## E.9 : ESSAI TOTEM

SYNOPSIS

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| **EudraCT Number** | 2008-001436-12 |
| **Clinical Study** | ITCC-013-TOTEM2 |
| **Title** | Phase 2 single-arm studies of Temozolomide in combination with Topotecan in refractory or relapsing neuroblastoma and other paediatric solid tumours |
| **Study cohorts** | 5 study cohorts:<br>- Neuroblastoma<br>- Brain tumours<br>- Medulloblastoma<br>- PNET<br>- Miscellaneous other solid tumours |
| **Sponsor** | Institut Gustave Roussy, Villejuif |
| **Principal Investigators** | Neuroblastoma: Dr H. Rubie - Toulouse<br>Brain tumours: Riccardo Riccardi - Roma<br>Miscellaneous other solid tumours: Huib Caron-Amsterdam |
| **Study centers** | 23 centres in Austria, France, Italy, The Netherlands, Spain. |
| **Objectives** | **Primary:**<br>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<br>**Secondary:**<br>- To determine duration of response, time to progressive disease, time to treatment failure and overall survival<br>- To assess adverse events and toxicity profile of the combination<br>- 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<br>- Neuroblastoma cohort: Up to 36 evaluable patients<br>- Brain tumours: 30 evaluable patients<br>- Medulloblastoma : 19 evaluable patients<br>- PNET : up to 19 patients<br>- Miscellaneous other solid tumours: 30 evaluable patients.<br>To be sure to have 134 evaluable patients, 2 additional patients will be included in each cohort. |
| **Diagnosis and criteria for inclusion** | **Inclusion criteria:**<br>- 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)<br>- Relapsed or refractory tumours in which correct standard treatment approaches have failed or tumours with no known conventional therapy<br>- No more than 2 lines of prior chemotherapy (monoclonal antibody therapies, e.g. IGF1R, are not considered as lines of treatment)<br>- Measurable primary and/or metastatic disease on CT/MRI: at least one bi-dimensionally measurable lesion<br>For patients with neuroblastoma, measurable disease on CT/MRI with at least one bi-dimensionally measurable lesion or at least 4 spots on |

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| | MIBG<br>- Age at inclusion: 6 months to ≤ 20 years<br>- Lansky play score ≥ 70% or ECOG performance status ≤ 1<br>- Life expectancy ≥ 3 months<br>- Adequate organ function:<br>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;<br>Adequate renal function: normal creatinine related to patient's age:<br>0 – 1 year: ≤ 40 µmol/L<br>1 – 15 years: ≤ 65 µmol/L<br>15 – 20 years: ≤ 110 µmol/L<br>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)<br>- 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<br>- Patients previously treated with only one of the 2 drugs or none are eligible<br>- Able to comply with scheduled follow-up and with management of toxicity<br>- 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<br>- Written informed consent from patient, parents or legal guardian.<br>**Exclusion criteria:**<br>- Concurrent administration of any other anti-tumour therapy<br>- 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<br>- History of allergic reaction to the compounds or their solvents<br>- History of allergic reaction to Dacarbazine (DITC)<br>- Galactosemia, Glucose-galactose malabsorption or lactase deficiency<br>- Pregnant or breast feeding young women<br>- Presence of symptomatic brain metastases in patients with solid non-CNS tumours. |
| **Treatment, dose and mode of administration** | 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.<br>1 cycle is defined as a 28-day period.<br>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.<br>Pneumocystis Carinii Pneumonia prophylaxis is recommended, as well as premedication with anti-emetics (Setrons) during the 5 days of chemotherapy. |
| **Duration of treatment** | Maximum planned treatment duration will be 12 cycles, i.e. 12 months of treatment. |
| **Criteria for evaluation** | **Efficacy:**<br>The main efficacy criterion is tumour response after 2 cycles = 8 weeks of therapy. |

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| | **The same radiological method should be used for evaluation at study entry and for response evaluations.**<br>- Neuroblastoma: CT scan, MRI, MIBG scan. Recommended: bone marrow aspirations and biopsies.<br>- Brain tumours: MRI<br>Optional: Functional MRI, Thallium scintigraphy, and Methionine PET scan<br>- Other solid tumours: CT, MRI<br>Optional: Scintigraphy, glucose PET-scan, Bone Marrow aspirates and biopsies.<br>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.<br><br>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.<br><br>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.<br>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.<br><br>**Safety:**<br>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%, $\alpha$ = 10%, $\beta$ = 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.<br>- Medulloblastoma cohort: Fleming one stage design (p0 = 20%, p1 = 50%, $\alpha$ = 10%, $\beta$ = 10%), 19 evaluable patients will be included. If at least 7 responses are observed, it will be concluded that the combination is interesting.<br>- 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 then p0 = 20% with p-value = 0.033.<br>- 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<br>Treatment duration per patient: 12 months<br>Follow up period: 12 months<br>Planned study duration: 57 months. |