Efficacy and tolerance of pazopanib in desmoid tumors : a randomised phase 2 study

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Study Title	**Efficacy and tolerance of pazopanib in desmoid tumors : a randomised phase 2 study**
Acronym	**DESMOPAZ**
Sponsor	**Institut Bergonié, Bordeaux, France**
Coordinating investigator	**Antoine Italiano, MD, PhD** **Département d'oncologie médicale** **Institut Bergonié, Bordeaux**
Sites of investigation	13 Sites : – Institut Bergonié, Bordeaux – Centre François Baclesse, Caen – Centre Georges Francois Leclerc, Dijon – Centre Oscar Lambret, Lille – Centre Léon Bérard, Lyon – Centre René Gauducheau, Nantes – Centre Antoine Lacassagne, Nice – Institut Curie, Paris – Institut Gustave Roussy, Villejuif – Institut Claudius Régaud, Toulouse – Institut Paoli Calmettes, Marseille – Assistance Publique des Hôpitaux de Paris : Hôpital ST Louis – Assistance Publique des Hôpitaux de Paris - Hôpital Saint Antoine – Centre Paul Papin – ICO Angers
Study design	**Multicentric Randomised Phase 2 Study (Simon design with 2 steps)**
Number of patients	72 patients (arm pazopanib: 43 patients ; arm méthotrexate-vinblastine : 22 ; + 10 %)
Study milestones	Inclusion of the first patient: September 2012 Inclusion period: 60 months Follow-up: 24 months Study duration: 84 months
Indication	**Adult patients with a progressive desmoid tumor**
Objectifs	➢ **<u>Main endpoint</u>** Evaluation of efficacy of: - pazopanib in terms of non-progression rate at 6 months (RECIST criteria v.1.1) - methotrexate-vinblastine in terms of non-progression rate at 6 months (RECIST criteria v.1.1) ➢ **<u>Secondary endpoints</u>** **For each arm** - Evaluation of efficacy in terms of: o Best overall response RECIST o Progression-free survival o Overall survival - Evaluation of safety (before each cycle and at the end of treatment)

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- Evaluation of pain: D0, before each cycle for the first three months, then every three months; at progression of disease and at the end of treatment (Brief Pain Inventory)
- Quality of life : D0, before each cycle for the first three months, then every three months ; at progression of diease and at the end of treatment (EORTC QLQ-C30)
- Pharmacogenomic analysis.

For patients included in arm pazopanib
- Pharmacokinetics: assessment of variability of Cmin concentration of pazopanib and correlation with outcome.
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<tr><td>Inclusion criteria</td><td>
Inclusion criteria:
1) Subjects must provide written informed consent
2) Age ≥ 18 years or legal age of consent if greater than 18 years
3) ECOG ≤ 1
4) Histologically confirmed diagnosis of desmoid tumor (central review)
5) Documented disease progression (as per RECIST) before study entry with two imaging obtained at less than 6 months interval
6) Patients must have measurable disease (outside any previously irradiated field) defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with spiral CT scan.
7) Normal LVEF
8) Adequate organ system function as defined in Table 1
Table 1: Definitions for Adequate Organ Function
<table>
<tr><th>System</th><th>Laboratory Values</th></tr>
<tr><td colspan="2">Hematology</td></tr>
<tr><td>Absolute neutrophil count (ANC)</td><td>≥1.5 X 10^9/L</td></tr>
<tr><td>Hemoglobina</td><td>≥9 g/dL (5.6 mmol/L)</td></tr>
<tr><td>Platelets</td><td>≥100 X 10^9/L</td></tr>
<tr><td>Prothrombin time (PT) or international normalized ratio (INR)[b]</td><td>≤1.2 X ULN</td></tr>
<tr><td>Activated partial thromboplastin time (aPTT)</td><td>≤1.2 X ULN</td></tr>
<tr><td colspan="2">Hepatic</td></tr>
<tr><td>Total bilirubin</td><td>≤1.5 X ULN</td></tr>
<tr><td>Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)[c]</td><td>≤2.5 X ULN</td></tr>
<tr><td colspan="2">Renal</td></tr>
<tr><td>Serum creatinine</td><td>≤1.5 mg/dL (133 µmol/L)</td></tr>
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Or, if >1.5 mg/dL: Calculated creatinine clearance (Cl_{CR}) (appropriate appendix)	≥50 mL/min
Urine Protein to Creatinine Ratio (UPC; appropriate appendix)[d]	<1

a. Subjects may not have had a transfusion within 7 days of screening assessment.
b. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.
c. Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted.
d. If UPC ≥1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible.

9)A female is eligible to enter and participate in this study if she is of:

a. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had:
   - A hysterectomy
   - A bilateral oophorectomy (ovariectomy)
   - A bilateral tubal ligation
   - Is post-menopausal

Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

Subjects using HRT must have experienced total cessation of menses for >= 1 year and be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT

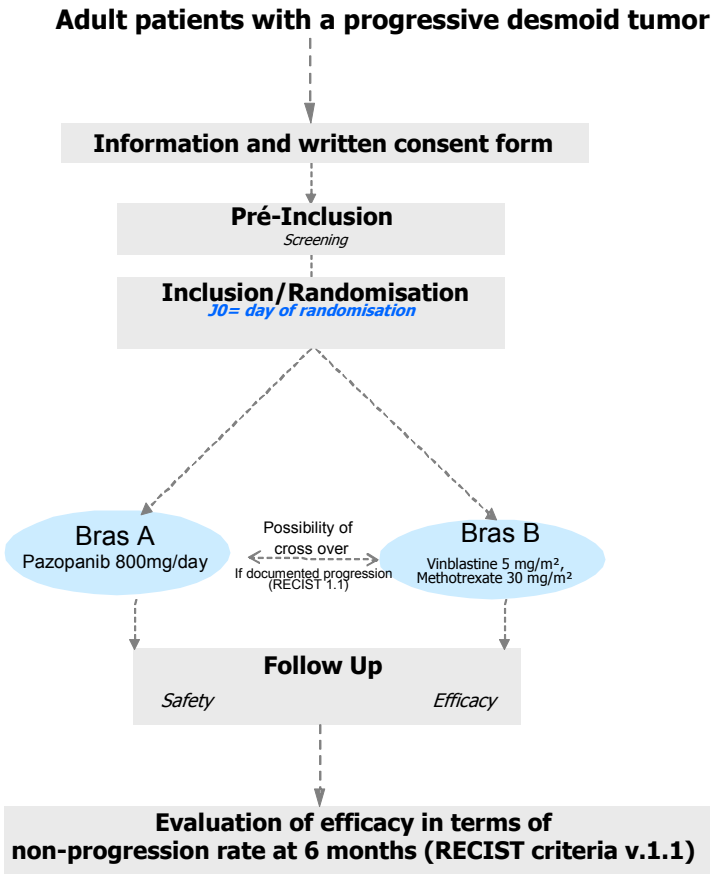
b. Childbearing potential, including any female who has had a negative serum pregnancy test within a week prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception.

   Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

   - Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product
   - Oral contraceptive, either combined or progestogen alone
   - Injectable progestogen
   - Implants of levonorgestrel
   - Estrogenic vaginal ring
   - Percutaneous contraceptive patches
   - Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year

	• Male partner sterilization (vasectomy with documentation of azoospermia) prior to the **female subject's entry** into the study, and this male is the sole partner for that subject • Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository) Female subjects who are lactating should discontinue nursing prior to the first dose of study drug and should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug. 10. Affiliation to a Social Security System
Exclusion criteria	Exclusion Criteria: 1. Patient with a history of a prior malignancy with the exception of cervical intraepithelial neoplasia; basal cell carcinoma of the skin; adequately treated localized prostate carcinoma with PSA <1.0 ng/ml; or who has undergone potentially curative therapy with no evidence of that disease for two years, and who is deemed at low risk for recurrence by his/her treating physician 2. Prior treatment by pazopanib or methotrexate-vinblastine 3. Allergy to pazopanib, methotrexate or vinblastine 4. Tumor tissue sample not available for pathological review and/or correlative studies. 5. Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to: • Known intraluminal tumor with risk of bleeding • Inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), or other gastrointestinal conditions with increased risk of perforation 6. Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to: • Malabsorption syndrome • Major resection of the stomach or small bowel. 7. Presence of uncontrolled infection. 8. Corrected QT interval (QTc) > 480 msecs using Bazett's formula 8. History of any one or more of the following cardiovascular conditions within the past 6 months: • Cardiac angioplasty or stenting • Myocardial infarction • Unstable angina • Coronary artery bypass graft surgery • Symptomatic peripheral vascular disease 10. Class II, III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) 11. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg]. Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. BP must be re-assessed on two occasions that are separated by a minimum of 1 hour; on each of these occasions, the mean (of 3 readings) SBP / DBP values from each BP assessment must be <140/90 mmHg in order for a subject to be eligible for the study

	12. History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible 13. Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major). 14. Evidence of active bleeding or bleeding diathesis. 15. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels 16. Hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks of first dose of study drug. 17. Respiratory impairment, asthma, emphysema, COPD, pneumonia, pneumothorax, pulmonary injury, 18. Severe renal insufficiency ; 19. Severe liver insufficiency; 20. History of psoriasis, rhumatoïd arthritis, alcoolism, 21. Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures. 22. Unable or unwilling to discontinue use of prohibited medications for at least 14 days or five half-lives of a drug prior to the first dose of study drug and for the duration of the study. 23. Treatment with any of the following anti-cancer therapies: • radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of pazopanib OR • chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of Pazopanib 24. Any ongoing toxicity from prior anti-tumor therapy that is >Grade 1 and/or that is progressing in severity, except alopecia. 25. Pregnancy or breast feeding 26. Concomitant therapy that can not be discontinued or substituted and is a contraindication to methotrexate: a. Probenecid (alone or in combination with sulfamethoxazole), b. Trimethoprim, c. Acetylsalicylic acid (for doses of methotrexate greater than 20 mg per week and with acetylsalicylic acid used at analgesic or antipyretic doses (≥ 500 mg per dose and / or <3 g daily) or anti-inflammatory (≥ 1 g per dose and / or> 3 g per day), d. Phenylbutazone. e. Yellow fever vaccine

Treatment plan	- Arm A : Pazopanib 800 mg orally once daily without food (at least 1 hour before or 2 hours after a meal) until disease progression with a maximum of 12 months of treatment. - Arm B : vinblastine 5 mg/m², méthotrexate 30 mg/m² IV (D1, D8, D15, D21, for the first 6 months and D1,D15 after 6 months) 28 days cycle, until disease progression and for a maximum of 12 months. • **In case of disease progression according to RECIST criteria:** . Patients initially included in arm A will have the possibility to receive arm B treatment or to stop study participation . Patients initially included in arm B will have the possibility to receive arm A treatment or to stop study participation  • **Follow-up of patients** The baseline assessment should be performed in the two weeks before study drug administration (potassium blood level should be assessed during the 24 hours before study drug administration) Baseline radiological assessment should be performed during the 4 weeks before first study drug administration. Safety evaluation will be performed at every visit : D0, D14±3, D28±5, and then every

	four weeks; as well as in the case of progression or dose adjustment. Tumor radiological assessment should be performed every 12 weeks by using RECIST (version 1.1) [Eur L Ca 45 :228-47, 2009].
Evaluation criteria	• **Main endpoint** The main endpoint is the non-progression rate at 6 months. A patient will be considered as non-progressive if he is alive without progressive disease according to RECIST v1.1. criteria at 6 months after the day of randomization. In case of cross-over before 6 months, the patients will be considered as progressive. Objective response should be confirmed by a radiological evaluation performed at least four weeks after the initial assessment. Radiological tumor evaluation should be performed by using the same technique all along the study. A blinded central review by a radiological expert will be performed to assess tumor response. The results of this review will be used for the statistical analysis. - **Secondary objective criteria** - The **best overall response is** defined as the best response observed between first study drug administration and the date of progression. In the case of cross-over, only the response observed with the first allocated arm will be considered. - The **Progression-free survival**, at 1 and 2 years, is defined as the interval between the date of randomisation and one the first following event: disease progression (RECIST v1.1) or death. Data related to patients loss of follow-up and without progression will be censored at the date of the last news. - The **overall survival** is defined as the interval between the date of randomization and the date of death. Data related to patients' loss of follow-up and alive will be censored at the date of the last news. - Safety will be assessed by using the NCICTCAE. - **Pain** will be assessed by using the Brief Pain Inventory questionnaire, at D0, and each month before the cycle (during the first three months of treatment) and then every three months, at progression and at the end of treatment. - **Quality of life** is assessed by using the QLQC30 questionnaire (EORTC) at D0, and each month before the cycle (during the first three months of treatment) and then every three months, at progression and at the end of treatment.
Statistical Analysis	• **Number of patients** This is a randomized non-comparative 2-arm phase II trial. Two groups of patients will be recruited in parallel. As such, each treatment arm will be analysed independently without any formal statistical comparison between them.

Arm A : pazopanib

We rely on an optimal two-stage Simon's design. Based on the following hypotheses:
- 60% 6-month non-progression rate (null hypothesis),
- 80% acceptable 6-month non-progression rate (alternative hypothesis),
- 5% type I error rate,
- 80% power,
a total of 43 assessable subjects/arm will be necessary, with 11 assessable subjects recruited to the first stage.

Stage 1: Following the inclusion of the first 11 assessable patients, if 7 or less patients are progression-free (complete response, partial response or stable disease),the study would be terminated early. Otherwise, the second group of 32 subjects will be recruited.

Stage 2: If at the end of recruitment, 31 patients or more are progression-free (out of the 43 evaluable patients), the corresponding treatment would be considered worthy of further testing in this disease.

To be evaluable, a subject must meet the eligibility criteria AND have received at least one administration of pazopanib (arm A) or one administration of methotrexate-vinblastine (arm B).

Arm B methotrexate + vinblastine

The randomization is based on a 2:1 ratio, with 2 patients in the pazopanib arm for 1 patient in the standard arm. Given that 43 eligible and evaluable patients are needed in the pazopanib arm and from a 2:1 randomization, 22 eligible and evaluable patients are needed in the reference arm (methotrexate-vinblastine).

Total inclusions

A total of 43 eligible and evaluable patients are needed in the pazopanib arm and 22 eligible and evaluable patients are needed in the reference arm (methotrexate-vinblastine), ie 65 eligible and evaluable patients in total. To take into account the inclusion of possible non-evaluable and / or ineligible patients (+/- 10%), we plan to include a total of 72 patients.

Statistical analysis

- *Analysis of the first endpoint*

  The 6-month non progression rate will be assessed for each arm by using the intent to treat population and will be reported with a 95% confidence interval.

- *Analysis of the secondary endpoints*

  . The first endpoint will also be assessed by using the per protocol study population.
  . The other endpoints related to efficacy (best objective response, overall survival and progression-free survival) will be assessed by using the per protocol and intent to treat population.
  . The efficacy rates will be calculated and reported for each arm with a 95% confidence interval.

	. Overall and Progression-free survivals will be estimated with the Kaplan Meier Method. Median survivals will be reported with a 95% confidence interval. The median follow-up will be estimated by using the reverse Kaplan Meier method.