DesmOVER

International randomized Phase II trial evaluating the efficacy and safety of oral methotrexate-vinorelbine combination in children, adolescents and young adults with progressive or symptomatic desmoid fibromatosis type tumor (DFT).

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DesmOVER rational: oral VNB

DESMORAL

Oral vinorelbine in advanced, progressive desmoid tumors: a national retrospective multicentric study on pediatric and adolescent patients.

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- Efficacy: **8 PR**/ **12 stabilizations** (3/3 pain control)/ **3 progressions**/
  - No CR
  - **PR: 8/23 = 35%**
  - **Tumor stabilization: 12/23 = 52%**
  - PD = 13%

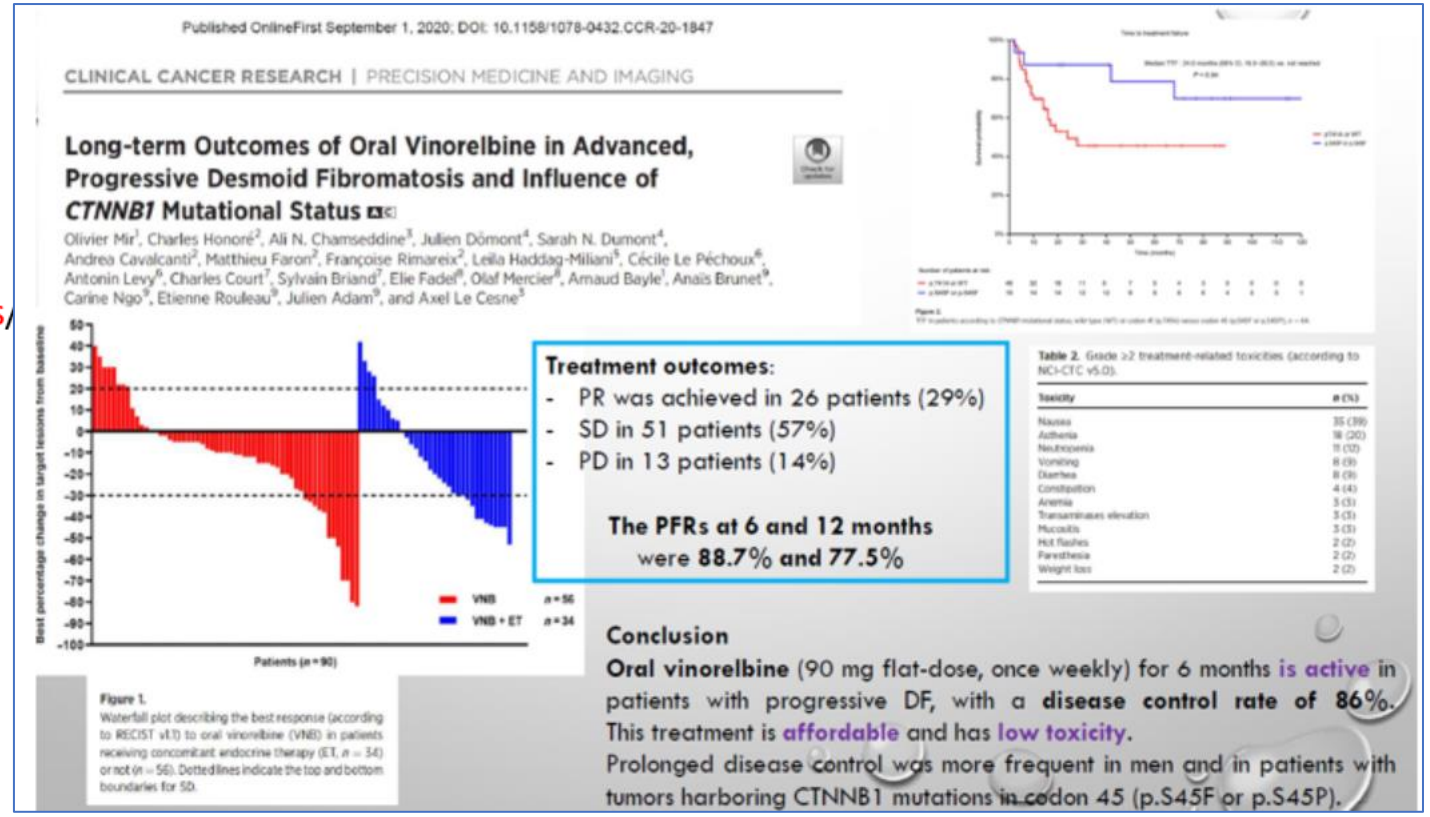
Conclusions: oral VNB

- **87% disease control**
  → Interesting to test prospectively

DESMOVER

But:

- **13% PD**
- Only 10/23 pts remained OFF therapy after this end of VNB
  → Difficulty in stopping the combination with Methotrexate
- Crucial importance of centralized **radiological review** and **MRI guidelines** needed to harmonize interpretation of tumor evolution.



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CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Long-term Outcomes of Oral Vinorelbine in Advanced, Progressive Desmoid Fibromatosis and Influence of *CTNNB1* Mutational Status

Olivier Mir[1], Charles Honoré[2], Ali N. Chamseddine[3], Julien Dômont[4], Sarah N. Dumont[4], Andrea Cavalcanti[2], Matthieu Faron[2], Françoise Rimareix[2], Leila Haddag-Miliani[5], Cécile Le Péchoux[6], Antonin Levy[6], Charles Court[7], Sylvain Briand[7], Elie Fadel[8], Olaf Mercier[8], Arnaud Bayle[1], Anais Brunet[9], Carine Ngo[9], Etienne Rouleau[9], Julien Adam[9], and Axel Le Cesne[3]

Treatment outcomes:
- PR was achieved in 26 patients (29%)
- SD in 51 patients (57%)
- PD in 13 patients (14%)

The PFRs at 6 and 12 months were 88.7% and 77.5%

Figure 1.
Waterfall plot describing the best response (according to RECIST v1.1) to oral vinorelbine (VNB) in patients receiving concomitant endocrine therapy (ET, $n = 34$) or not ($n = 56$). Dotted lines indicate the top and bottom boundaries for SD.

Conclusion
Oral vinorelbine (90 mg flat-dose, once weekly) for 6 months **is active** in patients with progressive DF, with a **disease control rate of 86%**. This treatment is **affordable** and has **low toxicity**.
Prolonged disease control was more frequent in men and in patients with tumors harboring CTNNB1 mutations in codon 45 (p.S45F or p.S45P).

Centres participants

EpSSG (European pediatric Soft Tissue Sarcoma Group):

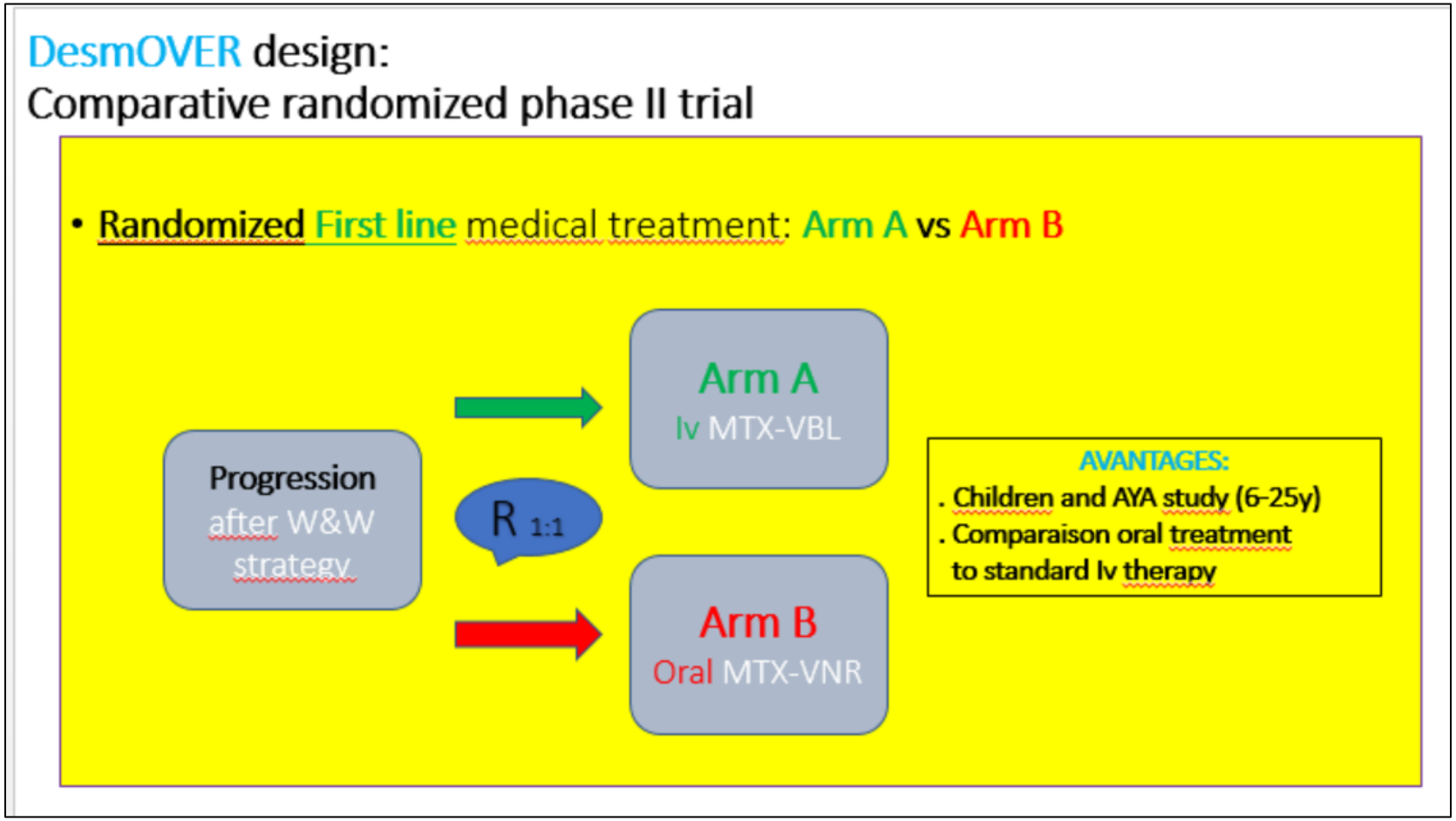
- Denmark
- France
- Italy
- Great Britain
- Israel
- Netherlands
- Spain

CWS (Cooperative Weichteilsarkom Studiengruppe):

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

*: to be confirmed

Molécules, schéma de traitement



104 patients : 52 pts / bras

Indication : 1ère ligne. Progressive or symptomatic 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 symptomatic 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 et stat succintes

- The **primary objective** is to compare **health-related quality of life** (HRQoL) and **efficacy** of oral chemotherapy (experimental arm) *versus* intravenous chemotherapy (control arm) in children, adolescent and young adults with progressive or symptomatic DFT.
- The primary endpoint (event-free survival, EFS) is a **composite criterion** combing **quality of life** and **PFS**.

  EFS will be defined as the duration between the date of randomization and the date of **first event** defined as:

  - a clinically significant **deterioration in HRQoL** compared to baseline

  OR: - a **progressive disease** 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 QoL were selected as targeted dimensions in the composite primary endpoint: overall assessment of health, pain (intensity and interference), and physical condition (mobility).

  A clinically significant deterioration in HRQoL will be defined as a decline of at least 2 points from the baseline evaluation, for at least 1 questionnaire (out of the 3 questionnaires assessing global health and pain), with confirmation of the deterioration at the subsequent evaluation.

  - **Others items**: Short additional evaluation by questionnaire & time in hospitalisation.

  EFS will be analysed using the Kaplan-Meier method and will be described in each arm in terms of 6-month EFS rate with the associated 95% CIs

Stat: - Given the 6-month **PFS rate is about 70-80%** with standard treatments, and assuming a rate of patients with QoL deterioration among progression-free patients of 30%, it appears clinically relevant to maintain an **overall success rate** (6-month EFS rate) of **70% in the experimental arm.**
- The rate of **patients with QoL deterioration** at 6 months is assumed to **decrease** from 30% in the standard arm to **10% in the experimental arm.**

Secondary objectives:

- To **compare QoL** between the **2 arms**.
- To describe **efficacy** according to **mutation types** (according to standard national practical).
- To establish a **local recurrence nomogram** (age, site, size, location, type of mutation…).
- 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.

Translational research objectives (ancillaries):

- **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-Montpellier/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: Link with APC germline mutations:

- 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

Financial aspects:

PHRC : lettre d'intention acceptée !

National cancer funding application in sep 2021: 584 k€

The budget requested aims to fund the French part of the study and a part of the European coordination fees.

RÉPUBLIQUE FRANÇAISE

INSTITUT NATIONAL DU CANCER

APPEL A PROJETS NATIONAL EN CANCEROLOGIE 2021- 2022

PHRC-K

Programme Hospitalier de Recherche Clinique en Cancérologie

LETTRE D'INTENTION – LETTER OF INTENT

Private national donation : 200 k€

FKC 2022 Project Proposals

Expression of Interest

Closing date 30th November 2021

Application soumise

Pending:
- CWS financial participation
- local data-base management in each country
- individual financing of each ancillary study

Time lines

December 2021

- Approval of final protocol (DESMOVER sub-committee working group)
- Meetings with subgroups:
  - radiology
  - ancillaries teams

Q1-2 2022

Medical Ethical Committee France
Opening of protocol first site

THANKS to all!

European Pediatric Soft Tissue Sarcoma Study Group EpSSG
Cooperative Weichteilsarkom Studiengruppe CWS der GPOH

DESMOVER

A randomised phase II trial of the European pediatric Soft Tissue Sarcoma Study Group and the Cooperative Weichteilsarkom Studiengruppe for Desmoid Tumours in children, adolescents, and young adults

EpSSG – NRSTS committee

DesmOVER study group committee

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