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Pharmacokinetic drug evaluation of ixazomib citrate for the treatment of multiple myeloma

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ABSTRACT

Introduction: multiple myeloma (MM) is a plasma cell disorder that represents the second most frequent hematologic cancer. Although MM is still an incurable disease, prognosis has improved in the last decade thanks to the introduction of novel agents such as proteasome inhibitors (PIs), immunomodulatory drugs, monoclonal antibodies, and histone deacetylase inhibitors.

Areas covered: ixazomib is the first oral PI recently approved by Food and Drug Administration (FDA) and European Medicine Agency (EMA) in combination with lenalidomide and dexamethasone as salvage therapy in MM patients. In this paper, we focus on its pharmacokinetics features, as well as its safety and efficacy in clinical studies.

Expert opinion: ixazomib can be considered an oral analogue of bortezomib, with 9.5-day half-life, 58% of oral bioavailability, and a large distribution volume of 543L. These features make it a versatile molecule, potentially useful both in combination and as single agent. Oral route of administration and good efficacy/safety profile are its winning characteristics, providing the rationale for a future role also in the maintenance setting.

KEY WORDS: ixazomib, maintenance therapy, multiple myeloma, pharmacokinetics, proteasome inhibitors.

1. Introduction

Multiple myeloma (MM) is a plasma cell dyscrasia that clinically manifests with hypercalcemia, renal insufficiency, anemia, and bone lesions [1]. It constitutes 13% of hematologic cancers and 2% of all cancers [2,3].

Prognosis has improved in the last decade thank to introduction of novel agents such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies (MoAbs), and histone deacetylase inhibitors.

Generally, young fit patients are treated with novel agent-based induction followed by autologous stem cell transplantation (ASCT), whereas therapy of elderly, ASCT-ineligible patients consists of triplet or doublet combinations including novel agents. More recently, consolidation and long-term therapies (LTTs) are under evaluation to be implemented in standard treatment [4]. New drug development is crucial for the treatment of the disease that is characterized by clonal evolution and onset of chemotherapy resistance [5].

Among PIs, ixazomib is the most recent to be approved by regulatory authorities in the relapse setting. In this paper, we focus on its pharmacokinetics features, as well as its safety and efficacy in clinical studies.

2. Overview of the Market

Bortezomib, approved by FDA in 2003 [6], was the first PI used in MM. At first, bortezomib was administered intravenously, subsequently, clinical trials showed improved safety with subcutaneous bortezomib, leading to approval of subcutaneous injection use [7,8]. In 2012, the second-generation, intravenous PI, carfilzomib received FDA approval for treatment of MM patients who have received ≥ 2 prior therapies including bortezomib and an IMiD and have demonstrated disease progression on or within 60 days of completion of the last therapy. In 2015, carfilzomib was approved also in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed/refractory MM (RRMM) who have received 1-3 prior lines of therapy [9].

In this scenario, also the new PI ixazomib received approval by regulatory authorities (details of approval are reported in section 8).

3. Introduction to the compound

Ixazomib citrate is the first orally available PI [10]. The standard dose is 4 mg on days 1, 8, 15 of 28-day cycles. Although sharing some structural motifs and the same target with the previous approved PIs, bortezomib and carfilzomib, ixazomib citrate is the first PI prodrug with a distinct affinity and selectivity profile [11,12] [Table 1].

3.1 Chemistry

Ixazomib citrate, is a prodrug that, on exposure to plasma, is rapidly hydrolyzed to ixazomib, that is the active form (MLN2238, IUPAC name: [(1R)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]boronic acid) [13].

Structurally, ixazomib is a dipeptidyl boronic acid-based compound consisting of an alanine-leucine dipeptide core with a citrate-protected boric acid [12].

The molecular formula for ixazomib citrate is C₂₀H₂₃BCl₂N₂O₉ and its molecular weight is 517.12 g/mol. The solubility of ixazomib citrate in 0.1N HCl (pH 1.2) at 37°C is 0.61 mg/mL. The solubility increases as the pH increases [14] (Box 1).

3.2 Pharmacodynamics

The ubiquitin-proteasome pathway, consisting of the ubiquitin-conjugating system and the 26S proteasome, is involved in polyubiquitination and subsequent degradation of proteins. The 26S proteasome is made up of the 19S regulatory units and the 20S core particle, subdivided in two α - and β -rings, carrying catalytic activities referred to as chymotrypsin-like (CT-L), trypsin-like (T-L), and caspase-like (C-L), also called β_5 , β_2 , and β_1 subunits, respectively [13,15]. Proteasome inhibition prevents degradation of I κ B, which binds to NF κ B in the cytoplasm, blocking nuclear entry of the transcription factor involved in cell-surviving, angiogenesis, bone remodeling, and cell invasiveness. Proteasomal activity suppression leads also to p27 accumulation, resulting in cell-cycle arrest and apoptosis. Another consequence of proteasome inhibition is up-regulation of pro-apoptotic factors - present at higher levels in myeloma cells due to increased amounts of misfolded immunoglobulin proteins - such as p53, Bax, and NOXA, together with reduction of anti-apoptotic factors like Bcl-2 and IAP. Finally, PIs can prevent degradation of misfolded proteins, largely produced by myeloma cells, leading to their accumulation in the endoplasmic reticulum, causing cell death [16–20].

Ixazomib is a selective, reversible and dose-dependent inhibitor of the 20S proteasome $\beta 5$ subunit, with half maximal inhibitory concentration (IC_{50}) value of 3.4 nmol/L [13].

Although ixazomib selectivity and potency are similar to bortezomib, the proteasome dissociation half-life ($t_{1/2}$) for ixazomib is approximately six times shorter than bortezomib, meaning a wider tissue distribution of the drug [13] [Table1].

3.3 Pharmacokinetics and metabolism

Ixazomib pharmacokinetics has been deeply explored in several studies. In this chapter we report the main features of ixazomib in terms of absorption, distribution, metabolism, and excretion.

3.3.1 Absorption and distribution

Ixazomib was initially dosed according to body-surface-area (BSA). Subsequently, a population pharmacokinetics model-based analysis of patients enrolled in four phase I studies showed that BSA did not influence ixazomib clearance or systemic exposure, allowing the switching from BSA-scaled to fixed dosing.

Ixazomib is rapidly absorbed, with a median time to reach peak concentration (T_{max}) of approximately 1 h postdose [13,14,21] and a maximum observed plasma concentration (C_{max}) of 0,11 $\mu\text{g}/\text{ml}$ at the clinical dosage of 4 mg weekly [22].

Area-under-concentration curve (AUC) increases proportionally over a dose range of 0.2 to 10.6 mg with a dose-linear model.

A food effect study showed an AUC reduction by 28% after a high-fat meal [23]. For this reason, no food should be consumed for at least 2h before and 1h after drug administration. Analysis of data from 755 adult patients enrolled across ten studies established absolute oral bioavailability (F) to be 58% [24].

In *vivo* studies demonstrated that ixazomib is 99% bound to plasma proteins [21,22,24], explaining the rapid absorption and the long terminal half life [Table 2].

The steady-state volume of distribution reported by different studies is 543L [22,24], providing further evidence of wide tissue distribution [13,18].

3.3.2 Metabolism

Ixazomib citrate is a prodrug that, in aqueous solutions or plasma, rapidly hydrolyzes to its biologically active form, ixazomib. In vitro studies using human cDNA-expressed cytochrome P450 (CYP) isozymes showed that, at concentrations of 10 μ M, seven major human CYP isozymes were involved: CYP3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%), and 2C9 (1%). Whereas at closer to clinically relevant concentration of 0.1 and 0.5 μ M, non-CYP-mediated metabolism was observed, suggesting that, non-CYP proteins contribute to the clearance of ixazomib, and no specific CYP isozyme predominates [22,25].

Given the hepatic role in ixazomib metabolism, a study was conducted to characterize pharmacokinetics in patients with solid tumours and moderate or severe hepatic impairment [total bilirubin $>1.5 \times$ (upper limits of normal, ULN)]. In such patients, unbound and total systemic exposures of ixazomib were 27% and 20% higher, respectively, than in patients with normal hepatic function. Consequently, a reduced ixazomib starting dose of 3 mg is recommended for patients with moderate or severe hepatic impairment [26].

3.3.3 Excretion

Ixazomib is a low clearance drug with a terminal half-life of 9.5 days, and a plasma clearance value of 1.86 L/h [24,25].

The mean renal clearance for oral ixazomib is estimated to be 0.119 L/h, which represents 6.4% of the total body clearance. Furthermore, considering the evidence that approximately 62% of the oral dose is excreted into urine, about 22% in the feces, and only 3.2% is eliminated unchanged in the urine up to 168 hours after oral dosing, metabolism is expected to be the major clearance mechanism for ixazomib [14,24,25].

Since MM is a disease associated with renal impairment at diagnosis in 15-40% of cases [27], a study was designed to investigate pharmacokinetics in patients with severe renal impairment (SRI) or end-stage renal disease (ESRD) requiring haemodialysis. In SRI/ESRD patients unbound and total systemic exposures of ixazomib were 38% and 39% higher, respectively, compared to patients with normal renal function. Therefore, in case of SRI/ESRD a reduced starting dose of 3 mg is recommended [28].

4. Clinical efficacy

In phase I studies, ixazomib administered as single agent in heavily pre-treated patients, showed overall response rate (ORR) ranging between 15 and 18% [29,30]. Preclinical studies indicated a synergistic activity of ixazomib with lenalidomide. These results provided the basis for phase II trials in which ixazomib efficacy was explored both as single agent and in combination with lenalidomide and dexamethasone.

In a phase II trial, ixazomib as single-agent was given to relapsed MM patients not bortezomib-refractory, and the ORR was 34% [31].

Two doses of ixazomib (4 and 5.5 mg) given orally once-weekly (on days 1, 8 and 15 of a 28-day cycle) combined with dexamethasone were compared in RRMM patients. Both doses of ixazomib plus dexamethasone were safe and effective; ixazomib at the dose of 5.5 mg induced deeper responses (ORR: 38% vs 52%) but resulted in a higher rate of grade ≥ 3 adverse events (21% vs 54%) [32].

Clinical efficacy of ixazomib-lenalidomide-dexamethasone combination in RRMM patients was confirmed in the phase III TOURMALINE-MM1 study, which, besides higher ORR in ixazomib vs placebo group (78% vs 72%, p 0.04), showed longer median PFS in favor of ixazomib (21 vs 15 months, p 0.01). Moreover, by subgroup analysis, in high cytogenetics risk patients, PFS was 21 months in ixazomib arm while PFS decreased to 10 months in placebo arm. Median overall survival (OS) was not reached in either group and follow-up is ongoing [33].

In newly diagnosed (ND)MM a phase I/II trial enrolled 65 patients who were treated with ixazomib associated with lenalidomide and dexamethasone, leading to an ORR of 92% with complete response (CR) in 27% of patients. Estimated 2-year progression-free survival (PFS) was 66% [34].

A phase II study of ixazomib in combination with lenalidomide and dexamethasone was conducted also by the Intergroupe Francophone du Myélome (IFM) for NDMM patients. The combination was used both as induction prior to, and as consolidation following ASCT, showing an ORR of 81% after induction therapy. CR rate increased from 12% before ASCT, to 38% after transplantation, and to 44% following consolidation [35].

Oral route of administration, weekly dosing schedule, and good safety/efficacy profile encouraged the evaluation of ixazomib in the maintenance setting.

In the phase I/II trial mentioned above, 21 untreated MM patients not undergoing ASCT, who responded to induction therapy, started ixazomib maintenance: 33% deepened their responses, median time to best response was 7 months, and median duration of response was 26 months [36]. Ixazomib maintenance in combination with lenalidomide after ASCT was evaluated in 65 patients

enrolled in a phase II trial and the estimated 2-year PFS was 83% [37] [Table 3]. Currently, phase III trials TOURMALINE-MM3 and TOURMALINE-MM4 are ongoing to evaluate single-agent ixazomib as maintenance therapy in NDMM patients who received ASCT, and those who have not undergone ASCT, respectively [38].

5. Safety, tolerability, toxicity, and potential off-target effects related to safety liabilities

A phase I, dose-escalation trial evaluated weekly ixazomib tolerability in 60 RRMM patients. One dose limiting toxicity (DLT) was grade (G) 3 nausea, vomiting and diarrhea, and occurred at the dose of 2.97 mg/m². Two other DLTs were reported at the dose of 3.95 mg/m² and were G3 nausea, vomiting and diarrhea, and G3 erythema multiforme rash. Maximum tolerated dose (MTD) was established at 2.97 mg/m². Most relevant hematologic G_{≥3} drug-related adverse events (AEs) were: thrombocytopenia (28%), neutropenia (13%), and lymphopenia (9%); while most frequent non-hematologic drug-related G_{≥3} AEs were gastrointestinal, such as diarrhea (13%) and nausea (9%) [30].

Another phase I, dose-escalation study evaluated safety of the twice-weekly schedule in 60 RRMM patients. One patient experienced a DLT (G3 macular erythematous rash) at 2.23 mg/m² dose. G4 thrombocytopenia developed in another patient and it was considered as DLT, even though it did not formally meet all the definition criteria. MTD was determined to be 2.0 mg/m². Most common drug-related G_{≥3} AEs were hematologic: thrombocytopenia (37%) and neutropenia (17%); among non-hematologic drug-related G_{≥3} AEs the most frequent were dermatologic (8%) [29].

Safety profile of ixazomib in combination with lenalidomide and dexamethasone was evaluated both in NDMM and RRMM patients.

In a phase I/II trial, 65 NDMM patients were treated with ixazomib-lenalidomide-dexamethasone, followed by single-agent ixazomib as maintenance therapy. During phase I, four DLTs were experienced, one at 2.97 and three at 3.95 mg/m², and the MTD was established at 2.23 mg/m². G_{≥3} drug-related AEs were observed in 63% of patients, the most frequent were rash (17%), neutropenia (12%) and thrombocytopenia (8%).

More consistent data on toxicity of ixazomib-lenalidomide-dexamethasone combination were provided in the TOURMALINE-MM1 study. This study compared the triple oral combination vs placebo-lenalidomide-dexamethasone in 722 RRMM patients. Among hematologic toxicities, G_{≥3} thrombocytopenia was more frequent in the ixazomib group (19% vs 9%), whereas the most relevant G_{≥3} non-hematologic AEs included rash (7% vs 4%) and diarrhea (6% vs 3%). The incidence

of peripheral neuropathy (PN) was 27% in the ixazomib group and 22% in the placebo group. Only 2% of patients in each study arm had G3 events, and 4% in the ixazomib group and 3% in the placebo group had PN with pain. Discontinuation rate due to toxicity was 17% in ixazomib arm vs 14% in control one [33].

Maintenance therapy with single-agent ixazomib at weekly dosing schedule was evaluated in 21 NDMM patients enrolled in a phase I/II trial. Seventy-one percent had drug-related AEs, 10% were G \geq 3 (thrombocytopenia and hypokalemia) [36].

Combination of ixazomib and lenalidomide as maintenance therapy showed a high toxicity: the main hematologic G \geq 3 AEs were neutropenia (23%) and thrombocytopenia (11%), while the most frequent non-hematologic G \geq 3 AEs included infections (26%), rash (12%) and gastrointestinal toxicities [37] [Table 3].

6. Drug-drug interaction

Drug-drug interaction may lead to suboptimal efficacy due to reduced drug exposure, or toxicity due to excessive compound plasma concentration. Most oral drugs are CYP450 substrates and lots of them are inducers or inhibitors of such enzymes. Ixazomib is a CYP3A4 substrate, therefore, concomitant administration of strong CYP3A4 inducers, such as rifampicin, phenytoin, carbamazepine, and St. John's Wort (hypericum), is strictly prohibited. CYP1A2-modulatory drugs and smoking status were not found to influence ixazomib systemic clearance [14,24,39].

7. Dosing routes

Pharmacokinetic data from four phase 1 dose-escalation studies with MLN9708 showed that there was a rapid absorption of ixazomib after oral administration. Similar systemic exposures have been achieved during IV and oral administration of ixazomib [21]. For this reason, ixazomib has been administered orally since the first clinical phase I trials in MM. Intravenous administration was used only in two phase I studies in which ixazomib was evaluated in relapsed/refractory lymphoma and non-hematologic tumors [25,40,41].

8. Regulatory affairs

Ixazomib (Ninlaro), marketed by Takeda Pharmaceuticals, on 27th September 2011 was designated as “orphan medicine” for MM treatment. The FDA granted priority review because this application was considered of significant importance in terms of safety and efficacy for MM patients.

In November 2015, the US FDA approved ixazomib in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received at least one prior therapy [14].

In September 2016, ixazomib in combination with lenalidomide and dexamethasone received a conditional approval also by European Medicine Agency (EMA) [42].

9. Conclusion

Ixazomib, the first oral PI marketed in 2015, is administered on empty stomach, on day 1, 8, 15 of 28-day cycles at the dose of 4 mg. Starting dose reduction at 3 mg is required only in case of severe hepatic and renal impairment.

Ixazomib could be defined as an oral analogue of bortezomib, being a boronic acid that reversibly inhibits $\beta 5$ subunit of 20S proteasome. With a 9.5-day half-life, 58% of oral bioavailability, and a large distribution volume of 543 L, ixazomib is a versatile molecule, potentially useful both in combination with IMiDs, and as single-agent.

TOURMALINE-MM1 trial showed its good efficacy/safety profile, with ORR of 78%, median PFS of 21 months and a discontinuation rate due to AEs of 17% only, and led to FDA and EMA approval for use in combination with lenalidomide and dexamethasone as salvage treatment in RRMM.

G \geq 3 AEs with ixazomib are low and easily manageable. In addition, this drug can be safely administered during dialysis, and confirmed to be effective in high-risk cytogenetic MM patients, thus paving the way to its evaluation in other combinations and in the maintenance setting.

10. Expert Opinion

Ixazomib, compared to bortezomib and carfilzomib, has two particular advantages: the oral route of administration and a better toxicity profile. Indeed, its pharmacokinetic profile allows once-weekly administration, improving quality of life and patient compliance while reducing hospital admissions for treatment. Moreover, data from TOURMALINE-MM1 showed easy-management of G \geq 3 AEs, mostly thrombocytopenia, neutropenia, nausea, diarrhea and skin rash. Bortezomib toxicity profile is characterized by development of poorly reversible PN of any grade in about 37%

of patients, including 14% of patients with G \geq 3 clinical manifestations [43]. By comparison, in TOURMALINE-MM1 PN of any grade was reported in 27% of patients and only in 4% it was associated with pain.

The major concern with carfilzomib is the occurrence of cardiovascular toxicities, being hypertension and cardiac failure the most frequent G \geq 3 events, reported in 9% and 5% in the ENDEAVOR study, respectively, and in 4% in the ASPIRE trial [44,45]. In the TOURMALINE-MM1 study, G \geq 3 hypertension and cardiac failure were reported in 3% and 2% of patients, without significant differences with the placebo arm. These data strongly suggest that ixazomib is not characterized by frequent cardiovascular toxicity.

In terms of efficacy, in the TOURMALINE-MM1 study, ixazomib overcame the poor prognosis associated with high-risk cytogenetic abnormalities, especially del(17p) and t(4;14), thus improving PFS. Indeed, in high-risk patients treated with ixazomib-lenalidomide-dexamethasone, median PFS was 21.4 months while it was 9.7 months in the control arm (HR 0.543)[46]. In addition, ixazomib also improved PFS in patients with amp(1q21), although the benefit was minor.

The development of treatment-resistant clones is a possible cause of worsening in long-term outcomes, including PFS and OS, with increasing number of prior therapies. Although patients refractory to PIs or lenalidomide were excluded from TOURMALINE-MM1, the results of this trial demonstrated that PFS significantly improved by adding ixazomib to lenalidomide and dexamethasone in patients with 1 prior therapy without transplant (HR 0.60), and 2 or 3 previous lines of treatment (HR 0.58), regardless of previous exposure to PI or IMiDs. This benefit was reported also in patients refractory to their last therapy (HR 0.71)[47,48].

Easy oral administration, good safety/efficacy profile, and the need for newer therapeutic strategies to face MM intrinsic chemoresistance and genetic instability, provide the rationale to implement and evaluate ixazomib in novel agent-combinations, such as with thalidomide, pomalidomide [49], panobinostat, selinexor, daratumumab, and also in association with conventional, more economically sustainable chemotherapeutic drugs, such as cyclophosphamide, and melphalan . [50–56]

Preliminary results (reported in Table 4) confirmed the good safety/efficacy profile of the aforementioned combinations.

Maintenance therapy in the post-ASCT setting, and continuous therapy for ASCT-ineligible patients are defined LTTs and represent a new issue in MM therapeutic strategy. The goal of LTTs is to control minimal residual disease, thus prolonging PFS and OS. To be appropriate for LTTs, a drug should be

effective, safe, easy-to-take and, possibly, not excessively expensive. With the exception of cost issues, ixazomib seems to satisfy these requirements [57]. Furthermore, phase I and II trials showed promising results in the maintenance setting, both for ixazomib as single agent and in combination with lenalidomide.

Based on the aforementioned considerations, two are the most probable fields in which ixazomib could be employed in the future: all-oral combinations both as front-line and salvage therapies, and LTTs.

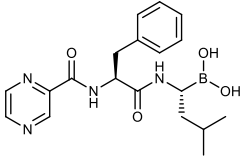
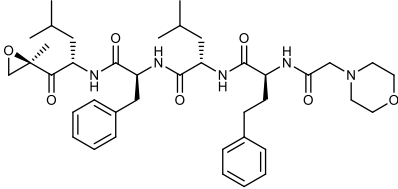
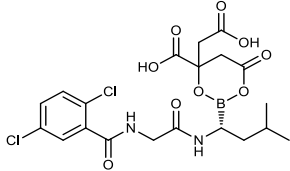
Data on long-range toxicity (including second primary malignancies) and chemoresistance stimulation are still needed and will be of crucial importance for the future role of this promising molecule.

Head-to-head comparisons in well-designed clinical trials are needed to evaluate ixazomib and carfilzomib or bortezomib and to define the best choice in terms of safety/efficacy[58].

Additionally, because modern anti-myeloma regimens typically combine a PI and an IMiD and could cost at least 100.000 USD per year, also pharmaco-economic considerations need to be carefully addressed. Therefore, clinical trials are also needed to evaluate the most appropriate sequence of agents to be used, to determine which drug is the best option in specific subsets of patients and disease settings, and to define the optimal duration of therapy, especially in the context of LTTs[58–60].

Conflicts of interest: Mario Boccadoro has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Abbvie, BMS, and research funding from Celgene, Janssen, Amgen, BMS, Mundipharma, Novartis, Sanofi. Alessandra Larocca has received honoraria from Amgen, BMS, Celgene and Janssen-Cilag. The other authors have no conflicts of interest

Table 1. Comparison between Bortezomib, Carfilzomib and Ixazomib [3]

	Bortezomib	Carfilzomib	Ixazomib
Chemical structure			
Mechanism of proteasome inhibition	Slowly-reversible inhibition of the $\beta 5$ CT-L and $\beta 1$ C-L subunit	Irreversible inhibition of the $\beta 5$ CT-L subunit	Reversible inhibition of the $\beta 5$ CT-L subunit
Proteasome dissociation half-life ($t_{1/2}$)	Slowly reversible: 110 minutes	Irreversible	Reversible: 18 minutes
Administration	Intravenous/Subcutaneous	Intravenous	Oral
Treatment indication	NDMM or RRMM	RRMM	RRMM

CT-L, chymotrypsin-like; **C-L**, caspase-like; **NDMM**, newly diagnosed multiple myeloma; **RRMM**, relapsed/refractory multiple myeloma;

Table 2. Pharmacokinetics characteristics of ixazomib at 4 mg weekly

Parameter	Value
C_{max} (µg/ml)	0,11
T_{max} (h)	1.0
t_{1/2} (days)	9.5
F (%)	58
PPB (%)	99
CL (L/h)	1.86

C_{max}, maximum observed plasma concentration; **T_{max}**, first time of C_{max}; **t_{1/2}**, half-life; **F**, oral bioavailability; **PPB**, plasma protein binding; **CL**, plasma clearance;

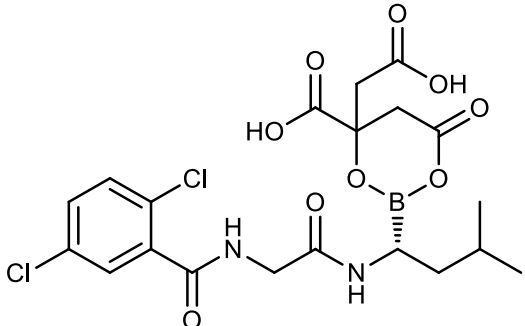
Box 1. Drug Summary	
Drug name	Ixazomib Citrate (Ninlaro, Takeda)
Indication	Multiple Myeloma
Phase	Approved by FDA in combination with lenalidomide and dexamethasone in relapsed/refractory patients that have received at least one prior therapy
Pharmacology	Inhibitor of $\beta 5$ subunit of 20S proteasome
Description	Proteasome inhibitor
Route of administration	Oral
Chemical structure	 <p>2,2'-{2-[(1R)-1-{[N-(2,5-Dichlorobenzoyl)glycyl]amino}-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl} diacetic acid</p>
Pivotal trial(s)	NCT01564537

Table 3: summary of most relevant clinical trials evaluating safety and efficacy of ixazomib both as single agent and in combination with lenalidomide and dexamethasone.

Authors of the study	Phase	N° of patients	Type of MM	Median number of prior therapies	Study design	Safety			Efficacy	
						DLTs/MTD	Main hematologic G≥3 AEs	Main non-hematologic G≥3 AEs	ORR	Median PFS
Kumar et al. [30]	I	60	RRMM	6	Ixazomib at 0.24, 0.48, 0.8, 1.2, 1.68, 2.23, 2.97, 3.95 mg/m ² orally on days 1, 8, and 15 of a 28-day cycle for 12 cycles	G3 nausea, vomiting and diarrhea at 2.97 and 3.95 mg/m ² G3 rash at 3.95 mg/m ² MTD at 2.97 mg/m ²	thrombocytopenia (28%) neutropenia (13%)	diarrhea (13%) nausea (9%)	18%	n.e.
Richardson et al. [29]	I	60	RRMM	4	Ixazomib at 0.24, 0.48, 0.8, 1.2, 1.68, 2.0, 2.23 mg/m ² orally on days 1, 4, 8, 11 of a 21-day cycle for 12 cycles	G3 rash at 2.23 mg/m ² G4 thrombocytopenia at 2.23 mg/m ² MTD at 2.0 mg/m ²	thrombocytopenia (37%) neutropenia (17%)	skin and subcutaneous tissue disorders (8%)	15%	n.e.
Kumar et al. [31]	II	33	RRMM	2	Ixazomib orally at a dose of 5.5 mg on days 1, 8 and 15 of a 28-day cycle. Dexamethasone at a dose of 20 mg orally was added on days 1, 2, 8, 9, 15 and 16 of the 28-day	n.e.	thrombocytopenia (45%)	diarrhea (20%)	34%	11 months*

					cycle for lack of minor response by end of cycle 2, lack of a PR by end of cycle 4, or disease progression at any time					
Moreau et al. [33]	III	722 randomized in 1:1 ratio	RRMM	Range 1-3	Oral ixazomib or placebo at a dose of 4 mg on days 1, 8, and 15; plus lenalidomide 25 mg orally on days 1-21 and dexamethasone 40 mg orally on days 1, 8, 15, and 22 of 28-day cycles until disease progression or development of unacceptable toxicities	n.e.	thrombocytopenia (19% vs 9%)	rash (7% vs 4%) diarrhea (6% vs 3%)	78% vs 72%, p 0.04	21 vs 15 months, p 0.01
Kumar et al. [34]	I/II	65 (15 in phase I and 50 in phase II)	NDMM	0	Phase I: oral ixazomib at 1.68, 2.23, 2.97, and 3.95 mg/m ² Phase II: oral ixazomib at 4 mg on days 1, 8, 15	1 DLT at 2.97 mg/m ² 3 DLTs at 3.95 mg/m ² MTD at 2.23 mg/m ² converted to fixed dose of 4	neutropenia (12%) thrombocytopenia (8%)	skin and subcutaneous tissue disorders (17%)	92%	67% (estimated 2-year)

					plus lenalidomide 25 mg orally on days 1–21 and dexamethasone 40 mg orally on days 1, 8, 15, 22 of a 28-day cycle for 12 cycles, followed by maintenance therapy with ixazomib alone	mg on the basis of pharmacokinetics results				
Kumar et al. [36]	I/II	21	NDMM	0	Maintenance with ixazomib 4 mg orally on days 1, 8, 15 of 28-day cycles	n.e.	thrombocytopenia (5%)	hypokalemia (5%)	2 VGPR to n-CR, 3 VGPR to CR, 1 VGPR to sCR, 1 CR to sCR	n.e.
Shah et al. [37]	II	65	NDMM	0	Maintenance with ixazomib 4 mg orally on days 1, 8, 15, and lenalidomide 10 mg orally (increased to 15 mg after 3 months if well tolerated) on days 1-28 of 28-day cycles	n.e.	neutropenia (23%) thrombocytopenia (11%)	infections (26%) rash (12%)	n.e.	83% (estimated 2-year)

Legend: N°: number; MM: multiple myeloma; DLT: dose limiting toxicity; MTD: maximum tolerated dose; G: grade; AEs: adverse events; ORR: overall response rate; PFS: progression-free survival; RRMM: relapsed/refractory multiple myeloma; NDMM: newly diagnosed multiple myeloma; n.e.: not evaluated; *: event-free survival (EFS); VGPR: very good partial response; nCR: near complete response; CR: complete response; sCR: stringent complete response.

Table 4: summary of most relevant clinical trials evaluating safety and efficacy of ixazomib in novel, all oral combinations.

Authors of the study	Phase	n of patients	Type of MM	Median number of prior therapies	Study design	Safety	Efficacy
San Miguel et al[55]	I	38	NDMM	n.a.	Arm A: Ixa 3.0-3.7 mg (days 1, 4, 8, 11, 22, 25, 29, 32) plus M 9 mg/m ² and P 60 mg/m ² (days 1-4) in 42-day cycles (max 9 cycles); Arm B: Ixa 3.0-4.0 mg (days 1, 8, 15) plus M 6 mg/m ² and P 60 mg/m ² (days 1-4) in 28-day cycles (max 13 cycles); Arm C/D: Ixa 3.0-4.0 mg (days 1, 8, 15, 22, 29)/Ixa 4.0 mg (days 1, 8, 22, 29) plus M 9 mg/m ² and P 60 mg/m ² (days 1-4) in 42-day cycles (max 9 cycles)	10 DLTs: G3 rash (n=2, Arm A), G≥3 thrombocytopenia (n=4, 1 pt in each Arm), G≥3 neutropenia (n=1, Arm A; n=4, Arm C; n=1, Arm D), G4 hemorrhagic esophageal ulcer (n=1, Arm B), G3 ileus/neurogenic bladder (n=1, Arm B), G3 vomiting/diarrhea (n=1, Arm B), and G3 respiratory infection (n=1, Arm C)	n.e.
San Miguel et al[55]	II	61	NDMM	n.a.	Ixa 4.0 mg (days 1, 8, 15) plus M 6 mg/m ² and P 60 mg/m ² (days 1-4) in 28-day cycles (max 13 cycles) followed by Ixa maintenance (days 1, 8, 15; 28-day cycles)	G≥3 thrombocytopenia: 49%, G≥3 neutropenia: 44%, G≥3 infections: 13%, G≥3 diarrhea: 11%, G≥3 rash: 7%	ORR 66% (CR 26%), median PFS 23.5 m
Dimopoulos et al[56]	II	70	NDMM	n.a.	Ixa 4.0 mg plus Cy 300 mg/m ² (Arm A) or 400 mg/m ² (Arm B) on days 1, 8, and 15, and D 40 mg on days 1, 8, 15, and 22, for up to 13 28-day cycles followed by Ixa maintenance therapy	G≥3 neutropenia: 31%, G≥3 anemia: 14%, G≥3 respiratory infections: 13%, G≥3 supraventricular arrhythmias: 7%	ORR 76% (CR 13%), median PFS n.r.
Voorhees et al[52]	I	17	RRMM	≥2	Pom 2-4 mg on days 1-21 plus Ixa 3-4 mg on days 1, 8 and 15 and D 40 mg (20 mg if age >75 years) on days 1, 8, 15 and 22 of 28-day	2 DLTs: 1 febrile neutropenia at Pom 4 mg and Ixa 3 mg, 1 G4 thrombocytopenia at Pom 4 mg and Ixa 4 mg	ORR 62%

					cycles until disease progression or unacceptable toxicity	G≥3 neutropenia: 35%, G≥3 lymphopenia: 29%, G≥3 thrombocytopenia: 18%	
Krishnan et al[61]	I/II	21	RRMM	3	Ixa 3-4 mg on days 1, 8 and 15 plus Pom 4 mg on days 1-21 and D 40 mg of 28-day cycles until disease progression or unacceptable toxicity	1 DLT: G3 lung infection at Ixa 3 mg MTD: Ixa 4 mg	ORR 40%
Reu et al[50]	I	11	RRMM	5	Ixa 3-4 mg on days 1, 8, 15 plus Pan 20 mg (days 1, 3, 5, 15, 17, 19) and D 20 mg (days 1, 2, 8, 9, 15, 16) of 28-day cycles	No DLTs G≥3 neutropenia: 18%, G≥3 thrombocytopenia: 9%	n.a.
Ludwig et al[49]	II	77	RRMM	1	Ixa 4 mg on days 1, 8 and 15 plus T 100 mg/day, and D 40 mg on days 1, 8, 15. If age ≥75 years T 50 mg/day and D 20 mg. Max 8 cycles followed by Ixa maintenance for 1 year (Ixa 4 mg or 3 mg if age ≥75 years on days 1, 8, 15; 28-day cycles)	G≥3 anemia: 13%, G≥3 thrombocytopenia: 9%, G≥3 neutropenia: 6%, all grades pneumonia: 9%	ORR 63%, median PFS 11.6 m
<p>Legend: n: number; MM: multiple myeloma; NDMM: newly diagnosed multiple myeloma; n.a.: not available; Ixa: ixazomib; M: melphalan; P: prednisone; DLT: dose limiting toxicity; G: grade; n.e.: not evaluated; ORR: overall response rate; CR: complete response; PFS: progression-free survival; m: months; Cy: cyclophosphamide; D: dexamethasone; n.r.: not reached; RRMM: relapsed/refractory multiple myeloma; T: thalidomide; Pom: pomalidomide; MTD: maximum tolerated dose; Pan: panobinostat</p>							

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Annotations:

Ref 24. **Important study of ixazomib pharmacokinetics.

Ref 26. *Pharmacokinetic analysis of ixazomib in hepatic impairment and consequences for clinical safety.

Ref 28. *Pharmacokinetic analysis of ixazomib in renal failure and consequences for clinical safety.