Gesellschaft für Pädiatrische Onkologie und Hämatologie

NB2004 Trial Protocol

for Risk Adapted Treatment of Children with Neuroblastoma

Principal investigator:

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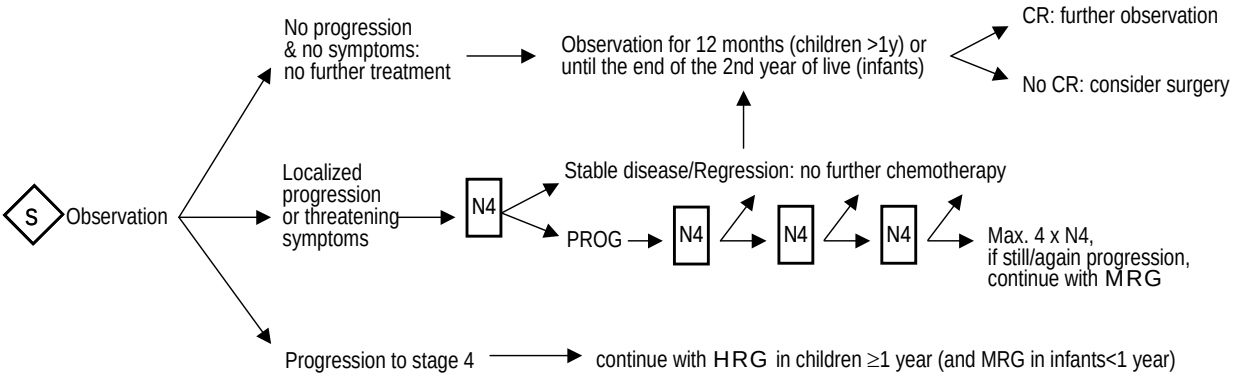
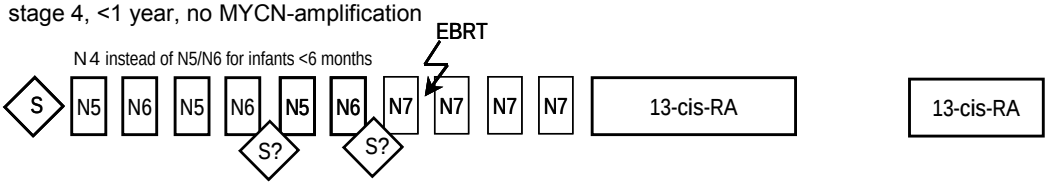
Status: final

1 NB2004 GENERAL OVERVIEW

OBSERVATION GROUP (OG)
stage 1, 0-21 years, no MYCN-amplification
stage 2, 0-21 years, no 1p aberration, no MYCN-amplification
stage 3, 0-2 years, no 1p aberration, no MYCN-amplification
stage 4S, 0-1 year, no MYCN-amplification



MEDIUM RISK GROUP (MRG)
stage 3, ≥2 years; no MYCN-amplification
stage 3, 0-21 years, 1p aberration, no MYCN-amplification
stage 2, 0-21 years, 1p aberration, no MYCN-amplification
stage 4, <1 year, no MYCN-amplification



HIGH RISK GROUP (HRG)
stage 4, ≥1-21 years,
Any stage, age 0-21 years, presence of MYCN amplification

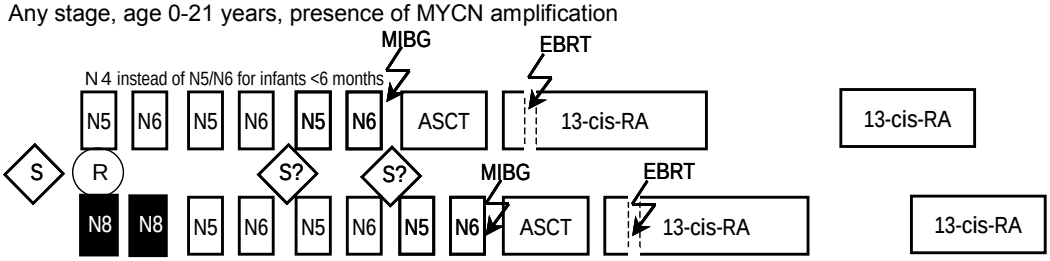


Figure 1: Overview over NB2004 treatment (S=surgery, R=randomization, N4/5/6/7/8=chemotherapy cycles, MIBG=MIBG treatment, EBRT=external beam radiation therapy, 13-cis-RA=13-cis-retinoic acid)

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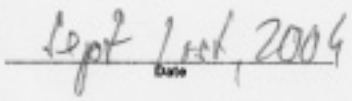
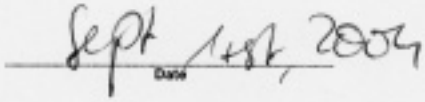
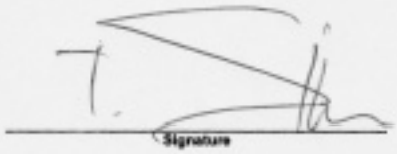
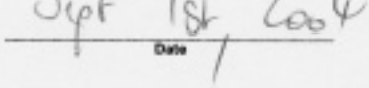
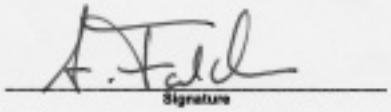
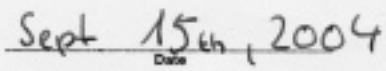
3 SIGNATURES

Prof. Dr. F. Berthold Principal investigator	 Signature	 Date
Dr. B. Hero Trial coordinator	 Signature	 Date
Dr. T. Simon Trial coordinator	 Signature	 Date
Dr. A. Faldum Biostatistics	 Signature	 Date

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Prof. Dr. M.	Schrappe	Hannover
Dr. T.	Simon	Köln
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Prof. Dr. D.	von Schweinitz	München
Prof. Dr. J.	Wolff	Regensburg

6 IMPORTANT NOTE

This clinical trial protocol for the risk adapted treatment of neuroblastoma in children and adolescents does not represent a guideline for standard treatment of neuroblastoma. Patients can only be treated according to the protocol in hospitals which have signed the cooperation form. Inclusion and exclusion criteria must be met by any individual patient prior to admission. Each patient must be registered by the trial office.

The protocol has been written carefully. Despite this, errors cannot entirely be discounted. Each investigator is fully responsible for the treatment. All recommendations given in this protocol, particularly drug doses, must be compared with commonly accepted guide lines. If questions arise, do not hesitate to contact the trial office.

The content of the protocol is confidential. It can only be passed to hospitals not participating in the trial by the trial office.

7 TABLE OF CONTENTS

8 GLOSSARY

ADR	Adriamycin
AMG	Arzneimittelgesetz
ASCT	Autologous stem cell transplantation
AT III	Antithrombin III
CARBO	Carboplatin
CI	Confidence interval
CPM	Cyclophosphamide
CR	Complete remission
CRF	Case report forms (attached to the clinical trials protocol)
CT	Chemotherapy
CTV	Clinical target volume (radiation therapy)
DDP	Cisplatinum
DMC	Data monitoring committee
DOX	Doxorubicin = Adriamycin
DTIC	Dacarbacin
EANM	European association of nuclear medicine
EBRT	External beam radiation therapy
ECG	Echocardiogram
EFS	Event free survival
EFS_D	Event free survival
EFS_L	Locoregional event free survival
EFS_R	Event free survival after begin of regression
$EFS_{stage\ 4}$	Survival free from transition to stage 4
FISH	Fluorescence in vitro hybridization
G-CSF	Granulocyte colony stimulating factor
GGT	Glutamyl transpeptidase
GOT	Serum glutamic oxaloacetic transaminase
GPOH	Gesellschaft für Pädiatrische Hämatologie und Onkologie
GPT	Serum glutamic pyruvic transaminase
Hb	Hemoglobin
HCG	Historic control group
HRG	NB2004 High risk group
HVA	Homovanillic acid
IFO	Ifosfamide
INPC	International Neuroblastoma Pathology Committee
INSS	International neuroblastoma staging system
KM	Bone marrow
LDH	Lactate dehydrogenase
MACS	Magnetic-activated cell sorting = CD34 positive selection
MBq	Mega-Bequerel
MEL	Melphalan

MIBG	Meta-iodo-benzylguanidine
MKI	Mitosis karyorrhexis index
MR	Mixed response
MRG	NB2004 Medium risk group
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MYCN	Oncogen MYCN
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NMA	MYCN amplification
NR	Non-response
NSE	Neuron specific enolase
OG	NB2004 Observation group
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PLT	Platelets
PR	Partial remission
RA	13-cis-retinoic acid
RT	radiation therapy
SAE	Severe adverse event
SD	Stable disease
SPECT	Single photon emission computed tomography
SUSARS	Suspected unexpected severe adverse reaction
TBI	Total body irradiation
TOPO	Topotecan
TTND	Time to no evidence of disease
TTNT	Time to normalization of tumor markers
TTPR	Time to primary regression
VBL	Vinblastine
VCR	Vincristine
VGPR	Very good partial response
VMA	Vanillymandelic acid
VOD	Venous occlusive disease
VP-16	Etoposide
WBC	White blood cells

9 NB2004 RISK GROUP DEFINITION

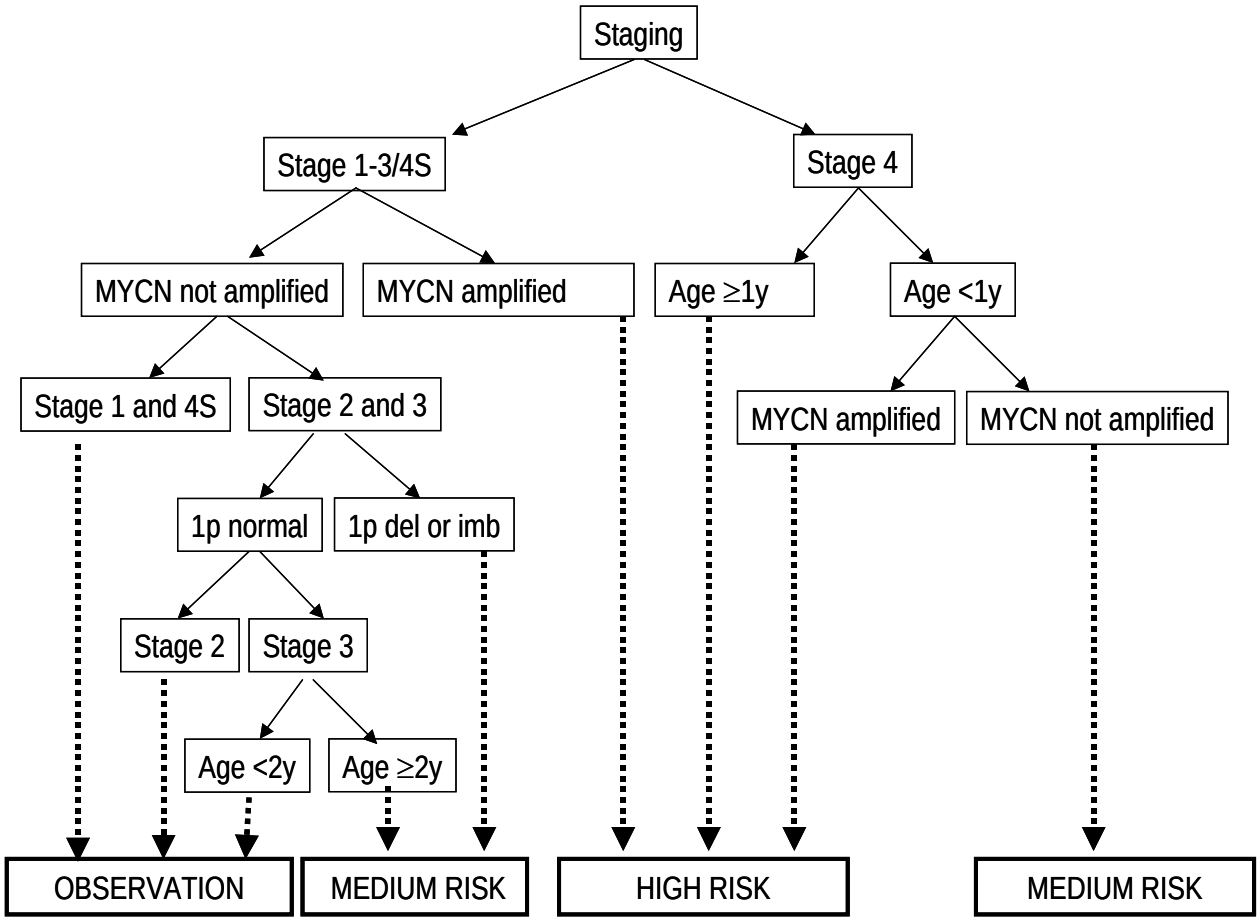


Figure 2: Risk group classification in NB2004

10 DIAGNOSIS AND FOLLOW-UP

10.1 Initial (=preoperative) staging

Initial assessment of the patient must establish the diagnosis of neuroblastoma and must reveal the extent of the disease. The complete staging should be performed prior to any chemotherapy or surgery. It has to include each of the following procedures (see page 180):

10.1.1 Basic assessment

- History
- Clinical status
- Full blood count
- Electrolytes, liver function tests (GOT, GPT, GGT, bilirubin, coagulation: prothrombine time, activated partial thomboplastin time, fibrinogen, AT III, D-dimers), kidney function (creatinine, urea, uric acid)
- blood type
- HLA class I typing
- transfusion associated viral status (i.e., hepatitis A, B, and C, HIV, CMV, Parvovirus B19)
- consider karyogram if unexplained morphologic or developmental abnormalities of the patient are found.

10.1.2 Tumor marker

- **Lactate dehydrogenase (LDH).** The results depend on patient's age. According to the NB90 trial,[6] the following enzyme activities are defined as abnormal:
    - patients age <1 year: >400 U/l
    - patients age 1-17 years: >300 U/l
    - patients age >17 years: >200 U/l
- **Ferritine**. The result depends on patient's age and on the test used. Therefore, categorization "normal" or "elevated" according to the reference values of the local laboratory has to be documented in the case report files.
- **Neuron-specific enolase (NSE).** NSE results are influenced by hemolysis and degradation at room temperature. Therefore, a non-hemolytic blood sample should be assessed within 2-6 hours in the local hospital laboratory. If the sample is sent to other laboratories, please separate the serum and send the serum only. The

result depends on patient's age and on the test used. Therefore, categorization "normal" or "elevated" according to the reference values of the local laboratory has to be documented in the case report files.

- **Catecholamine metabolites** vanillymandelic acid (VMA) and homovanillic acid (HVA) in serum and urine.[72] Urine collection is not necessary, when the results are normalized by urine creatinine concentration. Categorization "normal" or "elevated" according to the reference values of the laboratory has to be documented in the case report files. It is recommended to send the serum and urine samples to the laboratory of Dr. D.H. Hunneman in Göttingen (shipping form on page 231).

10.1.3 Imaging required for initial diagnosis

10.1.3.1 Ultrasound

Ultrasound assessment of the **involved region** is mandatory unless anatomical reasons do not allow ultrasound (e.g., thoracic neuroblastoma). Also, the size of skin or soft tissue metastasis can be documented by ultrasound.

Routine ultrasound assessment is required as a base line investigation in all children. It must include examination of neck, abdomen, particularly liver (small liver metastasis may be overlooked unless high frequency transducer is used), retroperitoneum, and brain (if the fontanel is still open).

10.1.3.2 X-ray

Chest x-ray but no other routine X-ray is required during initial staging.

In some cases, **thoracic neuroblastoma** may be detected by chest x-ray for pulmonary symptoms. Since ultrasound assessment of the chest is limited by the air filled lungs, follow-up of thoracic neuroblastoma includes routine chest x-rays instead of ultrasound.

Bone lesions due to metastases can be seen on x-ray but bone scan gives information about the whole skeleton. Therefore, bone x-ray is only recommended for documentation and follow-up of selected lesions critical for stability of the skeletal system.

10.1.3.3 MRI of the involved regions

MRI assessment of the **primary tumor** is required at initial diagnosis.

If neuroblastoma is found in the paravertebral region, a **spinal MRI** is required to document or to rule out intraforaminal or intraspinal involvement even in patients without neurological signs. Computed tomography is not appropriate since small intraspinal tumor masses can be missed.

In all stage 4 patients regardless of MIBG uptake pattern, **MRI of the cranium** is needed to demonstrate or exclude intracranial or orbital involvement.

Minimum of MRI sequences required:

Cranium:

- T1-weighted (T1w) sequence and T1w contrast enhanced sequence, transversal;
- T1w sequence and T1w contrast enhanced sequence, coronal;
- T2w sequence, transversal;
- FLAIR sequence, transversal;

Chest:

- T2w sequence, coronal;
- T1w sequence and T1w contrast enhanced sequence, transversal;
- T2w sequence, transversal;

Abdomen:

- T2w sequence, coronal;
- T1w sequence, transversal;
- T1w contrast enhanced fat suppression sequence, transversal;
- T2w fat suppression sequence, transversal;

Spinal MRI (for all paravertebral tumors):

- T1w sequence and T1w contrast enhanced sequence, sagittal;
- fat suppression sequence, sagittal;
- T2w or T1w contrast enhanced sequence, transversal (depending on signal intensity of the primary tumor).

MRI should not be substituted by computed tomography for the following reasons: detailed resolution, better soft tissue contrast, better detection of intraspinal or intraforaminal tumor tissue, and no exposure to radiation. In children under the age of about 6 years, general anesthesia should be considered for MRI assessment.

Central review of MRI films is not mandatory but in case of equivocal MRI results, the trial office will arrange central review. MRI films from initial diagnosis, the most recent films, and films made prior to the recent assessment are required for review. Please include the local radiologist's result. The request form is found on page 222. In observation patients with macroscopic residual tumor, central review of the MRI´s is required. Please send all MRI films to the trial office using the shipping form on page 222. The complete set will be returned to you after review. Ultrasound films are not standardized and, therefore, not appropriate for reference radiology.

10.1.3.4 Scintigraphy with ^{123}I-MIBG including SPECT reconstruction.

About 85% of neuroblastoma take up ^{123}I-MIBG. The uptake is specific for neuroblastoma, ganglioneuroma, and pheochromocytoma. Therefore, ^{123}I-MIBG scintigraphy is an important tool for initial diagnosis and follow-up of neuroblastoma.

Prior to ^{123}I-MIBG scintigraphy, **thyroid blockage** with Na-Perchlorate (Irenat ®) in a dose of 1 drop/kgxd divided in 4-6 doses given from day -1 (the day prior to the MIBG-scintigraphy) to day +3 after MIBG-scintigraphy is required. In case of intolerance to Na-Perchlorate or insufficient blockage of thyroid gland during previous assessments, potassium iodide as recommended by the EANM (32 mg for children between 1 month and 3 years of age, 65 mg for children of 3-13 years, and 130 mg for older children) should be considered.[127, 169]

According to the EANM, a minimum dose of 80 MBq ^{123}I-MIBG is recommended for the investigation. Scans must be done 4 hours and 24 hours after injection of ^{123}I-MIBG. In case of equivocal results, extra scans may be necessary after 48 hours.[127]

The urinary bladder should be emptied prior to each scan to allow clear interpretation of pelvic organs particularly in patients with pelvic primary tumors.

Since tumor tissue might be located near organs with physiological uptake (i.e., liver, heart, bladder, bowl, and salivary glands), routine *single photon emission computed tomography* (SPECT) is strongly recommended and should be used routinely.[142]

10.1.3.5 Bone scan with ^{99m}Tc

Bone scan can distinguish bone metastasis and bone marrow involvement in ^{123}I-MIBG positive skeletal spots. Additional conventional x-ray might demonstrate bone lesions but negative x-ray does not exclude early stage bone metastasis.

Bone scan results in a high radiation exposure of the epiphysis. Therefore it is reserved for **initial diagnosis** of

- stage 4 neuroblastoma patients with ^{123}I-MIBG positive skeletal ^{123}I-MIBG uptake
- all ^{123}I-MIBG negative neuroblastoma regardless of stage to find bone metastasis. Two thirds of all primary neuroblastoma take up the ^{99m}Tc tracer. Therefore, some but not all of ^{123}I-MIBG negative primary tumors may be seen in the bone scan.[50]

Bone scan should be restrictively used during follow-up of all patients.

10.1.3.6 Scintigraphy with ^{111}In-Octreotide

In general, sensitivity of ^{111}In-Octreotide scintigraphy is lower than ^{123}I-MIBG scintigraphy.[146] It is recommended as second line scintigraphy in MIBG-negative neuroblastoma.

Scans must be done 4 hours and 24 hours after injection of ^{111}In-Octreotide. In case of equivocal results, extra scans may be necessary after 48 hours. The urinary bladder should be emptied prior to each scan to allow clear interpretation of the pelvis particularly in pelvic primary tumors.

10.1.4 Bone marrow assessment

Bone marrow involvement is focal in neuroblastoma. Therefore, a single bone marrow puncture is not appropriate. Bone marrow aspirates from **at least 4 different puncture sites** are mandatory. If the aspirates appear not representative, two aspirates and two trephine biopsies or 4 bone marrow biopsies may be used instead.

Bone marrow of all NB2004 patients will be assessed centrally by conventional microscopy and anti-GD2-immunocytology. For central cytology, bone marrow smears must by prepared from each puncture site. **At least 5 unstained smears** from each puncture site are requested by the bone marrow laboratory in Cologne. If the bone marrow involvement exceeds 60%, molecular analysis can be done from bone marrow aspirates, too, but requires a total of ≥10 smears from each puncture site. For immunocytology, additional 2-3 ml of **heparinized bone marrow** samples must be collected from each of the four puncture sites.

These bone marrow samples should be sent to Cologne within 24 hrs by overnight express mail. **Do not freeze** the samples. A shipping form is found on page 232. If the samples are expected to arrive Saturday, please inform the laboratory in advance.

In case of any questions, do not hesitate to contact the trial laboratory:

bone marrow lab hotline
+ 49 (0) 221 - 478 4390

10.1.5 Pathology

Tumor histology and molecular genetics are crucial for stratification of localized disease, stage 4S disease, and stage 4 disease in infants. Therefore, tumor biopsy is always required in localized disease.

In stage 4 patients, the status of MYCN and chromosome 1p can be assessed in bone marrow if it contains ≥60% tumor cells. The assessment of other parameters (e.g. tumor

associated antigens) is not possible using bone marrow samples. Therefore, open biopsy tissue sampling is strongly recommended even in stage 4 disease.

The pediatric oncologist should take care for collecting the tumor material. Close collaboration between pediatric oncologist and pathologist is a prerequisite for sufficient tissue sampling and shipping. The tumor handling and sectioning should be performed by the local pathologist. The tumor material has to be transferred from the operation theatre to the pathology department immediately and should be **processed within 30 minutes** to avoid RNA degradation. The local pathologist has to decide which part of the tumor tissue can be frozen without impairing the diagnosis. If possible, he should collect samples from at least two macroscopically different areas (if present).

Touch prints should be performed before the tumor is put into formalin.

In addition, peripheral blood for molecular analysis has to be collected.

The remaining tissue after freezing samples is fixed in (buffered) 4% formalin for **diagnostic histology**. Multiple blocks from all macroscopically different areas should be collected (page 229), particularly tumor nodules. Necroses and regressive tumor tissue should be collected according to their relative amount of the whole tumor to allow a correct estimation of the regression grade.

The **local pathologist** should classify the neuroblastic tumor according to the INPC (International Neuroblastoma Pathology Committee) classification on page 166 including the mitosis-karyorrhexis index (MKI, page 167). In addition, the modified Hughes classification should be mentioned (page 168). The grade of regression and differentiation and the involvement of resection margins have to be evaluated according to the criteria given on page 169.

After chemotherapy the tumor should be classified according to the two classification schemes mentioned above with a statement in the report whether or not a preoperative therapy has been applied.

The histological report of removed lymph nodes should include the number of positive lymph nodes and the categorization of the infiltration according to the classification schemes mentioned above.

Reference histology is required for all patients at initial diagnosis and relapse. For reference examination, it is recommended to send either all blocks or representative slides from all blocks accompanied by 1 representative paraffin blocks to one of the reference pathology laboratories listed on page 5. The request form for the local pathologist is found on page 224, the shipping form on page 225.

10.1.6 Genetic markers: MYCN- and 1p-Status

In general, risk patients are identified by the presence of either MYCN amplification, 1p deletion, 1p imbalance, or 1p LOH. Lack of MYCN amplification, lack of 1p deletion or imbalance, 1p heterozygous, and MYCN gain indicate normal risk.

For therapy stratification, the status of the MYCN oncogene and the status of distal chromosome 1p (1p36) are supposed to be investigated using two different techniques (FISH and Southern Blot *or* FISH and PCR) preferentially (not exclusively) in two different laboratories. The transfer of tissue, RNA, or DNA samples is organized by the laboratories.

The technique used for marker assessment is outlined on page 170. The test results for each parameter will be given according to the criteria of the European Neuroblastoma Pathology, Biology, and Bone Marrow Group.[4] The results of the investigation are mailed directly to the clinic and to the trial office in Cologne. In the case of discrepant results the trial office is in charge to contact the laboratories, in order to exchange the samples and reinvestigate the tissue.

10.1.7 Tumor tissue dispatch organization

Detailed guidelines for collection of tumor and other samples are found on page 229. The samples are sent to the **tumor bank in Cologne** using the *Tumorbox* as quickly as possible by courier service (not on the weekend). The shipping form is found on page 227. The tumor bank will assess the tumor cell content in an area close the one chosen for molecular analysis. This is necessary for a reliable result of the molecular markers. After assessment, the Cologne tumor bank will forward the frozen tissue, RNA, or DNA samples to the collaborating molecular laboratories as requested by the submitting hospital. This has been agreed by all NB2004 molecular genetics labs at a meeting on 14. October 2003 in Cologne.

Frozen tissue samples not actually needed for investigation will be stored in the **tumor bank** of the GPOH.

10.1.8 Diagnosis in infants <3 months in good clinical condition

Newborns or young infants have an excellent prognosis even without treatment. A suprarenal mass seen in routine ultrasound in a clinically well child may be a neuroblastoma as well as a suprarenal hemorrhage. In these clinically well infants, the initial staging may be divided into two steps:

10.1.8.1 Assessment immediately required in all infants <3 months

The assessment to be done **immediately** in all infants includes:

- Clinical status particularly of the entire integument,
- Full blood count, electrolytes, liver function tests (GOT, GPT, GGT), kidney function (creatinine, urea, uric acid), and coagulation,

- Tumor markers: lactate dehydrogenase (LDH), ferritine, neuron-specific enolase (NSE), urinary (and blood) catecholamines (vanillymandelic acid and homovanillic acid),
- Ultrasound assessment of neck, abdomen (particularly liver), pelvis, and brain.

10.1.8.2 Assessment required for persisting tumor >3 months of age

Other investigations **may be delayed** in young infants with good clinical condition but must be done until the child is 3 months old and prior to any anti-tumor treatment:

- MRI of the involved region,
- ^{123}I-MIBG scintigraphy including SPECT reconstruction,
- Bone scan, if ^{123}I-MIBG scan reveals ^{123}I-MIBG-positive skeletal lesions or if the primary tumor is ^{123}I-MIBG negative but tumor markers suggest neuroblastoma,
- Bone marrow aspirates from at least 4 different puncture,
- Tumor biopsy for histology (investigated locally and centrally) and for molecular genetics.

10.2 Postoperative assessment of observation patients

Three months after operation, each observation patient regardless of residual tumor must undergo complete staging to have a base line for further follow up. If relapse or progression is suspected during further follow-up, results can be compared with the postoperative status. The postoperative staging must include:

- clinical examination
- tumor markers
- MRI
- ^{123}I-MIBG-scintigraphy (if positive preoperatively)

Observation patients have no chemotherapy and, therefore, enter follow-up after postoperative assessment (for details see page 32). If N4 chemotherapy is required to control symptoms, clinical examination, tumor markers, ultrasound, and ECG/echocardiography are required prior to each N4 cycle. MRI and MIBG must be repeated after the last N4 cycle or earlier, if necessary (for details see page 181).

10.3 Assessment during chemotherapy

During chemotherapy, response and toxicity must be assessed at regular intervals.

Each relapse, progression, or death requires an **event report**. The report form is found on page 252. It must be completely filled in and then sent to the trial office immediately after the patient has experienced the event and staging has been completed.

Any suspected unexpected severe adverse event according to the definitions in section 19 on page 117 requires an **SAE-report** by fax within 24 hrs after the investigator becomes aware of it. The report form is found on page 253.

The assessment during treatment must include (see pages 181-185):

- **clinical assessment** prior to each treatment element, i.e., each chemotherapy cycle, ASCT, and 14 days retinoic acid cycle.
- **tumor markers:** NSE in serum, VMA and HVA in urine (and/or serum) prior to every second chemotherapy cycle, prior to autologous stem cell transplantation (ASCT), prior to every second maintenance cycle, and every 3 months during retinoic acid consolidation.
- **MRI** of the involved region (i.e., primary tumor and cranium for intracranial or retroorbital metastasis) is mandatory
    - prior to 3rd cycle (HRG and MRG),
    - prior to ASCT (HRG) or maintenance treatment (MRG),
    - 3, 6, and 9 months after ASCT (HRG),
    - after maintenance treatment and after retinoic acid course 1 (MRG)
    - at the end of treatment (HRG and MRG)
    - It may be required for planning surgery at shorter intervals.
- **Ultrasound** of the involved region must be done prior to every second chemotherapy cycle, ASCT, and every 6 weeks during retinoic acid consolidation unless MRI is scheduled instead. It is recommended, to repeat ultrasound prior to each chemotherapy cycle of induction chemotherapy. For thoracic primary tumors, ultrasound must be substituted by chest X-ray at least prior to every second chemotherapy cycle.
- **MIBG scintigraphy** must be repeated for all ^{123}I-MIBG positive neuroblastoma until no abnormal uptake is found. Thereafter, MIBG scintigraphy should be done if relapse or progression are suspected:
    - prior to the 3rd cycle,
    - prior to ASCT (HRG) or maintenance treatment (MRG),
    - 3 months after ASCT (HRG),
    - after maintenance treatment (MRG),

- thereafter every 6 months until normal.

- **bone marrow follow-up assessment** is required for stage 4 and 4S:
  - prior to the 3rd chemotherapy cycle (send smears and heparinized marrow to Cologne for reference assessment),
  - prior to the 5th chemotherapy cycle (for local assessment, shipping to Cologne is not mandatory but allowed)
  - and prior to ASCT or maintenance treatment (send smears and heparinized marrow to Cologne for reference assessment).
  - Further bone marrow examinations may be necessary if the bone marrow is not free of tumor cells thereafter.
- **side effect monitoring**: echocardiography, electrocardiography, audiometry, kidney function and other as outlined separately for each treatment element in the flow sheets (section 14 starting on page 87).

Figures 3 (medium risk group) and 4 (high risk group) show the timing of examinations during treatment. All investigations must be repeated any if time non-response, progression, relapse, or treatment side effects are suspected.

10.3.1 Diagnostics during MRG treatment

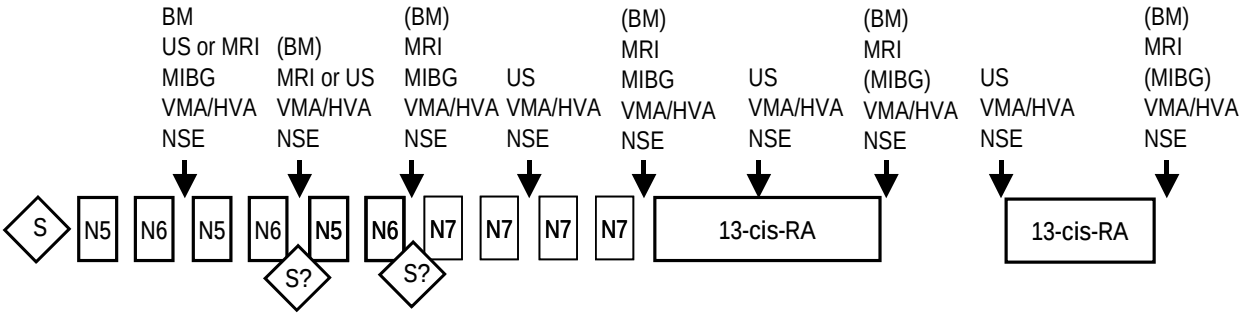


Figure 3: Follow-up during medium risk group treatment: the arrows represent staging, BM=bone marrow for stage 4 infants, (BM)=only if previous bone marrow was not free of tumor cells in stage 4 infants, US=ultrasound mandatory, it is recommended to repeat an ultrasound examination prior to every chemotherapy cycle, MRI=MRI mandatory, VMA/HVA=catecholamines metabolites in urine and/or serum, NSE=neuron specific enolase, S=surgery, N4/5/6/7=chemotherapy, 13-cis-RA=13-cis-retinoic acid)

10.3.2 Diagnostics during HRG treatment

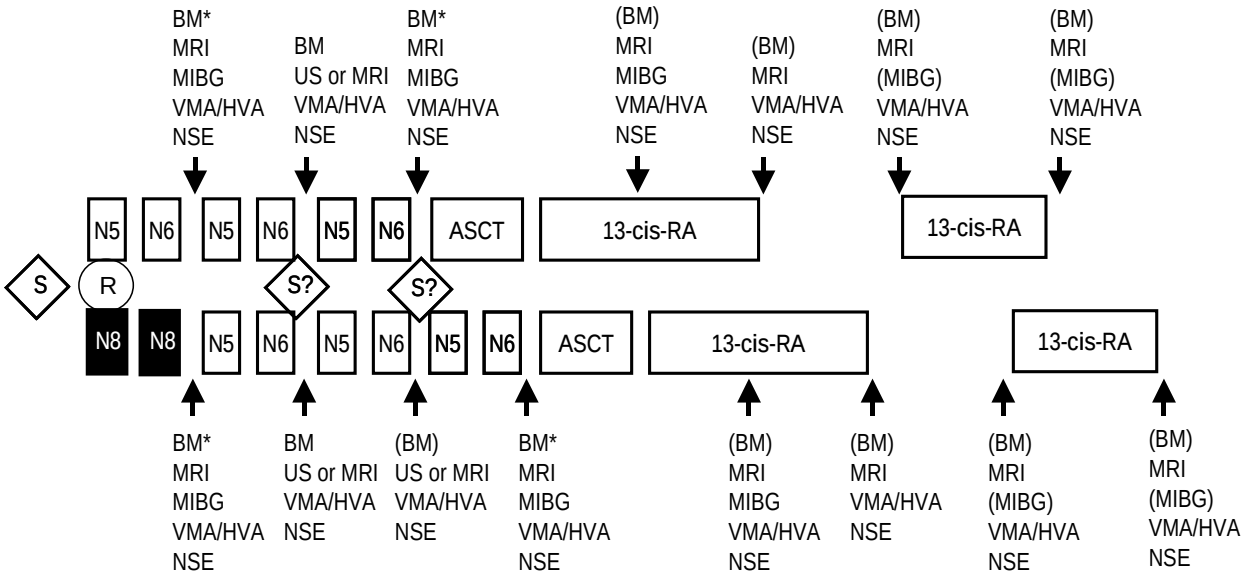


Figure 4: Follow-up during high risk group treatment: the arrows represent staging, BM=bone marrow, (BM)=only if previous bone marrow was not free of tumor cells, BM*=send bone marrow samples to Cologne for central review, US=ultrasound, MRI=MRI mandatory, VMA/HVA=catecholamines metabolites in urine and/or serum, NSE=neuron specific enolase, S=surgery, R=randomization, N5/6/8=chemotherapy cycles, 13-cis-RA=13-cis-retinoic acid

10.4 Follow-up assessment after treatment

10.4.1 Observation group

The follow-up assessment of the observation group begins right after the postoperative staging (page 28). It includes clinical assessment, tumor markers and imaging (table1 and 2). Tumor markers alone are able to detect only about 25-50% of relapses or progressions, more events are diagnosed by clinical examination and imaging.[151]

In general, the recommended assessment intervals are shorter in the first five years after treatment, and longer thereafter since life table analysis shows a lower event rate 5 years or more after diagnosis. Of course, in case of any unclear symptom or abnormal test result, follow-up assessments are to be repeated at shorter intervals or must include a complete staging (MRI, scintigraphy, or bone marrow assessment) to rule out or to identify disease recurrence or treatment induced late effect.

10.4.1.1 Observation patients <u>without</u> residual tumor

Table 1: Recommended follow-up assessment of <u>observation patients</u> without postoperative residual after the postoperative staging has been done

	1st year	2nd – 5th year	After the 5th year
Clinical assessment Urinary catecholamines Ultrasound/chest-x-ray*	**Every 6 weeks**	**Every 3 months**	**Every 6-12 months**
LDH and NSE	**With every venous blood sample required for MRI or scintigraphy**		
MRI**	**3 month after surgery, thereafter only if ultrasound or chest x-ray gives equivocal results**		
Scintigraphy	**Only if ultrasound or chest x-ray gives equivocal results**		

***) For thoracic tumors ultrasound is not the appropriate technique and is substituted by chest X ray.**

****) A higher MRI frequency might be appropriate if intraspinal/intraforaminal residual tumor is present**

10.4.1.2 Observation patients with residual tumor

Table 2: Recommended follow-up assessment of observation patients with postoperative residual after the postoperative staging has been done

	1st year	2nd – 5th year	After the 5th year
Clinical assessment Urinary catecholamines Ultrasound/chest-x-ray*	**Every 6 weeks**	**Every 3 months**	**Every 6 months**
LDH and NSE	**With every venous blood sample required for MRI or scintigraphy**		
MRI**	**Every 6 months if primary clearly seen in ultrasound, otherwise consider 3 months**	**every 12 months**	**not routinely if normal**
Scintigraphy	**every 6 months until normalization, thereafter not routinely**		

***) For thoracic tumors ultrasound is not the appropriate technique and is substituted by chest X ray.**

****) A higher MRI frequency might be appropriate if intraspinal/intraforaminal residual tumor is present**

10.4.2 Medium and high risk group

10.4.2.1 End of treatment assessment

The follow-up assessment begins after the end of the treatment plan with a staging in order to define the extent of residual disease. This staging must include

- Clinical status
- Full blood count
- Electrolytes, liver function tests (GOT, GPT, GGT), kidney function (Creatinine, Urea), and coagulation
- Tumor markers: Lactate dehydrogenase (LDH), Ferritine, Neuron-specific enolase (NSE), urinary (and blood) catecholamines (Vanillylmandelic acid and homovanillic acid)[72]
- MRI of the involved region,
- ^{123}I-MIBG scintigraphy including SPECT reconstruction (or ^{111}In-Octreotide in MIGB-negative, ^{111}In-Octreotide-positive neuroblastoma),
- bone marrow assessment from 4 puncture sites if the last assessment gave an abnormal result or if relapse is suspected.

10.4.2.2 Long term follow-up

Follow-up assessment includes clinical assessment, tumor markers and imaging as outlined in table 3. Tumor markers alone are able to detect only about 25-50% of relapses or progressions, more events are diagnosed by clinical examination and imaging.[151]

In general, the recommended assessment intervals are shorter in the first five years after treatment, and longer thereafter since life table analysis shows a lower event rate 5 years or more after diagnosis. Of course, in case of any unclear symptom or abnormal test result, follow-up assessments are to be repeated in shorter intervals and include a complete staging (MRI, scintigraphy, and bone marrow assessment x4) to rule out or to identify disease recurrence or treatment induced late effect.

After the 5th year, follow-up of the chemotherapy patients is important for late effects surveillance. These late effects may involve the auditory system, the kidneys, secondary malignant disease, or other. It is strongly recommended to follow the patients in a pediatric oncology clinic. If the long term follow-up is transferred to the local pediatrician, please get patients' consent to allow the trial office to contact that physician for further follow-up.

Table 3: Recommended follow-up assessment of medium and high risk group patients

	1st year	2nd – 5th year	After the 5th year
Clinical assessment **Urinary catecholamines** **Ultrasound or chest x-ray***	**Every 6 weeks**	**Every 3 months**	**Every 6 months**
LDH and NSE	**With every venous blood sample required for MRI or scintigraphy**		
MRI**	**Every 3 months**	**every 6 months only if previous assessment gave abnormal results**	
Scintigraphy	**every 6 months until normalization, thereafter not routinely**		
bone marrow 4 sites	**every 6 months until normalization, thereafter not routinely**		
ECG/Echocardiography **Audiometry** **Kidney function test** **TSH, fT3, fT4** **growth chart** **puberty assessment**	**at the end of every year**		**every 2nd year**

***) For thoracic tumors ultrasound is not the appropriate technique and is substituted by chest X ray.**

****) A higher MRI frequency might be appropriate if intraspinal/intraforaminal residual tumor is present**

11 OBSERVATION PATIENTS

11.1 Observation patients protocol outline

Indication	Low risk neuroblastoma stages 1, 2, 3, and 4S
Design	Prospective multicenter nonrandomized observation trial
Primary objectives	event free survival of a newly defined observation group
Secondary objectives	time from diagnosis to an event, time to a locoregional event, time from the begin of regression to an event, time to transition to stage 4, overall survival, time to begin of primary tumor regression, time to the normalization of tumor markers, time to no evidence of disease (stage 4S), status of the primary at 12 months, best status of the primary tumor within 12 months, molecular marker (chromosome 1p, chromosome 11q, neuroblastoma gene chip), surgery (initial surgery, best surgery, complications), chemotherapy (need for and intensity required)
Trial medication	None, if no threatening symptoms or tumor progression occurred, N4 cycles for patients with threatening symptoms/progression
Inclusion criteria	STAGE 1: age 0-21 years, no MYCN-amplification STAGE 2: age 0-21 years, no MYCN-amplification, no del1p or imb1p (=1p aberration) STAGE 3: age 0-2 years, no MYCN-amplification, no 1p aberration STAGE 4S: age 0-1 year, no MYCN-amplification
Exclusion criteria	Concomitant non-protocol anti-tumor therapy
Treatment schedule	Complete resection is indicated initially only when the risk of operation related complication appears low. Otherwise, incomplete resection or biopsy is appropriate. After initial surgery, the patients will undergo follow-up. In case of threatening tumor associated symptoms, progression, or relapse, patients will receive a maximum of 4 N4 chemotherapy cycles until stop of progression and symptom relief. If this fails, the patients continue with medium risk treatment.
Cooperating hospitals	≥80 pediatric-oncology departments of German & Swiss children's hospitals
Trial schedule	Pilot phase begin: 01. October 2004 Trial start: 01. June 2005 Trial closing: 30. September 2010

11.2 Observation group introduction

11.2.1 General results of low risk neuroblastoma

In general, prognosis of stage 1-3/4S neuroblastoma is excellent (figure 5). In infants, spontaneous regression is possible in localized and in stage 4S disease.[8, 21, 25, 97] In the NB95-S trials, among 55 infants with residual tumor after surgery, we have observed spontaneous regression without chemotherapy in 30 patients. Regression of localized tumor has been observed beyond the 1st year of life as well.[25, 70] Particularly stage 2 patients had a good outcome after surgery alone regardless of age.[116] Over-diagnosis of localized neuroblastoma found by screening programs indicates a substantial number of spontaneous regressions during and after the 1st year of life, too.[144, 147, 176]

Due to these encouraging data, the NB2004 trial will extend the observation group by including all stage 2 patients regardless of the size of residual, and stage 3 neuroblastoma up to 2 years of age who do not have molecular risk markers (i.e. MYCN-amplification and aberrations in chromosome 1p).

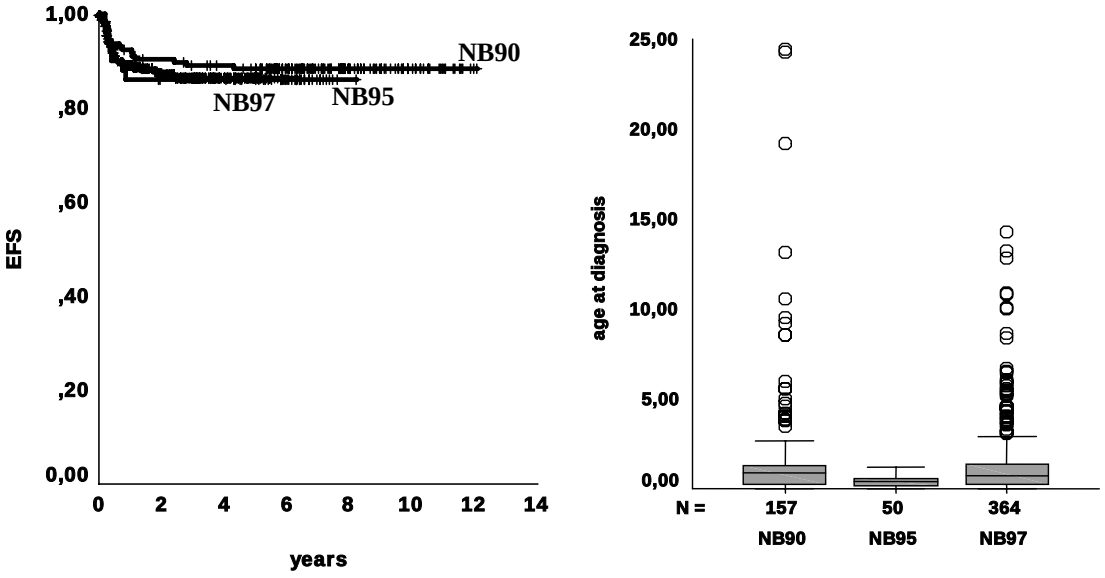


Figure 5: Stage 1-3/4S patients without chemotherapy of the trials NB90-95. LEFT EFS plot: NB90 n=157, 5-y-EFS 88±3%, NB95 n=50, 5-y-EFS 86±5%, and NB97 n=364, 5-y-EFS 86±2%, logrank p=.742; OS (plot not shown: NB90 5-y-OS 97±1%, NB95 98±2%, NB97 97±1%; RIGHT: age distribution of these patients.

11.2.2 Rationale for the extended age definition of the observation group

In general, age is an important risk factor in neuroblastoma. Figure 6 shows the event free and overall survival of stage 1-3/4S, MYCN not amplified patients by age regardless of

treatment. Age is less important in stage 1-2 neuroblastoma. But in stage 3, patients ≥2 years have a worse prognosis than younger stage 3 patients (figure 7). Therefore, Stage 3 patients are included in the observation group if they are <2 years old. All stage 1-2 patients regardless of residual tumor size and age will enter the observation group.

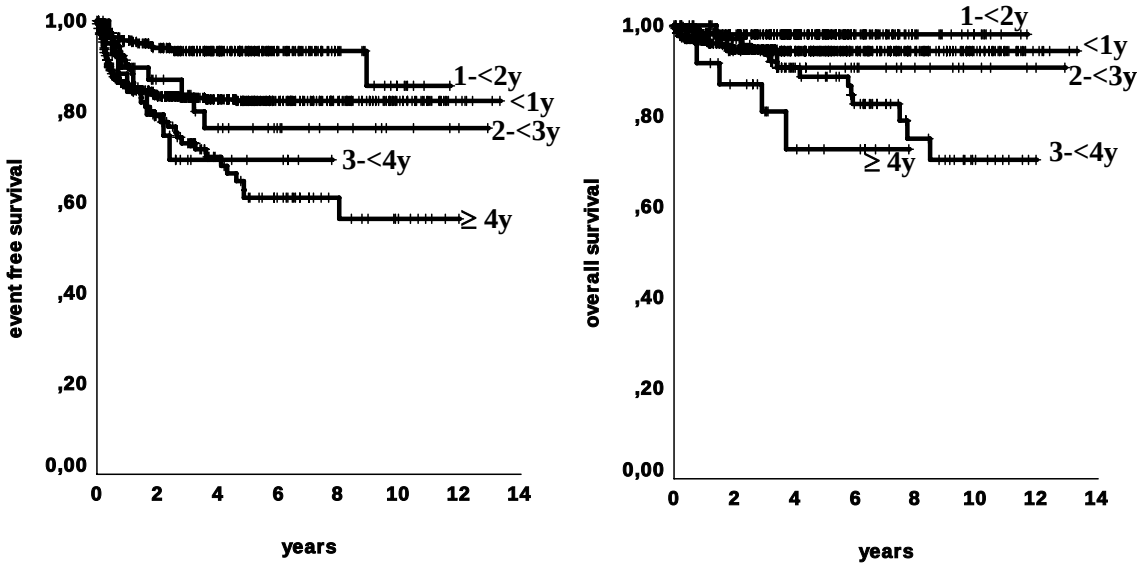


Figure 6: EFS and OS of 908 stage 1-3/4S neuroblastoma patients of trails NB90-97 with normal MYCN by age (0-1 years n=483, 1-<2 years n=244, 2-<3 years n=40, 3-<4 years n=28, and ≥4 years n=113) regardless of administration and intensity of chemotherapy: left EFS (p<.001) and right OS (p=<.001)

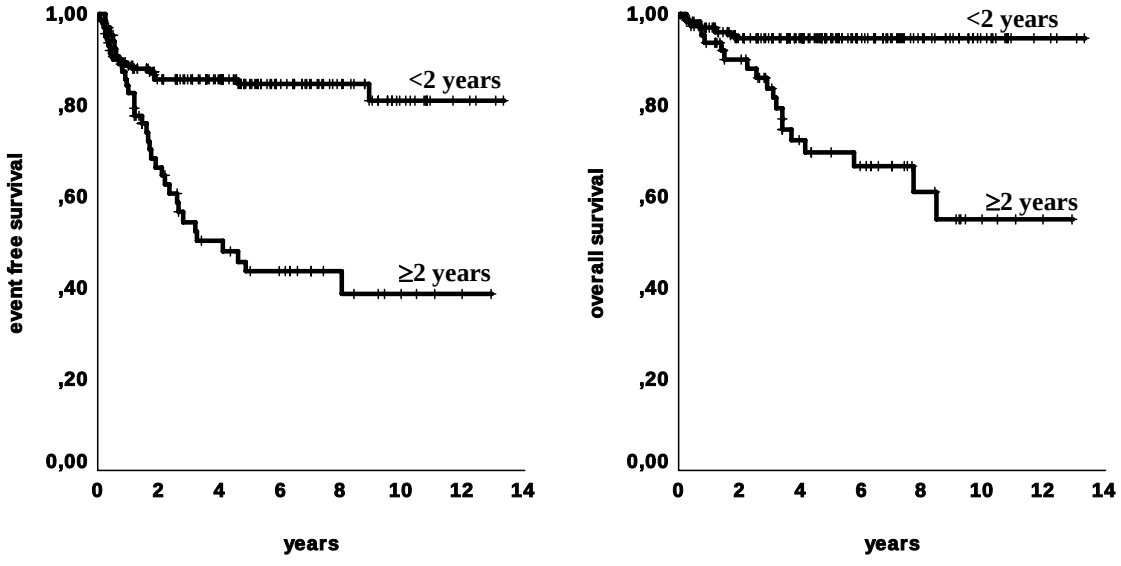


Figure 7: Outcome of 227 stage 3 neuroblastoma patients of the trials NB90-97 with normal MYCN by age (<2 years n=161 vs. ≥2 years n=66) regardless of administration and intensity of chemotherapy: left EFS (3-y-EFS 86±3% vs. 54±7%, logrank p<0.001) and right OS (3-y-OS 95±1.8% vs. 84+5%, logrank p<0.001). Of note, some events and deaths were observed far later than 3 years after diagnosis.

11.2.3 Rationale for the molecular markers in low risk neuroblastoma

11.2.3.1 Univariate analysis

Amplification of MYCN (NMA) is a well known indicator of poor prognosis in localized and metastatic neuroblastoma.[11, 140, 148] Despite intensive treatment of localized NMA tumors, the prognosis of these patients is still unsatisfactory. In the German NB trials, the 3-year-EFS of 89 stage 1-3/4S neuroblastoma patients with NMA was only 43±6% compared to 86±1% in 910 patients without NMA (p<0.001). The OS of NMA patients was 61±6% compared to 96±1% in patients without NMA (p<0.001). Therefore, all NMA patients will be included into the high risk group of NB2004.

Aberrations of chromosome 1 often coincide with NMA [41, 107] but there is a group of patients with normal MYCN and abnormal 1p. Caron et al. found a poor prognosis of stage 1, 2, and 4S neuroblastoma with 1p-deletions by univariate analysis (3-y-EFS 35±15% for del 1p regardless of MYCN-status compared to 100% in normal 1p, p<0.001) and multivariate analysis (hazard ratio 6.7, p<0.001).[22] Maris et al. reported a 3-y-EFS of 48.4% for patients with 1p deletion regardless of MYCN status compared to 77.3% in normal 1p (p<0.001) and found 1p-status prognostic in multivariate analysis (hazard ratio 1.9, p=0.005).[107]

1p status assessment may by performed by PCR or FISH technology. PCR is unable to detect 1p-deletions in homozygous individuals. It may give false normal results if the tumor cell content is low in the tissue specimen. FISH analysis allows to distinguish tumor cells and normal cells, is independent of heterozygous status and able to detect the new feature of 1p-imbalance (i.e. at least 2 intact chromosomes 1p and an additional variable number of deleted copies of chromosome 1p). In a series of unselected neuroblastoma patients of all stages assessed by FISH technique, patients with 1p-imbalance (3-year-EFS 41±15%) had a similarly poor outcome as patients with 1p-deletion (3-year-EFS 33±15%) compared to patients with normal 1p (3-year-EFS 70±5%).[153]

Analysis of 233 stage 1-3/4S patients without MYCN amplification analyzed by FISH technique for 1p status demonstrated a better EFS (logrank p<0.001) and OS (logrank p=0.027) for patients with normal 1p (n=215) compared to patients with deletion or imbalance of 1p (n=18, NB90-97, unpublished results).

Aberrations of chromosome 11q indicate poor prognosis in neuroblastoma.[53, 71, 105, 106, 152] Spitz et al. showed a trend towards a better EFS for patients with normal 11q (n=102, 3-year-EFS 63±7%) compared to patients with 11q-deletion (n=30, 3-year-EFS 42±13%) and 11q-imbalance (n=12, 3-year-EFS 38±12%, p=0.086). In stage 1-3/4S non-NMA neuroblastoma, the difference between normal 11q (3-year-EFS 84±6%) and abnormal 11q (3-year-EFS 43±18%) was significant (p<0.001).[152]

Analysis of 230 stage 1-3/4S, non-NMA patients for 11q status showed a better EFS (logrank p<0.001) and OS (logrank p=0.011) for patients with normal 11q (n=207) compared to patients with deletion or imbalance of 11q (n=23, NB90-97, unpublished results).

Aberrations of 3p were reported to have a prognostic impact in neuroblastoma.[152] Among 157 stage 1-3/4S, non-NMA patients, a better EFS (logrank p<.001) but not OS (logrank p=0.268) for patients with normal 3p (n=149) was found compared to patients with deletion or imbalance of 3p (n=8). We could demonstrate a high event rate in patients with abnormal 3p but the majority of serious events (metastatic relapse or death of disease) were observed in the group of normal 3p (NB90-97, unpublished results).

Expression of TrkA has been reported to correlate with a good prognosis in neuroblastoma. [36, 119, 158] Analysis of our stage 1-3/4S non-NMA patients revealed a poor outcome of patients without TrkA expression (n=39, 3-year-EFS 54±9%) compared to patients with TrkA expression (n=221, 3-year-EFS 88±2%, p<0.001, NB90-97, unpublished results). Since TrkA assessment is not standardized so far and for economical reasons, the NB2004 trial does not use TrkA as a stratifying parameter.

Lack of ***CD44-Expression*** correlates with a poor prognosis but CD44 is expressed by >90% of localized neuroblastoma. [51, 93] Among the patients of trials NB90-97, we found a low EFS for stage 1-3/4S non-NMA patients (n=11, 3-year-EFS 36±14%) compared to patients with CD44 expression (n=251, 3-year-EFS 85±2%, p<.001). But most of the serious events and most of the disease related deaths were observed in patients with normal CD44. Since CD44 assessment is not standardized, the NB2004 trial will not use CD44 as a stratifying marker.

Telomerase has been identified as a prognostic marker by some authors.[75, 95, 138] In a recent report, full length hTERT transcripts were of prognostic value but not the presence of spliced length transcripts.[95] In contrast, analysis of stage 1-3/4S non-NMA neuroblastoma patients by telomerase quantitative PCR showed no disadvantage for high hTERT expressing patients (n=5, 3-year-EFS 80±18% vs. n=73, 3-year-EFS 87±4% in normal hTERT). These data do not justify the exclusion of high telomerase expressing tumors from observation group.

11.2.3.2 Multivariate analysis of relevant molecular factors

Due to univariate results, stage 1 and 2 patients (all ages), stage 3 (<2 years), and stage 4S were regarded as a potential new observation group. Stage 3 patients ≥2 years were excluded since these patients showed a poor prognosis in univariate analysis and could not be described reliably on the basis of MYCN and 1p status only.

Multivariate analysis was performed to identify the most relevant molecular risk markers among these patients including all markers available for the large number of trial patients: age, lactate dehydrogenase (LDH), and status of chromosome 1p, 11q, and 3p. Assessment of the three molecular markers will be available in the trial reference laboratories on a high quality level. Other known prognostic markers (e.g., TrkA, CD44, telomerase) were excluded since assessment is available only in research laboratories with limited resources or assessment is not standardized yet. Chemotherapy intensity (no chemotherapy vs. 1-5 cycles vs. more than 5 cycles) was included in the multivariate analysis in order to reflect the different treatment intensity given to the patients according to the treatment protocols.

For EFS, 1p status (p=0.009, hazard ratio=4.0) and 11q status (p=0.028, hazard ratio=3.1) proved to be prognostic. For OS, only 1p status (p=0.022, hazard ratio=3.6) showed prognostic impact.

Since the frequency of patients with 11q aberration was low among stage 1 and 4S patients, the subgroup of 346 patients stage 2 (all ages) and stage 3 (<2 years) was analyzed separately. In this group, 1p status only had an impact on the prognosis (p=0.002, hazard ratio=6.6). Multivariate analysis of OS in stage 2 and stage 3 (<2 years) was impossible due to the low death rate among these patients. Therefore, 1p will be used as stratifying marker in stage 2 (all ages) and stage 3 (<2 years). Stage 1 patients are resected completely and stage 4S have a very good prognosis. Aberrations of chromosome 1p will not be used as stratifying maker in stage 1 and 4S.

We suggest a definition of low risk neuroblastoma by the following criteria:

- **stage 1 (all ages, no MYCN-amplification),**
- **stage 2 (all ages, no MYCN-amplification, no 1p aberrations),**
- **stage 3 (<2 years, no MYCN-amplification, no 1p aberration),**
- **stage 4S (<1 year by definition [19], no MYCN-amplification).**

By retrospectively classifying the patients of NB90 and NB97 according to this definition, the 710 patients classified as observation patients had a 3-y-EFS of 87±1% and a 3-y-OS of 96±1%. The 72 patients excluded from the new observation group (i.e., stage 2 & 3 with aberrations of 1p and all stage 3 ≥2 years) had a 3-y-EFS of 52±6% (logrank p<0.001) and a 3-y-OS of 83±5% (logrank p<0.001). Detailed results for stage 2-3 and stage 1&4S are found in figure 8a and 8b:

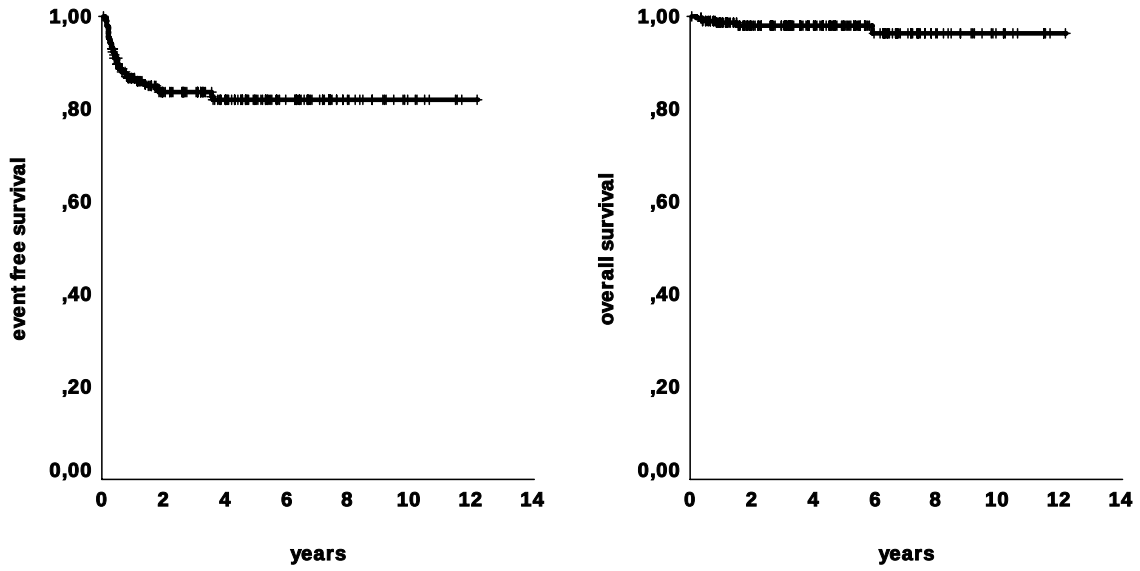


Figure 8a: Outcome of 214 stage 2-3 patients of the trials NB90 and NB97 retrospectively classified according to the new observation group definition (3-y-EFS 84±3%, 3-y-OS 98±1%)

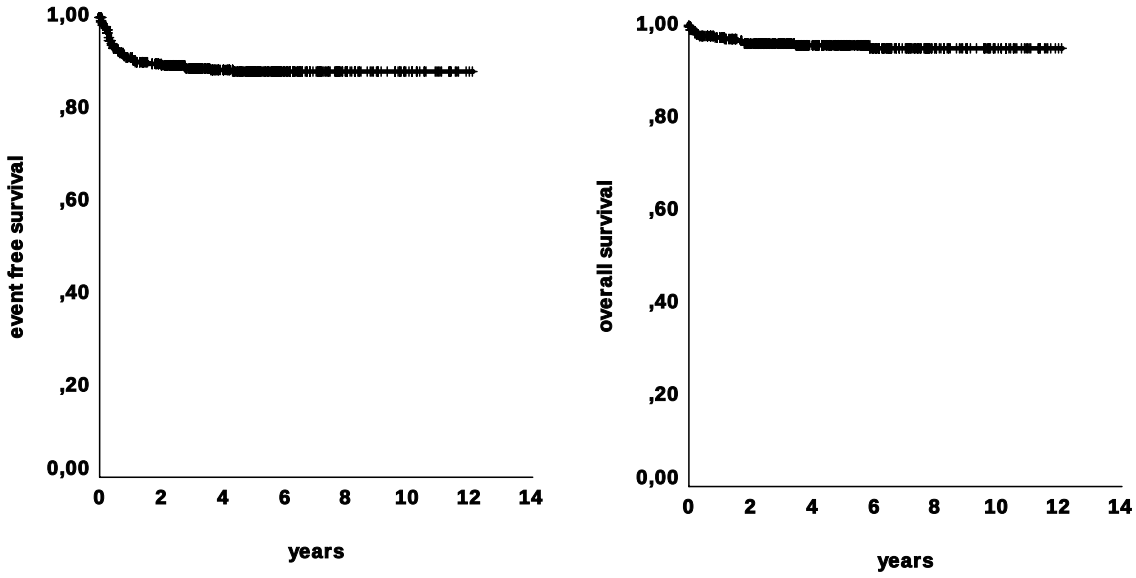


Figure 8b: Outcome of 496 stage 1/4S patients of the trials NB90 and NB97 retrospectively classified according to the new observation group definition (3-y-EFS 88±1%, 3-y-OS 97±1%)

11.3 Differences between NB97 and NB2004

Table 4: Differences of the NB2004 observation group vs. NB97 (NMA=MYCN amplification)

definition according to NB97	definition according to NB2004
stage 1, no NMA	stage 1, no NMA
stage 2a/b with residual <10% or 5ml, no NMA	stage 2a/b, any residual, no NMA, no 1p aberration
stage 3 <1 year, no NMA	stage 3 <2 years, no NMA, no 1p aberration
stage 4S, no NMA	stage 4S, no NMA

11.4 Trial objectives of the observation group

The focus of the NB2004 observation group is

- to extend the number of neuroblastoma patients not receiving any postoperative chemotherapy by application of an extended observation group definition excluding patients defined by presence of MYCN-amplification, 1p aberration (imbalance or deletion), and age (in stage 3),
- to manage tumor associated symptoms or progression of residual tumor by mild chemotherapy.

Statistics are outlined from page 121. Event, regression and detailed trial objectives are defined as follows:

11.4.1 Definition of event

Since transient progression before definite regression is a known phenomenon, not every tumor size increase can be regarded as event. Therefore, **an event is defined as**

- Stage 1-3: occurrence of any distant metastasis
- Stage 4S: progression of bone marrow involvement exceeding 10% or occurrence of metastasis other than skin or liver, i.e. transition into stage 4 disease.
- Any local growth of the primary (stages 1-3) or organomegaly (stage 4S) which leads to threatening clinical symptoms as estimated by the local oncologist:
  - severe deterioration of the general condition,
  - serious feeding difficulties leading to weight loss,
  - respiratory failure defined by oxygen requirement or carbon dioxide retention exceeding 60 mmHg,
  - circulatory failure defined by hypotension or hypertension according to the age related blood pressure reference values,
  - hepatic failure defined by grade 3 toxicity of bilirubin, fibrinogen, or thrombin time according to the NCI-CTC toxicity criteria,
  - renal failure defined by impaired blood urea or creatinine, new development of hydroureter/hydronephrosis or deteriorating preexistent hydronephrosis,
  - new development of intraspinal involvement documented by MRI regardless of symptoms,
  - failure of other organ systems,
- Death of any reason,
- Any secondary malignant disease.

11.4.2 Definition of regression

Regression is defined and categorized as follows:

i. **progression** according to the criteria for event outlined on page 42,

ii. **no change:** not meeting the definition of progression but regression <10% in all dimensions,

iii. **minimal regression:** regression of the primary ≥10% and <25% in one or more diameters and <10% in all other diameters seen by ultrasound, MRI, or computed tomography (provided the next investigation is able to confirm that regression),

iv. **unequivocal regression:** regression ≥25% in one or more diameters and <25% in all other diameters seen by ultrasound, MRI, or computed tomography,

v. **complete regression:** no sign of residual primary by imaging (=complete response according INSS criteria on page 160).

11.4.3 Trial objectives

The trial objectives of the OG are:

- **EFS_D:** Event free survival measured from the time of diagnosis up to an event or last follow-up for patients without event. Definition of event is given on page 42.
- **EFS_L:** locoregional EFS measured from the time of diagnosis up to a locoregional event or last follow-up for patients without locoregional event. A locoregional event is defined as (i) death related to locoregional disease, (ii) local progression of residual primary tumor, (iii) locoregional relapse following previous complete remission of the primary tumor as defined on page 160.
- **EFS_R for patients with regression:** event free survival measured from the begin of regression up to an event or last follow-up for patients without event. The begin of the regression is defined as the time, at which regression of the primary tumor >10% in at least one diameter and no growth in any diameter is documented by ultrasound, MRI or computed tomography for the first time (provided that the following investigation is able to confirm that regression). The definition of event is given on page 42.
- **EFS_{stage4}:** time from diagnosis to transition to stage 4, to death of disease, or to last follow-up if no transition to stage 4 is observed and the patient is surviving.
- **OS:** Overall survival measured from the time of diagnosis up to death of any reason or last follow-up for surviving patients.
- **TTPR:** Time to begin of primary tumor regression measured from the time of diagnosis to begin of tumor regression or last follow-up if no regression occurs. The begin of regression is defined as outlined in the definition of EFS_R.

- **TTNT:** Time to the normalization of tumor markers HVA and VMA in urine measured from time of diagnosis to the time of the first investigation with normal VMA and HVA results. VMA and HVA results must be categorized according to age specific reference values given by the investigating laboratory.
- For stage 4S patients:
  TTND: Time to no evidence of disease measured from the time of diagnosis to the time of complete regression or to last follow-up if the patient has no complete regression. Complete regression is defined as no evidence of primary tumor plus normalization of tumor markers plus no sign of liver metastases (confirmed by normal ultrasound of the liver) plus no skin metastases.
- Status of the primary tumor 12 months after diagnosis. The status of the primary tumor is defined as outlined in section 11.4.2.
- Best status of the primary tumor within the first 12 months after diagnosis defined according to section 11.4.2.
- Molecular marker: status of chromosome 1p (open) and status of chromosome 11q (blinded, for interim analysis see page 126) categorized according to criteria published by Ambros.[4] Tumor tissue is collected and stored in the tumor bank for future evaluation of other molecular markers which will be considered having prognostic impact during the ongoing trial.
- Prospective molecular analysis of defined molecular markers by the neuroblastoma gene chip.
- Surgery:
  - Extent of **initial surgery** categorized in: biopsy vs. incomplete resection vs. macroscopic complete resection. Initial surgery is the first tumor operation done in a patient.
  - Extent of **best surgery** up to time t performed during the protocol treatment categorized in: biopsy vs. incomplete resection vs. macroscopic complete resection. Best surgery is the operation performed up to time t during treatment which achieves the most extensive tumor resection.
  - Complications related to surgery considered separately for: nephrectomy, bleeding, infection, intestinal obstruction, or other according to the documentation form (page 216 and 248).
- Chemotherapy:
  - Need for chemotherapy to control progression (definition according to page 42),
  - Chemotherapy intensity required categorized as (i) progression and symptoms controlled after 1 x N4 cycle, (ii) progression and symptoms controlled after 2 x N4, (iii) progression and symptoms controlled after 3 x N4, (iv) progression and symptoms controlled after 4x N4, (v) progression and symptoms not controlled after 4 x N4, no transition to stage 4, treatment continued with MRG, (vi)

transition to stage 4 at any time, treatment continued with HRG (children ≥1 year at diagnosis) or MRG (infants <1 years at diagnosis).

11.5 Selection of subjects

11.5.1 Inclusion criteria

For admission into the observation group of NB2004, each patient must meet all of the following criteria:

- Neuroblastoma newly diagnosed according to the accepted criteria: histological diagnosis from tumor tissue (INSS stages 1-3 and 4S, for stages see page 159) or presence of distinct neuroblastoma cells in the bone marrow and elevated catecholamine metabolites (HVA, VMA) in blood or urine (only in stage 4S).[19]
- Age: 0-21 years (INSS stages 1 and 2), <2 years (INSS stage 3), and <1 year (INSS stage 4S).
- Molecular markers:
    - MYCN not amplified (all OG patients),
    - no deletion or imbalance of chromosome 1p (only stage 2 and 3).
- Guardians' informed consent and patient's informed consent if appropriate according to age and status of psycho-intellectual development.
- No pregnancy and sufficient contraception during chemotherapy in all female adolescents who might become pregnant.

11.5.2 Exclusion criteria

Any concomitant non-protocol anticancer therapy.

These patients will be registered in the NB2004 trial but will not be included in the interims and final analysis.

11.6 Treatment in the observation group

11.6.1 Overview

OBSERVATION GROUP (OG)
stage 1, 0-21 years, no MYCN-amplification
stage 2, 0-21 years, no 1p aberration, no MYCN-amplification
stage 3, 0-2 years, no 1p aberration, no MYCN-amplification
stage 4S, 0-1 year, no MYCN-amplification

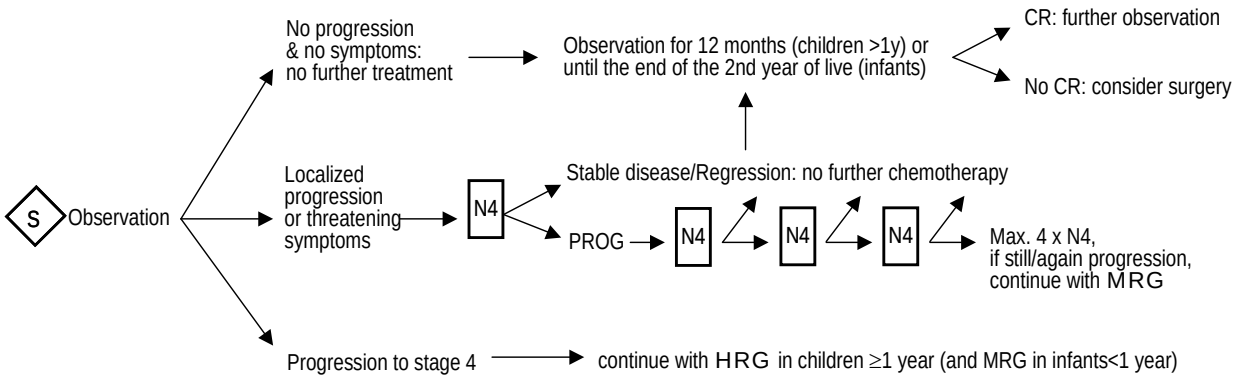


Figure 9: Overview over the NB2004 observation group (S=surgery, N4=chemotherapy cycles)

11.6.2 Stage 1-3 neuroblastoma without threatening initial symptoms

These patients will not have any postoperative chemotherapy regardless of the extent of surgery and size of residual tumor.

They will undergo surgery only. The extent of the tumor resection is decided by the surgeon. Complete resection is indicated only when the risk of any complication appears low. Tumor nephrectomy (a priori) or other mutilating operations are not acceptable. If the risk of complication appears high, partial resection or even biopsy might be appropriate. During any operation, tumor tissue must be collected for histological and molecular investigations. For details of tumor tissue collection see chapter 29.3 on page 161.

The initial operation is documented at the first documentation form of the German Children's Cancer Registry, Mainz, Germany (page 216).

11.6.2.1 Stage 1 and 2 without macroscopic residual

Follow up according to page 32 is appropriate.

11.6.2.2 Stage 2 and 3 with macroscopic residual

Observation of the residual tumor requires reassessment of tumor size and tumor markers every 6 weeks. MRI must be repeated at least after 12 months of observation. For documentation, use the form found on page 254.

Regular observation is finished at the end of the 2nd year of life (age at diagnosis <1 year) or 12 months after first operation (age at diagnosis ≥1 year).

If the residual tumor underwent **complete regression**, follow-up according to page 32 is appropriate.

If the residual tumor has **not** vanished completely, secondary surgery should be discussed with the trial office. MRI films are required for discussion. Please send all MRI films to the trial office using the shipping form on page 222. The complete set will be returned to you as soon as a decision has been made. Ultrasound films are not standardized and, therefore, not appropriate for reference radiology.

11.6.3 Management of relapse or progression during observation

If a relapse or progression is diagnosed during follow-up, a **complete staging** (tumor markers, MRI, MIBG-scintigraphy, bone marrow assessment) is required. Each relapse, progression, or death requires an **event report**. The report form is found on page 252. It must be completely filled in and sent to the trial office immediately after the patient has experienced the event.

Please contact the trial office to discuss further options. In general, the following situations are possible:

11.6.3.1 Local relapse after stage 1 neuroblastoma:

Secondary surgery and chemotherapy should be discussed with the trial office. MRI films are required for discussion. Please send all MRI films available to the trial office using the shipping form on page 222. The complete set will be returned to you as soon as a decision has been made. Ultrasound films are not standardized and, therefore, not appropriate for reference radiology.

11.6.3.2 Local progression of residual stage 2 or 3

Local progression must be confirmed by **reference radiology**. Please send the MRI films to the trial office using the shipping form on page 222. The complete set will be returned to you as soon as a decision has been made.

If the progression has been confirmed by reference radiology or threatening tumor associated symptoms develop, the patients will receive **N4 cycles** for regression induction (for details of N4 cycles see page 87 and 234). As soon as tumor growth is stopped and the symptoms are relieved, no further chemotherapy cycles will be given. The patients will be followed-up closely.

Regular observation is finished at the end of the 2nd year of life (age at diagnosis <1 year) or 12 months after first operation (age at diagnosis ≥1 year). If the residual tumor has **not** vanished completely after 12 months, surgery should be discussed with the trial office. MRI films are required for discussion. Please send all MRI films available to the trial office using the shipping form on page 222. The complete set will be returned to you as soon as a decision has been made.

If **progression or symptoms are not controlled** after 4 N4 cycles, the patient will enter the medium risk group. Please contact the trial office to discuss details. Prior to medium risk group chemotherapy, a new biopsy or resection followed by complete histology and molecular assessment is recommended. Histology and molecular analysis results are necessary to distinguish non-responding tumors from differentiating or regressing tumors. Further treatment can only be decided based on these results.

The toxicity of each chemotherapy cycle must be documented at the chemotherapy form which is found on page 239. If toxicity other than listed in the report form occurs, please use the CTCAE-toxicity grading system issued 12 December 2003 by NCI. It can be downloaded from http://ctep.cancer.gov/forms/CTCAEv3.pdf. If toxicity appears unexpected or severe, contact the trial office and consider **SAE report** (for details see pages 117-120, the report form is found on page 253).

11.6.3.3 Relapse or progression to stage 4

A metastatic relapse or progression to stage 4 requires intense treatment. **Children ≥1 year** will be treated according to the high risk group (page 65). **Infants <1 year** who develop metastasis not compatible with stage 4S definition (i.e., progression of bone marrow involvement exceeding 10% or occurrence of metastasis other than skin or liver) will be treated according to the MRG (page 53).

11.6.4 Stage 1-3 neuroblastoma with threatening initial symptoms

These patients will undergo surgery first. The extent of the tumor resection is decided by the surgeon. Complete resection is indicated only when the risk of any complication appears low. Tumor nephrectomy (a priori) or other mutilating operations are not

acceptable. If the risk of complication appears high, partial resection or even biopsy might be appropriate. During any operation, tumor tissue must be collected for histological and molecular investigations. For details of tumor tissue collection see chapter 29.3 on page 161.

The initial operation is documented at the first documentation form of the German Children's Cancer Registry, Mainz, Germany (page 216).

Threatening symptoms are **tumor associated symptoms** which **persist after tumor resection** (i.e., are not solved by tumor resection) and lead to:

- deterioration of the general condition,
- feeding difficulties leading to weight loss,
- respiratory failure defined by oxygen requirement or carbon dioxide retention exceeding 60 mmHg,
- circulatory failure defined by hypotension or hypertension according to the age specific blood pressure reference values,
- hepatic failure defined by grade 3 toxicity of bilirubin, fibrinogen, or thrombin time according to the NCI-CTC toxicity criteria,
- renal failure defined by impaired blood urea or creatinine, new development of hydroureter/hydronephrosis or deteriorating preexistent hydronephrosis,
- symptomatic intraspinal involvement documented by MRI,
- failure of other organ systems.

Only the local physician can definitely estimate the severity of symptoms. Therefore, the list can only be a guide. Please, do not hesitate to contact the trial office to discuss cases which appear equivocal.

The patients will receive a postoperative **chemotherapy of N4 cycles** (for details of N4 cycles see page 87 and 234) for induction of regression. As soon as tumor growth and symptoms are under control (i.e. stable disease or induction of regression), no further chemotherapy cycles will be given. The patients will be followed closely.

If **progression or symptoms are not controlled** after 4 N4 cycles, the patient will enter the medium risk group. Please contact the trial office to discuss details. Prior to medium risk group chemotherapy, a new biopsy or resection followed by complete histology and molecular assessment is recommended. Histology and molecular analysis results are necessary to distinguish non-responding tumors from differentiating or regressing tumors. Further treatment can only be decided based on these results.

The toxicity of each chemotherapy cycle must be documented at the chemotherapy forms which are found on page 239. If toxicity other than listed in the report form occurs, please use the CTCAE-toxicity grading system issued 12 December 2003 by NCI. It can be downloaded from http://ctep.cancer.gov/forms/CTCAEv3.pdf. If toxicity appears unexpected or severe, contact the trial office and consider **SAE report** (for details see pages 117-120, the report form is found on page 253).

Asymptomatic patients with intraspinal involvement found by MRI should undergo resection of the intraspinal tumor whenever possible without risk. The resected tissue must be collected for histology and molecular analysis. The extraspinal portion of the tumor does not require chemotherapy and will be observed according to NB2004 observation group unless molecular risk markers are detected.

11.6.5 Stage 4S

In stage 4S, progression is not uncommon.[52, 121] Therefore, growth of primary tumor, of liver involvement, or skin metastasis without clinical deterioration will not necessarily require surgery or chemotherapy. But any relevant clinical deterioration may require mild chemotherapy with N4 cycles to induce regression. Only the local physician can definitely estimate any symptom as threatening. Therefore, the following list can only be a guide. Please, do not hesitate to contact the trial office to discuss cases which appear equivocal:

- deterioration of the general condition,
- feeding difficulties leading to weight loss,
- respiratory failure defined by oxygen requirement or carbon dioxide retention exceeding 60 mmHg,
- circulatory failure defined by hypotension or hypertension according to the age specific blood pressure reference values,
- hepatic failure defined by grade 3 toxicity of bilirubin, fibrinogen, or thrombin time according to the NCI-CTC toxicity criteria,
- renal failure defined by impaired blood urea or creatinine, new development of hydronephrosis or deteriorating preexistent hydronephrosis,
- symptomatic or asymptomatic intraspinal involvement documented by MRI
- failure of other organ systems.

Patients meeting these criteria will be treated with **N4 chemotherapy cycles** starting every 21st day after day 1 of the preceding cycle until progression is stopped. Therefore, once stable disease is achieved, no further chemotherapy is required. It is not necessary to induce a partial or complete response to this mild chemotherapy. Further wait-&-see is sufficient after stopping the progression by N4 chemotherapy. The details of the N4 cycle are outlined on page 87 and 234. All patients treated with N4 cycles will still be followed according to the observation group of this protocol.

If **progression or symptoms are not controlled** after 4 N4 cycles, do not continue N4 chemotherapy and contact the trial office to discuss the options.

In some patients, progression may be very fast. Hepatomegaly may lead to respiratory failure due to high intraabdominal pressure. Laparatomy and transient insertion of a silastic patch into the abdominal wall can reduce the intra-abdominal pressure. The abdominal wall can be closed later after liver enlargement has regressed.[118]

Any case of pre-existing or developing distant lymph node metastasis, bone lesion, orbital involvement or bone marrow involvement exceeding 10% in an infant is not compatible with the diagnosis of stage 4S. These patients are treated according to the medium risk group of NB2004 (section 12.2.3 on page 56) as long as they are <1 year of age ad MYCN is not amplified.

Regular observation is finished at the end of the 2nd year of life. If the residual primary tumor has **not** vanished completely, surgery should be discussed with the trial office. MRI films are required for discussion. Please send all MRI films available to the trial office using the shipping form on page 222. The complete set will be returned to you as soon as a decision has been made.

11.7 Patient drop-out

The patient's guardians and the patient (if appropriate to her/his psycho-intellectual development) can refuse further observation by individual decision at any time without giving any reasons and without any negative consequences for the further treatment.

Observation can be stopped by decision of the local pediatric oncologist in case of any medical reason.

All patients not under observation anymore and receiving any treatment will still be followed until death, lost to follow-up, or until they withdraw their consent for data collection.

11.8 Premature termination of trial

The trial can be closed prematurely by the principal investigator when the event rate is unacceptably high. As this is an observational trial, the cut off event rate is defined for stage 1/4S and stage 2/3 OG patients separately by the sequential probability ratio test by Wald (page 126 and 127). Additionally, a stopping rule for the status of chromosome 11q has been defined.

12 MEDIUM RISK PATIENTS

12.1 Medium risk patients protocol outline

Indication	Medium risk neuroblastoma stages 2, 3, and stage 4 infants
Design	Prospective multicenter nonrandomized historical controlled trial
Primary objectives	event free survival rate of the newly defined and more intensive treated medium risk group compared to a historical control group
Secondary objectives	time from diagnosis to an locoregional event, time to transition to stage 4, overall survival, molecular marker (chromosome 1p, 11q, neuroblastoma gene chip), external beam radiation therapy (acute side effects, late effects), surgery (initial and best surgery, frequency of complications)
Trial medication	3 x N5 cycle (cisplatin, etoposide, and vindesine) 3 x N6 cycle (vincristine, dacarbacin, ifosfamide, and doxorubicin), 4 x N7 cycle (low dose cyclophosphamid orally) 9 x Retinoic acid 14-day cycles supportive care (PCP/fungal prophylaxis, transfusions, G-CSF)
Inclusion criteria	STAGE 2/3 age 0-21 years, del1p or imb1p in tumor tissue, no MYCN-amplification STAGE 3: age ≥2-21 years, no MYCN-amplification STAGE 4: age <1 year, no MYCN-amplification
Exclusion criteria	Concomitant non-protocol anticancer therapy
Treatment schedule	initial tumor biopsy or resection, 6 cycles of alternating N5 and N6 starting every 21 days, second look tumor resection when appropriate for tumor size, surgical risk, and presumed respectability, external beam radiation therapy for active residual tumor tissue, oral maintenance therapy with 4 x N7, retinoic acid for 12 months (6 months, 3 months break, 3 months)
Cooperating hospitals	≥80 pediatric-oncology departments of German and Swiss children's Hospitals
Trial schedule	Pilot phase begin: 01. October 2004 Trial start: 01. June 2005 Trial closing: 30. September 2010

12.2 Background for the MRG definition

12.2.1 Results of localized neuroblastoma in previous trials

In NB90, the standard risk group included, regardless of MYCN, all stage 2 patients and stage 3 low risk patients (i.e., if the patient met none or only one of these risk factors: elevated LDH, initial biopsy only, age>9 months). If response to chemotherapy was not satisfactory, low risk stage 3 patients were allowed to shift to the high risk group during treatment.

In NB97, only unresectable stage 2 >1 year of age with residual tumor more than 10% of initial volume and stage 3 neuroblastoma >1 year received standard risk therapy. Patients with MYCN amplification (NMA) were excluded. Here, we have analyzed patients classified as standard risk patient of trials NB90 and NB97 stratified by stage and age:

In **stage 2 ≥1 year** without NMA, **no difference** between NB90 (n=44, 3-y-EFS 88.5±4.8%, 3-y-OS 97.7±2.3%) and NB97 (n=64, 3-y-EFS 86.8±4.8%, logrank p=0.7635 and 3-y-OS 98.0±1.9%, logrank p=0.9094) was detected. A total of 46 stage 2 patients ≥1 year did not receive chemotherapy. Two of these patients died of disease and 3 are alive after treatment for progression.

In **stage 3 <1 year** without NMA, there was **no difference** between NB90 (n=31, 3-y-EFS 83.9±6.6%, 3-y-OS 87.1±6.0%) and NB97 (n=47, 3-y-EFS 75.9±6.3%, logrank p=0.3022; 3-y-OS 93.3±3.7%, logrank p=0.4602).

In **stage 3 ≥1 year** without NMA, we found a trend toward better EFS in NB90 (n=62, 3-y-EFS 81.9±4.9%) compared to NB97 (n=72, 66.5±6.6%, logrank p=0.0853). But the survival was identical between both trials (NB90 3-y-OS 91.8±3.5% vs. NB97 3-y-OS 92.0±3.5%, logrank p=0.8120). This clearly demonstrates that reduction in chemotherapy resulted in more events but did not influence the survival rate of these patients so far.

12.2.2 Rationale for the treatment intensification of the MRG

Many patients of the NB97 standard risk group are classified as observation patients in NB2004. The new defined medium risk group contains the remaining patients with a higher risk profile: The patients of NB90-NB97 classified retrospectively as medium risk patients (i.e., stage 2 and 3 with 1p alterations and stage 3 ≥2 years) had a 3-y-EFS of 52±6% (logrank p<0.001) and a 3-y-OS of 83±5% (logrank p<0.001, figure 10). The median time to relapse/progression was 1.54 years (range 0.15-4.87 years).

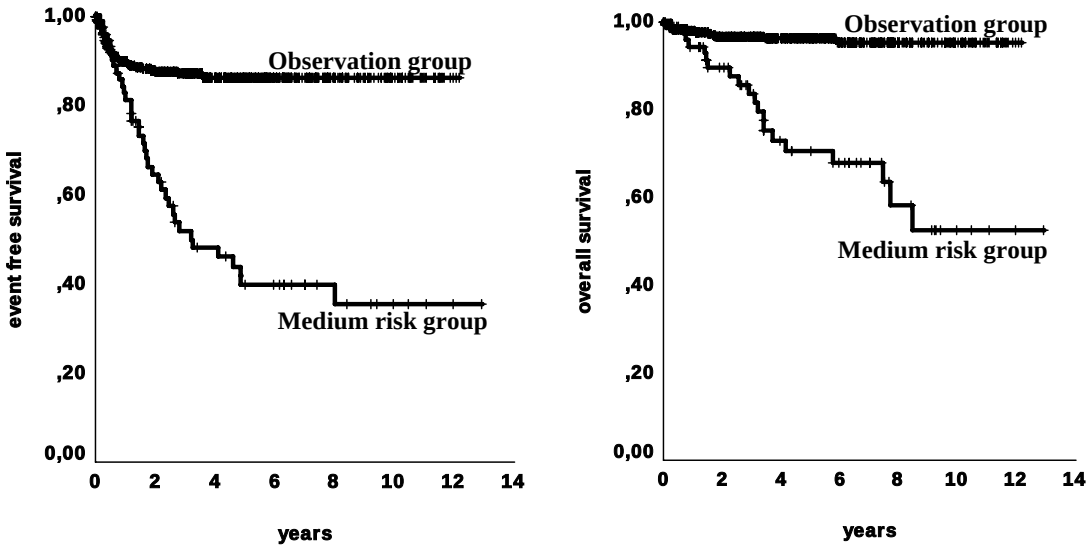


Figure 10: Outcome of stage 1-3/4S patients of the trials NB90 and NB97 classified according to the new risk definition retrospectively (observation group n=710, new medium risk group n=72).

The event and death rate is considerably high in the new medium risk group. Therefore, treatment intensification is required. Chemotherapy intensification seems to have limited value: In NB90, stage 2 and stage 3 A/B were scheduled for 4 chemotherapy cycles and were allowed to shift into high risk group if response was not complete after 4 cycles. By separate retrospective analysis of 38 patients ≥2 years or with 1p-aberration initially classified as stage 3 C/D in the trials NB90 and NB97, the number of intensive chemotherapy cycles was not prognostic (1-5 cycles n=15, >5 cycles n=15, EFS logrank p=0.544, OS logrank p=0.843).

The extent of surgical resection (figure 11) and radiation therapy (figure 12) had no influence on the outcome, either.

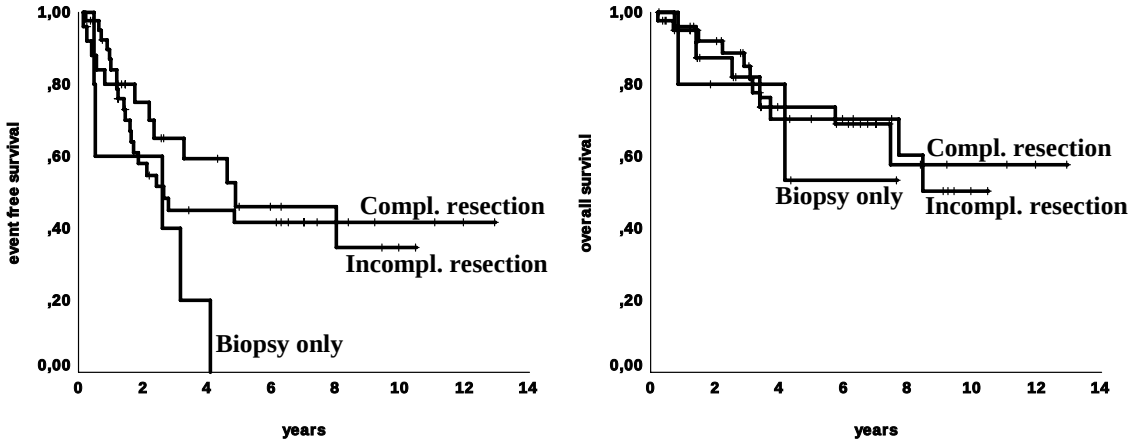


Figure 11: EFS and OS of 72 patients (stage 2 and 3 with 1p alteration and stage 3 ≥2 years of trials NB90 and NB97) by extent of best resection (biopsy only n=5, incomplete resection n=26, complete resection n=41, EFS logrank p=0.1393, OS logrank p=0.8152).

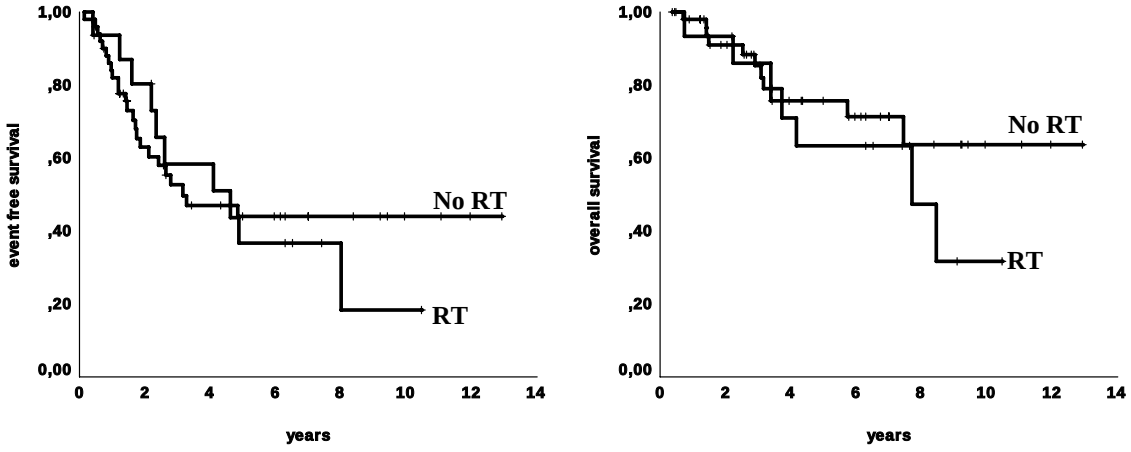


Figure 12: EFS and OS of 68 patients (stage 2 and 3 with 1p alteration and stage 3 >2 years of trials NB90 and NB97) by radiation therapy. No radiotherapy includes all patients who completed initial treatment until radiotherapy was possible: n=52, 3-y-EFS 52.5±7.7%, 3-y-OS 85.3±5.6%; radiotherapy given n=16, 3-y-EFS 58.5±13.1%, 3-y-OS 86.1±9.1%, EFS logrank p=0.813, OS logrank p=0.359).

Up to now, there are no data which justify highly aggressive chemotherapy with ASCT, aggressive radiation therapy or aggressive surgery for medium risk patients. Since relapses have been observed as long as 4.87 years after first diagnosis (figure 10), a treatment prolongation seems the appropriate way to improve outcome with expected low additional toxicity. Therefore, medium risk patients (i.e., stage 2 and 3 with 1p aberrations and stage 3 patients ≥2 years) will receive 6 chemotherapy cycles (N5 and N6 alternating), followed by four N7 maintenance cycles and a 6+3 months retinoic acid consolidation treatment (figure 13):

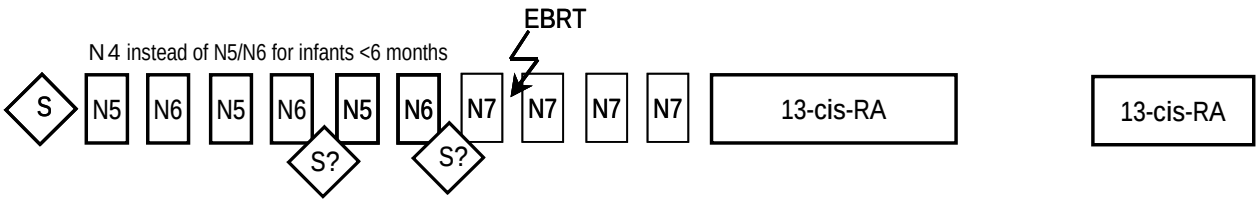


Figure 13: Overview of the medium risk group treatment (S=surgery, N5/6/7=chemotherapy cycles, EBRT=external beam radiation therapy, 13-cis-RA=13-cis-retinoic acid)

12.2.3 Treatment of stage 4 infants in the medium risk group

In NB97, infants <1 year with stage 4 disease, MYCN not amplified, were treated in the high risk arm but had N7 maintenance instead of ASCT. The outcome results are satisfying (figure 14). Therefore, treatment intensification with increased toxicity is not

required. Since the NB97 high risk maintenance arm is identical to the NB2004 medium risk group, these infants will be treated according to the NB2004 medium risk group.

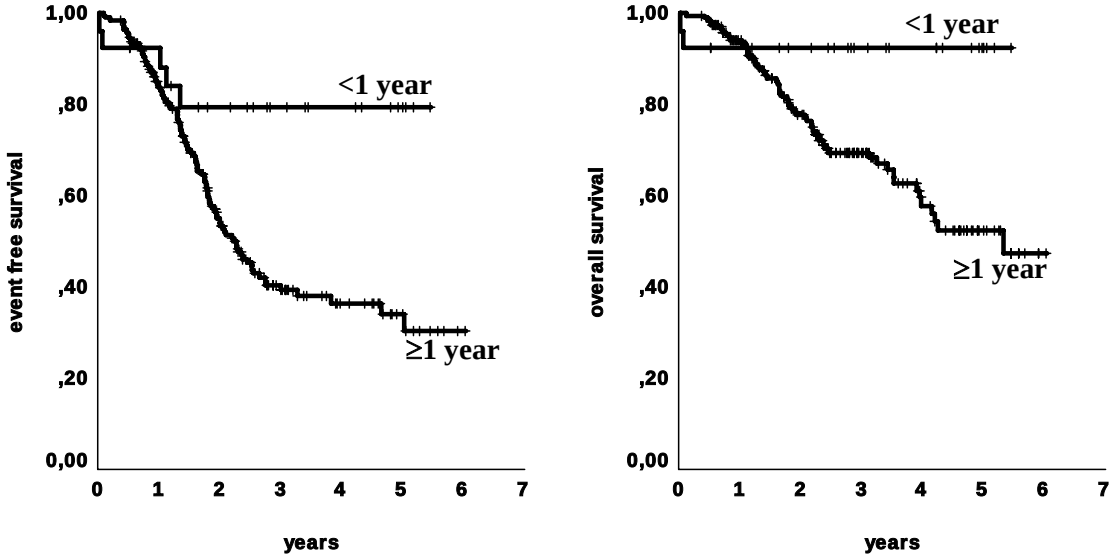


Figure 14: EFS and OS of 218 stage 4 patients, MYCN not amplified of trial NB97. Infants (n=26) had a better EFS (79±8%) and OS (92±5%) compared to older children (n=192, EFS 40±4%, logrank p=0.004; OS 69±4%, logrank p=.012)

12.3 Differences between NB97 and NB2004

Table 5: Modifications of the NB2004 medium risk group vs. NB97 standard risk

definition according to NB97	definition according to NB2004
stage 2nr, residual >10% or >5ml, no NMA	stage 2, no NMA, presence of 1p aberration
stage 3 >1 year, no NMA	stage 3, no NMA, presence of 1p aberration OR stage 3 >2 years, no NMA
stage 2-3 all ages with threatening symptoms	stage 1-3 all ages with threatening symptoms or progression resistant to 4 cycles of N4 chemotherapy

12.4 Trial objectives of the medium risk group

12.4.1 Primary objectives

The medium risk group includes all localized patients with considerable risk of relapse/progression or death. The NB2004 treatment has been intensified compared to the preceding trial NB97.

The primary objective is the event free survival. It is expected to be superior to the results of the historic control group outlined on page 55. An event is defined as death of any reason, occurrence of any distant disease, reappearance of primary after complete response, or growth of residual exceeding 25% after partial response according to the criteria of the INSS (see page 160).[19]

12.4.2 Secondary objectives

- **EFS_L:** locoregional EFS measured from the time of diagnosis up to an locoregional event or last follow-up for patients without locoregional event. A locoregional event is defined as (i) death (related to locoregional disease), (ii) local progression of residual primary tumor, (iii) locoregional relapse following previous complete remission of the primary tumor as defined on page 160.
- **EFS_{stage4}:** time from diagnosis to transition to stage 4, to death of disease, or to last follow-up if no transition to stage 4 is observed and the patient is surviving.
- **OS:** Overall survival measured from the time of diagnosis up to death of any reason or last follow-up for surviving patients.
- **Molecular markers:** status of chromosome 1p and status of chromosome 11q categorized according to criteria published by Ambros.[4] Tumor tissue is collected and stored in the tumor bank for future evaluation of other molecular markers which will be considered having prognostic impact during the ongoing trial.
- Prospective molecular analysis of defined molecular markers by the neuroblastoma gene chip.
- **External beam radiation therapy:**
    - **Acute side effects** of EBRT considered separately according to the radiation therapy documentation form (page 250).
    - **Late effects** of EBRT considered separately according to the long term follow-up forms (page 258).
- **Surgery:**
    - Extent of the **initial surgery** categorized in: biopsy vs. incomplete resection vs. macroscopic complete resection. Initial surgery is the first tumor operation done in a patient.

- Impact or the **best surgery** up to time t categorized in: biopsy vs. incomplete resection vs. macroscopic complete resection. Best surgery is the operation performed from diagnosis up to time t which achieves the most extensive tumor resection.
- Frequency of complications related to surgery considered separately for the items: nephrectomy, bleeding, intestinal obstruction, and other.

12.4.3 Study design

This is a multi-center, single-arm, non-randomized, un-blinded trial. The event rate is monitored continuously. The final analysis to answer the primary and secondary trial objective will be done 3 years after entry of the last trial patient (for details see section 20.2 on page 128).

12.5 Selection of subjects

12.5.1 Inclusion criteria

- Neuroblastoma diagnosed histologically from tumor tissue.[19]
- Molecular markers MYCN and 1p status available from tumor tissue,
- Complete initial staging by MRI, MIBG-scintigraphy, bone marrow assessment, and tumor markers.
  - STAGE 2: age 0-21 years, no MYCN-amplification, presence of chromosome 1p deletion or imbalance
  - STAGE 3: age <2 years, no MYCN-amplification, presence of chromosome 1p deletion or imbalance
  - STAGE 3: age ≥2-21 years, no MYCN amplification, regardless of 1p status
  - STAGE 4 age <1 year, no MYCN amplification
- Guardians' informed consent and patient's informed consent (if appropriate according to his/her age and status of psycho-intellectual development).
- No pregnancy and sufficient prevention of pregnancy in fertile female adolescents.

12.5.2 Exclusion criteria

- Any concomitant non-protocol anticancer therapy

12.6 Medium risk group treatment

12.6.1 Overview

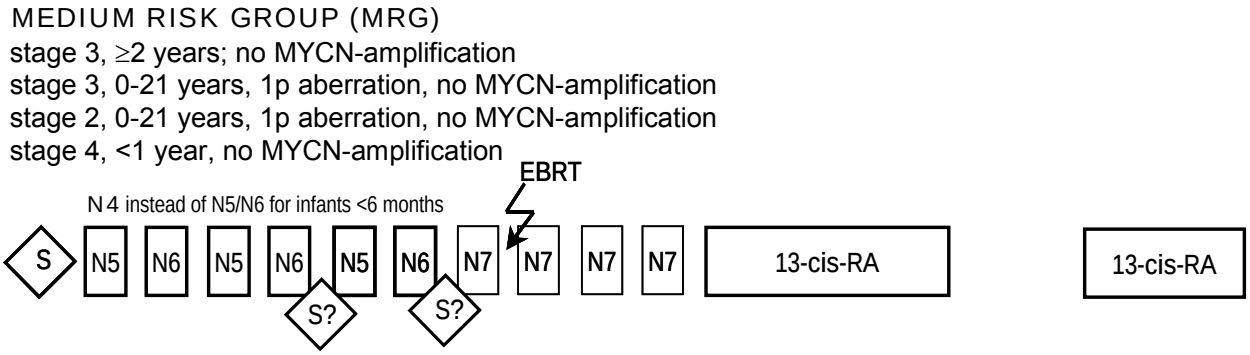


Figure 15: Overview of the medium risk group treatment (S=surgery, N5/6/7=chemotherapy cycles, EBRT=external beam radiation therapy, 13-cis-RA=13-cis-retinoic acid)

12.6.2 Intensive chemotherapy in the MRG

Patients **younger than 6 months** at diagnosis start with N4 cycles instead of N5/N6. For details see pages 87 and 234. As soon as the infant is 6 months old, the remaining cycles are given as N5 and N6 for a total of 6 chemotherapy cycles followed by the N7 maintenance therapy and retinoic acid.

All **patients ≥6 months** at diagnosis receive alternating N5 and N6 cycles for a total of six chemotherapy cycles. Details of the chemotherapy cycles are found on pages 88, 89, 235 and 236. A 21-day-interval between the first days of two consecutive cycles is attempted. Shorter intervals are allowed. Longer intervals are sometimes necessary to overcome bone marrow depression.

In general, prior to each cycle the following criteria must be fulfilled:

- leukocytes >2000/µl, lymphocytes >1000/µl,
- platelets >50,000/µl,
- no sign of infection

If these criteria are not met, the start of a cycle must be delayed. If the delay exceeds 7 days or infection grade ≥3 occurred, the doses of the next cycle should be modified. Dose reduction rules are outlined for each cycle on pages 87-89.

The toxicity of each chemotherapy cycle must be documented on the chemotherapy forms which are found on page 239. If toxicity other than listed in the report form occurs, please use the CTCAE-toxicity grading system issued 12 December 2003 by NCI. It can be downloaded from http://ctep.cancer.gov/forms/CTCAEv3.pdf. If toxicity appears

unexpected or severe, contact the trial office and consider **SAE report** (for details see pages 117-120, the report form is found on page 253).

12.6.3 Maintenance chemotherapy in the MRG

After intensive chemotherapy, all patients will receive four N7 cycles of oral cyclophosphamid. Details of this chemotherapy are found on page 90.

The toxicity of each N7 cycle must be documented on the chemotherapy forms which are found on page 239. If toxicity other than listed in the report form occurs, please use the CTCAE-toxicity grading system issued 12 December 2003 by NCI. It can be downloaded from http://ctep.cancer.gov/forms/CTCAEv3.pdf. If toxicity appears unexpected or severe, contact the trial office and consider **SAE report** (for details see pages 117-120, the report form is found on page 253).

12.6.4 Retinoic acid consolidation treatment in the MRG

13-cis-retinoic acid (RA) treatment begins 21 days after the last N7 maintenance cycle. Retinoic acid is available in Germany as **Roaccutan®** capsules. The capsules contain oil. For younger children, the capsules can be opened or punctured and the oil can be taken in milk or ice cream. 13-cis-retinoic acid is given in a dose of 160 mg/m²xd in 2-(3) divided doses for subsequent 14 days followed by 14 day rest. Then the next cycle is started. After 6 cycles, the patient has a 3 months rest without any treatment. Then, 13-cis-retinoic acid is restarted for additional 3 cycles (page 93).

Since **increased light sensitivity** has been reported, avoid sunlight exposure during 13-cis-retinoic acid treatment.

Given during pregnancy, 13-cis-retinoic acid can cause **severe birth malformations** (hydrocephalus, microcephalus, ear abnormalities, cardiovascular abnormalities, facial dysmorphia, endocrine abnormalities, cerebellar malformations, and other). Therefore, contraception starting 1 month prior to 13-cis-retinoic acid treatment is mandatory in all female adolescents who might become pregnant.

For further toxicity and drug information see page 111.

The toxicity of each RA cycle must be documented at the forms found at pages 256 and 257. If toxicity other than listed in the report form occurs, please use the CTCAE-toxicity grading system issued 12 December 2003 by NCI. It can be downloaded from http://ctep.cancer.gov/forms/CTCAEv3.pdf. If toxicity appears unexpected or severe, contact the trial office and consider **SAE report** (for details see pages 117-120, the report form is found on page 253).

12.6.5 Radiation therapy in the MRG

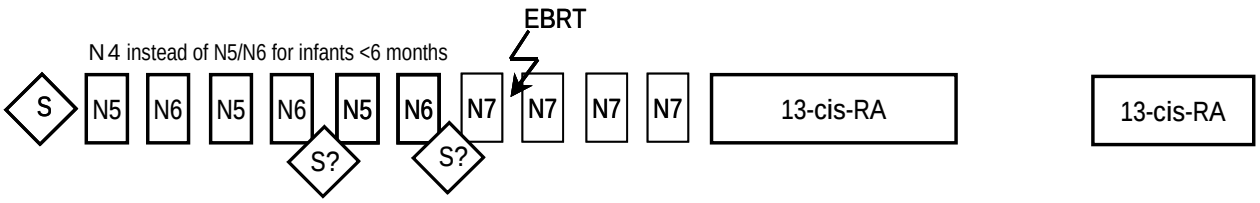


Figure 16: Timing of external beam radiation therapy in the medium risk group (S=surgery, N5/6/7=chemotherapy cycles, EBRT=external beam radiation therapy, 13-cis-RA=13-cis-retinoic acid)

Radiation therapy is reserved for patients with active residual tumor after 6 cycles of induction chemotherapy, i.e. prior to maintenance chemotherapy. Active residual tumor tissue is defined as:

- residual MIBG-uptake (tumors initially MIBG positive),
- residual Octreotide-uptake (tumors initially MIBG negative but Octreotide positive),
- or clear MRI-contrast enhancement (only tumors which have been completely negative in initial scintigraphy).

Residual non-progressing non-active mass seen only in MRI, CT, or ultrasound does not require radiation therapy.

Radiation therapy should be done during the maintenance chemotherapy. It must be finished at least 1, better 4 weeks prior to retinoic acid consolidation therapy to avoid possible negative interactions between radiation and retinoic acid.

Radiation therapy in the medium risk group is external beam radiation therapy (EBRT). MIBG therapy is not scheduled for the medium risk group because of potential bone marrow toxicity.

For details of the EBRT see section 14.9 on page 98.

Each EBRT must be documented at the radiation therapy form found on page 250. Toxicity must be reported according to the CTCAE-toxicity grading system issued 12 December 2003 by NCI. It can be downloaded from the internet from http://ctep.cancer.gov/forms/CTCAEv3.pdf.

12.6.6 Surgery in the MRG

During any operation, tumor tissue must be collected for histological and molecular investigations. For details of tumor tissue collection see chapter 29.3 on page 161.

12.6.6.1 Initial surgery

Initially, a tumor biopsy for histology and molecular analysis is required. Complete resection of the primary tumor is not necessary. It might be done in selected patients where the risk of surgical complications appears very low. Extended operations in order to remove the primary tumor should not be attempted. Nephrectomy, injury of large vessels, or other complications should be avoided during initial surgery unless threatening symptoms due to compression of airways, nerves, or large vessels may require immediate tumor resection in selected cases. For details see page 94.

For symptomatic intraspinal involvement, immediate start of chemotherapy is preferred since chemotherapy has less late effects than surgery in these patients (page 115).

The initial operation (i.e., extent of resection, complications) is documented at the initial documentation form of the German Children's Cancer Registry, Mainz, Germany found on page 216.

12.6.6.2 Secondary surgery

After **chemotherapy**, resection can be done with a lower risk of tumor rupture. Therefore, resection of the primary should be attempted after the 4th or 6th chemotherapy cycle. The risk of operation has to be balanced against the benefits of radical resection. Radical microscopic complete resection is not required. Microscopic or even macroscopic residual tumor tissue is accepted despite the fact, that macroscopic complete resection was associated with a better outcome in localized neuroblastoma patients older than 1 year.[174]

After **radiotherapy**, resection can be more difficult due to radiation induced fibrosis in the tumor area. Therefore, resection should be attempted prior to radiation therapy.

Since tumor spillage is unlikely after chemotherapy, incision of the tumor is permissible in order to facilitate resection during secondary surgery.

Secondary and further surgery must be reported to the trial office using the report form on page 248.

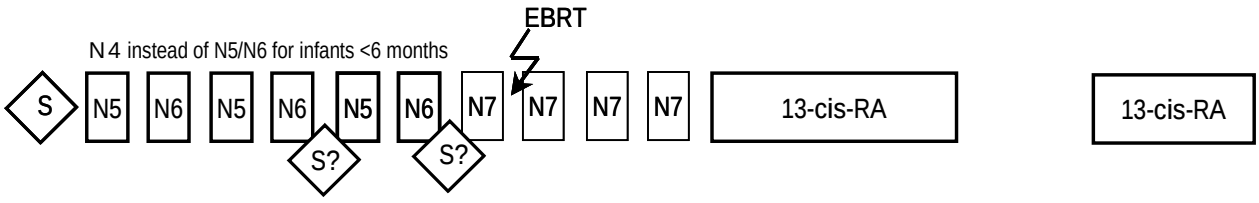


Figure 17: Surgery in the MRG. Initial surgery aims to obtain a sufficient biopsy for histological and molecular diagnosis. Tumor resection is scheduled after 4 or 6 chemotherapy cycles. Incomplete resection is accepted (S=surgery, N5/6/7=chemotherapy, 13-cis-RE=retinoic acid, EBRT=external radiation therapy)

12.7 Patient drop-out

The patient's guardians and the patient (if appropriate to her/his psycho-intellectual development) can refuse further trial treatment by individual decision at any time without giving any reasons and without any negative consequences for the further treatment.

Investigational treatment can be stopped by decision of the local pediatric oncologist in case of any individual medical reason.

All patients not under trial treatment anymore and receiving any other treatment will still be followed until death, lost to follow-up, or until they withdraw their consent for data collection.

12.8 Premature termination of trial

The trial can be closed prematurely by the principal investigator when the event rate is unacceptably high. Stopping rules follow the criteria outlined in section 20.2 at page 128. If the MRG is closed due to an unacceptably high event rate, the medium risk group patients will be treated according to the high risk group.

13 HIGH RISK PATIENTS

13.1 High risk patients protocol outline

Indication	neuroblastoma stage 4 (≥1 year) or MYCN-amplification of any stage/age
Design	Prospective, multicenter, unblinded, randomized, window-design
Primary objectives	Event free survival of both randomized treatment arms
Secondary objectives	time from diagnosis to an local event, overall survival, early response after two cycles of chemotherapy, response to induction therapy, chemotherapy toxicity (cycle 1, cycle 2, frequency of chemotherapy cycles with toxicity grade ≥ 3 or 4 during induction chemotherapy), surgery (initial and best surgery, complications), external beam radiation therapy (acute side effects, late effects), MIBG therapy (activity and whole body dose), molecular marker (chromosome 1p, 11q, MYCN, neuroblastoma gene chip)
Trial medication	**Experimental arm:** 2 x N8 cycle (topotecan, cyclophosphamide, and etoposide) followed by standard arm treatment **Standard arm:** 3 x N5 cycle (cisplatin, etoposide, and vindesine) 3 x N6 cycle (vincristine, dacarbacin, ifosfamide, and doxorubicine), ASCT (melphalan, carboplatin, etoposide) 9 x Retinoic acid cycles supportive care (PCP/fungal prophylaxis, transfusions, G-CSF)
Inclusion criteria	Stage 4 neuroblastoma ≥1-21 years of age OR MYCN-amplification regardless of stage, 0 – 21 years (infants <1 year with MYCN-amplification are not randomized)
Exclusion criteria	Concomitant non-protocol anti-tumor therapy
Treatment schedule	initial tumor biopsy or resection, induction chemotherapy according to the randomization result, second look tumor resection when appropriate for tumor size, surgical risk, and presumed resectability, ASCT, combined with MIBG radiation therapy for active tumor residuals, external beam radiation therapy after ASCT for active residuals, retinoic acid for 12 months (6 months, 3 months break, 3 months) Follow-up of all patients for a minimum of 10 years.
Cooperating hospitals	≥80 pediatric-oncology departments of German and Swiss children's Hospitals
Trial schedule	Pilot phase begin: 01. October 2004 Trial start: 01. June 2005 Trial closing: 30. September 2010

13.2 Background of the HRG treatment

13.2.1 Results of previous trials

High risk neuroblastoma definition may vary between different international trials. This group contains all stage 4 patients over 1 year and patients with MYCN-amplification. Some protocols include high risk stage 3 or patients defined by other risk markers like ferritine and unfavorable Shimada histology. In general, treatment includes induction chemotherapy, maintenance or high dose chemotherapy, and consolidation treatment. For induction treatment, several protocols have been employed but the improvement of the event free and overall survival is still unsatisfactory.[154] Figure 18 demonstrates the progress made during the German NB trials since 1979.[9]

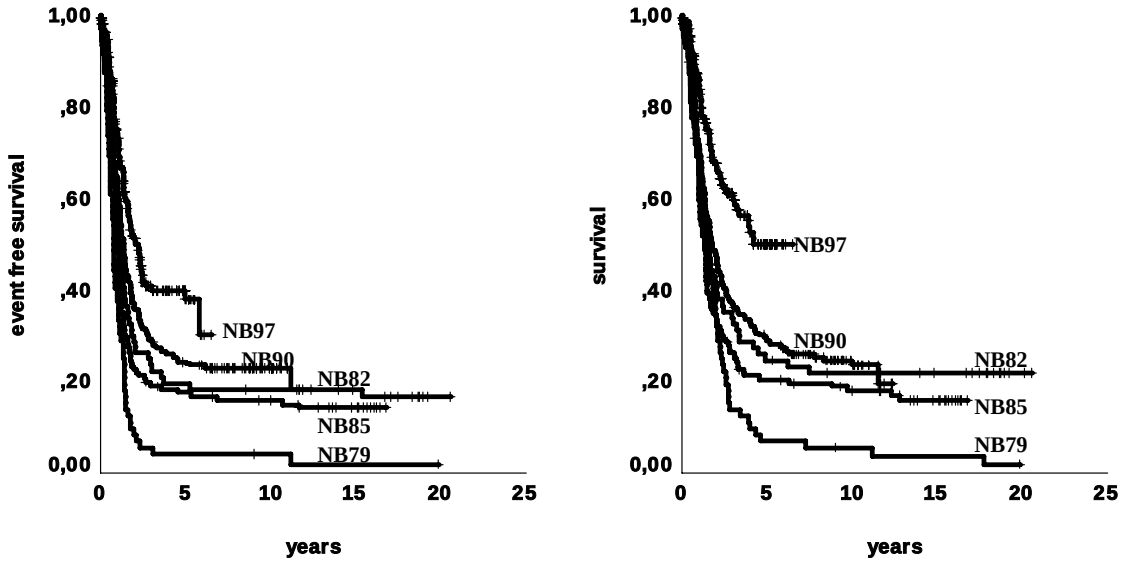


Figure 18: EFS and OS of 746 stage 4 protocol patients by trial. NB79 n=72, NB82 n=79, NB85 n=141, NB90 n=228, NB97 n=226. LEFT EFS, logrank p<0.001, RIGHT OS, logrank p<0.001.

13.2.2 Rationale of the induction chemotherapy

13.2.2.1 Induction treatment in the standard arm

The number of drugs available and effective in neuroblastoma is limited. Induction therapy of the most international protocols contains combinations of cisplatin, carboplatin, cyclophosphamide, ifosfamide, doxorubicine, etoposide, teniposide, vincristine, and/or vinblastine.[7, 23, 30, 43, 98, 112, 133, 165] Table 6 gives an overview over the drugs and the cumulative doses of selected induction protocols. The EFS rates must be interpreted with

great caution since the treatment following induction chemotherapy differs substantially between all these protocols, and selection of patients does play a role not only in small pilot protocols.

Table 6: Overview over different induction chemotherapy regimens[23, 27, 30, 43, 85, 98, 112, 132, 165]

	Castel 2001	Coze 1997 NB87	DeBernardi 2003 ICGNB-89	DeBernardi 2003 ICGNB-92	Frappaz 2002 LMCE5	Kaneko 2002 MYCN <10	Kaneko 2002 MYCN ≥10	Kushner 1994 N6	Matthay 1999 CCG3891	Pearson 1992	Tweddle 2001 OPEC/ OJEC	HR-NBL-1 Protocol Rapid COJEC	**NB04** HR standard arm	**NB04** HR N8 arm
ADR		120			180[only<PR]	240	240	300	150				180	180
CDDP	400	400	400		400	540	715	600	300	360	320	320	480	480
CADDP	4,000			4,000	1,600						1,500	1,500		
CYC	8,400	3,000	1,200	2,400	12,000	7,200	13,200	16,800	10,000	1,000	4,200	4,200		1,400
IFO													22,500	22,500
DTIC													3,000	3,000
Peptichemio			1,000											
Thiotepa				120										
VCR	4	6	3					18		6	10.5	12	9	9
VDS													9	9
VM26	450													
VP16	300	1,000		1,200	2,500	3,000	3,000	1,800	1,000	800	1,400	1,400	1,200	1,800
topotecan														14
deferoxamine				2,000										
No. of patients	81	183	65	159	24	133	88	24	434	12	95			
CR/VGPR/PR after induction	79%	74%	69%	69%	87%	93%	95%	96%	73%	75%	n.rep.		87%	
Toxic deaths	3.7%	2.7%	4.6%	3.1%	0%	3.0%	1.1%	0%	n.rep.	0%	1%		1%	
General EFS	4y 33%	n.rep.	5y 17%	5y 17%	6y 8%	5y 32%	5y 36%	n.rep.	3y 30%	n.rep.	2y 46%		3y 45%	

13.2.2.1.1 Toxicity of NB97 induction chemotherapy

Chemotherapy has been detoxified from NB90 to NB97 by reduction of the total number of cycles from 8 to 6, by reduction of the etoposide dose from 125 mg/m²xd to 100 mg/m²xd, by reduction of doxorubicine infusion time from 48 hours continuous infusion to 4 hours infusion at 2 consecutive days, and by application of G-CSF to all high risk patients.

The toxicities registered after N5/N6 cycles are outlined in table 7. The rate of myelosuppression grade ≥3 was considerably high. Fever and infection grade 1-2 were frequent but fever or infection grade ≥3 were rare (4.1% and 7.3% for fever and infection, respectively). Moderate mucositis was observed in 25.2% but severe grade ≥3 mucositis was only seen in 3.9%. No severe unexpected toxicity occurred.

The median interval between the chemotherapy cycles was 32 days (range 9 to 46 days) in NB90, and 27 days (range 17 to 64) in NB97 (Mann-Whitney-U-test $p<0.001$). This treatment intensification may be one reason for better outcome of NB97 high risk patients compared to the previous trials.

In NB90, 21 deaths (5.4%) were clearly treatment related and 8 deaths (2.1%) were possibly related to the treatment. Thirteen deaths occurred during induction chemotherapy. In NB97, 10 deaths (2.7%) were clearly related to and 2 deaths (0.5%)

were possibly related to treatment (table 8). Only 2 deaths occurred during induction chemotherapy.

Table 7: Toxicities according to the WHO grading observed during 683 cycles N5/N6 given in the induction chemotherapy of the NB97 high risk group.

	grade 1-2 reported in % of N5/N6 cycles	grade 3-4 reported in % of N5/N6 cycles
anemia	25.3	71.8
leukopenia	13.9	81.7
infection	39.7	7.3
fever	54.8	4.1
thrombopenia	12.5	71.2
abnormal GOT/GPT	46.7	3.9
bilirubin	4.7	1.4
creatinine	5.8	0
cardiac toxicity	2.8	1.1
general condition	68.9	11.6
diarrhea	26.4	2.4
mucositis	25.2	3.9
peripheral neurotoxicity	7.1	0.9

Table 8: Causes of death among 759 stage 4 patients of the trials NB90 and NB97

	NB90		NB97	
	n	%	n	%
tumor	211	54.2	123	33.2
initial treatment	21	5.4	10	2.7
ASCT	4	1.0	6	1.6
chemotherapy	13	3.3	4	1.1
maintenance therapy	2	0.5	0	0.0
surgery	2	0.5	0	0.0
relapse treatment	5	1.3	2	0.5
tumor & treatment	8	2.1	2	0.5
secondary malignant disease	11	2.8	1	0.3
not known/not to decide	5	1.3	4	1.1
total patients	389		370	

13.2.2.1.2 Response to NB97 induction chemotherapy

In NB90, 230 high risk patients were strictly treated according to the protocol and evaluable for response analysis. After 4 chemotherapy cycles, 31% were in CR and 44% PR. Prior to ASCT/Maintenance therapy (i.e. after 8 chemotherapy cycles) 58% were in CR and 11% PR (table 9). In NB97, 204 high risk patients were evaluable for analysis. After 4 chemotherapy cycles 26% were in CR and 62% in PR. ASCT/maintenance therapy was started after 6 chemotherapy cycles. Therefore, assessment prior to ASCT/maintenance therapy was done about 6 weeks earlier in NB97. 63% CR and 24% PR were observed (table 9).

There was a better response rate (CR+PR) in NB97 of 87% compared to 69% in NB90 despite the fact, that NB97 assessment was done earlier missing further CR/PR achievements for about 6 weeks. Of course, some relapses might be missed as well.

Table 9: Response to induction treatment comparing per protocol treated patients of NB90 (n=230) and NB97 (n=204)

		NB90	NB97
after 4 chemotherapy cycles	**CR**	**31%**	**26%**
	PR	**44%**	**62%**
	MR	**9%**	**5%**
	SD	**4%**	**1%**
	Relapse/progression	**1%**	**1%**
	alive, status not reported	**2%**	**3%**
	died	**9%**	**2%**
prior to ASCT/maintenance	**CR**	**58%**	**63%**
	PR	**11%**	**24%**
	MR	**2%**	**2%**
	SD	**0%**	**0%**
	Relapse/progression	**4%**	**4%**
	alive, status not reported	**2%**	**3%**
	died	**23%**	**4%**

In conclusion, dose reduction of NB97 compared to NB90 resulted in less treatment related deaths but response was not compromised. Therefore, the NB97 induction treatment was chosen as the standard induction therapy for the randomized trial to assess the additional impact of Topotecan containing chemotherapy in NB2004.

13.2.2.2 Experimental induction with topotecan (N8)

The NB2004 trial will assess the value of additional Topotecan, Cyclophosphamide, and Etoposide (N8) cycles in the induction treatment of high risk neuroblastoma in a randomized window trial design.

Topotecan (SK&F 104864, 9-dimethylaminomethyl-10-hydroxycamptotecin, Hycamtin® GlaxoSmithKline) is a derivate of the alkaloid camptothecin which has not been used in the first line treatment of neuroblastoma so far. The compound is a potent inhibitor of topoisomerase I.[49, 109, 137]

Clinical response seems to be correlated to the formation of topoisomerase-DNA-complexes.[1, 84] Glycoprotein p expression can mediate resistance to topotecan but this effect is smaller than observed in other drugs.[65, 81, 108]

Topotecan proved to be effective in neuroblastoma xenografts in mice[171, 180] and in phase I-II trials. In vitro data with Rhabdomyosarcoma xenografts suggest higher efficiency of prolonged administration.[77]

In untreated pediatric rhabdomyosarcoma patients, 4% CR and 42% PR was seen after 2 cycles topotecan 2.0 – 2.4 mg/m²xday intravenous push for 5 days.[129] In a phase II trial with 37 relapsed or progressing neuroblastoma patients treated with topotecan (2.0 mg/m²xd 30-min-infusion day 1 to 5), 2 CR, 5 MR and 8 SD were observed.[123] In 13 neuroblastoma patients 2 PR were seen.[100] With 72-hour continuous topotecan infusion (dose escalation 1.0 to 1.3 mg/m²xday) one CR was observed in 26 children with relapsed or resistant neuroblastoma.[14]

The toxicity of topotecan monotherapy regardless of the application schedule was grade 3-4 myelotoxicity, mild to moderate nausea and vomiting, and in higher doses mucositis, and diarrhea after oral application[1, 14, 15, 18, 42, 76, 83, 94, 100, 123, 164].

Topoisomerase I and II are expressed reciprocally, suggesting enhanced sensitivity to topoisomerase II inhibitor after treatment with topoisomerase I inhibitor.[17, 88, 156, 157, 159, 175] This up regulation of topoisomerase II by pretreatment with topoisomerase I inhibitors was demonstrated in humans.[54 57]

The sequential combination of topotecan (0.5 – 1.25 mg/m²/day for 5 days or 0.68 mg/m²/day continuous infusion for 72 hours) followed by etoposide (40-100 mg/m²/day orally for 3 - 12 days or 60 – 75 mg/m²/day intravenously for 3 - 5 days) was tolerable in adults.[28, 34, 57, 68, 78, 114, 128] Dose limiting toxicity was hematological in all studies and mucositis in some studies.[28, 34, 68, 69, 84, 114, 172] In one study 2 patients died of septicemia following treatment induced neutropenia.[114] Cross resistance of topotecan and etoposide was found to be small in small cell lung carcinoma cell lines.[81]

In a multicenter trial, we treated relapsed neuroblastoma patients with a combination of topotecan and etoposide. Topotecan was given in three dose levels: (1) 1.0 mg/m²xd 30 min infusion for 5 days, (2) 0.7 mg/m²xd continuous infusion for 7 days, and (3) 1.0 mg/m²xd continuous infusion for 7 days. It was followed by etoposide in a dose 100 mg/m²xd for 3 additional days. Grade 4 toxicity was only hematological. Neutropenic fever occurred after 62/236 (26%) cycles (table 10, first results of the study published in[101]). A response better than SD was seen in 24/56 (43%) of evaluable patients (table 11).

In a pilot trial, a total of 14 relapsed high risk neuroblastoma patients have been treated with N8, i.e., a combination of topotecan (1.0 mg/m²xd for 7 days), cyclophosphamide (100 mg/m²xd for 7 days), and etoposide (100 mg/m²xd). This combination was considerably myelosuppressive. Leukopenia and thrombopenia grade 4 were observed after 85% of cycles. Neutropenic fever occurred after 27/40 evaluable cycles (table 10). No patient died due to chemotherapy related complications. No unexpected toxicity occurred. Few patients complained about mucositis and emesis. Complete or partial response was achieved in 8/14 patients after chemotherapy with topotecan, etoposide, and cyclophosphamide (table 11).

Table 10: Toxicity of topotecan containing chemotherapy in relapsed neuroblastoma patients

	Topotecan 1.0 mg/m² 30 min + VP16		Topotecan 0.7 mg/m² continuous + VP16		Topotecan 1.0 mg/m² continuous + VP16		N8		Chi² p
	n	%	N	%	n	%	n	%	
thrombopenia °3	18/85	21	16/106	15	11/77	14	6/44	14	.000
thrombopenia °4	43/85	51	59/106	56	58/77	75	37/44	85	
leukopenia °3	39/85	46	44/103	43	22/77	29	6/44	14	.000
leukopenia °4	23/85	27	17/103	16	33/77	43	37/44	85	
fever > 38.5%	13/75	17	25/91	27	24/70	34	27/40	67	.000
gen. condition°3 & 4	1/79	1	3/109	3	6/69	9	10/33	30	.000
nausea °3	0/81	0	1/107	1	0/77	0	5/44	11	.000
mucositis °3	1/78	1	1/108	1	1/78	1	1/40	2	.316
skin toxicity °3 & 4	0/79	0	0/106	0	0/77	0	0/40	0	n.d.

Table 11: Best response achieved after different topotecan containing chemotherapy cycles in relapsed neuroblastoma patients.

	Topotecan 1.0 mg/m² 30 min + VP16	Topotecan 0.7 mg/m² continuous + VP16	Topotecan 1.0 mg/m² continuous + VP16	N8
CR/VGPR	2	1	1	3
PR	2	8	9	5
MR	0	0	1	0
NR/SD	5	6	6	2
PROG	3	8	4	4
Response (>SD)	33%	39%	52%	57%
total	12	23	21	14

Therefore, the use of topotecan in the first line treatment of neuroblastoma might improve event free survival rates. The good CNS penetration of topotecan [5, 12, 13, 15, 83, 179] might help to prevent CNS relapses of neuroblastoma which are not uncommon after intensive treatment of stage 4 neuroblastoma. Among 334 patients of the trials NB90-97 who completed induction therapy without event, 45 (13%) had intracranial involvement during relapse of the disease.

13.2.3 Rationale for megatherapy (ASCT)

It has been shown in retrospective analyses[73, 79, 126, 155] and prospective trials[112, 135], that autologous stem cell transplantation (ASCT) is superior in the treatment of advanced neuroblastoma. The NB97 trial demonstrated an advantage for ASCT compared to three months mild maintenance chemotherapy. Intent-to-treat analysis demonstrated a better EFS (45±5% vs. 29±4%, logrank p=0.016) for patients who underwent ASCT (figure 19). As-treated and treated-as-randomized analysis confirmed these results for EFS and for OS. Subgroup analysis showed superiority of ASCT for patients defined either by elevated LDH, by MYCN-amplification, by normal MYCN, or who reached CR/VGPR prior to ASCT.[10]

Therefore, all NB2004 stage 4 patients >1 year at diagnosis and all MYCN amplified neuroblastoma patients regardless of age will undergo ASCT.

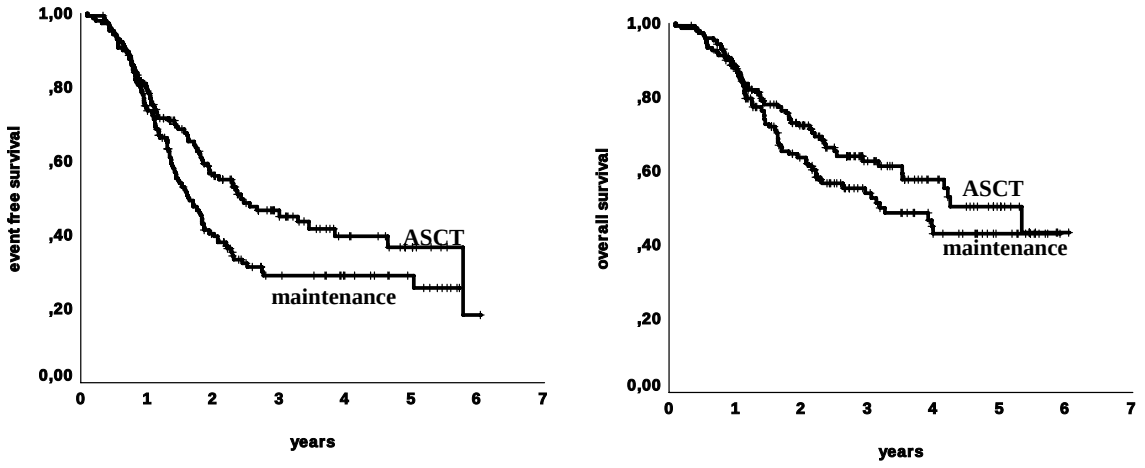


Figure 19: Intent-to-treat analysis of 295 high risk neuroblastoma patients of NB97 randomly assigned to ASCT or maintenance treatment: ASCT patients n=149, 3-y-EFS 45±5%, 3-y-OS 63±5%; maintenance treatment patients n=146, 3-y-EFS 29±4% (logrank p=0.016), 3-y-OS 54±5% (logrank p=0.180)

There are reports of etoposide + melphalan[168], carboplatin + etoposide + melphalan [7, 37, 73], carboplatin + etoposide + melphalan + TBI[112], busulfan + melphalan[167], busulfan + melphalan + cyclophosphamide[63] based conditioning regimens in the ACST of high risk neuroblastoma. In a retrospective analysis, busulfan containing regimens were regarded

more effective than other regimens[64] but the carboplatin + etoposide + melphalan regimen was not included in this analysis. Other reports on busulfan containing regimens demonstrated a considerable number of treatment related deaths (8% - 9,5%[63, 64, 167]) and venous occlusive disease (VOD, up to 75% in infants[167]). Of note, the ongoing European HR-NBL-1 randomized trial compares busulfan + melphalan with carboplatin + etoposide + melphalan.

In 164 ASCT performed in the NB97 trial, we observed 6 deaths related to the ASCT (3.7%, the 95%-confidence-interval [CI] 1.4–7.5%). VOD was observed in 8 patients (4.8%, the 95%-CI 2.1-9.0%), 3/8 VOD-patients had received carboplatin + etoposide + melphalan and 5/8 have had busulfan + melphalan as conditioning regimen confirming the higher potential for VOD induction by the busulfan/melphalan combination. One of these 8 patients died 80 days after transplantation due to toxicity and disease progression, the other VOD´s resolved without residual.

Due to the encouraging survival data and the acceptable toxicity, carboplatin + etoposide + melphalan conditioning regimen will be used in NB2004 for all patients undergoing ASCT.

^{131}I-MIBG-therapy with external beam irradiation boost for a residual active primary is scheduled in MIBG up taking residuals in order to improve efficiency of the ASCT without significant additional toxicity (for indication and details see section 14.10 on page 101).[89, 110, 177]

13.2.4 Rationale for radiotherapy

Neuroblastoma is considered a radiosensitive tumor since patients respond to palliative radiotherapy. Therefore, several high risk treatment protocols include external beam radiation and/or ^{131}I-MIBG therapy.

13.2.4.1 External beam radiation therapy (EBRT)

Stage 4 neuroblastoma is not a localized disease and requires systemic treatment. The value of radiotherapy in modern high dose chemotherapy protocols has not been proven yet. The potential benefits from radiation therapy must be balanced against late effects (e.g., growth delay, scoliosis, and secondary malignant diseases).[3, 130]

A recent report of the CCG-3891 trial could only confirm the superiority of ASCT compared to continuation chemotherapy but found similar local relapse rates among the ASCT patients (local relapse rate 22±12% with 10-20 Gy local radiation plus 10 Gy TBI for ASCT vs. 35±10% without external radiation, p=0.36) and among the continuation therapy patients (52±8% with 10-20 Gy local radiation vs. 50±7%, p=0.55).[56] Analysis of the German neuroblastoma trial NB90 failed to show a benefit from external radiation (unpublished results). Therefore, in NB97 radiation therapy was reserved only for residual tumor tissue with MIBG uptake or clear MRI contrast enhancement. Due to the good results of the NB97 trial, EBRT will be reserved for active residual primary tumors in NB2004 as in NB97.

There are reports about intra-operative radiation therapy (IORT).[55, 103, 178] The technique seems feasible and tolerable. But its value in the treatment concept of high risk neuroblastoma has not been proven since only small numbers of neuroblastoma patients have been treated. Of note, one renal artery stenosis and one mesentery artery occlusion were observed after IORT.[178]

13.2.4.2 131-I-MIBG therapy

^{131}I-MIBG therapy has been used for many years in the therapy of neuroblastoma. Initial studies demonstrated response rates between 20% and 60%.[90] Good pain relief has been documented, too. [91]

The therapeutic effect of ^{131}I-MIBG depends on the radiation dose delivered to the tumor tissue. Neuroblastoma was shown to take up about 0.026% of injected ^{123}I-MIBG dose per gram tissue.[117] In another study, ^{131}I-MIBG uptake of neuroblastoma ranged between 0.04 and 10.0% of the injected dose leading to a calculated tumor dose between 4.4 and 45.4 Gy.[16] Dose escalation in order to deliver a higher dose to the tumor tissue is limited by the toxicity to other tissues (whole body exposure, organ dose).

Unfortunately, there is only a weak correlation between the ^{131}I-MIBG activity [MBq] administered and the resulting whole body or organ exposure [Gy] (Spearman rank correlation r_S=0.59, p<0.0001).[111] Bolster[16] et al reported

- whole body exposures of 0.25 $\pm$ 0.09 mGy/MBq,
- liver dose of 0.58 $\pm$ 0.29 mGy/MBq,
- lung dose of 0.35 $\pm$ 0.12 mGy/MBq
- bladder wall dose of 0.76 $\pm$ 0.32 mGy/MBq (influenced by voiding times, frequent voiding reduced the contact time to the bladder wall)

Protocols vary considerably between centers. In general, the maximum tolerable whole body dose is 2.0 Gy without stem-cell rescue and 4.0 Gy with stem-cell rescue. These doses showed no other short-term organ toxicity.[102] Garaventa et al. administered 2.5 – 3.7 GBq for patients under 15 kg, 3.7 to 4.7 GBq for patients between 15 and 20 kg and 5.5 GBq for patients over 20 kg. Mastrangelo et al. suggested a fixed activity of 7.4 GBq [200 mCi].[46] Doses of 12 mCi/kg were tolerable without stem cell rescue. Doses of 18 mCi/kg resulted in myelosuppression, particularly prolonged thrombocytopenia requiring long term transfusion or stem cell rescue.[110]

In the NB2004 protocol, ^{131}I-MIBG therapy is immediately followed by ASCT. Therefore, potential ^{131}I-MIBG myelotoxicity does not require separate management. A single injection of 12 mCi/kg [0.44 GBq/kg] ^{131}I-MIBG is scheduled. In view of the cumulative toxicity of combined MIBG therapy, ASCT, and EBRT, a higher dose is not recommended. This dose will result in a whole body dose of about 2 Gy.

Dosimetric calculations to determine the individual whole body dose and tumor dose are required in NB2004. For details see page 102.

13.2.5 Rationale for the consolidation treatment

In general, different consolidation regimens for potential minimal residual neuroblastoma exist. In the NB97 trial, monoclonal chimeric anti-GD2-antibody ch14.18 has been given to all high risk patients. In a first analysis comparing ch14.18 treated patients of NB90-97 with patients who had no further treatment and patients who underwent NB90 maintenance therapy, the survival analysis showed no difference in EFS between the groups but the group treated with ch14.18 had a better OS.[150] Since better OS might be influenced by many factors, EFS was not better after ch14.18, and antibody ch14.18 is not available commercially, the NB2004 high risk patients will not receive antibody treatment.

13-cis-Retinoic acid (Isotretionin, Roaccutan®) is effective in neuroblastoma *in vitro*[160, 161, 162] and *in vivo*[2]. *In vitro*, prolonged arrest of cell proliferation was seen after 10 days exposure to 10 µM 13-cis-retinoic acid.[139] The maximum tolerated RA dose in children after ASCT was 160 mg/m²xd which resulted in peak drug levels of 7 µM and trough levels of 4 µM.[87, 173] Accordingly, the clinical effect seems to be dose dependent, since 13-cis-retinoic acid treatment with 100 mg/m²xd in refractory patients[40] or 0.75 mg/kgxd as maintenance therapy in a randomized trial[92] failed to be effective. High dose treatment with 160 mg/m²xd was effective in the randomized CCG-3891 trial.[112] Therefore, the NB2004 high risk patients will receive 13-cis-retinoic acid cycles in a dose of 160 mg/m²xd for days 1-14 followed by a rest days 15-28. According to the CCG3891 trial, a first course of 6 months is given. After a 3 months break, a second 3-months-course is scheduled since the CCG group observed relapses after stopping 13-cis-retinoic acid (P. Reynolds, personal communication). The second 3-months-course should help to control the growth of residual minimal disease after the end of the first retinoic acid course.

For toxicity of retinoic acid see page 111.

13.3 Differences between NB97 and NB2004

Compared to the preceding NB97 trial, the following modifications have been made in the high risk group:

- ASCT for all high risk patients, since NB97 demonstrated an advantage for patients who underwent ASCT. Stage 4 infants without MYCN-amplification have a good prognosis without ASCT and are, therefore, treated according to the NB2004 medium risk group.
- Assessment of a new topotecan containing chemotherapy regimen in a randomized window trial setting for high risk patients >1 year at diagnosis.
- Consolidation with 13-cis-retinoic acid in a dose of 160 mg/m²xd for 14 consecutive days (day 1-14), followed by a 14 days rest (day 15-28) for a total of 9 cycles. After the 6th cycle a prolonged rest of 3 months is scheduled, followed by additional 3 cycles.

13.4 Trial objectives of the high risk group

The NB2004 high risk group aims to improve the best results of the previous trial NB97 be randomized evaluation of additional topotecan based chemotherapy (cycle N8). All patients undergo ASCT followed by retinoic acid biotherapy.

13.4.1 Primary objectives

Primary objective of the trial is the comparative assessment of the EFS of neuroblastoma patients treated in the two different arms. An event is defined as:

- relapse of disease after complete initial response defined according to the INSS[19],
- progression of residual disease after initial incomplete response defined according to the INSS[19],
- any death,
- any secondary malignant disease.

13.4.2 Secondary objectives

- **EFS_L:** locoregional EFS measured from the time of diagnosis up to an locoregional event or last follow-up for patients without locoregional event. A locoregional event is defined as (i) death (related to locoregional disease), (ii) local progression of residual primary tumor (defined on page 160), (iii) locoregional relapse following previous complete remission of the primary tumor as defined on page 160.
- **OS:** Overall survival measured from the time of diagnosis up to death of any reason or last follow-up for surviving patients.
- **Early response** measured after two cycles of chemotherapy (either N5+N6 for the high risk standard arm or 2xN8 for the high risk experimental arm) or after 60 days if the second cycle is not yet finished: Complete response, very good partial response, partial response, mixed response, stable disease, progression, or relapse defined according to the INSS criteria (page 160).[19]
- **Response to induction therapy** measured prior to ASCT or after 280 days if the induction chemotherapy is not yet finished: Complete response, very good partial response, partial response, mixed response, stable disease, progression, or relapse defined according to the INSS criteria (page 160).[19]
- **Chemotherapy toxicity** categorized according to the grading tables in the case report forms of the protocol (page 239). For toxicity not included in the tables of the case report forms, categorization according to the NCI-CTCAE scale (http://ctep.cancer.gov/forms/CTCAEv3.pdf) is required.
    - Grade of toxicity observed during and after chemotherapy cycle 1 (N5 for the high risk standard arm or N8 for the high risk experimental arm),

- Grade of toxicity observed during and after chemotherapy cycle 2 (N6 for the high risk standard arm or N8 for the high risk experimental arm),
- Frequency of chemotherapy cycles with toxicity grade ≥ 3 observed during the last 6 chemotherapy cycles in each patient (3x (N5+N6) for the high risk standard arm and for the high risk experimental arm): 0 – 6 counts per patient are possible,
- Frequency of chemotherapy cycles with toxicity grade 4 observed during the last 6 chemotherapy cycles in each patient (3x (N5+N6) for the high risk standard arm and for the high risk experimental arm): 0 – 6 counts per patient are possible.

- **Surgery:**
  - Extent of the **initial surgery** categorized in: biopsy vs. incomplete resection vs. macroscopic complete resection. Initial surgery is the first tumor operation done in a patient.
  - Extent of the **best surgery** up to time t categorized in: biopsy vs. incomplete resection vs. macroscopic complete resection. Best surgery is the operation performed from diagnosis up to time t which achieves the most extensive tumor resection.
  - Frequency of complications related to surgery considered separately for the items: nephrectomy, bleeding, infection, intestinal obstruction, or other.
- **External beam radiation therapy:**
  - **Acute side effects** of EBRT considered separately according to the radiation therapy documentation form (page 250).
  - **Late effects** of EBRT considered separately according to the long term follow-up forms (page 258).
- **MIBG therapy:** activity [MBq] and whole body dose [Gy] assessed according to the dosimetry protocol (section 13.10.5).
- **Molecular marker:** status of chromosome 1p, status of chromosome 11q, and MYCN categorized according to criteria published by Ambros.[4] Tumor material is collected and stored in the tumor bank for future evaluation of other molecular markers which will be considered having prognostic impact.
- Prospective molecular analysis of defined molecular markers by the neuroblastoma gene chip.

13.4.3 Trial design

This is an randomized, un-blinded, multi-center, window-design clinical trial. The patients are randomly assigned to the high risk standard or experimental arm. They will undergo initial induction treatment according to the randomization result. The standard arm patients will get a total of 6 induction chemotherapy cycles; the high risk experimental arm

will get a total of 8 induction chemotherapy cycles. The event rate is monitored continuously. The final analysis to answer the primary and secondary trial objective will be done 3 years after entry of the last trial patient. For details see section 20.3 on page 134.

13.5 Selection of subjects

13.5.1 Inclusion criteria

Each patient must meet the following criteria:

- Neuroblastoma diagnosed according to the accepted criteria: histological diagnosis from tumor tissue or presence of distinct neuroblastoma cells in the bone marrow and elevated catecholamine metabolites (HVA, VMA) in blood or urine,[19]
- Initial staging by MRI, MIBG-scintigraphy, bone marrow assessment, and tumor markers (VMA and HVA in serum or urine),
- Stage 4: ≥1-21 years regardless of the MYCN-status (stage 4 infants without MYCN-amplification are treated according to the NB2004 MRG (page 53),
- Stage 1-3/4S with MYCN-amplification: 0-21 years,
- Informed consent of guardians and the patient (if appropriate according to age and status of psycho-intellectual development),
- No pregnancy and sufficient prevention of pregnancy in fertile female adolescents.

13.5.2 Exclusion criteria

- Any concomitant non-protocol anticancer treatment.

13.6 High Risk Treatment

13.6.1 Overview

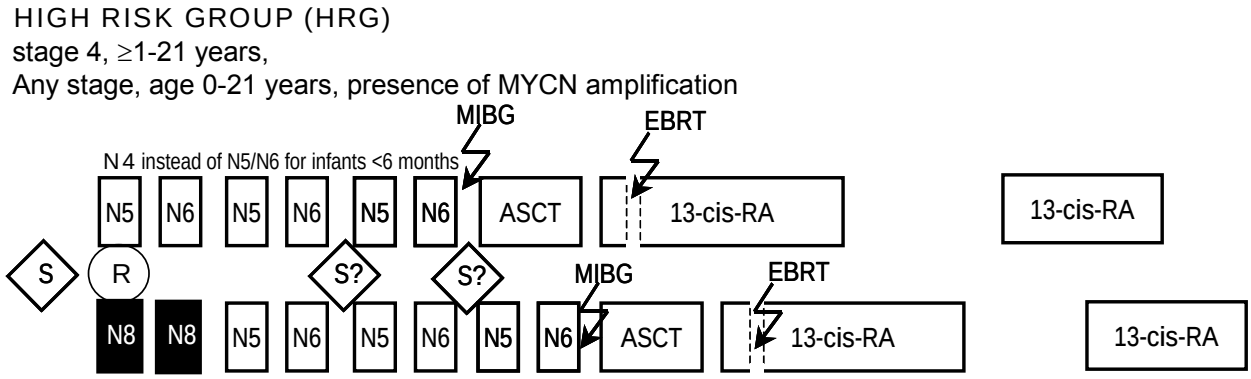


Figure 20: Overview over NB2004 high risk group treatment (S=surgery, R=randomization, N4/5/6/8=chemotherapy cycles, MIBG=MIBG treatment, EBRT=external beam radiation therapy, 13-cis-RA=13-cis-retinoic acid)

13.6.2 Induction chemotherapy

13.6.2.1 Randomization

The trial will compare the standard induction chemotherapy with a new topotecan containing induction therapy. All high risk neuroblastoma patients **older than 1 year** will undergo randomization. **Infants** with MYCN-amplification are classified as high risk patients, too, but will **not** undergo randomization and are treated according to the high risk standard arm. They will not receive N8 cycles.

As soon as the initial staging indicates high risk neuroblastoma, the randomization must be performed. After informed consent of the patients' guardians (page 211) is obtained, call the randomization hot line which is on call every day between 8:00 am and 06:00 pm including all bank holidays. Please fax the randomization form to the trial office the next regular working day. The form is found on page 220. It will be returned with the written randomization result for the patients´ files. If guardians' refuse randomization the child will be treated according to the standard arm.

Initial staging might classify some patients as MRG but MYCN-amplification will be available later after MRG chemotherapy had already started. These patients can not undergo randomization and must be treated according to the high risk standard arm (without N8).

Randomization Hotlines

+49 (0) 221 - 478 6853

+ 49 (0) 175 – 38 29 512

FAX +49 (0) 221 – 478 6851

7 days a week between 08:00 am and 06:00 pm

13.6.2.2 Induction chemotherapy

13.6.2.2.1 High risk experimental arm

Induction chemotherapy of the experimental arm starts with 2 cycles N8 in a window design. Details of the N8 cycles are found on page 91 and 238.

After these two cycles, the complete standard arm treatment (3 cycles N5 and 3 cycles N6) is scheduled. **Infants <1 year** with MYCN-amplification are classified as high risk patients, too. But they will **not undergo randomization** and are always treated according to the high risk standard arm (figure 20).

Details of each chemotherapy cycle are found on pages 87-92 and 234-238. The cycles should be given every 21 days (i.e., 21 days interval between the 1st day of each cycle). Prior to each cycle the following criteria must be fulfilled:

- leukocytes >2000/µl, lymphocytes >1000/µl,
- platelets >50,000/µl,
- no sign of infection

If these criteria are not met, the start of a cycle must be delayed. If the delay exceeds 7 days or infection grade ≥3 occurred, the doses of the next cycle should be modified. Dose reduction rules are outlined for each cycle on pages 87-92 and 234-238.

The toxicity of each chemotherapy cycle must be documented on the chemotherapy forms which are found on page 239. If toxicity other than listed in the report form occurs, please use the CTCAE-toxicity grading system issued 12 December 2003 by NCI. It can be downloaded from http://ctep.cancer.gov/forms/CTCAEv3.pdf. If toxicity appears unexpected or severe, contact the trial office and consider **SAE report** (for details see pages 117-120, the report form is found on page 253).

13.6.2.2.2 High risk standard arm

Infants <6 months with MYCN-amplification are not randomized and are treated according to the high risk standard arm. They will start with N4 cycles instead of N5/N6.

For details see pages 87 and 234. As soon as they are 6 months old, the remaining cycles are given as N5 and N6 for a total of 6 chemotherapy cycles followed by ASCT and retinoic acid consolidation.

All patients ≥6 months at diagnosis receive 6 chemotherapy cycles (alternating N5 and N6). Details to the chemotherapy cycles are found on page 89, 90, 235 and 236. This induction chemotherapy will be followed by ASCT and retinoic acid consolidation.

A 21 day interval between the first day of two consecutive cycles is approached. Shorter intervals are allowed. Longer intervals are sometimes necessary to overcome bone marrow depression. Prior to each cycle the following criteria must be fulfilled:

- leukocytes >2000/µl, lymphocytes >1000/µl,
- platelets >50,000/µl,
- no sign of infection

If these criteria are not met, the start of a cycle must be delayed. If the delay exceeds 7 days or infection grade ≥3 occurred, the doses of the next cycle should be modified. Dose reduction rules are outlined for each cycle at pages 88-89.

The toxicity of each chemotherapy cycle must be documented on the toxicity form which is found on page 239. If toxicity other than listed in the report form occurs, please use the CTCAE-toxicity grading system issued 12 December 2003 by NCI. It can be downloaded from http://ctep.cancer.gov/forms/CTCAEv3.pdf. If toxicity appears unexpected or severe, contact the trial office and consider **SAE report** (for details see pages 117-120, the report form is found on page 253).

13.6.3 Myeloablative high-dose-chemotherapy (ASCT)

13.6.3.1 Stem cell mobilization, harvesting, and CD34-selection

Stage 4 neuroblastoma does involve bone marrow in 87% and bone in 66% of patients. Stem cell mobilization is only possible after response of initial bone marrow involvement has been demonstrated. Therefore, bone marrow assessment must be repeated at least prior to the 3rd and 5th chemotherapy cycle as outlined on page 25. As soon as the bone marrow is free of neuroblastoma cells (i.e. less than 0.1% neuroblastoma cells by immunocytology, shipping form on page 232), stem cell apheresis should be scheduled after the next chemotherapy cycle.

For **stem cell mobilization**, G-CSF is started 2 days after the end of the preceding chemotherapy cycle. It is given in a dose of 10 µg/kgxd divided in two daily doses. Subcutaneous injection is strongly recommended. Intravenous infusion over 4 hrs is acceptable but might be less effective.

For **stem cell harvesting**, peripheral apheresis by a continuous flow separator according to the policy of the local pediatric oncology center should be followed.[124, 166] A vial of the

apheresis product should be sent unfrozen to the bone marrow lab in Cologne for immunocytology within 24 hours. Please use the bone marrow shipping form on page 232.

Processing of the apheresis product is necessary since minimal bone marrow involvement is not excluded by normal bone marrow cytology and immunocytology. Data on residual minimal tumor cell contamination are conflicting which is mainly due to great differences in the sensitivity of methods used for investigation of the apheresis product including overestimation due to well known unspecific bindings of secondary antibodies and over-amplification of PCR products.[39, 58, 60] In general, CD34-selection can sufficiently reduce the tumor cell content.[33, 58] For all NB2004 high risk patients, a **CD34-positive selection** of the apheresis product by magnetic-activated cell sorting (MACS) is required.[59] Immunocytology of the CD34-positive fraction after MACS is not recommended since the presence of antibodies used during the selection process interferes with immunocytology.

13.6.3.2 Conditioning chemotherapy regimen

After complete staging (i.e., clinical status, tumor marker, MRI, MIBG-scintigraphy, and bone marrow from 4 sites), ASCT is scheduled for all high risk patients.

The conditioning regimen is the melphalan, etoposide, and carboplatin regimen similar to NB97. An outline of the chemotherapy is found on page 92. Prior to ASCT, **audiometry**, **ECG/echocardiography**, and **kidney function** assessment are required. In case of grade ≥3 toxicity, alternative condition regimen or maintenance treatment instead of ASCT must be considered. Please, contact the trial office to discuss the options.

Special facilities for patients' isolation and experiences in autologous or allogenous bone marrow transplant are a prerequisite for every hospital performing ASCT. It is strongly recommended to transplant the patients in centers specialized in ASCT.

The toxicity of ASCT must be documented on the ASCT forms which are found on pages 240 and 241. If toxicity other than listed in the report form occurs, please use the CTCAE-toxicity grading system issued 12 December 2003 by NCI. It can be downloaded from http://ctep.cancer.gov/forms/CTCAEv3.pdf. If toxicity appears unexpected or severe, contact the trial office and consider **SAE report** (for details see pages 117-120, the report form is found on page 253).

13.6.3.3 Stem cell re-infusion

In general, all protocols and policies of the local transplantation unit must be followed. Stem cells are thawed immediately prior to re-infusion. Pre-medication of the patient with Atropine, Morphine, and Paracetamol is strongly recommended to prevent pain and abnormal circulatory reaction to infusion of the cold transplant.

After stem cell reinfusion, about 10 – 14 days of severe myelosuppression are expected. Transfusion of irradiated blood products, parenteral nutrition, PCP prophylaxis, CMV

prophylaxis, Herpes prophylaxis, mucositis management, and infection management are to be done according to the local transplantation protocols.

13.6.4 Radiotherapy

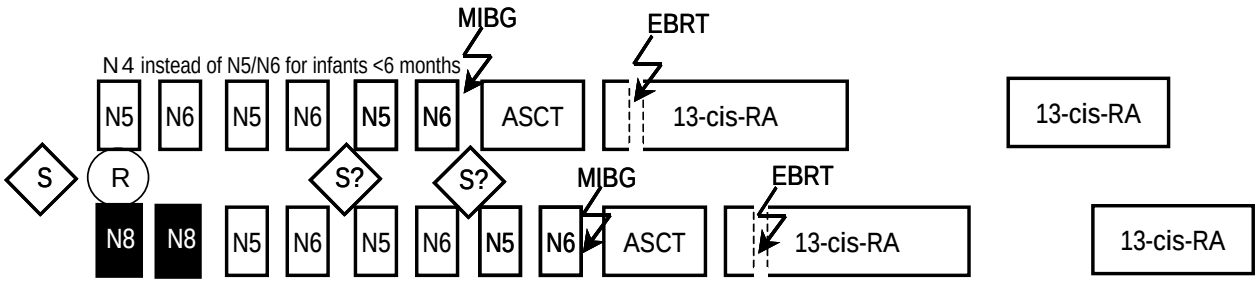


Figure 21: Timing of radiation therapy (S=surgery, R=randomization, N5/6/8=chemotherapy cycles, MIBG=MIBG treatment, EBRT=external beam radiation therapy, 13-cis-RA=13-cis-retinoic acid)

Radiation therapy is reserved for patients with active residual primary tumor after 6 cycles of induction chemotherapy, i.e., prior to ASCT. Active residual tumor tissue is defined as

- residual MIBG-uptake (tumors initially MIBG positive),
- or residual Octreotide-uptake (tumors initially MIBG negative but Octreotide positive),
- or unequivocal MRI-contrast enhancement (only tumors which have been completely negative in initial scintigraphy).

Residual non-progressing non-active mass seen only in MRI, CT, or ultrasound does not require radiation therapy.

In general, a combined radiation therapy of ^{131}I-MIBG-therapy and external beam radiation therapy (EBRT) is scheduled. Patients with MIBG negative neuroblastoma at initial diagnosis will only receive EBRT.

^{131}I-MIBG-therapy should be done prior to ASCT. As soon as the patient is able to leave the nuclear medicine department, ASCT has to start (figure 21).

EBRT should be done as soon as the patient has stabilized after ASCT. A combination with retinoic acid is not recommended in order to avoid possible negative interactions between radiation and retinoic acid. Since retinoic acid treatment should start 30 days after ASCT (for criteria see page 93) retinoic **acid must be interrupted during radiation therapy**.

For details of the ^{131}I-MIBG-therapy see page 101. Please complete a MIBG therapy documentation form (page 249) for each MIBG cycle separately.

For details of the EBRT see page 98. Please report each radiation therapy to the trial office using the form on page 250.

13.6.5 Consolidation treatment with retinoic acid

13-cis-retinoic acid (isotretionine) treatment begins day 30 post ASCT according to the criteria found on page 93.

In order to avoid possible negative interactions, the patients should not receive retinoic acid during EBRT. Since EBRT is unlikely to start within 30 days after ASCT, give the first 14-days-RA cycle(s), **discontinue RA treatment during EBRT** and restart it about 1 week after EBRT end.

13-cis-retinoic acid is available in Germany as **Roaccutan® capsules**. The capsules contain oil. For younger children, the capsules can be opened or punctured and the oil can be taken in milk or ice cream. 13-cis-retinoic acid is given in a dose of 160 mg/m²xd in 2-(3) divided doses for subsequent 14 days followed by 14 day rest. Then the next cycle is started. After 6 cycles, the patient has a 3 months rest without any treatment. Then, 13-cis-retinoic acid is restarted for additional 3 cycles (figure 22).

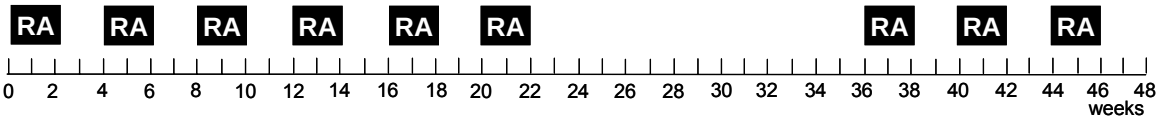


Figure 22: Time course of RA treatment

Since increased light sensitivity has been reported, avoid sunlight exposure during 13-cis-retinoic acid treatment.

During pregnancy, 13-cis-retinoic acid can cause **severe birth malformations** (hydrocephalus, microcephalus, ear abnormalities, cardiovascular abnormalities, facial dysmorphia, endocrine abnormalities, cerebellar malformations, and other). Therefore, contraception starting 1 month prior to 13-cis-retinoic acid treatment is mandatory in all female adolescents who might become pregnant.

For toxicity details and drug information see page 111.

The toxicity of each RA cycle must be documented on the forms found on pages 256 and 257. If toxicity other than listed in the report form occurs, please use the CTCAE-toxicity grading system issued 12 December 2003 by NCI. It can be downloaded from http://ctep.cancer.gov/forms/CTCAEv3.pdf. If toxicity appears unexpected or severe, contact the trial office and consider **SAE report** (for details see pages 117-120, the report form is found on page 253).

13.6.6 Surgery in the HRG

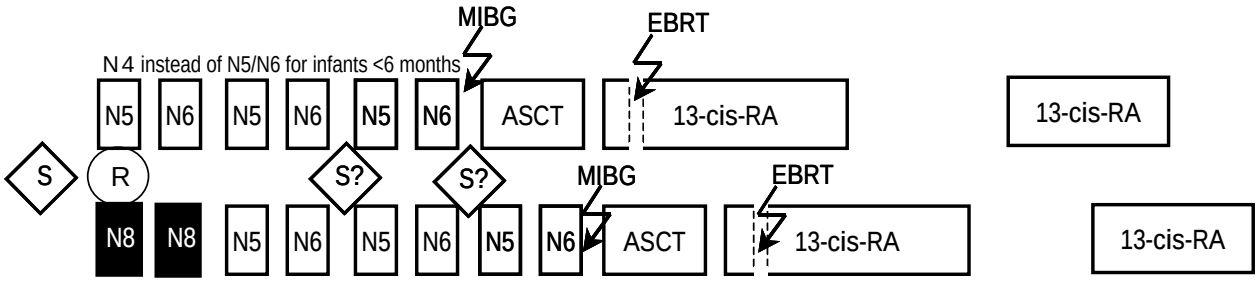


Figure 23: Timing of surgery during the high risk group treatment (S=surgery, R=randomization, N5/6/8=chemotherapy cycles, 13-cis-RA=13-cis-retinoic acid)

13.6.6.1 Initial surgery

Initial surgery aims to collect tumor tissue for histological and molecular assessment. Incomplete resection or open biopsy of the primary or a metastatic lesion is appropriate. Complete resection of the primary tumor is not necessary. It might be done in selected patients where the risk of surgical complications appears very low. Extended operations in order to remove the primary tumor should be avoided. Nephrectomy, injury of large vessels, or other complications of initial surgery are unacceptable.

For tissue collection and shipping guidelines see pages 161 and 229.

In very few cases, threatening symptoms due to compression of airways, nerves, or large vessels may require immediate tumor resection.

In symptomatic intraspinal involvement, immediate start of chemotherapy is preferred since chemotherapy has less late effects than surgery in these patients.

The initial operation is documented at the first documentation form of the German Children's Cancer Registry, Mainz, Germany. It is found on page 216.

13.6.6.2 Secondary surgery

If the staging during induction chemotherapy reveals a complete or very good partial response of the primary and locoregional lymph nodes, no further tumor resection is required.

After **chemotherapy**, resection can be done with a lower risk of tumor rupture. Therefore, resection of the primary should be attempted after the 4th or 6th chemotherapy cycle.

After **radiotherapy**, resection can be more difficult due to radiation induced fibrosis in the area of the tumor. Therefore, resection should be attempted prior to radiation therapy. In addition, the surgically achieved reduction of tumor volume may result in a smaller radiation field or completely avoid irradiation.

In localized tumors with MYCN-amplification, there was a tendency towards better event free survival after complete resection (5-y-EFS 46±9% after complete resection vs. 20±18% after incomplete resection and 5-y-EFS 13±12% after biopsy, logrank p=0.08).[174] Since the difference is small, the risk of complete resection must be balanced against the possible small benefit.

In intensively treated stage 4 disease, no benefit of complete resection compared to incomplete tumor removal was demonstrated (5-y-EFS 32±4%, 28±7%, and 37±11% for complete resection, incomplete resection, and biopsy only, respectively).[174] Therefore, complete resection should only be performed, when no other organs are injured. Tumor nephrectomy or mutilation of other organs should be avoided.

Even in stage 4 disease with MYCN-amplification, prognosis was equal after complete resection (5-y-EFS 20±6%) and incomplete resection (5-y-EFS 18±8%). Patients with biopsy only had a worse prognosis (5-y-EFS 10±9%).[174]

Secondary and further surgery must be reported to the trial office using the report form on page 248.

13.7 Patient drop-out

The patient's guardians and the patient (if appropriate to her/his psycho-intellectual development) can refuse further trial treatment by individual decision at any time without giving any reasons and without any negative consequences for the further treatment.

Investigational treatment can be stopped by decision of the local pediatric oncologist in case of any individual medical reason.

All patients not under trial treatment anymore and receiving any other treatment will still be followed until death, lost to follow-up, or until they withdraw their consent for data collection.

13.8 Premature termination of trial

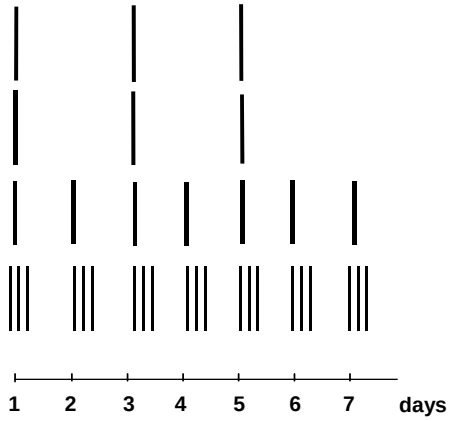
The trial can be closed prematurely by the principal investigator when the toxicity or the event rate is unacceptably high. Stopping rules follow the criteria outlined on page 140.

14 TREATMENT ELEMENTS

14.1 N4 cycle

14.1.1 Criteria for the start of N4

- Progression of observation patients during follow up or presence of threatening symptoms in observation patients at initial diagnosis
- Infants <6 months classified as medium or high risk patient
- Blood count: WBC >2,000/µl, granulocytes > 500/µl, platelets >50,000/µl



Doxorubicine	**15 mg/m²xd**	**d 1, 3, and 5**	**30 min**
Vincristine	**0.75 mg/m²xd**	**d 1, 3, and 5**	**push**
Cyclophosphamide	**300 mg/m²xd**	**d 1 to 7**	**30 min**
MESNA	**3 x 60 mg/m²xd**	**d 1 to 7**	**push**
	0, 4, and 8 hrs after cyclophosphamide		

doses for children ≥1 year, for infants see text

14.1.2 Doses in infants and children

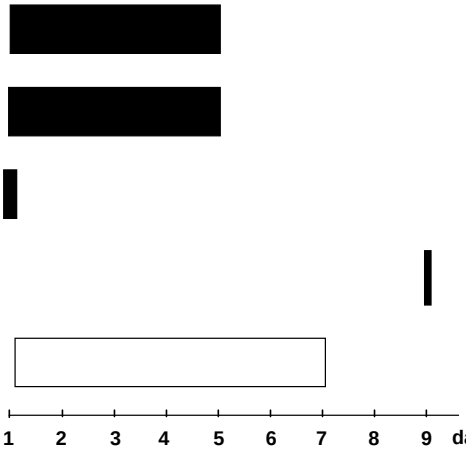
(for details see infusion plans on page 234)

	infants ≤1 year and children <10 kg	**children ≥1 year**	
doxorubicine	**0.5 mg/kgxd**	**15 mg/m²xd**	**day 1,3 and 5 infusion 30 min**
vincristine	**0.025 mg/kgxd**	**0.75 mg/m²xd maximum 2 mg**	**day 1, 3, and 5 iv. push**
cyclophosphamide	**10 mg/kgxd**	**300 mg/m²xd**	**day 1-7 infusion 30 min**
MESNA[66]	**3x2 mg/kg**	**3x60 mg/m²**	**day 1-7 iv. push 0, 4, 8 hrs after CYC**
hydration	**50 ml/kgxd plus orally ad lib.**	**2000 ml/m²xd**	**day 1-7**

14.2 N5 cycle

14.2.1 Criteria for the start of N5

- WBC >2,000/µl, lymphocytes >1,000/µl, platelets >50,000/µl (except patients with extensive bone marrow involvement)
- Ototoxicity grade ≤2 (i.e., loss of ≤30 dB at 2 kHz, **audiometry required**)
- Creatinine ≤150% of upper limit of normal; Creatinine clearance ≥70ml/minx1.73m²
- no sign of infection
- age >6 months



Cisplatin	**40 mg/m²xd**	**d 1 to 4**	**96 hrs**
Etoposide	**100 mg/m²xd**	**d 1 to 4**	**96 hrs**
Vindesine	**3 mg/m²xd (maximum 6 mg)**	**d 1**	**1 hr**
G-CSF	**5 µg/kgxd s.c.**	**≥d 9 until WBC >10/nl**	
	10 µg/kgxd for stem cell mobilization		
Hydration	**3000 ml/m²xd**	**day 1 to 6**	
	doses for children ≥1 year, for infants see text		

14.2.2 Doses in infants and children

(for details see infusion plans on page 235)

	infants ≤1 year and children <10 kg	**children >1 year**	
Cisplatinum	**1.3 mg/kgxd**	**40 mg/m²xd**	**day 1-4 continuous infusion 96 hrs**
Etoposide	**4.2 mg/kgxd**	**100 mg/m²xd**	**day 1-4 continuous infusion 96 hrs**
Vindesine	**0.1 mg/kgxd**	**3 mg/m²xd maximum 6 mg**	**day 1 infusion 1 hr**
Hydration containing Mg, Ca, and K	**3000 ml/m²xd**	**3000 ml/m²xd**	**day 1-6**

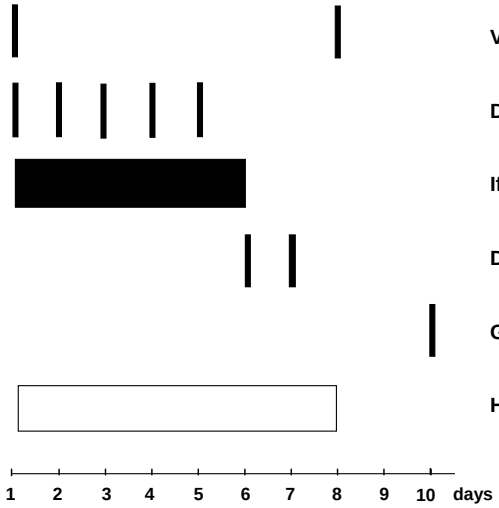
14.2.3 Dose reduction

- If **delayed bone marrow restitution** leads to an interval of ≥28 days to the 1st day of subsequent cycle OR infection grade 4 ➔ reduction of etoposide to 3.2 mg/kgxd in infants and 80 mg/m²xd in children >1 year in the next N5 cycle is recommended. Please note, that infant etoposide doses are derived from plasma level and are higher than in children ≥1year.
- **Ototoxicity** >grade 2 ➔ Substitution of cisplatin by carboplatin 100 mg/m²xd 96 hrs continuous infusion.

14.3 N6 cycle

14.3.1 Criteria for the start of N6

- WBC > 2,000/µl, lymphocytes >1,000/µl, platelets >50,000/µl (except patients with extensive bone marrow involvement)
- Creatinine ≤150% of upper limit of normal, Creatinine clearance ≥70ml/minx1.73m²
- no sign of infection
- no evidence of cardiomyopathy **(ECG and echocardiography required)**



Vincristine	**1.5 mg/m²xd (maximum 2mg)**	**d 1 and 8**	**1 hr**
Dacarbacine	**200 mg/m²xd**	**d 1 to 5**	**1 hr**
Ifosfamide	**1500 mg/m²xd** discontinue during dacarbacine infusion	**d 1 to 5**	**120 hrs**
Doxorubicine	**30 mg/m²xd**	**d 6 and 7**	**4 hrs**
G-CSF	**5 µg/kgxd s.c.** 10 µg/kgxd for stem cell mobilization	**≥d 10 until WBC >10/nl**	
Hydration	**3000 ml/m²xd** with MESNA 900 mg/m²xd	**day 1 to 7**	

doses for children ≥1 year, for infants see text

14.3.2 Doses in infants and children

(for details see infusion plans on page 236)

	infants ≤1 year and children <10 kg	**children >1 year**	
Vincristine	**0.05 mg/kgxd**	**1,5 mg/m²xd maximum 2 mg**	**day 1 and 8 infusion 1 hr**
Dacarbacin	**6.7 mg/kgxd**	**200 mg/m²xd**	**days 1-5 infusion 1 hr**
Ifosfamide	**50 mg/kgxd**	**1500 mg/m²xd**	**days 1-5 continuous infusion 120 hrs**
Doxorubicine	**1 mg/kgxd**	**30 mg/m²xd**	**day 6 and 7 infusion 4 hrs**
MESNA[66]	**30 mg/kgxd**	**900 mg/m²xd**	**days 1-7 continuous infusion 120 hrs**

14.3.3 Dose reduction

If **delayed bone marrow** restitution leads to an interval of ≥28 days to the 1st day of subsequent cycle OR **infection grade 4** occurred

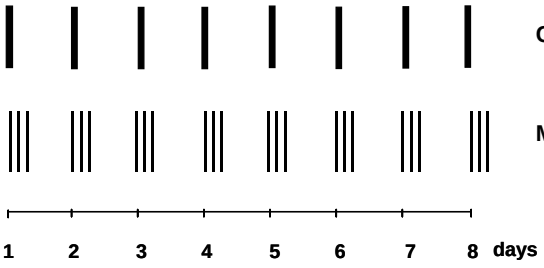
➔ 1st step: reduction of ifosfamide to 1000 mg/m²xd infusion;

➔ 2nd step: omit DTIC in the next N6 cycle and contact trial office

14.4 N7 Cycle

14.4.1 Criteria for the start of N7

- WBC > 2,000/µl, lymphocytes >1,000/µl, platelets >50,000/µl
- no serious infection



Cyclophosphamide	**150 mg/m²xd**	**d 1 to 8**
MESNA	**3 x 30 mg/m²xd** 0, 4, and 8 hrs after cyclophosphamide	**d 1 to 8**

14.4.2 Doses in infants and children

	infants ≤1 year and children <10 kg	children >1 year	
Cyclophosphamide	**5 mg/kgxd**	**150 mg/m²xd**	**days 1-8 orally (or 1hr infusion)**
MESNA[66]	**3x1 mg/kgxd**	**3 x 30 mg/m²**	**days 1-8 orally 0, 4, 8 hours after CYC**

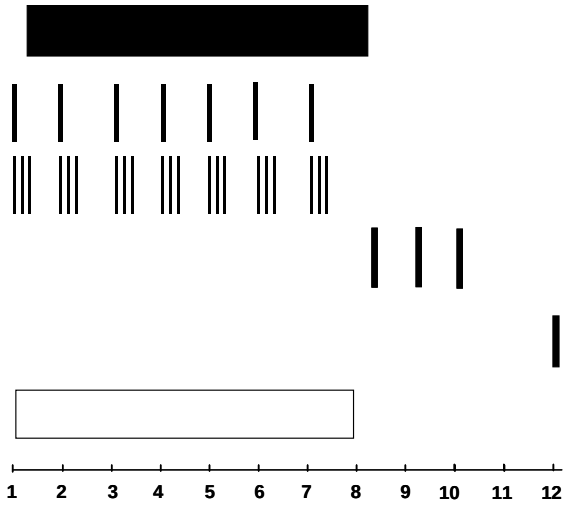
14.4.3 Dose reduction

not applicable

14.5 N8 Cycle

14.5.1 Criteria for the start of N8

- only patients >1 year in the high risk experimental arm
- WBC >2,000/µl, lymphocytes >1,000/µl, platelets >50,000/µl, (except patients with extensive bone marrow involvement)
- Creatinine clearance ≥70ml/minx1.73m²
- hepatic toxicity grade ≤2
- no sign of infection



Topotecan	**1.0 mg/m²xd d 1-7 168 hrs** starts 6 hrs after CYC day 1
Cyclophosphamide	**100 mg/m²xd d 1-7 1 hr** starts 6 hrs prior to Topotecan day 1
MESNA	**3 x 20 mg/m² d 1-7 push** 0, 4, and 8 hrs after cyclophosphamide
Etoposide	**100 mg/m²xd, d 8-10 1hr**
G-CSF	**5 µg/kgxd s.c. ≥d 12 until WBC >10/nl**
Hydration	**2000 ml/m²xd d 1-7**

14.5.2 Doses in infants and children

(for details see infusion plans on page 238)

	infants ≤1 year	**children >1 year for children <10 kg use dose per kg body weight (1m²~30kg)**	
Topotecan	**not applicable**	**1.0 mg/m²xd**	**days 1-7 continuous infusion 168 hrs starts 6 hrs after cyclophosphamide**
Cyclophosphamide	**not applicable**	**100 mg/m²xd**	**days 1-7 infusion 1 hr, starts 6 hrs prior to topotecan**
Etoposide	**not applicable**	**100 mg/m²xd**	**infusion 1 hr**
MESNA[66]	**not applicable**	**3 x 20 mg/m²**	**days 1-7 iv.-push at 0,4, and 8 hrs after CYC**

14.5.3 Dose reduction

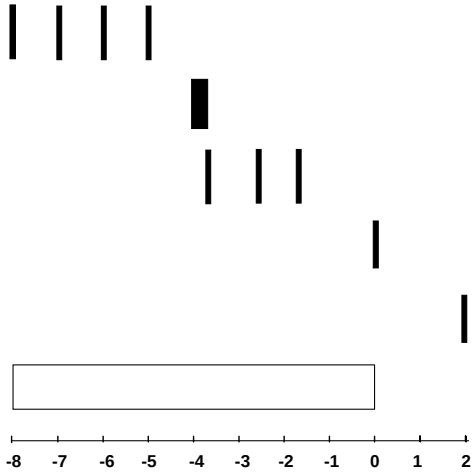
If **delayed bone marrow restitution** leads to an interval of ≥28 days to the 1st day of the subsequent cycle OR infection grade 4 occurred

➔ Reduction of topotecan to 0.7 mg/m²xd in the second cycle

14.6 ASCT = Megatherapy

14.6.1 Criteria for start of megatherapy (ASCT)

- WBC >2,000/µl, lymphocytes >1,000/µl, platelets >50,000/µl
- Creatinine ≤150% of upper limit of normal, Creatinine clearance ≥70ml/minx1.73m²
- Ototoxicity grade ≤2 (i.e., loss of ≤30 dB at 2 kHz, **audiometry required**), if grade ≥3 ototoxicity is present, contact trial office.
- Hepatic toxicity grade ≤2
- Cardiomyopathy grade ≤1 (**ECG and echocardiography required**)
- no sign of infection



Melphalan	**45 mg/m²xd**	**d -8 to -5**	**30 min**
Etoposide	**40 mg/kgxd**	**d -4**	**4 hrs**
Carboplatin	**500 mg/m²xd**	**d -4 to -2**	**1 hr**
CD34+ stem cells	**≥2 x 10^6/kg**	**d 0**	
G-CSF	**10 µg/kgxd s.c.**	**≥d 2 until >10/nl WBC**	
Hydration	**3000 ml/m²xd**	**day -8 to -1**	

doses for children ≥1 year, for infants see text

For any residual MIBG uptake: MIBG therapy prior to ASCT
For residual MIBG uptake by primary: additional external radiation 36-40 Gy after megatherapy

14.6.2 Doses in infants and children

(for details see infusion plans on page 240)

	infants ≤1 year and <10 kg with MYCN amplification	**children >1 year**	
melphalan	**1.5 mg/kgxd**	**45 mg/m²xd**	**days –8 to –5 infusion 30 min**
etoposide	**40 mg/kgxd**	**40 mg/kgxd**	**day –4 infusion 4 hrs**
carboplatin	**16.6 mg/kg**	**500 mg/m²xd**	**day –4 to –2 infusion 1 hr**
stem cells	**≥2 x 10^6 CD34 cells/kg**	**≥2 x 10^6 CD34 cells/kg**	**day 0**

ASCT must be documented using to the EBMT and Pediatric Stem Cell Registry (PRST) form found on page 242. Details are found at http://www.uni-essen.de/prst. The PRST data will available to the NB2004 trial. Therefore, extra documentation for NB2004 is not required unless PRST documentation is not completed.

14.7 Retinoic acid

14.7.1 Criteria for start of retinoic acid

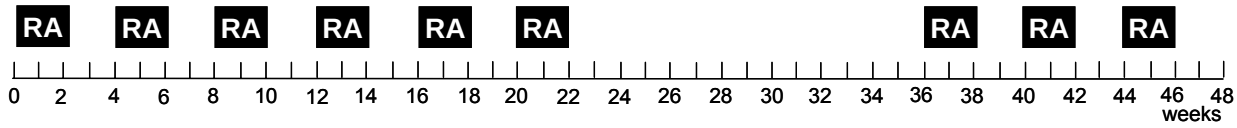
- Retinoic acid (RA) starts 30 days after ASCT day 0.
- To avoid possible negative interactions, RA should not be given during EBRT. Since EBRT is unlikely to start within 30 days after ASCT in patients undergoing EBRT, give the first 14-days-RA cycle(s), discontinue RA treatment during EBRT and restart it about 1 week after EBRT end.
- WBC >1.000/µl; Hepatic toxicity grade ≤2; normal serum calcium.
- no serious infection, no residual mucositis or dermatitis after ASCT.

14.7.2 Monitoring during retinoic acid

blood count, electrolytes (particularly calcium), creatinine, liver function tests, and triglycerides at day 1, 8, and 15 of each cycle.

14.7.3 Dose

160 mg/m²xd in 2-(3) divided doses for subsequent 14 days followed by 14 day rest for a total of 6 cycles, then 3 months rest followed by 3 additional cycles:



13-cis-retinoic acid is available in Germany as **Roaccutan® capsules**. The capsule contains oil. It can be opened or punctured and the oil can be taken in milk or ice cream.

Dose modification

If **skin toxicity** is not tolerable ➔ local treatment with vitamin E crème. If this fails ➔ local corticoid containing crèmes or ➔ oral vitamin E (not recommended due to possible interaction with RA antitumor effect). If the side effects of RA are not tolerable ➔ stop the cycle earlier than day 14 (reduction of daily dose is not recommended).[40, 92]

Hypercalcemia (>3.0 mmol/l) ➔ stop the ongoing cycle. The next RA cycle can be started according to the schedule if the serum calcium is back to normal. If hypercalcemia develops again, stop the cycle and contact the trial office.

14.7.4 Warnings

Since **increased light sensitivity** has been reported, avoid sunlight exposure during RA treatment. Given during pregnancy, RA can cause **severe birth malformations.** Therefore, contraception starting 1 month prior to RA treatment is mandatory in all female adolescents who might become pregnant.

14.8 Surgery

Surgery should be performed by pediatric surgeons experienced in neuroblastoma. Therefore, patient's transfer to specialized hospital is strongly recommended.

Prior to any operation, resectability of the tumor must be estimated by ultrasound, CT, or MRI. All results of initial staging and – for chemotherapy patients - follow up assessment must be available to the surgeon. A decision about time and risk of tumor resection should be based on localization of the primary tumor, its relation to surrounding organs, midline crossing, and potentially involved lymph nodes.

14.8.1 Initial surgery

Initially, only a tumor biopsy for histology and molecular analysis is required. For details of tissue collection and shipping see section 29.3 (starting on page 161). Complete resection of the primary tumor may be attempted in selected patients where the risk of surgical complications appears very low. This applies in particular to patients with localized disease where complete resection of the primary may result in stage 1.

In localized tumors and in patients with stage 4, any extended operation in order to remove the primary tumor should be avoided. Nephrectomy, injury of large vessels, or other complications of initial surgery are unacceptable since most of the localized tumors have a good prognosis even if residual tumor is present. Since metastatic disease (stage 4 and 4S) is not cured by radical surgery, operation appears to have a limited role.[174]

In very few cases, threatening symptoms due to compression of airways, nerves, large vessels, or transverse myelopathy may require immediate tumor resection.

In asymptomatic **intraspinal involvement**, resection of the intraspinal tumor tissue is recommended if the patient is classified as observation patient (see page 115). In symptomatic intraspinal involvement and in all medium/high risk patients, immediate start of chemotherapy is preferred since chemotherapy has less late effects than surgery in these patients.

The initial operation is documented at the first documentation form of the German Children's Cancer Registry, Mainz, Germany (page 216).

14.8.2 Secondary surgery

14.8.2.1 Second look surgery in observation patients

In observation patients with non-progressing residual tumors, routine resection is not recommended but might be done if the tumor tissue is not regressing any further at the end of the 2nd year of live (patients <1 years at diagnosis) of after 1 year of observation (patients ≥1 year at diagnosis) if the risk of surgery appears low. If a considerable risk is expected, further observation is strongly recommended.

Secondary surgery should be discussed with the trial office. MRI films are required for discussion. Please send all MRI films to the trial office using the shipping form on page

220. The complete set will be returned to you as soon as a decision has been made. Ultrasound films are not standardized and, therefore, not appropriate for reference radiology.

14.8.2.2 Second look surgery in chemotherapy patients

After **chemotherapy**, resection can be done with a lower risk of tumor rupture. Therefore, resection of the primary should be attempted after the first chemotherapy cycles. The risk of operation must be balanced against the benefits of radical resection. Radical microscopic complete resection is not required in any patient. Microscopic or even macroscopic residual tumor tissue is accepted. Macroscopic complete resection was correlated with a better outcome only in localized neuroblastoma ≥1 year, but not in localized neuroblastoma of infants <1 year or in stage 4 disease.[174]

Since tumor spillage is unlikely after chemotherapy, incision of the tumor is permissible in order to reduce the risk during resection.

After **radiotherapy**, resection can be more difficult due to radiation induced fibrosis in the area of the tumor. Therefore, resection should be attempted prior to radiation therapy.

14.8.3 Technique

14.8.3.1 Access for tumor resection

- retroperitoneal neuroblastoma: transversal laparatomy,
- pelvic neuroblastoma: median lower abdominal cut or transversal suprasymphysic access,
- pelvic retrorectal neuroblastoma: perineal sagittal access,
- neuroblastoma in the low mediastinum and the retroperitoneum: thoracoabdominal access,
- thoracic neuroblastoma: lateral thoracotomy, bilateral thoracotomy for large tumors,
- cervical neuroblastoma: transversal lateral access,
- large neuroblastoma in the upper chest: thoraco-cervical access,
- intraspinal neuroblastoma: dorsal laminotomy or laminectomy.

14.8.3.2 Lymph node evaluation and collection

It is important to examine the regional lymph nodes of the following regions. If a node appears abnormal, is should be removed for histology.

- cervical primary: jugular chain and supraclavicular area
- thoracic primary: mediastinal lymph nodes above and below the tumor

- abdominal primary: lymph nodes located medially, superior, and inferior to the tumor. Additionally, lymph nodes from the contralateral side must be examined/collected.

14.8.3.3 Special considerations

14.8.3.3.1 Thoracic neuroblastoma

Thoracic neuroblastoma usually is located paravertebrally. Often, it is large and can involve subclavian vessels, the thoracic duct, the aorta, the vena cava, the right atrium, trachea, bronchi, the esophagus, *nervus recurrens*, and *nervus phrenicus.*

It is particularly important to restrict ligation of intervertebral arteries to a maximum of two arteries since discontinuation of more intervertebral arteries can lead to transversal myelopathy. Complete resection of tumor tissue in the intervertebral foramina is not necessary. In order to avoid injury of spinal nerves, tumor tissue present in the intervertebral foramina should be left.

Thoraco-abdominal neuroblastoma can be resected after incision of the diaphragm via abdominal access or via additional thoracic access.

14.8.3.3.2 Retroperitoneal/abdominal neuroblastoma

In the upper retroperitoneal space, neuroblastoma can encase or infiltrate important structures as: *vena cava*, *truncus coeliacus*, upper mesenterial artery and vein, the lower mesenterial artery, the *ligamentum hepatoduodenale*, the pancreas, the lower surface of the liver, the renal vessels. During preparation, compression or discontinuation of the renal vessels should be avoided. Spasms of the renal arteries during surgery can be avoided by flushing the situs with vasodilating compounds (e.g., lidocain or papaverine). Extensive preparation of the mesenteric root or the *truncus coeliacus* can lead to protracted postoperative diarrhea. Discontinuation of $\geq$2 intervertebral arteries or veins can cause transversal myelopathy.

For large or centrally located retroperitoneal neuroblastoma, bilateral retroperitoneal access from the left and the right side should be considered. An additional third access via *bursa omentalis* or via *ligamentum gastrocolicum* is possible. Caudal access to the upper retroperitoneum can be achieved by lifting the gastrocolic ligament, right colon and the mesenterium. The most upper part of the retroperitoneum and diaphragm are reached after complete mobilization of the liver.

Extensive resection of a retroperitoneal neuroblastoma can lead to lymphatic leakage. Lymph node collection is easier done starting from the most inferior nodes and moving upward.

Occasionally, neuroblastoma involves the outer layer of vessels. Resection of these infiltrated layers should be avoided since perforation of the vessel and persisting disturbance of perfusion are potential hazards.

14.8.3.3.3 Presacral neuroblastoma

Presacral neuroblastoma often involves the sacral plexus. During surgery, the risk of bladder or bowl paralysis, or injury of large vessel or nerves is considerably high. Therefore, complete resection should not be attempted. An additional perineal access might help to remove the most inferior tumor tissue.

14.8.4 Complications

Table 8 shows the frequency of complications observed during 1193 operations done in first line treatment in the NB97 trial. The most important were: bleeding (4.9%), postoperative fever (3.3%), pulmonary complications (3.3%), Horner's syndrome (2.5%), intestinal obstruction/ileus (1.6%), renal deterioration (1.6%), and tumor rupture (1.4%). Nephrectomy was done in 4.1% of all operations in order to achieve a complete tumor resection. A secondary operation for the management of surgical complications was necessary in 4% of patients. A total of 4 patients died due to surgical complications (3 stage 3 and 1 stage 4S).

Table 8: Frequency of surgery related complications during first line treatment of neuroblastoma in the NB97 trial (diagnosis prior to 01.07.2003)

	all stages		stages 1-3		stage 4	
	n	%	n	%	n	%
bleeding	59	4.95	25	3.57	30	6.93
nephrectomy	49	4.11	31	4.42	17	3.93
fever	40	3.35	22	3.14	16	3.70
pulmonary complications	39	3.27	22	3.14	16	3.70
Horner	30	2.51	21	3.00	6	1.39
intestinal obstruction	19	1.59	9	1.28	10	2.31
renal problems	19	1.59	8	1.14	11	2.54
perforation of tumor	17	1.42	11	1.57	4	0.92
perfusion disturbance	14	1.17	8	1.14	6	1.39
hypertension	10	0.84	2	0.29	8	1.85
ascites	9	0.75	4	0.57	5	1.15
injury of peripheral nerves	8	0.67	3	0.43	4	0.92
wound healing problems	7	0.59	2	0.29	4	0.92
wound infection	7	0.59	6	0.86	1	0.23
septicemia	6	0.50	3	0.43	3	0.69
fits	2	0.17	2	0.29		0.00
pneumonia	2	0.17	1	0.14	1	0.23
transverse myelopathy	2	0.17	1	0.14	1	0.23
peritonitis	1	0.08	1	0.14		0.00
total number of operations	1193	100.00	701	100.00	433	100.00

14.9 External beam radiotherapy (EBRT)

14.9.1 Indication

External beam radiotherapy of the primary tumor site is reserved for patients of MRG and HRG with active residual primary tumor present after induction chemotherapy and surgery. The decision about radiation therapy is based on the patient's status prior to maintenance treatment (MRG) or ASCT (HRG).

The activity of residual tumor tissue is defined as:

- MIBG uptake (in tumors initially MIBG positive),
- Octreotide uptake (in tumors initially MIBG negative but ^{111}In-Octreotide positive),
- or unequivocal MRI contrast enhancement (if the tumor was initially completely negative in scintigraphy).

In HRG, combination radiotherapy with ^{131}I-MIBG prior to ASCT and EBRT after ASCT is scheduled. Tumors which were initially MIBG-negative will undergo EBRT without ^{131}I-MIBG-therapy, if other means (e.g., MRI contrast enhancement, ^{111}In-Octreotide scintigraphy) clearly demonstrated residual metabolic activity of the tissue.

The systematic irradiation of metastases is not intended in the trial. It is reserved for individual palliative treatment.

14.9.2 Timing of external beam radiotherapy

14.9.2.1 Medium risk group

For medium risk patients with residual active primary, radiotherapy should be done during the N7 maintenance cycles (figure 24). It must be finished prior to the start of 13-cic-retinoic acid to avoid possible negative interactions between retinoic acid and external beam radiation therapy. MRG patients will **not** receive MIBG therapy.

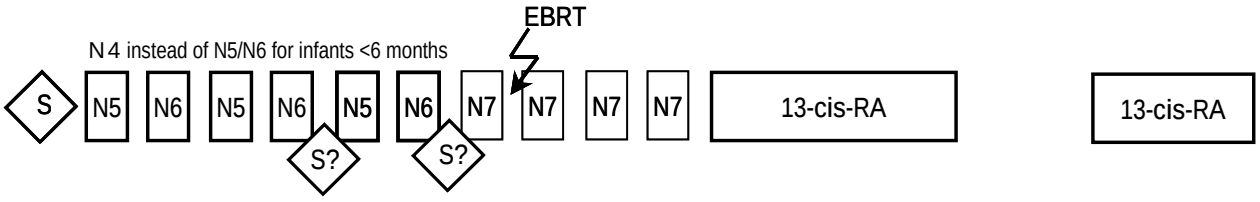


Figure 24: Radiotherapy in the medium risk group (S=surgery, N5/6/7=chemotherapy cycles, EBRT=external beam radiation therapy, 13-cis-RA=13-cis-retinoic acid)

14.9.2.2 High risk group

Radiotherapy in the high risk group includes MIBG therapy (see page 101) given prior to ASCT conditioning chemotherapy and EBRT given after ASCT as soon as the patient has stabilized. In order to avoid possible negative interactions, the patients should not receive retinoic acid during EBRT. Since EBRT will not be finished 30 days after ASCT, give the first 14-days-retinoic acid cycle(s), discontinue retinoic acid treatment during EBRT and restart retinoic acid about 1 week after EBRT end.

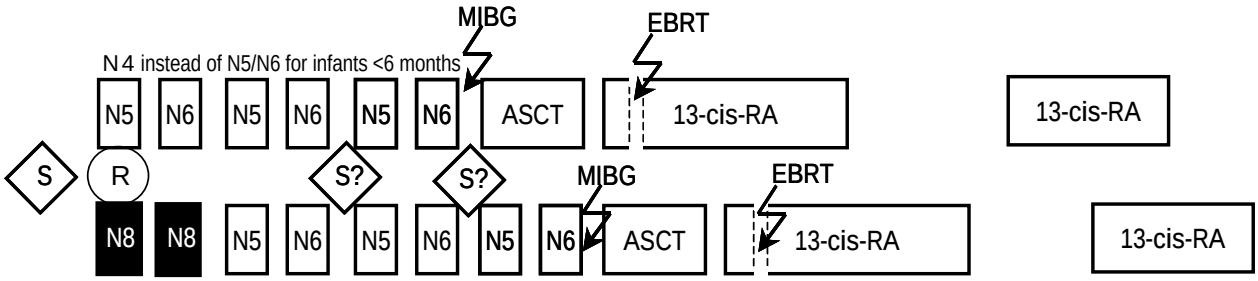


Figure 25: MIBG Therapy and EBRT in the high risk group (S=surgery, R=randomization, N5/6/8=chemotherapy cycles, MIBG=MIBG treatment, EBRT=external beam radiation therapy, 13-cis-RA=13-cis-retinoic acid)

14.9.3 Technical requirements

Linear accelerator; photons from 4 MeV to 8 MeV

14.9.4 Target volume

As in trial NB97, the clinical target volume (CTV) includes the above mentioned active residual tumor with an appropriate safety margin of 1 to 2 cm.

14.9.5 Dose and fractionation

A total dose of 36 – 40 Gy should be delivered to the target volume in daily fractions of 1.6 – 2.0 Gy (as clinically indicated by age of the patient or the extend of the irradiated volume). Radiation dose has to be specified according to the ICRU 50/62 – recommendations.

14.9.6 Planning and technique

The radiation must be planned using the most recent CT and/or MRI scan. The tolerance doses of surrounding critical organs must be considered. The irradiated volume should be kept as small as possible. In most cases, two opposed fields may be appropriate. In

special situations, a subtle 3-D-planning and conformal therapy may be necessary. Details of the given radiotherapy should be reported in the RT-forms found on page 250.

The following dose-limits are recommended:

- **Kidney:** doses to single kidney should not exceed 15 Gy; doses to parts of one of two kidneys should be kept below 20 Gy, although that may be impossible if active residual tumor has to be treated.
- **Liver:** more than 50% of the liver should not receive more than 20 Gy.
- **Bone:** vertebrae should be irradiated symmetrically to avoid scoliosis
- **Spinal cord:** if possible the dose to the spinal cord should not exceed 30 Gy for a short part (i.e. 2-3 vertebrae) or 20 Gy for longer parts, particularly in younger children.
- **Other sites:** problems with other critical organs will occur very rarely e.g. if there are larger residual masses in the mediastinum. These situations should be discussed individually with the radiotherapy reference-center (address see page 3).

14.9.7 Side effects of external radiotherapy

Acute side effects as vomiting, diarrhea or changes in blood count may occur depending on the irradiated volume, but mostly can be avoided by an appropriate supportive care. Late effects depend on the irradiated site, the total dose and the age of the child. Serious late effects should be rare because of small target volumes and modern individual planning. In some cases skeletal deformations could develop; serious spine deformations as scoliosis may be avoided in most of the cases by symmetric irradiation. Spinal cord injuries are not expected, if the tolerance doses are respected.

Secondary malignant disease is possible after high-dose-chemotherapy and radiotherapy.

For children treated in GPOH-trials the possible late effects of radiotherapy are prospectively registered in an own trial, conducted by Prof. Dr. Willich and Dr. Schuck in Münster. (Department of Radiotherapy, University of Münster; phone 0049 (0) 251 – 83 47 384). The forms can be downloaded from

http://www.muenster.de/institute/radonk/radtox.htm.

14.10 131-I-MIBG therapy

14.10.1 Indication

^{131}I-MIBG-therapy is reserved for high risk patients with residual tumor tissue (primary or metastasis) with clear MIBG uptake present at the end of induction chemotherapy (i.e., after the last N6 cycle). Residual non-progressing non-active mass seen only in MRI, CT, or ultrasound does not require any radiation therapy. Tumors without MIBG uptake at initial diagnosis will not undergo ^{131}I-MIBG-therapy regardless of metabolic activity diagnosed by other means (MRI contrast, Octreotide scintigraphy etc.).

14.10.2 Timing of the MIBG therapy

^{131}I-MIBG-therapy should be done prior to ASCT. As soon as the patient is able to leave the nuclear medicine department, ASCT has to start. Additional EBRT should be performed after ASCT as soon as the patient has stabilized (figure 26).

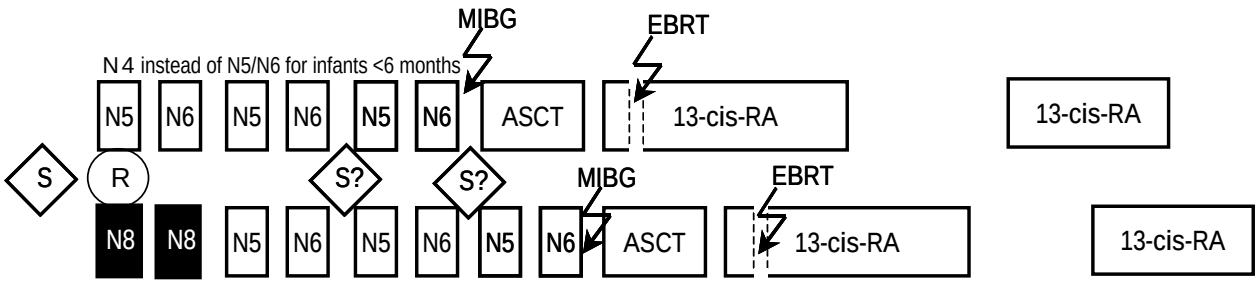


Figure 26: Timing of 131I-MIBG-therapy in MIBG positive residual tumor in high risk patients

14.10.3 Technical considerations

^{131}I-MIBG therapy requires patient's admission to the nuclear medicine ward and close cooperation between pediatric oncology and nuclear medicine departments.

Prior to ^{131}I-MIBG therapy, complete tumor staging as outlined in section 10.3 on page 30 is mandatory in order to demonstrate active residual tumor requiring combined ^{131}I-MIBG and external beam radiation therapy.

Prior to admission in the nuclear medicine, additional analyses are necessary:

- full blood count
- liver function tests
- kidney function tests
- thyroid hormone analysis, i.e. TSH, fT3 and fT4

All drugs taken by the patient must be known since some of these might interfere with MIBG uptake (e.g., labetalol, reserpine, calcium-channel blockers, tricyclic antidepressants, sympathomimetics[35]).

Na-Perchlorate (Irenat ®) in a dose of 1 drop/kgxd orally divided in 3-4 doses from day -1 (the day prior to the ^{131}I-MIBG therapy) to day +14 after ^{131}I-MIBG therapy is given for **thyroid blockage**. In case of intolerance to Na-perchlorate, 100 mg potassium iodide daily given from day –1 (the day prior to the ^{131}I-MIBG therapy) to day +10 or +14 after the ^{131}I-MIBG therapy is an alternative.[35]

In order to reduce the radiation exposure of the bladder epithelium, hydration (2000 mg/m²xd) is recommended until discharge from the nuclear ward.

14.10.4 131-I-MIBG activity

A single ^{131}I-MIBG activity of **12 mCi/kg body weight** infused over 2 hours is recommended. This activity corresponds with a whole body dose of about 2 Gy. According to radiation protection regulations, most hospitals have the license to deal with a maximum activity of 300 mCi = 11.1 GBq ^{131}I-MIBG. Therefore, the maximum dose for children >25 kg to be given is 300 mCi. Dosimetry in order to determine the exact whole body and tumor dose is mandatory.

14.10.5 Whole-body dosimetry protocol

For dosimetry, register the body activity according to the following protocol:

1. Acquire background reading prior to administration of ^{131}I-MIBG.
2. Ensure geometry is the same for all readings.
3. Acquire first patient reading immediately following administration and before first void.
4. First void.
5. Acquire second reading immediately after first void.
6. Subsequent readings are recommended to be taken every 2 hours for the first 24 hours and every 4 – 6 hours thereafter. Patient must void before each reading. However, it is unreasonable to wake the patient for readings overnight. Therefore readings should be taken last thing at night before the patient retires and as soon as he/she awakes in the morning.
7. Plot activity-time data and fit decay phases to the data. Integrate to determine the cumulated activity **Ã**. If calculation of **Ã** is not possible, please report the single time dependent readings to the trial office.
8. Determine the relevant MIRD **S** value from the patient weight.
9. Calculate the whole-body dose using standard MIRD, i.e. **D =Ã x S**.

It is important that the patient voids immediately prior to administration. This ensures that no activity is lost before the first whole body retention measurement. If the patient has to

void during administration the activity in this void must be measured and taken into account in subsequent calculations.

The MIRD S value (wb → wb) is determined according to the patient's weight. MIRD S values are available for newborn, 1 year old, 5 year old, and adults (on the internet: http://www.dosisinfo-radar.com/RADARphan.html). From these, an (empirical) equation may be generated to determine a patient-specific S value by:

$S = 1.96^{-0.6} \times 70 \times \text{body weight [kg]}^{-0.918}$ Gy/(MBq h).

If there are further questions, do not hesitate to contact the consulting nuclear medicine department (for address see page 3).

14.10.6 Important possible side effects of ^{131}I-MIBG-therapy

Paravenous infusion of ^{131}I-MIBG can lead to dermal necrosis and potential limb loss.

Short term side effects: Adrenergic side effect may include nausea and vomiting but are rare when ^{131}I-MIBG is given slowly as an infusion over 2 hours. Thyroid dysfunction may be possible even if thyroid blockage is performed. Thoracic pain and fever may occur and interstitial pneumonia has been reported.[46] Bone marrow toxicity is accepted in the NB2004 protocol, since ^{131}I-MIBG therapy is followed by ASCT with stem cell rescue. Oral mucositis has been observed after ^{131}I-MIBG therapy. [29]

Late effects: Lifelong thyroid dysfunction requiring hormone replacement therapy.[134] Impotence may occur because of ^{131}I-MIBG therapy; however chemotherapy may play a more significant role. Secondary malignancies have been reported after combined chemotherapy and ^{131}I-MIBG therapy.[47]

The radiation can harm the unborn. Therefore, contraception is mandatory for all adolescent females who might become pregnant.

15 DRUG INFORMATION

15.1 Chemotherapeutic drugs

Source of information: German drug information "Fachinformation" unless otherwise stated. Brand names are given since formulation and stability may vary between different brands. Of course, similar drugs from other manufacturers can be used instead. Please refer to manufacturers' information.

15.1.1 Carboplatin (CARBO, Carboplat®)

Formulation: solution in dextrose 5%

Dose/Administration:

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
ASCT	**16.6 mg/kg**	**500 mg/m²xd**	**day –4 to –2 infusion 1 hr**
N5 as substitute for Cisplatin		**100 mg/m²xd**	**day 1 to 4 continuous infusion 96 hr**

Stability/Storage: Vials stable for 18 months; infusion preparation with dextrose 5% is stable 28 d if prepared under sterile conditions,[163] otherwise only 8hrs at room temperature and 24 hrs refrigerated.

Pharmacokinetics: intravenous infusion only, after short infusion $t_{½}\alpha$ 90-100 min, $t_{½}\beta$ 6 hrs for bound platinum and 24-40-139 hrs for free platinum. Plasma binding >90%. Renal elimination by glomerular filtration dependent on the creatinine clearance.[82]

Known important incompatibilities: aluminum, amphotericin B, $NaHCO_3$.

Main toxicity: transient myelosuppression, reversible hair loss, renal, hypomagnesaemia, other electrolyte disturbances, auditory, peripheral neuropathy, transient increase of liver function tests, nausea and vomiting, allergy (rare).

15.1.2 Cisplatin (CDDP, Cisplatin medac®)

Formulation: dry powder vials or ready-to-use solution, reconstitute with normal saline only

Dose/Administration in N5 cycle:

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
N5	**1.3 mg/kgxd**	**40 mg/m²xd**	**day 1-4 continuous infusion 96 hrs**

Stability/storage: Unopened vials: protected from light at room temperature (+15 to +25°C). Injection preparation: store at room temperature, stabile for 28 days if prepared under aseptic conditions.[163]

Pharmacokinetics: intravenous application only, 90% protein bound, $t_{½}\alpha$ 20-30 min, $t_{½}\beta$ 48-67 min, $t_{½}\gamma$ 24-129 hrs, elimination by tubular secretion and filtration (90%) and hepatic excretion (10%).[82]

Known important incompatibilities: aluminum, amifostin, amphotericin B, MESNA, $NaHCO_3$, metoclopramide, thiotepa.[163]

Main toxicities: renal, hypomagnesaemia, hypocalcaemia, ototoxicity, peripheral neuropathy, transient myelosuppression, nausea and vomiting, diarrhea, abdominal pain, mucositis (rare), elevation of liver function tests, allergy (rare), arrhythmia, reversible hair loss.

Dialysis: about 8% are eliminated by immediate hemodialysis; late hemodialysis is less effective due to 90% protein binding.

15.1.3 Cyclophosphamide (CPM, Cyclostin®)

Formulation: dry powder vials plus saline solution vials

Dose/Administration

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
N4	**10 mg/kgxd**	**300 mg/m²xd**	**day 1-7 infusion 30 min**
N7	**5 mg/kgxd**	**150 mg/m²xd**	**days 1-8 orally (or 1hr infusion)**
N8	**not applicable**	**100 mg/m²xd**	**days 1-7 infusion 1 hr, starts 6 hrs prior to topotecan**

Stability/Storage: Vials: 5 years; prepared solution 4 d at room temperature and 28 d refrigerated if prepared under sterile conditions. Otherwise only 12 hrs at room temperature and 48 hrs at +5°C; Cyclophosphamide is compatible with the commercially available topotecan (Hycamtin®) solution.[113, 163] Therefore, topotecan infusion can continue during cyclophosphamide infusion.

Pharmacokinetics: Oral bioavailability about 90%; Plasma half life 4 – 6.5 hrs; Hepatic elimination by cytochrome P 450 and by aldehyde oxidase.[62]

Known important incompatibilities: amphotericin B, bencylalcohol

Main toxicity: transient myelosuppression, reversible hair loss, nausea and vomiting, hemorrhagic cystitis due to accumulation of acrolein in the urine, water retention[20], cardio toxicity in high doses used with stem cell rescue.[62]

Dialysis: possible (low protein binding).

Precaution of Hemorrhagic Cystitis: hydration, concomitant application of sodium-2-mercaptoethane (MESNA) at 60% of cyclophosphamide-dose.[66]

15.1.4 Dacarbacin (DTIC, Detimedac®)

Formulation: dry powder vials to dissolve with sterile water

Dose/Administration:

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
N6	**6.7 mg/kgxd**	**200 mg/m²xd**	**days 1-5 infusion 1 hr**

Stability/storage: Vials: protected from light, not over +25°C; Reconstituted solution is stable for 8 hrs at room temperature if protected from light.

Pharmacokinetics: intravenous application only, protein binding 5%, terminal plasma half time 0.5-3.5 hrs, hepatic elimination by hydroxylation/de-methylation and renal elimination about 20-50%.

Known important incompatibilities: heparin, hydrocortisone, L-cystein, $NAHCO_3$, piperacillin/tazobactam.

Main toxicity: transient myelosuppression, reversible hair loss, nausea and vomiting, transient elevated liver function tests (rare), veno-occlusive disease (rare), renal (rare), allergy (rare), seizures (rare).

15.1.5 Doxorubicine (DOX, Adriblastin ®)

Formulation: dry powder, and saline solution for dissolving

Dose/Administration:

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
N4	**0.5 mg/kgxd**	**15 mg/m²xd**	**day 1,3 and 5 infusion 30 min**
N6	**1 mg/kgxd**	**30 mg/m²xd**	**day 6 and 7 infusion 4 hrs**

Stability/storage: Vial: 4 years; Reconstituted solution: protected from light 24 hrs at room temperature and 48 hrs at +4°C

Pharmacokinetics: intravenous application only, protein binding 75%, plasma half time biphasic with 3 and 30-50 hrs, transformation to doxorubincinol and 7-deoxyglycon, conjugation with glucuronic acid, excretion via bile.[182]

Known important incompatibilities: allopurinol, aluminum, cephalotin, dexamethasone, ganciclovir, diazepam, fluorouracil, furosemide, heparin, hydrocortisone, MTX, $NaHCO_3$, piperacilline, theophylline, vincristine

Main toxicity: transient myelosuppression, reversible hair loss, cardiotoxicity (acute arrhythmias and late cardiomyopathy), nausea and vomiting, mucositis, transient increase of liver function tests, allergic reactions (rare).

15.1.6 Etoposide-phosphate (VP16, Etopophos®)

Formulation: dry powder vials to dissolve with either sterile water, 5% dextrose, or normal saline

Dose/Administration:

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
N5	**4.2 mg/kgxd**	**100 mg/m²xd**	**day 1-4 continuous infusion 96 hrs**
N8	**not applicable**	**100 mg/m²xd**	**infusion 1 hr**
ASCT	**40 mg/kgxd**	**40 mg/kgxd**	**day –4 infusion 4 hrs**

Stability/storage: Vials: 3 years refrigerated and protected from light; reconstituted solution stable for 28 days at room temperature or refrigirated.[163]

Pharmacokinetics: Oral bio-availability 29–100%, Plasma half life after intravenous injection 4.4–6.4 hrs, poor penetration of the intact blood brain barrier, renal elimination by excretion of unchanged drug (30-40% of the dose given) and of the glucuronide (20%).[32]

Known important incompatibilities: amphotericin B, cefepim, chlorpromazine, imipenem, methyprednisolone, mitomycin[163]

Main toxicity: myelosuppression, reversible hair loss, fever and hypotension, anaphylactic reactions, nausea and vomiting, diarrhea, mucositis, hepatocellular enzyme elevation, secondary malignant diseases.[32, 120, 131]

Precaution: cardiovascular monitoring (ECG and blood pressure) during infusion for early detection of anaphylactic reactions.

15.1.7 Ifosfamide (IFO, Holoxan®, Holoxan Lösung®)

Formulation: dry powder vials to dissolve with sterile water (Holoxan®), or vials with 4% ifosfamide solution (Holoxan Lösung ®)

Dose/Administration:

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
N6	**50 mg/kgxd**	**1500 mg/m²xd**	**days 1-5 continuous infusion 120 hrs**

Stability/storage: Dry powder vials (Holoxan®): 5 years; reconstituted solution: 24 hrs refrigerated (+2 to +8°C); Solution vials (Holoxan Lösung®): 6 months

Pharmacokinetics: intravenous application only; plasma half life 4-7 (-15) hrs; renal excretion of ifosfamide and 4-hydroxy-metabolite.[44, 62]

Known important incompatibilities: none

Main toxicity: transient myelosuppression, reversible hair loss, nausea and vomiting, hemorrhagic cystitis, renal, encephalopathy (about 10-20% with agitation, nightmares, loss of consciousness, or seizures), transient increased liver function tests (rare).

Precaution of hemorrhagic cystitis: hydration, concomitant application of sodium-2-mercaptoethane (MESNA) at 60% of ifosfamide-dose.[66]

Management of encephalopathy: Discontinuation of ifosfamide-infusion, methylene-blue injection 1-2 mg/kgxd (max. 50 mg) dissolved in 5% dextrose over 30 min up to 6 times a day. Methylene blue is contraindicated in glucose-6-phosphate dehydrogenase deficiency, pregnancy/lactation, known sensitivity to the drug, and severe renal impairment. [44, 96, 122, 181]

15.1.8 Melphalan (MEL, Alkeran®)

Formulation: dry powder vials and a separate vial of special diluents (sodium citrate, propylene glycol, ethanol, and sterile water)

Dose/Administration:

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
ASCT	**1.5 mg/kgxd**	**45 mg/m²xd**	**days –8 to –5 infusion 30 min**

Storage: protected from light, under +30°C but not refrigerated (precipitates when stored refrigerated), the reconstituted solution diluted with normal saline is stable for 3 hrs at room temperature and 24 hrs refrigerated.[163]

Pharmacokinetics: low oral bio-availability (20-50%), terminal plasma half life 86.5±48.8 min, elimination by spontaneous hydrolysis and renal excretion of intact drug (15%).[62]

Known important incompatibilities: amphotericin B, dextrose

Main toxicity: transient myelosuppression, reversible hair loss (rare), nausea and vomiting, mucositis, diarrhea, allergy (rare), elevated liver function tests, venous occlusive disease (rare),

15.1.9 Topotecan (TOPO, Hycamtin®)

Formulation: dry powder vials

Dose/Administration in N8 cycle:

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
N8	**not applicable**	**1.0 mg/m²xd**	**days 1-7 continuous infusion 168 hrs starts 6 hrs after cyclophosphamide**

Stability/storage: Stable for 28 days at room temperature and at 2-8°C; storage: cool and dark; chemically compatible with cyclophosphamide[113, 163]

Pharmacokinetics: oral bio-availability of about 30% with low individual variability,[48] plasma elimination half-life 2.2-3.18 hrs,[18, 170] good CSF penetration, rate dependent from the infusion time (0.25 ± 0.15 after 30-min-infusion, 0.29 ± 0.02 after 4 h infusion, 0.29 after 24-h infusion, and 0.39 - 0.42 after 72h infusion [5, 12, 13, 15, 83, 179]), Elimination by conversion of the active lactone form to the inactive hydroxyl acid and by renal excretion dependent from creatinine clearance [45, 67, 115, 170], clearable by hemodialysis [74]

Known important incompatibilities: dexamethasone, fluorouracil, mitomycin, $NaHCO_3$[163]

Main toxicity: transient myelosuppression, nausea and vomiting, mucositis, [14, 42, 83, 100, 123]

15.1.10 Vincristine (VCR, Vincristinsulfat-GRY®)

Formulation: ready-to-use solution vials

Dose/Administration:

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
N4	**0.025 mg/kgxd**	**0.75 mg/m²xd maximum 2 mg**	**day 1, 3, and 5 iv. push**
N6	**0.05 mg/kgxd**	**1,5 mg/m²xd maximum 2 mg**	**day 1 and 8 infusion 1 hr**

Stability/storage: stable for 2 years at +2 to +8°C protected from light, stable for 28 d at room temperature[163]

Pharmacokinetics: intravenous application only, terminal plasma half life 85 hrs, 44% plasma protein binding, hepatic elimination via bile system (80%) and renal (20%)

Known important incompatibilities: all solutions with pH other than 3.5 to 5.0

Main toxicity: **Only for intravenous injection!**, peripheral neuropathy, central neurotoxicity (rare), constipation, venous occlusive disease (rare), polyuria, dysuria, inadequate ADH secretion, transient myelosuppression, reversible hair loss, necrosis after para-venous injection

15.1.11 Vindesine (VDS, Eldisine®)

Formulation:

dry powder vials to dissolve with sterile water, 5% dextrose, or normal saline

Dose/Administration:

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
N5	0.1 mg/kgxd	3 mg/m²xd maximum 6 mg	day 1 infusion 1 hr

Stability/storage: prepared solution stable for 28 d at room temperature and refrigirated[163]

Pharmacokinetics: intravenous application only, terminal plasma half life 24.2 hrs, hepatic elimination via bile system and renal (about 13%).

Known important incompatibilities: all solutions with pH other than 3.5 to 5.0

Main toxicity: transient myelosuppression, constipation, nausea and vomiting, peripheral neuropathy, polyuria, dysuria, inadequate ADH secretion, brochospasm (rare), reversible hair loss, necrosis after para-venous injection

15.2 Other important drugs

15.2.1 13-cis-Retinoic acid = Isotretionin (Roaccutan®)

Formulation: soft capsules containing 10 mg or 20 mg 13-cis-retinoic acid

Dose/Administration: 160 mg/m²xd in 2 (or 3) divided doses for 14 days followed by a 14 day rest.

Stability/storage: 3 years stable, do not store >25°C

Pharmacokinetics: 60% oral bioavailability, 99% albumin bound, terminal half life of intact isotretionine 19 hrs, excretion of intact isotretionine and metabolites in urine and stool, enterohepatic reabsorption circle

Known important incompatibilities: none

Main toxicity: **frequent:** cheilitis, mucocutane xerosis, conjunctivitis, itching, hair loss, hypertriglyceridaemia, transient increase of GOT and GPT, **occasionally:** hypercalcemia, bone pain, bone decalcification, bone marrow depression; **rare:** night blindness, headache, depression, abdominal pain, diarrhea, vertigo, tinnitus, bone marrow necrosis, pulmonary infiltration, vasculitis.

Warnings: Since **increased light sensitivity** has been reported, avoid sunlight exposure during 13-cis-retinoic acid treatment.

Given during pregnancy, 13-cis-retinoic acid can cause **severe birth malformations** (hydrocephalus, microcephalus, ear abnormalities, cardiovascular abnormalities, facial dysmorphia, endocrine abnormalities, and cerebellar malformations). Therefore, contraception starting 1 month prior to 13-cis-retinoic acid treatment is mandatory in all female adolescents who might become pregnant.

15.2.2 MESNA (Uromitexan®)

Formulation: Solution 100 mg/1.0 ml

Dose/Administration:

In general 60% of the ifosfamide/cyclophosphamide dose. Clear evidence exists for ifosfamide use, evidence for cyclophosphamide use is less clear.[66]

cycle	infants ≤1 year and children <10 kg	children ≥1 year	
N4	**3x2 mg/kg**	**3x60 mg/m²**	**day 1-7 iv. push, 0, 4, 8 hrs after CYC**
N6	**30 mg/kgxd**	**900 mg/m²xd**	**days 1-7, continuous infusion 120 hrs**
N7	**3x1 mg/kgxd**	**3 x 30 mg/m²**	**days 1-8 orally, 0, 4, 8 hours after CYC**
N8	**not applicable**	**3 x 20 mg/m²**	**days 1-7 iv.-push, 0,4, and 8 hrs after CYC**

Stability/storage: vials 3 years at room temperature, open vials 8 days at 8°C

Pharmacokinetics: oral bioavailability 40-50%, transformation to MESNA-disulphide, half life about 1 hr, peak urinary concentration following iv. and oral administration 1 hr and 3 hrs, respectively, nearly complete renal excretion within 8 hrs.[104]

Known important incompatibilities: in vitro not compatible with carboplatin, cisplatin, and nitrogen mustard

Main toxicity: no toxicities known

15.2.3 G-CSF (Neupogen®, Granocyte ®)

Formulation:

- Neupogen ® 30 (300 µg/1.0ml Filgrastim = 30 million units) solution
- Neupogen ® 48 (480 µg/1.6 ml Filgrastim = 48 million units) solution
- Granocyte ® 13 (105 µg/1.0ml Lenograstim = 13.4 million units) powder
- Granocyte ® 34 (263 µg/1.0ml Lenograstim = 33.6 million units) powder

Dose/Administration:

- after each N5, N6, and N8 cycle: 5 µg/m²xd subcutaneously starting 2 days after chemotherapy until leucocytes >10.000/µl or granulocytes >5000/µl.
- for autologous stem cell mobilization prior to stem cell apheresis: 10 µg/kgxd in 2 divided doses subcutaneously (or 4 hr infusion intravenously).
- after ASCT 10 µg/kgxd subcutaneously (or 4 hr infusion intravenously).

Stability/storage:

- Neupogen: vial stable for 2 years at 2-8°C, diluted solution stable for 24 hrs at 2-8°C
- Granocyte: vial stable at room temperature for 2 years, prepared solution stable for 24 hrs at 5-25°C

Pharmacokinetics: after subcutaneous or intravenous injection serum half life 3.0-3.5 hrs, after subcutaneous injection of Filgrastim effective serum concentration of ≥10 ng/ml for 8-16 hrs.

Known important incompatibilities: Filgrastim: normal saline

Main toxicity: headache, backache, bone pain, abdominal pain, local reaction at the injection site, transient abnormal liver function tests; very rare: spleen rupture, pulmonary infiltration, respiratory failure, vasculitis, Lyell-syndrome

16 SUPPORTIVE CARE

During the first chemotherapy cycles, adequate hydration and monitoring of uric acid levels and kidney function are strongly recommended. **Tumor lysis syndrome** well known from lymphoma and leukemia has been observed occasionally in neuroblastoma, too.[99]

G-CSF (Neupogen® or Granucyte®) is mandatory after each block. The dose recommended is 5 µg/kgxd. G-CSF should start 2 days after the last chemotherapeutic drug of each cycle was given. G-CSF should continue until the WBC are ≥10,000/µl or granulocytes ≥5,000/µl. As outlined earlier, the double dose is recommended for stem cell mobilization.

Antiemetic drugs are strongly recommended for the cycles N5 and N6. Ondansetron bolus 4 mg/m² followed by continuous ondansetron infusion 16 mg/m²xd will be appropriate in most of the patients. If nausea and/or vomiting are not controlled, dimenhydrinate, addition of glucocorticoids to Ondansetron, and midazolam-metoclopramide bypass should be considered.

Topotecan has shown a low emetic potential.[100] Therefore, routine antiemetic drugs might not be necessary during topotecan infusion. Ondansetron 2x4 mg/m² might be appropriate as prophylaxis.

All commonly used **analgesic drugs** are allowed.

During chemotherapy and ASCT, **prophylaxis against fungal infections** (Fluconazol 1-2 mg/kgxd single dose or Amphotericin suspension 25-50 mg/kgxd divided into 3 doses) and ***Pneumocystis jovanii*** (150 mg/m²xd trimethoprim with sulfamethoxazole 750 mg/m²xday in two divided doses on three consecutive days each week[24]) are strongly recommended.

Treatment of **neutropenic fever** or neutropenic infection should be done according to the individual policy of every participating hospital. Prior to the start of antibiotics, blood culture, urine culture, and throat swab are required.

Blood cell components should be leukocyte depleted and irradiated prior to transfusion.

17 SPECIAL SITUATIONS

17.1 Opsomyoclonus (Kinsbourne syndrome)

The *opsomyoclonus-ataxia-syndrome (OMS, Kinsbourne syndrome)* is characterized by rapid, irregular movements of the eyes ("dancing eyes", may continue during sleep) and/ or by myoclonus and ataxia of the limbs ("dancing feet"), the trunk and the eyelids. OMS may occur with or without neuroblastoma. The pathogenesis is still unclear. Extensive lymphocyte infiltration of the tumor tissue (compared to neuroblastoma patients without OMS[26]) and the presence of antineural antibodies[141] suggest an immune-mediated mechanism. The pharmacological treatment of the neurological symptoms includes glucocorticoids (prednisone, dexamethasone, or ACTH), high dose immunoglobulins and cytostatic drugs. In short term, 60-80 % of the symptoms responded to the treatment with no detectable superiority of one approach, but long term neurodevelopmental results still appear to be poor. Many patients demonstrated developmental delays including cognitive and motor delays, language deficits and behavioral abnormalities.[143] [141] The survival chances of children with OMS are favorable because of their lower stages of the disease at presentation.[141]

Patients with OMS are treated according to the appropriate risk group as outlined in the NB2004 protocol. Immunosuppression therapy will be necessary for most of the patients. An international protocol for patients with OMS will be available soon. Please contact the trial office for details.

17.2 Transverse myelopathy

The *transverse myelopathy* results from growth of cervical, intrathoracic or intraabdominal neuroblastoma through neuroforamina into to the spinal canal. Only half of them show neurological symptoms[86] but may develop myelopathy soon afterwards, e.g. during surgery. Thus, the intraspinal degree of tumor extension has to be investigated by MRI before surgery in order to avoid decompensation of a labile steady state. The neurological abnormalities included motor deficit (> 95%), radicular or back pain (54%), sphincteric (34%) and sensory (12%) deficits.[31] The frequency of complete neurological recovery was inversely correlated with the severity of the presenting neurological deficits.[86] About 40-50% of the severely affected surviving children experienced long-term neurological sequeals.[86] [31] Longer duration of symptoms (>1 week) made permanent neurological dysfunction also more likely. Chemotherapy, radiotherapy and laminectomy proved to be similar effective for short term relief, but chemotherapy appears to be associated with somewhat less long term sequelae.[86] [31]

Therefore, all children with clinical signs of transverse myelopathy need immediate chemotherapy. If intraspinal involvement of localized tumor is only seen in MRI but no clinical signs are found, resection is recommended for children classified as observation patients as outlined in section 9 on page 19.

18 CONSIDERATIONS FOR RELAPSE MANAGEMENT

In case of relapse, progression or death, **immediate event report** using the form on page 252 is required. Do not hesitate to contact the trial office for discussion of further treatment options. Complete documentation is a crucial prerequisite for discussion of relapse management. Make sure that all previous treatment is well documented.

Relapse management can not be standardized by a single protocol. The trial office will give information about current phase I-II protocols which are open for neuroblastoma relapse patients. The trial office will consider the individual situation of a patient, his/her life expectancy, his/her previous treatment, drug intolerances or late effects of the previous treatment, the initial extend of the disease, and the relapse/progression pattern.

The following options might be appropriate for selected relapse/progression patients:

- First consider surgery to remove the bulk of recurrent disease. The tissue must be processed as required for initial diagnosis. For details of tissue handling see chapter 29.3 on page 161. It is strongly recommended, to handle all snap frozen material absolutely sterile to facilitate its use for tumor lysate vaccination.
- N8 treatment for all patients which were not in the N8 arm of the high risk protocol. Topotecan containing chemotherapy has proven tolerable and effective in many relapse patients in the topotecan protocols. [100]
- Radiation therapy for patients who have not had irradiation before.
- Carboplatin/etoposide chemotherapy.
- Tumor vaccination protocols (tumor lysate, tumor antigen peptides, or combination). Please contact the trial office to discuss the most recent protocol.

19 PATIENTS SAFETY

19.1 Adverse event monitoring

Each subject must be carefully monitored for adverse events. This includes clinical and laboratory test variables. An assessment must be made of the seriousness, intensity and relationship to the administration of the trial medication.

At each presentation in the in- or outpatient clinic, the patient and the guardians will be asked whether they experienced any adverse events during the time from one visit to the other (open questions). The results of the laboratory measurements will be checked for any abnormalities immediately after they have been received. The investigator will carefully assess whether any lab abnormalities have to be regarded as adverse events.

19.2 Adverse event definitions

19.2.1 Adverse event (AE)

Any adverse event associated with the use of a drug in humans, whether or not considered drug related, includes the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from an overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

19.2.2 Serious adverse event (SAE)

A serious adverse event includes an adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the 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.

Life-threatening means that the patient was, in the view of the investigator, at immediate risk of death from the reaction as it occurred. This does not include an AE that, had it occurred in a more serious form, might have caused death.

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

In cases of overdose only events consequent to an overdose are reportable.

19.2.3 Expected adverse events

In general, all known side effects of the applied drugs listed in the drug information of the manufacturer are by definition expected adverse events. The most important toxicities are found in detail in section 15 at pages 105-113.

During the infusion of chemotherapeutic drugs, emesis, vomiting, and allergic reaction may occur and, therefore, are considered as expected. Hematological toxicity grade 3-4 is expected. Leukopenia may lead to infectious complication in a certain number of cycles. Therefore, grade 4 infections are referred as expected adverse events, too. Thrombopenia may lead to bleeding; platelet transfusions will be given according to the policy of every participating hospital. Severe treatment induced anemia may cause circulation problems; packed red cell transfusions will be given according to the policy of every participation hospital. Severe mucositis can be expected. It can lead to constipation, abdominal pain, and severe diarrhea.

19.2.4 Unexpected adverse events

Any adverse drug experience, the specificity or severity of which is not consistent with the current Investigators' Brochure (or Package Insert for marketed products).

19.2.5 Relationship to investigational therapy

The assessment of the relationship of an adverse event to the administration of study drug (none, unlikely (remote), possible, probable, not assessable) is a clinical decision based on all available information at the time of the completion of the case report form.

- **None -** includes: (1) the existence of a clear alternative explanation (e.g. mechanical bleeding at surgical site); or (2) non-plausibility (e.g., the patient is struck by an automobile at least where there is no indication that the drug caused disorientation that my have led to the event; cancer developing a few days after drug administration).
- **Unlikely (remote)** - a clinical event, including lab abnormality, with an improbable time sequence to drug administration and in which other drugs, chemicals or underlying disease provide plausible explanation.
- **Possible** - a clinical event, including lab abnormality, with a reasonable time sequence to administration of the drug, which could also be explained by concurrent disease, or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Probable** - a clinical event including lab abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge).

- **Not assessable** - a report of an AE which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Concurrent disease includes concomitant, intercurrent and underlying disease/condition. Concomitant disease - any other illness the subject may have at the time of entering the clinical trial. Intercurrent disease - any other illness the subject may develop during the clinical trial. Underlying disease - the illness which is the indication for study drug therapy.

Factors to be considered include:

- The temporal sequence from drug administration (The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.)
- Recovery on discontinuation (dechallenge), recurrence on reintroduction (rechallenge) (Subject's response after drug discontinuation (dechallenge) or subjects response after drug re-introduction (rechallenge) should be considered in the view of the usual clinical course of the event in question.)
- Underlying, concomitant, intercurrent diseases (Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.)
- Concomitant medication or treatment (The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be recognized to cause the event in question.)
- Known response pattern for this class of drug (Clinical/preclinical.)
- Exposure to physical and/or mental stresses (The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.)
- The pharmacology and pharmacokinetics of the trial medication (The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the trial medication the subject is taking, coupled with the individual subject's pharmacodynamics should be considered.)

19.2.6 Intensity (severity) of the event

The following classification should be used:

- **Mild** - usually transient in nature and generally not interfering with normal activities;
- **Moderate** - sufficiently discomforting to interfere with normal activities;
- **Severe** - prevents normal activities.

19.3 Adverse event documentation

All adverse events occurring during the trial and follow-up period must be fully recorded in the subject's case record.

All patients receiving the trial medication for any time should be followed-up for at least 30 days after (premature or regular) stop of study medication.

Documentation must be supported by an entry in the subject's file. Laboratory test abnormalities considered to be clinically relevant, e.g., causing the subject to stop study medication out of the trial, requiring treatment, causing apparent clinical manifestations, or if the investigator believes the event to be relevant, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, intensity, relationship to investigational product, action taken and outcome.

19.4 Reporting of SAE's/SUSAR's

All suspected SAE's which are unexpected (according to section 19.2.3 and 19.2.4) and serious (according to section 19.2.2) observed during trial must be reported to the **national trial coordinator** as suspected unexpected serious adverse reaction (SUSARS). The telephone number and FAX number are found in chapter 27 on page 148 concerning national variations of this multinational trial. Each national trial coordinator will report the events to the German trial study office.

The reporting of SAE to the trial office is in addition to and does not supplant the reporting of toxicities as part of the data reporting for this study.

20 STATISTICS

20.1 Observation group

20.1.1 Design of the trial

Spontaneous regression of neuroblastoma is well known in infants. The NB97 trial has indicated, that small residual tumor in stage 2 disease does not require postoperative chemotherapy. The aim of the NB2004-OG trial is the collection of data about the frequency, the time frame, and molecular basis of relapse free survival and regression in stage 1, stage 2 disease without 1p aberrations regardless of the extent of the residual tumor, in stage 3 disease without 1p aberrations in children <2 years, and in stage 4S disease (patient eligibility criteria see section 10.5).

This observation trial is multicenter, non-blinded and prospective.

In accordance with the therapy optimization trial of high risk neuroblastoma patients NB2004, the accrual period of the trial is 6 years followed by an observation period of 3 years. Based on the experience of the previous trials, an accrual of 64 patients per year is expected. Compared to the previous trial, the observation group definition has been changed by two different criteria which are (i) extension of age definition which is expected to increase the event risk and (ii) exclusion of status 1p alterations which is expected to decrease the event risk. Patient numbers are too small for confirmatory statistics. All statistics can only be descriptive. For stopping rules, two subgroups were considered separately (group 1: stage 1 all ages and 4S <1 year, 39 patients/year and group 2: stage 2 all ages without 1p aberrations and 3 <2 years without 1p aberrations, 25 patients/year). Additionally, a stopping rule for chromosome 11q status was defined.

As soon as the diagnosis of low risk neuroblastoma has been established according to inclusion and exclusion criteria (page 45), the child will be included into the observation trial NB2004-OG.

Within this trial, the principals of the ICH-guidelines of good clinical practice (GCP) (http://www.emea.eu.int/index/indexh1.htm) as well as the declaration of Helsinki (http://www.wma.net/e/ethicsunit/helsinki.htm) will be respected.

20.1.2 End points and patients characteristics of the OG

According to the different questions, the following end points are defined:

- **EFS_D:** Event free survival measured from the time of diagnosis up to an event or last follow-up for patients without event. Definition of event is given on page 42.
- **EFS_L:** locoregional EFS measured from the time of diagnosis up to an locoregional event or last follow-up for patients without locoregional event. A locoregional event is defined as (i) death (related to locoregional disease), (ii) local progression of residual

primary tumor, (iii) locoregional relapse following previous complete remission of the primary tumor as defined on page 160.

- **EFS_R for patients with regression:** event free survival measured from the begin of regression up to an event or last follow-up for patients without event. The begin of the regression is defined as the time, at which regression of the primary tumor >10% in at least one diameter and no growth in any diameter is documented by ultrasound, MRI or CT for the first time (provided that the following investigation is able to confirm that regression). The definition of event is given on page 42.
- **EFS_{stage4}:** time from diagnosis to transition to stage 4, to death of disease, or to last follow-up if no transition to stage 4 is observed and the patient is surviving.
- **OS:** Overall survival measured from the time of diagnosis up to death of any reason or last follow-up for surviving patients.
- **TTPR:** Time to begin of primary tumor regression measured from the time of diagnosis to begin of tumor regression or last follow-up if no regression occurs. The begin of regression is defined as outlined in the definition of EFS_R.
- **TTNT:** Time to the normalization of tumor markers HVA and VMA in urine measured from time of diagnosis to the time of the investigation with first normal VMA and HVA results. VMA and HVA results must be categorized according to age specific reference values given by the investigating laboratory.
- For stage 4S patients:
  TTND: Time to no evidence of disease measured from the time of diagnosis to the time of complete regression or to last follow-up if the patients has no complete regression. Complete regression is defined as no evidence of primary tumor plus normalization of tumor markers plus no sign of liver metastases (confirmed by normal ultrasound of the liver) plus no skin metastases.
- Status of the primary tumor 12 months after diagnosis. The status of the primary tumor is defined as outlined on page 43.
- Best status of the primary tumor according to the criteria defined on page 43 within the first 12 months after diagnosis.
- Molecular marker: status of chromosome 1p (unblinded) and status of chromosome 11q (blinded) categorized according to criteria published by Ambros.[4] Tumor material is collected and stored in the tumor bank for future evaluation of other molecular markers which will be considered having prognostic impact during the ongoing trial. A neuroblastoma gene chip will be developed and applied.
- **Surgery:**
  - Extent of **initial surgery** categorized in: biopsy vs. incomplete resection vs. macroscopic complete resection. Initial surgery is the first tumor operation done in a patient.
  - Extent of **best surgery** up to time t performed during the protocol treatment categorized in: biopsy vs. incomplete resection vs. macroscopic complete

resection. Best surgery is the operation performed up to time t during treatment which achieves the most extensive tumor resection.

- Complications related to surgery considered separately for the items: nephrectomy, bleeding, infection, intestinal obstruction, or other according to the documentation form (page 216 and 248).

- **Chemotherapy:**
  - Need for chemotherapy to control progression (definition according to 42),
  - Chemotherapy intensity required categorized as (i) progression and symptoms controlled after 1 x N4 cycle, (ii) progression and symptoms controlled after 2 x N4, (iii) progression and symptoms controlled after 3 x N4, (iv) progression and symptoms controlled after 4x N4, (v) progression and symptoms not controlled after 4 x N4, no transition to stage 4, treatment continued with MRG, (vi) transition to stage 4 at any time, treatment continued with HRG (children ≥1 year at diagnosis) or MRG (infants <1 years at diagnosis).

20.1.3 Collectives of the OG

Collective A: all patients of the NB2004-OG.

Collective B: patients of the NB2004-OG with stage 2 (all ages) and stage 3 (<2 years).

Collective C: patients of the NB 2004-OG with stage 1 (all ages) and stage 4S (<1 year)

Collective R: patients with residual primary after initial surgery (residual primary is defined as a mass seen in ultrasound, MRI or computed tomography)

20.1.4 Questions of the OG

1 Do the following factors influence EFS_D, EFS_L, EFS_R (only patients with regression), EFS_{stage4}, OS, TTPR (only patients with regression), TTNT, TTND (only stage 4S) in collectives A, B, C, and R?:

- age,
- stage (INSS stage 1, 2, 3, or 4S; page 159),
- LDH,
- extent of initial surgery,
- extent of best surgery,
- application of chemotherapy,
- status of chromosome 1p,
- status of chromosome 11q,
- gene expression profile pattern (signature: yes vs. no).

2 Which are the proportions of primary tumor status at 12 months in collectives B and R?

3 Which are the proportion of best tumor status during the first 12 months in collectives B and R?

4 Does the extent of initial surgery (biopsy vs. incomplete resection) influence the status of primary tumor at 12 months in collectives B and R?

5 What is the frequency of complications related to surgery?

6 What is the proportion of patients with the need for chemotherapy?

7 What chemotherapy intensity is required for control of progression and symptoms?

20.1.5 Statistical analysis of the OG

The analysis will be done according to the intention-to-treat principle, i.e., all patients included in the NB2004-OG will be analyzed. Additionally, a per-protocol analysis will be performed for explorative reasons.

Per-protocol-patients are patients meeting the following criteria:

- all patients eligible according to inclusion and exclusion criteria (page 45),
- receiving no postoperative chemotherapy or chemotherapy according to the protocol (i.e., N4 cycles for localized events and stage 4S patients or HRG treatment after transition to stage 4).

Expecting low recruitment and event rates within the NB 2004-OG trial, all analyses are regarded as explorative and the p-values are stated descriptively. Consequently, no significance level is fixed.

1 Cox regression models will be built for EFS_D, EFS_L, EFS_R (only patients with regression), EFS_{stage4}, OS, TTPR (only patients with regression), TTNT, TTND (only stage 4S) separately for the collectives A, B, C, and R including the following potential influential factors.

- age (continuous),
- stage (INSS stage *1,* 2, 3, or 4S as defined on page 159),
- LDH (elevated vs. *normal* according to page 21),
- extent of initial surgery (biopsy vs. incomplete vs. *complete resection*),
- extent of best surgery (biopsy vs. incomplete vs. *complete resection*),
- chemotherapy (yes vs. *no*),
- status of chromosome 1p (deletion or imbalance vs. *no aberration*),
- status of chromosome 11q (deletion or imbalance vs. *no aberration*),

- gene expression profile pattern (signature: yes vs. *no*).

The item given in *italics* is regarded as the reference. For description of categorical factors, Kaplan Meier curves, the quartiles of the survival times with the 95 % CI and the different survival rates at 3 and 5 years with the 95 % CI will be given.

2 Absolute and relative frequencies of the primary tumor status **at 12 months** are given for the collectives A, B, C, and R of the NB2004-OG trial. For the relative frequencies 95% confidence intervals will be calculated.

3 Absolute and relative frequencies of the best primary tumor status **during** the first 12 months are given for the collectives A, B, C, and R of the NB2004-OG trial. For the relative frequencies 95% confidence intervals will be calculated.

4 Cross tables with extend of surgery (biopsy vs. incomplete resection) as potential influence and primary status at 12 months or best primary status within the first 12 months as dependent variables will be given for collective B and R. χ^2-tests will be performed.

5 Cross tables with extend of surgery (biopsy vs. incomplete vs. complete resection) as potential influence and occurrence of complication as dependent variable will be given for each type of complication and for collective A-C separately. χ^2-tests will be performed.

6 Absolute and relative frequency of patients with the need for chemotherapy are given for the collectives A, B, C, and R of the NB2004-OG trial. For the relative frequencies 95% confidence intervals will be calculated.

7 Absolute and relative frequency of chemotherapy intensity for patients who received chemotherapy. For the relative frequencies 95% confidence intervals will be calculated.

20.1.6 Final analysis of the OG

The final analysis will be performed after 9 years. After 3, 5 and 7 years interim analyses will be performed. Expecting only small numbers of patients, all analyses are regarded as explorative. The results of the analyses will be discussed with the data monitoring committee (DMC).

20.1.7 Stopping for toxicity

In general, the observation trial aims to avoid chemotherapy. Therefore, mere observation does not expose the patients to chemotherapy toxicity. If progression or relapse has been diagnosed according to the protocol criteria (page 47), mild N4 chemotherapy is scheduled. Experience of the previous trials demonstrated no threatening toxicity of these cycles. Therefore, toxicity stopping rules are not applicable for the OG.

20.1.8 Stopping for events related to 11q aberrations

Univariate analysis and clinical experience gave evidence for increased risk of event for patients with 11q aberration. Retrospective multivariate analysis of patients of the trial NB90-97 meeting the NB2004 OG definition failed to confirm an prognostic impact of the status of 11q (page 39).

Therefore, this factor will be registered blinded during the trial and analyzed in an interim analysis after 2 and 4 years by logrank test. Expecting about 10% of patients having abnormal 11q (i.e., deletion or imbalance), one-sided question, α=0.025, an accrual of 64 patients per year, the probability to detect an influence of 11q status on event is 74% after 2 years and 94% after 4 years if the survival rate is 90% for patients with normal 11q and 60% for patients with abnormal 11q after half a year and a relevant decrease of the survival rates occurred thereafter. The simulations were performed with nQuery 3.0.

The result of the logrank test must be reviewed by the DMC. If logrank test shows inferiority for patients with 11q aberrations, these patients must be excluded from NB2004-OG from this time on.

20.1.9 Stopping for events: stage 2 (all ages), stage 3 (<2 years), normal 1p

On the basis of NB97 accrual rates, about 150 stage 2 (all ages) and stage 3 ($\leq$2 years) without 1p aberration are expected during 6 years. In the trials NB90-97, the 3-year-EFS rate and 3-year-OS rate were 84$\pm$3% and 98$\pm$1%, respectively (n=214). Events occurred early after diagnosis.

Therefore, an event probability of 15% is expected in this NB2004 subgroup (H_0 p$\leq$0.15). An event probability of 30% is considered to be unacceptably high. The criterion for stopping will be controlled by a sequential design according to Wald plotted in figure 27. It shows the maximum tolerable number of events in relation to the number of patients registered in this NB2004-OG subgroup. The trial must be stopped for stage 2 (all ages) and stage 3 (<2 years) with normal 1p status, if the number of patients with event exceeds 3.376 + 0.219 x (number of registered patients) of the subgroup. The probability of rejection is 3.8% for an event probability of 15%, 76.4% for an event probability of 25%, and 97.5% for an event probability of 30%.

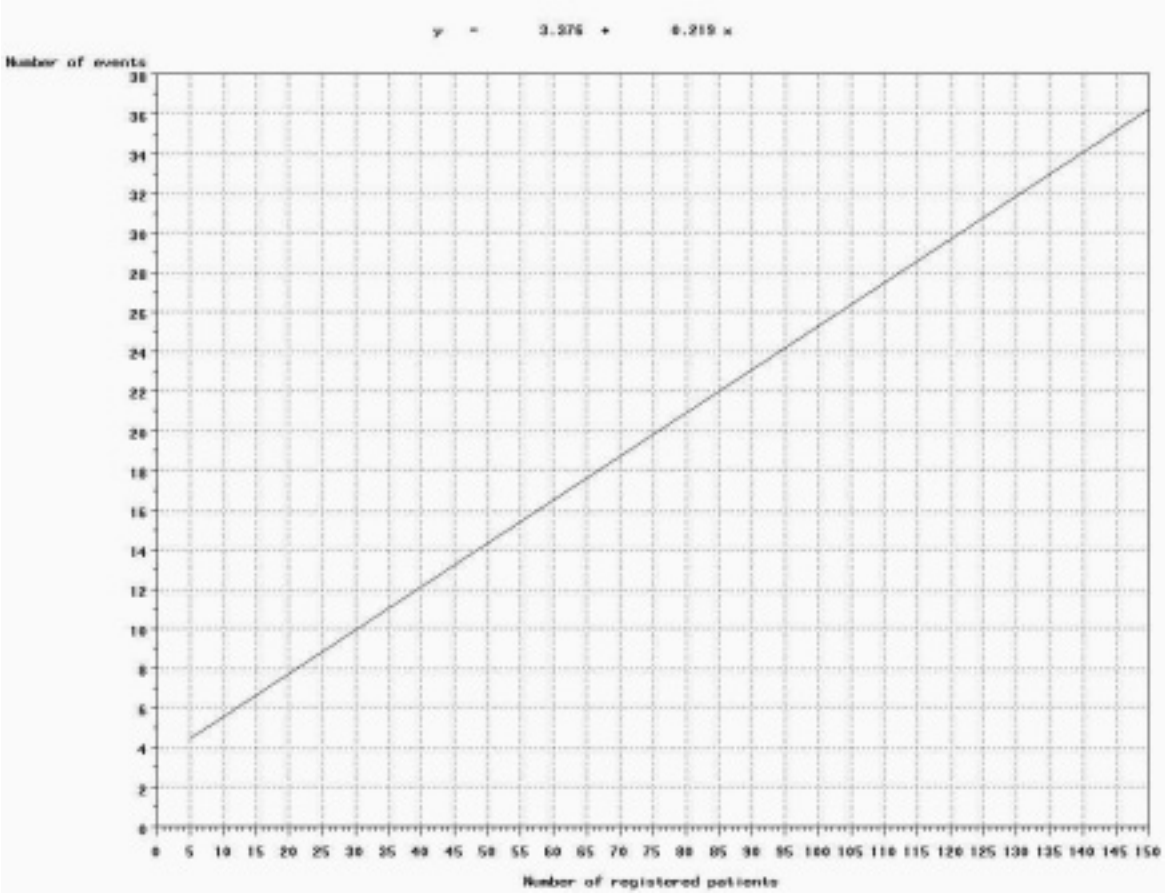


Figure 27: Maximum tolerable event number by number of patients registered for stage 2 (all ages) and stage 3 (<2 years) calculated according to the sequential probability ratio test by Wald.

20.1.10 Stopping for events: stage 1 (all ages) and stage 4S (<1 year)

On the basis of NB97 accrual rates, about 234 patients are expected during 6 years. The 3-year-EFS rate of this group was 88±1% in the NB90 and NB97 trials and the 3-year-OS rate 97±3%. Events occurred early after diagnosis.

Therefore, an event probability of 10% is expected in this NB2004 subgroup (H_0 $p \leq 0.10$). An event probability of 30% is considered to be unacceptably high. The criterion for stopping will be controlled by a sequential design according to Wald plotted in figure 28. It shows the maximum tolerable number of events in relation to the number of patients registered in this NB2004-OG subgroup. The trial must be stopped for this subgroup if the number of patients with event exceeds 2.219 + 0.186 x (number of registered patients). The probability of rejection is 3.4% for an event probability of 10%, 81.4% for an event probability of 20%, and 100% for an event probability of 30%.

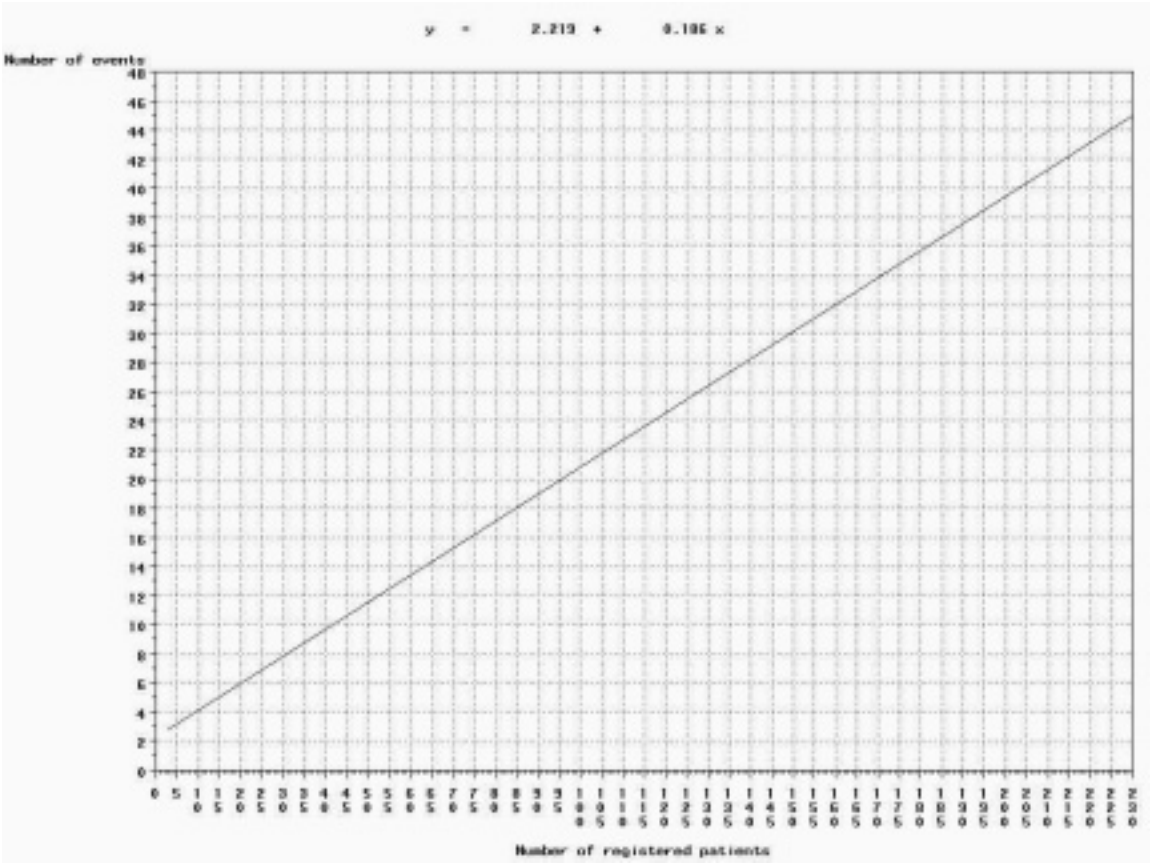


Figure 38: Maximum tolerable event number by number of patients registered for stage 1 (all ages) and stage 4S (<1 year) calculated according to the sequential probability ratio test by Wald.

20.1.11 Modifications of the OG protocol

The design of this trial may be changed, if necessary, in case of new important discoveries. Modifications of the protocol will be made only in form of written amendments and with agreement of the trial committee. The respective ethic commissions have to be informed of the modifications. The patient information has to be changed according to the modifications of the protocol.

20.2 Medium risk group

20.2.1 Design of the trial

The aim of the trial is to evaluate an intensified treatment for a new defined medium risk group defined by age, stage, and molecular markers. Retrospective analysis of patients of the trials NB90-97 classified according to the new medium risk group definition showed an unsatisfactory event free and overall survival. In general, these patients had a less intensive treatment. Therefore, the treatment will be extended by two additional

chemotherapy cycles, by four maintenance chemotherapy cycles, and by retinoic acid consolidation therapy over 1 year (6 months, 3 months break, and 3 months).

This observation trial is multicenter, non-blinded, non-randomized and historical controlled. The historical control group (HCG) contains patients of the trials NB90 and NB97 of stage 2 and 3 with 1p aberration (all ages) and stage 3 regardless of the 1p status (≥2 years).

In accordance with the therapy optimization trial of high risk neuroblastoma patients NB2004 the accrual period of the trial is 6 years followed by an observation period of 3 years. Based on the accrual rates of the previous trial, a total of 8 patients per year is expected.

As soon as the patient meets the inclusion criteria (section 11.5) the child will be included into the NB2004-MRG trial.

Within this trial, the principals of the ICH-guidelines of good clinical practice (GCP) (http://www.emea.eu.int/index/indexh1.htm) as well as the declaration of Helsinki (http://www.wma.net/e/ethicsunit/helsinki.htm) will be respected.

20.2.2 End points of the MRG

According to the different questions, the following end points are defined:

- **EFS_D:** Event free survival measured from the time of diagnosis up to an event or last follow-up for patients without event. An event is defined as death (for all reasons), progression, or relapse following previous remission (according to the INSS criteria on page 160).
- **EFS_L:** locoregional EFS measured from the time of diagnosis up to an locoregional event or last follow-up for patients without locoregional event. A locoregional event is defined as (i) death (related to locoregional disease), (ii) local progression of residual primary tumor, (iii) locoregional relapse following previous complete remission of the primary tumor as defined on page 160.
- **EFS_{stage4}:** time from diagnosis to transition to stage 4, to death of disease, or to last follow-up if no transition to stage 4 is observed and the patient is surviving.
- **OS:** Overall survival measured from the time of diagnosis up to death of any reason or last follow-up for surviving patients.
- **Molecular markers:** status of chromosome 1p and status of chromosome 11q categorized according to criteria published by Ambros.[4].
- External beam radiation therapy:
    - **Acute side effects** of EBRT considered separately according to the radiation therapy documentation form (page 250).
    - **Late effects** of EBRT considered separately according to the long term follow-up forms (page 258).

- Surgery:
    - Extent of the **initial surgery** categorized in: biopsy vs. incomplete resection vs. macroscopic complete resection. Initial surgery is the first tumor operation done in a patient.
    - Extent of the **best surgery** up to time t categorized in: biopsy vs. incomplete resection vs. macroscopic complete resection. Best surgery is the operation performed from diagnosis up to time t which achieves the most extensive tumor resection.
    - Frequency of complications related to surgery considered separately for the items: nephrectomy, bleeding, infection, intestinal obstruction, or other.

20.2.3 Questions of the MRG

By means of this trial the following questions shall be answered:

Main question of the trial

1 Does intensified treatment lead to a better event free survival EFS_D compared to the historical control group (HCG)? The historical control group is defined as outlined in section 12.2.2 on page 54.

Secondary questions:

2 Does intensified treatment lead to a better overall survival OS compared to the HCG?

3 Do the following factors influence EFS_D, EFS_L, EFS_{stage4}, and OS?:

- age,
- stage (INSS stage 2, 3, or 4; page 159),
- LDH,
- extent of initial surgery,
- extent of best surgery,
- external beam radiation therapy,
- status of chromosome 1p,
- status of chromosome 11q,
- gene expression profile pattern.

4 External beam radiation therapy (EBRT):

4.1 What is the frequency of **acute side effects** related to radiation therapy?

4.2 What is the frequency of **late effects** related to radiation therapy?

5 What is the frequency of complications related to surgery?

20.2.4 Statistical analysis of the MRG

The analysis will be done according to the intention-to-treat principle.

Additionally, a per-protocol analysis will be performed for explorative reasons.

Per-protocol-patients must meet all of the following criteria:

- eligibility according to inclusion and exclusion criteria (page 59),
- induction treatment: 6±2 cycles N5/N6,
- maintenance treatment: 4±2 cycles N7,
- retinoic acid: a total of 9±3 months treatment,
- no ASCT,
- no other non protocol anti-tumor treatment.

The main question will be analyzed within the intention-to-treat population on a significance level of α=0,05. The p-values corresponding to the secondary questions and per-protocol-analyses are regarded as explorative.

According to the questions of the trial the following analyses are performed:

Main question of the trial

1 Null hypothesis: The EFS_D of children with intensified treatment of the NB 2004-MRG trial is not better than the EFS_D of children of the HCG. This hypothesis will be analyzed by a one sided log-rank test on difference. For descriptive reasons, the Kaplan Meier curves of the EFS_D, the quartiles of the EFS_D with the 95 % CI, the EFS_D -rates at 3 and 5 years with the 95 % CI will be illustrated.

Secondary questions:

2 Null hypothesis: The OS of children with intensified treatment of the NB 2004-MRG trial is not better than the OS of children of the HCG. This hypothesis will be analyzed by a one sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the OS, the quartiles of the OS with the 95 % CI, the OS-rates at 3 and 5 years with the 95 % CI will be illustrated.

3 Cox regression models will be built for EFS_D, EFS_L, EFS_{stage4}, and OS including the following potential influential factors:

- age (continuous),
- stage (INSS stage *1*, 2, or 3 as defined at page 159),
- LDH (elevated vs. *normal* categorized according to page 21),
- extent of initial surgery (biopsy vs. incomplete vs. *complete resection*),
- extent of best surgery (biopsy vs. incomplete vs. *complete resection*),
- EBRT (yes vs. *no*),

- status of chromosome 1p (deletion or imbalance vs. *no aberration*),
- status of chromosome 11q (deletion or imbalance vs. *no aberration*),
- gene expression profile pattern (signature: yes vs. *no*).

The item given in *italics* is regarded as the reference. For description of categorical factors, Kaplan Meier curves, the quartiles of the survival times with the 95 % CI and the rates of the different survival times at 3 and 5 years with the 95 % CI will be given.

4 External beam radiation therapy (EBRT):

4.1 Null hypotheses: EBRT has no influence on the occurrence of acute complications. Cross tables with EBRT (yes vs. no) as potential influence and dichotomized occurrence of **acute complication** as dependent variable will be given for each type of complication for the NB 2004-trial. Fisher's exact test will be performed.

4.2 Null hypotheses: EBRT has no influence on the occurrence of late effects. Cross tables with EBRT (yes vs. no) as potential influence and dichotomized occurrence of **late effects** as dependent variable will be given for each type of complication for the NB 2004-trial. Fisher's exact test will be performed.

5 Null hypotheses: The extent of surgery has no influence on the occurrence of acute complications. Cross tables with extend of surgery (biopsy vs. incomplete vs. complete resection) as potential influence and dichotomized occurrence of complication as dependent variable will be given separately for each type of complication. χ^2-test will be performed.

20.2.5 Interim analyses and final analysis of the MRG

The final analysis will be performed after 9 years. After 3, 5 and 7 years interim analyses will be performed. All interim analyses are regarded as explorative. The results of the analyses will be discussed with the DMC.

20.2.6 Stopping for events in the MRG

A total of 8 MRG patients are expected per year. This number is to small too establish a stopping rule according to Emrich[38] comparing the NB2004-MRG with the historical control group (HCG). Since time to relapse/progression is approximately exponentionally distributed in the HCG, a sequential quote test according to Wald is not appropriate.

Retrospective analysis of NB90-97 patients classified as MRG patients according to the NB2004 criteria revealed a 3-year-EFS of 52±6% (page 54). This is virtually as low as the expected 3-year-EFS for the NB2004-HRG standard arm (3-year-EFS 45%). The main difference between MRG and HRG is the use of ASCT in the HRG. But if the event rate of

the MRG exceeds the event rate of the HRG standard arm, MRG treatment must be stopped immediately. Therefore, MRG and HRG standard arm will be compared for stopping criterion.

This stopping criterion will be examined by logrank tests of the event free survival time (EFS_D) between the MRG and the HRG standard arm. Events are progression, relapse or death of any reason. Definitions of progression and relapse are found on page 160.

Two analyses with a one-sided logrank test will be performed after 3 and 5 years. The significance level for each of the analyses is given by 0.10. A correction for multiple testing is not initiated since the analyses focus on the detection of an inferiority of the median risk group therapy.

The 3 year EFS_D-rate for the high risk standard arm is supposed to be 45% (figure 18, page 72). With a significance level of 10%, a one-sided question, the assumption of exponential distributed EFS_D, a recruitment of 30 patients per year in high risk standard arm and of 8 patients per year in the median risk group, a reduction of this EFS_D-rate by 15% in the MRG can be detected with a power of 44% after 3 years and 65% after 5 years. A reduction of this EFS_D-rate by 10% in the MRG can be detected with a power of 30% after 3 years and 42% after 5 years. The power was calculated with nQuery Advisor 3.0.

When one of the logrank tests shows a significant inferiority of the median risk group the group results will be discussed with the DMC.

20.2.7 Sample size calculation of the MRG

This trial assesses an intensified treatment for patients with medium risk compared to the historical control group (HCG). The EFS of the NB2004-MRG and HCG are considered to be exponentially distributed. The hazard rate of the HCG is approximated by 0.1837. The hazard ratio of the HCG was estimated using the observed 3-year-EFS rate (52%) as well as the ratio of the observed events (n=37) and the sum of the observed times (248 years). Both estimates were averaged. This results in an averaged curve which acceptably fits the observed curve. It has a 3-year-EFS rate of 58%.

The 3-year-EFS rate is expected to be improved by 15% using the intensified MRG treatment. Hence, the 3-year-EFS rate of the NB2004-MRG is supposed to be 73% resulting in a hazard ratio of 0.1049.

With a significance level of 5 %, an accrual period of 6 years, a follow-up period of 3 years, no drop-outs, and a recruitment rate of 8 patients per year a power of 71% is achieved for the one-sided log-rank test on difference.

The power was calculated for a historically controlled trial according to Emrich.[38]

The stated recruitment rate corresponds with the experience of NB97 trial.

20.2.8 Modifications of the MRG protocol

The design of this trial may be changed, if necessary, in case of new important discoveries. Modifications of the protocol will be made only in form of written amendments and with agreement of the study committee. The respective ethic commissions have to be informed of the modifications. The patient information has to be changed according to the modifications of the protocol.

20.3 High risk group statistics

20.3.1 Design of the trial

The aim of the trial is to compare the **high risk standard arm** consisting of 3 x (N5 + N6) with the **intensified high risk experimental arm** consisting of 2 x N8 + 3 x (N5 + N6) in children with high risk neuroblastoma (stage 4 older than 1 year, or MYCN amplified of any age) according to patient eligibility criteria (section 13.5). This treatment optimization trial is a multicenter, non-blinded, randomized, and prospective trial. The accrual period is 6 years followed by an observation period of 3 years.

As soon as diagnosis of high risk neuroblastoma has been established, stage 4 patients (≥1 year) and patients with MYCN-amplification (≥1 year) will be randomized to one of the two induction regimens. Randomization lists will be provided by the Institute for Medical Biostatistics, Epidemiology and Informatics, University Hospital of Mainz. Randomization will be done by blocks and will be stratified according to the following 4 groups:

- stage 4, LDH not elevated at diagnosis (definition see page 21), age ≥1-21 years, regardless of MYCN;
- stage 4, LDH elevated, age at diagnosis ≥1-<2 years, regardless of MYCN;
- stage 4, LDH elevated, age at diagnosis ≥2-21 years, regardless of MYCN;
- MYCN amplification of localized neuroblastoma (≥1 year)

Within this trial, the principals of the ICH-guidelines of good clinical practice (GCP) (http://www.emea.eu.int/index/indexh1.htm) as well as the declaration of Helsinki (http://www.wma.net/e/ethicsunit/helsinki.htm) will be respected.

20.3.2 End points of the HRG

According to the different questions the following end points are defined:

- **EFS_D:** Event free survival measured from the time of diagnosis up to an event or last follow-up for patients without event. An event is defined as death (for all reasons), progression, relapse following previous complete remission (according to the INSS criteria on page 160), or secondary malignant disease.

- **EFS_L:** locoregional EFS measured from the time of diagnosis up to an locoregional event or last follow-up for patients without locoregional event. A locoregional event is defined as (i) death (related to locoregional disease), (ii) local progression of residual primary tumor, (iii) locoregional relapse following previous complete remission of the primary tumor as defined on page 160.
- **OS:** Overall survival measured from the time of diagnosis up to death of any reason or last follow-up for surviving patients.
- **Early response** measured after two cycles of chemotherapy (either N5+N6 for the high risk standard arm or 2 x N8 for the high risk experimental arm) or after 60 days if the second cycle is not yet finished: Complete response, very good partial response, partial response, mixed response, stable disease, and progression/relapse according to the INSS (page 160).[19]
- **Response to induction therapy** measured prior to ASCT or after 280 days if the induction chemotherapy is not yet finished: Complete response, very good partial response, partial response, mixed response, stable disease, and progression/relapse according to the INSS (page 160).[19]
- **Chemotherapy toxicity** categorized according to the grading tables in the case report forms of the protocol (page 239). For toxicity not included in the tables of the case report forms, categorization according to the NCI-CTCAE scale (http://ctep.cancer.gov/forms/CTCAEv3.pdf) is required.
    - Grade of toxicity observed from the 1st day of chemotherapy cycle 1 (N5 for the high risk standard arm or N8 for the high risk experimental arm) until the start of the subsequent chemotherapy cycle,
    - Grade of toxicity observed from the 1st day of chemotherapy cycle 2 (N6 for the high risk standard arm or N8 for the high risk experimental arm) until the start of the subsequent chemotherapy cycle,
    - Frequency of chemotherapy cycles with toxicity grade ≥ 3 observed during the last 6 chemotherapy cycles in each patient (3x (N5+N6) for the high risk standard arm and for the high risk experimental arm): 0 – 6 counts per patient are possible,
    - Frequency of chemotherapy cycles with toxicity grade 4 observed during the last 6 chemotherapy cycles in each patient (3x (N5+N6) for the high risk standard arm and for the high risk experimental arm): 0 – 6 counts per patient are possible.
- **Surgery:**
    - Extent of the **initial surgery** categorized in: biopsy vs. incomplete resection vs. macroscopic complete resection. Initial surgery is the first tumor operation done in a patient.
    - Extent of the **best surgery** up to time t categorized in: biopsy vs. incomplete resection vs. macroscopic complete resection. Best surgery is the operation

performed from diagnosis up to time t which achieves the most extensive tumor resection.

- Frequency of complications related to surgery considered separately for the items: nephrectomy, bleeding, infection, intestinal obstruction, or other.

- **External beam radiation therapy:**
  - **Acute side effects** of EBRT considered separately according to the radiation therapy documentation form (page 250).
  - **Late effects** of EBRT considered separately according to the long term follow-up forms (page 258).
- **MIBG therapy**: activity [MBq] and whole body dose [Gy] assessed according to the dosimetry protocol (section 13.10.5).
- **Molecular markers:** MYCN, status of chromosome 1p and status of chromosome 11q (categorized according to criteria published by Ambros[4]). Tumor material is collected and stored in the tumor bank for future evaluation of other molecular markers which will be considered having prognostic impact during the ongoing trial. A neuroblastoma gene chip will be developed and applied.

20.3.3 Questions of the HRG

By means of this trial the following questions shall be answered:

Main question of the trial:

1 Does intensified induction chemotherapy lead to a different EFS_D than the standard induction therapy?

Secondary questions:

2 Does intensified induction chemotherapy lead to a different EFS_L than the standard induction therapy?

3 Does intensified induction chemotherapy lead to a different OS than the standard induction therapy?

4 Do the following factors influence EFS_D, EFS_L, and OS?:

- age,
- stage,
- LDH,
- metastatic pattern,
- treatment arm according to the randomization result,
- MYCN status,
- status of chromosome 1p,

- status of chromosome 11q,
- gene expression profile pattern,
- extent of initial surgery,
- extent of best surgery,
- EBRT,
- MIBG therapy?

5 Does early response depend on the type of induction therapy (standard or intensified induction) ?

6 Does the response to the complete induction therapy depend on the type of induction therapy (standard or intensified induction)?

7 Chemotherapy toxicity:

7.1 Does the intensified induction chemotherapy lead to a different grade of toxicity of chemotherapy cycle 1 than the standard induction chemotherapy?

7.2 Does the intensified induction chemotherapy lead to a different grade of toxicity of chemotherapy cycle 2 than the standard induction chemotherapy?

7.3 Does the intensified induction chemotherapy lead to a different frequency of chemotherapy cycles with toxicity grade $\geq$ 3 observed during the last 6 chemotherapy cycles than the standard induction chemotherapy?

7.4 Does the intensified induction chemotherapy lead to a different frequency of chemotherapy cycles with toxicity grade 4 observed during the last 6 chemotherapy cycles than the standard induction chemotherapy?

8 Surgery: What is the frequency of complications related to surgery?

9 External beam radiation therapy (EBRT):

9.1 What is the frequency of **acute side effects** related to radiation therapy?

9.2 What is the frequency of **late effects** related to radiation therapy?

10 Does the whole body dose correlate with the activity given in MIBG therapy?

20.3.4 Statistical analysis of the HRG

The analysis will be done according to the intention-to-treat principle. Additionally, a per-protocol analysis will be performed for explorative reasons. Per-protocol-patients must meet all following criteria:

- eligibility according to inclusion and exclusion criteria (page 78),

- induction treatment according to the treatment arm:
    a. standard arm: 6±2 cycles N5/N6,
    b. experimental arm: 2xN8 plus 6±2 cycles N5/N6,
- ASCT,
- retinoic acid: a total of 9±3 months treatment (regardless of the break scheduled after 6 months),
- no other anticancer treatment.

The main question will be analyzed on a significance level of α=0.05 within the intention-to-treat population. The p-values corresponding to the secondary questions and the per-protocol-analyses are regarded as explorative.

According to the questions of the trial the following null hypothesis and test statistics follow:

Main question of the trial

1 Null hypothesis: The EFS_D of children treated with intensified induction chemotherapy does not differ from the EFS_D of children treated with standard induction chemotherapy. This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the EFS_D, the quartiles of the EFS_D with the 95% CI, the EFS-rates at 3 and 5 years with the 95% CI will be illustrated.

Secondary questions:

2 Null hypothesis: The EFS_L of children treated with intensified induction chemotherapy does not differ from the EFS_L of children treated with standard induction chemotherapy. This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the EFS_L, the quartiles of the EFS_L with the 95% CI, the EFS_L-rates at 3 and 5 years with the 95% CI will be illustrated.

3 Null hypothesis: The OS of children treated with intensified induction chemotherapy does not differ from the OS of children treated with standard induction chemotherapy. This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the OS, the quartiles of the OS with the 95% CI, the OS-rates at 3 and 5 years with the 95% CI will be illustrated.

4 Cox regression models will be built for EFS_D, EFS_L, and OS including the following potential influential factors:

- age (continuous),
- stage (localized vs. stage 4S vs. *stage 4*)
- LDH (elevated vs. *normal* defined according to page 21),

- metastatic pattern (isolated bone marrow metastasis vs. *combined bone marrow and bone metastasis* vs. all other metastatic patterns vs. no metastases),
- treatment arm according to the randomization result (experimental arm vs. *standard arm*),
- treatment arm as realized (experimental vs. *standard arm*)
- status of MYCN (amplified vs. *not amplified*)
- status of chromosome 1p (deletion or imbalance vs. *no aberration*),
- status of chromosome 11q (deletion or imbalance vs. *no aberration*),
- gene expression profile pattern (signature: yes vs. *no*).
- extent of initial surgery (biopsy vs. incomplete vs. *complete resection*),
- extent of best surgery (biopsy vs. incomplete vs. *complete resection*),
- EBRT (yes vs. *no*),
- MIBG therapy (yes vs. *no*),

The items given in *italics* are regarded as reference. For description of categorical factors, Kaplan Meier curves, the quartiles of the survival times with the 95 % CI and the rates of the different survival rates at 3 and 5 years with the 95 % CI will be given.

5 Null hypothesis: the early response does not differ between standard and experimental induction therapy. This hypothesis will be analyzed by a two-sided Mann-Whitney U test. For descriptive reasons the respective frequency table will be illustrated.

6 Null hypothesis: the response to complete induction does not differ between standard and experimental induction therapy. This hypothesis will be analyzed by a two-sided Mann-Whitney U test. For descriptive reasons the respective frequency table will be illustrated.

7 Chemotherapy toxicity:

7.1 Null hypothesis: the median grade of toxicity in chemotherapy cycle 1 does not differ between standard and experimental induction. This hypothesis will be analyzed by a two-sided Mann-Whitney U test. For descriptive reasons the respective table will be illustrated.

7.2 Null hypothesis: the median grade of toxicity in chemotherapy cycle 2 does not differ between standard and experimental induction. This hypothesis will be analyzed by a two-sided Mann-Whitney U test. For descriptive reasons the respective table will be illustrated.

7.3 Null hypothesis: the frequency of chemotherapy cycles with toxicity grade $\geq$ 3 observed during the last 6 chemotherapy cycles does not differ between the two types of induction therapy (standard or intensified induction). This

hypothesis will be analyzed by a two-sided Mann-Whitney U test. For descriptive reasons the respective table will be illustrated.

7.4 Null hypothesis: the frequency of chemotherapy cycles with toxicity grade 4 observed during the last 6 chemotherapy cycles does not differ between the two types of induction therapy (standard or intensified induction). This hypothesis will be analyzed by a two sided Mann-Whitney U test. For descriptive reasons the respective table will be illustrated.

8 Null hypotheses: The extent of surgery has no influence on the occurrence of complications. Cross tables with extend of surgery (biopsy vs. incomplete vs. complete resection) as potential influence and dichotomized occurrence of complication as dependent variable will be given separately for each type of complication. χ^2-test will be performed.

9 External beam radiation therapy (EBRT):

9.1 Null hypotheses: EBRT has no influence on the occurrence of acute complications. Cross tables with EBRT (yes vs. no) as potential influence and dichotomized occurrence of **acute complication** as dependent variable will be given for each type of complication for the NB 2004-trial. Fisher's exact test will be performed.

9.2 Null hypotheses: EBRT has no influence on the occurrence of late effect. Cross tables with EBRT (yes vs. no) as potential influence and dichotomized occurrence of **late effects** as dependent variable will be given for each type of complication for the NB 2004-trial. Fisher's exact test will be performed.

10 MIBG therapy: Null hypothesis: the whole body dose does not correlate with the activity given in MIBG therapy. This hypothesis will be analyzed by Spearman's rank correlation coefficient and the respective p-value. For descriptive reasons the scatter plot will be given.

20.3.5 Interim and final analysis, stopping rule for HRG

Analyses will be performed after 1/3, 2/3 and all expected events occurred, unless the trial was stopped before. Both induction therapy arms are added up to evaluate the number of occurred events with respect to the expected number of events.

With an accrual period of 6 years, a follow-up period of 3 years, an accrual rate of 60 children per year, a 3-year EFS of 45% for children with standard induction therapy and expected 57.5% for patients with the experimental induction therapy, no drop outs and the assumption of exponential distributed EFS, a total number of 257 events is expected after 9 years. Therefore, the first interim analysis is scheduled to take place after 85 events and the second after 171 events. The final analysis will be performed after 257 events.

The trial will be terminated after an interim analysis, if the main question can already be answered at this interim analysis or the chance to answer the main question is low while continuing the trial.

The criteria for stopping the trial after an interim analysis are given by a 3-step group sequential plan according to Pampallona & Tsiatis with the possibility to stop the trial in favor for the alternative and the null hypothesis.[80] The bounds of the 3-step group sequential design result from α=5%, power=80%, hazard ratio =1.443, event free survival rates after 3 years of 45% and 57.5% for the two groups and an α-spending approach according to O'Brien & Fleming ($\Delta = 0$).[125]

20.3.6 Stopping for death of toxicity in the HRG

The potential difference between both treatment arms in death of toxicity is considered to be based on the additional toxicity of the N8 cycles. The proportion of death of toxicity will be analyzed each year 1.5, 2.5, 3.5, 4.5 and 5.5 years after the start of the trial. It will be computed as ratio of the number of study patients, which already had died of toxicity and the number of patients, who entered the trial 6 month prior to the analyses. A toxic death is defined as death related to chemotherapy toxicity.

The high risk experimental arm has to be closed if the proportion of death of toxicity exceeds the proportion of death of toxicity in the high risk standard arm relevantly.

This stopping criterion will be examined by a two-sample χ^2-test for equal proportions of death of toxicity without continuity correction between the high risk experimental arm and the high risk standard arm.

5 analyses with a one-sided two-sample χ^2-test for equal proportions without continuity correction will be performed after 1.5, 2.5, 3.5, 4.5, and 5.5 years. The overall significance level for all analyses is given by 10%. The correction for multiple testing is done by a group sequential test design according to Pocock.[136]

The proportion of death of toxicity is supposed to be 1% in the high risk standard arm. A increase of this proportion by factor 5 in the high risk experimental arm is not acceptable.

With a significance level of 10%, a one-sided question, the null hypothesis of no difference between the proportion of death of toxicity in both induction arms, a recruitment of 60 patients per year in the high risk group, a design with a maximum of k=5 stages, the critical values of the group sequential test design for Δ = 0.5 according to Pocock,[136] a power of 69% results to detect the unacceptable increase of the proportion of death of toxicity from 1% to 5%. The power was calculated with ADDPLAN 2.0.

When one of the analyses shows a significant inferiority of the high risk experimental arm the trial will be closed and all high risk patients will be treated according to the high risk standard arm.

20.3.7 Sample size calculation for the HRG

The trial will assess an intensified induction chemotherapy. According to the results of the previous trial, the 3 year EFS-rate for the standard induction chemotherapy is supposed to be 45%. The 3 year EFS-rate for the intensified chemotherapy is assumed to be 57.5%. With a significance level of 5%, an accrual period of 6 years, a follow-up period of 3 years, no drop-outs and on the assumption of exponential distributed EFS, 360 patients are necessary to obtain a power of 80% while performing a three step group sequential design according to Pampallona & Tsiatis explained on page 140 for the two-sided log-rank-test on difference. This corresponds with an annual recruitment rate of 60 patients. This rate has been achieved in the NB97 trial.

The sample size was calculated for an one-step design with nQuery Advisor 3.0 and the sample size was adapted to the 3-step group sequential design according to Jennison[80].

20.3.8 Modifications of the HRG protocol

The design of this trial may be changed, if necessary, in case of new important discoveries. Modifications of the protocol will be made only in form of written amendments and with agreement of the study committee. The respective ethic commissions have to be informed of the modifications. The patient information has to be changed according to the modifications of the protocol.

If an adaptation of the group sequential design is necessary – e.g. because of a low recruitment rate – the respective changes of the time points, number of interim analyses, maximal sample size and α-spending function will be done according to the conditional rejection error probability method by Schäfer and Müller.[145] The modifications can be done during a planned or unplanned interim analysis on the basis of the observed survival and treatment data collected so far. The corresponding conditional rejection error probability functions are defined by Schäfer and Müller.[145] If a design change is made the time point, the data file of the trial, all calculations and the description of the new group sequential design have to be recorded in an amendment.

21 TRIAL ORGANISATION

21.1 Cooperation with the local investigators

Prior to the entry of the first patient, each pediatric oncologist representing his/her participating hospital has to sign a hospital trial participation form. The form is enclosed in the CRF´s and must be sent to the trial office after signing.

By signing this form, the participating centers agree to fulfill all legal end ethical needs of the trial, e.g., patient information, data collection, data transmission, SAE reporting without delay. Each hospital needs to inform the health authorities and the local ethics committee about this trial. Every local investigator must apply for approval of the local ethics committee if this fits the policy of the local hospital.

21.2 Patient registration

All hospitals will report all patients to the trial office in Cologne using the early registration form (page 215) as soon as the diagnosis of neuroblastoma has been established. Each patient is given a consecutive four digit NB patient number for patient identification.

Registration of German patients is coordinated with the German Childhood Cancer Registry of the Institute for Medical Biostatistics, Epidemiology, and Informatics, University of Mainz. After establishing the diagnosis of neuroblastoma, the hospital will send the early registration form (page 215) to the German Childhood Cancer Registry in Mainz. Then, the hospital will receive the initial status report form (page 216).

For Swiss patients, these forms are used as well regardless the fact, that these patients are not registered in the German registry. The German Childhood Cancer registry will not get any data of these patients.

All other nations find nation specific early registration and initial status form on pages 215 and 216. These are to be filled in and sent to the trial office in Cologne. Details of national patients registration are outlined in section 27 concerning national variations.

22 DATA MANAGEMENT AND DOCUMENTATION

22.1 Case report forms (CRF)

All patient data are documented in the patient's file of the local hospital. Data relevant for the investigational treatment must be documented in the CRF-forms as well. There are forms for initial staging, for each treatment element, and for follow up either under treatment and after treatment. The forms are found on pages 179 to 258.

In general, there are different forms:

- Treatment/documentation overviews (pages 180-185)

- Patient information (pages 187-211)
- Documentation of the patient status (215-216),
- Randomization (pages 220-221),
- Request forms and documentation of laboratory investigations (pages 224-232),
- Chemotherapy application forms (pages 234-238 and 240),
- Chemotherapy toxicity documentation forms (pages 239 and 241),
- Documentation of other treatment elements (pages 248-250),
- Follow up forms including event report and SAE (=SUSAR) report (pages 252-258).

The toxicity of each chemotherapy cycle must be documented on the chemotherapy forms. If toxicity other than listed in the report form occurs, please use the CTCAE-toxicity grading system issued 12 December 2003 by NCI. It can be downloaded from http://ctep.cancer.gov/forms/CTCAEv3.pdf. If toxicity appears unexpected or severe, contact the trial office and consider **SAE report** (for details see pages 117-120, the report form is found on page 253).

22.1.1 Observation patients

After surgery observation patients undergo follow up as outlined on pages 32 and 181. The first year must be documented on the form found on page 254. Thereafter, the trial office automatically will send a follow-up form for each patient once a year for documentation of the current disease status of the patient (page 258).

In case of relapse, progression or death, **immediate report** using the **event report form** on page 252 is required.

22.1.2 Chemotherapy patients of all treatment groups

Time, doses and toxicity of treatment element (chemotherapy cycle, ASCT, EBRT, MIBG-therapy, RA) must be documented using the appropriate forms (pages 234-241). Initial surgery is documented on the form of the German Children's Cancer Registry (Mainz) for German trial centers (page 216) and at the national form for other trial centers. Secondary or further surgery is documented on the appropriate form (page 248).

The disease status must be documented on the form found on page 255:

- after the 2nd chemotherapy cycle,
- after the 4th chemotherapy cycle,
- after the 6th chemotherapy cycle (high risk standard arm) or after the 8th chemotherapy cycle (high risk experimental arm),
- after ASCT
- after retinoic acid 1 and retinoic acid 2

After the end of treatment, the patients undergo follow-up as outlined on page 33. The trial office will send a follow-up forms for each patient once a year for documentation of the current disease status of the patient automatically (page 258).

In case of relapse, progression or death, **immediate event report** using the **event report form** on page 252 is required.

22.2 Data quality and confidentiality

The local investigator is responsible for the correct documentation and for the quality of all data. To guarantee confidentiality, the patient/the parents must give consent for data exchange between the local investigator, the study office and all in the trial participating institutions during admission into the trial. These personal data will not be accessible to other persons except for those specified in the informed consent.

22.3 Data entry and data management

All data are documented in the patients file and in the case report forms (CRF's) of this protocol. The CRF's must be completed and sent to the trial office in Cologne. Only individuals experienced with the NB trials will enter data into the data base. All data will be checked for plausibility and discussed during data entry by the trial office. Data are stored in an Oracle® computer database. Only authorized individuals will have password protected access to the system. The server has a backup system to a parallel server and stream backup is performed every night.

23 MONITORING AND AUDIT

Data must be reported to the trial office with minimal delay. Data quality and plausibility will be checked by the trial office during entry into the database. In general, monitoring will be performed centrally by discussion of equivocal data by the trial office and by discussion with the participating hospital. In selected cases where data quality appears inadequate the trial office will compare the data reported with the original data. The participating hospitals give consent for this monitoring performed by authorized individuals.

24 ETHICAL, LEGAL, REGULATORY ISSUES

24.1 Ethical issues

The trial is based on the current version of the declaration of Helsinki (2000, Edinburgh, 2002 Washington, http://www.wma.net/e/ethicsunit/helsinki.htm) and the ICH-guidelines of good clinical practice (http://www.emea.eu.int/index/indexh1.htm). It is strongly recommended to download and read the most recent version from the internet resources.

The trial protocol and particularly the patient information has been reviewed and evaluated by the Ethics Committee of the University of Cologne. Copies of the approvals of the Cologne ethics committee are enclosed in the appendix starting on page 171.

24.2 Patient information

A patient can only participate in the trial after his/her guardian and (if appropriate for his/her psycho-intellectual development) the patient have signed the informed consent form. All parents and/or patients must be handed out the patient information form enclosed in the CRF at pages 187 to 202. The informed consent can only be given after the parents and/or the patient have been informed about the disease, about the treatment according to the clinical trial, about the side and late effects of the investigational treatment, about the assessment required for the trial, and about alternative treatment options. The parents and/or the patient must have the opportunity to ask all questions concerning the trial treatment before they sign the consent form.

24.3 Legal issues

All legal issues are country specific and, therefore, are found in section 27 on page 147.

25 REPORTING

Report of preliminary results will be given at the neuroblastoma trial commission workshop twice a year and at the meeting of the participating trial centers (approximately September/October 2005). The final results of the trial will be published three years after entry of the last trial patient. The principal investigator is responsible for final analysis and for publication. He can pass the actual data analysis or writing to members of the trial committee. Submission of manuscripts always requires the written consent of the principal investigator.

26 AMENDMENTS TO THE TRIAL PROTOCOL

Amendments to the trial protocol might become necessary due to preliminary results of the trial, to recent reports of other groups, or to ethical reasons. Every amendment must be agreed by the trial committee. The amendments must be signed according to the signatures on page 3. A new evaluation by the ethics committee might be required when the investigational treatment is modified. All participating hospitals will be sent a written information.

27 NATIONAL VARIATIONS (GERMANY)

27.1 Regulatory obligations

All clinical trials in Germany have to be conducted according to the §§ 40,41 of the German Drug Law. Every trial has to be announced to the corresponding district government “Regierungspräsidenten” and to the German authorities (Bundesinstitut für Arzneimittel und Medizinprodukte and/or the Paul-Ehrlich-Institut, respectively) before start of the study.

27.2 Ethics committee

The approval of the independent Ethics Committee of the University of Cologne was available before the start of this study. The statements of the committee are found in the appendix starting on page 171. Each trial participant must get the approval of the local ethics committee if this fits the policy of the local hospital.

According to §40 of the German AMG, the ethics committee of the University of Cologne must be informed about all SAE´s which might affect the safety of the study participants or the progress of the trial by the principal investigator immediately. This information will enclose a statement of the principal investigator about the severity and the suspected causal relationship to the investigational treatment.

27.3 Insurance

All subjects taking part in a trial will be insured by the sponsor. Insurance cover is provided by HDI Industrie Versicherungen, Dürrenhofstr. 6, D 90402 Nürnberg, Germany. A copy of the certificate is found on page 172.

27.4 Investigators and centers

27.4.1 Principal investigator according to §40 German drug law

In accordance with § 40 para 1 sub-para 4 of the German Drug Law, a clinical trial in humans shall only be performed if and as long as it is running under the supervision of a physician, with proven experience of at least two years in the field of clinical drug trials.

The principal investigator in Germany according to §40 German Drug Law is:

Prof. Dr. F. Berthold;
Dept. Pediatric Oncology and Hematology;
Children’s Hospital; University of Cologne;
Kerpener Str. 62, D-50924 Köln, GERMANY,
Tel. +49 221 478 - 4380, FAX - 4689,
Email: frank.berthold@medizin.uni-koeln.de

27.4.2 Investigators

Investigators will be documented in the study file. In general, all hospitals participating in the previous NB97 trial will cooperate in the NB2004 trial.

27.5 Patients registration

Registration of German patients is coordinated with the German Childhood Cancer Registry of the Institute for Medical Biostatistics, Epidemiology, and Informatics, University of Mainz. Early registration form (page 215) and initial status report form (page 216) are found in the case report forms. By sending the early registration form, the local investigator has to get **patient's written informed consent** for data transmission. The patient information and the trial participation forms are found on pages 187 to 211.

27.6 Documentation and data safety

The case report forms, patient files and raw data are to be retained for at least 15 years following the end of the clinical study. The investigator will ensure that a correct assignment of the case report forms to the corresponding patient files and raw data is possible at any time.

In the NB2004 trial, personal data of each patient will be registered and reported to the study office in Cologne. All individuals who have access to these data are bound to and will respect medical secrecy. The name of a patient will never be made public. Due to surveillance of clinical trials by health authorities, independent representatives of these health authorities will have insight into patient files to guarantee correct data registration. These representatives are bound to and will respect medical secrecy, too. By signing the consent form the patient and/or the parents give consent for data registration, reporting, and insight by independent representatives of health authorities.

27.7 Patient information and informed consent

Before inclusion in the study, every patients' guardian and patient (if appropriate for his/her psycho-intellectual development) has to give in writing his/her informed consent to participate in that study according ICH (http://www.wma.net/e/ethicsunit/helsinki.htm). The informed consent must include transmission of personal data.

Master copies of local patient information and local informed consent forms are included in the countries' study files on pages 187 to 211. The version approved by the respective Ethics Committees will be used by the investigators.

27.8 Reporting procedure for SAE´s/SUSAR's

Suspected unexpected serious adverse events must be reported to the national trial office in Cologne immediately, i.e., within 24 hours of the investigator becoming aware.

SAE Report
Tel. +49 (0) 221 478 6853,
FAX +49 (0) 221 478 6851

A report form is enclosed in the CRF on page 253. According to the standard of procedure, the trial office will inform the principal investigator about every SAE within 48 hours. The principal investigator has to decide whether the SAE is relevant for other trial participants.

The principal investigator will report all suspected unexpected severe adverse reactions (SUSAR's) to the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) within 7 days by telephone or FAX. An additional written report must be sent to the institute within further 8 days. Non-serious AE´s and expected SAE´s must be documented in the CRF but are not subject to immediate report.

The principal investigator has to inform the local investigators about all SAE´s which in his opinion might have a consequence for other patients currently under investigational treatment.

According to §40 of the German AMG, the ethics committee of the University of Cologne must be informed about all SAE´s which might affect the safety of the study participants or the progress of the trial by the principal investigator immediately. This information will enclose a statement of the principal investigator about the severity and the suspected causal relationship to the investigational treatment.

The local ethics committee can be informed about all SAE´s which might affect the safety of the study participants or the progress of the trial by the local investigator if this fits the policy of the participating hospital. Therefore, during the trial evaluation process, each participating hospital needs a close cooperation with the local ethics committee.

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29 APPENDIX

29.1 INSS neuroblastoma stages [19]

Stage	Definition
Stage 1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph node negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive for the tumor). A *grossly resected* midline tumor without ipsilateral (with: → stage 2A) or contralateral (with: → stage 2B) lymph node involvement is considered stage 1.
Stage 2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
Stage 2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph node positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumor infiltrating across the midline with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement. The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or or other organs except as defined for stage 4S.
Stage 4S	Localized primary tumor (as defined for stage 1, 2A, or 2B) with dissemination limited to liver, skin and bone marrow (limited to infants <1 year of age). Marrow involvement in stage 4S should be minimal, i.e., <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The MIBG scan should be negative in the marrow.

Multifocal primary tumors (e.g., bilateral adrenal primary tumors) should be staged according to the greatest extend of disease as defined and followed by a subscript letter M (e.g., 3_M)

29.2 Response criteria of neuroblastoma patients[19]

Response	Primary tumor	Metastatic site
CR	No tumor	No tumor; catecholamines normal
VGPR	Decreased by 90-99%	No tumor; catecholamines normal; residual ^{99}Tc bone changes allowed
PR	Decreased by >50%	All measurable sites decreased by >50%. Bones and bone marrow: number of positive bone sites decreased by >50%; no more than 1 positive bone marrow site allowed (if this represents a decrease from the number of positive sites at diagnosis)
MR	No new lesions; >50% reduction of any measurable lesion (primary or metastasis) with <50% reduction in any other; <25% increase in any existing lesion	
NR	No new lesions; <50% reduction but <25% increase in any existing lesion	
PD	Any new lesion; increase of any measurable lesion by >25%; previous negative marrow positive for tumor	

29.3 Guidelines for the preparation of tumor tissue during biopsy or resection

29.3.1 Handling of tumor tissue

All neuroblastoma samples will be sent to the tumorbank in Cologne in a *Tumorbox.* The tumorbank will check the tumor cell content of the samples and forward samples to the other collaborating laboratories if required for trial purposes or by special request of the local hospital.

Tumor tissue not actually needed for investigations will be stored in the tumorbank of the GPOH.

The *Tumorbox* system was established by the German competence net (Kompetenznetzwerk Pädiatrische Onkologie und Hämatologie, KPOH). The *Tumorbox* is provided by the KPOH to most of the collaborating hospitals. If not available, please call the laboratory hotline for assistance. A box will be provided within about 3 days. The box contains all slides and tubes required for shipping. The local hospital has to fill it with dry ice prior to shipping. The *Tumorbox* is designed to keep the contents frozen up to 3 days in the large chamber and additional material (e.g., tumor touch preparations, anticoagulated blood samples) unfrozen in the small chamber of the lid.

tumor tissue lab hotline
+ 49 (0) 221 - 478 6843

29.3.1.1 Resectable tumor

After gross tumor resection, tissue must be collected for routine diagnostic histology and for molecular analysis. The tumor should be processed by the local pathologist. Therefore, the tumor material must be transferred from the operation theatre to the pathology department under sterile conditions immediately (i.e., within 30 minutes). A longer interval will lead to degradation of RNA and prevents many of the analyses.

At least two or more samples (size 1x1x1cm) from morphologically different areas (if present) should be collected. If tumor nodules are seen by macroscopic examination, these nodules and the surrounding tissue should be collected. Mark the samples from different areas with capitals A, B, etc. In very large or heterogeneous tumors, collection of further samples C, D, etc. is recommended. Only the pathologist can decide whether collection of samples C, D, and more is required or possible. Do not sample necrotic

areas or the capsule of the tumor. Since surgical margins must remain identifiable, do not take samples from tumor margin if ever possible. The tumor specimens (A, B…) should be divided in four equal parts. The parts should be marked as A1, A2, A3, and A4 as shown in figure 29.

From A1 and B1, 10 touch preparations are made. Slides are provided in the *Tumorbox.* These slides must dry on air. After making the touch preps, the tumor samples A1, B1,… are put into tubes with 4% formalin for histology for the local pathologist. These tubes are not found in the *Tumorbox*.

The samples A2, A3, A4 and B2, B3, B4 should be snap frozen in liquid nitrogen and then transferred into the separate tubes each. These tubes are provided in the *Tumorbox* as well. Please mark each tube according to the tumor sample (A2, A3, A4, B2 etc.). The complete set of frozen samples can be stored in liquid nitrogen or at –70 to -80°C until it is shipped to the neuroblastoma tumorbank of the GPOH. If more tissue has been frozen (C, D,…) follow the guidelines above. It is strongly recommended to collect C, D, and more from large tumors for scientific purposes.

The remaining tumor tissue is fixed in 4% buffered formalin for local routine histology.[4]

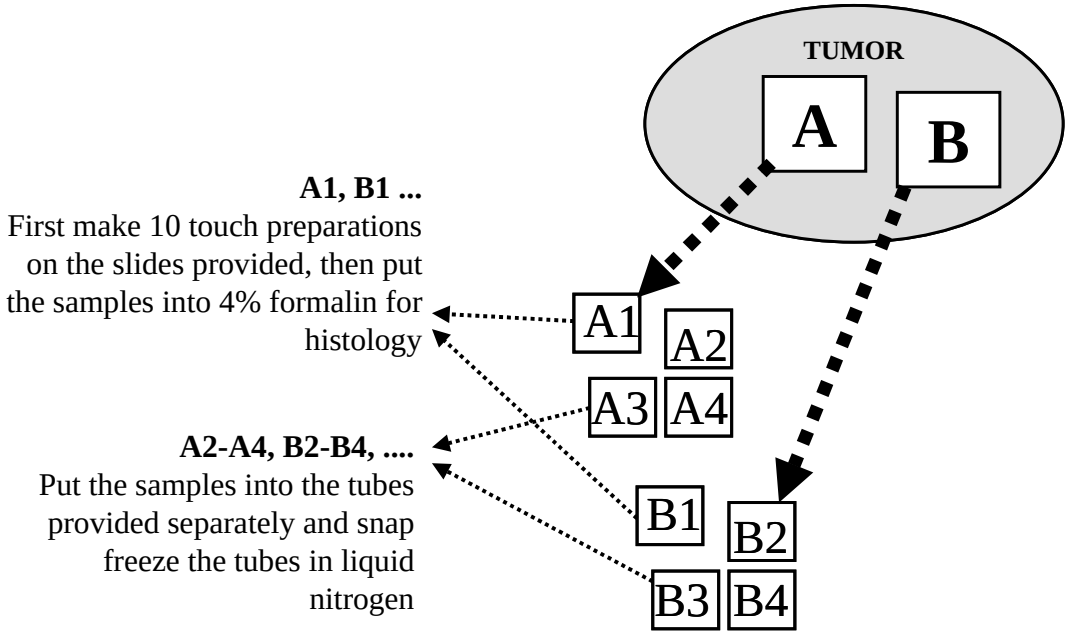

Figure 29: Preparation of the tissue samples during open surgery

29.3.1.2 Open biopsy or incomplete resection

The procedure strongly depends on the amount of tumor tissue. The tumor tissue should be processed by the local pathologist. Therefore, the tumor material must be transferred from the operation theatre to the pathology department under sterile conditions immediately (i.e., within 30 minutes).

In the case of open biopsy the surgeon should take biopsies from two different areas of the tumor (at least 1 cm³ each), if possible. The biopsies should be marked with capitals (A, B).

Depending on the size of the biopsy one sample should be used for touch preparations for FISH analysis and then put in 4% buffered formalin for diagnostic histology. The other samples should be snap frozen (for details see above). In the case of a very small biopsy the local pathologist has to decide whether a small part of the biopsy can be snap frozen for molecular analysis, which is strongly recommended and highly important for the treatment strategy decision.

29.3.1.3 Tru cut biopsies (not recommended)

Tru cut biopsies are not recommended because of the small amount gives no sufficient information on the macroscopic tumor structure which is important for the INPC classification (e.g., stroma-poor or stroma-rich, presence of nodules and necrosis, page 166) and may miss typical nodules in nodular ganglioneuroblastoma. In the case of very sick patients, however, tru cut may be the least disturbing procedure.

In general, six biopsies (at least two biopsies in case of very small lesions) of different areas of the tumor should be performed (at least 1 cm long and 0,1 cm thick). To avoid crush artifacts, do not scrape off the biopsy tissue from the needle. Put the needle into a tube with sterile RPMI 1640 or PBS and shake gently until the biopsy tissue is released into the solution. The local pathologist has to decide how much tissue is needed for diagnosis and if it is possible to and how much tissue can be snap frozen. Mark each biopsy with capitals (A, B, etc.). Put each biopsy in a petridish. If possible, each sample should be divided in two pieces. After removing the RPMI 1640 or PBS, one half is put in formalin and the other one is snap frozen. In case of 4-6 biopsies, 2 complete biopsy samples can be fixed in formalin for histological diagnosis and 2-4 biopsies can be snap frozen (without RPMI 1640 or PBS). In case of 2 biopsies, one biopsy can be fixed in formalin and the other one snap frozen. Touch imprints will be made from the Tumorbank laboratory from the frozen material.

The samples for diagnostic histology are fixed in 4% (buffered) formalin and processed as described.

29.3.1.4 Peripheral blood

About 5 ml of citrate blood should be collected from each patient as reference material for molecular investigations. The blood should be snap frozen. The tube is found in the *Tumorbox* set.

29.3.1.5 Other material

Normal tissue not infiltrated by the tumor can be used as reference material as well. If normal tissue has to be removed for surgical reasons during surgery, this normal tissue should be collected according to the guidelines above. **Extended resection only for collection of normal tissue is not accepted and must be avoided under all circumstances.**

If possible, peripheral heparin anti-coagulated blood for isolation of mononuclear blood cells should be collected in the glass vacutainer with the blue/black plug. It is found in the *Tumorbox*. This sample must be shipped by room temperature stored in the lid of the *Tumorbox*.

29.3.2 Shipping of tumor samples

After collection, the frozen material can be stored at –70 to –80 C for some days. Therefore, it is strongly recommended to avoid shipping over weekends.

The snap frozen tumor probes, the citrate blood and normal tissue must be send on dry ice. The inner of the *Tumorbox* should be filled with dry ice completely. The tubes with the tumor samples must be placed directly in the chamber under the dry ice. Place the citrate blood tube in the dry ice as well.

The touch preparations and the glass vacutainer with the blue/black plug are sent unfrozen and should be put in the lid of the *Tumorbox*.

The *Tumorbox* will be send to the central tumorbank in Cologne by express mail. Normal mail is not appropriate since sometimes it takes more than 3 days. The address is found at the shipping form on page 227. Please include a shipping form with all data filled in.

29.4 Guidelines for histology workup

After collecting tissue for molecular analysis (page 161), the local pathologist should collect multiple tissue blocks from the formalin fixed tumor tissue (minimum 1 block per centimeter of diameter of the tumor). All macroscopically different areas should be sampled (especially nodules). Necrosis and regressive tumor tissue should be sampled according to the their relative amount of the whole tumor to allow a correct estimation of regression grade.

The local pathologist should classify the neuroblastic tumor according to the INPC (International Neuroblastoma Pathology Committee) classification (page 166) including the mitosis-karyorrhexis index (MKI, page 167). It is suggested to indicate the proliferation rate by other means (e.g., Ki67 staining) additionally. The classification modified to Hughes should be mentioned (page 168). The grade of regression and differentiation has to be evaluated (page 169). If calcifications are present, it should be indicated. The pathologist has to comment if the resection margins are infiltrated by tumor cells.

After chemotherapy the tumor should be classified according to the above mentioned two classification schemes. It has to be mentioned in the diagnosis if a preoperative therapy has been applied.

The histological report of removed lymph nodes should include the number of positive lymph nodes and the categorization of the infiltrate according to the above mentioned classification schemes.

After the local pathologist has established the diagnosis, reference histology is required for all patients which are diagnosed for the first time and for relapsed patients. For reference histology, please send the pathology form (page 225) and either all available paraffin blocks or representative H&E slides from all available paraffin blocks plus at least one representative block to one of the reference laboratories:

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29.5 INPC Classification[149]

Neuroblastoma (Schwannian stroma-poor)

Neuroblastoma, undifferentiated

supplementary techniques (immuno-histochemistry, electron microscopy, and/or cytogenetics) usually required to establish diagnosis

tumor cells are undifferentiated

Neuroblastoma, poorly differentiated

most tumor cells are undifferentiated

only ≤5% of tumor cell population has cytomorphologic features of differentiation toward ganglion cells

background neuropil present

≤50% Schwannian stroma

Neuroblastoma, differentiating

>5% of tumor cell population has cytomorphologic features of differentiation toward ganglion cells with synchronous differentiation of the nucleus (enlarged eccentric nucleus with vesicular chromatin pattern and usually a single prominent nucleolus) and the conspicuous, eosinophilic or amphophilic cytoplasm

ganglion cell differentiation may be present

background neuropil present

≤50% Schwannian stroma

Ganglioneuroblastoma, intermixed (Schwannian stroma-rich)

proportion of ganglioneuromatous component to neuroblastic foci >50%

microscopic nests of neuroblastic cells are intermixed or randomly distributed in the ganglioneuromatous tissue

these nests are a mixture of neuroblastic cells in various stages of differentiation, usually dominated by differentiating neuroblasts and maturing ganglion cells

abundant background neuropil

Ganglioneuroma (Schwannian stroma-dominant)

Ganglioneuroma, maturing

predominantly ganglioneuromatous stroma

minor component of scattered, evenly or unevenly distributed collections of differentiating neuroblasts or maturing ganglion cells, no nests

Ganglioneuroma, mature

mature Schwannian stroma and ganglion cells

fascicular profile of neuritic processes, accompanied by Schwann cells and perineuritical cells

Ganglioneuroblastoma, nodular (Composite Schwannian stroma-rich/stroma-dominant and stroma-poor)

presence of macroscopic, usually hemorrhagic neuroblastic nodules (stroma-poor component) and coexisting ganglioneuroblastoma, intermixed (stroma-rich component) or ganglioneuroma (stroma-dominant component)

abrupt demarcation between nodules and stroma-rich/dominant component

proportion of stroma-rich/dominant to neuroblastic component not critical for diagnosis

stroma-rich/dominant component often located at the periphery of the tumor, can appear as thin or broad septa

if the tumor is ganglioneuroblastoma intermixed or ganglioneuroma and a lymph node metastasis is neuroblastoma, the case should be classified as ganglioneuroblastoma, nodular atypical

Neuroblastic tumor, unclassifiable

Neuroblastoma, NOS (not otherwise specified)

Ganglioneuroblastoma, NOS (not otherwise specified)

29.6 Mitosiskaryorrhexisindex (MKI)[149]

The MKI has to be evaluated in all subtypes of neuroblastoma and neuroblastic nodules of ganglioneuroblastoma nodular subtype including atypical nodular ganglioneuroblastoma.

For evaluation in highly cellular tumors count 6-8 HPF (about 700-900 cells/HPF) or for low cellularity tumors with abundant neuropil 20 HPF (about 100-300 cells /HPF).

Classification:

low MKI	<2% (<100/5000) cells in mitosis or karyorrhexis
intermediate MKI	2-4% (100-200/5000) cells in mitosis or karyorrhexis
high MKI	>4% (>200/5000) cells in mitosis or karyorrhexis

29.7 Hughes classification (modified)

grade 3	undifferentiated cells without signs of maturation
grade 2	Mixture of undifferentiated cells and at least some cells with partial differentiation toward ganglion cells (vesicular nuclei with prominent nucleolus, increased nucleus/cytoplasm-ratio, neuritic processes)
grade 1a	diffuse ganglioneuroblastoma, diffuse mixture of undifferentiated and differentiating cells and mature ganglion cells
grade 1b	ganglioneuroblastoma composite type ganglioneuroma with nodules of undifferentiated neuroblastoma with abrupt demarcation between both components

Harms et Wilke, 1979[61]

29.8 Grading of regression und differentiation

Regression grade

grade 1	no vital tumor cells
grade 2	<10% vital tumor cells
grade 3	10-50% vital tumor cells
grade 4	>50% vital tumor cells

Differentiation grade*

grade 1	ganglioneuroma
grade 2	<10% immature neuroblastic tissue
grade 3	10-50% immature neuroblastic tissue
grade 4	>50% immature neuroblastic tissue

* evaluated in the non-necrotic or regressive tumor tissue

29.9 Definition of molecular markers

MYCN-Status			
Technique	**Result**	**Definition**	**Recommended Probes**
FISH	Amplification	=over 4-fold MYCN copy number in relation to the copy number of chr. 2	n-myc (Q-Biogene) LSI N-myc (Abbott/Vysis) D2Z (Q-Biogene)
	Gain	=1.5-4-fold MYCN copy number in relation to the copy number of chr. 2	
	not amplified	=equal copy number of MYCN and chr. 2	
	Heterogeneous	=amplification only in a very small portion of the investigated tumor cells	
Southern Blot	Amplification	=over 4-fold increase of the band intensity of the MYCN band in relation to the internal reference	
	Gain	=2-4-fold increase of the MYCN band in relation to the internal reference	
	not amplified	=equal band intensities of the MYCN band and the internal reference	
1p-Status			
Technique	**Result**	**Definition**	**Recommended probes**
FISH	Deletion	=1 signal of the subtelomeric probe (D1Z2) in at least 33% of the investigated cells	D1Z2 (Q-Biogene) TelVysion 1p (Abbott/Vysis) D1Z1 (Q-Biogene) CEP satellite II/III DNA (Abbott/Vysis)
	Imbalance	=at least 2 signals of D1Z2 in combination with a higher number of reference signals in at least 33% of the investigated cells; ratio reference/subtelomeric probe = 3/2, 4/2, 4/3 etc.	
	No aberration	=equal number of subtelomeric and reference signals or aberration in less than 33% of the cells	
PCR	LOH	For single markers: hemizygous=loss of one allele in the tumor is indicated by the loss of the allele specific band in comparison with the blood-DNA reference	D1S243 (1p36.33) D1S468 (1p36.32) D1S253 (1p36.31) D1S244 (1p36.22) D1S436 (1p36.13) D1S199 (1p36.13) D1S234 (1p36.11) D1S513 (1p35.2) D1S80 (1p36.33)
	Heterozygous	=both alleles present in tumor-DNA	
	homozygous	=alleles indistinguishable (markers not informative)	

29.10 Vote of the ethics committee

13. SEP 2004

Prof. Dr. med. M. Staak
Vorsitzender der Ethik-Kommission
der Medizinischen Fakultät
der Universität zu Köln

50823 KÖLN, den 09.09.04
gl-mun
MELATENGÜRTEL 60 - 62
TELEFON 0221 - 478 - 4262
TELEFAX 0221 - 478 - 6751

Prof. Dr. med. M. Staak, Melatengürtel 60-62, 50823 Köln

Herrn
Prof. Dr. Berthold
Kinderonkologie

- im Hause -

04 – 049
Multizentrische Therapieoptimierungsstudie für die risikoadaptierte Behandlung von Kindern mit Neuroblastom.

Sehr geehrter Herr Kollege Berthold,

wir bestätigen den Eingang Ihres Schreibens vom 04.09.04, dem Sie eine Versicherungsbestätigung der HDI Industrieversicherung mit AVB beigefügt haben.

Gerne bestätigen wir Ihnen, dass hiermit die im Anschreiben der Ethik-Kommission vom 29.03.04 formulierten Anregungen umgesetzt worden sind, so dass seitens der Ethik-Kommission keine Bedenken gegen die Durchführung der Studie mehr bestehen.

Mit den besten Empfehlungen
und freundlichen Grüßen

(Univ.-Prof. Dr. med. M. Staak) (Dr. med. F. Glenewinkel)

29.11 Patients insurance

HDI

Versicherungsbestätigung

PROBANDENVERSICHERUNG

Versicherer:

HDI Industrie Versicherung AG
Riethorst 2

D-30659 Hannover

Versicherungsnehmer (Studienleitung)

Prof. Dr. Frank Berthold
Universitätsklinikum zu Köln
Zentrum für Kinderonkologie und -hämatologie
Joseph-Stelzmann-Str. 9
50924 Köln

Policen-Nr.:	85-403369-03016-390
Beginn der Studie:	**01.10.2004**
Ende der Studie:	**01.10.2012 (inklusive Rekrutierungs-, Behandlungs- und Nachbeobachtungsphase)**

Abweichend von Abschnitt A Ziff. 5 (2) der Allgemeinen Versicherungsbedingungen für klinische Prüfungen von Arzneimitteln (U 199) gilt der Vertrag nur für die o.g. Periode.
Der Versicherungsvertrag endet automatisch zum vorgenannten Zeitpunkt (Ende der Studie). Eine Verlängerung darüber hinaus erfordert vorherige Absprache mit dem Versicherer.
Weitere Studien werden vom Versicherungsschutz nur erfasst, wenn sie rechtzeitig vor Beginn angemeldet werden.

Klinische Prüfung:	Kooperative multizentrische Therapieoptimierungsstudie für die Behandlung von Säuglingen, Kindern und Jugendlichen mit Neuroblastom (NB 2004)
Prüfpräparat:	Block Topotecan/ Cyclophosphamid/ Etoposid für Hochrisikopatienten

- 2 -

Prüfzentrum:	Universitätsklinikum zu Köln, Zentrum für Kinderonkologie und –hämatologie, Joseph-Stelzmann-Straße 9, 50924 Köln
Geplante Patientenzahl:	800 Probanden

Wir bestätigen den Versicherungsschutz für die oben angeführte klinische Prüfung im Rahmen des mit dem Versicherungsnehmer abgeschlossenen Versicherungsvertrages. Die Deckung erstreckt sich auf alle Probanden bzw. Patienten, die an der klinischen Prüfung teilnehmen.

Je versicherte Person bilden **Euro 500.000,00** die Höchstgrenze für die Leistungen des Versicherers.

Die Höchstersatzleistung für alle Versicherungsfälle aus der klinischen Prüfung eines Arzneimittels beträgt:

a)	weniger als 1.000 Probanden	**Euro 5.000.000,00**
b)	bei 1.000 bis 3.000 Probanden	**Euro 10.000.000,00**
c)	bei mehr als 3.000 Probanden	**Euro 15.000.000,00**

Die Leistungen des Versicherers für die einzelnen versicherten Personen ermäßigen sich im entsprechenden Verhältnis, wenn die Summe der einzelnen Versicherungsleistungen diesen Höchstbetrag überschreiten würden.

Die Höchstersatzleistung für alle Versicherungsfälle aus den im Versicherungsjahr begonnenen klinischen Prüfungen beträgt **Euro 25.000.000,00**.

Nürnberg, 10.09.2004
fr, N-VG

HDI Industrie Versicherung AG
Niederlassung Nürnberg
Vertrieb Industrie-Großkunden

(Thamm) (Frank)

HDI

INDUSTRIE VERSICHERUNG

Allgemeine Versicherungsbedingungen für klinische Prüfungen von Arzneimitteln (Probandenversicherung/Arzneimittel)

– U 199 –

A Versicherte Gefahr

1. Gegenstand der Versicherung, Versicherungsfall

Der Versicherer gewährt Versicherungsschutz für den Fall, dass bei einer vom Versicherungsnehmer durchgeführten oder veranlassten klinischen Prüfung eines Arzneimittels eine Person, bei der die klinische Prüfung durchgeführt wurde (Versicherter), getötet oder ihr Körper oder ihre Gesundheit verletzt wird (Gesundheitsschädigung).

2. Versicherungsumfang

(1) Versicherungsschutz besteht für Gesundheitsschädigungen, die Folge von den bei der klinische Prüfung angewandten Arzneimitteln und/oder Stoffen sind.

(2) Unter den Versicherungsschutz fallen auch Gesundheitsschädigungen durch Maßnahmen, die an dem Körper des Versicherten im Zusammenhang mit der klinischen Prüfung des Arzneimittels durchgeführt werden.

(3) Soweit unabhängig von der klinischen Prüfung bestehende Krankheiten oder andere Ursachen bei der Gesundheitsschädigung mitgewirkt haben, besteht Versicherungsschutz nur für den entsprechenden ursächlichen Anteil der klinischen Prüfung an der Gesundheitsschädigung.

3. Ausschlüsse

Ausgeschlossen von der Versicherung sind:

(1) Gesundheitsschädigungen eines Versicherten, wenn er an einer Krankheit leidet, zu deren Behebung das zu prüfende Arzneimittel angewendet werden soll, und soweit diese Gesundheitsschädigungen

a) durch mit Sicherheit eintretende und dem Versicherten bekanntgemachte Wirkungen/Ereignisse verursacht worden sind und

b) über ein nach den Erkenntnissen der medizinischen Wissenschaft vertretbares Maß nicht hinausgehen.

(2) Gesundheitsschädigungen und Verschlimmerungen bereits bestehender Gesundheitsschädigungen, die auch dann eingetreten wären oder fortbestünden, wenn der Versicherte nicht an der klinischen Prüfung teilgenommen hätte;

(3) genetische Schädigungen (Veränderungen am Erbgut [Genom], an den Chromosomen, an den Genen oder an einzelnen Nukleotiden). Versicherungsschutz besteht jedoch, soweit die Veränderung beim Versicherten organische Gesundheitsschädigungen mit Auswirkungen auf das klinische Erscheinungsbild (Phänotyp) zur Folge haben;

(4) Gesundheitsschädigungen, soweit sie eingetreten sind, weil der Versicherte vorsätzlich den ausdrücklichen Anweisungen der Personen, die mit der Durchführung der klinischen Prüfung beauftragt sind, zuwidergehandelt hat.

4. Örtliche und zeitliche Geltung

(1) Die Versicherung umfasst klinische Prüfungen, die innerhalb der Bundesrepublik Deutschland durchgeführt werden.

(2) Vom Versicherungsschutz sind Gesundheitsschädigungen aus solchen klinischen Prüfungen erfasst, die während der Wirksamkeit des Vertrages begonnen wurden, unabhängig davon, ob der Vertrag vor Eintritt des Versicherungsfalles beendet wird.

(3) Versicherungsschutz besteht für Gesundheitsschädigungen, die spätestens 5 Jahre nach Abschluss der beim Versicherten durchgeführten klinischen Prüfung eingetreten sind und nicht später als 10 Jahre nach Beendigung der klinischen Prüfung dem Versicherer gemeldet werden.

Die Gesundheitsschädigung gilt als in dem Zeitpunkt eingetreten, in dem der Geschädigte erstmals einen Arzt wegen Symptomen konsultiert hat, die sich bei diesem Anlass oder später als Symptome der betreffenden Gesundheitsschädigung erweisen.

5. Beginn der Leistungspflicht, Vertragsdauer

(1) Die Leistungspflicht des Versicherers beginnt, wenn nicht ein späterer Zeitpunkt im Versicherungsschein selbst bestimmt oder ein früherer Zeitpunkt von dem Versicherer schriftlich zugesagt ist, mit der Einlösung des Versicherungsscheines. Wird der erste Beitrag erst nach dem als Beginn der Versicherung festgesetzten Zeitpunkt auf Anforderung ohne Verzug gezahlt, so beginnt der Versicherungsschutz mit dem vereinbarten Zeitpunkt.

(2) Der Vertrag ist zunächst für die in dem Versicherungsschein festgesetzte Zeit abgeschlossen. Beträgt die Dauer des Vertrages mindestens ein Jahr, so kann er schriftlich gekündigt werden. Die Kündigung muss spätestens drei Monate vor dem jeweiligen Ablauf des Vertrages der anderen Partei zugegangen sein. Sie soll durch eingeschriebenen Brief erfolgen. Wird die rechtzeitige Kündigung unterlassen, so verlängert sich der Vertrag jeweils um ein Jahr.

(3) Ein Versicherungsverhältnis, das für eine Dauer von mehr als fünf Jahren eingegangen ist, kann zum Ende des fünften Jahres oder jedes darauf folgenden Jahres unter Einhaltung einer Frist von drei Monaten gekündigt werden.

B Leistungen des Versicherers

6. Versicherungsleistung, Höchstleistung

I. (1) Der Versicherer leistet den Geldbetrag, der zum Ausgleich des durch die Gesundheitsschädigung eingetretenen materiellen Schadens des Versicherten erforderlich ist.

(2) Schaden ist der Unterschiedsbetrag zwischen der tatsächlichen Vermögenslage des Versicherten und der Vermögenslage, die bestehen würde, wenn die Gesundheitsschädigung nicht eingetreten wäre.

(3) Im Falle der Verletzung des Körpers oder der Gesundheit leistet der Versicherer

a) Heilbehandlungskosten im Rahmen des Angemessenen,

b) eine Geldrente, wenn infolge der Gesundheitsschädigung die Erwerbsfähigkeit des Versicherten aufgehoben oder gemindert wird, oder eine Vermehrung seiner Bedürfnisse eintritt.

Im Einvernehmen von Versicherer und Versichertem kann anstelle einer Rentenleistung eine Kapitalabfindung gewährt werden.

(4) Im Falle des Todes des Versicherten ersetzt der Versicherer demjenigen die Kosten der Beerdigung, welchem die Verpflichtung obliegt, die Kosten zu tragen. Stand der Versicherte zu diesem Zeitpunkt zu einem Dritten in einem Verhältnis, aufgrund dessen er diesem gegenüber kraft Gesetzes unterhaltspflichtig war oder unterhaltspflichtig werden konnte, und ist dem Dritten infolge der Tötung das Recht auf den Unterhalt entzogen, so erbringt der Versicherer Unterhaltsleistungen insoweit, als der Versicherte während der mutmaßlichen Dauer seines Lebens zur Gewährung des Unterhalts verpflichtet gewesen sein würde. Der Versicherer erbringt die Leistungen auch dann, wenn der Dritte zur Zeit des Todes des Versicherten gezeugt, aber noch nicht geboren war.

Im Einvernehmen von Versicherer und Versichertem kann anstelle einer Rentenleistung eine Kapitalabfindung gewährt werden.

434-0199 7. 03 (VR. 03. 300 U)

II. Die Höchstleistung beträgt für alle Versicherungsfälle aus der klinischen Prüfung eines Arzneimittels

5 Mio €, wenn bis zu 1.000 Personen,
10 Mio €, wenn mehr als 1.000 Personen bis zu 3.000 Personen,
15 Mio €, wenn mehr als 3.000 Personen

an der klinischen Prüfung teilnehmen. Die Versicherungsleistungen für die einzelnen versicherten Personen ermäßigen sich im entsprechenden Verhältnis, wenn die Summe der einzelnen Versicherungsleistungen diesen Höchstbetrag überschreiten würde.

III. Je versicherte Person bilden 500.000 € die Höchstgrenze für die Leistung des Versicherers.

IV. Die Höchstleistung für alle Versicherungsfälle aus den im Versicherungsjahr begonnenen klinischen Prüfungen beträgt 25 Mio €.

7. Nebenleistungen

Der Versicherer übernimmt auch die auf seine Anweisung oder mit seinem Einverständnis erwachsenden notwendigen Kosten einer medizinischen Begutachtung.

8. Erklärung über die Leistungspflicht

(1) Der Versicherer ist verpflichtet, sich innerhalb von zwei Monaten darüber zu erklären, ob und inwieweit eine Entschädigungspflicht anerkannt wird. Die Frist beginnt mit dem Eingang der Unterlagen, die zur Feststellung des Schadens dem Grunde und der Höhe nach beizubringen sind.

(2) Hat der Versicherer die Entschädigungspflicht anerkannt, so ist die Entschädigung binnen zwei Wochen zu leisten.

9. Verfahren bei Meinungsverschiedenheiten

I. (1) Im Falle von Meinungsverschiedenheiten über Art und Umfang der Gesundheitsschädigung oder darüber, ob und in welchem Umfang die Gesundheitsschädigung auf die klinische Prüfung im Sinne der Ziff. 2. zurückzuführen ist, entscheidet ein Ärzteausschuss; für alle sonstigen Streitpunkte sind die ordentlichen Gerichte zuständig.

(2) Die Entscheidung des Ärzteausschusses ist von dem Versicherten bis zum Ablauf von sechs Monaten, nachdem ihm die Erklärung des Versicherers nach Ziff. 8. zugegangen ist, zu beantragen. Versicherer und Versicherter können jedoch bis zum Ablauf dieser Frist verlangen, dass anstelle des Ärzteausschusses die ordentlichen Gerichte entscheiden. Wird dieses Verlangen gestellt, so kann der Versicherte nur Klage erheben.

(3) Lässt der Anspruchserhebende die unter (2) genannte Frist verstreichen, ohne dass er entweder die Entscheidung des Ärzteausschusses verlangt oder Klage erhebt, so sind weitergehende Ansprüche, als sie vom Versicherer anerkannt sind, ausgeschlossen. Auf diese Rechtsfolge hat der Versicherer in seiner Erklärung hinzuweisen.

II. Für den Ärzteausschuss gelten folgende Bestimmungen:

(1) Zusammensetzung:

a) Der Ärzteausschuss setzt sich zusammen aus zwei Ärzten, von denen jede Partei einen benennt, und einem Obmann. Dieser wird von den beiden von den Parteien benannten Ärzten gewählt und muss ein auf dem medizinischen Fachgebiet, in das die klinische Prüfung fällt, erfahrener Arzt sein, der nicht in einem Abhängigkeitsverhältnis zu einer der Parteien steht. Einigen sich die von den Parteien gewählten Ärzte nicht binnen eines Monats über den Obmann, so wird dieser auf Antrag einer Partei von dem Vorsitzenden der für den letzten inländischen Wohnsitz des Versicherten zuständigen Ärztekammer benannt. Hat der Versicherte keinen inländischen Wohnsitz, so ist die für den Sitz des Versicherers zuständige Ärztekammer maßgebend. Der Obmann kann einen auf dem betroffenen Fachgebiet besonders erfahrenen medizinischen oder pharmakologischen Sachverständigen als Gutachter hinzuziehen.

b) Benennt eine Partei ihr Ausschußmitglied nicht binnen eines Monats, nachdem sie von der anderen Partei hierzu aufgefordert ist, so wird dieses Ausschußmitglied gleichfalls durch den Vorsitzenden der Ärztekammer ernannt.

(2) Verfahren:

a) Sobald der Ausschuss zusammengesetzt ist, hat der Versicherer unter Einsendung der erforderlichen Unterlagen den Obmann um die Durchführung des Verfahrens zu ersuchen.

b) Der Obmann bestimmt im Benehmen mit den beiden Ausschußmitgliedern Ort und Zeit des Zusammentritts und gibt hiervon den Parteien mindestens eine Woche vor dem Termin Nachricht. Es bleibt ihm unbenommen, sich wegen weiterer Aufklärung des Sachverhalts an die Parteien zu wenden.

Im Rahmen der Sitzung ist der Versicherte, soweit möglich, zu hören und erforderlichenfalls zu untersuchen. Erscheint der Versicherte unentschuldigt nicht, so kann der Ausschuss aufgrund der Unterlagen entscheiden.

c) Die Entscheidung ist schriftlich zu begründen und vom Obmann zu unterzeichnen.

(3) Kosten:

Ist die Entscheidung des Ärzteausschusses für den Versicherten günstiger als es dem vor seinem Zusammentritt abgegebenen Angebot des Versicherers entspricht, so sind die Kosten voll von diesem zu tragen. Anderenfalls werden sie bis zu 10 % der geforderten Entschädigung, höchstens bis zu 5.000 € dem Versicherten auferlegt.

C Pflichten des Versicherungsnehmers

10. Vorvertragliche Anzeigepflichten des Versicherungsnehmers

I. (1) Der Versicherungsnehmer hat bei der Schließung des Vertrages alle ihm bekannten Umstände, die für die Übernahme der Gefahr erheblich sind, dem Versicherer anzuzeigen. Erheblich sind die Gefahrumstände, die geeignet sind, auf den Entschluss des Versicherers, den Vertrag überhaupt oder zu dem vereinbarten Inhalt abzuschließen, einen Einfluss auszuüben. Ein Umstand, nach welchem der Versicherer ausdrücklich und schriftlich gefragt hat, gilt im Zweifel als erheblich.

(2) Ist die Anzeige eines erheblichen Umstandes unterblieben, so kann der Versicherer von dem Vertrag zurücktreten. Das gleiche gilt, wenn die Anzeige eines erheblichen Umstandes deshalb unterblieben ist, weil sich der Versicherungsnehmer der Kenntnis des Umstandes arglistig entzogen hat.

(3) Der Rücktritt ist ausgeschlossen, wenn der Versicherer den nicht angezeigten Umstand kannte oder wenn die Anzeige ohne Verschulden des Versicherungsnehmers unterblieben ist.

II. (1) Der Versicherer kann von dem Vertrag auch dann zurücktreten, wenn über einen erheblichen Umstand eine unrichtige Anzeige gemacht worden ist.

(2) Der Rücktritt ist ausgeschlossen, wenn die Unrichtigkeit dem Versicherer bekannt war oder die Anzeige ohne Verschulden des Versicherungsnehmers unrichtig gemacht worden ist.

III. Hatte der Versicherungsnehmer die Gefahrumstände anhand schriftlicher, von dem Versicherer gestellter Fragen anzuzeigen, kann der Versicherer wegen unterbliebener Anzeige eines Umstandes, nach welchem nicht ausdrücklich gefragt worden ist, nur im Fall arglistiger Verschweigung zurücktreten.

IV. Wird der Vertrag von einem Bevollmächtigten oder von einem Vertreter ohne Vertretungsmacht geschlossen, so kommt für das Rücktrittsrecht des Versicherers nicht nur die Kenntnis und die Arglist des Vertreters, sondern auch die Kenntnis und die Arglist des Versicherungsnehmers in Betracht. Der Versicherungsnehmer kann sich darauf, dass die Anzeige eines erheblichen Umstandes ohne Verschulden unterblieben oder unrichtig gemacht ist, nur berufen, wenn weder dem Vertreter noch ihm selbst ein Verschulden zur Last fällt.

V. (1) Der Rücktritt kann nur innerhalb eines Monats erfolgen. Die Frist beginnt mit dem Zeitpunkt, in welchem der Versicherer von der Verletzung der Anzeigepflicht Kenntnis erlangt.

(2) Der Rücktritt erfolgt durch Erklärung gegenüber dem Versicherungsnehmer. Im Fall des Rücktritts sind, soweit das Versicherungsvertragsgesetz nicht in Ansehung des Beitrages ein anderes bestimmt, beide Teile verpflichtet, einander die empfangenen Leistungen zurückzugewähren; eine Geldsumme ist von dem Zeitpunkt des Empfangs an zu verzinsen.

VI. Tritt der Versicherer zurück, nachdem der Versicherungsfall eingetreten ist, so bleibt die Verpflichtung zur Leistung gleichwohl bestehen, wenn der Umstand, in Ansehung dessen die Anzeigepflicht verletzt ist, keinen Einfluss auf den Eintritt des Versicherungsfalles und auf den Umfang der Leistung des Versicherers gehabt hat.

VII. Das Recht des Versicherers, den Vertrag wegen arglistiger Täuschung über Gefahrumstände anzufechten, bleibt unberührt.

11. Gefahrerhöhung

Der Versicherungsnehmer ist verpflichtet, dem Versicherer unverzüglich alle nach Vertragsschluss eintretenden, die übernommene Gefahr erhöhenden Umstände mitzuteilen. Dies gilt sowohl für vom Versicherungsnehmer als auch von Dritten mit Duldung des Versicherungsnehmers verursachte Gefahrerhöhungen.

Die Anzeigepflicht besteht auch für Gefahrerhöhungen, die nach Antragstellung und vor Annahme des Antrages eintreten. Unrichtige Angaben zu den Gefahrumständen oder das arglistige Verschweigen sonstiger Gefahrumstände können den Versicherer berechtigen, den Versicherungsschutz zu versagen.

12. Beitragszahlung

I. (1) Der erste oder einmalige Beitrag wird, wenn nichts anderes bestimmt ist, sofort nach Abschluss des Versicherungsvertrages fällig. Zu dem Beitrag gehören auch die aus dem Versicherungsschein oder der Beitragsrechnung ersichtlichen Kosten (Ausfertigungsgebühr) und etwaige öffentliche Abgaben (Versicherungsteuer).

(2) Wird der erste oder einmalige Beitrag nicht rechtzeitig gezahlt, so ist der Versicherer, solange die Zahlung nicht bewirkt ist, berechtigt, vom Vertrage zurückzutreten. Es gilt als Rücktritt, wenn der Anspruch auf den Beitrag nicht innerhalb von drei Monaten vom Fälligkeitstage an gerichtlich geltend gemacht wird.

(3) Ist der Beitrag zur Zeit des Eintritts des Versicherungsfalles noch nicht gezahlt, so ist der Versicherer von der Verpflichtung zur Leistung frei. Wird der erste Beitrag erst nach dem als Beginn der Versicherung festgesetzten Zeitpunkt eingefordert, alsdann aber ohne Verzug gezahlt, so beginnt der Versicherungsschutz mit dem vereinbarten Zeitpunkt.

II. (1) Die nach Beginn des Versicherungsschutzes zahlbaren regelmäßigen Folgebeiträge sind, soweit nichts anderes vereinbart wurde, am Monatsersten des jeweiligen Beitragszeitraumes, sonstige Beiträge bei Bekanntgabe an den Versicherungsnehmer einschließlich etwaiger öffentlicher Abgaben (Versicherungsteuer) und einer Hebegebühr zu entrichten.

(2) Unterbleibt die Zahlung, so ist der Versicherungsnehmer auf seine Kosten unter Hinweis auf die Folgen fortdauernden Verzugs schriftlich zur Zahlung innerhalb einer Frist von zwei Wochen aufzufordern.

(3) Ist der Versicherungsnehmer nach Ablauf dieser Frist mit der Zahlung des Beitrages oder der Kosten im Verzug, gilt folgendes:

Bei Versicherungsfällen, die nach Ablauf dieser Frist eintreten, ist der Versicherer von der Verpflichtung zur Leistung frei, wenn der Versicherungsnehmer in der Fristbestimmung auf diese Rechtsfolge hingewiesen wurde.

Der Versicherer ist berechtigt, das Vertragsverhältnis ohne Einhaltung einer Kündigungsfrist zu kündigen. Die Kündigung kann bereits bei der Bestimmung der Zahlungsfrist ausgesprochen werden. In diesem Fall wird die Kündigung zum Fristablauf wirksam, wenn in dem Kündigungsschreiben darauf hingewiesen wurde. Die Wirkungen der Kündigung fallen fort, wenn der Versicherungsnehmer innerhalb eines Monats nach der Kündigung oder, falls die Kündigung mit der Fristbestimmung verbunden worden ist, innerhalb eines Monats nach dem Ablauf der Zahlungsfrist die Zahlung nachholt, sofern nicht der Versicherungsfall bereits eingetreten ist.

Kündigt der Versicherer nicht, ist er für die gerichtliche Geltendmachung der rückständigen Beiträge nebst Kosten an eine Ausschlussfrist von 6 Monaten seit Ablauf der zweiwöchigen Frist gebunden.

(4) Bei Teilzahlung des Jahresbeitrages werden die noch ausstehenden Raten des Jahresbeitrages sofort fällig, wenn der Versicherungsnehmer mit der Zahlung einer Rate in Verzug gerät.

13. Ergänzende Bestimmungen zur Beitragsberechnung

(1) Der Versicherungsnehmer meldet dem Versicherer zum Zweck der vorläufigen Beitragsberechnung vor Beginn eines jeden Versicherungsjahres, welche klinischen Prüfungen im Laufe des Versicherungsjahres voraussichtlich von ihm durchgeführt oder veranlasst werden, und nach Ablauf eines Versicherungsjahres, welche klinischen Prüfungen darüber hinaus noch begonnen wurden. Mit diesen Meldungen teilt der Versicherungsnehmer auch die voraussichtliche Zahl der von den Prüfungen betroffenen Personen (Versicherte) mit.

(2) Innerhalb eines Monats nach Ablauf eines Versicherungsjahres teilt der Versicherungsnehmer dem Versicherer zur Berechnung des endgültigen Beitrages mit:

a) welche klinischen Prüfungen welcher Arzneimittel im abgelaufenen Versicherungsjahr beendet wurden,

b) in welchem Versicherungsjahr diese klinischen Prüfungen jeweils begonnen haben und

c) wie viele Personen (Versicherte) an diesen Prüfungen teilgenommen haben.

(3) Der Versicherungsnehmer ist verpflichtet, dafür zu sorgen, dass geordnete Aufzeichnungen über die Versicherten geführt werden.

Die Aufzeichnungen müssen insbesondere so geführt werden, dass bei Eintritt einer versicherten Gesundheitsschädigung ein Zweifel über die Zugehörigkeit einzelner Personen zum versicherten Personenkreis nicht entstehen kann und dass der Ablauf und die Ergebnisse der klinischen Prüfung im Einzelfall rekonstruierbar sind.

14. Obliegenheiten

I. des Versicherungsnehmers

(1) Soweit der Versicherungsnehmer die klinische Prüfung selbst durchführt, ist er verpflichtet,

a) die Vorschriften der §§ 40 und 41 des Arzneimittelgesetzes (AMG) einzuhalten und die Arzneimittelprüfrichtlinien (§ 26 AMG) in ihrer jeweils gültigen Fassung zu beachten;

b) die Versicherten über das Bestehen des Vertrages und die Obliegenheiten gem. Abs. II. (1) und (2) zu unterrichten, soweit nicht § 41 Ziff. 7 AMG eingreift.

(2) Soweit der Versicherungsnehmer die klinische Prüfung durch von ihm beauftragte Dritte durchführen lässt, hat er diese zur Wahrung der Pflichten gem. Ziff. (1) anzuhalten.

(3) Im Schadenfall ist der Versicherungsnehmer im Rahmen seiner Möglichkeiten verpflichtet, den Versicherer bei der Aufklärung des Sachverhaltes und der Minderung des Schadens zu unterstützen.

II. des Versicherten

(1) Während der Dauer der klinischen Prüfung darf sich die versicherte Person einer anderen medizinischen Behandlung nur nach Rücksprache mit dem klinischen Prüfer unterziehen. Dies gilt nicht in einem medizinischen Notfall; der klinische Prüfer ist von einer Notfallbehandlung unverzüglich zu unterrichten.

(2) Eine Gesundheitsschädigung, die als Folge der klinischen Prüfung eingetreten sein könnte, ist dem Versicherer unverzüglich anzuzeigen.

(3) Der Versicherte hat alle zweckmäßigen Maßnahmen zu treffen, die der Aufklärung der Ursache und des Umfangs des eingetretenen Schadens und der Minderung dieses Schadens dienen.

(4) Auf Verlangen des Versicherers ist der behandelnde Arzt – als solcher gilt auch ein Konsiliararzt oder ein gutachterlich tätiger Arzt – zu veranlassen, einen Bericht über die Gesundheitsschädigung und, nach Abschluss der ärztlichen Behandlung, einen Schlussbericht zu erstatten; außerdem ist dafür Sorge zu tragen, dass alle etwa weiter noch von dem Versicherer geforderten Berichte des behandelnden Arztes geliefert werden. Alternativ kann der Versicherte den behandelnden Arzt von der ärztlichen Schweigepflicht entbinden, damit der Versicherer die vorab genannten Berichte direkt beim Arzt anfordern kann.

(5) Die behandelnden Ärzte, auch diejenigen, von denen der Versicherte aus anderen Anlässen behandelt oder untersucht worden ist, und die Sozialversicherungsträger sowie andere Versicherer, wenn dort die Gesundheitsschädigung gemeldet ist, sind zu ermächtigen, dem Versicherer auf Verlangen Auskunft zu erteilen.

(6) Hat der Versicherungsfall den Tod zur Folge, so ist dies unverzüglich anzuzeigen (Ziff. 17.), und zwar auch dann, wenn eine Meldung nach Abs. (2) bereits erfolgt ist. Dem Versicherer ist das Recht zu verschaffen, eine Obduktion durch einen von ihm beauftragten Arzt vornehmen zu lassen.

15. Rechtsverhältnis Dritter

(1) Die Ausübung der Rechte aus dem Versicherungsvertrag steht dem Versicherungsnehmer zu. Den Anspruch auf die Versicherungsleistung kann auch der Versicherte unmittelbar geltend machen.

(2) Alle für den Versicherungsnehmer bzw. Versicherten geltenden Vorschriften finden auf dessen Rechtsnachfolger Anwendung.

(3) Die Versicherungsansprüche können vor ihrer endgültigen Feststellung ohne ausdrückliche Zustimmung des Versicherers weder übertragen noch verpfändet werden.

16. Folgen von Obliegenheitsverletzungen

I. des Versicherungsnehmers

(1) Verletzen der Versicherungsnehmer oder dessen mit der Leitung der klinischen Prüfung verantwortlich Beauftragte (soweit sie betriebsangehörig sind) vorsätzlich eine Obliegenheit, die nach dem Eintritt des Versicherungsfalles zu erfüllen ist, so kann der Versicherer beim Versicherungsnehmer Rückgriff nehmen. Das Recht zum Rückgriff besteht nicht, wenn die Verletzung weder Einfluss auf den Eintritt oder die Feststellung des Versicherungsfalles noch auf die Feststellung oder den Umfang der dem Versicherer obliegenden Leistung gehabt hat. Unter denselben Voraussetzungen besteht ein Recht zum Rückgriff, wenn eine Obliegenheit verletzt ist, die vor dem Eintritt des Versicherungsfalles zu erfüllen war, und der Vertrag nach Abs. (2) gekündigt wurde.

(2) Verletzen der Versicherungsnehmer oder dessen mit der Leitung der klinischen Prüfung verantwortlich Beauftragte (soweit sie betriebsangehörig sind) eine Obliegenheit, die vor dem Eintritt des Versicherungsfalles dem Versicherer gegenüber zu erfüllen ist, so kann der Versicherer innerhalb eines Monats, nachdem er von der Verletzung Kenntnis erlangt hat, ohne Einhaltung einer Kündigungsfrist kündigen, es sei denn, dass die Verletzung als eine unverschuldete anzusehen ist.

II. des Versicherten

Verletzt der Versicherte vorsätzlich oder grob fahrlässig eine Obliegenheit, die nach dem Eintritt des Versicherungsfalles zu erfüllen ist, so ist der Versicherer von der Verpflichtung zur Leistung frei. Bei grob fahrlässiger Verletzung bleibt der Versicherer zur Leistung insoweit verpflichtet, als die Verletzung Einfluss weder auf die Feststellung des Versicherungsfalles noch auf die Feststellung oder den Umfang der dem Versicherer obliegenden Leistung gehabt hat.

D Sonstige Bestimmungen

17. Anzeigen und Willenserklärungen

(1) Alle für den Versicherer bestimmten Anzeigen und Erklärungen sind schriftlich abzugeben und sollen an die Hauptverwaltung des Versicherers oder an die im Versicherungsschein oder in dessen Nachträgen als zuständig bezeichnete Geschäftsstelle gerichtet werden. Die Vertreter sind zu deren Entgegennahme nicht bevollmächtigt.

(2) Hat der Versicherungsnehmer seine Anschrift geändert, die Änderung aber dem Versicherer nicht mitgeteilt, so genügt für eine Willenserklärung, die dem Versicherungsnehmer gegenüber abzugeben ist, die Absendung eines eingeschriebenen Briefes an die letzte dem Versicherer bekannte Anschrift. Die Erklärung wird in dem Zeitpunkt wirksam, in welchem sie ohne die Anschriftenänderung bei regelmäßiger Beförderung dem Versicherungsnehmer zugegangen sein würde.

18. Widerspruchsrecht des Versicherungsnehmers

Werden die für den Vertrag geltenden Versicherungsbedingungen oder die weitere für den Vertragsinhalt maßgebliche Verbraucherinformation erst zusammen mit dem Versicherungsschein übersandt, hat der Versicherungsnehmer ein gesetzliches Widerspruchsrecht, über das er belehrt werden muss.

Fehlt diese Belehrung oder liegen dem Versicherungsnehmer der Versicherungsschein, die Versicherungsbedingungen oder die Verbraucherinformation nicht vollständig vor, kann dieser noch innerhalb eines Jahres nach Zahlung des ersten Beitrages widersprechen.

19. Gerichtsstände

(1) Für Klagen, die aus dem Versicherungsvertrag gegen den Versicherer erhoben werden, bestimmt sich die gerichtliche Zuständigkeit nach dem Sitz des Versicherers oder seiner für den Versicherungsvertrag zuständigen Niederlassung. Hat ein Versicherungsagent am Zustandekommen des Vertrages mitgewirkt, ist auch das Gericht des Ortes zuständig, an dem der Versicherungsagent zur Zeit der Vermittlung oder des Abschlusses seine gewerbliche Niederlassung oder – bei Fehlen einer gewerblichen Niederlassung – seinen Wohnsitz hatte.

(2) Klagen des Versicherers gegen den Versicherungsnehmer können bei dem für den Wohnsitz des Versicherungsnehmers zuständigen Gericht erhoben werden. Soweit es sich bei dem Vertrag um eine betriebliche Versicherung handelt, kann der Versicherer seine Ansprüche auch bei dem für den Sitz oder die Niederlassung des Versicherungsnehmers zuständigen Gericht geltend machen.

20. Verjährung, Klagefrist

(1) Die Ansprüche aus diesem Versicherungsvertrag verjähren in zwei Jahren. Die Verjährung beginnt mit dem Schluss des Jahres, in welchem die Leistung verlangt werden kann.

Ist ein Anspruch des Versicherungsnehmers bei dem Versicherer angemeldet worden, so ist die Verjährung bis zum Eingang der schriftlichen Entscheidung des Versicherers gehemmt.

(2) Hat der Versicherer den Versicherungsanspruch abgelehnt, so ist der bestrittene Versicherungsanspruch bei Meidung des Verlustes durch Erhebung der Klage binnen einer Frist von sechs Monaten geltend zu machen. Die Frist beginnt mit dem Tage, an dem der Anspruchsberechtigte durch eingeschriebenen Brief unter Hinweis auf die Rechtsfolgen der Fristversäumung davon in Kenntnis gesetzt worden ist, inwieweit sein Anspruch auf Versicherungsschutz bestritten wird.

Erläuterungen zu den Allgemeinen Versicherungsbedingungen für klinische Prüfungen von Arzneimitteln

zu Ziff. 1:

Als versicherte Person gilt auch die bei der Durchführung der klinischen Prüfung bereits gezeugte Leibesfrucht der Versicherten.

zu Ziff. 6. I.:

Bedingungsgemäß ersetzt der Versicherer den konkret eingetretenen materiellen Schaden des Versicherten. Der Umfang des Schadens ist so beschrieben, dass der Versicherte dasjenige ersetzt bekommt, was er auf der Grundlage des § 249 BGB bekäme, wenn ein Schädiger ihm gegenüber haftpflichtig wäre.

Wird infolge der Gesundheitsschädigung die Erwerbsfähigkeit des Versicherten aufgehoben oder gemindert oder kommt es zu einer Vermehrung seiner Bedürfnisse, ist eine Geldrente entsprechend § 843 BGB zu gewähren.

Da der Umfang des Schadens durch Vergleich der Vermögenslagen vor und nach Eintritt der Gesundheitsschädigung ermittelt werden soll, tritt insoweit kein Schaden ein, als dem Versicherten oder seinen Hinterbliebenen ein Anspruch auf Leistung aus einer Sozialversicherung, gegen einen Krankenversicherer oder ein gesetzlicher Anspruch auf Lohn- und Gehaltsfortzahlung, auf Fortzahlung von Dienst- oder Amtsbezügen oder auf Gewährung von Versorgungsbezügen zusteht. Bei Streit über die Entstehung solcher Ansprüche wird der Versicherer gegen Abtretung der strittigen Ansprüche die Leistungen vorab gewähren.

Eine Ersatzpflicht besteht nach Ziff. 2. nur für solche Schäden, die durch die klinische Prüfung verursacht sind.
Nicht ersatzpflichtig sind dabei Schäden, die lediglich im Anschluss an die klinische Prüfung infolge psychogener Störungen des Versicherten auftreten, ohne dass die klinische Prüfung eine objektive Ursache hierfür gesetzt hat.

INITIALE DOKUMENTATION (DEUTSCH)

Übersicht: Initiale Diagnostik und Dokumentation

		Wo durchführen?	Bemerkungen
Anamnese und Klinische Untersuchung			
Labor	Blutbild, Elektrolyte, Leber, Niere, Gerinnung	lokal	
	Blutgruppe	lokal	
	HLA-1-Klasse	lokal	
	Karyogramm	lokal	bei konstitutionellen Auffälligkeiten
Virologie	Hepatitis, HIV, CMV, Parvovirus B19	lokal	
EKG/ECHO		lokal	wenn Chemotherapie geplant
EEG		lokal	wenn Chemotherapie geplant
Audiometrie		lokal	wenn Chemotherapie geplant
Tumormarker	LDH, NSE, Ferritin	lokal	
	Katecholamine HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
Bildgebung	Sono Primärtumor	lokal	
	Sono übrige Organe	lokal	
	Röntgen Thorax	lokal	
	MRT Primärtumor	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	MRT Schädel	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	nur bei Stadium 4 Formular ↗ Seite 220
	MRT Wirbelsäule (WS)	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	bei paravertebralem Tumor Formular ↗ Seite 220
	MIBG-Szintigraphie	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	
	evtl. Octreotid-Szintigraphie		bei MIBG negativem Primärtumor
	Skelettszintigraphie	lokal	nur bei MIBG negativem Primärtumor oder bei MIBG positiven Skelettherden
Knochenmark (4 Stellen)	Zytologie	lokal	
	Zytologie ≥5 Ausstriche	Köln	Bei KM-Befall >60% **≥10 Ausstriche** je Punktionsstelle beilegen; Formular ↗ Seite 232
	Immunzytologie	Köln	Heparin-Knochenmark, 2-3 ml pro Punktionsstelle, Versand in 24h ungekühlt; Formular ↗ Seite 232
Tumormaterial	Histologie	lokal	Bitte Kopie des Befunds an Studienleitung schicken
	Referenzhistologie	Köln oder Kiel	Formular ↗ Seite 224
	Molekulargenetik und Tumorbank	über Köln nach Heidelberg, Köln, Marburg, Stuttgart oder Zürich	**Tumorboxsystem** (Materialverarbeitung im OP ↗ Seite 161 und 229) Versandformular ↗ Seite 227 Befunde beilegen, wenn lokal molekulargenetische Untersuchungen durchgeführt wurden
Dokumentation	Einwilligungserklärung		↗ Seite 187 bis 211
	Erstmeldung	Mainz und Köln	Formular ↗ Seite 215
	Ersterhebung	Köln und Mainz	Formular ↗ Seite 216 Bitte Befunde der lokalen Histologie beilegen
	Randomisation	Köln	nur Stadium 4 >1 Jahr und MYCN-amplifizierte >1 Jahr ☎ +49 (0) 221 – 478 6853 ☎ +49 (0) 175 – 38 29 512 Formular ↗ Seite 220

Übersicht: Beobachtungsgruppe

Zeitpunkt nach OP	Maßnahme	Wo durchführen	Bemerkungen
Woche 6	Klinische Untersuchung HVA/VMA in **Urin**/Serum Sonographie PT+Mets (Stadium 4S) **Dokumentation** Formular ↗ Seite 254	 Göttingen 	 Formular ↗ Seite 231
3 Monate	Klinische Untersuchung HVA/VMA in **Urin**/Serum postoperatives MRT (PT+ ggf. Mets) **Dokumentation** Formular ↗ Seite 254	 Göttingen Referenzbeurteilung bei Rest	 Formular ↗ Seite 231
4 ½ Monate	Klinische Untersuchung HVA/VMA in **Urin**/Serum Sonographie PT+Mets (Stadium 4S) **Dokumentation** Formular ↗ Seite 254	 Göttingen 	 Formular ↗ Seite 231
6 Monate	Klinische Untersuchung HVA/VMA in **Urin**/Serum evtl. MRT Primärtumor Sono Metastasen (St.4S) **Dokumentation** Formular ↗ Seite 254	 Göttingen Referenzbeurteilung bei Rest	 Formular ↗ Seite 231 Formular ↗ Seite 220
7 ½ Monate	Klinische Untersuchung HVA/VMA in **Urin**/Serum Sonographie PT+Mets (Stadium 4S) **Dokumentation** Formular ↗ Seite 254	 Göttingen 	 Formular ↗ Seite 231
9 Monate	Klinische Untersuchung HVA & VMA in **Urin**/Serum Sonographie PT+Mets (Stadium 4S) **Dokumentation** Formular ↗ Seite 254	 Göttingen 	 Formular ↗ Seite 231
10 ½ Monate	Klinische Untersuchung HVA/VMA in **Urin**/Serum Sonographie PT+Mets (Stadium 4S) **Dokumentation** Formular ↗ Seite 254	 Göttingen 	 Formular ↗ Seite 231
12 Monate	Klinische Untersuchung HVA/VMA in **Urin**/Serum MRT des Primärtumors MIBG-Szintigraphie **Dokumentation** Formular ↗ Seite 254	 Göttingen Referenzbeurteilung bei Rest Referenzbeurteilung bei Rest 	 Formular ↗ Seite 231 Formular ↗ Seite 220
Wenn Chemotherapie: Vor jedem N4 Block	Klinische Untersuchung, LDH, NSE HVA & VMA in **Urin**/Serum Sonographie PT+Mets (Stadium 4S) EKG/Echo **Dokumentation** • jeder Chemoblock (Formular ↗ Seite 234) • dessen Toxizität (je Chemoblock ein Formular ↗ Seite 239) vervollständigen; • Tumorstatus nach jedem Block (Formular ↗ Seite 255) **Jede unerwartete vermutete schwere Nebenwirkung der Chemotherapie (SUSAR) erforderte eine SAE-Meldung (↗ Seite 253)**	lokal Göttingen lokal lokal	 Formular ↗ Seite 231
Bei jeder OP	Histologie Referenzhistologie Molekulargenetik und Tumorbank **Dokumentation** 2. und folgende Operation(en) (Formular ↗ Seite 248, bitte OP Bericht, lokale Histologie und Referenzhistologie beilegen)	lokal Köln oder Kiel über Köln	 Formular ↗ Seite 224 und 225 Anweisung ↗ Seite 229, Formular ↗ Seite 227
follow-up	**entsprechend Übersicht Seite 32.** **Die jährliche Statuserhebung (↗ Seite 258) wird den Kliniken vom Studienbüro NB2004 automatisch zugeschickt.** **Erleidet der Patient ein Rezidiv/Progress, dann bitte umgehend Ereignismeldung (↗ Seite 252) vollständig ausfüllen und zuschicken.** **Jede unerwartete vermutete schwere Nebenwirkung der Chemotherapie (SUSAR) erforderte eine SAE-Meldung (↗ Seite 253)**		

Übersicht: Mittlere Risikogruppe (MRG) 1 von 2

Zeitpunkt	Maßnahme	Wo durchführen	Bemerkungen
Vor jedem N4, N5 und N6	Klinische Untersuchung, BB, CRP, Elektrolyte, Leber, Gerinnung, Niere, LDH, Sonographie Primärtumor	lokal	
Vor jedem N4 und N6	EKG/Echo	lokal	
Vor jedem N5	Audiometrie	lokal	
Nach 2 Blöcken	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT (wenn OP geplant) oder Sono des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	Knochenmarkzytologie (≥5 Ausstriche)	Köln	nur Stadium 4 <1 Jahr Formular ↗ Seite 232
	Immunzytologie	Köln	nur Stadium 4 <1 Jahr Heparin-Knochenmark, 2-3 ml pro Punktionsstelle, Versand ungekühlt Formular ↗ Seite 232
	Dokumentation • erste Chemoblöcke (N5/N6, Formulare ↗ Seiten 234-238), • deren Toxizität (je Chemoblock ein Formular ↗ Seite 239), • Tumorstatus vor 3. Chemoblock (Formular ↗ Seite 255)		
Nach 4 Blöcken	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT (wenn OP geplant) oder Sono des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	Knochenmarkzytologie	lokal	nur Stadium 4 <1 Jahr
Bei ZweitOP	Histologie	lokal	
	Referenzhistologie	Köln oder Kiel	Formular ↗ Seite 224-226
	Molekulargenetik und Tumorbank	über Köln	Anweisung ↗ Seite 229, Formular ↗ Seite 227
	Dokumentation (Formular ↗ Seite 248, bitte OP Bericht und lokale Histologie beilegen)		
Vor Erhaltungstherapie	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	MIBG-Szintigraphie	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	
	Knochenmarkzytologie	lokal	nur Stadium 4 <1 Jahr
	Knochenmarkzytologie (≥5 Ausstriche)	Köln	nur Stadium 4 <1 Jahr Formular ↗ Seite 232
	Immunzytologie	Köln	nur Stadium 4 <1 Jahr Heparin-Knochenmark, 2-3 ml pro Punktionsstelle, Versand ungekühlt Formular ↗ Seite 232
	Dokumentation • gesamte Induktionstherapie (6 Blöcke, Formulare ↗ Seiten 234-238), • deren Toxizität (je Chemoblock ein Formular ↗ Seite 239), • Tumorstatus vor Erhaltungstherapie (Formular ↗ Seite 255)		

Übersicht: Mittlere Risikogruppe (MRG) 2 von 2

Zeitpunkt	Maßnahme	Wo durchführen	Bemerkungen
nach 2 N7-Blöcken	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	Sonographie Primärtumor	lokal	
nach Erhaltungstherapie	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	MIBG-Szintigraphie	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	
	Knochenmark	wie oben	nur wenn bei Voruntersuchung noch befallen
	Dokumentation • Durchführung der Erhaltungstherapie (Formular ↗ Seite 237), • Toxizität der Erhaltungstherapie (Formular ↗ Seite 239), • Tumorstatus nach Erhaltungstherapie (Formular ↗ Seite 255); • weitere Operationen (Formular ↗ Seite 248, bitte OP-Bericht und lokale Histologie beilegen), • externe Radiotherapie, wenn erfolgt (Formular ↗ Seite 250)		
nach 3 Monaten Retinsäure	Katecholamine HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	Sono Primärtumor	lokal	
nach 6 Monaten Retinsäure = Ende Kurs 1	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	Dokumentation Retinsäure follow-up (↗ Seiten 256-257)		
vor Start Retinsäure Kurs 2	Katecholamine HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	Sono Primärtumor	lokal	
Ende Retinsäure Kurs 2 = Therapieende	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	MIBG-Szintigraphie	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	nur, wenn bei vorangehender Untersuchung noch auffällig!
	Dokumentation Retinsäure follow-up (↗ Seiten 256-257)		
follow-up	**entsprechend Übersicht Seite 34** **Die jährliche Statuserhebung (↗ Seite 258) wird den Kliniken vom Studienbüro NB2004 automatisch zugeschickt.** **Erleidet der Patient ein Rezidiv/Progress, dann bitte umgehend Ereignismeldung (↗ Seite 252) vollständig ausfüllen und zuschicken.** **Jede unerwartete vermutete schwere Nebenwirkung der Chemotherapie (SUSAR) erforderte eine SAE-Meldung (↗ Seite 253)**		

Übersicht: Hochrisikogruppe (HRG) 1 von 2

Zeitpunkt	Maßnahme	Wo durchführen	Bemerkungen
Vor jedem Block	Klinische Untersuchung, BB, CRP, Elektrolyte, Leber, Niere, LDH; Sonographie (PT + Mets) empfohlen (jeden 2. Block nötig)	lokal	
Vor jedem N4, N6 und ASCT	EKG/Echo	lokal	
Vor jedem N5 und ASCT	Audiometrie	lokal	
Nach 2 Blöcken	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	MRT Schädel/WS	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	wenn initial auffällig, Formular ↗ Seite 220
	MIBG-Szintigraphie	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	
	Knochenmarkzytologie	lokal	
	Knochenmarkzytologie (≥5 Ausstriche)	Köln	Formular ↗ Seite 232
	Immunzytologie	Köln	Heparin-Knochenmark, 2-3 ml pro Punktionsstelle, Versand ungekühlt (↗ Seite 232)
	Dokumentation • erste Chemoblöcke (2xN8 bzw. N5/N6, Formulare ↗ Seiten 234-238), • deren Toxizität (je Chemoblock ein Formular ↗ Seite 239), • Tumorstatus vor 3. Chemoblock (Formular ↗ Seite 255).		
nach 4 Blöcken	Knochenmarkzytologie	lokal, Untersuchung in Köln (Zytologie + Immunzytologie), wenn gewünscht	
	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	Sonographie	lokal	
nach 6 Blöcken (N8-Arm)	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	Sonographie	lokal	
Bei ZweitOP	Histologie	lokal	
	Referenzhistologie	Köln oder Kiel	Formular ↗ Seite 224-226
	Molekulargenetik und Tumorbank	über Köln	Anweisung ↗ Seite 229, Formular ↗ Seite 227
	Dokumentation (Formular ↗ Seite 248, bitte OP-Bericht und lokale Histologie beilegen)		
Vor ASCT (Megatherapie)	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	MRT Schädel/WS	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	nur, wenn bei vorangehender Untersuchung auffällig!
	MIBG-Szintigraphie	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	
	Knochenmarkzytologie	lokal	
	Knochenmarkzytologie (≥5 Ausstriche)	Köln	Formular ↗ Seite 232
	Immunzytologie	Köln	Heparin-Knochenmark, 2-3 ml pro Punktionsstelle, Versand ungekühlt (↗ Seite 232)
	Dokumentation • gesamte Induktionstherapie (6 bzw. 8 Blöcke, Formulare ↗ Seiten 234-238), • deren Toxizität (je Chemoblock ein Formular ↗ Seite 239), • Tumorstatus vor Megatherapie (Formular ↗ Seite 255)		

Übersicht: Hochrisikogruppe (HRG) 2 von 2

Zeitpunkt	Maßnahme	Wo durchführen	Bemerkungen
3 Monate nach ASCT	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	MRT Schädel/WS	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	nur, wenn bei vorangehender Untersuchung auffällig!
	MIBG-Szintigraphie	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	
	Knochenmark	lokal, Untersuchung in Köln (Zytologie + Immunzytologie), wenn gewünscht	nur, wenn bei vorangehender Untersuchung befallen!
	Dokumentation • Durchführung der Megatherapie (PRST-Formular Tag 100 ↗ Seite 242), • Toxizität der Megatherapie (Formular ↗ Seite 241), • Tumorstatus nach Megatherapie (Formular ↗ Seite 255); • weitere Operationen (Formular ↗ Seite 248, bitte OP Bericht und lokale Histologie beilegen), • MIBG Therapie, wenn erfolgt (Formular ↗ Seite 249), • externe Radiotherapie, wenn erfolgt (Formular ↗ Seite 250)		
6 Monate nach ASCT = Ende Retinsäurekurs 1	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	MRT Schädel/WS	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	nur, wenn bei vorangehender Untersuchung noch auffällig!
	Dokumentation: Retinsäure Follow-up 1 (↗ Seiten 256-257)		
9 Monate nach ASCT = Start Retinsäurekurs 2	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	MRT Schädel/WS	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	nur, wenn bei vorangehender Untersuchung noch auffällig!
	MIBG-Szintigraphie	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	nur, wenn bei vorangehender Untersuchung noch auffällig!
	Knochenmark	lokal, Untersuchung in Köln (Zytologie + Immunzytologie), wenn gewünscht	nur, wenn bei vorangehender Untersuchung befallen!
Ende Retinsäure = Therapieende	HVA & VMA in **Urin**/Serum	Göttingen	Formular ↗ Seite 231
	NSE	lokal	
	MRT des Primärtumors	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	Formular ↗ Seite 220
	MRT Schädel/WS	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	nur, wenn bei vorangehender Untersuchung noch auffällig!
	MIBG-Szintigraphie	lokal, Referenzbeurteilung in Köln nur bei unklarem Befund	nur, wenn bei vorangehender Untersuchung noch auffällig!
	Knochenmark	lokal, Untersuchung in Köln (Zytologie + Immunzytologie), wenn gewünscht	nur, wenn bei vorangehender Untersuchung befallen!
	Dokumentation: Retinsäure Follow-up 2 (↗ Seiten 256-257)		
follow-up	**entsprechend Übersicht Seite 34** **Die jährliche Statuserhebung (↗ Seite 258) wird den Kliniken vom Studienbüro NB2004 automatisch zugeschickt.** **Erleidet der Patient ein Rezidiv/Progress, dann bitte umgehend Ereignismeldung (↗ Seite 252) vollständig ausfüllen und zuschicken.** **Jede unerwartete vermutete schwere Nebenwirkung der Chemotherapie (SUSAR) erforderte eine SAE-Meldung (↗ Seite 253)**		

NB2004 Klinik-Einwilligung zur Studienteilnahme

Bitte senden an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

An
Prof. Dr. F. Berthold
Studienleitung NB2004
Zentrum für Kinderonkologie- und Hämatologie
des Universitätsklinikums Köln
Kerpener Straße 62
50924 Köln

Als die/der für die Behandlung onkologischer Erkrankungen verantwortliche Ärztin/Arzt der Klinik

_____
Name des Arztes

_____
Name der Klinik

_____ _____ _____
Telefon **Telefax** **Email**

erkläre ich in Kenntnis des Studienprotokolls NB2004 die Teilnahme unseres Zentrums an der Therapieoptimierungsstudie NB2004. Unser Zentrum verpflichtet sich:

- die Notwendigkeit eines Ethikvotums der lokalen Ethikkommission abzuklären und dieses gegebenenfalls einzuholen,
- diese Studie den kooperierenden Fachabteilungen unseres Zentrums (z.B. Chirurgie, Strahlentherapie, Nuklearmedizin, Pathologie) zur Verfügung zu stellen,
- die Eltern und gegebenenfalls den Patienten vor Eintritt in die Studie eingehend über das Ziel der Studie, die geplante Behandlung, deren Nebenwirkungen und alternative Behandlungsmöglichkeiten aufzuklären,
- die Eltern und gegebenenfalls den Patienten auf die Freiwilligkeit der Studienteilnahme hinzuweisen,
- alle Patienten mit Neuroblastom, die ihr schriftliches Einverständnis zur Datenweitergabe gegeben haben, der Studienleitung zu melden,
- die gewünschten Daten an die Studiendokumentation unverzüglich weiterzuleiten,
- bei auftretenden schwerwiegenden unerwarteten Nebenwirkungen (SAE) die Studienleitung innerhalb 24 Stunden nach Bekanntwerden zu informieren. Eine Weitermeldung an die zuständige Landes- und Bundesoberbehörden übernimmt die Studienleitung,
- autorisierten Personen im Rahmen des Monitoring Zugang zu den Patientenakten zu gewähren.

Es besteht eine Patientenversicherung bei HDI Versicherung, der Nachweis ist im Protokoll enthalten.

_____ _____ _____
Stempel mit Name/Adresse/Telefon **Datum** **Unterschrift**

NB2004 Patienteninformation - Beobachtungsgruppe

Patient Name	Patient Vorname	geboren	NB Nummer

Studienname: Kooperative multizentrische Therapieoptimierungsstudie für die Behandlung von Säuglingen, Kindern und Jugendlichen mit Neuroblastom (NB2004) – Beobachtungsgruppe

Studienleiter: Prof. Dr. F. Berthold
Studienbüro: Zentrum für Kinderonkologie und –hämatologie,
Universitätsklinikum zu Köln, Kerpener Straße 62, 50924 Köln

Liebe Eltern,

bei Ihrem Kind wurde die Diagnose eines Neuroblastoms gestellt. Das Neuroblastom ist eine grundsätzlich bösartige Erkrankung des Kindesalters. Der Verlauf der Erkrankung kann jedoch sehr unterschiedlich sein. Beim Fehlen von Risikofaktoren (z.B. wenig fortgeschrittenes Stadium, junges Alter, keine MCYN-Amplifikation und keine Veränderungen am Chromosom 1) kann sich die Erkrankung sogar ohne Chemotherapie zurückbilden. Ihr Kind wird aus folgenden Gründen der Beobachtungsgruppe zugeordnet:

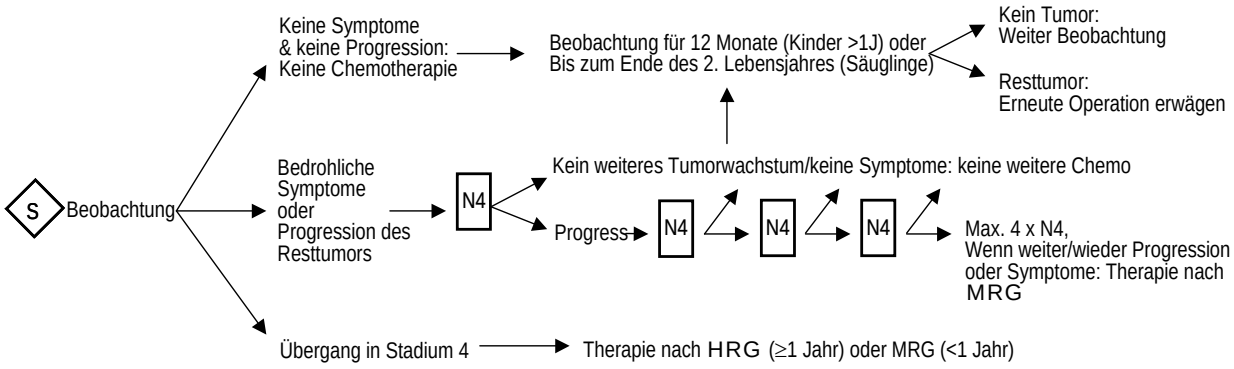
- ☐ Stadium 1
- ☐ Stadium 2, keine Veränderungen an Chromosom 1p
- ☐ Stadium 3, <2 Jahre, keine Veränderungen an Chromosom 1p
- ☐ Stadium 4S

Bitte lesen Sie diese Patienteninformation sorgfältig durch. Ihr Arzt wird mit Ihnen auch direkt über diese Studie sprechen. Bitte fragen Sie Ihn, wenn Sie etwas nicht verstehen oder wenn Sie zusätzlich etwas wissen möchten.

Was soll in dieser Studie untersucht werden?

Frühere Untersuchungen haben gezeigt, dass beim Fehlen von Risikofaktoren auf eine Chemotherapie des Neuroblastoms verzichtet werden kann. Dabei hat man sich zunächst nur auf Säuglinge beschränkt. Einige Tumoren verschwanden spontan, andere Tumoren haben bis heute eine stabile Größe. Einige Tumoren zeigten eine Größenzunahme, so dass diese Patienten eine Chemotherapie erhalten mussten. Der spätere Beginn dieser Chemotherapie hatte keine negativen Auswirkungen auf die Heilungsraten. Bei den übrigen Patienten konnte vollständig auf eine Chemotherapie verzichtet werden.

In der Neuroblastomstudie NB97 wurden auch ältere Kinder mit kleinem Tumorrest nach Operation nur beobachtet und erhielten keine Chemotherapie. Gründliche Analysen dieser Krankheitsverläufe geben Hinweise, dass auch bei älteren Kindern und größeren Resttumoren auf eine Chemotherapie verzichtet werden kann, ohne die Heilungsraten zu gefährden. Wir sind der Meinung, dass Kinder nur dann eine Chemotherapie erhalten sollen, wenn dies unumgänglich ist.



Ablaufschema für Beobachtungspatienten (S = Operation, N4 = Chemotherapie)

Welche anderen Behandlungsmöglichkeiten gibt es?

Beim Fehlen von Risikofaktoren erhalten Patienten nach vollständiger operativer Tumorentfernung (Stadium 1) weltweit keine Chemotherapie. Dazu gibt es keine sinnvolle Alternative. Kann der Tumor nicht oder nur unvollständig entfernt werden, kann man eine Chemotherapie geben. Der genaue Ablauf dieser Chemotherapie variiert zwischen einzelnen Ländern. Wir würden Chemotherapie entsprechend dem vorangehendem Behandlungsprotokoll NB97 in Betracht ziehen.

Wie wird die Studie ablaufen?

Während der ohnehin notwendigen Tumoroperation wird so viel Tumor wie möglich entfernt. Manchmal ist der Tumor gut abgekapselt und lässt sich ohne Risiko vollständig entfernen. Manchmal liegen wichtige Gefäße, Nerven oder Organe im Tumor oder in unmittelbarer Nachbarschaft des Tumors, so dass die komplette oder teilweise Tumorentfernung gefährlich ist. Dann wird nur eine kleine Probe entnommen. Diese Probe wird gründlich untersucht, um die feingewebliche Diagnose zu stellen und spezielle molekulare Risikofaktoren am Tumorgewebe zu untersuchen.

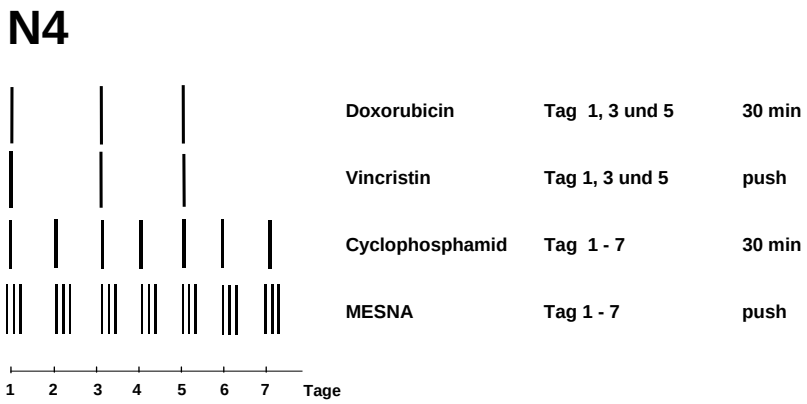
Tumormaterial, welches aktuell nicht für die Untersuchung benötigt wird, wird in der Tumorbank „Embryonale Tumoren“ der Gesellschaft Pädiatrische Hämatologie und Onkologie aufbewahrt. Es steht damit ausschließlich zur Erforschung der Tumoreigenschaften zur Verfügung. Mit diesen Erkenntnissen soll es in Zukunft möglich werden, aus der anfangs entnommenen Tumorprobe für jeden Patienten die bestmögliche Therapie vorherzusagen.

Etwa 8-12 Wochen nach der Tumoroperation ist eine erneute gründliche Untersuchung des Patienten erforderlich, um die Größe des verbliebenen Resttumors zu bestimmen. Danach erfolgen regelmäßige Kontrolluntersuchungen (klinische Untersuchung, Blutuntersuchung, Urinuntersuchung, Ultraschall, in größeren Abständen auch Kernspintomographie, Szintigraphie und wenn

erforderlich Knochenmarkpunktion). Das Ausmaß dieser Diagnostik entspricht den üblichen Kontrolluntersuchungen für alle derartigen Patienten. Keinesfalls werden im Rahmen der Studie zusätzliche Untersuchungen oder Gewebeentnahmen über das aus medizinischer Sicht notwendige Maß hinaus erforderlich.

Zeigt der Resttumor eine stabile Größe oder eine Größenabnahme, erfolgen Nachuntersuchungen in zunehmendem zeitlichem Abstand.

Zeigt sich zu irgend einem Zeitpunkt eine deutliche Größenzunahme des Resttumors ohne dass Ihr Kind Beschwerden (wie Schmerzen, Darmverstopfung, Atemnot, Gewichtsstillstand, Fieber ungeklärter Ursache) oder klinische Krankheitszeichen zeigt, müssen die Kontrollen unter Umständen in kürzeren Abständen durchgeführt werden. Kommt es infolge einer Größenzunahme zu Krankheitszeichen, die Ihr Kind beeinträchtigen oder gefährden, ist eine Chemotherapie erforderlich. Für diesen Fall ist eine milde Chemotherapie mit „N4“ Blöcken vorgesehen. Sobald das Tumorwachstum gestoppt und die Symptome beherrscht sind, wird diese Chemotherapie beendet. Wächst der Tumor erneut oder bestehen die Symptome weiter, erhält der Patient eine stärkere Chemotherapie entsprechend der mittleren Risikogruppe des Protokolls NB2004. Diese Therapie kann Ihnen Ihr Arzt erklären.



Ablaufplan des Chemotherapieblocks N4

Mit welchen Nebenwirkungen ist zu rechnen?

Durch den Verzicht auf eine Chemotherapie können den meisten Patienten deren mögliche Nebenwirkungen erspart werden.

Wird dennoch eine Chemotherapie erforderlich, kann es zu folgenden Nebenwirkungen kommen, die in ihrer Ausprägung je nach Chemotherapiezyklus und individueller Medikamentenverträglichkeit variieren können:

- Übelkeit, Erbrechen, gelegentlich auch Schwindel, Kreislaufprobleme oder allergische Reaktionen während der Infusion der Medikamente,
- Vorübergehende Beeinträchtigung der Blutbildung: Infolge des Mangels an weißen Blutkörperchen (Leukozyten) wird die Körperabwehr geschwächt. Der Patient wird anfällig für Infektionen. Diese können einen bedrohlichen Verlauf nehmen und erfordern unter Umständen eine Antibiotikatherapie unter stationären Bedingungen. Ein Mangel an roten Blutkörperchen (Erythrozyten) beeinträchtigt das körperliche Leistungsvermögen des Patienten. Bei fast allen Patienten werden während der Behandlung Bluttransfusionen notwendig. Der Mangel an Blutplättchen (Thrombozyten) führt zu einer Blutungsneigung. Lebensbedrohliche Blutungen können nur durch die Transfusion von Blutplättchen vermieden werden.
- Vorübergehende Schleimhautschädigung: Der gesamte Verdauungstrakt kann betroffen sein. Dadurch kann es zu Mundschmerzen, Schluckbeschwerden, Bauchschmerzen, Verstopfung oder Durchfall kommen.
- Vorübergehender Haarausfall.

Ist unser Kind versichert?

Wie für alle klinischen Prüfungen gesetzlich vorgeschrieben, wurde für diese Studie eine Patientenversicherung bei der HDI Industrie Versicherungs- AG, Riethorst 2, 30659 Hannover, Niederlassung Nürnberg, Telefon 0911–2012-0 abgeschlossen. Die Police-Nummer ist 85-403369-03016-390. Die Versicherungshöchstsumme pro Einzelfall beträgt € 500.000,00. Die allgemeinen

Versicherungsbedingungen sind im Studienprotokoll enthalten und können Ihnen auf Wunsch ausgehändigt werden. Schadenersatzansprüche, die über etwaige Versicherungsleistungen hinausgehen, sind ausgeschlossen. Die Versicherungszeit beträgt 2 Jahre vom Zeitpunkt der Diagnose (Studienaufnahme) an gerechnet.

Um den Versicherungsschutz nicht zu gefährden, hat der Versicherte folgende Pflichten:

- Während der Dauer der Studie darf sich die versicherte Person einer anderen medizinischen Behandlung nur nach Rücksprache mit dem behandelnden Arzt unterziehen. Dies gilt nicht für Notfälle. Der behandelnde Arzt ist von einer Notfallbehandlung unverzüglich zu unterrichten.
- Eine Gesundheitsschädigung, die als Folge der Studie eingetreten sein könnte, ist dem Versicherer unter oben genannter Adresse unverzüglich anzuzeigen.

Was passiert mit den Daten unseres Kindes?

Im Rahmen der Studie NB2004 werden personenbezogene krankheits- und behandlungsrelevante Daten vom Patienten erhoben und an die Studienzentrale in Köln zur Auswertung weitergegeben. Dabei handelt es sich nur um Daten über die Krankheit Ihres Kindes. Verantwortlich für die Datenverarbeitung ist der Leiter der Studie. Alle Personen, die Einblick in die gespeicherten Daten haben, sind zur Wahrung des Datenschutzes verpflichtet. Der Name des Patienten wird zu keinem Zeitpunkt öffentlich gemacht.

Auf Grund gesetzlicher Regelungen haben bestimmte Personen (autorisierte Dritte) ein Recht auf Einsichtnahme in die personenbezogenen Daten. Dazu zählen Vertreter der zuständigen Überwachungsbehörden oder der Bundesoberbehörde. Die Einsichtnahme erfolgt um sicherzustellen, dass die Daten dieser Studie korrekt erhoben wurden. Diese Personen sind jedoch von Amtes wegen ebenfalls zur Verschwiegenheit verpflichtet.

Daten über Langzeitverläufe sind eine wichtige Grundlage für die Weiterentwicklung der Behandlung des Neuroblastoms im Kindesalter. Die Daten bleiben deshalb über die Laufzeit der Studie hinaus gespeichert. Die Daten werden allerdings umgehend anonymisiert, wenn uns das Einverständnis zur Datenspeicherung entzogen wird.

Mit der Unterzeichnung der Einwilligungserklärung zur Studienteilnahme geben Sie Ihre Einwilligung zur Erhebung und Weitergabe der Daten sowie zur Einsichtnahme durch autorisierte Dritte.

Beendigung der Studienteilnahme

Diese Studie wurde von der Ethikkommission der Universität zu Köln ethisch geprüft und zustimmend bewertet. Eine Teilnahme daran ist freiwillig. Das erteilte Einverständnis zur Teilnahme an der Studie kann jederzeit und ohne Angabe von Gründen widerrufen werden, ohne dass daraus Nachteile im Hinblick auf die Behandlung oder Ihr Verhältnis zum behandelnden Arzt entstehen. Ihr Kind kann durch Ihren behandelnden Arzt aus NB2004 ausgeschlossen werden, wenn medizinische oder organisatorische Gründe dies notwendig machen.

Nach Beendigung der Studienteilnahme sollen von den Patienten weiter Verlaufsdaten erhoben werden, um später Aussagen über den langfristigen Behandlungserfolg und die Verträglichkeit der Behandlung machen zu können. Ihr Kind profitiert von dieser Nachsorge durch rechtzeitige Erkennung und gegebenenfalls Behandlung von Gefährdungen durch das Neuroblastom (Rückfall) und durch die Behandlung (Behandlungsfolgen).

NB2004 Patienteninformation – Mittlere Risikogruppe

Patient Name	Patient Vorname	geboren	NB Nummer

Studienname: Kooperative multizentrische Therapieoptimierungsstudie für die Behandlung von Säuglingen, Kindern und Jugendlichen mit Neuroblastom (NB2004) – Mittlere Risikogruppe

Studienleiter: Prof. Dr. F. Berthold
Studienbüro: Zentrum für Kinderonkologie und –hämatologie,
Universitätsklinikum zu Köln, Kerpener Straße 62, 50924 Köln

Liebe Eltern,

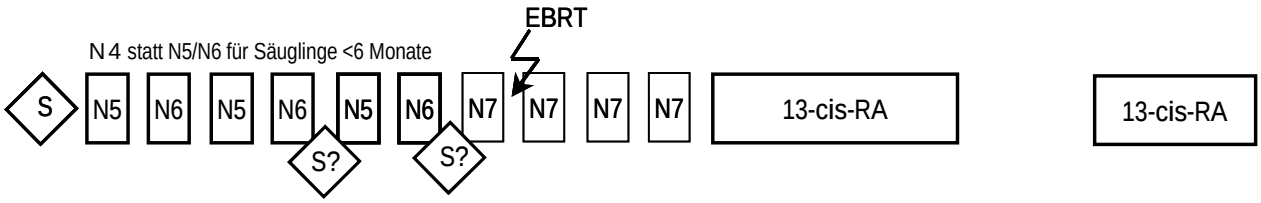
bei Ihrem Kind wurde die Diagnose eines Neuroblastoms gestellt. Das Neuroblastom ist eine bösartige Erkrankung des Kindesalters. Der Verlauf der Erkrankung kann sehr unterschiedlich sein. Beim Vorliegen bestimmter Risikofaktoren (z.B. Stadium 2 und 3, Alter über 2 Jahre, genetische Faktoren wie Veränderungen am Chromosom 1p im Tumorgewebe) kann auf eine Chemotherapie nicht verzichtet werden. Aufgrund der vorliegenden Befunde wird Ihr Kind in die mittlere Risikogruppe der Therapiestudie NB2004 eingeordnet:

- ☐ Stadium 2 oder 3, Nachweis von Veränderungen an Chromosom 1p
- ☐ Stadium 3, ≥2 Jahre
- ☐ Stadium 4, < 1 Jahr

Bitte lesen Sie diese Patienteninformation sorgfältig durch. Ihr Arzt wird mit Ihnen auch direkt über diese Studie sprechen. Bitte fragen Sie Ihn, wenn Sie etwas nicht verstehen oder wenn Sie zusätzlich etwas wissen möchten.

Was soll in dieser Studie untersucht werden?

Üblicherweise erhalten Neuroblastompatienten im Anschluss an die Tumoroperation eine Chemotherapie, wenn der Tumor nicht vollständig operativ entfernt werden konnte. Gründliche Analysen vieler Krankheitsverläufe geben Hinweise, dass eine kleine Gruppe von Patienten mit bestimmten Risikofaktoren trotz der bisher üblichen Chemotherapie ein deutlich höheres Risiko eines Rückfalls hat. Diese Patienten werden in der Studie NB2004 der mittleren Risikogruppe zugeordnet. Im Vergleich zur bisherigen Behandlung (Therapieprotokoll NB97) wurde die Chemotherapie auf sechs Blöcke (drei „N5“-Blöcke und drei „N6“-Blöcke) verlängert. Sie wurde außerdem um eine Erhaltungstherapie mit dem Medikament Cyclophosphamid und eine anschließende Retinsäurebehandlung erweitert. Dadurch sollen Rückfälle vermieden werden.



Übersicht über die Therapie der mittleren Risikogruppe (S = Operation, N4, N5, N6 = Chemotherapieblöcke, N7 = Erhaltungschemotherapieblöcke, EBRT = Strahlentherapie bei aktivem Resttumor, 13-cis-RA = Retinsäurebehandlung über 6 und 3 Monate)

Welche anderen Behandlungsmöglichkeiten gibt es?

Eine allgemein akzeptierte Standardbehandlung für Neuroblastompatienten der mittleren Risikogruppe in NB2004 gibt es nicht. Eine Alternative zur vorgeschlagenen Therapie ist die Behandlung entsprechend der Vorläuferstudie

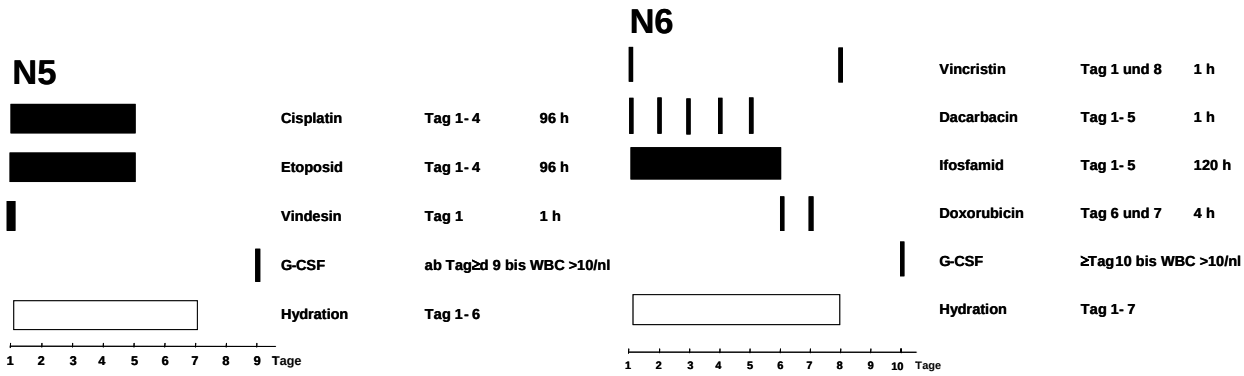
NB97. Diese besteht nur aus 4 Chemotherapieblöcken (zwei „N5“-Blöcke und zwei „N6“-Blöcke). Die Ergebnisse dieser Behandlung sind für die Mehrzahlen der Patienten der mittleren Risikogruppe in der Studie NB2004 nicht zufriedenstellend.

Wie wird die Studie ablaufen?

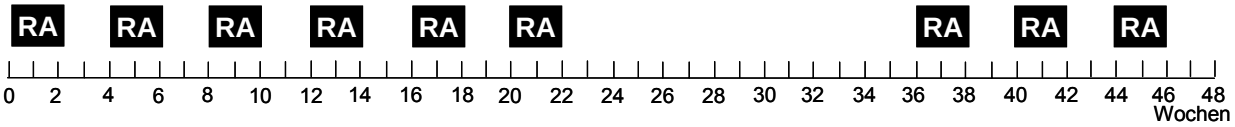
Während der ohnehin notwendigen Tumoroperation wird so viel Tumor wie möglich entfernt. Manchmal ist der Tumor gut abgekapselt und lässt sich ohne Risiko vollständig entfernen. Manchmal liegen wichtige Gefäße, Nerven oder Organe im Tumor oder in unmittelbarer Nachbarschaft des Tumors, so dass die komplette oder teilweise Tumorentfernung riskant ist. Dann wird nur eine kleine Probe entnommen. Diese Probe wird gründlich untersucht, um die feingewebliche Diagnose zu stellen und spezielle molekulare Risikofaktoren am Tumorgewebe zu untersuchen.

Tumormaterial, welches aktuell nicht für die Untersuchung benötigt wird, wird in der Tumorbank „Embryonale Tumoren“ der Gesellschaft für Pädiatrische Hämatologie und Onkologie aufbewahrt. Es steht damit ausschließlich zur Erforschung der Tumoreigenschaften zur Verfügung. Mit diesen Erkenntnissen soll es in Zukunft möglich werden, aus der anfangs entnommenen Tumorprobe für jeden Patienten die bestmögliche Therapie vorherzusagen.

Zunächst erhält Ihr Kind sechs Chemotherapieblöcke (je drei „N5“ und drei „N6“ Blöcke im Wechsel). Diese intensive Therapie muss unter stationären Bedingungen durchgeführt werden. Danach sind vier Erhaltungsblöcke „N7“ geplant. Diese „N7“-Blöcke erfordern grundsätzlich keinen stationären Aufenthalt. Ist zu diesem Zeitpunkt noch ein stoffwechselaktiver Tumorrest vorhanden, ist parallel zu den „N7“ Blöcken eine Bestrahlung der Tumorregion vorgesehen. Daran schließt sich eine Retinsäurebehandlung über insgesamt 1 Jahr (6 Monate, dann 3 Monate Pause, dann noch einmal 3 Monate Retinsäure) an. Retinsäure ist in Kapselform verfügbar und erfordert keine Infusionen.



Übersicht über die Chemotherapieblöcke N5 und N6



Zeitschema der Retinsäurebehandlung: jeweils 14 Tage zwei (bis drei) tägliche Einnahmen, dann 14 Tage Pause.

Für die Dauer der Therapie und danach sind regelmäßige Untersuchungen Ihres Kindes erforderlich, um die Menge des verbliebenen Tumors zu bestimmen. Auch nach Therapieabschluss erfolgen regelmäßige Kontrolluntersuchungen (klinische Untersuchung, Blutuntersuchung, Urinuntersuchung, Ultraschall, in größeren Abständen auch Kernspintomographie, Szintigraphie und, wenn erforderlich, Knochenmarkpunktion). Das Ausmaß dieser Diagnostik entspricht den üblichen Kontrolluntersuchungen für alle derartigen Patienten. Keinesfalls werden im Rahmen der Studie zusätzliche Untersuchungen oder Gewebeentnahmen über das aus medizinischer Sicht notwendige Maß hinaus erforderlich.

Mit welchen therapiebedingten Nebenwirkungen ist zu rechnen?

Eine Chemotherapie kann Auswirkungen auf den gesamten Organismus haben. Besonders betroffen sind alle stoffwechselaktiven Gewebe. Deshalb kann es zu folgenden Nebenwirkungen kommen, die in ihrer Ausprägung je nach Chemotherapiezyklus und der individuellen Medikamentenverträglichkeit variieren können:

- Übelkeit, Erbrechen, gelegentlich auch Schwindel, Kreislaufprobleme oder allergische Reaktionen während der Infusion der Medikamente,
- Vorübergehende Beeinträchtigung der Blutbildung: Infolge des Mangels an weißen Blutkörperchen (Leukozyten) wird die Körperabwehr geschwächt. Der Patient wird anfällig für Infektionen. Diese können einen bedrohlichen Verlauf nehmen und erfordern unter Umständen eine Antibiotikatherapie unter stationären Bedingungen. Ein Mangel an roten Blutkörperchen (Erythrozyten) beeinträchtigt das körperliche Leistungsvermögen des Patienten. Bei fast allen Patienten werden während der Behandlung Bluttransfusionen notwendig. Der Mangel an Blutplättchen (Thrombozyten) führt zu einer Blutungsneigung. Lebensbedrohliche Blutungen können nur durch die Transfusion von Blutplättchen vermieden werden.
- Vorübergehende Schleimhautschädigung: Der gesamte Verdauungstrakt kann betroffen sein. Dadurch kann es zu Mundschmerzen, Schluckbeschwerden, Bauchschmerzen, Verstopfung oder Durchfall kommen.
- Vorübergehender Haarausfall
- Spezielle Nebenwirkungen einzelner Medikamente:
    - Cisplatin und Carboplatin: Bleibende Beeinträchtigung des Innenohrs oder der Niere bei einem Teil der Patienten.
    - Etoposid: Gelegentlich allergische Reaktionen.
    - Cyclophosphamid und Ifosfamid: Blutige Blasenschleimhautentzündung. Diese kann durch Gabe des Schutzmedikaments MESNA in den allermeisten Fällen vermieden werden.

- Retinsäure: Hauttrockenheit, Hautreizung, Lippentrockenheit, Verminderung der Tränenflüssigkeit, Nachtblindheit, Schwankungen der Stimmung, erhöhte Lichtempfindlichkeit, Kopfschmerzen, Laborwertveränderungen (Kalzium, Leberwerte, Blutfette) und Knochenveränderungen.

Im Falle einer unter Therapie eintretenden Schwangerschaft kann jede Chemotherapie zu Schädigungen des Embryos führen. Dies gilt auch für Retinsäure (Roaccutan®). Bei Mädchen im gebärfähigen Alter ist deshalb eine sichere Schwangerschaftsverhütung für die Dauer der Behandlung erforderlich.

Bei Jungen kann nach einer Chemotherapie die spätere Zeugungsfähigkeit beeinträchtigt werden.

Medikamente zur Behandlung bösartiger Erkrankungen (Zytostatika) können in seltenen Fällen selbst zum Entstehen bösartiger Erkrankung führen. Deshalb kann es in einigen Fällen Jahre nach einer derartigen Behandlung zum Auftreten sogenannter sekundärer Leukämien oder Zweittumoren kommen. Eine Vorhersage, welchen Patienten diese Spätkomplikationen betreffen werden, ist nicht möglich.

Ist unser Kind versichert?

Wie für alle klinischen Prüfungen gesetzlich vorgeschrieben, wurde für diese Studie eine Patientenversicherung bei der HDI Industrie Versicherungs- AG, Riethorst 2, 30659 Hannover, Niederlassung Nürnberg, Telefon 0911–2012-0 abgeschlossen. Die Police-Nummer ist 85-403369-03016-390. Die Versicherungshöchstsumme pro Einzelfall beträgt € 500.000,00. Die allgemeinen Versicherungsbedingungen sind im Studienprotokoll enthalten und können Ihnen auf Wunsch ausgehändigt werden. Schadenersatzansprüche, die über etwaige Versicherungsleistungen hinausgehen, sind ausgeschlossen. Die Versicherungszeit beträgt 2 Jahre vom Zeitpunkt der Diagnose (Studienaufnahme) an gerechnet.

Um den Versicherungsschutz nicht zu gefährden, hat der Versicherte folgende Pflichten:

- Während der Dauer der Studie darf sich die versicherte Person einer anderen medizinischen Behandlung nur nach Rücksprache mit dem behandelnden Arzt unterziehen. Dies gilt nicht für Notfälle. Der behandelnde Arzt ist von einer Notfallbehandlung unverzüglich zu unterrichten.
- Eine Gesundheitsschädigung, die als Folge der Studie eingetreten sein könnte, ist dem Versicherer unter oben genannter Adresse unverzüglich anzuzeigen.

Was passiert mit den Daten unseres Kindes?

Im Rahmen der Studie NB2004 werden personenbezogene krankheits- und behandlungsrelevante Daten vom Patienten erhoben und an die Studienzentrale in Köln zur Auswertung weitergegeben. Dabei handelt es sich nur um Daten, die die Krankheit Ihres Kindes betreffen. Verantwortlich für die Datenverarbeitung ist der Leiter der Studie. Alle Personen, die Einblick in die gespeicherten Daten haben, sind zur Wahrung des Datenschutzes verpflichtet. Der Name des Patienten wird zu keinem Zeitpunkt öffentlich gemacht.

Auf Grund gesetzlicher Regelungen haben bestimmte Personen (autorisierte Dritte) ein Recht auf Einsichtnahme in Ihre personenbezogenen Daten. Dazu zählen Vertreter der zuständigen Überwachungsbehörden oder der Bundesoberbehörde. Die Einsichtnahme erfolgt um sicherzustellen, dass die Daten dieser Studie korrekt erhoben wurden. Diese Personen sind jedoch von Amtes wegen zur Verschwiegenheit verpflichtet.

Daten über Langzeitverläufe sind eine wichtige Grundlage für die Weiterentwicklung der Behandlung des Neuroblastoms im Kindesalter. Die Krankheitsdaten bleiben deshalb über die Laufzeit der Studie hinaus gespeichert. Die Daten werden allerdings umgehend anonymisiert, wenn uns das Einverständnis zur Datenspeicherung entzogen wird.

Mit der Unterzeichnung der Einwilligungserklärung zu Studienteilnahme geben Sie Ihre Einwilligung zur Erhebung und Weitergabe der Daten sowie zur Einsichtnahme durch autorisierte Dritte.

Beendigung der Studienteilnahme

Diese Studie wurde von der Ethikkommission der Universität zu Köln ethisch geprüft und zustimmend bewertet. Eine Teilnahme an der Studie ist freiwillig. Ein gegebenes Einverständnis zur Teilnahme kann jederzeit und ohne Angabe von Gründen widerrufen werden, ohne dass daraus Nachteile im Hinblick auf die Behandlung oder Ihr Verhältnis zum behandelnden Arzt entstehen. Ihr Kind kann durch Ihren behandelnden Arzt aus NB2004 ausgeschlossen werden, wenn medizinische oder organisatorische Gründe dies notwendig machen.

Nach Beendigung der Studienteilnahme sollen von den Patienten weiter Verlaufsdaten erhoben werden, um später Aussagen über den langfristigen Behandlungserfolg und die Verträglichkeit der Behandlung machen zu können. Ihr Kind profitiert von dieser Nachsorge durch rechtzeitige Erkennung und gegebenenfalls Behandlung von Gefährdungen durch das Neuroblastom (Rückfall) und durch die Behandlung (Behandlungsfolgen).

NB2004 Patienteninformation – Hochrisikogruppe

Patient Name	Patient Vorname	geboren	NB Nummer

Studienname: Kooperative multizentrische Therapieoptimierungsstudie für die Behandlung von Säuglingen, Kindern und Jugendlichen mit Neuroblastom (NB2004) – Hochrisikogruppe

Studienleiter: Prof. Dr. F. Berthold
Studienbüro: Zentrum für Kinderonkologie und –hämatologie,
Universitätsklinikum zu Köln, Kerpener Straße 62, 50924 Köln

Liebe Eltern,

bei Ihrem Kind wurde die Diagnose eines Neuroblastoms gestellt. Das Neuroblastom ist eine bösartige Erkrankung des Kindesalters. Der Verlauf der Erkrankung kann allerdings sehr unterschiedlich sein. Beim Vorliegen gewisser Risikofaktoren (z.B. Ausbreitung der Krankheit, genetische Faktoren wie MYCN-Amplifikation) kann auf eine Chemotherapie nicht verzichtet werden. Die bisherigen Befunde zeigen, dass Ihr Kind aufgrund folgender Faktoren in die Hochrisikogruppe der Therapiestudie NB2004 eingeordnet wird:

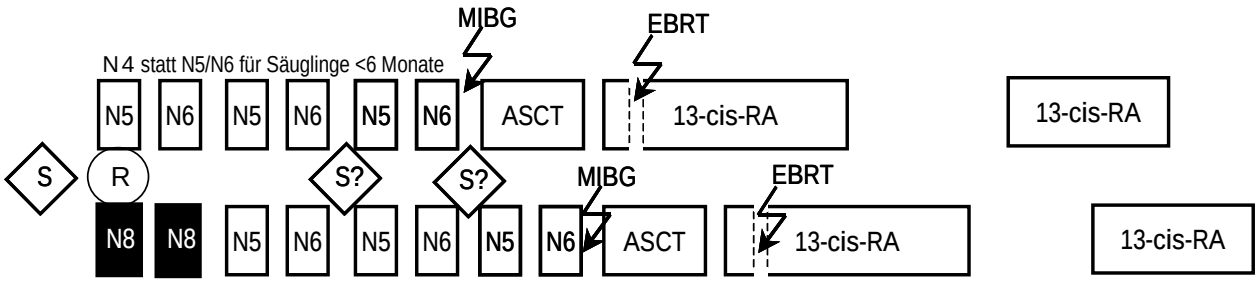
- ☐ Stadium 4, >1 Jahr
- ☐ MYCN-Amplifikation und Stadium 1, 2, 3 oder 4S

Bitte lesen Sie diese Patienteninformation sorgfältig durch. Ihr Arzt wird mit Ihnen auch direkt über diese Studie sprechen. Bitte fragen Sie Ihn, wenn Sie etwas nicht verstehen oder wenn Sie zusätzlich etwas wissen möchten.

Was soll in dieser Studie untersucht werden?

Die Heilungschancen bei Neuroblastom Stadium 4 oder Neuroblastom mit MYCN-Amplifikation konnten in den zurückliegenden Jahren schrittweise verbessert werden. Dennoch erleiden viele Patienten einen Rückfall. Aufbauend auf den Erkenntnissen früherer Studien aus dem In- und Ausland möchten wir die Heilungsraten weiter verbessern.

In der Behandlung von Patienten mit Neuroblastomrückfall hat sich ein neuer Chemotherapieblock („N8“) als wirksam erwiesen. Die Studie NB2004 soll klären, ob zwei zusätzliche „N8“-Blöcke die Heilungsraten im Vergleich zur Vorstudie weiter verbessern. Eine Hälfte der Hochrisikopatienten wird deshalb zusätzlich zwei „N8“ Blöcke erhalten, die andere Hälfte nicht. Die Auswahl der Patienten erfolgt nach dem Zufallsprinzip (sogenannte **Randomisation**). Erst der Vergleich der Patienten ohne und mit „N8“ wird zeigen, ob die Mehrbelastung der Patienten durch zusätzliche Chemotherapiezyklen zur gewünschten Verbesserung der Heilungsraten führt oder nicht.



Übersicht über die Therapie der Hochrisikogruppe (R = Randomisierung, S = Operation, N4, N5, N6, N8 = Chemotherapieblöcke, ASCT = Hochdosischemotherapie mit Rückgabe von patienteneigenen Blutstammzellen, EBRT = Strahlentherapie bei aktivem Resttumor, MIBG = MIBG-Therapie bei aktiven Resten, 13-cis-RA = Retinsäurebehandlung über 6 und 3 Monate)

Welche anderen Behandlungsmöglichkeiten gibt es?

Eine Alternative ist der Verzicht auf die vorgeschlagene Randomisierung und damit die Behandlung entsprechend dem Standardarm der Hochrisikogruppe

NB2004. Dieser entspricht dem erfolgreichsten Arm der Hochrisikogruppe aus der Vorläuferstudie NB97.

Wie wird die Studie ablaufen?

Während der ohnehin notwendigen Tumoroperation wird so viel Tumor wie möglich entfernt. Manchmal ist der Tumor gut abgekapselt und lässt sich ohne Risiko vollständig entfernen. Manchmal liegen wichtige Gefäße, Nerven oder Organe im Tumor oder in unmittelbarer Nachbarschaft des Tumors, so dass die komplette oder teilweise Tumorentfernung zu riskant ist. Dann wird nur eine kleine Probe entnommen und gründlich untersucht, um die feingewebliche Diagnose zu stellen und spezielle molekulare Risikofaktoren am Tumorgewebe zu untersuchen.

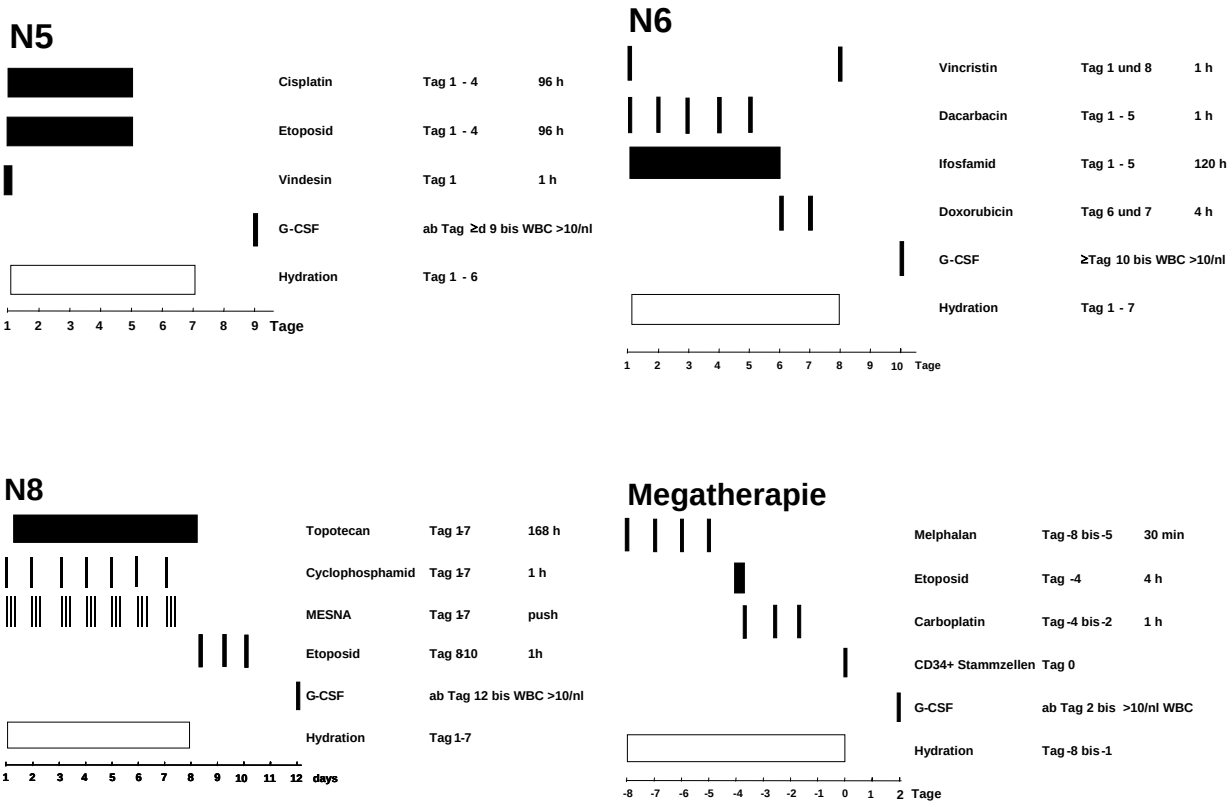
Tumormaterial, welches aktuell nicht für die Untersuchung benötigt wird, wird in der „Tumorbank Embryonale Tumoren der Gesellschaft für Pädiatrische Hämatologie und Onkologie“ gelagert. Es steht damit ausschließlich zur Erforschung der Tumoreigenschaften zur Verfügung. Mit diesen Erkenntnissen soll es in Zukunft möglich werden, aus der anfangs entnommenen Tumorprobe für jeden Patienten die bestmögliche Therapie vorherzusagen.

Bei Patienten der Hochrisikogruppe, die älter als 1 Jahr sind, erfolgt gleich zu Therapiebeginn eine **Randomisierung.** Dabei wird per Zufall festgelegt, ob der Patient ohne „N8“ Blöcke oder mit „N8“ Blöcken behandelt wird. Grundlage dafür sind Listen, die das Institut für Medizinische Biometrie, Epidemiologie und Informatik der Universität Mainz vor dem Start der Studie erstellt hat. Die Studienleitung und Ihr Arzt haben keinen Einfluss auf das Ergebnis der Randomisierung. Sie haben selbstverständlich das Recht, das Randomisierungsergebnis anzunehmen oder abzulehnen. Bitte bedenken Sie aber, dass wir die Behandlungsergebnisse in den zurückliegenden Jahren nur deshalb verbessern konnten, weil die Mehrheit unserer Patienten ähnlichen Randomisierungen zugestimmt hat.

Patienten des „N8“-Armes erhalten zunächst zwei Blöcke „N8“. Daran schließt sich die komplette Therapie des sogenannten Standardarmes an. Patienten des „N8“-

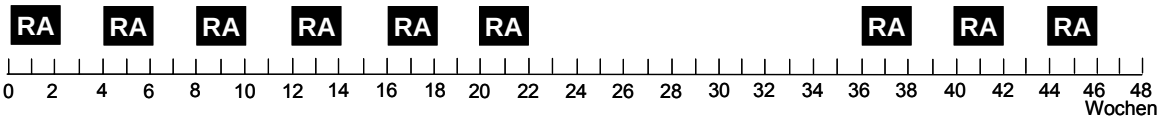
Armes haben also schon zwei Blöcke „N8“ hinter sich, bevor sie mit „N5“ und „N6“ im Wechsel weiterbehandelt werden.

Patienten des Standardarmes starten gleich mit den „N5“ und „N6“ Blöcken und erhalten so insgesamt sechs Chemotherapieblöcke. Diese intensive Therapie muss unter stationären Bedingungen durchgeführt werden. Danach erhalten alle Patienten eine Hochdosischemotherapie mit Transplantation von patienteneigenen (autologen) Blutstammzellen. Diese Blutstammzellen werden nach einem der ersten Chemotherapieblöcke aus dem Blut des Patienten gewonnen, sobald das Knochenmark des Patienten frei von Tumorzellen ist. Ist zum Zeitpunkt der Hochdosistherapie noch ein stoffwechselaktiver Tumorrest vorhanden, erhält der Patient unmittelbar vor der Hochdosistherapie eine MIBG-Therapie mit radioaktiv markiertem ^{131}I-MIBG und nach Hochdosistherapie eine ergänzende Bestrahlung der Tumorregion.



Übersicht über die verschiedenen Chemotherapieblöcke der NB 2004 Hochrisikogruppe

Daran schließt sich eine Retinsäurebehandlung über 1 Jahr entsprechend dem unten stehenden Schema an. Retinsäure ist in Kapselform verfügbar und erfordert keine Infusionen.



Zeitschema der Retinsäurebehandlung: jeweils 14 Tage zwei (bis drei) drei tägliche Einnahmen, dann 14 Tage Pause.

Für die Dauer der Therapie und danach sind regelmäßige Untersuchungen des Patienten erforderlich, um die Menge des verbliebenen Tumors zu bestimmen. Auch nach Therapieabschluss erfolgen regelmäßige Kontrolluntersuchungen (klinische Untersuchung, Blutuntersuchung, Urinuntersuchung, Ultraschall, in größeren Abständen auch Kernspintomographie, Szintigraphie und, wenn erforderlich, Knochenmarkpunktion). Das Ausmaß dieser Diagnostik entspricht den üblichen Kontrolluntersuchungen für alle derartigen Patienten. Keinesfalls werden im Rahmen der Studie zusätzliche Untersuchungen oder Gewebeentnahmen über das aus medizinischer Sicht notwendige Maß hinaus erforderlich.

Mit welchen Nebenwirkungen ist zu rechnen?

Eine Chemotherapie kann Auswirkungen auf den gesamten Organismus haben. Besonders betroffen sind alle stoffwechselaktiven Gewebe. Deshalb kann es zu folgenden Nebenwirkungen kommen, die in ihrer Ausprägung je nach Chemotherapiezyklus und zwischen den Patienten variieren können:

- Übelkeit, Erbrechen, gelegentlich auch Schwindel, Kreislaufprobleme oder allergische Reaktionen während der Infusion der Medikamente,
- Vorübergehende Beeinträchtigung der Blutbildung: Infolge des Mangels an weißen Blutkörperchen (Leukozyten) wird die Körperabwehr geschwächt. Der Patient wird anfällig für Infektionen. Diese können einen bedrohlichen Verlauf nehmen und erfordern unter Umständen eine Antibiotikatherapie unter

stationären Bedingungen. Ein Mangel an roten Blutkörperchen (Erythrozyten) beeinträchtigt das körperliche Leistungsvermögen des Patienten. Bei fast allen Patienten werden während der Behandlung Bluttransfusionen notwendig. Der Mangel an Blutplättchen (Thrombozyten) führt zu einer Blutungsneigung. Lebensbedrohliche Blutungen können nur durch rechtzeitige Transfusion von Blutplättchen vermieden werden.

- Vorübergehende Schleimhautschädigung: Der gesamte Verdauungstrakt kann betroffen sein. Dadurch kann es zu Mundschmerzen, Schluckbeschwerden, Bauchschmerzen, Verstopfung oder Durchfall kommen.
- Vorübergehender Haarausfall
- Spezielle Nebenwirkungen einzelner Medikamente:
    - Cisplatin und Carboplatin: Bleibende Beeinträchtigung des Hörvermögens oder der Nierenfunktion bei einem Teil der Patienten.
    - Etoposid: Gelegentlich allergische Reaktionen.
    - Cyclophosphamid und Ifosfamid: Blutige Blasenschleimhautentzündung. Diese kann durch Gabe des Schutzmedikaments MESNA in den allermeisten Fällen vermieden werden.
    - Retinsäure: Hauttrockenheit, Hautreizung, Lippentrockenheit, Verminderung der Tränenflüssigkeit, Nachtblindheit, Schwankungen der Stimmung, erhöhte Lichtempfindlichkeit, Kopfschmerzen, Laborwertveränderungen (Kalzium, Leberwerte, Blutfette) und Knochenveränderungen.

Im Falle einer unter Therapie eintretenden Schwangerschaft kann jede Chemotherapie zu Schädigungen des Embryos führen. Dies gilt auch für Retinsäure (Roaccutan®). Bei Mädchen im gebärfähigen Alter ist deshalb eine sichere Schwangerschaftsverhütung für die Dauer der Behandlung erforderlich.

Bei Jungen kann nach einer Chemotherapie die spätere Zeugungsfähigkeit beeinträchtigt werden.

Medikamente zur Behandlung bösartiger Erkrankungen (Zytostatika) können in seltenen Fällen selbst zum Entstehen bösartiger Erkrankung führen. Deshalb kann es in einigen Fällen auch noch Jahre nach einer derartigen Behandlung zum Auftreten sogenannter sekundärer Leukämien oder Zweittumoren kommen. Eine Vorhersage, welchen Patienten diese Spätkomplikationen betreffen werden, ist nicht möglich.

Ist unser Kind versichert?

Wie für alle klinischen Prüfungen gesetzlich vorgeschrieben, wurde für diese Studie eine Patientenversicherung bei der HDI Industrie Versicherungs- AG, Riethorst 2, 30659 Hannover, Niederlassung Nürnberg, Telefon 0911–2012-0 abgeschlossen. Die Police-Nummer ist 85-403369-03016-390. Die Versicherungshöchstsumme pro Einzelfall beträgt € 500.000,00. Die allgemeinen Versicherungsbedingungen sind im Studienprotokoll enthalten und können Ihnen auf Wunsch ausgehändigt werden. Schadenersatzansprüche, die über etwaige Versicherungsleistungen hinausgehen, sind ausgeschlossen. Die Versicherungszeit beträgt 2 Jahre vom Zeitpunkt der Diagnose (Studienaufnahme) an gerechnet.

Um den Versicherungsschutz nicht zu gefährden, hat der Versicherte folgende Pflichten:

- Während der Dauer der Studie darf sich die versicherte Person einer anderen medizinischen Behandlung nur nach Rücksprache mit dem behandelnden Arzt unterziehen. Dies gilt nicht für Notfälle. Der behandelnde Arzt ist von einer Notfallbehandlung unverzüglich zu unterrichten.
- Eine Gesundheitsschädigung, die als Folge der Studie eingetreten sein könnte, ist dem Versicherer unter oben genannter Adresse unverzüglich anzuzeigen.

Was passiert mit den Daten unseres Kindes?

Im Rahmen der Studie NB2004 werden personenbezogene krankheits- und behandlungsrelevante Daten vom Patienten erhoben und an die Studienzentrale

in Köln zur Auswertung weitergegeben. Dabei handelt es sich nur um Daten, die die Krankheit Ihres Kindes betreffen. Verantwortlich für die Datenverarbeitung ist der Leiter der Studie. Alle Personen, die Einblick in die gespeicherten Daten haben, sind zur Wahrung des Datenschutzes verpflichtet. Der Name des Patienten wird zu keinem Zeitpunkt öffentlich gemacht.

Auf Grund gesetzlicher Regelungen haben bestimmte Personen (autorisierte Dritte) ein Recht auf Einsichtnahme in Ihre personenbezogenen Daten. Dazu zählen Vertreter der zuständigen Überwachungsbehörden oder der Bundesoberbehörde. Die Einsichtnahme erfolgt um sicherzustellen, dass die Daten dieser Studie korrekt erhoben wurden. Diese Personen sind jedoch von Amtes wegen ebenfalls zur Verschwiegenheit verpflichtet.

Daten über Langzeitverläufe sind eine wichtige Grundlage für die Weiterentwicklung der Behandlung des Neuroblastoms im Kindesalter. Die Daten bleiben deshalb über die Laufzeit der Studie hinaus gespeichert. Die Daten werden allerdings umgehend anonymisiert, wenn uns das Einverständnis zur Datenspeicherung entzogen wird.

Mit der Unterzeichnung der Einverständniserklärung geben Sie Ihre Einwilligung zur Erhebung und Weitergabe der Daten sowie zur Einsichtnahme durch autorisierte Dritte.

Beendigung der Studienteilnahme

Diese Studie wurde von der Ethikkommission der Universität zu Köln ethisch geprüft und zustimmend bewertet. Eine Teilnahme daran ist freiwillig. Ein gegebenes Einverständnis zur Teilnahme an der Studie kann jederzeit und ohne Angabe von Gründen widerrufen werden, ohne dass daraus Nachteile im Hinblick auf die Behandlung oder Ihr Verhältnis zum behandelnden Arzt entstehen. Ihr Kind kann durch Ihren behandelnden Arzt aus NB2004 ausgeschlossen werden, wenn medizinische oder organisatorische Gründe dies notwendig machen.

Nach Beendigung der Studienteilnahme sollen von den Patienten weiter Verlaufsdaten erhoben werden, um später Aussagen über den langfristigen

Behandlungserfolg und die Verträglichkeit der Behandlung machen zu können. Ihr Kind profitiert von dieser Nachsorge durch rechtzeitige Erkennung und gegebenenfalls Behandlung von Gefährdungen durch das Neuroblastom (Rückfall) und durch die Behandlung (Behandlungsfolgen).

NB2004 Einwilligung zur Studienteilnahme

Patient Name	Patient Vorname	geboren	NB Nummer

Studienname: Kooperative multizentrische Therapieoptimierungsstudie für die Behandlung von Säuglingen, Kindern und Jugendlichen mit Neuroblastom (NB2004)

Studienleiter: Prof. Dr. F. Berthold
Studienbüro: Zentrum für Kinderonkologie und –hämatologie,
Universitätsklinikum zu Köln, Kerpener Straße 62, 50924 Köln

Wir sind von Dr. ……. ausführlich und verständlich über die Art der Erkrankung, die durchzuführende Behandlung, deren Wirkungen und Nebenwirkungen, deren mögliche Spätfolgen und Risiken sowie über Ziel und Bedeutung der oben genannten Therapieoptimierungsstudie informiert worden.

Oben genannter Patient wurde folgender Behandlungsgruppe zugeordnet.

☐ Beobachtungsgruppe (Informationsschreiben Seite 187 bis 193)

☐ Mittlere Risikogruppe (Informationsschreiben Seite 194 bis 201)

☐ Hochrisikogruppe (Informationsschreiben Seite 202 bis 210)

Auf andere Behandlungsmethoden außerhalb dieser Studie wurden wir hingewiesen. Über die mündliche Aufklärung hinaus haben wir den Text der Patienteninformation und diese Einwilligungserklärung gelesen und verstanden. Ich/wir hatten Gelegenheit, Fragen zu stellen. Aufgetretene Fragen wurden uns vom behandelnden Arzt verständlich und ausreichend beantwortet. Ein Ansprechpartner für weitere zukünftige Fragen wurde uns benannt.

Folgende Themen wurden zusätzlich im mündlichen Aufklärungsgespräch behandelt:

.....

.....

.....

Wir wurden darüber aufgeklärt, dass regelmäßige Nachuntersuchungen unter Umständen über viele Jahre durchgeführt werden müssen. Hierdurch sollen rechtzeitig Rückfälle, Zweittumore und therapiebedingte Beeinträchtigungen erkannt werden. Wir wurden ebenfalls darüber informiert, dass die in der Studie eingesetzten Substanzen möglicherweise das ungeborene Leben schädigen können. Bei Mädchen im gebärfähigen Alter muss deshalb durch sicheren Empfängnisschutz für die Dauer der Behandlung eine Schwangerschaft ausgeschlossen werden.

Wir wurden über die bestehende Patientenversicherung bei HDI Versicherungen sowie über die sich daraus für uns ergebenden Anforderungen aufgeklärt.

Datenschutz:

Wir wurden über unsere Datenschutzrechte informiert. Wir erklären uns einverstanden mit der im Rahmen von NB2004 erfolgenden Aufzeichnung und Speicherung von krankheits- und behandlungsrelevanten Daten und ihrer nichtanonymisierten Weitergabe an die Studienzentrale in Köln zur Auswertung. Alle Personen, die Einblick in die gespeicherten Daten haben, sind zur Wahrung des Datenschutzes verpflichtet. Der Name des Patienten wird zu keinem Zeitpunkt öffentlich gemacht. Wir erklären uns einverstanden mit der anonymisierten Weitergabe von Krankheitsdaten/Studiendaten zur Überprüfung an die zuständige Überwachungsbehörde oder die zuständige Bundesoberbehörde und, soweit es sich um personenbezogene Daten handelt, mit deren Einsichtnahme durch zur Verschwiegenheit verpflichtete Beauftragte der Behörden.

Folgende Zentren erhalten im Rahmen der Studie Zugang zu Patientendaten:

- Studienleitung NB2004: Prof. Dr. F. Berthold,
- Tumorbank Embryonale Tumoren der GPOH: Prof. Dr. F. Berthold
  (Zentrum für Kinderonkologie und -hämatologie, Kerpener Str. 62; D-50924 Köln),
- Kinderkrebsregister für die Bundesrepublik Deutschland
  (IMBEI, Universität Mainz, Obere Zahlbacher Straße 69, D-55101 Mainz),
- Referenzpathologie: Dr. K. Ernestus
  (Institut für Pathologie, Universität zu Köln, Kerpener Str. 62, D-50924 Köln),
- Referenzpathologie: Dr. U. Jänig und PD Dr. I. Leuschner (Institut für Pathologie, Universität des Landes Schleswig-Holstein, Michaelisstraße 11, D-24105 Kiel),
- Molekulargenetisches Referenzlabor: Prof. Dr. H. Christiansen
  (Universitätskinderklinik, Deutschhausstraße 12, D-35055 Marburg),
- Molekulargenetisches Referenzlabor: PD Dr. Niggli
  (Universitätskinderklinik, Steinwiesstraße 75, CH-8032 Zürich),
- Molekulargenetisches Referenzlabor: Dr. F. Schilling
  (Olgahospital, Bismarckstraße 8, D-70176 Stuttgart),
- Molekulargenetisches Referenzlabor: Prof. Dr. M. Schwab
  (Deutsches Krebsforschungszentrum, Im Neuheimer Feld 280, D-69120 Heidelberg)
- Molekulargenetisches Referenzlabor: Dr. R. Spitz
  (Zentrum für Kinderonkologie und –hämatologie, Kerpener Str. 62, D- 50925 Köln),
- Projektgruppe Spätfolgen nach Strahlentherapie maligner Erkrankungen im Kindes- und Jugendalter: Prof. Dr. Willich, Dr. Schuck (Klinik und Poliklinik für Strahlentherapie, Universitätsklinikum, Albert-Schweitzer-Str. 33; D-48149 Münster),
- Pädiatrisches Register für Stammzelltransplantationen: Prof. Dr. T. Klingebiel
  (Klinikum der Johann W. Goethe Universität, Theodor Stern Kai 7, D-60590 Frankfurt a. M.).

Wir erklären hiermit die Teilnahme unseres Kindes an der oben genannten Studie. Wir wurden darauf hingewiesen, dass die Teilnahme freiwillig ist und dass wir das Recht haben, diese jederzeit ohne Angabe von Gründen zu beenden, ohne dass sich dadurch Nachteile für die Behandlung unseres Kindes ergeben. Eine Kopie dieser Einverständniserklärung und der dazugehörigen Patienteninformation haben wir erhalten.

Wir sind einverstanden mit der Weitergabe behandlungsrelevanter personenbezogener Daten an das Studienbüro der Studie NB2004 und die oben genannten kooperierenden Einrichtungen der Studie.

Wir sind damit einverstanden, dass Tumorgewebe unseres Kindes ausschließlich zur Erforschung der Krankheit in ihren molekularen, genetischen, immunologischen und anderen Eigenschaften untersucht wird und ggf. auch für die Entwicklung neuer Behandlungsverfahren eingesetzt wird. Die Entnahme des

Tumorgewebes erfolgt schmerzlos im Rahmen der für mein Kind notwendigen chirurgischen Tumorentfernung bzw. während der zur Diagnosestellung erforderlichen Probeentnahme aus dem Tumor. Falls bei der Tumorentfernung aus medizinisch chirurgischen Notwendigkeiten gesundes Gewebe mitentfernt werden muss, darf dieses als Vergleichsgewebe für die Tumoreigenschaften eingesetzt werden. Eine medizinisch nicht notwendige Erweiterung des chirurgischen Eingriffs erfolgt dazu nicht.

Zugestimmt wird der Entnahme einer Blutprobe während der Narkose (je nach Alter 2—10 ml) als Vergleichsmaterial für die Eigenschaften des Tumors. Tumor, Vergleichsgewebe und Vergleichsblut werden zentral in einer Tumorbank der Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) gelagert und anonymisiert Wissenschaftlern, die in universitären Einrichtungen oder in Krankenhäusern tätig sind und in GPOH-Studie kooperativ eingebunden sind, für die oben genannten krankheitsbezogenen Untersuchungen zur Verfügung gestellt. Auf diese Weise sollen die Diagnosestellung sicherer gemacht werden, das biologische Verständnis der Erkrankung verbessert und neue therapeutische Ansätze gefunden werden.

Wir sind darüber informiert, dass wir jederzeit und ohne Angabe von Gründen unsere Einwilligung zur wissenschaftlichen Erforschung an dem Tumor- und Vergleichsgewebe auch später beschränken oder ganz widerrufen und die Vernichtung der gelagerten Untersuchungsproben verlangen können.

…….	…….
Ort und Datum	Unterschrift aufklärender Arzt
…….	…….
Ort und Datum	Unterschrift Vater
…….	…….
Ort und Datum	Unterschrift Mutter
…….	…….
Ort und Datum	Unterschrift Patient (wenn angemessen)
…….	…….
Ort und Datum	Unterschrift Zeuge

NB2004 Meldebogen des Kinderkrebsregisters

- Bitte beachten Sie die Erläuterungen auf der Rückseite - Version 16 01.01.2003

MALIGNOME* IM KINDESALTER - Meldebogen

Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)
Deutsches Kinderkrebsregister (DKKR)
am Institut für Medizinische Biometrie, Epidemiologie und Informatik (IMBEI)

Bitte senden Sie die weißen Bögen an: Deutsches Kinderkrebsregister am IMBEI, 55101 Mainz
Telefon: 06131/17-3227 oder -6808, Telefax: 06131/17-4462

Adresse der Klinik (Stempel), Telefon:

Adressette:

Aufnahmenr. der Klinik:

Nachname:

Vorname:

Geschlecht: 1=m, 2=w

Geburtsdatum:

Adresse (ständiger Wohnsitz zur Zeit der Erkrankung):

Straße:

PLZ: **Wohnort:**

Geburtsort:

im Ausland erkrankt: ❑ Nein ❑ Ja

GPOH-PID:

Diagnose:

Lokalisation:

Stadium: **Malignitätsgrad:**

Diagnosedatum:

Sicherung der Diagnose durch:
- ❑ Klinik (incl. bildgeb. Verfahren)
- ❑ Spezifische Diagnostik (z.B. biochem./immunol. Tests)
- ❑ Zytologie
- ❑ Histologie
- ❑ Autopsie
- ❑ unbekannt

Seite:
- ❑ rechts
- ❑ links
- ❑ beidseitig
- ❑ Mittellinie
- ❑ Systemerkrankung
- ❑ unbekannt

Studienteilnahme: ❑ Nein ❑ Ja: **Studienname:**
(Meldebogendurchschlag wird vom DKKR an die Studienleitung geschickt)

Die schriftliche Einwilligung zur Datenübermittlung an das KKR (siehe Rückseite):
- ❑ liegt vom Patienten vor (zwingend bei mind. 16-jährigen)
- ❑ liegt vom Sorgeberechtigten vor
- ❑ wurde verweigert
- ❑ wird baldmöglichst nachgereicht

Der Elternfragebogen wurde ausgehändigt:
- ❑ Nein
- ❑ Ja - nur bei unter 15-Jährigen erforderlich -

Name des dokumentierenden Arztes (Stempel) **Datum** **Unterschrift**

*incl. benigne ZNS-Tumoren, LCH, SAA; auch für Sekundärmalignome

NB2004 Ersterhebungsbogen des Kinderkrebsregisters

Weiße und gelbe Seiten bitte direkt an die Studienleitung schicken - grüne Seiten für die Patientenakte ! NB 1/4

STUDIE NEUROBLASTOM NB 2004 - ERSTERHEBUNG

Studienleitung: Prof. Dr. F. Berthold, Universitäts-Kinderklinik, Joseph-Stelzmann-Str. 9,
50924 Köln, Tel.: 0221/478-4380, Fax: 0221/478-4689
in Zusammenarbeit mit dem Deutschen Kinderkrebsregister am IMBEI, 55101 Mainz
Tel.: 06131/17-3227 Fax: 06131/17-4462

Name/Aufnahmenummer | Pat.-Nr. | Klinik | Identifikationszahl

! Bitte beachten Sie, dass vor der Weiterleitung dieses Bogens die schriftliche Einwilligung zur Übermittlung der Daten und zur Speicherung vorliegen muss ! !

GPOH-PID

Vorausgegangene Tumorerkrankung:
☐ Nein ☐ Ja, welche: _____

Syndrome / hereditäre Grunderkrankungen / schwere dauerhafte Erkrankungen:
(z. B. Vitium cordis, Diabetes, Neurofibromatose etc.)
☐ Nein ☐ Ja, welche: _____

Familiäre Belastung (Leukämie-, Tumor- oder Immunmangelerkrankung, Syndrome):
☐ Nein ☐ Eltern ☐ Geschwister ☐ Sonstige

Falls ja, Art der Erkrankung: _____

Anzahl der Geschwister des Patienten: ☐☐

Ist der Patient ein Zwillingskind: ☐ Nein ☐ Ja, eineiig ☐ Ja, zweieiig ☐ nicht bekannt

Besonderheiten während der Schwangerschaft: ☐ Nein
☐ Rauchen ☐ Alkohol ☐ Drogen ☐ Strahlenbelastung ☐ Medikamente
☐ Sonstiges: _____

Allgemeinzustand bei Diagnosestellung:
☐ Normale Aktivität, keine Beeinträchtigung
☐ Geringe Beeinträchtigung, jedoch keine zusätzliche Hilfe erforderlich
☐ Altersentsprechende Aktivität stark eingeschränkt (z.B. kein regelmäßiger Kindergarten- bzw. Schulbesuch möglich)
☐ Bettlägerig, pflegebedürftig
☐ Intensive Behandlung notwendig, schwerstkrank, moribund

Anlaß der Diagnosestellung:
☐ Tumorsymptomatik führte zum Arztbesuch, Art der Erstsymptomatik:
☐ Tumorschwellung ☐ Gewichtsabnahme / -stillstand ☐ Durchfall, therapieresistent
☐ Metastasenschwellung ☐ Schmerzen ☐ Querschnitt: ☐ kompl. ☐ inkompl.
☐ Lymphknotenschwellung ☐ Ataxie, Opsomyoklonus ☐ Horner-Syndrom
☐ Fieber ☐ Brillenhämatom ☐ Hypertonie
☐ Reduz. d. Allgemeinzustandes ☐ pathologische Fraktur
☐ Sonstiges: _____

☐ primär keine Tumorsymptomatik vorhanden, Anlaß:
☐ Vorsorgeuntersuchung (U1-U9): U___ ☐ Intrauterine Sonographie, Schwangerschaftswoche: _____
☐ Befunde bei anderweitiger Untersuchung: _____
☐ Sonstiges: _____

Datum des 1. Auftretens eines Symptoms: ☐☐.☐☐.☐☐☐☐
Datum der definitiven Diagnosestellung (z.B. histologische Sicherung): ☐☐.☐☐.☐☐☐☐

Version 1

NB 2/4

Vorbehandlung in auswärtiger Klinik: ☐ Nein ☐ Ja, wie: _____

wo: _____

Weitere Therapie in anderer Klinik: ☐ Nein ☐ Ja, wo: _____

Internationale Stadieneinteilung des Neuroblastoms (J Clin Oncol 11: 1466-1477, 1993):

☐ Stadium 1: Lokalisierter Tumor mit makroskopisch kompletter Entfernung (mit oder ohne mikroskopischem Resttumor); repräsentative ipsi- und kontralaterale Lymphknoten sind histologisch ohne Tumorbefall. Lediglich unmittelbar am Tumor adhärente, chirurgisch entfernte Lymphknoten dürfen positiv sein. Auch bilaterale Tumoren, die makroskopisch komplett exstirpiert werden können und keinen regionalen Lymphknotenbefall aufweisen, gehören zum Stadium 1.

☐ Stadium 2a: Unilateraler Tumor mit makroskopisch inkompletter Entfernung; repräsentative ipsi- oder kontralaterale (nicht am Tumor adhärente) Lymphknoten sind histologisch ohne Tumorbefall.

☐ Stadium 2b: Unilateraler Tumor; regionale ipsilaterale nichtadhärente Lymphknoten zeigen Tumorbefall, kontralaterale Lymphknoten sind histologisch negativ.

☐ Stadium 3: Nichtresektabler, bilateraler Tumor mit oder ohne Lymphknotenbefall oder unilateraler Tumor mit kontralateralem Lymphknotenbefall. Überschreiten der Mittellinie ist definiert durch infiltratives Erreichen/Überschreiten der Wirbelkante der Gegenseite.

☐ Stadium 4: Dissemination des Tumors zu Knochenmark, Knochen, entfernten Lymphknoten, Leber, Haut und/oder anderen Organen.

☐ Stadium 4S: Lokalisierter Primärtumor wie beim Stadium 1 oder 2 mit Disseminierung nur in Leber, Haut und/oder Knochenmark. Nur Säuglinge im ersten Lebensjahr. Die Knochenmarkinfiltration ist gering (weniger als 10% Tumorzellen im Ausstrich, mIBG für Knochenmark negativ)

Lokalisation des Primärtumors:

☐ Nebenniere
☐ abdominal, sicher nicht adrenal (z.B. Grenzstrang)
☐ abdominal, unklar, ob adrenal oder nicht adrenal
☐ Becken
☐ Thorax
☐ Hals
☐ nicht auffindbar

Seite: ☐ rechts ☐ links ☐ Mittellinie

☐ Sonstiges: _____

Fernmetastasen bei Diagnosestellung:

☐ Nein Ja: ☐ Knochenmark ☐ Knochen ☐ Fern-Lymphknoten, Lokalisation: _____ ☐ Leber ☐ Haut

☐ Sonstiges: _____

Tumorinfiltration im Knochenmark:

	nicht durchgeführt	normal	pathologisch		
Zytologie	☐	☐	☐ ➨	☐ diffus	☐ Nester

Tumorzellen: ___ %

Befunde weiterer Untersuchungen bitte beifügen (wenn nicht von Köln durchgeführt)

Prätherapeutische diagnostische Verfahren:

	unauffällig	pathologisch	nicht eindeutig	nicht durchgeführt
Sonographie/CT/NMR (PRIMÄRTUMOR)	☐	☐	☐	☐
J-Benzylguanidin-Szinti (mIBG)				
Ergebnis für Primärtumor	☐	☐	☐	☐
Ergebnis für Metastasen	☐	☐	☐	☐
Skelett - Szintigramm	☐	☐	☐	☐
CT/NMR/Sonographie Schädel	☐	☐	☐	☐
Sonstige: _____	☐	☐	☐	☐

Tumorvolumen: Länge: ___,___ cm Breite: ___,___ cm Tiefe: ___,___ cm

Volumen: ___,___ ml $\left(\frac{\text{Länge x Breite x Tiefe}}{2}\right)$ ☐ gemessen ☐ errechnet

NB 3/4

Tumormarker im Serum (vor Therapie): * Falls andere Einheit, bitte angeben.

	unauffällig	pathologisch	nicht eindeutig	nicht durchgeführt	Wert		Faktor
LDH	☐	☐	☐	☐	_____	U/l*	
Ferritin	☐	☐	☐	☐	_____	ng/ml*	
NSE	☐	☐	☐	☐	_____	ng/ml*	
Katecholamine i. Serum:							
HVA	☐	☐	☐	☐	_____	ng/ml*	_____
VMA	☐	☐	☐	☐	_____	ng/ml*	_____
Katecholamine i. Urin:							
HVA	☐	☐	☐	☐	_____	nmol/µmol Krea*	_____
VMA	☐	☐	☐	☐	_____	nmol/µmol Krea*	_____

Blutbild (initial):

Leukozyten: ___,___ /µl Lymphozyten: ___ % Granulozyten: ___ %

Thrombozyten: ____ /µl Hb - Wert: ___,___ g/dl

Operation vor Chemotherapiebeginn durchgeführt: ☐ Nein ☐ Ja

Bitte Kopie des OP-Berichts beilegen!

Operationsdatum: ____.____.____

Radikalität:
- ☐ makroskopisch u. mikroskopisch komplett
- ☐ mikroskopisch inkomplett
- ☐ makroskopisch inkomplett
- ☐ Probeexzision:
  - ☐ Primärtumor
  - ☐ Metastase(n)

Komplikationen: ☐ Nein

(Wenn ja, Zeitpunkt in Wochen nach Op. angeben)

- ☐ Nephrektomie
- ☐ Blutung, Zeitpunkt: _____
- ☐ Ileus, Zeitpunkt: _____
- ☐ Infektion (bitte näher bezeichnen): _____ Zeitpunkt: _____
- ☐ Sonstiges (bitte näher bezeichnen): _____ Zeitpunkt: _____

Tumorinfiltration über die Mittellinie: ☐ Nein ☐ Ja ☐ nicht untersucht

(per def.: infiltratives Überschreiten der Wirbelkante der Gegenseite)

Lymphknoten makroskopisch auffällig: ☐ Nein ☐ Ja ☐ nicht untersucht

Histologischer Befall der regionären Lymphknoten:

homolaterale Lymphknoten:	☐ Nein	☐ Ja	☐ nicht untersucht
kontralaterale Lymphknoten: (jenseits der Mittellinie)	☐ Nein	☐ Ja	☐ nicht untersucht
anhängende Lymphknoten:	☐ Nein	☐ Ja	☐ nicht untersucht

Histologische Untersuchung (Bitte histologische Befunde und Befunde von molekulargenetischen Untersuchungen beilegen, wenn nicht in Marburg, Heidelberg, Stuttgart, Zürich oder Köln untersucht.):

☐ örtlicher Pathologe ☐ Referenzpathologe ☐ nicht durchgeführt

Bei Verstorbenen: Sterbedatum: ____.____.____

Todesursache: _____

- ☐ bedingt durch Primärtumor
- ☐ bedingt durch Rezidiv/Metastase
- ☐ bedingt durch Therapie
- ☐ andere Todesursache
- ☐ Tumorabhängigkeit nicht entscheidbar

Autopsie: ☐ Nein ☐ Ja

NB 4/4

Postoperative diagnostische Verfahren: (nicht ausfüllen nach Biopsie)

Datum: ☐☐.☐☐.☐☐☐☐

	unauffällig	pathologisch	nicht eindeutig	nicht durchgeführt
Sonographie/CT/NMR (PRIMÄRTUMOR)	☐	☐	☐	☐
J-Benzylguanidin-Szinti (mIBG)	☐	☐	☐	☐
Ergebnis für Primärtumor	☐	☐	☐	☐
Ergebnis für Metastasen	☐	☐	☐	☐

Sonstige: _____

Tumorvolumen: Länge: ☐☐,☐ cm Breite: ☐☐,☐ cm Tiefe: ☐☐,☐ cm

Volumen: ☐☐☐,☐ ml ($\frac{\text{Länge x Breite x Tiefe}}{2}$)

☐ gemessen
☐ errechnet

Tumormarker im Serum (nach Operation):

* Falls andere Einheit, bitte angeben.

	unauffällig	pathologisch	nicht eindeutig	nicht durchgeführt	Wert		Faktor
LDH	☐	☐	☐	☐	_____	U/l*	
Ferritin	☐	☐	☐	☐	_____	ng/ml*	
NSE	☐	☐	☐	☐	_____	ng/ml*	
Katecholamine i. Serum:							
HVA	☐	☐	☐	☐	_____	ng/ml*	_____
VMA	☐	☐	☐	☐	_____	ng/ml*	_____
Katecholamine i. Urin:							
HVA	☐	☐	☐	☐	_____	nmol/µmol Krea*	_____
VMA	☐	☐	☐	☐	_____	nmol/µmol Krea*	_____

Der Patient ist:

☐ Studienpatient
- ☐ Beobachtungspatient
- ☐ Mittlere Risikogruppe
- ☐ Hochrisikopatient
  - ☐ N8-Arm
  - ☐ Arm ohne N8

☐ Nicht-Studienpatient, wegen:
- ☐ Therapieverstoß
- ☐ Vorbehandlung, welche: _____

wie lange: _____

- ☐ Ablehnung der Therapie
- ☐ Sonstiges: _____

Chemotherapiebeginn: ☐☐.☐☐.☐☐☐☐

Bitte Kopien beilegen:
- ☐ Op-Bericht
- ☐ Histologie-Befund des örtlicher Pathologen
- ☐ Arztbriefe
- ☐ Befunde molekulargenetischer Untersuchungen, falls nicht in Marburg, Heidelberg, Stuttgart, Zürich oder Köln untersucht
- ☐ Knochenmarkbefunde (wenn nicht in Köln untersucht)
- ☐ radiologische Bildgebung (nur für Beobachtungspatienten mit postoperativem Rest)

Bemerkungen:

Stempel: Datum: Unterschrift:

NB2004 Randomisation

Bitte faxen an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

An
Prof. Dr. F. Berthold
Studienleitung NB2004
Zentrum für Kinderonkologie- und Hämatologie
Universitätsklinikum zu Köln
Kerpener Straße 62
50924 Köln
FAX 0221 478 6851

Patient

Patient Name	Patient Vorname	geboren	NB Nummer

Sehr geehrter Herr Professor Berthold,

o.g. Patient wird als Hochrisikopatient im Rahmen der Neuroblastomstudie NB2004 behandelt. Wir bitten ergänzend zur telefonischen Randomisierung um schriftliche Bestätigung des Randomisierungsergebnisses. Das Einverständnis der Eltern (des Patienten wenn zutreffend) liegt vor. Der Patient hat folgende Charakteristika:

- ☐ **Stadium 4, LDH nicht erhöht, Alter ≥1-21 Jahre, ungeachtet des MYCN Status**
- ☐ **Stadium 4, LDH erhöht, Alter zwischen ≥1 und <2 Jahre, ungeachtet des MYCN Status**
- ☐ **Stadium 4, LDH erhöht, Alter ≥2 Jahre, ungeachtet des MYCN Status**
- ☐ **MYCN amplifizierter lokalisierter Tumor, Alter ≥1-21 Jahre**
  Patienten <1 Jahre mit MYCN-Amplifikation werden nicht randomisiert und erhalten immer den Hochrisiko-Standardarm ohne N8

Mit freundlichen Grüßen

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

Rückmeldung der Studienleitung

Der Patient wurde randomisiert für
- ☐ Hochrisiko Standardarm ohne N8-Blöcke
- ☐ Hochrisiko experimenteller Arm mit N8-Blöcken

NB2004 Randomisation Rückmeldung an Klink

Bitte ausgefüllt zurückfaxen oder per Post an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie, Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

An
Prof. Dr. F. Berthold
Studienleitung NB2004
Zentrum für Kinderonkologie- und Hämatologie
Universitätsklinikum zu Köln
Kerpener Straße 62
50924 Köln
FAX 0221 478 6851

Sehr geehrte/geehrter

Die Patientin/der Patient:

Patient Name	Patient Vorname	geboren	NB Nummer

wurde im Rahmen der Neuroblastomstudie NB2004 Hochrisikogruppe randomisiert.

Er/sie wurde randomisiert für

☐ Hochrisiko Standardarm ohne N8-Blöcke

☐ Hochrisiko experimenteller Arm mit N8-Blöcken

Bitte teilen Sie uns mit, ob das Randomisierungsergebnis angenommen wurde:

☐ Randomisierung angenommen

☐ Randomisierung **nicht** angenommen

Mit freundlichen Grüßen

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

NB2004 Referenzradiologie Begleitschreiben

Bitte senden an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

An
Prof. Dr. F. Berthold
Studienleitung NB2004
Zentrum für Kinderonkologie- und Hämatologie
Universitätsklinikum zu Köln
Kerpener Str. 62
50924 Köln

Referenzbeurteilung radiologischer Aufnahmen des Patienten

Patient Name	Patient Vorname	geboren	NB Nummer

Sehr geehrte Studienleitung,

Wir bitten Sie um Ihre Beurteilung der radiologischen Aufnahmen und einen Vorschlag für das weitere therapeutische Vorgehen o.g. Patienten betreffend. In der Anlage finden Sie **Bilder und Befunde** folgender Untersuchungszeitpunkte:

Minimalanforderung: (i) initiale Bilder, unmittelbare Voraufnahmen und aktuelle Bilder zuschicken; (ii) für jeden Zeitpunkt jeweils komplette Serie (d.h., T1w, T1w mit KM, T2w; axial, sagittal, koronar; CT nativ, CT mit KM usw.)

	Datum	Art: MRT/CT/Röntgen/MIBG und Kommentar
Diagnosezeitpunkt		
unmittelbar Voraufnahme		
Aktuelle Aufnahmen		
andere:		
andere:		

Fragestellung _____

☐ Wir bitten um Rücksendung der Originale.

☐ Es handelt sich um Kopien zum Verbleib bei der Studienleitung.

Mit freundlichen Grüßen

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

LABORUNTERSUCHUNGEN (DEUTSCH)

NB2004 Referenzhistologie

Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, 🗐 -6851, neuroblastomstudie@uk-koeln.de

An den
Direktor des Instituts
für Pathologie

im Hause

Referenzbeurteilung histologischer Schnitte von:

NB Nummer	Patient Name	Patient Vorname	geboren

OP-Datum	Ihre Eingangsnummer

Sehr geehrte Frau Kollegin, sehr geehrter Herr Kollege,

o.g. Patient wird nach den Richtlinien der Neuroblastomstudie NB2004 behandelt. Zur Anerkennung als Protokollpatient ist für die Erstdiagnose und im Rezidiv die einheitliche zentrale Begutachtung durch ein Panel ausgewählter Pathologen erforderlich. Wir bitten Sie daher höflich, den Pathologiebogen, alle Blöcke oder HE Schnitte von allen Blöcken plus wenigstens einen repräsentativen Block an eine der beiden Adressen zu senden, um eine einheitliche Beurteilung der Klassifikation nach Hughes und INPC sowie die Einschätzung von Regressions- und Differenzierungsgrad zu ermöglichen:

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Kindertumorregister der GPOH
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Dr. K. Ernestus
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Universität zu Köln

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🗐 +49 (0) 221/478-6360
karen.ernestus@uni-koeln.de

Mit bestem Dank im Voraus für Ihre Bemühungen und

mit freundlichen Grüßen

Prof. Dr. F. Berthold
Studienleiter NB2004

Pädiatrischer Onkologe

NB2004 Pathologie-Bogen Teil 1

Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie, J-Stelzmann-Straße 9, D-50924 Köln
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An den
Referenzpathologen

Pathologie-Bogen zur Referenzbeurteilung histologischer Schnitte von:

NB Nummer	Patient Name	Patient Vorname	geboren

OP-Datum	Eingangsnummer

Diesen Bogen soll der lokale Pathologe ausfüllen.

Lokaler Pathologe: ..... oder Stempel
Klinik: .....
.....
Straße: .....
PLZ, Ort: .....

Chirurgische Information erhalten: ☐ ja ☐ nein

Vorbehandlung des Patienten:
☐ primäre Biopsie/Resektion
☐ OP nach Chemotherapie
☐ Rezidiv

Tumorlokalisation: .....

Tumormaterial:
☐ Biopsie
☐ Teilresektion des Tumors
☐ komplette Tumorresektion
☐ anderes: .....

Tumorgewicht: .....g Tumorgröße: .....x.....x.....cm³

Tumor am Resektionsrand:
makroskopisch ☐ ja ☐ nein ☐ unklar
mikroskopisch ☐ ja ☐ nein ☐ unklar
minimaler Abstand zum Resektionsrand:.....cm
falls ja, Lokalisation und Paraffinblock:.....

regionäre Lymphknotenmetastasen: ☐ ja ☐ nein ☐ unklar
wenn ja, Lokalisation: ☐ homolat. ☐ kontralateral ☐ anhängend

Bemerkungen:.....

NB2004 Pathologie-Bogen Teil 2

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Tumorskizze

Bitte zeichnen Sie in die Tumorskizze die genaue Lage der Gewebeblöcke mit Buchstaben oder Ziffern ein oder verwenden Sie ein (Digital-)Photo.

schockgefrorenes Gewebe asserviert:	☐ ja	☐ nein	☐ unklar
schockgefrorenes Gewebe an Tumorbank versandt:	☐ ja	☐ nein	☐ unklar

---

Bitte schicken Sie an den Referenzpathologen:

☐ diesen ausgefüllten Pathologie-Bogen

☐ alle Blöcke oder HE-Schnitte von allen Blöcken

☐ mindestens einen repräsentativen Paraffinblock

Die Referenzpathologie soll eine einheitliche Beurteilung der Klassifikation nach INPC und Hughes sowie die Einschätzung vom Regressions- und Differenzierungsgrad ermöglichen, wobei insbesondere für die exakte Festlegung des Regressions- und Differenzierungsgrades alle Blöcke bzw. Schnittpräparate nötig sind.

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

NB2004 Tumorbank-Einsendebogen

Kompetenznetz Pädiatrische Onkologie und Hämatologie
Molekularbiologische Marker bei embryonalen Tumoren

Patientendaten: Patientenetikett:

Name:.....

Vorname:.....

Geburtsdatum:.....

Geschlecht: [ ]w [ ]m

Diagnose:.....

[ ] Erstdiagnose [ ] Verlaufskontrolle [ ] Rezidiv [ ] nach Chemotherapie [ ] nach KMT

Therapie-Studie:.....

Bemerkungen (z.B. 2. Rez.):.....

.....

Untersuchungsmaterial: Entnahme-Datum:.....

Bitte ankreuzen: Lokalisation:

0 Tumor ..... Zeit bis zum Einfrieren:.....
0 Tumortupfpräparate .....
0 Blut (Monovette grün) für DNA-Extraktion
0 Blut (Glasmonovette) für Leukozytenisolation und Serum
0 Serum
0 Normalgewebe .....
0 tumorzellhaltiges Knochenmark für Molekularbiologie
(Ausstriche und Heparinblut für Immunzytologie beim Neuroblastom bitte extra einsenden)
0 Sonstiges:.....

Ansprechpartner: ..... Telefon-Nr.....

(Stempel) Datum:..... Unterschrift:.....

Präferenzlabor für das Neuroblastom

Primär das Material nach Köln senden. Bitte ankreuzen, welches zweite Labor, insbesondere für die N-myc-Bestimmung bevorzugt wird. Falls keine Angabe vorliegt, wird die Entscheidung von der Tumorbank vorgenommen.

	Prof. Schwab, Heidelberg		**Vergleichsblut unbedingt erforderlich**
	Prof. Christiansen, Marburg		**Vergleichsblut unbedingt erforderlich**
	Prof. Berthold, Köln		
	PD Dr. Niggli, Zürich		
	Dr. Schilling, Stuttgart		

seltene Tumoren, Keimzelltumoren

	nur Asservierung

bitte wenden

Name:.....**Vorname:**.....**geb.:**.....

Adressen:

Hirn- und Lebertumoren:
Prof. Dr. T. Pietsch
Institut für Neuropathologie der Universität Bonn
Sigmund-Freud-Str. 25
53105 Bonn
Tel.: 0228-287 4398

Nierentumoren:
Prof. Dr. M. Gessler
Institut für physiologische Chemie an der
Universität Würzburg
Am Hubland
97074 Würzburg
Tel.: 0931-888 4159

Neuroblastom, Keimzelltumoren,
seltene embryonale Tumoren:
Prof. Dr. F. Berthold
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50924 Köln
Tel.: 0221-478 6843

CWS-Studie:
PD Dr. E. Koscielniak
Olgaspital Stuttgart
Onkologisches Labor
Bismarckstr. 8
70176 Stuttgart
Tel.: 0711/9923504

Lagerhanszell-Histiozytose:
St. Anna Kinderspital
Kinderspitalgasse 6
A-1090 Wien
Tel.: +43-40170476
Fax: +43-40170430
e-mail: LCH@stanna.at

Wird vom Labor ausgefüllt:

Eingangsdatum: ..... Patientennummer:.....

Materialart	Menge	Lagerort	Zustand bei Eintreffen

Anleitung zur Asservierung von Tumorgewebe

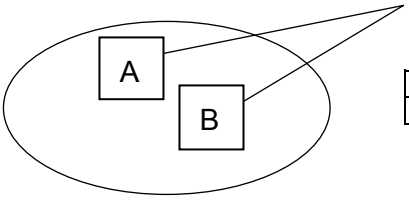
Quelle: Kompetenznetz Pädiatrische Onkologie und Hämatologie, Molekularbiologische Marker bei embryonalen Tumoren

A. Benötigtes Material

1. diese Anleitung
2. Tumorgewebe-Set:
- 20 Superfrost-Objektträger für Tumortupfpräparate
- 5 Objektträger-Boxen
- 1 50 ml Becher für das Handling mit flüssigem Stickstoff
- 7 1,8 ml Standröhrchen für tiefgefrorenes Frischgewebe (6 x ROT für Tumor, 1 x GRÜN für Normalgewebe)
- 1 5 ml Citrat-Monovette für Vergleichsblut (DNA-Extraktion)
- 1 4ml Glasmonovette (blau-schwarzer Stopfen) für Leukozytenisolation
- 1 Einsendebogen

3. Bleistift und Permanentmarker (fein) zum Beschriften von Objektträgern und Röhrchen
4. Tumorbox
5. *Sterile* Kompressen, Skalpell, Pinzette, Handschuhe, Deuwer für Stickstoff
Die Sicherheitsvorschriften beim Arbeiten mit flüssigem Stickstoff müssen eingehalten werden.

B. Vorgehensweise



A und B werden jeweils in vier gleiche Stücke geteilt mindestens zwei Tumorstücke A/ B sollten von morphologisch unterschiedlichen Arealen entnommen werden.

1	2
3	4

1 bevor das Tumorstück in Formalin fixiert wird (für Histologie, örtlicher Pathologe), 10 Tupfpräparate (z. B. für FISH) machen
2,3,4 Einfrieren in flüssigem Stickstoff

Resektabler Tumor:

1. Aufteilen des Tumormaterials

Gemeinsam mit dem zuständigen Pathologen Tumor aufschneiden, der Pathologe soll die Aufteilung des Tumors vornehmen. Gewebeproben aus unterschiedlichen, aber mindestens zwei repräsentativen Arealen gewinnen **A** und **B** (Größe 1 cm^3, wenn möglich mehr Tumorproben gewinnen: **C**, **D** etc.; nicht vom Tumorrand (Resektionsränder!), kein Bindegewebe, keine nekrotischen Bezirke asservieren, beim Neuroblastom noduläre Areale immer asservieren). Falls mehr Stücke (C, D) gewonnen werden, neues Tumor-Röhrchenset verwenden. Die Stücke dann jeweils in 4 gleiche Stücke **A1**, **A2**, **A3**, **A4** und **B1**, **B2**, **B3**, **B4** (**C1**, **C2**, **C3**, **C4** etc.) teilen. Vor der Weiterverarbeitung vorsichtig steril Blut vom Tumorgewebe abtupfen. So schnell wie möglich verarbeiten (optimal: innerhalb von 30 Minuten nach der chirurgischen Entnahme). Übriges Tumorgewebe für die histologische Diagnostik in Formalin geben (örtlicher Pathologe).

Falls bei einem größeren Operationspräparat der Pathologe nicht das gesamte restliche Tumorgewebe zur Diagnostik braucht, übrig gebliebenes Tumorgewebe klein schneiden, in 50 ml Becher einfrieren und versenden. Welches Tumorgewebe zusätzlich eingefroren werden kann, entscheidet der Pathologe!

2. Frischgewebe schockgefrieren

50 ml Becher mit flüssigem Stickstoff füllen und Deckel locker auflegen, damit die Verdunstung gering bleibt, jedoch auch kein Druck entsteht.

1,8 ml Standröhrchen (rot) mit Namen, Geburtsdatum, Operationsdatum und Tumorlokalisation (**A2**, usw.) beschriften.

Danach aufschrauben. Deckel auf sterile Kompresse legen, Röhrchen im Deuwer mit flüssigem Stickstoff vorkühlen.

Kompressen, Pinzette und Skalpell steril auspacken und bereitlegen.

Sterile Handschuhe anziehen (zum Schutz des Gewebes vor RNAsen an den Händen und zur Erhaltung der Sterilität)

Tumorteile **A, B** in 4 Teile **A1**, **A2**, **A3**, **A4**, **B1**, **B2**, **B3** und **B4** teilen (s. Skizze) und **A2**, **A3**, **A4**, **B2**, **B3**, und **B4** rasch, steril schockgefrieren. Falls die Stücke nicht in die Röhrchen passen teilen bzw. in kleine Stücke schneiden.

Schockgefrieren des Gewebes durch Fallenlassen der Tumorstücke in den flüssigen Stickstoff (im 50ml Becher). Dabei *nicht* mit der Pinzette eintauchen, weil dabei das Tumorgewebe an der Pinzette haften bliebe. Darauf achten, dass die Gewebestücke *nicht* an der Wand des 50 ml Bechers haften.

Aus vorgekühlten 1,8 ml Röhrchen flüssigen Stickstoff dekantieren. Dabei darauf achten, dass sich kein flüssiger Stickstoff mehr im 1,8ml Röhrchen befindet.

Schockgefrorenes Tumorgewebe aus dem 50ml Becher in die roten 1,8 ml Röhrchen transferieren, dabei nach **A** und **B** trennen, verschließen (Schraubdeckel) und im flüssigen Stickstoff gefroren halten.

Auf dem Einsendebogen die Dauer vom Zeitpunkt der Entnahme des Tumorgewebes bis zum Einfrieren notieren.

3. Herstellung von Tupfpräparaten und Formalinfixierung von Gewebe

2 Gefäße für die Histologie mit Namen, Geburtsdatum und Operationsdatum beschriften und mit gepufferter 4%iger Formalinlösung füllen. (Diese Gefäße sind nicht im Tumorgewebe-Set enthalten.)

Von den Tumorteilen **A1** und **B1** jeweils zehn Tumortupfpräparate herstellen. *Behutsames* Abtupfen der oberflächlichen Zellschicht der Tumorprobe auf *Superfrost-Objektträger* (ca. 6 Tupfungen pro Schnittfläche, max. 10 Objektträger pro Stück, nicht wischen). Präparate beschriften und *lufttrocknen*.

Danach die Tumorteile **A1** und **B1** unzerkleinert (!) in je 1 Histologiegefäß mit 4%iger Formalin-Lösung einbringen für den örtlichen Pathologen zur Bestimmung des Tumorzellgehalts.

Nichtresektabler Tumor:

1. Aufteilung des Tumormaterials

Die Aufteilung des Tumorgewebes hängt von der Größe der Biopsie ab und soll vom *Pathologen* vorgenommen werden. Falls möglich, sollte der Chirurg beim Neuroblastom 2 unterschiedliche Areale **A** und **B** (Größe ca. 1cm^3) entnehmen. Vor der Weiterverarbeitung vorsichtig und steril Blut vom Tumorgewebe abtupfen. Abhängig von der Biopsiegröße einen Teil für die histologische Diagnostik asservieren und restliche Tumorteile tiefgefrieren (s. o.). Bei kleinen Biopsien entscheidet der Pathologen, wie viel Gewebe eingefroren werden kann, was möglichst geschehen sollte.

2. und 3.

Verfahren wie bei resektablem Tumor.

C. Gewinnen von Vergleichs-DNA und Leukozyten aus Citratblut und/oder Normalgewebe

Blut:

5-10 ml Begleitblut vom Patienten in Vacutainer-Citrat-Monovetten **(grün)** gewinnen, gut durchmischen (nicht schütteln) und unsepariert im Thermogefäß mit flüssigem Stickstoff einfrieren.

Tumorarten: alle

Glasmonovette **(blau-schwarzer Stopfen)** mit 4ml Blut füllen. Die Glasmonovette **NICHT** tieffrieren sondern im Deckel der Tumorbox (zusammen mit Tumortupf) verschicken.

Tumorarten: alle

Normalgewebe:

Wenn bei der gleichen Operation (z.B. Nephrektomie, Leberteilresektion) normales Gewebe aus chirurgisch technischen Gründen mitentfernt werden **muss**, eignet sich dies als Vergleichsgewebe noch besser. ***Das darf aber keinesfalls zu einer zusätzlichen Resektion oder Erweiterung der Resektionsränder führen.***

Tumorarten: alle

Das Vergleichsgewebe wird wie das Tumorgewebe im **grünen** Röhrchen in flüssigem Stickstoff eingefroren.

D. Versand

1. Einsendebogen vollständig ausfüllen und mit dem Material in der Tumorbox an das zuständige Labor senden.
2. Tumorteile **A1** und **B1** bzw. **C1**, **D1** usw. (in 4% Formalin) und übriges Tumorgewebe vom zuständigen örtlichen Pathologen befunden lassen, evtl. mit Bitte um Referenzhistologie.
3. Schockgefrorene Tumorteile **A2**, **A3**, **A4** sowie **B2**, **B3**, **B4** (evtl. **C2**, **C3**, **C4** etc.) und Vergleichsblut bzw. Normalgewebe bis zum Versand bei –70 bzw. –80°C oder in flüssigem Stickstoff lagern. Der Versand erfolgt per Express tiefgefroren auf Trockeneis in der Tumorbox an das zuständige molekulargenetische Labor. Die gesamte Kammer der Tumorbox muss mit Trockeneis aufgefüllt werden. Die luftgetrockneten Tumortupfpräparate, Glasmonovette und evtl. Serum, Knochenmark im Deckel der Tumorbox (nicht auf Trockeneis) beilegen.

E. Adressen:

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Sigmund-Freud-Str. 25
53105 Bonn
Tel.: 0228-287 4398

Nierentumoren:
Prof. Dr. M. Gessler
Institut für physiologische Chemie an der Universität Würzburg
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Tel.: 0931-888 4159

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NB2004 Katecholamine in Blut und Urin

Georg-August-Universität Göttingen ● Bereich Humanmedizin
Universitätsklinikum ● Medizinische Fakultät
Zentrum Kinderheilkunde
Pädiatrie II mit Schwerpunkt Neuropädiatrie, Direktorin Prof.Dr.med. Jutta Gärtner

PROBEN AN:

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Fax.: 0551-396236
hunneman@med.uni-goettingen.de

Absender (Adresse für Befund)

Etikett oder

NAME_____

VORNAME:_____

Geb.:_____

UNTERSUCHUNGSAUFTRAG FÜR KATECHOLAMINE UND METABOLITE IM URIN oder PLASMA / SERUM

O Plasma oder Serum 0,5 ml ungekühlt DATUM:_____

O Spontanurin (2-5 ml) DATUM:_____

O Sammelurin (2-5 ml) DATUM :_____ Vol.:_____

Zeit:_____

Kostenträger
O Ambulant
O Stationär

Privatpatient O**
Selbstzahler O**
Kassenpatient O

**Rechnungsempfänger angeben

Verantwortlicher Arzt _____

O Bekannter Patient mit NEUROBLASTOM (Stadium _____).

O Unter Therapie O Rezidivverdacht O Persistierender Tumor
O Keine Änderung seit letzter Untersuchung. Routine Verlaufskontrolle

O Initiale diagnostische Untersuchung: Verdacht auf:
O Neuroblastom O Phaeochromocytom O Carcinoid
O Andere:

Symptome : O Hypertonie O Durchfall O Flushing O Schwitzen
O Raumforderung O Klinisch unauffällig

NB2004 Knochenmark Einsendeformular

Bitte senden an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, 🖷 -6851, neuroblastomstudie@uk-koeln.de

An das
Hämatologisch-Onkologische Labor
Zentrum für Kinderonkologie und -hämatologie
Klinik für allgemeine Kinderheilkunde
Kerpener Str. 62
50924 Köln

Betr.:

Patient Name	Patient Vorname	geboren	NB Nummer

Entnahme-Datum: .....

Krankheitsstatus:
- ☐ Initialdiagnostik
- ☐ nach ..... Blöcken Chemotherapie
- ☐ vor Erhaltungstherapie
- ☐ vor Megatherapie
- ☐ vor Retinsäure-Konsolidierung 1 (6 Monate)
- ☐ vor Retinsäure-Konsolidierung 2 (3 Monate)
- ☐ bei Therapieende
- ☐ Rezidiv-Verdacht
- ☐ Routineverlaufskontrolle ohne Rezidiv-Verdacht
- ☐ **Apherisat** (vor Positivselektion) nach peripherer Stammzellapherese
- ☐ Sonstiges: .....

Hiermit bitten wir um den Nachweis von Neuroblastomzellen im Knochenmark (4 Punktionsstellen):

Punktionsort 1.....

Punktionsort 2.....

Punktionsort 3.....

Punktionsort 4.....

Je Punktionsort sind 3-5 ml **Heparin-Knochenmark** und ≥5 **Ausstriche** erforderlich. Das Material kann ungekühlt verschickt werden, muss das Labor aber innerhalb von 24 h erreichen. Expressversand über Nacht ist ausreichend. Eine Versendung am Freitag ist nur nach telefonischer Voranmeldung (+49 221 478 4390) möglich. Von einer Versendung am Samstag bitten wir abzusehen.

Mit freundlichen Grüßen

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

THERAPIEDOKUMENTATION (DEUTSCH)

NB2004 Chemotherapieplan Block N4

Bitte **diesen Bogen oder den klinikintern verwendeten Medikamentenplan** senden an:
Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Gewicht (kg)	Größe (cm)	KOF (m²)

Adriamycin (ADR): 15 mg/m²xd (Säuglinge 0,5 mg/kgxd)

Tage 1, 3 und 5 als intravenöse 30 Minuten-Kurzinfusion

Datum Tag 1

falls kein zentralvenöser Katheter: sorgfältige Beobachtung der Infusionseintrittsstelle zur Vermeidung lokaler Nekrosen

Datum Tag 3

Datum Tag 5	Tagesdosis	Volumen der Lösung	Geschwindigkeit
	mg	ml	ml/h

Vincristin (VCR): 0,75 mg/m²xd (Maximal 2 mg; Säuglinge 0,025 mg/kgxd)

Tage 1, 3, 5 intravenös als push

Datum Tag 1

Datum Tag 3

Datum Tag 5	Tagesdosis	Volumen der Lösung	Geschwindigkeit
	mg	ml	ml/h

Cyclophosphamid (CPM): 300 mg/m²xd (Säuglinge 10 mg/kgxd)

Tage 1-7 als 30 Minuten-Kurzinfusion oder oral

Datum Tag 1

Datum Tag 2	CP Einzeldosis	Volumen der CP Lösung	Geschwindigkeit
	mg	ml	ml/h

Datum Tag 3

Mesna 6mg/kgxd Tage 1-8
in der Begleitinfusion ODER 3 Einzeldosen iv. push Stunde 0, 4 und 8 nach CP

Datum Tag 4

Datum Tag 5	MESNA Einzeldosis	Volumen der MESNA Lösung
	3 x mg	3 x ml

Datum Tag 6

Datum Tag 7

NB2004 Chemotherapieplan Block N5

Bitte **diesen Bogen oder den klinikintern verwendeten Medikamentenplan** senden an:
Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, 🖷 -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Gewicht (kg)	Größe (cm)	KOF (m²)

Vindesin (VDS): 3 mg/m²xd (Maximal 6 mg, Säuglinge 0,1 mg/kgxd)

Tag 1 als Infusion über 1 Stunde in NaCl 0,9%

Datum Tag 1	Einzeldosis	Volumen der Lösung	Geschwindigkeit
	mg	ml	ml/h

Cisplatin (DDP): 40 mg/m²xd (Säuglinge 1,3 mg/kgxd)

Tag 1-4 als 96h-Dauerinfusion (4x 24h) in NaCl 0,9%

Datum Tag 1			
Datum Tag 2	**Tagesdosis**	**Volumen der Lösung**	**Geschwindigkeit**
	mg	ml	ml/h
Datum Tag 3			
Datum Tag 4			

Etoposid (VP16): 100 mg/m²xd (Säuglinge 4,2 mg/kgxd)

Tag 1-4 als 96h-Dauerinfusion (4x 24h) in NaCl 0.9%

Datum Tag 1			
	Bei Verzögerung>28 Tage oder Infektion Grad ≥3: Dosisreduktion auf 80%		
Datum Tag 2			
	mg	ml	ml/h
Datum Tag 3	**Tagesdosis**	**Volumen der Lösung**	**Geschwindigkeit**
Datum Tag 4			

Parallelinfusion 3000 ml/m²xd (Maximal 5000 ml/d) Tag 1-6

Datum Tag 1	**Zusammensetzung**	**ml/1000 ml**	**ml/24 h**
	NaCl 0.9%	469 ml	.....
	Glukose 5%	468 ml	.....
	$MgSO_4$ 10%	26 ml	.....
	Calciumglukonat 10%	12 ml	.....
	KCl 7,45%	25 ml	.....
Datum Tag 6			ml/h .....

Mannit-DTI 1 g/kgxd (maximal 1,5 g/kg) = 6,7 ml Mannit 15%/kgxd

Tag 1-4 als 96h-Dauerinfusion (4x 24h) in NaCl 0,9%

Datum Tag 1			
	mg	ml	ml/h
Datum Tag 4	**Tagesdosis**	**Volumen der Lösung**	**Geschwindigkeit**

G-CSF 5 µg/kg x d (zur Stammzellmobilisierung 10 µg/kgxd)

ab Tag 9 bis Leukos >10 000/µl (bzw. Granulozyten >5000/µl) subkutan (oder als 4-h-Infusion)

NB2004 Chemotherapieplan Block N6

Bitte **diesen Bogen oder den klinikintern verwendeten Medikamentenplan** senden an:
Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Gewicht (kg)	Größe (cm)	KOF (m²)

Vincristin (VCR): 1,5 mg/m²xd (Maximal 2 mg, Säuglinge 0,05 mg/kgxd)

Tag 1 und Tag 8 als **separate** 1h-Infusion in NaCl 0,9%

Datum Tag 1

Datum Tag 8	Einzeldosis	Volumen der Lösung	Geschwindigkeit
	mg	ml	ml/h

Dacarbacin (DTIC): 200 mg/m²xd (Säuglinge 6,7 mg/kgxd)

Tag 1-5 als 1h-Infusion **lichtgeschützt** in NaCl 0,9%

Schritt 2 bei erneuter Verzögerung>28 Tage oder Infektion Grad ≥3:
DTIC ersatzlos streichen!

Datum Tag 1

Datum Tag 2	Einzeldosis	Volumen der Lösung	Geschwindigkeit
	mg	ml	ml/h

Datum Tag 3

Datum Tag 4

Datum Tag 5

Ifosfamid (IFO): 1500 mg/m²xd (Säuglinge 50 mg/kgxd)

Tag 1-5 als 115h-Dauerinfusion (= 5 x 23h, Unterbrechung für DTIC) in NaCl 0.9%

Datum Tag 1

Schritt 1 bei Verzögerung>28 Tage oder Infektion Grad ≥3:
Dosisreduktion auf 1000 mg/m²xd

Datum Tag 2

Datum Tag 3	Tagesdosis	Volumen der Lösung	Geschwindigkeit
	mg	ml	ml/h

Datum Tag 4

Datum Tag 5

Adriamycin (ADR): 30 mg/m²xd (Säuglinge 1 mg/kgxd)

Tag 6-7 als **separate** 4 h-Infusion in NaCl 0.9%

Datum Tag 6

Datum Tag 7	Einzeldosis	Volumen der Lösung	Geschwindigkeit
	mg	ml	ml/h

Parallelinfusion 3000 ml/m²xd (Maximal 5000 ml/d) Tag 1-7

Zusammensetzung	ml/1000 ml	ml/24 h
MESNA 100 mg/ml	3 ml	.....
NaCl 0.9%	485 ml	.....
Glukose 5%	485 ml	.....
KCl 7,45%	25 ml	.....
		ml/h .....

Datum Tag 1

Datum Tag 7

G-CSF 5 µg/kg x d (zur Stammzellmobilisierung 10 µg/kgxd)

ab Tag 10 bis Leukos >10 000/µl (bzw. Granulozyten >5000/µl) subkutan (oder als 4-h-Infusion)

NB2004 Chemotherapieplan Block N7

Bitte **diesen Bogen oder den klinikintern verwendeten Medikamentenplan** nach dem letzten N7 senden an:
Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Gewicht (kg)	Größe (cm)	KOF (m²)

Cyclophosphamid (CP): 150 mg/m²xd (Säuglinge 5 mg/kgxd)

Tage 1-8 oral

errechnete Cyclophosphamid Einzeldosis in mg/Tag

MESNA 3 x 30 mg/m² (Säuglinge 3 x 1 mg/kgxd)

Tage 1-8 oral jeweils zur Stunde 0, 4 und 8 nach Cyclophosphamid

errechnete MESNA Einzeldosis in mg

		Datum Tag 1		Datum Tag 8
1. Block N7	**von**		**bis**	
2. Block N7	**von**		**bis**	
3. Block N7	**von**		**bis**	
4. Block N7	**von**		**bis**	

NB2004 Chemotherapieplan Block N8

Bitte **diesen Bogen oder den klinikintern verwendeten Medikamentenplan** senden an:
Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Gewicht (kg)	Größe (cm)	KOF (m²)

Cyclophosphamid (CP): 100 mg/m²xd (<10 kg KG nach kg dosieren)

Tag 1 **Start 6 h vor Topotecan** über 1 Stunde in NaCl 0,9%;
Tag 2-7 parallel zu Topotecan als 1h Infusion in NaCl 0,9%

Datum Tag 1: _____

Datum Tag 7	Einzeldosis	Volumen der Lösung	Geschwindigkeit
	mg	ml	ml/h

MESNA: 3 x 20 mg/m² x d

Tag 1-7 als intravenöse Injektion zur Stunde 0, 4 und 8 nach Cyclophosphamid
Topotecan während Injektion stoppen und Leitung mit NaCl 0,9% vor- und nachspülen!

Datum Tag 1: _____

Datum Tag 7	Einzeldosis	Volumen der Lösung
	3 x mg	3 x ml

Topotecan (TOPO): 1.0 mg/m²xd (<10 kg KG nach kg dosieren)

Tag 1-7 als 168 h Dauerinfusion (7x24h) in NaCl 0.9%; Tag 1 Start 6 h nach Cyclophosphamid

Bei Verzögerung>28 Tage oder Infektion Grad ≥3: Dosisreduktion auf 70%

Datum Tag 1: _____

Datum Tag 7	Tagesdosis	Volumen der Lösung	Geschwindigkeit
	mg	ml	ml/h

Etoposid (VP16): 100 mg/m²xd (<10 kg KG nach kg dosieren)

Tag 8-10 als 1 h-Infusion in NaCl 0.9%

Datum Tag 8: _____

Datum Tag 9	Einzeldosis	Volumen der Lösung	Geschwindigkeit
	mg	ml	ml/h

Datum Tag 10: _____

Parallelinfusion 2000 ml/m²xd (Maximal 5000 ml/d), Tag 1-7

Datum Tag 1: _____

Zusammensetzung	ml/1000 ml	ml/24 h
NaCl 0.9%	485 ml	.....
Glukose 5%	485 ml	.....

ml/h .....

Datum Tag 7: _____

G-CSF 5 µg/kg x d (zur Stammzellmobilisierung 10 µg/kgxd)

ab Tag 12 bis Leukos >10 000/µl (bzw. Granulozyten >5000/µl) subkutan (oder als 4-h-Infusion)

NB2004 Toxizitätsbogen Chemotherapie

Bitte senden an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie, Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Datum Start des Blocks: .....

Welcher Block ☐ **N4** ☐ **N5** ☐ **N6** ☐ **N7** ☐ **N8** ☐ anderer:.....

Bitte die maximale Toxizität, die vom ersten Tag des Blocks bis zum Start des nachfolgenden Blocks beobachtet wurde, ankreuzen und mit einer Kopie des Therapieplans an die Studienleitung senden

Grad	0	1	2	3	4
Allgemeinzustand	Normale Aktivität	Geringe Beeinträchtigung	Altersentspr. Aktivität stark eingeschränkt	Bettlägerig, pflegebedürftig	Intensive Behandlung schwerstkrank
Hämoglobin	Altersnorm	> 100%	80-100%	65-79%	< 65%
Leukozyten (/nl)	> 4,0	3,0-3,9	2,0-2,9	1,0-1,9	< 1,0
Granulozyten (/nl)	> 2,0	1,5-1,9	1,0-1,4	0,5-0,9	< 0,5
Thrombozyten (/nl)	> 100	75-100	50-74,9	25-49,9	< 25
Infektion	keine	leicht	mäßig: ohne Erregernachweis, i.v. Antibiotika	schwer: mit Erregernachweis, i.v. Antibiotika	lebensbedrohlich, mit Hypotonie
Fieber (°C)	keins	37,1-38	38,1-40	> 40 für < 24 Std.	> 40 für ≥ 24 Std.
Stomatitis/ orale Mucositis	keine	schmerzlose Ulzera, Erythem	schmerzendes Erythem oder Ulzerationen, kann aber essen	schmerzendes Erythem oder Ulzerationen, nur flüssige Nahrung möglich	TPN wegen Stomatitis erforderlich
Diarrhöe (Anstieg Stuhl-frequenz/Tag)	keine	2-3	4-6 o. nächtl. Stuhl o. leichte Bauchkrämpfe	7-9 oder Inkontinenz oder starke Bauchkrämpfe	≥ 10 o. blutiger Durchfall o. TPN erforderlich
Kreatinin	Altersnorm	< 1,5 x Norm	1,5-3,0 x Norm	3,1-6,0 x Norm	> 6,0 x Norm
Bilirubin	Altersnorm	-	< 1,5 x Norm	1,5-3 x Norm	> 3 x Norm
SGOT/SGPT	Altersnorm	≤ 2,5 x Norm	2,6-5,0 x Norm	5,1-20 x Norm	> 20 x Norm
Kardiotoxizität: Echo LV-SF	> 30%	> 25 und ≤ 30%	> 20 und ≤ 25%	> 15 und ≤ 20%	≤ 15%
Ototoxizität: Hörverlust bei 2kHz	keine	< 15 dB	16-30 dB	31-60 dB	> 60 dB
Neurotoxizität peripher	keine	Parästhesien	schwere Parästhesien und/oder milde Schwäche	unerträgliche Parästhesien, deutliche motorische Verluste	Paralyse
Neurotoxizität zentral	keine		Somnolenz oder Müdigkeit	Stupor, schwer erweckbar	Koma
Obstipation	keine oder keine Veränderung	mild	moderat	schwer	Ileus > 96 h
Sonstiges					

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

NB2004 Megatherapieplan

Bitte **diesen Bogen, PRST Bogen oder den klinikintern verwendeten Medikamentenplan** senden an:
Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name | Patient Vorname | geboren | NB Nummer

Melphalan (MEL): 45 mg/m²xd (<10 kg Körpergewicht 1,5 mg/kgxd)

Tag –8 bis –5 als 30-min-Infusion in NaCl 0,9%

Datum Tag –8

Datum Tag –7 | Einzeldosis (mg) | Volumen der Lösung (ml) | Geschwindigkeit (ml/h)

Datum Tag –6

Datum Tag –5

Etoposid (VP16): 40 mg/kg Körpergewicht

Tag –4 als 4-h-Infusion vor Carboplatin

Datum Tag –4 | Einzeldosis (mg) | Volumen der Lösung (ml) | Geschwindigkeit (ml/h)

Carboplatin (CARBO): 500 mg/m²xd (<10 kg Körpergewicht 16,6 mg/kgxd)

Tag –4 bis –2 als 1-h-Infusion in NaCl 0.9%, Gabe Tag –4 nach Etoposidinfusion!

Datum Tag –4

Datum Tag –3 | Einzeldosis (mg) | Volumen der Lösung (ml) | Geschwindigkeit (ml/h)

Datum Tag –2

Parallelinfusion 3000 ml/m²xd (Maximal 5000 ml/d)

Datum Tag –8

Zusammensetzung	ml/1000 ml	ml/24 h
Glukose 50%	100 ml	.....
Glukose 5%	795 ml	.....
NaCl 5,85%	40 ml	.....
$MgSO_4$ 10%	30 ml	.....
CaGlukonat 20%	15 ml	.....
KCl 7,45%	20 ml	.....
		ml/h .....

Datum Tag –1

Stammzell-Reinfusion, Dosis >2 x 10^6 CD34 pos. Zellen/kg

Tag 0

☐ autolog ☐ allogen ☐ KM ☐ periph. Stammzellen ☐ CD34 Separation

Datum Tag 0 | CD 34 pos. Zellen absolut ($x10^6$) | CD 34 pos. Zellen pro kg ($x10^6$/kg)

G-CSF 10 µg/kg x d

Tag 2 bis Leukos >10 000/µl (bzw. Granulozyten >5000/µl) subkutan (oder als 4-h-Infusion)

Datum Tag 1 | Präparat | Dosis G-CSF absolut (µg/d) | letzter Tag G-CSF

NB2004 Toxizitätsbogen Megatherapie

Bitte **zusammen mit PRST Bogen** senden an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie, Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, 🗐 -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Tag 0: ..... **Konditionierung** ☐ MEL/VP16/CARBO ☐ andere: .....

Bitte die maximale Toxizität im Verlauf und **nach** dem Therapiekurs ankreuzen und mit Therapieplan als Kopie an die Studienleitung senden

Grad	0	1	2	3	4
Allgemeinzustand	Normale Aktivität	Geringe Beeinträchtigung	Altersentspr. Aktivität stark eingeschränkt	Bettlägerig, pflegebedürftig	Intensive Behandlung schwerstkrank
Hämoglobin	Altersnorm	> 100%	80-100%	65-79%	< 65%
Leukozyten (/nl)	> 4,0	3,0-3,9	2,0-2,9	1,0-1,9	< 1,0
Granulozyten (/nl)	> 2,0	1,5-1,9	1,0-1,4	0,5-0,9	< 0,5
Thrombozyten (/nl)	> 100	75-100	50-74,9	25-49,9	< 25
Infektion	keine	leicht	mäßig: ohne Erregernachweis, i.v. Antibiotika	schwer: mit Erregernachweis, i.v. Antibiotika	lebensbedrohlich, mit Hypotonie
Fieber (°C)	keins	37,1-38	38,1-40	> 40 für < 24 Std.	> 40 für ≥ 24 Std.
Stomatitis/ orale Mucositis	keine	schmerzlose Ulzera, Erythem	schmerzendes Erythem oder Ulzerationen, kann aber essen	schmerzendes Erythem oder Ulzerationen, nur flüssige Nahrung möglich	TPN wegen Stomatitis erforderlich
Diarrhöe (Anstieg Stuhl-frequenz/Tag)	keine	2-3	4-6 o. nächtl. Stuhl o. leichte Bauchkrämpfe	7-9 oder Inkontinenz oder starke Bauchkrämpfe	≥ 10 o. blutiger Durchfall o. TPN erforderlich
Hautveränderung	keine	Erythem	trockene Desquamation, Vaskulitis Pruritus	feuchte Desquamation, Ulzerationen	exfoliative Dermatitis, Nekrosen
Kreatinin	Altersnorm	< 1,5 x Norm	1,5-3,0 x Norm	3,1-6,0 x Norm	> 6,0 x Norm
Bilirubin	Altersnorm	-	< 1,5 x Norm	1,5-3 x Norm	> 3 x Norm
SGOT/SGPT	Altersnorm	≤ 2,5 x Norm	2,6-5,0 x Norm	5,1-20 x Norm	> 20 x Norm
Kardiotoxizität: Echo LV-SF	> 30%	> 25 und ≤ 30%	> 20 und ≤ 25%	> 15 und ≤ 20%	≤ 15%
Ototoxizität: Hörverlust bei 2kHz	keine	< 15 dB	16-30 dB	31-60 dB	> 60 dB
Neurotoxizität peripher	keine	Parästhesien	schwere Parästhesien und/oder milde Schwäche	unerträgliche Parästhesien, deutliche motorische Verluste	Paralyse
Neurotoxizität zentral	keine		Somnolenz oder Müdigkeit	Stupor, schwer erweckbar	Koma
Obstipation	keine oder keine Veränderung	mild	moderat	schwer	Ileus > 96 h
Sonstiges					

Leukozyten >1/nl _____ Datum

Thrombozyten >20/nl (unsubstituiert) _____ Datum

Entlassung nach Hause _____ Datum

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

PRST Dokumentationsbogen Tag 100

Form 3: Autograft

Center |_____|

Patient, name |_____|

and/or UPN |_____| Sex: m ☐ f ☐

Date of birth |__|__|__|__|__|__|

Diagnosis |_____|

Date of diagnosis: |__|__|__|__|__|__|

Patient

ABO group ☐ A ☐ B ☐ AB ☐ 0

☐ Rhpos ☐ rhneg

Viral status ☐ CMV pos ☐ CMV neg ☐ unknown

☐ HBV pos ☐ HBV neg ☐ unknown

☐ HCV pos ☐ HCV neg ☐ unknown

☐ HIV pos ☐ HIV neg ☐ unknown

Collection

Source of stem cells ☐ BM ☐ PBSC ☐ Cord Blood

Date of collection/cytapheresis |__|__|__|__|__|__|

If PBSC preparation ☐ none ☐ cytokines alone

☐ chemotherapy alone

☐ cytokines + chemotherapy

if cytokines ☐ G-CSF ☐ GM-CSF ☐ SCF

☐ MGDF/TPO

☐ other |_____|

if chemotherapy ☐ Cyclophosphamide ☐ VP16

☐ other |_____|

number of mobilisation courses |__|

date of last mobilisation course |__|__|__|__|__|__|

Purging ☐ Y ☐ N

if yes, ☐ **positive selection** ☐ **negative selection**

if **negative** selection ☐ mafosfamide/4HC standard dose

☐ mafosfamide/4HC adjusted dose

☐ chemoprotective agent ☐ monoclonal antibodies

if monoclonals ☐ CD2 ☐ CD3 ☐ CD14 ☐ CD15

☐ CD19 ☐ CD20 ☐ other

if other _____

if **positive** selection ☐ CD34+ ☐ CD38- ☐ DR-

☐ Thy1+ ☐ other

if other _____

percentage of positive selected cells [____] %

Relapse before transplantation ☐ Y ☐ N

1. Relapse date(dd/mm/yy) [__][__] [__][__] [__][__]

hematological: ☐ marrow/blood ☐ extramedullary ☐ both

cytogenetic: ☐ Y ☐ N **molecular:** ☐ Y ☐ N

*** Solid tumor** ☐ local ☐ distant ☐ combined ☐ unknown

2. Relapse date(dd/mm/yy) [__][__] [__][__] [__][__]

hematological: ☐ marrow/blood ☐ extramedullary ☐ both

cytogenetic: ☐ Y ☐ N **molecular:** ☐ Y ☐ N

*** Solid tumor** ☐ local ☐ distant ☐ combined ☐ unknown

3. Relapse date(dd/mm/yy) [__][__] [__][__] [__][__]

hematological: ☐ marrow/blood ☐ extramedullary ☐ both

cytogenetic: ☐ Y ☐ N **molecular:** ☐ Y ☐ N

*** Solid tumor** ☐ local ☐ distant ☐ combined ☐ unknown

Conditioning regime

Body weight: _____ kg **Body surface area:** _____ m^2

Therapy (Drugs, ATG, mono AB)	**Daily dose** (mg/kg/day or mg/m^2/day)			**Total dose** (mg)	**Days of adminstration**
		kg	**m2**		

TBI ☐ N ☐ Y total dose ___|___ Gy number of fractions ___|___

TLI ☐ N ☐ Y total dose ___|___ Gy number of fractions ___|___

other ☐ N ☐ Y, total dose ___|___ Gy number of fractions ___|___

specify _____

Transplantation

Date of transplantation (dd/mm/yy) ___|___|___|___|___|___|

Number of this transplantation ___|

Status at transplantation _____

Double graft programme ☐ Y ☐ N

Cells infused Number of nucleated cells _____ $*10^8$/kg

$CD34^+$ cells _____ $*10^6$/kg

$CD3^+$ cells _____ $*10^4$/kg

Complications < 100 days ☐ no complication

	yes	no	un-known		yes	no	un-known
Pneumonia				Systemic fungal infection			
Bacterial Sepsis				Parasitic infection			
CMV Infection				Documented fungal pneumonitis			
CMV Disease				Idiopathic pneumonitis			
HIV				VOD			
Hepatitis B				Haemorrhagic cystitis			
Hepatitis C				Cataract			
Other severe viral infection				Secondary malignancy			

Cytokines in the immediate post transplant period

☐ Y ☐ N

Day, when started (dd/mm/yy) |__|__|__|__|__|__|

. if yes, specify ☐ G-CSF ☐ IL2 ☐ GM-CSF
☐ MGDF/TPO ☐ EPO ☐ SCF
☐ IL3 ☐ other:

if other, specify |_____|

Total length of cytokines treatment |_____| days

Engraftment ☐ Y ☐ N

Hematopoietic reconstitution (dd/mm/yy)

Leucocytes	>1,000/µl	_____
Neutrophiles	>500/µl	_____
Platelets	>20,000/µl	_____
Platelets	**>50,000/µl**	_____
Last platelet transfusion		_____

Lost graft:
date of graft failure (dd/mm/yy) _____

If engraftment failure ☐ no specific treatment ☐ cytokines
☐ subsequent transplant
if subsequent transplant, date _____ (dd/mm/yy)
☐ auto ☐ allo
☐ related ☐ unrelated

Response of disease

Best response at 90 days ☐ CR maintained ☐ PR
☐ relapse ☐ death ☐ unknown

Relapse after transplantation ☐ Y ☐ N
if yes, date (dd/mm/yy) _____

*** Acute leukemia, lymphoma**
hematological ☐ marrow/blood ☐ extramedullary ☐ both
cytogenetic ☐ Y ☐ N
molecular ☐ Y ☐ N

*** Solid tumor** site of relapse ☐ local ☐ distant ☐ combined ☐ unknown

Treatment after SCT

Chemotherapy: ☐ Y ☐ N
if yes, specify _____

Other therapy: _____

Last follow up

Date (dd/mm/yy) |__|__|__|__|__|__|

|___| % Karnofsky scale

|___| % Lansky scale

Disease status ☐ CR maintained ☐ PR ☐ relapse

☐ autologous reconstitution

☐ unknown

Survival status ☐ alive ☐ dead

☐ lost to follow up

If dead, date |__|__|__|__|__|__|

Cause ☐ relapse ☐ transplant related

☐ secondary malignancy ☐ unknown

☐ other:_____

if transplant related ☐ rejection/poor graft function

☐ interstitial pneumonitis ☐ VOD

☐ cardiac toxicity ☐ haemorrhage

☐ infection:

☐ viral ☐ bacterial ☐ parasitic

☐ fungal ☐ unknown

Notes

_____

_____

_____

_____

Person completing the form:

|__|__|__|__|__|__|
Date

_____
Signature*

NB2004 Dokumentation 2. oder folgende OP

Bitte **mit OP-Bericht** senden an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie, Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Op-Datum: _____

Radikalität:

- ☐ makroskopisch/mikroskopisch komplett
- ☐ mikroskopisch inkomplett
- ☐ makroskopisch inkomplett
- ☐ Probeexcision

Was wurde operiert:

- ☐ Primärtumor
- ☐ Metastase, welche: _____

Tumorausdehnung

Tumorinfiltration über Mittellinie:	☐ nein	☐ ja	☐ nicht untersucht
Lymphknoten makroskopisch auffällig:	☐ nein	☐ ja	☐ nicht untersucht

Histologischer Befall der regionären Lymphknoten:

anhängende LK	☐ nein	☐ ja	☐ nicht untersucht
homolaterale LK	☐ nein	☐ ja	☐ nicht untersucht
kontralaterale LK (jenseits der Mittellinie):	☐ nein	☐ ja	☐ nicht untersucht

OP Komplikationen:

- ☐ **Keine**
- ☐ Nephrektomie Zeitpunkt :
- ☐ Blutung (bitte näher bezeichnen): ....
- ☐ Infektion (bitte näher bezeichnen): ....
- ☐ Ileus .....
- ☐ Sonstiges: ....

Histologie:

- ☐ örtlicher Pathologe (Bitte Kopie des Berichts beilegen)
- ☐ Referenzpathologe
- ☐ Keine Histologie erstellt

Remissionsstatus vor OP:

	Primärtumor	Metastasen
Vollremission	☐	☐
sehr gute Teilremission	☐	☐
Teilremission	☐	☐
gemischte Remission	☐	☐
kein Ansprechen	☐	☐
Progression/Rezidiv	☐	☐

Ereignismeldung (S. 252) erledigt?

Remissionsstatus nach OP

	Primärtumor	Metastasen
Vollremission	☐	☐
sehr gute Teilremission	☐	☐
Teilremission	☐	☐
gemischte Remission	☐	☐
kein Ansprechen	☐	☐
Progression/Rezidiv	☐	☐

dann bitte **Ereignismeldung** (S. 252) ausfüllen und zusenden

Bemerkungen

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

NB2004 Dokumentation MIBG-Therapie

Bitte **Bericht der Klinik für Nuklearmedizin** beilegen und senden an:
Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie, Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Datum der MIBG Gabe

Datum MIBG Gabe

Applizierte Aktivität

(Gesamtaktivität bei fraktionierter Gabe innerhalb von mehreren Tagen)

MBq = mCi = mCi/kg

Gesamtaktivität absolut | Gesamtaktivität absolut | Gesamtaktivität/kg KG

errechnete Ganzkörperdosis

Gesamtkörperdosis (Gy)

Siehe Seite 102.

errechnete Tumordosis

(falls Angabe möglich)

Tumordosis eines repräsentativen Herdes (Gy)

Siehe Seite 102.

Schilddrüsenblockade: ☐ Keine ☐ Irenat® ☐ Kaliumjodid

Komplikationen: ☐ Keine ☐ Ja, welche:.....

Stammzellrückgabe: ☐ nein ☐ Ja, Dosis .....x10^6/kg, Datum.....
nur ausfüllen, wenn keine Megatherapie unmittelbar nach MIBG Therapie folgt

Remissionsstatus

vor MIBG, Datum .....

	Primärtumor	Metastasen
Vollremission	☐	☐
sehr gute Teilremission	☐	☐
Teilremission	☐	☐
gemischte Remission	☐	☐
kein Ansprechen	☐	☐
Progression/Rezidiv	☐	☐

Ereignismeldung (S. 252) erledigt?

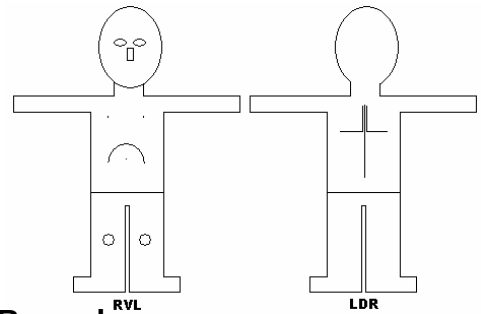
ca. 3 Monate nach MIBG, Datum .....
diese Angabe ist nur erforderlich, wenn keine Megatherapie folgt
bei MIBG vor Megatherapie reicht der Bogen nach Mega (Seite 255)

	Primärtumor	Metastasen
Vollremission	☐	☐
sehr gute Teilremission	☐	☐
Teilremission	☐	☐
gemischte Remission	☐	☐
kein Ansprechen	☐	☐
Progression/Rezidiv	☐	☐

dann bitte **Ereignismeldung** (S. 252) ausfüllen und zusenden

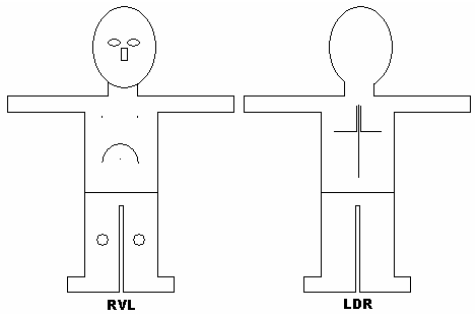
Restherde vor MIBG (ggf. Skizze)

.....



Restherde ca. 3 Monate nach MIBG (ggf. Skizze)

.....



Bemerkungen:

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

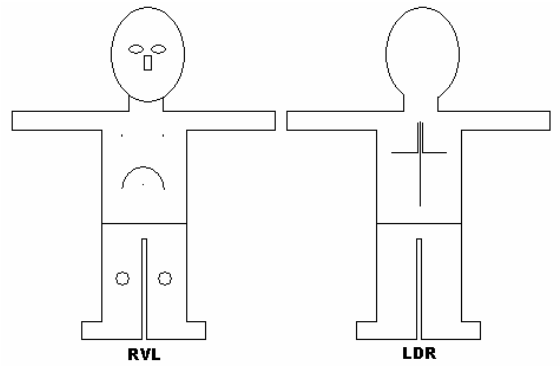
NB2004 Dokumentation Strahlentherapie

Bitte **Bericht der Strahlenklinik** beilegen und senden an:
Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Datum der Strahlentherapie _____ (Erster Tag der Radiatio) _____ (letzter Tag der Radiatio)

Lokalisation des Strahlenfelds
Lokalisation in Schema eintragen _____
Bitte hier beschreiben und/oder im Schema skizzieren



Herddosis
Lokalisation in Schema eintragen _____ Gy (Gesamtherddosis) = _____ Gy (Dosis Einzelfraktion) x _____ (Anzahl der Sitzungen n)

Indikation:

☐ aktiver Primärtumorrest ☐ Andere: _____

Komplikationen:

☐ Nein ☐ Ja, welche: _____

Remissionsstatus

vor RT, Datum .....

	Primärtumor	Metastasen
Vollremission	☐	☐
sehr gute Teilremission	☐	☐
Teilremission	☐	☐
gemischte Remission	☐	☐
kein Ansprechen	☐	☐
Progression/Rezidiv	☐	☐

Ereignismeldung (S. 252) erledigt?

3 Monate **nach RT**, Datum .....
diese Angabe ist nur bei Rezidivpatienten erforderlich,
ansonsten reicht der Bogen nach Mega bzw. Erhaltung (Seite 255)

	Primärtumor	Metastasen
Vollremission	☐	☐
sehr gute Teilremission	☐	☐
Teilremission	☐	☐
gemischte Remission	☐	☐
kein Ansprechen	☐	☐
Progression/Rezidiv	☐	☐

dann bitte **Ereignismeldung** (S. 252) ausfüllen und zusenden

Bemerkungen:

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

VERLAUFSDOKUMENTATION (DEUTSCH)

NB2004 Meldung: Rezidiv, Progression, Tod

Bitte bei jedem Ereignis sofort senden an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie, Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, 🖷 -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Datum ....., **Ereignisart:**
- ☐ Rezidiv (nach Vollremission)
- ☐ Progression (von Resttumor oder Metastasenresten)
- ☐ Zweitmalignom, welches.....
- ☐ Tod (bitte Ursache angeben, siehe unten)

Ereignis diagnostiziert?
- ☐ Routinekontrolle Tumormarker
- ☐ Routinekontrolle Bildgebung
- ☐ Symptome, welche:.....

Rezidiv/Progression lokal? ☐ Ja ☐ Nein

Im ehemaligen Primärtumorgebiet?	☐ Ja	☐ Nein	☐ Nicht zu entscheiden
Im ehemaligen Bestrahlungsfeld?	☐ Ja	☐ Nein	☐ ist vorher nie bestrahlt worden ☐ ist nicht zu entscheiden

Rezidiv/Progression systemisch? ☐ Ja ☐ Nein

Befallsmuster bitte spezifizieren:

Knochenmark:	☐ Ja	☐ Nein	☐ Nicht untersucht
Knochen:	☐ Ja	☐ Nein	☐ Nicht untersucht
Fernlymphknoten, wo.....	☐ Ja	☐ Nein	☐ Nicht untersucht
Leber:	☐ Ja	☐ Nein	☐ Nicht untersucht
Haut:	☐ Ja	☐ Nein	☐ Nicht untersucht
ZNS:	☐ Ja	☐ Nein	☐ Nicht untersucht
Lunge:	☐ Ja	☐ Nein	☐ Nicht untersucht

Sonstige: .....

Geplante Therapie:
- ☐ N4 Blöcke entsprechend NB2004 Beobachtungsgruppe
- ☐ Chemotherapie entsprechend NB2004 Mittlere Risikogruppe
- ☐ Chemotherapie entsprechend NB2004 Hochrisikogruppe
- ☐ andere, welche: .....
- ☐ keine Tumortherapie mehr, nur noch symptomatisch/palliativ

Bei Verstorbenen:

Sterbedatum: .....

Todesursache: .....
- ☐ bedingt durch Tumorerkrankung
- ☐ bedingt durch Therapie
- ☐ Tumor/Therapieabhängigkeit nicht zu entscheiden
- ☐ andere Todesursache, nicht im Zusammenhang mit Tumor

Autopsie durchgeführt? ☐ ja (bitte Bericht beilegen) ☐ nein

Bemerkungen:

Stempel	Datum	Unterschrift

NB2004 Meldung: Schweres unerwartetes Ereignis

Bitte **innerhalb von 24 Stunden** senden an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie, Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	Geschlecht	Gewicht (kg)	Größe (cm)	NB Nummer

Beobachtete SAE

Beobachtung/Laborveränderungen, ggf. Extrablatt beilegen	Datum, Zeit des Beginns	Dauer

Art des SAE

☐ Todesfall ☐ Verlängerung Hospitalisierung ☐ Angeborene Anomalie
☐ Lebensbedrohend ☐ Erhebliche/dauerhafte geist. Behinderung ☐ Medizinisch relevant

Alle Medikamente bei Auftreten des SAE:

Medikament & Charge	mg/Tag	Route	Gegeben von ... bis	Indikation	Zusammenhang zwischen Medikament und SAE					
					gesichert	wahr-scheinlich	möglich	unwahr-scheinlich	kein	nicht zu beurteilen
1										
2										
3										
4										
5										
6										

Betreffende Medikamente früher gegeben? ☐ ja ☐ nein und vertagen? ☐ ja ☐ nein

Therapie/Maßnahmen zur Behandlung des SAE

Medikament/Maßnahme	Dosis/Tag	Route	Gegeben von ... bis	Indikation

Ausgang des SAE?:

☐ wiederhergestellt ☐ bleibender Schäden ☐ noch nicht wieder hergestellt ☐ unbekannt
☐ Tod, wann..... Sektion ☐ ja ☐ nein ggf. Befund beilegen/nachreichen
Todesursache.....

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

NB2004 Follow-up Beobachtungspatienten

Bitte senden an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie, Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name _____ Patient Vorname _____ geboren _____ NB Nummer [ ]

Datum: ....., Zeitpunkt
- ☐ nach 6 Wochen
- ☐ nach 3 Monaten
- ☐ nach 4 ½ Monaten
- ☐ nach 6 Monaten
- ☐ nach 7 ½ Monaten
- ☐ nach 9 Monaten
- ☐ nach 10 ½ Monaten
- ☐ nach 12 Monaten
- ☐ anderer Zeitpunkt.....

Primärtumor (Sonographie/MRT)
bitte Befunde beilegen
- ☐ Progression, ...%
- ☐ Regression, ...%
- ☐ unverändert zur Voruntersuchung

Tumorvolumen
- ☐ gemessen
- ☐ errechnet: _____ (Länge (cm)) X _____ (Breite (cm)) X _____ (Tiefe (cm)) = _____ (Volumen = (LxBxT) x 0.5)

Lebermetastasen (Stadium 4S)
- ☐ Progression
- ☐ Regression
- ☐ unverändert zur Voruntersuchung

Hautmetastasen (Stadium 4S)
- ☐ Progression
- ☐ Regression
- ☐ unverändert zur Voruntersuchung

Tumormarker
kann entfallen, wenn Befundkopien beiliegen
ggf. abweichende Einheiten angeben

	Wert	Faktor		
HVA (Urin)	_____ nmol/µmol Crea	_____ Faktor	☐ pathologisch ☐ gebessert	☐ normal ☐ nicht durchgeführt
VMA (Urin)	_____ nmol/µmol Crea	_____ Faktor	☐ pathologisch ☐ gebessert	☐ normal ☐ nicht durchgeführt
HVA (Serum)	_____ ng/ml	_____ Faktor	☐ pathologisch ☐ gebessert	☐ normal ☐ nicht durchgeführt
VMA (Serum)	_____ ng/ml	_____ Faktor	☐ pathologisch ☐ gebessert	☐ normal ☐ nicht durchgeführt
NSE (Serum)	_____ ng/ml		☐ pathologisch ☐ gebessert	☐ normal ☐ nicht durchgeführt

Bemerkungen:

Stempel mit Name/Adresse/Telefon _____ Datum _____ Unterschrift _____

NB2004 Chemotherapie/Megatherapie Follow-up

Bitte senden an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie, Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, 🖷 -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Behandlungsgruppe ☐ Mittleres Risiko ☐ HR Standardarm ohne N8 Blöcke ☐ HR experimenteller Arm mit N8 Blöcken

Erhebungszeitpunkt ☐ nach 2 Blöcken ☐ nach 4 Blöcken Chemotherapie ☐ nach 6 Blöcken ☐ nach 8 Blöcken Chemotherapie ☐ nach Megatherapie ☐ nach Erhaltung (MRG)

Diagnostik zum Erhebungszeitpunkt

verglichen mit Voruntersuchung, vor einer evtl. OP, bei Zunahme pathologischer Befunde handelt es sich um einen Progress, dann ist eine **Ereignismeldung (S. 252)** erforderlich	**Datum**	**völlig unauffällig**	**gebessert, aber noch nicht normal**	**unverändert pathologisch**	**nicht durchgeführt**
Sonographie/CT/MRT Primärtumor		☐	☐	☐	☐
MIBG-Szintigraphie Primärtumor		☐	☐	☐	☐
MIBG-Szintigraphie Metastasen		☐	☐	☐	☐
Schädel-CT/MRT		☐	☐	☐	☐
Knochenmark – Zytologie		☐	☐	☐	☐
Sonstige Untersuchungen, welche		☐	☐	☐	☐

Tumorvolumen ☐ gemessen ☐ errechnet: _____ (Länge (cm)) X _____ (Breite (cm)) X _____ (Tiefe (cm)) = _____ (Volumen =(Länge x Breite X Tiefe) x 0.5

Tumormarker zum Erhebungszeitpunkt (vor einer evtl. Operation):

	Datum	**Wert**	**Einheit***	**Faktor**	**völlig unauffällig**	**gebessert, aber noch nicht normal**	**unverändert pathologisch**	**nicht durchgef**
NSE im Serum			ng/ml		☐	☐	☐	☐
HVA im Serum			ng/ml		☐	☐	☐	☐
VMA im Serum			ng/ml		☐	☐	☐	☐
HVA im Urin			nmol/µmol Crea		☐	☐	☐	☐
VMA im Urin			nmol/µmol Crea		☐	☐	☐	☐

***Falls andere Einheit, bitte angeben**

Therapieerfolg zum Erhebungszeitpunkt (vor einer evtl. Operation), Stichtag: .....

	Primärtumor	**Metastasen**		**Primärtumor**	**Metastasen**
Vollremission	☐	☐	sehr gute Teilremission	☐	☐
Teilremission	☐	☐	gemischte Remission	☐	☐
stabile Erkrankung	☐	☐	Progression/Rezidiv	☐	☐

dann bitte **Ereignismeldung** (S. 252) ausfüllen und zusenden

Geplante weitere Therapie:

☐ Fortführung der Chemotherapie ☐ Radiotherapie, welche?: ☐ externe Bestrahlung ☐ MIBG
☐ Megatherapie ☐ Operation ☐ Erhaltungstherapie
☐ Retinsäure ☐ anderes: .....

Stempel mit Name/Adresse/Telefon	Datum	Unterschrift

NB2004 Retinsäure Follow-up 1/2

Bitte senden an: Prof. Dr. F. Berthold, Studienleitung NB2004, Zentrum für Kinderonkologie und –hämatologie,
Kerpener Straße 62, D-50924 Köln, ☎ +49 (0) 221/478-6853, -6851, neuroblastomstudie@uk-koeln.de

Patient Name	Patient Vorname	geboren	NB Nummer

Behandlung

☐ Mittleres Risiko ☐ HR Standardarm ohne N8 Blöcke ☐ HR experimenteller Arm mit N8 Blöcken

Erhebungszeitpunkt

Bitte je einen Bogen nach Retinsäure 1 und 2 und nach jedem zusätzlichen Retinsäurezyklus ausfüllen

☐ nach Retinsäure 1 = nach 6 Monaten Retinsäure
☐ nach Retinsäure 2 = nach weiteren 3 Monaten Retinsäure
☐ anderes, ...

	1./7. Zyklus Woche 1-2 Woche 36-37	**2./8. Zyklus Woche 4-5 Woche 40-41**	**3./9. Zyklus Woche 8-9 Woche 44-45**	**4. Zyklus Woche 12-13**	**5. Zyklus Woche 16-17**	**6. Zyklus Woche 20-21**
Startdosis (mg/m²)	mg/m²	mg/m²	mg/m²	mg/m²	mg/m²	mg/m²
Start des 14-d-Zyklus (Datum)						
Dosisreduktion ab? (Datum)						
Dosisreduktion? (um ...%)						
vorzeitiger Abbruch? (Datum)						

Nebenwirkungen

Grad	0	1	2	3	4
Allgemeinzustand	Normale Aktivität	Geringe Beeinträchtigung	Altersentspr. Aktivität stark eingeschränkt	Bettlägerig, pflegebedürftig	Intensive Behandlung schwerstkrank

Hämoglobin	Altersnorm	> 100%	80-100%	65-79%	< 65%
Leukozyten (/nl)	> 4,0	3,0-3,9	2,0-2,9	1,0-1,9	< 1,0
Granulozyten (/nl)	> 2,0	1,5-1,9	1,0-1,4	0,5-0,9	< 0,5
Thrombozyten (/nl)	> 100	75-100	50-74,9	25-49,9	< 25

Infektion	keine	leicht	mäßig: ohne Erregernachweis, i.v. Antibiotika	schwer: mit Erregernachweis, i.v. Antibiotika	lebensbedrohlich, mit Hypotonie
Fieber (°C)	keins	37,1-38	38,1-40	> 40 für < 24 Std.	> 40 für ≥ 24 Std.

Haut/Exanthem	keine	Erythem	trockene Desquamationen, Vascularisation, Pruritus	feuchte Desquamationen, Ulcerationen	exfoliative Dermatitis, Nekrosen
Bilirubin	Altersnorm	-	< 1,5 x Norm	1,5-3 x Norm	> 3 x Norm
SGOT/SGPT	Altersnorm	≤ 2,5 x Norm	2,6-5,0 x Norm	5,1-20 x Norm	> 20 x Norm

Kopfschmerz	kein	tolerabel ohne Behandlung	stark, Behandlung erforderlich	sehr stark, Abbruch oder Verzögerung der Therapie	
Cheilitis	keine	tolerabel ohne Behandlung	stark, Behandlung erforderlich	sehr stark, Abbruch oder Verzögerung der Therapie	
Konjunctivitis	keine	tolerabel ohne Behandlung	stark, Behandlung erforderlich	sehr stark, Abbruch oder Verzögerung der Therapie	

Sonstiges	

Bitte auch Folgeseite ausfüllen!

NB2004 Retinsäure Follow-up 2/2

NB Nummer

Hyperglyceridämie ☐ nicht gemessen ☐ nein ☐ ja, maximal .....Einheit.....

Hyperkalzämie ☐ nicht gemessen ☐ nein ☐ ja, maximal .....Einheit.....

Nachtblindheit ☐ nicht evaluierbar ☐ nein ☐ ja.

Vitamin E Gabe: ☐ nein ☐ ja, Grund: .....
☐ wenn lokal : ☐ teilweise ☐ durchgehend
☐ wenn systemisch: ☐ teilweise ☐ durchgehend

Diagnostik zum Erhebungszeitpunkt

verglichen mit Voruntersuchung, vor einer evtl. OP, bei Zunahme pathologischer Befunde handelt es sich um einen Progress, dann ist eine **Ereignismeldung (S. 252)** erforderlich	**Datum**	**völlig unauffällig**	**gebessert, aber noch nicht normal**	**unverändert pathologisch**	**nicht durchgeführt**
Sonographie/CT/MRT Primärtumor		☐	☐	☐	☐
MIBG-Szintigraphie Primärtumor		☐	☐	☐	☐
MIBG-Szintigraphie Metastasen		☐	☐	☐	☐
Schädel-CT/MRT		☐	☐	☐	☐
Knochenmark – Zytologie		☐	☐	☐	☐
Sonstige Untersuchungen, welche		☐	☐	☐	☐

Tumorvolumen ☐ gemessen
☐ errechnet: _____ (Länge (cm)) X _____ (Breite (cm)) X _____ (Tiefe (cm)) = _____ (Volumen =(Länge x Breite X Tiefe) x 0.5)

Tumormarker zum Erhebungszeitpunkt (abweichende Einheiten bitte angeben):

	Datum	**Wert**	**Einheit**	**Faktor**	**normal**	**pathologisch**	**nicht untersucht**
NSE im Serum			ng/ml		☐	☐	☐
HVA im Serum			ng/ml		☐	☐	☐
VMA im Serum			ng/ml		☐	☐	☐
HVA im Urin			nmol/µmol Crea		☐	☐	☐
VMA im Urin			nmol/µmol Crea		☐	☐	☐

Therapieerfolg zum Erhebungszeitpunkt (vor einer evtl. Operation), Stichtag: .....

	Primärtumor	**Metastasen**		**Primärtumor**	**Metastasen**
Vollremission	☐	☐	sehr gute Teilremission	☐	☐
Teilremission	☐	☐	gemischte Remission	☐	☐
stabile Erkrankung	☐	☐	Progression/Rezidiv	☐	☐

dann bitte **Ereignismeldung** (S. 252) ausfüllen und zusenden

Geplante weitere Therapie:

☐ weitere Retinsäurezyklen
☐ Radiotherapie, welche?: ☐ externe Bestrahlung ☐ MIBG
☐ Operation
☐ Erhaltungstherapie
☐ anderes: .....

Stempel mit Name/Adresse/Telefon **Datum** **Unterschrift**

NB2004 Follow-up nach Abschluss Protokolltherapie

Wird elektronisch generiert und den Kliniken automatisch jährlich von der Studienleitung NB2004zugeschickt.

Folgeerhebungsbogen für Neuroblastompatienten (NB2004)

für geb.: Patnr:

Diagnosedatum: Stadium:

Remissionsbeurteilung (Kriterien siehe Protokoll) für Zeitraum: ca.

	PT	Metastasen
Vollremission	o	o
sehr gute Teilremission	o	o
Teilremission	o	o
gemischte Remission	o	o
kein Ansprechen	o	o
nicht evaluiert	o	o

letzte Vorstellung: _____

o **Rezidiv / Progression**
Datum: : _____
(bitte **Ergebnismeldebogen** ausfüllen)

o wird nicht mehr von uns betreut, Adresse letzter Hausarzt _____

Wurde nach der letzten Dokumentation eine weitere Therapie durchgeführt ?

letzte Dokumentation:

o keine Therapie
o Chemotherapie
o Radiotherapie
o Operation - bitte OP-Bericht und Histologie-Befund als Kopie beifügen -
o andere Therapie _____

Spätschäden bekannt:

weitere Spätschäden:
o Nierenschädigung
o Kardiomyopathie oder sonst. Schädigung des Herzens
o Innenohrschädigung
o Sonstiges: _____

Bei Verstorbenen:

Sterbedatum: _____

o bedingt durch Primärtumor
o bedingt durch Rezidiv/Metastase
o bedingt durch Therapie

Todesursache: _____

o andere Todesursache
o Tumorabhängigkeit nicht zu entscheiden

Autopsie durchgeführt ? ja/nein

Bemerkungen:

Stempel:

Datum und Unterschrift:

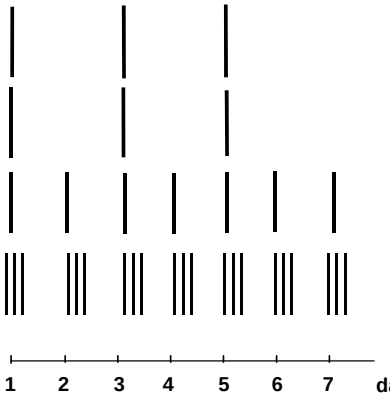
Folgende Unterlagen liegen der Studie noch nicht vor:

o Kopie des Op-Berichts (Operation vom)
o Kopie des histologischen Befundes (Operation vom)
o Kopie des Befundes des Referenzpathologen
o Folgeerhebungsbogen

Bitte senden an: Neuroblastomstudie, Prof. Dr. F. Berthold, Universitätskinderklinik Köln,
Joseph-Stelzmann-Str. 9, 50924 Köln
Tel.: 0221-478-6853, Fax: 0221-478-6851

30 INDEX

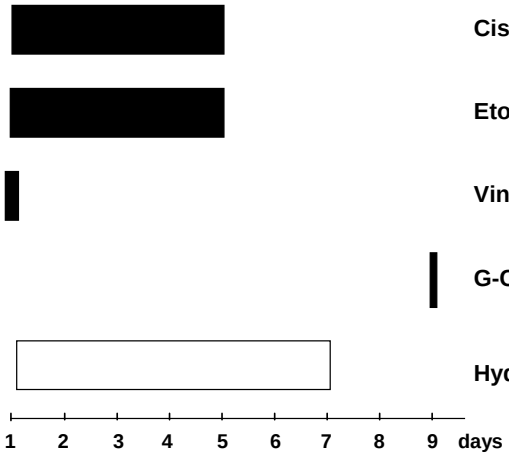
Cycle N4



Doxorubicine	**15 mg/m²xd**	**d 1, 3, and 5**	**30 min**
Vincristine	**0.75 mg/m²xd**	**d 1, 3, and 5**	**push**
Cyclophosphamide	**300 mg/m²xd**	**d 1 to 7**	**30 min**
MESNA	**3 x 60 mg/m²xd**	**d 1 to 7**	**push**
	0, 4, and 8 hrs after cyclophosphamide		

doses for children ≥1 year, for infants see text

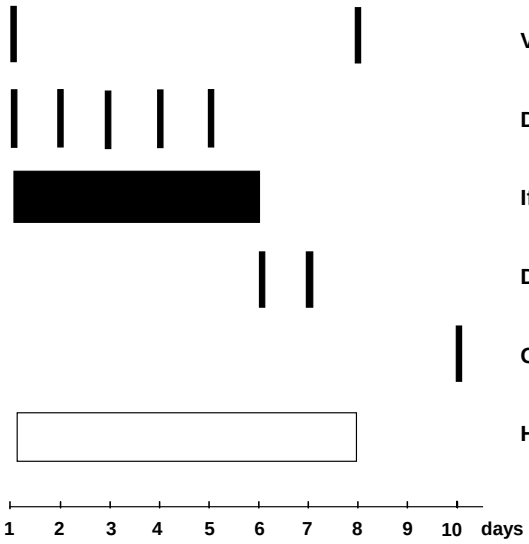
Cycle N5



Cisplatin	**40 mg/m²xd**	**d 1 to 4**	**96 hrs**
Etoposide	**100 mg/m²xd**	**d 1 to 4**	**96 hrs**
Vindesine	**3 mg/m²xd (maximum 6 mg)**	**d 1**	**1 hr**
G-CSF	**5 µg/kgxd s.c.**	**≥d 9 until WBC >10/nl**	
	10 µg/kgxd for stem cell mobilization		
Hydration	**3000 ml/m²xd**	**day 1 to 6**	

doses for children ≥1 year, for infants see text

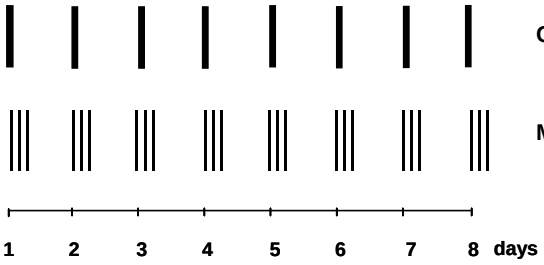
Cycle N6



Vincristine	**1.5 mg/m²xd (maximum 2mg)**	**d 1 and 8**	**1 hr**
Dacarbacine	**200 mg/m²xd**	**d 1 to 5**	**1 hr**
Ifosfamide	**1500 mg/m²xd**	**d 1 to 5**	**120 hrs**
	discontinue during dacarbacine infusion		
Doxorubicine	**30 mg/m²xd**	**d 6 and 7**	**4 hrs**
G-CSF	**5 µg/kgxd s.c.**	**≥d 10 until WBC >10/nl**	
	10 µg/kgxd for stem cell mobilization		
Hydration	**3000 ml/m²xd**	**day 1 to 7**	
	with MESNA 900 mg/m²xd		

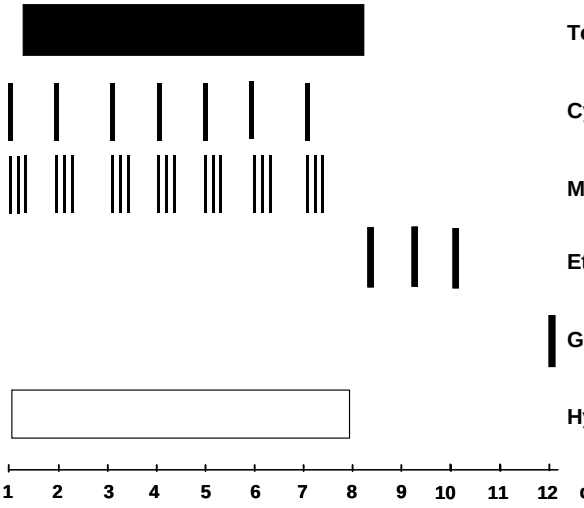
doses for children ≥1 year, for infants see text

Cycle N7



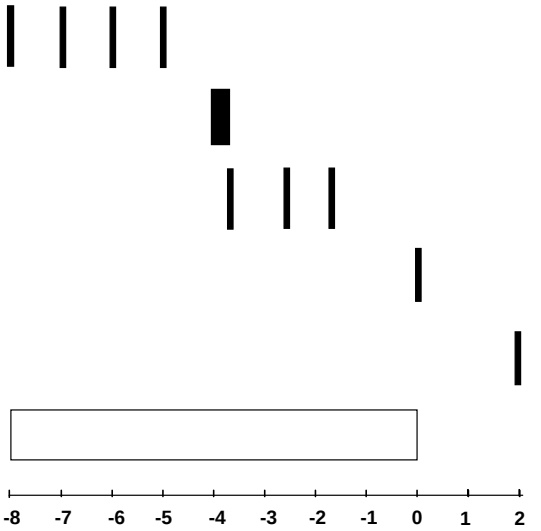
Cyclophosphamide	**150 mg/m²xd**	**d 1 to 8**
MESNA	**3 x 30 mg/m²xd** 0, 4, and 8 hrs after cyclophosphamide	**d 1 to 8**

Cycle N8



Topotecan	**1.0 mg/m²xd** starts 6 hrs after CYC day 1	**d 1-7**	**168 hrs**
Cyclophosphamide	**100 mg/m²xd** starts 6 hrs prior to Topotecan day 1	**d 1-7**	**1 hr**
MESNA	**3 x 20 mg/m²** 0, 4, and 8 hrs after cyclophosphamide	**d 1-7**	**push**
Etoposide	**100 mg/m²xd,**	**d 8-10**	**1hr**
G-CSF	**5 µg/kgxd s.c.**	**≥d 12 until WBC >10/nl**	
Hydration	**2000 ml/m²xd**	**d 1-7**	

Megatherapy



Melphalan	**45 mg/m²xd**	**d -8 to -5**	**30 min**
Etoposide	**40 mg/kgxd**	**d -4**	**4 hrs**
Carboplatin	**500 mg/m²xd**	**d -4 to -2**	**1 hr**
CD34+ stem cells	**≥2 x 10^6/kg**	**d 0**	
G-CSF	**10 µg/kgxd s.c.**	**≥d 2 until >10/nl WBC**	
Hydration	**3000 ml/m²xd** doses for children ≥1 year, for infants see text	**day -8 to -1**	

For any residual MIBG uptake: MIBG therapy prior to ASCT
For residual MIBG uptake by primary: additional external radiation 36-40 Gy after megatherapy