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Pomalidomide for the treatment of relapsed-refractory multiple myeloma: a review of biological and clinical data

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Abstract

Despite the improvements thanks to the introduction of proteasome inhibitors and immunomodulatory drugs (IMiDs), nearly all myeloma patients eventually become refractory to these drugs. Consequently, the outcome of these patients is very poor. Pomalidomide is a new IMiD with a similar structure to the commonly used IMiDs thalidomide and lenalidomide. Pomalidomide exhibited more potent anti-myeloma activity and a similar favorable safety profile compared with thalidomide and lenalidomide. In phase 1-2 studies Pomalidomide plus low-dose dexamethasone demonstrated activity in myeloma patients refractory to both bortezomib and IMiDs. Based on the results of a phase 3 trial, the FDA and EMA agencies granted accelerated approval to Pomalidomide, which is now considered a new effective strategy for relapsed and/or refractory myeloma patients. Very promising results were obtained when Pomalidomide-dexamethasone was used in combination with other compounds. This review provides updated information about pharmacokinetics, mechanism of action, resistance, clinical efficacy and safety of Pomalidomide.

Key words: Pomalidomide, IMiDs, multiple myeloma, relapsed, refractory, treatment

1. Introduction

Multiple Myeloma (MM) is a lymphoproliferative disorder characterized by monoclonal plasma cells expansion and accumulation in the bone marrow. Symptomatic MM is characterized by the so called CRAB features, that include hyperCalcemia, Renal impairment, Bone lesions, Anaemia[1].

The pathogenesis of MM is characterized by a progressive acquisition of genetic lesions such as translocations, deletions and mutations in the regulating genes of plasma cells, promoting, in the early stage, the binding with bone marrow stromal cells. The mutations that occur during MM progression activates NFkB. NFkB up-regulates cell-surface adhesion molecules and increases growth, anti-apoptotic and angiogenic cytokines production (IL-6, TNF−α, IGF-1, VEGF) as well as IL-10 and TGF-β secretion by tumor plasma cells, leading to dysregulation of B- and T-cells immune surveillance. This whole process supports survival, proliferation and chemoresistance of tumor plasma cells[2]. Genetic lesions occurred in a Darwinian fashion, leading to intraclonal heterogeneity and increasing the genetic complexity of MM. Therefore, genetic lesions also have an important effect on treatment strategies[2].

MM affects 4 to 7 / 100.000 inhabitants in the developed countries. In the United States, the estimated number of new cases of MM in 2014 is 24,050 and the expected number of deaths due to myeloma is 11,090 [3]. In Europe, the incidence of MM was 3.8 / 100,000 inhabitants in 2012, and Italy was one of the ten countries with the highest incidence (5.5 / 100,000 inhabitants)[4].

Despite the introduction of effective novel agents and strategies in the front-line therapy of MM, virtually all MM patients have a different amount of residual disease leading to cyclic relapse and finally to refractory disease. The optimal treatment of patients with relapsed refractory MM (rrMM) remains an unanswered question, particularly the optimal sequence, number and dose of drugs, and duration of therapies need to be appropriately defined. To date, treatment decision is based on the characteristics of the disease and of the patients, as well as on the efficacy and toxicity of prior therapy and drugs availability[5]. Although re-treatment with previously used agents[6] or the use of a different class of first-generation novel agents can be a sensible strategy, patients who become refractory to Thalidomide, Lenalidomide and Bortezomib have limited salvage therapeutic options and a dismal outcome[7]. These patients represent an unmet medical need. Fortunately, advances in the understanding of the biology, cytogenetic and the molecular pathways of MM[8] have led to

developments of various novel agents, including monoclonal antibodies[9-11], histone-deacetylase inhibitors[12-15], signal transduction modulators[16], new proteasome inhibitors such as Carfilzomib[17-19] and new immunomodulators (IMiDs)[20] such as Pomalidomide. Pomalidomide has been recently approved by the Food and Drugs Administration (FDA) in USA and European Medicine Agency (EMA) in Europe for the treatment of patients who have progressed after previous treatment with at least two prior therapies including Lenalidomide and Bortezomib but whose disease progressed on therapy or within 60 days after the most recent cycle of therapy[21,22].

This review will provide an overview of the chemistry of Pomalidomide and the clinical results achieved with this agent for the treatment of relapse/refractory MM.

2. Chemistry, pharmacokinetics, pharmacodynamics

The chemical name of Pomalidomide is (RS)-4-Amino-2-(2,6-dioxo-piperidin-3-yl)-isoindoline-1,3-dione[23]. Following administration of single doses of Pomalidomide, the oral absorption is more than 70% and the Cmax occurs at 2 and 3 hours post dose. Half-life of Pomalidomide ranges from 6.5 to 8.0 hours and it is eliminated for the most part within 48 hours. Pomalidomide is primarily eliminated through the kidneys (~73%) but it is extensively metabolized prior to excretion and the main metabolic processes consist in cytochrome P450-mediated hydroxylation (CYP1A2 and CYP3A2) with subsequent glucuronidation and glutarimide ring hydrolysis. Only 10% of the compound administered is excreted unchanged (renal and fecal). Pomalidomide may be removed by dialysis[24]. In vitro studies to test the direct inhibition of MM cells and the immunomodulatory property of Pomalidomide metabolites showed low activity. Differently from Lenalidomide that is eliminated in urine mostly as unchanged compound, Pomalidomide is eliminated primarily as metabolities[24]. The phase 1 MM-008 study[25] assessed the pharmacokinetics and safety of Pomalidomide plus low-dose Dexamethasone in patients with relapsed/refractory MM and with impaired renal function. Preliminary results suggest that dose-normalized exposure in patients with severe renal impairment is similar to that of patients with normal to mildly impaired renal function.

3. Mechanism of action and resistance

Similarly to Thalidomide and Lenalidomide, Pomalidomide exerts its antitumor activity by direct antiproliferative and pro-apoptotic effects on plasma cells, by bone marrow microenvironment modulation (anti-angiogenic and anti-inflammatory effects) and by immunomodulation (increase in T and NK cell activity, suppression of regulatory T-cells). Of note, Pomalidomide showed to be more active than the two previous IMiDs[26] (Table 1).

Pomalidomide arrests cell cycle in G1/G0 phase by up-regulation of the expression of both p21 and p53 tumor suppressor genes, independently[27]. Moreover, it exerts pro-apoptotic effect via a caspase-8-dependent mechanism[27] and by sensitizing Fas- and TRAIL/Apo2L-induced apoptosis[28]. This pro-apoptotic effect is enhanced by Dexamethasone and by proteasome inhibitors, showing the clinical synergistic effects of Pomalidomide is combined with these agents[29,30].

In the bone marrow microenvironment, Pomalidomide, mainly by inhibition of TNF-α secretion, reduces the cell adhesion molecules LFA-1, ICAM-1, VCAM-1 and VLA-4 on both plasma cells and stromal cells, thereby inhibiting their interaction...Consequently, the secretion of survival, angiogenetic and inflammatory cytokines such as IL-6, bFGF, VEGF, cyclooxygenase-2 and prostaglandin by stromal cells is inhibited, leading to plasma cell death [31,32].

Pomalidomide has a more potent immunomodulatory effect compared with Thalidomide and Lenalidomide. Pomalidomide strongly stimulates the secretion of Th-1 cytokines, such as IL-2 and Interferon-γ that stimulates CD4+, CD8+ T-cells and activates NK and NKT thus improving cellular immunity[33]. Moreover, Pomalidomide inhibits the proliferation of regulatory T-lymphocytes and their suppressor functions, enhancing cytotoxic tumor cell killing[34]. These immunomodulatory effects were observed in vivo, in patients with relapsed/refractory MM enrolled in a phase 1 clinical trial[35].

Although further studies are warranted, Pomalidomide seems to be also effective to prevent bone resorption by down-regulating PU.1 transcription factor that inhibits cytokines-mediated differentiation of osteoclasts[36].

Recently, the protein cereblon (CRBN) has been found to mediate the antiproliferative and immunomodulatory activities of lenalidomide and pomalidomide[37]. The reduction of CRBN expression, occurring in MM cells that acquired resistance to IMiDs, was associated with loss of antiproliferative potency of lenalidomide and pomalidomide[38]. On the other hand, patients with newly diagnosed MM receiving Thalidomide maintenance with CRBN expression above the median demonstrated longer PFS compared with patients with CRBN

expression below the median. No correlation between CRBN expression and PFS was found in patients receiving Bortezomib maintenance[39]. However, a recent study[40] demonstrated that intrinsically resistant fresh plasma cells and myeloma cell-lines do not show CRBN mutations. This suggests that resistance to IMiDs is a more complex and widely unknown phenomenon involving other genetic and epigenetic pathways. To date, there are several technical limitations to CRBN measurement. Therefore, only validated and standardized assays will be able to assess the role of CRBN as predictive or prognostic biomarker in MM[41].

4. Clinical studies

***4.1** Phase 1 studies*

The first phase 1 study[35] aimed to evaluate safety and maximum-tolerated dose (MTD) of Pomalidomide. Pomalidomide was given at doses of 1, 2, 5 and 10 mg daily and 24 patients were enrolled. Dose-limiting toxicities included grade 3-4 neutropenia and deep vein thrombosis occurring in 25% and 16% of patients, respectively. The MTD was defined as 2 mg daily. Fifty-four percent of patients achieved at least a partial response (PR), 17% achieved a complete response (CR) and the median progression-free survival (PFS) was 9.7 months. Of note, patients had not previously received IMiDs. In a subsequent study[42], 20 patients with progressive disease who had received at least one prior therapy were treated with Pomalidomide at 1, 2, 5 and 10 mg every other day. These patients had received a median of 4 prior lines of therapy and 85% of them had received thalidomide. Grade 3-4 neutropenia occurred in 45% of patients. Constipation was the other main toxicity, it occurred in 20% of patients but was limited in severity to grade. No thromboembolic events or neurological toxicity were reported. The MTD was defined as 5 mg. Fifty percent of patients obtained at least a PR. After a median follow-up of 35 months, the median PFS was 10.5 months, the median overall survival (OS) was 35.9 months. Recently, Richardson et al[43] reported the results of a phase 1 dose-escalation study in which Pomalidomide was given for 21 days of each 28-day cycle at doses ranging from 2 mg to 5 mg. The MTD was defined as 4 mg. Thirty-eight relapsed/refractory MM patients were enrolled. All patients had been previously treated with either Lenalidomide or Bortezomib and 63% of them were refractory to both drugs. In addition, twelve patients (32%) had been treated with Carfilzomib and then became refractory to this drug. Patients

received a median of 5 cycles of Pomalidomide. In 22 patients, Dexamethasone was added after a median of 2.8 months due to the suboptimal response. The most common grade 3-4 hematologic side effects were neutropenia (53%), anemia (21%) and thrombocytopenia (18%). Three patients (8%) developed pneumonia and 2 patients (5%) grade 3 deep vein thrombosis. The overall response rate (ORR) was 21% and, among 24 patients (63%) refractory to both Lenalidomide and Bortezomib, at least PR was documented in 6 patients (25%). The median PFS was 4.6 months and OS 18.3 months.

4.2 *Phase 2 studies*

Several phase 2 trials[29,44-46] evaluated Pomalidomide at different doses and schedules in combination with Dexamethasone. Sixty patients[29, 44]. who had received 1-3 prior regimens (only 35% had previously been treated with Lenalidomide and 33% with Bortezomib), were treated with Pomalidomide at 2 mg daily on days 1 through 28 of a 28-day cycles, in association with Dexamethasone at 40 mg daily on days 1, 8, 15 and 22 of each cycle. Sixty-five percent of patients obtained at least a PR, with 10% achieving stringent CR (sCR), 13% CR, 41% very good partial response (VGPR) and 36% PR. After a median follow-up of 30 months, the median PFS was 13 months and 2-yr OS 76%. Grade 3-4 neutropenia (20%) was the most common side effect, whereas only 3% of patients experienced severe thrombocytopenia. Grade 3-4 fatigue occurred in 18% and pneumonia in 12% of patients. Lacy and colleagues[45] evaluated the combination Pomalidomide plus Dexamethasone, at the same doses and schedules as the previous study, in patients refractory to Lenalidomide. Thirty-four patients were accrued. Patients had received a median number of 4 previous therapies. Thirty-two percent of patients achieved at least a and no patient attained a CR. Grade 3-4 hematologic toxicity included neutropenia (29%) and thrombocytopenia (9%) whereas severe non-hematologic side effects were rare. No patient developed thromboembolic events but 26% of subjects experienced grade 1-2 peripheral neuropathy. With a median follow-up of 8 months, the median PFS and OS were 4.8 and 13.9 months, respectively. In a randomized phase 2 study[46], two schedules of pomalidomide were compared. Pomalidomide was administered at doses of 2 or 4 mg daily on days 1-28 of a 28-day cycle and Dexamethasone was given at a dose of 40 mg daily on days 1, 8, 15 and 22. In each cohort 35 patients were enrolled and they were all refractory to Lenalidomide and Bortezomib. The higher dose of Pomalidomide was not associated with improved efficacy: the at least PR rate was 25% for patients receiving Pomalidomide at 2 mg and

29% for those treated with Pomalidomide at 4 mg. The median PFS was 6.5 with Pomalidomide at 2 mg and 3.2 months with Pomalidomide at 4 mg, whereas the median OS was not reached in both groups. Neutropenia was the most common grade 3-4 hematologic side effect, and occurred in 51% of patients with pomalidomide 2 mg and 66% of those treated with pomalidomide 4 mg daily. Severe non-hematologic toxicity mainly consisted in fatigue and occurred in 9% of patients in both cohorts. Approximately 10% of patients enrolled in the 4 mg cohort discontinued treatment due to side effects, while discontinuation was lower (3% only) in the 2 mg cohort[46]. Recently, results of 6 sequential phase 2 trials including 345 relapsed/refractory MM patients treated with the combination Pomalidomide, at differing doses, and weekly Dexamethasone have been assessed[47]. In patients refractory to Lenalidomide (214 patients), 21-32% of patients achieved at least a PR, with a median PFS of up to 8 months. In the multivariate analysis, lactate dehydrogenase (LDH) value > upper limit of normal (ULN), more than 3 prior regimens and prior Bortezomib were associated with a shorter time-to-progression (TTP). Moreover, patients who had received Thalidomide or Lenalidomide immediately before Pomalidomide had a lower response rate compared with those who had not received IMiDs as their last therapy (29% *vs* 44%, p=0.04). Of note, these patients also had a shorter median duration of Pomalidomide treatment (5.7 months *vs* 7.3 months, p=0.02)[48]. In the MM-002 phase 2 study[49], 221 patients with relapsed/refractory MM who had received at least 2 prior therapies including Bortezomib and Lenalidomide were randomized to receive Pomalidomide in combination with Dexamethasone (113 patients) or Pomalidomide alone (108 patients). Pomalidomide was administered at 4 mg daily on days 1-21 of a 28-day cycle, whereas Dexamethasone was given at 40 mg weekly. Overall, patients received a median of 5 treatment cycles and at least a PR was documented in 33% (PR 30%, CR 3%) of patients receiving Pomalidomide with Dexamethasone and in 18% (PR 16%, CR 2%) of those treated with Pomalidomide alone. After a median follow-up of 14.2 months, the median PFS was 4.2 months for Pomalidomide with Dexamethasone and 2.7 months for Pomalidomide alone (HR 0.68, 95%CI, 0.51-0.90, p=0.003), whereas the respective median OS times were 16.5 and 13.7 months (HR 0.94, 95%CI, 0.70-1.28, p=0.709). In patients older than 65 years, response rate and PFS were not significantly different if compared with younger patients. No difference between the two arms was seen in terms of safety profile. Grade 3-4 neutropenia and thrombocytopenia occurred in 41% and 19% of patients receiving Pomalidomide plus Dexamethasone vs 48% and 22% in those receiving Pomalidomide alone. The most frequent grade 3-4 non-hematologic toxicities were

pneumonia (22% in the Pomalidomide plus Dexamethasone arm *vs* 15% in the Pomalidomide only arm), fatigue (14% vs 11%) and dyspnea (13% vs 8%). Patients treated with Pomalidomide and Dexamethasone who had received more than three prior therapies had a worse ORR (30%) compared with those less heavily pretreated (48%)[50].. Similarly, patients with high-risk cytogenetics, defined as the presence of del (17p13) and/or t(4;14), had a lower ORR (23%) if compared with patients with standard-risk cytogenetics (40%). Consistently, high-risk patients had a shorter PFS (median 3.1 vs 5.5 months) and OS (median 13.2 vs 21.7 months)[51]. Renal function at baseline appeared not to impact on the efficacy and safety profile of the combination Pomalidomide plus Dexamethasone[52]. The IFM 2009-02 phase 2 trial[53] evaluated two different treatment schedules of the combination Pomalidomide and Dexamethasone. Eighty-four patients with relapsed/refractory MM were randomized to receive Pomalidomide 4 mg orally on days 1-21 of each 28-day cycle (arm 21/28 days) or continuously (arm 28/28 days) whereas Dexamethasone was given at 40 mg weekly in both arms. Patients had received a median of 5 prior lines of therapies and 76% of them were refractory to lenalidomide and bortezomib. No significant difference in terms of ORR between the two arms was seen (ORR 35% in the 21/28 arm *vs* 34% in the 28/28 arm), and the median TTP (5.8 *vs* 4.8 months) and the median OS (14.9 *vs* 14.8 months) were also similar. Although no difference was found in terms of grade 3-4 hematologic toxicity between the two arms, infections (27% in the 28/28 arm *vs* 19% in the 21/28 arm) and pneumonia (19.5% in the 28/28 arm *vs* 7% in the 21/28 arm) occurred more frequently in patients receiving Pomalidomide continuously. The results of the main trials of Pomalidomide in combination with Dexamethasone are reported in Table 2.

4.3 *Phase 2 studies: triplet therapies*

Recently, a phase 1-2 study[54] explored the 3-drug combination Pomalidomide-Cyclophosphamide-Prednisone (PCP) followed by maintenance with Pomalidomide-Prednisone in patients with MM who relapsed after or were refractory to lenalidomide. Patients had received 1-3 prior lines of therapy. In the phase 1 portion of this study, 24 patients were enrolled in 6 cohorts to determine the MTD, and Pomalidomide was administered at doses ranging from 1 to 2.5 mg. The MTD was established at 2.5 mg/day continuously when associated with Cyclophosphamide at 50 mg every other day and Prednisone 50 mg every other day. In the phase 2 portion of study, another 55 patients were enrolled. PCP induced at least a PR rate of 51% and a CR rate of 5%. Similar

responses were reported in the subgroups of patients who relapsed after or were refractory to lenalidomide, or those who were refractory to both lenalidomide and bortezomib. After a median follow-up of 15 months, the median PFS was 10.4 months and the 1-year OS was 69%. In the multivariate analysis, the achievement of at least a PR and younger age were associated with longer PFS, whereas refractoriness to Lenalidomide, to Lenalidomide and Bortezomib or high-risk cytogenetics seemed not to affect PFS. Severe neutropenia occurred in 41% of patients whereas thrombocytopenia in only 10%. Infection (9%), skin rash (7%) and worsening of neuropathy (7%) were the main severe non-hematological adverse events. They led to dose-reduction in 30% of patients and therapy discontinuation 10% of patients .

Several trials have assessed the role of Pomalidomide-Dexamethasone in combination with standard chemotherapeutic agents or new drugs[30,55-60]. A phase 1-2 randomized study[55] evaluated the combination of Pomalidomide (4 mg days 1-21), Dexamethasone [40 mg (20 mg for patients ≥ 75 years) days 1, 8, 15, 22] with or without Cyclophosphamide (400 mg on days 1, 8, 15 of a 28-day cycle). All patients were refractory to Lenalidomide, 79% were refractory also to bortezomib. The aggregate results of 70 patients randomized in the phase 2 portion of study showed at least a PR rate of 48.5% and a median PFS of 6.4 months. The median duration of response was 10.4 months. Grade 3-4 side effects were neutropenia (30%), febrile neutropenia (13%), pneumonia (13%) and thrombocytopenia (11%). Thromboembolic events were rare (4%).

A phase 1-2 study[56] evaluated Pomalidomide-Dexamethasone in combination with Pegylated liposomal doxorubicin (PLD) in patients refractory to Lenalidomide. In the phase 1 portion, the MTD of Pomalidomide was established at 3 mg on days 1-21 when combined with Dexamethasone at 40 mg and PLD at 5 mg, both on days 1, 4, 8 and 11 in a 28-day cycle. In the 29 evaluable patients who had received a median of 5 prior therapies, at least a PR was achieved in 35% of patients. Severe neutropenia, the main adverse event, decreased from 37.5% to 0 when the dose of Pomalidomide was lowered from 4 to 3 mg/day.

A single institution study[57] assessed Pomalidomide-Dexamethasone (Pomalidomide at 4 mg on days 1-21 and Dexamethasone at 40 mg on days 1, 8, 15, 22 of a 28-day cycle) in combination with Clarithromycin (500 mg twice day). One-hundred and fourteen patients treated with a median of 5 prior therapies (range 3-15) had completed at least one cycle and could be evaluated for response. Eighty-five percent of them were refractory to Lenalidomide, 82% to Bortezomib, 68% to both drugs. The at least PR rate was 61.4% and

the VGPR rate was 20.2%. After a median follow-up of 13 months, the median PFS was 8.67 months and OS was 57%. Response, PFS and OS were not significantly different between patients who were double refractory and those who were not. Grade 3-4 neutropenia (51%) and thrombocytopenia (41%) were quite frequent whereas febrile neutropenia was uncommon (2%). No patients developed grade 3-4 peripheral neuropathy and deep vein thrombosis occurred in one patient only. Discontinuation due to toxicity was only 3.5%.

Another phase 1 study (MM-005 study)[30] evaluated Pomalidomide in combination with intravenous (iv) Bortezomib at 1.3 mg/m^2 on days 1, 4, 8, and 11 and Dexamethasone at 20 mg on days 1, 2, 4, 5, 8, 9, 11, 12 in patients who had received 1-4 prior lines of therapies, were refractory to lenalidomide and had been exposed to bortezomib. The MTD of Pomalidomide was established at 4 mg on days 1-14 in a 28-day cycle. In the cohort of 22 patients who received iv Bortezomib, 71% achieved at least a PR and 38% at least a VGPR. Responses improved over the follow-up period, also in patients with high-risk cytogenetics. Neutropenia and thrombocytopenia were the most common grade 3-4 adverse events whereas no severe neuropathy was reported. This study provided the basis for a randomized phase 3 study comparing Pomalidomide-Bortezomib-Dexamethasone (PVD) with Bortezomib-Dexamethasone (MM-007 study), which is currently ongoing.

A similar study[58] was conducted to explore the role of PVD in patients who had received 1-4 lines of previous therapy and were resistant or refractory to Lenalidomide. In the phase 1 portion of this study, Bortezomib dose was escalated from 1 mg/m^2 weekly (days 1, 8, 15, 22) to 1.3 mg/m^2 weekly associated with fixed dose of Pomalidomide at 4 mg on days 1-21 and Dexamethasone at 40 mg on days 1, 8, 15, 22 of a 28-day cycle. Sixteen patients entered the phase 2 portion of the study, in which the MTD of Bortezomib was used (1.3 mg/m^2 weekly). Fifteen patients (94%) achieved at least a PR, including 9 patients (56%) with at least a VGPR. Neutropenia (36%) was the most common severe complication.

Pomalidomide-Dexamethasone in combination with Carfilzomib was tested in a phase 1-2 study including 79 patients[59]. In the first portion of the trial, the MTD was defined as Pomalidomide 4 mg on days 1-21, Carfilzomib 20/27 mg/m^2 on days 1-2, 8-9, 15-16 and Dexamethasone 40 mg on days 1, 8, 15, 22 of a 28-day cycle. Patients had previously received a median of 5 therapies, were all refractory to Lenalidomide and most of them had been exposed to Bortezomib. Seventy percent achieved at least a PR, 27% at least a VGPR, the,median PFS was 9.7 months and the median OS was longer than 18 months,.

High-risk cytogenetics did not affect response rate and PFS duration. Grade 3-4 adverse events were neutropenia (29%), anemia (17%) and thrombocytopenia (14%) .

Carfilzomib followed by Pomalidomide or Pomalidomide followed by Carfilzomib were evaluated to define the best sequential approach to obtain the maximum tumor reduction in relapsed/refractory MM. In one study[60], 14 patients who had received Carfilzomib-based therapy and then received salvage therapy with Clarithromycin-Pomalidomide-Dexamethasone (ClaPd) were compared with 20 patients who had been initially treated with ClaPd and then received salvage treatment with Carfilzomib-based therapy at relapse-progression. Both sequences were effective, and deeper responses were detected with the first approach, although patients had received more prior lines of therapy. Table 3 shows the results of the most relevant Pomalidomide-based combinations in realapsed/refractory MM.

4.4 *Phase 3 study and sub-studies*

The first phase 3 trial (MM-003 trial) [61] comparing the efficacy and safety of Pomalidomide plus low-dose Dexamethasone (Pd) *vs* high-dose Dexamethasone (Hi-Dex) in patients with refractory or relapsed/refractory MM has been recently published. Patients were randomized to Pd (arm A: 302 patients treated with Pomalidomide at 4 mg/day for 21 days every 28 days; Dexamethasone at 40 mg on days 1, 8, 15, 22 of a 28-day cycle) or to Hi-Dex (arm B: 153 patients treated with Dexamethasone at 40 mg on days 1-4, 9-12- 17-20 of a 28-day cycle) until progression or unacceptable toxicity. Patients had received a median of 5 prior lines of treatment (94% had received more than two lines of therapy), more than 80% had refractory disease, three quarter of patients were refractory to both bortezomib and lenalidomide. After a median follow-up of 10 months, the median PFS (the primary endpoint of the study) was 4.0 months in the Pd arm *vs* 1.9 months in the Hi-Dex arm (HR 0.48; p<0.0001). PFS was significantly longer in the Pd arm regardless of age, cytogenetics, and last therapy with or refractoriness to either lenalidomide, bortezomib, or both lenalidomide and bortezomib. The median OS was still significantly longer in the Pd arm (12.8 *vs* 8.1 months; HR 0.74, p=0.028). Response rate was higher in the Pd arm (at least PR rate 31% *vs* 10%; p<0.001).

Grade 3-4 haematological adverse events in the Pd arm included neutropenia (48%) and thrombocytopenia (22%). Infections (34%) pneumonia (14%) and febrile neutropenia (10%)

were the most common non-hematological severe adverse events and the main causes of treatment-related deaths and therapy discontinuation. Both grade 3-4 neuropathy and deep-vein thrombosis/ pulmonary embolism occurred in 1% of patients with thromboprophylaxis.
Based on this study, the FDA (February 2013) and the EMA (August 2013) granted accelerated approval to Pd.
Updated data and several sub-studies of the MM-003 trial have been recently presented[62-66]. After a median follow-up of 15.4 months[62] the median PFS (4 months *vs* 1,9 months; HR 0.50, p<0.001) and the median OS (13.1 months vs 8.1 months; HR 0.72, p=0.009) were improved with Pd arm versus Hi-Dex. Moreover, Pd was significantly more effective than Hi-Dex regardless of low-risk or high-risk FISH defined as t(4;14) or del17[62]. Another substudy[63] showed that Pd was effective regardless of the number of prior therapies, but the the benefit more rponounce when Pd was given earlier in therapy and immediately following the development of Lenalidomide-refractory disease. In another analysis[64], age (cut-off 65 years) was confirmed to impact on outcome. Pd induced better response, PFS and, marginally enhanced OS compared with Hi-Dex in both patients older and younger than 65 years. This may be attributable to the fact that the same median relative dose intensity of Pomalidomide (90%) was administered in both age groups. Another substudy[65] found that health-related Quality of life (HR-QoL) was significantly better in any considered domain (Global health Status, Physical Functioning, Fatigue Emotional Function) with Pd compared with Hi-Dex, except for pain either as cross-sectional or longitudinal measurement.
Finally, the two randomized trials MM-002 and MM-003 were analyzed side-by-side[66]. The results with Pd in the two studies were very similar and significantly better than pomalidomide alone or Hi-Dex in terms of response, PFS and OS.

4.5 *Particular clinical situations (High-risk, Extramedullary disease)*

In a recent phase 2 study[67], Pd was administered to patients with relapsed/refractory MM and del(17p) and/or t(4;14). Fifty patients were enrolled and all patients had previously been exposed to lenalidomide, 84% were refractory to lenalidomide. At least a PR was obtained in 20% of patients and after a median follow-up of 5 months the median TTP was 3 months in the whole population, 8 months in patients with del17p and 3 months in those with t(4;14). Several phase 2 studies[30, 54, 59, 62] of Pd with or without chemotherapeutic

agents or new drugs showed that high-risk patients have a similar outcome in terms of response rate or duration of response compared with standard-risk subjects. However, these results are preliminary and further confirmation is needed.

Extramedullary localization is uncommon in frontline MM but it is frequent in advanced disease stages. Lymphnodes, soft tissue, skin, muscle and lung were mainly involved but extramedullary disease can occur near in all organs[68-70]. In one study[71], extramedullary disease was present in 7.5% of 174 patients assessed at diagnosis. Thirteen patients with extramedullary disease treated with Pomalidomide during relapsed-refractory disease achieved a response, including 4 (31%) with a PR and 2 (15%) with a CR. This demonstrated that Pomalidomide could be still effective in extramedullary MM. In a case report[72], a patient with central nervous system myelomatosis obtained a cerebral spinal fluid clearance of plasma cells with Pomalidomide treatment, thus suggesting that Pomalidomide could be effective also in this rare and critical clinical situation.

5. Safety profile

In relapsed/refractory MM, Pd has a good safety profile. Haematological toxicity, particularly neutropenia, was the main adverse event and could be easily managed. Haematological toxicity was dose-dependent (2-4 mg), related to the number of prior therapies and occurred mainly in the first cycles of therapy[29, 44-47].

Fatigue and infections, particularly pneumonia, were the major non-haematological adverse events but rarely led to therapy discontinuation or death[45]. Worsening of neuropathy was inconsistently seen[43, 45, 53].

Thromboembolic complications were low in all studies and could be successfully prevented with prophylaxis according to the guidelines used for the other IMiDs[73].

Skin rash was more rarely seen with Pomalidomide compared with Lenalidomide and Thalidomide[74].

Pd in combination with Cyclophosphamide or other new drugs may slightly increase the rate of neutropenia, thrombocytopenia and infections[54-56]. The association with proteasome inhibitors seems to not increase the rate of severe neuropathy, whereas gastrointestinal toxicity, particularly diarrhoea, and fatigue are higher[59]. Considering that infections are the most frequent adverse events, antibiotic prophylaxis should be considered in patients receiving any Pomalidomide-based combinations.

6. Conclusions

Pomalidomide is a new IMiD, it has a peculiar and strong activity in relapsed/refractory MM, directly or by modulating bone marrow microenvironment. Phase 1-2 studies suggest that Pomalidomide at daily dose of 2-4 mg orally plus low-dose Dexamethasone is effective in heavily pretreated patients who are also refractory to Lenalidomide and/or Bortezomib. However, the recommended dose of Pomalidomide is 4 mg/day for 21 days of 28 day cycle. One phase 3 study demonstrated that Pd combination significantly prolonged PFS and OS in patients who were refractory to Bortezomib and Lenalidomide compared with high-dose Dexamethasone. This study led to the Pd approval as a new standard treatment in this setting. In small or retrospective studies, Pd demonstrated activity also in high-risk or extramedullary diseases but these data are very preliminary and they need to be confirmed in larger trials including newly diagnosed MM patients. Promising results were seen when Pd was combined with alkylating agents, proteasome inhibitors or other compounds in phase 1-2 studies in relapsed/refractory MM. Pomalidomide showed to have a good safety profile, as it was associated with manageable haematological toxicity; non-hematological toxicity was rare and manageable as well.

Further studies are awaited to define the role of Pomalidomide in less heavily pretreated or newly diagnosed MM patients.

7. Expert commentary

So far, the available studies with Pomalidomide have not shown a clear relationship between dose-schedule, response rate and toxicity, although neutropenia and infections seem to be more frequent when Pomalidomide is give at higher doses and for a prolonged time. Compared with Lenalidomide, Pomalidomide induces more rapid response with a similar toxicity profile.

The number and type of prior therapies strongly predict response and survival also after Pomalidomide treatment. However, the positive results obtained in patients with advanced and refractory disease, the good safety profile and the oral bioavaliabilty make Pomalidomide one of the most important recent options in the treatment of relapsed/refractory MM. Pomalidomide is particularly advantageous for patients who did not benefit from Lenalidomide and Bortezomib and thus represent an unmet medical need.

Alkylating agents and proteasome inhibitors strongly enhanced the activity of Pd combination, and were associated with a manageable toxicity also in patients with advanced MM.
Although preliminary results showed that Pomalidomide was effective also in high-risk MM, further trials in this subset of patients are needed. .

8. Five-year view

Despite the good activity and toxicity profile of Pomalidomide with the currently approved schedule, the optimal dose-schedule that achieves maximal activity with minimal toxicity should be further investigated in order to build future long-term combination therapies.
Studies exploring Pd with or without other compounds should be implemented. Indeed, combinations including Pd showed promising results in the treatment of MM patients with less advanced disease and in newly diagnosed MM, as induction before transplantation, as consolidation therapy, or, particularly, as continuous therapy in patients not eligible for transplantation.
Finally, studies to confirm the effectiveness of Pomalidomide as maintenance are urgently needed.

9. Key issues

- Pomalidomide is a new oral IMiD exerting a potent anti-myeloma activity by direct antiproliferative and pro-apoptotic effects, by bone marrow microenvironment modulation and by immunomodulation
- Although the optimal schedule has not been yet established, Pomalidomide at 2-4 mg orally for 21-28 days alone or with low-dose Dexamethasone showed to be effective in relapsed/refractory MM. Yet, the recommended dose is 4 mg/day.
- In several phase 2 studies, Pd was effective in patients with advanced disease, with disease refractory to Lenalidomide, to Bortezomib or both
- In a phase 3 study, Pd demonstrated significantly better response rate, PFS and OS compared with Hi-Dex in patients with MM who became resistant to both Lenalidomide and Bortezomib
- Pomalidomide in combination with “old” and novel drugs has a very promising activity in relapsed/refractory MM

- Pomalidomide alone or in combination, similarly to lenalidomide, has a manageable safety profile: haematological toxicity, pneumonia and fatigue are the most common adverse events, whereas thromboembolic complications and neurologic toxicity are very rare
- Pd has been recently approved in USA and in Europe for the treatment of patients with MM who have received at least two prior therapies including Lenalidomide and Bortezomib and progressed on the last therapies
- The efficacy of combinations including Pomalidomide in less advanced disease stages, in first-line therapy and in maintenance strategies should be urgently explored

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Table 1. Main mechanisms of action of IMiDs

Effect	Thalidomide	Lenalidomide	Pomalidomide
Anti-angiogenesis	++++	+++	+++
Anti-inflammatory properties	+	++++	+++++
CD4+ and CD8+ T-cell stimulation	+	++++	+++++
NK and NKT cell activation	+	++++	+++++
Th1 cytokine production	+	++++	+++++
Treg suppression	-	+	+
Antibody-dependent cellular cytotoxicity (ADCC)	-	++++	++++
Anti-proliferative activity	+	+++	+++

Table 2. Pomalidomide plus Dexamethasone trials in relapsed-refractory Multiple Myeloma

	Lacy et al[29]	Lacy et al[45]	Lacy et al[46]	Lacy et al[46]	Richardson et al[49]	Leleu et al[53]	Leleu et al[53]
Patient population	Rel, 1-3 reg	Len ref	Len , Bor ref	Len ,Bor ref	Len, Bor ref	Len, Bor ref	Len, Bor ref
No patients	60	34	35	35	113	43	41
Age (median)	65.5	62	62	61	64	60	60
Previous lines of therapy							
1-2 (%)	65	29	0	6	-	-	-
> 2 (%)	35	71	100	94		-	-
Previous therapy (%)							
Thalidomide	47	58	63	57	68	73*	73*
Lenalidomide	35	100	100	100	100	100	100
Bortezomib	33	59	100	100	100	100	100
ASCT	65	68	77	80	73	81*	81*
Schedule							
Pomalidomide	2 mg days 1-28	2 mg days 1-28	2 mg days 1-28	4 mg days 1-28	4 mg days 1-21	4 mg days 1-21	4 mg days 1-28
Desametasone	40 mg/wk	40 mg/wk	40 mg/wk	40 mg/wk	40 mg/wk	40 mg/wk	40 mg/wk
ORR (≥ PR) (%)	65	32	25	29	33	35	34
sCR/CR	15	0	0	3	3	2	5
VGPR	27	9	14	9	0	2	2
PR	23	23	11	17	30	30	27
PFS (median, months)	13	4.8	6.5^	3.2^	4.2	5.4^^	3.7^^
OS (median, months)	76% at 2 yr	13.9	78% at 6 mo	67% at 6 mo	16.5	14.9	14.8
Median follow-up (months)	30	8	9.7	6.6	14.2	23	23
Grade 3-4 Toxicity							
Neutropenia	20	29	51	66	41	65	58.5
Thrombocytopenia	3	9	32	31	19	28	27
Infection	18	3	26	40	31	26	46.5
Peripheral neuropathy	0	0	0	8	0	0	0

* referred to the whole study population of 84 patients
^ p = ns

Table 3. Most relevant phase 1-2 trials of Pomalidomide-based combinations in relapsed/refractory MM

	Larocca et al[54]	Baz et al[55]	Mark et al[57]	Shah et al[59]
No patients	55*	70	114	79
Age (median)	69	65	-	64
Previous lines of therapy (median,range)	3 (1-3)	5 (2-14)	5 (3-15)	6 (2-15)
Combination schedule	Pom 2.5 mg days 1-28 Cy 50 mg QOD PDN 50 mg QOD	Pom 4 mg days 1-21 Dex 40 mg/wk ± Cy 400 mg days 1,8,15	Pom 4 mg days 1-21 Dex 40 mg/wk Cla 500 mg BID	Pom 4 mg days 1-21 Dex 40 mg/wk Carf 20/27 mg/m^2 days 1-2, 8-9,15-16
ORR (≥ PR) (%)	51	48.5	61	70
sCR/CR	5	1.5	5	NR
VGPR	18	15	15	27**
PR	27	32	41	43
PFS (median, months)	10.4	6.4	8.7	9.7
OS (median, months)	69% at 1 yr	-	57% at 1 yr	> 18
Median follow-up (months)	14.8	-	13	-
Grade 3-4 Toxicity				
Neutropenia	41	30	51	29
Thrombocytopenia	10	11	41	14
Infection	9	26	2	5
Peripheral neuropathy	4	0	0	0
Thromboembolic events	0	4	1	1

* patients of phase 2 study
** at least VGPR