Management of adverse events induced by next-generation immunomodulatory drug and proteasome inhibitors in multiple myeloma

MANAGEMENT OF ADVERSE EVENTS INDUCED BY NEXT-GENERATION IMMUNOMODULATORY DRUG AND PROTEASOME INHIBITORS IN MULTIPLE MYELOMA

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Abstract

Introduction. In the last decade the introduction of novel agents has strongly improved multiple myeloma prognosis by doubling median overall survival. Unfortunately disease relapse is very common and patients may become refractory to previous drugs. Therefore, new therapeutic strategies are urgently needed.

Areas covered. We have reviewed the available data on next generation novel agents, particularly immunomodulatory drug pomalidomide and proteasome inhibitors carfilzomib and ixazomib, the latter being the first-in-class orally available. We focused on adverse events associated with such agents and described how they should be managed. The main grade ≥3 adverse events correlated with these drugs are hematologic, myelosuppression-related and reversible; non-hematologic grade ≥3 toxicities are less frequent, with an incidence of <10%.

Expert commentary. These agents showed to have a good tolerability. The great majority of adverse events are easily manageable with dose-adjustment and appropriate treatment, and drug discontinuation is not frequent. Favorable safety profile and high efficacy, especially in combination, confer to these drugs a central role in development of new lines of therapy against multiple myeloma. Further investigation is certainly needed to determine the best combinations including these agents.

Keywords

Multiple myeloma

Novel agents

Adverse events management

Immunomodulatory drugs

Proteasome inhibitors

Pomalidomide

Carfilzomib

Ixazomib

1. Introduction

Multiple myeloma represents 1% of all cancers and 13% of all hematologic malignancies. It primarily affects individuals with median age at diagnosis of 70 years. In 2012 multiple myeloma caused ≈21000 deaths in United States and Europe. The median survival has improved from 3-4 to 7-8 years over the past decade thanks to introduction of novel agents including immunomodulatory drugs such as thalidomide and lenalidomide, and the proteasome inhibitor bortezomib [1-4]. Next generation drugs recently approved include the immunomodulatory drug pomalidomide and the proteasome inhibitors carfilzomib and ixazomib.

The aim of this review is to provide practical guidance to help hematologists and oncologists maximize efficacy and minimize safety risks through appropriate dosing, monitoring and intervention for adverse events with pomalidomide, carfilzomib and ixazomib treatment.

2. Immunomodulatory agents

2.1 Pomalidomide

Pomalidomide is a new-generation immunomodulatory agent approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on their last therapy.
Pomalidomide is administered orally at the starting dose of 4 mg on day 1 through 21 of 28-day cycles until disease progression or unacceptable toxicity. European Medicines Agency approved its use only in combination with low-dose-dexamethasone, given orally at the dose of 40 mg weekly (20 mg in patients older than 75 years) on days 1, 8, 15 and 22 of 28-day cycles [5,6].

MM-003 phase-III trial (Table 1) compared pomalidomide plus low-dose-dexamethasone to high-dose-dexamethasone in relapsed and refractory multiple myeloma patients [7]. Another study, MM-010 "STRATUS", analyzed the role of pomalidomide plus low-dose dexamethasone. This is the largest phase-III single-arm study assessing this combination: 682 heavily pretreated (median prior therapy lines: 5) relapsed-refractory-multiple-myeloma patients were enrolled, and 676 received treatment [8]. In both trials the most frequent grade≥3 adverse events were hematologic with a low incidence of febrile neutropenia. Neutropenia was the most frequent grade≥3 hematologic adverse event, and it occurred in 48% and 50% of patients enrolled in MM-003 and MM-010, respectively. The incidence of grade≥3 pneumonia observed in MM-010 and MM-003 was similar, 11% and 14%, respectively. Pomalidomide discontinuation rate due to adverse events was 9% in MM-003 and 6% in MM-010; dose interruptions were 67% and 66%, while dose reductions were 27% and 22%, respectively, and occurred most often as a result of neutropenia or thrombocytopenia [7,8].
In summary safety analysis shows that the most common adverse events associated with pomalidomide are myelosuppression, infections and fatigue [7-12].
These toxicities can be prevented with an adequate prophylaxis and are generally easily manageable with appropriate treatment and pomalidomide dose adjustment (Tables 2 and 7).

2.1.1 Hematologic adverse events.

In MM-003 hematological adverse events were the most frequent grade ≥3 adverse events with pomalidomide, and they were generally due to myelosuppression. Therefore it is recommended to monitor complete-blood-count every 1-2 weeks [13].

2.1.1.1 Neutropenia

Neutropenia was the most common adverse event occurring in patients treated with pomalidomide. Of note, in the MM-003 study, 94% of cases were grade ≥3, they occurred more frequently within the first cycles of therapy and they were generally short-lived. Moreover, 9% of patients experienced grade ≥3 febrile neutropenia [7].

FDA recommends that the absolute-neutrophil-count required to start a new cycle of pomalidomide should be ≥500/mm^3 [5]; whereas, according to EMA, and also to an expert panel consensus statement on optimal use of pomalidomide, the absolute-neutrophil-count should be ≥1000/mm^3 [6,13].
In the occurrence of grade 4 neutropenia or neutropenic fever pomalidomide should be interrupted until absolute-neutrophil-count ≥500/mm^3 [5] or ≥1000/mm^3 [6]; subsequently, it may be restarted reducing the

dose by one level.
The use of granulocyte-colony-stimulating-factor is a sensible choice to accelerate absolute-neutrophil-count rise and it is recommended to prevent neutropenia when the patient is at high risk of developing neutropenic fever [5,6,13].

2.1.1.2 Anemia

Anemia is common in multiple myeloma. Many factors are involved in its pathogenesis, such as bone marrow infiltration by clonal tumor cells and low level of erythropoietin due to renal impairment; furthermore all drugs commonly used in therapy, including immunomodulatory agents, can induce anemia through myelosuppression.

Although no specific indications for anemia management are available to date, weekly complete-blood-count monitoring and eventually administration of erythropoiesis-stimulating-agents and/or red-blood-cells transfusions are the strategies currently adopted. If hemoglobin concentration is ≤10 g/dl erythropoietin can be administered at the lowest dose to maintain hemoglobin concentration between 10-12 g/dl. Hemoglobin concentration should not be ≥12 g/dl because of the increased risk of thromboembolic events. Treatment with erythropoiesis-stimulating-agents should be discontinued after 6-8 weeks if there is no response [13,14].

2.1.1.3Thrombocytopenia

In the MM-003 study, grade ≥3 thrombocytopenia occurred in 22% and was generally cyclic and reversible.

Pomalidomide treatment should be started with a platelet count ≥50000/mm^3 [5,6]; however, an expert panel consensus statement on pomalidomide optimal use recommends that pomalidomide therapy should be started with a platelet count ≥75000/mm^3 or ≥30000/mm^3 if ≥50% of bone-marrow nucleated cells are plasma cells [13].
In case of grade 4 thrombocytopenia, pomalidomide should be interrupted until resolution to grade ≤2, then it can be resumed at a reduced dose level [5,6].

2.1.2 Non-hematologic adverse events.

2.1.2.1 Infections

Infection was one of the most common adverse events in the MM-003 trial, with 34% of patients reporting a grade ≥3 infection, including 14% of grade ≥3 pneumonia [7].

To prevent infections it is recommended that patients undergo annual routine vaccinations against influenza-virus. Antibacterial prophylaxis may be considered for the first three months of therapy, and it should be continued for the whole treatment duration if the patient is considered to be at high risk of infection (low blood counts and/or severe prior infection during treatment). Different agents can be used for prophylaxis and the choice should be made according to local guidelines. However, some quinolones such as ciprofloxacin and enoxacin should be avoided since they strongly inhibit CYP1A2, the main metabolizer of pomalidomide, thus increasing the exposure to the drug.
In the occurrence of infection, pomalidomide should be stopped and then resumed after the event resolution. In addition, to appropriately manage this adverse event, immediate initiation of empirical antibiotic is needed [13].

2.1.2.2 Venous thromboembolism

Multiple myeloma patients treated with immunomodulatory drugs show an increased risk of venous thromboembolism, especially during the first months of therapy [14,15]. On the basis of previous experiences with thalidomide and lenalidomide, in pomalidomide clinical trials thromboprophylaxis was mandatory, therefore the frequency of venous thromboembolism was low (the incidence of grade ≥3 events was ≤1% in the MM-003 study).

Thromboprophylaxis should be based on a thorough assessment of the patient, particularly considering patient-related factors (history of venous thromboembolism, obesity, immobilization, recent surgery, constitutional thrombophilia, hyperviscosity and presence of central venous catheter), and treatment-related factors (erythropoiesis-stimulating-agents, hormone replacement therapy, exposure to tamoxifen/stilboestrol, doxorubicin or high-dose steroids). If the patient is at low risk, prophylaxis with aspirin is recommended for the whole duration of treatment. If the patient is at high risk, initial prophylaxis should consist of low-molecular-weight-heparin or oral vitamin-K-antagonists (at proper dosage to achieve International Normalized Ratio 2-3). After the first 4 months of therapy venous thromboembolism risk can be reassessed and prophylaxis may be re-evaluated and switched to aspirin if appropriate.
In case of thromboembolic event despite prophylaxis, treatment with pomalidomide should be interrupted and anticoagulation therapy should be started. Management of venous thromboembolism should follow good clinical practice guidelines. The optimal timing to resume pomalidomide was not determined, but few weeks seem to be sufficient [13,14,15].

2.1.2.3 Peripheral neuropathy

The incidence of peripheral neuropathy was quite low among MM-003 patients, with grade ≥3 events occurring in ≤1% of patients. The rate of any grade peripheral neuropathy was 15%, but 52% of these cases had grade 1 peripheral neuropathy at baseline [7].

If grade 3 peripheral neuropathy occurs, pomalidomide should be stopped until peripheral neuropathy resolution to grade ≤1 and then resumed at lower dose level. In case of grade 4 peripheral neuropathy treatment should be permanently discontinued.

In addition, calcium channel blockers (e.g. gabapentin and pregabalin), sodium channel blockers (e.g. oxcarbazepine) and serotonin-norepinephrine reuptake inhibitors (e.g. duloxetine) can be effective if peripheral neuropathy is associated with pain [13,14,16].

2.1.2.4 Rash

Rash is a clinically relevant non-hematologic adverse event, even if it is not a frequent toxicity. Patients with previous dermatological reactions to immunomodulatory agents are at increased risk and should be carefully monitored.

In case of grade ≤2 rash pomalidomide may be continued with addition of antihistamines and low-dose prednisone. In case of grade 3 rash, treatment needs to be held and resumed at reduced dose level after resolution, whereas in case of grade 4 rash, pomalidomide should be definitively discontinued [13].

2.1.2.5 Other adverse events

Acute pulmonary toxicity is a very rare and serious pomalidomide adverse event: a case-report described 2 patients who developed dyspnea, fever, hypoxia, and ground-glass opacities on CT scan in a context of negative work-up for infectious causes. Prognosis was excellent with prompt removal of medication. Methylprednisolone, 1 g/d for 3 days may be used in severe settings, otherwise tapering doses of

prednisone could be sufficient. Moreover, empiric antibiotic treatment is a sensible approach until infectious sources have been excluded. At resolution, pomalidomide could be reduced by one dose level and resumed but, in case of new onset of acute pulmonary toxicity, it should be permanently discontinued [17].
In MM-003 and MM-010 all grades muscle spasms were reported in 16% and 14% of patients treated with pomalidomide, respectively, and among them <1% were grade ≥3 [7,8]. Calcium and magnesium supplementation or quinine may ameliorate muscle cramps [13].

In MM-003, 4 (1.3%) second primary malignancies occurred in the pomalidomide and low-dose dexamethasone group versus 1 (0.7%) in the high-dose dexamethasone group. In MM-010 trial, second primary malignancies were reported in 15 patients (2.2%) [7,8].

It is worth underling that pomalidomide is a thalidomide analogue, that can cause fetal harm. Females must avoid pregnancy beginning 4 weeks before initiating treatment, while taking pomalidomide and for at least one month after discontinuation. Males should use contraception for the whole treatment duration and up to 28 days after discontinuation. Pregnancy test must be performed before starting pomalidomide then every month until 30 days after discontinuation. The drug cannot be administered during pregnancy or lactation [5,6].

3. Proteasome inhibitors

3.1 Carfilzomib

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome [18,19].

Carfilzomib is approved by FDA and EMA in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received at least one line of therapy.
Carfilzomib 20/27 mg/m^2 is administered intravenously as a 10 minute infusion while at the dose of 56 mg/m^2 as 30 minute infusion, on two consecutive days, each week for three weeks. When used in combination with lenalidomide and dexamethasone, carfilzomib is given at the dose of 20 mg/m^2 on days 1 and 2 of cycle 1 then, if tolerated, the dose is escalated to 27 mg/m^2. When used in combination with dexamethasone, carfilzomib dose is escalated to 56 mg/m^2 [20,21].

Toxicities in combination regimens were described in 2 phase-III trials (Table 3) in which carfilzomib was associated with dexamethasone (ENDEAVOR) [21] or lenalidomide plus dexamethasone (ASPIRE) [20]. In both studies treatment discontinuation rate due to therapy-related adverse events was lower in the carfilzomib group than in the control group (Figure 1). In the ASPIRE trial, the incidence of several adverse events (diarrhea, dyspnea, pyrexia, any cardiovascular toxicity, hypertension, upper respiratory tract infection) was higher in the carfilzomib group. This resulted in more frequent dose modifications in the carfilzomib arm (11% for carfilzomib, 43% for lenalidomide) over the lenalidomide-dexamethasone arm (39%) [22].

3.1.1 Hematologic adverse events.

The most frequent hematologic adverse events detected in the ENDEAVOR and ASPIRE studies were: anemia, neutropenia, lymphopenia and thrombocytopenia. Generally they were cyclic and reversible. Normal blood count at baseline is associated with a reduced probability to develop grade ≥3 hematologic toxicities. In the aforementioned studies, hematologic adverse events rarely (≤1%) caused carfilzomib discontinuation [22,23].

3.1.1.1 Neutropenia

Grade ≥3 neutropenia was reported in 2% of patients treated with carfilzomib-dexamethasone and was more frequent when carfilzomib was associated with lenalidomide, reaching a rate of 30% [22,23]. A neutrophil count ≤500/mm^3 requires carfilzomib temporary suspension and, if needed, treatment with granulocyte-colony-stimulating-factor should be started. Depending on the absolute-neutrophil-count trend it may be possible to schedule a prophylactic treatment with granulocyte-colony-stimulating-factor [20,21,24].

3.1.1.2 Thrombocytopenia

Grade ≥3 thrombocytopenia was 8% with carfilzomib-dexamethasone and 17% with carfilzomib-dexamethasone plus lenalidomide [22,23]. Any grade thrombocytopenia associated with bleeding requires prompt, temporary suspension of carfilzomib, adequate bleeding etiology recognition and treatment [20]. If no bleeding occurs, in case of grade 4 thrombocytopenia carfilzomib should be withheld. Platelet transfusion may be necessary according to standard protocols [20,21,24].

3.1.2 Non-hematologic adverse events.

Non-hematologic adverse events with carfilzomib were generally grade ≤2. Grade ≥3 adverse events were not usual (≤11%); the more frequent toxicities were: pneumonia (7%), hypertension (4-9%), cardiac failure (4-5%) and dyspnea (3-5%) [22,23].

The appropriate approach to manage severe non-hematologic adverse events with carfilzomib should include drug interruption, proper diagnostic evaluation and adequate therapy until improvement and/or resolution of the toxicity. Subsequently, on the basis of patient recovery and clinical features, carfilzomib may be restarted at full dose, at reduced dose or definitively suspended (Tables 4 and 7).

3.1.2.1 Cardiovascular and vascular adverse events

Proteasome inhibitors are associated with an elevated risk of cardiovascular toxicity. Bortezomib has also been reported to be cardiotoxic, but the incidence was apparently very low.

Both ENDEAVOR and ASPIRE trials showed increased frequency of cardiovascular adverse events in the carfilzomib group [22,23]. These toxicities may present in various forms: new onset or worsening of pre-existing hypertension, congestive heart failure, restrictive cardiomyopathy, myocardial ischemia, myocardial infarction, sudden cardiac death and thromboembolism [19,22,23,25-27].
The higher risk of some cardiovascular toxicities is probably due to multifactorial etiology: pre-existing comorbidities, disease characteristics, volume overload, carfilzomib dose and duration of infusion.
There is increasing evidence that a deficient proteasome activity has a crucial role in the impairment of cardiac function. The most important mechanism that mediates this effect is the accumulation of unfolded, damaged and undegraded proteins inside myocytes. Cardiovascular toxicity appears to have also an endothelial component [27].

Prevention of cardiotoxicity has a crucial role. The use of a screening echocardiogram or other cardiac testing before carfilzomib initiation is not validated [23,25-27]. It is recommended to monitor blood pressure in all patients at baseline and regularly during treatment. All patients with cardiac comorbidities should undergo cardiac evaluation before starting treatment and thromboprophylaxis is necessary when carfilzomib is associated with lenalidomide and/or dexamethasone.
In cases of grade ≥3 cardiovascular toxicities, carfilzomib should be withheld until recovery; if resumed,carfilzomib should be administered at a lower dose, without preinfusion hydration, and administration over 30 min is suggested.[20,21,24].

Both ENDEAVOR and ASPIRE trials showed a higher incidence of venous thromboembolic events such as deep-vein thrombosis and pulmonary embolism among patients treated with carfilzomib.
In ENDEAVOR trial, all grades deep-vein thrombosis and pulmonary embolism were reported in 4% and 3% of patients receiving carfilzomib-dexamethasone, respectively. In ASPIRE, rates were: 7% for deep-vein thrombosis and 4% for pulmonary embolism among patients treated with carfilzomib-lenalidomide-dexamethasone (Table 3).
Therefore thromboprophylaxis is recommended for patients treated with the combination of carfilzomib plus dexamethasone or with lenalidomide plus dexamethasone. In particular, thromboprophylaxis regimen should be based on an assessment of patient's underlying risks [21].

3.1.2.2 Respiratory adverse events

The main respiratory adverse event reported in clinical trials was dyspnea. Any grade dyspnea was reported in 19 and 28% of ASPIRE and ENDEAVOR patients, respectively, and the rate of grade ≥3 was 3 and 5% [22,23].

It is necessary to pay particular attention to respiratory symptoms. Drug administration should be stopped in case of dyspnea with minimal exertion, desaturation at rest and labored breathing. Careful evaluation is necessary also to distinguish between cardiac and respiratory etiology.
When symptoms resolved, carfilzomib therapy can be restarted at the physician's discretion [20,21,24].

3.1.2.3 Renal adverse events

Grade ≥3 acute renal failure was low and was detected in 3 and 4% of ASPIRE and ENDEAVOR patients [22,23]; a cross-trial safety analysis, in which a total of 526 patients enrolled in four phase-II trials were treated with carfilzomib as single agent, showed that 13% of patients experienced a worsening of their renal function over their course of treatment. In 6% of them the deterioration was reversible and lasted a median of 10 days; in the remaining 7% it was permanent [19].
However renal adverse events often have a multifactorial etiology and they are more probable in patients presenting with a reduced estimated creatinine clearance at baseline.

Dosing guidelines from the carfilzomib prescribing information recommend not to start adjusting the dose in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis. However, it is mandatory for all patients to monitor renal function regularly.
Generally transient increases in serum creatinine may be managed with oral and intravenous hydration; in cases of grade ≥3 renal adverse events carfilzomib dose may be modified or discontinued.
For patients on dialysis receiving carfilzomib, the dose should be administered after the dialysis procedure [20,21,24].

3.1.2.4 Infusion reactions

Infusion reactions were rare (<5%), and symptoms include: fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina [19,22,23].

Prevention of infusion reactions, in terms of both incidence and severity, could be a valid strategy and can be done with dexamethasone premedication administered orally or intravenously 1-4 hours before carfilzomib treatment in the first cycles. This procedure may be repeated if necessary in the subsequent cycles. Carfilzomib must be given as 10 or 30 minutes infusion, depending on dose regimen, never as a bolus [20,21,24].

3.1.2.5 Tumor lysis syndrome

Patients with multiple myeloma and high tumor burden should be considered at greater risk for tumor lysis syndrome.

Prevention of this event is simply based on adequate hydration and clinical monitoring. The prophylactic use of uric acid-lowering drugs could be considered in high risk patients. In case of tumor lysis syndrome, carfilzomib administration should be suspended until resolution [20,21,24].

3.1.2.6 Infections

Varicella-Zoster-Virus prophylaxis is recommended for all the proteasome inhibitors [14]. Antibacterial prophylaxis is suggested particularly for patients who are at risk for certain infections, such as urinary tract infections or pneumonia [24].

3.2 Ixazomib

Ixazomib is the biologically active boronic acid form of ixazomib citrate. It is the first oral reversible proteasome inhibitor to be evaluated for treatment of multiple myeloma.
Ixazomib at lower doses preferentially binds and inhibits the CT-L proteolytic (β_5) site of the 20S proteasome, with inhibition of β_1 and β_2 sites at higher concentrations [28].

Phase I and II studies showed that this agent is safe and effective [28-30], thus providing the basis for the phase III, double-blind, placebo-controlled TOURMALINE-MM1 trial (Table 5) in which the all oral ixazomib, lenalidomide and dexamethasone combination therapy was compared to placebo, lenalidomide and dexamethasone [31]. On the basis of this phase III trial results, FDA approved ixazomib in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy.

Ixazomib is administered at the dose of 4 mg once a week on days 1, 8, 15 of 28-day cycle, in association with lenalidomide 25 mg on day 1 through 21 and dexamethasone 40 mg on days 1, 8, 15 and 22 [32].

Because bortezomib has typically been administered twice-weekly, oral ixazomib was also evaluated in with the twice-weekly administration in a phase I study [33]. Despite no differences in efficacy, the less frequent administration of ixazomib certainly had a more favorable effect on the toxicity profile; moreover, pharmacokinetic data support the weekly schedule [28-30,33].

3.2.1 Hematologic adverse events.

The most frequent grades ≥3 toxicities with ixazomib described in the TOURMALINE-MM1 were hematologic, mostly thrombocytopenia and neutropenia (Table 5).

3.2.1.1 Thrombocytopenia

Grade ≥3 thrombocytopenia incidence was 19% in the ixazomib group vs. 9% in the placebo group. Platelet count reduction was cyclic and reversible, with nadir between day 14 and 21 of 28-day cycles. Discontinuation of therapy due to thrombocytopenia was 1% in each study group [31].

To prevent high grade thrombocytopenia, it is recommended to monitor platelet count at least once monthly during treatment and to start a new treatment cycle with platelet count ≥75000/mm^3.
It is generally agreed that in cases of platelet count <30000/mm^3 ixazomib and lenalidomide should be suspended until thrombocytes ≥30000/mm^3, then lenalidomide may be resumed at next lower dose and ixazomib may be restarted at its most recent dose. When thrombocytopenia occurs again, it is recommended to alternate dose modification of lenalidomide and ixazomib [32] (Tables 6 and 7).

3.2.1.2 Neutropenia

Safety data from ixazomib trials showed minimal myelosuppression caused by this drug, with a similar incidence of grade ≥3 neutropenia in the ixazomib (22%) and placebo groups (24%) [31].

To prevent severe neutropenia, a new treatment cycle should be started when the patients have an absolute-neutrophil-count ≥1000/mm^3.
In cases of absolute-neutrophil-count <500/mm^3 it is recommended to withhold ixazomib and lenalidomide until neutrophils recovers to ≥500/mm^3, then lenalidomide may be resumed at the next lower dose level and ixazomib may be restarted at its most recent dose. Also in this case, when neutropenia occurs again, it is recommended to alternate dose modification of lenalidomide and ixazomib. In addition, granulocyte-colony-stimulating-factor could be a valid option [32].

3.2.2 Non-hematologic adverse events.

The incidence of non-hematologic adverse events was limited in clinical trials and they were mostly grade ≤2. Grades ≥3 were not usual (<10%); among them the most frequent were: diarrhea (6%), arrhythmias (5%), rash (5%), nausea and vomiting (3%) and peripheral neuropathy (2%). No cardiac, renal, or respiratory safety signals were associated with the use of ixazomib [31].
Specific recommendations to manage rash, peripheral neuropathy and gastrointestinal toxicities are available. Whereas, for other grade ≥3 non-hematologic adverse events, the general indication is to withhold ixazomib until toxicity recovers at least to grade 1. Subsequently, if the adverse event is drug-related, ixazomib may be resumed at the next lower dose [32] (Tables 6 and 7).

3.2.2.1 Rash

Rash may clinically present in the form of some erythematous areas, macular and/or small papular bumps that may or may not be itchy, over limited or also more general areas of the body [31].

In case of grade 2-3 rash, the strategy consists in withholding lenalidomide until the event recovers at least to grade 1. After resolution, lenalidomide can be resumed at the next lower dose. If grade 2-3 rash occurs again, ixazomib and lenalidomide should be withheld until rash recovers at least to grade 1. For additional occurrences, alternate dose modifications of lenalidomide and ixazomib is the recommended approach. The use of antihistamines, topical or oral steroid is also suggested. In case of grade 4 rash, treatment should be discontinued [32].

3.2.2.2 Peripheral neuropathy

Peripheral neuropathy is generally of grade ≤2, rarely of higher grades. In most of the cases, it clinically develops as peripheral sensory neuropathy. This adverse event is a relatively common and serious consequence associated with multiple myeloma treatment, mainly with bortezomib and thalidomide. Therefore, many patients with progressive disease have baseline peripheral neuropathy as a consequence of previous therapy. Compared with bortezomib, ixazomib appears to have a better toxicity profile in terms of peripheral neuropathy indeed 2% of patients in the ixazomib group had grade ≥3 events, as compared with 6% of patients who received subcutaneous bortezomib [23,34] and 3% of patients who received carfilzomib [22] in other studies.

There are no guidelines for the management of neurotoxicity caused by ixazomib, but given its low frequency, guidelines from bortezomib neurotoxicity can be followed. When grade 1 peripheral neuropathy with pain or grade 2 peripheral neuropathy occur, it is recommended to withhold ixazomib until peripheral neuropathy recovers at least to grade 1, or to the baseline value, without pain. After resolution, ixazomib may be resumed at its most recent dose. In the case of grade 2 peripheral neuropathy with pain or grade 3 peripheral neuropathy, the recommendation is similar, but ixazomib may be resumed at the next lower dose. In the case of grade 4 peripheral neuropathy, treatment should be discontinued [32].

3.2.2.3 Gastrointestinal adverse events

Safety data from ixazomib trials show that this drug causes gastrointestinal toxicity. Any grade diarrhea was reported in 45% of patients, including 6% with grade ≥3 [31]. This side effect should be managed according to best clinical practice [32].Nausea was reported in 29% of patients, vomiting in 23%. Grade ≥3 nausea and vomiting accounted for 2% and 1%, respectively [31]. Standard anti-emetics, including 5-hydroxytryptamine 3 serotonin receptor (5-HT_3) antagonists, are recommended for emesis if it occurs after treatment start; prophylactic anti-emetics may also be considered. [32].

4. Expert commentary

Proteasome inhibitors represent a mainstay in the treatment of multiple myeloma, either at diagnosis and at relapse. In addition, the broad spectrum of activities and the high efficacy exerted by thalidomide and lenalidomide paved the way for the development of newer compounds such as pomalidomide.

Clinical trials showed that new active agents are emerging for the treatment of relapsed/refractory multiple myeloma and they may play a role also in the frontline setting. Pomalidomide, carfilzomib and ixazomib have already be granted FDA approval in the relapse/refractory disease, since they were active as a single agent and in combination with other anti-myeloma agents. Thus, it is likely that such agents will be widely used in the next future. Their toxicity profile is well defined and physicians should promptly recognize adverse events associated with these drugs in order to allow patients to stay on treatment for a longer time and benefit from it.

Pomalidomide, carfilzomib and ixazomib are rarely associated with serious adverse events. In phase III clinical trials few patients discontinued treatment because of therapy-related adverse events (Figure 1). The majority of toxicities are easily manageable through temporary dose interruptions and adjustments, associated with proper etiology treatment and adequate supportive care (Tables 2, 4, 6 and 7).

The safety and efficacy profile of these agents confer them a central role in development of new combinations regimens containing a proteasome inhibitor and immunomodulatory drug to be used both in relapsed/refractory multiple myeloma and as frontline therapy in transplant ineligible patients.

NCT02046070 is a phase II study that combines ixazomib, cyclophosphamide and low-dose-dexamethasone in newly diagnosed transplant ineligible patients. This all oral triplet combination showed good tolerability and efficacy [35]. In a phase I/II trial the association of pomalidomide with cyclophosphamide has been evaluated for relapsed/refractory multiple myeloma and it showed to be safe and effective [36].

Pomalidomide is also under evaluation in association with carfilzomib and dexamethasone in relapsed/refractory multiple myeloma patients: results of the phase I NCT01464034 trial demonstrated good tolerability and high-activity of this combination [37], and further investigation is ongoing.

Impressive results, including high rates of minimal-residual-disease-negative responses, have been reported with carfilzomib-lenalidomide-dexamethasone without up-front autologous stem-cell transplantation in phase I/II and phase II studies in patients with newly diagnosed multiple myeloma [38,39]. Moreover, Jakuboviak et al also showed the cost-effectiveness of adding carfilzomib to lenalidomide and dexamethasone [40].

The question regarding the best partners in combination regimens and their role in multiple myeloma treatment is still open: the optimal combination is going to be established in clinical trials, based not only on efficacy and toxic effects but also other relevant factors, such as regimen cost and treatment impact on patient quality of life.

5. Five-year view

Next generation proteasome inhibitors and pomalidomide are an effective treatment option for patients who have exhausted lenalidomide- and bortezomib-based therapies. However, patients refractory to immunomodulatory agents and proteasome inhibitors have a median survival of 9 months, therefore it is extremely important to investigate new therapeutic strategies incorporating new mechanisms of action [41]. In 2015 FDA approved drugs belonging to novel classes of agents such as monoclonal antibodies (elotuzumab and daratumumab) and histone-deacetylase-inhibitors (panobinostat) [42-44]. A recent meta-analysis of 5 randomized-clinical-trials consisting of 3197 patients (PANORAMA-1 [panobinostat-bortezomib-dexamethasone vs bortezomib-dexamethasone], MMVAR [bortezomib-thalidomide-dexamethasone vs thalidomide-dexamethasone], ASPIRE, ELOQUENT-2 [elotuzumab-lenalidomide-dexamethasone vs lenalidomide-dexamethasone], TOURMALINE) showed that triplet regimens improved response rates and progression-free-survival [45]. The major efficacy and acceptable safety profile of triplet combinations was also shown by pre-specified interim analysis of CASTOR trial in which daratumumab-bortezomib-dexamethasone combination doubled both very-good-partial-response and (stringent-)complete-response rates vs. bortezomib-dexamethasone association [46]. Similarly, POLLUX trial showed that daratumumab-lenalidomide-dexamethasone regimen significantly prolonged progression-free survival among patients with relapsed or refractory multiple myeloma compared with lenalidomide-dexamethasone alone. Higher rates of neutropenia and infusion-related reactions (generally grade 1-2 during the first infusion) did not result into higher rates of treatment discontinuation or death [47].These results support the hypothesis that triplet regimens combining steroid, monoclonal antibody and proteasome inhibitor, or immunomodulatory drug, or other potentially novel agents will become a new standard of care in the future [46,48-60].

Ongoing trials are evaluating pomalidomide as backbone drug for combination with newer agents including monoclonal antibodies, such as anti-CD38 daratumumab [56] and MOR202 [50], anti-SLAMF7 elotuzumab [52] and anti-PD-L1 durvalumab [54].

In the future other pomalidomide-based combinations including checkpoint inhibitors will be tested to achieve durable remissions, and to improve treatment tolerability.

Carfilzomib is generally well tolerated, but its use is associated with cardiovascular adverse events. Therefore, patients with pre-existing thrombotic risk, heart failure, or poorly controlled hypertension should be monitored closely. Carfilzomib is particularly attractive in patients with significant neuropathy, although consecutive days of intravenous administration may be a disadvantage.

Based on promising results of carfilzomib, lenalidomide and dexamethasone association in relapsed multiple myeloma, this triplet regimen is likely to become a suitable option also as frontline therapy.

Ixazomib, being administrated orally, represents an appealing agent. In fact, it can be taken at home by patients without attending hospital visits and requires only monthly medical control. Therefore, it is associated with lower costs also for health care system. These advantages make ixazomib potentially ideal for long-term administration, since maintenance treatment is increasingly being integrated in modern multiple myeloma therapeutic algorithm, both in the transplant and non-transplant settings [61,62].

Because ixazomib has a good safety profile with low rate of gastrointestinal and skin adverse events, most studies are evaluating weekly dosing of this drug, both as a single agent or in combination regimens. Results are encouraging for the possibility of highly efficacious, oral triplet-regimens to be used both at diagnosis or relapse.

In conclusion, the combination of proteasome inhibitors, immunomodulatory drugs and corticosteroids is going to be a standard of care in multiple myeloma patients, both at the onset of the disease and at

relapse. Novel next-generation agents belonging to these drug-classes such as carfilzomib, ixazomib and pomalidomide are under evaluation or will be evaluated in newer combinations, including also drugs with different mechanisms of action. Because novel agent-based continuous therapy prolongs progression-free-survival and overall-survival [6163], the safety profile of these combinations will play a determinant role in this setting, and a deep knowledge of the toxicities of these drugs will help hematologists and oncologists to early recognize adverse events and to minimize their impact on efficacy.

Key issues

- Multiple myeloma is a plasma cell dyscrasia that accounts for 86000 new cases per year, represents 1% of all cancers and 13% of all hematologic malignancies. It primarily affects patients with median age at diagnosis of 70 years. In 2012 it caused ≈21000 deaths in the United States and Europe.
- In the last decade, prognosis has improved with introduction of novel agents including immunomodulatory drugs such as thalidomide and lenalidomide, and the proteasome inhibitor bortezomib.
- Pomalidomide is a 3rd generation immunomodulatory drug, carfilzomib and ixazomib represent next-generation proteasome inhibitors, the latter being the first-in-class orally available.
- In phase III trials pomalidomide, carfilzomib and ixazomib showed high efficacy and good safety.
- Adverse events are generally low-grade and they infrequently lead to treatment discontinuation. The main grade ≥3 adverse events are hematological, due to myelosuppression, and they are cyclic and reversible. Grade ≥3 non-hematologic adverse events are infrequent (<10%) and easily manageable with temporary treatment interruption, proper therapy according to best clinical practice, and dose adjustments.
- Because of the safety and efficacy profile of novel agents, these drugs play a crucial role in defining new therapeutic strategies for multiple myeloma, also taking into account patient quality of life and costs for Health-Care System.

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Figures / Tables

Table 1. Main pomalidomide-induced adverse events.

MM-003				
Arms	**POMALIDOMIDE plus low-dose dexamethasone**		**HIGH-DOSE DEXAMETHASONE**	
Number of patients	300		150	
Schedule	pomalidomide 4 mg orally on days 1 through 21 plus dexamethasone 40 mg (20 mg if age >75 years) orally on days 1, 8, 15, 22 of 28-day cycles until disease progression or unacceptable toxicities		dexamethasone 40 mg (20 mg if age >75 years) orally on days 1-4, 9-12, and 17-20 of 28-day cycles until disease progression or unacceptable toxicities	
Adverse event	**All grades %**	**Grades ≥3 %**	**All grades %**	**Grades ≥3 %**
Hematologic				
Anemia	52	33	51	37
Neutropenia	51	48	21	16
Thrombocytopenia	30	22	29	26
Infections				
Upper respiratory tract infection	16	2	8	1
Pneumonia	15	14	11	10
Bronchitis	10	1	5	0
Febrile neutropenia	10	9	1	0
Gastrointestinal				
Diarrhea	22	1	19	1
Constipation	22	2	15	0
Respiratory				
Dyspnea	20	5	14	5
Other				
Fatigue	34	5	27	6
Muscle spasms	16	<1	7	<1
Dizziness	12	1	8	1

Table 2. Management of pomalidomide-induced adverse events.

ADVERSE EVENT	RECOMMENDATION
Grade 4 neutropenia (absolute neutrophil count <500/mm^3) or febrile neutropenia (absolute neutrophil count <1000/mm^3 with a single temperature of 38.3 °C or a temperature ≥38.0 °C for ≥1 hour)	Interrupt pomalidomide and monitor complete-blood-count weekly. When neutrophils ≥1000/mm^3 resume pomalidomide at reduced dose level. Consider treatment with granulocyte-colony-stimulating-factor. Consider granulocyte-colony-stimulating-factor as primary prophylaxis for patients at high risk of severe neutropenia or febrile neutropenia, and as secondary prophylaxis in case of neutropenic complications in previous cycles.
Grade ≤3 anemia (hemoglobin <8.0 g/dl)	Interrupt pomalidomide and monitor complete-blood-count weekly. When anemia resolves to grade 2 resume pomalidomide at reduced dose. Consider red blood cells transfusions and/or treatment with erythropoiesis-stimulating-agents.
Grade 4 thrombocytopenia (platelet count <25000/mm^3)	Interrupt pomalidomide and perform complete-blood-count weekly. When platelet count ≥50000/mm^3 resume pomalidomide at reduced dose. Consider platelet transfusions.
Infections	Prevention: consider annual influenza virus vaccination; consider antibacterial prophylaxis at least for the first 3 months of treatment. Antiviral and antifungal prophylaxis is not routinely recommended. Management: interrupt pomalidomide, start proper antimicrobial therapy and resume at resolution.
Venous thromboembolism	Prevention: it is mandatory with acetylsalicylic acid if standard risk or prophylactic dose of low-molecular-weight-heparin/vitamin-K-antagonist if high risk. Management: interrupt pomalidomide and start anticoagulation therapy; resume pomalidomide after event resolution and risk-reassessment.
Peripheral neuropathy	Grade 3: interrupt pomalidomide and resume at reduced dose level when peripheral neuropathy returns to grade ≤1. Grade 4: discontinue pomalidomide. Consider treatment of neuropathic pain with proper drugs.
Rash	Grade ≤2: consider antihistamines and steroids. Grade 3: interrupt pomalidomide and resume at reduced dose level when rash returns to grade ≤1. Grade 4: discontinue pomalidomide.
Other grade ≥3 toxicities	Hold dose. At resolution to grade ≤2, resume pomalidomide at reduced dose level.

Table 3. Main carfilzomib-induced adverse events, with in-depth focus on cardiovascular toxicities.

Studies	**ENDEAVOR**				**ASPIRE**			
Type of study	Phase III Carfilzomib and dexamethasone vs. bortezomib and dexamethasone				Phase III Carfilzomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone			
Number of Carfilzomib treated patients	463				392			
Schedule	Carfilzomib 20 mg/m^2 on days 1, 2 of cycle 1; 56 mg/m^2 given thereafter as 30-minute infusion on days 1, 2, 8, 9, 15, 16 of 28-day cycles. Dexamethasone 20 mg orally on days 1, 2, 8, 9, 15, 16, 22 and 23.				Carfilzomib 27 mg/m^2 as a 10-minute infusion on days 1, 2, 8, 9, 15, 16 for 12 28-day cycles, then on days 1, 2, 15, 16 until cycle 18. Starting dose: 20 mg/m^2 on days 1 and 2 of cycle 1. Lenalidomide 25 mg orally on days 1 through 21. Dexamethasone 40 mg orally on days 1, 8, 15 and 22.			
Dose	56 mg/m^2				27 mg/m^2			
Adverse event	**All grades %**		**Grades ≥3 %**		**All grades %**		**Grades ≥3 %**	
Hematologic								
Anemia	39		14		43		18	
Neutropenia	8		2		38		30	
Thrombocytopenia	20		8		29		17	
Infection								
Upper respiratory tract infection	20		2		29		2	
Pneumonia	9		7		n.a.		n.a.	
Respiratory								
Dyspnea	28		5		19		3	
Pulmonary hypertension	1		1		n.a.		n.a.	
Gastrointestinal								
Diarrhea	31		4		42		4	
Constipation	15		0		20		0	
Renal								
Acute renal failure	8		4		8		3	
Elevated creatinine	6		2		7		1	
Neurologic								
Peripheral neuropathy	19		2		17		3	
Other								
Second primary malignancy	1		1		3		2	
Cardiovascular adverse events	**Carfilzomib group**		**Bortezomib group (n = 456)**		**Carfilzomib group**		**Control group (n = 389)**	
	All grades %	**Grade ≥3 %**	**All grades %**	**Grade ≥3 %**	**All grades %**	**Grade ≥3 %**	**All grades %**	**Grade ≥3 %**
Hypertension	25	9	9	3	14	4	7	2
Cardiac failure†	8	5	3	2	6	4	4	2
Deep vein thrombosis	4	1	1	0	7	2	4	1
Ischemic heart disease∫	3	2	2	1	6	3	5	2
Pulmonary embolism	3	2	1	1	4	3	2	2

†Include: cardiac failure, congestive cardiac failure, pulmonary edema, hepatic congestion, cardiopulmonary failure, acute pulmonary edema, acute cardiac failure, and right ventricular failure.

∫Include: angina pectoris, myocardial infarction, acute myocardial infarction, increased blood creatinine phosphokinase, coronary artery disease, myocardial ischemia, coronary artery occlusion, increased troponin, increased troponin T, acute coronary syndrome, abnormal cardiac stress test, cardiomyopathy stress, unstable angina, coronary artery stenosis, abnormal electrocardiogram ST-T segment, and abnormal electrocardiogram T-wave.

Table 4. Management of carfilzomib-induced adverse events.

ADVERSE EVENT	RECOMMENDATION
Anemia	If grade ≤2 (hemoglobin 8-10 g/dl) treat with erythropoiesis-stimulating-agents. If grade ≥3 (hemoglobin <8 g/dl) consider transfusions, carfilzomib can be administered followed by transfusion. Consider dose adjustment on the basis of recovery.
Grade ≥3 neutropenia (absolute-neutrophil-count <1000/mm^3)	Withhold dose, consider granulocyte-colony-stimulating-factor until absolute-neutrophil-count ≥1000/mm^3. If fully recovered before next scheduled dose, continue carfilzomib without dose reduction. If recovered to grade 2, reduce dose by one level; if tolerated, dose may be escalated at physician's discretion.
Febrile neutropenia (absolute-neutrophil-count <1000/mm^3 with a single temperature of 38.3 °C or a temperature ≥38.0 °C for ≥1 hour)	Withhold dose and manage according to standard protocols.
Lymphopenia	Consider antimicrobial prophylaxis.
Platelet count ≤25000/mm^3 or evidence of bleeding with thrombocytopenia.	Withhold dose, consider platelet transfusion. If fully recovered before next scheduled dose, continue carfilzomib without dose reduction. If recovered to grade 3 (platelet count: 25000-50000/mm^3), reduce dose by one level; if tolerated, dose may be escalated at physician's discretion.
Cardiovascular adverse events	Monitor blood pressure regularly in all patients. In hypertensive patients consider adjustment of hypertensive medication. Patients with cardiac risk factors should be evaluated by a cardiologist before treatment and fluid overload should be avoided. If grade ≥3, withhold dose, at resolution consider resuming reduced by one level, or treatment interruption.
Respiratory adverse events	If grade ≥3 withhold dose until recovery, consider resuming on the basis of a benefit/risk assessment. In case of dyspnea stop carfilzomib until resolution or baseline and etiology evaluation established: fluid overload should be investigated and properly treated.
Renal adverse events	If serum creatinine ≥ 2Xbaseline or creatinine-clearance ≤15 ml/min, or decrease ≥50% of baseline, withhold dose and monitor renal function: when recovers to within 25% of baseline, restart reduced by one level. If on dialysis carfilzomib should be administered after dialysis procedure.
Infusion reactions	Prophylactic medication prior to carfilzomib administration.
All other grade ≥3 non-hematological toxicities	Withhold until resolved or returned to baseline. Start on proper treatment. Consider dose adjustment or discontinuation on the basis of clinical context and recovery.

Table 5. Main ixazomib-induced adverse events.

TOURMALINE-MM1				
Arms	**IXAZOMIB-LENALIDOMIDE-DEXAMETHASONE**		**PLACEBO-LENALIDOMIDE-DEXAMETHASONE**	
Number of patients	361		359	
Schedule	ixazomib 4 mg orally on days 1, 8, 15 plus lenalidomide 25 mg orally on days 1 through 21 plus dexamethasone 40 mg orally on days 1, 8, 15, 22 of 28-day cycles until disease progression or unacceptable toxicities		placebo on days 1, 8, 15 plus lenalidomide 25 mg orally on days 1 through 21 plus dexamethasone 40 mg orally on days 1, 8, 15, 22 of 28-day cycles until disease progression or unacceptable toxicities	
Adverse event	**All grades %**	**Grades ≥3 %**	**All grades %**	**Grades ≥3 %**
Hematologic				
Neutropenia	33	22	31	24
Thrombocytopenia	31	19	16	9
Anemia	28	9	27	13
Gastrointestinal				
Diarrhea	45	6	39	3
Constipation	35	0	26	0
Nausea	29	2	22	0
Vomiting	23	1	12	1
Dermatologic				
Rash	36	5	23	2
Neurologic				
Peripheral neuropathy	27	2	22	2
Cardiovascular				
Arrhythmias	16	5	15	3
Hypertension	6	3	5	1
Heart failure	4	2	4	2
Myocardial infarction	1	1	2	1
Thromboembolism	8	3	11	3
Renal				
Acute renal failure	9	3	11	4
Other				
Fatigue	29	4	28	3
Upper respiratory tract infection	23	1	19	1

Table 6. Management of ixazomib-induced adverse events.

ADVERSE EVENT	RECOMMENDATION
Platelet count <30000/mm^3	Withhold ixazomib and lenalidomide until platelet count ≥30000/mm^3. At resolution resume lenalidomide at the next lower dose, restart ixazomib at its most recent dose. If platelet count falls <30000/mm^3 again, withhold ixazomib and lenalidomide until platelet count ≥30000/mm^3. At resolution resume ixazomib at the next lower dose, restart lenalidomide at its most recent dose. For additional occurrences, alternate dose modification of lenalidomide and ixazomib.
Grade 4 neutropenia (absolute neutrophil count <500/mm^3)	Withhold ixazomib and lenalidomide until absolute-neutrophil-count ≥500/mm^3. Consider adding granulocyte-colony-stimulating-factor. At resolution resume lenalidomide at the next lower dose, restart ixazomib at its most recent dose. If absolute-neutrophil-count falls <500/mm^3 again, withhold ixazomib and lenalidomide until neutrophils ≥500/mm^3. Consider adding granulocyte-colony-stimulating-factor. At resolution resume ixazomib at the next lower dose, restart lenalidomide at its most recent dose. For additional occurrences, alternate dose modification of lenalidomide and ixazomib.
Grade 2-3 rash (macules/papules covering >10% of body-surface-area with or without symptoms limiting instrumental and/or self-care activities of daily living)	Withhold lenalidomide until rash recovers to grade ≤1, then resume lenalidomide at the next lower dose. If grade 2-3 rash occurs again, withhold ixazomib and lenalidomide until rash recovers to grade ≤1. At resolution resume ixazomib at the next lower dose, restart lenalidomide at its most recent dose. For additional occurrences, alternate dose modification of lenalidomide and ixazomib.
Grade >3 rash	Discontinue treatment.
Grade 1 peripheral neuropathy (loss of deep tendon reflexes or paresthesia) with pain or grade 2 peripheral neuropathy (moderate symptoms limiting instrumental activities of daily living)	Withhold ixazomib until peripheral neuropathy recovers to grade ≤1, or baseline, without pain. At resolution restart ixazomib at its most recent dose.
Grade 2 peripheral neuropathy with pain or grade 3 peripheral neuropathy (severe symptoms limiting self-care activities of daily living)	Withhold ixazomib until peripheral neuropathy recovers to grade ≤1 or baseline. At resolution restart ixazomib at the next lower dose.
Grade >3 peripheral neuropathy	Discontinue treatment.
Other grade ≥3 non-hematologic adverse events	Withhold ixazomib until toxicity recovers to grade ≤1, or baseline. If ixazomib-related, at resolution restart ixazomib at next lower dose.

Table 7. Pomalidomide, carfilzomib and ixazomib dose-level-reductions before discontinuation.

Drugs	Regimen	Starting dose	First reduction	Second reduction	Third reduction
Pomalidomide	Pomalidomide from day 1 through 21 of 28 days cycles plus low-dose dexamethasone.	4 mg	3 mg	2 mg	1 mg
Carfilzomib	Carfilzomib, lenalidomide and dexamethasone (20/27 mg/m^2)	27 mg/m^2	20 mg/m^2	15 mg/m^2	-
	Carfilzomib and dexamethasone (20/56 mg/m^2)	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2
Ixazomib	All oral ixazomib, lenalidomide, dexamethasone combination therapy.	4 mg†	3 mg	2.3 mg	-

†Recommended starting dose in patients with moderate or severe hepatic impairment, severe renal impairment or end-stage-renal-disease requiring dialysis is 3 mg.

Figure 1. Efficacy/safety results of MM-003, ENDEAVOR, ASPIRE and TOURMALINE-MM1 phase III trials.