Promotion Centre Léon Bérard

Portfolio études onco sarcomes - Juin 2021

DESMOVER

Multicenter prospective non-comparative randomized Phase II trial evaluating the efficacy and safety of oral methotrexate-vinorelbine versus IV methotrexate-vinblastine in children, adolescents and young adults with progressive desmoid fibromatosis type tumor.

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Groupes participants

EpSSG (European pediatric Soft Tissue Sarcoma Group):

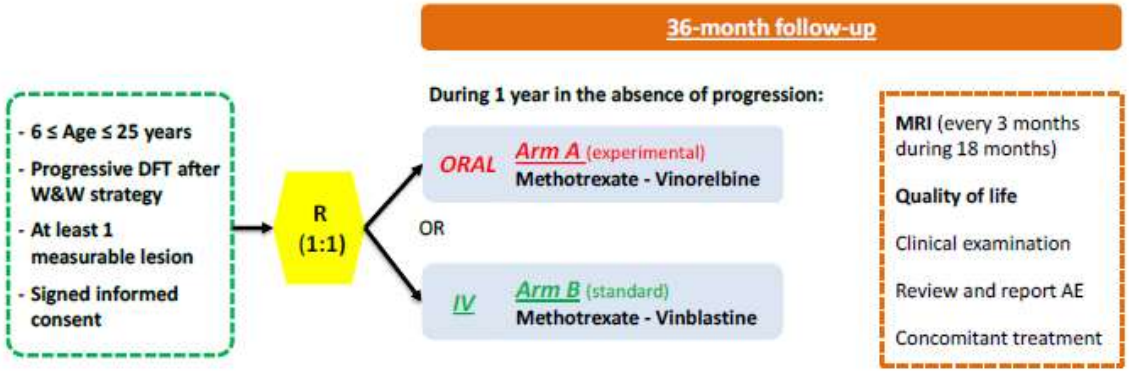
- France
- Italy
- Spain
- Netherlands
- Great Britain
- Israel

CWS (Cooperative Weichteilsarkom Studiengruppe):

- GPOH - Gesellschaft für Pädiatrische Onkologie und Hämatologie (Germany, Austria, Switzerland)
- The Swedish Working Group for Pediatric Solid Tumours (Sweden)
- PPSTSG – Polish Paediatric Solid Tumour Study Group (Poland)
- Finnish Paediatric Solid Tumour Study Group (Finland)
- Austrian Paediatric Solid Tumour Study Group (Austria)
- Swiss Paediatric Solid Tumour Study Group (Switzerland)

Molécules, schéma de traitement

Expected number of participants	**106** evaluable patients (53 patients/arm)
Study scheme	After signature of informed consent form and verification of the eligibility criteria, patients will be randomized (1:1 ratio) to receive one of the following treatments: - ***Arm A:*** **ORAL MTX/VNR *(i.e. experimental treatment).*** - ***Arm B:*** **INTRAVENOUS MTX/VBL *(i.e standard treatment).***



Nb of patients: 53 patients/arm

Indication : progressive desmoid fibromatosis type tumor

Principaux critères d'inclusion

- **Histollogically proven desmoid fibromatosis type tumor** (diagnosis by (inter-)national referent pathologist). DFT with germline *APC* carrier or non β-catenin mutated tumors are allowed.
- **Progressive disease** according to RECIST v1.1, between 2 successive MRI or CT-scans no more than 6 months apart OR **clinical progression**, documented by an MRI within the last 3 months or symptomatic and/or life threatening tumor concerns.
- At least **1 measurable lesion** according to RECIST v1.1.
- **6 years <Age ≤ 25 years** at the time of randomization.
- **Not previously treated** except with surgery and/or NSAIDs and/or hormonal therapy.

Endpoint

- The **primary objective** is to determine the **efficacy** of oral CT (experimental arm) *versus* IV CT (standard arm) in children, adolescent and young adults with **progressive or symptomatic DFT**.
- The primary endpoint is the 6-month **success rate** (binary variable), a success being defined as a patient with:
  - a clinically significant **improvement in health-related quality of life** (i.e., improvement compared to the score at baseline)

  AND
  - a **complete response (CR), partial response (PR) or stable disease (SD)** according to RECIST criteria (version 1.1).
- **Health-related Quality of life** will be evaluated using:
  - **PROMIS** (Patient-Reported Outcomes Measurement Information System): **4 questionnaires** exploring **3 areas of quality of life** were selected: overall assessment of health, pain (x2: qualitative assessment / intensity and interference), and physical condition (mobility).
  - **Others items**: Short additional evaluation by questionnaire & time in hospitalisation.

Stat: - to maintain an overall success rate of 70% of patients with significant improvement in quality of life and without progression of their disease within 6 months of starting treatment.
- to improve quality of life by 15-20% at best compared to standard treatment.

Objectifs secondaires

- To describe **progression-free rate (PFR) at 6 months (patients with a CR, PR or SD at 6 months)** according to **mutation types** (according to standard national practical).
- To establish a **local recurrence nomogram** (age, site, size, location, type of mutation…).
- To establish **European consensus on risk-stratification** for DFT within the network of EpSSG and CWS.
- To evaluate progression-free survival (PFS) of **second line treatment with homogeneous treatment strategy** based on **oral tyrosine kinase inhibitor** (TKI) (according to standard national practical).
- To **compare the results of DESMOVER** with respect to PFS, short- and long-term toxicities and quality of life with the results of **previous trials** within the desmoid-network.
- To evaluate the **safety** using the NCI-CTC AE grading scale version 5. Adverse events will be described by their intensity and severity.

Etudes ancillaires

- **Functional imaging**: **Functional MRI/radiomic** tumor evaluation for few patients, and harmonization/guidelines of radiologic evaluation for all patients (radiologists group from **CWS** and from **Utrecht/EpSSG**).
- **Prognostic value** of the plasmatic concentration of **circulating cell free DNA using ddPCR** (French team from **Marseille/EpSSG** + **CWS lab** with the same procedure).
- **Medico-economic study:** To determine **medico-economic differences** between the two treatment arms: costs of medication, costs of port-a-cath, costs of regular visists at hospital, costs of laboratory controls (**Lyon/EpSSG**).
- **PK oral VNR**: PK during first cycle in some patients from French centers (French team from **Marseille/EpSSG**).
- **Other biological proposal**:

CWS:

- To determine ***APC* germline mutation rates** in a prospective cohort of patients diagnosed with DFT, and to correlate *APC* germline mutations with family history of tumors and *CTNNB1* staining in tumor tissue.
- To characterize **potential differences** in the clinical manifestation of DFT and response to chemotherapy in patients with and **without *APC* germline mutations**.
- To explore the **somatic mutational landscape** of DFT in patients with and without *APC* germline mutations.

Curie/EpSSG**: RNAseq** and **methylation profile** analyzes to compare genomic profile between tumor with and without response (research team in Curie).

Etat d'avancement

Study calendar	• **Start:** T1 2022. • **Recruiting period:** 3 years. • **Follow-up period:** 3 years. • **Total study duration:** minimum 6 years (01.01.2022 – 31.12.2027).