SYNOPSIS
PROTOCOL TOMMY - N°ICO-2012-04

A) CLINICAL TRIAL IDENTIFICATION	
SPONSOR STUDY CODE: **VERSION AND DATE:** **NCT NUMBER:**	ICO-2012-04 PROTOCOL V3.1 DU 11/10/17 NCT01794572
STUDY TITLE:	Phase I/II Study of the Combination of Escalated Total Marrow Irradiation Using Helical Tomotherapy and Fixed High-Dose Melphalan (140 mg/m2) Followed by Autologous Stem Cell Transplantation at First Relapse in Multiple Myeloma
SHORT TITLE:	TOMMY
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NUMBER OF CENTRES:	5 CHU (hematology department) et 5 CLCC (radiotherapy)
NUMBER OF PATIENTS:	MAXIMUM 44
B) SPONSOR IDENTIFICATION	
SPONSOR:	ICO, DRCI-Cellule de Promotion
SPONSOR CONTACT:	Dr François Pein Institut Cancérologie de l'Ouest, site René Gauducheau DRCI Bvd J Monod - 44805 Saint-Herblain, France. Tel: + 33.(0)2.40.67.99.08 ; Fax: + 33.(0)2.40.67.97.05 ; E-mail : francois.pein@ico.unicancer.fr
C) STUDY INFORMATION	
INDICATION:	Patients under 65 years old experiencing a first relapse of multiple myeloma.
METHODOLOGY:	Phase I/II Study of the Combination of Escalated Total Marrow Irradiation (TMI) and High-Dose Melphalan.
PRIMARY OBJECTIVE:	Determine the Maximum Tolerated Dose (MTD) of Total Marrow radiotherapy administered via TOMOTHERAPY HI-ART™ in combination with Melphalan 140 mg/m², followed by autologous stem cell transplantation (ASCT) for the consolidation of Multiple Myeloma in first relapse, in patients who previously responded to conventional chemotherapy (achieving Complete Response or Very Good Partial Response). Define the Dose-Limiting Toxicities (DLTs) at the different dose levels explored.
SECONDARY OBJECTVES:	- Acute and delayed toxicity will be assessed according to NCI-CTCAE v4 grading. - Determine the recommended dose of TMI radiotherapy for Phase II. - Efficacy will be expressed as the percentage of Complete Responses (CR) and Very Good Partial Responses (VGPR). - Additional analysis of short- and medium-term toxicity, with systematic patient follow-up until death. - In the Phase II expansion cohort at the Recommended Dose, evaluate the response rate, duration of response, and 1-year progression-free survival (PFS).

INCLUSION CRITERIA:	1. Multiple Myeloma in first relapse after either intensive treatment (excluding total body irradiation) or non-intensive treatment, whether or not initially treated under the IFM/DFCI PHRC 2009 protocol. 2. Patients with measurable disease at the time of first relapse, defined by a serum monoclonal component >5 g/L or urinary monoclonal component >200 mg/24h, who have shown a response to salvage chemotherapy (regimen at the investigator's discretion). 3. Age: 18 to 65 years. 4. Performance Status: ECOG < 2. 5. HIV seronegative. 6. Availability of an autologous graft containing at least 2.5×10^6 CD34+ cells/kg. 7. Signed informed consent.
EXCLUSION CRITERIA:	1. Multiple Myeloma at first presentation or Multiple Myeloma in second or subsequent relapse. 2. History of cancer, except for cutaneous basal cell carcinoma and in-situ cervical carcinoma. 3. History of total body irradiation. 4. History of focal irradiation resulting in a cumulative dose that, combined with TMI, would exceed 45 Gy equivalent to the spinal cord. 5. Severe cardiac history and any uncontrolled vascular disease or diabetes. 6. Pregnant patient or women of childbearing potential not using effective dual contraception. 7. Amyloidosis or MM complicated by amyloidosis. 8. Cerebral metastases from MM. 9. Platelet count < 50,000/mm³, neutrophils < 1,000/µL, hemoglobin < 8 g/dL (away from transfusion). 10. Bilirubin > 1.5× ULN, SGOT/SGPT/Alkaline phosphatase > 2× ULN. 11. Creatinine clearance < 60 mL/min. 12. Inability to ensure regular follow-up. 13. Legally incapacitated patients (under guardianship) or deprived of liberty.
PRIMARY ENDPOINT:	- Determination of the Maximum Tolerated Dose (MTD) of the combination of Total Marrow Irradiation (TMI) with Melphalan 140 mg/m², followed by reinfusion of autologous stem cells > 2.5×10^6 CD34+ cells/kg. - Types of toxicities considered as Dose-Limiting Toxicities (DLTs).
SECONDARY ENDPOINTS:	- Determination of the Recommended Dose for Phase II, defined as the dose level immediately below the Maximum Tolerated Dose (MTD). - Sterilization of osteo-medullary lesions identified as FDG-avid on PET scan prior to treatment, through the combination of TMI + Melphalan. - Phase II expansion cohort including a total of 14 patients treated at the dose level defined as the Recommended Phase II Dose. - Global toxicity analysis at short- and medium-term across all dose levels. - Analysis of 1-year progression-free survival (PFS) and overall survival (OS).

D) TREATMENT / INVESTIGATIONAL PROCEDURES DESCRIPTION

TOTAL BODY IRRADIATION: TOMOTHÉRAPY HI-ART™	The principle of Helical Tomotherapy (HT) is based on the use of a linear accelerator mounted on a CT scanner gantry, producing 6 MV photons. During treatment, the gantry rotates around the patient, who is positioned on a couch that moves longitudinally. Radiation is thus delivered in a helical mode, through successive spirals of 40 cm in length and 1, 2.5, or 5 cm in width. The energy deposition (fluence)—which defines the intensity modulation—can be adjusted using an additional collimation system composed of 64 opposing leaves, each 0.61 cm wide, operating in a binary open/closed mode.

The originality of Helical Tomotherapy (HT) compared to conventional linear accelerators lies in three key aspects:

- Helical Intensity-Modulated Radiation Therapy (IMRT): This helical delivery mode enables a continuous 360° rotation around the patient, unlike conventional accelerators which perform IMRT using either fixed beams (step-and-shoot technique) or sequential moving beams (dynamic technique).
- Image-Guided Radiotherapy (IGRT) integrated into the machine: The degradation of photon energy from 6 MV to 3 MV allows for high-quality imaging before each treatment session, enabling precise patient repositioning identical to the dosimetric CT scan.

Extended treatment length: The longitudinal movement of the treatment couch within the gantry allows for irradiation over a length of up to 1.60 meters, compared to only 40 cm with a conventional linear accelerator.

TREATMENTS:

Treatment name	Brand name	Pharmaceutical Form	Route of administration	Dosage per Administration
Melphalan	Alkeran	ALKERAN 50 mg/10 ml	intravenous	140 mg/m²

TREATMENT DESIGN :

At each TMI dose level, the patient will receive treatment according to the following procedures:

Dose level	Total dose of TMI	TMI by Tomotherapy HI-ART™	Melphalan (Mel) followed by autologous stem cell transplantation (Peripheral Blood Stem Cells (PBSCs))
1	**8 Grays**	2 sessions of **1** Gy per day, separated by 6 hours, over **4** consecutive days (total of 8 sessions).	Mel. : 140 mg/m² followed by PBSCs $\geq$ 2.5*10^6 cells CD34/Kg
2	**10 Grays**	2 sessions of **1.25** Gy per day, separated by 6 hours, over **4** consecutive days (total of 8 sessions).	Mel. : 140 mg/m² followed by PBSCs $\geq$ 2.5*10^6 cells CD34/Kg
3	**12 Grays**	2 sessions of **1.50** Gy per day, separated by 6 hours, over **4** consecutive days (total of 8 sessions).	Mel. : 140 mg/m² followed by PBSCs $\geq$ 2.5*10^6 cells CD34/Kg
4	**14 Grays**	2 sessions of **1.75** Gy per day, separated by 6 hours, over **4** consecutive days (total of 8 sessions).	Mel. : 140 mg/m² followed by PBSCs $\geq$ 2.5*10^6 cells CD34/Kg
5	**16 Grays**	2 sessions of **2** Gy per day, separated by 6 hours, over **4** consecutive days (total of 8 sessions).	Mel. : 140 mg/m² followed by PBSCs $\geq$ 2.5*10^6 cells CD34/Kg

This Phase I/II study will include the following steps:

- Collection of Peripheral Blood Stem Cells (PBSCs), unless a sufficient cryopreserved graft is already available from the first disease episode.
- Day –6 to Day –3: Total Osteo-Medullary Irradiation (IOMT) using Tomotherapy HI-ART™: 8 sessions over 4 days, with 2 sessions per day, separated by at least 6 hours, at dose levels of 1, 1.25, 1.50, 1.75, and 2 Gy. Organs at risk will be contoured and must not receive more than 8 Gy, corresponding to 50% of the IOMT dose. In particular, the total cumulative dose to the lungs must not exceed 8 Gy.
- Day –2: Administration of Melphalan 140 mg/m².
- Day 0: Reinfusion of PBSCs.

TREATMENT DURATION	The average hospitalization duration for a patient is approximately one month in a protected environment, starting immediately after the 6-day radio-chemotherapy conditioning regimen followed by autologous hematopoietic stem cell transplantation, and continuing until full hematologic recovery (toxicity < Grade 2).
E) STATISTICAL CONSIDERATIONS	
STATISTICAL METHOD :	Dose escalation will follow a modified Fibonacci scheme. At each IOMT dose level, 3 patients will be enrolled. Escalation to the next dose level will depend on the absence of Dose-Limiting Toxicity (DLT) observed during the course of treatment with IOMT + Melphalan, followed by PBSC transfusion. • If no DLT is observed among the 3 patients in the cohort, 3 additional patients will be enrolled at the next dose level. • If 1 DLT is observed among the initial 3 patients, 3 more patients will be enrolled at the same dose level. • If no additional DLT is observed among these 6 patients, dose escalation will proceed to the next level. • If 2 or more DLTs are observed among the 6 patients at a given dose level, that level will be considered to have exceeded the Maximum Tolerated Dose (MTD), and 3 additional patients will be enrolled at the previous lower dose level. ⇨ *If necessary, and based on observed toxicities and pharmacokinetic data, the protocol monitoring committee may decide to explore intermediate dose levels.*
	Definition of Dose-Limiting Toxicities (DLTs): For each cohort, DLTs will be assessed during the 90 days following PBSC transfusion, with particular attention to hematologic recovery. DLTs will be defined according to the NCI-CTCAE v4 grading scale. **Hematologic Toxicities:** • Grade 4 neutropenia lasting more than 15 days. • Grade 4 thrombocytopenia lasting more than 28 days. **Non-Hematologic Toxicities:** • Any Grade 3 or 4 non-hematologic toxicity, except: - Nausea - Vomiting - Alopecia - Mucositis - Reactions attributable to PBSC transfusion, whether immediate (e.g., post-transfusion reaction) or noisy aplasia recovery events attributable to PBSC transfusion and growth factors. **Definition of the Recommended Phase II Dose:** The Recommended Dose corresponds to the dose level immediately below the Maximum Tolerated Dose (MTD). At this dose level, 14 patients will be enrolled to further evaluate tolerability and efficacy (including complete response rate, VGPR rate, and progression-free survival). The study may include up to a maximum of 44 patients at this dose level.
F) BIOLOGICAL MATERIALS COLLECTED FOR THE ANCILLARY STUDY	
SAMPLE TYPES	Frozen plasma samples stored at –80°C. Analysis of ceramide and sphingosine-1-phosphate as predictive biomarkers of response to radiotherapy.
QUANTITY COLLECTED	80 mL in 4 collections of 2 × 10 mL each
G) STUDY DURATION	
DURATION OF INCLUSION PERIOD:	**78 months**.
TREATMENT DURATION:	The average hospitalization lasts approximately one month (until full hematologic recovery), but safety monitoring continues until Day 90 (3 months) post-transplant due to the Total Medullary Irradiation (TMI).
FOLLOW-UP PERIOD:	17 months or until disease progression or unacceptable toxicity.

ESTIMATED TIME FRAME UNTIL ANALYSIS OF THE PRIMARY OBJECTIVE:	**78 months**
STUDY COMPLETION DURATION (INCLUDING FOLLOW-UP PERIOD):	**8 years**