Horizon Scanning in Oncology

Ixazomib (Ninlaro®) in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma (MM)

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The HTA Core Model® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

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Table of contents

List of tables

1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA
HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is ixazomib?
A0022	Who manufactures ixazomib?
A0007	What is the target population in this assessment?
A0020	For which indications has ixazomib received marketing authorisation?
Health problem and current use	
A0002	What is multiple myeloma?
A0004	What is the natural course of multiple myeloma?
A0006	What are the consequences of multiple myeloma for the society?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of multiple myeloma?
A0003	What are the known risk factors for multiple myeloma?
A0024	How is multiple myeloma currently diagnosed according to published guidelines and in practice?
A0025	How is multiple myeloma currently managed according to published guidelines and in practice?
Clinical effectiveness	
D0001	What is the expected beneficial effect of ixazomib on mortality?
D0005	How does ixazomib affect symptoms and findings (severity, frequency) of multiple myeloma?
D0006	How does ixazomib affect progression (or recurrence) of multiple myeloma?
D0011	What is the effect of ixazomib on patients' body functions?
D0012	What is the effect of ixazomib on generic health-related quality of life?
D0013	What is the effect of ixazomib on disease-specific quality of life?
Safety	
C0008	How safe is ixazomib in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying ixazomib?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of ixazomib?
A0021	What is the reimbursement status of ixazomib?

2 Drug description

Generic/Brand name/ATC code:

Ixazomib/Ninlaro®/L01XX50

B0001: What is ixazomib?

orally bioavailable, reversible and selective inhibitor of the 20S proteasome

Ixazomib (Ninlaro®) is an orally bioavailable, reversible and selective proteasome inhibitor [2-5]. It binds to the beta 5 subunit of the 20S proteasome and thereby inhibits its chymotrypsin-like activity. In vitro studies have shown that ixazomib induces apoptosis of multiple myeloma cell lines [2, 5].

28-day cycle: 4mg on days 1, 8 and 15

The recommended dose of ixazomib for one 4-week cycle (28 days) is 4 mg administered orally on days 1, 8, and 15. Treatment with ixazomib should be continued until disease progression or unacceptable toxicity [2].

A0022: Who manufactures ixazomib?

Millennium Pharmaceuticals, Inc. (Takeda Oncology)

3 Indication

A0007: What is the target population in this assessment?

indicated for relapsed and/or refractory MM

Ixazomib, combined with lenalidomide and dexamethasone, is indicated for the treatment of patients who are refractory to prior therapy or who exhibit relapsed as well as relapsed and refractory multiple myeloma (MM).

4 Current regulatory status

A0020: For which indications has ixazomib received marketing authorisation?

FDA approval for MM since 2015

Ixazomib, in combination with lenalidomide and dexamethasone, was approved by the US Food and Drug Administration (FDA) on 20 November 2015 for the treatment of patients with MM who have received at least one prior therapy [2].

In November 2016 ixazomib has received marketing authorisation by the European Medicines Agency (EMA) for the following indication: ixazomib in combination with lenalidomide and dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy [6].

approved for the treatment of MM since November 2016

5 Burden of disease

A0002: What is multiple myeloma?

MM is a heterogeneous disease of various cytogenetically distinct plasma cell malignancies [7, 8]. Molecular characterisation and classification allows nowadays to distinguish prognostic relevant subgroups, which will have increasing influence in the choice of treatment [9].

heterogeneous disease → plasma cell malignancies

A0004: What is the natural course of multiple myeloma?

MM is thought to arise from the malignant transformation of post-germinal centre plasma cells. This appears to be the consequence of a two-step model of progression. In the first step, an asymptomatic pre-malignant stage of clonal plasma cell proliferation termed monoclonal gammopathy of undetermined significance (MGUS) is established. In the second step different progression events can occur, such as dysregulation of cell cycle controls, escapes from normal apoptotic pathways, or changes in the stromal microenvironment which induces the malignant clonal proliferation that is characteristic of MM [8, 10, 11].

MM appears to rise from the malignant transformation of post-germinal centre plasma cells

Commonly, end organ damage, including hypercalcemia, renal dysfunction, anaemia, or lytic bone lesions are characteristics of MM. However, MM sometimes occurs in an intermediately asymptomatic manner or as a more advanced pre-malignant stage that is referred to as smouldering MM (SMM) [8, 10, 11].

end organ damage is characteristic of MM

A0006: What are the consequences of multiple myeloma for the society?

Though MM is an orphan disease, the age peak in the early elderly age suggests that rising numbers of patients will occur. In addition, the longer survival rates of affected people, due to new therapeutic options will be challenging future considerations on pharmacoeconomic consequences worldwide, and especially in countries with ageing societies. Considering migration the differences between the ethnicities must also be taken into account [12, 13].

pharmacoeconomic consequences

A0023: How many people belong to the target population?

incidence rate in Austria 3.0 per 100,000/year

In Austria, the incidence for plasmacytomas and plasma cell malignancies, including MM, is 3.0 per 100,000 persons per year (based on the WHO-world population 2011). In 2012, 471 persons were newly diagnosed, of whom 245 were men and 226 were women. 1.2% of all malignant neoplasm cases in Austria are due to plasmacytomas and plasma cell malignancies. The survival rate (2010-2012) for three years after diagnosis is 58% [14]. Myeloma is most commonly diagnosed between the ages of 65 and 74 (median age 69) [12].

median age at diagnosis: 69

A0005: What are the symptoms and the burden of multiple myeloma?

most common presentations: fatigue, anaemia, bone pain, renal dysfunction, changes in electrophoreses

Signs and symptoms in MM patients are mostly related to the infiltration of plasma cells into the bone marrow. For the diagnosis evidence of organ damage attributable to the clonal plasma cell disorder is necessary. The most common symptoms comprise fatigue with or without anaemia, bone pain, changes in electrophoreses (monoclonal proteins in serum and/or urine) and renal dysfunction. Rare but critical symptoms in the beginning of MM are hypercalcemia hyper viscosity syndrome or spinal cord compression [9, 15].

A0003: What are the known risk factors for multiple myeloma?

associated risk factors: age, BMI, ethnicity, family history

Risk factors associated with MM are older age, body mass index (BMI), ethnicity and, in a small but unknown number of instances, family history. In addition, persons with MGUS or solitary plasmacytoma have a chance to develop MM [9].

A0024: How is multiple myeloma currently diagnosed according to published guidelines and in practice?

diagnosis according to the criteria of the International Myeloma Working Group

The diagnosis of MM proceeds in accordance with the current criteria of the International Myeloma Working Group [16]. In addition to the evidence of ≥ 10% clonal plasma cells in a bone marrow examination or a biopsy-proven plasmacytoma, the diagnosis of MM involves the presentation of monoclonal proteins in the serum and/or urine. For the diagnosis of symptomatic MM myeloma defining events (MDE) that comprise of defined CRAB (C = hyper calcemia, R = renal insufficiency, A = anaemia, B = bone lesions) features are required [8, 17].

6 Current treatment

A0025: How is multiple myeloma currently managed according to published guidelines and in practice?

risk stratification includes prior cytogenetic abnormalities

To stratify the risk of MM, the Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) can be applied. This risk stratification also takes prior cytogenetic abnormalities, determined by a fluorescence *in situ* hybridisation (FISH), into account. It is classified in three different risk stages: high-risk, intermediate-risk and standard-risk. In addition, time to relapse should also be considered in risk determination. Depending on the result of the risk stratification, the subsequently described treatment options should be applied [18, 19].

treatment options for ASCT candidates: Rd, KRD, VDT-PACE, bortezomib-containing regimes (VCD, VDT)

In patients who are eligible for autologous stem cell transplantation (ASCT) the following treatment options can be used [8, 17, 20]:

- Lenalidomide low-dose dexamethasone (Rd)
- Bortezomib-containing regimes (like bortezomib-cyclophosphamide-dexamethasone [VCD], bortezomib-thalidomide-dexamethasone [VTD])
- Carfilzomib-lenalidomide-dexamethasone (KRD)
- Multi-drug combinations (multiagent combination chemotherapy, like bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide [VDT-PACE])

To reduce toxicity, the low-dose dexamethasone regimen (40 mg weekly) is favourably used in all treatment regimens. It has not yet been established whether post-transplant maintenance therapy should be administered and which patient population should receive it. However, possible options are lenalidomide maintenance therapy or maintenance therapy with a proteasome inhibitor (like bortezomib) [8].

treatment options for patients who are not eligible for ASCT: MPT, Rd, VCD and VDT

Treatment options for patients who are not eligible for ASCT are the following: melphalan in combination with prednisone and thalidomide (MPT), bortezomib-based regimens (like VCD and VDT) and Rd. Subsequent treatment options are available for patients who have relapsed/refractory MM [8, 17, 18, 21]:

treatment options for relapse/refractory MM

- ASCT
- Bortezomib- and lenalidomide-based regimens (like VCD and VDT)
- Carfilzomib, lenalidomide and dexamethasone or dexamethasone alone
- Pomalidomide and dexamethasone
- Panobinostat, bortezomib and dexamethasone
- Daratumumab

Although, there is improvement of survival in patients with MM by disease control, eradication of the malignant plasma cell clone is still a rare event. Since, subsequent therapies increase the risk of development of resistance. Therefore, new drugs are still warranted, especially for MM subtypes with poor prognosis [22].

7 Evidence

systematic literature search in 5 databases: 204 hits

A literature search was conducted on 25 October 2016 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “Ixazomib”, “mln9708”, “Ninlaro”, “multiple myeloma”, “plasma cell myeloma”, “relapsed” and “refractory”. The manufacturer who submitted six references (five of which had already been identified by systematic literature search) was also contacted. A manual search identified 15 additional references (web documents and journal articles). Overall, 221 references were identified. Included in this report are:

- One phase III study, assessing the addition of ixazomib to lenalidomide and dexamethasone in the treatment of patients who have relapsed, refractory, or relapsed and refractory MM [23, 24].
- One phase II study, assessing the safety, tolerability, and activity of weekly oral ixazomib combined with lenalidomide and low-dose dexamethasone in patients with newly diagnosed MM [25].

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

The methodological quality of the evidence was conducted to assess the risk of bias at the study level based on EUnetHTA internal validity for RCTs [26]. Evidence was assessed based on the adequate generation of randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 4 of the Appendix.

7.1 Clinical efficacy and safety – phase III studies

TOURMALINE-MM1: randomised phase III study

The TOURMALINE-MM1 trial, a randomised, double-blind, multicentre, placebo-controlled phase III study, was conducted to assess the addition of ixazomib to lenalidomide and dexamethasone for the treatment of patients who have relapsed, refractory, or relapsed and refractory MM [23, 24]. Although follow-up is ongoing, the results of two pre-specified interim analyses are reported. Progression-free survival (PFS) and the overall response rate (ORR) were evaluated in the first analysis. The median follow-up at the time of the first interim analysis was 14.8 months in the ixazomib group and 14.6 months in the placebo group. 129 events of disease progression or death occurred in the ixazomib arm and 157 in the placebo group at the time of the first interim analysis. The second interim analysis was performed at a median follow-up of about 23 months. At this point in time, overall survival (OS) and adverse events (AEs) were analysed. At the time of the 23-month analysis 171 deaths had occurred, 81 in the ixazomib group and 90 in the placebo group.

efficacy and safety of ixazomib-lenalidomide-dexamethasone vs. placebo-lenalidomide-dexamethasone

A total of 722 patients were randomly assigned in a 1:1 ratio to either receive 4 mg of ixazomib or a placebo on days 1, 8 and 15 of a 28-day treatment cycle. Additionally, all patients received 25 mg of oral lenalidomide on days 1 through 21 and 40 mg of dexamethasone on days 1, 8, 15 and 22. The stratification of randomisation was based on the number of prior therapies, the prior treatment with proteasome inhibitors and the International Staging System disease stage. The median number of treatment cycles in the ixazomib group were 17 (1-34) and 15 (1-34) in the placebo group.

Enrolled patients had a median age of 66, and ranged from 30-91. The study population had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and had received at least one prior therapy. Cytogenetic analyses were available for 76% of patients, 19% of whom had high-risk cytogenetic abnormalities. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 3.

median age of 66 and ECOG performance status of 0–2

The primary outcome of TOURMALINE-MM1 was PFS; secondary outcomes included overall ORR, OS, and PFS in patients with high-risk cytogenetic abnormalities. Other evaluated study endpoints were the change in global health status and safety. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE), version 4.03.

primary outcome: PFS
secondary outcomes: ORR, OS, safety

7.1.1 Clinical efficacy

D0001: What is the expected beneficial effect of ixazomib on mortality?

At the time of the second interim analysis (23 months), the median OS had not yet been reached in either of the two study groups; follow-up is ongoing. At that time 171 deaths had occurred, 81 in the ixazomib group and 90 in the placebo arm.

secondary endpoint: OS had not yet been reached

D0006: How does ixazomib affect progression (or recurrence) of multiple myeloma?

PFS, the primary endpoint, was significantly improved (p = 0.01) in the intention-to-treat population of the ixazomib group. The median PFS was 20.6 months in the ixazomib group and 14.7 months in the placebo group. The hazard ratio (HR) for disease progression of ixazomib compared to placebo was 0.74 (95% CI 0.59–0.94).

primary endpoint: PFS

positive difference in median PFS: 5.9 months

The median PFS for patients with high-risk cytogenetic abnormalities, of whom 75 patients were in the ixazomib group and 62 patients in the placebo group, was 21.4 months and 9.7 months respectively. The HR for disease progression among patients with high-risk cytogenetic abnormalities was 0.54 (95% CI 0.32–0.92, p = 0.02)

positive difference in median PFS among patients with HCR: 11.7 months

D0005: How does ixazomib affect symptoms and findings (severity, frequency) of multiple myeloma?

The overall rates of response (ORR) were 78.3% (n = 282, ixazomib) and 71.5% (n = 259, placebo); a complete response (CR) occurred in 42 patients (12%) in the ixazomib group and in 24 patients (7%) in the placebo group. 240 patients (67%) in the ixazomib group and 235 (65%) in the placebo group showed partial responses (PR). Stable disease (SD) could be observed in 40 patients (11%) in the ixazomib group and in 59 patients (16%) of the placebo group. The median time to response was 1.1 and 1.9 months in patients receiving ixazomib and in patients receiving placebo respectively. The corresponding median duration of response was 20.5 months and 15.0 months.

ORR
ixazomib: 78.3%
placebo 71.5%

median duration of response
ixazomib: 20.5 months
placebo: 15.0 months

D0011: What is the effect of ixazomib on patients'body functions?

No evidence was found to answer this research question.

D0012: What is the effect of ixazomib on generic health-related quality of life?

D0013: What is the effect of ixazomib on disease-specific quality of life?

no significant difference in QoL

At a median follow-up of about 23 months, patient-reported quality of life (QoL) was maintained with the addition of ixazomib to the treatment regimen lenalidomide-dexamethasone. A trend toward better physical functioning, emotional functioning and fatigue scores in the ixazomib group compared to the placebo group could be observed. Nausea and vomiting symptoms were similar in both study groups and stable during treatment. Diarrhoea seemed to be worsening in later cycles of patients receiving ixazomib. However, no significant difference in QoL could be observed.

Table 1: Efficacy results of the TOURMALINE-MM1 trial

Descriptive statistics and estimate variability	Treatment group	Ixazomib-lenalidomide-dexamethasone	Placebo
	Number of subjects	360	362
	Median PFS (overall), months	20.6	14.7
	Median PFS (HCR), months	21.4	9.7
	Median OS, months	NR	NR
	ORR, % CR PR SD	78.3 12 67 11	71.5 7 65 16
Effect estimate per comparison	*Comparison groups*		Ixazomib-lenalidomide-dexamethasone vs. placebo
	PFS (overall)	HR	0.74
		95% CI	0.59–0.94
		Log-rank test p value	0.01
	PFS (HCR)	HR	0.54
		95% CI	0.32–0.92
		Log-rank test p value	0.02

Abbreviations: CI = confidence interval, CR = complete response, HR = hazard ratio, HCR = high cytogenetic risk patients, NR = not reached, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, PR = partial response, SD = stable disease

7.1.2 Safety

C0008: How safe is ixazomib in relation to the comparator(s)?

any grade AEs
ixazomib: 98%
placebo: 99%

AEs of any grade were reported in 98% (ixazomib) and 99% (placebo) of patients. The most common AEs of any grade in the ixazomib group were diarrhoea (45%), rash (36%), constipation (35%), fatigue (29%) and nausea (29%).

Grade ≥3 AEs could be observed in 74% of patients in the ixazomib group and in 69% of patients in the placebo group. Serious AEs occurred in 47% (ixazomib) and in 49% (placebo) of patients. Permanent discontinuation due to AEs of any agent occurred in 25% of patients in the ixazomib group and in 20% of patients in the placebo group. All common AEs and other AEs of clinical importance can be found in Table 2.

grade ≥3 AEs
ixazomib: 74%
placebo: 69%

C0002: Are the harms related to dosage or frequency of applying ixazomib?

Dose reductions of any drug appeared in 56% of patients in the ixazomib group and in 50% of patients in the placebo group. Dose adjustments to manage symptoms occurred in regard to the management of diarrhoea and rash.

dose reductions
ixazomib: 56%
placebo: 50%

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of ixazomib?

Administration of ixazomib to pregnant woman can cause foetal harm based on earlier studies on animals. However, there are no controlled trials that have investigated ixazomib in pregnant women. Patients with hepatic impairment or renal impairment should receive a reduced initial dose of ixazomib [2].

reduced starting dosage of ixazomib in patients with renal and hepatic impairment

Table 2: Most frequent adverse events

Adverse Event (according to CTCAE version 4.03)	**Ixazomib-lenalidomide-dexamethasone** (n = 361)			**Placebo** (n = 359)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Common hematologic AEs of any cause*						
Neutropenia	118 (33)	64 (18)	17 (5)	111 (31)	63 (18)	22 (6)
Thrombocytopenia	112 (31)	43 (12)	26 (7)	57 (16)	19 (5)	13 (4)
Anaemia	103 (29)	34 (9)	0 (0)	98 (27)	48 (13)	0 (0)
Common non-hematologic AEs of any cause*						
Diarrhoea	164 (45)	23 (6)	0 (0)	139 (39)	9 (3)	0 (0)
Rash Standardised MedDRA query High-level term	 131 (36) 72 (20)	 18 (5) 9 (2)	 0 (0) 0 (0)	 82 (23) 45 (13)	 6 (2) 6 (2)	 0 (0) 0 (0)
Constipation	126 (35)	1 (<1)	0 (0)	94 (26)	1 (<1)	0 (0)
Fatigue	106 (29)	13 (4)	0 (0)	102 (28)	10 (3)	0 (0)
Nausea	104 (29)	6 (2)	0 (0)	79 (22)	0 (0)	0 (0)
Peripheral edema	101 (28)	8 (2)	0 (0)	73 (20)	4 (1)	0 (0)
Peripheral neuropathy	97 (27)	9 (2)	0 (0)	78 (22)	6 (2)	0 (0)
Back pain	87 (24)	3 (<1)	0 (0)	62 (17)	9 (3)	0 (0)
Vomiting	84 (23)	4 (1)	0 (0)	42 (12)	2 (<1)	0 (0)
Upper respiratory tract infection	83 (23)	2 (<1)	0 (0)	70 (19)	3 (<1)	0 (0)
Nasopharyngitis	81 (22)	0 (0)	0 (0)	73 (20)	0 (0)	0 (0)
Insomnia	73 (20)	7 (2)	0 (0)	98 (27)	11 (3)	0 (0)
Muscle spasms	66 (18)	0 (0)	0 (0)	95 (26)	2 (<1)	0 (0)

Other AEs of clinical interest						
Arrhythmias[A]	56 (16)	17 (5)	3 (<1)	53 (15)	10 (3)	1 (<1)
Thromboembolism[A]	29 (8)	9 (2)	2 (<1)	38 (11)	11 (3)	1 (<1)
Liver impairment	26 (7)	7 (2)	0 (0)	21 (6)	4 (1)	0 (0)
Hypertension Any Hypertension crisis	 22 (6) 1 (<1)	 11 (3) 0(0)	 0 (0) 0 (0)	 18 (5) 0 (0)	 4 (1) 0 (0)	 0 (0) 0 (0)
Hypotension[A]	22 (6)	4 (1)	0 (0)	21 (6)	1 (<1)	0 (0)
Heart failure	16 (4)	7 (2)	2 (<1)	14 (4)	4 (1)	2 (<1)
Acute renal failure[A]	31 (9)	7 (2)	2 (<1)	41 (11)	12 (3)	4 (1)
Myocardial infarction[A]	5 (1)	0 (0)	3 (<1)	8 (2)	2 (<1)	2 (<1)
Encephalopathy	2 (<1)	2 (<1)	0 (0)	4 (1)	0 (0)	0 (0)
Interstitial lung disease	4 (1)	1 (<1)	1 (<1)	7 (2)	2 (<1)	0 (0)
New primary malignant tumour	17 (5)	NA	NA	14 (4)	NA	NA

*Abbreviations: [A] = reported grade 5 AEs: arrhythmia was reported in two patients in the ixazomib group and in three in the placebo group, thromboembolism was reported in one patient in each group, hypotension was reported in one patient in the ixazomib group, heart failure was reported in one patient in the ixazomib group and in three patients in the placebo group, myocardial infarction was reported in one patient in the ixazomib group and in two patients in the placebo group; AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; * = AEs reported in at least 20% of patients in either group.*

7.2 Clinical effectiveness and safety – Further studies

safety, tolerability, and activity of ixazomib in combination with lenalidomide and low-dose dexamethasone

An open-label, non-randomised, phase I/II trial [25] was conducted to assess the safety, tolerability, and activity of weekly oral ixazomib combined with lenalidomide and low-dose dexamethasone in patients with newly diagnosed MM. Included were 65 newly diagnosed MM patients (15 in phase I and 50 in phase II). To establish the recommended dose of ixazomib, patients received escalating doses of ixazomib (1.68–3.95 mg/m^2) in phase I of the study. In phase II of the study, enrolled patients received 2.23 mg/m^2 of oral ixazomib (days 1, 8, 15) plus 25 mg of lenalidomide (days 1–21) and 40 mg of dexamethasone (days 1, 8, 15, 22) for up to twelve 28-day cycles, followed by maintenance therapy with ixazomib alone. The primary endpoints were the maximum tolerated dose of ixazomib (phase I), and the rate of very good partial response or better (phase II). Secondary outcomes were safety, the characterisation of the pharmacokinetics of ixazomib, and the evaluation of response rates.

phase II recommended fixed dose 4.0 mg

One dose-limiting toxic event in phase I was noted at a dose of 2.97 mg/m^2 of ixazomib and three events at 3.95 mg/m^2. The maximum tolerated dose of ixazomib was defined at 2.97 mg/m^2. In addition, based on population pharmacokinetic results the recommended phase II fixed dose of ixazomib was 4.0 mg (2.23 mg/m^2). Drug-related grade ≥ 3 AEs were reported in 41 (63%) patients, including skin and subcutaneous tissue disorders (17%), neutropenia (12%), and thrombocytopenia (8%). Grade 3 or higher drug-related peripheral neuropathy occurred in four (6%) patients. Five patients discontinued because of AEs. 58% (95% CI 45–70) of patients had at least a very good partial response.

grade ≥ 3 AEs related to any drug: 63% of patients

8 Estimated costs

A0021: What is the reimbursement status of ixazomib?

estimated costs for 28-day treatment cycle of ixazomib: € 8,572.3

In Austria, ixazomib is available as 2.3, 3, and 4-mg hard capsules in packages of 3 pieces each at € 8,572.3 [27]. The recommended dose of ixazomib is 4 mg orally on days 1,8 and 15 of a 28-day cycle. According to this dosing recommendation, the costs for a 28-day treatment cycle would be € 8,572.3. Costs for about 17 treatment cycles may occur, since in the TOURMALINE-MM1 trial [23] patients received 17 (1–34) and 15 (1–34) treatment cycles in the ixazomib group and in the placebo group, respectively. Additional costs for lenalidomide and dexamethasone would arise for the triplet combination treatment.

9 Ongoing research

3 phase III studies are ongoing, investigating ixazomib in patients with MM

In November 2016 a search in databases http://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ctr-search/ was conducted. The following ongoing phase III trials are investigating ixazomib in different regimes in patients with MM:

- **NCT02181413:** A phase III, randomised, placebo-controlled, double-blind study of oral ixazomib citrate (MLN9708) maintenance therapy in patients with multiple myeloma following autologous stem cell transplant. Estimated study completion date is July 2023.
- **NCT02312258:** A phase III, randomised, placebo-controlled, double-blind study of oral ixazomib maintenance therapy after initial therapy in patients with newly diagnosed multiple myeloma not treated with stem cell transplantation. Estimated study completion date is July 2019.
- **NCT01850524:** A phase III, randomised, double-blind, multicentre study comparing oral ixazomib (MLN9708) plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma. Estimated study completion date is February 2021.

numerous ongoing phase I and II trials in different indication and treatment lines

Various phase I and II studies are currently ongoing in different treatment lines in patients with MM, using ixazomib in different regimes (e.g. NCT02477215, NCT01217957, NCT02004275, NCT01383928, NCT02057640, NCT02057640, and NCT02542657) In addition, ixazomib is also currently being investigated for other indications such as mantle cell lymphoma, renal cell carcinoma, non-Hodgkin lymphoma, follicular lymphoma and acute myeloid leukaemia.

10 Discussion

positive CHMP opinion in Europe, licensed in the USA

On 20 November 2015 ixazomib, in combination with lenalidomide and dexamethasone, was approved by the FDA for the treatment of patients with MM who have received at least one prior therapy [2]. The EMA has granted marketing authorisation to ixazomib in November 2016 for the combination therapy with lenalidomide and dexamethasone in adult patients with MM who have received at least one prior therapy [6].

TOURMALINE-MM (interim analysis): significantly improved PFS and ORR, but OS was not yet reached

The FDA approval was based on the interim results of three study endpoints of the TOURMALINE-MM1 [23, 24] trial, a randomised, double-blind, multicentre, placebo-controlled phase III study. 722 previously treated patients were randomised in a 1:1 ratio to either receive ixazomib in combination with lenalidomide and dexamethasone or placebo in combination with lenalidomide and dexamethasone. The primary endpoint PFS showed a significant increase of 5.9 months (median) compared to the placebo arm. ORR was also significantly improved among patients who received ixazomib combination therapy: 78.3% in the ixazomib group versus 71.5% in the placebo group. However, median OS had not yet been reached in either study group; the follow-up, however, is ongoing.

+5% grade 3–4 AEs and+5% discontinuation in the ixazomib group; no difference in QoL

In terms of safety, grade 3–4 AEs occurred more often (+5%) in the ixazomib group than in the placebo arm. The most frequent AEs of any grade in the ixazomib group were diarrhoea, rash, constipation, fatigue and nausea. Permanent discontinuation due to AEs of any agent occurred more commonly (+5%) in the ixazomib group. QoL was maintained with the addition of ixazomib to the treatment regimen of lenalidomide-dexamethasone.

long-term data on safety and efficacy are required

Since only results based on the interim analysis of the trial are available, a lack of data in long-term efficacy and safety exists. Thus, further follow-up of the study population is required especially because median OS was not reached in either treatment arm. In terms of safety, the potential occurrence of late side effects, as well as long-term effects on QoL, needs to be evaluated.

age group 65 to 75 did not benefit

Although a positive difference in median PFS in the intention-to-treat population could be observed, the subgroup analysis showed that patients between 65 and 75 years of age do not benefit from the ixazomib regimen (17.5 vs. 17.6 months). This patient group is of high importance, because myeloma is most frequently diagnosed between the ages of 65 and 74 (median age 69) [12].

benefit for patients with high-risk cytogenetic abnormalities

Patients with high-risk cytogenetic abnormalities showed a greater positive difference in median PFS than the intention-to-treat population (11.7 vs. 5.9 months). This patient population should be further investigated, since MM is characterised by chromosomal instability, and cytogenetic abnormalities have an effect on prognosis [28].

two other triplet combination regimens for MM have been approved since 2015: carfilzomib elotuzumub

Two other triplet combination regimens with lenalidomide and dexamethasone for the treatment of MM have received marketing authorisation from the EMA and the FDA since 2015. One of the approved treatment regimens included the proteasome inhibitor carfilzomib. This treatment option was investigated in the phase III trial ASPIRE [29], in which a significant improvement in median PFS compared to the control arm (26.3 vs. 17.6 months, 8.7 months gain) was shown. However, no results for OS are available at the moment. The other approved regimen was a combination regimen

with a monoclonal antibody, elotuzumab. This antibody was examined in the ELOQUENT-2 trial [30]. In this phase III study a significant increase in median PFS in the intervention arm compared to the control arm could be observed (19.4 vs. 14.9 months, 4.5 months gain). Nevertheless, no mature data for OS was also available in this trial.

direct comparison of ixazomib combination therapy to the two other triplet combination regimens

Direct comparison of the ixazomib regimen to the two already approved regimens (carfilzomib and elotuzumab) with lenalidomide and dexamethasone are needed to investigate which treatment option MM patients benefit the most from. Furthermore, subgroup analysis in these comparative trials for patients with high-risk cytogenetic abnormalities as well as older patients (> 65 years) would be of high relevance. In addition, the comparison of toxic effects of these treatments, should be compared since patients treated carfilzomib in clinical trials have been associated with a ~5% incidence of unexplained and unpredictable cardiovascular toxicity as well as ixazomib treated patients show increased neurotoxicity's. Indirect trial comparisons are insufficient, due to differences in the study designs, patient populations and methods.

treatment cost for ixazomib for a 28-day cycle: € 8,572.3

The costs per 28-day treatment cycle would be € 8,572.3 [27]. Costs for about 17 treatment cycles may arise, since the median number of treatment cycles in the ixazomib group were 17 (1-34) and 15 (1-34) in the placebo group. Moreover, additional costs for the treatment of AEs as well as the combination therapies (lenalidomide and dexamethasone) would arise in all mentioned triplet combination regimes.

significant PFS improvement

long-term data required

direct comparison to recently approved triplet combination regimens

In conclusion, the treatment with ixazomib in combination with lenalidomide and dexamethasone offers a significant improvement in PFS (median gain 5.9 months, intention-to-treat population), even for patients with high-risk cytogenetic abnormalities. However, the missing data for OS and the lack of benefit for the actual patient population most affected by MM in clinical practice (> 65 years) highlight the requirement for long-term data. Finally, the direct comparison of ixazomib to the carfilzomib and elotuzumab triplet combination regimens is necessary to identify the best treatment option for MM patients who received prior therapies.

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12 Appendix

Table 3: Characteristics of the TOURMALINE-MM1 trial

Title: Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma [23, 24]			
Study identifier	NCT01564537, EudraCT number 2011-005496-17, TOURMALINE-MM1		
Design	Phase III, randomised, multicentre, placebo-controlled, double-blind trial		
	Duration		Data cut-off of the 1st analysis: 30 October 2014 Median follow-up of the 1st analysis: 14.8 months (ixazomib), 14.6 months (placebo) Data cut-off of subsequent analysis: 12 July 2015 Median follow-up of subsequent analysis: 23 months
Hypothesis	Superiority The study was designed to show a prolonged PFS in patients treated with ixazomib plus lenalidomide and dexamethasone compared to those who received placebo plus lenalidomide and dexamethasone. The primary endpoint (PFS) was based on central laboratory results and International Myeloma Working Group 11 criteria and evaluated by an independent review committee, with 80% power at a two-sided alpha level of 0.05.		
Funding	Millennium Pharmaceuticals, Inc. (Takeda Oncology)		
Treatments groups	Intervention (n = 360)		Oral ixazomib was administered at a dose of 4 mg on days 1, 8 and 15 of a 28-day treatment cycle. Oral lenalidomide was administered at a dose of 25 mg on days 1 through 21 and on days 1, 8, 15 and 22 patients additionally received 40 mg of dexamethasone.
	Control (n = 362)		Placebo was administered on days 1, 8 and 15 of a 28-day treatment cycle. Additionally, patients received 25 mg of oral lenalidomide on days 1 through 21 and 40 mg of dexamethasone on days 1, 8, 15 and 22.
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Time from the date of randomisation to the date of first documentation of disease progression or death from any cause, as assessed by an independent review committee.
	Overall survival	OS	Defined as the time from the date of randomisation to the date of death.
	overall response rate	ORR	Defined as the percentage of participants with complete response (CR) including stringent complete response (sCR), very good partial response (VGPR) and partial response (PR) assessed by the IRC using IMWG criteria.
Results and Analysis			
Analysis description	**Primary Analysis** All primary and secondary efficacy analyses were performed in the intention-to-treat population (all patients who underwent randomisation). For the safety analysis all patients who received at least one dose of a study drug or placebo were investigated.		
Analysis population	Inclusion		❁ Male or female participants 18 years of age or older ❁ Relapsed, refractory, primary refractory or relapsed and refractory MM ❁ Measurable levels of disease ❁ ECOG performance status score of 0 to 2 ❁ One to three prior therapies ❁ Adequate hematologic and hepatic function ❁ Mild-to-moderate impairment of renal function

Title: Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma [23, 24]				
Study identifier	NCT01564537, EudraCT number 2011-005496-17, TOURMALINE-MM1			
Analysis population (continuation)	Exclusion	❁ Peripheral neuropathy of grade 1 with pain or grade 2 or higher or had disease that was refractory to prior lenalidomide therapy or proteasome inhibitor-based therapy ❁ Patients who have failed to recover from effects of prior chemotherapy ❁ Any central nervous system involvement ❁ Evidence of current uncontrolled cardiovascular conditions ❁ Comorbid systematic illness or other severe concurrent disease ❁ Patients were excluded for the following reasons (within 14 days before randomisation): - undergone major surgery - received radiotherapy - had an infection requiring systematic antibiotic therapy or other serious infections - had received systematic treatment with strong CYP1A2, strong CYP3A inhibitors or strong CYP3A inducers or had used Ginko biloba or St. John's wort		
	Characteristics		Intervention (n = 360)	Control (n = 362)
	Median age (range), years >65, n (%)		66 (38–91) 192 (53)	66 (30–89) 186 (51)
	Gender, n (%)		♂ 207 (58) ♀ 153 (42)	♂ 202 (56) ♀ 160 (44)
	White race, n (%)		310 (86)	301 (83)
	ECOG performance status, n/total (%) 0 1 2		 180/354 (51) 156/354 (44) 18/354 (5)	 170/358 (47) 164/358 (46) 24/358 (7)
	ISS disease stage at study entry, n (%) I II III		 226 (63) 89 (25) 45 (12)	 233 (64) 87 (24) 42 (12)
	Median time since initial diagnosis of MM (range), months		44.2 (3–281)	42.2 (4–306)
	Cytogenetic features, n (%) Standard-risk High-risk Data not available		 199 (55) 75 (21) 86 (24)	 216 (60) 62 (17) 84 (23)
	Number of prior therapies, n (%) 1 2 3		 224 (62) 97 (27) 39 (11)	 217 (60) 111 (31) 34 (9)
	Disease category, n/total (%) Relapsed Refractory Relapsed and Refractory Primary refractory		 276/359 (77) 42/359 (12) 41/359 (11) 24/359 (7)	 280/362 (77) 40/362 (11) 42/362 (12) 22/362 (6)
	Prior proteasome inhibitor therapy, n (%) Bortezomib Carfilzomib		 248 (69) 1 (<1)	 250 (69) 4 (1)
	Disease refractory to any prior therapy, n (%)		4 (1)	8 (2)
	Prior immunomodulatory drug therapy, n/total (%) Lenalidomide Thalidomide Disease refractory to any prior immunomodulatory drug therapy		193/360 (54) 44/360 (12) 157/360 (44) 41/193 (21)	204/362 (56) 44/362 (12) 170/362 (47) 50/204 (25)

Abbreviations: ECOG = Eastern Cooperative Oncology Group, IMWG = International Myeloma Working Group, IRC = Independent Review Committee, MM = multiple myeloma

Table 4: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [26]

Criteria for judging risk of bias		risk of bias
Adequate generation of randomisation sequence: no information available		unclear
Adequate allocation concealment: no information available		unclear
Blinding: double-blind	**Patient**	yes
	Treating Physician	yes
Selective outcome reporting unlikely: confidence intervals of the median PFS values for both treatment arms are not available		no
No other aspects which increase the risk of bias: no aspects which increase the risk of bias were found		yes
Risk of bias – study level		low