesem Fall werden wir versuchen, eine **Wahrscheinlichkeit** für das Auftreten der o.g. Erkrankung bzw. eine Veranlagung bei Ihnen bzw. Ihren Angehörigen abzuschätzen. Manchmal werden Genvarianten nachgewiesen, deren Bedeutung unklar ist. Dies wird dann im Befund angegeben und mit Ihnen besprochen. Eine umfassende Aufklärung über alle denkbaren genetisch (mit-)bedingten Erkrankungsursachen ist nicht möglich. Es ist auch nicht möglich, jedes Erkrankungsrisiko für Sie selbst oder Ihre Angehörigen (insbesondere für Ihre Kinder) durch genetische Analysen auszuschließen.
Prinzipiell können bei allen Untersuchungstechniken Ergebnisse auftreten, die nicht mit der eigentlichen Fragestellung im direkten Zusammenhang stehen, aber trotzdem von medizinischer Bedeutung für Sie oder Ihre Angehörigen sein können (sog. **Zufallsbefunde**). Insbesondere bei den Übersichtsmethoden wie Array-Analysen und Genomsequenzierungen können Zufallsbefunde auftreten, welche auf (Ihnen möglicherweise noch nicht bewusste) erhöhte Risiken für eventuell schwerwiegende, nicht vermeidbare oder nicht behandelbare Erkrankungen hinweisen. Sie können im Rahmen der Einwilligung bestimmen, ob bzw. unter welchen Umständen Sie über derartige Zufallsbefunde informiert werden möchten. Werden mehrere Familienmitglieder untersucht, ist eine korrekte Befundinterpretation davon abhängig, dass die angegebenen Verwandtschaftsverhältnisse stimmen. Sollte der Befund einer genetischen Analyse zum Zweifel an den angegebenen Verwandtschaftsverhältnissen führen, können Sie vorab darüber entscheiden, ob Ihnen die Untersuchungsergebnisse bzw. Teile davon nicht mitgeteilt werden sollen.
.
Widerrufsbelehrung
Sie können Ihre Einwilligung zur Analyse jederzeit ohne Angaben von Gründen ganz oder teilweise zurückziehen. Sie haben das Recht, Untersuchungsergebnisse nicht zu erfahren (Recht auf Nichtwissen), eingeleitete Untersuchungsverfahren bis zur Ergebnismitteilung jederzeit zu stoppen und die Vernichtung allen Untersuchungsmaterials sowie aller bis dahin erhobenen Ergebnisse zu verlangen.

Briefkopf der behandelnden Klinik

IV.5.1.11 Einwilligung zur Ausführung genetischer Analysen gemäß Gendiagnostikgesetz (GenDG) – Diagnostische und prädiktive Gentests

Das Gendiagnostikgesetz (GenDG) fordert für alle genetischen Analysen eine ausführliche Aufklärung und eine schriftliche Einwilligung sowie vor vorgeburtlichen und prädiktiven (vorhersagenden) Analysen zusätzlich eine genetische Beratung. Die Deutsche Gesellschaft für Humangenetik (GfH) und der Berufsverband Deutscher Humangenetiker (BVDH) empfehlen darüber hinaus, die u.g. Sachverhalte im Rahmen der Einwilligung zu klären.
Bitte lesen Sie diese Einwilligung sorgfältig durch und kreuzen Sie die für Sie zutreffenden Antworten an:

Ich habe eine allgemeine schriftliche Aufklärung (und ggf. zusätzlich spezielle schriftliche Aufklärungen) zu genetischen Analysen gemäß GenDG erhalten, gelesen und verstanden. Über die in Frage stehende Erkrankung und deren genetische Grundlage sowie die Aussagemöglichkeiten und Aussagegrenzen der Gendiagnostik in meinem speziellen Fall bin ich umfassend von einem Facharzt/einer Fachärztin, der/die sich im Rahmen seines/ihres Fachgebietes qualifiziert hat, aufgeklärt worden.
Mit meiner Unterschrift gebe ich meine Einwilligung zu den genetischen Analysen, die zur Klärung der in Frage stehenden Diagnose eines Prädispositions-Syndroms bei rhabdoiden Tumoren (RTPS) durch das beauftragte Labor bzw. von diesem beauftragten Kooperationspartner notwendig sind, sowie zu den dafür erforderlichen Blutentnahmen (maximal 2 x 9 ml). Es stand mir eine angemessene Bedenkzeit zur Verfügung und ich hatte ausreichend Gelegenheit, offene Fragen zu besprechen.
Der Gesetzgeber schreibt vor, dass Ihre personenbezogenen Daten und medizinischen Ergebnisse/Befunde nach 10 Jahren vollständig vernichtet werden müssen. Diese Informationen können jedoch auch danach noch für Sie oder Ihre Angehörigen (z.B. für Ihre Kinder) von großer Bedeutung sein. Mit Ihrer Einwilligung erlauben Sie, dass wir diese Daten auch über die gesetzlich vorgeschriebene Frist von 10 Jahren hinaus aufbewahren können.

	Ja	Nein
Sind Sie damit einverstanden, dass die für Sie oder Ihre Angehörigen relevanten Daten / Unterlagen bis zu 30 Jahre aufbewahrt und erst dann vernichtet werden?	☐	☐
Ich bin einverstanden, dass von mir erhobene Daten / Ergebnisse über die Erkrankung der rhabdoiden Tumoren in verschlüsselter (pseudonymisierter) Form für wissenschaftliche Zwecke genutzt und anonymisiert in Fachzeitschriften veröffentlicht werden.	☐	☐

Das Gendiagnostikgesetz verlangt, dass nicht verbrauchtes Untersuchungsmaterial nach Abschluss der Untersuchung vernichtet wird. Mit Ihrer Einwilligung darf es jedoch aufbewahrt werden. Bitte entscheiden Sie, ob und wie nicht verbrauchtes Untersuchungsmaterial verwendet werden darf:

Ich bin einverstanden mit der Aufbewahrung (Mehrfachnennungen möglich):

	Ja	Nein
- zum Zwecke der Nachprüfbarkeit der erhobenen Ergebnisse	☐	☐
- zur Verwendung für zukünftige neue Diagnosemöglichkeiten für meine o.g. Fragestellung	☐	☐
- Ich möchte über klinisch bedeutsame Ergebnisse informiert werden	☐	☐
- Übermittlung des Befundes durch einen in gleicher Weise kompetenten Vertreter der verantwortlichen ärztlichen Person, kann in Ausnahmefällen erfolgen	☐	☐
- zur Verwendung zum Zwecke der Qualitätssicherung, der studentischen Lehre, der Erforschung der o.g. Erkrankung und der Verbesserung der Diagnostik und Behandlung genetisch bedingter Erkrankungen in verschlüsselter (pseudonymisierter) Form.	☐	☐

Oder:

Ich wünsche die sofortige Vernichtung des nicht verbrauchten Untersuchungsmaterials nach endgültigem Abschluss der Untersuchung entsprechend GenDG.	☐	☐

Ich wurde darauf hingewiesen, dass ich meine Einwilligung jederzeit ohne Angaben von Gründen ganz oder teilweise zurückziehen kann, ohne dass mir daraus Nachteile entstehen und dass ich das Recht habe, Untersuchungsergebnisse nicht zu erfahren (Recht auf Nichtwissen). Mir ist bekannt, dass ich eingeleitete Untersuchungsverfahren bis zur Ergebnismitteilung jederzeit stoppen, die Vernichtung des Untersuchungsmaterials einschl. aller daraus gewonnenen Komponenten sowie aller bis dahin erhobenen Ergebnisse und Befunde verlangen kann.

Patient/in Name, Vorname	Datum	Unterschrift
Sorgeberechtigte/r Name, Vorname	Datum	Unterschrift
Sorgeberechtigte/r Name, Vorname	Datum	Unterschrift
Aufklärender Arzt/Ärztin Name	Datum	Unterschrift
Zeuge/in Name, Vorname	Datum	Unterschrift

Molekular Genetik	**Zytogenetik und Molekurargenetik**
Prof. Dr. R. Schneppenheim/PD Dr. Kordes Klinik und Poliklinik für Pädiatr. Hämatologie und Onkologie Universitätsklinikum Hamburg-Eppendorf Martinistr. 52 20246 Hamburg Telefon: 040 7410-54270 Telefax: 040 7410-54601 schneppenheim@uke.uni-hamburg.de	Prof. Dr. med. Reiner Siebert Institut für Humangenetik Institutsdirektor Universitätsklinikum Ulm EU-RHAB Referenzzentrum Albert-Einstein-Allee 11 89081 Ulm Telefax: 0731-500-65402 Telefon: 0731-500-65400 sekretariat.humangenetik@uni-ulm.de

Briefkopf der behandelnden Klinik

IV.5.1.12
Einwilligungserklärung zur zytogenetischen/molekular-zytogenetischen Untersuchung an Tumorgewebe (Chromosomenanalyse/ FISH-Analyse)

Bei zytogenetischen Untersuchungen werden die Chromosomen aus bestimmten Körperzellen - in diesem Fall Tumorgewebe - unter dem Lichtmikroskop analysiert. Untersuchungsziel ist der Nachweis oder der Ausschluss eines zahlenmäßig oder strukturell auffälligen Chromosomensatzes (Karyotyps). Bei rhabdoiden Tumoren, der bei Ihnen diagnostizierten Tumorerkrankung, findet sich in über 90% der Fälle eine Mutation des Chromosoms 22. Bei der molekularzytogenetischen Untersuchung (FISH-Analyse) wird mit Hilfe farbmarkierter DNA-Sonden, welche für bestimmte Chromosomen bzw. Chromosomenabschnitte spezifisch sind, die Anzahl bestimmter Chromosomen bzw. das Vorhandensein bestimmter Chromosomenabschnitte überprüft. Diese genetischen Untersuchungen erhöhen die Diagnosesicherheit Ihrer Tumorerkrankung und werden deshalb regelmäßig in Ergänzung zur feingeweblichen (histopathologischen) Untersuchung am Tumorgewebe durchgeführt.

Es kann gelegentlich vorkommen, dass die Chromosomensätze in verschiedenen Körperzellen oder Körpergeweben unterschiedlich sind. Man bezeichnet diesen Zustand als „chromosomales Mosaik". Ein unauffälliger Chromosomensatz in dem untersuchten Gewebe schließt deshalb nicht aus, dass in diesem Gewebe oder in anderen Geweben Zellen mit einem auffälligen Chromosomensatz vorliegen. Umgekehrt bedeutet ein auffälliger Befund im untersuchten Gewebe nicht notwendigerweise, dass der Chromosomensatz in allen anderen Zellen oder Geweben ebenfalls auffällig ist. Zur Chromosomenuntersuchung müssen in der Regel die Zellen zunächst in einer Zellkultur im Labor vermehrt werden. Durch diesen Vorgang können in einzelnen Zellen Chromosomenstörungen neu entstehen. Man spricht in diesen Fällen von „Kulturartefakten". Die Unterscheidung von Kulturartefakten ohne klinische Bedeutung von Mosaiken mit klinischer Bedeutung ist nicht in allen Fällen sicher möglich.

Strukturelle Chromosomenaberrationen (Veränderungen in der Struktur der Chromosomen) können nur soweit erkannt werden, wie es die Qualität des jeweiligen Präparates erlaubt.

Bei der Untersuchung des Chromosomensatzes wird regelmäßig auch das chromosomale Geschlecht der untersuchten Person festgestellt. In sehr seltenen Fällen stimmen das chromosomale und das äußerlich sichtbare Geschlecht nicht überein. Dies hat in der Regel biologische Ursachen und wird gegebenenfalls mit Ihnen besprochen.

Eine mögliche Fehlerquelle bei der medizinischen Labordiagnostik liegt in Probenverwechslungen. Es werden alle üblichen Sicherungsvorkehrungen getroffen, um Probenverwechslungen zu vermeiden.

Die Information zur zytogenetischen/ molekularzytogenetischen Untersuchung (Chromosomenanalysel/FISH-Analyse) habe ich gelesen, zur Kenntnis genommen und davon eine Kopie erhalten. Über die in Frage stehenden Störungen sowie die Aussagemöglichkeiten und Aussagegrenzen der Diagnostik in meinem speziellen Fall bin ich umfassend aufgeklärt

worden. Es wurde mir ausreichend Bedenkzeit sowie die Möglichkeit, offene Fragen zu besprechen, eingeräumt. Ich wurde darüber informiert, dass ich meine Einwilligung jederzeit widerrufen kann.

Ich wünsche die Durchführung einer zytogenetischen / molekularzytogenetischen Diagnostik am Tumorgewebe

❒ bei meinem Kind
❒ bei der von mir betreuten Person .....

Nicht verbrauchtes Untersuchungsmaterial soll nach Abschluss der molekulargenetischen Diagnostik

❒ nach der gesetzlichen Aufbewahrungspflicht von 10 Jahren vernichtet werden. Die aufbewahrte Probe wird ausschließlich bei erneutem Untersuchungsauftrag und erneuter Einwilligung verwendet
❒ für ggf. weitere wissenschaftliche Untersuchungen zu rhabdoiden Tumoren ohne zeitliche Befristung aufbewahrt werden.

Mir ist bekannt, dass ich meine Zustimmung zur Aufbewahrung der Probe jederzeit ohne Angabe von Gründen und ohne persönliche Nachteile widerrufen kann.

Patient/in Name, Vorname	Datum	Unterschrift
Sorgeberechtigte/r Name, Vorname	Datum	Unterschrift
Sorgeberechtigte/r Name, Vorname	Datum	Unterschrift
Aufklärender Arzt/Ärztin Name	Datum	Unterschrift
Zeuge/in Name, Vorname	Datum	Unterschrift

Falls Sie zusätzliche Informationen wünschen, können Sie mit den Leitern des EU-RHAB-Registers Kontakt aufnehmen:

Prof. Dr. Dr. Michael Frühwald I. Klinik für Kinder und Jugendliche Klinikum Augsburg Stenglinstraße 2 86156 Augsburg E-mail: michael.fruehwald@klinikum-augsburg.de Tel.: (0821) 400-9201 Fax.: (0821) 400-179201	PD Dr. Rhoikos Furtwängler Dept. of Pediatric Hematology and Oncology Saarland University Hospital 66421 Homburg/Saar Tel: (06841) 1628399 Fax: (06841) 1628424 E-Mail: rhoikos.furtwaengler@uks.eu

Briefkopf der behandelnden Klinik

IV.5.1.13 Aufklärung zur Verwendung von Liquor-Proben für das Forschungsprojekt Etablierung von Tumormarkern für Rhabdoidtumoren des Gehirns (AT/RT)

Herrn
Dr. med. K.Kerl
Tumorbiologie EURHAB
Institut für molekulare Tumorbiologie
Robert-Koch-Straße 43
48149 Münster

E-mail:
kornelius.kerl@ukmuenster.de

FAX: 0251 83 55318
Tel.: 0251 83 55303

Name des Patienten: _____

Geburtsdatum: _____

Sehr geehrte/r Frau/Herr _____

Bei Ihrem Sohn/Ihrer Tochter wird heute „Hirnwasser“ (Liquor) entnommen. Dabei wird aus technischen Gründen meist mehr Probenmaterial gewonnen, als für die Analysen notwendig ist. Wir bitten Sie, dass Sie das bei Ihrem Sohn/Ihrer Tochter entnommene Hirnwasser/Blut, das nicht für die Diagnostik gebraucht wird, für ein wissenschaftliches Forschungsprojekt zur Verfügung stellen.

Falls sich bei Ihrem Kind herausstellt, dass keine Auffälligkeiten im Hirnwasser nachzuweisen sind, wollen wir dieses gerne als „Kontrollgruppe“ für folgendes Forschungsprojekt verwenden.

Bei dem Forschungsprojekt mit dem Titel „Etablierung von Tumormarkern für Rhabdoidtumoren des Gehirns“ befassen wir uns mit der Untersuchung möglicher Marker für Hirntumoren, an denen Ärzte das Therapieansprechen im Hirnwasser beurteilen können.

Bei der Verwertung des Materials und der wissenschaftlichen Forschungsergebnisse werden die Bestimmungen zum Datenschutz streng beachtet. So wird der Name Ihres Kindes durch

eine Codenummer ersetzt, die eine Zuordnung zur Person nur über eine entsprechende Liste ermöglicht. Im Rahmen der Datenveröffentlichung wird der Name Ihres Kindes vollständig verschlüsselt (anonymisiert).

Nicht verarbeitete Proben werden in den Laboren der Universitätsklinik Münster in eingefrorenem Zustand in Stickstofftanks aufbewahrt und nach Abschluss des Projekts, frühestens jedoch nach 10 Jahren, vernichtet.

Aus den geplanten Experimenten ergibt sich keine Konsequenz für die Therapie Ihres Kindes. Es können aus den Ergebnissen auch keine Rückschlüsse auf den weiteren Verlauf der Erkrankung bei Ihrem Kind gezogen werden. Selbstverständlich können Sie Ihr Einverständnis jederzeit und ohne Angabe von Gründen und ohne nachteilige Folgen zurückziehen.

Briefkopf der behandelnden Klinik

IV.5.1.14 Einwilligung zur Verwendung von Liquor-Proben für das Forschungsprojekt Etablierung von Tumormarkern für Rhabdoidtumoren des Gehirns (AT/RT)

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48149 Münster

E-mail:
kornelius.kerl@ukmuenster.de

FAX: 0251 83 55318
Tel.: 0251 83 55303

Name des Patienten: _____

Geburtsdatum: _____

Hiermit erkläre ich mich einverstanden damit, dass Hirnwasser- und Blutproben, die meinem Sohn/meiner Tochter im Rahmen der Diagnostik entnommen werden, für oben genannte wissenschaftliche Studie verwendet werden können.

Es entstehen für meinen Sohn/meine Tochter keine zusätzlichen Risiken. Mir wird zugesichert, dass die entnommenen Proben nicht kommerziellen Zwecken dienen, ferner bleibt die ärztliche Schweigepflicht gewahrt. Ich bin darüber aufgeklärt worden, dass ich mein Einwilligung jederzeit und ohne Angabe von Gründen und ohne nachteilige Folgen widerrufen kann. Es wurde mir ausreichend Bedenkzeit sowie die Möglichkeit, offene Fragen zu besprechen, eingeräumt.

_____, den _____ _____

Ort, Datum Unterschrift Patient/Erziehungsberechtigter

_____, den _____ _____

Ort, Datum Aufklärender Arzt/Ärztin

_____

Unterschrift Arzt

IV.5.2 Information and Consent Forms – English

IV.5.2.1 Parents information

IV.5.2.2 Consent form data registration, exchange, participation in research projects and tumour banking
(form see chapter 9.4.2.1 Page 65)

IV.5.2.3 Consent form registry participation and standardized chemotherapy
(form see chapter 9.4.2.2 Page 69)

IV.5.2.4 Consent form autologous stem-cell harvest

IV.5.2.5 Consent form high-dose chemotherapy with autologous stem-cell-rescue

IV.5.2.6 ***Genetic testing as appropriate for individual countries***

Letter head of the treating facility

IV.5.2.1 Information for Parents and Patients

Dear patient, dear parents!

This document is intended to inform you about rhabdoid tumours, the current clinical treatment approaches, the aim and structure of our European Rhabdoid Registry and all associated affairs. We kindly ask for your cooperation in our endeavour to further our understanding of this enigmatic disease by participation in the European Rhabdoid Registry. The information contained herein is meant to supplement information given to you by your treating physician. Please highlight those sections you do not understand and need further explanation for discussion with your treating physicians.

What are Rhabdoid Tumors?

Rhaboid tumours are highly aggressive, difficult to treat tumours. In the current literature on these tumours inconsistent data are found on incidence, gender predominance, origin of disease and unified successful therapeutic strategies. Most published analyses consist of small case series or limited institutional experiences. Common treatment approaches are currently developed in the USA and in parallel in Europe. EU-RHAB thus contains a consented recommendation for treatment of rhabdoid tumours regardless of origin.

Rhabdoid tumours may be diagnosed in almost any anatomical region. Most commonly these tumours are detected in the brain, kidneys or soft tissue such as the liver or muscles. In the brain they are termed AT/RT (atypical teratoid, rhabdoid tumour), in the kidney RTK (rhabdoid tumour kidney) and in soft tissues MRT (malignant rhabdoid tumour). Rhabdoid tumours almost exclusively affect infants and other young children. 85% of RTK are diagnosed before the age of 2 years. The same is true for AT/RT. Rhaboid tumours of soft tissue (MRT) are in 60% diagnosed before the age of 10.

The signs and symptoms leading to the diagnosis are not different from other malignant disease. Children with RTK usually present with abdominal swelling, pain or blood in the urine. MRT are usually found when swelling of a certain region in the body appears. Infants with AT/RT present with lethargy, vomiting, failure to thrive or headaches. Often paralysis of cranial nerves or torticollis is noted. These signs usually lead to initiation of imaging studies such as ultrasound, MRI or CT scanning. This is usually succeeded by a diagnostic operation including tissue asservation. The histological diagnosis of a rhabdoid tumour may at times be challenging. Advances in genetic diagnoses have alleviated this problem in a way that a combination of histological stains and genetic analyses helps make the diagnosis in most cases.

Rhabdoid tumours are generally characterized by a mutation in all tumor cells of a gene called *SMARCB1/hSNF5/INI1*, which is located on chromosome 22. For a certain percentage of patients this defined mutation is detectable in all cells of their body. The evaluation of a blood sample from the patient, which helps to confirm this diagnosis, is called a diagnostic gene test according to the German gene diagnostics law “Gendiagnostikgesetz”. Unfortunately there seems to be a higher risk for the siblings of such patients, thus it is advisable to analyse also

the blood of the parents and all siblings. The investigation of healthy relatives is called a predictive gene test according to the German “Gendiagnostikgesetz”. A qualified doctor will give you detailed information about these tests and the possible consequences. After sufficient time for consideration you may decide about consenting to these investigations on a separate informed consent form.

Asservation of tissue and blood samples for the European Rhabdoid Registry

Tissue samples will be obtained at surgery and blood samples or cerebrospinal fluid will be taken for routine testing. We ask you that tissue and blood or CSF sample needed for diagnosis may be taken for research purposes. No unnecessary procedures will be performed to reach this goal. Tissue, blood and CSF samples will be collected in the different institutions listed under “Pathology” in your consent form until you revoke your consent. Tissue, blood and CSF will bei used for further analyses. We thus aim at improving save diagnosis, a better understanding of the origin of the disease and to evaluate future hopefully more successful therapeutic advances.

Current treatment approaches for affected children

Due to the rarity of cancer in children and to assure quality of clinical management children are in general treated on cooperative trials. These are organized by different groups of institutions. The common aim of these groups is to register patients in a uniform fashion and to treat patients on a consented schedule.

Despite aggressive treatment approaches including high dose chemotherapy and radiotherapy in small children the outcome of children with rhabdoid tumours remains dismal. Young age and inoperable lesions as well as metastases make therapy difficult. Children who can not be made free of tumour in general do not survive the disease for more than 2 years.

RTK have until recently been treated on protocols for Wilms tumours comprising intensive chemotherapy, aggressive surgery and local radiotherapy. Patients with MRT have been treated on soft tissue sarcoma protocols such as those issued by the CWS or EpSSG group and AT/RT have been treated on protocols for medulloblastoma. Most of these approaches have been proven unsatisfactory indicating the need for different treatment measures and a unified European concept.

The European Rhabdoid Registry – EU-RHAB - has been founded by a group of physicians with a special focus on rhabdoid tumours. These researchers and clinicians have defined the current status of our knowledge on rhabdoid tumours and thus summarized remaining questions. These are sought to be answered by registering data from affected patients within EU-RHAB. Furthermore a consensus therapeutic strategy has been formulated based on the current literature and the specialist´s experience.

Only with the help of affected patients and their families has it been possible to lay the foundation for our current knowledge, which is far from being complete or nearly satisfying our needs to treat our patients in the best possible way.

EU-RHAB - Therapeutic recommendations for patients with rhabdoid tumors
(All therapies described below have already been used for the treatment of rhabdoid tumors before opening the EU-RHAB Registry)

Ultimate goal of all approaches is the maximal safe surgical removal of all tumour tissue. Especially in the brain this may not be possible in all situations and tumour tissue must be left in place to safe the child from severe lasting damage.

Following surgery block-like chemotherapy is recommended using a rapid sequence of drugs. Once the child has reached at least 18 months radiotherapy is added to chemotherapy to improve local control.

Surgical removal is of very high importance. As this is often impossible in CNS rhabdoid tumours (AT/RT), it is recommended to supplement the intensive chemotherapy by intraventricular chemotherapy. This is done via a plastic reservoir (Ommaya or Rickham) implanted onto the skull connected to a tubing with direct access to the cerebrospinalfluid. In this way the tumour and cells that have been shed are directly exposed to the chemotherapeutic drugs.

Chemotherapy

Drugs which have been shown to be efficient in rhabdoid tumours are recommended for therapy. These are i.e. vincristin, doxorubicin, ifosfamide, carboplatinum, etoposide, cyclophosphamide and actinomycin-D. For rhabdoid tumours of the brain (AT/RT) it is also recommended to apply Methotrexate directly into the cerebrospinal fluid (CSF). Your physician will provide you with a detailed plan which medication will be given at which time points. It is recommended, that block-like chemotherapy is given until a safe age has been reached for radiotherapy to ensue. Currently it is unclear whether children who receive high dose chemotherapy fare better than those who receive conventional block-like chemotherapy. The decision which way to go will be discussed with you by your treating physician.

High dose chemotherapy is a form of chemotherapy which relies on very high doses which under normal circumstances damage the normal bone marrow in a way that makes regeneration very slow and puts the patient at risk due to prolonged periods of aplasia (absence of blood cells) and consequently infection. This obstacle is overcome by infusing previously generated stem cells from the affected child, which are reinfused following high dose chemotherapy.

Chemotherapy with or without high dose chemotherapy takes up to 20 weeks. The child will be able to leave the hospital for a few days in between blocks. An important aspect in the treatment of rhabdoid tumours is to not delay therapy for too long in order to prevent the tumour tissue from recovering.

Side effects of chemotherapy

Chemotherapeutic medications comprise a group of cell poisons which affect not only tumour cells but also other healthy tissues and organs. Apart from hair loss the following organs and organ systems may be affected: mucous membranes (inflammation), bone marrow (infection, anaemia, bleeding), kidneys, ears (hearing), nervous system (tremor, numbness…). Furthermore testes and ovaries may be affected. A rare but notable side effect is the formation of secondary malignancies. Drug doses according to age and body surface, exact timing and limiting the cumulative dose are attempts at minimizing the risk for such deleterious side effects. Supportive and preventive measures are taken to avoid symptoms such as nausea, vomiting or infection.

Radiotherapy

Radiotherapy is performed once age permits. This is highly dependent upon the age of the child and the extent of the disease. In general RT should be performed as early as possible. The radiotherapist will give you exact details on how radiotherapy is applied and what the potential side effects are.

Supportive Measures

Before, during and after therapy the patient will be assessed thoroughly for any signs of persistent or recurrent tumour but also for side effects of therapy. Adolescent girls and young women should undergo a pregnancy test before initiating chemotherapy to avoid damaging an unborn baby. Contraceptive measures should be taken until at least 6 months after administering chemotherapy.

Contributing data to EU-RHAB and being treated on a consensus treatment approach

Participation in EURHAB and adhering to the treatment suggested in this protocol is completely voluntary. Consent may be revoked at any time without any disadvantage to the patient. In case you revoke your consent you may also demand the destruction of the tissue and blood samples.

Confidentiality

To improve the diagnosis and management of children all over Europe affected by this rare disease hospitals and institutions all over Europe have agreed to pool data on the diagnosis, therapy, side effects of therapy and outcome of affected children. This is the only way how we can improve therapy in the long run. In order to pass the necessary information on to the EURHAB centre we ask for your kind consent that your treating physician may submit the data to our data centre. This also includes the data of genetic diagnostic and predictive tests, which - according to the German gene diagnostics law "Gendiagnostikgesetz" – are usually transmitted to the treating physician. The information will be used for scientific analyses only and will be handled with strict confidentiality. Your consent is again voluntary and may be revoked at any time without any disadvantages.

Alternative Treatments

Once novel developments indicating more successful therapeutic approaches are published, we will immediately inform you and potentially suggest a change in treatment.

Ethics committee approval

This protocol has been approved by the local ethics committee of the University of Muenster, Germany in the current form.

Address for questions about this protocol and rhabdoid tumours in general:

EU-RHAB

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E-mail: michael.fruehwald@klinikum-augsburg.de

Dr. Rhoikos Furtwängler
Dept. of Pediatric Hematology and
Oncology
Saarland University Hospital
66421 Homburg/Saar
Tel: (06841) 1628399
Fax: (06841) 1628424
E-Mail:
rhoikos.furtwaengler@uks.eu

Letter head of the treating facility

IV.5.2.4 Consent form autologous stem-cell harvest

Patient:

Surname: _____

Name:_____ Date of birth:_____

Gesprächspartner:

□ Legal representative:_____

□ Patient:_____

□ Principal investigator:_____

□ Witness:_____

What are „stem cells“?

Stem-cells are the „mother-cells“ of blood formation. Through multiplication and maturation they provide the renewal of the three different cell types: leucocytes, erythrocytes and platelets. Normally you find only a very limited number of stem-cells in the peripheral blood. To collect stem-cells one has to stimulate their mobilisation from the bone marrow into the peripheral blood. This is made possible through the application of so-called growth factors (i.e. G-CSF). Partly previous chemotherapy courses are used in stimulation, because it is well known that after chemotherapy an increased number of stem-cells can be detected in the peripheral blood. There is the possibility at any time or after a chemotherapy-course to stimulate the mobilisation of stem-cells in order to collect them from the blood.

Why do we collect stem cells?

In some types of malignant diseases in children and adults the conventional – „normally dosed“ -therapy unfortunately has only low chance of long-term healing. It is a well established method to increase the dose and with this the chance of healing. The increase of dose is only possible in substances which have as major side effect a suppression of the bone marrow. With very high doses of the cytotoxic compounds the patient would not be able to create blood-cells for a couple of weeks or not recover at all. With an autologous stem-cell-rescue these risk can be averted. This means that we can in propose a high-dose therapy if sufficient stem-cells have been collected in advance. Stem-cells are stored in fluid nitrogen at a temperature of -170° C.

How do we collect stem-cells?

The stem cells are mobilized by the application of a growth factor. Two big venous catheters are needed, which in case of small arm veins makes the implantation of a double-lumen central venous catheter necessary for separation and the following high dose therapy. Blood is taken of one lumen, flows through a cell separator which divides the blood in its components. The stem cells are collected separately followed by the re-infusion of the rest of the blood.

The 2 – 3 fold of the blood volume is separated. This takes about 4 hours. The stem cell separation does not hurt the children, sometimes it is however unpleasant or tiresome because the children have to lie still for a long time. To collect a sufficient number of stem-cells, 5 – 6 separations (two cycles) will be necessary. Enough platelets and sufficient haemoglobin are the requirements for a successful separation. Transfusion of red blood cells or platelets may be necessary before or in between the separations.

Stem cell separation is performed as in-patient only.

Effects of the application of growth factor:

1. flu-like symptoms, rise in temperature
2. The growth factor is injected into the subcutis (like insulin). Infections may occur at the site of injections.
3. In rare cases mobilisation of stem-cells is not possible despite the application of growth factor. In these cases high-dose therapy is not possible.

Risks of stem cell harvest:

4. Circulation problems may occur because of possible blood volume variation. These can be treated with positioning or with medical treatment.
5. Coagulation of the blood is inhibited with citrate flowing into the separation system. A side effect of citrate is the binding of calcium in the blood. This can lead to a calcium deficiency with prickling sensations or numbness of the face or the hands. Nausea, muscle cramps and arrhythmias can occur as well. To prevent this, the patient is supplied with calcium during the cell-separation.
6. Another electrolyte variation is a momentary deficiency of potassium, which normally needs no therapy.
7. The blood is centrifugated which implies the risk of damage to the blood cells. This can lead to haemolysis and can make a transfusion of erythrocytes necessary.
8. Sometimes a transfusion of red blood cells or platelets is necessary, because during the cell separation these cells are withdrawn, too.
9. In case of slow blood flow thrombi may form within the tubing. In these cases the separation has to be interrupted, the system has to be flushed and may potentially have to be removed.

□ I have understood the information about the stem cell harvest and have no further questions.

□ I agree, that the stem cell harvest will be performed.

_____

Date/Signature of patient and all legal representatives

_____ _____

Date/Signature of pricipal investigator Date/Signature of witness

Letter head of the treating facility

IV.5.2.5 Consent form high-dose chemotherapy with autologous stem-cell-rescue

Patient:

Surname: _____

Name: _____Date of birth: _____

Correspondence:

☐ Legal representative: _____

☐ Patient: _____

☐ Principal investigator: _____

☐ Witness: _____

In some types of malignant diseases in children the conventional – „normally dosed“ chemotherapy unfortunately has only low chances for long-term cure, especially in recurrent disease, primary metastases or tumors resistant to conventional therapies.

In some of these cases long term healing or relevant prolongation of life can be achieved with intensified therapy i.e. application of high doses of chemotherapy with following autologous stem cell rescue. Up to now the experiences with this therapy are limited. This treatment still is an individual attempt at a cure.

Requirements for the beginning of high-dose therapy:

1. Relevant reduction or total elimination of the tumor with conventional therapy.
2. Sufficient number of stem cells, regarding quality and quantity.
3. Stable general and nutritional condition of the patient. No signs of severe organ deficiencies or severe complications under conventional therapy must be found in clinical, chemical or radiological examinations (for example of the heart, lung, liver, kidney or seizures).

The high-dose therapy always is adapted to the individual course of the disease of the patient, based on the results of conventional dosed therapy and therefore is individually designed for the patient. The high dose therapy is applied over four days followed by the re-infusion of stem-cells after 96 to 120 hours. The stem cells are frozen until the re-infusion and are given over a central-venous or a peripheral-venous catheter.

During the application of the high-dose-therapy the following side-effects or complications may occur:

1. Nausea, vomiting, weakness, lack of appetite
2. Circulatory disorders of cardiac rhythm, hypertension or drop of blood pressure
3. Disorder of renal excretion
4. Allergic reaction
5. Headache

After re-infusion of stem cells, these find their way to the bone marrow and constitute a novel bone marrow, which is able to generate mature blood cells (red blood cells, neutrophiles and platelets). The renewal of blood cells starts about 10 to 21 days after stem cell rescue. During the time between stem cell rescue and sufficient own renewal of blood cells, the bone marrow is highly affected by the high-dose therapy. Therefore transfusions of erythrocytes in case of anemia and transfusions of platelets to prevent bleeding are inevitable.

Changes in the white blood count lead to relevant immunosuppression of the patient. Fever, severe infections of respiratory tract, of intestinal tract or of the blood can be the result and can make an antibiotic, antimycotic or antiviral therapy necessary. Therefore prophylactic measures are taken at the beginning of the high-dose-therapy in order to minimize pathogens on skin and mucosa.

With the simultaneous application of a growth factor (G-CSF) it is intended to accelerate the renewal of neutrophil leukocytes.

Following the high-dose-therapy the following short-term or long-term side effects may occur:

Short-term side effects:

1. Alopezia
2. Rash
3. Ulceration of the mucosa of mouth and entire GI-tract, which may make the application of analgetics and/or nutrition via infusion necessary.
4. Infection of skin, intestinum (diarrhea), kidney, ureter and bladder, lung (pneumonia) or of central-venous-catheter
5. Damage of kidney, liver and/or heart
6. Incompatibility reaction towards blood products in case of transfusions
7. Disorder of the clotting of the blood with the risk of bleeding
8. Damage of the central nervous system or seizures

Long-term side effects:

1. Disturbance of growth
2. Disturbance of fertility
3. increased risk of secondary malignancies
4. chronic damage of liver, kidney, heart or central nervous system

Until complete recovery of the patient the treatment will be performed as in-patient only (normally 4 – 6 weeks). Before, during and following the high-dose-chemotherapy with stem-cell-rescue regular blood samples will be taken as well as regular microbiological examinations. In some cases sonographic or radiologic examinations will be necessary.

☐ I have understood the information about the high-dose-chemotherapy and have no further questions.

☐ I agree, that the high-dose-therapy with stem-cell-rescue will be performed according to the recommendations of the European Rhabdoid Registry.

_____

Date/Signature of patient and/or all legal representatives

_____ _____

Date/Signature of principal investigator Date/Signature of witness

IV.5.2.6 Genetic testing as appropriate for individual countries

IV.6 Therapeutic interventions (overview)

IV.6.1 AT/RT (< 18 months)

IV.6.2 AT/RT (> 18 months)

IV.6.3 DOX – AT/RT

IV.6.4 ICE – AT/RT

IV.6.5 VCA – AT/RT

IV.6.6 High-dose AT/RT

IV.6.7 RTK/MRT (< 18 months)

IV.6.8 RTK/MRT (> 18 months)

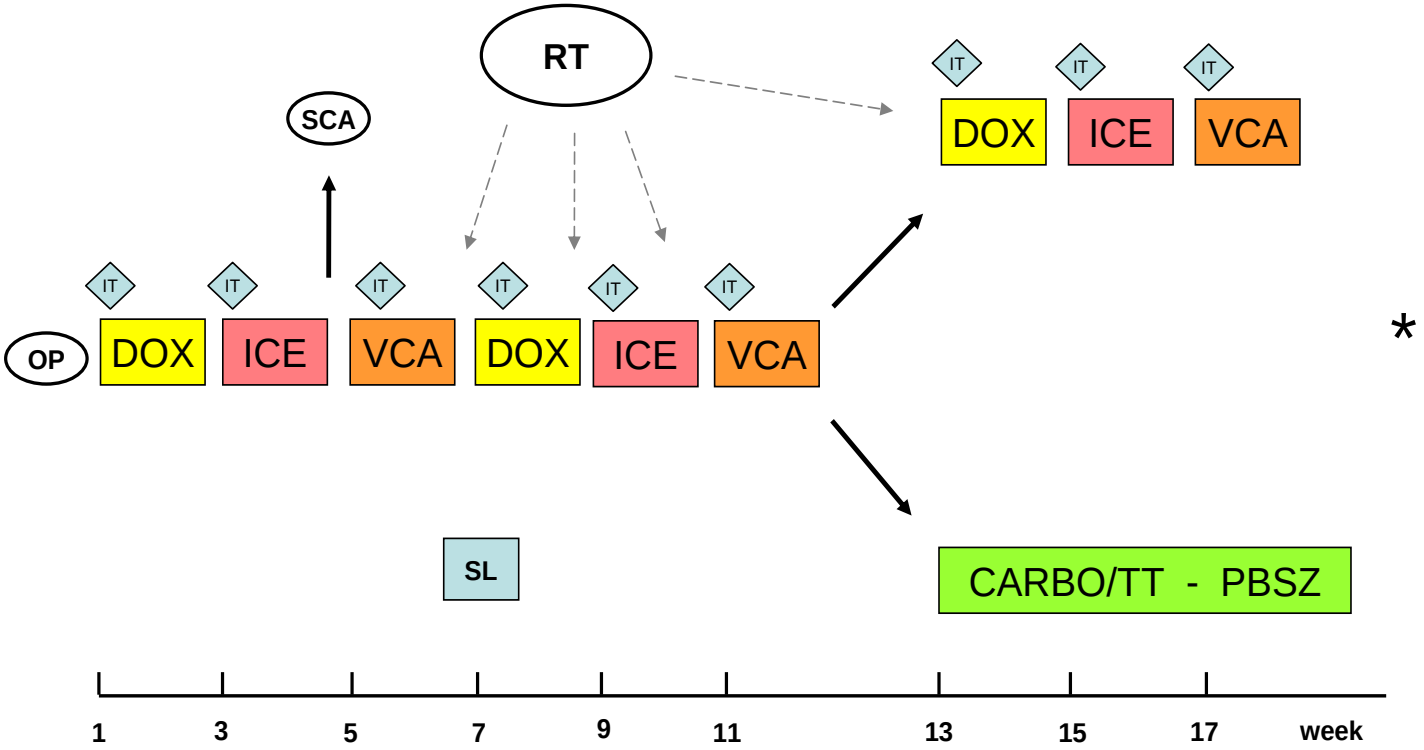
IV.6.9 DOX – RTK/MRT

IV.6.10 ICE – RTK/MRT

IV.6.11 VCA – RTK/MRT

IV.6.12 High-dose – RTK/MRT

IV.6.1 AT/RT (<18 months)



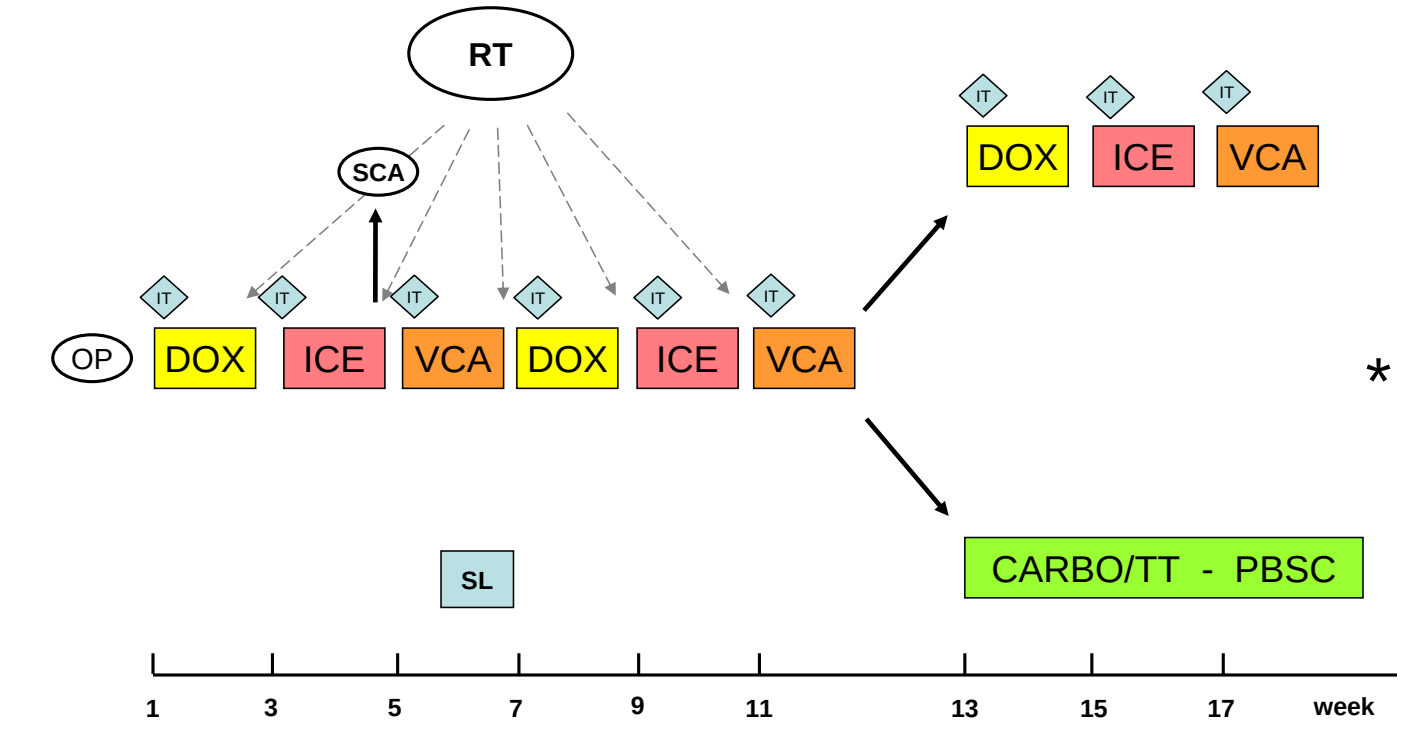
RT **Earliest opportunity, not in children below 18 months (delay DOX and actinomycin-D, replace by ICE and VC)**

SL **Consider second look surgery after each cycle**

* **In selected cases maintenance therapy may be considered**

IT **STOP once RT initiated**

IV.6.2 AT/RT (>18 months)



RT **Earliest opportunity (delay DOX and actinomycin-D, replace by ICE and VC)**

SL **Consider second look surgery after each cycle**

* **In selected cases maintenance therapy may be considered**

IT **STOP once RT initiated**

IV.6.3 DOX chemotherapy AT/RT

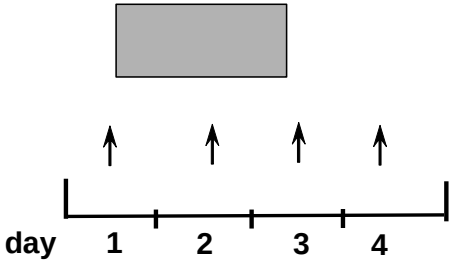
Weight = _____ kg
Height = _____ cm
BSA = _____ m ^{2}

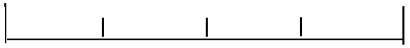
DOX (AT/RT)

Hospital:

Name: _____

dob: _____





date

Doxorubicin (24h) 37,5 mg/m² x 2 = |__|__|__| mg

MTX i.ventr. = |__|__| mg

Dose :	**<2Y**	**2-3Y**	**>3Y**
MTX (CSF levels)	**0,5**	**1**	**2 mg**

Please report CTC toxicity !!!

Dose reduction in children < 6 months or < 10 kg!
Dose in mg/kg: (Dose/m² divided by 30 x kg BW)

_____

signature
Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

IV.6.4 ICE chemotherapy AT/RT

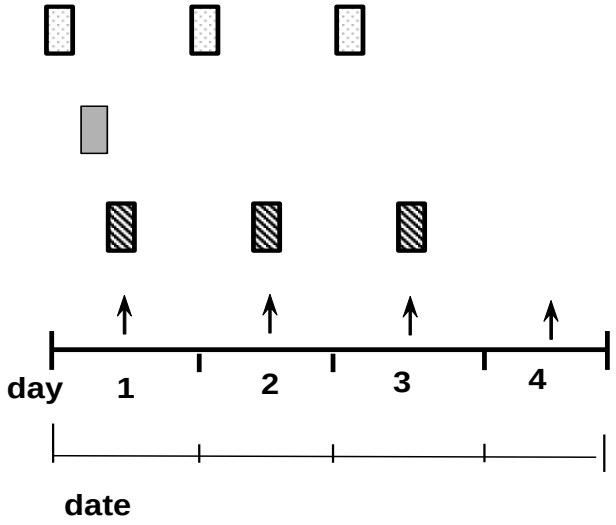
Weight = _____ kg
Height = _____ cm
BSA = _____ m ²

ICE (AT/RT)

Hospital:

Name: _____

dob: _____



Ifosfamide p.i. (1h) 2000mg/m² x 3 = |__|__|__|__| mg/D
with MESNA:
2.000mg/m² with hydration 3.000ml/m2/d

Carboplatinum (1h) 500mg/m² = |__|__|__| mg

Etoposide (1h) 100mg/m² x 3 = |__|__|__| mg/D

MTX i.ventr. = |__|__| mg

Dose :	**<2Y**	**2-3Y**	**>3Y**
MTX (CSF levels)	**0,5**	**1**	**2 mg**

Dose reduction in children < 6 months or < 10 kg!
Dose in mg/kg: (Dose/m² divided by 30 x kg BW)

Please report CTC toxicity !!!

signature

Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

IV.6.5 VCA chemotherapyAT/RT

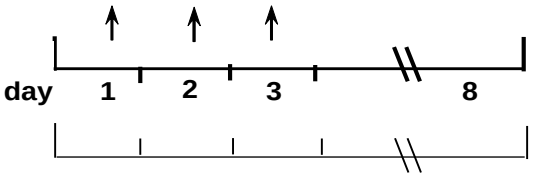
VCA (AT/RT)

Weight	= _____	kg
Height	= _____	cm
BSA	= _____	m ^{2}

Hospital:

Name: _____

dob: _____



VCR i.v. (max. 2mg) 1,5mg/m² x 2 = |__| , |__|__| mg

Act-D i.v. 25 µg/kg x 2 = |__| , |__|__| mg
Not during RT!

CPM p.i. (1h) 1500mg/m² = |__|__|__|__| mg
with MESNA:
day 1: 500 mg/m² bolus
day 1+2: 1500 mg/m² 24-h-infusion

MTX i.ventr. = |__|__| mg

Dose :	**<2y**	**2-3y**	**>3y**
MTX (CSF levels)	**0,5**	**1**	**2 mg**

Dose reduction in children < 6 months or < 10 kg!
Dose in mg/kg: (Dose/m² divided by 30 x kg BW)

Please report CTC toxicity !!!

_____

signature

Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

Dose reduction Actinomycin-D: For infants < 1 year or < 10 kg only 2/3 of the already reduced Actinomycin-D dose should be administered. If tolerated well individual increase of the dose in the next cycle may be considered.

IV.6.6 High-dose chemotherapy AT/RT

Weight = _____ kg
Height = _____ cm
BSA = _____ m ²

AT/RT
High-dose: Carbo / Thio

Hospital:

Name: _____

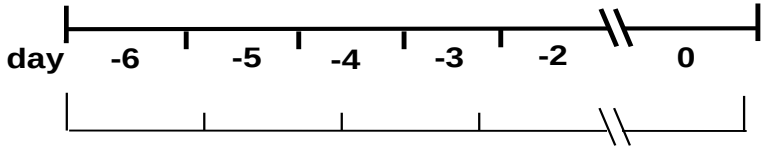
dob: _____

Carboplatinum 500mg/m²/d = |__|__|__| mg/d
day -6 to -4

Thiotepa 300 mg/m²/d 1 h = |__|__|__| mg/d
day -6 to -4

X

ASCT



date

Please report CTC toxicity !!!

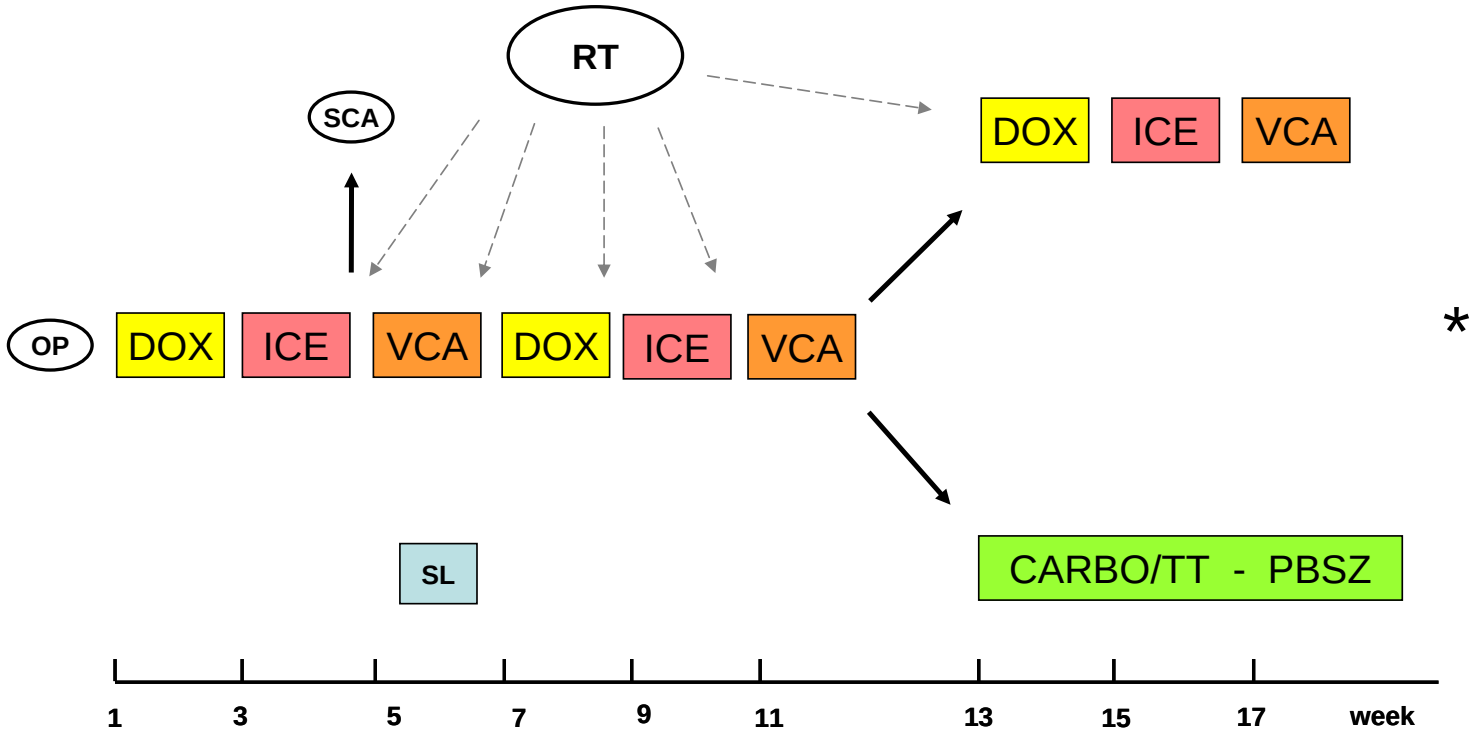
G-CSF: 150 µg/m²/d or 5 µg/kg/d s.c. day +5 until ANC > 1000/µl for 3 days

_____

signature

Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

IV.6.7 RTK / MRT < 18 months

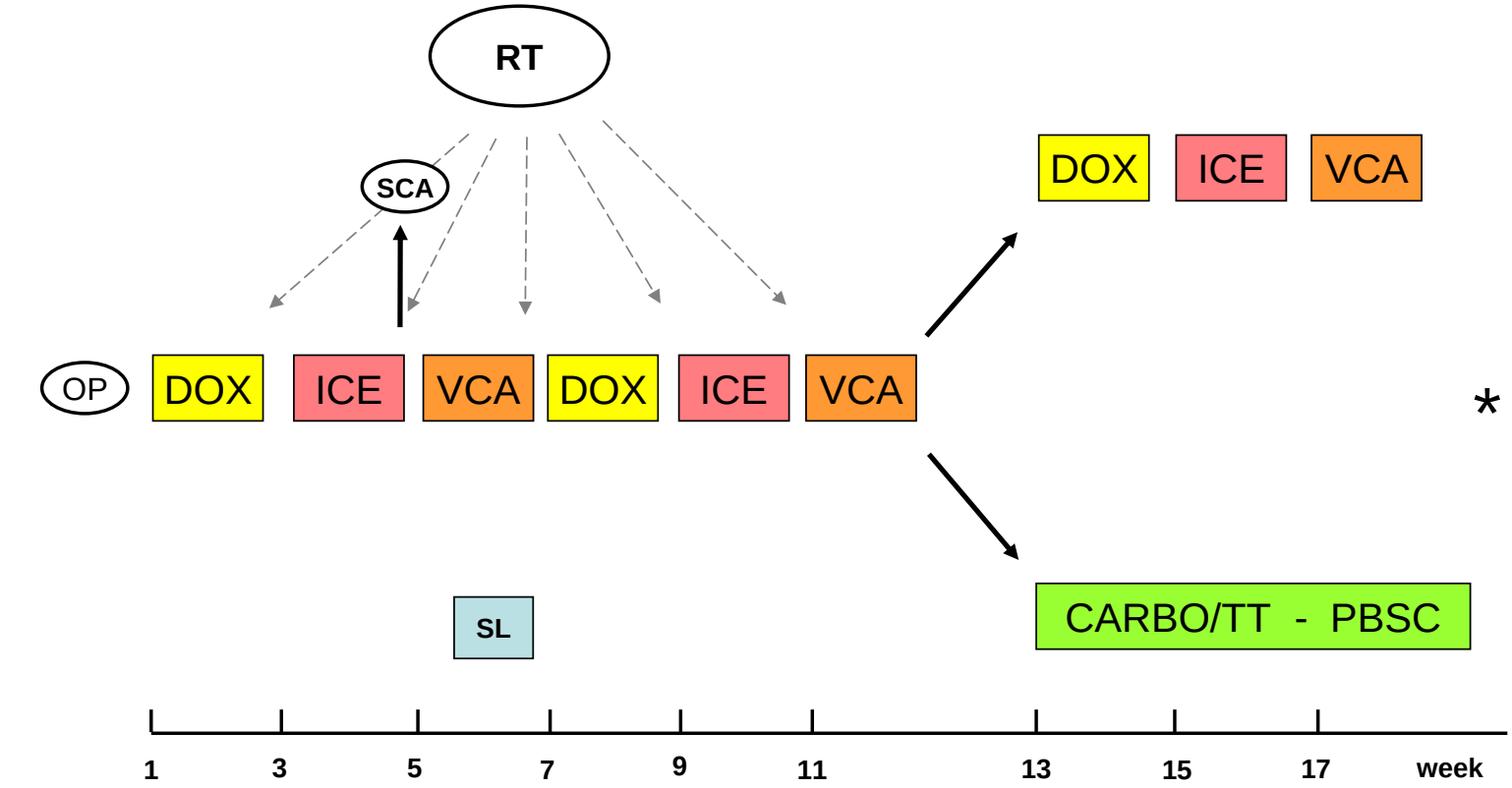


RT Earliest opportunity, not in children below 18 months (delay DOX and actinomycin-D, replace by ICE and VC)

SL Consider second look surgery after each cycle

* In selected cases maintenance therapy may be considered

IV.6.8 RTK / MRT > 18 months



RT **Earliest opportunity (delay DOX and actinomycin-D, replace by ICE and VC)**

SL **Consider second look surgery after each cycle**

* **In selected cases maintenance therapy may be considered**

IV.6.9 DOX chemotherapy RTK / MRT

Weight = _____ kg
Height = _____ cm
BSA = _____ m²

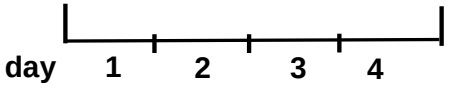
DOX (RTK / MRT)

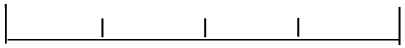
Hospital:

Name: _____

dob: _____

Doxorubicin (24h) 37,5 mg/m² x 2 = |__|__|__| mg





date

Please report CTC toxicity !!!

Dose reduction in children < 6 months or < 10 kg!
Dose in mg/kg: (Dose/m² divided by 30 x kg BW)

signature

Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

IV.6.10 ICE chemotherapy RTK / MRT

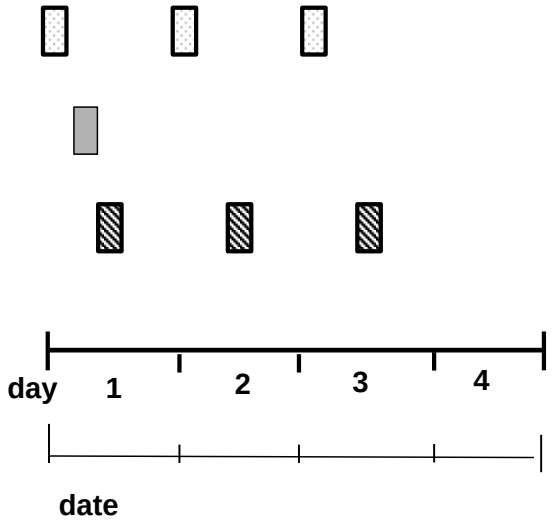
Weight = _____ kg
Height = _____ cm
BSA = _____ m^2

ICE (RTK / MRT)

Hospital:

Name: _____

dob: _____



Ifosfamide p.i. (1h) 2000mg/m^2 x 3 = |__|__|__|__| mg/D
with MESNA:
2.000mg/m^2 with hydration 3.000ml/m2/d

Carboplatinum (1h) 500mg/m^2 = |__|__|__| mg

Etoposide (1h) 100mg/m^2 x 3 = |__|__|__| mg/D

Dose reduction in children < 6 months or < 10 kg!
Dose in mg/kg: (Dose/m^2 divided by 30 x kg BW)

Please report CTC toxicity !!!

signature

Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

IV.6.11 VCA chemotherapy RTK / MRT

Weight = _____ kg
Height = _____ cm
BSA = _____ m^2

VCA (RTK / MRT)

Hospital:

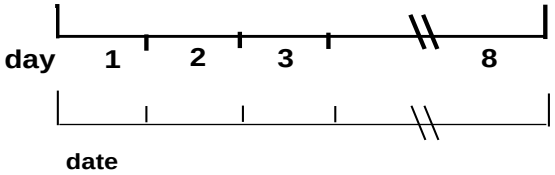
Name: _____

dob: _____

VCR i.v. (max. 2mg) 1,5mg/m² x 2 = |__| , |__|__| mg

Act-D i.v. 25 µg/kg x 2 = |__| , |__|__| mg
Not during RT!

CPM p.i. (1h) 1500mg/m² = |__|__|__|__| mg
with MESNA:
Day 1: 500 mg/m² bolus
Day 1+2: 1500 mg/m² 24-h-infusion



Dose reduction in children < 6 months or < 10 kg!
Dose in mg/kg: (Dose/m² divided by 30 x kg BW)

Please report CTC toxicity !!!

_____
signature
Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

Dose reduction Actinomycin-D: For infants < 1 year or < 10 kg only 2/3 of the already reduced Actinomycin-D dose should be administered. If tolerated well individual increase of the dose in the next cycle may be considered.

IV.6.12 High-dose chemotherapy RTK / MRT

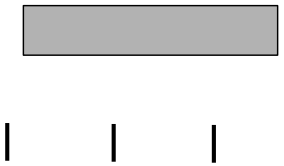
Weight	= _____	kg
Height	= _____	cm
BSA	= _____	m ^{2}

RTK / MRT
High-dose: Carbo / Thio

Hospital:

Name: _____

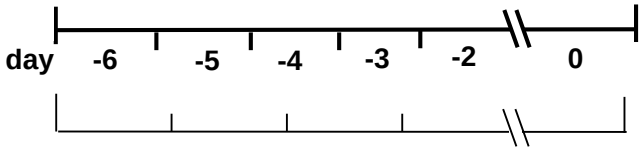
dob: _____



Carboplatinum 500mg/m²/d = |__|__|__| mg/d
day -6 to -4

Thiotepa 300 mg/m²/d 1 h = |__|__|__| mg/d
day -6 to -4

X **ASCT**



date

Please report CTC toxicity !!!

G-CSF: 150 µg/m²/d or 5 µg/kg/d s.c. day +5 until ANC > 1000/µl for 3 days

_____

signature

Send copy to local study centre or international coordinator
Prof. Dr. Dr. M. Frühwald, Augsburg

IV.7 Case Report Forms

IV.7.1 Case report forms - German

IV.7.1.1 Meldung

EU-RHAB
Meldung

Von Studienleitung auszufüllen:

EU-RHAB Pat.-Nr.....

Klinik: _____ Ort: _____

VERANTWORTLICHER ARZT: .....

NACHNAME D. PATIENTEN/IN: .....

VORNAME D. PATIENTEN/IN: .....

GEBURTSDATUM ..... Tag Monat Jahr

GESCHLECHT

☐ männlich
☐ weiblich

DATUM DER DIAGNOSTISCHEN BIOPSIE ODER INITIALEN OP	Tag Monat Jahr
Histologische Diagnose	☐ MRT (Weichteil) ☐ RTK (Niere) ☐ AT/RT (ZNS) ☐ Sonstiges: _____
Vorbehandlung (außer OP) ?	☐ **Nein** ☐ **Ja**
Maligne Vorerkrankung	☐ **Nein** ☐ **Ja**
Medizinische Kontraindikation gegen Chemotherapie	☐ **Nein** ☐ **Ja**
Einverständniserklärung zur Studienteilnahme und zur Übermittlung/Speicherung der Daten **liegt vor**	☐ **Nein** ☐ **Ja**

_____ _____ _____

Stempel der Klinik **Datum** **Unterschrift**

Meldung durch:

Name: _____ **Telefon:** _____

Fax: _____ **Email:** _____

Bitte senden Sie diesen Bogen per Fax an: 0821 400 179340

IV.7.1.2 Ersterhebung

EU-RHAB
Ersterhebung

Studienzentrale:
Kinderklinik für Kinder und Jugendliche, Klinikum Augsburg, Stenglinstr.2, 86156 Augsburg,
Tel.: 0821/400-9340, FAX: 0821/400-179340, E-mail: eurhab@klinikum–augsburg.de
- in Zusammenarbeit mit dem Deutschen Kinderkrebsregister am IMBEI, 55101 Mainz -
- in Zusammenarbeit mit der GPOH -

Name/Vorname _____ **Geschlecht** ⌊_⌋ (m = 1, w = 2) **Geburtsdatum** ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (TT.MM.JJJJ)

Pat. Nr. *(Studie)* ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Klinik *(DKKR)* ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

MaligID *(DKKR)* ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

GPOH-PID ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

!! Bitte beachten Sie, dass vor der Weiterleitung dieses Bogens die schriftliche Einwilligung zur Übermittlung der Daten und zur Speicherung vorliegen muss!!

Anamnese

Anlass der Erfassung

- ☐ Tumorsymptomatik führte zum Arztbesuch
- ☐ Vorsorgeuntersuchung (U1-U9)
- ☐ Befunde bei anderweitiger Untersuchung
- ☐ Pränatale Diagnostik

Allgemeinzustand bei Diagnosestellung

- ☐ Normale Aktivität, keine zusätzliche Hilfe erforderlich
- ☐ Geringe Beeinträchtigung der Aktivität, jedoch keine zusätzliche Hilfe erforderlich
- ☐ Altersentsprechende Aktivität stark eingeschränkt (z. B. kein regelmäßiger Kindergarten-/Schulbesuch möglich)
- ☐ Bettlägerig, pflegebedürftig
- ☐ Intensive Behandlung notwendig, schwerstkrank, moribund

Diagnose in anderer Klinik ☐ Nein ☐ Ja, in: _____

Teilnahme an Therapiestudie ☐ Nein ☐ Ja, an EU-RHAB ☐ Ja, an: _____

Vortherapie in anderer Klinik ☐ Nein ☐ Ja, in _____

Art der Vortherapie

- ☐ Chemotherapie
  - ☐ nach CWS ☐ nach HIT
  - ☐ nach SIOP 2001 (Nephroblastom)
  - ☐ Andere: _____
- ☐ Operation
  - ☐ Biopsie ☐ komplette Resektion
  - ☐ inkomplette Resektion
- ☐ Strahlentherapie

Frühestes Auftreten des eindeutig auf den Tumor zu beziehenden Symptoms Wann? ⌊_⌊_⌊_ Wochen vor Klinikaufnahme

Welches? _____

Vorausgegangene Tumorerkrankung ☐ Nein ☐ Ja, welche: _____

Hämatologische Vorerkrankung ☐ Nein ☐ Ja, welche: _____

Immundefekt ☐ Nein ☐ Ja, welcher: _____

Chronischer Virusinfekt ☐ Nein ☐ Ja, welcher: _____

Chromosomenaberration ☐ Nein ☐ Ja, welche: _____

Syndrom (z. B. M. Down, Rhabdoid-Tumor-Prädispositions-Syndrom) ☐ Nein ☐ Ja, welches: _____

Andere dauerhafte Vorerkrankungen ☐ Nein ☐ Ja, welche: _____

Familienanamnese

Mehrfachnennung möglich

Familiäre Belastung (Leukämie, Tumor-, Immunmangel-Erkrankungen, Syndrome)

☐ Nein

☐ Ja, Eltern Wer? Welche? _____

☐ Ja, Geschwister Wer? Welche? _____

☐ Ja, Sonstige Wer? Welche? _____

Geburtsjahr der Eltern Mutter: ⌊_⌊_⌊_⌊_ Vater: ⌊_⌊_⌊_⌊_

Anzahl Geschwister ⌊_⌊_ Eineiiger Mehrling? ☐ Nein ☐ Ja

Diagnose

Datum der stat. Aufnahme ⌊_⌊_ . ⌊_⌊_ . ⌊_⌊_⌊_⌊_ (TT.MM.JJJJ)

Datum der Diagnose (Tumorerkrankung) ⌊_⌊_ . ⌊_⌊_ . ⌊_⌊_⌊_⌊_ (TT.MM.JJJJ)

Datum der Diagnose Rhabdoid-Tumor *(Referenzhistologie!)* ⌊_⌊_ . ⌊_⌊_ . ⌊_⌊_⌊_⌊_ (TT.MM.JJJJ)

Art der Diagnose

☐ Primärdiagnose

☐ Rezidivdiagnose / Zweitmalignom

Histologischer Befund – Lokaler Pathologe (bitte beifügen)

Datum des Befundes ⌊⌊⌋⌊⌋⌋.⌊⌊⌋⌊⌋⌋.⌊⌊⌋⌊⌋⌊⌋⌊⌋⌋ (TT.MM.JJJJ) **Journal-Nr.** ⌊⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌋

Institut _____

Beurteilung Immunhistochemie (lokaler Pathologe)

- ☐ INI1 Expression erhalten
- ☐ INI1 Expression verloren

Beurteilung Histologie (lokaler Pathologe)

- ☐ MRT (Weichteil)
- ☐ RTK (Niere)
- ☐ AT/RT (ZNS)
- ☐ Sonstiges _____

Histologischer Befund – Referenzpathologe (bitte beifügen)

Versand an Referenzpathologen

- ☐ Nein
- ☐ Ja, ist geplant
- ☐ Ja, ist erfolgt
  - ☐ nach Bonn
  - ☐ nach Kiel
  - ☐ nach Münster
  - ☐ Sonstige _____

Datum des Befundes ⌊⌊⌋⌊⌋⌋.⌊⌊⌋⌊⌋⌋.⌊⌊⌋⌊⌋⌊⌋⌊⌋⌋ (TT.MM.JJJJ) **Journal-Nr.** ⌊⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌋

Institut _____

Beurteilung Immunhistochemie (Referenzpathologe)

- ☐ INI1 Expression erhalten
- ☐ INI1 Expression verloren

Beurteilung Histologie (Referenzpathologe)

- ☐ MRT (Weichteil)
- ☐ RTK (Niere)
- ☐ AT/RT (ZNS)
- ☐ Sonstiges _____

Primärtumor – Bildgebung initial (Befunde bitte beifügen)

Datum der Bildgebung ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Mit welchem bildgebenden Verfahren wurde der Primärtumor diagnostiziert?

Primärtumor ☐ CT nativ ☐ CT mit KM ☐ MRT nativ ☐ MRT mit KM ☐ andere Methode_____

Primärtumor – Tumorvolumen initial

Tumorgröße ⌊_⌊_⌋ , ⌊_⌋ **x** ⌊_⌊_⌋ , ⌊_⌋ **x** ⌊_⌊_⌋ , ⌊_⌋ cm (Schicht mit größter Tumorausdehnung)

Bilder an Referenzradiologie versandt: ☐ Nein ☐ Ja

Primärtumor - Lokalisation

ZNS
☐ Großhirn-Hemisphäre ☐ Pons
☐ Cerebellum ☐ Spinal
☐ Stammganglien
☐ Sonstige (bitte Angabe) _____
☐ rechts ☐ links ☐ beidseits ☐ Mittellinie

Niere ☐ rechts ☐ links ☐ beidseits

Weichteile ☐ rechts ☐ links ☐ beidseits ☐ Mittellinie

Bitte genaue Lokalisation in nachfolgender Tabelle ankreuzen:

Region	Lokalisation	Code	Region	Lokalisation	Code
Becken	Beckenweichgewebe	15		Gesicht	56
	Gesäß	16		Sonstige *	50
	Hüfte / Inguinalregion	17	Obere Extremitäten	Oberarm	67
	Perineum	18		Ellbogen	68
	Sonstige *	10		Unterarm	69
Abdomen	Leber	21		Handgelenk	70
	Intra-abdominell (außer Leber)	22		Hand	71
	Retroperitoneal	23		Sonstige *	60
	Abdominalwand	24	Untere Extremitäten	Oberschenkel	88
	Sonstige *	20		Knie	89
Thorax	Schulter	45		Unterschenkel	90
	Axilla	46		Knöchel	91
	Thoraxwand	47		Fuß	92
	Sonstige *	40		Sonstige *	80
Kopf-Hals-Bereich	Kopfhaut	54	Primärtumor nicht bekannt		99
	Hals	55			

* Bei „Sonstige“ bitte nähere Angabe hier: _____

Metastasen – Bildgebung

☐ MRT-Ganzkörper ☐ CT (Region)_____ ☐ PET - CT

☐ MRT-Schädel ☐ CT-Thorax ☐ PET - MRT

☐ MRT-Abdomen ☐ CT-Ganzkörper ☐ Knochenszintigraphie

☐ MRT-Spinal ☐ Andere_____

Metastasen – Lokalisationen außerhalb des ZNS

Mehrfachnennung möglich

☐ Nein

☐ Ja, Knochen / Wo? _____

☐ Ja, Lymphknoten / Wo?_____

☐ Ja, Knochenmark ☐ Ja, Leber ☐ Ja, Mediastinum

☐ Ja, Lunge ☐ links ☐ rechts ☐ beidseits

☐ Ja, Niere ☐ links ☐ rechts ☐ beidseits

☐ Ja, Sonstige (bitte Angabe) _____

☐ Nicht untersucht

wenn ja, Anzahl der Metastasen ⌊_⌊_⌋

Metastasen – Lokalisationen im ZNS (solide)

Mehrfachnennung möglich

☐ Nein

☐ Ja, supratentoriell

☐ Ja, infratentoriell (Ø Hirnstamm)

☐ Ja, Pons

☐ Ja, Sonstige (bitte Angabe) _____

☐ Nicht untersucht

☐ Ja, Medulla oblongata

☐ Ja, spinal extramedullär

☐ Ja, spinal intramedullär

wenn ja, Anzahl der Metastasen ⌊_⌊_⌋

Meningeose (Bildgebung)

Mehrfachnennung möglich

☐ Nein

☐ Ja, supratentoriell

☐ Ja, infratentoriell

☐ Nicht untersucht

☐ Ja, spinal

☐ Ja, Sonstige (bitte Angabe) _____

Tumorzellen im Liquor (nur AT/RT)

Bitte luftgetrocknete Liquorzytozentrifugenpräparate - möglichst ungefärbt - an Studienzentrale schicken !

Liquor verschickt? ☐ Nein ☐ Ja

Datum der Liquorentnahme ⌊_⌊_⌋.⌊_⌊_⌋.⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Tumorzellen im Liquor unmittelbar vor Beginn der postoperativen Therapie

Lumbal ☐ Nein ☐ Ja ☐ Nicht untersucht

Ventrikulär ☐ Nein ☐ Ja ☐ Nicht untersucht

Primäres chirurgisches Vorgehen (OP-Bericht bitte beifügen)

Datum der Operation ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Operateur / Klinik _____

Art der Operation

- ☐ Biopsie, offen
- ☐ Biopsie, stereotaktisch
- ☐ Partielle Resektion (< 50%)
- ☐ Partielle Resektion (> 50%)
- ☐ Subtotale Resektion (< 10% Rest)
- ☐ Totale Resektion (kein sichtbarer Resttumor)

Wenn primär Metastasen nachgewiesen wurden:

Metastasenresektion ☐ Nein ☐ Ja, komplett ☐ Ja, inkomplett

Datum ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Liquorableitung bleibend ☐ Nein ☐ Ja, v. p. ☐ Ja, v. a.

Verstümmelnde Operation/ Amputation ☐ Nein ☐ Ja, _____

Operationsfolgen / Komplikationen

- ☐ Nein
- ☐ Ja, neurologisch (bitte nähere Angabe) _____
- ☐ Ja, nicht neurologisch (bitte nähere Angabe) _____

Frühe postoperative Bildgebung Primärtumor (Befunde bitte beifügen)

Datum der Bildgebung ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Verfahren Primärtumor ☐ CT nativ ☐ CT mit KM ☐ MRT nativ ☐ MRT mit KM

Größe ⌊_⌊_⌋ , ⌊_⌋ cm senkrecht dazu ⌊_⌊_⌋ , ⌊_⌋ cm

Laborbefunde bei Diagnosestellung

Tumormarker:

Katecholamine im Serum	☐ erhöht	☐ nicht erhöht	☐ nicht durchgeführt
Katecholamine im Urin	☐ erhöht	☐ nicht erhöht	☐ nicht durchgeführt

SMARCB1/hSNF5/INI1-Deletion:

Bitte Material (**Blut, Tumorgewebe**) **AT/RT** an Prof. Hasselblatt schicken
Bitte Material (**Tumorgewebe**) **MRT/RTK** an Dr. Vokuhl schicken
Bitte Material (**Blut**) **MRT/RTK** an Prof. Siebert und PD Dr. Kordes schicken

aus Tumorgewebe:	☐ erfolgt, in: _____		☐ nicht eingeleitet
Methode	☐ Immunhistochemie	☐ Molekulargenetik	☐ Zytogenetik
aus Blut oder DNA	☐ erfolgt, in: _____		☐ nicht eingeleitet
Methode	☐ Immunhistochemie	☐ Molekulargenetik	☐ Zytogenetik

Organfunktion bei Diagnose

Herzfunktion ☐ normal ☐ verändert: _____

Nierenfunktion ☐ normal ☐ verändert: _____

Beginn der Protokolltherapie EU-RHAB

Datum ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Mit: ☐ Chemotherapie ☐ Operation ☐ Radiatio ☐ andere: _____

Bemerkungen:

Patient lebt am: ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Patient verstorben am: ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Stempel der Klinik	Datum	Unterschrift

Angaben durch:

Name: _____ **Telefon:** _____

Fax: _____ **Email:** _____

Anhang für AT/RT – Teil 1

PRÄoperative neurologische Untersuchung (nur auszufüllen bei AT/RT)

Datum der Untersuchung ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Hirndrucksymptome ☐ Nein ☐ Erbrechen ☐ Vorgewölbte Fontanellen
Mehrfachnennung möglich ☐ Kopfschmerzen ☐ Wesensveränderung
☐ Stauungspapillen

Bewußtseinsstörungen ☐ Nein ☐ Somnolenz
☐ Stupor
☐ Coma

Cerebrale Anfälle ☐ Nein ☐ Ja

Störungen neuropsychologischer Funktionen ☐ Nein ☐ Ja, welche _____

Hirnnervenausfälle ☐ Nein ☐ Ja, Symptom/Seite _____ HN-Nr. _____
☐ Ja, Symptom/Seite _____ HN-Nr. _____
☐ Ja, Symptom/Seite _____ HN-Nr. _____

Störung der Grobmotorik ☐ Nein ☐ Monoparese - Arm rechts ☐ Monoparese - Arm links
☐ Monoparese - Bein rechts ☐ Monoparese - Bein links
☐ Hemiparese rechts ☐ Hemiparese links
☐ Paraparese ☐ Tetraparese

falls Querschnittslähmung ☐ Inkomplett ☐ Komplett
Höhe der Qu.-lähmung _____

Störung der Koordination ☐ Nein ☐ Extremitätenataxie ☐ Nystagmus
Mehrfachnennung möglich ☐ Intentionstremor ☐ Rumpfataxie
☐ Sonstige Störung _____

Extrapyramidale Bewegungsstörung ☐ Nein ☐ Ja _____

Störung der Sensibilität ☐ Nein ☐ Ja _____

Störung vegetativer Funktionen ☐ Nein ☐ Ja _____

Somatische Auffälligkeiten ☐ Nein ☐ Ja _____

Neuroendokrinologische Auffälligkeiten ☐ Nein ☐ Ja _____

Körperlänge ⌊_⌊_⌊_⌋ Cm **Körpergewicht** ⌊_⌊_⌋ , ⌊_⌋ kg **Kopfumfang** ⌊_⌊_⌋ , ⌊_⌋ cm

Anhang für AT/RT- Teil 2

POSToperative neurologische Untersuchung (nur auszufüllen bei AT/RT)

Datum der Untersuchung ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Hirndrucksymptome ☐ Nein ☐ Erbrechen ☐ Vorgewölbte Fontanellen
Mehrfachnennung möglich ☐ Kopfschmerzen ☐ Wesensveränderung
☐ Stauungspapillen

Bewußtseinsstörungen ☐ Nein ☐ Somnolenz
☐ Stupor
☐ Coma

Cerebrale Anfälle ☐ Nein ☐ Ja

Störungen neuropsychologischer Funktionen ☐ Nein ☐ Ja, welche _____

Hirnnervenausfälle ☐ Nein ☐ Ja, Symptom/Seite _____ HN-Nr. _____
☐ Ja, Symptom/Seite _____ HN-Nr. _____
☐ Ja, Symptom/Seite _____ HN-Nr. _____

Störung der Grobmotorik ☐ Nein ☐ Monoparese - Arm rechts ☐ Monoparese - Arm links
☐ Monoparese - Bein rechts ☐ Monoparese - Bein links
☐ Hemiparese rechts ☐ Hemiparese links
☐ Paraparese ☐ Tetraparese

falls Querschnittslähmung ☐ Inkomplett ☐ Komplett
Höhe der Qu.-lähmung _____

Störung der Koordination ☐ Nein ☐ Extremitätenataxie ☐ Nystagmus
Mehrfachnennung möglich ☐ Intentionstremor ☐ Rumpfataxie
☐ Sonstige Störung _____

Extrapyramidale Bewegungsstörung ☐ Nein ☐ Ja _____

Störung der Sensibilität ☐ Nein ☐ Ja _____

Störung vegetativer Funktionen ☐ Nein ☐ Ja _____

Somatische Auffälligkeiten ☐ Nein ☐ Ja _____

Neuroendokrinologische Auffälligkeiten ☐ Nein ☐ Ja _____

Körperlänge ⌊_⌊_⌊_⌋ Cm **Körpergewicht** ⌊_⌊_⌋ , ⌊_⌋ kg **Kopfumfang** ⌊_⌊_⌋ , ⌊_⌋ cm

IV.7.1.3 Chemotherapie

EU-RHAB
Konventionelle Block-Chemotherapie

Patientennummer:	⌊⌊⌊⌊
Klinik: _____ **Ort:** _____	⌊⌊⌊
Nachname des Patienten:	⌊⌊⌊
Geburtsdatum:	⌊⌊ . ⌊⌊ . ⌊⌊⌊⌊ Tag Monat Jahr

Kurs Nr. ⌊⌊ **Tag 1 dieses Kurses** ⌊⌊ . ⌊⌊ . ⌊⌊⌊⌊ (TT.MM.JJJJ)

Körpergröße bei Kursbeginn (in cm) ⌊⌊⌊ **Körpergewicht bei Kursbeginn (in g)** ⌊⌊⌊⌊⌊

Verzögerung > 5 Tage ☐ Nein

☐ Ja ☐ wegen Toxizität des vorhergehenden Kurses

☐ aus anderen Gründen (bitte angeben):_____

Dosismodifikation ☐ Nein

☐ Ja ☐ wegen Toxizität des vorhergehenden Kurses

☐ aus anderen Gründen (bitte angeben):_____

Kumulative Gesamtdosis pro Kurs DOX

Doxorubicin ⌊⌊⌊⌊ mg

MTX i.ventr. (nur bei AT/RT) → Bitte Bogen „Chemotherapie: „intraventrikuläre MTX-Injektionen“ ausfüllen!

Kumulative Gesamtdosis pro Kurs ICE

Ifosfamid ⌊⌊⌊⌊ mg

Carboplatin ⌊⌊⌊ mg

Etoposid ⌊⌊⌊ mg

MTX i.ventr. (nur bei AT/RT) → Bitte Bogen „Chemotherapie: „intraventrikuläre MTX-Injektionen“ ausfüllen!

Kumulative Gesamtdosis pro Kurs VCA

Vincristin ⌊ , ⌊ mg

Cyclophosphamid ⌊⌊⌊⌊ mg

Actinomycin-D ⌊⌊⌊ µg

MTX i.ventr. (nur bei AT/RT) → Bitte Bogen „Chemotherapie: „intraventrikuläre MTX-Injektionen“ ausfüllen!

EU-RHAB **Chemotherapie: Hauptphase, Seite 2/5**

Leukozytenzahl zu Beginn ⌊_⌋⌊_⌋ , ⌊_⌋ x 10^9/L

Thrombozytenzahl zu Beginn ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ x 10^9/L

Resttumor/Metastasen

Untersuchungen obligat nach den Kursen 2, 4, 6 und 9!

Datum der Untersuchung ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (TT.MM.JJJJ)

Untersuchungsmethode ☐ MRT ☐ CT ☐ Sonographie ☐ andere Methode _____

Primärtumorgröße
im Vergleich zur vorangegangenen Untersuchung

☐ Nicht untersucht
☐ Nicht mehr nachweisbar
☐ Reduziert um mehr als 50 %
☐ Reduziert zwischen 25 und 50 %
☐ Unverändert nachweisbar
☐ Progredient/Rezidiv (≥ 25% Zunahme)

Metastase(n)
im Vergleich zur vorangegangenen Untersuchung

☐ keine
☐ Nicht untersucht
☐ Nicht mehr nachweisbar
☐ Reduziert um mehr als 50 %
☐ Reduziert zwischen 25 und 50 %
☐ Unverändert nachweisbar
☐ Progredient/Rezidiv (≥ 25% Zunahme)

Tumorzellen im Liquor
Untersuchung obligat !

☐ Nicht untersucht ☐ Nein ☐ Ja

Therapiefortsetzung (geplant):

☐ **gemäß Protokoll**

☐ **Salvage** *bei ungenügendem Ansprechen oder Progredienz bzw. Metastasierung*

- ☐ Hochdosistherapie
- ☐ Lokale Strahlentherapie
- ☐ Second-look-OP → Bitte Bogen "OP" ausfüllen!
- ☐ Sonstiges

  Bitte nähere Angabe: _____

☐ **Therapieabbruch**

Bitte Bogen „Abschluss-Erhebung" ausfüllen!

EU-RHAB **Chemotherapie: Hauptphase, Seite 3/5**

Bemerkungen:

Stempel der Klinik	Datum	Unterschrift

Angaben durch:

Name: _____ **Telefon:** _____

Fax: _____ **Email:** _____

Bitte senden Sie diesen Bogen an:

EU-RHAB
Studienzentrale
I. Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg
FAX: 0821 400 179340

Toxizitätsskala: CTC modifiziert Angaben nach Chemotherapiekurs Nr. ☐☐

Bitte tragen Sie den Toxizitätsgrad in der letzten Spalte ein oder kreuzen Sie jeweils das entsprechende Kästchen an

Kategorie	Grad 0	Grad 1	Grad 2	Grad 3	Grad 4	Code	Grad
Allgemeinzustand	normal	geringe Einschränkung	altersgemäße Aktivität stark eingeschränkt	bettlägerig, pflegebedürftig	Intensivpflege, sehr krank	**01**	
Hämatologische Toxizität							
Hämoglobin (g/dl)	Altersnorm (N)	10,0 - < N	8,0 – < 10,0	6,5 – < 8,0	< 6,5	**11**	
Leukozyten (x 10^9/l)	≥ 4,0	3,0 – < 4,0	2,0 – < 3,0	1,0 – < 2,0	< 1,0	**12**	
Granulozyten (x 10^9/l)	≥ 2,0	1,5 – < 2,0	1,0 – < 1,5	0,5 – < 1,0	< 0,5	**13**	
Thrombozyten (x 10^9/l)	≥ 100	75 – < 100	50 – < 75	10 – < 50,0	< 10	**14**	
Infektionen							
Infektion	keine	leichte Infektion	mäßiggradig, Erreger nicht identifiziert; i.v. Antibiotika	schwer, Erreger identifiziert; i.v. Antibiotika	lebensbedrohlich mit Hypotonie	**21**	
Fieber (°C)	< 38	38 - 39	> 39 – 40	> 40 für < 24 h.	> 40 für ≥ 24 h.	**22**	
Verdauungstrakt							
Stomatitis	keine	schmerzloses Ulkus, Erythem	schmerzhaftes Erythem oder Ulkus Nahrungsaufnahme möglich	schmerzhaftes Erythem oder Ulkus, Nahrungs-aufnahme nicht möglich	TPN erforderlich, wg. Stomatitis	**31**	
Erbrechen (Anzahl Episoden pro 24h**)**	0	1	2 - 5	6 - 10	> 10 oder TPN erforderlich	**32**	
Diarrhoe (Stuhlfrequenz/Tag**)**	keine	2 - 3	4 – 6 oder nächtliche Stühle oder leichte Bauchkrämpfe	7 - 9 oder Inkontinenz oder schwere Bauchkrämpfe	≥ 10 oder blutiger Durchfall oder TPN erforderlich	**33**	
Hauttoxizität							
Hautveränderungen	keine	Erythem	trockene Desquamation, Vaskulitis, Pruritus	feuchte Desquamation, Ulzerationen	exfoliative Dermatitis, Nekrosen	**40**	
Nierentoxizität							
Kreatinin	Altersnorm (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 6,0 x N	> 6,0 x N	**51**	
Proteinurie (g/l)	keine	< 3	3 – 10,0	> 10	nephrot. Syndrom	**52**	
Hämaturie	keine	mikroskopisch	makroskopisch, ohne Koagel	makroskopisch, mit Koagel	Transfusion erforderlich	**53**	
Kreatinin-Clearence (ml/min/1,73m²)	≥ 90	60 - 89	40 - 59	20 - 39	≤ 19	**54**	
Lebertoxizität							
Bilirubin	Altersnorm (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 10,0 x N	> 10,0 x N	**61**	
SGOT / SGPT	Altersnorm (N)	> N – 2,5 x N	> 2,5 – 5,0 x N	> 5,0 – 20,0 x N	> 20 x N	**62**	
Kardiale Toxizität							
Arrhythmie	Keine	Asympt., keine Therapie	Rekurr./persist., keine Therapie	Therapie erforderlich	Hypotension, ventr. Arrhyth., Defibrillation	**70**	
Herzfunktion	normal	asymptomat., EF ↓ (Ruhe) ≥ 10 % aber < 20 % vom Ausgangswert	asymptomat., aber EF ↓ (Ruhe) unter dem unteren Normwert für EF (Arbeit) oder EF ↓ ≥ 20 % vom Ausgangswert	Milde CHF, therapeutisch kompensiert	schwere/ refraktäre CHF oder Notwendigkeit der Intubation	**71**	
ECHO: LV-SF (%)	≥ 30	≥ 24 - < 30	≥ 20 - < 24	> 15 - < 20	≤ 15	**72**	

Fortsetzung Toxizitätsskala: CTC modifiziert Angaben nach Chemotherapiekurs Nr. ☐☐

Bitte tragen Sie den Toxizitätsgrad in der letzten Spalte ein oder kreuzen Sie jeweils das entsprechende Kästchen an

Kategorie	Grad 0	Grad 1	Grad 2	Grad 3	Grad 4	Code	Grad
Ototoxizität							
Hörvermögen	normal	asymptomat. Hörverlust, nur audiometrisch fassbar	mäßige Symptomatik: Tinnitus, geringe Hypakusis bei Audiometrie	stark beeinträchtigender Hörverlust, Korrektur mit Hörgerät nötig	nicht korrigierbare Ertaubung	**80**	
Audiometrie	kein Hörverlust	≤ 15 dB bei ≤2 kHz	16 – 30 dB bei ≤2 kHz	31 – 60 dB bei ≤2 kHz	> 60 dB bei ≤2 kHz	**81**	
Kategorie	**Grad 0**	**Grad 1**	**Grad 2**	**Grad 3**	**Grad 4**	**Code**	**Grad**
Neurotoxizität							
Zentrale Neurotoxizität	Keine	Vorübergehende Lethargie	Somnolenz < 50% der Zeit, mäßige Desorientierung	Somnolenz > 50% der Zeit, erhebliche Desorientierung, Halluzinationen	Koma, Krämpfe	**85**	
Periphere Neurotoxizität	Keine	Parästhesien	schwere Parästhesien und/oder milde Schwäche	unerträgliche Parästhesien, deutliche motorische Verluste	Paralyse	**86**	

Sonstige Toxizität

nein = 0 ja = 1 ☐	Welche ? (Text)	90	Grad

Nach **anthrazyklinhaltigen** Kursen bitte noch folgende zusätzliche Angaben zur kardialen Toxizität:

Untersuchungsdatum ☐☐.☐☐.☐☐☐☐ (TT.MM.JJJJ)

Herzrhythmus Pulsfrequenz: ☐☐☐ Antiarrhythmische Therapie ☐ Nein ☐ Ja

Herzfunktion Syst. / diast. RR: ☐☐☐ / ☐☐☐ LV-SF: ☐☐ % Diastolische Parameter pathologisch? ☐ Nein ☐ Ja

Gabe von Digitalis? ☐ Nein ☐ Ja Gabe von Diuretika? ☐ Nein ☐ Ja Gabe von Betablockern? ☐ Nein ☐ Ja

Weiterführende Diagnostik
- ☐ MUGA
- ☐ EPO-Spiegel
- ☐ Troponin
- ☐ Sonstige _____

IV.7.1.4 intrathekale MTX-Therapie

EU-RHAB
Chemotherapie: Intraventrikuläre Methotrexat-Injektionen

Patientennummer:	⌊⌊⌊⌊
Klinik: _____ **Ort:** _____	⌊⌊⌊
Nachname des Patienten:	⌊⌊⌊
Geburtsdatum:	⌊⌊ . ⌊⌊ . ⌊⌊⌊⌊ Tag Monat Jahr

Kurs Nr. ⌊⌊ **Tag 1 MTX** ⌊⌊ . ⌊⌊ . ⌊⌊⌊⌊ (TT.MM.JJJJ)

Tag 1: MTX intraventrikulär ☐ Nein ☐ Ja ⌊ , ⌊⌊ mg
MTX-Spiegel: _____ µmol/L Eiweiß _____ mg/dl

Tag 2: MTX intraventrikulär ☐ Nein ☐ Ja ⌊ , ⌊⌊ mg
MTX-Spiegel: _____ µmol/L Eiweiß _____ mg/dl

Tag 3: MTX intraventrikulär ☐ Nein ☐ Ja ⌊ , ⌊⌊ mg
MTX-Spiegel: _____ µmol/L Eiweiß _____ mg/dl

Tag 4: MTX intraventrikulär ☐ Nein ☐ Ja ⌊ , ⌊⌊ mg
MTX-Spiegel: _____ µmol/L Eiweiß _____ mg/dl

MTX-Spiegel / Eiweißgehalt immer aus Liquor ermitteln!

Weitere MTX-/Eiweißspiegel:

Tag ____: MTX-Spiegel: _____ µmol/L Eiweiß _____ mg/dl

Tag ____: MTX-Spiegel: _____ µmol/L Eiweiß _____ mg/dl

Tag ____: MTX-Spiegel: _____ µmol/L Eiweiß _____ mg/dl

Tag ____: MTX-Spiegel: _____ µmol/L Eiweiß _____ mg/dl

MTX-Spiegel / Eiweißgehalt immer aus Liquor ermitteln!

EU-RHAB **Chemotherapie: Intrathekale Methotrexat-Injektionen, Seite 2/3**

Toxizitäten / Komplikationen (durch MTX intraventrikulär / Rickham-Reservoir / Ommaya-Kapsel verursacht)

Hirnblutung	☐ Nein	☐ Ja
ZNS-Infektion	☐ Nein	☐ Ja
Neurotoxizität	☐ Nein	☐ Ja
Überdosierung / toxische MTX-Spiegel	☐ Nein	☐ Ja
Sonstige Toxizität	☐ Nein	☐ Ja

Bitte schildern Sie möglichst ausführlich

1. die Toxizitäten bzw. aufgetretenen Symptome

2. die therapeutischen Maßnahmen

3. den Verlauf

Fortsetzung ggf. auf Seite 3

EU-RHAB **Chemotherapie: Intraventrikulär Methotrexat-Injektionen, Seite 3/3**

Bemerkungen:

Stempel der Klinik	Datum	Unterschrift

Angaben durch:

Name: _____ **Telefon:** _____

Fax: _____ **Email:** _____

Bitte senden Sie diesen Bogen an:

EU-RHAB
Studienzentrale
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg
FAX: 0821 400 179340

IV.7.1.5 Stammzellapherese

EU-RHAB
Stammzellapherese

Patientennummer:	⌊_⌊_⌊_⌊_⌋
Klinik: _____ **Ort:** _____	⌊_⌊_⌊_⌋
Nachname des Patienten:	⌊_⌊_⌊_⌋
Geburtsdatum:	⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ Tag Monat Jahr

Körpergewicht bei Apherese (in g) ⌊_⌊_⌊_⌊_⌊_⌋

Datum der ersten Stammzellapherese/ -sammlung ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Anzahl der Apheresen ⌊_⌋

Chemotherapie vor Mobilisation ☐ keine ☐ DOX ☐ ICE ☐ VCA

Mobilisation nach Kurs Nr. ⌊_⌊_⌋ Tag 1 des Mobilisationskurses ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Progenitorzellen ☐ autolog, peripheres Blut ☐ autolog, Knochenmark

Mobilisation ☐ Chemotherapie + HGF ☐ Steady state + HGF ☐ Nur Chemotherapie

Hämatologische Wachstumsfaktoren ☐ keine ☐ G-CSF ☐ GM-CSF

☐ Sonstiges (Bitte Angabe!): _____

Purging ☐ Kein Purging ☐ CD34 Selektion

☐ Sonstiges (Bitte Angabe!): _____

Anzahl gesammelter Stammzellen vor dem Einfrieren

⌊_⌊_⌋ , ⌊_⌊_⌋ X 10^6 CD34+/kg

⌊_⌊_⌋ , ⌊_⌊_⌋ X 10^8 ANC/kg

⌊_⌊_⌋ , ⌊_⌊_⌋ X 10^4 CD3+/kg

EU-RHAB **Stammzellapherese, Seite 2/2**

Bemerkungen:

Stempel der Klinik	**Datum**	**Unterschrift**

Angaben durch:

Name: _____ **Telefon:** _____

Fax: _____ **Email:** _____

Bitte senden Sie diesen Bogen an:
EU-RHAB
Studienzentrale
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg
FAX: 0821 400 179340

IV.7.1.6 Hochdosis-Chemotherapie (HDCT)

EU-RHAB
Chemotherapie: Hochdosistherapie

Patientennummer:	☐☐☐☐
Klinik: _____ **Ort:** _____	☐☐☐
Nachname des Patienten:	☐☐☐
Geburtsdatum:	☐☐ . ☐☐ . ☐☐☐☐ Tag Monat Jahr

Status vor Hochdosistherapie:

Tumorstatus:

Komplette Remission	☐
Teilremission	☐
Stable Disease	☐
Progress	☐
Nicht evaluierbar	☐

Allgemeinzustand:

Normale Aktivität, keine Beeinträchtigung	☐
Geringe Beeinträchtigung, zusätzliche Hilfe erforderlich	☐
Altersentsprechende Aktivität stark eingeschränkt	☐
Bettlägerig, pflegebedürftig	☐
Intensive Behandlung notwendig, schwerstkrank	☐

Organfunktionen vor HDCT:

Herz

Nicht untersucht ☐ Echokardiographisch untersucht ☐ Szintigraphisch untersucht ☐

Wenn untersucht:

LV-SF ☐☐ **%** EF ☐☐ **%**

Niere

GFR Nicht ermittelt ☐ Ermittelt per Kreatinin-Clearance ☐ Ermittelt per EDTA ☐

Ergebnis:

☐☐☐ **ml/min/1,73 m²**

Tubuläre Funktion Nicht ermittelt ☐ ermittelt ☐

Ergebnis: TP/CCrea oder Tmp/GFR

☐ , ☐☐ mmol/l

HCO3 ☐☐ , ☐ mmol/l

EU-RHAB **Chemotherapie: Hochdosistherapie, Seite 2/8**

Leber

SGOT ⌊_⌊_⌊_⌊_⌋ Oberer SGOT-Grenzwert des untersuchenden Labors ⌊_⌊_⌊_⌊_⌋

Lunge

Nicht untersucht ☐ Normal ☐ Eingeschränkt ☐

Pulmonale Compliance ⌊_⌊_⌊_⌋ **%** CO-Diffusion ⌊_⌊_⌊_⌋ **%**

Virusserologie vor HDCT:

CMV	negativ	☐	positiv	☐	nicht bekannt ☐
HBV	negativ	☐	positiv	☐	nicht bekannt ☐
HCV	negativ	☐	positiv	☐	nicht bekannt ☐
HIV	negativ	☐	positiv	☐	nicht bekannt ☐

Blutgruppe:

Blutgruppe 0 ☐

Blutgruppe A ☐

Blutgruppe B ☐

Blutgruppe AB ☐

Rhesusfaktor:

Rhesusfaktor positiv ☐

Rhesusfaktor negativ ☐

Tag 1 dieses Elements ⌊⌊⌋⌊⌊⌋⌊⌊⌊⌊⌋ (TT.MM.JJJJ)

☐ 1. HDCT ☐ 2. HDCT

Körpergröße bei Kursbeginn (in cm) ⌊⌊⌋ **Körpergewicht bei Kursbeginn (in g)** ⌊⌊⌊⌊⌋

Verzögerung > 5 Tage

☐ Nein

☐ Ja ☐ wegen Toxizität des vorhergehenden Kurses

☐ aus anderen Gründen (bitte angeben)

_____

Dosismodifikation

☐ Nein

☐ Ja ☐ wegen Toxizität des vorhergehenden Kurses

☐ aus anderen Gründen (bitte angeben)

_____

Kumulative Gesamtdosis

Carboplatin ⌊⌊⌊⌊⌋ mg

Thiotepa ⌊⌊⌊⌊⌋ mg

Etoposid ⌊⌊⌊⌊⌋ mg

Sonstige ⌊⌊⌊⌊⌋ mg

Transplantat ☐ PBSC ohne Aufreinigung ☐ PBSC mit CD 34 Selektion ☐ Knochenmark

Anzahl kernhaltiger Zellen ⌊⌊⌋,⌊⌋ x 10^8/kg KG

Anzahl CD 34+ Zellen ⌊⌊⌋,⌊⌋ x 10^6/kg KG

Leukozytenzahl zu Beginn ⌊⌊⌋,⌊⌋ x 10^9/L

Thrombozytenzahl zu Beginn ⌊⌊⌊⌊⌋ x 10^9/L

Bei Tandem – HDCT bitte 2. Bogen ausfüllen

EU-RHAB **Chemotherapie: Hochdosistherapie, Seite 4/8**

GCSF ⌊_⌋⌊_⌋ µg/kg KG/d

Gabe vom ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (TT.MM.JJJJ) bis zum ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (TT.MM.JJJJ)

Engraftment

Leukozyten > 1000/µl am ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (TT.MM.JJJJ)

Neutrophile Granulozyten > 500/µl am ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (TT.MM.JJJJ)

Thrombozyten > 50.000/µl am ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (TT.MM.JJJJ)

Resttumor/Metastasen

Untersuchungen obligat nach HDCT!

Datum der Untersuchung ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (TT.MM.JJJJ)

Untersuchungsmethode ☐ MRT ☐ CT ☐ Sonographie ☐ andere Methode _____

Primärtumorgröße
im Vergleich zur vorangegangenen Untersuchung

☐ Nicht untersucht
☐ Nicht mehr nachweisbar
☐ Reduziert um mehr als 50 %
☐ Reduziert zwischen 25 und 50 %
☐ Unverändert nachweisbar
☐ Progredient/Rezidiv (≥ 25% Zunahme)

Metastase(n)
im Vergleich zur vorangegangenen Untersuchung

☐ keine
☐ Nicht untersucht
☐ Nicht mehr nachweisbar
☐ Reduziert um mehr als 50 %
☐ Reduziert zwischen 25 und 50 %
☐ Unverändert nachweisbar
☐ Progredient/Rezidiv (≥ 25% Zunahme)

Tumorzellen im Liquor
Untersuchung obligat !

☐ Nicht untersucht ☐ Nein ☐ Ja

EU-RHAB **Chemotherapie: Hochdosistherapie, Seite 5/8**

Toxizität der Hochdosistherapie:

Parenterale Analgesie erforderlich ?	Nein ☐	Ja ☐	Wenn ja, Dauer ⌊⌊⌋ Tage
Parenterale Ernährung erforderlich	Nein ☐	Ja ☐	Wenn ja, Dauer ⌊⌊⌋ Tage
Parenterale Antibiose erforderlich ?	Nein ☐	Ja ☐	Wenn ja, Dauer ⌊⌊⌋ Tage
VOD ?	Nein ☐	Ja ☐	Wenn ja, Grad (Bearman) ⌊⌋
VOD-Prävention ?	Nein ☐	Ja ☐	Wenn ja, mit Defibrotide ☐ Heparin ☐

1= leichte Leberfunktionsstörung	2 mg% ≤ Bilirubin ≤ 6 mg% **oder** 2.5% ≤ Gewichtszunahme ≤ 5% gegenüber Ausgangswert **oder** SGOT-Anstieg > 2-fach, aber < 5-fach gegenüber niedrigstem Wert vor Hochdosistherapie
2= mäßiggradige Leberfunktionsstörung	6 mg% < Bilirubin ≤ 20 mg% **oder** SGOT-Anstieg > 5-fach gegenüber niedrigstem Wert vor Hochdosistherapie **oder** klinisch manifester oder radiologisch nachgewiesener Aszites **oder** Gewichtszunahme > 5% gegenüber Ausgangswert
3= schwere Leberfunktionsstörung	Bilirubin > 20 mg% **oder** hepatische Enzephalopathie **oder** Aszites, der die Atmung beeinträchtigt

Pulmonale Toxizität	Nein ☐	Ja ☐	
Wenn ja, Pneumonitis?	Nein ☐		
	Ja ☐	Radiologische Veränderungen, keine Steroide erforderlich	☐
		Steroide erforderlich	☐
		Sauerstoffgabe erforderlich	☐
		Beatmung erforderlich	☐
Sonstige pulmonale Toxizität?	Nein ☐	Ja ☐	wenn ja, welche: _____

EU-RHAB **Chemotherapie: Hochdosistherapie, Seite 6/8**

Bemerkungen:

Stempel der Klinik	Datum	Unterschrift

Angaben durch:

Name: _____ **Telefon:** _____

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Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg
FAX: 0821 400 179340

Zu den Toxizitäten bitte Angaben im Anhang nicht vergessen!

Toxizitätsskala: CTC modifiziert **Angaben nach Hochdosistherapie Nr.** ☐☐

Bitte tragen Sie den Toxizitätsgrad in der letzten Spalte ein oder kreuzen Sie jeweils das entsprechende Kästchen an

Kategorie	Grad 0	Grad 1	Grad 2	Grad 3	Grad 4	Code	Grad
Allgemeinzustand	normal	geringe Einschränkung	altersgemäße Aktivität stark eingeschränkt	bettlägerig, pflegebedürftig	Intensivpflege, sehr krank	**01**	
Hämatologische Toxizität							
Hämoglobin (g/dl)	Altersnorm (N)	10,0 - < N	8,0 – < 10,0	6,5 – < 8,0	< 6,5	**11**	
Leukozyten (x 10^9/l)	≥ 4,0	3,0 – < 4,0	2,0 – < 3,0	1,0 – < 2,0	< 1,0	**12**	
Granulozyten (x 10^9/l)	≥ 2,0	1,5 – < 2,0	1,0 – < 1,5	0,5 – < 1,0	< 0,5	**13**	
Thrombozyten (x 10^9/l)	≥ 100	75 – < 100	50 – < 75	10 – < 50,0	< 10	**14**	
Infektionen							
Infektion	keine	leichte Infektion	mäßiggradig, Erreger nicht identifiziert; i.v. Antibiotika	schwer, Erreger identifiziert; i.v. Antibiotika	lebensbedrohlich mit Hypotonie	**21**	
Fieber (°C)	< 38	38 - 39	> 39 – 40	> 40 für < 24 h.	> 40 für ≥ 24 h.	**22**	
Verdauungstrakt							
Stomatitis	keine	schmerzloses Ulkus, Erythem	schmerzhaftes Erythem oder Ulkus Nahrungsaufnahme möglich	schmerzhaftes Erythem oder Ulkus, Nahrungs-aufnahme nicht möglich	TPN erforderlich, wg. Stomatitis	**31**	
Erbrechen (Anzahl Episoden pro 24h**)**	0	1	2 - 5	6 - 10	> 10 oder TPN erforderlich	**32**	
Diarrhoe (Stuhlfrequenz/Tag**)**	keine	2 - 3	4 – 6 oder nächtliche Stühle oder leichte Bauchkrämpfe	7 - 9 oder Inkontinenz oder schwere Bauchkrämpfe	≥ 10 oder blutiger Durchfall oder TPN erforderlich	**33**	
Hauttoxizität							
Hautveränderungen	keine	Erythem	trockene Desquamation, Vaskulitis, Pruritus	feuchte Desquamation, Ulzerationen	exfoliative Dermatitis, Nekrosen	**40**	
Nierentoxizität							
Kreatinin	Altersnorm (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 6,0 x N	> 6,0 x N	**51**	
Proteinurie (g/l)	keine	< 3	3 – 10,0	> 10	nephrot. Syndrom	**52**	
Hämaturie	keine	mikroskopisch	makroskopisch, ohne Koagel	makroskopisch, mit Koagel	Transfusion erforderlich	**53**	
Kreatinin-Clearence (ml/min/1,73m²)	≥ 90	60 - 89	40 - 59	20 - 39	≤ 19	**54**	
Lebertoxizität							
Bilirubin	Altersnorm (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 10,0 x N	> 10,0 x N	**61**	
SGOT / SGPT	Altersnorm (N)	> N – 2,5 x N	> 2,5 – 5,0 x N	> 5,0 – 20,0 x N	> 20 x N	**62**	
Kardiale Toxizität							
Arrhythmie	Keine	Asympt., keine Therapie	Rekurr./persist., keine Therapie	Therapie erforderlich	Hypotension, ventr. Arrhyth., Defibrillation	**70**	
Herzfunktion	normal	asymptomat., EF ↓ (Ruhe) ≥ 10 % aber < 20 % vom Ausgangswert	asymptomat., aber EF ↓ (Ruhe) unter dem unteren Normwert für EF (Arbeit) oder EF ↓ ≥ 20 % vom Ausgangswert	Milde CHF, therapeutisch kompensiert	schwere/ refraktäre CHF oder Notwendigkeit der Intubation	**71**	
ECHO: LV-SF (%)	≥ 30	≥ 24 - < 30	≥ 20 - < 24	> 15 - < 20	≤ 15	**72**	

Toxizitätsskala: CTC modifiziert **Angaben nach Hochdosistherapie Nr.** ☐☐

Bitte tragen Sie den Toxizitätsgrad in der letzten Spalte ein oder kreuzen Sie jeweils das entsprechende Kästchen an

Kategorie	Grad 0	Grad 1	Grad 2	Grad 3	Grad 4	Code	Grad
Ototoxizität							
Hörvermögen	normal	asymptomat. Hörverlust, nur audiometrisch fassbar	mäßige Symptomatik: Tinnitus, geringe Hypakusis bei Audiometrie	stark beeinträchtigender Hörverlust, Korrektur mit Hörgerät nötig	nicht korrigierbare Ertaubung	**80**	
Audiometrie	kein Hörverlust	≤ 15 dB bei ≤2 kHz	16 – 30 dB bei ≤2 kHz	31 – 60 dB bei ≤2 kHz	> 60 dB bei ≤2 kHz	**81**	
Neurotoxizität							
Zentrale Neurotoxizität	keine	Vorübergehende Lethargie	Somnolenz < 50% der Zeit, mäßige Desorientierung	Somnolenz > 50% der Zeit, erhebliche Desorientierung, Halluzinationen	Koma, Krämpfe	**85**	
Periphere Neurotoxizität	keine	Parästhesien	schwere Parästhesien und/oder milde Schwäche	unerträgliche Parästhesien, deutliche motorische Verluste	Paralyse	**86**	

Sonstige Toxizität

nein = 0 **ja = 1** ☐	**Welche ? (Text)**	**90**	**Grad**

IV.7.1.7 OP

EU-RHAB
OP

Patientennummer:	⌊⌊⌊⌊⌋
Klinik: _____ **Ort:** _____	⌊⌊⌊⌋
Nachname des Patienten:	⌊⌊⌊⌋
Geburtsdatum:	⌊⌊⌋ . ⌊⌊⌋ . ⌊⌊⌊⌊⌋ Tag Monat Jahr

Datum der Operation ⌊⌊⌋ . ⌊⌊⌋ . ⌊⌊⌊⌊⌋ (TT.MM.JJJJ)

Operateur / Klinik _____

Art der Operation

- ☐ Biopsie, offen
- ☐ Biopsie, stereotaktisch
- ☐ Partielle Resektion (< 50%)
- ☐ Partielle Resektion (> 50%)
- ☐ Subtotale Resektion (< 10% Rest)
- ☐ Totale Resektion (kein sichtbarer Resttumor)

Anlass zur Operation

- ☐ Unvollständige Erstoperation des Primärtumors
- ☐ Lokalrezidiv
- ☐ Solide Metastase ☐ primär vorhanden ☐ im Verlauf entstanden
- ☐ Synchroner Tumor
- ☐ Sonstiges _____

Liquorableitung bleibend ☐ Nein ☐ Ja, v. p. ☐ Ja, v. a.

Verstümmelnde Operation/ Amputation ☐ Nein ☐ Ja, _____

Histologischer Befund – Lokaler Pathologe (bitte beifügen)

Datum des Befundes ⌊⌊⌋ . ⌊⌊⌋ . ⌊⌊⌊⌊⌋ (TT.MM.JJJJ) **Journal-Nr.** ⌊⌊⌊⌊⌊⌊⌊⌊⌊⌋

Institut _____

Beurteilung Immunhistochemie (lokaler Pathologe)

- ☐ INI1 Expression erhalten
- ☐ INI1 Expression verloren

Beurteilung Histologie (lokaler Pathologe)

- ☐ MRT (Weichteil)
- ☐ RTK (Niere)
- ☐ AT/RT (ZNS)
- ☐ Sonstiges _____

Histologischer Befund – Referenzpathologe (bitte beifügen)

Versand an Referenzpathologen

- ☐ Nein
- ☐ Ja, ist geplant
- ☐ Ja, ist erfolgt
  - ☐ nach Bonn
  - ☐ nach Kiel
  - ☐ nach Münster
  - ☐ Sonstige _____

Datum des Befundes ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ) **Journal-Nr.** ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Institut _____

Beurteilung Immunhistochemie (Referenzpathologe)

- ☐ SMARCB1/hSNF5/INI1 erhalten
- ☐ SMARCB1/hSNF5/INI1 verloren

Beurteilung Histologie (Referenzpathologe)

- ☐ MRT (Weichteil)
- ☐ RTK (Niere)
- ☐ AT/RT (ZNS)
- ☐ Sonstiges _____

Radiologische Kontrolle nach der OP

Datum der Bildgebung ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Verfahren Primärtumor ☐ CT nativ ☐ CT mit KM ☐ MRT nativ ☐ MRT mit KM

Größe ⌊_⌊_⌋ , ⌊_⌋ cm senkrecht dazu ⌊_⌊_⌋ , ⌊_⌋ cm

Verfahren Metastase(n) ☐ CT nativ ☐ CT mit KM ☐ MRT nativ ☐ MRT mit KM

Größe* ⌊_⌊_⌋ , ⌊_⌋ cm senkrecht dazu ⌊_⌊_⌋ , ⌊_⌋ cm

* Wenn >1 Metastase bitte Maße der <u>größten</u> Metastase angeben und lokalradiologischen Befund beifügen.

Bilder an Referenzradiologie versandt: ☐ Nein ☐ Ja

Operationsfolgen / Komplikationen

- ☐ Nein
- ☐ Ja, neurologisch (bitte nähere Angabe) _____
- ☐ Ja, nicht neurologisch (bitte nähere Angabe) _____

EU-RHAB **OP, Seite 3/5**

Bemerkungen:

Stempel der Klinik	**Datum**	**Unterschrift**

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EU-RHAB **Anhang für AT/RT – Teil 1** **OP, Seite 4/5**

PRÄoperative neurologische Untersuchung (nur auszufüllen bei AT/RT)

Datum der Untersuchung ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Hirndrucksymptome ☐ Nein ☐ Erbrechen ☐ Vorgewölbte Fontanellen
Mehrfachnennung möglich ☐ Kopfschmerzen ☐ Wesensveränderung
☐ Stauungspapillen

Bewußtseinsstörungen ☐ Nein ☐ Somnolenz
☐ Stupor
☐ Coma

Cerebrale Anfälle ☐ Nein ☐ Ja

Störungen neuropsychologischer Funktionen ☐ Nein ☐ Ja, welche _____

Hirnnervenausfälle ☐ Nein ☐ Ja, Symptom/Seite _____ HN-Nr. _____
☐ Ja, Symptom/Seite _____ HN-Nr. _____
☐ Ja, Symptom/Seite _____ HN-Nr. _____

Störung der Grobmotorik ☐ Nein ☐ Monoparese - Arm rechts ☐ Monoparese - Arm links
☐ Monoparese - Bein rechts ☐ Monoparese - Bein links
☐ Hemiparese rechts ☐ Hemiparese links
☐ Paraparese ☐ Tetraparese

falls Querschnittslähmung ☐ Inkomplett ☐ Komplett
Höhe der Qu.-lähmung _____

Störung der Koordination ☐ Nein ☐ Extremitätenataxie ☐ Nystagmus
Mehrfachnennung möglich ☐ Intentionstremor ☐ Rumpfataxie
☐ Sonstige Störung _____

Extrapyramidale Bewegungsstörung ☐ Nein ☐ Ja _____

Störung der Sensibilität ☐ Nein ☐ Ja _____

Störung vegetativer Funktionen ☐ Nein ☐ Ja _____

Somatische Auffälligkeiten ☐ Nein ☐ Ja _____

Neuroendokrinologische Auffälligkeiten ☐ Nein ☐ Ja _____

Körperlänge ⌊_⌊_⌊_⌋ cm **Körpergewicht** ⌊_⌊_⌋ , ⌊_⌋ kg **Kopfumfang** ⌊_⌊_⌋ , ⌊_⌋ cm

EU-RHAB **Anhang für AT/RT- Teil 2** **OP, Seite 5/5**

POSToperative neurologische Untersuchung (nur auszufüllen bei AT/RT)

Datum der Untersuchung ☐☐.☐☐.☐☐☐☐ (TT.MM.JJJJ)

Hirndrucksymptome ☐ Nein ☐ Erbrechen ☐ Vorgewölbte Fontanellen
Mehrfachnennung möglich ☐ Kopfschmerzen ☐ Wesensveränderung
☐ Stauungspapillen

Bewußtseinsstörungen ☐ Nein ☐ Somnolenz
☐ Stupor
☐ Coma

Cerebrale Anfälle ☐ Nein ☐ Ja

Störungen neuropsychologischer Funktionen ☐ Nein ☐ Ja, welche _____

Hirnnervenausfälle ☐ Nein ☐ Ja, Symptom/Seite _____ HN-Nr. _____
☐ Ja, Symptom/Seite _____ HN-Nr. _____
☐ Ja, Symptom/Seite _____ HN-Nr. _____

Störung der Grobmotorik ☐ Nein ☐ Monoparese - Arm rechts ☐ Monoparese - Arm links
☐ Monoparese - Bein rechts ☐ Monoparese - Bein links
☐ Hemiparese rechts ☐ Hemiparese links
☐ Paraparese ☐ Tetraparese

falls Querschnittslähmung ☐ Inkomplett ☐ Komplett
Höhe der Qu.-lähmung _____

Störung der Koordination ☐ Nein ☐ Extremitätenataxie ☐ Nystagmus
Mehrfachnennung möglich ☐ Intentionstremor ☐ Rumpfataxie
☐ Sonstige Störung _____

Extrapyramidale Bewegungsstörung ☐ Nein ☐ Ja _____

Störung der Sensibilität ☐ Nein ☐ Ja _____

Störung vegetativer Funktionen ☐ Nein ☐ Ja _____

Somatische Auffälligkeiten ☐ Nein ☐ Ja _____

Neuroendokrinologische Auffälligkeiten ☐ Nein ☐ Ja _____

Körperlänge ☐☐☐ cm **Körpergewicht** ☐☐,☐ kg **Kopfumfang** ☐☐,☐ cm

IV.7.1.8 Abschluss-Erhebung

EU-RHAB
Abschluss-Erhebung

Patientennummer:	☐☐☐☐
Klinik: _____ **Ort:** _____	☐☐☐
Nachname des Patienten:	☐☐☐
Geburtsdatum:	☐☐ . ☐☐ . ☐☐☐☐ Tag Monat Jahr

Therapiebeginn ☐☐ . ☐☐ . ☐☐☐☐ (TT.MM.JJJJ)

Therapieende ☐☐ . ☐☐ . ☐☐☐☐ (TT.MM.JJJJ)

Status bei Therapieende	**Primärtumor**	**Metastasen**	**Liquor**
Komplette Remission	☐	☐	☐
Teilremission (Reduktion ≥ 50%)	☐	☐	☐
Stable Disease (Reduktion < 50% oder Zunahme < 25%)	☐	☐	☐
Progress (Zunahme > 25%)	☐	☐	☐
Nicht beurteilbar	☐	☐	☐
Keine Angaben	☐	☐	☐

Therapieverlauf

Operation	☐ Nein	☐ Ja	
Weitere Operation	☐ Nein	☐ Ja	
Wenn ja, welche	☐ Second Look	☐ LK	☐_____
Bestrahlung	☐ Nein	☐ Ja	Dosis in Gy: ☐☐ , ☐
Chemotherapie	☐ Nein	☐ Ja	Anzahl der verabreichten Kurse (auch wenn modifiziert):
			DOX ☐☐
			ICE ☐☐
			VCA ☐☐
			MTX (i.t.) ☐☐
Orale Erhaltung	☐ Nein	☐ Ja	wenn "ja"→ TI ☐☐
			TE ☐☐
			TMZ ☐☐
Stammzellapherese	☐ Nein	☐ Ja	
Hochdosistherapie	☐ Nein	☐ Ja	wenn "ja" ☐ Tandem
			☐ Sonstige _____

EU-RHAB **Abschluss-Erhebung, Seite 2/2**

Gründe für Beendigung der Therapie

☐ protokollgemäß

☐ vorzeitig aufgrund
- ☐ Toxizität
- ☐ Tumorprogress
- ☐ Entscheidung des Patienten / der Eltern
- ☐ Entscheidung des Arztes
- ☐ Tod des Patienten
- ☐ Keine Angaben
- ☐ Sonstiges (bitte Angabe) _____

Bemerkungen:

Stempel der Klinik	**Datum**	**Unterschrift**

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Name: _____ **Telefon:** _____

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IV.7.1.9 Status-Erhebung

EU-RHAB
Statuserhebung

Patientennummer:	☐☐☐☐
Klinik: _____ **Ort:** _____	☐☐☐
Nachname des Patienten:	☐☐☐
Geburtsdatum:	☐☐ . ☐☐ . ☐☐☐☐ Tag Monat Jahr

Status zum Zeitpunkt der letzten Untersuchung

☐ Patient lebt
Datum der letzten klinischen Untersuchung ☐☐ . ☐☐ . ☐☐☐☐ (TT.MM.JJJJ)
Datum der letzten bildgebenden Untersuchung, wenn abweichend ☐☐ . ☐☐ . ☐☐☐☐ (TT.MM.JJJJ)

☐ Patient verstorben
Todesdatum ☐☐ . ☐☐ . ☐☐☐☐ (TT.MM.JJJJ)

Remissionsstatus

☐ Vollremission / tumorfrei
☐ Resttumormanifestation lokal
  ☐ *ohne* Progression
  ☐ *in* Progression, d. h. Größenzunahme >= 25%
☐ Resttumormanifestation Metastase/Meningeose
  ☐ *ohne* Progression
  ☐ *in* Progression, d. h. Größenzunahme >= 25%

Auftreten von Rezidiv/sekundärer Metastasierung

☐ Nein
☐ Ja

Auftreten eines Sekundärmalignoms

☐ Nein
☐ Ja

Bei Tod des Patienten sowie bei Auftreten von Rezidiv/sekundärer Metastasierung/Sekundärmalignom bitte Bogen „Ereignismeldung“ ausfüllen.

EU-RHAB **Statuserhebung, Seite 2/4**

Therapie

Wurde seit dem Therapieende / der letzten Erhebung eine spezielle Therapie begonnen/durchgeführt?

☐ Nein ☐ Ja, Operation
Histologische Diagnose bestätigt? ☐ Ja ☐ Nein ***
☐ Ja, Radiotherapie
☐ Ja, Chemotherapie ***
☐ Ja, Sonstige ***

*** **Falls zutreffend, bitte nähere Angaben auf Seite 3 im Feld „Bemerkungen".**

Langzeitfolgen *(seit dem Therapieende / der letzten Erhebung erhobene Befunde)*

Nephrotoxizität ☐ Nicht untersucht ☐ Nein ☐ Ja, Tubulopathie
☐ Ja, Glomerulopathie

Befund _____

Ototoxizität ☐ Nicht untersucht

Audiometrie:
☐ Kein Hörverlust
☐ Hörstörung, ≤ 15 dB bei ≤ 2 kHz
☐ Hörstörung, 16-30 dB bei ≤ 2 kHz
☐ Hörstörung, 31-60 dB bei ≤ 2 kHz
☐ Hörstörung, > 60 dB bei ≤ 2 kHz

Hörgerät: ☐ Nein ☐ Ja

Hämatotoxizität ☐ Nicht untersucht ☐ Nein ☐ Ja
Thrombozyten ⌊_⌊_⌊_⌊_⌋ x 10^9/L
Leukozyten ⌊_⌊_⌋,⌊_⌋ x 10^9/L
Granulozyten ⌊_⌊_⌋,⌊_⌋ x 10^9/L

Ophtalmologie ☐ Nicht untersucht ☐ Normalbefund ☐ Visus pathologisch
☐ Gesichtsfeld pathologisch

Befund _____

Sonstige Folgen ☐ Nein ☐ Ja

Bitte spezifizieren: _____
_____
_____

EU-RHAB **Statuserhebung, Seite 3/4**

Bemerkungen:

Stempel der Klinik	**Datum**	**Unterschrift**

Angaben durch:

Name: _____ **Telefon:** _____

Fax: _____ **Email:** _____

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Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg
FAX: 0821 400 179340

EU-RHAB **Anhang für AT/RT** **Statuserhebung,**
Seite 4/4

Neurologische Untersuchung (nur auszufüllen bei AT/RT)

Datum der Untersuchung ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Hirndrucksymptome ☐ Nein ☐ Erbrechen ☐ Vorgewölbte Fontanellen
Mehrfachnennung möglich ☐ Kopfschmerzen ☐ Wesensveränderung
☐ Stauungspapillen

Bewußtseinsstörungen ☐ Nein ☐ Somnolenz
☐ Stupor
☐ Coma

Cerebrale Anfälle ☐ Nein ☐ Ja

Störungen neuropsychologischer Funktionen ☐ Nein ☐ Ja, welche _____

Hirnnervenausfälle ☐ Nein ☐ Ja, Symptom/Seite _____ HN-Nr. _____
☐ Ja, Symptom/Seite _____ HN-Nr. _____
☐ Ja, Symptom/Seite _____ HN-Nr. _____

Störung der Grobmotorik ☐ Nein ☐ Monoparese - Arm rechts ☐ Monoparese - Arm links
☐ Monoparese - Bein rechts ☐ Monoparese - Bein links
☐ Hemiparese rechts ☐ Hemiparese links
☐ Paraparese ☐ Tetraparese

falls Querschnittslähmung ☐ Inkomplett ☐ Komplett
Höhe der Qu.-lähmung _____

Störung der Koordination ☐ Nein ☐ Extremitätenataxie ☐ Nystagmus
Mehrfachnennung möglich ☐ Intentionstremor ☐ Rumpfataxie
☐ Sonstige Störung _____

Extrapyramidale Bewegungsstörung ☐ Nein ☐ Ja _____

Störung der Sensibilität ☐ Nein ☐ Ja _____

Störung vegetativer Funktionen ☐ Nein ☐ Ja _____

Somatische Auffälligkeiten ☐ Nein ☐ Ja _____

Neuroendokrinologische Auffälligkeiten ☐ Nein ☐ Ja _____

Körperlänge ⌊_⌊_⌊_⌋ cm **Körpergewicht** ⌊_⌊_⌋ , ⌊_⌋ kg **Kopfumfang** ⌊_⌊_⌋ , ⌊_⌋ cm

IV.7.1.10 Ereignismeldung

EU-RHAB
Ereignismeldung

Patientennummer:	☐☐☐☐
Klinik: _____ **Ort:** _____	☐☐☐
Nachname des Patienten:	☐☐☐
Geburtsdatum:	☐☐ . ☐☐ . ☐☐☐☐ Tag Monat Jahr

Datum des Ereignisses: ☐☐ . ☐☐ . ☐☐☐☐ (TT.MM.JJJJ) **Nummer des Ereignisses:** ☐☐

Bitte je Ereignis einen Bogen ausfüllen.

Diagnose von Rezidiv oder sekundärer Metastasierung an o.g. Datum
- ☐ Nein
- ☐ Ja
  - ☐ Progression
  - ☐ Lokalrezidiv
  - ☐ Fernmetastase
  - ☐ Lokalrezidiv und Fernmetastase

Falls Metastasen:
- ☐ ZNS ☐ zerebral ☐ spinal
- ☐ Liquor
- ☐ Lunge ☐ rechts ☐ links ☐ beidseits
- ☐ Leber
- ☐ Niere ☐ rechts ☐ links ☐ beidseits
- ☐ Knochenmark
- ☐ Knochen Welche? _____
- ☐ andere Welche? _____

Diagnose eines Sekundärmalignoms an o.g. Datum
- ☐ Nein
- ☐ Ja Art _____
  Lokalisation _____

Tod des Patienten an o.g. Datum
- ☐ Nein
- ☐ Ja

Todesursache:
- ☐ malignombedingt
  - ☐ Primärerkrankung
  - ☐ Rezidiv/sekundäre Metastasierung
  - ☐ Sekundärmalignom
- ☐ therapiebedingt
- ☐ nicht entscheidbar, ob Tumorerkrankung oder Therapie
- ☐ Sonstige
  Bitte nähere Angabe: _____

Autopsie:
- ☐ Nein
- ☐ Ja

EU-RHAB **Ereignismeldung, Seite 2/2**

Bemerkungen:

Stempel der Klinik	Datum	Unterschrift

Angaben durch:

Name: _____ **Telefon:** _____

Fax: _____ **Email:** _____

Bitte senden Sie diesen Bogen an:

EU-RHAB
Studienzentrale
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg
FAX: 0821 400 179340

IV.7.1.11 SAE-Meldung

EU-RHAB
Serious adverse event

Patientennummer:	⌊⌊⌊⌊⌋
Klinik: _____ **Ort:** _____	⌊⌊⌊⌋
Nachname des Patienten:	⌊⌊⌊⌋
Geburtsdatum:	⌊⌊⌋.⌊⌊⌋.⌊⌊⌊⌊⌋ Tag Monat Jahr

Beginn des Ereignisses: ⌊⌊⌋.⌊⌊⌋.⌊⌊⌊⌊⌋ (TT.MM.JJJJ) **Nummer des Ereignisses:** ⌊⌊⌋

Ende des Ereignisses: ⌊⌊⌋.⌊⌊⌋.⌊⌊⌊⌊⌋ (TT.MM.JJJJ)

nach Chemo-Kurs Nr. ⌊⌊⌋ **verabreicht am** ⌊⌊⌋.⌊⌊⌋.⌊⌊⌊⌊⌋ (TT.MM.JJJJ)

Bitte je Ereignis einen Bogen ausfüllen.

Größe: ⌊⌊⌊⌋ (cm) **Gewicht:** ⌊⌊⌊⌊⌊⌋ (g) **KOF:** ⌊⌊⌊⌋ (m^2)

Medikament: **Dosierung:**

Chargennummer des Medikamentes: _____

Meldung an BfArm erfolgt: ☐ ja ☐ nein

wenn „ja“, bitte BfArm-Nummer eintragen:_____

Beschreibung des SAE, im Anhang Toxizität eintragen:

EU-RHAB **SAE, Seite 2/5**

Kommentar zur Natur oder Ursache des SAE:

Toxizitätsgrad nach NCI: □ **3** □ **4**

Beginn: ⌊⌊⌋⌋ . ⌊⌊⌋⌋ . ⌊⌊⌋⌋⌊⌋⌋ **Ende:** ⌊⌊⌋⌋ . ⌊⌊⌋⌋ . ⌊⌊⌋⌋⌊⌋⌋ **Oder weiter-bestehend:** □

Tag Monat Jahr Tag Monat Jahr

Kausalität

Ist der anfängliche Zustand des Patienten oder eine andere Erkrankung für dieses Ereignis verantwortlich?

□ ja □ wahrscheinlich □ möglich □ unwahrscheinlich □ nein

Glauben Sie, dass das Ereignis mit der Therapie zusammenhängt?

□ ja □ wahrscheinlich □ möglich □ unwahrscheinlich □ nein

Klassifikation (Schweregrad)

□ Tod innerhalb von 4 Wochen nach letzter Therapie
□ Lebensbedrohlich
□ Persistierende oder schwere Folgeschäden
□ Klinikaufenthalt oder Verlängerung des Klinikaufenthaltes notwendig

Verlauf

□ vollständige Erholung □ noch fehlende Erholung □ Spätfolgen □ Tod □ unbekannt

EU-RHAB **SAE, Seite 3/5**

Bemerkungen:

Stempel der Klinik	**Datum**	**Unterschrift**

Angaben durch:

Name: _____ **Telefon:** _____

Fax: _____ **Email:** _____

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Studienzentrale
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg

FAX: 0821 400 179340

Toxizitätsskala: CTC modifiziert Angaben nach Chemotherapiekurs Nr. ☐☐

Bitte tragen Sie den Toxizitätsgrad in der letzten Spalte ein oder kreuzen Sie jeweils das entsprechende Kästchen an

Kategorie	Grad 0	Grad 1	Grad 2	Grad 3	Grad 4	Code	Grad
Allgemeinzustand	normal	geringe Einschränkung	altersgemäße Aktivität stark eingeschränkt	bettlägerig, pflegebedürftig	Intensivpflege, sehr krank	**01**	
Hämatologische Toxizität							
Hämoglobin (g/dl)	Altersnorm (N)	10,0 - < N	8,0 – < 10,0	6,5 – < 8,0	< 6,5	**11**	
Leukozyten (x 10^9/l)	≥ 4,0	3,0 – < 4,0	2,0 – < 3,0	1,0 – < 2,0	< 1,0	**12**	
Granulozyten (x 10^9/l)	≥ 2,0	1,5 – < 2,0	1,0 – < 1,5	0,5 – < 1,0	< 0,5	**13**	
Thrombozyten (x 10^9/l)	≥ 100	75 – < 100	50 – < 75	10 – < 50,0	< 10	**14**	
Infektionen							
Infektion	keine	leichte Infektion	mäßiggradig, Erreger nicht identifiziert; i.v. Antibiotika	schwer, Erreger identifiziert; i.v. Antibiotika	lebensbedrohlich mit Hypotonie	**21**	
Fieber (°C)	< 38	38 - 39	> 39 – 40	> 40 für < 24 h.	> 40 für ≥ 24 h.	**22**	
Verdauungstrakt							
Stomatitis	keine	schmerzloses Ulkus, Erythem	schmerzhaftes Erythem oder Ulkus Nahrungsaufnahme möglich	schmerzhaftes Erythem oder Ulkus, Nahrungs-aufnahme nicht möglich	TPN erforderlich, wg. Stomatitis	**31**	
Erbrechen (Anzahl Episoden pro 24h**)**	0	1	2 - 5	6 - 10	> 10 oder TPN erforderlich	**32**	
Diarrhoe (Stuhlfrequenz/Tag**)**	keine	2 - 3	4 – 6 oder nächtliche Stühle oder leichte Bauchkrämpfe	7 - 9 oder Inkontinenz oder schwere Bauchkrämpfe	≥ 10 oder blutiger Durchfall oder TPN erforderlich	**33**	
Hauttoxizität							
Hautveränderungen	keine	Erythem	trockene Desquamation, Vaskulitis, Pruritus	feuchte Desquamation, Ulzerationen	exfoliative Dermatitis, Nekrosen	**40**	
Nierentoxizität							
Kreatinin	Altersnorm (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 6,0 x N	> 6,0 x N	**51**	
Proteinurie (g/l)	keine	< 3	3 – 10,0	> 10	nephrot. Syndrom	**52**	
Hämaturie	keine	mikroskopisch	makroskopisch, ohne Koagel	makroskopisch, mit Koagel	Transfusion erforderlich	**53**	
Kreatinin-Clearence (ml/min/1,73m²)	≥ 90	60 - 89	40 - 59	20 - 39	≤ 19	**54**	
Lebertoxizität							
Bilirubin	Altersnorm (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 10,0 x N	> 10,0 x N	**61**	
SGOT / SGPT	Altersnorm (N)	> N – 2,5 x N	> 2,5 – 5,0 x N	> 5,0 – 20,0 x N	> 20 x N	**62**	
Kardiale Toxizität							
Arrhythmie	Keine	Asympt., keine Therapie	Rekurr./persist., keine Therapie	Therapie erforderlich	Hypotension, ventr. Arrhyth., Defibrillation	**70**	
Herzfunktion	normal	asymptomat., EF ↓ (Ruhe) ≥ 10 % aber < 20 % vom Ausgangswert	asymptomat., aber EF ↓ (Ruhe) unter dem unteren Normwert für EF (Arbeit) oder EF ↓ ≥ 20 % vom Ausgangswert	Milde CHF, therapeutisch kompensiert	schwere/ refraktäre CHF oder Notwendigkeit der Intubation	**71**	
ECHO: LV-SF (%)	≥ 30	≥ 24 - < 30	≥ 20 - < 24	> 15 - < 20	≤ 15	**72**	

Fortsetzung Toxizitätsskala: CTC modifiziert

Bitte tragen Sie den Toxizitätsgrad in der letzten Spalte ein oder kreuzen Sie jeweils das entsprechende Kästchen an

Kategorie	Grad 0	Grad 1	Grad 2	Grad 3	Grad 4	Code	Grad
Ototoxizität							
Hörvermögen	normal	asymptomat. Hörverlust, nur audiometrisch fassbar	mäßige Symptomatik: Tinnitus, geringe Hypakusis bei Audiometrie	stark beeinträchtigender Hörverlust, Korrektur mit Hörgerät nötig	nicht korrigierbare Ertaubung	**80**	
Audiometrie	kein Hörverlust	≤ 15 dB bei ≤2 kHz	16 – 30 dB bei ≤2 kHz	31 – 60 dB bei ≤2 kHz	> 60 dB bei ≤2 kHz	**81**	
Neurotoxizität							
Zentrale Neurotoxizität	keine	Vorübergehende Lethargie	Somnolenz < 50% der Zeit, mäßige Desorientierung	Somnolenz > 50% der Zeit, erhebliche Desorientierung, Halluzinationen	Koma, Krämpfe	**85**	
Periphere Neurotoxizität	keine	Parästhesien	schwere Parästhesien und/oder milde Schwäche	unerträgliche Parästhesien, deutliche motorische Verluste	Paralyse	**86**	

Sonstige Toxizität

nein = 0 ja = 1 ☐	Welche ? (Text)	90	Grad

Nach **anthrazyklinhaltigen** Kursen bitte noch folgende zusätzliche Angaben zur kardialen Toxizität:

Untersuchungsdatum ☐☐ . ☐☐ . ☐☐☐☐ (TT.MM.JJJJ)

Herzrhythmus Pulsfrequenz: ☐☐☐

Antiarrhythmische Therapie ☐ Nein ☐ Ja

Herzfunktion Syst. / diast. RR: ☐☐☐ / ☐☐☐ LV-SF: ☐☐ %

Diastolische Parameter pathologisch? ☐ Nein ☐ Ja

Gabe von Digitalis? ☐ Nein ☐ Ja

Gabe von Diuretika? ☐ Nein ☐ Ja

Gabe von Betablockern? ☐ Nein ☐ Ja

Weiterführende Diagnostik
- ☐ MUGA
- ☐ EPO-Spiegel
- ☐ Troponin
- ☐ Sonstige

IV.7.1.12 Radiotherapie - Basisdaten

EU-RHAB
Strahlentherapie - Basisdaten

Patientennummer:	☐☐☐☐
Klinik: _____ **Ort:** _____	☐☐☐
Nachname des Patienten:	☐☐☐
Geburtsdatum:	☐☐ . ☐☐ . ☐☐☐☐ Tag Monat Jahr

Durchführung der Primärtumorbestrahlung

Beginn der Strahlentherapie ☐☐ . ☐☐ . ☐☐☐☐ (TT.MM.JJJJ)

Abschluss der Strahlentherapie ☐☐ . ☐☐ . ☐☐☐☐ (TT.MM.JJJJ)

☐ konventionelle Bestrahlung ☐ Protonen-Bestrahlung

Gleichzeitige Chemotherapie?

□ Nein

□ Ja

wenn ja, bitte auch entsprechende Chemotherapie-Bögen ausfüllen

Bestrahlungsfeld

☐ Tumorbett

☐ craniospinal

☐ Sonstige_____

Dosis und Fraktionierung

Gesamtdosis ☐☐ **Gy**

Boost? Wenn ja, Gesamtdosis incl. Boost ☐☐ **Gy**

Hyperfraktionierung?

□ Nein

□ Ja

EU-RHAB **Strahlentherapie – Basisdaten Seite 2/2**

Bemerkungen:

Stempel der Klinik	**Datum**	**Unterschrift**

Angaben durch:

Name: _____ **Telefon:** _____

Fax: _____ **Email:** _____

Bitte senden Sie diesen Bogen an:

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Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg
FAX: 0821 400 179340

IV.7.13 Dauertherapie

EU-RHAB

Dauertherapie

Dr. Kornelius Kerl, Universität Münster, Institute of Molecular Tumorbiology,
Robert-Koch-Straße 43, 48149 Münster
Professor Dr. M. Frühwald PhD, Klinikum Augsburg, Klinik für Kinder und Jugendliche, Stenglinstr. 2, 86156 Augsburg,
Email: michael.fruehwald@klinikum-augsburg.de

- in Zusammenarbeit mit dem Deutschen Kinderkrebsregister am IMBEI, 55101 Mainz -

- in Zusammenarbeit mit der GPOH -

EURHAB-No. ⌊_⌊_⌊_⌊_⌋

Behandelnde Klinik _____

Nachname _____ **Vorname** _____ **Geburtsdatum** _____

1. Allgemeine Fragen

Wurde eine Dauertherapie im Anschluss an die intensive Therapie durchgeführt? □ **nein** □ **ja**

Gründe keine Dauertherapie durchzuführen, waren:

☐ Es gibt keine generelle Empfehlung

☐ Rezidiv des Patienten vor Gabe der Dauertherapie

☐ Der Patient ist vor Beginn einer Dauertherapie gestorben

☐ Der Patient/die Eltern des Patienten haben einer Dauertherapie nicht zugestimmt

2. Evaluation vor Beginn der Dauertherapie

2.1. Radiologische Evaluation vor Beginn der Dauertherapie

Datum der letzten radiologischen Evaluation vor Beginn der Dauertherapie ⌊_⌊_ . ⌊_⌊_ . ⌊_⌊_⌊_⌊_ (TT.MM.JJJJ)

Welche Methode wurde verwendet?

CT nativ ☐ CT mit KM ☐ MRT nativ ☐ MRT mit KM ☐ Ultraschall

Residualer Tumor vor Start der Dauertherapie? ☐ nein ☐ ja ☐ nicht evaluiert

Versand an Referenzradiologie erfolgt? ☐ nein ☐ ja

2.2 Evaluation des Liquors vor dem Start der Dauertherapie

Evaluation des Liquors vor dem Start der Dauertherapie? ☐ nein ☐ ja

Datum der Liquorentnahme ⌊⌊⌋⌋.⌊⌊⌋⌋.⌊⌊⌋⌋⌊⌊⌋⌋ (TT.MM.JJJJ)

Tumorzellen im Liquor (bei Beginn der Dauertherapie)

Lumbal ☐ nein ☐ ja ☐ nicht evaluiert

Ventrikulär ☐ nein ☐ ja ☐ nicht evaluiert

Versand einer Liquorprobe an das EURHAB/RHABDOID 2007-Register ☐ nein ☐ ja

3. Dauertherapie

3.1 Allgemeine Fragen

Beginn der Dauertherapie

⌊⌊⌋⌋.⌊⌊⌋⌋.⌊⌊⌋⌋⌊⌊⌋⌋ (TT.MM.JJJJ)

Ende der "intensiven Therapie" ⌊⌊⌋⌋.⌊⌊⌋⌋.⌊⌊⌋⌋⌊⌊⌋⌋ (TT.MM.JJJJ)

Welche Art von Dauertherapie wurde dem Patienten verabreicht?

konventionelle Chemotherapie ☐ nein ☐ ja

Intrathekale Therapie ☐ nein ☐ ja

Andere Therapie (z.B.. epigenetisch wirksame Therapie...) ☐ nein ☐ ja, bitte spezifizieren

_____

EU-RHAB **Dauertherapie, Seite 3/9**

3.2 Dauertherapie "Systemische Therapie"

Welche Medikamente wurden als systemische Therapie (i.v. oder p.o.) während der Dauertherapie (inklusive alternativer Therapieansätze) verabreicht?

Medikamentenname	Datum	Applikation pro Tag (mg/kg)	Kumulative Dosis	Dauer der Dauertherapie (in Wochen	i.v.	p.o.

Wurde die Dauertherapie verzögert gegeben oder musste die Dosis modfiziert werden?

Verzögerung > 3 Tage ☐ nein

☐ ja ☐ aus folgenden Gründen: _____

Anpassung der Dosis ☐ nein

☐ ja ☐ aus folgenden Gründen: _____

Kommentare:

EU-RHAB

3.3 Dauertherapie-i.th. Therapie

Wurde eine intrathekale Therapie während der Dauertherapie verabreicht?

☐ ja ☐ nein

Welche Medikamente wurden i.th. während der Dauertherapie verabreicht?

Name des Medikaments	Tag der Gabe	Dosis
1._____	……..	␣␣ , ␣␣␣ mg
2._____	……..	␣␣ , ␣␣␣ mg
3._____	……..	␣␣ , ␣␣␣ mg
4._____	……..	␣␣ , ␣␣␣ mg

Wurde die i.th. Dauertherapie verzögert gegeben oder musste die Dosis der Dauertherapie modfiziert werden?

Verzögerung > 3 Tage ☐ nein

☐ ja Gründe:_____

Anpassung der Dosis ☐ nein

☐ ja Gründe:_____

3.4 Warum wurde die Dauertherapie beendet?

Die geplante kumulative Dosis/Zeit wurde erreicht	☐ nein	☐ ja
Toxizität der Therapie	☐ nein	☐ ja, bitte spezifizieren:_____
Rezidiv	☐ nein	☐ ja, bitte spezifizieren:_____
Tod des Patienten	☐ nein	☐ ja, bitte spezifizieren:_____
Andere Gründe	☐ nein	☐ ja, bitte spezifizieren:_____

EU-RHAB **Dauertherapie, Seite 5/9**

4. Toxizität-welche Toxizitäten traten während der Dauertherapie auf?

☐ es traten keine toxischen Nebenwirkungen auf *(bitte mit 5.fortfahren)*

☐ toxische Nebenwirkungen traten auf *(bitte in der folgenden Tabelle spezifizieren)*

Toxizitätsskala: CTC modifiziert Bitte tragen Sie den Toxizitätsgrad in der letzten Spalte ein oder kreuzen Sie jeweils das entsprechende Kästchen an

Kategorie	Grad 0	Grad 1	Grad 2	Grad 3	Grad 4	Code	Grad
Allgemeinzustand	normal	geringe Einschränkung	altersgemäße Aktivität stark eingeschränkt	bettlägerig, pflegebedürftig	Intensivpflege, sehr krank	**01**	
Hämatologische Toxizität							
Hämoglobin (g/dl)	Altersnorm (N)	10,0 - < N	8,0 – < 10,0	6,5 – < 8,0	< 6,5	**11**	
Leukozyten (x 10^9/l)	≥ 4,0	3,0 – < 4,0	2,0 – < 3,0	1,0 – < 2,0	< 1,0	**12**	
Granulozyten (x 10^9/l)	≥ 2,0	1,5 – < 2,0	1,0 – < 1,5	0,5 – < 1,0	< 0,5	**13**	
Thrombozyten (x 10^9/l)	≥ 100	75 – < 100	50 – < 75	10 – < 50,0	< 10	**14**	
Infektionen							
Infektion	keine	leichte Infektion	mäßiggradig, Erreger nicht identifiziert; i.v. Antibiotika	schwer, Erreger identifiziert; i.v. Antibiotika	lebensbedrohlich mit Hypotonie	**21**	
Fieber (°C)	< 38	38 - 39	> 39 – 40	> 40 für < 24 h.	> 40 für ≥ 24 h.	**22**	
Verdauungstrakt							
Stomatitis	keine	schmerzloses Ulkus, Erythem	schmerzhaftes Erythem oder Ulkus Nahrungsaufnahme möglich	schmerzhaftes Erythem oder Ulkus, Nahrungs-aufnahme nicht möglich	TPN erforderlich, wg. Stomatitis	**31**	
Erbrechen (Anzahl Episoden pro 24h)	0	1	2 - 5	6 - 10	> 10 oder TPN erforderlich	**32**	
Diarrhoe (Stuhlfrequenz/Tag)	keine	2 - 3	4 – 6 oder nächtliche Stühle oder leichte Bauchkrämpfe	7 - 9 oder Inkontinenz oder schwere Bauchkrämpfe	≥ 10 oder blutiger Durchfall oder TPN erforderlich	**33**	
Hauttoxizität							
Hautveränderungen	keine	Erythem	trockene Desquamation, Vaskulitis, Pruritus	feuchte Desquamation, Ulzerationen	exfoliative Dermatitis, Nekrosen	**40**	
Nierentoxizität							
Kreatinin	Altersnorm (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 6,0 x N	> 6,0 x N	**51**	
Proteinurie (g/l)	keine	< 3	3 – 10,0	> 10	nephrot. Syndrom	**52**	
Hämaturie	keine	mikroskopisch	makroskopisch, ohne Koagel	makroskopisch, mit Koagel	Transfusion erforderlich	**53**	
Kreatinin-Clearence (ml/min/1,73m²)	≥ 90	60 - 89	40 - 59	20 - 39	≤ 19	**54**	
Lebertoxizität							
Bilirubin	Altersnorm (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 10,0 x N	> 10,0 x N	**61**	
SGOT / SGPT	Altersnorm (N)	> N – 2,5 x N	> 2,5 – 5,0 x N	> 5,0 – 20,0 x N	> 20 x N	**62**	
Kardiale Toxizität							
Arrhythmie	Keine	Asympt., keine Therapie	Rekurr./persist., keine Therapie	Therapie erforderlich	Hypotension, ventr. Arrhyth., Defibrillation	**70**	
Herzfunktion	normal	asymptomat., EF ↓ (Ruhe) ≥ 10 % aber < 20 % vom Ausgangswert	asymptomat., aber EF ↓ (Ruhe) unter dem unteren Normwert für EF (Arbeit) oder EF ↓ ≥ 20 % vom Ausgangswert	Milde CHF, therapeutisch kompensiert	schwere/ refraktäre CHF oder Notwendigkeit der Intubation	**71**	
ECHO: LV-SF (%)	≥ 30	≥ 24 - < 30	≥ 20 - < 24	> 15 - < 20	≤ 15	**72**	

Fortsetzung Toxizitätsskala: CTC modifiziert
Bitte tragen Sie den Toxizitätsgrad in der letzten Spalte ein oder kreuzen Sie jeweils das entsprechende Kästchen an

Kategorie	Grad 0	Grad 1	Grad 2	Grad 3	Grad 4	Code	Grad
Ototoxizität							
Hörvermögen	normal	asymptomat. Hörverlust, nur audiometrisch fassbar	mäßige Symptomatik: Tinnitus, geringe Hypakusis bei Audiometrie	stark beeinträchtigender Hörverlust, Korrektur mit Hörgerät nötig	nicht korrigierbare Ertaubung	**80**	
Audiometrie	kein Hörverlust	≤ 15 dB bei ≤2 kHz	16 – 30 dB bei ≤2 kHz	31 – 60 dB bei ≤2 kHz	> 60 dB bei ≤2 kHz	**81**	
Neurotoxizität							
Zentrale Neurotoxizität	keine	Vorübergehende Lethargie	Somnolenz < 50% der Zeit, mäßige Desorientierung	Somnolenz > 50% der Zeit, erhebliche Desorientierung, Halluzinationen	Koma, Krämpfe	**85**	
Periphere Neurotoxizität	keine	Parästhesien	schwere Parästhesien und/oder milde Schwäche	unerträgliche Parästhesien, deutliche motorische Verluste	Paralyse	**86**	

Sonstige Toxizität			
nein = 0 **ja = 1** ☐	**Welche ? (Text)**	**90**	**Grad**

Kommentare:

Weitere Nebenwirkungen:

5. Dauer der Hospitalisierung während der Dauertherapie

Anzahl der Tage im Krankenhaus gesamt während der Dauertherapie (inklusive Medikamentengaben, Behandlung von Nebenwirkungen…) **Tage** ⌊⌊⌋

Anzahl der Tage im Krankenhaus zur Gabe der Dauertherapie **Tage** ⌊⌊⌋

Anzahl der Tage im Krankenhaus zur Behandlung der Nebenwirkungen während der Dauertherapie **Tage** ⌊⌊⌋

6. Evaluation nach Beendigung der Dauertherapie

6.1. Radiologische Evaluation nach Beendigung der Dauertherapie

Datum der radiologischen Untersuchung nach Beendigung der Dauertherapie

⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Welche Methode wurde verwendet?

☐ CT nativ ☐ CT mit KM ☐ MRT nativ ☐ MRT mit KM ☐ Ultraschall

Versand an Referenzradiologie erfolgt? ☐ nein ☐ ja

☐ Progression ☐ Lokalrezidiv

☐ Fernmetastase ☐ Lokalrezidiv u. Fernmetastase

☐ CR

6.2. Evaluation des Liquors nach Beendigung der Dauertherapie (nur für AT/RT Patienten)

Datum der Liquorprobe nach Beendigung der Dauertherapie ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (TT.MM.JJJJ)

Tumorzellen im Liquor (nach Beendigung der Dauertherapie)	**Lumbal**	☐ nein	☐ ja	☐ nicht evaluiert
	Ventrikulär	☐ nein	☐ ja	☐ nicht evaluiert

Versand von Liquor an das „EURHAB/RHABDOID 2007“ Register? ☐ nein ☐ ja

EU-RHAB **Dauertherapie, Seite 8/9**

7. Outcome

Patientenstatus bei der letzten Untersuchung

☐ Patient am Leben

Datum der letzten Untersuchung ⌊⌊⌋⌊⌋.⌊⌋⌊⌋.⌊⌋⌊⌋⌊⌋⌊⌋ (TT.MM.JJJJ)

Datum der letzten radiologischen Untersuchung ⌊⌊⌋⌊⌋.⌊⌋⌊⌋.⌊⌋⌊⌋⌊⌋⌊⌋ (TT.MM.JJJJ)

☐ Patient verstorben

Todesdatum ⌊⌊⌋⌊⌋.⌊⌋⌊⌋.⌊⌋⌊⌋⌊⌋⌊⌋ (TT.MM.JJJJ)

Tumorstatus

☐ Komplette Remission

☐ Lokale Erkrankung

- ☐ *ohne* Progression
- ☐ *mit* Progression (>=25% Zunahme)

☐ Disseminierte Erkrankung

- ☐ *ohne* Progression
- ☐ *mit* Progression (>= 25% Zunahme)

Rezidiv

☐ nein

☐ ja

Neuaufgetretene Zweittumore

☐ nein

☐ ja

War die Dauertherapie bis zum Zeitpunkt dieser Evaluation beendet

☐ **nein, die Dauertherapie war zum Zeitpunkt dieser Evaluation noch nicht beendet**

☐ **ja, die Dauertherapie wurde vor _____ Wochen beendet**

Kommentare:

EU-RHAB **Dauertherapie, Seite 9/9**

Kommentare:

Stempel der behandelnden Klinik	Datum	Unterschrift

Bitte senden Sie dieses Formblatt an:

EU-RHAB
Studienzentrale
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg
FAX: 0821 400 179340

IV.7.2 Case report forms - English

IV.7.2.1 Registration

EU-RHAB
Registration

Shaded areas for trial office use only:

EU-RHAB Pat.-Nr.....

Treatment centre: _____ Town: _____

RESPONSIBLE CLINICIAN: .....

PATIENT´S SURNAME: .....

PATIENT´S FIRST NAME: .....

DATE OF BIRTH ..... Day Month Year

SEX

☐ male

☐ female

DATE OF DEFINITIVE BIOPSY OR INITIAL SURGERY..... Day Month Year

Histological diagnosis	☐ MRT (soft tissue) ☐ RTK (kidney) ☐ AT/RT (CNS) ☐ Other: _____
Previous treatment other than surgery?	☐ **no** ☐ **yes**
Previous malignancy	☐ **no** ☐ **yes**
Medical contraindications for chemotherapy?	☐ **no** ☐ **yes**
Informed consent signed?	☐ **no** ☐ **yes**

Treatment centre (stamp) **Date** **Signature**

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

Please fax this form to the trial office: 0049 821 400 179340

IV.7.2.2 Clinical extent at diagnosis

EU-RHAB
Clinical extent at diagnosis

Data Center and Study Coordination:
I. Klinik für Kinder und Jugendliche, Stenglinstr. 2, 86156 Augsburg,
Phone: 0049 821 400 9340 , FAX: 0049 821 400 17 9340, email: eurhab@klinikum-augsburg.de
- in Cooperation with Deutschen Kinderkrebsregister am IMBEI, 55101 Mainz -
- in Cooperation GPOH -

Pat.-No. **Treatment centre**

⌊_⌊_⌊_⌊_⌋ _____

Surname **First name** **date of birth**

Informed consent registration and transmission of personal data

- ☐ has been signed by patient (necessary in patients above the age of 16, in patients below the age of 16 if understanding)
- ☐ has been signed by the legal guardian
- ☐ could not be obtained yet
- ☐ was refused

History

Cause for medical consultation:

- ☐ Tumor symptoms leaded to medical consultation
- ☐ Preventive Examination (U1-U9)
- ☐ Result of other examination
- ☐ Pre-natal diagnostic

General condition at diagnosis:

- ☐ Normal no complaint
- ☐ mild complaints, but needs no assistance
- ☐ age-appropriate activity severely impaired (e.g. no regular school visits)
- ☐ confined to bed, needs nursing care
- ☐ needs intensive care, seriously ill, moribund

Diagnosis in other institution: ☐ No ☐ Yes, in: _____

Participation in trial: ☐ No ☐ Yes, EU-RHAB ☐ Yes, other: _____

Therapy in other institution: ☐ No ☐ Yes, in: _____

Kind of therapy:

- ☐ Chemotherapy ☐ CWS ☐ HIT ☐ other
- ☐ SIOP 2001 (Nephroblastoma)
- ☐ Surgery ☐ biopsy ☐ complete resection
- ☐ incomplete resection
- ☐ Radiation

EU-RHAB **Clinical extent at diagnosis, page 2/9**

Earliest appearance of symptoms caused by the tumor When? ⌊_⌊_⌊_ Weeks before admission to hospital

Which? _____

Preceding tumor disease	☐ No	☐ Yes, please specify:	_____
Hematologic diseases	☐ No	☐ Yes, please specify:	_____
Immuno deficiency	☐ No	☐ Yes, please specify:	_____
Chronic virus infection	☐ No	☐ Yes, please specify:	_____
Chromosome aberration	☐ No	☐ Yes, please specify:	_____
Syndrome (eg. M. Down, Rhabdoid-tumor-predisposition-syndrome)	☐ No	☐ Yes, please specify:	_____
Other chronic preceding diseases	☐ No	☐ Yes, please specify:	_____

Family history

more than one possible

Family predisposition (Leukemia, tumor, Immuno deficiency, syndrome)

☐ No

☐ Yes, parents — Who? please specify _____

☐ Yes, brothers and sisters — Who? please specify _____

☐ Yes, other — Who? please specify _____

Birth year of parents: mother: ⌊_⌊_⌊_⌊_ father: ⌊_⌊_⌊_⌊_

Number of brothers and sisters: ⌊_⌊_ Identical twin?? ☐ No ☐ Yes

Diagnosis

Date of admission to hospital ⌊_⌊_ . ⌊_⌊_ . ⌊_⌊_⌊_⌊_ (DD.MM.YYYY)

Date of diagnosis (tumor) ⌊_⌊_ . ⌊_⌊_ . ⌊_⌊_⌊_⌊_ (DD.MM.YYYY)

Date of diagnosis Rhabdoid-tumor *(Reference pathology!)* ⌊_⌊_ . ⌊_⌊_ . ⌊_⌊_⌊_⌊_ (DD.MM.YYYY)

Type of diagnosis

☐ Primary diagnosis

☐ Relapse / secondary malignancy

EU-RHAB **Clinical extent at diagnosis, page 3/9**

Histopathology – Local pathologist`s report (please enclose)

Date of report ⌊⌊⌋⌊⌋⌋.⌊⌊⌋⌊⌋⌋.⌊⌊⌋⌊⌋⌊⌋⌊⌋⌋ (DD.MM.YYYY) **Journal-Nr.** ⌊⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌋

Institution _____

Immunhistochemistry (localer pathologist)

- ☐ SMARCB1/hSNF5/INI1 retained
- ☐ SMARCB1/hSNF5/INI1 lost

Histopathology (local pathologist)

- ☐ MRT (soft tissuel)
- ☐ RTK (kidney)
- ☐ AT/RT (CNS)
- ☐ Other _____

Histopathology – Reference pathologist`s report (please enclose)

Dispatch to reference pathologist

- ☐ No
- ☐ Yes, planned
- ☐ Yes, has been made
  - ☐ to Bonn
  - ☐ to Kiel
  - ☐ to Münster
  - ☐ other _____

Date of report ⌊⌊⌋⌊⌋⌋.⌊⌊⌋⌊⌋⌋.⌊⌊⌋⌊⌋⌊⌋⌊⌋⌋ (DD.MM.YYYY) **Journal-Nr.** ⌊⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌋

Institution _____

Immunhistochemistry (Reference pathologist)

- ☐ SMARCB1/hSNF5/INI1 retained
- ☐ SMARCB1/hSNF5/INI1 lost

Histopathology (Reference pathologist)

- ☐ MRT (soft tissuel)
- ☐ RTK (kidney)
- ☐ AT/RT (CNS)
- ☐ Other _____

EU-RHAB **Clinical extant at diagnosis, page 4/9**

Primary tumor – initial radiologic evaluation

Date of radiologic evaluation ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)

Which method has been used?

Primary site ☐ CT native ☐ CT with contrast ☐ MRT native ☐ MRT with contrast

Primary site – initial tumor volume

Dimension ⌊_⌊_⌋ , ⌊_⌋ **x** ⌊_⌊_⌋ , ⌊_⌋ **x** ⌊_⌊_⌋ , ⌊_⌋ cm (plane with largest diameter)

Dispatch to reference radiology: ☐ No ☐ Yes

Site of primary tumor

CNS
☐ Cerebral Hemisphere ☐ Pons
☐ Cerebellum ☐ Spinal
☐ Stem Ganglia
☐ Other (please specify) _____
☐ right ☐ left ☐ both sides

Kidney ☐ right ☐ left ☐ both sides

Soft tissue ☐ right ☐ left ☐ both sides

Please mark localisation in the following table:

Region	Localisation	Code	Region	Localisation	Code
Pelvis	Palvic soft tissue	15		Face	56
	Buttock	16		Other *	50
	Hip / Inguinal region	17	Upper extremity	Upper arm	67
	Perineum	18		Elbow	68
	Other *	10		Forearm	69
Abdomen	Liver	21		Wrist	70
	Intra-abdominall (exept liver)	22		Hand	71
	Retroperitoneal	23		Other *	60
	Abdominal wall	24	Lower extremity	Thigh	88
	Other *	20		Knee	89
Chest	Shoulder	45		Leg	90
	Axilla	46		Ankle	91
	Chest wall	47		Foot	92
	Other *	40		Other *	80
Head and neck	Scalp	54	Unknown primary tumor		99
	Neck	55			

* Other – please specify: _____

EU-RHAB **Clinical extent at diagnosis, page 5/9**

Metastases – radiologic evaluation

☐ MRI-body
☐ MRI-cranial
☐ MRI-abdomen
☐ MRI-spinal
☐ CT (region)_____
☐ CT-thorax
☐ CT-whole body
☐ Others_____
☐ PET - CT
☐ PET - MRI
☐ Bone scintigraphy

Metastases – localisation outside CNS

More than one possible

☐ No
☐ Yes, bone / localisation _____
☐ Yes, lymph nodes / localisation_____
☐ Yes, bone marrow ☐ Yes, liver ☐ Yes, mediastinum
☐ Yes, lung ☐ left ☐ right ☐ both sides
☐ Yes, kidney ☐ left ☐ right ☐ both sides
☐ Yes, other localisation (please specify) _____
☐ Not evaluated

if yes, number of metastases ⌊_⌋⌊_⌋

Metastases – localisation CNS (solid)

More than one possible

☐ No
☐ Yes, supratentorial
☐ Yes, infratentorial (Ø Brain stem)
☐ Yes, Pons
☐ Yes, other (please specify) _____
☐ Not evaluated
☐ Yes, Medulla oblongata
☐ Yes, spinal extramedullar
☐ Yes, spinal intramedullar

if yes, number of metastases ⌊_⌋⌊_⌋

Meningeosis (radiology)

More than one possible

☐ No
☐ Yes, supratentorial
☐ Yes, infratentorial
☐ Not evaluated
☐ Yes, spinal
☐ Yes, other (please specify) _____

Tumor cells in CSF (AT/RT only)

Please send unstained CSF cyto spins to study coordinator!

Dispatch of CSF to study coordinator? ☐ No ☐ Yes

Date of CSF sample ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (DD.MM.YYYY)

Tumor cells in CSF (directly before beginning of post-surgery treatment)

Lumbal	☐ No	☐ Yes	☐ Not evaluated
Ventricular	☐ No	☐ Yes	☐ Not evaluated

EU-RHAB **Clinical extent at diagnosis, page 6/9**

Primary surgery

Date of sugery ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)

Institution / Surgeon _____

Type of surgery

- ☐ Biopsy, open
- ☐ Biopsy, stereotactic
- ☐ Partial resection (< 50%)
- ☐ Partial resection (> 50%)
- ☐ Subtotal resektion (< 10%)
- ☐ Total resection (no visible residuals)

In case of primary metastases:

Resection of metastases ☐ No ☐ Yes, complete ☐ Yes, incomplete

Date ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)

Persisting VP/VA-shunt? ☐ No ☐ Yes, v. p. ☐ Yes, v. a.

Mutilating surgery/amputation ☐ No ☐ Yes, _____

Surgical complications

☐ No

☐ Yes, neurologic (please specify) _____

☐ Yes, not neurologic (please specify) _____

Early radiologic evaluation after surgery

Date of radiologic evaluation ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)

Primary site ☐ CT native ☐ CT with contrast ☐ MRT native ☐ MRT with contrast

Extension ⌊_⌊_⌋ , ⌊_⌋ cm X ⌊_⌊_⌋ , ⌊_⌋ cm

Laboratory findings at diagnosis

Tumormarker:

Catecholamines (serum)	☐ raised	☐ not raised	☐ not performed
Catecholamines (urine)	☐ raised	☐ not raised	☐ not performed

SMARCB1/hSNF5/INI1-Deletion:

Tumor:	☐ performed, in: _____		☐ not performed
Method	☐ Immunhistochemistry	☐ Moleculargenetics	☐ Cytogenetics
From Blood or DNA	☐ performed, in: _____		☐ not performed
Method	☐ Immunhistochemistry	☐ Moleculargenetics	☐ Cytogenetics

EU-RHAB **Clinical extent at diagnosis, page 7/9**

Organ function at diagnosis

Cardiac function ☐ normal ☐ changed: _____

Renal function ☐ normal ☐ changed: _____

Beginning of therapy (EU-RHAB)

Date ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)

with: ☐ Window ☐ Chemotherapy ☐ Surgery ☐ Radiatio ☐ other: _____

Comments:

Treatment centre (stamp) **Date** **Signature**

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

EU-RHAB Attachment for AT/RT – part 1 Clinical extent at diagnosis, page 8/9

PRE-operative neurological examination (to be filled for AT/RT–patients only)

Date of examination ⌊⌊⌋⌋.⌊⌊⌋⌋.⌊⌊⌋⌋⌊⌊⌋⌋ (DD.MM.YYYY)

Symptoms of increased intracranial pressure ☐ No ☐ Emesis ☐ Raised fontanelle
More than one possible ☐ Headache ☐ Behavioural changes
☐ Raised optic disc

Disorder of conciousness ☐ No ☐ Somnolence
☐ Stupor
☐ Coma

Seizures ☐ No ☐ Yes

Neuropsychological disorder ☐ No ☐ Yes, _____

Failure of cranial nervs ☐ No ☐ Yes, symptom/side _____ CN # ⌊⌊⌋⌋
☐ Yes, symptom/side _____ CN # ⌊⌊⌋⌋
☐ Yes, symptom/side _____ CN # ⌊⌊⌋⌋

Disorder of gross motor function ☐ No ☐ Monoparesis – right arm ☐ Monoparesis – left arm
☐ Monoparesis – right leg ☐ Monoparesis – left leg
☐ Hemiparesis right ☐ Hemiparesis left
☐ Paraparesis ☐ Tetraparesis

In case of paraplegia ☐ incomplete ☐ complete
Level of paraplegia _____

Disorder of coordination ☐ No ☐ Ataxia of extremities ☐ Nystagmus
More than one possible ☐ Intention tremor ☐ Ataxia of trunk
☐ other _____

Extrapyramidal movement disorder ☐ No ☐ Yes _____

Disorder of sensibility ☐ No ☐ Yes _____

Disorder of vegetative functions ☐ No ☐ Yes _____

Somatic disorders ☐ No ☐ Yes _____

Neuroendocrine disorders ☐ No ☐ Yes _____

Hight ⌊⌊⌋⌋⌊⌋ cm **Weight** ⌊⌊⌋⌋,⌊⌋ kg **Head circumference** ⌊⌊⌋⌋,⌊⌋ cm

EU-RHAB Attachement for AT/RT- part 2 Clinical extend at diagnosis, page 9/9

POST-operative neurological examination (to be filled for AT/RT-patients only)

Date of examination ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (DD.MM.YYYY)

Symptoms of increased intracranial pressure ☐ No ☐ Emesis ☐ Raised fontanelle
More than one possible ☐ Headache ☐ Behavioural changes
☐ Raised optic disc

Disorder of conciousness ☐ No ☐ Somnolence
☐ Stupor
☐ Coma

Seizures ☐ No ☐ Yes

Neuropsychological disorder ☐ No ☐ Yes, _____

Failure of cranial nervs ☐ No ☐ Yes, symptom/side _____ CN # ⌊_⌋⌊_⌋
☐ Yes, symptom/side _____ CN # ⌊_⌋⌊_⌋
☐ Yes, symptom/side _____ CN # ⌊_⌋⌊_⌋

Disorder of gross motor function ☐ No ☐ Monoparesis – right arm ☐ Monoparesis –left arm
☐ Monoparesis – right leg ☐ Monoparesis – left leg
☐ Hemiparesis right ☐ Hemiparesis left
☐ Paraparesis ☐ Tetraparesis

In case of paraplegia ☐ incomplete ☐ complete
Level of paraplegia _____

Disorder of coordination ☐ No ☐ Ataxia of extremities ☐ Nystagmus
More than one possible ☐ Intention tremor ☐ Ataxia of trunk
☐ Other _____

Extrapyramidal movement disorders ☐ No ☐ Yes _____

Disorder of sensibility ☐ No ☐ Yes _____

Disorder of vegetative functions ☐ No ☐ Yes _____

Somatic disorders ☐ No ☐ Yes _____

Neuroendocrine disorders ☐ No ☐ Yes _____

Height ⌊_⌋⌊_⌋⌊_⌋ cm **Weight** ⌊_⌋⌊_⌋ , ⌊_⌋ kg **Head circumference** ⌊_⌋⌊_⌋ , ⌊_⌋ cm

IV.7.2.3 Chemotherapy

EU-RHAB
Conventional chemotherapy

Patient number:	⌊⌊⌊⌊⌋
Treatment centre: _____ **Town:** _____	⌊⌊⌊⌋
Patient´s surname:	⌊⌊⌊⌋
Date of birth:	⌊⌊⌋ . ⌊⌊⌋ . ⌊⌊⌊⌊⌋ Day Month Year

Course No. ⌊⌊⌋ **Day 1 of this course** ⌊⌊⌋ . ⌊⌊⌋ . ⌊⌊⌊⌊⌋ (DD.MM.YYYY)

Height at start of course (in cm) ⌊⌊⌊⌋ **Weight at start of course (in g)** ⌊⌊⌊⌊⌊⌋

Delay > 5 days ☐ no

☐ yes ☐ Due to toxicity of previous course

☐ Due to other reasons (please specify):_____

Dosemodification ☐ no

☐ yes ☐ Due to toxicity of previous course

☐ Due to other reasons (please specify):_____

Cumulative dose per course <u>DOX</u> Doxorubicine ⌊⌊⌊⌊⌋ mg

MTX i.ventr. (AT/RT only) → **Please fill file: „Chemotherapy: intraventricular MTX-Injections"**

Cumulative dose per course <u>ICE</u> Ifosfamide ⌊⌊⌊⌊⌋ mg

Carboplatinum ⌊⌊⌊⌋ mg

Etoposid ⌊⌊⌊⌋ mg

MTX i.ventr. (AT/RT only) → **Please fill file:" intrathecal MTX"**

Cumulative dose per course <u>VCA</u> Vincristine ⌊⌋ , ⌊⌋ mg

Cyclophosphamide ⌊⌊⌊⌊⌋ mg

Actinomycin-D ⌊⌊⌊⌋ µg

MTX i.ventr. (only AT/RT) → **Please fill file: "intrathecal MTX"**

EU-RHAB **Conventional chemotherapy, page 2/5**

WBC ot strat of course ⌊_⌋⌊_⌋ , ⌊_⌋ x 10^9/L

Platelets at start of course ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ x 10^9/L

Evaluation of primary tumor/metastases

obligatory after course 2, 4, 6 and 9!

Date of evaluation ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (DD.MM.YYYY)

Method of evaluation ☐ MRI ☐ CT ☐ Ultrasound ☐ others _____

Primary tumor

Compared to previous evaluation

☐ Not evaluated

☐ Complete remission
☐ Partial remission (> 50 % decrease)
☐ Stable disease (< 50% but > 25 % decrease)
☐ No changes
☐ Progression/Relapse (≥ 25% increase)

Metastases

Compared to previous evaluation

☐ none
☐ Not evaluated

☐ Complete remission
☐ Partial remission (> 50 % decrease)
☐ Stable disease (< 50% but > 25 % decrease)
☐ No changes
☐ Progression/Relapse (≥ 25% increase)

Tumor cells in CSF
Evaluation obligatory!

☐ Not evaluated ☐ No ☐ Yes

Continuation of therapy (planned):

☐ **According to protocol**

☐ **Salvage** *(in case of insufficient response or or progress or metastases)*

- ☐ High-dose-chemotherapy
- ☐ Local radiotherapy
- ☐ Second-look-Surgery → **Please fill file "Surgery"!**
- ☐ Other

  Please specify: _____

☐ **Discontinuation of treatment**

Please fill file „End of treatment"

EU-RHAB **Conventional chemotherapy, page 3/5**

Comments:

Treatment centre (stamp)	Date	Signature

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

Please send this form to:

EU-RHAB
Data Center and Study Coordination
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg- GERMANY
FAX: 0049 821 400 179340

Toxicity scale: CTC modified Report after conventional chemotherapy No._____

Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Code	Grade
General condition	normal	Mild impairement	Age-related activities strongly decreased	Bedridden, in need of care	Intensive care, very sick	**01**	
Haematological toxicity							
Haemoglobin (g/dl)	Normal for age (N)	10,0 - < N	8,0 – < 10,0	6,5 – < 8,0	< 6,5	**11**	
WBC (x 10^9/l)	≥ 4,0	3,0 – < 4,0	2,0 – < 3,0	1,0 – < 2,0	< 1,0	**12**	
Granulocytes (x 10^9/l)	≥ 2,0	1,5 – < 2,0	1,0 – < 1,5	0,5 – < 1,0	< 0,5	**13**	
Platelets (x 10^9/l)	≥ 100	75 – < 100	50 – < 75	10 – < 50,0	< 10	**14**	
Infections							
Infection	none	mild	Moderate, pathogen not identified; i.v. antibiotics	Severe, pathogen identified; i.v. antibiotics	Life threatening, with hypotension	**21**	
Fever (°C)	< 38	38 - 39	> 39 – 40	> 40 for < 24 h.	> 40 for ≥ 24 h.	**22**	
Gut toxicity							
Stomatitis	none	Painless ulcer, erythema	Painful erythema or ulceration, can still eat	Painful erythema or ulceration, cannot eat	TPN required due to stomatitis	**31**	
Vomiting (no. Of episodes in 24 h**)**	0	1	2 - 5	6 - 10	> 10 or TPN necessary	**32**	
Diarrhoea (Stools/day**)**	none	2 - 3	4 – 6 or nightly stool or light cramps	7 - 9 or incontinence or severe cramps	≥ 10 or bloody diarhoeal or TPN required	**33**	
Skin toxicity							
Changes in the skin	none	erythema	Dry desquamation, vasculitis, pruritus	moist desquamation, ulceration	Exfoliativ dermatitis, necrosis	**40**	
Renal toxicity							
Creatinine	normal for age (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 6,0 x N	> 6,0 x N	**51**	
Proteinuria (g/l)	none	< 3	3 – 10,0	> 10	nephrot. Syndrom	**52**	
Hämaturia	none	microskopic	macroskopic, no clotsl	macroskopic, clots	transfusion required	**53**	
Creatinine-Clearence (ml/min/1,73m²)	≥ 90	60 - 89	40 - 59	20 - 39	≤ 19	**54**	
Liver toxicity							
Bilirubin	Normal for age (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 10,0 x N	> 10,0 x N	**61**	
SGOT / SGPT	Normal for age (N)	> N – 2,5 x N	> 2,5 – 5,0 x N	> 5,0 – 20,0 x N	> 20 x N	**62**	
Cardiac toxicity							
Arrhythmia	none	Asympt., no therapy	Recurr./persist., no therapy	Therapy necessary	Hypotension, ventr. arrhyth., defibrillation	**70**	
Cardiac function	normal	asymptomat., EF ↓ (Ruhe) ≥ 10 % but < 20 % of baseline	asymptomat., but EF ↓ ≥ 20 %of baseline	Mild congestive heart failure, therapeutically compensated	Severe / refractory congestive heart failure	**71**	
ECHO: LV-SF (%)	≥ 30	≥ 24 - < 30	≥ 20 - < 24	> 15 - < 20	≤ 15	**72**	
Ototoxicity							
hearing	normal	asymptomat. Hearing loss, nur audiometrisch fassbar	Hearing loss not requiering hearing aid or intervention	Hearing loss requiring hearing aid or intervention	Profound bilateral hearing loss	**80**	
Audiometry	No hearing loss	≤ 15 dB at ≤2 kHz	16 – 30 dB at ≤2 kHz	31 – 60 dB at ≤2 kHz	> 60 dB at ≤2 kHz	**81**	

Continuation toxicity scale: CTC modified Report following conventional therapy
No._____

Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Code	Grade
Neurotoxicity							
Central neurotoxicity	none	Transient lethargia	Somnolence < 50% of time, mild disorientation	Somnolence > 50% of time, severe disorientation, hallucinations	Coma, seizures	**85**	
Peripheral neurotoxicity	none	paraesthesia	Severe paraesthesia and/or weakness	Unbearable paraesthesia, deficits in motor function	paralysis	**86**	
Other toxicity							
no = 0 **yes = 1** ☐	**Please specify**					**90**	**Grad**

After courses containing **anthracyclines** please give information according cardiac toxicity:

Date of evaluation ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY)

Rhythm Pulse: ☐☐☐ Antiarrhythmic therapy? ☐ No ☐ Yes

Cardiac function Pressure syst. / diast. ☐☐☐ / ☐☐☐ LV-SF: ☐☐ % Pathologic diastolic parameters? ☐ No ☐ Yes

Application of digitalis? ☐ No ☐ Yes Application of diuretics? ☐ No ☐ Yes Application of beta-blockers? ☐ No ☐ Yes

Further diagnostic evaluation
☐ MUGA
☐ EPO-level
☐ Troponin
☐ Other

IV.7.2.4 intrathecal MTX

EU-RHAB
Chemotherapy: Intraventricluar Methotrexat-injection

Patient number:	␣␣␣␣
Treatment centre: _____ **Town:** _____	␣␣␣
Patient´s surname:	␣␣␣
Date of birth:	␣␣ . ␣␣ . ␣␣␣␣ Day Month Year

Course No. ␣␣ **Day 1 MTX** ␣␣ . ␣␣ . ␣␣␣␣ (DD.MM.YYYY)

Day 1:	MTX intraventricular	☐ No	☐ Yes	␣ , ␣␣	mg	
	MTX-level:	_____ µmol/L		protein	_____ mg/dl	
Day 2:	MTX intraventricular	☐ No	☐ Yes	␣ , ␣␣	mg	
	MTX-level:	_____ µmol/L		protein	_____ mg/dl	
Day 3:	MTX intraventricular	☐ No	☐ Yes	␣ , ␣␣	mg	
	MTX-level:	_____ µmol/L		protein	_____ mg/dl	
Day 4:	MTX intraventricular	☐ No	☐ Yes	␣ , ␣␣	mg	
	MTX-level:	_____ µmol/L		protein	_____ mg/dl	

MTX-level / protein level of CSF!

Further MTX-/protein level:

Day ____**:**	MTX-level:	_____ µmol/L	protein	_____ mg/dl
Day ____**:**	MTX-level:	_____ µmol/L	protein	_____ mg/dl
Day ____**:**	MTX-level:	_____ µmol/L	protein	_____ mg/dl
Day ____**:**	MTX-level:	_____ µmol/L	protein	_____ mg/dl

MTX-level / protein level of CSF!

EU-RHAB **Chemotherapy: Intraventricular Methotrexat-Injection, page 2/3**

Toxicity / Complications (due to MTX intrathecal / Rickham-Reservoir / Ommaya-Reservoir)

CNS bleeding	☐ No	☐ Yes
CNS infection	☐ No	☐ Yes
Neurotoxicity	☐ No	☐ Yes
Overdose / toxic MTX-level	☐ No	☐ Yes
Other toxicity	☐ No	☐ Yes

Please describe in detail

1. the toxicity - symptoms

2. the therapeutic measurements

3. the course of the toxicity/complication

EU-RHAB **Chemotherapy: Intraventricular Methotrexat-Injections, page 3/3**

Comments:

Treatment centre (stamp)	Date	Signature

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

Please send this form to:

EU-RHAB
Data Center and Coordination
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg - GERMANY
FAX: 0049 821 400 179340

IV.7.2.5 Stem-cell harvest

EU-RHAB
Stem cell harvest

Patient number:	☐☐☐☐
Treatment centre: _____ **Town:** _____	☐☐☐
Patient´s surname:	☐☐☐
Date of birth:	☐☐ . ☐☐ . ☐☐☐☐ Day Month Year

Body weight at apheresis (g) ☐☐☐☐☐

Date of first stem cell apheresis/harvest ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY)

Number of apheresis ☐

Chemotherapy prior to mobilisation ☐ none ☐ Dox ☐ ICE ☐ VCA

Mobilisation after course no. ☐☐ Day 1 of mobilisation course ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY)

Progenitor cells ☐ autologous, peripheral blood ☐ autologous, bone marrow

Mobilisation ☐ Chemotherapy + HGF ☐ Steady state + HGF ☐ Chemotherapy only

Hematologic growth factors ☐ none ☐ G-CSF ☐ GM-CSF

☐ other (please specify): _____

Purging ☐ no purging ☐ CD34 selection

☐ other (please specify): _____

Number of collected stem cells before freezing ☐☐ , ☐☐ X 10^6 CD34+/kg

☐☐ , ☐☐ X 10^8 ANC/kg

☐☐ , ☐☐ X 10^4 CD3+/kg

EU-RHAB **Stem cell harvest, page 2/2**

Comments:

Treatment centre (stamp)	Date	Signature

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

Please send this form to:

EU-RHAB
Data Center and Coordination
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg - GERMANY
FAX: 0049 821 400 179340

IV.7.2.6 High-dose-chemotherapy (HDCT)

EU-RHAB
Chemotherapy: High-dose therapy

Patient number:	☐☐☐☐
Treatment centre: _____ **Town:** _____	☐☐☐
Patient`s surname:	☐☐☐
Date of birth:	☐☐ . ☐☐ . ☐☐☐☐ Day Month Year

Status prior to HDCT:

Tumorstatus:		**General condition of health:**	
Complete remission	☐	**Normal activity, no complaints**	☐
Partial remission	☐	**Mild complaints, but needs no assistance**	☐
Stable Disease	☐	**Age-appropriate activity, severely impaired**	☐
Progress	☐	**Confined to bed, needs nursing care**	☐
Not evaluable	☐	**Needs intensive care, seriously ill, moribund**	☐

Organ functions prior to HDCT:

Cardiac function

Not evaluated ☐ Evaluated by echokardiography ☐ Evaluated by scintigraphy ☐

If evaluated:

LV-SF ☐☐ **%** EF ☐☐ **%**

Kidney

GFR Not evaluated ☐ Evaluated by creatinine clearance ☐ Evaluated by EDTA ☐

result:

☐☐☐ **ml/min/1,73 m²**

Tubular function Not evaluated ☐ Evaluated ☐

result: TP/CCrea oder Tmp/GFR HCO3

☐ , ☐☐ mmol/l ☐☐ , ☐ mmol/l

EU-RHAB **Chemotherapy: High-dose therapy, page 2/8**

Liver

SGOT ⌊⌊⌊⌊ Upper value of SGOT fort the lab ⌊⌊⌊⌊

Lung function

Not evaluated ☐ normal ☐ reduced ☐

Lung Compliance ⌊⌊⌊ % CO-diffusion ⌊⌊⌊ %

Viral status prior to HDCT:

CMV	**negative**	☐	**positive**	☐	**unknown**	☐
HBV	**negative**	☐	**positive**	☐	**unknown**	☐
HCV	**negative**	☐	**positive**	☐	**unknown**	☐
HIV	**negative**	☐	**positive**	☐	**unknown**	☐

Blood ABO-group:

0 ☐
A ☐
B ☐
AB ☐

Rhesus factor:

Rhesus factor positive ☐
Rhesus factor negative ☐

EU-RHAB **Chemotherapy: High-dose therapy, page 3/8**

Day 1 of high-dose ⌊⌊⌋⌋.⌊⌊⌋⌋.⌊⌊⌋⌋⌊⌊⌋⌋ (DD.MM.YYYY)

☐ 1st HDCT ☐ 2nd HDCT

Height (cm) ⌊⌊⌋⌋⌊⌋ **Weight (g)** ⌊⌊⌋⌋⌊⌊⌋⌋⌊⌋

Delay > 5 days

☐ No

☐ Yes

- ☐ Due to toxicity of previous course
- ☐ Due to other reasons (please specify)

_____

Dose modification

☐ No

☐ Yes

- ☐ Due to toxicity of previous course
- ☐ Due to other reasons (please specify)

_____

Cumulative dose

Carboplatin	⌊⌊⌋⌋⌊⌊⌋⌋⌊⌋	mg
Etoposid	⌊⌊⌋⌋⌊⌊⌋⌋⌊⌋	mg
Thiotepa	⌊⌊⌋⌋⌊⌊⌋⌋⌊⌋	mg
other	⌊⌊⌋⌋⌊⌊⌋⌋⌊⌋	mg

Stem cell rescue: ☐ PBSC ☐ PBSC with CD 34 selection ☐ Bone marrow

Number of stem cells given ⌊⌊⌋⌋,⌊⌋ x 10^8/kg KG

or

Number of Cd 34+ Cells ⌊⌊⌋⌋,⌊⌋ x 10^6/kg KG

WBC at beginning ⌊⌊⌋⌋,⌊⌋ x 10^9/L

Platelets at beginning ⌊⌊⌋⌋⌊⌋⌋ x 10^9/L

By Tandem HDCT – please fill out second form

EU-RHAB **Chemotherapy: High-dose therapy, page 4/8**

GCSF ⌊_⌋⌊_⌋ µg/kg KG/d

Application from ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (DD.MM.YYYY) to ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (DD.MM.YYYY)

Engraftment

WBC > 1000/µl at ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (DD.MM.YYYY)

Neutrophiles > 500/µl at ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (DD.MM.YYYY)

Platelets > 50.000/µl at ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (DD.MM.YYYY)

Evaluation of primary tumor/metastases

Date of evaluation ⌊_⌋⌊_⌋.⌊_⌋⌊_⌋.⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (DD.MM.YYYY)

Method of evaluation ☐ MRT ☐ CT ☐ Ultrasound ☐ others _____

Primary tumor

Compared to previous evaluation

☐ Not evaluated

☐ Complete remission
☐ Partial remission (> 50 % decrease)
☐ Stable disease (< 50% but > 25 % decrease)
☐ No changes
☐ Progression/Relapse (≥ 25% increase)

Metastases

☐ none

Compared to previous evaluation

☐ Not evaluated

☐ Complete remission
☐ Partial remission (> 50 % decrease)
☐ Stable disease (< 50% but > 25 % decrease)
☐ No changes
☐ Progression/Relapse (≥ 25% increase)

Tumor cells in CSF
Evaluation obligatory!

☐ Not evaluated ☐ No ☐ Yes

EU-RHAB **Chemotherapy: High-dose therapy, page 5/8**

Toxicity from HDCT:

Parenteral analgesia required ?	No ☐	Yes ☐	If yes, duration ⌊⌊⌋⌋ days
Parenteral nutrition required?	No ☐	Yes ☐	If yes, duration ⌊⌊⌋⌋ days
Parenteral antibiotics reqiured ?	No ☐	Yes ☐	If yes, duration ⌊⌊⌋⌋ days
VOD ?	No ☐	Yes ☐	If yes, grade (Bearman) ⌊⌋
VOD-Prevention ?	No ☐	Yes ☐	If yes, with Defibrotide ☐ Heparin ☐

1=mild hepatic dysfunction	2 mg% ≤ bilirubin ≤ 6 mg% **or** 2.5% ≤ weight gain ≤ 5% from baseline **or** SGOT-increase > 2-fold, but < 5-fold from lowest preconditioning
2= moderate hepatic dysfunction	6 mg% < bilirubin ≤ 20 mg% **or** SGOT-increase > 5-fold from lowest preconditioninig **or** clinical or image-documented ascites **or** weight gain > 5% from baseline
3= severe hepatic dysfunction	bilirubin > 20 mg% **or** hepatic encephalopathy **or** ascites compromising respiratory function

Pulmonary toxicity	No ☐	Yes ☐	
If yes, pneumonitis?	No ☐		
	Yes ☐	Radiographic changes, symptoms do not require steroids	☐
		Steroids required	☐
		Oxygen required	☐
		Assisted ventilation required	☐
Other pulmonary toxicity?	No ☐	Yes ☐	if yes, specify: _____

EU-RHAB **Chemotherapy: high-dose therapy, page 6/8**

Comments:

Treatment centre (stamp)	Date	Signature

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

Please send this form to:

EU-RHAB
Data Center and Coordination
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg - GERMANY
FAX: 0049 821 400 179340

Toxicity scale: CTC modified Report after high dose therapy No. _____

Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Code	Grade
General condition	normal	Mild impairement	Age-related activities strongly decreased	Bedridden, in need of care	Intensive care, very sick	**01**	
Haematological toxicity							
Haemoglobin (g/dl)	Normal for age (N)	10,0 - < N	8,0 – < 10,0	6,5 – < 8,0	< 6,5	**11**	
WBC (x 10^9/l)	≥ 4,0	3,0 – < 4,0	2,0 – < 3,0	1,0 – < 2,0	< 1,0	**12**	
Granulocytes (x 10^9/l)	≥ 2,0	1,5 – < 2,0	1,0 – < 1,5	0,5 – < 1,0	< 0,5	**13**	
Platelets (x 10^9/l)	≥ 100	75 – < 100	50 – < 75	10 – < 50,0	< 10	**14**	
Infections							
Infection	none	mild	Moderate, pathogen not identified; i.v. antibiotics	Severe, pathogen identified; i.v. antibiotics	Life threatening, with hypotension	**21**	
Fever (°C)	< 38	38 - 39	> 39 – 40	> 40 for < 24 h.	> 40 for ≥ 24 h.	**22**	
Gut toxicity							
Stomatitis	none	Painless ulcer, erythema	Painful erythema or ulceration, can still eat	Painful erythema or ulceration, cannot eat	TPN required due to stomatitis	**31**	
Vomiting (no. Of episodes in 24 h**)**	0	1	2 - 5	6 - 10	> 10 or TPN necessary	**32**	
Diarrhoea (Stools/day**)**	none	2 - 3	4 – 6 or nightly stool or light cramps	7 - 9 or incontinence or severe cramps	≥ 10 or bloody diarhoeal or TPN required	**33**	
Skin toxicity							
Changes in the skin	none	erythema	Dry desquamation, vasculitis, pruritus	moist desquamation, ulceration	Exfoliativ dermatitis, necrosis	**40**	
Renal toxicity							
Creatinine	normal for age (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 6,0 x N	> 6,0 x N	**51**	
Proteinuria (g/l)	none	< 3	3 – 10,0	> 10	nephrot. Syndrom	**52**	
Hämaturia	none	microskopic	macroskopic, no clotsl	macroskopic, clots	transfusion required	**53**	
Creatinine-Clearence (ml/min/1,73m²)	≥ 90	60 - 89	40 - 59	20 - 39	≤ 19	**54**	
Liver toxicity							
Bilirubin	Normal for age (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 10,0 x N	> 10,0 x N	**61**	
SGOT / SGPT	Normal for age (N)	> N – 2,5 x N	> 2,5 – 5,0 x N	> 5,0 – 20,0 x N	> 20 x N	**62**	
Cardiac toxicity							
Arrhythmia	none	Asympt., no therapy Therapie	Recurr./persist., no therapy	Therapy necessary	Hypotension, ventr. arrhyth., defibrillation	**70**	
Cardiac function	normal	asymptomat., EF ↓ (resting) ≥ 10 % but < 20 % of baseline	asymptomat., but EF ↓ ≥ 20 %of baseline	Mild congestive heart failure, therapeutically compensated	Severe / refractory congestive heart failure	**71**	
ECHO: LV-SF (%)	≥ 30	≥ 24 - < 30	≥ 20 - < 24	> 15 - < 20	≤ 15	**72**	

Continuation toxicity scale: CTC modified Report following high dose therapy Nr.__

Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Code	Grade
Ototoxicity							
hearing	normal	asymptomat. Hearing loss, by audiometry only	Hearing loss not requiering hearing aid or intervention	Hearing loss requiring hearing aid or intervention	Profound bilateral hearing loss	**80**	
Audiometry	No hearing loss	≤ 15 dB at ≤2 kHz	16 – 30 dB at ≤2 kHz	31 – 60 dB at ≤2 kHz	> 60 dB at ≤2 kHz	**81**	
Neurotoxicity							
Central neurotoxicity	none	Transient lethargia	Somnolence < 50% of time, mild disorientation	Somnolence > 50% of time, severe disorientation, hallucinations	Coma, seizures	**85**	
Peripheral neurotoxicity	none	paraesthesia	Severe paraesthesia and/or weakness	Unbearable paraesthesia, deficits in motor function	paralysis	**86**	
Other toxicity							
no = 0 **yes = 1** ☐	**Please specify**					**90**	**Grad**

IV.7.2.7 Surgery

EU-RHAB
Surgery

Patient number:	☐☐☐☐
Treatment centre: _____ **Town:** _____	☐☐☐
Patient`s surname:	☐☐☐
Date of birth:	☐☐ . ☐☐ . ☐☐☐☐ Day Month Year

Date of surgery ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY)

Institution / Surgeon _____

Type of surgery

- ☐ Biopsy, open
- ☐ Biopsy, stereotactic
- ☐ Partial resection (< 50%)
- ☐ Partial resection (> 50%)
- ☐ Subtotal resection (< 10%)
- ☐ Total resection (no visible residuals)

Cause of operation

- ☐ Incomplete surgery of primary tumor
- ☐ Local recurrence
- ☐ Solid metastasis ☐ primary ☐ secondary
- ☐ Synchron Tumor ☐ Other

Persisting VP/VA-shunt ☐ No ☐ Yes, v. p. ☐ Yes, v. a.

Mutilating surgery/ amputation ☐ No ☐ Yes, _____

Histopathology – Local pathologist`s report (please enclose)

Date of report ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY) **Journal-Nr.** ☐☐☐☐☐☐☐☐☐☐

Institution _____

Immunhistochemistry (localer pathologist)

- ☐ SMARCB1/hSNF5/INI1 retained
- ☐ SMARCB1/hSNF5/INI1 lost

Histopathology (local pathologist)

- ☐ MRT (soft tissue)
- ☐ RTK (kidney)
- ☐ AT/RT (CNS)
- ☐ Other _____

EU-RHAB **Surgery, page 2/5**

Histopathology – Reference pathologist`s report (please enclose)

Dispatch to reference pathologist

- ☐ No
- ☐ Yes, planned
- ☐ Yes, has been made
  - ☐ to Bonn
  - ☐ to Kiel
  - ☐ to Münster
  - ☐ other _____

Date of report ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY) **Journal-Nr.** ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Institution _____

Immunhistochemistry (Reference pathologist)

- ☐ SMARCB1/hSNF5/INI1 retained
- ☐ SMARCB1/hSNF5/INI1 lost

Histopathology (Reference pathologist)

- ☐ MRT (soft tissuel)
- ☐ RTK (kidney)
- ☐ AT/RT (CNS)
- ☐ Other _____

Radiologic evaluation after surgery

Date of radiologic evaluation ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)

Primary site ☐ CT native ☐ CT with contrast ☐ MRT native ☐ MRT with contrast

Extension ⌊_⌊_⌋ , ⌊_⌋ cm X ⌊_⌊_⌋ , ⌊_⌋ cm

Metastases ☐ CT native ☐ CT with contrast ☐ MRT native ☐ MRT with contrast

Extension* ⌊_⌊_⌋ , ⌊_⌋ cm X ⌊_⌊_⌋ , ⌊_⌋ cm

* If more than 1 metastatic lesion please dimensions of the largest (please enclose report of local radiologist)

Images have been sent to reference neuroradiologist: ☐ Yes ☐ No

Surgical complications

- ☐ No
- ☐ Yes, neurologic (please specify) _____
- ☐ Yes, not neurologic (please specify) _____

EU-RHAB **Surgery, page 3/5**

Comments:

Treatment centre (stamp)	Date	signature

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

Please send this form to:

EU-RHAB
Data Center and Coordination
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg - GERMANY
FAX: 0049 821 400 179340

EU-RHAB **Attachment for AT/RT – part 1** **Surgery, page 4/5**

PRE-operative neurological examination (to be filled for AT/RT–patients only)

Date of examination ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)

Symptoms of increased intracranial pressure ☐ No ☐ Emesis ☐ Raised fontanelle
More than one possible ☐ Headache ☐ Behavioural changes
☐ Raised optic disc

Disorder of conciousness ☐ No ☐ Somnolence
☐ Stupor
☐ Coma

Seizures ☐ No ☐ Yes

Neuropsychological disorder ☐ No ☐ Yes, _____

Failure of cranial nervs ☐ No ☐ Yes, symptom/side _____ CN # ⌊_⌊_⌋
☐ Yes, symptom/side _____ CN # ⌊_⌊_⌋
☐ Yes, symptom/side _____ CN # ⌊_⌊_⌋

Disorder of gross motor function ☐ No ☐ Monoparesis – right arm ☐ Monoparesis – left arm
☐ Monoparesis – right leg ☐ Monoparesis – left leg
☐ Hemiparesis right ☐ Hemiparesis left
☐ Paraparesis ☐ Tetraparesis

In case of paraplegia ☐ incomplete ☐ complete
Level of paraplegia _____

Disorder of coordination ☐ No ☐ Ataxia of extremities ☐ Nystagmus
More than one possible ☐ Intention tremor ☐ Ataxia of trunk
☐ other _____

Extrapyramidal movement disorder ☐ No ☐ Yes _____

Disorder of sensibility ☐ No ☐ Yes _____

Disorder of vegetative functions ☐ No ☐ Yes _____

Somatic disorders ☐ No ☐ Yes _____

Neuroendocrine disorders ☐ No ☐ Yes _____

Hight ⌊_⌊_⌊_⌋ cm **Weight** ⌊_⌊_⌋ , ⌊_⌋ kg **Head circumference** ⌊_⌊_⌋ , ⌊_⌋ cm

POST-operative neurological examination (to be filled for AT/RT-patients only)

Date of examination ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋ . ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (DD.MM.YYYY)

Symptoms of increased intracranial pressure ☐ No ☐ Emesis ☐ Raised fontanelle
More than one possible ☐ Headache ☐ Behavioural changes
☐ Raised optic disc

Disorder of conciousness ☐ No ☐ Somnolence
☐ Stupor
☐ Coma

Seizures ☐ No ☐ Yes

Neuropsychological disorder ☐ No ☐ Yes, _____

Failure of cranial nervs ☐ No ☐ Yes, symptom/side _____ CN # ⌊_⌋
☐ Yes, symptom/side _____ CN # ⌊_⌋
☐ Yes, symptom/side _____ CN # ⌊_⌋

Disorder of gross motor function ☐ No ☐ Monoparesis – right arm ☐ Monoparesis –left arm
☐ Monoparesis – right leg ☐ Monoparesis – left leg
☐ Hemiparesis right ☐ Hemiparesis left
☐ Paraparesis ☐ Tetraparesis

In case of paraplegia ☐ incomplete ☐ complete
Level of paraplegia _____

Disorder of coordination ☐ No ☐ Ataxia of extremities ☐ Nystagmus
More than one possible ☐ Intention tremor ☐ Ataxia of trunk
☐ Other _____

Extrapyramidal movement disorders ☐ No ☐ Yes _____

Disorder of sensibility ☐ No ☐ Yes _____

Disorder of vegetative functions ☐ No ☐ Yes _____

Somatic disorders ☐ No ☐ Yes _____

Neuroendocrine disorders ☐ No ☐ Yes _____

Height ⌊_⌋⌊_⌋⌊_⌋ cm **Weight** ⌊_⌋⌊_⌋ , ⌊_⌋ kg **Head circumference** ⌊_⌋⌊_⌋ , ⌊_⌋ cm

IV.7.2.8 End of treatment

EU-RHAB
End of treatment

Patient number:	☐☐☐☐
Treatment centre: _____ **Town:** _____	☐☐☐
Patient`s surname:	☐☐☐
Date of birth:	☐☐ . ☐☐ . ☐☐☐☐ Day Month Year

Beginning of therapy ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY)

End of therapy ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY)

Tumor Status at end of treatment	**Primary Tumor**	**Metastases**	**Liquor**
Complete Remission	☐	☐	☐
Partial remission (decrease ≥ 50%)	☐	☐	☐
Stable Disease (decrease < 50% or increase < 25%)	☐	☐	☐
Progressive disease (increase >= 25%)	☐	☐	☐
Not evaluable	☐	☐	☐
No information	☐	☐	☐

Therapy

Surgery ☐ No ☐ Yes

Other surgeries ☐ No ☐ Yes

if yes, which one ☐ Second look ☐ LK ☐_____

Radiotherapy ☐ No ☐ Yes dose in Gy: ☐☐ , ☐

Chemotherapy ☐ No ☐ Yes number of courses (even if modified):

DOX ☐☐

ICE ☐☐

VCA ☐☐

MTX (i.th.) ☐☐ ☐☐

Oral maintenance ☐ No ☐ Yes ⟶ TI ☐☐

TE ☐☐

TMZ ☐☐

Stem cell apheresis ☐ No ☐ Yes

High dose therapy ☐ No ☐ Yes If yes: ☐ Tandem

☐ other (please specify)_____

EU-RHAB **End of treatment, page 2/2**

Reasons for end of treatment

☐ according to protocol

☐ Early, because…

- ☐ toxicity
- ☐ progression
- ☐ patient´s/parent`s choice
- ☐ physician`s choice
- ☐ death
- ☐ lost to follow-up
- ☐ other (please specify) _____

Comments:

Treatment centre (stamp) **Date** **Signature**

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

Please send this form to:

EU-RHAB
Data Center and Coordination
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg- GERMANY
FAX: 0049 821 400 179340

IV.7.2.9 Follow-up

EU-RHAB
Follow-up

Patient number:	☐☐☐☐
Treatment centre: _____ **Town:** _____	☐☐☐
Patient`s surname:	☐☐☐
Date of birth:	☐☐ . ☐☐ . ☐☐☐☐ Day Month Year

Patients status at last presentation

☐ Patient alive

Date of last clinical examination ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY)

Date of last radiologic examination ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY)

☐ Patient deceased

Date of death ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY)

Tumor status

- ☐ Complete remission
- ☐ Local disease
  - ☐ *without* progression
  - ☐ *with* progression (>= 25% increase)
- ☐ Disseminated disease
  - ☐ *without* progression
  - ☐ *with* progression (>= 25% increase)

New relapse/secondary metastases

- ☐ No
- ☐ Yes

New secondary malignancy

- ☐ No
- ☐ Yes

In case of death, relapse, secondary metastases or secondary malignancy please fill form Event-report.

EU-RHAB **Follow-up, page 2/4**

Therapy

Has a specific treatment been started since the last presentation/follow-up?

☐ No ☐ Yes, surgery
Confirmation of histological diagnosis? ☐ Yes ☐ No ***
☐ Yes, radiotherapy
☐ Yes, chemotherapy ***
☐ Yes, other ***

*** Please specify on page 3 (comments).

Long term sequelae *(since end of therapy/last follow up)*

Nephrotoxicity ☐ Not examined ☐ No ☐ Yes, tubulopathy ☐ Yes, glomerulopathy

Result: _____

Ototoxicity ☐ Not examined

Audiometry:
☐ No hearing loss
☐ hearing loss, ≤ 15 dB bei ≤ 2 kHz
☐ hearing loss, 16-30 dB bei ≤ 2 kHz
☐ hearing loss, 31-60 dB bei ≤ 2 kHz
☐ hearing loss, > 60 dB bei ≤ 2 kHz

Hearing aid: ☐ No ☐ Yes

Hematotoxicity ☐ Not examined ☐ No ☐ Yes

Platelets ⌊_⌊_⌊_⌊_⌋ x 10^9/L
WBC ⌊_⌊_⌋,⌊_⌋ x 10^9/L
Neutrophiles ⌊_⌊_⌋,⌊_⌋ x 10^9/L

Ophtalmology ☐ Not examined ☐ normal ☐ Pathologic visus ☐ Pathologic visual field

Result: _____

Other effects ☐ No ☐ Yes

Please specify: _____
_____
_____

EU-RHAB **Follow-up, page 3/4**

Comments:

Treatment centre (stamp)	Date	Signature

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

Please send this form to:

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Data Center and Coordination
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg - GERMANY
FAX: 0049 821 400 179340

EU-RHAB **Attachment for AT/RT – part 1** **Follow-up, page 4/4**

Neurological examination (to be filled for AT/RT–patients only)

Date of examination ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)

Symptoms of increased intracranial pressure ☐ No ☐ Emesis ☐ Raised fontanelle
More than one possible ☐ Headache ☐ Behavioural changes
☐ Raised optic disc

Disorder of conciousness ☐ No ☐ Somnolence
☐ Stupor
☐ Coma

Seizures ☐ No ☐ Yes

Neuropsychological disorder ☐ No ☐ Yes, _____

Failure of cranial nervs ☐ No ☐ Yes, symptom/side _____ CN # ⌊_⌊_⌋
☐ Yes, symptom/side _____ CN # ⌊_⌊_⌋
☐ Yes, symptom/side _____ CN # ⌊_⌊_⌋

Disorder of gross motor function ☐ No ☐ Monoparesis – right arm ☐ Monoparesis – left arm
☐ Monoparesis – right leg ☐ Monoparesis – left leg
☐ Hemiparesis right ☐ Hemiparesis left
☐ Paraparesis ☐ Tetraparesis

In case of paraplegia ☐ incomplete ☐ complete
Level of paraplegia _____

Disorder of coordination ☐ No ☐ Ataxia of extremities ☐ Nystagmus
More than one possible ☐ Intention tremor ☐ Ataxia of trunk
☐ other _____

Extrapyramidal movement disorder ☐ No ☐ Yes _____

Disorder of sensibility ☐ No ☐ Yes _____

Disorder of vegetative functions ☐ No ☐ Yes _____

Somatic disorders ☐ No ☐ Yes _____

Neuroendocrine disorders ☐ No ☐ Yes _____

Hight ⌊_⌊_⌊_⌋ cm **Weight** ⌊_⌊_⌋ , ⌊_⌋ kg **Head circumference** ⌊_⌊_⌋ , ⌊_⌋ cm

IV.7.2.10 Event report

EU-RHAB
Event-report

Patient number:	☐☐☐☐
Treatment centre: _____ **Town:** _____	☐☐☐
Patient`s surname:	☐☐☐
Date of birth:	☐☐ . ☐☐ . ☐☐☐☐ Day Month Year

Date of event: ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY) **Number of event:** ☐☐

Please fill form for each event.

Diagnosis of recurrence or new metastases on date above
- ☐ No
- ☐ Yes
  - ☐ progression
  - ☐ local recurrence
  - ☐ new metastases
  - ☐ local recurrence and new metastases

If metastases:
- ☐ CNS ☐ cerebral ☐ spinal
- ☐ CSF
- ☐ Lung ☐ right ☐ left ☐ both sides
- ☐ Liver
- ☐ Kidney ☐ right ☐ left ☐ both sides
- ☐ Bone marrow
- ☐ Bone Which? _____
- ☐ other Which? _____

Diagnosis of secondary malignancy on date above
- ☐ No
- ☐ Yes
  - Type _____
  - Localisation _____

Death of patient on date above
- ☐ No
- ☐ Yes

Cause:
- ☐ cancer
  - ☐ primary disease
  - ☐ relapse/ secondary metastases
  - ☐ secondary malignancy
- ☐ treatment-related
- ☐ unknown if cancer or treatment
- ☐ other
  - please specify: _____

Autopsy:
- ☐ No
- ☐ Yes

EU-RHAB **Event report, page 2/2**

Comments:

Treatment centre (stamp)	Date	Signature

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

Please send this form to:

EU-RHAB
Data Center and Coordination
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg - GERMANY
FAX: 0049 821 400 179340

IV.7.2.11 SAE

EU-RHAB
Serious adverse event

Patient number:	⌊_⌊_⌊_⌊_⌋
Treatment centre: _____ **Town:** _____	⌊_⌊_⌊_⌋
Patient`s surname:	⌊_⌊_⌊_⌋
Date of birth:	⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ Day Month Year

begin of the event: ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYY) **number of event:** ⌊_⌊_⌋

end of the event: ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYY)

after chemo cycle ⌊_⌊_⌋ **administered on** ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYY)

Please fill form for each event.

height: ⌊_⌊_⌊_⌋ (cm) **weight:** ⌊_⌊_⌊_⌊_⌊_⌋ (g) **CS:** ⌊_⌊_⌊_⌋ (m^2)

drug: **dose:**

charge number of the drug: _____

SAE forwarded to health authorities ☐ yes ☐ no

if "yes" health authorities report number _____

forwarded on ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYY)

Description of SAE, fill toxicity grade on next pages:

EU-RHAB **SAE, page 2/5**

Comment on nature and cause of SAE:

Toxicity grade according to NCI: □ **3** □ **4**

Onset: ⌊⌊⌋⌋.⌊⌊⌋⌋.⌊⌊⌋⌋⌋⌋ (Day . Month . Year) **End:** ⌊⌊⌋⌋.⌊⌊⌋⌋.⌊⌊⌋⌋⌋⌋ (Day . Month . Year) **Persisting:** □

Cause

Is the pre-existing condition or the medical history responsible for the SAE?

□ yes □ probably □ possibly □ unlikely □ no

Do you think the SAE is related to therapy?

□ yes □ probably □ possibly □ unlikely □ no

Classification (seriousness)

- □ Death within 4 weeks after therapy
- □ Life-threatening
- □ Persistant or severe disability/incapacity
- □ Requires inpatient hospitalization or prolongation

Outcome

□ Recovered/resolved □ Not recovered □ Late sequelae □ Death □ Unknown

EU-RHAB **SAE, page 3/5**

Comments:

Treatment centre (stamp)	Date	Signature

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

Please send this form to:

EU-RHAB
Data Center and Coordination
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg - GERMANY
FAX: 00 49 821 400 179340

Toxicity scale: CTC modified

After chemo cycle Nr. ☐☐

Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Code	Grade
General condition	normal	Mild impairement	Age-related activities strongly decreased	Bedridden, in need of care	Intensive care, very sick	**01**	
Haematological toxicity							
Haemoglobin (g/dl)	Normal for age (N)	10,0 - < N	8,0 – < 10,0	6,5 – < 8,0	< 6,5	**11**	
WBC (x 10^9/l)	≥ 4,0	3,0 – < 4,0	2,0 – < 3,0	1,0 – < 2,0	< 1,0	**12**	
Granulocytes (x 10^9/l)	≥ 2,0	1,5 – < 2,0	1,0 – < 1,5	0,5 – < 1,0	< 0,5	**13**	
Platelets (x 10^9/l)	≥ 100	75 – < 100	50 – < 75	10 – < 50,0	< 10	**14**	
Infections							
Infection	none	mild	Moderate, pathogen not identified; i.v. antibiotics	Severe, pathogen identified; i.v. antibiotics	Life threatening, with hypotension	**21**	
Fever (°C)	< 38	38 - 39	> 39 – 40	> 40 for < 24 h.	> 40 for ≥ 24 h.	**22**	
Gut toxicity							
Stomatitis	none	Painless ulcer, erythema	Painful erythema or ulceration, can still eat	Painful erythema or ulceration, cannot eat	TPN required due to stomatitis	**31**	
Vomiting (no. Of episodes in 24 h**)**	0	1	2 - 5	6 - 10	> 10 or TPN necessary	**32**	
Diarrhoea (Stools/day**)**	none	2 - 3	4 – 6 or nightly stool or light cramps	7 - 9 or incontinence or severe cramps	≥ 10 or bloody diarhoeal or TPN required	**33**	
Skin toxicity							
Changes in the skin	none	erythema	Dry desquamation, vasculitis, pruritus	moist desquamation, ulceration	Exfoliativ dermatitis, necrosis	**40**	
Renal toxicity							
Creatinine	normal for age (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 6,0 x N	> 6,0 x N	**51**	
Proteinuria (g/l)	none	< 3	3 – 10,0	> 10	nephrot. Syndrom	**52**	
Hämaturia	none	microskopic	macroskopic, no clotsl	macroskopic, clots	transfusion required	**53**	
Creatinine-Clearence (ml/min/1,73m²)	≥ 90	60 - 89	40 - 59	20 - 39	≤ 19	**54**	
Liver toxicity							
Bilirubin	Normal for age (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 10,0 x N	> 10,0 x N	**61**	
SGOT / SGPT	Normal for age (N)	> N – 2,5 x N	> 2,5 – 5,0 x N	> 5,0 – 20,0 x N	> 20 x N	**62**	
Cardiac toxicity							
Arrhythmia	none	Asympt., no therapy Therapie	Recurr./persist., no therapy	Therapy necessary	Hypotension, ventr. arrhyth., defibrillation	**70**	
Cardiac function	normal	asymptomat., EF ↓ (resting) ≥ 10 % but < 20 % of baseline	asymptomat., but EF ↓ ≥ 20 %of baseline	Mild congestive heart failure, therapeutically compensated	Severe / refractory congestive heart failure	**71**	
ECHO: LV-SF (%)	≥ 30	≥ 24 - < 30	≥ 20 - < 24	> 15 - < 20	≤ 15	**72**	
Ototoxicity							
hearing	normal	asymptomat. Hearing loss, by audiometry only	Hearing loss not requiering hearing aid or intervention	Hearing loss requiring hearing aid or intervention	Profound bilateral hearing loss	**80**	
Audiometry	No hearing loss	≤ 15 dB at ≤2 kHz	16 – 30 dB at ≤2 kHz	31 – 60 dB at ≤2 kHz	> 60 dB at ≤2 kHz	**81**	

Continuation toxicity scale: CTC modified therapy — Report following high dose

Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Code	Grade
Neurotoxicity							
Central neurotoxicity	none	Transient lethargia	Somnolence < 50% of time, mild disorientation	Somnolence > 50% of time, severe disorientation, hallucinations	Coma, seizures	**85**	
Peripheral neurotoxicity	none	paraesthesia	Severe paraesthesia and/or weakness	Unbearable paraesthesia, deficits in motor function	paralysis	**86**	

Other toxicity			
no = 0 **yes = 1** ☐	**Please specify**	**90**	**Grad**

After courses containing **anthracyclines** please give information according cardiac toxicity:

Date of evaluation ☐☐ . ☐☐ . ☐☐☐☐ (DD.MM.YYYY)

Rhythm Pulse: ☐☐☐ Antiarrhythmic therapy? ☐ No ☐ Yes

Cardiac function Pressure syst. / diast. ☐☐☐ / ☐☐☐ LV-SF: ☐☐ % Pathologic diastolic parameters? ☐ No ☐ Yes

Application of digitalis? ☐ No ☐ Yes Application of diuretics? ☐ No ☐ Yes Application of beta-blockers? ☐ No ☐ Yes

Further diagnostic evaluation
- ☐ MUGA
- ☐ EPO-level
- ☐ Troponin
- ☐ Other

IV.7.2.12 Radiotherapy – basic data

EU-RHAB
Radiotherapy, basic data

Patient number:	⌊⌊⌊⌊⌋
Treatment centre: _____ **Town:** _____	⌊⌊⌊⌋
Patient´s surname:	⌊⌊⌊⌋
Date of birth:	⌊⌊⌋.⌊⌊⌋.⌊⌊⌊⌊⌋ Day Month Year

Radiotherapy of primary tumor

Date: treatment started ⌊⌊⌋.⌊⌊⌋.⌊⌊⌊⌊⌋ (DD.MM.YYYY)

Date: treatment completed ⌊⌊⌋.⌊⌊⌋.⌊⌊⌊⌊⌋ (DD.MM.YYYY)

□ conventional radiation

□ Proton ratiation

Concurrent chemotherapy?

□ No

□ Yes,

if "yes", please fill corresponding form

Radiation field:

□ Tumor bed

□ Cranio spinal

□ other, please specify_____

Dose and fractionation

Total dose ⌊⌊⌋ **Gy**

Boost? If yes, please specify total dose including boost ⌊⌊⌋ **Gy**

Hyperfractionation?

□ No

□ Yes

EU-RHAB **Radiotherapy – basic data, page 2/2**

Comments:

Treatment centre (stamp)	Date	Signature

Information submitted by:

Name: _____ **Phone:** _____

Fax: _____ **E-mail:** _____

Please send this form to:

EU-RHAB
Data Center and Coordination
I.Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg - GERMANY
FAX: 0049 821 400 179340

IV.7.2.13 Maintenance Therapy

EU-RHAB
Maintenance Therapy

Dr. Kornelius Kerl, Universität Münster, Institute of Molecular Tumorbiology,
Robert-Koch-Straße 43, 48149 Münster
Professor Dr. M. Frühwald PhD, Klinikum Augsburg, Klinik für Kinder und Jugendliche, Stenglinstr. 2, 86156 Augsburg,
email: michael.fruehwald@klinikum-augsburg.de
- in Cooperation with Deutsches Kinderkrebsregister am IMBEI, 55101 Mainz -
- in Cooperation with GPOH -

EURHAB-No. ⌊_⌊_⌊_⌊_⌋ **Treatment Center** _____

Surname _____ **First name** _____ **Date of birth** _____

3. General questions

Maintenance therapy was applied after intensive therapy ☐ **no** ☐ **yes**

…if no maintenance therapy was applied, what were the reasons

Reasons for not applying maintenance therapy

☐ Not generally recommended

☐ Relapse before end of intensive therapy

☐ Patient died before end of intensive therapy

☐ Parents/patient did not agree with maintenance therapy

☐ needs intensive care, seriously ill, moribund

2. Evaluation before starting maintenance therapy

2.1. Radiologic evaluation before starting maintenance therapy

Date of last radiologic evaluation before starting maintenance therapy ⌊_⌊_⌋.⌊_⌊_⌋.⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)

hich method was employed?

☐ CT native ☐ CT with contrast ☐ MRT native ☐ MRT with contrast ☐ Ultra Sound

Residual tumor before starting maintenance therapy? ☐ no ☐ yes ☐ not evaluated

Dispatch to reference radiology: ☐ no ☐ yes

Cerebrospinal fluid (CSF) evaluation before starting maintenance therapy (AT/RT only)

Evaluation of CSF before starting maintenance therapy?	☐ no	☐ yes		
Date of CSF sample	⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)			
Tumor cells in CSF (at start of maintenance therapy)	**Lumbal**	☐ no	☐ yes	☐ not evaluated
	Ventricular	☐ no	☐ yes	☐ not evaluated
Dispatch of CSF to study coordinator?	☐ no	☐ yes		

5. Maintenance therapy

5.1. General questions

Date of starting maintenance therapy ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)

End of intensive therapy ⌊_⌊_⌋ . ⌊_⌊_⌋ . ⌊_⌊_⌊_⌊_⌋ (DD.MM.YYYY)

What kind of maintenance therapy was applied?

conventional chemotherapy	☐ no	☐ yes
Intrathecal therapy	☐ no	☐ yes
Other kind of therapy (e.g. epigenetic therapy...)	☐ no	☐ yes, please specify _____

5.2. Maintenance "Systemic therapy"

Which drugs have been (e.g., i.v. or p.o.) applied during maintenance therapy (including alternative drugs, e.g. epigenetically active compounds)?

Name of the Drug	Date	Application p. day (mg/kg)	i.v.	p.o.	cumulative dose	Duration (Days)
			☐	☐	└┴┴┴┘ mg	
			☐	☐	└┴┴┴┘ mg	
			☐	☐	└┴┴┴┘ mg	
			☐	☐	└┴┴┴┘ mg	
			☐	☐	└┴┴┴┘ mg	
			☐	☐	└┴┴┴┘ mg	
			☐	☐	└┴┴┴┘ mg	

HAS THE MAINTENANCE THERAPY BEEN DELAYED OR THE DOSE BEEN MODIFIED AT ANY TIME?

Delay > 3 days ☐ no

☐ yes ☐ Due to the following reasons:

____

Dose modification ☐ no

☐ yes ☐ Due to the following reasons:

____

Comment:

5.3. Maintenance intrathecal therapy

Has intrathecal therapy been administered during maintenance therapy?

☐ no ☐ yes

Which drugs have been applied i.th. during maintenance therapy?

Name of the drug	Days of administration		
1._____	……	␣ , ␣␣	mg
2._____	……	␣ , ␣␣	mg
3._____	……	␣ , ␣␣	mg
4._____	……	␣ , ␣␣	mg

HAS THE I.TH. MAINTENANCE THERAPY BEEN DELAYED OR THE DOSE BEEN MODIFIED AT ANY TIME?

Delay > 3 days ☐ no

☐ yes ☐ Due to the following reasons:

_____

Dose modification ☐ no

☐ yes ☐ Due to the following reasons:

_____

3.4 Why has maintenance therapy finally been stopped?

The cumulative time/dosis was reached	☐ no	☐ yes
Toxicity of therapy	☐ no	☐ yes, please specify_____
Relapse	☐ no	☐ yes, please specify_____
Death of the patient	☐ no	☐ yes, please specify_____
Other reasons	☐ no	☐ yes, please specify_____

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4. Toxicity- What kind of toxicity occurred during maintenance therapy?

☐no toxic side effects occurred *(please continue with 5.)* ☐ side effects occurred *(please specify in the following table)*

Toxicity scale: CTC modified after maintenance therapy

Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Code	Grade
General condition	normal	Mild impairement	Age-related activities strongly decreased	Bedridden, in need of care	Intensive care, very sick	**01**	
Haematological toxicity							
Haemoglobin (g/dl)	Normal for age (N)	10,0 - < N	8,0 – < 10,0	6,5 – < 8,0	< 6,5	**11**	
WBC (x 10^9/l)	≥ 4,0	3,0 – < 4,0	2,0 – < 3,0	1,0 – < 2,0	< 1,0	**12**	
Granulocytes (x 10^9/l)	≥ 2,0	1,5 – < 2,0	1,0 – < 1,5	0,5 – < 1,0	< 0,5	**13**	
Platelets (x 10^9/l)	≥ 100	75 – < 100	50 – < 75	10 – < 50,0	< 10	**14**	
Infections							
Infection	none	mild	Moderate, pathogen not identified; i.v. antibiotics	Severe, pathogen identified; i.v. antibiotics	Life threatening, with hypotension	**21**	
Fever (°C)	< 38	38 - 39	> 39 – 40	> 40 for < 24 h.	> 40 for ≥ 24 h.	**22**	
Gut toxicity							
Stomatitis	none	Painless ulcer, erythema	Painful erythema or ulceration, can still eat	Painful erythema or ulceration, cannot eat	TPN required due to stomatitis	**31**	
Vomiting (no. Of episodes in 24 h**)**	0	1	2 - 5	6 - 10	> 10 or TPN necessary	**32**	
Diarrhoea (Stools/day**)**	none	2 - 3	4 – 6 or nightly stool or light cramps	7 - 9 or incontinence or severe cramps	≥ 10 or bloody diarhoeal or TPN required	**33**	
Skin toxicity							
Changes in the skin	none	erythema	Dry desquamation, vasculitis, pruritus	moist desquamation, ulceration	Exfoliativ dermatitis, necrosis	**40**	
Renal toxicity							
Creatinine	normal for age (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 6,0 x N	> 6,0 x N	**51**	
Proteinuria (g/l)	none	< 3	3 – 10,0	> 10	nephrot. Syndrom	**52**	
Hämaturia	none	microskopic	macroskopic, no clotsl	macroskopic, clots	transfusion required	**53**	
Creatinine-Clearence (ml/min/1,73m²)	≥ 90	60 - 89	40 - 59	20 - 39	≤ 19	**54**	
Liver toxicity							
Bilirubin	Normal for age (N)	> N – 1,5 x N	> 1,5 – 3,0 x N	> 3,0 – 10,0 x N	> 10,0 x N	**61**	
SGOT / SGPT	Normal for age (N)	> N – 2,5 x N	> 2,5 – 5,0 x N	> 5,0 – 20,0 x N	> 20 x N	**62**	
Cardiac toxicity							
Arrhythmia	none	Asympt., no therapy Therapie	Recurr./persist., no therapy	Therapy necessary	Hypotension, ventr. arrhyth., defibrillation	**70**	
Cardiac function	normal	asymptomat., EF ↓ (Ruhe) ≥ 10 % but < 20 % of baseline	asymptomat., but EF ↓ ≥ 20 %of baseline	Mild congestive heart failure, therapeutically compensated	Severe / refractory congestive heart failure	**71**	
ECHO: LV-SF (%)	≥ 30	≥ 24 - < 30	≥ 20 - < 24	> 15 - < 20	≤ 15	**72**	

Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Code	Grade
Ototoxicity							
hearing	normal	asymptomat. Hearing loss, nur audiometrisch fassbar	Hearing loss not requiering hearing aid or intervention	Hearing loss requiring hearing aid or intervention	Profound bilateral hearing loss	**80**	
Audiometry	No hearing loss	≤ 15 dB at ≤2 kHz	16 – 30 dB at ≤2 kHz	31 – 60 dB at ≤2 kHz	> 60 dB at ≤2 kHz	**81**	
Neurotoxicity							
Central neurotoxicity	none	Transient lethargia	Somnolence < 50% of time, mild disorientation	Somnolence > 50% of time, severe disorientation, hallucinations	Coma, seizures	**85**	
Peripheral neurotoxicity	none	paraesthesia	Severe paraesthesia and/or weakness	Unbearable paraesthesia, deficits in motor function	paralysis	**86**	
Other toxicity							
no = 0 **yes = 1** ☐	**Please specify**					**90**	**Grad**

Comments:

Other side effects:

5. Duration of hospitalisation

Days in hospital in total during maintenance therapy (including drug administration, treatment of side effects…) ⌊⌊⌋ **days**

Days in hospital for drug administration during maintenance therapy ⌊⌊⌋ **days**

Days in hospital during maintenance therapy due to side effects ⌊⌊⌋ **days**

6. Evaluation after finishing maintenance therapy

6.1. Radiologic evaluation after finishing maintenance therapy

Date of radiologic evaluation after finishing maintenance therapy

|_|_| . |_|_| . |_|_|_|_| (DD.MM.YYYY)

Which method has been used?

☐ CT native ☐ CT with contrast ☐ MRT native ☐ MRT with contrast ☐ Ultra sound

Dispatch to reference radiology? ☐ no ☐ yes

☐ Progression ☐ Local relapse

☐ Distant metastasis ☐ Local relapse and distant metastasis ☐ Complete remission

6.2. Cerebrospinal fluid (CSF) evaluation after finishing maintenance therapy (AT/RT only)

Date of CSF sample (after finishing maintenance therapy) |_|_| . |_|_| . |_|_|_|_| (DD.MM.YYYY)

Tumor cells in CSF (after end of maintenance therapy)	**Lumbal**	☐ no	☐ yes	☐ not evaluated
	Ventricular	☐ no	☐ yes	☐ not evaluated

Dispatch of CSF to study coordinator? ☐ no ☐ yes

7. Outcome

Patients status at last presentation

☐ Patient alive

Date of last clinical examination ⌊⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋ (DD.MM.YYYY)

Date of last radiologic examination ⌊⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋ (DD.MM.YYYY)

☐ Patient deceased

Date of death ⌊⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋ (DD.MM.YYYY)

Tumor status

☐ Complete remission

☐ Local disease

- ☐ *without* progression
- ☐ *with* progression (>= 25% increase)

☐ Disseminated disease

- ☐ *without* progression
- ☐ *with* progression (>= 25% increase)

Relapse

☐ no

☐ yes

New secondary malignancy

☐ no

☐ yes

Has the maintenance therapy been applied/finished until date of evaluation?

☐ **no, maintenance therapy has not been finished until date of evaluation**

⌊⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋ (DD.MM.YYYY)

☐ **yes, maintenance therapy has been finished _____ weeks ago**

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Comments:

Treatment centre (stamp)	Date	Signature

Please send this form to:

EU-RHAB
Professor Dr. Dr. Michael Frühwald
1. Klinik für Kinder und Jugendliche
Klinikum Augsburg
Stenglinstraße 2
86156 Augsburg

Or fax to:

EU-RHAB REGISTRY OFFICE

+49 (0)821 400-179340

IV.8 Forms for reference evaluation

IV.8.1 Forms for reference evaluation – German

see chapter 9.5

IV.8.2 Forms for reference evaluation – English

see chapter 9.5

IV.9 Checklists for documentation and evaluation of patients

Checklist rhabdoid tumors of the CNS (AT/RT)

Pre-treatment evaluation

	Procedure / Consult
Laboratory work-up, clinical evaluation	
	Complete medical and psychosocial history
	Physical and neurologic examination, height, weight, pubertal status
	Informed consent
	Complete blood count, serum chemistries, T3/T4/TSH, IGF1, IGFBP3, Cortisol, DHEA*
	Material for molecular genetic analysis, reference (neuro)pathology
	Spinal CSF analysis
Imaging and other apparative diagnostics	
	Cranial MRI or cCT
	Spinal MRI
	Chest x-ray/ chest-CT (PET-CT)
	ECG
	Echocardiography
	Renal Function
	Bone Age
	Ultrasound thyroid gland
	Ophthalmology
	Audiometry, ENT consult
Facultative, depending on stage	
	Chest-CT
	Bone scan
	Lung-function
Documentation	
	Registration form for Cancer registry (IMBEI in Germany)
	Initial evaluation form incl. neurostatus
	Central neuroradiology review

Checklist rhabdoid tumors of the CNS (AT/RT)

Examination during treatment

Time	Measurement
Following initial surgery	Tumor material for local and central neuropathology
	Material for molecular-genetic evaluation
	Fill out form for extent of disease
	Radiotherapy consult (reference RT planning)
During chemotherapy	Physical and neurologic examination weekly
	Complete blood count and serum chemistries prior to each course
	Echocardiography prior to each course with doxorubicin (idarubicin in maintenance)
After course 2	MRI cranial, central radiological review
	Chest X-ray
	Documentation of courses 1 and 2
After course 4	MRI cranial, central radiological review
	Documentation of courses 3 and 4
After course 6	MRI cranial, central radiological review
	Chest X-ray
	Documentation of courses 5 and 6
After course 9 or after HD	MRI cranial, central radiological review
	Chest X-ray
	ECG and Echocardiography
	Documentation of courses 7,8 and 9, or documentation of HD
	Physical and neurologic examination
	Serum chemistries and CBC
	Audiometry
	Form: End of treatment

Checklist rhabdoid tumors of the CNS (AT/RT)

Documentation

Time	Measurement
At diagnosis	Informed consent forms
	Registration form for German Childhood Cancer Registry
	Central radiology review
	Form: Clinical extent at diagnosis
	Neuropathology
	Central neuropathology review
	CSF examination (centralized and local)
	Molecular Genetics
	Cytogenetics
During chemotherapy	Form: Documentation chemotherapy
	Form: Documentation intraventricular therapy
	Form: Documentation of radiotherapy
	Poss. Form: Documentation of stem cell harvest
	Poss. Form: Documentation of high-dose therapy
	Form: Toxicity incl. cardiotoxicity
In case of SAE	Form: SAE
In case of any event (progress, relapse, second malignancy, death)	Form: Event report
End of therapy	Form: End of treatment
After the end of therapy	Form: Follow-up at recommended intervals

Check list rhabdoid tumors of kidney or extra-renal soft tissue

Pre-treatment evaluation

	Procedure / Consult
Laboratory work-up, clinical evaluation	
	Complete medical and psychosocial history
	Physical and neurologic examination, height, weight, pubertal status
	Information und Einverständnisse
	Complete blood count, serum chemistries, T3/T4/TSH, IGF1, IGFBP3, Cortisol, DHEA*
	Material for moleculargenetic analysis
Imaging and other apparative diagnostics	
	MRI or CT of tumor
	Sonography and measurement of tumor volume
	Chest x-ray/ chest-CT (ggf. PET-CT)
	ECG
	Echocardiography
	Renal Function
	Bone Age
	Sono thyroid gland
	Ophthalmology
	Audiometry, ENT consult
Facultative, depending on stage	
	Chest-CT
	Cranial MRI
	Bone scan (PET/CT)
	Lung-function
Dokumentation	
	Registration form for national cancer registry (e.g. IMBEI)
	Initial evaluation form incl. neurostatus
	Central radiology review

Checklist rhabdoid tumors of kidney or extra-renal soft tissue

Examination during treatment

Time	Measurement
After initial surgery	Material for local and central pathology
	Material for molecular-genetic evaluation
	Form: Clinical extend at diagnosis
	Radiotherapy consult and planning of RT
During chemotherapy (including maintenace therapy)	Physical and neurologic examination weekly
	Complete blood count and serum chemistries prior to each course
	Echocardiography prior to each course containing doxorubicin
After course 2	MRI or ultrasound of tumor region, central radiological review
	Chest X-ray
	Documentation of courses 1 and 2
After course 4	MRI or sonography of tumor region, central radiological review
	Documentation of courses 3 and 4
After course 6	MRI or sonography of tumor region, central radiological review
	Chest X-ray
	Documentation of courses 5 and 6
After course 9 or after HD	MRI or sonography of tumor region, central radiological review
	Chest X-ray
	Echocardiography
	Documentation of courses 7,8 and 9, or documentation of HD
	Physical and neurologic examination
	Blood chemsitries and CBC
	ECG and Echocardiography
	Audiometry, ENT consult
	Form: End of treatment

Checklist rhabdoid tumors of kidney or extra-renal soft tissue

Documentation

Time	Measurement
At diagnosis	Informed consent forms
	Registration form for German Childhood Cancer Registry
	Central radiological review
	Form: Clinical extend at diagnosis
	Pathology
	Central pathological review
	Moleculare Genetics
	Cytogenetics
During chemotherapy	Form: Documentation chemotherapy
	Form: Documentation of radiotherapy
	Poss. Form: Documentation of stem cell harvest
	Poss. Form: Documentation of high-dose therapy
	Form: Toxicity incl. cardiotoxicity
In case of SAE	Form: SAE
In case of any event (progress, relapse, second malignancy, death)	Form: Event report
End of therapy	Form: End of treatment
After the end of therapy	Form: Follow-up at recommended intervals

IV.10 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be

performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
• The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or • Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of
serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

IV.11 Ethics committee approval

Ärztekammer Westfalen-Lippe
Körperschaft des öffentlichen Rechts

Ethik-Kommission Münster • Von-Esmarch-Straße 62 • 48149 Münster

Herrn Prof. Dr. med. Dr. (USA)
Michael Frühwald
Klinik und Poliklinik für Kinder- und Jugendmedizin
- Pädiatrische Hämatologie und Onkologie -
Universitätsklinikum Münster
Albert-Schweitzer-Str. 33
48149 Münster

ETHIK-KOMMISSION
der Ärztekammer Westfalen-Lippe
und der Medizinischen Fakultät der
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Von-Esmarch-Str. 62
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gedruckt: 01. März 2010

Unser Aktenzeichen: **2009-532-f-S** (bitte immer angeben!)
Studiencode: **EU-RHAB**
Titel des Forschungsvorhabens:
„Europäisches Rhabdoid Register EU-RHAB. Multinationales Register für rhabdoide Tumoren jeglicher anatomischen Lokalisation"

Sehr geehrter Herr Prof. Frühwald,

für das oben genannte Forschungsvorhaben haben Sie die Beratung durch die Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster („Ethik-Kommission") beantragt.

Die Ethik-Kommission hat in ihrer Sitzung am 08.01.2010 über Ihren Antrag beraten, ergänzend vorgelegte Unterlagen in einem Ausschuss nach § 5 Abs. 1 Satz 3 ihrer Satzung geprüft, und beschlossen:

Die Ethik-Kommission hat keine grundsätzlichen Bedenken ethischer oder rechtlicher Art gegen die Durchführung des Forschungsvorhabens.

Die vorliegende Einschätzung gilt für das Forschungsvorhaben, wie es sich auf Grundlage der in Anhang 1 genannten Unterlagen darstellt.

Für die Entscheidung der Ethik-Kommission erhebt die Ärztekammer Westfalen-Lippe Gebühren nach Maßgabe ihrer Verwaltungsgebührenordnung. Auf Ihren Antrag gewährt Ihnen die Ethik-Kommission in Übereinstimmung mit dem Dekanat der Medizinischen Fakultät eine Ermäßigung der Verwaltungsgebühr auf 50 Prozent des regulären Gebührensatzes. Über die Gebühren erhalten Sie von der Ärztekammer einen gesonderten Bescheid.

Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster
unser Az.: 2009-532-f-S
Studiencode: EU-RHAB
Abschließendes Votum vom 01. März 2010

Allgemeine Hinweise:

Mit der vorliegenden Stellungnahme berät Sie die Ethik-Kommission zu den mit Ihrem Forschungsvorhaben verbundenen berufsethischen und berufsrechtlichen Fragen gemäß § 15 Abs. 1 Satz 1 Berufsordnung Ärztekammer Westfalen-Lippe.
Die Einschätzung der Kommission ist als ergebnisoffene Beratung für den Antragsteller nicht bindend. Die Ethik-Kommission weist darauf hin, dass unabhängig von der vorliegenden Stellungnahme die medizinische, ethische und rechtliche Verantwortung für die Durchführung des Forschungsvorhabens bei dessen Leiter und bei allen an dem Vorhaben teilnehmenden Ärzten bzw. Forschern verbleibt.

An der Beratung und Beschlussfassung haben die in Anhang 2 aufgeführten Mitglieder der Ethik-Kommission teilgenommen. Es haben keine Kommissionsmitglieder teilgenommen, die selbst an dem Forschungsvorhaben mitwirken oder deren Interessen davon berührt werden.

Die Ethik-Kommission empfiehlt nachdrücklich die Registrierung klinischer Studien in einem öffentlich zugänglichen Register, das die von der Weltgesundheitsorganisation (WHO) geforderten Voraussetzungen erfüllt, insbesondere deren Mindestangaben enthält. In Betracht kommende Register sowie ausführliche weiterführende Informationen stehen im Internetangebot der WHO zur Verfügung:
http://www.who.int/ictrp/en/
Zu den von zahlreichen Fachzeitschriften aufgestellten Anforderungen wird hingewiesen auf:
http://www.icmje.org/clin_trialup.htm

Die Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster ist organisiert und arbeitet gemäß den nationalen gesetzlichen Bestimmungen und den GCP-Richtlinien der ICH.

Die Kommission wünscht Ihrem Forschungsvorhaben gutes Gelingen und geht davon aus, dass Sie nach Abschluss des Vorhabens über die Ergebnisse berichten werden.

Mit freundlichen Grüßen

Univ.-Prof. Dr. med. Heidi Pfeiffer
Stellv. Vorsitzende der Ethik-Kommission

Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster
unser Az.: 2009-532-f-S
Studiencode: EU-RHAB
Abschließendes Votum vom 01. März 2010

Anhang 1

Folgende Unterlagen haben bei der Beschlussfassung vorgelegen:

Eingang	Datierung	Anlage	Version
14.12.2009	10.12.2009	Anschreiben Antragsteller	
14.12.2009	10.12.2009	Antrag auf Begutachtung 11.12.2009	
14.12.2009	10.12.2009	Schreiben Prof. Jürgens/UKM	09.12.2009
14.12.2009	10.12.2009	IV.5.1.1 Patienten- und Elterninformation	
14.12.2009	10.12.2009	European Rhabdoid Registry EU-RHAB	07.12.2009
17.12.2009		B_Empfehlung Jürgens	
17.12.2009		C_Aufklärung und Einverständnisse	
17.12.2009		D_EURHAB 091207	
26.02.2010	10.02.2010	Anschreiben des Antragstellers mit Stellungnahme	
26.02.2010	10.02.2010	Patienten und Elterninformation (dt.+engl.)	
26.02.2010	10.02.2010	Aufklärung für Kinder bis 8 Jahre sowie für Kinder	von 8-14 Jahre
26.02.2010	10.02.2010	Einverständnis zur Registrierung, Weitergabe und Verarbeitung von Patientendaten und Untersuchungsmaterial (dt. + engl.)	23.02.2010
26.02.2010	10.02.2010	Einverständniserklärung zur Teilnahme an der Konsensus-Therapie des European Rhabdoid Registry (dt.+engl.)	23.02.10

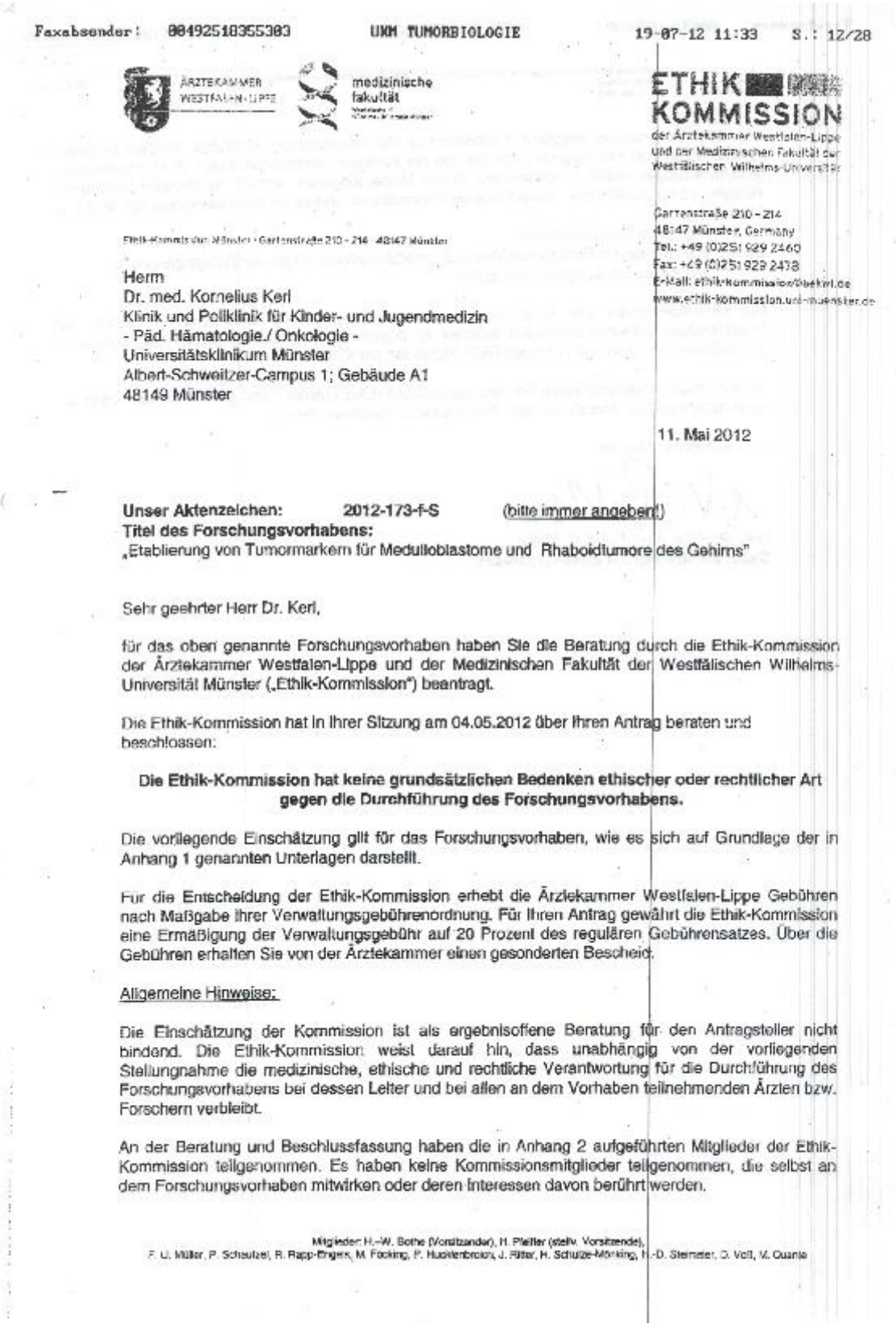
Anhang 2

Folgende Mitglieder der federführenden Ethik-Kommission haben an der Beratung und Beschlussfassung in der Sitzung vom 08.01.2010 teilgenommen:

Prof. Dr. jur. Heinz-Dietrich **Steinmeyer** Direktor des Instituts für Arbeits-, Sozial- und Wirtschaftsrecht (Abt. III) Westfälische Wilhelms-Universität Münster	Prof. Dr. phil. Ludwig **Siep** Direktor des Philosophischen Seminars Westfälische Wilhelms-Universität Münster
Prof. Dr. med. Gerhard A. E. **Rudolf** Univ.-Prof. a.D. (Psychiatrie, Schwerpunkt Klinische Psychopathologie)	Prof. Dr. med. Hans-Werner **Bothe** M.A. Klinik und Poliklinik für Neurochirurgie Universitätsklinikum Münster
Frau Dr. rer. nat. Dorothea **Voß** Apothekerin Apotheke des UKM Universitätsklinikum Münster	Prof. Dr. med. Dr. phil. Peter **Hucklenbroich** Institut für Ethik, Geschichte und Theorie der Medizin Universitätsklinikum Münster
Frau Mechthild **Föcking** Landesarbeitsgemeinschaft der Selbsthilfe Behinderter e.V.	Prof. Dr. med. Frank U. **Müller** Institut für Pharmakologie und Toxikologie Universitätsklinikum Münster
Prof. Dr. med. Dr. rer. nat. Otmar **Schober** Direktor der Klinik und Poliklinik für Nuklearmedizin Universitätsklinikum Münster ***(Vorsitz)***	Prof. Dr. med. Jörg **Ritter** Klinik und Poliklinik für Kinderheilkunde - Pädiatrische Hämatologie und Onkologie - Universitätsklinikum Münster
Frau Dr. med.Inge **Wolf** Frauenärztin	Prof. em. Dr. med. Jürgen **Horst** Institut für Humangenetik Universitätsklinikum Münster

S. 3 von 3

IV.12 Ethics committee approval for ancillary studies (see chapter 6.4)



Faxabsender: 00492518355383 UKM TUMORBIOLOGIE 19-07-12 11:33 S.: 12/28

ÄRZTEKAMMER WESTFALEN-LIPPE

medizinische fakultät

ETHIK KOMMISSION
der Ärztekammer Westfalen-Lippe
und der Medizinischen Fakultät der
Westfälischen Wilhelms-Universität

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Fax: +49 (0)251 929 2478
E-Mail: ethikkommission@ekwl.de
www.ethik-kommission.uni-muenster.de

Ethik-Kommission Münster · Gartenstraße 210 - 214 · 48147 Münster

Herrn
Dr. med. Kornelius Kerl
Klinik und Poliklinik für Kinder- und Jugendmedizin
- Päd. Hämatologie./ Onkologie -
Universitätsklinikum Münster
Albert-Schweitzer-Campus 1; Gebäude A1
48149 Münster

11. Mai 2012

Unser Aktenzeichen: 2012-173-f-S (bitte immer angeben!)
Titel des Forschungsvorhabens:
„Etablierung von Tumormarkern für Medulloblastome und Rhaboidtumore des Gehirns"

Sehr geehrter Herr Dr. Kerl,

für das oben genannte Forschungsvorhaben haben Sie die Beratung durch die Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster („Ethik-Kommission") beantragt.

Die Ethik-Kommission hat in Ihrer Sitzung am 04.05.2012 über Ihren Antrag beraten und beschlossen:

Die Ethik-Kommission hat keine grundsätzlichen Bedenken ethischer oder rechtlicher Art gegen die Durchführung des Forschungsvorhabens.

Die vorliegende Einschätzung gilt für das Forschungsvorhaben, wie es sich auf Grundlage der in Anhang 1 genannten Unterlagen darstellt.

Für die Entscheidung der Ethik-Kommission erhebt die Ärztekammer Westfalen-Lippe Gebühren nach Maßgabe ihrer Verwaltungsgebührenordnung. Für Ihren Antrag gewährt die Ethik-Kommission eine Ermäßigung der Verwaltungsgebühr auf 20 Prozent des regulären Gebührensatzes. Über die Gebühren erhalten Sie von der Ärztekammer einen gesonderten Bescheid.

Allgemeine Hinweise:

Die Einschätzung der Kommission ist als ergebnisoffene Beratung für den Antragsteller nicht bindend. Die Ethik-Kommission weist darauf hin, dass unabhängig von der vorliegenden Stellungnahme die medizinische, ethische und rechtliche Verantwortung für die Durchführung des Forschungsvorhabens bei dessen Leiter und bei allen an dem Vorhaben teilnehmenden Ärzten bzw. Forschern verbleibt.

An der Beratung und Beschlussfassung haben die in Anhang 2 aufgeführten Mitglieder der Ethik-Kommission teilgenommen. Es haben keine Kommissionsmitglieder teilgenommen, die selbst an dem Forschungsvorhaben mitwirken oder deren Interessen davon berührt werden.

Mitglieder: H.-W. Bothe (Vorsitzender), H. Pfeiffer (stellv. Vorsitzende),
F. U. Müller, P. Schulze, B. Rapp-Engels, M. Focking, P. Hucklenbroich, J. Ritter, H. Schulze-Mosking, H.-D. Stemster, O. Voß, M. Quante

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Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster S. 2 von 5
unser Az.: 2012-175f-S
Schreiben vom: 11. Mai 2012

Die Ethik-Kommission empfiehlt nachdrücklich die Registrierung klinischer Studien in einem öffentlich zugänglichen Register, das die von der Weltgesundheitsorganisation (WHO) geforderten Voraussetzungen erfüllt, insbesondere deren Mindestangaben enthält. In Betracht kommende Register sowie ausführliche weiterführende Informationen stehen im Internetangebot der WHO zur Verfügung:

http://www.who.int/ictrp/en/

Zu den von zahlreichen Fachzeitschriften aufgestellten Anforderungen wird hingewiesen auf:

http://www.icmje.org/clin_trialup.htm

Die Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster ist organisiert und arbeitet gemäß den nationalen gesetzlichen Bestimmungen und den GCP-Richtlinien der ICH.

Die Kommission wünscht Ihrem Forschungsvorhaben gutes Gelingen und geht davon aus, dass Sie nach Abschluss des Vorhabens über die Ergebnisse berichten werden.

Mit freundlichen Grüßen

i.V.

Univ.-Prof. Dr. med. Frank U. Müller
Stellv. Vorsitzender der Ethik-Kommission

Anhang 1

Folgende Unterlagen haben bei der Beschlussfassung vorgelegen:

Eingang	Datierung	Anlage	Version
13.04.2012	23.03.2012	Antrag Ethikkommission Tumormarkerscreening_KK 20120321	
13.04.2012	23.03.2012	attachment	
13.04.2012	23.03.2012	Aufklärung ATRT und Medulloblastome Eltern	
13.04.2012	23.03.2012	Aufklärungsbogen Eltern gesunde Patienten	

Anhang 2

Folgende Mitglieder der Ethik-Kommission haben an der Beratung und Beschlussfassung in der Sitzung vom 04. Mai 2012 teilgenommen:

Prof. Dr. med. Torsten **Hausamen**
Facharzt für Innere Medizin
Dortmund

Univ.-Prof. Dr. Michael **Quante**
Philosophisches Seminar
Westfälische Wilhelms-Universität Münster

Univ.-Prof. em. Dr. med. Jörg **Ritter**
Klinik und Poliklinik für Kinder- und Jugendmedizin
- Pädiatrische Hämatologie und Onkologie -
Universitätsklinikum Münster

Frau Univ.-Prof. Dr. med. dent.
Petra **Scheutzel**
Poliklinik für Zahnärztliche Prothetik und Werkstoffkunde
Universitätsklinikum Münster

Frau Univ.-Prof. Dr. sc. hum. Monika **Stoll**
Leibniz-Institut für Arteriosklerosеforschung
Münster

Univ.-Prof. Dr. med. Frank U. **Müller**
Institut für Pharmakologie und Toxikologie
Universitätsklinikum Münster

Frau Ursula **Rheinlaender**
Sonderschulpädagogin
Maximilian-Kolbe-Schule, Nordkirchen

Univ.-Prof. Prof. Dr. jur. Ingo **Saenger**
Institut für Internationales Wirtschaftsrecht (IWS)
Westfälische Wilhelms-Universität Münster

Prof. Dr. med. Heinrich **Schulze-Mönking**
St. Rochus-Hospital Telgte

Frau Dr. rer. nat. Dorothea **Voß**
Apotheke des UKM
Universitätsklinikum Münster

IV.13 Ethics committee approval Protocol Amendment

ÄRZTEKAMMER WESTFALEN-LIPPE

medizinische fakultät
Westfälische Wilhelms-Universität Münster

ETHIK KOMMISSION
der Ärztekammer Westfalen-Lippe
und der Medizinischen Fakultät der
Westfälischen Wilhelms-Universität

Gartenstraße 210 – 214
48147 Münster, Germany
Tel.: +49 (0)251 929 2460
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E-Mail: ethik-kommission@aekwl.de
www.ethik-kommission.uni-muenster.de

Ethik-Kommission Münster · Gartenstraße 210 – 214 · 48147 Münster

Herrn
Prof. Dr. Dr. Michael Frühwald
I. Klinik für Kinder und Jugendliche
Klinikum-Augsburg
Stenglinstraße 2
86156 Augsburg

24. Juli 2014

Unser Aktenzeichen: **2009-532-f-S** (bitte immer angeben!)
Studiencode: EU-RHAB
Sponsor / Finanzierung: Universitätsklinikum Münster / Deutsche Kinderkrebsstiftung
Titel des Forschungsvorhabens:
„Europäisches Rhabdoid Register EU-RHAB. Multinationales Register für rhabdoide Tumoren jeglicher anatomischen Lokalisation"

Hier: **Protocol Amendment vom 10./17.07.2014**

Votum

Sehr geehrter Herr Prof. Frühwald,

für das oben genannte Forschungsvorhaben mit Schreiben vom 10.07.2014 für nachträgliche Änderungen die Beratung durch die Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster („Ethik-Kommission") beantragt.

Die Ethik-Kommission hat durch einen Ausschuss nach § 5 Abs. 1 Satz 3 ihrer Satzung über Ihren Antrag beraten, ergänzend vorgelegte Unterlagen (Patientenaufklärung und –einwilligungserklärung zur Registrierung, Weitergabe und Verarbeitung von Patientendaten und Untersuchungsmaterial) in einem Ausschuss nach § 5 Abs. 1 Satz 3 ihrer Satzung geprüft, und beschlossen:

Die Ethik-Kommission hat weiterhin keine grundsätzlichen Bedenken ethischer oder rechtlicher Art gegen die Durchführung des Forschungsvorhabens.

Die vorliegende Einschätzung gilt für das Forschungsvorhaben, wie es sich auf Grundlage der in Anhang 1 genannten Unterlagen darstellt.

Für die Entscheidung der Ethik-Kommission erhebt die Ärztekammer Westfalen-Lippe Gebühren nach Maßgabe ihrer Verwaltungsgebührenordnung. Für Ihren Antrag gewährt die Ethik-Kommission eine Ermäßigung der Verwaltungsgebühr auf 50 Prozent des regulären Gebührensatzes. Über die ermäßigte Gebühr erhalten Sie von der Ärztekammer einen gesonderten Bescheid.

Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster
unser Az.: 2009-532-f-S
Schreiben vom: 24. Juli 201424. Juli 2014

Allgemeine Hinweise:

Mit der vorliegenden Stellungnahme berät Sie die Ethik-Kommission zu den mit Ihrem Forschungsvorhaben verbundenen berufsethischen und berufsrechtlichen Fragen gemäß § 15 Abs. 1 Satz 1 Berufsordnung Ärztekammer Westfalen-Lippe.
Die Einschätzung der Kommission ist als ergebnisoffene Beratung für den Antragsteller nicht bindend. Die Ethik-Kommission weist darauf hin, dass unabhängig von der vorliegenden Stellungnahme die medizinische, ethische und rechtliche Verantwortung für die Durchführung des Forschungsvorhabens bei dessen Leiter und bei allen an dem Vorhaben teilnehmenden Ärzten bzw. Forschern verbleibt.

An der Beratung und Beschlussfassung haben keine Mitglieder der Ethik-Kommission teilgenommen, die selbst an dem Forschungsvorhaben mitwirken oder deren Interessen davon berührt werden.

Die Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster ist organisiert und arbeitet gemäß den nationalen gesetzlichen Bestimmungen und den GCP-Richtlinien der ICH.

Die Kommission wünscht Ihrem Forschungsvorhaben gutes Gelingen und geht davon aus, dass Sie nach Abschluss des Vorhabens über die Ergebnisse berichten werden.

Mit freundlichen Grüßen

Univ.-Prof. Dr. med. Hans-Werner Bothe M.A.
Vorsitzender der Ethik-Kommission

Anhang 1

Folgende Unterlagen haben bei der Beschlussfassung neu vorgelegen:

Eingang	Datierung	Anlage
14.07.2014	10.07.2014	Protokoll Stand 10.07.2014
24.07.2014	17.07.2014	Änderungen Amendment für Ethik
24.07.2014	17.07.2014	EU-RHAB Protokoll Stand 17.07.2014 Änderungen Ethikkommission Münster

IV.14 Ethics committee approval Protocol Amendment

Patientenschutz | Forschungsfreiheit

ÄRZTEKAMMER WESTFALEN-LIPPE

WESTFÄLISCHE WILHELMS-UNIVERSITÄT MÜNSTER

Klinikum Augsburg
I. Klinik f. Kinder u. Jugendliche
Eing. 23. Sep. 2015
zugeteilt an/am:

ETHIK KOMMISSION
der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität

Ethik-Kommission Münster · Gartenstraße 210 – 214 · 48147 Münster

Gartenstraße 210 – 214
48147 Münster, Germany
Tel.: +49 (0)251 929 2460
Fax: +49 (0)251 929 2478
E-Mail: ethik-kommission@aekwl.de
www.ethik-kommission.uni-muenster.de

Herrn
Prof. Dr. Dr. Michael Frühwald
Klinikum-Augsburg
I. Klinik für Kinder und Jugendliche
Stenglinstraße 2
86156 Augsburg

18. September 2015

Unser Aktenzeichen: **2009-532-f-S** (bitte immer angeben!)
Studiencode: EU-RHAB
Sponsor / Finanzierung: Universitätsklinikum Münster / Deutsche Kinderkrebsstiftung
Titel des Forschungsvorhabens:
„Europäisches Rhabdoid Register EU-RHAB. Multinationales Register für rhabdoide Tumoren jeglicher anatomischen Lokalisation"

Beratung und Bewertung

Sehr geehrter Herr Professor Frühwald,

für das oben genannte Forschungsvorhaben haben Sie mit Schreiben vom 10.09.2015 die Beratung durch die Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster („Ethik-Kommission") beantragt.

Die Ethik-Kommission hat durch einen Ausschuss nach § 5 Abs. 1 Satz 3 ihrer Satzung über Ihren Antrag beraten, und beschlossen:

Die Ethik-Kommission hat keine grundsätzlichen Bedenken ethischer oder rechtlicher Art gegen die Durchführung des Forschungsvorhabens.

Die vorliegende Einschätzung gilt für das Forschungsvorhaben, wie es sich auf Grundlage der in Anhang 1 genannten Unterlagen darstellt.

Für die Entscheidung der Ethik-Kommission erhebt die Ärztekammer Westfalen-Lippe Gebühren nach Maßgabe ihrer Verwaltungsgebührenordnung. Über die auf 50% ermäßigten Gebühren erhalten Sie von der Ärztekammer einen gesonderten Bescheid.

Allgemeine Hinweise:

Mit der vorliegenden Stellungnahme berät die Ethik-Kommission die der Ärztekammer Westfalen-Lippe angehörenden Ärztinnen und Ärzte zu den mit dem Forschungsvorhaben verbundenen berufsethischen und berufsrechtlichen Fragen gemäß § 15 Abs. 1 Berufsordnung ÄKWL.
Die Einschätzung der Kommission ist als ergebnisoffene Beratung für den Antragsteller nicht bindend. Die Ethik-Kommission weist darauf hin, dass unabhängig von der vorliegenden Stellungnahme die medizinische, ethische und rechtliche Verantwortung für die Durchführung des Forschungsvorhabens bei dessen Leiter und bei allen an dem Vorhaben teilnehmenden Ärzten bzw. Forschern verbleibt.

Es haben keine Mitglieder teilgenommen, die selbst an dem Forschungsvorhaben mitwirken oder deren Interessen davon berührt werden.

Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster
unser Az.: 2009-532-f-S
Schreiben vom: 18. September 2015

Die Ethik-Kommission empfiehlt im Einklang mit der Deklaration von Helsinki nachdrücklich die Registrierung klinischer Studien vor Studienbeginn in einem öffentlich zugänglichen Register, das die von der Weltgesundheitsorganisation (WHO) geforderten Voraussetzungen erfüllt, insbesondere deren Mindestangaben enthält. Ausführliche Informationen zur International Clinical Trials Registry Platform (ICTRP) stehen im Internetangebot der WHO zur Verfügung:
http://www.who.int/ictrp/about/en/
Zu den Kriterien des International Committee of Medical Journal Editors (ICMJE) sei beispielsweise verwiesen auf die Informationen unter:
http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html
Das WHO Primär-Register für Deutschland ist das Deutsche Register für Klinische Studien (DRKS) in Freiburg. Es erfüllt die Forderungen der Fachzeitschriften:
http://www.drks.de/index.html

Die Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster ist organisiert und arbeitet gemäß den nationalen gesetzlichen Bestimmungen und den GCP-Richtlinien der ICH.

Die Kommission wünscht Ihrem Forschungsvorhaben gutes Gelingen und geht davon aus, dass Sie nach Abschluss des Vorhabens über die Ergebnisse berichten werden.

Mit freundlichen Grüßen

Univ.-Prof. Dr. med. Hans-Werner Bothe M.A.
Vorsitzender der Ethik-Kommission

Anhang 1

Folgende Unterlagen haben bei der Beschlussfassung vorgelegen:

Eingang	Datierung	Anlage
17.09.2015	10.09.2015	Amendment 10.09.2015 EU-RHAB Protokoll
17.09.2015	10.09.2015	Amendment 10.09.2015 EU-RHAB Protokoll
17.09.2015	10.09.2015	Auflisting Änderungen EU-RHAB Protokoll Amendement vom 10.09.2015
17.09.2015	10.09.2015	Auflisting Änderungen EU-RHAB Protokoll Amendement vom 10.09.2015
17.09.2015	10.09.2015	EU-RHAB Protokoll Stand 17.07.2014
17.09.2015	10.09.2015	EU-RHAB Protokoll Stand 17.07.2014
17.09.2015	10.09.2015	Änderungen EU-RHAB Protokoll Amendement vom 10.09.2015
17.09.2015	10.09.2015	Überarbeitungen im EU-RHAB Protokoll vom 10.09.2015
17.09.2015	10.09.2015	Überarbeitungen im Protokoll vom 10.09.2015

S. 2 von 2

IV.15 Ethics committee approval Protocol Amendment

16/02/2017 15:50 +492519292478 EK MS S. 01/02

Patientenschutz | Forschungsfreiheit

ÄRZTEKAMMER WESTFALEN-LIPPE

WESTFÄLISCHE WILHELMS-UNIVERSITÄT MÜNSTER

ETHIK KOMMISSION
der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität

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E-Mail: ethik-kommission@aekwl.de
www.ethik-kommission.uni-muenster.de

Ethik-Kommission Münster · Gartenstraße 210 – 214 · 48147 Münster

Herrn
Prof. Dr. Dr. Michael Frühwald
Klinikum-Augsburg
I. Klinik für Kinder und Jugendliche
Stenglinstraße 2
86156 Augsburg

Fax: 0821-400-174243

8. Februar 2017

Unser Aktenzeichen: **2009-532-f-S** **(bitte immer angeben!)**
EudraCT- oder DIMDI Nummer:
Prüfplancode: EU-RHAB
Sponsor: Universitätsklinikum Münster / Deutsche Kinderkrebsstiftung
Titel des Forschungsvorhabens / der klinischen Prüfung:
„Europäisches Rhabdoid Register EU-RHAB. Multinationales Register für rhabdoide Tumoren jeglicher anatomischen Lokalisation"

Sehr geehrter Herr Professor Frühwald,

vielen Dank für Ihr Schreiben vom 08.12.2016. Nach Rücksprache mit dem Studiensekretariat am 08.02.2017 bestätigen wir Ihnen gerne, zusätzlich zu der Kenntnisnahme des Eingangs vom 30.12.2016, dass wir keine Einwände haben gegen den Umzug des Leiters einer der Referenzlaboratorien sowie Änderung im Bereich der Referenzneuropathologie.
Anmerkung: Sollten wesentliche Änderungen erfolgen aufgrund der erwähnten Kommentare der verschiedenen lokalen Ethikkommissionen, bitten wir um Mitteilung und Markierung der Änderungen.

Mit freundlichen Grüßen

Univ.-Prof. Dr. med. Hans-Werner Bothe M.A.
Vorsitzender der Ethik-Kommission

Folgende Unterlagen haben uns vorgelegen:
Bei mehreren Versionen eines Dokumentes bezieht sich unsere Bewertung stets auf die letzte Version.

Eingang	Datierung	Anlage	Version:
12.12.2016	08.12.2016	Amendment zum EU-RHAB Protokoll Stand 06.12.2016	
12.12.2016	08.12.2016	Anschreiben Ethikkommission Amendment 08.12.2016	

16/02/2017 15:50 +492519292478 EK MS S. 02/02

Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster
EudraCT- oder DIMDI Nummer:
unser Az.: 2009-532-f-S
Schreiben EK vom 8. Februar 2017

S. 2 von 2

Eingang	Datierung	Anlage	Version:
12.12.2016	08.12.2016	Änderungsliste Amendment zum Protokoll 06.12.2016	
12.12.2016	08.12.2016	Überarbeitungen im Dokument EU-RHAB Protokoll vom	08.12.2016

IV.16 Checklist Cancer Predisposition Syndrome

(Fragebogen Krebsdispositionssyndrom)

Krebserkrankung im Kindesalter: Genetische Beratung indiziert?

adaptiert nach Jongmans et al. Eur J Med Genet 59 (2016) 116-125 und Ripperger et al., submitted (2016)

Ist mindestens ein Kriterium erfüllt, könnte die Familie von einer genetischen Beratung profitieren

1. Familienanamnese (Stammbaum über 3 Generationen erfragen)

O ≥2 Krebsdiagnosen vor dem 18. Lebensjahr innerhalb der Familie, einschließlich Indexpatient
O Ein Elternteil oder ein Geschwisterkind des an Krebs erkrankten Kindes hat oder hatte eine Krebserkrankung vor dem 45. Lebensjahr
O ≥2 erst- oder zweitgradig Verwandte einer Elternseite mit Krebs vor dem 45. Lebensjahr
O Die Eltern des an Krebs erkrankten Kindes sind konsanguin

2. Bei dem erkrankten Kind wurde eine der folgenden Diagnosen gestellt (Indikator Tumore):

O Adrenokortikales Karzinom / Adenom
O ALL (Robertson'sche Translokation 15;21)
O ALL (Ringchromosom 21)
O ALL (niedrig hypodiploid)
O ALL Rezidiv (*TP53* mutiert)
O AML (Monosomie 7)
O Basalzellkarzinom
O Botryoides Rhabdomyosarkom des Urogenitaltrakts (Fusions-negativ)
O Chondromesenchymales Hamartom
O Choroid-Plexus-Karzinom / Tumor
O Endolymphatischer-Sack-Tumor
O Fötales Rhabdomyom
O Gastrointestinaler Stromatumor
O Gonadoblastom
O Großzelliger kalzifizierender Sertoli-Zell-Tumor
O Hämangioblastom
O Hepatoblastom (*CTNNB1* Wildtyp)
O Hepatozelluläres Karzinom
O Hypophysäres Blastom
O Hypophysenadenom / -tumor
O Infantile Myofibromatose
O Juvenile myelomonozytäre Leukämie
O Juvenile polyposis
O Keratozytisch odontogener Tumor
O Keimstrang-Stroma-Tumor mit anulären Tubuli
O Kleinzelliges hyperkalzämisches Ovarialkarzinom
O Kolorektales Karzinom
O Maligner peripherer Nervenscheidentumor
O Medulläres Schildrüsenkarzinom
O Medulläres Nierenzellkarzinom
O Medulloblastom (SHH aktiviert)
O Medulloblastom (WNT aktiviert, *CTNNB1* Wildtyp)
O Medulloepitheliom
O Melanom
O Meningeom
O Myelodysplastisches Syndrom
O Myeloproliferative Neoplasie (Ausnahme: CML)
O Myxom
O Nebenschilddrüsenkarzinom / -adenom
O Neuroendokriner Tumor
O Nierenzellkarzinom
O Paragangliom / Phäochromozytom
O Pineoblastom
O Plattenepithelkarzinom
O Pleuropulmonales Blastom
O Retinoblastom
O Rhabdoid-Tumor
O Rhabdomyosarkom mit diffuser Anaplasie
O Schilddrüsenkarzinom (nicht-medullär)
O Schwannom
O Schwannomatose
O Sehbahngliom (mit klinischen NF1-Zeichen)
O Sertoli-Leydig-Zell-Tumor
O Subependymales Riesenzellastrozytom
O Transiente myeloproliferative Erkrankung
O Zystisches Nephrom
O Andere bei Kindern seltene Entitäten oder eher bei Erwachsenen typische Tumore bzw. ungewöhnlich frühes Erkrankungsalter

3. O Tumoranalysen zeigen genetische Alteration, die auf Prädisposition hindeutet

4. O Ein Kind mit ≥2 Primär-Neoplasien (z.B. sekundär, bilateral, multifokal, metachron)

5. O Bei dem an Krebs erkrankten Kind bestehen kongenitale oder andere Auffälligkeiten

Zeichen	*Denke an*
O Kongenitale Anomalien	Organfehlbildungen, Skelettanomalien, Lippen-Kiefer-Gaumen-Spalten, Zahnanomalien, urogenital Anomalien, Hör-/Sehstörungen etc.
O Auffällige Fazies	
O Herabgesetzte intellektuelle Fähigkeiten / Entwicklungsretardierung	Lernstörungen, Verhaltensauffälligkeiten
O Wachstumsauffälligkeiten	Größe, Kopfumfang, Geburtsgewicht, Asymmetrie, Wachstumskurve
O Hautauffälligkeiten	Auffällige Pigmentierung, z.B. ≥2 Café-au-lait Flecken, vaskuläre Läsionen, Überempfindlichkeit gegenüber Sonne, mehrere gutartige Hauttumore
O Hämatologische Auffälligkeiten (nicht durch aktuelle Krebserkrankung erklärt)	Panzytopenie, Anämie, Thrombozytopenie, Neutropenie, Leukopenie, Makrozytose der Erythrozyten
O Immundefizienz	Häufigkeit von Infektionen, Lymphopenie
O Endokrine Auffälligkeiten	z.B. primärer Hyperparathyreoidismus, vorzeitige Pubertät, Gigantismus/Akromegalie, Cushing Syndrom

6. O Es besteht bei dem krebskranken Kind im Verlauf der Therapie eine exzessive Toxizität

Version 1, 7. Dezember 2016, AG Genetische Krebsprädisposition der GPOH

IV.17 Checklist
Cancer Predisposition Syndrome

Childhood cancer: Indication for genetic counseling?

* adapted from Jongmans et al. Eur J Med Genet 59 (2016) 116-125 and Ripperger et al., submitted (2016)

if at least one criterion is fulfilled, your patient may benefit from genetic counseling

1. Family history (3 generation pedigree)

O ≥2 malignancies occurred in family members before age 18 years, including index patient
O Parent or sibling with current or history of cancer before age 45 years
O ≥2 first or second degree relatives in the same parental lineage with cancer before age 45 years
O The parents of the child with cancer are consanguineous

2. One of the following Neoplasms was diagnosed:

O Adrenocortical carcinoma / adenoma
O ALL (low hypodiploid)
O ALL (ringed chromosome 21)
O ALL (Robertsonian translocation 15;21)
O ALL relapse (*TP53* mutated)
O AML (Monosomy 7)
O Basal cell carcinoma
O Botryoid rhabdomyosarcoma of the urogenital tract (fusion-negative)
O Chondromesenchymal harmatoma
O Choroid plexus carcinoma / tumor
O Colorectal carcinoma
O Cystic nephroma
O Endolymphatic sack tumor
O Fetal rhabdomyoma
O Gastrointestinal stromal tumor
O Glioma of the optic pathway (with signs of NF1)
O Gonadoblastoma
O Hemangioblastoma
O Hepatoblastoma (*CTNNB1* wildtype)
O Hepatocellular carcinoma
O Infantile myofibromatosis
O Juvenile myelomonocytic leukemia
O Keratocystic odontogenic tumor
O Large cell calcifying Sertoli-cell-tumor
O Malignant peripheral nerve sheath tumor
O Medullary thyroid carcinoma
O Medulloblastoma (SHH activated)
O Medulloblastoma (WNT activated, *CTNNB1* wildtype)
O Medullary renal cell carcinoma
O Medulloepithelioma
O Melanoma
O Meningioma
O Myelodysplastic syndrome
O Myeloproliferative neoplasms (except CML)
O Myxoma
O Neuroendocrine tumor
O Paraganglioma / pheochromocytoma
O Parathyroid carcinoma / adenoma
O Pineoblastoma
O Pituitary adenoma / tumor
O Pituitary blastoma
O Pleuropulmonary blastoma
O Renal cell carcinoma
O Retinoblastoma
O Rhabdoid tumor
O Rhabdomyosarcoma with diffuse anaplasia
O Schwannoma
O Schwannomatosis
O Sertoli-Leydig cell tumor
O Sex cord stromal tumor with annular tubules
O Small cell carcin. of the ovary hypercalcemic type
O Squamous cell carcinoma
O Subependymal giant cell astrocytoma
O Thyroid carcinoma (non-medullary)
O Transient myeloproliferative disease
O **Other rare cancers or cancers that typically occur in adults, unusually early manifestation age**

3. O Genetic tumor analysis reveals defect suggesting a germline predisposition

4. O A patient with ≥2 malignancies (e.g. secondary, bilateral, multifocal, metachronous)

5. O A child with cancer and congenital or other anomalies

Sign	*Think of*
O Congenital anomalies	Abnormal organs, skeletal anomalies, oral clefting, abnormal teeth, urogenital anomalies, abnormal hearing or vision, etc.
O Facial dysmorphism	
O Mental impairment, developmental delay	Abnormal behavior, learning difficulties
O Abnormal growth	Height, head circumference, birth weight, hemihyperplasia, growth chart
O Skin anomalies	Abnormal pigmentation such as ≥2 café-au-lait spots, vascular lesions, hypersensitivity to sun, benign tumors, etc.
O Hematological abnormalities (not explained by current cancer)	Pancytopenia, anemia, thrombocytopenia, neutropenia, leukopenia, macrocytic erythrocytes
O Immune deficiency	Frequency of infections, lymphopenia
O Endocrine anomalies	Primary hyperparathyroidism, precocious puberty, Gigantism/acromegaly, Cushing syndrome

6. O The patient suffers from excessive toxicity of cancer therapy

Version 1, December 7 2016, Cancer Predisposition Working Group of the GPOH

IV.18 CRF SIOP Umbrella Study

SIOP Renal Tumour Study Group RTSG	**UMBRELLA Study**	PATHOLOGY FORM *FORM 4* *Page 1 of 5*

Patient Identifier	Centre	SIOP 2016 Study Number
☐☐☐☐☐	_____	☐☐☐☐☐

Name of Pathologist: _____

Date of surgery ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y)

Pathology specimen number(s) .....

.....

.....

PLEASE SEND ***TWO SEPARATE FORMS*** FOR ***BILATERAL CASES***

Primary nephrectomy (1) Pre-operative chemotherapy (2) ☐

Tumour site: Right (1) Left (2) Extra-renal (4) ☐

Type of specimen: (send **two forms** whenever tissue is available from both kidneys) ☐

Unilateral	Left or right	Complete nephrectomy	(1)
	Left or right	Partial nephrectomy	(2)
Bilateral	Left	Complete nephrectomy	(3)
		Partial nephrectomy	(4)
	Right	Complete nephrectomy	(5)
		Partial nephrectomy	(6)

Specimen Weight (gram) ☐☐☐☐ **Tumour diameters (mm)** ☐☐☐

(For multifocal tumours, indicate the diameter of the largest single tumour)

Renal capsule grossly intact? (before opening specimen)
No (1) Yes (2) Uncertain (3) ☐

Tumour multifocal?
No (1) Yes (2) Uncertain (3) ☐

Resection margin involved by tumour?
(Microscopically) No (1) Yes (2) Uncertain (3) ☐

If Yes, please specify viability of tumour at resection margin
Viable (1) Non-viable (2) ☐

In case of partial nephrectomy:
minimal distance of viable tumour to resection line (mm): ☐☐

Renal vein thrombosis
(Microscopically) No (1) Yes (2) Uncertain (3) ☐

Percentage of necrosis/regressive changes on gross examination % ☐☐☐

Percentage of necrosis/regressive changes on histological examination % ☐☐☐

Percentage of blastema in viable tumour component % ☐☐☐

Nephrogenic rests
No (1) Yes (2) Uncertain (3) ☐

If anaplastic nephroblastoma, please subclassify
Focal (1) Diffuse (2) Uncertain (3) ☐

SIOP Renal Tumour Study Group RTSG	**UMBRELLA Study**	PATHOLOGY FORM ***FORM 4*** ***Page 2 of 5***

Patient Identifier	Centre	SIOP 2016 Study Number
☐☐☐☐☐	_____	☐☐☐☐☐

Number of lymph nodes examined **(hilar, peri-aortic or other abdominal sites):** ☐☐

Lymph node status

Positive for tumour (1) Negative for tumour (2)
Uncertain (3) None examined (4) ☐

Number of lymph nodes with viable tumour ☐☐

Number of lymph nodes with non-viable tumour ☐☐

Your diagnosis (please enter the code of the appropriate classification from the list below) ☐☐☐

Low Risk	CPDN	(110)	**High Risk**	Blastemal	(212)
	Completely necrotic	(140)		Diffuse anaplasia	(312)
	Mesoblastic nephroma	(150)			
Intermediate Risk	Non anaplastic and variants	(210)	**Other**	CCSK	(320)
	Epithelial type	(211)		MRTK	(330)
	Stromal type	(213)		RCC	(340)
	Mixed type	(214)		Other (specify below)	(500)
	Regressive type	(216)		Undeterminable	(600)
	Focal anaplasia	(311)		Nephroblastomatosis	(450)

If Other (code 500) please specify: .....

Abdominal tumour stage based on pathological examination ☐

Reason(s) for staging (see coding on the last page of this form) ☐☐ ☐☐ ☐☐

Material stored for biological studies?

No (1) ☐ If yes, Stored as: Frozen Only (1)
Yes (2) Research paraffin block only (2) ☐
Both (3)

If yes, sent to: _____

Form completed by (please print): _____

Please sign: _____

Tel/Fax:_____ **Email Address:** _____ **Date** _____

Please indicate here date path sent direct ___/___/___

If not using eCRFs in ALEA or ObTiMA please send form immediately to:

SIOP Nephroblastoma Office: Princess Maxima Center, Tav MM van den Heuvel-Eibrink, Lundlaan 6, 3584 EA, Utrecht, The Netherlands. Phone ++ 31-(0)88 -9727007	**For GPOH:** Studienzentrale Nephroblastom, UKH, Kinderonkologie, Gebäude 9, 66421 Homburg Phone: ++49-6841-1628025, Fax: ++49-6841-1628024

SIOP Renal Tumour Study Group RTSG	**UMBRELLA Study**	PATHOLOGY FORM *FORM 4* *Page 3 of 5*
Patient Identifier ☐☐☐☐☐	Centre _____	SIOP 2016 Study Number ☐☐☐☐☐

For central review, please submit a full set of H&E slides and one paraffin block immediately after the operation. Do not delay sending the sections for pathology review for whatever reason, even if you are not sure whether the patient will be entered into the study.

SEND **SLIDES**, **BLOCK**, THIS *FORM AND A COPY OF YOUR REPORT
IF READY, TO YOUR NATIONAL REFERENCE PATHOLOGIST

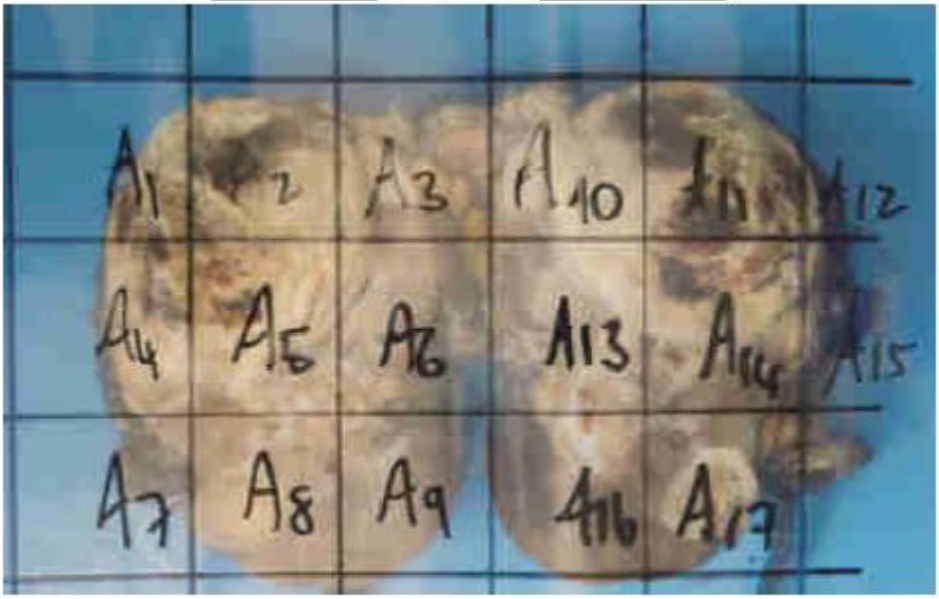
THE SLIDES AND THE PARAFFIN BLOCK WILL BE KEPT IN THE REFERENCE CENTER!

List of Addresses at the last page of this form!

**Please note a copy of this form should also be kept by the reporting centre,*

Please ensure your data manager has a copy.

Left Kidney Right Kidney



Please draw or photograph the tumour and document the exact site (by using numbers or letters) of each section taken.

SIOP Renal Tumour Study Group RTSG	**UMBRELLA Study**	PATHOLOGY FORM *FORM 4* *Page 4 of 5*

Staging criteria

Stage I

a) The tumour is limited to kidney or surrounded with a fibrous (pseudo)capsule if outside of the normal contours of the kidney. The renal capsule or pseudo capsule may be infiltrated by the tumour but it does not reach the outer surface.
b) The tumour may be protruding ('bulging') into the pelvic system and 'dipping' into the ureter but it is not infiltrating their walls.
c) The vessels or the soft tissues of the renal sinus are not involved.
d) Intrarenal vessel involvement may be present.

Notes:

- *Be aware of mature tubules within the sinus or hilar region which usually represent perilobar nephrogenic rests. Intralobar nephrogenic rest may grow within the sinus, too. Genuine infiltration of the sinus/hilar structures is usually seen as blastemal foci closely related to nerves.*
- *Fine needle aspiration or percutaneous core needle ('tru-cut') biopsy does not upstage the tumour.*
- *The presence of necrotic tumour or chemotherapy-induced change in the renal sinus, renal veins and/or within the perirenal fat should not be regarded as a reason for upstaging a tumour*
- *Infiltration of the adrenal gland does not upstage tumour if the external capsule of the adrenal gland is intact*
- *Liver: tumour might be attached to the liver capsule and this should not be regarded as infiltration of the adjacent organ; only if clear infiltration of the liver parenchyma is present, tumour should be regarded as stage III*

Stage II

a) Viable tumour penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins 'clear')
b) Viable tumour infiltrates the soft tissues of the renal sinus
c) Viable tumour infiltrates blood and lymphatic vessels of the renal sinus or renal veins or is present in the perirenal tissue but it is completely resected.
d) Viable tumour infiltrates the ureter's wall.
e) Viable tumour infiltrates adjacent organs or vena cava but is completely resected.

Stage III

a) Viable tumour extends to the resection margins. If there is only non-viable tumour at inked resection line, it is regarded as stage III only if viable tumour is <5 mm to the inked margin. If the viable tumour is >5 mm from the resection line and only regressive changes are found at inked margin it does not upstage the tumour (the minimal distance of 5 mm tissue without viable has to be documented with several blocks of this area).
b) Any abdominal lymph nodes are involved with either viable or non-viable tumour.
c) Pre- or intra-operative tumour rupture, if visible at pathological examination (irrespective of other criteria for staging).
d) Tumour thrombus is present at resection margins of ureter, renal vein or vena cava inferior (always discuss resection margins with a surgeon)
e) Tumour thrombus which is attached to the IVC wall is removed piecemeal by surgeon
f) Tumour has been biopsied (wedge/open biopsy) prior to pre-operative chemotherapy or surgery
g) Tumour implants (viable and/or non-viable) are found anywhere in the abdomen
h) Tumour (viable and/or non-viable) has penetrated through the peritoneal surface

Notes:

- *Renal vein retraction issue: Often a thrombus bulges out of the resection line of the renal vein. This is even marked by retraction of the vein after resection and fixation. Such cases have to be discussed with surgeon who needs to clarify whether thrombus was at resection margin before cutting off the vein.*
- *The presence of necrotic tumour or chemotherapy-induced changes in a lymph node is regarded as proof of previous tumour with microscopic residue and therefore the tumour is assigned stage III (because of the possibility that some viable tumour is left behind in the adjacent lymph node). The regressive changes in the lymph nodes should have an appearance of a tumour-like area having the shape of previous tumour infiltration. Groups of macrophages in the sinus should not regarded as previous tumour infiltration.*
- *Mature tubules can be found in lymph nodes often associated with Tamm-Horsfall protein deposits, but also without it. This should not be regarded as lymph node metastasis.*
- ***The presence of ruptures at diagnosis is only considered as pathological stage III if it can be seen at nephrectomy. If not, tumour should be staged on the basis of other criteria seen, and the final treatment stage should be decided after discussion at multidisciplinary team /tumour board meeting.***

Stage IV

Haematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdomino-pelvic region.

Stage V

Bilateral renal tumours at diagnosis. Each side should be sub-staged according to the above criteria.

SIOP Renal Tumour Study Group RTSG	**UMBRELLA Study**	PATHOLOGY FORM *FORM 4* *Page 5 of 5*

ADDRESSES TO SEND **SLIDES**, **BLOCK**, THIS ***FORM** AND A COPY OF **YOUR REPORT**
TO YOUR NATIONAL REFERENCE PATHOLOGIST

United Kingdom: Gordan M. Vujanic E-mail: vujanic@cf.ac.uk	**Germany:** Ivo Leuschner E-mail: ileuschner@path.uni-kiel.de
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Italy: Paola Collini E-mail: paola.collini@istitutotumori.mi.it	**Spain:** Enrique de Alava E-mail: Enrique.alava.sspa@juntadeandalucia.es
Brazil: Isabela Werneck Cuhna E-mail: iwerneck0210@gmail.com	**Scandinavia:** Ivo Leuschner E-mail: ileuschner@path.uni-kiel.de
All other countries: Gordan Vujanic and Ivo Leuschner	

Chairs of the Pathology Panel:

United Kingdom: Professor Gordan M. Vujanic Department of Pathology, University Hospital of Wales, Heath Park, Cardiff, CF4 14XN, UK Tel.: 029 2074 2706; Fax: 029 2074 8490 E-mail: vujanic@cf.ac.uk	**Germany:** Prof. Dr. Ivo Leuschner Universitätsklinikum Schleswig Holstein Campus Kiel, Arnold-Heller-Str. 3, Haus 14, 24105 Kiel, Germany Tel.: +49 431 597-3450; Fax +49 431 597-3486 E-mail: ileuschner@path.uni-kiel.de

SIOP Renal Tumour Study Group RTSG	**UMBRELLA Study**	**BIOMATERIAL** ***FORM 5*** ***Page 1 of 3***
Patient Identifier ☐☐☐☐☐	**Centre** _____	**SIOP 2015 Study Number** ☐☐☐☐☐

BIOMATERIAL: PATIENT

Date when blood was sampled: ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y)

Was any of the following biomaterial from the patient stored?

Blood sample(s)

EDTA No (1), Yes (2) ☐

If yes, specify biobank/lab:.....

At what time point were EDTA samples collected?

At diagnosis No (1), Yes (2) ☐

During treatment No (1), Yes (2) ☐

If yes, when:

- After preoperative chemotherapy ☐
- After surgery ☐
- At the end of treatment ☐
- After the end of treatment, during follow-up ☐
- At relapse ☐
- At another time point ☐

Please specify: .....

PAXgene™ tube No (1), Yes (2) ☐

If yes, specify biobank/lab: .....

At what time point were PAXgene™ samples collected?

At diagnosis No (1), Yes (2) ☐

During treatment No (1), Yes (2) ☐

If yes, when:

- After preoperative chemotherapy ☐
- After surgery ☐
- At the end of treatment ☐
- After the end of treatment, during follow-up ☐
- At relapse ☐
- At another time point ☐

Please specify: .....

SIOP Renal Tumour Study Group RTSG	**UMBRELLA Study**	**BIOMATERIAL** ***FORM 5*** ***Page 2 of 3***

Patient Identifier	Centre	SIOP 2015 Study Number
☐☐☐☐☐	_____	☐☐☐☐☐

Urine sample(s) No (1), Yes (2) ☐

If yes: date when tissue is sampled: D D M M Y Y Y Y

If yes, specify biobank/lab: .....

At what time point were urine samples collected?

At diagnosis No (1), Yes (2) ☐

During treatment No (1), Yes (2) ☐

If yes, when:

- After preoperative chemotherapy ☐
- After surgery ☐
- At the end of treatment ☐
- After the end of treatment, during follow-up ☐
- At relapse ☐
- At another time point ☐

Please specify: .....

Tumour tissue No (1), Yes (2) ☐

If yes: date when tissue is sampled: D D M M Y Y Y Y

Type of sample(s):

Frozen ☐

Please specify biobanks, where sample is stored: .....

Please specify number of samples: .....

Please specify type of sample: Primary tumour ☐

Relapsed tumour ☐

Research paraffin block ☐

Please specify biobanks, where sample is stored: .....

Please specify number of samples: .....

Please specify type of sample: Primary tumour ☐

Relapsed tumour ☐

SIOP Renal Tumour Study Group RTSG	**UMBRELLA Study**	**BIOMATERIAL** ***FORM 5*** ***Page 3 of 3***

Patient Identifier	Centre	SIOP 2015 Study Number
☐☐☐☐☐	_____	☐☐☐☐☐

Normal kidney tissue No (1), Yes (2) ☐

If yes: date when tissue is sampled: D D M M Y Y Y Y

Type of sample(s): **Frozen** ☐

Please specify biobanks, where sample is stored: .....

Please specify number of samples: .....

Please specify type of sample: Primary tumour ☐

Relapsed tumour ☐

Research paraffin block ☐

Please specify biobanks, where sample is stored: .....

Please specify number of samples: .....

Please specify type of sample: Primary tumour ☐

Relapsed tumour ☐

BIOMATERIAL: PARENTS

Was biomaterial from the parents stored? No (1), Yes (2) ☐

If yes: Blood ☐ Urine ☐ other ☐ If other, please specify: .....

If **blood**: EDTA PAXgene ™ ☐ other ☐ If other, please specify: .....

From whom: Mother ☐ Father ☐

Please specify biobank: .....

If **urine**: From whom: Mother ☐ Father ☐

Please specify biobank: .....

If **other**: From whom: Mother ☐ Father ☐

Please specify other: .....

Please specify biobank: .....

Please send form immediately to:

SIOP Nephroblastoma Office: Princess Máxima Center for Pediatric Oncology, Lundlaan 6, 3584EA Utrecht Phone: +31(0)88-9727007	**For GPOH:** Studienzentrale Nephroblastom, UKH, Kinderonkologie, Gebäude 9, 66421 Homburg Phone: ++49-6841-1628025, Fax: ++49-6841-1628024