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Running Head:

Transplant program with IRD combination in myeloma

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Letter

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DATA SHARING STATEMENT

The authors make original data and study protocol available to other investigators without unreasonable restrictions.

CLINICAL TRIAL REGISTRATION INFORMATION

EUDRACT number: n° 2013-001443-31

High-dose therapy with autologous stem cell transplantation (ASCT) is considered as a standard of care for patients with transplant-eligible (TE) symptomatic newly-diagnosed multiple myeloma (NDMM).[1] The benefit of ASCT in TE NDMM patients has been recently confirmed by two phase 3 randomized trials demonstrating progression free survival (PFS) and/or overall survival (OS) advantage in the transplant arm. [2–4] In the past decades, induction therapy before ASCT has been dramatically improved, resulting in deeper response and prolonged PFS. The triplet combination of bortezomib, lenalidomide and dexamethasone (VRD) is one of the standard of care induction regimens in the context of transplantation.[1,2,5] Ixazomib is the first-in-class oral proteasome inhibitor approved for relapsed/refractory (RR) MM patients in combination with lenalidomide and dexamethasone. [6] Here, we report the results of the multicenter, open-label, phase II study by the Intergroupe Francophone du Myelome (IFM) 2013-06 evaluating the efficacy and safety of IRD used as an induction and consolidation regimen followed by ixazomib maintenance in TE NDMM patients.

This study included TE patients with previously untreated symptomatic NDMM. Key selection criteria are indicated in the supplementary Figure. All patients provided written informed consent. The study was approved by relevant national health authority, ethics committee and was conducted in accordance with the International Conference on Harmonization of Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. This clinical trial is registered at www.clinicaltrials.gov as NCT01936532.

Induction therapy comprised three 28-day cycles of oral ixazomib (4 mg on days 1,8,15), oral lenalidomide (25 mg on days 1–21) and oral dexamethasone (40 mg on days 1,8,15,22). Stem cell harvest was planned for all patients after high-dose cyclophosphamide ($3g/m^2$) plus granulocyte-colony stimulating factor (G-CSF). Patients proceeded to transplant using melphalan 200 mg/m^2 as the conditioning regimen. Non-progressive patients then proceeded to early consolidation therapy

with two 28-day IRD cycles, followed by late consolidation (six 28-day cycles of ixazomib (4 mg on days 1,8,15) and lenalidomide (25 mg on days 1–21) without dexamethasone. Patients subsequently received maintenance therapy with ixazomib (4 mg/day on days 1,8,15) for one year.

The primary endpoint was stringent complete response (sCR) rate at the completion of extended consolidation. Secondary endpoints included response at each step of the program, time to response, quality of stem cell harvest, PFS, OS, and safety. Myeloma response assessment was based on the International Myeloma Working Group uniform response criteria. [7] sCR was defined as CR in addition with normal serum free light chain ratio and absence of clonal BMPC assessed by flow cytometry analysis. All patients were followed until death or end of the study (June 2020).

Forty-two eligible patients were enrolled between November 2014 and May 2015. Patients characteristics are summarized in Table 1. Median age was 60 years. A high-risk cytogenetic profile–was present in 8 (19%) patients. Patient disposition is summarized in the supplemental Figure. Overall, 40 (95%) patients completed induction and 37 (88%) underwent ASCT. One patient experienced stem cell collection failure. Plerixafor was needed for stem cell mobilization in 5 patients.

By the end of induction (n=42), overall response rate (ORR) was 80% (n=33), including 30% (n=10) very good partial response (VGPR) and 12% (n=5) CR/sCR (Figure A). At the end of consolidation (primary endpoint) (n=37), the sCR rate was 41% (33% in an intention-to-treat analysis) . The median time to PR and CR was 1 and 8 months, respectively. As of June 2020, the median follow-up from start of therapy was 62.6 months. Twenty nine patients progressed and 7 patients died due to myeloma progression. The median PFS was 41.8 months (95% CI: 33.2-62) and the 3-year OS was 92.8% (95% CI: 85.3-100) (Figure B et C).

There were no IRD-related deaths. Overall, 7 (16.6%) patients discontinued treatment permanently due to treatment related toxicity: 1 patient during induction (skin rash), 3 during consolidation (1 skin rash, 2 thrombocytopenia) and 3 patients during maintenance (colon cancer, thrombocytopenia, pneumonia). For these patients, the median time to ixazomib discontinuation was 227 days. Overall, 33 (79%) patients had at least one dose modification of one of the study drugs. Dose reduction of ixazomib, lenalidomide or dexamethasone occured in 60%, 67% and 29%, respectively. Adverse events (AEs) reported for at least 10% of patients are described in Table 2. During induction, grade 3-4 neutropenia was the most frequent treatment related AE, occurring in 8 (19%) patients. Skin rash was reported in 12 (29%), including 5% grade 3 or 4. During consolidation, neutropenia and thrombocytopenia were the most frequent AEs, with grade 3-4 occuring in 14 (38%) and 8 (22%) patients, respectively. During maintenance, thrombocytopenia and lung infection were the most frequent AEs, occurring in 10 (32%) and 12 (39%) patients, respectively. Grade 1/2 sensory peripheral neuropathy was reported in 12 (29%) patients, including 2 patients with grade 2 peripheral neuropathy. Deep-vein thrombosis occurred in one patient.

The primary objective of this phase 2 study was to evaluate the efficacy of a transplant program with the oral triplet IRD as induction and consolidation in NDMM patients. In the intention-to-treat (ITT) population (n=42), the ORR was 92.3%, including 70.3% $\geq$ VGPR. Our study showed that responses continuously deepened throughout the program. At the completion of extended consolidation, the per protocol CR/sCR rate was 44% (37% in ITT analysis). These response rates are close to those obtained with VRD as the induction/consolidation regimen in the IFM-2009 and GEM2012 trials.[2,5] However, patients in the present study received a higher number of cycles (induction, n=3; early consolidation, n=2; late consolidation, n=6) in comparison with patients from IFM-2009 (5 cycles of VRD) or GEM2012 (8 cycles of VRD). In the present study, patients received ixazomib maintenance for one year, with no significant improvement in CR/sCR rates.

The phase 3, placebo-controlled TOURMALINE-MM3 trial demonstrated a modest PFS benefit in NDMM patients receiving post ASCT ixazomib maintenance for 2 years (26.5 vs 21.3 months at the start of maintenance). [8] After a median follow-up of nearly 5 years, the median PFS observed in the present study was 41.8 months with a 3-year OS of 92.8%. Continuous ixazomib therapy following ASCT in combination with lenalidomide and dexamethasone maintenance has been evaluated (versus lenalidomide dexamethasone) by the randomized phase 3 trial GEM2014 (n=332). After a median follow-up of 56 months, the addition of ixazomib did not result in a PFS benefit.[9] At the time of study design, continuous lenalidomide maintenance after ASCT did not demonstrated OS benefit and was not appoved. [10] In the present study, a fixed-duration maintenance with ixazomib alone appears as a suboptimal approach in TE NDMM patients.

Safety was an important objective of the present phase 2 trial. The strategy was feasible with 7 (16.6%) patients that discontinuated therapy due to treatment toxicity and no IRD-related mortality. Overall, 33 (79%) patients had at least one dose modification of one study drug. The hematological toxicities were predictable and manageable. The most common hematological toxicity related to IRD was thrombocytopenia with grade >3 occuring in 29 (69%) patients. Thrombocytopenia related to the IRD combination was expected and has previously been described. [6,8,11]

Considering non-hematological toxicities, skin rash occurred in 23 (54%) patients, with only 2 (5%) grade 3/4 AEs. Grade $\geq$2 peripheral neuropathy occurred in 2 patients and one patient had grade $\geq$3. These results compare favorably with VRD strategies with a rate of grade >3 peripheral neuropathy of 12% and 4% in the IFM-2009 and GEM2012 studies, respectively. [2,5] The triplet combination of carfilzomib, lenalidomide and dexamethasone (KRD) with transplantation demonstrated strong efficacy results but is associated with substantial cardiac events. [12] In the present study, no patient developed treatment related cardiac failure.

To conclude, a transplant program with all-oral IRD as induction and consolidation, followed by 1-year ixazomib maintenance is effective in NDMM patients and has a favorable safety profile.

However, these results are inferior to those achieved with VRD ASCT and lenalidomide maintenance with respect to PFS. To date, ixazomib-based combinations failed to significantly improve the outcome of TE NDMM.[8,9] This suboptimal efficacy can be partially explained by inferior *in vitro* proteasome inhibition with ixazomib in comparison with other PIs.[13] In NDMM patients, Ixazomib could however be suitable for a specific subset of frail, comorbid patients (i.e. preexisting neuropathy, cardiac insufficiency), deemed to not tolerate bortezomib or carfilzomib-based combinations. Recently, daratumumab in combination with bortezomib, thalidomide and dexamethasone has been approved for TE NDMM and is now considered as a standard of care. [1,14] The phase 2 randomized study GRIFFIN also demonstrated strong efficacy results (without a safety signal) with daratumumab in combination with VRD in TE NDMM. [15] One way of improving IRD efficacy in the context of transplantation could be the addition of anti-CD38 antibody. The convenience and efficacy profile of IRD in TE NDMM patients led to the design of the IFM phase 2 study 2018-01 (NCT03669445) to evaluate the efficacy and safety of IRD in combination with daratumumab in TE NDMM. Based on their efficacy/safety profile, bortezomib or carfilzomib-based induction regimen with anti-CD38 should be considered as a standard of care in TE NDMM patients.

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TABLE

Table 1. Legend

Legend : Ig, immunoglobulin; ECOG, Eastern Cooperative Oncology Group; PS, performance status ; ISS, International Staging System. * High-risk cytogenetics was defined by the presence of t(4;14) (with a positive 30% cut-off) and/or 17p deletion (with a positive 50% cut-off)

Table 1. Patient demographic and baseline disease characteristics

Characteristic	n=42
Gender: Male/Female, n	21/21
Median age, years (range)	60 (43–66)
ECOG PS, n (%) 0, 1, 2	 23 (55), 15 (36), 4 (9)
Isotype, n (%) IgG, IgA, Light chain only	 27 (64), 9 (22), 6 (14)
ISS stage, n (%) I, II, III	12 (29), 23 (55), 7 (17)
Median creatinine (µmol/l), (range)	72 (48-134)
Cytogenetic risk profile, n (%) High-risk* Standard	 8 (19) 34 (81)
Stem-cell collection Median CD34+ cell yield (x 10^6/kg)	 7,2 (1.4 – 14.6).

Table 2. Legend

Safety was monitored until 30 days after the last dose of study drug, except for secondary malignancies (monitored continuously during follow-up). Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria of Adverse Events (version 4.03; Bethesda, MD).

Table 2. Adverse events reported through induction, consolidation and maintenance

Adverse Event	**Induction (n=42)**		**Consolidation (n=37)**		**Maintenance (n=31)**	
	Any grade Patients (%)	Grade 3/4 Patients (%)	Any grade Patients (%)	Grade 3/4 Patients (%)	Any grade Patients (%)	Grade 3/4 Patients (%)
Hematologic						
Neutropenia	8 (19)	8 (19)	14 (38)	14 (38)	2 (6)	2 (6)
Thrombocytopenia	1 (2)	0	11 (30)	8 (22)	10 (32)	7 (23)
Non-hematologic						
Constipation	8 (19)	0	7 (19)	1 (3)	1 (3)	0
Diarrhea	8 (19)	0	6 (16)	1 (3)	4(13)	0
Nausea	10 (24)	0	6 (16)	2 (5)	5(16)	0
Pneumonia/bronchitis	8 (19)	5 (12)	8 (22)	0	12 (39)	0
Skin rash	12 (29)	2 (5)	10 (27)	0	3(9)	0
Peripheral neuropathy	6 (13)	0	8(22)	1(3)	6(19)	0

FIGURES LEGEND

Figure. Efficacy of All oral ixazomib lenalidomide dexamethasone transplant program

A : Response rate

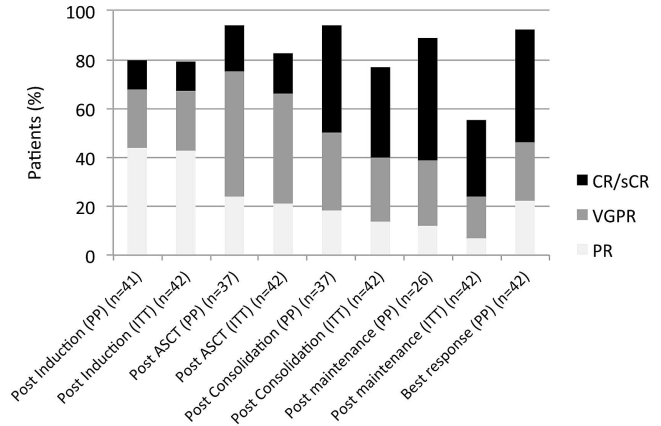
ASCT, autologous stem cell transplantation; CR, complete remisison; sCR, stringent complete remission; VGPR, very good partial response; PR, partial response. ITT, intention-to-treat, PP, per protocol

B : Progression-free survival

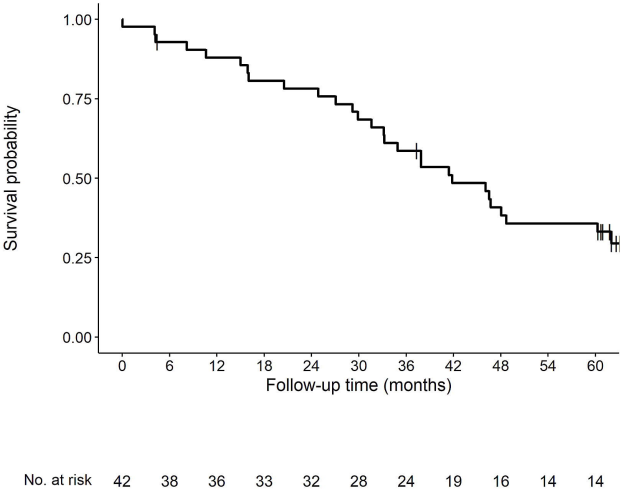
C: Overall survival

Median follow-up duration was estimated using the reverse Kaplan-Meier method. PFS was calculated as the time from start of treatment to the first documentation of PD, or death if the patient died due to any cause before progression. OS was calculated as the time from the start of treatment to death. The Kaplan-Meier method was used to estimate the survival distribution. All analyses were conducted using R - version 4.0.

A


100
80
60
40
20
0
Patients (%)
CR/sCR
VGPR
PR
Post Induction (PP) (n=41)
Post Induction (ITT) (n=42)
Post ASCT (PP) (n=37)
Post ASCT (ITT) (n=42)
Post Consolidation (PP) (n=37)
Post Consolidation (ITT) (n=42)
Post maintenance (PP) (n=26)
Post maintenance (ITT) (n=42)
Best response (PP) (n=42)

B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Follow-up time (months)
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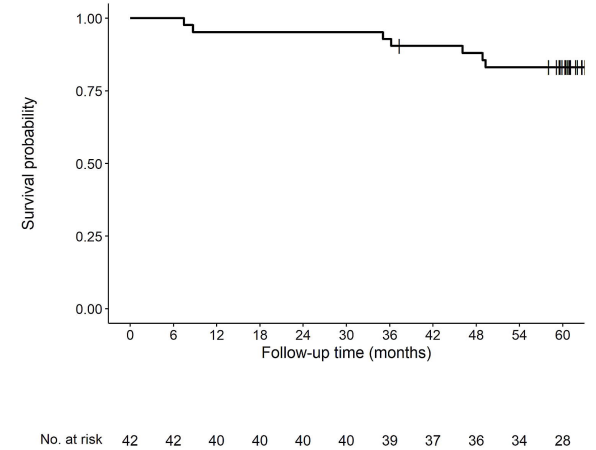
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Survival probability
0 6 12 18 24 30 36 42 48 54 60
Follow-up time (months)
No. at risk 42 42 40 40 40 40 39 37 36 34 28

Supplemental Figure.

IRD, ixazomib, lenalidomide, dexamethasone; IR, ixazomib, lenalidomide; dexamethasone

* Key inclusion criteria were : 65 years of age or younger, newly diagnosed MM with measurable paraprotein in the serum ($\geq$ 0.5 g/dL) or urine (> 0.2 g/24 hours), transplant-eligible, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2, and adequate renal function. Key exclusion criteria were: HIV, HBV, HCV positivity, history of other malignancy (other than basal cell carcinoma and carcinoma of the cervix *in situ*), grade $\geq$2 peripheral neuropathy

Figure 1: Patient disposition