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Ixazomib, pomalidomide and dexamethasone in relapsed or refractory multiple myeloma characterized with high-risk cytogenetics: the IFM 2014-01 study

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Ixazomib, pomalidomide and dexamethasone in relapsed or refractory multiple myeloma characterized with high-risk cytogenetics: the IFM 2014-01 study

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Running title. Ixazomib, Pomalidomide and Dexamethasone in high risk RRMM, IFM 2014-01

Key words. Multiple Myeloma; relapse setting; high risk; triplet-based combination

This trial is registered at www.clinicaltrials.gov (#NCT03683277)

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Data-sharing information.
Data supporting this article are part of an ongoing clinical trial and are not publicly available. Data will be considered for sharing, with restriction due to data privacy regulations, and the informed consent. Requests for de-identified patient data by researchers with proposed use of the data can be made to the corresponding author with specific data needs, analysis plans and dissemination plans. Those requests will be reviewed by a study steering committee (IFM group) and the study sponsor for release upon publication. Response will typically be given in 3 months.

The definition of high-risk (HR) Multiple Myeloma (MM) is constantly evolving [1], the presence of a deletion of 17p13 (del[17p]) and/or translocation (4;14) (t[4;14]), which represents approximately 20% to 25% of patients in the series remains the main definition of HR MM[2]. These patients are characterized with shorter survivals, related to an early relapse rate (median time to progression [TTP] <4 months) and rapid development of mechanisms of resistance to treatments[2].

The multicenter phase 2, IFM 2010-02 study, evaluated pomalidomide plus dexamethasone (Pd) in RRMM characterized with del(17p) and/or t(4;14) demonstrated limited activity, with an median TTP at 3.0 months, at 7.3 and 2.8 months in case of del(17p) and of t(4;14), respectively[3]. The development of triplet or quadruplet-based regimens has improved survival, with limitations to these treatment regimens because of the safety profile issues that can be experienced as difficult [4–6]. We hypothesized that addition of Ixazomib (a boronate acid oral proteasome inhibitor) at increased dose density to Pd (IxPd) in HR RRMM would provide a triplet-based treatment approach with improved convenience and safety profile, and thus adherence to treatment to ease the continuous treatment until progression.

This study is a multicenter, open-label, single arm, phase 2 study of IxPd in RRMM with adverse genomic abnormalities. The main eligibility criteria were RRMM in line 2 or 3, refractory to lenalidomide, but not to pomalidomide and ixazomib, a measurable disease[7], a platelet count ≥75 $\times 10^9$/L, neutrophil count ≥1.0 $\times 10^9$/L, and creatinine clearance (MDRD) >30 mL/min. The cytogenetic analysis was performed centrally by Pr Avet Loiseau/Pr Corre Jill on sorted bone marrow plasma cells. HR was define as presence of either del(17p) and/or t(4;14) since diagnosis or at study entry to compare IxPd to Pd from the IFM 2010-02 study. The study was sponsored by the Intergroupe Francophone du Myélome (IFM) in accordance with national regulations in France (Eudract number 2016-002650-20). This trial is registered at www.clinicaltrials.gov (#NCT03683277). The patients received 17 induction 21-days'-based cycles, consisting of ixazomib 3mg/day (days 1, 4, 8 and 11), pomalidomide 4mg/day (days 1 to 14) and weekly dexamethasone (40mg day 1, 8 and 15, 20mg ≥75years old), followed by a maintenance phase of 28-day-based cycles with ixazomib 4mg/day (days 1, 8 and 15) and pomalidomide 4mg/day (days 1 to 21), given until progression. The primary endpoint was time to progression (TTP)[7]. Secondary endpoints included the safety profile of the regimen using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), the response rates, response durations, overall survival time (OS) and progression-free survival (PFS). Sparse pharmacokinetic (PK) samples were collected from patients on days 1 and 11 of cycle 1, then pre-dose for cycles 2 to 5. We studied whether PK analysis would differ in HR RRMM from previous studies using the same dose schedule of Ixazomib (MLN2238). We considered a 100% improvement in median TTP from the median TTP at 3 months in IFM 2010-02 as clinically relevant in IFM 2014-01. The number of patients to be included is 26 patients if using a 2-sided test with a type I error of 5% and ensuring a

power of 80%[8]. Considering the median TTP would differ across HR RRMM[9], and under the assumption that we would study separately the 2 populations of HR RRMM, the statistical design considered the inclusion of 70 patients with a power slightly above 90, assuming a minimum of 40% of patients would be included in the least represented population[8]. We recruited 26 patients then the study was terminated prematurely on December 31, 2022 due to lack of recruitment. A safety analysis was performed when 15 patients had completed at least 1 cycle at ANSM (agence nationale de securite du medicament) request. The DMC (Data Monitoring Committee) confirmed the treatment was safe and allowed the study to fully recruit. The primary analysis was conducted on an intention-to-treat basis (ITT). All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC) and R software version 4.0.4 (The R Foundation for Statistical Computing, Vienna, Austria).

Of the 32 screened patients, 26 were included and started the protocol induction phase, 8 received the maintenance according to protocol (Supp figure 1). At end of study, 25 patients had discontinued the study treatment, 22 for progressive disease, 15 patients died, all of them related to MM, and 1 patient remains on treatment with commercial products. At study entry, 12 patients presented with del(17p), 9 with t(4;14), and 5 with del(17p) and t(4;14). Fifteen patients had 2 prior lines. All patients were refractory to lenalidomide. The patients' characteristics are summarized in Table 1.

With a median follow-up time of 27 months [23-29], the median TTP time improved by more than 3 times at 10.2 months (CI95%. 4.4;13.0). The median OS time was 23.7 (CI95%. 12.2;not evaluable (NE)) months. Survival times are shown in Figure 1. The patients with t(4;14) had longer median survival times compared to IFM 2010-02, the benefit appeared limited in other subgroups of interest. The response rates were similar at the end of induction and at study completion (Supp table 1). The median duration of response was 10.0 [3.4-13.6] months, similar across HR subgroups. Dose-normalized PK concentrations were comparable across patient response subgroups; a slight trend toward higher values was observed in patients with PR/VGPR response (Figure 1E).

At the data cutoff, 25 patients (96%) had discontinued treatment and the most common reason was disease progression (n=18, 70%). All patients experienced at least one AE, with a median frequency of 10 occurrences per patient [4-15], and 85% (n=22) experienced AE of grade $\geq$3, with a median frequency of 2 occurrences per patient [1-4] (Supp table 2). There were no observed differences across study phases, induction and maintenance, and across HR subgroups. The summary of the dose relative intensity of Ixazomib and Pomalidomide is provided in Table 2.

Our study met its primary endpoint, however, it is fair to conclude that the benefit brought to these patients is limited with our IxPd regimen. The other approved regimens available to these patients lenalidomide refractory, across high-risk and even non-high risk RRMM patients, also showed limited activity, with median PFS from 7.8 months to 28.1 months[10]. These data confirm that we have recruited patients that were truly high-risk being lenalidomide refractory RRMM, even in early

relapse L2 and L3, and on top cytogenetic high-risk, thus characterized with a very poor outcome. Our results demonstrate that new drug developments are needed for this population.

Our study results appear to confirm the added value of a PI in HR MM with t(4;14) compared to Pd doublet-based regimen. This raises questions on whether the effect seen with IxPd was only explained by the triplet-based regimen, triplet expectedly performing better, or whether there is a true biological effect, yet to be demonstrated. In our study, not all t(4;14) HR MM benefited from the study treatment, also questioning on certain t(4;14) being of lesser HR profile compared to other[11].

There are 3 different PIs available in MM in various indications, Ixazomib and Bortezomib that belong to the boronate acid-based family and Carfilzomib an epoxyketone-based PI. The bortezomib's safety profile remains difficult for a long period of time in HR MM, whom tend to relapse rapidly when treatments are stopped, despite the subcutaneous and weekly developments[12,13]. When IFM 2014-01 started, carfilzomib was available only as a bi-weekly schema, with an increasing risk of cardio vascular safety concerns. Ixazomib appeared an interesting PI to study given its oral bioavailability and its favorable safety profile. Ixazomib was therefore the most appealing PI to improve the adherence of patients to a prolonged study treatment for responders and to combine with IMiDs[14].

We believe our study results support our hypothesis that the twice-weekly ixazomib concentrations with 12 mg total given per 21 days-based cycle of Ixazomib, with reduced doses (3mg at days 1, 4, 8 and 11), in the induction phase might be of importance in HR RRMM, compared to Tourmaline-MM1 study[15]. Our study population was harder to treat, and we have observed ORR and VGPR rates at 60% at end of induction phase, while ORR and ≥ VGPR rates were 78% and 48% in Tourmaline-MM1 study. It would be of interest to further develop this design in future and larger Ixazomib studies.

As a conclusion, the study IFM 2014-01, a phase 2 study of the triplet-based combination of ixazomib plus pomalidomide and dexamethasone, in high-risk early RRMM refractory to lenalidomide, met its primary end point objective. We have observed an increase of the median TTP with the addition of ixazomib to pomalidomide and dexamethasone in this very hard to treat population characterized with a very poor outcome. This data confirms the importance of introducing a proteasome inhibitors in HR RRMM treatment's regimens, particularly in t(4;14). This phase 2 study needs confirmation in a larger cohort.

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Table 1. Patients' characteristics, according to their abnormalities, t(4;14) and Del(17p), at inclusion, median [Q1-Q3] or n (%) and description of prior lines of therapy, n (%). Data presented as a whole and according to their abnormalities, t(4;14) and Del(17p), at inclusion.

	All (n=26)	t(4;14) (n=9)	Del(17p) (n=12)	Del(17p) and t(4;14) (n=5)
Age, median [Q1-Q3]**	72 [67-78]	67 [67-76]	74 [67-80]	73 [68-75]
≥75 years	12 (46)	4 (44)	6 (50)	2(40)
Two prior lines**	15 (58)	7 (78)	6 (50)	2 (40)
Time from diagnosis to study entry	4 [2-5]	4 [3-5]	3 [2-6]	3 [1-4]
Time from relapse to treatment start, days (Q1-Q3)	34 [26-48]	29 [21-35]	42 [26-67]	47 [34-47]
ß2-microglobulin (mg/L)*	5 [4-7]	5 [4-8]	4 [3-5]	6 [4-8]
ISS Stage III*	9 (36)	4 (44)	3 (25)	2 (50)
LDH abnormal*	6 (27)	1 (12)	3 (30)	2 (50)
Circulating plasma cells^{+}**	5 (19)	2 (22)	3 (25)	0 (0)
Cytogenetic*				
t(4;14)	7 (27)	7 (78)	0 (0)	5 (100)
Del(17p)	7 (27)	0 (0)	7 (70)	3 (60)
Del(17p) and t(4;14)	3 (11)	0 (0)	0 (0)	3 (60)
+1q gain	4 (15)	2 (22)	1 (8)	1 (20)
+Del1p32	4 (15)	2 (22)	2 (17)	0 (0)
Plasmacytomas**				
Paraskeletal (PMD)	4 (15)	1 (11)	2 (17)	1 (20)
Soft tissue (EMD)	2 (8)	0 (0)	2 (17)	0 (0)
Line 1, n (%)	**26**	**9**	**12**	**5**
Bortezomib-based*				
VMP	6 (23)	3 (33)	3 (25)	0 (0)
VCyd	5 (19)	2 (22)	2 (17)	1 (20)
VTd	3 (12)	1 (11)	2 (17)	0 (0)
Lenalidomide-based**				
Rd	4 (15)	1 (11)	2 (17)	1 (20)
RCyd	1 (4)	0 (0)	0 (0)	1 (20)
VRd	4 (1)	2 (22)	1 (8)	1 (20)

DRd	1 (4)	-	1 (8)	0 (0)
AntiCD38VRd	2 (8)	-	1 (8)	1 (20)
Autologous transplantation-based				
	6 (23)	3 (33)	3 (25)	-
	1 (4)	0 (0)	1 (8)	-
Line 2, n (%)	**15**	**7**	**6**	**2**
VMP	1	1	0	0
Rd	4	1	2	1
VRd	3	1	1	1
DRd	6	3	3	0
KRd	1	1	0	-

*at diagnosis; ** at inclusion
[+]Circulating plasma cells were identified and counted by regular flow analysis.
Quantitative data were expressed as means ± standard deviation (SD) or median (25th-75th percentiles). Qualitative variables are given as number (percentage) of patients.

Table 2. Number of cycles, Relative dose intensity of Ixazomib and Pomalidomide, and Patients with more than 12 cycles of treatment, as a whole and according to their abnormalities, t(4;14) and Del(17p), at inclusion.

	All (n=26)	t(4;14) (n=9)	Del(17p) (n=12)	Del(17p) and t(4;14) (n=5)
Ixazomib				
Number of cycles, median [Q1-Q3]				
All study long	9 [4-19]	13 [6-20]	9.5 [3.5-19.5]	8 [5.5-12]
Induction	9 [4-17]	13 [6-17]	9.5 [3.5-17]	8 [5.5-12]
Maintenance*	4.5 [2-7]	6 [3-8]	4.5 [2.5-7]	1 [1-1]
Relative dose intensity, median [Q1-Q3]				
Induction	80.0 [69.2-90.6]	79.4 [69.0-87.7]	77.7 [68.3-94.2]	87.5 [71.9-95.9]
Maintenance*	69.4 [60.0-74.2]	72.1 [64.9-73.0]	66.2 [56.3-87.5]	66.7 (n=1)
Patients with >12 cycles, n (%)				
	12 (46)	5 (56)	6 (50)	1 (20)
Pomalidomide				
Number of cycles, median [Q1-Q3]				
All study long	9 [4-19]	13 [6-20]	9.5 [3.5-19.5]	8 [5.5-12]
Induction	9 [4-17]	13 [6-17]	9.5 [3.5-17]	8 [5.5-12]
Maintenance*	4.5 [2-7]	6 [3-8]	4.5 [2.5-7]	1 [1-1]
Relative dose intensity, median [Q1-Q3]				
Induction	89.6 [73.7-97.9]	84.7 [71.1-97.8]	87.3 [71.9-98.9]	91.7 [82.5-94.2]
Maintenance*	89.3 [58.1-100.0]	97.6 [85.1-112.5]	84.3 [58.1-100.0]	0 (n=1)
Patients with >12 cycles, n (%)				
	12 (46)	5 (56)	6 (50)	1 (20)

*The number of patients analyzed at maintenance phase were overall 8 patients, breakdown as t(4;14) n=3, Del(17p) n=4, and Del(17p) and t(4;14) n=1

The relative dose intensity of pomalidomide and ixazomib drugs' administrations was calculated as the dose concentration received by patients over the protocol-planned doses concentrations across the study induction and maintenance phases.

Figure legend.

Survival from study entry (n=26). Time to progression. (A) Overall population. (**B).** According to HR RRMM population, either del(17p), or t(4;14) or del(17p) and t(4;14). **Overall survival. (C)** Population as a whole. (**D).** According to HR RRMM population, either del(17p), or t(4;14) or del(17p) and t(4;14). The median TTP and OS were at 10.5 (CI95%. 7.9;NE) and NE (CI95%. 27.1;NE), as a whole, respectively.

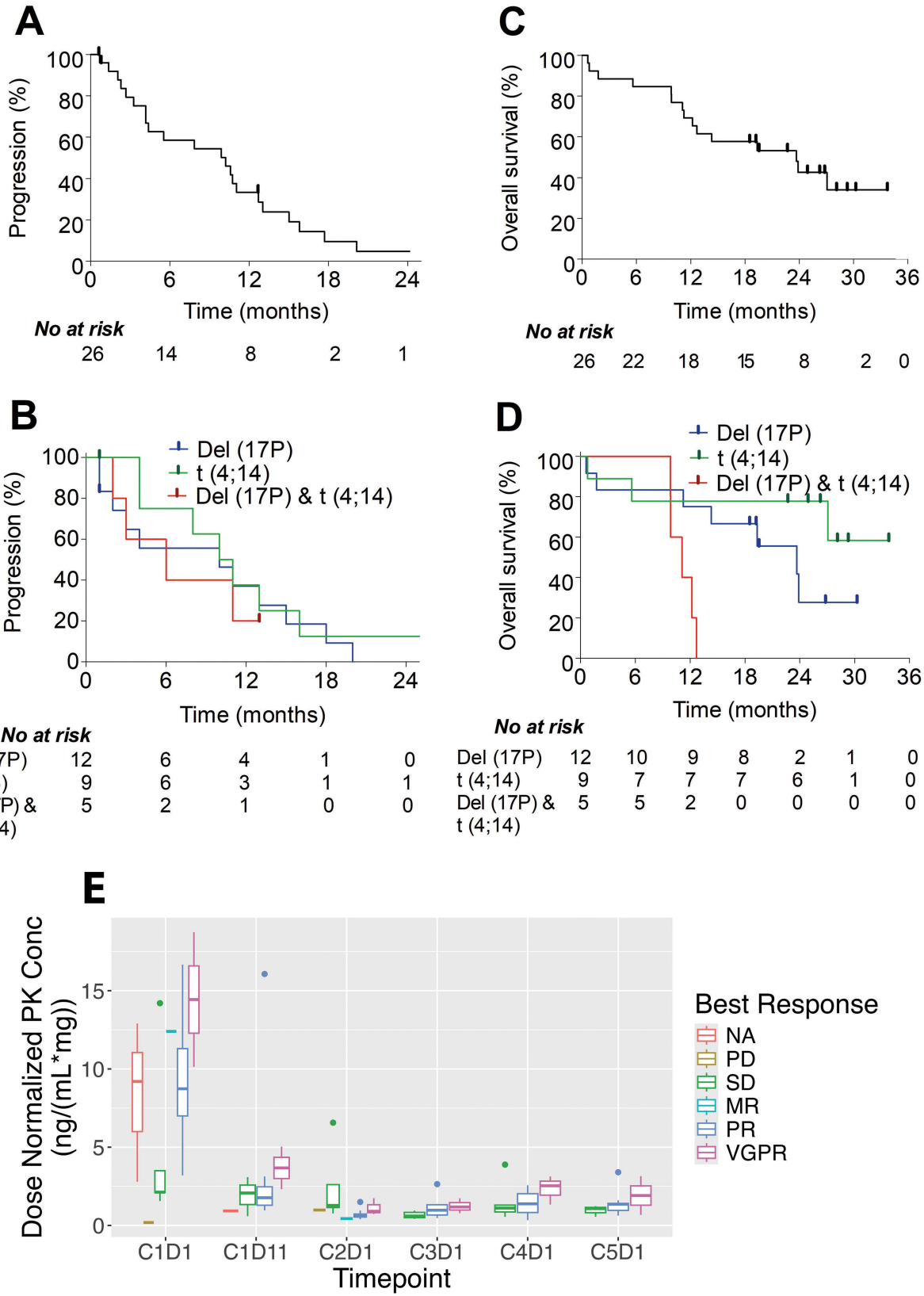
Kaplan-Meier method was used to analyze time-to-event data. Results were expressed as median time-to-event in months and 95% confidence interval (95%CI).

PK analysis (n=26). (E) The patients are stratified by best response over the course of the study**.**

Sparse pharmacokinetic (PK) samples were collected from patients on days 1 and 11 of cycle 1, then pre-dose for cycles 2 to 5. The objective was to study whether PK analysis would differ in HR RRMM from previous studies using the same dose schedule of Ixazomib (MLN2238). The systemic ixazomib concentrations were quantified from patient plasma samples using a validated liquid chromatography/tandem mass spectrometry assay with a range of 0.5 to 500 ng/mL. Given that ixazomib exhibits dose-proportional PK, all PK concentrations in this analysis were normalized by the corresponding dose administered; these normalized values enable the comparison across studies and dose levels.

The dose-normalized PK concentrations in our study were comparable with a previous single-agent dose escalation trial which utilized the same dose regimen (#NCT00932698) and the dose-normalized PK concentrations were comparable across patient response subgroups. These results are consistent with previous model-driven exposure-response analyses that concluded ixazomib exposures were not a statistically significant predictor of CR, ≥VGPR, or ≥PR rate [Gupta N, Yang H, Hanley MJ, et al (2017) Dose and Schedule Selection of the Oral Proteasome Inhibitor Ixazomib in Relapsed/Refractory Multiple Myeloma: Clinical and Model-Based Analyses. Target Oncol. https://doi.org/10.1007/s11523-017-0524-3]. Despite a slight trend toward higher values observed in patients who experienced a PR/VGPR response, this data supports that HR RRMM patients don't seem to have different PK concentrations' of Ixazomib, independently of the dose density or intensity of the drug. This data does not support, therefore, the use of the serum concentration of Ixazomib as a potential biomarker to tailor treatment schema of Ixazomib and better determine dose density over intensity in order to optimize the activity of Ixazomib in RRMM HR.

MR. Minor response. NA. Not applicable. PD. Progressive disease. PR. Partial response. SD. Stable disease. VGPR. Very good partial response.


A
Progression (%)
100
80
60
40
20
0
0
6
12
18
24
Time (months)
No at risk
26 14 8 2 1
C
Overall survival (%)
100
80
60
40
20
0
0
6
12
18
24
30
36
Time (months)
No at risk
26 22 18 15 8 2 0
B
Progression (%)
Del (17P)
t (4;14)
Del (17P) & t (4;14)
Time (months)
No at risk
Del(17P) 12 6 4 1 0
t(4;14) 9 6 3 1 1
Del(17P) & t(4;14) 5 2 1 0 0
D
Overall survival (%)
Del (17P)
t (4;14)
Del (17P) & t (4;14)
Time (months)
No at risk
Del (17P) 12 10 9 8 2 1 0
t (4;14) 9 7 7 7 6 1 0
Del (17P) & t (4;14) 5 5 2 0 0 0 0
E
Dose Normalized PK Conc (ng/(mL*mg))
15
10
5
0
C1D1
C1D11
C2D1
C3D1
C4D1
C5D1
Timepoint
Best Response
NA
PD
SD
MR
PR
VGPR

Ixazomib, Pomalidomide and dexamethasone in Relapsed or refractory Multiple Myeloma characterized with High-risk cytogenetics. IFM 2014-01.

Supplemental materials.

Supp Table 1. Patients' median survival time-to-event after a median follow-up time of 27 months, and response rates, as a whole and according to their abnormalities t(4;14) and Del(17p), at inclusion.

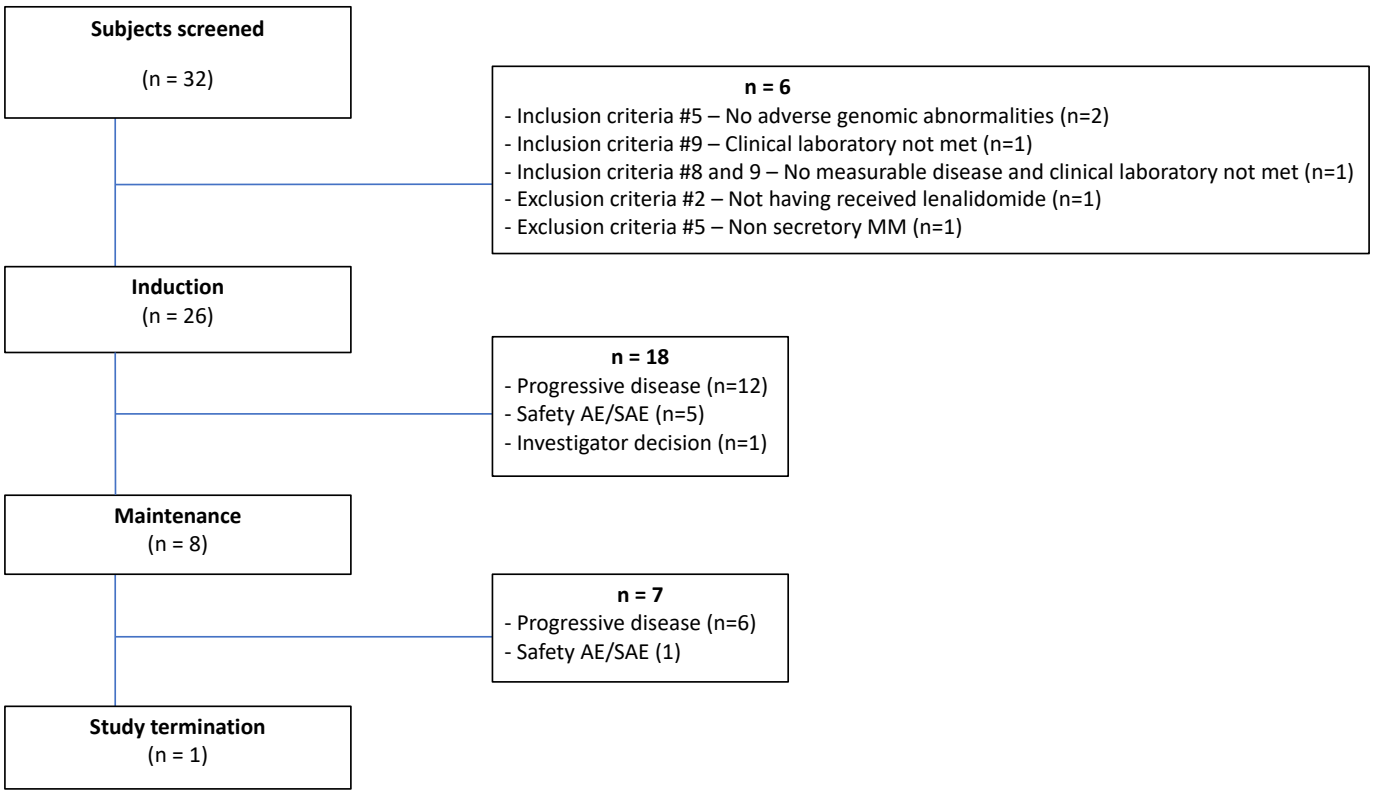
	All (n=26)	t(4;14) (n=9)	Del(17p) (n=12)	Del(17p) and t(4;14) (n=5)
Progression, n	22	7	11	4
Death, n	15	3	7	5
Months (95%CI)				
TTP	10.2 (4.4;13.0)	10.5 (7.9;NE)	9.9 (3.3;NE)	5.5 (2.7;NE)
PFS	8.9 (4.2;12.7)	10.2 (4.4; NE)	7.03 (2.3; NE)	5.5 (2.7; NE)
OS	23.7 (12.2; NE)	NE (27.1; NE)	23.7 (14.3; NE)	11.1 (9.9; NE)
Response rates at end of study, n (%)				
ORR	15 (60)	5 (62)	7 (58)	3 (60)
≥ VGPR	7 (28)	3 (38)	1 (8)	3 (60)
CBR	18 (72)	7 (88)	8 (67)	3 (60)

ORR. Overall response rate; VGPR. Very good partial response; CBR. Clinical beneficial rate; responses per IMWG criteria [11]. NE. not estimable. TTP. Time to progression. PFS. Progression free survival. OS. Overall survival. n. numbers
Kaplan-Meier method was used to analyze time-to-event data. Results were expressed as median time-to-event in months and 95% confidence interval (95%CI).

Supp Table 2. Summary of adverse events of grade 3 or higher according to MedDRA Hierarchy preferred term, as a whole and according to their abnormalities, t(4;14) and Del(17p), at inclusion, n (%).

	All (n=26)	t(4;14) (n=9)	Del(17p) (n=12)	Del(17p) and t(4;14) (n=5)
Neutropenia	52 (68)	34 (76)	4 (40)	14 (64)
Neoplasms benign, malignant and unspecified	4 (5)	0 (0)	2 (20)	2 (9)
Dyspnea	3 (4)	1 (2)	0 (0)	2 (9)
Infection	3 (4)	3 (7)	0 (0)	0 (0)
General physical health deterioration	3 (4)	2 (4)	1 (10)	0 (0)
Rash	3 (4)	0 (0)	1 (10)	2 (9)
Peripheral sensory neuropathy	2 (3)	2 (4)	0 (0)	0 (0)
Muscle spasms	2 (3)	1 (2)	1 (10)	0 (0)
Diarrhea	2 (3)	1 (2)	0 (0)	1 (5)
Renal and urinary disorder	1 (1)	0 (0)	0 (0)	1 (5)
Cardiac disorder	1 (1)	0 (0)	1 (10)	0 (0)
Psychiatric disorder	1 (1)	1 (2)	0 (0)	0 (0)

Supp Figure 1. CONSORT Patient Flow Diagram. (n=26)



n: number; AE/SAE: adverse event, serious adverse event; ANSM: medical agency France; #number per protocol