Clinical Study Report – Synopsis
IFM 2005-02

2 Synopsis

SYNOPSIS OF RESEARCH REPORT

Name of Sponsor /COMPANY: CHU Toulouse NAME OF FINISHED PRODUCT: Revlimid® NAME OF ACTIVE INGREDIENT(S): Lenalidomide	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY	BENEFIT OF A MAINTENANCE TREATMENT WITH LENALIDOMIDE FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH MYELOMA AGED LESS THAN 65 YEARS		
INVESTIGATORS	Coordinating investigator: Investigators: a total of 76 principal investigators enrolled patients at their sites (please refer to for a list of investigators).		
STUDY CENTERS	A total of 80 centers have participated (or are participating) in the study, in France, Belgium and Switzerland.		
PUBLICATIONS (REFERENCES)	Lenalidomide After Autologous Transplantation for Myeloma: First Analysis of a Prospective, Randomized Study of the Intergroupe Francophone Du Myelome (IFM 2005 02). Attal et al. *Blood*. 2009 **114**:Abstract #529. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. Attal et al. *N. Eng. J. Med.* 2012 **366**(19):1782-1791. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma: follow-up analysis of the IFM 2005-02 trial. Attal et al. *Blood*. 2013 **122**(21):Abstract #406. Prognostic factors affecting progression free survival for multiple myeloma patients receiving lenalidomide maintenance after autologous transplantation. Follow-up analysis of the IFM 2005-02 trial. Marit et al. *Blood*. 2013 **122**(21):Abstract #3312.		
PERIOD OF TRIAL	June 2006 to December 2017 (estimated)	CLINICAL PHASE	III
OBJECTIVES	- **Primary objective**: to evaluate the efficacy of lenalidomide in extending post-transplantation progression-free survival - **Secondary objectives:** • Progression-free survival from the date of diagnosis • Overall survival • Time to progression • Response assessment o Response rate (at least PR) o Response duration (at least PR) o Duration of complete response (CR) o Time to best response		

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	o Quantitative variation of the monoclonal peak • To assess the long-term safety of lenalidomide in post-transplantation consolidation and maintenance treatment.
STUDY DESIGN/ METHODOLOGY	A phase III, multicenter, randomized, double-blind, placebo-controlled, 2-arm parallel study conducted in France, Belgium and Switzerland to evaluate the efficacy of a maintenance treatment with lenalidomide following autologous stem cell transplantation (ASCT) in extending progression-free survival. The study consisted of 2 treatment phases: a consolidation phase, and a maintenance phase. Patients who met all eligibility criteria were randomized (1:1) to 1 of 2 treatment arms: • 2 cycles of consolidation treatment with lenalidomide 25 mg/day for 21 consecutive days of a 28-day cycle, followed by single-agent placebo maintenance therapy (Placebo Arm); • 2 cycles of consolidation treatment with lenalidomide 25 mg/day for 21 consecutive days of a 28-day cycle, followed by single-agent lenalidomide 10 mg/day starting dose maintenance therapy for 28 days per 28-day cycle (Lenalidomide Arm). Patients were stratified at randomization according to the following: • beta2 microglobulin at diagnosis (≤ 3 mg/L versus > 3 mg/L), • presence/absence of deletion in chromosome 13 (del13) at diagnosis, • response to last ASCT (CR/very good partial response [VGPR] versus PR/stable disease). Patient monitoring consisted of a baseline visit and then visits every 28 days until disease progression, and then follow-up visits every 3 months for survival. At each visit, clinical and biological variables were to be assessed. Disease response was to be evaluated by the investigator every 3 months according to International Myeloma Working Group (IMWG) criteria (Durie *et al.* 2006). All patients who discontinued the study treatment for any reason other than progression of disease, loss to follow-up, new anti-cancer treatment, death, or withdrawal of consent were to continue to be followed for PD and/or survival.
NUMBER OF PATIENTS	614 patients were planned and were randomized (307 in each arm).

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Patients were included in the study after undergoing ASCT. Information concerning the induction treatment and transplantation procedures was collected retrospectively.

Eligibility requirements were as follows:

Before autologous transplantation

- de novo myeloma
- Durie-Salmon stage: III, II, I with symptomatic bone lesion (imaging)
- Aged 18 to 65 years
- Affiliated to a social security regimen
- No symptomatic cardiac failure or coronary disease, and ventricular ejection fraction > 40%
- No liver disorders: bilirubin < 35 µmol/L, and aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase < 4 x ULN
- No pulmonary disorders: ventilation tests and diffusing capacity of the lung for carbon monoxide (DLCO) > 50% normal value (N)
- No history of renal disorder not related to the disease and defined by a creatinine > 160 µmol/L
- No history of malignancies except for basal cell carcinoma and stage I carcinoma of the cervix
- HIV negative
- Women of child bearing potential were to have a negative urine or serum pregnancy test (performed within 7 days prior to treatment start). Effective contraception was to be used during the entire treatment period (oral, injectable, transcutaneous or implantable contraceptive, surgical sterilization, intra uterine device, barrier contraceptive using spermicides, or vasectomy of partner).

Autologous transplantation period

- Good performance status (WHO 2)
- Creatinine < 250 µmol/L
- Good quality transplantation according to each center's standards (e.g., 5 x 10^6 CD34/kg for 1 transplantation)
- No other exclusion criteria

Inclusion in the study

- Written informed consent signed by the patient
- Within 6 months post-transplantation

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– No signs of progression after the transplantation (IMWG, (Durie *et al.* 2006))

– Women of child bearing potential were to have a negative urine or serum pregnancy test (performed within the 3 days prior to treatment start). Effective contraception was to be used during the entire treatment period (oral, injectable, transcutaneous or implantable contraceptive, surgical sterilization, intra uterine device, barrier contraceptive using spermicides, or vasectomy of partner). An additional method of contraception (condom) was strongly recommended during the entire treatment period. The treatment was to be dispensed within 7 days of the test being performed.

– No active chronic infection

– Satisfactory hematological recovery: PNN > 1000/mm^3 and platelets > 75000/mm^3.

– Bilirubin < 35 µmol/L and AST/ALT/AP < 3N

– Creatinine < 160 µmol/L.

TRIAL DRUG / BATCH No.	Lenalidomide (Revlimid®) (CC-5013) Capsules of 5 and 25 mg. Batch numbers: Open-label supplies (consolidation phase and after study unblinding approval): Lots 06F0152, 06F0153, 06F0188, 06F0189, 07F0141, 07F0142, 08F0014. Blinded supplies (maintenance phase prior to unblinding approval): Lots 05F0025, 06F0052, 06F0080, 06F0187, 07F0053, 07F0140, 07F0159, 08F0218, 08F0259, 09F0132, 09F0133, 09F0167, 10F0111, 10F0117.
DOSE / ROUTE / REGIMEN / DURATION	Lenalidomide was to be taken orally once daily. The consolidation treatment initial dose was 25 mg/day, for 21 consecutive days of a 28-day cycle. The initial dose of the maintenance treatment was 10 mg/day for 28 consecutive days of a 28-day cycle.
REFERENCE DRUG / STROKE (BATCH) No.	Not applicable/ placebo. Capsules of 5 mg.
DOSE / ROUTE / REGIMEN / DURATION	Placebo was to be taken orally once daily. The initial dose of the maintenance treatment was 10 mg/day for 28 consecutive days of a 28-day cycle.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary:** Progression-free survival (PFS) assessed by the Independent Review Committee (IRC) calculated for all patients

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	from the date of randomization to the date of progression or death (whatever the cause). **Secondary:** • Progression-free survival from diagnosis calculated for all patients from the date of diagnosis to the date of progression or death (whatever the cause). • Overall survival calculated from the date of randomization to the date of death. • Response duration calculated for all randomized patients with a complete or partial response (including VGPR) from the date of response criteria were met to the date of progression. • Complete response duration calculated for all randomized patients with a complete response from the date that complete response criteria were first met to the date of progression. • Time to progression calculated for all patients from the date of randomization to the date of progression. • Time to the best response calculated for all patients from the date of randomization to the date of the best response. • The percentage of the different types of response determined both locally and centrally before and after consolidation and during the maintenance phase. • The variation of the monoclonal peak calculated before and after the consolidation phase and before and after the maintenance phase best response in relation to the pre-consolidation value. Disease Responses were assessed according to the IMWG criteria by the local investigators. All Responses were reviewed by a medical monitor. In addition an IRC was set up to review the data independently.
PHARMACODYNAMICS:	Not applicable
PHARMACOKINETICS:	Not applicable
SAFETY:	Safety was to be evaluated on the basis of adverse events (graded according to the World Health Organization [WHO] toxicity criteria) reported by the investigator. All Adverse Events (AE) and Serious Adverse Events (SAE) (irrespective of their relationship to study drug) were reported and their causality determined by the investigator. However, hematologic abnormalities of grade 1 and 2 according to WHO criteria were not to be reported as AEs unless they were clinically significant. Pregnancies occurring while the patient was receiving study treatment, or within 4 weeks of the last study dose, were considered as events. The pregnancy, the favorable or unfavorable

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	evolution, and all events defined as SAEs (spontaneous abortion and any fetal malformations, stillbirth, neonatal death up to 30 days after birth, congenital anomalies) were reported.
STATISTICAL METHODS	Progression-free survival was analyzed using the survival data analysis methods of Kaplan-Meier estimation, log-rank test, and the Cox model for adjustments. The known prognostic parameters of this disease and parameters for which an imbalance was observed at randomization were investigated to determine factors predictive of survival. The initial calculation evaluated that approximately 267 subjects in each treatment group would have 90% power to detect the difference in 2 survivorship functions with a hazard rate ratio of 1.42 (placebo arm vs. lenalidomide arm) using a one-sided log rank test with overall significance level of 0.05 (adjusted for 4 interim analyses). Expecting a drop out rate of 15%, 614 subjects were to be enrolled. Full information necessary for a log-rank test to have 90% power would be achieved when approximately 300 subjects had progressed or died (PFS). Approximately 614 subjects would also have 85% power to detect the difference in 2 survivorship functions with a hazard rate ratio of 1.42 (placebo arm vs. lenalidomide arm) using a one-sided log-rank test with overall significance level of 0.025 (adjusted for one interim analysis) with a final alpha equal to 2.4%. Full information necessary for a log-rank test to have 85% power would be achieved when approximately 300 subjects had progressed or died (PFS).

KEY STUDY MILESTONES

During the conduct of the study, several events and amendments were implemented, which led to study modifications. The main milestones are summarized below:

- Accrual occurred between 12 June 2006 to 29 August 2008;
- Data Monitoring Committee (DMC) recommendation to unblind the study, following the results of a pre-planned interim analysis (September 2009 dataset) that showed significant benefit in the lenalidomide arm (Amendment #8). First unblinding occurred on 07 July 2010; patients in the placebo group were recommended to not cross over to lenalidomide treatment;
- Median follow-up (FU) of surviving patients for this cut-off: 31.2 months;
- With Amendment #9 (21 Mar 2011), the decision was made to stop treatment for all patients still on therapy after reports showed a higher level of second primary malignancies (SPMs) in the lenalidomide arm;
- Following a good survival outcome in both treatment arms, the FU period of the study was extended to obtain mature OS data (Amendments #10 and #12).

EFFICACY RESULTS:

Demography and disease characteristics: Overall, 614 patients (57% men, 43% women), aged 22-68 years (median 57 years) at randomization, mostly with a WHO Performance Status (PS) of 0 (65.0%) or 1 (33.7%), were randomized and analyzed in the ITT population. Patient characteristics and disease history (including prognostic factors) were generally well balanced between the 2 treatment arms, although analysis of CRAB criteria (calcium, renal, anemia, bone) at diagnosis showed a higher rate of anemia (hemoglobin < 10 g/dL) in the lenalidomide arm than the placebo arm (35.2% and 24.8%, respectively), and there was an imbalance in the proportion of patients with serum creatinine ≤ 177 μmol/L (90.8% and 95.3%, respectively). Overall, 76.4% of patients had Durie-Salmon stage III disease; 8.2% of patients had Durie-Salmon grade B disease, with a higher number in the lenalidomide arm than the placebo arm (11.1% and 5.2%, respectively). Adverse cytogenetics (t[4;14] or del17p) were seen in more patients in the lenalidomide arm (16.9%) than in the placebo arm (10.0%). A total of 59.7% of patients had a CR or VGPR to their last ASCT.

Primary efficacy endpoint: At the date of study unblinding (cut-off date of 07 July 2010), the primary endpoint of median PFS (IRC assessment) was significantly longer in the lenalidomide arm than the placebo arm ($p < 0.001$), hazard ratio (HR) 0.50 (95% CI: 0.39; 0.64). Analysis was based on 263 events (placebo 160; lenalidomide 103). The median PFS, estimated from Kaplan-Meier curves, was 23.0 months (95% confidence interval (CI): 21.2; 28.0) for the placebo arm and 41.2 months (95% CI: 38.3; —) for the lenalidomide arm. Sensitivity analyses, including the use of different censoring rules to comply with FDA and EMA guidance, were consistent with the primary analysis, demonstrating the robustness of this analysis.

A repeat of the analysis using data from the 01 March 2015 cut-off date continued to show a significant improvement in PFS in the lenalidomide arm (46.3 months, 95% CI: 40.4; 56.6) over the placebo arm (23.8 months, 95% CI: 21.0; 27.3) (HR 0.53, $p < 0.001$). Sensitivity analyses were again consistent with the primary analysis, demonstrating the robustness of this analysis. Subgroup analysis of PFS was performed with the 01 March 2015 cut-off date (investigator assessment) based on stratification factors (beta2 microglobulin, del13 status, reponse to last ASCT), and prognostic factors.

A significant treatment effect with respect to PFS in favor of lenalidomide-treated patients was seen in all subgroups based on stratification factors. Results in most other subgroup analyses (based on age, gender, ISS stage at diagnosis, induction therapy, number of transplants, adverse cytogenetics [del17p and/or t(4;14)], response to transplant, and prior DCEP therapy) also favoured lenalidomide treatment. However, in a proportional hazards regression model, a significant interaction with treatment was observed with post-ASCT response (with a significant treatment effect in favour of lenalidomide observed in patients who experienced VGPR/PR/SD after transplant, but not CR) and with adverse cytogenetics (with a significant treatment effect observed only in patients who did not have del17p and/or t[4;14]). In multivariate analysis, male gender, beta2 microglobulin > 3 mg/L at diagnosis, presence of del13, poorer response (PR/SD) after ASCT (investigator assessment), and inclusion of DCEP in induction therapy were all independent risk factors for PFS, associated with an increase in relative risk. A significant interaction

was observed between treatment and achieving CR during the study (p = 0.0192) meaning that this factor could be considered as a predictive factor related to treatment. No further heterogeneity of treatment effect was reported for this endpoint.

Secondary efficacy endpoints: At the cut-off date of 01 March 2015, 44.3% of patients had died: 128 (41.7%) in the lenalidomide arm and 144 (46.9%) in the placebo arm. In Kaplan-Meier analysis, the median overall survival was 90.9 months (95% CI: 81.0; —) in the placebo arm, but had not been reached in the lenalidomide arm. There was no statistically significant difference between the 2 treatment arms (HR 0.91, p = 0.423). Subgroup analysis according to stratification factors showed no difference between treatment arms in any subgroup. Multivariate analysis of OS based on various prognostic factors (as described for PFS) showed a significant interaction between treatment and gender (p = 0.0046), and between treatment and del13 status at diagnosis (p = 0.0718).

The median time to progression was 23.8 months (95% CI: 21.0; 27.3) for the placebo arm and 47.2 months (95% CI: 40.9; 58.6) for the lenalidomide arm (HR 0.51, p < 0.001).

The overall response rate (CR or VGPR per IRC assessment) after ASCT was 55.1% in the lenalidomide arm and 53.2% in the placebo arm; after completion of lenalidomide consolidation, the reponse rate was 63.9% in the lenalidomide arm and 65.0% in the placebo. Following maintenance treatment (i.e., best reponse on study), a greater depth of response was noted on study for patients in the lenalidomide arm (84.1% with CR/VGPR) compared to the placebo arm (73.0%). The median response duration for responders (patients who achieved at least a PR, investigator assessment) was 23.7 months (95% CI: 20.7; 26.9) for the placebo arm and 46.3 months (95% CI: 40.1; 56.6) for the lenalidomide arm (HR 0.53, p < 0.001).

In analysis in patients who had already experienced progression and had received a second line of therapy, median second PFS (calculated from the time of starting the second antimyeloma therapy to disease progression or death) was significantly longer in the placebo arm (18.1 months) than in the lenalidomide arm (11.4 months, HR: 1.67, p < 0.001), although since these patients were not randomized, the number of patients included in the second PFS analysis and adverse cytogenetic at baseline was imbalanced between treatment arms. Moreover, second PFS is driven largely by the type of therapy that patients received in second line. In the placebo arm, 44.2% patients received lenalidomide as second line treatment, compared to 18.9% in the lenalidomide arm (p<0.001).

Due to the prolonged treatment period in the present study, analysis of PFS2 was performed, defined as the time from randomization to objective disease progression on next-line treatment or death from any cause. Primary analysis of PFS2 showed a median PFS2 of 71.7 months (95% CI: 61.0; 87.5) in the lenalidomide arm and 59.9 months (95% CI: 51.1;69.3) in the placebo arm, with log-rank test showing a significant difference between treatment arms (HR 0.80, p = 0.041) in favour of lenalidomide. In multivariate analysis, heterogeneity of treatment effect was observed between male and female patients (p = 0.0687).

SAFETY RESULTS:

The safety population consisted of 608 treated patients; 6 patients did not receive any study treatment and were excluded from the safety analysis.

The median overall treatment duration (consolidation plus maintenance) was 116.4 weeks in the lenalidomide arm and 92.4 weeks in the placebo arm; patients received a median of 29.0 cycles and 24.0 cycles, respectively. During the overall treatment period (consolidation plus maintenance), the median cumulative dose was lower in the lenalidomide arm (7752.5 mg) than in the placebo arm (8355.0 mg, active drug during consolidation, not active drug during maintenance), with a median relative dose intensity of 0.798 in the lenalidomide arm compared to 0.939 in the placebo arm. In the lenalidomide arm, more patients had at least 1 dose reduction than in the placebo arm (75.8% versus 58.3%), and more patients had at least 1 dose interruption (79.7% versus 64.9%); the number of patients with at least 1 dose increase was similar in the lenalidomide arm and the placebo arm (13.2% and 11.8%, respectively).

As might be expected, there was little difference in AE incidence between the 2 arms during the consolidation period because all patients were to be treated with 2 cycles of lenalidomide. The main difference between the 2 arms was observed during the maintenance period, when patients received either placebo or lenalidomide maintenance treatment. Most serious treatment-emergent AEs (TEAEs) occurred during the maintenance period.

During the consolidation period, 66.9% of patients reported a treatment-related TEAE, 32.9% reported a grade 3-4 TEAE, 28.8% experienced a treatment-related grade 3-4 TEAE and 6.4% had a treatment-related serious TEAE. Thirty-one patients (31, 5.4%) discontinued treatment during the consolidation period due to TEAEs.

During the maintenance period (median of 88.6 weeks for the placebo arm and 104.6 weeks for the

lenalidomide arm), the proportion of patients reporting TEAEs was comparable in the lenalidomide and placebo arms (99.3% and 97.1%, respectively); however, grade 3-4 TEAEs (75.1% versus 32.1%), SAEs (44.7% versus 22.9%), and discontinuations due to TEAE (27.6% versus 10.0%) were reported in more patients in the lenalidomide arm than the placebo arm.

During the overall treatment period, TEAEs were reported in 99.7% of patients in the lenalidomide arm and 98.3% of patients in the placebo arm, with grade 3-4 events reported in 75.5% and 43.0%, respectively. At the SOC level, blood and lymphatic system disorders, gastrointestinal disorders, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders, nervous system disorders, and general disorder and administration site conditions were reported in more patients in the lenalidomide arm than in the placebo arm (> 10% difference). The most frequently reported TEAEs overall were neutropenia (43.8%), bronchitis (43.1%), asthenia (36.0%), nasopharyngitis (32.6%), muscle spasms (31.9%) and diarrhea (31.4%); in addition, leukopenia and thrombocytopenia were reported in 23.8% and 20.2% of patients overall, respectively, with a higher incidence in the lenalidomide arm (≥ 10% difference). Neutropenia was often severe, with grade 3-4 events reported in 53.9% of patients in the lenalidomide arm and in 17.5% of the placebo; however, these events were not often serious (lenalidomide arm 3.9%, placebo arm 0.3%) and did not often lead to treatment discontinuation (lenalidomide arm 2.3%, placebo arm 0.3%). Infections and infestations were reported in 82.7% of patients in the lenalidomide arm and 76.5% in the placebo arm, with the most frequently reported being bronchitis, nasopharyngitis and gastroenteritis (all grades), each reported in more patients in the lenalidomide arm than in the placebo arm. The most frequent grade 3-4 infections were herpes zoster (1.3% overall) and gastroenteritis (1.0% overall), both reported in more patients in the lenalidomide arm than in the placebo arm.

Despite the fact that no prophylactic antithrombotic treatment was planned in this trial, the rate of venous thromboembolic events proved to be low (lenalidomide 4.2%, placebo 2.3%). Pulmonary embolism occurred in 5 patients (1.6%) in the lenalidomide arm (versus 0 in the placebo arm), and deep vein thrombosis occurred in 4 patients in the lenalidomide arm (versus 0 in the placebo arm). No fatal thromboembolic events were reported.

Peripheral neuropathy (all grades) was reported in 13.1% of patients in the lenalidomide arm during the overall study period, and in 7.0% of the placebo arm; these were primarily grade 1-2, with grade 3-4 events reported in 0.7% and 1.3% of patients, respectively. Other neurotoxicity events, including neuralgia and peripheral sensory neuropathy, were reported with comparable incidence in the 2 treatment arms.

Serious adverse events were reported in 47.1% of the lenalidomide arm and 27.2% of the placebo arm. Serious adverse events that occurred in ≥ 2% of patients in either treatment arm were lung disorder (7.2% lenalidomide arm versus 2.3% placebo arm), neutropenia (3.9% lenalidomide arm versus 0.3% placebo arm), thrombocytopenia (2.0% lenalidomide arm versus 0.7% placebo arm), febrile neutropenia (2.3% lenalidomide arm versus 0.3% placebo arm), and bronchitis (2.0% lenalidomide arm versus 0.0% placebo arm).

A total of 272 patients in the ITT population had died during the overall study period, before the 01 March 2015 cut-off date: 128 patients (41.7%) died in the lenalidomide arm and 144 (46.9%) patients died in the placebo arm. Most of the deaths were due to progressive disease (27.4% lenalidomide arm, 34.5% placebo arm). In 9 patients (2 in the placebo arm, 7 in the lenalidomide arm), the primary cause of death was reported as toxicity. However, a total of 16 patients experienced grade 5 adverse events, with 5 in the placebo arm and 11 in the lenalidomide arm; 6 of these patients died within 30 days of their last dose of study treatment (4 in the lenalidomide arm and 2 in the placebo arm). Five of the deaths due to grade 5 AEs in the lenalidomide arm were considered to be related to study treatment (acute mesenteric and colonic ischemia, esophageal carcinoma, *Staphylococcal* sepsis, myelodysplastic syndrome, and acute leukemia).

A total of 136 patients (22.4%) discontinued study treatment due to TEAEs during the overall study period (29.7% lenalidomide arm, 14.6% placebo arm). In general, few events led to treatment discontinuation in more than 1 patient. Treatment-emergent AEs that led to treatment discontinuation in more than 3 patients overall included neutropenia, thrombocytopenia and asthenia (8 patients each overall, 1.3%), peripheral neuropathy (6 patients, 1.0%), diarrhea (6 patients, 1.0%), lung disorder (5 patients, 0.8%), gastrointestinal disorder (4 patients, 0.7%), and drug eruption (4 patients, 0.7%).

Maintenance treatment in this trial was initially to be continued until disease progression. However, due to the occurrence of a higher incidence of second primary malignancies (SPMs) in the lenalidomide arm compared to the placebo arm, maintenance treatment was discontinued for all patients still receiving study treatment (Amendment #9, 21 March 2011). The sponsor modified patient follow-up to ensure a complete record of all SPMs, to include patients who had already left the study, to ensure equivalent collection of these data in both treatment arms.

Seventy-six (76) patients in the safety population (12.5%) presented a total of 105 SPMs. Invasive SPMs

were reported in 41 patients (13.4%) in the lenalidomide arm and in 22 patients (7.3%) in the placebo arm; this was equivalent to an incidence rate of 2.57 per 100 person-years in the lenalidomide arm, compared to 1.33 per 100 person-years in the placebo arm. These included 30 patients overall (4.9%) with hematologic malignancies (21 [6.9%] in the lenalidomide arm and 9 [3.0%] in the placebo arm) and 34 patients overall (5.6%) with solid tumors (21 [6.9%] in the lenalidomide arm and 13 [4.3%] in the placebo arm). In addition, 10 patients (3.3%) in the lenalidomide arm and 7 patients (2.3%) in the placebo arm developed non-invasive skin cancers. Cox model analysis showed an increased risk in time-to-invasive SPM with lenalidomide treatment (HR 1.945, log-rank test p = 0.01037). Univariate Cox analysis of time-to-SPM showed an increased risk in patients aged ≥ 55 years, patients with ISS 3 at diagnosis, the del13 mutation at diagnosis, and induction therapy with VD over VAD. Multivariate Cox analysis showed an increased risk in time-to-SPM in female patients treated with lenalidomide, but not in male patients.

PHARMACODYNAMIC RESULTS: Not applicable.

PHARMACOKINETIC RESULTS: Not applicable.

CONCLUSIONS:

Lenalidomide maintenance with 10-15 mg daily showed a highly significant increase of PFS compared to placebo treatment. A risk reduction (for progression or death) of 50% was observed for patients who received maintenance treatment with lenalidomide (HR 0.50 [95% CI: 0.39; 0.64], p < 0.001).

This effect was demonstrated in several key prognostic subgroup analyses: this trial investigated the effect of lenalidomide on PFS in patients with low versus high beta2 microglobulin at diagnosis, patients with or without deletion in chromosome 13, and in patients who achieved a response of at least VGPR after transplant versus those who did not achieve VGPR. In all these subgroups the PFS gain proved to be highly significant for patients being treated with lenalidomide versus those treated with placebo.

Treatment with lenalidomide monotherapy seemed to be generally safe and clinically manageable. The AE reported most often in the lenalidomide arm was neutropenia (61.4% of patients during the overall treatment period), but this did not translate into febrile neutropenia (2.3% of lenalidomide-treated patients). Neurotoxicity was less marked than that observed with thalidomide, and the rate of VTEs (4.2% in the lenalidomide arm) was low despite the lack of thromboprophylaxis.

Maintenance treatment was discontinued due to TEAEs in 27.6% of the patients in the lenalidomide arm, compared to 10.0% in the placebo arm.

Invasive second primary malignancies occurred more often in the lenalidomide arm (13.4%, 2.57 per 100 person-years) than the placebo arm (7.3%, 1.33 per 100 patient years). Lenalidomide treatment was associated with an increase risk of SPM. With this increased risk of SPM in mind, the benefit-risk assessment for lenelidomide favors the benefit seen with treatment in terms of the PFS improvement. Continued follow-up for survival will be important.

ATTACHMENT

SPONSOR

CHU de Toulouse
Toulouse University Hospital Centre
Hôtel Dieu - 2 rue Viguerie –
31052 TOULOUSE Cedex

LISTE INVESTIGATEURS DES CENTRES FRANÇAIS

AIX-EN-PROVENCE
Hémato-Oncologie – CH Aix-en-Provence – Avenue des tamaris – 13 616 AIX-EN-PROVENCE

ALBI
Clinique Claude Bernard – Service d'Oncologie – 1 rue du Père
Colombier – 81 000 ALBI

AMIENS I
Hématologie clinique - CHRU - Hôpital Sud - avenue Laennec – 80054 Amiens cedex 1

AMIENS II
Médecine interne – CHRU – 1 place Victor Pauchet – 80 054 Amiens cedex 1

ANGERS
Hématologie - CHRU - Hôpital du Bocage - 4 rue Larrey - 49033 Angers cedex 01

ANNECY
Hématologie - Centre Hospitalier de la région d'Annecy – 1 avenue de l'Hôpital METZ-TESSY – BP 90074
74374 PRINGY cedex

ARGENTEUIL
Hématologie – SIDA – Centre Hospitalier Argenteuil Victor Dupouy – 69, rue du Lieutenant-Colonel Prud'hon –
95100 ARGENTEUIL

ARRAS
Hématologie clinique – CH d'Arras – 57 ave Winston Churchill – sac postal 6 – 62 022 ARRAS Cedex

AUCH
Service de Médecine – Centre hospitalier – Route de Tarbes – BP 382 - 32 000
AUCH

AVIGNON
Hématologie - Centre Hospitalier H.Duffaut - 305 rue R.Follereau - 84902 Avignon cedex 09

BAYONNE
Hématologie - Centre Hospitalier de la côte basque - 13 av Interne Jacques Loëb – 64109 Bayonne

BESANÇON
Hématologie - Hôpital Jean Minjoz - boulevard Fleming - 25030 Besançon
cedex

BLOIS
Médecine interne - Centre Hospitalier - 41016 Blois cedex

BOBIGNY
Hématologie - Hôpital Avicenne - 125 route de Stalingrad - 93009 Bobigny cedex

BORDEAUX PESSAC
Maladies du sang - CHRU - Hôpital du Haut Lévêque - Centre François Magendie - avenue de Magellan –33604 Pessac

BORDEAUX BERGONIE
Hématologie - Institut Bergonié - 229 cours de l'Argonne - 33076 Bordeaux cedex

BORDEAUX NORD
Polyclinique Bordeaux Nord Aquitaine - Onco-Hématologie - 15 à 33 rue Claude Boucher - 33300 BORDEAUX

BREST
Hématologie - Hôpital A.Morvan - 5 avenue Foch - 29609 Brest cedex

BRIIS-SOUS-FORGES
Service d'Hématologie Soins de suite – Département Onco-Hématologie – Centre médical de Bligny – 91640 BRIIS-SOUS-FORGES

CAEN CFB
Hématologie – IHBN CHU Côte de Nacre - 4e Etage Bât FEH - Avenue Côte de Nacre - 14033 CAEN cedex

CAEN CHU
Hématologie – CHU - avenue G.Clemenceau - 14033 Caen cedex

CAEN LE PARC
Polyclinique du Parc – 20 avenue G. Guynemer – 14 052 CAEN cedex 4

CHALON sur SAONE
Service d'Hématologie Oncologie – Centre Hospitalier William Morey – 4 rue du Capitaine Drillien 71100 CHALON-SUR-SAONE

CHARTRES
Hématologie Oncologie médicale – CH de Chartres – BP 407 – 28 018 CHARTRES cedex

CLAMART - PERCY
Hématologie - Hôpital d'instruction des armées Percy - 101 avenue H.Barbusse - 92141 Clamart cedex

CLAMART - BECLERE
Service de médecine interne et d'immunologie clinique - Hôpital Antoine Béclère - Université Paris Sud - 157 rue de la porte de Trivaux - 92140 Clamart

CLERMONT – FERRAND
CHU Estaing - Service de thérapie cellulaire et Hématologie clinique adulte - 1 Place Lucie Aubrac – 63000 Clermont-Ferrand

CLERMONT – FERRAND Pôle Santé République
Unité d'Oncologie Médicale – Pole Santé République – 105 avenue de la République - 63050

COLMAR
Oncohématologie - CH Louis Pasteur - 39 avenue de la liberté - 68024
Colmar cedex

CRETEIL
Unité Hémopathies Lymphoïdes – CHU Henri Mondor – 51, avenue du Maréchal de Lattre de Tassigny – 94010 Créteil

DIJON
Hématologie Clinique – CHRU Dijon - Hôpital des Enfants – 10 bd du Maréchal De Lattre de Tassigny – 21000 Dijon

DUNKERQUE
Hématologie – Centre Hospitalier Général – BP 6 – 367 rue L. Herbeaux – 59 385
Dunkerque

GRENOBLE I
Hématologie - CHRU - Hôpital A.Michallon - CS10217- 38043 Grenoble cedex 09

GRENOBLE II
Convention : Groupe Hospitalier Mutualiste de Grenoble – 8 rue Docteur Calmette – 38 028 GRENOBLE cedex 1
Groupe Hospitalier Mutualiste de Grenoble -Institut Daniel Hollard - 12 rue Docteur Calmette - 38028 GRENOBLE Cedex -

LA ROCHE SUR YON
Médecine Onco-Hématologie - Centre hospitalier départemental - 85025 La Roche sur Yon cedex

LAVAL
Médecine interne - Centre Hospitalier - 33 rue du haut rocher - 53015 Laval
cedex

LE HAVRE
Service de Rhumatologie – Centre Hospitalier du Havre – Avenue Pierre Mendes France – 76 290 MONTIVILLIERS

LE MANS CH
Médecine interne - Centre hospitalier - 194 avenue Rubillard - 72037 Le Mans cedex

LE MANS CJB
Onco-hématologie - Centre Jean Bernard - 9 rue Beauverger - 72000 Le Mans

LIBOURNE
Médecine Interne – Hématologie – Hôpital Robert Boulin – 112 rue de la Marne – BP 199 – 33 505 Libourne cedex

LILLE
Maladies du sang - CHRU - Hôpital Claude Huriez - 1 place de Verdun - 59037 Lille cedex

LORIENT
Service Hématologie – Hôpital Du Scorff -- 5, Avenue Choiseul – BP12233 - 56322 LORIENT Cedex
Hôpital Du Scorff - Service d'Oncologie - Recherche Clinique - 2ème étage - 5, Avenue Choiseul – BP 12233 -
56322 LORIENT Cedex

LYON HEH
Hématologie – Centre Hospitalier Lyon Sud – Pavillon Marcel Bérard, secteur 1G, 1er étage – 165 chemin du Grand
Revoyet - 69495 Pierre – Bénite cedex

LYON SUD
Hématologie - Centre Hospitalier Lyon sud – Pavillon 1F- 165 chemin du Grand Revoyet - 69495 Pierre – Bénite cedex

LYON CLB
Centre Léon Bérard - 28 rue Laennec - 69008 Lyon

MARSEILLE IPC
Hématologie - Institut Paoli Calmette - 232 boulevard Sainte Marguerite - 13273 Marseille cedex

MARSEILLE CHU
Service d'Hématologie – Hôpital de la Conception – 147 Bld Baille - 13385 Marseille cedex 05

METZ
Service d'Hématologie - Hôpital de Mercy - 1 allée du Château - CS 45001 -
57085 METZ cedex 03

NANCY
Hématologie - CHRU - Hôpitaux de Brabois - rue du Morvan, 54511 Vandoeuvre cedex

NANTES CHRU
Hématologie - CHRU - Hôtel Dieu – 1 place A.Ricordeau - 44093 Nantes cedex 01

NANTES CCS
Centre Catherine de Sienne – 2 rue Eric Tabarly – BP 20215 – 44 202 NANTES cedex 2

NICE MI
Médecine interne - Oncologie - Hôpital de l'Archet 1 - 151 route de Saint Antoine de Ginestière - BP 3079 - 06202 Nice cedex 3

NICE Hémato
Hématologie Clinique – Hôpital Archet 1 – 151 route de Saint Antoine de la Ginestière – BP 3079 – 06 202 NICE cedex 3

NICE CAL
Oncologie médicale et Hématologie - Centre Antoine Lacassagne - 33 avenue de Valombrose,

PARIS St-Antoine
Maladies du sang - CHU - Hôpital St-Antoine - 184 rue du Faubourg St-Antoine - 75571 Paris cedex 12

PARIS Hôtel-Dieu
Département d'hématologie du Pr M. MOHTY - Hôpital St-Antoine - 184 rue du Faubourg St-Antoine – 75571 Paris cedex 12

PARIS Cochin
Hôpital Cochin - Hématologie Clinique - Pavillon Achard - 27, rue du Faubourg Saint-Jacques - 75679 PARIS Cedex 14

PARIS Necker
Hématologie Adulte – Hôpital Necker – 149 rue de Sèvres –
75015 PARIS

PARIS St-Louis
Service d'Immuno-Hématologie – Hôpital Saint-Louis – 1 avenue Claude Vellefaux – 75475 PARIS cedex 10

POITIERS
Hématologie - CHRU - Hôpital Jean Bernard - 350 avenue Jacques Coeur - 86021 Poitiers cedex
Pôle régional de Cancérologie – Secteur tertiaire – CHU de la Milétrie – 2 rue de la Milétrie – BP 577 – 86 021 Poitiers

REIMS
Hématologie - Hôpital R.Debré – Avenue du Général Koenig – 51092 Reims cedex

RENNES MI
Médecine interne - CHRU - Hôpital Sud - 16 boulevard de Bulgarie - BP 5612 – 35056 Rennes cedex 02

RENNES Pontchaillou
Hématologie - CHRU - Hôpital de Pontchaillou – 2 rue Henri le Guillou - 35033 Rennes cedex

ROANNE
Service d'Oncologie médicale – Centre Hospitalier de Roanne – 28, rue de Charlieu – BP 511 – 42 328 ROANNE cedex

RODEZ
Cancérologie - Centre hospitalier - 1 rue Combarel - BP 815 - 12008 Rodez cedex

ROUEN II
Hématologie - Centre Henri Becquerel - rue d'Amiens - 76038 Rouen cedex

ST-BRIEUC
Hémato-Oncologie – Centre Hospitalier Yves le Foll – BP 2367 - 22 027 St-Brieuc cedex 1

ST-ETIENNE
Département d'Hématologie – Institut de Cancérologie de la Loire – 108 bis, avenue Albert Raimond – 42 271 ST-PRIEST-EN-JAREZ cedex

STRASBOURG
Hématologie - CHRU - Hôpital de Hautepierre - BP 428 - 67098 Strasbourg cedex

TARBES l'Ormeau
Oncologie - Clinique de l'Ormeau - 10 chemin de l'Ormeau - 65000 Tarbes

TARBES CH
Médecine interne - Centre hospitalier - boulevard de Tassigny – BP 1330 - 65013 Tarbes cedex

TOULOUSE Hémato
Hématologie, IUCT-Oncopole, 1 avenue Irène Joliot-Curie - 31059 TOULOUSE cedex 9

TOULOUSE Rhumato
Rhumatologie - CHRU - Hôpital Rangueil - 1 avenue Jean Poulhès – TSA 50032 – 31403 Toulouse cedex 9

TOULOUSE MI
Médecine Interne IUCT-Oncopole – 1 avenue Irène Joliot-Curie – 31059 TOULOUSE cedex9

TOURS
Onco-hématologie - CHRU - Hôpital Bretonneau - 2 bis boulevard Tonnelé - 37044 Tours cedex

TROYES
Hématologie Clinique – Centre Hospitalier de Troyes – 101, avenue Anatole France – 10003 TROYES cedex

VALENCE
Hématologie – Centre Hospitalier – 179 Bd Maréchal Juin – 26 953 Valence

VANNES
Médecine interne - CH P.Chubert – 20 bd du général M.Guillaudot – BP 70555 - 56017 Vannes cedex

VILLEFRANCHE/SAÔNE
Service de Rhumatologie, Médecine Interne et Cancérologie Osseuse – Hôpital de Villefranche/Saône – BP 436 – 69 655 VILLEFRANCHE/SAÔNE cedex

VILLEJUIF
Institut Gustave Roussy – Hématologie – 39, rue Camille Desmoulins – 94 805 Villejuif cedex

LA REUNION – SAINT PIERRE
Groupe Hospitalier Sud Réunion – Service de Médecine et d'Hématologie – Avenue du Président Mitterrand – BP 350 – 97 448 SAINT-PIERRE cedex

LA REUNION – ST DENIS
Service d'Hématologie – Oncologie – Centre Hospitalier Départemental – Allée des Topazes – Bellepierre –
97 405 ST-DENIS cedex

GLOBAL AMENDMENTS:

Amendment 12 Date: 18 December 2014	• Included details associated with prolongation of the study for an additional 3 years. • Added patient follow-up details: all patients will be monitored for progression and survival except where consent has been withdrawn. For the latter, only the date of death should be collected. • All patients monitored for development of secondary primary malignancies (SPM). • A first analysis was scheduled for 15 May 2015. The final analysis was scheduled for the end of the study, December 2017. • Other administrative changes.

Amendment 11 Date: 12 July 2013	• Included administrative, editorial changes.

Amendment 10 Date: 27 February 2012	• Included details associated with prolongation of the duration after analysis in October 2011 showed 4-year survival at greater than 75% with no difference between treatment arms. • A summary of pharmacovigilance data on 21 December 2011 showed an increase in the incidence of SPMs in the lenalidomide arm versus placebo. • Modified the follow-up of patients. • Modified the collection of adverse event (AE) data and concomitant medication data. Justified the collection of data on date of death and incidence of SPM for the database in patients who had withdrawn. • Patients still on study were to give consent again • Patients were to undergo clinical and biological disease assessments every 3 months. • Serious Adverse Events (SAEs) were to be reported as SPMs. All SPMs were to be reported on the CRF regardless of the date of the occurrence, the randomization arm or the patient's study status. • Patients who had discontinued the study were to be followed according to standard practice.

	• Investigators to provide date of death on case report form and asked to provide biological information on these cancers. Myeloma diagnosis slides were to be re-examined.

Amendment 09 Date: 21 March 2011	• Incorporated the recommendations of the Data Monitoring Committee (DMC) in according with the options of the IFM and CPP to implement an urgent safety measure (discontinuation of treatment with lenalidomide and notification of the patients), following the reporting of the higher occurrence of SPM in the lenalidomide arm compared to placebo arm. • The amendment specified to discontinue maintenance of lenalidomide since all patients had received 2 years of therapy; to continue the study in order to analyze survival and monitor toxicity in relation of occurrence of SPMs; to analyze risk factors; to determine the actions to be implemented to reduce the risks; the DMC recommended a careful investigation of the possibility that differences in reporting of SPMs may have occurred between patients on protocol therapy versus patients who went off study following progression (or any other cause); the DMC requested a follow-up report to be sent with the results of the investigation and with SPM rates expressed in person-years of follow-up; physicians were to discuss with patients on the trial the results so far, making sure patients understand that further data were needed before making any firm conclusions regarding the link between lenalidomide and SPM.

Amendment 08 Date: 26 April 2010	• Incorporated the recommendations of the DMC following the interim analysis performed in Dec 2009, after 180 events had been observed and reported with a cut-off date of 04 September 2009. The recommendations included: based on the significant differences in the primary end point, the DMC recommends that the study be unblended and participants be informed of the results and that the decision to use lenalidomide maintenance be made after discussing with patients the risks and benefits with such intervention. Following a decision from AFSSAPS, the amendment specified the protocol continue and analyze survival; the study was to be unblinded and the treatment continued in an open phase after a favorable decision had been obtained from the respective ethics committee and health authorities in the three participating countries.

	• The date of unblinding was to be taken as the date of the final analysis and an analysis of survival was to be performed every 6 months until the end of the study. • The patients were to be informed and asked to sign a new informed consent. • Patients were to be maintained in the same treatment arm; however, those in the placebo arm were to be offered the option of receiving lenalidomide maintenance if they desired. • Patients in the lenalidomide arm were to be informed of the risks and benefits and advised to continue the same treatment until progression. • Patients in the placebo arm were to be informed of the risks and benefits and advised to receive no maintenance treatment until progression.

Amendment 07 Date: 24 August 2009	• Further specify the primary endpoint of the study, the stratification factors, the contraceptive methods and the compliance monitoring. • The primary and secondary endpoint criteria were clarified; the population used for the analysis and timing of the interim analysis were re-defined; it specified that patients' involvement in the study was to start after the induction chemotherapy and autologous stem cell transplant (ASCT); • An interim analysis of efficacy was planned when 60% information fraction had been reached. If the p-value from the log-rank test was less than 0.004, then the independent DMC could consider stopping and/or unblinding the study and declaring the lenalidomide arm superior. • The treatment strategy for <90% response following the first autologous transplantation was specified. • Dose modifications of the protocol were to be applied to the placebo arm during the consolidation and maintenance periods; also, the use of growth factors presenting with febrile neutropenia was standardized. • Further details on the DMC members and the timing of the safety analysis were given with a safety analysis to be performed following the inclusion of 300 patients. • A specific "unblinding" procedure was inserted. • The IMWG terminology was used to formalize the study objectives. The secondary objective of "event-free survival" was deleted as the definition of events was redundant with the primary objective.

	• A window for the visits (+/- 14 days or +/- 28 days) was inserted. • Study withdrawal criteria were modified. • The toxicity criteria were changed from CTCAE to WHO criteria. • An independent response review committee (IRC) was created. • The study duration was modified to include the follow-up of patients for survival. • The ICF was modified to inform the patient that the data would be monitored, audited and published: to provide information on the sample sent to Professor Avet-Loiseau; to provide information on the planned number of patients for the study and the study duration; to update safety data and the contraceptive methods to comply with the Summary of Product Characteristics (SPC) for lenalidomide; to specify the inclusion in the study and the signing of the ICF would occur following the autologous transplantation.

Amendment 06 Date: 07 July 2008	• Administrative changes regarding centers and investigators.

Amendment 05 Date: 19 November 2007	• Administrative changes regarding centers and investigators

Amendment 04 Date: 20 August 2007	• New response criteria as set out by the IMWG (Durie et al. 2006) were to be taken into account, replacing the European Society for Blood and Marrow Transplantation (EBMT) criteria (Blade et al. 1998). • Randomizations were stratified by "post-transplantation response" rather than "number" of transplantations." • Patients would no longer be stratified according to the number of ACSTs (1 versus 2) but by their response to their last ASCT prior to randomization (CR/VGPR versus PR/SD). • Depending on the baseline survival after the interim analysis, the number of patients required would be re-calculated; if more patients were required due to the exclusion rate observed, a decision would be made to either increase the number of patients enrolled or reduce the number of interim analyses. • Systematic monitoring of erythrocyte sedimentation (ESR) was removed; an assay of thyroid hormones (T3, T4,

	TSH), ferritin and testosterone was included before the consolidation treatment in order to obtain baseline levels before treatment.

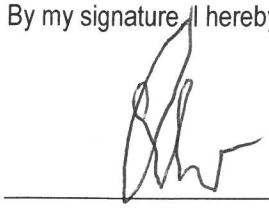
Amendment 03 Date: 19 February 2007	• The treatment was to be discontinued before restarting at the lower dose, if the platelet count was below 30,000/mm3. • If the chromosome 13 deletion was not available at diagnosis, it was to be considered as negative for the stratification during randomization.

Amendment 02 Date: 04 October 2006	• Two contraceptive methods were recommended for women for childbearing potential with frequent pregnancy tests for precautions. • A systemic post-transplantation consolidation treatment of lenalidomide 25 mg/day for 2 months after transplantation. • The permitted survival from transplantation to randomization was increased from 3 months to 6 months in order to limit the number of exclusions after double transplantation.

Amendment 01 Date: 12 December 2005	• The information to be collected concerning the induction treatment and transplantation procedures was clarifie.; patients were to be included after transplantation and the information concerning the induction treatment and transplantation procedures would be collected retrospectively. • The monitoring during study treatment was redefined; and a table on dose modification according to grade of observed toxicities was provided. • The procedure for monitoring SAEs was specified, including expected and unexpected SAEs, and how to submit a pregnancy declaration form.

STATEMENT OF DATA QUALITY

By my signature, I hereby confirm that the data reported in the results report were collected properly and are correct.



Thorsten Sperber, M.Sc.
Executive Director, US Medical Affairs

May 23-17
Date