E.4 : ESSAI MEVITEM

Clinical Trial Protocol - MEVITEM

SYNOPSIS

Study title	MEVITEM: An international, randomized, open-label Phase I/II study of vismodegib in combination with temozolomide versus temozolomide alone in adult patients with recurrent or refractory medulloblastomas presenting an activation of the Sonic Hedgehog (SHH) pathway
Sponsor	Centre Léon Bérard
EudraCT Number	2011-003372-37
Coordinating Investigator	Dr Didier Frappaz
Number of patients / centers	38 patients
Design	International, randomized, open-label, multicentric phase I/II study
Study rationale	*Background* Adult medulloblastoma is a rare disease for which there is no internationally accepted standard of care. In adults, treatment regimens have typically been modelled following pediatric protocols and consist of surgical resection followed by radiotherapy and chemotherapy. However, for patients with recurrent or refractory disease the therapeutic options are limited. Medulloblastoma is thought to arise from stem cells or early progenitor cells in the cerebellum. A critical developmental process in cerebellar maturation involves expansion, migration, and differentiation of immature precursor cells from the external granule-cell layer to form the internal granule-cell layer. This process is spatially and temporally regulated by activation of the hedgehog pathway in granule-cell precursors. The Sonic Hedgehog (SHH) signalling pathway is a crucial mediator of embryogenesis and is normally inactive in most normal adult tissue. Interestingly, SHH pathway reactivation has been implicated in the pathogenesis of several cancers including medulloblastoma. *Hedgehog signalling pathway* SHH signalling is initiated by the binding of the secreted morphogen Hedgehog (Hh), to its receptor patched 1 (PTCH1). In the resting state, PTCH1 inhibits the activity of Smoothened (SMO) by preventing its localization to the cell surface. Upon Hh ligand binding, the Hh-PTCH1 complex is internalized and the repression of PTCH1 on SMO is relieved leading to SHH pathway activation. Such pathway activation leads to transcription of downstream target genes including the glioma-associated (Gli) family of transcription factors involved in proliferation, survival, and angiogenesis, Ptch1 and secreted frizzled-related protein 1 (SFRP1). In human, aberrant SHH signalling was initially shown in patients with Gorlin syndrome, a genetic disorder associated with predisposition to basal cell carcinomas (BCC) and medulloblastomas. Up to 70% of BCC patients exhibit a mutation in at least one component of the SHH pathway: either loss-of-function of PTCH1 or gain-of-function of SMO. In animal models, mice with a heterozygous deletion of *ptch1*$^{+/-}$ develop cutaneous lesion similar to those of BCC and are also susceptible to develop medulloblastoma medulloblastoma that are highly responsive to inhibition by SMO antagonists, strongly suggesting that these tumors are "addicted" to SMO activity. Indeed, inhibition of the hedgehog pathway by SMO inhibitors such as cyclopamine or Hh antagonists results in regression of medulloblastoma in PTCH1$^{+/-}$ mice. Recent studies have demonstrated an overactivation of the SHH pathway in several types of cancers: medulloblastoma, ovarian and pancreatic cancers. Such overactivation is either mutation-driven (mainly loss of function of PTCH1 or gain of function of SMO) or ligand-driven. Up to 30 to 50% of medulloblastoma showed a gene expression signature that is indicative of SHH pathway activation, but only 50% of these are associated with loss of PTCH1, loss of SUFU or gain-of-function SMO mutations (1, 2). In fact, a subset of medulloblastomas exhibits SHH pathway activation without evidence of mutations in PTCH1, SMO or SUFU. In addition to mutation-driven medulloblastoma, paracrine-driven SHH pathway activations have been described in medulloblastoma. Aberrant Hh ligand production by some tumor cells can promote

	the tumor growth through activation of the SHH pathway in the tumor stroma via a paracrine mechanism (3). *Vismodegib : a novel SMO antagonist* Vismodegib is a small-molecule antagonist of the SHH signal pathway. Specifically, vismodegib binds to and inhibits SMO, thus blocking SHH signal transduction. *In vitro* and *in vivo* preclinical studies have demonstrated inhibition of SHH signalling following vismodegib administration. Vismodegib has demonstrated efficacy against a variety of primary human tumor xenografts, including colorectal cancer (CRC) and pancreatic adenocarcinoma, and tumor cell-line xenograft models. The first clinical trial of vismodegib in solid tumors included 33 patients with locally advanced or metastatic BCC. In this study, the objective response rate for these 33 unselelected patients was 55%. Median duration of response had not yet been reached, but was 8.8 months at the time of the data cut-off for that report. RNA profiling of tumor biopsies from these patients showed increased *GLI1* mRNA expression. The most common adverse events included fatigue, weight loss, muscle spasms, hyponatremia, and dysgeusia, with only one patient being withdrawn from the study due to adverse events. In the same Phase I study, a 26-year-old man with metastatic medulloblastoma that was refractory to multiple lines of prior therapies was treated with vismodegib (540mg/day). This patient had rapid regression of the tumor and reduction of symptoms under vismodegib therapy. This partial response lasted 3 months before a new progression in extra central nervous system (CNS) sites. This case report provides the proof of concept that SMO antagonist may be an interesting therapeutic option to treat medulloblastoma patients. A phase II study leads by Dr Amar Gajjar is ongoing in adult medulloblastoma (NCT00939484). *Current therapeutic options in relapsing /refractory medulloblastoma and study proposal* Temozolomide (Temodal®) has some efficacy in paediatric medulloblastomas: an Italian phase II has reported a 47% response rate among 32 medulloblastomas and 2 supratentorial PNET, with a 67% PFS rate at 6 months. Although temozolomide is not used in the initial standard treatment of adult medulloblastomas, it is part of therapeutic options for relapsing or refractory medulloblastoma. We have currently no data on the response rate and duration of response in adults with relapsing medulloblastomas. Blocking tumor cells proliferation at different molecular levels may generate synergistic effects by killing more tumor cells. Combination therapy is therefore an attractive approach in oncology especially for patients with relapsing or refractory tumor. Several studies are currently ongoing to evaluate the clinical interest of the combination of vismodegib with chemotherapy agents in different indications (NCT00878163, NCT01064622) We propose to evaluate the safety and the activity of the combination of vismodegib + temolozomide in adult patients with recurrent, progressive, or refractory to standard therapy medulloblastoma for which there is no known curative therapy and with activated SHH pathway. The study will be a randomized, open-label, Phase I/II multicentric International study.
Study Objective	**Primary Objectives** PHASE I To evaluate the safety of a fixed dose of vismodegib in combination with temozolomide in adult patients with recurrent, progressive, or refractory to standard therapy medulloblastoma. PHASE II To estimate the efficacy of vismodegib in combination with temozolomide in adult patients with recurrent, progressive, or refractory to standard therapy medulloblastoma ↳ *measured by the 6-month progression-free rate (Complete response + Partial Response + Stable disease according to Response Evaluation Criteria In Solid Tumours – WHO criteria)).* **Secondary Objectives** PHASE I ▪ To collect preliminary results on the 6-month progression-free rate of the combination

	vismodegib + temozolomide PHASE II To estimate in the two study arms: ▪ The objective response rate (Complete response + Partial Response according to WHO criteria) after 6 months of treatment ▪ The duration of treatment response ▪ The best overall response obtained during the study ▪ The progression-free survival (PFS) ▪ The time to progression (TTP) ▪ The time to treatment failure (TTF) In the combination arm (vismodegib + temozolomide): to further evaluate the safety of the combination
Study population	**Inclusion criteria** I_1. Age ≥ 18 years I_2. Patients must have histologically confirmed medulloblastoma (including posterior fossa primitive neuroectodermal tumor) for which no known curative therapy exists I_3. Patients must have recurrent or refractory disease I_4. Patients must have evidence of measurable disease or lesion in pre-inclusion MRI. Patients with measurable spinal disease are eligible. NB: Patients with complete resection for recurrence are not eligible. I_5. Activation of the SHH pathway validated by IHC. I_6. ECOG performance status 0, 1 or 2 (Appendix 3). I_7. Life expectancy ≥ 12 weeks I_8. Patients must have normal organ and marrow function as defined below: ▪ Neutrophils ≥ 1. 5 G/L ▪ Platelets ≥ 100 G /L ▪ Hemoglobin ≥ 10g/dL ▪ Creatinine clearance ≥ 50 mL/min (calculated by Cockcroft-Gault formula or MDRD formula for patients older than 65 years) or serum creatinine within normal limits or less than 1.5 x upper limit of normal (ULN) ▪ Total bilirubin ≤ 1.5 ULN ▪ ALAT and ASAT ≤ 2.5 ULN ▪ Serum albumin ≥ 25 g/L. I_9. Patients recovered from prior treatment-related toxicity (persistent treatment related toxicity <Grade 2 are allowed (NCI-CTCAE v4.0). I_{10}. Prior therapy: ▪ No prior hedgehog antagonist vismodegib or other antagonists of the hedgehog pathway, and no prior temozolomide treatment. ▪ More than 4 weeks since prior myelosuppressive chemotherapy (6 weeks for nitrosoureas, 6 months after high dose therapy) or immunotherapy ▪ At least 3 months since prior craniospinal irradiation (≥ 23 Gy) ▪ At least 8 weeks since prior local irradiation to primary tumor ▪ At least 2 weeks since prior focal irradiation for symptomatic metastatic sites. ▪ At least 1 week since prior colony-stimulating factors (e.g., G-CSF, GM-CSF, or erythropoietin) I_{11}. Women of childbearing potential* are required to have a negative serum pregnancy test within 72 hours prior to study treatment initiation (i.e. Cycle 1 Day 1). *: Female patients who meet at least one of the following criteria are defined as women of non-childbearing potential: o ≥50 years old and naturally amenorrheic for ≥ 1 year o Permanent premature ovarian failure confirmed by a specialist gynaecologist o Previous bilateral salpingo-oophrectomy o XY genotype, Turner's syndrome, or uterine agenesis Female patient who do not meet at least of the above criteria are defined as women of childbearing potential. I_{12}. An embryo-fetal development study in rats has confirmed the teratogenic potential of vismodegib. Therefore, women of child-bearing potential and men must use two forms of effective contraception (including one barrier method- refer to Appendix 4 for acceptable method of contraception) at least 4 weeks prior to study entry, during the study period and for at least 7 months post-treatment. Prior to dispensing vismodegib, the investigator must confirm

	and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of the teratogenic potential of vismodegib. I_{13}. Ability to understand and willingness to comply to follow-up visits. I_{15}. Covered by a medical insurance (in countries where applicable) **Exclusion criteria** E_1. Tumor tissue sample not available for biological studies (from the initial diagnosis and/or relapse) E_2. Pregnant or breastfeeding women are not eligible. E_3. History of allergic reactions attributed to compounds of similar chemical composition to vismodegib. E_4. Any contraindications to temozolomide treatment as per Temodal® SPC (see Appendix 5). E_5. Patients with malabsorption syndrome or other condition that would interfere with intestinal absorption. Patients must be able to swallow capsules. E_6. Uncontrolled hypocalcemia, hypomagnesemia, hyponatremia, or hypokalemia, defined as less than the lower limit of normal despite adequate electrolyte supplementation. E_7. History of congestive heart failure. E_8. History of ventricular arrhythmia requiring medication. E_9. Congenital long QT syndrome. E_{10}. Clinically significant unrelated systemic illness (e.g., serious infection or significant cardiac, pulmonary, hepatic, or other organ dysfunction) that would compromise the patient's ability to tolerate study treatment or would likely interfere with study procedures or results. E_{11}. Patients using prohibited concomitant and/or concurrent medications (see section "Prohibited concomitant/concurrent treatments.
Study treatments	**Investigational product: vismodegib** *Class*: vismodegib is a Hedgehog pathway antagonist. *Dosage:* 150 mg orally with or without food at the same time every day. For the purposes of scheduling and evaluations, a treatment cycle is defined as 28 days of continuous vismodegib treatment. Treatment will be continued until disease progression, unacceptable toxicity or willingness to stop. *Dosage modifications*: Patients who experience grade ≥3 toxicity must have treatment withheld until recovery to grade ≤ 1. A maximum delay of four weeks is allowed for recovery from toxicity. If toxicities have not recovered after ≥4 weeks, the patient should discontinue the treatment. *Missed doses:* If a patient misses a dose or if vomiting occurs after the dose is administered, a second dose should not be administered that day. **Reference treatment: temozolomide (Temodal®) - TMZ** *Class:* alkylating agent *Dosage:* Dose in Cycle 1 is 150 mg/m^2 orally once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200mg/m^2 orally once daily for 5 days if the CTC non-haematological toxicity for Cycle 1 is ≤ Grade 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥1.5 x 10^9/L, and the thrombocyte count is ≥100 x 10^9/L. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs (refer to temozolomide SPC). *Dosage modifications:* Dose reductions and discontinuations should be applied in case of toxicity. *Missed doses*: If a patient misses a dose or if vomiting occurs after the dose is administered, a second dose should not be administered that day. **Supportive care treatment** Nausea and vomiting are very commonly associated with TMZ. Anti-emetic therapy will be

	administered prior to and/or following administration of TMZ. **Concomitant/concurrent treatments** ▪ Other concurrent anticancer or investigational agents or therapies are not allowed. ▪ No specific concomitants medications are prohibited.
Experimental Plan	*Pre-screening phase*: Before randomisation, FFPE archival tumor samples will be collected for pathological review and assessment of SHH pathway activation by immunohistochemistry (SFRP1, Gab1, Filamin A, YAP1, β-catenin). Only patients with confirmed medulloblastoma presenting an activation of the SHH pathway validated by IHC will be randomized. For patients with no activation of the SHH pathway, medical team will choose the best therapeutic options. *Treatment phase*: In the first step of the study (Phase I), 9 adult patients with relapsing or refractory medulloblastoma will be randomized (randomization ratio 2:1) to receive ▪ Arm A: the combination of vismodegib (150 mg/day continuously) with temozolomide (150 mg/m^2 during Cycle 1 [day 1 to day 5/ 28 day-cycle] and 200 mg/m^2 during subsequent cycles) (6 patients) or ▪ Arm B: temozolomide alone (150 mg/m^2 day1 to day 5/ 28 day-cycle during Cycle 1 and 200 mg/m^2 day 1 to day 5/ 28 day-cycle during subsequent cycles) (3 patients). Two interim analyses are planned during the study : - An interim safety data analysis will be performed after 3 months of follow-up of the first 9 patients. If the results are acceptable in terms of safety, 5 additional patients will be randomized in a second step of the study (Phase II – First stage): 3 in the arm A and 2 in the arm B. - The, an interim analysis of the efficacy (6-month progression-free rate) of the combination will be performed on the 9 patients included in the arm A (Phase I: 6 patients + Phase II –First stage: 3 patients). If the number of successes is ≥ 3/9, 24 additional patients will be randomized, 16 in the arm A and 8 in the arm B, in order to proceed to the second stage of the Phase II. Finally, a total of 38 patients (arm A: 25 pts + arm B: 13 pts) has to be enrolled in the study. Patient enrolment and treatment will not be stopped during the interim analysis. **NB**: At progression, a treatment with vismodegib could be proposed to patients enrolled in Arm B (compassionate use) following approval of the Steering Committee. Major and relevant eligibility criteria should be re-checked before initiation of vismodegib monotherapy. These patients will be followed-up as outlined in study flow-chart beginning at Cycle 1. The Data collected during this compassionate part will not be considered for formal statistical analysis.