RESEARCH PROTOCOL

Phase II trial of the addition of gemcitabine to $^{131}$I-MIBG therapy in paediatric patients with relapsed or progressive neuroblastoma

Sponsor:
Academic Medical Centre AMC
Meibergdreef 9
1105 AZ Amsterdam
The NETHERLANDS

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**PROTOCOL SIGNATURE SHEET**

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**STUDY SYNOPSIS**

<table>
<thead>
<tr>
<th>Protocol Title</th>
<th>Protocol MiBG-gem: A single arm phase II study of the addition of gemcitabine to $^{131}$I-MIBG therapy in paediatric patients with relapsed or progressive neuroblastoma</th>
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<tr>
<td>Approval date</td>
<td>16 July 2009</td>
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</table>
| Study period   | Planned start date: 11-2010
Planned enrolment end date: 02-2015                                                                                                                                                                  |
| Study population| Paediatric patients, 1 to 18 years of age, with relapsed or progressive neuroblastoma.                                                                                                               |
| Rationale      | Neuroblastoma is the most common extra cranial solid tumour in children. Depending on the stage of the disease treatment consists of a combination of chemotherapy and targeted therapy with $^{131}$I-MIBG. MiBG therapy has proven its efficacy in relapsed neuroblastoma patients with response rates from 10-50%. Stage IV disease in children over 2 years of age has a 5 year survival rate of 30% - 40%. Due to this poor survival rate more effective treatment needs to be developed. In vitro gemcitabine has shown anti-tumour effect in neuroblastoma cell lines. In adult solid tumours, gemcitabine has shown radiosensitizing effect. This has led to combination therapy of gemcitabine and radiotherapy for adult solid tumours. In this study the hypothesis will be tested that gemcitabine has a radiosensitizing effect in addition to $^{131}$I-MIBG therapy which will lead to increased anti-tumour effect in neuroblastoma. |
| Study design   | Phase II multi-centre, open-label, single arm study of the combination of gemcitabine and $^{131}$I-MIBG therapy in paediatric patients with relapsed or progressive neuroblastoma. Two dosages of gemcitabine will be tested in combination with $^{131}$I-MIBG therapy. At each dose-level patients will be stratified based on previous MiBG therapy. In this study there will be 4 strata: 1A – gemcitabine 375 mg/m², MiBG-naïve patients, 1B – gemcitabine 375 mg/m², MiBG pre-treated patients, 2A – gemcitabine 500 mg/m², MiBG naïve patients, 2B – gemcitabine 500 mg/m², MiBG pre-treated patients. In this study gemcitabine is considered to be the IMP and referred to as study drug. |
| Objectives     | The main objective is to evaluate the efficacy of the addition of gemcitabine to $^{131}$I-MIBG therapy in paediatric patients with relapsed or progressive neuroblastoma. The secondary objective to evaluate the safety and toxicity profile of the addition of gemcitabine to $^{131}$I-MIBG therapy in paediatric patients with relapsed or progressive neuroblastoma. |
| Endpoints      | Primary endpoint: determination of efficacy as measured by response rate (and time-to-event measurements). Secondary endpoint: characterization of safety and toxicity profile. |
| Inclusion criteria | 1. Histological proven neuroblastoma
2. Measurable primary and/or metastatic disease
3. Relapsed or progressive neuroblastoma in which standard approaches to treatment have failed
4. Evidence of sufficient MiBG uptake in bone or soft tissue
5. 1 year to 18 years of age
6. Lansky play score ≥ 70%, or ECOG performance status ≤ 1 |
### Inclusion criteria

- Life expectancy ≥ 6 weeks
- Adequate organ function including:
  - Bone marrow: leukocytes > 2.0 x $10^9$/L, ANC ≥ 1.0 x $10^9$/L, platelets > 100 x $10^9$/L (in case of bone marrow disease: > 75 x $10^9$/L)
  - Hepatic: Bilirubin ≤ 1.5x upper limit of normal (ULN); AST, ALT ≤ 5.0x ULN
  - Renal: Serum creatinine ≤ 1.5x ULN for age (15 years: < 65µmol/L; > 15 years: < 110µmol/L) If serum creatinine is > 1.5 x ULN for age, then creatinine clearance (or radioisotope GFR) must be > 70 ml/min/1.73 m²

### Exclusion criteria

- Having received treatment with an investigational or conventional anti-cancer drug within the last 21 days
- Concurrent administration of any other anti-tumour therapy
- Serious concomitant disorders that would compromise patient safety
- Symptomatic brain metastases
- Contra-indication for nuclear isolation
- Are pregnant or breastfeeding
- 131I-MIBG treatment in prior 3 months
- Known hypersensitivity to gemcitabine

### Number of patients and Definitions

The number of patients to meet protocol objectives is calculated according to an adapted Bryant and Day design with early stopping rules for severe toxicity or poor response. Up to 47 (with a maximum of 66) evaluable patients will be enrolled and stratified based on pre-treatment of MIBG.

The study aims at a combined evaluation of safety and efficacy. For safety assessment of a given dose of gemcitabine we will apply the regular 3x3 rules and DLT-assessment to determine safety in the first 6 patients. If a safe dose is established, we will enrol more patients and assess safety under the definition of ‘severe toxicity’ (see below). Moreover, efficacy will be determined. In the sample size calculation given below, response is defined as CR and PR.

Dose-limiting toxicities (DLT) are adverse events (AEs) considered at least possibly related to the study drug (gemcitabine) and occurring in the 1st course of study treatment in the first 6 patients at each dose level.

DLT will be defined as:...
Severe toxicity are adverse events (AEs) occurring in the 1st course of study treatment in the expansion cohort (patient 7 and further) at each dose level.

Severe toxicity is defined as:
- grade 4 thrombocytopenia > 14 days, considered related to the study treatment,
- grade 4 neutropenia > 7 days, considered related to the study treatment or
- grade 4 life threatening non-hematological event which is considered related to the study treatment

Toxicities that are encountered in the 2nd or greater course in any given patient will be tabulated as cumulative toxicity. They may lead to dose-adaptations in the 2nd or greater course when deemed necessary.

If in the first 6 patients treated with 375 mg/m² gemcitabine dose-limiting toxicity is encountered in two or more patients, the trial will be stopped or amended.

If at interim analysis (after 19 patients) ≤ 6 responses are seen or if ≥ 10 severe toxicity is seen, enrolment will be stopped.

If at that stage ≥ 10 responses are seen and < 10 severe toxicity is seen, enrolment will be continued up till 47 patients. If > 6 but < 10 responses are seen and if toxicity is acceptable with < 10/19 patients with severe toxicity, the dose of gemcitabine will be escalated to 500 mg/m².

Again, at first, 6 patients will be treated at 500 mg/m². If in two or more of the patients treated with 500 mg/m² dose-limiting toxicity is encountered, the trial will be stopped or amended. After treatment of 19 patients at 500 mg/m² interim analysis will be performed. If in the first 19 patients ≤ 6 responses are seen or if ≥ 10 severe toxicity is seen, enrolment will be stopped or the trial will be amended. If at that stage ≥ 10 responses are seen and < 10 severe toxicity is seen, enrolment will be continued up till 47 patients.

If at final analysis > 17 responses are seen out of 47 and < 27 severe toxicity is seen, this regimen will be recommended for further study. If patients are not equally divided per stratum, enrolment will be continued until a minimum of 6 patients per stratum at interim analysis (19 pat) or 14 patients at end of study (47 patients).

**Treatment schedule**

Gemcitabine infusion on day 1 and 8 in a cycle of 28 days, combined with 131I-MIBG on day 1. Gemcitabine will be given as a 30 min intravenous infusion, 3 hours prior to 131I-MIBG infusion. A dose of 375 mg/m² (or 500 mg/m²) gemcitabine will be used in combination...
with $^{131}$I-MIBG. The dose of $^{131}$I-MIBG will be based on dosimetry and we will aim at a whole body dose of 4 Gy after 2 cycles.

<table>
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<th>Day</th>
<th>1</th>
<th>8</th>
<th>15</th>
<th>22</th>
<th>29/1</th>
<th>8</th>
<th>15</th>
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<tbody>
<tr>
<td>Gemcitabine</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{131}$I-MIBG</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
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To start treatment on Day 1, patients must have an absolute neutrophil count (ANC) of $\geq 1.0 \times 10^9/L$ and a platelet count of $\geq 100 \times 10^9/L$ ($\geq 75 \times 10^9/L$ in case of bone marrow disease). Prior to gemcitabine administration on day 8, an ANC of $\geq 0.5 \times 10^9/L$ is necessary.

Duration of treatment

Each patient is scheduled for two 28-day cycles of gemcitabine/MIBG. Treatment must be discontinued earlier if progression or dose limiting toxicity occurs. The treatment with gemcitabine/MIBG can continue if objective response is observed and/or if there is clinical benefit (stable disease with reduction of pain). After response assessment after the second cycle gemcitabine/MIBG, i.e. week 9, other off protocol treatments are allowed, leading to withdrawal of patients. There is a maximum of 6 cycles.

Pharmaceutical information

**Gemcitabine hydrochloride**

Mode of action:
Antineoplastic agent in the class of pyrimidine analogs

How supplied:
White lyophilized powder in a single use vial to be dissolved with NaCl 0.9%

Storage:
Store at controlled room temperature (15 - 25°C). Gemcitabine solutions are stable for 24 hours.

Toxicity assessment

Toxicity will be graded according to NCI-Common Terminology criteria AE v3.0.
The adverse events which are not reported in the NCI-Common Terminology criteria will be graded as mild, moderate, severe or life-threatening.

Efficacy assessment

Assessment of efficacy will be obtained after 2 cycles and will be recorded as complete response, partial response, stable disease or progressive disease, according to modified International Neuroblastoma Response Criteria (Brodeur et al, 1993).

A central review committee will review all the observations to validate responses or stable disease. Standard methods for response assessment will be used: MRI/CT, MIBG scintigraphy, bone marrow (aspirates $\geq 4$ sites or biopsy $\geq 2$ sites) and clinical examination (if indicated). Urine catecholamines (VMA/HVA, dopamine) will be performed at baseline and to confirm CR. If bone marrow biopsies are negative at baseline, they are not to be repeated unless disease progression is suspected. Duration of response, duration of stable disease, overall survival, time to treatment failure, and time to progressive disease will be measured.
**Supportive care guidelines**  
Anti-emetic prophylaxis:  
- Ondansetron 5 mg/m² iv (max 8 mg) or granisetron 0,25 μg/kg (max 1 mg) iv daily, start 30-60 min prior to gemcitabine infusion on day 1/2 and 8/9. Additional anti-emetics (such as domperidone and/or dexamethasone) are strongly recommended.  
- Acetaminophen (paracetamol) and/or prednisolon can be used during 1-2 days after gemcitabine infusion in case of fever or flu-like symptoms.  
- Use of granulocyte colony stimulating factor (G-CSF) may be used in life-threatening neutropenic infections.

**Special aspects**  
After finishing treatment with gemcitabine lymphocytopenia still can develop up to 12 months. For 12 months after treatment with gemcitabine the use of irradiated blood products is required.

**Post-study follow up**  
Patients will be followed up 4 weeks after study end and then every 8 weeks for 6 months.
# TABLE OF CONTENTS

1 INTRODUCTION AND RATIONALE................................................................................. 14
  1.1 Neuroblastoma .................................................................................................... 14
  1.2 Metaiodobenzylguanidine ..................................................................................... 14
  1.3 Gemcitabine ........................................................................................................ 17
  1.4 Gemcitabine and neuroblastoma ........................................................................... 18
  1.5 Gemcitabine in pediatric patients ........................................................................ 18
  1.6 Gemcitabine and radiotherapy ............................................................................. 20
  1.7 Rationale for the combination of Gemcitabine and $^{131}$I-MIBG in pediatric patients with neuroblastoma............................................................................................................. 21

2 OBJECTIVES.................................................................................................................. 23

3 SELECTION OF STUDY PATIENTS .............................................................................. 24
  3.1 Study patients ..................................................................................................... 24
  3.2 Inclusion criteria ................................................................................................. 24
  3.3 Exclusion criteria ................................................................................................. 25

4 OVERALL STUDY PLAN ................................................................................................ 27
  4.1 Description of the design ..................................................................................... 27
  4.2 Study centers ..................................................................................................... 31
  4.3 Study period ....................................................................................................... 31
  4.4 Premature discontinuation of the study ................................................................ 31

5 PATIENT REGISTRATION ............................................................................................. 32

6 STUDY TREATMENT ..................................................................................................... 34
  6.1 Treatment schedule ............................................................................................ 34
  6.2 Treatment duration .............................................................................................. 34
  6.3 Discontinuation of patients ................................................................................ 35
  6.4 Substitution of patients ....................................................................................... 35
  6.5 Investigational medicinal product – gemcitabine ................................................ 35
      6.5.1 Summary of findings from non-clinical studies ............................................ 36
      6.5.2 Summary of findings from clinical studies ............................................... 36
      6.5.3 Summary of adverse reactions ................................................................... 36
  6.6 Concomitant medication ...................................................................................... 36
      6.6.1 Anti-emetic prophylaxis .............................................................................. 36
      6.6.2 Colony stimulating factors ........................................................................ 37
      6.6.3 Therapy for febrile neutropenia .................................................................. 37
      6.6.4 Supportive care .......................................................................................... 37
      6.6.5 Autologues hematopoietic stem cells ....................................................... 37
  6.7 MIBG therapy (considered standard treatment) ................................................... 37
      6.7.1 Whole body dosimetry ............................................................................... 38
      6.7.2 MIBG therapy, patient preparation ............................................................ 38
      6.7.3 MIBG therapy, use of co-medications ....................................................... 39
      6.7.4 MIBG post therapeutic imaging ................................................................. 39
      6.7.5 MIBG therapy, possible side effects .......................................................... 39
LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
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<td>AR</td>
<td>Adverse Reaction</td>
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<tr>
<td>ASCT</td>
<td>Autologous stem cell transplantation</td>
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<tr>
<td>CA</td>
<td>Competent Authority</td>
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<tr>
<td>CCMO</td>
<td>Central Committee on Research Involving Human Subjects</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CR</td>
<td>Complete remission</td>
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<td>CRF</td>
<td>Case report forms</td>
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<td>CT</td>
<td>Chemotherapy and/or computed tomography</td>
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<td>DCOG-ECTC</td>
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<td>DLT</td>
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<td>DSMB</td>
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<td>EU</td>
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<td>EudraCT</td>
<td>European drug regulatory affairs Clinical Trials GCP Good Clinical Practice</td>
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<td>EBRT</td>
<td>External Beam Radiotherapy</td>
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<td>G-CSF</td>
<td>Granulocyte colony-stimulating factor</td>
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<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
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<td>MBq</td>
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<tr>
<td>MIBG</td>
<td>Meta-iodobenzylguanidine</td>
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<tr>
<td>MR</td>
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<tr>
<td>MREC</td>
<td>Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance tomography</td>
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<tr>
<td>MTD</td>
<td>Maximal tolerated dose</td>
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<tr>
<td>NCI-CTCAE</td>
<td>National Cancer Institute – Common Terminology Criteria for Adverse Events</td>
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<tr>
<td>NR</td>
<td>Non-response</td>
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**PD**  Progressive disease  
**PR**  Partial remission  
**RR**  Response rate  
**RT**  Radiation therapy  
**(S)AE**  (Serious) Adverse Event  
**SD**  Stable Disease  
**SPC**  Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)  
**SUSAR**  Suspected Unexpected Serious Adverse Reaction  
**VGPR**  Very good partial response  
**VMA**  Vanillyl mandelic acid  
**WBC**  White blood cells  
**Wbp**  Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)  
**WMO**  Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)
1 INTRODUCTION AND RATIONALE

1.1 Neuroblastoma

Neuroblastoma is a malignant paediatric tumour derived from the sympathetic nervous system. It is the most common extra cranial solid tumour in children, accounting for 10% of all childhood cancers (1). The primary tumour may be located in different anatomic sites such as abdomen (65%), thorax (19%), pelvis (2%), and cervix (1%). Neuroblastoma is usually staged according to the categories of the International Neuroblastoma Staging System (2). Stage 4 neuroblastoma in patients older than 1 year of age represents the most frequent form. Depending on the stage at diagnosis, the age of the child and the operability of the tumour, treatment will consist of chemotherapy, radiotherapy and/or surgery. Stage 4S patients generally display spontaneous regression without intensive intervention. Patients with stage 1 and 2 disease can usually be treated with surgery, without the need for radiotherapy and/or chemotherapy. But patients with Stage 3 and 4 disease require intensive treatments involving combinations of high-dose myeloablative chemotherapy (with or without total body irradiation) and stem cell rescue followed by high dose retinoic acid treatment. The most frequently used chemotherapeutic drugs are alkylating agents and platinum compounds, anthracyclines, topoisomerase II inhibitors and vinca-alcaloids.

The outcome of patients with neuroblastoma depends on disease stage, age at onset, the presence of bone metastasis, MYCN amplification and histology. Localized disease and those arising in infants have a 90% survival rate except in cases of MYCN amplification, where survival is below 30% (3). Despite the intensive multimodal approaches prognosis in patients > 1 year of age with stage 3 or 4 disease remains poor. Those children have a 5-year survival rate of only 30%-40%, even if there is a favourable response to initial therapy (4). Children with aggressively treated high-risk neuroblastoma may develop recurrences even more than 5 years after completion of therapy (5). High-risk neuroblastoma patients who relapse following myeloablative consolidation chemotherapy have a dismal prognosis, with no realistic hope for cure(6). One of the accepted treatment options in the relapsed patients is targeted radiotherapy with the radiopharmaceutical $^{131}$I-MIBG (see section 1.2). Objective response rates in heavily pretreated patients with neuroblastoma may be as high as 30-50% (7). Due to poor survival probability of children with metastatic neuroblastoma, it is important to develop more effective treatment either by introducing new agents or by improving existing treatments.

1.2 Metaiodobenzylguanidine

Metaiodobenzylguanidine (MIBG) is a guanethidine derivative with specific affinity for neural crest tissues. It is taken up by an active transport process involving the noradrenalin transporter molecule. Once iodinated, MIBG can be used for diagnostic or therapeutic strategies. MIBG labelled with iodine-123 ($^{123}$I-MIBG) has become an integral component
of staging and response evaluation in neuroblastoma. Since $^{131}$I-MIBG concentrates in neuroblastoma cells, it is suitable for targeted radiotherapy. Its uptake is tissue specific and a prolonged intracellular concentration is maintained at tumour sites compared to normal tissues (8). From 1985 on, $^{131}$I-MIBG has been used as a therapeutic agent in neuroblastoma in Europe and in a few centres in the United States. Treatment with $^{131}$I-MIBG as a single agent has shown encouraging results not only in the treatment of patients with chemo-resistant disease (7), but also in patients at diagnosis (9). An impressive palliative effect was also noted (6, 10). The most prominent response was obtained in patients with a large tumour burden at the time of treatment. In the United States $^{131}$I-MIBG therapy has been studied as a salvage treatment for refractory/recurrent disease or after an incomplete response after induction chemotherapy. As a single agent at doses of 3-18 mCi/kg $^{131}$I-MIBG shows activity against refractory neuroblastoma with varying response rates (table 1 addendum).

Garaventa and others used $^{131}$I-MIBG in the treatment of 43 stage 3 and 4 neuroblastoma patients with residual disease after first-line treatment. With a MIBG dose ranging from 2.5 to 5.5 GBq (median 3.7) a number of 3 (range 1-5) courses were given. CR was documented in 1 stage 4 patient, PR in 12 (2 stage 3, 10 stage 4), mixed or no response in 25 (10 stage 3, 15 stage 4) and disease progression in 5 (one stage 3, four stage 4). Twenty-four patients (12/13 stage 3, 12/30 stage 4) are alive at 22-153 months (median 59) from diagnosis (11).

Matthay and others have used $^{131}$I-MIBG in combination with myeloablative chemotherapy and autologous stem-cell support. In a phase I dose escalation study (12-18 mCi/kg) in 22 refractory patients, they observed 1 CR and 5 PR (total responses 6/22; 27%). The median overall survival (OS) interval was 48.1 months (95% CI; ranging 18.7-49.5 months). The median event free survival (EFS) was 18.0 months (95% CI; ranging 13.5 to 34.2 months) (12).

In 5 relapsed patients using the same myeloablative chemotherapy and a fixed dose of 12 mCi/kg $^{131}$I-MIBG, 3 patients achieved CR and 2 PR at day 100 after transplantation. The median times to neutrophil (0.5 x 10^3/ul) and platelet (>20 x 10^3/μl) engraftment were 10 and 28 days resp. (13).

In our centre Tytgat and others treated recurrent neuroblastoma patients with $^{131}$I-MIBG in combination with vitamin C and hyperbaric oxygen in a phase II study with dose escalation of vitamin C. A dose of 100-150 mCi $^{131}$I-MIBG was used in 22 heavily pre-treated patients. 12/22 patients received at least 2 MIBG treatments and were evaluated for response, 9/22 did not complete treatment because of progressive disease. An overall response rate of 32% was found (1 VGPR, 6 PR) and a good effect on pain relief and weight gain was reported. No adverse events or toxicities were reported (Tytgat et al, unpublished data). Berthold and others treated 32 stage III and IV neuroblastoma patients refractory to conventional high dose chemotherapy with $^{131}$I-MIBG. Mean applied activity was 128 mCi per course (35-300 mCi), 360 mCi cumulatively per patient (80-1033 mCi) and 19.2 mCi/kg per patient (3.2-37.9 mCi/kg), respectively. A total of 84 courses were given (mean 2.6 per patient). Pain relief was noticed in 14/14 patients with bone pain. An overall response rate of 50% (5 CR and VGPR, 11 PR) was achieved. Main side effect was
transient thrombocytopenia, which became more severe with increasing number of courses (14).

In a palliative setting and in the absence of harvested stem cells, Howard and others treated patients with recurrent neuroblastoma with multiple $^{131}$I-MIBG infusions in a lower dose (3-19 mCi/kg). They administered 62 infusions in 28 heavily pre-treated patients (16 after prior high dose chemotherapy with autologous stem cell rescue). Objective responses were seen in 11/28 patients (39%). Ten patients were alive 5-51 months after therapy, including 1 CR, 1 VGPR, 6 SD and 2 progressive diseases. Median time from treatment to last follow-up was 11.3 months (range 3.4-136.6 months). Median time to progression was 47 days (range 27-146 days). The estimated probability to overall survival at 50 months was 0.2 (15).

In a phase II study, Matthay and others evaluated the effect of disease sites and prior therapy on response and toxicity after $^{131}$I-MIBG therapy of patients with resistant neuroblastoma. 164 relapsed or refractory high-risk neuroblastomas were treated with 18 mCi/kg or 12 mCi/kg $^{131}$I-MIBG (depending on availability of hematopoietic stem cells). The overall complete plus partial response rate was 36%. The response rate was significantly higher for patients with disease limited either to bone and bone marrow, or to soft tissue (compared to patients with both) for patients with fewer than three prior treatment regimens and for patients older than 12 years. The event-free survival (EFS) and overall survival (OS) times were significantly longer for patients achieving response, for those older than 12 years and with fewer than three prior treatment regimens. The OS was 49% at 1 year and 29% at 2 years; EFS was 18% at 1 year (16).

$^{131}$I-MIBG single agent therapy is usually well tolerated, which is mainly due to its targeted activity towards neuroblastoma cells. The primary toxicity related to $^{131}$I-MIBG treatment includes transient myelosuppression, which is more common in case of bone marrow involvement; mostly platelets and neutrophils/granulocytes to a lesser extent. In a phase II study of the effect of disease sites and prior therapy to $^{131}$I-MIBG response in 164 relapsed or refractory neuroblastoma Matthay described 33% of patients treated with 18 mCi/kg $^{131}$I-MIBG received autologous stem cell support because of hematologic toxicity (ANC < 200 µl for more than 2 weeks or prolonged dependence on platelet transfusions). Non-hematologic toxicity grade 3 or 4 was rare, with 5% of patients experiencing hepatic, 3.6% pulmonary, 10.9% infectious toxicity and 9.7% with febrile neutropenia (16). Bone marrow disease at time of treatment is the most useful predictor of haematological toxicity (17). Dose-escalation studies have shown that a dose of 15 mCi/kg leads to haematological toxicity requiring stem cell rescue (18). To prevent thyroid dysfunction during MIBG therapy, thyroid blockage must be obtained and thyroid hormones should be replaced (19).

In addition, 6 patients have been described with secondary myelodysplastic syndrome and/or secondary leukemia after treatment with $^{131}$I-MIBG (20). In Europe, $^{131}$I-MIBG therapy is standard treatment in newly diagnosed neuroblastoma (upfront) and is commonly used in relapsed or progressive disease.
1.3 Gemcitabine

Gemcitabine (2',2'-difluorodeoxycytidine, dFdC), a nucleoside antimetabolite, is a cytotoxic agent that has a wide spectrum of anti-tumour activity in both murine and human solid tumour models. As a prodrug, gemcitabine requires intracellular phosphorylation by deoxycytidine kinase (dCK), resulting in the accumulation of the active forms, difluorodeoxycytidine diphosphate (dFdCDP) and difluorodeoxycytidine triphosphate (dFdCTP). dFdCDP inhibits ribonucleotide reductase (RR), reducing the concentrations of natural deoxynucleotides, including deoxycytidine triphosphate (dCTP). At the same time, dFdCTP competes with deoxycytidine triphosphate (dCTP) for incorporation into deoxyribonucleic acid (DNA) and subsequently inhibits DNA synthesis, resulting in cell death. Gemcitabine is metabolized to the pharmacologically inactive metabolite 2',2'-difluorodeoxyuridine (dFdU) by cytidine deaminase (CDA) in plasma and several organs, such as the liver. The rate-limiting step in the activation of gemcitabine is the conversion of the nucleoside into the monophosphate by the enzyme deoxycytidine kinase (dCK). The phosphorylating activity of dCK is inhibited by high concentrations of dCTP.

The antiproliferative activity of gemcitabine is mediated through its effects on DNA synthesis in rapidly dividing cells. Gemcitabine is cell cycle specific and blocks cells in the Gap1 (G1) and synthesis (S) phase. The concentration of the drug and the duration of exposure both play a crucial role in the ultimate cytotoxic effect. Optimal accumulation of the active metabolite dFdCTP is dependent on achieving plasma concentrations of gemcitabine that use the full capacity of dCK without exceeding the concentration where the enzyme is saturated (20µmol/l) (21). This concentration of gemcitabine is achieved in plasma when gemcitabine is infused at a dose rate of 6-10 mg/m²/min (22). Whenever the gemcitabine plasma level is below the saturation level, it is increased infusion time rather than increased dose that may increase intracellular dFdCTP (23). As a surrogate marker for tumour uptake and activation of gemcitabine, levels of dFdCTP can be measured in patients' peripheral blood mononuclear cells (PBMCs).

The therapeutic window of gemcitabine is characterized by predominantly dose and schedule dependent myelosuppression (thrombocytopenia and neutropenia) and only low to moderate and less schedule dependent non-hematologic toxicity (nausea, vomiting, abnormal liver function tests). Gemcitabine as single agent therapy has most commonly been administered as a 30-min infusion in a weekly schedule for 3 weeks, with one week rest.

Gemcitabine is approved in a variety of solid tumours in adults, including pancreas, non-small cell lung, bladder, breast, and ovarian cancers. None of these tumours are typically seen in a paediatric population.
1.4 Gemcitabine and neuroblastoma

Since neuroblastoma tends to quickly exhibit resistance to chemical agents through over-expression of a multi-drug resistant protein (24), there’s an urgent need for novel agents which can overcome chemo resistance. Gemcitabine may have an advantage in the treatment. First, deoxycytidine analogue have a unique mechanism of antineoplastic action that differs from those drugs commonly used against neuroblastoma (25). Second, gemcitabine is not a substrate for plasma membrane drug efflux pumps, such as P-glycoprotein or multidrug resistance-associated protein, which are closely related to multidrug resistance in neuroblastoma. Furthermore, recent studies (26) suggest that P-glycoprotein or multidrug resistance-associated protein overexpression induces an up-regulation of dCK, resulting in an increase in intracellular active metabolites of gemcitabine. In vitro studies proved that gemcitabine, as a single-agent, has high potential in the treatment of neuroblastoma even in patients refractory to chemotherapy (27). Both MYCN-amplified and MYCN-single-copy neuroblastoma cell lines were highly sensitive to gemcitabine, with concentration of the drug resulting in 50% effect when compared to untreated controls (ED50) values in the nanomolar range after a 3-h exposure to gemcitabine. There was no correlation of the observed ED50 with the dCK activity. The LD50 values of MYCN-amplified cell lines varied between 16 and 202 nM. In none of the MYCN-single copy cell lines LD50 values could be established. Treatment with gemcitabine induced cell death in MYCN-amplified cells whereas MYCN-single-copy-cell lines underwent neuronal differentiation. Ogawa examined the activity of gemcitabine against neuroblastoma in vitro and in vivo. The IC50s for gemcitabine in 11 neuroblastoma lines ranged between 3 nmol/L and 4 μmol/L. The high activity of gemcitabine against neuroblastoma was confirmed in animal models (athymic mice). Furthermore, gemcitabine-induced apoptosis was observed irrespective of the caspase-8 status of neuroblastoma cells, which indicates that apoptosis depends on the mitochondrial pathway. They concluded that neuroblastoma is highly sensitive to gemcitabine (28). These results suggest that clinical application of gemcitabine to the treatment of neuroblastoma is warranted.

1.5 Gemcitabine in pediatric patients

Initially, gemcitabine was evaluated in a phase I dose finding study in paediatric patients with leukemia. In this study performed by the COG (0955) gemcitabine was administered as a single agent to 14 heavily pre-treated, refractory patients with leukemia. The age range of study patients included infants 1 year of age to 20 years of age. The maximum tolerated dose (MTD) was defined as 3600 mg/m² (administered as 10 mg/m²/min for 360 min) when weekly administered for 3 weeks with 1 week rest. In this study 4 patients experienced positive changes in their bone marrow scores, but had insufficient changes in their peripheral blood counts to be considered complete or partial responders. One patient had ALL and an M1 marrow with persistent thrombocytopenia, and 3 patients had M2
marrows (2 with AML and 1 with ALL) with persistent neutropenia or thrombocytopenia (29).

A Phase 2 Study (ADVL0022) enrolled 20 evaluable patients with acute lymphoblastic leukaemia (ALL) and 10 patients with acute myelogenous leukaemia (AML). The age range of study patients included infants 1 year of age to adolescents ≤ 20. The dosage and administration schedule was used as in the Phase 1 study (0955). Primary study endpoint was complete response (CR) rate. Here to, patients were separated into two strata patients with AML and patients with ALL. There was one CR (ALL). As in the phase 1 study, haematological toxicity was dose-limiting. Other observed gemcitabine toxicities included febrile neutropenia, elevation of serum transaminases, nausea, vomiting and rash/desquamation. This toxicity spectrum was similar to that reported in adults. The conclusion of this phase 2 study was that gemcitabine at the dose and schedule studied was not effective for children with relapsed ALL or AML.

Gemcitabine was tested in solid tumours as well. A Phase 1 Study (0954) examined paediatric patients with advanced solid tumours at a starting dose of gemcitabine 1000 mg/m$^2$ (to 1500 mg/m$^2$) as a 30-minute infusion in a 3-weekly for 4 weeks schedule and at a starting dose of 1500 mg/m$^2$ (to 2100 mg/m$^2$) in a 2-weekly for 4 weeks schedule. Forty patients were treated on study. The MTD of gemcitabine given weekly for 3 weeks was 1200 mg/m$^2$/dose. In the 2-weekly for 4 weeks all dose levels were considered tolerable. The major toxicity was myelosuppression. Some patients with osteogenic sarcoma, Ewing’s sarcoma and soft tissue sarcoma had stable disease (SD) despite extensive prior chemotherapy; one patient with pancreatic tumour showed partial response (PR). The PR occurred in 1 of the 2 patients with pancreatic cancer, which is an approved indication for adult patients. The effects of gemcitabine on the various solid tumours in these paediatric patients suggest there may be activity in a paediatric population (30).

Another single-agent gemcitabine study in paediatric patients with solid tumours was conducted to determine the efficacy of gemcitabine and to evaluate the tolerability in pre-treated children. In this Phase 2 study 20 patients were enrolled with pre-treated soft tissue sarcoma, Ewing’s sarcoma, neuroblastoma, hepatoblastoma, osteosarcoma, or nephroblastoma. The age range of study patients included infants 2 years of age to adolescents 23 years of age (mean 15.8 year). Gemcitabine was administered at a dose of 1200 mg/m$^2$/dose for 3 weeks in a 4 week cycle. The tolerability was consistent with that expected in adults. Only 2 evaluable patients (neuroblastoma and Ewing’s sarcoma) had stable disease, and no responses were seen. Patients discontinued early, mostly because of progressive disease (31).

In paediatric patients variation of duration of infusion of gemcitabine was tested in a phase 1 study in patients with leukaemia (29). Duration of infusion of 360 min with an infusion rate of 10 mg/m$^2$/min was recommended for a phase 2 study, as was reported by Angiolillo in 2005. Studies performed in paediatric patients with solid tumours all used short infusions of gemcitabine (30 min).
Single-agent gemcitabine appears to have only minimal activity in the types of cancers typical in paediatric patients with relapsed or refractory tumours. However, gemcitabine as part of a combination therapy could still prove to be effective in these paediatric patients. An ongoing Phase 2 study of gemcitabine plus oxaliplatin is currently enrolling paediatric patients with relapsed or refractory neuroblastoma or miscellaneous non-brain tumours.

1.6 Gemcitabine and radiotherapy

Preclinical studies have demonstrated gemcitabine to be a potent radiosensitizer in human pancreatic, colorectal, and other solid tumour cell lines, with dose-enhancement ratios of 1.6 – 2.0 (32). This enhancement effect seems to depend on the concentration and duration of exposure and the timing of irradiation. Radio sensitization occurs at non-cytotoxic concentrations, increases with prolonged drug exposure and the maximal effect is observed when the drug is administered before radiation therapy without any delay. In vivo studies (mice, xenografts) confirmed the radiosensitization of gemcitabine. The effect is increased with increasing concentration and duration of exposure of gemcitabine, but radio-enhancement is already seen using gemcitabine doses well below the MTD. Different regimens (once or twice weekly) have been compared showing different enhancement ratios and therapeutic indices (33) (34). In preclinical studies, gemcitabine administered 24 hours before the start of radiotherapy showed the highest therapeutic gain (35). There also appears to be an inverse linear relationship between the MTD of gemcitabine and the radiation dose used (36).

In various phase 1 studies in adult patients with pancreatic cancer (table 2 in addendum) tolerability of different schedules (once or twice weekly) of gemcitabine and concurrent external beam radiation was determined. When administered twice-weekly, MTD was 40–50 mg/m² (37) (38). Once-weekly dose schedule of gemcitabine with concurrent radiotherapy for 6 weeks (39) or 7 weeks (40) suggested a MTD of gemcitabine in the range of 250-350 mg/m². Worrisome late GI toxicities have been observed in the once-weekly regimens, but either at high doses or with larger radiation dose fractions. In phase I studies in lung cancer patients similar dose ranges of gemcitabine have been proposed using once-weekly dose schedule (41) (42). The dose of gemcitabine which patients with head and neck cancer can tolerate on a weekly basis during radiotherapy are generally lower (43).

In different phase II studies efficacy (and tolerability) of the schedules and doses was determined. In a study of gemcitabine combined with radiation in patients with localized unresectable pancreatic cancer, gemcitabine was given once weekly at a dose of 1000 mg/m² for 7 weeks as an induction phase. Patients who showed clinical benefit and in whom reduction or stabilization of tumour size was confirmed, entered the chemoradiation phase. This consisted of gemcitabine 400 mg/m² weekly (day 1, 8, 15) for 2 cycles, given concurrently with radiotherapy (total dose 50.4 Gy). This treatment schedule was well tolerated and can provide prolonged clinical benefit (44).
Other phase II studies with gemcitabine (50 mg/m²/wk, 100 mg/m²/wk or 300 mg/m²/wk) concurrent with radiotherapy in patients with cervical or head and neck cancer showed that the combination was well tolerated and effective (45), (46).

A small randomized controlled trial by Li et al. showed that gemcitabine (600 mg/m² two times a week) concurrent with radiotherapy was superior over the standard in terms of response, quality-adjusted life month survival, progression-free survival, and overall survival and was comparable to the standard in terms of tolerability (47).

The radiosensitizing effect of gemcitabine has led to combination treatment of gemcitabine and radiation therapy in pancreatic cancer, lung cancer, ovary cancer and head- and neck sarcoma in adult patients.

1.7 Rationale for the combination of Gemcitabine and $^{131}$I-MIBG in pediatric patients with neuroblastoma

Despite intensive treatment schedules and changes, prognosis of neuroblastoma remains poor. Since it has been established that neuroblastoma tumours are radiosensitive (48), $^{131}$I-MIBG treatment has proven its efficacy in relapsed neuroblastoma patients with response rates from 10-50%. The high response rate and low non-hematological toxicity with $^{131}$I-MIBG suggest that incorporation of this agent into future multimodal therapy of neuroblastoma may be useful.

Gemcitabine is proven as a radiosensitizer when used in combination with radiotherapy. Moreover, gemcitabine has proven tolerability in children with cancer. The relatively mild toxicity profile of gemcitabine at radiosensitizing doses makes the combination treatment of gemcitabine and $^{131}$I-MIBG promising and worthwhile studying.

The combination of gemcitabine and $^{131}$I-MIBG has not been studied clinically yet. Pharmacokinetics of both agents does not differ significantly in children from those in adults and an interaction between the two drugs is not expected with the proposed dosing scheme.

The proposed regimen (dosages and schedule) is derived from the results of the phase II studies of gemcitabine and external beam radiotherapy in adult solid tumors. The gemcitabine doses in this pediatric trial will be administered on Day 1 and 8 of a 28-day cycle since the radiosensitizing effect of gemcitabine is expected in the first week of the MIBG treatment.

For these reasons we assume that the proposed combination regimen will increase the efficacy of $^{131}$I-MIBG therapy in pediatric patients with neuroblastoma and that the combination treatment will be tolerable and efficacious. In the event of therapeutic benefit
seen in this study, the combination of gemcitabine and $^{131}$I-MIBG will be studied in the complete group of neuroblastoma patients in an upfront setting.
2 OBJECTIVES

The main objective of this study is to evaluate the efficacy of gemcitabine in addition to $^{131}$I-MIBG therapy in paediatric patients with relapsed or progressive neuroblastoma.

The secondary objective is to evaluate the safety and toxicity profile.
3 SELECTION OF STUDY PATIENTS

3.1 Study patients

The study will be conducted in paediatric patients 1 to 18 years of age with relapsed or progressive neuroblastoma that have previously been treated with standard treatments and are considered candidates for gemcitabine chemotherapy and $^{131}$I-MIBG-therapy.

3.2 Inclusion criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

1. Histological proven neuroblastoma (at initial diagnosis).

2. Measurable primary and/or metastatic disease:
   - Measurable disease will be defined by the modified International Neuroblastoma Staging System and International Neuroblastoma Response Criteria (2).

3. Relapsed or progressive neuroblastoma in which standard approaches to treatment (including established salvage therapy) have failed:
   - **Relapsed neuroblastoma**: neuroblastoma which has responded to front-line treatment and achieves a remission (CR/VGPR) but the disease recurs later on.
   - **Progressive neuroblastoma**: neuroblastoma which has responded to front-line high-risk treatment (first or second line) but did not achieve a remission and shows progression (new lesions or >25% increase) later on.

4. Evidence of sufficient MIBG uptake on diagnostic $^{123}$I-MIBG scanning in bone lesions or soft tissue before study entry to justify treatment with $^{131}$I-MIBG.
   - **Sufficient MIBG uptake** is defined as any pathological uptake in a given organ or tissue with a higher uptake as compared to the MIBG uptake of the liver.

5. 1 year to 18 years of age.

6. Modified Lansky play score ≥ 70%, or ECOG performance status ≤ 1 (where more appropriate).

7. Life expectancy > 6 weeks.

8. Adequate organ function including the following:
Haematological function: leukocytes >2.0 x 10^9/L, absolute neutrophil (segmented and bands) count (ANC) ≥1.0 x 10^9/L, platelets >100 x 10^9/L (in case of bone marrow disease: >75 x 10^9/L)

Hepatic function: bilirubin ≤1.5x upper limit of normal (ULN), aspartate transaminase (AST) and alanine transaminase (ALT) ≤5 x ULN.

Renal function: serum creatinine ≤1.5 x ULN for age (1 to 15 years: <65 µmol/L; >15 years:<110 µmol/L). If serum creatinine is > 1.5 x ULN of age, then creatinine clearance (or radioisotope GFR) must be > 70 ml/min/1.73 m^2

[9] Wash out of 3 weeks for prior chemotherapy or radiotherapy (1 week if prior chemotherapy was single-agent vincristine), 6 weeks if the prior chemotherapy contained nitrosoureas, 6 months since ASCT was given.

[10] Able to comply with scheduled follow up and with management of toxicity.

[11] All patients with reproductive potential must use effective contraception. Female patients with childbearing potential must have a negative pregnancy test within 7 days before study treatment.

[12] Written informed consent from patients or from parents or legal guardians for minor patients, according to local law and regulations.

### 3.3 Exclusion criteria

Patients will be excluded from the study if they meet any of the following criteria:

[1] Have received treatment with an investigational or conventional anticancer drug for any indication within the last 21 days at the time of study entry.


[3] Have a serious concomitant systemic disorder (that is, active infection including HIV, or cardiac disease) that, in the opinion of the investigator, would compromise the patient’s ability to complete the study.


[7] $^{131}$I-MIBG treatment in prior 3 months

[8] Known hypersensitivity to gemcitabine
4 OVERALL STUDY PLAN

4.1 Description of the design

This is a phase II, multi-centre, open-label, single-arm study with two dose-levels of gemcitabine: 375 mg/m² and 500 mg/m².

For safety we will apply 3 definitions:

**Dose Limiting Toxicity (DLT):** are adverse events (AEs) considered at least possibly related to the study drug (gemcitabine) and occurring in the 1st course of study treatment in the first 6 patients at each dose level.

DLT will be defined as:
- grade 4 thrombocytopenia > 14 days, considered related to the study drug,
- grade 4 neutropenia > 7 days, considered related to the study drug or
- grade 4 life threatening non-hematological event which is considered related to the study drug.

**Severe toxicity:** are adverse events (AEs) occurring in the 1st course of study treatment in the expansion cohort (patient 7 and further) at each dose level.

Severe toxicity is defined as:
- grade 4 thrombocytopenia > 14 days, considered related to the study treatment,
- grade 4 neutropenia > 7 days, considered related to the study treatment or
- grade 4 life threatening non-hematological event which is considered related to the study treatment.

**Cumulative toxicities** are toxicities that are encountered in the 2nd or greater course in any given patient. Cumulative toxicity will be descriptive and tabulated separately.

For this study the number of patients to meet protocol objectives is calculated according to a modified Bryant and Day two stage design with early stopping rules for severe toxicity or poor response (figure 1 and 2).

In the first stage safety and efficacy of gemcitabine in combination with ¹³¹I-MIBG will be assessed at the first dose level (375 mg/m²). After 6 patients have been treated at this dose, a safety analysis will be performed (figure 1). If 2 patients develop dose-limiting toxicities (DLT), the trial will be stopped or amended. Otherwise, enrolment will be continued until 19 patients have been treated at this dose-level (expansion cohort). At the end of the first stage, interim analysis will be performed. Depending on the number of responses and the safety at the interim analysis, the dose which will be used in the second stage will be determined.
If at interim analysis (figure 2) the first dose-level has proven to be safe (<10 patients with severe toxicity) and response rates are very high (≥ 10 responses), the study will continue with this dose in the second stage. If, on the other hand at interim analysis the response rates are intermediate (<10 responses) and there are no severe toxicity concerns (<10/19 patients with severe toxicity), the dose to be used in the second stage will be escalated to the second dose level (500 mg/m²). If at interim analysis ≤ 6 responses are seen or if ≥ 10 severe toxicity is seen, further enrolment will be stopped or the trial will be amended.

When the dose of gemcitabine has been escalated in the second stage, another safety analysis will be performed after 6 patients have been treated at 500 mg/m². Again, if in 2 or more of these patients dose-limiting toxicity is encountered, the trial will be stopped or amended. Otherwise, enrolment will be continued until 19 patients have been treated at 500 mg/m². A second interim analysis is performed after treatment of 19 patients at 500 mg/m². If at this interim analysis ≤ 6 responses are seen or if there are ≥ 10 patients with severe toxicity, enrolment will be stopped or the trial will be amended. If at that stage ≥ 10 responses are seen and <10 patients with severe toxicity are seen, enrolment will be continued up till 47 patients.

At the end of the second stage a final analysis will be performed after treatment of 47 patients at a dose-level. If at this analysis >17 responses are seen and < 27 severe toxicity is seen, this regimen will be recommended for further study.

In this study there is a stratified enrolment based on ¹³¹I-MIBG prior treatment status. There will be 4 strata: 1A – gemcitabine 375 mg/m², MIBG-naïve patients; 1B – gemcitabine 375 mg/m², MIBG pre-treated patients; 2A – gemcitabine 500 mg/m², MIBG naïve patients; 2B – gemcitabine 500 mg/m², MIBG pre-treated patients. Patient numbers will be balanced per stratum. If patient numbers are not equally divided per stratum, enrolment will be continued for that stratum until a minimum of 6 patients per stratum at interim analysis (19 patients) or 14 patients at end of study (47 patients) is enrolled.
Figure 1: Study design first dose level – first stage

**Gemcitabine 375 mg/m²**

- Safety analysis (6 patients)

**Dose-limiting toxicity**
- < 2 patients → Further accrual → 19 patients → 47 patients
- ≥ 2 patients → Trial stops or will be amended
Figure 2: Study design expansion cohort– modified Bryant and Day design

- **First stage**
  - Gemc 375 mg/m²
  - N = 19 pat

  - **Response**
    - ≤ 6/19
    - AND/OR
    - Severe Toxicity
      - ≥ 10/19
      - Stop study or amend dosing
  
  - **Response**
    - ≥ 10/19
    - AND
    - Severe Toxicity
      - < 10/19
      - Continue at 375 mg/m²
      - Up till 47 patients

  - **Response**
    - > 6/19
    - < 10/19
    - AND
    - Severe Toxicity
      - < 10/19
      - Continue at 500 mg/m²
      - Safety analysis (6 pat)
      - Interim analysis after 19 pat
      - Final analysis after 47 patients

- **Interim analysis**

- **Second stage**
4.2 Study centers

Study will be performed in different centers in 2 countries: the Netherlands (in collaboration with the Dutch Childhood Cancer Group, DCOG) and Germany, (in collaboration with German Pediatric Oncology Hematology Group GPOH).

Coordinating international Sponsor:
    Academic Medical Centre (AMC), Amsterdam, the Netherlands
Co-sponsor Netherlands:  Academic Medical Centre (AMC), Amsterdam
Co-sponsor Germany:  University of Cologne, Cologne

International Trial Office: Clinical Trial Bureau AMC Pediatric Oncology
    Amsterdam, the Netherlands

Centers:
See participating centers list.

4.3 Study period

Duration of study: 2010 – 2015
    LPLV: 05 – 2015
    End of trial = LPLV

Final study report: 2016

4.4 Premature discontinuation of the study

The sponsor has the right to prematurely discontinue the study for significant efficacy or safety problems and will notify the investigator in writing, as well as the IRB/ethic committees and the competent authorities according to local law and regulations.
5 PATIENT REGISTRATION

Patients will be recruited from a population of children treated at or referred to one of the participating study sites. A study site can only start enrolling patients once the appropriate ethical committee and other relevant authorities have agreed with the study and if the contract with the sponsor (and co-sponsor if applicable) has been signed and the site has fulfilled all obligations as requested by the sponsor and is initiated for enrolment.

Patients will be enrolled to receive gemcitabine plus \(^{131}\)I-MIBG in an open-label manner.

The study site will be able to enrol patients into the study by procedure of registration available via the website http://www.skion.nl/dcoq-ectc/studies

This method of registration will be done utilizing a web-based service called TenALEA. This web-based registration program will provide continuous service during 24 hours 7 days per week. Each study site will request a login for the local person responsible for the registration of the patients. Detailed instructions will be provided to the participating sites.

The following information will be required to register a patient:

1. Gender, date of birth
2. review of eligibility criteria
3. prior \(^{131}\)I-MIBG therapy
4. expected date of treatment start

Alternatively, patient registration may be done by faxing the signed Enrolment Form to:

Clinical Trial Bureau AMC Pediatric Oncology
Fax:+ 31-20-566 9021
In case assistance is needed: Tel: +31-20- 566 8985
e-mail: dc-ectc@amc.uva.nl

In case enrolment issues need to be discussed prior to faxing the enrolment forms, please send an e-mail to both PI and coordinating investigator simultaneously for discussion: h.n.caron@amc.uva.nl and n.k.vaneijkelenburg@amc.uva.nl with a copy to dc-ectc@amc.uva.nl and for German patients to thorsten.simon@uk-koeln.de.

It is the responsibility of the Principle Investigator to ensure that the subject is eligible for the study before enrolling the subject.
At the end of the enrolment process, notification of a registration will be send automatically to all involved parties. A subject number will be assigned at this time together with the dose gemcitabine which should be used. The subject number will be used on all Case Report Form (CRF) pages and on all documentation and correspondence referencing that patient. No patient shall receive drug until the entire registration process has been completed.

For this trial balanced accrual based on MIBG-treatment status will be followed. If patient numbers are not equally divided per stratum, that stratum will be closed for enrolment of further patients. Sites will be informed by e-mail.
6 STUDY TREATMENT

6.1 Treatment schedule

Treatment will consist of gemcitabine and $^{131}$I-MIBG in a cycle of 28 days according to the following schedule:

Table 6.1 Treatment schedule

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>8</th>
<th>15</th>
<th>22</th>
<th>29/1</th>
<th>8</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine t = 0</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>start</td>
<td>start</td>
<td></td>
<td>start</td>
<td>start</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>stop</td>
<td>stop</td>
<td></td>
<td>stop</td>
<td>stop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{131}$I-MIBG t = 180 min</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>start</td>
<td></td>
<td></td>
<td>start</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gemcitabine will be infused over 30 min over a central venous line, 3 hours prior to the start of $^{131}$I-MIBG therapy (in 100 mCi/hour infusion). Dose of gemcitabine will start at 375 mg/m$^2$ and may be escalated to 500 mg/m$^2$ in the second stage (see section 10 for statistical considerations).

To start treatment on Day 1, patients must have an absolute neutrophil count (ANC) of $\geq 1.0 \times 10^9$/L and a platelet count of $>100 \times 10^9$/L ($>75 \times 10^9$/L in case of bone marrow disease). Prior to gemcitabine administration on day 8, an ANC of $\geq 0.5 \times 10^9$/L is necessary.

6.2 Treatment duration

Each patient is scheduled for two 28-day cycles of gemcitabine/$^{131}$I-MIBG. Treatment must be discontinued earlier if progression or dose limiting toxicity occurs. In the absence of disease progression (PD), study treatment can be continued for a maximum of 6 cycles as long the patient has clinical benefit (at the discretion of the investigator), does not experience major cumulative toxicity, and is able to be exposed to study treatment.

For assessment of study efficacy endpoints, a minimum of 2 cycles of treatment per patient is necessary. Response assessment will be performed according to procedures described in section 8.1.2). Due to this response assessment after cycle 2, cycle 3 or any other treatment will only start after a $^{123}$I-MIBG scan is performed at least 4 weeks after the last $^{131}$I-MIBG therapy has been started.

For the first 6 patients at each dose level, DLT's will be assessed after the first cycle. The other safety endpoints will be assessed through all cycles.
After response assessment after the second cycle gemcitabine/\textsuperscript{131}I-MIBG, other off protocol treatments are allowed leading to withdrawal of patients.

6.3 Discontinuation of patients

Patients will be discontinued from the study in the following circumstances:

- The investigator decides that the patient should be withdrawn from the study. This decision can be made because of progressive disease, toxicity or patient’s inability to be exposed to this study treatment.
- The patient or its legal representative requests that the patient will be withdrawn from the study.
- The sponsor decides to discontinue the study due to significant safety or efficacy concerns.
- The patient had two dose reductions and experiences a toxicity that would cause a third dose reduction.
- The patient cannot receive study treatment within 3 weeks after the intended date of the next cycle.
- The patient becomes pregnant.
- The patient is noncompliant with study procedures.

6.4 Substitution of patients

In the first 6 patients at each dose level patients will be substituted if:

- Patient shows pulmonary toxicity grade 2 or more before the end of 2 cycles of treatment and will thus discontinue treatment before efficacy can be assessed

Patients who encounter a DLT as is defined in chapter 4 and section 9.1.2 will not be substituted.

6.5 Investigational medicinal product – gemcitabine

\textbf{Description:} Commercially available gemcitabine will be used. The drug is supplied as a lyophilized powder in sterile vials containing either 200 mg or 1 g of gemcitabine as the hydrochloride salt, mannitol, and sodium acetate. The lyophilized product should be stored at room temperature.

\textbf{Preparation:} Drug will be reconstituted with normal saline added to the vial to make a solution ideally containing 10 mg/mL (not to exceed 40 mg/mL). Once the drug has been reconstituted it should be stored at room temperature (15 – 25 °C) and used within 24 hours. Any unused portion of a vial must not be stored for future use and must be discarded.
Drug accountability: it is the responsibility of the Investigator to keep a record of Investigational Medicinal product disposition. This should at least include batch number, use date and expiry date.

6.5.1 Summary of findings from non-clinical studies


6.5.2 Summary of findings from clinical studies

Gemcitabine was evaluated in children in different phase I and II trials. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which were similar to those reported in adults. No meaningful clinical activity was observed in these trials (29), (49), (30), (31), (50).

6.5.3 Summary of adverse reactions

Gemcitabine may cause bone marrow suppression, resulting in anemia, leucopenia and thrombocytopenia. Myelosuppression is usually dose-limiting. Disturbances in liver transaminases occur in approximately 66% of the patients, but are always mild and reversible. Gemcitabine should be carefully dosed to patients with decreased liver function. Nausea and vomiting occur in 33% of the patients and can usually adequately be treated with standard emetics. Mild proteinuria and hematuria has been reported in approximately 50% of the patients, but was rarely clinically significant, and was generally not associated with changes in serum creatinine or urea levels. Skin rash has been seen in approximately 25% of the patients, is not dose-limiting and mild. Pulmonary toxicity has been reported with the use of gemcitabine.

Gemcitabine is contraindicated in those patients with a known hypersensitivity to the drug.

6.6 Concomitant medication

All concomitant medications taken by the patient are to be recorded in the Case Report Forms (CRF), including those taken in the 2 weeks before the first course. No other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation therapy, surgery for cancer, or experimental medications will be permitted while the patients are participating in this study. The use of some specific drugs has to be excluded before administration of MIBG, see section 6.6.3.

6.6.1 Anti-emetic prophylaxis

Conventional anti-emetic guidelines must be used for prophylaxis. This means the use of ondansetron 5 mg/m² (max 8 mg) i.v. 3 times a day or granisetron 0,25 μg/kg (max 1 mg)
iv daily, 30-60 min prior to gemcitabine infusions on day 1 and 8 for 2 days. Additional anti-emetic medication (such as domperidone and/or dexamethasone) is strongly recommended. The choice on anti-emetic medication will be left to hospital guidelines, provided this medication does not interact with the influx of $^{131}$I-MIBG.

### 6.6.2 Colony stimulating factors

Routine use of colony stimulating factor (CSF) is not permitted during this study. ASCO guidelines for use of CSF should be followed (51), see addendum.

G-CSF may be used for patients who have life-threatening infections while neutropenic. The use of G-CSF in uncomplicated neutropenia is not recommended and should be discussed with the PI. G-CSF must be discontinued at least 24 hours prior to the start of the next cycle of chemotherapy.

### 6.6.3 Therapy for febrile neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy.

### 6.6.4 Supportive care

Acetaminophen (paracetamol) and/or prednisolon can be used during 1-2 days after gemcitabine infusion in case of fever or flu-like symptoms. Patients are allowed to receive full supportive care therapies concomitantly during the study, including corticosteroids.

### 6.6.5 Autologues hematopoietic stem cells

Collected autologues hematopoietic stem cells (when available) might be useful in case of prolonged neutropenia. The use of these stem cells will be left at the discretion of the physician. If stem cells will be used because of prolonged neutropenia, the principal investigator should be notified and withdrawal from study will be discussed.

### 6.7 MIBG therapy (considered standard treatment)

Commercially available $^{131}$I-MIBG will be used in this study. The infusion solution is prepared according to manufacturer’s prescription using NaCl 0.9%. The dosage of $^{131}$I-MIBG of the first cycle will be $444\, \text{MBq/kg bodyweight}$. The dosage of the second cycle will be an adjusted amount of $^{131}$I-MIBG to aim at $4\, \text{Gy whole body dose}$. For cycle 3 and further, a fixed dose of $296\, \text{MBq/kg bodyweight}$ or $8\, \text{mCi/kg bodyweight}$ will be used. The maximum single dose administered to children is restricted to an activity of $11100\, \text{MBq/300 mCi}$ $^{131}$I-MIBG. For some sites the maximum single dose is restricted to an activity of $7400\, \text{MBq/200 mCi}$. Such sites are advised to refer patients > 16 kg (who require a higher dose) to a site where the maximum dose that can be delivered is up to $11100\, \text{MBq/300 mCi}$ $^{131}$I-MIBG.
The radiolabeled MIBG will be administered through a readily running infusion (central venous line) by a 100 mCi/hour administration through a lead-shielded infusion system equipped with a pump. Infusions will always contain less than 5% free $^{131}$I.

### 6.7.1 Whole body dosimetry

To reduce bone marrow toxicity the dose regimen is aimed at a whole body exposure of 4 Gy for the combined 2 cycles of $^{131}$I-MIBG. To optimize radiation dose to the neuroblastoma sites, the second dose is adjusted based on the whole body dose of the first cycle. Moreover, whole body dosimetry is performed to determine the whole body radiation dose for the combined two cycles of $^{131}$I-MIBG. Whole body dosimetry will not be used for cycle 3 and further.

Whole body dosimetry (see also chapter 31).

For the assessment of the whole body dose the exact activity administered should be measured by taking into account the residue in the vials and tubes after the completion of infusion.

Whole body radiation will be calculated from the time-activity curve obtained from frequent whole body retention measurements. For this purpose a fixed and reproducible geometry is chosen. The distance from the bed to the measuring equipment should be the same within each therapy session and should at least be 2 m. The first whole body retention measurement will be taken immediately after completion of the administration of $^{131}$I-MIBG, before voiding of the bladder (100% measurement = administered amount of $^{131}$I-MIBG). Thereafter, whole body measurements are obtained frequently for the rest of the isolation period (see chapter 31). During the night (23 h - 7 h) no measurements have to be performed.

The whole body radiation dose is calculated using a dedicated excel based programme (see chapter 31) which is based on the Medical Internal Radiation Dose (MIRD) dose model.

### 6.7.2 MIBG therapy, patient preparation

Patients will be treated according to the national regulations and guidelines concerning the use of radionuclides for medical purposes and within the permission of the hospital to do so. Admission to a special nuclear medicine ward will be necessary.

Applicable for all patients:
The following thyroid blockage regimen must be prescribed:

One day before the MIBG therapy (day 0) thyroxine (125 µg/m² once daily) and thiamazol (0.25 mg/kg orally b.i.d.) will be started in the child and continued for 4 weeks (52). On the day of radioactive MIBG therapy, potassium iodide (30 mg orally three times a day) will be started and continued for a total of 14 days, to block the uptake of $^{131}$I in the thyroid.
Parents are advised to take potassium iodide as well (200 mg orally once a day), to start the
day for MIBG therapy and to continue for a total of 4 days, see also addendum.
For some children sedation may be necessary, but only after strict consideration of
indication and using appropriate monitoring and skilful personnel. Chloralhydrate (25-50
mg/kg oral/rectal t.i.d./q.i.d.) is then advised.
On day 1, patients are kept fasting until ≥ 2 hours after MIBG injection. Then (tube) feeding
is slowly restarted.

Regulations/guidelines applicable for the Netherlands:
If possible parents will be involved in nursing during the admission at the nuclear medicine
ward. Children need to be prepared for isolation by trained personnel. Daily registration of
whole body exposure rate is compulsory by regulations. Patient may be released from
the nuclear medicine ward if exposure rate < 20 μSv/h. If the patient is transferred to a
paediatric ward, special nursing regimen has to be installed. Duration of admission at
nuclear medicine ward: usually 3-5 days.

6.7.3 MIBG therapy, use of co-medications
Although prescription of interfering drugs is rare in paediatric patients, the use of the
following drugs should be preferably excluded (at least during 4 half lives of the co-
medication) before any MIBG administration or discussed with the PI:
- Bronchodilators: feneterol, salbutamol, terbutaline
- Nasal drops and sprays: xylometazoline
- Cardiac drugs: calcium channel blockers (nifedipine, nicardipine, amlodipine), ACE-
inhibitors (captopril, enalapril), adrenergic receptor blockers (labetolol, amiodarone),
inhibitor of sodium pump (digoxin).
DOI 10.1007/s00259-008-0715-3

6.7.4 MIBG post therapeutic imaging
Post therapeutic 131I-MIBG scan should be performed at least twice within the first week
after therapy, preferably at day 2 or 3 and at day 6 or 7. This scan will be used to assess
MIBG uptake and retention of that cycle.

6.7.5 MIBG therapy, possible side effects
Hypertension has been described during infusion of MIBG. This may be prevented by slow
infusion of the radiopharmaceutical. Most prominent adverse events in the first couple of
days post infusion are nausea, dehydration and pain. Prescription of anti-emetics and pain
medication will be done in consensus with paediatrician. Hydration regimen should be
prescribed in advance.
Expected toxicity in weeks post infusion related to $^{131}$I-MIBG therapy includes myelosuppression, mostly affecting platelets. Especially in patients with massive bone marrow invasion myelosuppression can be severe. Neutrophils are affected to a much lesser extent. Usually the nadir for platelet count is more pronounced than the nadir for neutrophils. Myelosuppression is almost always reversible but may be incomplete. Suppression may be more pronounced after the second treatment course in comparison to the first course. When available, collected autologues hematopoietic stem cells might be useful in case of prolonged neutropenia. Dry mouth may occur as a result of radiation to the salivary glands. Radiation sialoadenitis is reversible. Exposure of the thyroid to radiation can be prevented by adequate thyroid blocking when MIBG ($^{131}$I and $^{123}$I) is used (see addendum).

Exposure to radiation may cause secondary malignancies. Leukemia and myelodysplastic syndrome has been described after MIBG therapy (20) (53). As survival in this group of patients is still poor, little is known about the late effects of MIBG therapy.
7 DOSING SCHEMES

7.1 Description and justification of route of administration and dosages

The treatment schedule and dosages has been chosen based on results of Phase 1 and 2 studies with gemcitabine in children and the results of Phase 3 studies in adults with gemcitabine and external beam radiotherapy in several tumour types. Both dosages 375 mg/m² and 500 mg/m² are thought to be safe and tolerable as well as effective by radiosensitization. Gemcitabine will be administered as an intravenous infusion over 30 minutes over a central venous line which will give an infusion rate of approximately 10 mg/m²/min, which is the optimal infusion rate. The treatment schedule used in the present study is thought to be the optimal schedule for the combination of gemcitabine and MIBG. The dose of 444 MBq/kg ¹³¹I-MIBG has been shown tolerable in heavily pre-treated children. In our opinion, the most promising approach in dosing therapeutic amounts of MIBG has recently been reported by Gaze et al (54) and by Buckley et al (55). In this dosage regimen the aim is to limit whole body dose to 4 Gy for the combined series of two consecutive ¹³¹I-MIBG administrations. The first administration is based on a fixed dose/kg (444 MBq/kg). The second dose is based on the total body radiation dose calculated from the first therapeutic administration. In this way the highest possible dose is delivered to the tumour combined with an acceptable toxicity for other organs, especially bone marrow. Moreover, in this scheme one can compensate for inter-patient variation of biodistribution of MIBG. By law, the maximum single dose administered to children is restricted to an activity of 11100 MBq/300 mCi ¹³¹I-MIBG.

7.2 Dose modifications for toxicity

Toxicities will be managed by treatment interruption for a maximum of 3 weeks, to allow resolution of toxicity. If a patient’s treatment is delayed for longer than 3 weeks because of toxicity, the patient will discontinue study treatment.

After treatment interruption, dose of gemcitabine may be reduced according to maximum graded toxicity within the previous cycle as described below. If a dose has to be reduced for toxicity reasons, the patient will stay on this reduced dose for the remainder of the study. A second dose reduction is allowed before the patient discontinues from study treatment.

7.2.1 Hematologic toxicity

To start treatment on Day 1, patients must have an absolute neutrophil count (ANC) of ≥1.0 x 10⁹/L and a platelet count of ≥100 x 10⁹/L (>75 x 10⁹/L in case of bone marrow disease). Prior to gemcitabine administration on day 8, an ANC of ≥ 0.5 x 10⁹/L is necessary.
To start a new cycle (nr 2 and on) of gemcitabine and MIBG, patients must have an absolute neutrophil count (ANC) of $\geq 1.0 \times 10^9/L$ and a platelet count of $\geq 75 \times 10^9/L$ with an increasing trend (for all patients). On day 8 of each cycle, gemcitabine treatment will be continued if ANC $> 0.5 \times 10^9/L$. If the requirements are not met on day 8, treatment has to be delayed for a maximum of 7 days. If gemcitabine can not be administered at day 15, this dose should be omitted.

The dose of gemcitabine will be modified according to granulocyte and platelet counts during the previous cycle (see table 7.2-1).

### Table 7.2-1. Dosing reductions for Hematologic Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dosing scheme for subsequent cycle according to NCI CTCAE Grades within the previous cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Gemcitabine 100%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Gemcitabine 100%</td>
</tr>
</tbody>
</table>

#### 7.2.2 Non-hematologic toxicity

Any Grade 3 or greater non-hematologic toxicity experienced during a cycle must resolve to Grade 1 or lower before the next cycle may be administered. Grade 2 or greater alanine transaminase (ALT) and aspartate transaminase (AST) must resolve to Grade 1 or lower before the next cycle may be administered, unless the patient has liver metastases.

Table 7.2-2 illustrates the dosing scheme for non-hematologic toxicities. Toxicities are graded within the previous cycle.
Table 7.2-2  Dosing Scheme for Non-hematologic Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dosing scheme for subsequent cycle according to NCI-CTCAE Grades within the previous cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Gemcitabine: 100%</td>
</tr>
<tr>
<td>Other nonhematologic toxicities</td>
<td>Gemcitabine: 100%</td>
</tr>
</tbody>
</table>

<sup>a</sup>CTCAE Grade 3 or 4 nonhematologic toxicity considered clinically relevant – at the discretion of the investigator

7.3 Delays for Subsequent Cycles

Delays of a new cycle due to holidays, or other unforeseen circumstances, are permitted and will not be counted as protocol violations. The maximum delay permitted is 3 weeks and should be mentioned on the CRF.
8 STUDY ASSESSMENTS

The patient's assessments will consist of:

1. Baseline assessment
2. On-trial assessments
3. Post-discontinuation period

For details of the schedule and nature of the assessments, see flowchart of study procedures (see addendum).

8.1 Baseline assessment

Baseline assessment (CT and/or MRI scan, \(^{123}\text{I}-\text{MIBG}\) scan, BM assessment, tumour markers, urine catecholamines) of the tumor should be performed as close to the trial start as possible and the interval should not exceed 7 days (except for radiological studies, where a period of up to 4 weeks prior is permitted). Staging of disease is determined according to the INSS criteria (see addendum). Recommended tests for assessment of extent of disease are listed in table 8.1-1. Tumour lesions on CT and/or MRI-scan should be measured in 3 dimensions and the largest diameter must be noted. Measurable lesions include all the lesions that can be measured with a diameter > 10 mm on CT and/or MRI scan. When multiple measurable lesions are present, all measurements should be noted.

At baseline inclusion/exclusion criteria will be reviewed, previous medical history and therapy will be recorded and physical examination will be performed (including notation of vital signs and Lansky performance status). Screening laboratory results will be reviewed and decision is made if the child is eligible for study. All scans should be digitally stored, encoded (patient identification number only), dated and sent to the Review Committee and certain time points. Scans performed at baseline do not need to be send separately, but should be included in the shipment for central review after 2 cycles. See for details section 9.3 and Procedure manual.
Table 8.1-1 Assessment of extent of disease (baseline)

<table>
<thead>
<tr>
<th>Tumour Site</th>
<th>Recommended Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Tumour</td>
<td>CT and/or MRI scan with 3D measurements; MIBG scan (with SPECT reconstruction); urine catecholamines; tumour markers (ferritin, LDH)</td>
</tr>
<tr>
<td>Metastatic Sites</td>
<td></td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>Bone marrow aspirates from $\geq 4$ sites or trephine (core) bone marrow biopsies $\geq 2$ sites are required to exclude marrow involvement. A single positive site documents marrow involvement. Core biopsies must include at least 1 cm of marrow (excluding cartilage) to be considered adequate.</td>
</tr>
<tr>
<td>Bone</td>
<td>MIBG scan with SPECT reconstruction is mandatory; plain radiographs of positive lesions are recommended.</td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>Clinical examination (palpable nodes), ultrasound, CT and/or MRI, MIBG whole body scan.</td>
</tr>
<tr>
<td>Abdomen/liver</td>
<td>CT and/or MRI scan with 3D measurements.</td>
</tr>
<tr>
<td>Chest</td>
<td>AP and lateral chest radiographs. CT/MRI necessary if chest radiograph positive, or if abdominal mass/nodes extend into chest.</td>
</tr>
</tbody>
</table>


8.1.1 Pharmacogenomics – CDA activity

Cytidine deaminase (CDA) is the major enzyme in gemcitabine detoxification in the body. Lower CDA activity might be correlated with a higher toxicity after gemcitabine treatment. A study of Ciccolini et al (56) retrospectively tested CDA activity in 130 patients. Twelve percent of the adult patients experienced severe toxicities after gemcitabine. A significant difference in CDA activities was observed between patients with and without toxicities. The patients who displayed particularly reduced CDA activity all experienced strong toxicities. At the start of the MIBG-gem treatment a serum sample in each patient will be taken for measurement of CDA activity. This serum sample will be collected in dry tubes and sent to the Laboratoire de Transfert en Oncologie (Pr Ouafik, Marseille, France). See Procedure Manual for details.

8.2 On-trial assessment – efficacy

Tumor assessment to determine response must be performed after 2 cycles. Response will be assessed by standard methods: MRI and/or CT scan, $^{123}$I-MIBG scintigraphy with SPECT and bone marrow aspirates or biopsies (if indicated). If there’s a palpable or visible lesion, clinical response will be measured.

As part of this assessment a diagnostic $^{123}$I-MIBG scan will be performed. This scan should be performed > 4 weeks after the start of the last $^{131}$I-MIBG therapy because of prolonged retention of $^{131}$I-MIBG and a long t½ of $^{131}$I-MIBG. Therefore, a third cycle can not start before week 9.

Urine catecholamines (VMA/HVA, dopamine) will be repeated if initially positive and to confirm CR as assessed by MRI/CT and MIBG scintigraphy. Bone marrow aspirates
producing negative results at baseline, do not need to be repeated unless disease progression is suspected. In the absence of progressive disease (PD according to Brodeur, table 8.1), cycle 3 can be started. After the first assessment, response will be assessed every 2 cycles (so after cycle 4, 6 etc). For dosing and imaging requirements of assessment methods, see addendum.

8.3 On trial assessment – safety

During the trial, toxicity will be assessed at regular intervals. Toxicity assessment consists of lab tests and review of signs and symptoms to detect any AE’s or SAE’s (see for definitions section 9.3). Any severe adverse event according to the definitions in section 9.3 requires an SAE-report by fax immediately after the investigator becomes aware of it. Each relapse, progression, or death requires an event report (see end of study form on CRF). The end of study form 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. Lansky performance status, weight and vital signs will be noted for each cycle. 1-3 days prior to each administration of therapy lab tests will be performed to check if there is a contra-indication to get study treatment. For toxicity assessment during treatment weeks, lab tests are performed once a week (haematology/chemistry). If clinically indicated, tests will be performed more often.

8.4 Post-discontinuation period

At end of study or discontinuation from treatment a final evaluation will be performed (if possible) in each enrolled patient. Assessment includes physical examination (including vital signs and performance status), laboratory tests, radiological evaluation by ultrasound, computed tomography and/or MRI, and a diagnostic MIBG scan (not in case of unequivocal progression). After completion of study treatment, patients are followed at approximately 4 weeks after $^{131}$I-MIBG administration and then every 8 weeks for up to 6 months, or until death. The follow up visit at 4 weeks will take place at the research centre, the other post therapy follow up visits can take place at a local hospital. During post therapy follow-up, information will be collected regarding date of disease progression, death, and any post study chemotherapy, radiotherapy, or surgical intervention. Adverse events will be noted until 30 days after treatment is ended. The date of first documented disease progression must be recorded on the CRF even if it occurs after the patient has started a new therapy.
8.5 Withdrawal of individual patients

Patients will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and are not obliged to state their reasons. Additionally, the Investigator may withdraw a patient at any time if he/she considers this to be in the patient's best interest.

If a patient fails to return for a scheduled visit/follow up, attempts should be made to contact the patient to ensure that the reason for not returning is not an adverse event (AE). Likewise if a patient declares his/her wish to discontinue from the study e.g. for personal reasons, an attempt should be made to establish that the true reason is not an AE (bearing in mind the patient is not obliged to state his/her reasons). If the study drug therapy is prematurely discontinued, the primary reason for discontinuation must be recorded in the appropriate section of the CRF and all efforts will be made to complete and report the observations as thoroughly as possible.

8.5.1 Follow-up of patients withdrawn from treatment

A complete final evaluation following the patient's withdrawal should be made 4 weeks after withdrawal (in order to detect delayed toxicity), and any AE’s should be followed up until resolution. For survival analysis, after withdrawal patients will have follow-up through their recruiting physician every 8 weeks for a maximum of 6 months or until death).
9 DEFINITIONS FOR SAFETY AND EFFICACY EVALUATION

9.1 Study endpoints

**Primary study endpoint:**
To determine the efficacy as measured by response rate (and time-to-event measures) of the combined modality treatment.

**Secondary study endpoint:**
To characterise the safety and toxicity profile of the combined modality treatment.

9.2 Safety and toxicity

Safety and tolerability of study treatment will be reported for all treated subjects. Safety assessments will be performed during screening, prior to treatment, on Days 8, Day 15, and Day 22 (and weekly thereafter until recovery from thrombocytopenia or neutropenia) during each treatment cycle, and at the End of Study visit. Safety assessments will include physical examinations, vital signs (systolic/diastolic blood pressure, pulse rate, body temperature), clinical laboratory tests (hematology, serum chemistry), and reported or observed adverse events.

Treatment interruptions and discontinuations, and dose reductions for toxicity will be analyzed by dose level and per stratum. Moreover, the frequency and severity of all laboratory abnormalities will be tabulated.

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the CRF.

9.2.1 Adverse events

Adverse event (AE) is defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug (=gemcitabine). AEs will be assessed continuously and graded according to NCI-Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 ([http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf](http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf)). If not applicable, the event will be graded as 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening. Frequency and severity, and outcomes of AEs will be determined.

9.2.2 Relationship to study treatment

The causality relationship of the combination treatment and in particular of gemcitabine to the AEs will be assessed by the investigator as either:
• Certain: There is a reasonable causal relationship between the combined drug treatment and the AE. The event responds to withdrawal of study treatment (dechallenge), and recurs with rechallenge when clinically feasible.

• Probable: There is a reasonable causal relationship between the treatment and the AE. The event responds to dechallenge. Rechallenge is not required.

• Possible: There is reasonable causal relationship between the treatment and the AE. Dechallenge information is lacking or unclear.

• Not likely: There is a temporal relationship to treatment administration, but there is not a reasonable causal relationship between the treatment and the AE.

• Not related: There is not a temporal relationship to treatment administration (too early, or late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.

If a report of an AE cannot be judged because information is insufficient or contradictory, and this information cannot be supplemented or verified, the causality should be classified as “possible”.

9.2.3 Follow-up of adverse events

The investigator will continually monitor any patient with an adverse and serious adverse event until either the event has returned to the baseline grade or ≤ grade 1; or if the AE is determined to be chronic or a cause is identified or until a new treatment has started for which the AE becomes unassessable.

Follow-up of all AEs must be documented in the patient’s medical record and on the CRF. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. A patient who experiences an adverse event may be withdrawn at any time from the study at the discretion of the investigator.

9.2.4 Serious adverse events

A serious adverse event (SAE) is any adverse drug experience that occurs at any dose and results in any of the following outcomes:

• Death (except death from progression of malignancy).
• Life-threatening adverse drug experience.
• Requires inpatient hospitalization or prolongation of existing hospitalization.
• Persistent or significant disability/incapacity.
• A congenital anomaly/birth defect.
• Requires medical or surgical intervention to prevent one of the outcomes listed above.

NOTE 1:

• Pregnancy: Incidence of pregnancy is not considered a SAE; pregnancy must, however, be reported immediately by e-mail to the principal investigators of this study;
- Overdose: All cases of overdose must be reported immediately by e-mail to the principal investigators of this study.

**NOTE 2:**
Criteria for hospitalizations not reported as SAEs include admissions for:
- Planned as per protocol medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status documentation
- Medical/surgical admission for purpose other than remedying ill health state (planned prior to entry into study trial; appropriate documentation required)
- Admission encountered for other life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)
- Admissions for protocol-scheduled procedures or blood product transfusions will not be considered SAEs.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

### 9.2.5 Suspected unexpected adverse events - SUSARs

Suspected and unexpected serious adverse reactions (SUSARs) are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (i.e. Summary of Product Characteristics (SPC) for an authorised medicinal product) and of which there is a reasonable suspected causal relation with the IMP (gemcitabine) or for which a causal relation to the IMP cannot be ruled out.

### 9.3 Efficacy

Assessment of **efficacy** will be recorded as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), using a modified version of the International Neuroblastoma Response Criteria, see table 9.1.

**Table 9.1: Modified International Neuroblastoma Response Criteria, adapted from Brodeur (2)**

<table>
<thead>
<tr>
<th>Response</th>
<th>Primary Tumour</th>
<th>Metastatic Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>No tumour</td>
<td>No tumour; catecholamines normal</td>
</tr>
</tbody>
</table>
| **PR**   | Decreased by >50% | All measurable sites decreased by >50%. Bones and bone marrow: number of positive sites decreased by >50%; no more than 1 positive bone marrow site allowed (if a
Tumor responses will be reviewed by a central review committee. MRI films, CT scans and 131I-MIBG scans performed after every 2 cycles are required for review. MRI, CT and MIBG images should be digitally stored, encoded (patient identification number only), dated and send to the Review Committee together with the clinical history (see Procedure Manual). The baseline scans do not need to be send separately but should be included in the first shipment.

9.3.1 Response definitions

Response will be measured by Modified International Neuroblastoma Response Criteria (table 9.1). The proportion of subjects who responded will be determined after the second cycle of study treatment. In this trial, responses are defined as:

- Complete response (CR)
- Partial response (PR)

The estimate of the objective response rate will be given by (CR + PR) divided by the number of patients qualified for tumour response analysis. The study objective response rate will be reported including a 95% confidence interval.

9.3.2 Time to and Duration of Responses

The duration of overall response is defined as the time from the first documented objective response (CR or PR) to disease progression or death. Patients who have not progressed or died will have their duration censored at the date of their last disease assessment.

The duration of a stable disease is defined as the time from the start of the treatment until the criteria for progression are met.

Overall survival (OS) will be calculated for all patients from the date of registration to the date of death from any cause. Patients with no documented death will be censored at the last date they were known to be alive.

The time to treatment failure (TtTF) is the time from the first day of study treatment to the first date between documentation of progression or treatment discontinuation due to toxicity (including toxicity leading to patient refusal, or withdrawal per investigator decision). Patients who discontinued treatment without progression due to reasons other than unmanageable toxicity will be censored at the time of treatment discontinuation.
The **time to progressive disease (TtPD)** is the time from the first day of study treatment to the date of first objective disease progression. Patients who are lost to follow-up without documentation of progression will be censored at the last date they were assessed and found progression-free. For patients who die from causes other than study disease and without progressive disease, TtPD will be censored at the date of death. For patients who receive subsequent chemotherapy (after discontinuation from the study chemotherapy) prior to disease progression, TtPD will be censored at the date of subsequent chemotherapy.
10 STATISTICAL CONSIDERATIONS

This is a phase II, single-arm, open label multicenter study in collaboration with German Pediatric Oncology Hematology group (GPOH). The results of this study will be compared to historical controls of MIBG therapy in relapsed neuroblastoma patients. A modified two stage Bryant-and-Day design will be used.

10.1 Sample size

Sample size is calculated according to a modified Bryant and Day two stage design, with early stopping rules for toxicity or poor response. In the first stage, 6 patients will be treated at the first dose level of gemcitabine (375 mg/m²). This dose-level will be expanded to 19 patients if < 2 patients develop dose-limiting toxicities (DLT). Safety and efficacy will be assessed if 19 patients have been treated at this dose-level (interim analysis). Once this dose has proven to be safe and efficacious in the expanded cohort, up to 47 patients will be accrued (second stage). If response rates are intermediate, the dose will be escalated (500 mg/m²). Maximum sample size is 66 patients (19 + 47). See figure 2.

This procedure tests the null hypothesis (H₀) that the true response rate of the given treatment is 30% versus the alternative response rate (Hₐ) that the true response rate is 50%. The probability of accepting the combination therapy with a poor response (αₚ) is 10% and the probability of accepting the combination therapy which is toxic (αₜ) is 10%. The power of this study design is 80%. The upper limit of number of patients who experience toxicity is 50%, the lower limit is 30%.

10.2 Safety analysis

Safety analysis includes frequency, severity and relatedness of all AEs, frequency and severity of all laboratory abnormalities, frequency of dose interruptions, dose reductions and treatment discontinuation for toxicity, and use of concomitant medications. The number of infusions with grade 3 or 4 toxicity type possibly, probably or likely related to gemcitabine will be calculated and divided by the total number of cycles reported, to estimate incidence rate of serious toxicity associated with the agent.

Analyses for data with discrete dates, for example, deaths, and concomitant medications, will be done through 30 days after each patient’s last dose of study treatment. Adverse events will also be analysed in this timeframe; that is, if an event starts within 30 days of discontinuation from study treatment, but after 30 days after the last dose of study treatment, it will not be included.

For safety analyses, three definitions will be used:
Dose Limiting Toxicity (DLT): are adverse events (AEs) considered at least possibly related to the study drug (gemcitabine) and occurring in the 1st course of study treatment in the first 6 patients at each dose level. DLT will be defined as:
- grade 4 thrombocytopenia > 14 days, considered related to the study drug,
- grade 4 neutropenia > 7 days, considered related to the study drug or
- grade 4 life threatening non-hematological event which is considered related to the study drug.

Severe toxicity: are adverse events (AEs) occurring in the 1st course of study treatment in the expansion cohort (patient 7 and further) at each dose level. Severe toxicity is defined as:
- grade 4 thrombocytopenia > 14 days, considered related to the study treatment
- grade 4 neutropenia > 7 days, considered related to the study treatment or
- grade 4 life threatening non-hematological event which is considered related to the study treatment.

Cumulative toxicities are toxicities that are encountered in the 2nd or greater course in any given patient. Cumulative toxicity will be descriptive and tabulated separately.

10.2.1 Qualifications for Safety Analysis
The first 6 patients at each dose level who receive at least one cycle with the study regimen, will be evaluated for safety (DLT’s). All other patients who receive at least two cycles with the study regimen will be evaluated for safety and toxicity.

10.3 Safety analysis (after first 6 patients)
After 6 patients have been treated at a dose-level, a safety analysis will be performed. If 2 patients develop dose-limiting toxicities (DLT), the trial will be stopped or amended. Otherwise, enrolment will be continued until 19 patients have been treated at this dose-level (expansion cohort). A Data Safety Monitoring Board (DSMB) will be established to provide recommendations to continue, amend or terminate the trial depending upon this analysis see also section 11.5.

10.4 Interim analysis
When 19 patients have received 2 cycles of study treatment at a dose level an interim analysis will be performed. Depending on the number of responses at interim analysis, the dose which will be used in the second stage will be determined. If at interim analysis the first dose-level has proven to be safe (<10 patients with severe toxicity) and response rates are very high (≥ 10 responses), study will continue with this
dose in the second stage. If, on the other hand at interim analysis the response rates are intermediate (<10 responses) and there are no serious toxicity concerns (<10/19 patients), the dose to be used in the second stage will be escalated to the second dose level (500 mg/m²). If at interim analysis ≤ 6 responses are seen or if ≥ 10 severe toxicity is seen, further enrolment will be stopped or trial will be amended.
A Data Safety Monitoring Board (DSMB) will be established to provide recommendations to continue, amend or terminate the trial depending upon this analysis, see also section 11.5.

10.5 Final analysis

After treatment of 47 patients at a dose-level, final analysis will be performed If at this analysis >17 responses are seen and < 27 severe toxicity is seen, this regimen will be recommended for further study.

A Data Safety Monitoring Board (DSMB) will be established to provide recommendations to continue, amend or terminate the trial depending upon this analysis, see also section 11.5.

10.6 Efficacy analysis

The following describes the methods to be used for analysis of time to event parameters: Proportions of response will be compared by the Fisher’s exact test and trend in proportions assessed by the Chi squared test (or Cochran-Armitage test). Multivariable analysis of the response rate will be calculated using logistic regression and generalized additive models. EFS and overall survival (OS) will be estimated by the Kaplan-Meier method and compared by log-rank test. Patients will be censored in the EFS analysis at the time of last follow-up or new therapy.

A secondary analysis of the effect of prior MIBG therapy status on response and toxicity will be performed by correlating the current response to MIBG/gemcitabine to previous response to MIBG as single therapy.

10.6.1 Qualifications for Efficacy Analysis

All patients who receive at least two cycles with the study regimen will be evaluated for efficacy (tumour response and time to event parameters).

10.7 Statistical analysis - General Considerations

Parameters will be described using the following descriptive statistics:
Quantitative variables: mean, standard deviation, median, minimum and maximum.
Qualitative variables: frequencies and percentages
All tests of treatment effects will be conducted at a two-sided alpha level of 0.1 unless otherwise stated.
11 REGULATORY AND REPORTING REQUIREMENTS

11.1 Adverse event documentation

All adverse events occurring during the trial and follow-up period must be fully recorded in the case report form. Documentation must be supported by an entry in the patient medical file.

11.2 Adverse Event Monitoring and Reporting

The principal investigator is responsible for monitoring the safety of patients who enroll in the study. Each patient must be carefully monitored for adverse events. This includes clinical and laboratory test variables. 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. An assessment must be made of the seriousness, intensity and relationship to the administration of the study medication, as described in section 9.2.2. The descriptions and grading scales found in the NCI CTCAE version 3.0 will be used for adverse event reporting. A copy of the CTCAE version 3.0 can be found http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf.

All AEs occurring after any administration of the treatment combination will be followed until resolution. 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.

Adverse events, as well as serious adverse events (see 9.2.4), need to be reported until 60 days after the last administration of study medication, or until another treatment regimen is started, whichever occurs first. However, in the case of AEs occurring later than this deadline but which are considered related to the study medication by the investigator, such AEs still need to be reported.

11.3 Reporting of SAE’s

For this study a centralised SAE reporting procedure will be used, according to GCP guidelines. The international safety desk will be located at the AMC data centre, Amsterdam. There will be a national trial office located in Cologne, Germany and in Amsterdam, the Netherlands.
All serious adverse events occurring during the trial should be reported within 24 hours to the international trial office (Clinical Trial Office), with a copy to the national office. If the SAE occurs in the weekend or a holiday, the event will be reported on the next working day. The telephone, fax number and e-mail address are found at the end of this section.

The report form is communicated to the international principal investigator. He/she decides (if time allows with consultation of the study committee) what action (is) are necessary for the safety of the included patients. This is then communicated to the national principal investigator. All participating centres are informed if relevant.

The international sponsor is responsible for the expedited reporting of SUSARs that have arisen in the clinical trial to the MREC, to the competent authorities and the Medicine Evaluation Board in its country. A copy of this report will be send to the national trial office in Cologne and to the international sponsor. The co-sponsors are responsible for reporting SUSARs in their country to their national competent authorities and the Medicine Evaluation Board.

The reporting of SUSARs will be done according to national law and ICH-GCP guidelines for Clinical Safety Data Management (Definitions and Standards for Expedited Reporting) within 7 or 15 days.

Reporting SAE’s:
Clinical Trial Bureau AMC Pediatric Oncology
Tel: +31-20- 566 8985
Fax: +31- (0)87 784 7912
e-mail: safetydesk_mibggem@dcog-ectc.eu

11.4 Data safety registration

Data safety registration, CRF completeness check and database data entry will be carried out by the international trial office (Clinical Trial Bureau) at the Academic Medical Centre (AMC) Amsterdam. It will be done at the responsibility of the principal investigator.

11.5 DSMB

An independent data and safety monitoring board (DSMB) will be assembled to review the safety data collected during the study. The mission of the DSMB is to protect the safety of the patients in the study and to ensure the ethical conduct of the study. The DSMB will review data from the study (and other relevant data) with emphasis on gemcitabine related deaths, discontinuations due to AEs, gemcitabine-specific events, serious AEs and grade 4 toxicities.
The DSMB will be responsible for monitoring all clinically significant safety events; this will be done on an ongoing basis, and the frequency of reviews may be adjusted according to the emerging safety profile. The DSMB will regularly review the emerging safety profile and will make a recommendation on the conduct of the trial. The members of the DSMB will be independent of the trial and familiar with the methodology of oncology trials with particular emphasis on children and neuroblastoma. They must be aware of the implications of conclusions made based on immature data and agree with the design and the goals of the study protocol. The DSMB will be composed of two clinicians and a statistician, all familiar with conducting clinical studies.

The meeting schedule and all other DSMB related activities are specified in the separate DSMB charter and will be adjusted according to the emerging safety profile. The DSMB will have written operating procedures as outlined in the DSMB charter. The DSMB will review all data in an unblinded way. All results are confidential and will not be divulged to non-members of the DSMB, including the Sponsor. All meetings will be summarized in written minutes and kept by the DSMB chair until the end of the study. The recommendations can be communicated to the Sponsor verbally, but have to be confirmed in writing in a predefined time-frame.

The advice(s) of the DSMB will be notified upon receipt by the sponsor to the METC that approved the protocol. With this notification a statement will be included indicating whether the advice will be followed.

11.6 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited MRECs, competent authorities, Medicine Evaluation Boards of the participating countries.

12 ETHICAL CONSIDERATIONS

12.1 Medical Research involving Human Subjects Act (Section 10)

In accordance to section 10, subsection 1, of the Medical Research involving Human Subjects Act (in Dutch: WMO), the investigator will inform the subjects and the reviewing accredited MREC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited MREC, except insofar as suspension would jeopardise the subjects’ health.


12.2 Regulation statement

The study will be carried out in accordance with all applicable national law and local requirements.

This study will be conducted in accordance with the ethical principles that have their origin in the ICH guidelines of Good Clinical Practice of the European Community (http://www.emea.europa.eu/pdfs/human/ich/013595en.pdf CPMP/ICH/135/95), the Declaration of Helsinki (http://www.wma.net/e/ethicsunit/helsinki.htm) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other local guidelines, regulations and Acts. A copy of the ICH-GCP-Guidelines is included in the Investigator’s Study File.

12.3 Recruitment and consent

The investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing any new information that may be relevant to the patient’s willingness to continue his or her participation in the trial in a timely manner.

The informed consent document will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The consent form includes all elements required by ICH, GCP and applicable regulatory requirements. The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.
A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable. As used in this protocol, the term "informed consent" includes all consent and assent given by patients and/or their legal representatives. Children from the age of 12 onwards need to sign as well.

Prior to the beginning of the study, the investigator must have the MREC/IRB’s approval of the written informed consent form and any other information to be provided to the subjects.

Whenever important new information becomes available that is relevant to the subject’s consent, the informed consent form should be revised. This revised form should receive MREC/IRB approval prior to use. During a subject’s participation in the trial, any updates to the consent form and any updates to the written information will be provided to the subject. Any update to the consent form need to be signed again by the patient and/or legal representative.

### 12.4 Objection by minors


The Netherlands Association for Paediatric Medicine (NVK) has accordingly drawn up the following code of conduct for use in the context of medical research with minors:

1. Individual children respond differently to diagnostic and treatment procedures and to participation in medical research.

2. Before seeking consent for a child’s participation in medical research, an investigator must fully inform the child’s custodial parent(s) or guardian about what is proposed. Information should be provided orally and in writing. The nature of the procedures involved in the research should be discussed with the parents and their views sought on the child’s likely response.

3. The consent statement signed by parents should stipulate that, if the child should object to participation in the research, consent for its further participation will be invalidated.

4. If prior to the research there is doubt as to whether a child should participate, consideration may be given to involving the patient in the research for an agreed pilot period.

5. While the research is in progress, the behaviour of the child should be continually assessed at the research location to determine whether the child’s behaviour is within the bounds normally associated with the child when confronted with situations not encountered in everyday life.
6 The parents, the investigator(s) and possibly a behavioural scientist should be involved in assessment of a child subject’s behaviour. Assessment of a child subject’s behaviour should not be a one-off exercise, but should continue through all phases of the research.

7 The parents of a child subject should be able to withdraw their consent at any point during the research. If a child subject expresses an objection, the child’s participation should be discontinued.

8 In all medical research involving child subjects, the burden associated with participation should be minimised. Medical studies often involve the combination of research procedures with diagnostic procedures necessary in connection with the subject’s treatment.

9 The following should be noted in the research file or the medical (status) report, as appropriate:
   - the outcome of any trial participation;
   - the consent of the custodial parent(s) or guardian, including the procedure to be followed in the event of a possible expression of objection;
   - an account of the subject’s participation in the research, stating whether objection was expressed;
   - an assessment as to whether the subject’s behaviour constitutes objection, as referred to above;
   - the names of the people responsible for assessing the subject’s behaviour, as described above;
   - an assessment as to whether the subject’s behaviour in the course of the study constitutes objection;
   - the steps taken to minimise the burden associated with participation.

10 The protocol for a medical research project in which minors are to be used as subjects should state that the NVK’s code of conduct for dealing with subjects’ expressions of objection in the course of the research will be adhered to.

11 This code of conduct will be evaluated in consultation with the research community two years after its initial publication and amended as necessary.

This code of conduct was approved by the Board of the Netherlands Association for Paediatric Medicine (NVK) on 21 May 2001 and published in NVK Newsletter no. 3, June 2001.

12.5 Approval of study protocol
Before the study initiation, the investigator must have written and dated approval/favourable opinion form the local MREC/IRB for the study protocol and/or other appropriate documents. The investigator should also provide the MREC/IRB with a copy of the Investigator Brochure or product labelling.

12.6 Compliance with the protocol

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by the principal investigator. The principal investigator should not implement any substantial deviation or change to the protocol without prior review and documented approval/favourable opinion from the MREC/IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining MREC/IRB approval/favourable opinion, as soon as possible the deviation or change will be submitted to:
- MREC/IRB for review and approval/favourable opinion;
- the (co-)sponsor;
- Regulatory Authority(ies), if required by local regulations.

Any investigator or co-investigator who signed this protocol agrees to carry out this research in accordance with the protocol approved by the ethic committee, GCP and regulatory requirements.

12.7 Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Since this tumour is specifically seen in children, this study will be carried out in minors. The benefit for the patient is one of the objectives in this study. In the event of therapeutic benefit with this combination therapy, it will be related to the complete group of neuroblastoma patients. For patients in this study the burden and risks consists of extra assessments in a period of 6 months. These assessments are clinical, radiological, laboratory investigations and bone marrow biopsy(s). To receive study treatment, patients will be admitted for ± 5 days every 28 days.

12.8 Patient insurance

The study sponsor ensures that insurance covering any damage to patients participating in this study is taken out. This is referred to as direct damage insurance. Hereto, the (co-)sponsor of each country will provide insurance or indemnity in accordance with the applicable regulatory requirements for all patients within that country.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.
13 REGULATORY ASPECTS

13.1 Handling and storage of data and documents

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements. All patient names will be kept secret. Patients will be identified throughout documentation and evaluation by the number allotted to them during the study. The patient or his legally accepted representative would be told that all study findings would be stored on computer and handled in strict confidence.

The signed informed consent forms remain with the investigator. By signing the protocol agreement form, the investigator agrees to obtain a correctly completed informed consent form for each patient included in the study. He/she also agrees to allow these to be inspected on request. The investigator must retain investigational product disposition records, copies of CRFs and source documents for the maximum period required by applicable regulations and guidelines. The investigator will maintain a personal list of patient numbers and patient names. Both the consent forms and the patient identification list will be kept for at least 15 years.

13.2 Monitoring

Monitors will ensure that the clinical trial is conducted, recorded, and reported in accordance with the protocol, ICH-GCP, and the applicable regulatory requirement(s).

The type and scope of monitoring will be defined in the Monitoring Manual and documented on study specific Source Data Verification Forms.

With his participation in the study the investigator is obligated to support the activities of the monitors, provide them with direct access to the files and give them the opportunity to inspect the storage of the investigational product, etc.

13.3 Quality assurance (QA)

The Dutch and German sponsors will implement procedures to assure the quality of every aspect of the study. To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. Participating in this study implies acceptance of potential inspection by national or foreign Health Authorities.
13.4 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the MREC/IRB application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the MREC/IRB and to the competent authority. Non-substantial amendments will be recorded and filed by the sponsor.

13.5 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited MREC/IRB once a year. Information will be provided on the date of inclusion of the first patient, numbers of patients included and numbers of patients that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

13.6 End of study report

The sponsor will notify the accredited MREC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the patient’s last visit. In case the study is ended prematurely, the coordinating sponsor will notify the accredited MREC/IRB and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the principal investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited MREC/IRB and the Competent Authority.

13.7 Public disclosure and publication policy

Once the study has been completed (irrespective of whether or not it was terminated prematurely), the sponsor must submit a summary of the research results within a period of 3 weeks – 3 months. The clinical trial will be registered in a public trial registry as is required by the International Committee of Medical Journal editors as a condition for consideration for publication.

Study results are the coordinating sponsor’s property. They will be communicated to health authorities and ethic committees by the co-sponsors according to each national law. All
Information related to the study is confidential at least until appropriate analysis and control have been made by the coordinating investigator and principal investigator. The results of the clinical trial will be published after complete data collection and evaluation. Results from the study may not be published or presented orally without the authorization of the principal investigator. The study results shall be presented and published in collaboration with the principal investigator. Any publication or abstract shall be submitted to the principal investigator for approval. Authorship for publications will be defined according to the "International Committee of Medical Journal Editors" criteria NEJM, 1997. The following persons have to be considered as co-authors:
- investigators who have recruited at least 2 patients into the trial
- co-investigators representing the co-sponsor country.
14 SPONSOR, CO-SPONSOR and INVESTIGATOR RESPONSIBILITIES

Academic Medical Centre (AMC) in Amsterdam, the Netherlands is the coordinating/international sponsor of the study. The University of Cologne in Cologne, Germany will be the co-sponsor of the study for Germany. The co-sponsorship in Germany is delegated to the Centre for Clinical Trials Cologne (ZKS).

The co-sponsor of each country will provide insurance or indemnity in accordance with the applicable regulatory requirements for all patients within that country or may delegate this to the different participating centers. The co-sponsor will send copies of the insurance certificates to the coordinating sponsor for filing. The co-sponsor of each country is responsible for ethical approval of the protocol in that country.

Any investigator or co-investigator who signed this protocol agrees to carry out this research in accordance with the protocol approved by the ethic committee, GCP and regulatory requirements. The investigator will maintain a delegation of authority form in the Trial Master File to document signatures and initials of all persons of the study staff to provide a legal delegation of study specific principal responsibilities.

The investigator should provide the sponsor with his CV and the co-investigator's ones.

The coordinating sponsor has the right to prematurely discontinue the study for significant efficacy or safety problems and will notify the co-sponsor in writing, as well as the ethics committees and the competent authorities according to national law and regulations.
ADDENDUM

15 Study protocol agreement form

Study Title: ‘Phase II trial of the combination of gemcitabine and $^{131}$I-MIBG therapy in paediatric patients with relapsed or progressive neuroblastoma’

The following persons declare their consent with the study protocol:

Principal investigators:

NKA van Eijkelenburg, MD  ___________________ __________________
(date, dd/MON/yy)  (signature)

T. Simon, MD, PhD        ___________________ __________________
(date, dd/MON/yy)  (signature)

Herewith I confirm that I read the study protocol carefully and declare my consent with it. I will treat and examine the patients in accordance with the study protocol, the national applicable laws, the international guidelines on good clinical practice (ICH-GCP) and the Declaration of Helsinki.

Investigator:

Prof. Dr.____________________  ___________________ __________________
(name)    (date, dd/MON/yy)  (signature)

Site:  _____________________
(name)
### 16 Flowchart of study procedures

<table>
<thead>
<tr>
<th>Relative Day in Cycle</th>
<th>BL</th>
<th>1</th>
<th>5</th>
<th>8</th>
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<th>22</th>
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<th>8</th>
<th>15</th>
<th>22</th>
<th>Response</th>
<th>PD</th>
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<tbody>
<tr>
<td>Procedure</td>
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<tr>
<td>Informed Consent (before all procedures/tests)</td>
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<td>MIBG scan (diagnostic, $^{123}$I)</td>
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<td>Radiologic imaging for tumor measurements</td>
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<td>Bone marrow aspiration and trephine biopsies</td>
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<td>Urinary catecholamines</td>
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<td>Tumour markers</td>
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<td>Hematology</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>Thyroid function</td>
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<td>CTCAE grading</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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</tr>
</tbody>
</table>

**Notes:**
- X: Required
- X: Optional
\textbf{131I-MIBG-Gem in relapsed/progressive NBL IST}

<table>
<thead>
<tr>
<th>Blood sample for CDA activity(^{a})</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
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</tr>
<tr>
<td>Gemcitabine</td>
<td>X</td>
</tr>
<tr>
<td>MIBG (\textsuperscript{131}I)</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: \textbf{BL} = Baseline; \textbf{PD} = Post-discontinuation

**Baseline:** as close to the trial as possible, no more than 4 weeks before study enrolment

**Response:** 4-5 weeks after start of cycle 2-4-6 and so on

**Cycle 3 will start after response assessment is performed in week 9**

**Post-discontinuation period:** up to approximately 4 (30 days) weeks after discontinuation of study therapy.

\(^a\)Height only at baseline

\(^b\)Lansky performance scale (see addendum) or ECOG scale where more appropriate

\(^c\)Including RR, pulse, temperature

\(^d\)Girls at reproductive age

\(^e\)Diagnostic MIBG scanning (\textsuperscript{123}I-MIBG) should be performed >4 weeks after the last MIBG therapy is started

\(^f\)Investigators must consistently use the same imaging modality: CT and/or MRI scan with 3D measurements. See addendum for imaging requirements.

\(^g\)Bone marrow tests producing negative results at baseline do not need to be repeated unless there is clinical evidence of disease progression needing further confirmation.

\(^h\)Twenty-four hour urine collection is not necessary, when the results of a single portion of urine are normalized by urine creatinine concentration. During the collection of urine for catecholamine excretion, specific food (banana) is to be eliminated from the diet. Urine investigation is to be repeated after cycle 2 only if positive at baseline and/or to confirm CR

\(^i\)Tumour markers: Serum ferritine, lactate dehydrogenase (LDH)

\(^j\)Visual measurement must be performed using a metric ruler or calipers, and a color medical photograph must be taken

\(^k\)Lab tests: within 7 days before study enrolment, then \(\pm\) 3 days before Day 8, 15 and 22 (for chemistry and hematology) and at the first postdiscontinuation visit. See addendum for laboratory tests to be performed

\(^m\)Thyroid function: FT4 and TSH. Before start prophylaxis, during prophylaxis (before 2\textsuperscript{nd} MIBG therapy) and at the end of prophylaxis (after 1 month, then every 3\textsuperscript{rd} month)

\(^n\)Toxicity rating using the NCI CTCAE scale (Version 3.0)

\(^o\)Blood sample for CDA activity: in each patient a serum sample will be taken for CDA activity. This sample can be send to France, preferably overnight. See chapter 8.1.1.1. for further details

\(^{a}\)If date of baseline is identical to day 1 (or within 7 days prior to day 1) no need to repeat the measurements.
Clinical laboratory tests

Clinical Laboratory Tests

<table>
<thead>
<tr>
<th>Hematology a:</th>
<th>Tumour markers b:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>Urine catecholamines: VMA/HVA, dopamine</td>
</tr>
<tr>
<td>WBC</td>
<td>Ferritin, LDH</td>
</tr>
<tr>
<td>ANC</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Chemistry a:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>FT4</td>
</tr>
<tr>
<td>Alanine aminotransaminase (ALT/SGPT)</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST/SGOT)</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
</tr>
</tbody>
</table>

a Refer to the Study Schedule.
b 24 h collection or ratio to creatinine on spot urine sample.
c Test done on urine or serum at the discretion of the investigator.
d Reference values: TSH 0,2-1,0 mU/L, FT4 12-30 pmol/L

Modified Lansky performance scale

<table>
<thead>
<tr>
<th>Modified Lansky Play - Performance Scale (For use with persons ages 1 - 16 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 % Fully active, normal</td>
</tr>
<tr>
<td>90 % Minor restrictions in physically strenuous activity</td>
</tr>
<tr>
<td>80 % Active, but tires more quickly</td>
</tr>
<tr>
<td>70 % Both greater restriction of, and less time spent in, play activities</td>
</tr>
<tr>
<td>60 % Up and around, but minimal active play; keeps busy with quieter activities</td>
</tr>
<tr>
<td>50 % Gets dressed but lies around much of the day; no active play; able to participate in all quiet play and activities</td>
</tr>
<tr>
<td>40 % Mostly in bed; participates in quiet activities</td>
</tr>
<tr>
<td>30 % In bed; needs assistance even for quiet play</td>
</tr>
<tr>
<td>20 % Often sleeping; play entirely limited to very passive activities</td>
</tr>
<tr>
<td>10 % No play; does not get out of bed</td>
</tr>
<tr>
<td>5 % Unresponsive</td>
</tr>
<tr>
<td>0 % Dead</td>
</tr>
</tbody>
</table>
19 ECOG Performance status

ECOG PERFORMANCE STATUS*

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

* As published in Am. J. Clin. Oncol. (57)

20 NCI-CTC toxicity version 3.0


21 Helsinki ICH-GCP


22 International Neuroblastoma Staging system, INSS (Brodeur 1993)

Stage | Definition
--- | ---
Stage 1 | Localized tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph node negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive for the tumour).

A *grossly resected* midline tumour without ipsilateral (with: → stage 2A) or contralateral (with: → stage 2B) lymph node involvement is considered stage 1.

Stage 2A | Localized tumour with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumour microscopically.

Stage 2B | Localized tumour with or without complete gross excision, with ipsilateral
nonadherent lymph node positive for tumour. Enlarged contralateral lymph nodes must be negative microscopically.

**Stage 3**
Unresectable unilateral tumour infiltrating across the midline with or without regional lymph node involvement; or localized unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement. The midline is defined as the vertebral column. Tumours originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column. Lymph nodes to the left side of the aorta are left sided nodes, and to the right side of the aorta are right sided nodes (that may however be located in between the IVC and the aorta, hence left to the IVC)

**Stage 4**
Any primary tumour 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 tumour (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.
Modified International Neuroblastoma Response Criteria, INRC
adapted from Brodeur 1993

<table>
<thead>
<tr>
<th>Response</th>
<th>Primary tumor&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Metastatic sites&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No tumor</td>
<td>No tumor; catecholamines normal</td>
</tr>
<tr>
<td>PR</td>
<td>Decreased by &gt;50%</td>
<td>All measurable sites decreased by &gt; 50%. Bones and bone marrow: number of positive bone sites decreased by &gt; 50%; no more than 1 positive bone marrow site allowed.</td>
</tr>
<tr>
<td>SD</td>
<td>No new lesions; &lt; 50% reduction but &lt; 25% increase in any existing lesion.</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>Any new lesion; increase of any measurable lesion by &gt; 25%; previous negative marrow positive for tumor.</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Evaluation of primary and metastatic disease by clinical examination, MIBG scan, CT- or MRI scan and bone marrow examination (see table 8.4-1). Tumour lesions should be measured in 3 dimensions and the largest diameter must be noted. When multiple measurable lesions are present, the largest diameter should be noted.

<sup>b</sup>One positive marrow aspirate or biopsy allowed for PR if this represents a decrease from the number of positive sites at diagnosis.

Thyroid blockage - MIBG scan

**Thyroid blockage - $^{123}$I-MIBG (diagnostic scan)**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Start</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrax (L-thyroxine)</td>
<td>125 $\mu$g/m² ones a day during 3 days</td>
<td>1 day before administration of $^{123}$I-MIBG</td>
</tr>
<tr>
<td>Strumazol (thiamzol)</td>
<td>0.5 mg/kg/day in 2 doses during 3 days</td>
<td>1 day before administration of $^{123}$I-MIBG</td>
</tr>
<tr>
<td>Kaliumjodide (potassium iodide)</td>
<td>3 times a day 0.3 ml 10% (100mg/ml) during 2 days</td>
<td>Start morning of $^{123}$I-MIBG</td>
</tr>
</tbody>
</table>

**Thyroid blockage - $^{131}$I-MIBG (therapy)**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Start</th>
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</thead>
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<tr>
<td>Thyrax (L-thyroxine)</td>
<td>125 $\mu$g/m² ones a day during 4 weeks</td>
<td>1 day before administration of $^{123}$I-MIBG</td>
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<tr>
<td>Strumazol (thiamzol)</td>
<td>0.5 mg/kg/day in 2 doses</td>
<td>1 day before administration of $^{123}$I-MIBG</td>
</tr>
</tbody>
</table>

Final 6-5: 20-02-2012 -confidential- 75 of 100
131I-MIBG-Gem in relapsed/progressive NBL IST

| PotassiumIodide | 3 times a day 0.3 ml 10% (100mg/ml) during 2 days | Start morning of 131I-MIBG | Stop after 2 weeks, if 2nd course of 131I-MIBG will be given, restart the morning of 131I-MIBG |

Prophylaxis for parents/caretakers (only for 131I-MIBG)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Start</th>
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</thead>
<tbody>
<tr>
<td>PotassiumIodide</td>
<td>200 mg (capsule) once a day during 4 days</td>
<td>Day before start of 131I-MIBG</td>
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</table>

Do not give to pregnant women!

25 ASCO Guidelines for use of G-CSF

Therapy of febrile patients with neutropenia:
- G-CSF should not routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia
- G-CSF should be considered in patients with fever and neutropenia who are at high risk for infections associates complications
  - Expected prolonged (> 10 days) and profound neutropenia (<0.1 x 10^-9/L)
  - Hypotension and multi-organ dysfunction (sepsis syndrome)
  - Invasive fungal infection

26 Summary of adverse reactions gemcitabine

Adverse reactions Gemcitabine single agent, doses ranged 800-1250 mg/m^2 weekly in 30 min – 979 patients, various malignancies – resulted in 10% discontinuation therapy

<table>
<thead>
<tr>
<th>WHO Grades (% incidence)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Leukopenia</td>
</tr>
<tr>
<td>Neutropenia</td>
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<tr>
<td>Thrombocytopenia</td>
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### Hepatic

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<th>Parameter</th>
<th>68</th>
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<th>72</th>
<th>10</th>
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<td>6</td>
<td>2</td>
<td>78</td>
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<tr>
<td>AST</td>
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<td>77</td>
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<td>4</td>
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<td>Alkaline Phosphatase</td>
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<td>2</td>
<td>&lt;1</td>
<td>26</td>
<td>6</td>
<td>2</td>
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<tr>
<td>Bilirubin</td>
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### Renal

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<th>&lt;1</th>
<th>0</th>
<th>&lt;1</th>
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</thead>
<tbody>
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<td>Proteinuria</td>
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<td>&lt;1</td>
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<td>23</td>
<td>0</td>
<td>0</td>
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<td>Hematuria</td>
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<td>15</td>
<td>0</td>
<td>0</td>
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<td>BUN</td>
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### Non-laboratory

<table>
<thead>
<tr>
<th>Parameter</th>
<th>69</th>
<th>13</th>
<th>1</th>
<th>71</th>
<th>10</th>
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<tbody>
<tr>
<td>Nausea &amp; Vomiting</td>
<td></td>
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<tr>
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<td>48</td>
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<td>42</td>
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<td>&lt;1</td>
<td>31</td>
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<td>0</td>
<td>30</td>
<td>3</td>
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<td>Hemorrhage</td>
<td>17</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>4</td>
<td>2</td>
<td>&lt;1</td>
<td>&lt;1</td>
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<tr>
<td>Infection</td>
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<td>1</td>
<td>&lt;1</td>
<td>10</td>
<td>2</td>
<td>&lt;1</td>
<td>&lt;1</td>
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<td>Alopecia</td>
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<td>0</td>
<td>16</td>
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<td>Stomatitis</td>
<td>11</td>
<td>&lt;1</td>
<td>0</td>
<td>10</td>
<td>&lt;1</td>
<td>0</td>
<td>&lt;1</td>
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<tr>
<td>Somnolence</td>
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<td>&lt;1</td>
<td>&lt;1</td>
<td>11</td>
<td>2</td>
<td>&lt;1</td>
<td>&lt;1</td>
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<tr>
<td>Paresthesias</td>
<td>10</td>
<td>&lt;1</td>
<td>0</td>
<td>10</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Grade based on criteria from the World Health Organization (WHO).

| Note: these safety data are based on Gemzar IB-text 2006. For information about latest safety data see the SPC of the respective generic gemcitabine. |

---

### Hematologic —

In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity with Gemzar, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was 16 reported in 16% of patients; less than 1% of patients required platelet transfusions.

### Gastrointestinal —

Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

### Hepatic —

In clinical trials, Gemzar was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs.
Renal — In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving Gemzar in clinical trials. Four patients developed HUS on Gemzar therapy, 2 immediately post-therapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemzar therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

Fever — The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash — Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

Pulmonary — In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar. The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

Edema — Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

Flu-like Symptoms — “Flu syndrome” was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection — Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

Alopecia — Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity — There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Extravasation — Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemzar is not a vesicant.

Allergic — Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemzar should not be administered to patients with a known hypersensitivity to this drug.

Cardiovascular — During clinical trials, 2% of patients discontinued therapy with Gemzar due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior history of cardiovascular disease.

27 Requirements for imaging

General considerations:
All tumoral lesions must be documented and all measurable lesions must be measured in 3 dimensions by CT or MRI. The neck, chest and pelvis are preferably examined by MRI. If neuroblastoma is detected in the paravertebral region, the spine should be examined in the same session, to document or to rule out intraforaminal or intraspinal involvement even in patients without neurological signs. MRI is superior to computed tomography for detection of intraspinal or intraforaminal tumour tissue. In children under the age of about 6 years,
general anaesthesia or patient-controlled sedation should be considered for MRI assessment. Computed tomography is a good alternative to MRI, and might even be superior in patients with small, calcified abdominal tumour. Follow-up imaging should be done with the same imaging technique as initially performed to allow better comparison.

**Chest x-ray:**
Chest x-ray (AP or PA and lateral view) can be performed for thoracic tumour localization.

**MRI:**
Contrast enhanced T1-W fat saturated sequences are recommended if the tumour is not well delineated on the non-enhanced sequences. Coils and FOV should be adapted to the size of the child and the localization of the tumour.

**Minimum of MRI sequences required (depending on the site to be explored):**

**Head:**
* Axial T1-weighted (T1-W) sequence  
* Coronal T1-W sequence  
* Sagittal T1-W sequence  
* Axial FLAIR sequence  
  Optional: contrast enhanced T1-W sequences  

**Neck:** From skull base to superior mediastinum
* Sagittal T1-W sequence  
* Axial T1-W SE and T2-W FSE fat saturated sequences  
* Coronal T1-W sequence in the plane of the cervical spine  
* Optional: Contrast enhanced T1-W sequences  

**Chest:**
* Sagittal T1-W sequence  
* Coronal FSE T2-W sequence: all foraminal extensions should be in the same image  
* Optional T1-W SE contrast enhanced fat saturated sequences  

**Abdomen:**
* Axial, coronal and sagittal T1-W SE sequences  
  Coronal T2-W FSE sequence  
* Axial T2-W fat suppression sequence  
* Optional: T1-W contrast enhanced fat suppression sequence(s)  
  In case of tumour extension in the pelvis, coronal planes should be parallel to the plane of the sacrum.

**Computed tomography:**
Paediatric CT protocols with child-adapted scanning parameters must be used to minimize radiation.
The examination must consist of a nonenhanced study to detect small calcifications and a study after injection of iodinated contrast (1.5 – 2 ml/kg body weight with a rate of 1-2 ml/sec, scan delay adapted to examined anatomic site). Coronal and/or sagittal reconstructions must be included.

123I-MIBG diagnostic scanning:
In consultation with paediatrician, thyroid blockage therapy has to be prescribed.
Dosage of 123I-MIBG: 01-11 year: 111 MBq (3 mCi), 12-18 year: 185 MBq (5 mCi)
All registered and commercially available radiopharmaceuticals are allowed. Intravenous administration by slow injection in a peripheral vein or via central venous catheters, followed by flushing with saline.
123I-MIBG scintigraphy will be performed at 24 ± 4 hours after injection. Delayed scintigraphy may be performed up to 48 hours, if indicated.

Gamma camera and computer acquisition set-up:
Energy window: 15-20% window centred at 159 keV
Collimator: MEAP
Whole body: Scan speed 10 cm/min (Matrix 512 x 256)
Standard activity: 2-3 MBq 123I-MIBG
SPECT: 60 views of 40 sec/view (Matrix 128 x 128)

Anterior and posterior whole body imaging followed by SPECT should be performed.
If available SPECT combined with CT is recommended. A standard will be scanned along with the patient. This standard will be used for assessment of tumour response by the central review committee.
Note: the head should be imaged in straight anterior/posterior direction.
Shipping of imaging material

For $^{123}$I-MIBG scans: SPECT and planar films should be digitally stored (encoded). MRI scans: coupes should be digitally stored (encoded). See for instructions: Procedure Manual

A CD with the patient identification number only and date of investigations together with clinical history and results of urinary catecholamines should be send to:

Review Committee MIBG-Gem trial
N.K.A. van Eijkelenburg, MD
AMC / Emma Children’s Hospital, room F8-207
Meibergdreef 9
1105 AZ Amsterdam
PATIENTS:

- Any patient likely to be treated with a pyrimidine nucleoside analogue.
- Regardless of age, sex, general condition.
- Regardless of protocol, co-medications, dosage.
- No acute inflammatory syndrome.

SAMPLING & SAMPLE TREATMENT:

- Sampling must be performed BEFORE the treatment starts. If a previous treatment has been given that included a nucleoside analogue (e.g., gemcitabine), a wash-out period of min. 10-15 days must be considered prior to sampling.
- Dry tube (red cap), 1-3 ml of blood.
- Blood Sample must be until processed:
  * Option 1: Centrifugation (4°C, 20min, 1 300 g) and isolation of the upper serum phase. Cell pellet and serum are kept at -80°C until they are sent to the lab.
  * Option 2: the whole blood sample is sent immediately and kept at 4°C.

SENDING THE SAMPLE:

Samples are sent in dry ice (frozen serum + cell pellet) or refrigerated (whole blood sample) to:

Laboratoire de Transfert Pr L.H. Ouafik  
c/o Dr J. Ciccolini « CDA »  
Faculté Médecine Nord  
Bd. Pierre Dramard – 13015 Marseille  
France  
Tel +33 (0)4.91.69.88.82

Please advice by mail prior to shipping:  
Joseph CICCOLINI: joseph.ciccolini@univmed.fr  
Arnauld VERSCHUUR: arnauld.verschuur@mail.ap-hm.fr
30 Local rules for safety monitoring during $^{131}\text{I}$-MIBG therapy

Precautions for treating children with targeted radiotherapy with $^{131}\text{I}$-MIBG

Local rules AMC Amsterdam the Netherlands

Indications:
The decision for starting MIBG therapy is made by the pediatric oncologist after consultation of the nuclear medicine physician. They discuss the medical condition of the child and decide if the child is eligible for isolation.

Transfer:
The patient will be transferred to the nuclear medicine ward on the day before MIBG will be infused. There will be an oral handover to the medical team on the nuclear medicine ward as well as an written one which is printed in the medical chart. Both patient and parents will be guided on the ward the day before therapy starts. They will receive specific instructions with regard to radiation safety precautions. Before treatment is started it will be discussed which part of the care parents will give. They will watch the child like they do at home, via a video system. Parents will be coached by the nuclear medicine personnel who will answer their questions. The nursing staff can rely on the pediatric oncologist and/or the pediatric registrar on call.

For children with limited physical condition:
Clinical observation of vital parameters every 3 hours by nursing staff (nuclear medicine) and by a nurse who is qualified in nursing children.

For children > 1 year of age and in good clinical condition:
No extra medical care than observation by parents is indicated.

Handovers:
During admission on the nuclear medicine ward the patient will be handed over every morning and evening to the pediatric registrar on call. These patients will be seen as special care patients who may need extra attention from the registrar on call. The pediatric oncologist will hand the patient over to the pediatric oncologist on call.

Nursing staff:
Since this treatment is not given regularly, nursing staff will get regularly teaching. They are taught by pediatric oncologist and nuclear medicine physician. Nursing staff will inform each other regularly how to use the monitor for vital parameters. The nursing staff is responsible for their regulations.

Medication:
Thyroid blockage → see above schedule
Anti-emetics: Ondansetron if necessary
Sedative medication: only after consultation with the responsible pediatric oncologist in limited cases.

**Central venous line:**
At least 24 hours before injection of MIBG a (central) venous line should be inserted. Besides the $^{131}$I-MIBG the selection of all other infusion fluids are the responsibility of the pediatric oncologist.

**Nasogastric tube:**
Babies and patients who can not eat themselves should have a nasogastric tube before they are transferred to the nuclear medicine ward. Feeding program is made by the pediatric oncologist.
The schedule for $^{131}$I-MIBG therapy is based on a total absorbed whole body dose of 4 Gy. The first dose is based on patient’s weight: 444 MBq/kg (12 mCi/kg). The second dose will be based on the total absorbed whole body dose calculated from whole body retention measurements after administration of the first therapeutic dose.

Whole body dosimetry. The activity administered is corrected for any residue in the vials or tubing system. This netto activity serves as the 100% whole body retention measurement performed immediately after the completion of infusion and before the first voiding of the bladder.

Measuring configuration:
Whole body measurements are performed by a fixed measuring configuration with a minimal distance between the measuring equipment and the child of at least 2 meters. It is advisable to use markers for the positioning of the bed (child) and measuring equipment. When measuring it is important that all redundant sources (radioactive diapers or waste) have been removed.
Except for the measurement at T=0, the child should void the bladder or diapers should be changed before each measurement.

Scheme of measurements:

- **Day 1**  
  $T = 0\text{h}$: At the end of infusion. At least 3 measurements after voiding.
- **Day 2**  
  3 times per day after voiding
- **Day 3**  
  In the morning and the end of the afternoon after voiding
- **Day 4**  
  In the morning and the end of the afternoon or at discharge

Calculation: To calculate the whole body dose, a dedicated Excel based programme will be used with the protocol. In this programme, the exact administered dose, the date/time of measurements and the results of exposure measurements have to be filled out.

Dosimetry (background)
The mean dose of a target organ is depended on the total administered dose and biodistribution.

To simplify dosimetric calculations, organ parameter $S$ is introduced. In Olinda $S$-values are tabulated for many nuclides in combination with many source and target organs. In this particular model, the total body or remainder body is the only source and target organ. Therefore, the whole body dose can be written as.
\[
\frac{\overline{D}}{A_0} = \tau_{wb} \cdot S_{wb}
\]  
(1)

With:

- \( S_{wb} \): dose per unit cumulative activity in the source organ [Gy·MBq\(^{-1}\)·h\(^{-1}\)]
- \( \overline{D} \): mean absorbed dose [Gy]
- \( A_0 \): administered activity [MBq]
- \( \tau \): residence time [h]

The residence time is the ratio between the accumulated number of desintegrations, \( \tilde{A}_{wb} \), and the administered activity, \( A_0 \):

\[
\tau_{wb} = \frac{\tilde{A}_{wb}}{A_0}
\]  
(2)

The software package Olinda/EXM is used to calculate the WB-EDE from equation (1).

**Calculations**

To determine the residence time \( \tau \), the integral \( \tilde{A}_{wb} \) has to be calculated. Since Equation 4 is valid, \( \tilde{A}_{wb} \) can be calculated by taking the area under time activity curve (TAC).

But since the patient will be measured until discharge, an assumption has to be made about the TAC after discharge (\( t_{dc} \)).

\[
\tilde{A}_{wb} = \int_0^\infty A \, dt = AUC_1 + AUC_2
\]  
(3)

where

\[
AUC_1 = \sum_{i=1}^{n} A
\]  
(4)

\[
AUC_2 = \frac{1}{m} \cdot b \cdot e^{-m \cdot t_w}
\]  
(5)

where \( m \) and \( b \) are parameters obtained fitting an exponential function through the measured time points.

Olinda/EXM has implemented several models for paediatric patients to determine \( S_{wb} \). These models vary between 0, 1, 5, 10 and 15 year old children. For adults, an age of 20 years is used. In our case, interpolation is required, since the typical patient age will be around 2.5 years. This results in the following interpolation.
Using the correct age-dependent Sₚᵦ-rate factor, Eq. 1 can be solved. This gives the effective dose equivalent in mSv/MBq. After multiplying with the administered activity, the effective dose $D$ is calculated and expressed in Gy.
Table 1: Responses of $^{131}$I-MIBG single agent in children with chemoresistant neuroblastoma

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Doses of MIBG</th>
<th>Toxicity</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matthay 2007 (16)</td>
<td>164</td>
<td>18 mCi/kg</td>
<td>33% ASCT</td>
<td>36%</td>
</tr>
<tr>
<td>Howard 2005 (15)</td>
<td>28</td>
<td>3-19 mCi/kg/infusion 2-4 infusions</td>
<td>78% - 82% thrombocytopenia 50% G 4 neutropenia</td>
<td>39%</td>
</tr>
<tr>
<td>Kang 2003 (59)</td>
<td>20 palliative 9.5 mCi/kg 32 courses</td>
<td>no</td>
<td>31% (4/13 PR) 13 pat evaluable for response</td>
<td></td>
</tr>
<tr>
<td>Yanik 2002 (13)</td>
<td>5</td>
<td>12 mCi/kg In combination with CT</td>
<td>Gr 2-3 oral mucositis</td>
<td>3 CR 2 PR</td>
</tr>
<tr>
<td>El Tannir 2000</td>
<td>30</td>
<td>3700 MBq 1-4 courses</td>
<td>Myelosuppression 70%</td>
<td></td>
</tr>
<tr>
<td>Garaventa 1999 (11)</td>
<td>43 Stage III and IV</td>
<td>2,5-5,5 GBq/course 1-5 courses</td>
<td>Thrombocytopenia severe interstitial pneumonia (1) acute myeloid leukaemia (2) reduced thyroid reserve (21)</td>
<td>1 CR 12 PR = 30%</td>
</tr>
<tr>
<td>Matthay 1998 (18)</td>
<td>30</td>
<td>12 mCi/kg 15 mCi/kg = MTD</td>
<td>Protracted gr 4 hematotox (80%) Secondary leukemia (1) Hypothyroid (3) 37%</td>
<td>36% (1 CR, 10 PR) 3 MR 10 SD</td>
</tr>
<tr>
<td>Shapiro 1995 (60)</td>
<td>53</td>
<td>MIBG + CT + TBI</td>
<td></td>
<td>67% (7 CR, 29 PR)</td>
</tr>
<tr>
<td>Gaze 1995 (61)</td>
<td>5</td>
<td>MIBG + CT + TBI</td>
<td>feasible</td>
<td></td>
</tr>
<tr>
<td>Lashford 1992 (62)</td>
<td>25</td>
<td>75 MBq 1 Gy</td>
<td></td>
<td>33%</td>
</tr>
<tr>
<td>Klingebiel 1991 (7)</td>
<td>47 Stage III and IV</td>
<td>8.9+6.7 mCi/kg/course 112 courses</td>
<td>Thrombocytopenia 5/23</td>
<td>19% (CR + VGPR)</td>
</tr>
<tr>
<td>Matthay 1991 (63)</td>
<td>11</td>
<td>100-400 mCi/m²/course Total 23 courses</td>
<td>Thrombocytopenia 5/23</td>
<td>18% (PR) 2/11 SD</td>
</tr>
<tr>
<td>Hoefnagel 1991 (10)</td>
<td>53</td>
<td></td>
<td></td>
<td>57% (7 CR, 23 PR) Impressive palliative effect</td>
</tr>
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### 131I-MIBG-Gem in relapsed/progressive NBL IST

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Activity</th>
<th>Dose</th>
<th>Courses</th>
<th>Side Effects</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Lumbroso 1991 (64)</td>
<td>III and IV</td>
<td>26</td>
<td>30-108 mCi</td>
<td>1-5 courses</td>
<td>12 hematotox (7 &lt; 50)</td>
<td>5/10 pain palliations, 10/24 SD, no OR</td>
</tr>
<tr>
<td>Hutchinson 1991 (65)</td>
<td>III and IV</td>
<td>14</td>
<td>1.85-8.14 Gbq</td>
<td>1-3 courses</td>
<td>4 OR, 5 subjective responses</td>
<td></td>
</tr>
<tr>
<td>Hoefnagel 1987 (66)</td>
<td></td>
<td>21</td>
<td>64 courses</td>
<td></td>
<td>Good effect on palliation</td>
<td></td>
</tr>
<tr>
<td>Hartmann O 1987 (67)</td>
<td></td>
<td>9</td>
<td>1.3-4 Gbq</td>
<td>35-108 mCi</td>
<td>2 objective effects, 3 subjective effects</td>
<td></td>
</tr>
<tr>
<td>Treuner 1986 (68)</td>
<td></td>
<td>6</td>
<td></td>
<td>19 courses</td>
<td>4/6 subjective responses</td>
<td></td>
</tr>
<tr>
<td>Berthold 1988 (14)</td>
<td>III and IV</td>
<td>32</td>
<td>35-300 mCi per course</td>
<td>84 courses (2.6 per patient)</td>
<td>Transient thrombocytopenia</td>
<td>Overall RR 50% (5 CR + VGPR, 11 PR, 6 SD)</td>
</tr>
<tr>
<td>Tytgat</td>
<td>IV</td>
<td>22</td>
<td>100-150 mCi MIBG in combination with vitamin C and hyperbaric oxygen</td>
<td></td>
<td>No AE’s Max tolerated dose of vit C at 250 mg/kg/day (intake problems)</td>
<td>12/22 evaluated: RR 32% (1 VGPR, 6 PR) 5 SD, 9 PD, 1 L-FU</td>
</tr>
</tbody>
</table>
Table 2: Phase I and II trials of concurrent gemcitabine and radiation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Phase</th>
<th>Type of malignancy</th>
<th>N pts</th>
<th>Treatment schedule</th>
<th>Toxicities</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackstock</td>
<td>I</td>
<td>Pancreas (adenoca)</td>
<td>19</td>
<td>Gemc 20-60 mg/m²</td>
<td>Nausea, vomiting, Neutropenia</td>
<td>MTD 40 mg/m²</td>
</tr>
<tr>
<td>(69)</td>
<td></td>
<td></td>
<td></td>
<td>for 30 min, 2x/wk,</td>
<td>Thrombocytopenia</td>
<td>DLT 60 mg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.5 weeks, 2h</td>
<td></td>
<td>3 PR, 12 SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>before RT, 50.4 Gy</td>
<td></td>
<td>follow-up 12 mths</td>
</tr>
<tr>
<td>Pipas et al</td>
<td>I</td>
<td>Pancreas (adenoca)</td>
<td>21</td>
<td>Gemc 10-60 mg/m²</td>
<td>G3 fatigue, G3 nausea/vom, G3-4</td>
<td>MTD 50 mg/m²</td>
</tr>
<tr>
<td>(38)</td>
<td></td>
<td></td>
<td></td>
<td>for 30 min, 2x/wk,</td>
<td>hematotox, Gastrointestinal bleeding</td>
<td>6 CR</td>
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<td>5.5 weeks, 30 min -</td>
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<td>2h before RT, 50.4</td>
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<td>Ikeda et al</td>
<td>I</td>
<td>Pancreas (locally</td>
<td>15</td>
<td>30 min infusion,</td>
<td>Neutropenia, Leucopenia</td>
<td>MTD 250 mg/m²</td>
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<tr>
<td>(39)</td>
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<td>advanced adenoca)</td>
<td></td>
<td>150-350 mg/m²,</td>
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<td>DLT 350 mg/m²</td>
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<td>before RT, 1x/wk,</td>
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<td>6 weeks</td>
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<td>Wolff et al</td>
<td>I</td>
<td>Pancreas (Locally</td>
<td>18</td>
<td>Gemc 350-500 mg/m²</td>
<td>G3-4 hematotox, Fatigue, Anorexia,</td>
<td>MTD 350 mg/m²</td>
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<td>(40)</td>
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<td>advanced adenoca)</td>
<td></td>
<td>1x/wk, 7 weeks,</td>
<td>Nausea/vomiting, dehydration</td>
<td>1 pt died</td>
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<td>RT 3000 cGy</td>
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<td></td>
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<td>median survival 6 months</td>
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<tr>
<td>Mc Ginn et al</td>
<td>I</td>
<td>Pancreas (unresectable or incompletely resected)</td>
<td>37</td>
<td>Gemc 1000 mg/m²</td>
<td>Hematological Vomiting, Gastric/duodenal Ulceration</td>
<td>MTD 36 Gy</td>
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<td>(70)</td>
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<td>d1, 8, 15. RT starts at d1, after gemc</td>
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<td>DLT 42 Gy</td>
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<td></td>
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<td>Median survival 11.6 months</td>
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<tr>
<td>De Lange et al</td>
<td>I</td>
<td>Pancreas (locally advanced pancreatic ca)</td>
<td>24</td>
<td>300 mg/m², concurrent RT, d1, 8,15</td>
<td>Nausea vomiting, Diarrhea, Ulceration</td>
<td>1 CR</td>
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<tr>
<td>(71)</td>
<td></td>
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<td>12 SD</td>
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<td>5 PD</td>
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<td>Neutropenia</td>
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<td>Study</td>
<td>Treatment</td>
<td>Tumor Type</td>
<td>Dose Range</td>
<td>Dosage Details</td>
<td>Side Effects</td>
<td>Additional Information</td>
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<tr>
<td>Crane et al (36)</td>
<td>I Pancreas (locally advanced)</td>
<td>51</td>
<td>250-500 mg/m², 24-48 hr before RT, 7 wks</td>
<td>Nausea, Vomiting, Abdominal pain</td>
<td>Median survival 11 months</td>
<td></td>
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<tr>
<td>Poggi et al (72)</td>
<td>I Pancreas (unresectable adenocarcinoma)</td>
<td>19</td>
<td>350-550 mg/m²/wk x5, 90 min before RT</td>
<td>Nausea, Vomiting, Neutropenia, Thrombocytopenia, G3 thrombosis, G3 infection, G3 nausea, G3 vomiting, G3 hypotension, G3 constipation, G3 fatigue</td>
<td>MTD 440 mg/m², Median survival 40.3 wks</td>
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<tr>
<td>Cesario et al (41)</td>
<td>I NSCLC (unresectable or advanced)</td>
<td>36</td>
<td>30 min infusion, 1x/wk, 100-350 mg/m² x5, 4h before RT</td>
<td>Esophageal, Lung, Haematological, Skin</td>
<td>MTD 350 mg/m², 3.7% CR, 59.2% PR, 33.4% SD, 3.7% PD</td>
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<tr>
<td>Van Putten et al (42)</td>
<td>I NSCLC (stage III)</td>
<td>27</td>
<td>300 mg/m² – 450 mg/m² – 600 mg/m² d1, 8, 15, 22, 29, 36 2h before RT</td>
<td>G3 oesophagitis, G3 pneumonitis</td>
<td>MTD 300 mg/m², 4 CR, 13 PR, 9 SD, 1 PD, RR 63%, Median survival 61 weeks</td>
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<tr>
<td>Trodella et al (73)</td>
<td>I NSCLC (unresectable)</td>
<td>36</td>
<td>Weekly 100-350 mg/m², concurrent with RT</td>
<td>Esophagitis, Pulmonary actinic interstitial disease</td>
<td>DLT 375 mg/m², 4 CR, 18 PR, 9 SD, 2 PD</td>
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<tr>
<td>Gagel (74)</td>
<td>I/II NSCLC (locally advanced, unresectable)</td>
<td>33</td>
<td>Gemc 1200 mg/m², vinorelbine 30 mg/m² d1,8,22,29 followed by RT 66 Gy and gemc every 2 weeks 300-500 mg/m²</td>
<td>G2 oesophagitis, Persistent dysphagia, Overall RR 64%, median OS 19.9 months, median DFS 8.7 months</td>
<td>MTD gemc 500 mg/m² every two weeks in 3 cycles, max 7 weeks RT</td>
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<tr>
<td>Eisbruch et al (43)</td>
<td>I Head and neck (unresectable)</td>
<td>29</td>
<td>30 min infusion (10-300 mg/m²/week) concurrent RT,</td>
<td>Mucositis, Dysphagia</td>
<td>66%-87% CR, DLT 50-300 mg/m²</td>
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<tr>
<td>Author</td>
<td>Year</td>
<td>Stage</td>
<td>Treatment Details</td>
<td>Toxicities</td>
<td>Results</td>
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<tr>
<td>Cengiz et al</td>
<td>2012</td>
<td>II</td>
<td>Pancreas (Locally advanced)</td>
<td>gemc 4 hr before RT, 400 mg/m²/wk; RT 50.4 Gy, 50.5 weeks</td>
<td>Abdominal discomfort, Nausea, G3 vomiting (14%), Toxicities → incomplete delivery of treatment</td>
<td>CR 9%, PR 41%, SD 32%, progressive 18%. Median survival 8.7 months</td>
</tr>
<tr>
<td>Van Laethem et al</td>
<td>2012</td>
<td>II</td>
<td>Pancreas (stage II and III, Post-operative)</td>
<td>Gemc 1000 mg/m² d1,8, 3 weeks 300 mg/m², 4h before RT</td>
<td>G3-4 hematological, G3-4 nausea, G3-4 vomiting</td>
<td>Median survival 15 months</td>
</tr>
<tr>
<td>Blackstock et al</td>
<td>2012</td>
<td>II</td>
<td>Pancreas (resected adenocarcinoma)</td>
<td>Gemc 40 mg/m², 2x week for 5.5 weeks, RT 50.4 Gy in 5.5 weeks. After CRT: gemc 1000 mg/m²/wk for 2 cycles</td>
<td>infrequent G3-4 haematological or gastrointestinal</td>
<td>Median survival 18.3 months, 42% alive after 3 yrs</td>
</tr>
<tr>
<td>Small et al</td>
<td>2012</td>
<td>II</td>
<td>Pancreas (nonmetastatic)</td>
<td>Gemc 1000 mg/m² D1,8 (cycle 1), D1,8,15 (cycle 2), D1,8 (cycle 3) with concurrent RT during cycle 2, 3 weeks Surgery 4-6 weeks after treatment</td>
<td>G3 neutropenia, G3 nausea, G3 vomiting</td>
<td>RR 5.1 %, Disease control rate 84.6 %, Reduction of CA19-9 levels 1y- Survival rate: 73% for all, 94% resectable, 76% borderline resectable, 47% unresectable patients</td>
</tr>
<tr>
<td>Epelbaum et al</td>
<td>2012</td>
<td>II</td>
<td>Pancreas (localized unresectable)</td>
<td>Gemc 1000 mg/m²/wk x7 (induction phase), 400 mg/m²/wk d1,8,15 x 2 concurrent with RT 50.4 Gy (5.5 weeks)</td>
<td>Neutropenia, Thrombocytopenia, Thrombosis, Infection, Nausea, Vomiting, Hypotension</td>
<td>4 PR, Pancreatectomy, 2 pt negative surgical margins, 1 fibrosis</td>
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<tr>
<td>Study</td>
<td>Phase</td>
<td>Tumor Type</td>
<td>Patients</td>
<td>Treatment Description</td>
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<tr>
<td>Li et al (47)</td>
<td>II</td>
<td>Pancreas</td>
<td>18</td>
<td>30 min infusion 2x/wk 600 mg/m², 60 min before RT</td>
<td>Diarrhea, Fatigue</td>
<td>RR 50% for gemc CCRT (4 CR; 5 PR) vs RR 13% (2 PR) for 5-FU CCRT</td>
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<tr>
<td>Belderbos (79)</td>
<td>II</td>
<td>NSCLC</td>
<td>158</td>
<td>Gemc (1250 mg/m² d1,8) + cispl (75 mg/m² d2) vs cispl daily (6 mg/m²) in combination with RT 66 Gy (6wks)</td>
<td>Neutropenia, G3-4 haematoma (S arm 30% vs 6% C arm), G3-4 oesoph (C arm 5% vs 14% S arm), Gr3 late oesoph 4% (S and C), G3-4 pneumon 14% (S), 18% (C).</td>
<td>Median survival, overall survival, progression, free survival: no significant differences</td>
</tr>
<tr>
<td>Hirsh (80)</td>
<td>II</td>
<td>NSCLC</td>
<td>45</td>
<td>Gemc 1000 mg/m2 d1,8 + carboplatin AUC 5 d1, RT d50 60 Gy + paclitaxel 50 mg/m2 + gemc 100 mg/m2 d1,8</td>
<td>Neutropenia (9), G3-4 oesoph (4), G3 anemia (3), G3 oesaphagitis (3), G4 pneumonitis (1), G5 oesaphagitis (1 → died)</td>
<td>After chemo-RT: CR 22%, PR 73%, progression 5% Median survival 25 months, 1yr survival rate 73.2%, 2yr survival rate 50.5%</td>
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<tr>
<td>Kosmidis (81)</td>
<td>II</td>
<td>NSCLC</td>
<td>43</td>
<td>Gemc 1000 mg/m² d1,8 + paclitaxel 200 mg/m² in 3h d1, 2 cycles; RT 63 Gy, 7 weeks + paclitaxel 60 mg/m²/wk</td>
<td>Neutropenia 12%, Neurotoxicity, Oesophagitis (6%)</td>
<td>15 pat responded: CR 2%, PR 33%, SD 46.5%. Median follow-up 44 months, median survival 20.8 months, time-to-progression 8.4 months</td>
</tr>
<tr>
<td>Aguilar-Ponce et al</td>
<td>II</td>
<td>Head and neck</td>
<td>27</td>
<td>50 or 100 mg/m²/wk, 1-2 hr</td>
<td>G3/4 mucositis, Nausea/vomiting</td>
<td>61% CR, 27% PR</td>
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131I-MIBG-Gem in relapsed/progressive NBL IST

<table>
<thead>
<tr>
<th>Specenier (82) II</th>
<th>Head and neck (locally advanced squamous cell ca)</th>
<th>26</th>
<th>Gemc 100 mg/m²/wk, 2h prior to RT, fractionated</th>
<th>Severe non-hematolog tox</th>
<th>RR 88%</th>
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<th>Weller et al (83) II</th>
<th>Glioblastoma (newly diagnosed)</th>
<th>21</th>
<th>Gemc 1000 mg/m² d1,8,15; 4 monthly cycle, RT after 4 cycles</th>
<th>Myelotoxicity</th>
<th>Median survival 11 months</th>
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<th>Pattaranutaporn et al (45) II</th>
<th>Cervical (stage IIIB)</th>
<th>19</th>
<th>300 mg/m²/wk gemc concurrent RT</th>
<th>Diarrhea</th>
<th>17 CR</th>
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</thead>
</table>

derived and modified from Pauwels et al (32)

RT = radiotherapy; gemc = gemcitabine; NSCLC = non-small lung cancer; cispl = cisplatin

34 Reference list

REFERENCES


