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**Safe and prolonged survival with Long-term exposure to Pomalidomide in Relapsed/Refractory Myeloma**

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### **Abstract.**

**Background:** The IFM2009-02 trial studied pomalidomide (4mg daily, 21/28 versus 28/28) and dexamethasone in very advanced relapsed or refractory multiple myeloma (RRMM). We observed that 40% of patients had a prolonged PFS and subsequently OS. We sought to analyze the characteristics of these patients and study the effect of long exposure to pomalidomide.

**Design.** We separated the studied population into 2 groups: 3 months to one year (<1 year) and more than one year ( $\geq 1$  year) of treatment with pomalidomide and dexamethasone based on clinical judgement and historical control studies. We then analysed the characteristics of patients according to duration of treatment.

**Results:** The overall response rate for the <1 year group was 43%, the median PFS 4.6 months (CI95% 3.8;6.4) with only 6% at 12 months, and the median OS was 15 months(11.7;20.3), and 40% at 18 months. For the  $\geq 1$  year group, the response rate and survival were strikingly different, overall response rate at 83%, median PFS 20.7 months(14.7;35.4), median OS not reached, and 91% at 18 months.

**Conclusion:** Pomalidomide and dexamethasone favoured prolonged and safe exposure to treatment in 40% of heavily treated and end stage RRMM, a paradigm shift in the natural history of RRMM characterized with a succession of shorter disease free intervals and ultimately shorter survival. Although an optimization of pomalidomide-dexamethasone regimen is warranted in advanced RRMM, we believe pomalidomide has proved once more to change the natural history of myeloma in this series, which should be confirmed in a larger study.

**Key words.** Multiple Myeloma, Pomalidomide, Long-term treatment, Continuous therapy

**Key message:** Pomalidomide and dexamethasone favoured prolonged and safe exposure to treatment, with prolonged OS in 40% of heavily and end stage relapse and refractory Multiple Myeloma, to the opposite of the natural history of Myeloma characterized with a succession of shorter disease free intervals and ultimately shorter survival. For the  $\geq 1$  year group, the response rate and survival were strikingly improved, translating into prolonged overall survival, 91% at 18 months, demonstrating a shift in paradigm in relapse refractory myeloma exposed to pomalidomide.

## **Introduction**

Relapsed disease in Multiple Myeloma (MM) is characterized by progressively lower remission rate and shorter survival despite salvage therapy. MM prognosis remains especially poor for patients who relapse and particularly who become refractory to the first generation of IMiDs (Immunomodulatory compounds, thalidomide and lenalidomide) and the proteasome inhibitor bortezomib, with a median overall survival (OS) of 9 months – and 3 months if no further treatment is given (“historical control study”)[1]. Therapeutic options remain limited for these patients with advanced relapsed or refractory MM (beyond 4 lines of treatment), often heavily pre-treated and refractory to proteasome inhibitors and IMiDs, and with significant comorbidities and cumulative treatment-related toxicity.

Pomalidomide, a second generation IMiD, has been proven effective in patients refractory to lenalidomide and bortezomib, and manageable in terms of safety profile for these frail patients. In MM003, which studied the association of pomalidomide and low-dose dexamethasone in relapsed or refractory MM (RRMM), the median overall survival (OS) was approximately 13 months, improving on the “historical control study” by approximately 4 months. The 1-year cut-off was thus since considered the new threshold to improve on for novel drugs developed on very advanced end stage RRMM. Consequently, pomalidomide was recently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [2, 3].

The IFM 2009-02 study randomized 84 end stage very advanced RRMM patients treated with pomalidomide (21/28 versus 28/28 days at 4 mg daily) and dexamethasone. Whilst the overall median progression free survival was 4.6 months in this population, we observed that 40% of the patients had a prolonged progression free survival, beyond one year, and subsequently prolonged overall survival, suggesting that some patients could significantly benefit from this combination therapy.

We sought to analyze the characteristics of the patients with prolonged exposure to pomalidomide and dexamethasone, to study the effect of long exposure to pomalidomide.

### **Material and Method.**

**IFM2009-02.** This multicentre phase 2 study was launched in 2009 and recruited 84 RRMM patients who had at best stable disease with the last course of bortezomib and of lenalidomide, or who were refractory to bortezomib and lenalidomide (as per IMWG criteria). Patients had a median of 5 prior lines of treatment, and 76% of the patients were refractory to bortezomib and lenalidomide (double refractory) [4]. The patients were randomized to receive pomalidomide (oral 4 mg daily) and dexamethasone (oral 40 mg weekly) given either 21 days out of 28 or continuously (28 days out of 28). All patients received prophylaxis against venous thromboembolism. FISH cytogenetic analysis was performed centrally in Nantes (Pr Avet-Loiseau) on bone marrow plasma cells.

**Prolonged exposure study.** We included the 58 patients that were exposed at least 3 months to pomalidomide. This analysis was performed on the intention-to-treat (ITT) population combining data from the 2 study arms. Overall, median age was 61 years (range 42-81), sex ratio M/F was 2.6. 10 patients (26%) had adverse cytogenetic (deletion 17p and/or translocation t(4;14)), and 19 patients (54%) were ISS 2 or 3. We then separated the studied population in 3 groups, [3-6months], ]6-1 year[ and more than 1 year, and finally retained 2 groups: 3 months to one year (<1 year) and more than one year ( $\geq 1$  year). We then analyzed the characteristics of patients according to the duration of treatment with pomalidomide and dexamethasone, 3 months to one year (< 1 year) or more than one year ( $\geq 1$  year).

**Statistical Analysis.** Descriptive data were collected for all patients. All response rates were determined according to IMWG criteria [5]. Duration of response was calculated from the date of the first response to the date of progression. Progression free survival (PFS) was defined as the time interval between diagnosis and progression or death whichever occurred earlier. Overall survival (OS) was defined as the time from diagnosis to death. All survival end points were evaluated through the Kaplan-Meier estimates and compared through the Log-rank test. The estimate of the relative risk of event and its 95% confidence interval (95%CI) were estimated through proportional hazard model. All analyses were performed with the SPSS 15.0 software.

**Results.**

35 patients (60%) and 23 patients (40%) were exposed to pomalidomide for <1 year (e.g. 3-12months) and  $\geq 1$  year, respectively.

**Characteristics of patients according to 1-year based exposure to pomalidomide.**

There was no significant difference between the 2 groups (<1 year and  $\geq 1$  year), neither concerning patients-based characteristics nor myeloma-based characteristics, although patients from the <1 year group seemed to display more adverse features, as discussed below.

The <1 year group indeed displayed more intrinsic adverse features of the tumor cells compared to the  $\geq 1$  year group (Table 1). Serum beta-2 microglobulin level was higher at diagnosis in the <1 year compared to the  $\geq 1$  year group, with more adverse cytogenetic profile: 35% versus 12%. Presence of plasmacytoma/extramedullary disease (EMD) was also greater in the <1 year group: 20% versus 4% in the  $\geq 1$  year group, respectively.

The time from diagnosis to IFM 2009-02 study entry was also similar across the cohorts, 5.8 and 6.5 years, respectively; nonetheless 26% versus 6% of patients entered the study with a time from diagnosis of less than 3 years since diagnosis in the  $\geq 1$  year group compared to the other group.

The median number of prior lines and the refractory status was similar across the two groups (<1 year and  $\geq 1$  year), as depicted in Table 1. Overall, the median number of prior lines was 5 (range 1-13); with 45 patients (78%) refractory to bortezomib, 51 (88%) to lenalidomide, 42 (73%) double refractory to both bortezomib and lenalidomide and 37 (64%) triple refractory (refractory to bortezomib, lenalidomide, and the last line of therapy).

**Response according to 1-year based exposure to pomalidomide.** In the series as a whole, the overall response rate (ORR, at least partial response) was 59%, including 4 complete responses (CR, 7%) and 4 very good partial responses (VGPR, 7%). 23 patients (40%) had a stable disease. The median time to best response was 8.1 months (range 7.3-97).

Interestingly, the ORR was 83% in the  $\geq 1$ -year group versus 43% in the <1-year group ( $p=0.005$ ). Response rates and survival across the two groups (<1 year and  $\geq 1$  year) are summarized in Table 2.

**Survival according to 1-year based exposure to pomalidomide.** For the study as a whole, the median progression free survival (PFS) was 8.3 months (IC95 6;12) and the 12-months PFS was 37%. Median overall survival (OS) was 22.6 months (IC95 16;40), 12-months OS was 79% and 18-months OS was 60%.

After a median follow-up of 36 months, 31 (89%) and 8 (35%) patients have died in the 2 groups, <1 year and  $\geq 1$  year, respectively ( $p=0.002$ ). For the <1 year group, the median PFS was 4.6 months (IC95 4;6) with a PFS at 12 months of only 6%. The median OS was 15 months (IC95 12;20), the OS at 12 months was 66% and the OS at 18 months was 40%. Conversely, the survival rates were strikingly different for the  $\geq 1$  year group, the median PFS was 20.7 months (IC95 15;35) and the PFS at 12 months was 83%. The median OS was not reached (IC95 40.5;NR), the OS at 12 months was 100% and the OS at 18 months was 91%.

Survival according to the length of exposure to pomalidomide is presented in Figure 1.

Of note, 30/31 (97%) and 4/8 (50%) of patients in the 2 groups respectively died of progression of myeloma, in line with ORR, showing that the patients exposed <1 year to pomalidomide-dexamethasone had a lower myeloma disease control compared to the  $\geq 1$  year group. This data anticipates that no safety issue was at the origin of the shorter exposure and benefit from pomalidomide in our series, the primary cause of death was related to myeloma and not to any pomalidomide-dexamethasone-related direct toxicity; but also that it was more difficult to salvage the patients of the <1 year group in the next line of therapy post pomalidomide.

**Predictive factors of long-term survival on pomalidomide in our series.** Amongst the factors that strongly predicted long term survival on pomalidomide in univariate analysis were the time from initial diagnosis to entry into pomalidomide therapy, particularly at the cut-off of >3 years [OR (CI95%) 4.0 (0.6;23.4),  $p=0.04$ ], serum beta-2 microglobulin level, adverse cytogenetic profile and presence of plasmacytoma/EMD, although the latter did not reach significance. Finally, the number of previous lines, particularly at the cut-off of more than 6 lines, also participated with no statistical significance; but interestingly not the refractory presentation to drugs, whichever, nor being refractory to last line of therapy. In multivariate analysis, solely the time from initial diagnosis to entry into pomalidomide therapy, particularly at the cut-off of >3 years, had a negative impact on long term survival on pomalidomide in our series [OR (CI95%) 5.4 (0.7;38),  $p=0.02$ ].

**Safety profile.** Safety profile was acceptable in these RRMM patients, as previously reported in the initial report of the IFM2009-02 and IFM2010-02 study trials, and consisted primarily of myelosuppression. There was no clear difference in terms of safety management of pomalidomide and/or dexamethasone across the two groups. 14.3% ( $n=5$ ) and 13.0% ( $n=3$ ) died in relation to safety issues.

All the patients in the study experienced an adverse event (AE). 85.7% ( $n=30$ ) and 95.7% ( $n=22$ ) of patients experienced at least one grade 3 or 4 AE, and 68.6% ( $n=24$ ) and 78.3% ( $n=18$ ) a serious adverse event (SAE) across groups ( $p=ns$ ). Nonetheless, the daily dose intensity of pomalidomide (median, 3.0 and 2.9 mg/day),

the relative dose intensity of pomalidomide, 89% and 84%, the rate of dose reduction and dose interruption due to treatment related AEs, 5.7% (n=2) and 13.0% (n=3), were not different across the 2 groups (p=ns).

The slightly greater percentage in the latter metric might be explained by the longer exposure to pomalidomide and dexamethasone in this group.

Overall, considering grade 3 and 4 AEs that occurred in more than 10% of cases in the pomalidomide “long runners” group ( $\geq 1$  year) compared to the other group ( $< 1$  year), we have noticed an excess of neutropenia (83% and 63%), thrombocytopenia (30% and 17%), anemia (26% and 29%), and bronchopneumoniae (13% and 11%).

### **Discussion.**

Pomalidomide is a new and potent immunomodulatory compound [6, 7]. It has been proven effective in patients with RRMM [8], and the association of pomalidomide with low dose dexamethasone demonstrated a clear synergy, compared with pomalidomide alone [9]. This synergy was also reported in lenalidomide resistant myeloma studies [10]. However, in advanced MM, periods of remission tend to be short and progression can occur rapidly even under effective treatment. The median progression free survival with pomalidomide and dexamethasone in RRMM is indeed short, 4 to 4.6 months, such as the median overall survival, 13.1 to 16.5 months [4, 9, 11]. However, a subgroup of these end stage patients seems to benefit from this therapy since they display sustained responses. For instance, in the IFM 2009-02 study, 40% of the patients had a prolonged progression free survival and subsequently overall survival [4].

We thus aimed to assess the efficacy and safety profile of pomalidomide and low dose dexamethasone in patients that had prolonged exposure to pomalidomide and low dose dexamethasone in this study. Given that the median PFS of end stage RRMM to pomalidomide and low dose dexamethasone was approximately greater than 3 months, and for the OS greater than one year, we have thought to separate our studied population in 2 groups. The first group had less than 1 year, e.g. 3 months to one year, of treatment with pomalidomide and low dose dexamethasone, considering that the median PFS on pomalidomide and low dose dexamethasone in end stage RRMM was published and reported in the range of 3 months, with a median OS at approximately 13 months. On the other hand, the second group was considered “long runners on pomalidomide” with a prolonged exposure greater than 1 year.

We found an impressive improved survival across groups, in favour for the long runners (exposed  $\geq 1$  year) compared to the other group ( $< 1$  year). The former category displayed a far better prognosis in terms of response rate: 40% improvement, progression free survival: 16.1 months improvement, and, most remarkably, overall survival: 51% improvement at 18 months. It has been reported that patients relapsing after therapy with immunomodulatory drugs and bortezomib have an ORR of 24% [12], at best 49% in the literature [4, 9, 11, 13-15]. A pooled analysis recently showed that the ORR is 31% with pomalidomide and low dose dexamethasone [16] – whereas we found an ORR of 83% in our study for patients able to receive  $\geq 1$  year of pomalidomide and dexamethasone. The 18 months-reported OS at 91% in our study also compared favorably to the “historical control” data reported by Kumar et al., median OS of 9 months [16], and with available data about pomalidomide and low dose dexamethasone reporting a median OS from 11.9 to 18.3 months in RRMM patients [16].

On the other hand, our  $< 1$  year group fell into the known range of published ORR, PFS and OS of patients with end stage RRMM treated with pomalidomide-based therapy. Interestingly, it seemed that this group had more intrinsic adverse features of the disease, which could explain their worse prognosis and the difficulty to maintain these patients under therapy compared to the group with  $\geq 1$  year. This may also explain that patients treated  $< 1$  year with pomalidomide and dexamethasone had a worse outcome in the post-pomalidomide period, suggesting that salvage therapy is less effective in these patients. This population is expected to perform poorly to any sort of treatment, including pomalidomide to some extent as well. It is thus interesting to notice that there is no specific mechanism of resistance to pomalidomide apparently in our study, but the general poor risk criteria already known. Beyond the usual biological / genomic characteristics of poor prognosis known in MM, we also found that patients that entered pomalidomide-dexamethasone end stage study with a time from diagnosis beyond 3 years also displayed very poor features, as expected. These patients would certainly need optimized pomalidomide-based therapy as they usually performed poorly at each line of therapy with poor response rates and/or early relapse presentations, independently of the line received, either proteasome inhibitors or IMiDs.

Our data confirm in some extent that pomalidomide’s mechanism of action in MM relies on its immunomodulatory properties, as a better outcome was observed if patients remained longer under therapy; and conversely, the death of most patients occurred rapidly after discontinuation of therapy, highlighting the fact that pomalidomide allowed control of the disease during the period on pomalidomide-based therapy.

Pomalidomide is efficient as a continuous treatment, and is indeed currently recommended until evidence of disease progression unless unacceptable toxicity [2, 3].

We also confirmed the favourable safety profile of pomalidomide and dexamethasone, even in these heavily pre-treated RRMM patients, interestingly similar across the 2 groups. Most importantly, we did not find any particular toxicity profile in patients on long-exposure to pomalidomide, as compared with shorter duration of therapy [17, 18] .

The main perspective that emerges from this study is therefore to try and optimize pomalidomide therapy in RRMM patients, in order to be able to maintain more patients under prolonged therapy and significantly improve overall survival for a greater population of patients. We already pointed out that the association of dexamethasone to pomalidomide remarkably enhanced its efficacy, but we should probably now look on a wider scale at triplet pomalidomide-based regimens to allow the achievement of a more rapid response, and optimize the control of mechanisms of resistance in tumor cells. For instance, Palumbo et al. have already reported an ORR of 49%, a median PFS of 10.4 months and a 1-year overall survival of 69% with the combination of pomalidomide, cyclophosphamide and prednisone [19]. Greater data could be reported in the near future with the combination of proteasome inhibitor of novel generation with pomalidomide, confirming the known synergy with IMiDs compounds; and in a more distant future with monoclonal antibodies, using the immunomodulatory property of pomalidomide.

However, pomalidomide-based therapies would probably show a greater efficacy if used earlier in the disease course, in less end stage MM patients. For instance, preliminary results for the combination of bortezomib, pomalidomide and dexamethasone (PVD) reported an impressive median PFS of 17.7 months (95%CI: 9.5-NA) in patients with 1 to 4 prior lines of therapy – which means that this association was used as soon as at first relapse [20], which is not yet allowed in Europe.

#### Conclusion.

Pomalidomide and dexamethasone are effective and well tolerated in heavily pre-treated RRMM patients refractory to bortezomib and lenalidomide, with approximately 40% of the patients having prolonged exposure to treatment, which translated into a significantly prolonged OS. However, our study suggests that patients with more intrinsic adverse features of MM tumor cells could not benefit from prolonged exposure to pomalidomide as they progressed within a year from start of pomalidomide. Future studies should

examine optimizing pomalidomide therapy in the patients unable to receive pomalidomide for greater than a year, such as using multi-drugs pomalidomide-based combination regimens to prolong exposure to pomalidomide and/or use pomalidomide-based therapy earlier in the disease course to improve the survival of these patients.

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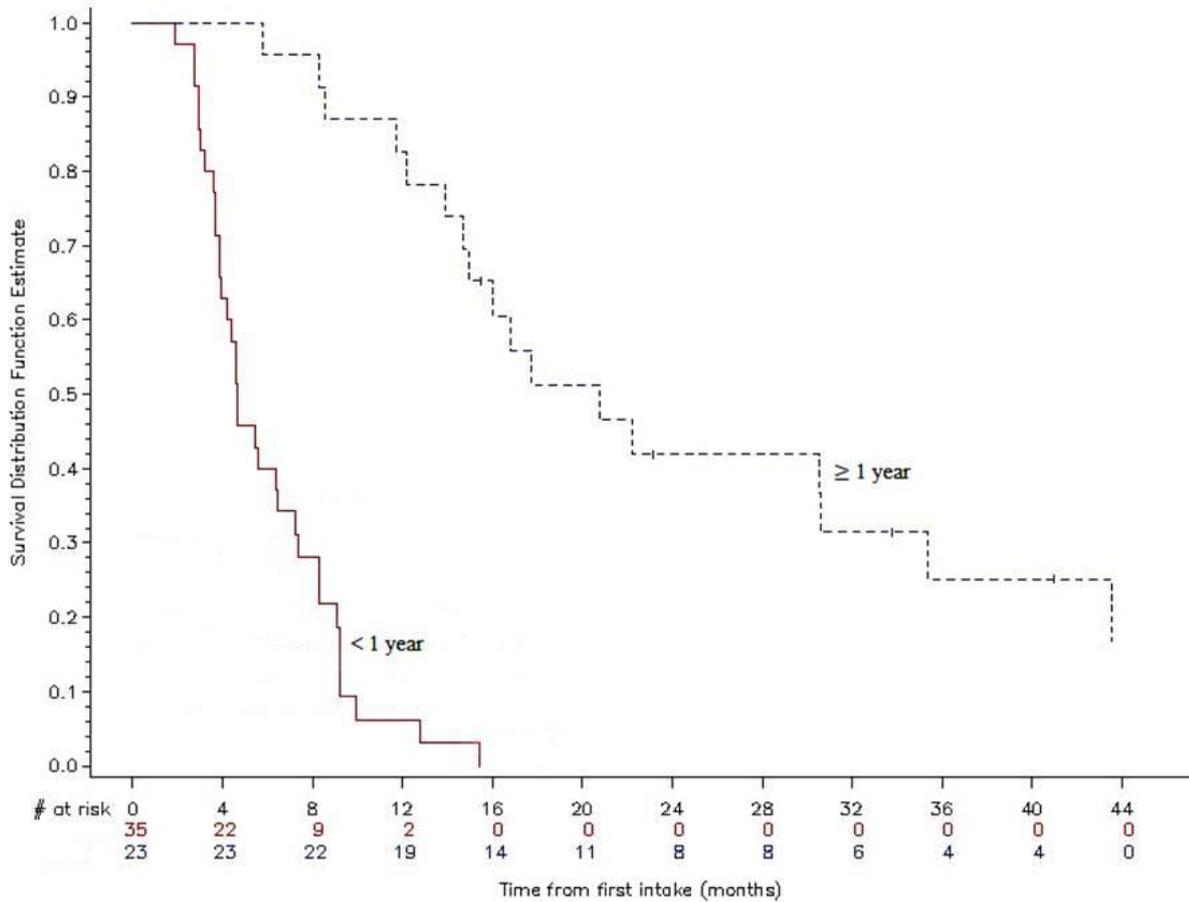
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Figure 1. Survival according to the length of exposure to Pomalidomide.

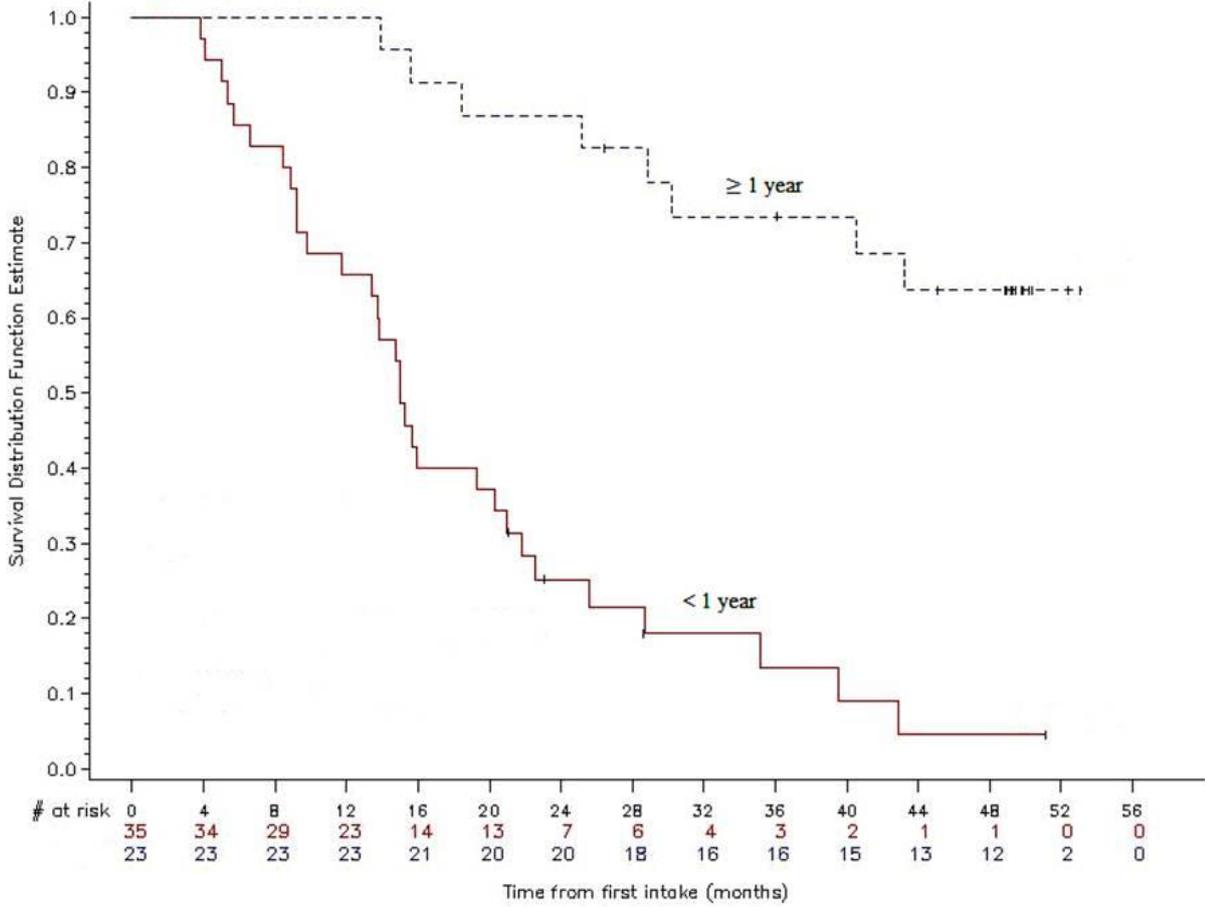
A. Progression free survival according to exposure to Pomalidomide < 1 year or  $\geq 1$  year

B. Overall survival according to exposure to Pomalidomide < 1 year or  $\geq 1$  year

**A. Progression free survival according to exposure to Pomalidomide <1 year or  $\geq 1$  year**



**B. Overall survival according to exposure to Pomalidomide <1 year or ≥1 year**



**Table 1. Characteristics of patients at baseline (n=58).**

<b>Exposure to Pomalidomide</b>	<b>&lt; 1 year (N=35)</b>	<b>≥ 1 year (N=23)</b>
Age, median (range)	61 (42-81)	60 (45-75)
Gender, M/F ratio	2.88	2.28
ECOG		
2, N (%)	3 (9)	3 (13)
Isotype		
IgA, N (%)	4 (12)	1 (4)
Light chains only, N (%)	5 (14)	1 (4)
Serum Beta 2m ≥ 5.5 mg/L, N (%)	5 (14)	2 (9)
ISS 2, N (%)	8 (23)	4 (17)
ISS 3, N (%)	5 (24)	2 (9)
Adverse FISH*, N (%)	8 (23)	2 (9)
Del(17p)	5 (14)	2 (9)
t(4;14)	3 (9)	0
Creatinine > 20mg/L (173μmol/L), N (%)	5 (14)	0
Hypercalcemia, N (%)	3 (9)	2 (9)
Osseous lesions, N (%)	26 (74)	17 (74)
Hemoglobin < 10 g/dL, N (%)	8 (23)	9 (39)
Platelet < 100 x10 <sup>9</sup> /L, N (%)	5 (14)	4 (17)
Plasmacytoma / EMD, N (%)	7 (20)	1 (4)
Median number of prior lines (range)	5 (2-13)	5 (1-10)
Exposition to > 3 lines, N (%)	31 (89)	18 (78)
Exposition to > 6 lines, N (%)	6 (17)	5 (22)
Refractory to Bortezomib, N (%)	28 (80)	17 (74)
Refractory to Lenalidomide, N (%)	31 (89)	20 (87)
Refractory to alkylating agent, N (%)	17/26 (65)	12/16 (75)
Double refractory (Bortezomib+Lenalidomide), N (%)	26 (74)	16 (70)
Triple refractory (Bortezomib + Lenalidomide + last line of therapy), N (%)	21 (60)	16 (70)

ISS. International staging system for MM; \*Adverse FISH. Del17p and/or t(4;14); EMD. Extramedullary disease.

**Table 2. Response rates and survival (n=58).**

<b>Exposure to Pomalidomide</b>	<b>&lt; 1 year (N=35)</b>	<b>≥ 1 year (N=23)</b>
<b>Overall response rate, N (%)</b>	15 (43)	19 (83)
VGPR, N (%)	1 (3)	3 (13)
CR, N (%)	0	4 (17)
<b>Median time to best response, months (range)</b>	8.1 (7.3-38.1)	9 (7.9-97)
<b>Median PFS, months (CI95%)</b>	4.6 (3.8;6.4)	20.7 (14.7;35.4)
PFS at 12 months (%)	6	83
<b>Median OS, months (CI95%)</b>	15 (11.7;20.3)	Not reached (40.5;-)
OS at 12 months (%)	66	100
OS at 18 months (%)	40	91