PROTOCOL ITCC -013- TOTEM2

PHASE 2 SINGLE-ARM STUDIES OF TEMOZOLOMIDE IN COMBINATION WITH TOPOTECAN IN REFRACTORY AND RELAPSED NEUROBLASTOMA AND OTHER PAEDIATRIC SOLID TUMOURS

Protocol Version 4.0 19 March 2012

EudraCT No: 2008-001436-12

N° CSET: 2008/1378

Confidentiality Statement

Information and data included in this protocol contain trade secrets and privileged or confidential information which is the property of the sponsor. No person is authorized to make it public without written permission of the sponsor. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential. This material may be disclosed to and used by your staff and associates as may be necessary to conduct the clinical study.
Clinical phase II studies of Temozolomide - Topotecan

STUDY PROTOCOL AGREEMENT FORM

I, _____________________, Investigator, have examined this


entitled:

“PHASE 2 SINGLE-ARM STUDIES OF TEMOZOLOMIDE IN COMBINATION WITH
TOPOTECAN IN REFRACTORY AND RELAPSED NEUROBLASTOMA
AND OTHER PAEDIATRIC SOLID TUMOURS”

and I have fully discussed the objectives of this trial and the contents of this protocol with the
Sponsor’s representative(s).

I agree to conduct the study according to this protocol and to comply with its requirements,
subject to ethical and safety considerations.

I understand that, should the decision be made by the Sponsor to terminate prematurely or
suspend the study, such decision will be communicated to me in writing. Conversely, should I
decide to withdraw from execution of the study I will communicate immediately such decision in
writing to the Sponsor.

INVESTIGATOR
Name:
Date:
Signature:
# SYNOPSIS

<table>
<thead>
<tr>
<th>EudraCT Number</th>
<th>2008-001436-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Study</td>
<td>ITCC-013-TOTEM2</td>
</tr>
<tr>
<td>Title</td>
<td>Phase 2 single-arm studies of Temozolomide in combination with Topotecan in refractory or relapsing neuroblastoma and other paediatric solid tumours</td>
</tr>
</tbody>
</table>
| Study cohorts | 5 study cohorts:  
- Neuroblastoma  
- Brain tumours  
- Medulloblastoma  
- PNET  
- Miscellaneous other solid tumours |
| Sponsor       | Institut Gustave Roussy, Villejuif |
| Principal Investigators | Neuroblastoma: Dr H. Rubie - Toulouse  
Brain tumours: Riccardo Riccardi - Roma  
Miscellaneous other solid tumours: Huib Caron-Amsterdam |
| Study centers | 23 centres in Austria, France, Italy, The Netherlands, Spain. |
| Objectives    | Primary:  
To assess the response rate of Temozolomide in combination with Topotecan in patients with relapsed or refractory neuroblastoma and in patients with medulloblastoma or PNET, and to describe response in patients with relapsed or refractory miscellaneous brain tumours and in patients with relapsed or refractory other solid tumours  
Secondary:  
- To determine duration of response, time to progressive disease, time to treatment failure and overall survival  
- To assess adverse events and toxicity profile of the combination  
- To evaluate MGMT expression on archived tumour material and correlate with response. |
| Study Design  | Prospective, non randomized, phase II trial |
| Number of patients | Up to 134 evaluable patients will be enrolled  
- Neuroblastoma cohort: Up to 36 evaluable patients  
- Brain tumours: 30 evaluable patients  
- Medulloblastoma : 19 evaluable patients  
- PNET : up to 19 patients  
- Miscellaneous other solid tumours: 30 evaluable patients.  
To be sure to have 134 evaluable patients, 2 additional patients will be included in each cohort. |
| Diagnosis and criteria for inclusion | Inclusion criteria:  
- Histologically or cytologically confirmed neuroblastoma, brain tumours, or other solid tumours (at diagnosis, no additional biopsy needs to be performed for the purpose of the study)  
- Relapsed or refractory tumours in which correct standard treatment approaches have failed or tumours with no known conventional therapy  
- No more than 2 lines of prior chemotherapy (monoclonal antibody therapies, e.g. IGF1R, are not considered as lines of treatment)  
- Measurable primary and/or metastatic disease on CT/MRI: at least one bi-dimensionally measurable lesion  
For patients with neuroblastoma, measurable disease on CT/MRI with at least one bi-dimensionally measurable lesion or at least 4 spots on...
- **MBG**
- Age at inclusion: 6 months to ≤ 20 years
- Lansky play score ≥ 70% or ECOG performance status ≤ 1
- Life expectancy ≥ 3 months
- Adequate organ function:
  - Adequate haematological function: haemoglobin ≥ 80 g/L, neutrophil count ≥ 1.0 x 10^9/L, platelet count ≥ 100 x 10^9/L; in case of bone marrow disease: neutrophils ≥ 0.5 x 10^9/L and platelets ≥ 75 x 10^9/L;
  - Adequate renal function: normal creatinine related to patient’s age:
    - 0 – 1 year: ≤ 40 µmol/L
    - 1 – 15 years: ≤ 65 µmol/L
    - 15 – 20 years: ≤ 110 µmol/L
  - Adequate hepatic function: bilirubin ≤ 1.5 x ULN; AST and ALT ≤ 2.5 x ULN (AST, ALT ≤ 5 x ULN in case of liver metastases)
- Wash out of 4 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas, 2 weeks in case of vincristine or retinoic acid alone; 6 weeks in case of prior radiotherapy (except palliative radiotherapy on non measurable lesions). Patients must have recovered from the acute toxic effects of all prior therapy before enrolment into the study
- Patients previously treated with only one of the 2 drugs or none are eligible
- Able to comply with scheduled follow-up and with management of toxicity
- All patients with reproductive potential must practice an effective method of birth control while on study. Female patients aged > 12 years must have a negative pregnancy test within 7 days before study treatment
- Written informed consent from patient, parents or legal guardian.

**Exclusion criteria:**
- Concurrent administration of any other anti-tumour therapy
- Serious concomitant systemic disorder (for example, active infection including HIV or cardiac disease) that in the opinion of the investigator, would compromise the patient’s ability to complete the study
- History of allergic reaction to the compounds or their solvents
- History of allergic reaction to Dacarbazine (DITC)
- Galactosemia, Glucose-galactose malabsorption or lactase deficiency
- Pregnant or breast feeding young women
- Presence of symptomatic brain metastases in patients with solid non-CNS tumours.

<table>
<thead>
<tr>
<th>Treatment, dose and mode of administration</th>
<th>Temozolomide will be administered per os at 150 mg/m^2, followed 1 hour later by Topotecan at 0.75 mg/m^2 as an intravenous infusion over 30 min, during 5 consecutive days. 1 cycle is defined as a 28-day period. Dose reductions and/or administration delays will be performed in case of severe haematological or organ toxicities. Routine use of Granulocyte Colony Stimulating factor (G-CSF) is not permitted during this study except for patient who presents a severe infection while neutropenic. Pneumocystis Carinii Pneumonia prophylaxis is recommended, as well as premedication with anti-emetics (Setrons) during the 5 days of chemotherapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of treatment</td>
<td>Maximum planned treatment duration will be 12 cycles, i.e. 12 months of treatment.</td>
</tr>
<tr>
<td>Criteria for evaluation</td>
<td>Efficacy: The main efficacy criterion is tumour response after 2 cycles = 8 weeks of therapy.</td>
</tr>
</tbody>
</table>
The same radiological method should be used for evaluation at study entry and for response evaluations.
- Neuroblastoma: CT scan, MRI, MIBG scan. Recommended: bone marrow aspirations and biopsies.
- Brain tumours: MRI
Optional: Functional MRI, Thallium scintigraphy, and Methionine PET scan
- Other solid tumours: CT, MRI
Optional: Scintigraphy, glucose PET-scan, Bone Marrow aspirates and biopsies.

The primary endpoint for efficacy is the percentage of patients achieving complete or partial response, after having received 2 cycles of Temozolomide - Topotecan (8 weeks). Any CR and PR should be confirmed 4-6 weeks later with the same radiological method.

For neuroblastoma cohort, tumour response will be assessed using the revised International Neuroblastoma Response Criteria completed with MIBG scoring. For other tumours, tumour response will be assessed according to WHO criteria. Efficacy will be assessed separately in the 5 cohorts.

An external response review committee will review all the observations to validate responses and failures. Continuing response/stable disease should be confirmed every 2 cycles (2 months) until tumour progression or study discontinuation. Further follow up will be performed every 3-4 months.

The secondary efficacy variables are the duration of response, the time to treatment failure, the time to progressive disease and the overall survival. Tumour response (complete or partial) that occurred after the evaluation of 2 cycles will be considered for the final analysis.

Safety:
Safety profile will be evaluated. Clinical and laboratory toxicities/symptomatology will be graded according to NCI-Common toxicity criteria AE v3.0. The adverse events which are not reported in the NCI-Common toxicity criteria will be graded as mild, moderate, severe, life-threatening.

Statistical considerations
- Neuroblastoma cohort: Two-stage Simon minimax design (p0 = 20%, p1 = 40%, α = 10%, β = 10%), 19 patients will be included in the first stage, and if at least 4 responses are confirmed, 17 additional patients will be included in the second stage. Total up to 36 evaluable patients. Conclusion of efficacy will be made if > 10 responses/36 patients are observed.
- Medulloblastoma cohort: Fleming one stage design (p0 = 20%, p1 = 50%, α = 10%, β = 10%), 19 evaluable patients will be included. If at least 7 responses are observed, it will be concluded that the combination is interesting.
- PNET cohort: no sample size calculation was performed due to the rarity of the disease. If among 10 evaluable enrolled patients 5 responses are observed, we will conclude that the response rate is greater than p0 = 20% with p-value = 0.033.
- Miscellaneous other solid tumours and brain tumours cohorts: There is no hypothesis testing. The anti-tumour activity will be assessed by describing the responses seen in each tumour type. Thirty patients will be enrolled in each cohort.

Post study Follow-up
Every 3-4 months up to death or study cut-off.

Study timetable
Planned recruitment period: 45 months
Treatment duration per patient: 12 months
Follow up period: 12 months
Planned study duration: 57 months.
## SCHEDULE OF ASSESSMENTS AND TREATMENTS

<table>
<thead>
<tr>
<th>Cycle/Visit</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5-6</th>
<th>7-8</th>
<th>9-10</th>
<th>11-12</th>
<th>30D</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Day in a Cycle</td>
<td>1-5</td>
<td>8-28</td>
<td>1-5</td>
<td>8-28</td>
<td>1-5</td>
<td>8-28</td>
<td>1-5</td>
<td>8-28</td>
<td>1-5</td>
<td>8-28</td>
</tr>
</tbody>
</table>

### Procedure
- **BL**: Baseline
- **FU**: Long-term follow-up

<table>
<thead>
<tr>
<th>Procedure</th>
<th>BL 1 2 3 4 5-6 7-8 9-10 11-12 30D FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent (before any study procedure)</td>
<td>X</td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination</td>
<td>X X X X X X X X X</td>
</tr>
<tr>
<td>Height, Weight, Body Surface Area</td>
<td>X X X X X X X X</td>
</tr>
<tr>
<td>Performance status</td>
<td>X X X X X X X X</td>
</tr>
<tr>
<td>Pregnancy test (if indicated) a</td>
<td>X</td>
</tr>
</tbody>
</table>

### Tumour evaluation
- **30 D**: 30-day post-discontinuation follow-up visit

<table>
<thead>
<tr>
<th>Procedure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5-6</th>
<th>7-8</th>
<th>9-10</th>
<th>11-12</th>
<th>30D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiological imaging b</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Safety assessment
- **Chemistry c** | X X X X X X X X X X |
- **Hematology d** | X X X X |
- **Thorax X-ray** | X |
- **CTCAE grading e** | X X X X X X X X |

### Treatment
- **Temozolomide** | X X X X X X X X |
- **Topotecan** | X X X X X X |

### Tumour biology (on archive material) | X |

Abbreviations: 30 D = 30-day post-discontinuation follow-up visit; BL = Baseline; FU = Long-term follow-up.

- a Within 7 days before study enrolment.
- b For radiological imaging: Investigators must consistently use the same imaging modality. **Baseline**: Preferably 1 to 3 weeks, but no more than 4 weeks before enrolment. **Study treatment period**: Every 2 cycles. **Post-discontinuation period**: Every 3 to 4 months until death or for at least one year if patient’s disease has not progressed. **Response confirmation**: Responses must be confirmed 4-6 weeks after initial response documentation. Thereafter, tumour response should be followed every 8 weeks until progression or discontinuation of study treatment. After discontinuation of study treatment, see Post-discontinuation period above.
- c Chemistry: Sodium, potassium, calcium, creatinine, AST (SGOT), ALT (SGPT), total bilirubin, albumin, urea, total protein. Within 7 days before study enrolment, then once a week during each cycle and if possible at the first post-discontinuation visit.
- d Haematology: Within 7 days before study enrolment, then once a week during each cycle and every 2 days in case of neutro- or thrombocytopenia, and if possible at the first post-discontinuation visit.
- e Toxicity rating using the NCI CTCAE scale (Version 3.0) after each cycle.
- f As necessary if patient's disease has not progressed (see Section 6.3, page 20).
- g As necessary to follow ongoing adverse events or to record new serious adverse events that are thought to be related to study treatment or protocol procedures (see Section 6.4, page 21).
## STUDY CONTACTS

<table>
<thead>
<tr>
<th>Role</th>
<th>Name and Address</th>
<th>Tel Number / Fax Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sponsor</strong></td>
<td><strong>Institut Gustave Roussy</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39 Rue Camille Desmoulins</td>
<td></td>
</tr>
<tr>
<td></td>
<td>94805 Villejuif Cedex</td>
<td></td>
</tr>
<tr>
<td><strong>Coordinating Investigator</strong></td>
<td>Dr Birgit Geoerger</td>
<td>Tel: +33 (0)1 42 11 46 61</td>
</tr>
<tr>
<td></td>
<td>Institut Gustave Roussy</td>
<td>Fax: +33 (0)1 42 11 53 08</td>
</tr>
<tr>
<td></td>
<td>Département de Pédiatrie</td>
<td><a href="mailto:geoerger@igr.fr">geoerger@igr.fr</a></td>
</tr>
<tr>
<td></td>
<td>39 Rue Camille Desmoulins</td>
<td></td>
</tr>
<tr>
<td></td>
<td>94805 Villejuif Cedex</td>
<td></td>
</tr>
<tr>
<td><strong>Investigators:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Dr Hervé Rubie</td>
<td>Tel: +33 (0)5 34 55 86 11/23</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Unité d’Hémato-Oncologie</td>
<td>Fax: +33 (0)5 34 55 86 12</td>
</tr>
<tr>
<td></td>
<td>Hôpital des Enfants</td>
<td><a href="mailto:rubie.h@chu-toulouse.fr">rubie.h@chu-toulouse.fr</a></td>
</tr>
<tr>
<td></td>
<td>330 Av de Grande Bretagne</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BP3119, 31026 TOULOUSE Cedex 3</td>
<td></td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Pr Riccardo Riccardi</td>
<td>Tel: +39 06 305 8203</td>
</tr>
<tr>
<td>Brain tumours</td>
<td>Università Cattolica di Roma</td>
<td>Fax: +39 06 305 2751</td>
</tr>
<tr>
<td></td>
<td>Divisione di Oncologia Pediadica</td>
<td><a href="mailto:riccardi@rm.unicatt.it">riccardi@rm.unicatt.it</a></td>
</tr>
<tr>
<td></td>
<td>Policlinico Universitario A. Gemelli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Largo A.Gemelli 8, 00168 Rome</td>
<td></td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Pr Huib Caron</td>
<td>Tel: +31 20 566 5655</td>
</tr>
<tr>
<td>Miscellaneous other solid tumours</td>
<td>Paediatric Oncology Department, Emma Childrens’ Hospital AMC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meibergdreef 9, 1105 AZ, Amsterdam</td>
<td><a href="mailto:h.n.caron@amc.uva.nl">h.n.caron@amc.uva.nl</a></td>
</tr>
<tr>
<td><strong>Co-chair:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chief Investigator Austria</td>
<td>Dr Ruth Landenstein</td>
<td>Tel: +43 (1)40470 4750</td>
</tr>
<tr>
<td></td>
<td>Children’s cancer Research Institute</td>
<td>Fax: +43 (1)40470 7430</td>
</tr>
<tr>
<td></td>
<td>St. Anna Kinderkrebsforschung e.V.</td>
<td><a href="mailto:ruth.ladenstein@ccri.at">ruth.ladenstein@ccri.at</a></td>
</tr>
<tr>
<td></td>
<td>Zimmermannplatz 10, 1090 Wien, Austria</td>
<td></td>
</tr>
<tr>
<td>Chief Investigator Spain</td>
<td>Dr Victoria Castel</td>
<td>Tel : +34 96 197 33 04</td>
</tr>
<tr>
<td></td>
<td>Hospital Universitario La Fe</td>
<td>Fax: + 34 96 197 33 04</td>
</tr>
<tr>
<td></td>
<td>Departamento de Oncologia Pediadica</td>
<td><a href="mailto:castel_vic@gva.es">castel_vic@gva.es</a></td>
</tr>
<tr>
<td></td>
<td>Hospital Infantil La Fe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Avda. Campanar N° 21, 46009 Valencia</td>
<td></td>
</tr>
<tr>
<td>Statistician</td>
<td>Dr Marie-Cecile Le Deley</td>
<td>Tel: +33 (0)1 42 11 54 44</td>
</tr>
<tr>
<td></td>
<td>Service de Biostatistique et Epidemiologie</td>
<td>Fax: +33 (0)1 42 11 52 58</td>
</tr>
<tr>
<td></td>
<td>Institut Gustave Roussy</td>
<td><a href="mailto:le_deley@igr.fr">le_deley@igr.fr</a></td>
</tr>
<tr>
<td>Study Coordinator</td>
<td>Dr Anna Ndiaye</td>
<td>Tel: +33 (0)1 42 11 41 17</td>
</tr>
<tr>
<td></td>
<td>Service de Biostatistique et Epidemiologie</td>
<td>Fax: +33 (0)1 42 11 52 04</td>
</tr>
<tr>
<td></td>
<td>Institut Gustave Roussy</td>
<td><a href="mailto:anna.ndiaye@igr.fr">anna.ndiaye@igr.fr</a></td>
</tr>
<tr>
<td>Data management</td>
<td>Katty Malekzadeh</td>
<td>Tel: +33 (0)1 42 11 41 96</td>
</tr>
<tr>
<td></td>
<td>Service de Biostatistique et Epidemiologie</td>
<td>Fax: +33 (0)1 42 11 52 04</td>
</tr>
<tr>
<td></td>
<td>Institut Gustave Roussy</td>
<td><a href="mailto:katty.malekzadeh@igr.fr">katty.malekzadeh@igr.fr</a></td>
</tr>
<tr>
<td>Quality Assurance</td>
<td>Claire Poullaouec</td>
<td>Tel: +33 (0)1 42 11 61 98</td>
</tr>
<tr>
<td></td>
<td>Clinical and Translational Research</td>
<td>Fax: +33 (0)1 42 11 62 90</td>
</tr>
<tr>
<td></td>
<td>Direction, Institut Gustave Roussy</td>
<td><a href="mailto:poullaouec@igr.fr">poullaouec@igr.fr</a></td>
</tr>
<tr>
<td>Trial Monitoring</td>
<td>Thibaud Motreff</td>
<td>Tel: +33 (0)1 42 11 66 43</td>
</tr>
<tr>
<td></td>
<td>Clinical and Translational Research</td>
<td>Fax: +33 (0)1 42 11 62 90</td>
</tr>
<tr>
<td></td>
<td>Direction, Institut Gustave Roussy</td>
<td><a href="mailto:thibaud.motreff@igr.fr">thibaud.motreff@igr.fr</a></td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>Dr Salim Laghouati</td>
<td>Tel: +33 (0)1 42 11 61 00</td>
</tr>
<tr>
<td></td>
<td>UF of Pharmaco-vigilance, Institut Gustave Roussy</td>
<td>Fax: +33 (0)1 42 11 61 00</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:philv@igr.fr">philv@igr.fr</a></td>
<td></td>
</tr>
<tr>
<td>Recherche Translationnelle</td>
<td>Dr Philippe Viel</td>
<td>Tel : 01 42 11 44 55</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>Département de Biologie et de pathologie médicale, Institut Gustave Roussy</td>
<td></td>
</tr>
</tbody>
</table>
7.5.5 Prophylaxis for Pneumocystis Carinii Pneumonia ................................................................. 24
7.5.6 Palliative radiotherapy .................................................................................................................. 25
7.6 Treatment Compliance ....................................................................................................................... 25

8 Research Assessments ......................................................................................................................... 25
MGMT, MSI and BER ................................................................................................................................. 25

9 Safety and Efficacy criteria .................................................................................................................. 25
9.1 Safety .................................................................................................................................................. 25
9.2 Response Assessment ........................................................................................................................ 25
9.2.1 Main efficacy criterion .................................................................................................................. 25
9.2.2 Response review committees ...................................................................................................... 26
9.2.3 Secondary endpoints for efficacy ................................................................................................. 26
9.2.4 Safety criteria .................................................................................................................................. 27

10 Statistical Methods ............................................................................................................................ 27
10.1 Trial plan and sample size ................................................................................................................. 27
10.1.1 Neuroblastoma ............................................................................................................................ 27
10.1.2 Brain tumours cohort .................................................................................................................. 28
10.1.3 Miscellaneous other solid tumours ............................................................................................. 28
10.1.4 Medulloblastoma cohort ............................................................................................................ 28
10.1.5 PNET cohort ............................................................................................................................... 28
10.2 Analysis ............................................................................................................................................. 28
10.3 Data-management .............................................................................................................................. 29

11 Adverse Events .................................................................................................................................... 29
11.1 Adverse events ................................................................................................................................. 29
11.1.1 Definition ...................................................................................................................................... 29
11.1.2 Recording of adverse events ...................................................................................................... 29
11.2 Serious adverse events ...................................................................................................................... 30
11.2.1 SAE definition .............................................................................................................................. 30
11.2.2 SAEs reporting ............................................................................................................................... 32
11.3 Adverse events follow-up ............................................................................................................... 34
11.4 Annual safety report ........................................................................................................................ 34

12 Study Discontinuation ........................................................................................................................ 34

13 Regulatory Aspects ............................................................................................................................. 34
13.1 Ethics and competent authorities .................................................................................................... 34
13.2 Patient information ........................................................................................................................... 35
13.3 Investigators/spoonor responsibilities ............................................................................................... 35
13.4 Authorization for computerization of the collected data ................................................................. 35
13.5 Quality Assurance ............................................................................................................................ 36

14 Monitoring ........................................................................................................................................... 36
14.1 Monitoring verification ...................................................................................................................... 36
14.2 Protection and development of study results .................................................................................... 36

References .................................................................................................................................................. 37

Appendix 1. Performance Scale and Lansky-Play Scale ........................................................................... 42
Appendix 2: Tumour response assessment according to WHO criteria .................................................. 43
Appendix 3: International criteria for diagnosis, staging and response to treatment .................................... 44
Appendix 4: MIBG Scoring ........................................................................................................................ 48
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event: any untoward medical occurrence in a patient administered a pharmaceutical product, without regard to the possibility of a causal relationship.</td>
</tr>
<tr>
<td>AGT</td>
<td>alkyl-guanine transferase</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>CCSG</td>
<td>Children's Cancer Study Group</td>
</tr>
<tr>
<td>CMP</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COG</td>
<td>Children’s Oncology Group</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form (sometimes referred to as Clinical Report Form). A printed or electronic form for recording study participants’ data during a clinical study, as required by the protocol.</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DLT</td>
<td>Dose-limiting toxicity</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>GCP</td>
<td>Good clinical practice</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Granulocyte colony stimulating factor</td>
</tr>
<tr>
<td>IGR</td>
<td>Institut Gustave Roussy</td>
</tr>
<tr>
<td>IEC/IRB</td>
<td>Institutional review board/ethical review board: a board or committee (institutional, regional, or national) composed of medical professional and non medical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical trial are protected.</td>
</tr>
<tr>
<td>INSS</td>
<td>International Neuroblastoma Staging System</td>
</tr>
<tr>
<td>MIBG</td>
<td>Meta-iodobenzylguanidine</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MTD</td>
<td>Maximum tolerated dose</td>
</tr>
<tr>
<td>MTIC</td>
<td>Monomethyl 5-triazeno imidazole carboxamide</td>
</tr>
<tr>
<td>MYCN</td>
<td>myc myelocytomatosis viral related oncogene</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NCI-CTCAE v3.0</td>
<td>NCI Common Terminology Criteria for Adverse Events version 3.0</td>
</tr>
<tr>
<td>NB</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>PNET</td>
<td>Primitive neuroectodermal tumour</td>
</tr>
<tr>
<td>POG</td>
<td>Paediatric Oncology Group</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>RBC</td>
<td>Red Blood Cells</td>
</tr>
<tr>
<td>RR</td>
<td>Response Rate</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>SD</td>
<td>Stable disease</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>TMZ</td>
<td>Temozolomide</td>
</tr>
<tr>
<td>TPT</td>
<td>Topotecan</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
1 INTRODUCTION

1.1 PAEDIATRIC CANCERS

Cancer occurs rarely in children and adolescents, with an incidence of 10 to 15 cases per 100,000 individuals under 19 years of age (NCI SEER paediatric monograph: http://seer.cancer.gov/publications/childhood/foreword.pdf). Two types of tumours are distinguished: leukemias, approximately 30% of all cases, and solid tumours. Current treatments for malignant paediatric solid tumours involve a combination of chemotherapy, surgery and, in certain cases, radiotherapy. This multidisciplinary approach leads to an overall cure of approximately 70%. Nevertheless, cancer mortality remains the leading cause of disease-related death in children and adolescents between 1 and 19 years. This is due to diseases with a poor prognosis, such as metastatic neuroblastoma, sarcoma in soft tissue and bone and brain tumours. New effective treatments must be found in order to continue to increase the cure rate of children and adolescents treated for cancer, as well as to improve the cured patients' quality of life. The methodology of early development of anticancer agents is well established and confirmed in paediatrics\(^1,2\).

Neuroblastoma (NB) is a malignant paediatric tumour derived from primordial neural crest cells. This tumour accounts for 8% to 10% of all cancers with a median age of onset of 22 months\(^3\). The primary tumour may be located in different anatomic sites such as abdomen (65%), thorax (19%), pelvis (2%), and cervix (1%). The strongest prognostic factors are age and stage\(^4,5\). Localized NB and those occurring in infants have a 90% survival rate when the biological profile is favorable\(^6,7\). Conversely, in case of Myc-N amplification, survival is around 30% after conventional treatment\(^7\) and 70% after intensification\(^8\). More than 50% of patients have a disseminated tumour at diagnosis, and Stage 4 neuroblastoma in patients older than 1 year of age represents the most frequent form. Neuroblastoma is a chemosensitive tumour. Chemotherapy is indicated in large primary tumours to reduce the volume and attempt a safe surgical resection\(^9,10\) and to eradicate tumour metastases in disseminated NB. The most frequently used drugs are alkylating and platinum agents (cyclophosphamide, melphalan, cisplatin, carboplatin), topoisomerase II inhibitors (doxorubicin, etoposide) and vinca-alkaloids (vincristine)\(^11\). High-dose chemotherapy (busulfan, melphalan, carboplatin, etoposide) with autologous bone marrow stem cell support is used as a consolidation treatment in patients with metastatic disease, as well as maintenance therapy with retinoid acid\(^12,13\). Although such an intensive strategy, the probability of survival of patients over 1 year of age with Stage 4 neuroblastoma is less than 40%. New drugs are urgently needed for patients with recurrent neuroblastoma.

Central nervous system (CNS) tumours as an entity represent the second most frequent malignancy in childhood and adolescents. The incidence rate of childhood primary benign and malignant brain tumours is 3.9 cases per 100,000 person-years, and appears to be increasing. Two thirds of the new cases are in children less than 15 years of age. The morbidity associated with CNS tumours exceeds those of other malignancies and is undoubtedly a result of the neurological and cognitive deficits associated with both the tumour itself and aggressive multimodal therapy. Current treatment involves surgical resection, mostly combined with irradiation and/or chemotherapy. This multidisciplinary approach leads to a cure in about 55% of all brain tumour patients. However, the outcome in small children and certain malignancies, such as
high grade astrocytomas, brain stem glioma and atypical teratoid/rhabdoid tumours and metastatic primary neuroectodermal tumours (PNET)/medulloblastoma is still dismal. In addition, treatment with irradiation and/or the combination of different chemotherapeutic agents is at the limit of tolerance inducing renal, hepatic, auditory, or hematological toxicity. Moreover, irradiation to the cerebral hemispheres, especially in small children, induces devastating sequelae. Clinical resistance to anticancer agents is the primary reason for treatment failure in childhood cancer and the development of new agents with a new profile of anti-tumour activity and toxicity is highly warranted.

Other relapsed/refractory non-CNS solid tumours include nephroblastoma, osteosarcoma, Ewing’s sarcoma, rhabdomyosarcoma and soft-tissue sarcomas, and rarer tumours, such as hepatoblastoma, retinoblastoma, nasopharyngeal carcinoma, and germ-cell tumours. For most of these tumours, treatment protocols are available for first-line therapy; to a lesser extent, treatment recommendations are proposed in case of relapse. Depending on the disease, type, and localization of relapse, treatment may include combinations of salvage chemotherapy, including high-dose chemotherapy with stem cell rescue, radiotherapy, and surgery. In several of these diseases, temozolomide (as well as topoisomerase I inhibitors, such as irinotecan and Topotecan) have shown single agent activity and may be used in combination schedules.

1.2 RATIONALE FOR STUDYING TEMOZOLOMIDE IN PAEDIATRIC PATIENTS

Temozolomide (TMZ) is a methylaing agent registered for the treatment of malignant glial tumours in adults and children. After oral administration, TMZ is quickly and completely absorbed and then hydrolysed in monomethyl 5-triazeno imidazole carboxamide (MTIC) which will generate an ion methyldiazonium methylating DNA, principally in O\textsuperscript{6} of guanine\textsuperscript{14}. These lesions are repaired by a nuclear protein, alkylguanine transferase (AGT), and by a system of bases mismatch repair or MMR\textsuperscript{15}. There is a correlation between the dose and the duration of administration of TMZ and the decrease O\textsuperscript{6} AGT activity in peripheral blood\textsuperscript{16-18}. In vitro studies on tumoural lines resistant to other anticancer drugs have suggested a good efficacy of TMZ\textsuperscript{19}.

The biotransformations of TMZ and MTIC are spontaneous (without enzymatic system), the first one in base the second one in acid. The oral biodisponibility of TMZ is complete. Pharmacokinetics (PK) of TMZ looks linear. These PK characteristics explain that the inter-individual variability is very low for TMZ and its metabolites. In addition, a PK interaction between TMZ and another drug is unlikely.

Temozolomide as a single drug administration

The recommended dose is 200 mg/m\textsuperscript{2}/d for 5 consecutive days in adults\textsuperscript{20,21}. The limiting toxicity is haematologic, reversible and not cumulative. Haematological recovery takes a few weeks, allowing a subsequent course at day 28. The efficacy of TMZ has been shown in adults' malignant gliomas and astrocytomas\textsuperscript{22-24}.

Preclinical studies, particularly in some models of paediatric tumour xenografts, have suggested a dose of 66 mg/kg/d or 200 mg/m\textsuperscript{2}/d for 5 consecutive days\textsuperscript{25}. Two phase I studies in children showed that the recommended dose was identical to adults: 200 mg/m\textsuperscript{2}/d for 5 consecutive days every four weeks\textsuperscript{26,27}. Haematologic toxicity, particularly thrombocytopenia, is the main toxicity, limiting dose escalation. In children presenting brain stem gliomas or supratentorial high-grade gliomas, no significant efficacy was observed\textsuperscript{28}. 
However, TMZ was active in 4 NB xenograft models. Its activity correlated with a low AGT activity in tumours. A clinical study confirmed these results showing that TMZ was active in NBs and CNS tumours. In a recent study, we reported encouraging results as 5 responses were observed among the 25 evaluable patients with refractory/relapsing NB.

**Temozolomide in combination**

In adults, phase I studies have shown the possibility to combine TMZ with VP-16, procarbazine or cisplatin. In adults brain tumours the activity of the combination of TMZ with CPT-11, BCNU and liposomal doxorubicin has been reported. In preclinical models, the association of TMZ and CPT-11 seems promising as the two drugs have a synergistic effect, in particular if TMZ is given before CPT-11. The efficacy of this combination has been reported in adults with malignant gliomas.

In children, a phase I study has allowed to determine the recommended doses of TMZ combined with cisplatin, respectively: 150 or 200 mg/m²/d TMZ and 80mg/m²/d cisplatin. A phase II using this combination in brain tumours is on-going.

Another phase I study using the combination of TMZ with CPT-11 has shown that the recommended doses were 100 mg/m²/d TMZ for 5 days and 10 mg/m²/d CPT-11 for 5 consecutive days during two weeks, every 3 weeks. Among 12 evaluable children, 1 complete and 2 partial responses were reported in Ewing sarcoma and NB. These observations confirm the interest of TMZ combined with topoisomerase I inhibitors. A phase II study in NB is on-going within the Children’s Oncology Group.

### 1.3 RATIONALE FOR STUDYING TOPOTECAN IN PAEDIATRIC PATIENTS

Topotecan (TPT) is a semi-synthetic analog of camptothecin able to block DNA and RNA synthesis in inhibiting topoisomerase I, a 100 kD nuclear enzyme implicated in DNA replication and reparation and facilitate cellular apoptosis.

Several schemes of administration have been evaluated in adults: an infusion every 3 weeks, a daily infusion for 5 consecutive days, a continuous infusion for 5 days, even 21 days, with Maximum Tolerated Dose (MTD) respectively of 0.68 mg/m²/d and 0.53 mg/m²/d. In these studies, the Dose Limiting Toxicity (DLT) was mainly haematological, suggesting supportive care with haematopoietic growth factors when administrating high or prolonged doses of TPT. TPT is partly eliminated intact by the kidney and partly by the liver after transformation and biliary secretion. In adults, pharmacokinetic-pharmacodynamic studies have shown a correlation between haematological toxicity and plasmatic exposure to TPT. These characteristics have been confirmed in children, with a wide inter-individual variability, leading some investigators to use methods of individual adaptations of the dose according to the results of the follow up of plasmatic drug concentration. This strategy of individual drug monitoring has shown to be relevant in term of response in NBs.

In children, the inter-individual variability of PK is partly explained by differences in renal function between the patients. In addition, some pharmacogenetic differences implicated in the elimination of TPT may play a role, as well as in paediatrics: CYP2C9 and transport proteins (ABCB1, ABCG2 and OATP1B1).

Pre-clinical studies in paediatric tumour xenografts have suggested the interest of TPT, particularly in NB, used as a single drug or combined with vincristin.
Topotecan as a single drug administration

Phase I studies reported in children confirm the relationship between the systemic exposure and haematological toxicity\textsuperscript{54}. They recommend either a 30 minutes infusion of 1.5 mg/m\textsuperscript{2}/d for 5 consecutive days or a continuous infusion of 1 mg/m\textsuperscript{2}/d over 72 h every 21 days\textsuperscript{55}. Finally, the optimal scheme of administration was reported by Paediatric Oncology Group (POG) after their phase I study and consists in a daily short infusion for 5 consecutive days\textsuperscript{56}.

POG reported the results of a phase II study in 37 children presenting with a refractory/relapsing NB, after a daily infusion of TPT (2 mg/m\textsuperscript{2}/d x 5 days), of whom a complete or mixed response was observed in 1 and 5 patients respectively, and a stable disease in 8\textsuperscript{57}. Using the same dosing, the German group reported 2 partial responses among 13 children with a NB\textsuperscript{58}, while the Children’s Cancer Study Group (CCSG) reported only 1 CR in 26 patients with a continuous infusion (TPT: 1-1.3 mg/m\textsuperscript{2}/d x 72 h)\textsuperscript{59}. More recently, the St Jude’s group reported a 60% response rate (RR) in 28 children with NB, after 2 courses of TPT given as a daily infusion 5 days a week, during 2 consecutive weeks\textsuperscript{60}. The Spanish group evaluated the efficacy of TPT given as a classical scheme (1.5 mg/m\textsuperscript{2}/d as a 30 min. infusion for 5 consecutive days in 20 patients with a NB (17 metastatic relapses and 3 refractory). Among the 17 evaluable patients, a response was observed in 8 (RR=47%) after 2 courses (Victoria Castel, personal communication).

TPT proved to be active also in children having medulloblastoma/supratentorial primitive neuroectodermal tumour\textsuperscript{60} and Wilms’ tumour\textsuperscript{61}.

Topotecan in combination

Some phase I studies have evaluated the combination of TPT with vincristine\textsuperscript{53}, cisplatin\textsuperscript{62}, carboplatin\textsuperscript{63} and vincristine-doxorubicin\textsuperscript{64}. The Italian group reported the results of a phase II study with this combination: TPT 1.5 mg/m\textsuperscript{2}/d with a 30 min infusion for 5 consecutive days, vincristine 2 mg/m\textsuperscript{2} and doxorubicin 45 mg/m\textsuperscript{2} both given as a continuous infusion over 48h repeated every 3 weeks. Among 25 patients presenting with NB and heavily pre-treated, 16 responses were observed (4 CR and 12 PR).

The German group evaluated the combination of TPT (with different doses and schemes of administration) with VP-16 and reported a 41% RR in 54 patients with NB\textsuperscript{65}. The same group evaluated the combination of TPT with VP-16 and cyclophosphamide in a subsequent study and observed 8 responses out of 14 patients (Frank Berthold, personal communication). The combination of TPT with paclitaxel, administered up-front has shown a 37% RR in 32 untreated children with NB\textsuperscript{66}.

The most commonly used combination is cyclophosphamide (CPM: 250 mg/m\textsuperscript{2} as short infusion at D1) followed by TPT (0.6 to 0.7 mg/m\textsuperscript{2}/d for 5 consecutive days) and G-CSF. The authors report 6 responses among 33 treated patients, of whom 2 out of 7 with NB\textsuperscript{67}. A subsequent phase II study published by the same group demonstrated significant activity in sarcomas, NBs\textsuperscript{68} and metastatic rhabdomyosarcoma\textsuperscript{69}. In a randomized phase II study in patients with NB, it was recently reported that combination of TPT with CPM was more efficient than TPT alone, with a RR of 31 and 19% respectively\textsuperscript{70}. Another study suggested that the combination of TPT (6 mg/m\textsuperscript{2} in a continuous infusion of 72 h) with high-doses of CPM (4200 mg/m\textsuperscript{2}/d in a continuous infusion of 48 h) followed by G-CSF was feasible\textsuperscript{71}.

Those results demonstrate that both TMZ and TPT have activity in paediatric tumours and justify their evaluation combined together.
1.4 CLINICAL RATIONALE FOR COMBINATION

Many reasons support the combination of TMZ with topoisomerase I inhibitors. A recent study evaluated the efficacy of CPT 11 (50 mg/m²/d, 1-hour infusion) combined with TMZ (150 mg/m²/d, oral) for 5 consecutive days. The authors reported 9 responses (2 CR) among 19 patients with a refractory NB and 3 (1 PR) out of 17 having a progressive NB. However, in terms of using topoisomerase inhibitors, TPT looks more attractive in our experience since activity of CPT 11 in the phase II in NBs was limited (1 response out of 32 patients).

1.5 PHASE 1 TRIAL OF TEMOZOLOMIDE IN COMBINATION WITH TOPOTECAN IN CHILDREN WITH REFRACTORY OR RELAPSED MALIGNANT TUMOURS

The combination of TMZ with TPT has never been used. A phase I trial in children was conducted to determine the MTD and RD. Sixteen patients were enrolled in the study. The recommended doses were: 150 mg/m²/d TMZ administered orally followed by 0.75 mg/m²/d TPT as a 30 min infusion for 5 consecutive days every 4 weeks. The combination was well tolerated. The main toxicity was haematological. Partial response was reported after 2 cycles in 2 out of 8 patients with neuroblatoma.

1.6 RATIONALE FOR EVALUATION OF MGMT, MSI AND BER

Tumour sensitivity to alkylating agents is affected by the activity of cellular DNA repair proteins, such as O(6)-methylguanine DNA methyltransferase (MGMT) and the DNA mismatch repair proteins. Chemosensitivity may be enhanced by reduced MGMT activity, however the frequency of MGMT promoter silencing through hypermethylation is largely unknown in paediatric cancers. Another mechanism of resistance to alkylating agents is the base excision repair (BER) pathway. Furthermore, low microsatellite instability (MSI) has been associated with poor prognosis in colon cancer and lack of response to topoisomerase I inhibitors (Kohonen-Corish et al. JCO 2005).

Consequently, we intend to detect MGMT expression, MGMT gene methylation, MSI and BER in patients treated with the temozolomide - Topotecan combination and to correlate these findings with responses observed in these paediatric solid malignancies.

1.7 DEVELOPMENT STATUS OF TEMOZOLOMIDE

Temozolomide is registered for treatment of malignant glioma including in children older than 3 years. Common side effects are: nausea, vomiting and constipation, neutropenia, lymphocytopenia, thrombocytopenia, headache, and fatigue. Mild effects such as weight loss, sleepiness, dizziness, paresthesia, dyspnoea, diarrhoea, skin rash, hair loss, fever, weakness, loss of appetite, muscle soreness can also be observed. Uncommon side effects reported with temozolomide include allergy and infections (pneumocystis carinii pneumonia).

For further information, please refer to the Summary of Product Characteristics (SPC).

1.8 DEVELOPMENT STATUS OF TOPOTECAN

Topotecan is registered for treatment of ovarian metastatic carcinoma where previous chemotherapies have failed.
The most common effects are neutropenia and thrombocytopenia, nausea, vomiting, diarrhoea and constipation, hair loss, fatigue. Uncommon side effects reported with Topotecan include allergy, skin rash, hyperbilirubinemia.

2 STUDY OBJECTIVES

2.1 PRIMARY
The primary study objective is to assess the response rate of Temozolomide in combination with Topotecan in patients with relapsed or refractory neuroblastoma and in patients with medulloblastoma or PNET, and to describe response in patients with relapsed or refractory miscellaneous brain tumours and in patients with relapsed or refractory miscellaneous other solid tumours.

2.2 SECONDARY
The secondary study objectives are:
- To assess the following time-to-event endpoints: duration of response, time to progressive disease, time to treatment failure and overall survival
- To characterize the safety and adverse event profile of the combination
- To evaluate MGMT expression on archive tumour material and correlate with response.

3 OVERALL STUDY PLAN

3.1 DESCRIPTION OF THE DESIGN
This is a multicentre, non randomized, Phase 2 trial with 5 study cohorts: Neuroblastoma, Brain tumours, Medulloblastoma, PNET, and Miscellaneous other solid tumours. A two-stage design will be followed in the neuroblastoma. After amendment, a Fleming one stage design will be used in the medulloblastoma cohort. Meanwhile brain tumour cohort and the miscellaneous other solid tumour cohort will act as a screening program to note interesting responses in several tumour types.

3.2 STUDY CENTERS
23 in Austria, France, Italy, the Netherlands and Spain.

3.3 EXPECTED NUMBER OF PATIENTS
Up to 36 evaluable patients in the neuroblastoma cohort
19 evaluable patients in the medulloblastoma cohort
Up to 19 evaluable patients in the PNET cohort
30 evaluable patients in the brain tumours cohort
30 evaluable patients in the miscellaneous other solid tumours
To be sure to have 134 evaluable patients, 2 additional patients will be included in each cohort.

3.4 STUDY PERIOD
The planned duration of the enrolment is 18 months. The planned duration of the entire study (i.e. enrolment period + treatment period + the follow-up period, if any) is 30 months.
4 SELECTION OF STUDY PATIENTS

4.1 INCLUSION CRITERIA

Patients are eligible to be included in the phase 2 trial only if they meet all of the following criteria:

- Histologically or cytologically confirmed neuroblastoma, brain tumour or other solid tumour (at diagnosis)
- Relapsed or refractory tumours in which correct standard treatment approaches have failed or Tumours with no known conventional therapy
- No more than 2 lines of prior chemotherapy (monoclonal antibody therapies, e.g. IGF1R, are not considered as lines of treatment)
- Measurable primary and/or metastatic disease on CT/MRI at least one bi-dimensionally measurable lesion.
  For patients with neuroblastoma, measurable disease on CT/MRI with at least one bi-dimensionally measurable lesion or at least 4 spots on MIBG.
- Age at inclusion: 6 months to ≤ 20 years
- Lansky play score ≥ 70% or ECOG performance status ≤ 1
- Life expectancy ≥ 3 months
- Adequate organ function:
  - Adequate haematological function: haemoglobin ≥ 80 g/l, neutrophil count ≥ 1.0 x 10⁹/L, platelet count ≥ 100 x 10⁹/L; in case of bone marrow disease: neutrophils ≥ 0.5 x 10⁹/L and platelets ≥ 75 x 10⁹/L;
  - Adequate renal function: normal creatinine related to patient’s age:
    - 0 – 1 year: ≤ 40 µmol/L
    - 1 – 15 years: ≤ 65 µmol/L
    - 15 – 20 years: ≤ 110 µmol/L
  - Adequate hepatic function: bilirubin ≤ 1.5 x ULN; AST and ALT ≤ 2.5 x ULN (AST, ALT ≤ 5xULN in case of liver metastases)
- Wash-out of 4 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas, 2 weeks in case of vincristine or retinoic acid alone; 6 weeks in case of prior radiotherapy (except palliative radiotherapy on non measurable lesions). Patients must have recovered from the acute toxic effects of all prior therapy before enrolment into the study.
- Patients previously treated with only one of the 2 drugs or none are eligible.
- Able to comply with scheduled follow-up and with management of toxicity.
- All patients with reproductive potential must practice an effective method of birth control while on study.
  Female patients aged > 12 years must have a negative pregnancy test within 7 days before study treatment.
- Written informed consent from patient, parents or legal guardian.

4.2 EXCLUSION CRITERIA:

- Concurrent administration of any other anti-tumour therapy.
- Serious concomitant systemic disorder (for example, active infection including HIV or cardiac disease) that in the opinion of the investigator, would compromise the patient’s ability to complete the study.
- History of allergic reaction to the compounds or their solvents.
• History of allergic reaction to Dacarbazine (DITC).
• Galactosemia, Glucose-galactose malabsorption or lactase deficiency.
• Pregnant or breast feeding young women.
• Presence of symptomatic brain metastases in patients with solid non-CNS tumours.

5 PATIENT REGISTRATION

A registration form documenting the patient’s fulfilment of the study entry criteria is to be completed, and signed by the investigator and faxed to the Institut Gustave Roussy (IGR) data centre at the following number:

+33 (0) 1 42 11 52 04  From Monday to Friday: 9 am – 5 pm

For all eligible patients, confirmation of inclusion and a patient study number will be provided to the site of enrolment. This patient study number should be used on all future documentation and correspondence which reference this patient.

Patient should be registered no more than 8 days before planned date of treatment initiation.

The study data manager can be called at following number: +33(0)1 42 11 60 91 or +33 (0)1 42 11 49 00, if absent.

6 STUDY ASSESSMENTS

The following exams will performed according to the schedule of assessments (page 6) after signature of written informed consent by patients or parents or legal representative.

6.1 CLINICAL ASSESSMENTS

6.1.1 Medical History
• Relevant past medical history, and current medical conditions not related to the current indication or disease for which patient entered into the study
• Information related to diagnosis of the disease under study
• Previous surgery, radiotherapy, systemic therapy, investigational therapy
• Any disease related symptoms present at baseline.

6.1.2 Physical examination
• Physical and Neurological Examination
• ECOG Performance Status or Lansky-Play score
• Vital signs (pulse, blood pressure, temperature)
• Height, Weight and Body Surface

Will be done within 7 days before study enrolment, once between day 8 and day 28 of cycle 1 and at the beginning of each cycle
• Thorax X-ray will be done before registration

6.2 LABORATORY ASSESSMENTS
• Pregnancy test (urine or serum) in females of childbearing potential within 7 days before study enrolment.
• Complete Blood Count: leukocyte, neutrophil, platelets and haemoglobin within 7 days before study enrolment, then once a week during each cycle and every 2 days in case of neutro- or thrombocytopenia, and if possible at the first post-discontinuation visit

• Serum Biochemistry: sodium, potassium, calcium, total protein, creatinine, urea, AST (SGOT), ALT (SGPT), total bilirubin, albumin within 7 days before study enrolment, then before each cycle, and if possible at the first post-discontinuation visit.

6.3 TUMOUR ASSESSMENTS

6.3.1 Tumour assessment schedule
Tumour assessment should be performed according to the schedule of assessments (page 6)
- Baseline assessment: should be done preferably 1 to 3 weeks, but no more than 4 weeks before enrolment.
- Evaluation of response for the primary objective: tumour assessment should be performed after 8 weeks (2 cycles) of therapy to determine response rate. To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks and before 6 weeks after the criteria for response are first met. Continuing response/stable disease should be confirmed every 2 cycles (2 months) until tumour progression or study discontinuation. After discontinuation of study treatment, evaluation will be done every 3 or 4 months until the patient's death or up to at least one year until study cut-off if patient's disease has not progressed.

6.3.2 Tumour assessment methods
Tumour measurements should assess the maximum of the two largest perpendicular diameters. If multiple sites of disease are present, all should be measured and recorded separately (up to six). Lesions will be reported in the Case Report Form (CRF) in the same order at study entry and during re-assessment to allow direct comparison of responses.

The same modality and technique for assessing disease at study entry is to be used for re-assessment, to allow direct comparison and accurate evaluation of disease response. Techniques producing negative results at initial evaluation do not need to be repeated unless there is clinical evidence of disease progression which may need further confirmation.

Patients with neuroblastoma
- MRI, CT scans.
- mIBG scan, Technetium scan is required if mIBG scan is negative.
- Bone marrow aspirates and biopsies recommended.
- Urinary catecholamine levels at study entry and at tumour assessment points only to confirm CR.

Patients with brain tumours
- Two-dimensional imaging (MRI scans) of all measurable lesions, including pre- and post-contrast enhanced films.
- Optional: functional MRI, Thallium scintigraphy, and Methionine PET scan.

Patients with miscellaneous other solid tumours
- MRI and CT scans.
• Optional: scintigraphy, glucose PET-scan, bone marrow aspirates and biopsies if abnormal at study entry and according to disease.

6.4 FOLLOW-UP
The follow-up period begins when the patient discontinues from study treatment (see Section 7.4 page 23). If feasible, one post-discontinuation visit will be performed 30 days after treatment discontinuation and follow-up in all patients must be pursued every 3-4 months until the patient's death or up to at least one year until study cut-off. Patients with adverse events at the end of the study related to temozolomide-Topotecan must be followed until recovery.

During post-therapy follow-up, information will be collected in the CRF regarding date of disease progression, further second line treatment (chemo, radiotherapy, surgery) and death. 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. All deaths will be recorded.

7 TREATMENTS
The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the site personnel, verifying that instructions are followed properly. Patient will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug(s) so that the situation can be assessed.

7.1 STUDY TREATMENTS
7.1.1 Description and preparation

Temozolomide
Description: Temozolomide is commercially available. The drug is supplied as bottles containing 5 capsules of 5, 20, 100 and 250 mg. The product should be stored at room temperature and temperature will not exceed 30°C.
Administration: Temozolomide will be administered orally each morning. Capsule will be swallowed with a glass of water before any food or drink absorption. Capsules should not be opened or chewed. Premedication with anti-emetics (Setrons) is recommended 30 minutes before Temozolomide administration. Breakfast should be given at least 30 minutes after Temozolomide administration.

Topotecan
Description: Topotecan (Hycamtin®) is commercially available. The drug is presented in the form of a lyophilisate for infusion in vials containing 4 mg.
Preparation: The lyophilized powder is reconstituted by adding 4 ml of water for injection. The Topotecan concentration in the reconstituted solution will be 1 mg/ml. The reconstituted solution must be further diluted in a 0.9% sodium chloride solution or in a 5% glucose (w/v) solution to obtain the appropriate final concentration of Topotecan i.e 25-50 microg/ml as per SPC.
Administration: one hour after Temozolomide administration, Topotecan will be administrated as intravenous infusion over 30 minutes.
Reconstituted Topotecan must be used immediately. If the dilution was performed in sterile conditions, the solution must be used (infusion completed) within 12 hours at room temperature or 24 hours at 2-8°C.
If vomiting occurs, a temozolomide capsule will only be replaced if the vomited capsule was still intact.

7.1.2 Drug supply

Topotecan will be provided by the sponsor. Initial supply will be ordered by the data centre. Subsequent supplies will be ordered to the data centre by the local pharmacy according to the recruitment of the centre and the number of patients under treatment. Temozolomide will be used from the Pharmacies commercial stocks.

7.1.3 Study treatment labelling

Topotecan will be labelled according to the regulatory requirements.

7.1.4 Drug reconciliation procedures

The pharmacist must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability log. Patients will return unused drug to the pharmacy. An accurate record of the date and amount of study drug dispensed to each patient and drug returned must be available for inspection at any time. Periodically or at the latest at the end of the trial all unused Topotecan vials will be destroyed and destruction will be documented on the destruction log. All drug supplies are to be used only for this protocol and not for any other purpose.

7.1.5 Dosing and Administration of study medication

The actual doses of Temozolomide and Topotecan to be administered will be determined by calculating the body surface area at the beginning of each cycle. A cycle is defined as a period of 28 days.

Patients receive during 5 days (Day 1 to Day 5):
- Temozolomide 150 mg/m$^2$/day per os, dose will be adjusted to the closest 5 mg, followed one hour later by
- Topotecan 0.75 mg/m$^2$/day as an intravenous infusion over 30 minutes.

In case of BSA higher than 2 m$^2$, the doses administered will be limited to doses corresponding to a BSA of 2m$^2$:
- Temozolomide 300 mg/day
  - Topotecan 1.50 mg/day

For children who have difficulties in swallowing, Temozolomide capsules should be placed in fruit juice or fruit compote and administered after the capsule has been allowed to soften. Temozolomide should be administered in in-patient setting.

7.2 TREATMENT DURATION

The maximum planned treatment duration in absence of toxicity or progression is up to 12 cycles.

7.3 DOSE ADJUSTMENTS OR DELAY FOR SUBSEQUENT CYCLES

If a dose has to be reduced for toxicity reasons, the patient will stay on this reduced dose for the remainder of the study.

Treatment may be delayed up to 3 weeks after the intended date of the next cycle 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. If treatment must be delayed, a new cycle is defined beginning the day of administration.
7.3.1 Haematologic toxicity

Patients must have an absolute neutrophil count $\geq 1.0 \times 10^{9}$/L and a platelet count $\geq 100 \times 10^{9}$/L or a neutrophil count $\geq 0.5 \times 10^{9}$/L and platelets $\geq 75 \times 10^{9}$/L in case of bone marrow disease prior to starting a new cycle of temozolomide and Topotecan.

The dose adjustment scheme for haematologic toxicities upon recovery to the minimum requirements outlined above is based on the maximum toxicity experienced in the previous cycle. In case of:

- CTC Grade 4 neutropenia lasting for $> 7$ days
- CTC Grade 4 neutropenia with documented febrile infection
- CTC Grade 4 thrombocytopenia lasting for $> 7$ days
- Platelets transfusion needs lasting for $> 7$ days
- 14 days delay in the start of a new cycle, because of slow recovery of the bone marrow

Subsequent dose adjustment will occur. Temozolomide will be given at $100 \text{ mg/m}^2$/day and Topotecan at $0.75 \text{ mg/m}^2$/day.

If necessary, a second dose reduction to Temozolomide $80 \text{ mg/m}^2$/day and Topotecan $0.5 \text{ mg/m}^2$/day will be allowed. Subsequent dose escalation to the level of the original doses will not be allowed.

Further dose reduction will not be allowed. If toxicity that would require a dose reduction occurs after two dose reductions, the patient will discontinue study treatment.

7.3.2 Non haematologic toxicities

Toxicities will be graded using the NCI common toxicity criteria (NCI-CTCAE v3.0; which can be downloaded at: http://ctep.info.nih.gov). Any 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 and aspartate transaminase must resolve to Grade 1 or lower before the next cycle may be administered, unless the patient has liver metastases.

7.4 TREATMENT DISCONTINUATION

Treatment should be discontinued if this is considered to be in the best interest of the patient. Treatment could be discontinued for the following reasons:

- Investigator’s decision: if this decision is made because of toxicity, a serious adverse event, or a clinically significant laboratory value, appropriate measures will be taken and IGR will be notified immediately (see Section 11.2.2, page 32).
- The patient, parents or legal representative’s refusal, withdrawal of patient consent.
- The patient requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from study treatment occurs immediately upon introduction of the new agent.
- The investigator or sponsor, for significant safety or efficacy reason, stops the study or stops the patient's participation in the study.
- Evidence of progressive disease exists.
- The patient becomes pregnant or fails to use adequate birth control (for those patients who are able to conceive).
- The patient is non compliant with study procedures.
- Life threatening toxicity.
- Unmanageable or unacceptable toxicity, including the need for more than 2 dose reductions, except in cases of obvious patient benefit in continuing the treatment.
- Treatment delay of more than 3 weeks for any reason except in cases of obvious patient benefit in continuing the treatment.

Study discontinuation, must be reported to IGR as soon as possible and immediately in case of discontinuation related to a serious adverse event. The primary reason and date of removal for all patients will be documented on the case report form (e.g. lost to follow-up, withdrawal of consent, patients wrongly included, adverse events, etc.). The final evaluation required by the protocol will be performed at the time of study discontinuation. Further follow-up should be reported. The investigator will attempt to complete all discharge procedures at the time a patient is removed from the treatment.

7.5 CONCOMITANT THERAPIES

Patients are allowed to receive full supportive care therapies concomitantly during the study. 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. Any disease progression requiring other forms of specific anti-tumour therapy will be cause for early discontinuation of study therapy. The following concomitant therapies warrant special attention.

7.5.1 Antiemetics

Premedication with anti-emetics (Setrons) per os is recommended 30 minutes before the administration of temozolomide according to local policy. In case of nausea or vomiting, additional treatment in compliance with the conventional antiemetic protocol of the individual treatment centre is allowed.

7.5.2 Colony Stimulating Factors

Routine use of granulocyte colony stimulating factor (G-CSF) is not recommended except for neutropenic patients who experienced life threatening infection. G-CSF must be discontinued at least 24 hours prior to the start of the next cycle of chemotherapy. Use of erythropoietin is allowed.

7.5.3 Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhoea or dyspnoea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy. This treatment will start as soon as the patient experienced fever ≥ 38°C and will be pursued until the disappearance of the fever and the recovery of neutrophils count > 0.5 10⁹/L, at least 48 hours.

7.5.4 Transfusions

Transfusions are recommended with irradiated blood products, i.e. red blood cells if haemoglobin is below 70 g/l and platelets if platelets count is below 20 x 10⁹/l (or 50 x 10⁹/l in case of brain tumour or a bleeding lesion). Such supportive care should be administered according to the centre practice.

7.5.5 Prophylaxis for Pneumocystis Carinii Pneumonia

Due to treatment related immunosuppression, it is recommended to provide cotrimoxazole prophylaxis: 20 to 30 mg/kg of sulfamethoxazole and 4 to 6 mg/kg trimethoprim given 3 times a week.
7.5.6 Palliative radiotherapy

If during the study patient develops a need for palliative radiotherapy, it should be ensured that this is not a manifestation of progressive disease (patients with progressive disease must discontinue study therapy). Palliative radiotherapy may be given for control of pain or for other reasons with no curative intent.

The irradiated area should be as small as possible and should never involve more than 20% of the bone marrow in any given 4-week period. Tumour progression should be ruled out by physical, biological, and radiological assessments of the tumour response. Not all measurable and/or evaluable lesions should be included in the irradiated field; otherwise the patient will be removed from the study and will not be evaluable for response. The irradiated area cannot be used as a parameter for response assessment.

7.6 TREATMENT COMPLIANCE

Temozolomide and Topotecan will be given only at the investigational sites. Thus, patient compliance monitoring is ensured.

8 RESEARCH ASSESSMENTS

MGMT, MSI AND BER

MGMT expression, MGMT gene hypermethylation, microsatellite instability (MSI) and Base Excision Repair (BER), mechanisms involved in resistance to alkylating agents and topoisomerase I inhibitors, will be analyzed by multiple techniques: MS-HRM, COBRA, HPLC and pyrosequencing on paraffin-embedded archive tumour tissue sections. Results will be correlated with response.

9 SAFETY AND EFFICACY CRITERIA

9.1 SAFETY

Each patient will be regularly assessed for any potential adverse events and disease related signs and symptoms which will be graded according to the NCI-Common Terminology Criteria AE v3.0 (can be downloaded at http://ctep.info.nih.gov) or, if not applicable, the event will be graded as 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening. All events, including those considered not related to the study treatment are reported.

All clinically significant nadir or apex laboratory values observed during the study treatment period require to be reported as adverse events in the case report form. The seriousness, the action taken regarding study drug medication and patient participation in the study, relation to study medication and the most likely cause, should then be recorded.

9.2 RESPONSE ASSESSMENT

9.2.1 Main efficacy criterion

The main efficacy criterion is tumour response after 2 cycles = 8 weeks of therapy assessed by methods described in 6.3.

Responses will be evaluated according to WHO criteria for brain tumours and miscellaneous other tumours. Definitions of measurable lesions and response criteria according to the WHO criteria are described in Appendix 2. For neuroblastoma response will be evaluated according to revised version of the International Neuroblastoma Response Criteria completed by MIBG scoring. Response criteria according this classification are described in Appendix 3.
A success is defined as CR or PR after 2 cycles of treatment. Complete and partial responses must be confirmed 4 to 6 weeks after the first response assessment. Responses leading to early surgery or a second line chemotherapy prior to confirmation at 4 weeks will be considered as responses.

9.2.2 Response review committees

Tumour responses will be reviewed by independent committees: one committee for neuroblastoma and miscellaneous other tumours cohorts and one committee for brain tumours cohort. These Committees will consist of experts in the evaluation of paediatric tumours: two paediatric radiologists, one expert in paediatric mIBG and scintigraphy and one paediatric oncologist.

The Review Committees should meet at least twice: first, when the number of evaluable patients required for the first step is reached in the neuroblastoma and secondly, at the end of the study.

For this reason, scans will be collected at the investigative sites and all patient identifiers (except for investigator number and patient number) will be removed from the scans. All documents regarding radiological tumour evaluation must be duplicated or copied on CD (format DICOM) and be available for the members of the committee within two weeks before the first review meeting.

9.2.3 Secondary endpoints for efficacy

Further re-evaluations are to be performed every 2 months to determine the best response, the durability of response and time to progression/death. The minimum necessary investigations to demonstrate persistence of response should be undertaken.

Best response is the best response designation recorded from the start of treatment until disease progression.

Regarding the time-to-event measures defined below, study enrolment refers to the date of first study therapy.

- The duration of overall response (CR or PR) is defined as the time from the date when the measurement criteria are met for CR or PR (whichever status is recorded first) until the date of first observation of objective disease progression. The duration of a CR is defined as the time from the date when the measurement criteria are met for CR until the date of first observation of objective disease progression. For responding patients not known to have died as of the data cut-off date and who do not have objective PD, duration of response will be censored at the date of the last objective progression-free disease assessment. For responding patients who receive subsequent systemic anticancer therapy (after discontinuation from the study chemotherapy) prior to objectively determined disease progression, duration of response will be censored at the date of the last objective progression-free disease assessment prior to post-discontinuation therapy.

- Time to Progressive Disease: Time to progressive disease (TtPD) is defined as the time from the date of study enrolment to the date of objectively determined PD. For patients not known to have died as of the data cut-off date and who do not have objective PD, TtPD will be censored at the date of the last objective progression-free disease assessment. For patients who receive subsequent systemic anticancer therapy (after discontinuation from the study chemotherapy) prior to objectively determined disease progression, TtPD will be censored at the date of the last objective progression-free disease assessment prior to post-discontinuation therapy.
• **Time to Treatment Failure:** Time to treatment failure (TtTF) is defined as the time from date of study enrolment to the first date among death from any cause, PD, or study treatment discontinuation due to any reason other than “protocol complete” or “satisfactory response”. For patients who discontinue due to protocol complete or satisfactory response, or for patient not known to have discontinued as of the data cut-off date, TtTF will be censored at the last contact date.

• **Overall Survival:** Overall survival time (OS) is defined as the time from the date of study enrolment to the date of death from any cause. For patients not known to have died as of the data cut-off date, OS will be censored at the last contact date.

9.2.4 **Safety criteria**

- maximum CTCAE grade (Version 3.0, NCI 2003) for laboratory and non laboratory adverse events that occur during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality.
- study discontinuations due to adverse events.
- death during the study treatment period or within 30 days of the last dose of study treatment.
- serious adverse events during the study treatment period or within 30 days of the last dose of study treatment.
- treatment-emergent adverse events during the study treatment period or within 30 days of the last dose of study treatment.

10 **STATISTICAL METHODS**

10.1 **TRIAL PLAN AND SAMPLE SIZE**

10.1.1 **Neuroblastoma**

We consider that this therapeutic combination would be of interest if the response rate (CR + PR) was superior or equal to 40%. We consider that this treatment would not be of interest if the response rate was less than or equal to 20%. A maximum of 36 evaluable patients are required for assessment of response according to a 2-stage Minimax Simon plan:

Up to 36 qualified patients will be enrolled in a two-stage sequential study with the possibility of stopping the study early for lack of efficacy. Nineteen qualified patients will be enrolled in the first stage. During this stage, if a tumour response is observed in less than 4 patients, the accrual will be stopped and the conclusion drawn that this therapy regimen is not worthy of further study in this tumour type, unless other tumour-specific clinical considerations suggest otherwise. If a tumour response is observed in at least 4 patients, accrual will continue until 17 additional qualified patients have been enrolled (a total of 36 patients). If responses are seen in fewer than 11 of 36 patients, this regimen will be deemed not worthy of any further investigation in this patient population, unless clinical considerations suggest otherwise. If responses are seen in 11 of 36 patients or more, this regimen will be recommended for further study.

The procedure described above tests the null hypothesis \(H_0\) that the true response rate is \(\leq 20\%\) against the alternative hypothesis \(H_1\) that the response rate is \(\geq 40\%\). The significance level (the probability of incorrectly rejecting \(H_0\) which is true) is 10% (computed alpha = 8.6%). The power (the probability of
rejecting $H_0$ when $H_1$ is true) is 90% (computed beta = 9.8%). If the treatment is ineffective (true response rate $\leq 20\%$), the probability of stopping at the end of the first step is 46%.

10.1.2 Brain tumours cohort
Patients will be heterogeneous in the cohort of brain tumours. Therefore, an overall response rate will not be provided. The cohort will act as a screening program to note interesting responses in several tumour types. Planned enrolment for this cohort is 30 patients.

10.1.3 Miscellaneous other solid tumours
Patients will be heterogeneous in the cohort of miscellaneous other solid tumours. Therefore, an overall response rate will not be provided. The miscellaneous other solid tumours cohort will act as a screening program to note interesting responses in several tumour types. Planned enrolment for this cohort is 30 patients.

10.1.4 Medulloblastoma cohort
Considering the results of previous studies in this disease (Temozolomide single agent: 14 responses / 40 patients, objective response rate= 35%, 95%CI, 21-52%, Riccardi personal communication; TEMIRI phase 2 study ORR = 15/46 = 33% (95% CI, 20% to 48%, Grill et al, Proceedings of ASCO 2009 and manuscript in preparation), we consider that the TOTEM combination would be of interest if the objective response rate (CR + PR) is significantly greater than 20%, equivalent to say that treatment would not be of interest if the response rate is less than or equal to 20% ($H_0$, $p_0=20\%$). Given the encouraging results already observed in the current TOTEM2 study, we want a 90% probability (beta=10%) of concluding a significant result if the response rate is 50% ($H_1$, $p_1=50\%$). Assuming a binomial distribution of the response rate, the test will be a one-sided exact test with alpha=10%. A Fleming one-stage design is chosen to evaluate the efficacy of the combination on this group of patients. Nineteen (19) evaluable patients are required. If at least 7 responses are observed, it will be concluded that this combination is sufficiently interesting to be considered in further treatment strategy evaluation in patients with medulloblastoma.

The procedure described above tests the null hypothesis $H_0$: $p_0=20\%$ against the alternative hypothesis $H_1$: $p_1=50\%$. The computed alpha error (the probability of incorrectly rejecting $H_0$ when $H_0$ is true) is 6.8%, and the power (the probability of rejecting $H_0$ when $H_1$ is true) is 91.6% (computed beta=8.4%).

10.1.5 PNET cohort
Relapsed or refractory PNET are rarer. It is thus decided to design the study as a single-arm phase 2 design for the medulloblastoma with an adequate sample size (see above), while allowing for an accrual of PNET in a separate cohort over the same recruitment period, with no sample size specification due to the rarity of the disease. However approximately 10 patients with a PNET may be recruited when 19 patients with a medulloblastoma are recruited. If 5 responses are observed among 10 PNET patients, we can conclude that the observed response rate is greater than $p_0=20\%$, with $p$-value=0.033.

10.2 ANALYSIS
The final analysis of efficacy will be made on an intention to treat basis, on all patients for whom tumour response is evaluable. Early death, before first tumour response assessment, will be considered as failure, if it is related or probably related to tumour progression or to treatment toxicity.

Exact 95% confidence intervals for the response rate will be calculated assuming a binomial distribution.
Time-to-events measures will be analyzed using the method of Kaplan and Meier.

In neuroblastoma cohort, one interim analysis is planned when data from 19 evaluable patients have been obtained. The interim analysis will be conducted to allow early stopping of the trial due to unpromising efficacy results and to explore the feasibility and safety of the temozolomide–Topotecan combination treatment. A steering committee will closely evaluate the risks and benefits of the study throughout its conduct.

In the Medulloblastoma and PNET cohorts, the observed response rate will be compared separately to the null hypothesis H0: p0=20% using exact test to provide a significance level. This analysis will be performed independently excluding the observed responses of the already recruited and evaluated patients in the TOTEM2 study (9 patients with a medulloblastoma and the 4 patients with a PNET). A secondary analysis will also be performed afterwards including those patients.

All patients who are treated with at least one component of the study regimen will be evaluated for safety. Safety analyses will include summaries of the criteria described in the 9.2.4 section.

Analyses for data with discrete dates, for example, deaths, and concomitant medications, will be done for 30 days after each patient’s last dose of study treatment. Adverse events will also be analyzed 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.

Additional analyses may be performed if deemed appropriate and will be further explained in the statistical analysis plan.

10.3 DATA-MANAGEMENT

Laboratory results and data obtained from CRF will be entered into a data base (MACRO). The data are then checked for discrepancies. Whenever necessary field visits will be made to clarify inconstancies. After checking, data files are imported into SAS, version 9.0 for Windows (SAS Institute, Cary, North Carolina, USA) and prepared for statistical analysis.

11 ADVERSE EVENTS

It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

11.1 ADVERSE EVENTS

11.1.1 Definition

An adverse event (AE) is the development of an undesirable medical condition or the worsening of a pre-existing medical condition in a clinical investigation subject. The event need not necessarily have a causal relationship with study drug and can occur at any time, including run-in or wash-out periods, even if no study treatment has been administered.

An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, x-ray, ECG).

11.1.2 Recording of Adverse Events

WHEN TO COLLECT AES
Any AE that occur from the time consent is given, during the study and in the 30 days following the last administration of study treatment should be recorded.

**WHAT AE TO COLLECT**

All observed AEs regardless of treatment group or suspected causal relationship to study drug will be assessed following NCI-CTC Criteria and recorded on the AE page(s) of the CRF, and in case of serious adverse event (SAE, refer section 11.2.1 ) in a SAE form too.

Worsening/exacerbation of sign and symptoms (in terms of severity and/or frequency, or the appearance of new manifestations/complications) of the malignancy under study or of a pre-existing illness should be reported as AE in the appropriate section of the CRF.

Lack of or insufficient clinical response, benefit, efficacy, therapeutic effect, or pharmacological action, should not be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., x-ray, ECG) should also be recorded as AE. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
- Test result leads to any of the outcomes included in the definition of a SAE, and/or
- Test result is considered to be an AE by the investigator or sponsor.

If an abnormal laboratory value is associated with a diagnosis or a clinical signs/symptoms, the diagnosis or sign/symptom should be reported as an AE and the associated laboratory result should be considered additional information to support the diagnosis.

For all AEs, the investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to IGR (see section 11.2.1, page 32). For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e., study drug or other illness). The investigator is required to assess causality and indicate that assessment on the CRF. All AEs and specially those that are serious, suspected to be related to study drug or considered significant by the investigator or clinical monitor must be followed after the time of therapy discontinuation until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and the clinical monitor or his/her designated representative.

All AEs will be recorded in the Case Reporting Form (CRF).

**11.2 SERIOUS ADVERSE EVENTS**

**11.2.1 SAE definition**

A Serious Adverse Event (SAE) is any adverse event occurring at any dose that:

- Is fatal (results in death);
- Is life-threatening;

- EudraCT: 2008-001436-12 - Confidential - Protocol v4.0, March 19, 2012
- Requires or prolongs inpatient hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect.
- Is medically significant or requires intervention to prevent one of the outcomes listed above. Any clinical event or laboratory result considered serious by the investigator and not corresponding to the criteria of seriousness defined above is nevertheless considered to be medically significant. Such an event/result can carry a risk for the patient and can require medical intervention to prevent one of the outcomes listed above (i.e. overdoses, second cancer and pregnancies can be considered medically significant).

Medical and scientific judgment should be exercised in deciding whether other situations such as important medical events that may not be immediately life-threatening or result in hospitalization but may jeopardize the safety of the patient or may require intervention to prevent one of the outcomes listed in the definition above.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A life-threatening AE is any adverse drug experience that places the patient/subject at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization is defined as in-patient hospital admission associated with an AE which occurs or worsens after the patient has been included in study. Thus attendance/ treatment at an emergency room/outpatient department does not meet hospitalization SAE criteria. However, an event which results in attendance / treatment at such a facility is an SAE if it is considered medically significant or required intervention to prevent one of the other seriousness criteria.

Note: The SAE is the diagnosis or sign /symptom, NOT the procedure or test defined as any inpatient admission.

Inpatient admission in the absence of a precipitating, treatment-emergent, clinical AE may meet criteria for “seriousness” but is not an adverse experience and thus is not subject to immediate reporting to IGR. For example:

A Pre-planned hospitalization for a condition which existed at the start of study drug and which did not worsen during the course of study drug treatment in not considered hospitalization for SAE reporting
Social admission (e.g., subject has no place to sleep; hospice facilities)
Administrative admission (e.g., for yearly physical exam)
Protocol-specified admission during a clinical trial (e.g., for a procedure required by the study protocol; clinical research. Phase I units)
Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
Inpatient admission does not include the following:
Emergency Room/Accident and Emergency/Casualty Department visits
Outpatient/same-day/ambulatory procedures
Observation/short-stay units
However, if a hospitalization for an unknown event occurs, it should be considered as a SAE.

**Prolongation of hospitalization** is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician. For protocol-specified hospitalizations in clinical trials, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e., not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to IGR.

Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient/subject.

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

### 11.2.2 SAEs reporting

Any SAE or SUSAR as defined above which occurs or comes to the attention of the investigator at any time during the study and through 30 days after the last administration of study drug, independent of the circumstances or suspected cause, must be reported immediately, within 24 hours of knowledge by fax via a SAE form to:

**UF pharmaco-vigilance at IGR: +33 (0) 1 42 11 61 50**

The Pharmacovigilance Unit at IGR will assess the adverse events in terms of seriousness, expectedness (IB), severity (NCI-CTCAE v3.0) and relationship to the study drug. All SAEs will be coded using medDRA.

Assessment of causality of SAEs may be reviewed during the study by the study coordinator.

In case of Suspected Unexpected Serious Adverse Reaction (or SUSAR), a Council for International Organization of Medical Sciences (CIOMS) form will be sent by the pharmacovigilance unit of IGR to each national sponsor within 72 hours. Each national sponsor is responsible for the declaration, to the National Ethic Committee (if required according to local regulation) and to the National competent authority. The time frame (starting from date of first knowledge of the SUSAR by the pharmacovigilance unit (mentioned in the CIOMS) is indicated in the table below.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Expected</th>
<th>Unexpected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal or life threatening</td>
<td>Annual safety report</td>
<td>7 days + 8 days (follow up report)</td>
</tr>
<tr>
<td>Others</td>
<td>Annual safety report</td>
<td>15 days</td>
</tr>
</tbody>
</table>

A copy will also be sent by the UF pharmacovigilance to all study investigators and Glaxo-SmithKline.
The pharmacovigilance unit will also send to Glaxo-SmithKline and to each national sponsor a quarterly summary table of the SAE not considered related to Temozolomide and Topotecan.

Information collected in the SAE form is crucial to assess the case and for this reason diligence in collecting as much verifiable and reliable information: BOTH QUALITY and TIMELINES are key factors.

All SAEs should be reported immediately (within 24 hours of knowledge of the event), regardless of time elapsed since last study drug dose (until 30 days after the last administration of study drug).

The investigator must provide any relevant information for the required 8 days follow up report for any SAE which is fatal or life threatening.

As far as possible, for each event, the following should be noted:

1. As clear as possible a description in medical terminology to allow for a complete medical assessment of the case and independent determination of possible causality
2. Its duration (start and end dates)
3. Action taken and the necessity for corrective treatment or not, stoppage of study drug(s) or not, and so on
4. Its intensity (grade 1-5), according to the NCI/NIH Common Terminology Criteria AE version 3.0 (a copy can be downloaded from the CTEP home page: http://ctep.info.nih.gov).
5. Its relationship to the study drug or treatment, the pathology treated, another pathology or another treatment, or to a constraint linked to the research (period without treatment, further tests required for the research, and so on). If causality is unknown and the investigator does not know whether or not study drug caused the event, it should be attributed to study drug. If the investigator's causality assessment is "unknown but not related to study drug", this should be clearly documented on study records.
6. Documentation of all co-medication and/or therapies
7. Documentation of all relevant medical history and/or co-existing diseases
8. The outcome (where applicable). For non fatal events, developments should be followed up until either recovery or recovery of a previous state of health or until the stabilization of possible after-effects.

The investigator must also attach the following to the serious adverse event report form, wherever possible:

- A copy of the summary of hospitalization or prolongation of hospitalization
- A copy of the post-mortem report
- A copy of all laboratory examinations and the dates on which these examinations were carried out, including relevant negative results, as well as normal laboratory ranges.
- All other document that he judges useful and relevant.

All these documents will remain anonymous.
Further information can be requested (by fax, telephone or when visiting) by the monitor and/or the safety manager.

All SAEs will be recorded in the Case Reporting Form (CRF) too.

11.3 ADVERSE EVENTS FOLLOW-UP
The investigator is responsible for the appropriate medical follow-up of patients until resolution or stabilization of the adverse event or until the patient's death. This may mean that follow-up should continue once the patient has left the trial.

Follow up information about a previously reported serious adverse event must be reported by the investigator to the pharmacovigilance unit within 48 hours of receiving it (on the serious adverse event report form, by ticking the box marked “Follow-up N°...”). The investigator also transmits the final report at the time of resolution or stabilization of the SAE.

He retains the documents concerning the supposed adverse event so that previously transmitted information can be completed if necessary.

11.4 ANNUAL SAFETY REPORT
The pharmacovigilance unit at IGR will issue once a year throughout the clinical trial, or on request, the annual safety report (ASR) of the study, in accordance with the detailed guidance issued by the European Commission on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use of April 2006 and the applicable revisions thereof.

The pharmacovigilance unit will send a copy of the ASR to Glaxo-SmithKline, the investigators and national sponsors.

Each national sponsor should submit the ASR within 60 days of the data lock point (date of the first authorisation of the concerned clinical trial by a competent authority in a member state) to the national competent authority and the national Ethic Committee of the concerned Member State, according to national legislation.

12 STUDY DISCONTINUATION
The study may be suspended or stopped by the sponsor in agreement with the Principal investigator and the competent authorities for following reasons:
- Significant safety or efficacy reasons
- Insufficient recruitment of patients

13 REGULATORY ASPECTS
This study will be conducted in accordance with the Declaration of Helsinki and will be consistent with Good Clinical Practice (GCP) and applicable regulatory requirements.

13.1 ETHICS AND COMPETENT AUTHORITIES
The protocol, any amendment and the subject informed consent will receive Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favourable opinion prior to initiation.
The decision of the IEC/IRB concerning the conduct of the study will be made in writing to the Sponsor before study initiation.

This protocol will also be submitted to competent authorities for approval if applicable.

### 13.2 PATIENT INFORMATION

Before agreeing to participate in this trial, all patients will be provided with sufficient information in the patient information notice/consent form prepared in the local language. This document will be submitted for approval to the IEC/IRB along with the protocol.

Because this study includes minor subjects who can only be enrolled with the consent of the subject’s legally acceptable representative, the subject must be informed about the study to the extent compatible with the subject’s understanding and, if capable, personally sign and date the consent form or patient information sheet according local regulations.

The investigator or a person designated by the Investigator must provide the subject with a copy of the consent form and full written information about the study in language that is non-technical and easily understood.

During a subject's participation in the trial, any update to the consent form and any update to the written information will be provided to the subject.

### 13.3 INVESTIGATORS/SPONSOR RESPONSIBILITIES

Institut Gustave Roussy is the coordinating sponsor of the study. There is a co-sponsor for each country involved in the study.

The (co)-sponsor of each country will provide insurance or indemnity in accordance with the applicable regulatory requirements for all patients within 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.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s).

The investigator should provide the Sponsor with his Curriculum Vitae and the co-investigator’s ones.

The Sponsor is responsible for keeping the IEC/IRB informed of significant new information about study drug. All protocol amendments will agreed upon by the sponsor and the investigator.

The sponsor has the right to prematurely discontinue the study for significant safety or efficacy reason and will notify the investigator in writing.

The sponsor and the investigational site must archive the entire documents for 15 years.

### 13.4 AUTHORIZATION FOR COMPUTERIZATION OF THE COLLECTED DATA

Before the data entry and the computerization of the collected study data the approval of applicable data protection committee will be requested.
13.5 QUALITY ASSURANCE

The Sponsor should implement procedures to assure the quality of every aspect of the study. During the course of the study, the quality assurance of IGR or external auditors contracted by the Sponsor may conduct an onsite audit visit.

Participating in this study implies acceptance of potential inspection by national or foreign health authorities.

14 MONITORING

The study will be monitored by regular site visits and telephone calls to the investigator by the coordinating sponsor clinical trial monitor.

14.1 MONITORING VERIFICATION

During site visits, the study monitor should:

- Review original patients records to verify that reported trial data are accurate, complete and verifiable from source documents. The study monitor will control for all the patients the consent forms, the eligibility criteria, the main efficacy criteria and the toxicity.

- Review drug accountability records and documented retention (study file).

- Verify that the conduct of the trial is in compliance with the currently approved protocol/amendment, procedures and GCP

Additionally, the monitor will discuss any problems with the Investigator.

Adequate time for these visits should be allocated by the investigator. The investigator should also ensure that the monitor is given direct access to source documents (i.e. hospital or private charts, original laboratory records, appointment books etc.) of the subject which support data entered in the case report forms. The investigator could designate someone to report corrections requested by the study monitor.

14.2 PROTECTION AND DEVELOPMENT OF STUDY RESULTS

Study results are the coordinating sponsor’s property. They will be communicated to health authorities and ethic committees by the sponsor and 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 sponsor, the coordinating investigator and the statistician of the study. Results from the study may not be published or presented orally without the authorization of the sponsor. The study results shall be presented and published in collaboration with the coordinating sponsor. Any publication or abstract shall be submitted to the coordinating sponsor for approval.

Authorship for publications will be defined according to the “International Committee of Medical Journal Editors” criteria NEJM, 1997 ».
REFERENCES


Clinical phase II studies of Temozolomide - Topotecan


54 HOUGHTON PJ, CHESHIRE PJ, MYERS L et al: Evaluation of 9-dimethylaminomethyl-10-
hydroxycamptothecin against xenografts derived from adult and childhood solid tumors. Cancer

55 PRATT CB, STEWART CF, SANTANA VM et al: Phase I study of Topotecan for pediatric patients with

56 TUBERGEN DG, STEWART CF, PRATT CB et al: Phase I trial and pharmacokinetic and
pharmacodynamic study of Topotecan using a five-day course in children with refractory solid tumors:

57 DAW NC, SANTANA VM, IACONO LC et al: Phase I pharmacokinetic study of Topotecan administered
orally once daily for 5 days for 2 consecutive weeks to pediatric patients with refractory solid tumors. J

58 LANGLER A, CHRISTARAS A, ABSHAGEN K et al.: Topotecan in the treatment of refractory
153-6.

59 BLANEY SM, NEEDLE MN, GILLEPSIE A et al.: Phase II trial of Topotecan administered as 72h-
continuous infusion in children with refractory solid tumors: a collaborative Pediatric Branch, National

60 STEWART CF, IACONO LC, CHINTAGUMPALA M et al.: Results of a phase II upfront window of
pharmacokinetically guided Topotecan in high-risk medulloblastoma and supratentorial primitive

61 METZGER ML, STEWART CF, FREEMAN BB et al.: Topotecan is active against Wilms’ tumor:

62 WELLS RJ, REID JM, AMES MM et al: Phase I trial of cisplatin and Topotecan in children with

63 ATHALE UH, STEWART CF, KUTTESCH JF et al: Phase I study of combination Topotecan and

64 GARAVENTA A, LUKSCH R, BIASOTTI S et al: A Phase II study of Topotecan with vincristine and

65 LANGLER A, HERO B, BERTHOLD F et al.: A phase II study with Topotecan and etoposide in

66 KRETSCHMAR C, KLETZEL M, MURRAY K et al: Paclitaxel, Topotecan, and Topotecan-
Cyclophosphamide in children with untreated neuroblastoma treated in an upfront phase II

67 SAYLORS RL, STEWART CF, ZAMBONI WC et al: Phase I study of Topotecan in combination with
cyclophosphamide in pediatric patients with malignant solid tumors: A Pediatric Oncology Group Study.

68 SAYLORS RL, STINE KC, SULLIVAN J et al.: Cyclophosphamide plus Topotecan in children with
recurrent or refractory solid tumors: A Pediatric Oncology Group phase II study. J. Clin. Oncol. 2001,

69 WATERHOUSE DO, LYDEN ER, BREITFELD PP et al.: Efficacy of Topotecan and Cyclophosphamide
given in a phase II window trial in children with newly diagnosed metastatic rhabdomyosarcoma: A

70 FRANTZ CN, LONDON WB, DILLER L et al: Recurrent neuroblastoma : Randomized treatment with
Topotecan + cyclophosphamide (T+C) vs. Topotecan alone (T). A POG/CCG Intergroup Study. ASCO
2005 meeting abstr. 22: 8512.


### APPENDIX 1. PERFORMANCE SCALE AND LANSKY-PLAY SCALE

For children aged 1 to 12 years old, a play performance scale according to LANSKY is recommended.

<table>
<thead>
<tr>
<th>ECOG Grade</th>
<th>Lansky-Play Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry out all normal activity without restriction.</td>
</tr>
<tr>
<td>100</td>
<td>Fully active, normal.</td>
</tr>
<tr>
<td>90</td>
<td>Minor restrictions in physically strenuous activity.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work.</td>
</tr>
<tr>
<td>80</td>
<td>Active, but tires more quickly.</td>
</tr>
<tr>
<td>70</td>
<td>Both greater restriction of, and less time.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50 % of waking hours.</td>
</tr>
<tr>
<td>60</td>
<td>Up and around, but minimal active play; keeps busy with quieter activities.</td>
</tr>
<tr>
<td>50</td>
<td>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>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50 % of waking hours.</td>
</tr>
<tr>
<td>40</td>
<td>Mostly in bed; participates in quiet activities.</td>
</tr>
<tr>
<td>30</td>
<td>In bed; needs assistance even for quiet play.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair.</td>
</tr>
<tr>
<td>20</td>
<td>Often sleeping; play entirely limited to very passive actualities.</td>
</tr>
<tr>
<td>10</td>
<td>No play; does not get out of bed.</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
<tr>
<td>0</td>
<td>Unresponsive</td>
</tr>
</tbody>
</table>
APPENDIX 2: TUMOUR RESPONSE ASSESSMENT ACCORDING TO WHO CRITERIA

DISEASE MEASURABILITY/EVALUABILITY

Bidimensionally measurable lesions (“measurable lesions”) include all lesions with at least one diameter > 10 mm on CT or MRI scan.

Unidimensionally measurable lesions include all the lesions that can be measured with only one diameter > 10 mm on CT or MRI scan.

Evaluable not measurable lesions include the bidimensionally and unidimensionally measurable lesions with the largest diameter below the cut-off defined previously.

RESPONSE CRITERIA

All lesions should be evaluated every 8 weeks. When multiple lesions are present, up to 6 measurable target lesions which are representative of all organs involved should be selected for the involved sites, giving the priority to bidimensionally measurable target lesions.

- Complete response (CR): disappearance of all known disease, determined by 2 observations not less than 4 weeks apart, or, if applicable, absence of residual tumour cells on histological examination. Patient has to be off steroids with stable or improving neurologic examination.

- Partial response (PR): in case of bidimensionally measurable disease, decrease by at least 50% of the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by 2 observations not less than 4 weeks apart. It is not necessary for all lesions to have regressed to qualify for partial response, but no lesion should have progressed and no new lesion should appear. If applicable, the presence of less than 10% vital tumour cells on histological examination. Steroid dose must be stable or decreasing and neurological examination stable or improving.

- No change (NC) or Stable disease (SD): for bidimensionally or unidimensionally measurable disease, < 50% decrease and < 25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by two observations not less than 4 weeks apart. No lesion should have progressed and no new lesions should appear. Patient with CNS tumour has to be on a stable or decreasing dose of steroids with a stable or improving neurologic examination.

- Progressive disease (PD): > 25% increase in the area of one or several lesions or appearance of a new lesion or CSF positivity.

DETERMINATION OF OVERALL RESPONSE

Best overall response is the best response designation recorded from the start of treatment until disease progression.
APPENDIX 3: INTERNATIONAL CRITERIA FOR DIAGNOSIS, STAGING AND RESPONSE TO TREATMENT


Table 1  DIAGNOSIS OF NEUROBLASTOMA

A diagnosis of neuroblastoma is established if:

1. An unequivocal pathological diagnosis is made from tumour tissue by light microscopy (with or without immunohistochemistry, electron microscopy, increased urine or serum catecholamines or metabolites)

OR

2. Bone marrow contains unequivocal tumour cells (eg syncitia or immunocytologically positive clumps of cells) and increased urine or serum catecholamines or metabolites

Notes

Ψ If histology is equivocal, karyotypic patterns or abnormalities in tumour cells characteristic of other tumours eg t(11:22), then exclude a diagnosis of neuroblastoma, whereas genetic features characteristic of neuroblastoma (1p deletion, N-myc amplification) would support this diagnosis.

* Catecholamines and metabolites must include dopamine, HVA and/or VMA; levels must be > 3SD above the mean for age (measured in μmol per mmol creatinine) to be considered increased, and at least two of these metabolites must be measured.

# Timed urine collections are difficult in young children so normalisation per mmol creatinine does away with the necessity for a timed collection and also avoids the problem of false negatives due to dilute urine.
Table 2 ASSESSMENT OF EXTENT OF DISEASE

<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 if available†</td>
</tr>
<tr>
<td>Metastatic sites</td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Bilateral posterior iliac crest marrow aspirates and trephine (core) bone marrow biopsies required to exclude marrow involvement. Core biopsies must contain at least 1cm of marrow (excluding cartilage) to be considered adequate.</td>
</tr>
<tr>
<td>Bone</td>
<td>MIBG† scan; ⁹⁹Tc scan is required if MIBG scan negative or unavailable, and plain radiographs of positive lesions are recommended.</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Clinical examination (palpable nodes), confirmed histologically. CT scan for non-palpable nodes (3D measurements)</td>
</tr>
<tr>
<td>Abdomen/liver</td>
<td>CT and/or MRI scan* with 3D measurements AP and lateral chest radiographs. CT/MRI necessary if chest radiograph positive, or if abdominal mass/nodes extend into the chest.</td>
</tr>
</tbody>
</table>

Notes

* Ultrasound examination considered suboptimal for accurate 3D measurements
† The MIBG scan is applicable to all sites of disease.
Table 3  INSS STAGING

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Localised tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive).</td>
</tr>
<tr>
<td>Stage 2A</td>
<td>Localised tumour with incomplete gross excision; representative ipsilateral non-adherent lymph nodes negative for tumour microscopically</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>Localised tumour with or without complete gross excision, with ipsilateral non-adherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes must be negative microscopically</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Unresectable unilateral tumours, infiltrating across the midline*, with or without regional lymph node involvement; or localised unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration or lymph node involvement.</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow liver and/or other organs (except as defined for Stage 4S).</td>
</tr>
<tr>
<td>Stage 4S</td>
<td>Localised primary tumour (as defined for Stage 1, 2A or 2B) with dissemination limited to liver, skin and/or bone marrow†. (limited to infants &lt; 1 year of age).</td>
</tr>
</tbody>
</table>

Notes

Multi-focal primary tumours (eg bilateral adrenal primary tumours) should be staged according to the greatest extent of disease, as defined above, and be followed by a subscript “M” (eg Stage 3M).

* 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.

† Marrow involvement in Stage 4S should be minimal, i.e. less than 10% nucleated cells on bone marrow biopsy or quantitative assessment of nucleated cells on marrow aspirate. More extensive marrow involvement should be considered Stage 4. The MIBG scan (if done) should be negative in the marrow for Stage 4S.
<table>
<thead>
<tr>
<th>Response</th>
<th>Primary tumour*</th>
<th>Metastatic sites*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No tumour</td>
<td>No tumour: catecholamines normal</td>
</tr>
<tr>
<td>VGPR</td>
<td>Decreased by 90-99%</td>
<td>No tumour; Residual ⁹⁹-Tc bone changes allowed</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 sites decreased by &gt; 50%; no more than 1 positive bone marrow site allowed†.</td>
</tr>
<tr>
<td>MR</td>
<td>No new lesions; &gt; 50% reduction of any measurable lesion (primary or metastases) with &lt; 50% reduction in any other; &lt; 25% increase in any existing lesion.</td>
<td></td>
</tr>
<tr>
<td>NR</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 tumour.</td>
<td></td>
</tr>
</tbody>
</table>

**Notes**
- CR: Complete Response
- VGPR: Very Good Partial Response
- PR: Partial Response
- MR: Mixed Response
- NR: No Response
- PD: Progressive Disease
- * Evaluation of primary and metastatic disease as outlined in Table 2
- † One positive marrow aspirate or biopsy is allowed for PR if this represents a decrease from the number of positive sites at diagnosis.
## APPENDIX 4: MIBG SCORING

<table>
<thead>
<tr>
<th>mIBG scoring</th>
<th>Not Done ☐</th>
<th>Done ☐</th>
<th>Date: ____________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumour uptake:</td>
<td>None ☐</td>
<td>Homogeneous ☐</td>
<td>Heterogeneous ☐</td>
</tr>
<tr>
<td>Primary tumour size:</td>
<td>Smaller than heart ☐</td>
<td>Equal to or larger than heart ☐</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skeleton</th>
<th>Score</th>
<th>Skeleton</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull and facial bones</td>
<td>Spine</td>
<td>Thoracic cage</td>
<td>Pelvis</td>
</tr>
<tr>
<td>Right humerus</td>
<td>Right femur</td>
<td>Left humerus</td>
<td>Left femur</td>
</tr>
<tr>
<td>Right forearm/hand</td>
<td>Right tibia/fibula/foot</td>
<td>Left forearm/hand</td>
<td>Left tibia/fibula/foot</td>
</tr>
</tbody>
</table>

Score definition:

0: No abnormality
1: 1 focal lesion
2: 2 focal lesions
3: 3 focal lesions
4: Diffuse < 50% of bone or > 3 focal lesions
5: Diffuse 50 – 95% of bone
6: Diffuse involving whole bone
X: Unevaluable

Total score: [___]