



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pepaxti

International non-proprietary name: melphalan flufenamide

Procedure No. EMEA/H/C/005681/II/0002

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AML	Acute myeloid leukaemia
AUC	Area under the curve
AUCinf	Area under the curve extrapolated to infinity
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CL	Clearance
CBR	Clinical benefit rate
Cmax	Maximum concentration
CR	Complete response
CrCl	Creatinine clearance
DOCB	Duration of clinical benefit
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EMD	Extramedullary disease
HRQoL	Health-related quality of life
IC50	Half maximal inhibitory concentration
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
ISS	Integrated Summary of Safety or International Staging System
IV	Intravenous
M-protein	Monoclonal protein spike
MAA	Marketing Authorisation Application
mAb	Monoclonal antibody
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MR	Minimal response
NCCN	National Comprehensive Cancer Network
NE	Not estimable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Proteasome inhibitor
PK	Pharmacokinetics
PO	Oral (per os)
PR	Partial response
PT	Preferred term
QoL	Quality of life
RRMM	Relapsed-refractory multiple myeloma
SAE	Serious adverse event
sCR	Stringent complete response
SCS	Summary of Clinical safety
SD	Stable disease
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
SOC	System organ class
SPM	Second primary malignancy

TCR	Triple-class refractory
TEAE	Treatment-emergent adverse event
TFI	Treatment-free interval
TSP	Targeted Safety Population
TTP	Time to progression
TTR	Time to response
URC	Uniform Response Criteria
VGPR	Very good partial response
WBC	White blood cell
WRO	Written Response Only

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Oncopeptides AB submitted to the European Medicines Agency on 28 November 2022 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of patients with Multiple Myeloma who have received at least two prior lines of therapies for PEPAXTI, based on final results from study OP-103 OCEAN; this is a randomized, open-label phase III study in patients with relapsed or refractory multiple myeloma following two to four lines of prior therapies and who were refractory to lenalidomide and the last line of therapy. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the SmPC.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Elita Poplavska

Subsequently, Peter Mol was appointed Rapporteur for the assessment of the product.

Timetable	Actual dates
Submission date	28 November 2022
Start of procedure	31 December 2022
CHMP Rapporteur's preliminary assessment report circulated on	24 February 2023
PRAC Rapporteur's preliminary assessment report circulated on	27 February 2023
CHMP Co-Rapporteur's Assessment circulated on	10 March 2023
PRAC RMP advice and assessment overview adopted by PRAC on	16 March 2023
CHMP Rapporteur(s) (Joint) assessment report circulated on	23 March 2023
Request for supplementary information adopted by the CHMP on	30 March 2023
MAH's responses submitted to the CHMP on	19 April 2023
Re-start of procedure	24 April 2023
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	23 May 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	24 May 2023
PRAC RMP advice and assessment overview adopted by PRAC on	8 June 2023
2 nd Request for supplementary information adopted by the CHMP on	22 June 2023
MAH's responses submitted to the CHMP on	6 July 2023
Re-start of procedure	17 July 2023
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	22 August 2023
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	7 September 2023
CHMP opinion adopted on	14 September 2023
The CHMP adopted a report on similarity of Pepaxti with Abecma, Carvykti, Blenrep, Darzalex, Farydak, Imnovid, Kyprolis and Ninlaro on	14 September 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Multiple myeloma (MM) is an incurable malignant plasma cell disorder. It is characterised by clonal proliferation of plasma cells in the bone marrow and the production of excessive amounts of a monoclonal immunoglobulin protein (Ig; usually of the IgG or IgA type or free light chain [paraprotein,

monoclonal protein spike (M-protein), or M-component]). MM predominantly affects the older patient, with a median age at onset of 72 years in Europe (Palumbo and Anderson 2011).

The most common criteria used in diagnosis of symptomatic MM are the presence of neoplastic plasma cells comprising greater than 10% of BM cells or presence of a plasmacytoma; paraprotein (M protein) in the serum and/or urine; and evidence of related organ or tissue impairment due to plasma cell disorder.

According to the International Myeloma Working Group (IMWG) criteria (Rajkumar et al. 2011), relapsed-refractory multiple myeloma (RRMM) is defined as disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously, before then progressing in their disease course. Patients who relapse during ongoing treatment or within 60 days of last dose of lenalidomide are per IMWG definition "lenalidomide refractory".

Claimed therapeutic indication

The claimed extension of indication in an earlier line of relapsed-refractory multiple myeloma (MM) treatment is:

*'Pepaxti is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least ~~three~~ **two** prior lines of therapies, whose disease is refractory to ~~at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody,~~ **lenalidomide** and ~~who have demonstrated disease progression on or after the last line of therapy.~~*

For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation (see section 4.4).'

Epidemiology

MM is the second most common haematologic malignancy, and accounts for approximately 1-2% of all new cancer cases, with a global incidence rate of 1.7 per 100,000 and an age-standardised incidence rate of 2.1-3.4 per 100,000 in France, Germany, Italy, Spain and the UK. An estimated 35,842 patients were diagnosed in the EU27 during 2020, with an estimated 23,275 deaths due to the disease (ECIS 2020). Multiple myeloma is more common in men than women (ECIS 2020) and in the US, twice as common in African Americans than in other races and ethnicities (SEER 2019).

Aetiology and pathogenesis

The initiating event driving malignant development is either the acquisition of hyperdiploidy or a translocation involving the immunoglobulin heavy chain gene locus. Such clonal events can occur in almost all cells, and are present in the precursor conditions monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma.

Clinical presentation, diagnosis and stage/prognosis

Sometimes patients are asymptomatic and identified with routine blood testing, although most patients with MM experience symptoms leading to significant decrement to quality of life, including bone pain, bone fractures, fatigue, anaemia, infections, hypercalcemia, hyperviscosity of the blood, and renal insufficiency.

Patients with MM may have symptom-free periods, but the disease always relapses, and patients may become refractory to all available treatment options due to mutations and/or clonal evolution of the tumour cells.

Clinical outcomes for patients with multiple myeloma depend on several factors, including intrinsic tumour cell characteristics (cytogenetic abnormalities, gene expression profile, extramedullary growth, lactate dehydrogenase levels), tumour burden (β 2-microglobulin [B2M], low platelet count), and patient features (age, comorbidities, frailty). Outcomes also depend on depth of response to therapy. Models combining patient and disease characteristics have been created, because individual prognostic factors do not capture the full heterogeneity in outcome. The original multiple myeloma International Staging System, based on serum albumin and B2M concentrations, reflects tumour burden and patient condition. This staging system has been updated as the Revised International Staging System, which includes information on the presence of high-risk genetic lesions—t(4;14), t(14;16), or del(17p), either alone or in combination—or increased lactate dehydrogenase concentration.

While the advent of novel treatment regimens has translated into improvements in outcomes over the past 15 years (Sonneveld 2017), the disease is ultimately fatal, with a 5-year survival around 50% (Seer 2019). Data from a multi-country European real-world study (N=4,997) provide a glimpse into the rate of relapse in MM (Yong et al. 2016). Although patients with relapsed disease can achieve responses to subsequent anti-myeloma regimens, the duration of response typically decreases with successive relapses until resistant disease develops. This observational study was a retrospective chart review conducted in Belgium, France, Germany, Italy, Spain, Switzerland, and the UK. Authors found that 95% of patients had received first-line, 61% had received second-line, 38% had received third-line, 15% had received fourth-line and 1% had received fifth-line or later treatment. Of interest is that the median time to progression decreased from 18 months in first line to 13, 7, and 5 months through lines 2, 3 and 4, respectively. Patients who develop disease refractory to immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and CD38- targeting monoclonal antibodies (mAbs), i.e., are triple-class refractory (TCR), have an overall survival of only a few months.

Management

The management of patients with relapsed/refractory disease represents a clinical challenge, as these patients suffer from continuing symptoms, complications of the disease (including renal failure, blood cytopenia or recurrent infections) and decreased quality of life. These patients typically receive salvage therapy until the next relapse, progression or the development of intolerable toxicity and then go onto the next salvage option. Current treatment strategies in pre-treated RRMM patients focus on controlling disease progression and prolonging survival. These strategies include glucocorticoids (dexamethasone, prednisolone, methylprednisolone); chemotherapy (primarily alkylating agents, including high dose chemotherapy followed by autologous stem cell transplantation [ASCT]); proteasome inhibitors (PIs, such as bortezomib, carfilzomib and ixazomib); immunomodulatory agents (such as thalidomide, lenalidomide and pomalidomide); monoclonal antibodies (such as daratumumab, isatuximab, elotuzumab and belantamab); the histone deacetylase inhibitor Panobinostat; selective inhibitors of nuclear export (SINE) (selinexor); chimeric antigen receptor T-cells (CAR-T; idecabtagene vicleucel, and ciltacabtagene autoleucel); and the recently approved bispecific antibody teclistamab. Among these treatment options, lenalidomide and bortezomib have a prominent role. Both are approved and used as frontline treatment of multiple myeloma and used in combination with other drugs at relapse. Lenalidomide is also approved as maintenance therapy after ASCT in patients with newly diagnosed MM.

The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior

treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e. clinical versus biochemical relapse). Switching to another class of MM therapy is a preferable approach but treatment with another drug in the same drug class, in a different combination, can also be considered. In young patients, a second ASCT may be considered, provided that the patient responded well to the previous ASCT and had a PFS of more than 24 months.

Treatment of RRMM patients who received two or more prior lines of therapy is becoming challenging. The ESMO guideline in MM (2021), recommends one of the following treatment options in second or subsequent relapse (Figure 1):

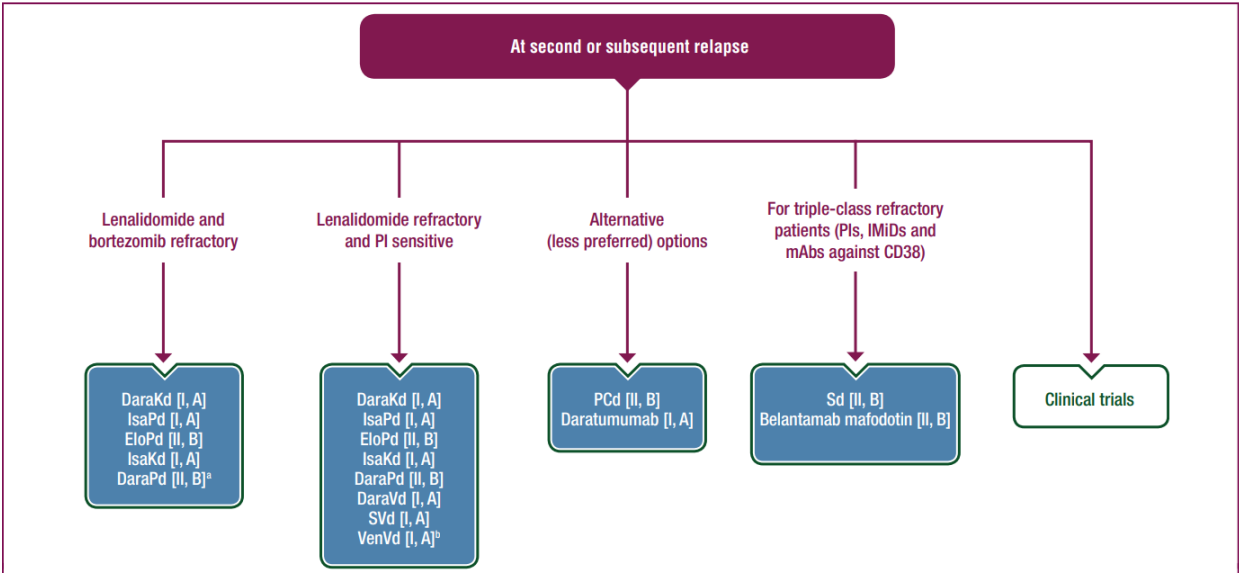


Figure 1. Recommendations for MM patients who receive a third or subsequent line of therapy (ESMO guideline 2021)

Triplet regimens are now standard in the treatment of MM. Nevertheless, pomalidomide plus dexamethasone (comparator therapy in the pivotal clinical trial for this application) is registered for RRMM patients who have received at least two prior regimens and is still an appropriate choice for patients who cannot tolerate triplets (such as frail patients) or those who may not have access to the newer agents included in triplet regimens.

None of the newly approved medicinal products (mainly combinations) has provided a cure. Ultimately patients relapse and treatment options are exhausted. As such, an unmet medical need remains, and new effective and convenient treatment options are needed .

2.1.2. About the product

Melphalan flufenamide (melflufen) is a lipophilic peptide conjugated alkylating drug designed for targeted delivery of alkylating moieties to tumour cells. The drug is composed of a di-peptide and an alkylating moiety of the bischloroethylamine group. It shares the bis (2-chloroethyl)amino alkylating group with the marketed compounds cyclophosphamide, bendamustine, chloroambucil and melphalan. Although melphalan is one of the metabolites of melflufen, melflufen has the intrinsic capacity to act as an alkylator without any activating step. The lipophilic characteristics of melflufen allow for a faster cellular uptake whereas the peptide hydrolysis mediated by aminopeptidases (like aminopeptidase N [APN]), allows for a potentiated effect in APN-rich environments, resulting in accumulation of alkylating moieties in cancer cells. According to the applicant, this is expected to result in improved efficacy without an increase in toxicity compared to melphalan. Similar to other nitrogen mustard drugs, cross-

linking of DNA is involved in the anti-tumour activity of melphalan flufenamide. In cellular assays, melphalan flufenamide inhibited proliferation and induced apoptosis of haematopoietic and solid tumour cells. Retained cytotoxic activity was demonstrated in multiple myeloma cells with absent or impaired p53 functionality. Melphalan flufenamide showed synergistic cytotoxicity with dexamethasone in melphalan resistant and non-resistant multiple myeloma cell lines.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Main clinical efficacy data is derived from Phase 3 Study **OP-103** (OCEAN), a randomised, open-label study in patients with relapsed or refractory multiple myeloma (RRMM) following 2 to 4 lines of prior therapies and who were refractory to lenalidomide and the last line of therapy. Key supportive data is derived from a supplementary clinical study report for Phase 2 Study **OP-106**, the pivotal study for the MAA of Pepaxti, with results from an additional data-cut-off (Oct 2021) as per Rapporteurs request during the initial Marketing Authorisation procedure.

Full clinical study reports for OP-103 and OP-106 (including additional analysis with data cut-off Oct 2021) were submitted as confirmatory data to EMA during the MAA for Pepaxti (EMA/H/C/005681/0000). Based on these data, a full approval in 3L+ MM was granted.

For convenience, study design details and results of the overall study population are repeated in this report. Results for the post-hoc defined target indication population (which comprised patients who had either not previously received an ASCT or patients with a prior transplant and whose time-to-progression of MM was >36 months post-ASCT) are presented separately from the overall study population.

The MAH did not seek scientific advice at the CHMP. The clinical development plan was discussed with the FDA and individual regulatory agencies (MPA [SE] and MHRA [UK]) in 2015 and 2016. This pertained the dose and primary endpoint of Phase 2 study OP-106, and design of the Phase 3 Study OP-103 intended to serve as confirmatory study after conditional marketing authorisation.

2.1.4. General comments on compliance with GCP

All clinical studies submitted were, as claimed by the MAH, conducted in accordance with the Sponsor's (or designee's) standard operating procedures, which are designed to ensure adherence to Good Clinical Practice guidelines.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Environmental risk assessment was provided in the initial MAA-submission and is still valid. Since the risk assessment was based on a worst case market penetration and considered the current treatment regimen, the proposed change in indication has no impact on the environmental risk assessment.

2.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of melflufen.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

Study	OP-103/OCEAN	OP-106/HORIZON
Phase	Phase 3	Phase 2
Population studied	RRMM, after 2-4 prior lines of therapy including lenalidomide and a PI and refractory to last line of therapy and lenalidomide.	RRMM, after at least 2 prior lines of therapy, including an IMiD and a PI and refractory to pomalidomide and/or an anti-CD38 mAb.
Design	Randomized	Single arm
Combination regimen	Combination (melflufen or pomalidomide) with 40 mg dexamethasone weekly	Combination with 40 mg dexamethasone weekly
Melflufen starting dose and frequency	40 mg Q4W	40 mg Q4W
Study status	Complete	Complete ^a
CSR available	Full CSR	Full CSR + CSR addendum (functional status and well-being) and Supplemental CSR
Planned enrollment (planned N)	450	150
Number of patients enrolled (N)	495	157
Number of prior treatments (median)	3	5
Primary endpoint	PFS	ORR
IRC assessment	Yes	Yes ^b
Pharmacokinetics	Yes	No

Abbreviations: CSR clinical study report; IRC Independent Review Committee; MTD maximum tolerated dose; ORR overall response rate; PFS progression-free survival; Q3W every 3 weeks; Q4W every 4 weeks; RRMM relapsed refractory multiple myeloma.

^a As of 14 January 2020, the data cutoff date for the CSR and functional status and well-being CSR addendum, all patients had at least 3 months of follow-up and most patients had at least 6 months of follow-up.

^b Primary endpoint was ORR as assessed by the investigator, but the IRC supporting the analyses on the primary endpoint based on the investigator assessment.

2.3.2. Pharmacokinetics

Melphalan flufenamide (melflufen) is a peptide-drug conjugate containing melphalan as an alkylating moiety. Due to its high lipophilicity, melflufen is passively and rapidly distributed into cells where it is metabolized by peptidases into the hydrophilic alkylator melphalan or by esterases into hydrophilic desethyl-melflufen, which also has alkylating properties.

For this extension of indication of melflufen, the Phase 3 Study OP-103 (Ocean) is the pivotal study. PK data from this study have already been evaluated at the initial marketing authorisation procedure (EMA/H/C/005681/0000). An updated popPK report (ONC0101F-Report Addendum-v1.1-Final, 2022-11-01) has been submitted to describe the pharmacokinetics of melphalan. Data from 4 additional patients with severe renal impairment are added. In addition, PK samples which were outside the established long term stability have been deleted. This has already been evaluated and agreed upon during the initial marketing authorisation. Consequently the changes to the popPK model are minor and the PK parameters have not changed compared to those of the initial marketing authorisation.

In short, melflufen PK is characterized by low plasma concentrations during the IV infusion and a very rapid disappearance after the end of infusion with a half-life of less than 5 minutes. Plasma concentrations of melphalan, the main active metabolite, increased rapidly and melphalan plasma concentrations exceed those of melflufen within 15 minutes after the start of the 30-minute melflufen infusion. Peak plasma concentrations of melphalan appear with a T_{max} of 34-45 min, a delay by 5 to 15 minutes after the end of the melflufen infusion. Melphalan C_{max} was approximately 3 to 4-fold higher than the C_{max} of melflufen and AUC of melphalan was almost 20-fold higher than the AUC of melflufen. Melphalan is eliminated by spontaneous degradation but also partly excreted unchanged in the urine. Plasma concentrations of the metabolite desethyl-melflufen remained very low during and after melflufen administration and PK of desethyl-melflufen could not be characterised well.

Updated popPK analysis. Melphalan pharmacokinetics was characterized by a three-compartment population PK model with dosing into the peripheral compartment and linear CL. Similar covariate effects on PK parameters were estimated: melphalan CL increased with increasing body weight and increasing eGFR.

Melphalan exposure was affected by body size, at a BW of 60 kg AUC was on average 40% higher compared to a BW of 95 kg. A 30 mg starting dose is therefore recommended in patients ≤ 60 kg to compensate for the higher melphalan exposure in patients with a lower body weight to reduce the risk for thrombocytopenia.

Melphalan CL increased with increasing eGFR resulting in a melphalan AUC on average 8% higher in patients with a mild renal impairment (eGFR 76 mL/min), 22% higher in patients with moderate renal impairment (eGFR 47 mL/min) and 56% higher in patients with severe renal impairment (eGFR 28 mL/min) compared to patients with normal renal function (eGFR 102 mL/min) based on population PK analysis.

As per the approved SmPC, a starting dose of 30 mg is recommended in patients with eGFR 30-45 mL/min/1.73 m² to compensate for the on average 56% higher melphalan AUC than in patients with normal renal function. There are insufficient data in patients with eGFR below 30 mL/min/1.73 m² to support a dose recommendation.

Overall, sections 4.2 and 5.2 of the SmPC regarding recommended starting dose in subjects with low bodyweight or moderate renal impairment and the PopPK remain the same.

2.3.3. Pharmacodynamics

Mechanism of action

Melphalan flufenamide (melflufen) is an optimized derivative of the classical nitrogen based alkylating agent melphalan. Owing to its high lipophilicity, melflufen freely and rapidly traverse the cell membrane. The rapid inflow of melflufen into cells is followed by rapid enzymatic hydrolysis of the ester/peptide bond leading to molecular trapping and high local concentration of primarily melphalan.

Nitrogen-based alkylating agents like melflufen exert their cytotoxic action through covalent interaction with intracellular nucleophiles, especially DNA, as a result of the spontaneous formation of reactive cyclic aziridinium ion intermediates. Cross-linking of DNA is probably the most important factor for the cytotoxic effect, resulting in inhibitory effects on DNA replication and transcription which subsequently triggers cell death.

Primary and secondary pharmacology

Melphalan flufenamide (melflufen) is an optimized derivative of the classical nitrogen based alkylating agent melphalan. Melphalan has been in clinical use as an antitumor agent for more than 60 years. Owing to its high lipophilicity, melflufen freely and rapidly traverses the cell membrane. The rapid inflow of melflufen into cells is followed by rapid enzymatic hydrolysis of the ester/peptide bond leading to molecular trapping and high local concentration of primarily melphalan.

Nitrogen-based alkylating agents like melflufen exert their cytotoxic action through covalent interaction with intracellular nucleophiles, especially DNA, as a result of the spontaneous formation of reactive cyclic aziridinium ion intermediates. Cross-linking of DNA is probably the most important factor for the cytotoxic effect, resulting in inhibitory effects on DNA replication and transcription which subsequently triggers cell death. The proof of concept for efficacy of melflufen was shown at the time of the marketing authorisation through non-clinical *in vitro* and *in vivo* experiments, and thereby the mode of action was sufficiently demonstrated.

No new PD data has been submitted for this extension of indication application.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics

For this extension of indication of melflufen, the Phase 3 Study OP-103 (Ocean) is the pivotal study. PK data from this study have already been evaluated at the initial marketing authorisation (EMA/H/C/005681/0000). For this application an updated popPK report (ONC0101F-Report Addendum-v1.1-Final, 2022-11-01) has been submitted to describe the pharmacokinetics of melphalan, however, the PK parameters have not been changed compared to those of the initial marketing authorisation.

PD

The proof of concept for efficacy of melflufen was shown at the time of the marketing authorisation through non-clinical *in vitro* and *in vivo* experiments, and thereby the mode of action was sufficiently demonstrated. No new PD data has been submitted for this extension of indication application, which is acceptable.

2.3.5. Conclusions on clinical pharmacology

Pharmacology data from the pivotal Phase 3 study OP-103 have already been evaluated at the initial marketing authorisation (EMA/H/C/005681/0000). No new data have been submitted, which is acceptable.

2.4. Clinical efficacy

Main clinical efficacy data is derived from Phase 3 Study **OP-103** (OCEAN), a randomised, open-label study in patients with relapsed or refractory multiple myeloma (RRMM) following 2 to 4 lines of prior therapies and who were refractory to lenalidomide and the last line of therapy. Key supportive data is derived from single arm trial Phase 2 Study **OP-106** investigating melflufen + dex in RRMM after at least 2 prior lines including an IMiD and PI and refractory to pomalidomide and/or an anti-CD38 mAb.

In addition, data from early terminated Study **OP-108** (LIGHTHOUSE), a randomised Phase 3 study investigating melflufen in combination with daratumumab and dexamethasone vs. daratumumab alone have been presented as supportive clinical data.

2.4.1. Dose response studies

No new dose response studies have been submitted. The proposed posology (similar to the approved posology in fourth line RRMM and to the posology used in pivotal trial OP-103) was selected based on data from Phase 1/2a Study O-12-M1. This study is discussed in detail in the EPAR of the MAA for Pepaxti. In brief, this study was designed to determine the maximum tolerated dose (MTD) of melflufen + dexamethasone (dex) in patients with RRMM and subsequently the efficacy and safety in patients treated at the MTD. In Phase 1 of the study, the MTD was determined at 40 mg melflufen Day 1 of each cycle in combination with 40 mg dexamethasone weekly, based on a total of 4 (66.7%) patients that experienced at least one DLT in the 55 mg cohort.

An additional 45 patients received melflufen + dex at the MTD in Phase 2a of the study, with an overall ORR of 31.1% (n=14). For an additional cohort of 13 patients who received single-agent melflufen, ORR was only 7.7% (n=1), and low dose dex was added back to the treatment regimen.

2.4.2. Main study

Study OP-103 – OCEAN

Randomized, controlled, open-label Phase 3 Study OP-103 investigated melflufen + dex with pomalidomide + dex in patients with relapsed refractory MM who were refractory to lenalidomide.

Methods

Study participants

Key inclusion criteria

- Male or female, age 18 years or older

- Prior diagnosis of multiple myeloma with documented disease progression in need of treatment at time of screening
- Measurable disease defined as any of the following:
 - Serum monoclonal protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP)
 - ≥ 200 mg/24 hours of monoclonal protein in the urine on 24-hour urine electrophoresis (UPEP)
 - Serum free light chain (SFLC) ≥ 10 mg/dL AND abnormal serum kappa to lambda free light chain ratio
- Received 2 to 4 prior lines of therapy including lenalidomide and a PI, either sequential or in the same line, and was refractory (relapsed and refractory or refractory) to both the last line of therapy and to lenalidomide (≥ 10 mg) administered within 18 months prior to randomization (refractory to lenalidomide included patients who relapsed while on lenalidomide therapy or within 60 days of last dose following at least 2 cycles of lenalidomide with at least 14 doses of lenalidomide per cycle)
- Life expectancy of ≥ 6 months
- ECOG performance status ≤ 2
- Females of childbearing potential had a negative pregnancy test or pomalidomide pregnancy prevention plan completed within 10 to 14 days prior to planned start of treatment. All patients had to agree to either commit to continued abstinence from heterosexual intercourse or begin two acceptable methods of birth control.
- 12-lead electrocardiogram (ECG) with corrected QT (QTc) interval calculated by Fridericia Formula (QTcF) interval of ≤ 470 msec
- The following laboratory results must have been met during screening (within 21 days) and also immediately before study drug administration on C1D1 ("inclusion criterion 10"):
 - Absolute neutrophil count (ANC) $\geq 1,000$ cells/mm³ (1.0×10^9 /L) (growth factors could not be used within 10 days prior to first drug administration)
 - Platelet count $\geq 75,000$ cells/mm³ (75×10^9 /L) (without required transfusions during the 10 days prior to first drug administration)
 - Hemoglobin ≥ 8.0 g/dl (red blood cell [RBC] transfusions were permitted)
 - Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), or patients diagnosed with Gilberts syndrome, that were reviewed and approved by the medical monitor
 - Aspartate transaminase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine transaminase/serum glutamic pyruvic transaminase (ALT/SGPT) $\leq 3.0 \times$ ULN
 - Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥ 45 mL/min
- Must be able to take antithrombotic prophylaxis

Key exclusion criteria

- Primary refractory disease (i.e., never responded with $\geq$ MR) to any prior therapy)

- Evidence of mucosal or internal bleeding and/or were platelet transfusion refractory (i.e., platelet count failed to increase by $> 10,000$ cells/mm³ after transfusion of an appropriate dose of platelets)
- Any medical conditions that, in the Investigator's opinion, would have imposed excessive risk to the patient or would have adversely affected his/her participating in this study.
- Prior exposure to pomalidomide
- Known intolerance to IMiDs ($\geq$ Grade 3 hypersensitivity reaction or at the Investigator's discretion)
- Known active infection requiring parenteral or oral anti-infective treatment within 14 days of randomization
- Other malignancy diagnosed or requiring treatment within the past three years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix or breast or very low and low risk prostate cancer in active surveillance
- Pregnant or breast-feeding females
- Serious psychiatric illness, active alcoholism, or drug addiction that may have hindered or confused compliance or follow-up evaluation
- Known human immunodeficiency virus or active hepatitis C viral infection
- Active hepatitis B viral infection
- Concurrent symptomatic amyloidosis or plasma cell leukemia
- POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein [M-protein], and skin changes)
- Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to randomization. The use of live vaccines within 30 days before randomization. IMiDs, PIs, or corticosteroids within 2 weeks prior to randomization. Other investigational therapies and monoclonal antibodies within 4 weeks of randomization. Prednisone up to but no more than 10 mg orally once daily or its equivalent for symptom management of comorbid conditions was permitted but dose should have been stable for at least 7 days prior to randomization
- Residual side effects to previous therapy $>$ Grade 1 prior to randomization (alopecia any grade and/or neuropathy Grade 2 without pain were permitted)
- Prior peripheral stem cell transplant within 12 weeks of randomization
- Prior allogeneic stem cell transplantation with active graft-versus-host-disease
- Prior major surgical procedure or radiation therapy within 4 weeks of randomization
- Known intolerance to steroid therapy

Treatments

Patients were randomized to receive:

- Melflufen 40 mg IV on Day 1 of every 28-Day cycle, or
- Pomalidomide (POM) 4 mg capsules orally on Days 1 to 21 in each 28-Day cycle.

Both treatment arms were administered 40 mg dexamethasone (dex) orally once weekly on Days 1, 8, 15 and 22 of each 28-Day cycle for patients <75 years of age or 20 mg for patients ≥75 years.

Dose modifications, including reductions, and delays for both melflufen and dex were implemented based on patient tolerability.

Patients received treatment until there was documented PD (confirmed on two consecutive assessments), unacceptable toxicity or the patient/treating physician determined it was not in the patient's best interest to continue.

Objectives

The primary objective of this Phase 3 trial was to compare PFS between both treatment arms as assessed by IRC according to IMWG-URC response criteria.

Key secondary objectives were to assess and compare ORR, OS, safety and tolerability in both treatment arms.

Outcomes/endpoints

The primary endpoint was PFS, defined as time (months) from date of randomization to the earlier of confirmed disease progression or death due to any cause. Progression dates were assessed by the IRC using the IMWG-URC.

The key secondary endpoints were:

- ORR, defined as the proportion of patients achieving a best confirmed response of sCR, CR, VGPR, or PR using local laboratory evaluation.
- OS, defined as time (months) from date of randomization to death due to any cause. Patients still alive at end of study, or lost to follow up, were censored at last day known alive.

Other secondary efficacy endpoints were:

Unless stated otherwise, response and progression status were to be assessed by the IRC using the IMWG-URC.

- DOR defined as the time from the first evidence of confirmed assessment of sCR, CR, VGPR, or PR to first confirmed disease progression, or to death due to any cause. Duration of response was defined only for patients with a confirmed PR or better.
- Clinical benefit rate (CBR), i.e., ≥ MR: is the rate of response evaluable patients that achieved a confirmed MR or better.
- TTR defined as the time from the date of randomization to the date of the first documented confirmed response in a patient that had responded with ≥ PR.
- TTP defined as the time from the date of randomization to the date of the first documented confirmed PD.

- Duration of clinical benefit (DOCB) defined as the time from the first evidence of confirmed assessment of sCR, CR, VGPR, PR, or MR to first confirmed disease progression, or to death due to any cause. DOCB was defined only for patients with a confirmed MR or better.
- Best response during the study (sCR, CR, VGPR, PR, MR, SD, or PD) using the IMWG-URC.
- Primary and secondary endpoints as assessed by investigators.

Exploratory endpoints were:

- Proportion of patients with MRD (yes/no) for patients that achieve a CR.
- Value and change from baseline in EORTC QLQ-C30 summary score, each scale of the EORTC QLQ-C30, each scale of the MY20, EQ-5D utility score, each dimension of the EQ-5D, and the VAS of the EQ-5D.
- Maximum post-baseline health related quality of life (HRQoL) scores (EORTC Global Health Status, EORTC summary score, EQ-5D-3L health utility score, EQ VAS).
- Relationship between concurrent IMWG response and time to maximum HRQoL score.

Sample size

The planned sample size was 450 patients based on 90% power with 0.05 two-sided significance level and HR of 0.70 (melflufen + dex/POM+dex), an accrual time of 24 months, ~15% early censor rate and a median PFS of POM+ dex of 3.6 months.

Randomisation

Patients were 1:1 randomized and stratified by age (≥ 75 years of age versus < 75 years of age), number of lines of prior therapy (2 versus 3 to 4 prior lines) and international staging system (ISS) Score (1 versus ≥ 2).

Blinding (masking)

The study was unblinded.

Statistical methods

Analysis sets - The Full analysis set (FAS) was defined as all subjects who were randomized. The Per Protocol (PP) analysis set was defined as all patients who received at least one dose of melflufen, pomalidomide, or dexamethasone, and had a baseline assessment of disease status and at least 1 post-baseline assessment for disease response. Patients who had major protocol deviations, related to critical eligibility criteria, the assessment of efficacy or the safety of the patient that could have significantly impacted the interpretation of study results, were excluded from the Per Protocol analysis set.

Efficacy analysis - The primary analysis of PFS was performed using a log-rank test stratified by the randomization stratification factors to compare treatment group survival distributions based on the FAS. Superiority of melflufen+dex over pomalidomide+dex with respect to the primary endpoints was claimed if the 2-sided p-value was <0.05 favoring melflufen+dex. In addition to a significant p-value for the treatment comparison based on the log-rank test, the superiority of melflufen+dexamethasone

versus pomalidomide+dexamethasone was demonstrated if the upper limit of the 95% CI for the hazard ratio was < 1.0.

Non-inferiority of melflufen+dex versus POM + dex was demonstrated if the upper limit of the 95% CI for the HR was < 1.2.

Multiplicity control - Superiority testing of melflufen+dex over pomalidomide+dex with respect to the key secondary endpoints performed using a gatekeeping procedure based on a closed fixed-sequence test, provided the primary efficacy endpoint comparison was statistically significant at an alpha level 0.05. In case of statistical superiority on the primary endpoint then ORR was tested for statistical superiority. In case of statistical superiority on ORR, then overall survival was tested for statistical superiority.

Interim analysis – No interim analysis were performed. Based on sample size assumptions, the final analysis was to take place when 339 patients had experienced PFS events.

Handling of missing values/censoring/discontinuations - Unconfirmed PD as the final response assessment for PFS was also assessed as confirmed PD and, therefore, an event. PFS was right-censored according to the conventions described in Table 2.

Table 1. Conventions for Censoring of PFS

Situation	Date of Progression or Censoring	Outcome
No post baseline response assessments	Date of randomization	Censored
Non-protocol systemic anticancer therapy started before documentation of PD or death	Date of last response assessment prior to start of new anticancer therapy	Censored
Death or PD after more than 1 consecutively missed response assessment	Date of last response assessment without documentation of PD that is before the first missed visit	Censored
Unconfirmed PD as the final response assessment	Date of latest PD assessment	Progressed
Alive and without PD documentation	Date of last response assessment	Censored
Death or PD between scheduled response assessments	Date of death or preceding response assessment showing PD, whichever occurs first	Progressed
Death before first response assessment	Date of death	Progressed

PD = disease progression; PFS = progression-free survival

Results

Participant flow

A total of 495 patients were randomized in the study. Of these, 21 patients were randomized, but not treated; 18 patients randomized to melflufen+dex and 3 patients randomized to pom+dex. The most common reasons were low laboratory values in both treatment arms.

Approximately 18% of patients were still receiving treatment as of the data cut-off (3 Feb 2021).

The most common reason for treatment discontinuation was progressive disease (n=257, 54.2%), followed by adverse event (n=73, 15.4%; Table 3; Figure 2).

Table 2. Summary of Patient Disposition

	Melflufen+Dexamethasone N=246 n (%)	Pomalidomide+Dexamethasone N=249 n (%)	Overall N=495 n (%)
Number of screened patients in the Enrolled Analysis Set ^a	—	—	644
Number of screen failures	—	—	149
Number of randomized patients in the Full Analysis Set ^b	246	249	495
Number of patients randomized not treated	18	3	21
Number of treated patients in the Safety Analysis Set ^c	228 (92.7%)	246 (98.8%)	474 (95.8%)
Number of treated patients in the Per Protocol Analysis Set ^d	218 (88.6%)	236 (94.8%)	454 (91.7%)
Number of treated patients in the PRO Analysis Set ^e	77 (31.3%)	81 (32.5%)	158 (31.9%)
Number of treated patients in the PK Analysis Set ^f	224 (91.1%)	—	224 (45.3%)
Treatment Status ^g			
Ongoing	42 (18.4%)	46 (18.7%)	88 (18.6%)
Discontinued	186 (81.6%)	200 (81.3%)	386 (81.4%)
Primary reason for treatment discontinuation			
Progressive disease	116 (50.9%)	141 (57.3%)	257 (54.2%)
Adverse event	38 (16.7%)	35 (14.2%)	73 (15.4%)
Lack of efficacy	6 (2.6%)	8 (3.3%)	14 (3.0%)
Physician decision	17 (7.5%)	9 (3.7%)	26 (5.5%)
Withdrawal by patient	9 (3.9%)	6 (2.4%)	15 (3.2%)
Lost to follow up	0	1 (0.4%)	1 (0.2%)
Number of treated patients in PFS follow-up ^g	10 (4.4%)	1 (0.4%)	11 (2.3%)
Number of treated patients in OS follow-up ^g	70 (30.7%)	82 (33.3%)	152 (32.1%)
Study Status			
Ongoing	126 (51.2%)	129 (51.8%)	255 (51.5%)
Discontinued	120 (48.8%)	120 (48.2%)	240 (48.5%)
Primary reason for study discontinuation ^h			
Death	116 (47.2%)	108 (43.4%)	224 (45.3%)
Lost to follow-up	1 (0.4%)	2 (0.8%)	3 (0.6%)
Withdrawal by patient	3 (1.2%)	10 (4.0%)	13 (2.6%)

OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PRO = patient-reported outcomes.

^a The Enrolled Analysis Set was defined as all patients who were assigned a unique patient number by Interactive Response Technology system at the time of enrollment (signing of consent).

^b The Full Analysis Set was defined as all randomized patients.

^c The Safety Analysis Set was defined as all patients who received at least one dose of melflufen, pomalidomide, or dexamethasone.

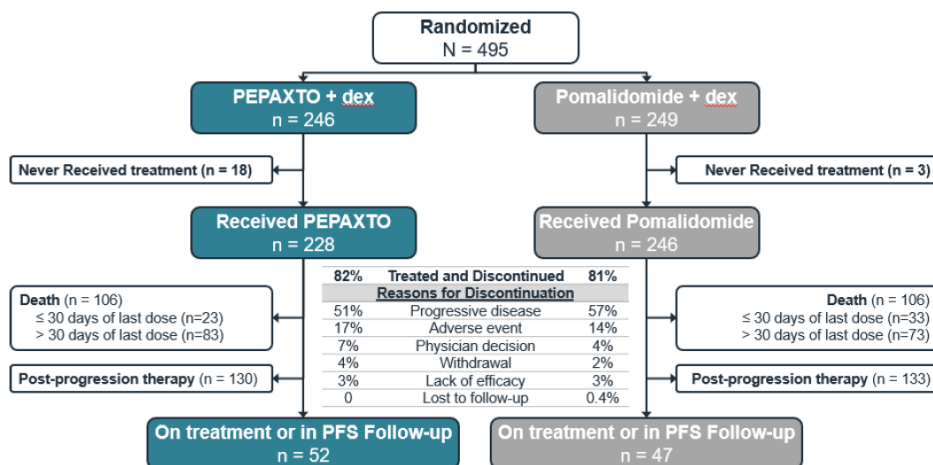
^d The Per Protocol Analysis Set was defined as all patients who received at least one dose of melflufen, pomalidomide, or dexamethasone, and had a baseline assessment of disease status and at least one post-baseline assessment for disease response. Patients with major protocol deviations, related to critical eligibility criteria, the assessment of efficacy or the safety that could significantly impact the interpretation of study results, were excluded from the Per Protocol Analysis Set.

^e The PRO Analysis Set was defined as all patients who enrolled on or after protocol version 4.1 and had completed the same PRO questionnaire at baseline and post-baseline.

^f The PK Analysis Set was defined as all patients in the Full Analysis Set who received at least 1 dose of melflufen and had 3 samples with measurable concentrations in at least one treatment cycle.

^g Percentage calculations used the Safety Analysis Set as denominator.

^h Patients reporting more than one screen failure reason were counted more than once.

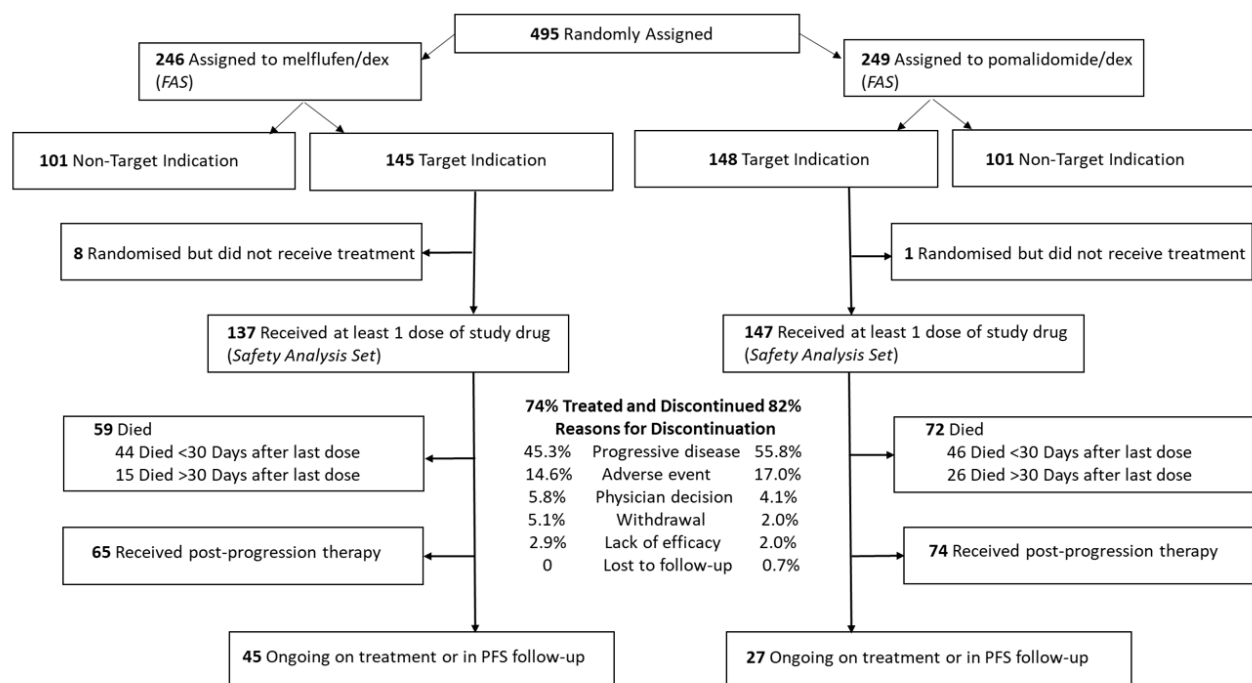


Abbreviations: dex dexamethasone; PFS progression-free survival.
PEPAXTO=melflufen.

Figure 2. Study OP-103 – Patient Disposition

Similar to the approved indication, the proposed extension of indication reflects the time to progression of at least 36 months after ASCT post-hoc defined subgroup of the overall study population. Of the 495 patients in Study OP-103, 145 patients in the melflufen+dex arm and 148 patients in the pomalidomide+dex arm had no prior ASCT or had progressed >36 months after ASCT, and comprised the target indication population, while 101 patients in each of the melflufen+dex and the pomalidomide+dex arms had a prior ASCT with progression <36 months following the transplant (Figure 3).

Compared with the overall population in Study OP-103, a lower percentage of melflufen+dex treated patients in the target indication discontinued treatment (74% vs. 82%) and discontinued treatment due to progressive disease (45% vs. 51%). These proportions were similar in the pomalidomide + dex arm. The reasons for discontinuation remained more or less similar in both treatment arms.



Abbreviations: Dex dexamethasone; FAS Full Analysis Set; PFS Progression-free survival
Note. Target indication includes patients who had no ASCT or progressed >36 months after an ASCT

Figure 3. Study OP-103 – Disposition of Patients in the Target Indication

Recruitment

The first patient was enrolled to initiate study treatment in June 2017. The last patient enrolled in September 2020.

Conduct of the study

The original protocol (version 1.1) was approved on 07 Dec 2016. There were 5 protocol amendments. Key changes pertained to a change of inclusion criteria 4 to allow patients that received lenalidomide and a proteasome inhibitor during the first line of therapy and were refractory to lenalidomide in the first line to potentially enroll in the study to improve accrual; addition of PRO as exploratory endpoint; and an increase in number of sites to ~100 as well as added Asia/Pacific region.

Changes to the planned analyses per the protocol were made in Apr and Jun 2021, following FDA feedback. Key changes pertained to: primary endpoint based on stratified log-rank test; DOR moved from key to other secondary endpoint removing it from multiplicity assessment; addition of 'time from prior ASCT to randomization subgroup analysis' for PFS, ORR and OS as well as imputation rules for this subgroup.

Protocol deviations

Overall, a total of 154 major protocol deviations were identified during the study as of the data cutoff: 61 deviations related to study procedure or assessment (Table 4).

Table 3. Major Protocol Deviations

Deviation Category	Melphalan Flufenamide + Dexamethasone (N=246)	Pomalidomide + Dexamethasone (N=249)	Overall (N=495)
Study Procedure or Assessment	38 (15.4%)	23 (9.2%)	61 (12.3%)
Study Medication	21 (8.5%)	14 (5.6%)	35 (7.1%)
Other: GCP	7 (2.8%)	12 (4.8%)	19 (3.8%)
Inclusion/Exclusion Criteria	6 (2.4%)	7 (2.8%)	13 (2.6%)
Randomization Procedure	7 (2.8%)	2 (0.8%)	9 (1.8%)
Excluded Concomitant Medication	2 (0.8%)	6 (2.4%)	8 (1.6%)
Withdrawal Criteria	3 (1.2%)	1 (0.4%)	4 (0.8%)
Other: Source Documentation	2 (0.8%)	1 (0.4%)	3 (0.6%)
Informed Consent	2 (0.8%)	0	2 (0.4%)

Baseline data – Overall study population

Demographics

Of the 495 patients in the FAS, the median age (years) was 68.0 years (Table 5). Approximately 36% of patients were <65 years of age. There were slightly more male than female patients (56.4% vs 43.6%) and 90.1% of patients were white. Around 90% of patients had ECOG 0 or 1.

Table 4. Demographics and Baseline Characteristics (FAS)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide + Dexamethasone N=249	Overall N=495
Age (years) ^a			
n	246	249	495
Mean (SD)	66.1 (8.98)	66.5 (8.83)	66.3 (8.89)
Median	68.0	68.0	68.0
Min, max	41, 91	39, 87	39, 91
Age category (years), n (%)			
< 65 years	96 (39.0%)	85 (34.1%)	181 (36.6%)
65 to <75 years	113 (45.9%)	125 (50.2%)	238 (48.1%)
≥75 years	37 (15.0%)	39 (15.7%)	76 (15.4%)
Sex, n (%)			
Male	139 (56.5%)	140 (56.2%)	279 (56.4%)
Female	107 (43.5%)	109 (43.8%)	216 (43.6%)
Race, n (%)			
Asian	8 (3.3%)	13 (5.2%)	21 (4.2%)
Black or African American	4 (1.6%)	4 (1.6%)	8 (1.6%)
White	224 (91.1%)	222 (89.2%)	446 (90.1%)
Other	1 (0.4%)	0	1 (0.2%)
Unknown	9 (3.7%)	9 (3.6%)	18 (3.6%)
Not Reported	0	1 (0.4%)	1 (0.2%)
Ethnicity, n (%)			
Hispanic or Latino	8 (3.3%)	5 (2.0%)	13 (2.6%)
Not Hispanic or Latino	232 (94.3%)	237 (95.2%)	469 (94.7%)
Not reported	6 (2.4%)	7 (2.8%)	13 (2.6%)
Baseline ^b ECOG Performance Status ^c , n (%)			
0	90 (36.6%)	92 (36.9%)	182 (36.8%)
1	130 (52.8%)	136 (54.6%)	266 (53.7%)
2	26 (10.6%)	21 (8.4%)	47 (9.5%)

ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; Max = maximum; Min = minimum;
SD = standard deviation

^a Age was calculated relative to the date of informed consent.

^b Baseline was defined as the most recent assessment prior to administration of the first dose of study drug.

^c For ECOG Performance Status: 0 – Fully active, able to carry on all predisease performance without restriction;
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature,
e.g., light housework, office work; 2 - Ambulatory and capable of all self-care but unable to carry out any work
activities. Up and about more than 50% of waking hours.

Disease Characteristics

The median time since initial diagnosis was close to 4 years in both arms (Table 6). At study entry, most patients had ISS stage I (49.1%) or II (38%) and extramedullary disease was present in 12.5%. Bone lesions were present in slightly fewer patients in the melflufen+ dex arm (74.8%) compared to the pom+dex arm (82.7%). Other disease characteristics at study entry were generally consistent between treatment arms.

Table 5 Selected Myeloma Disease Characteristics at Study Entry and Baseline (FAS)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide +Dexamethasone N=249	Overall N=495
Time since initial diagnosis, years ^a			
N	246	249	495
Mean (SD)	4.88 (3.542)	4.82 (3.424)	4.85 (3.480)
Median (Min, Max)	3.98 (0.5, 26.3)	3.88 (0.4, 25.2)	3.93 (0.4, 26.3)
ISS stage at study entry, n (%)			
I	119 (48.4%)	124 (49.8%)	243 (49.1%)
II	94 (38.2%)	94 (37.8%)	188 (38.0%)
III	33 (13.4%)	31 (12.4%)	64 (12.9%)
R-ISS stage of disease at study entry, n (%)			
R-I	69 (28.0%)	69 (27.7%)	138 (27.9%)
R-II	129 (52.4%)	138 (55.4%)	267 (53.9%)
R-III	24 (9.8%)	17 (6.8%)	41 (8.3%)
Unknown/missing	24	25	49
Bone lesions present at study entry			
Yes	184 (74.8%)	206 (82.7%)	390 (78.8%)
No	62 (25.2%)	43 (17.3%)	105 (21.2%)
Extramedullary disease present at study entry			
Yes	31 (12.6%)	31 (12.4%)	62 (12.5%)
No	215 (87.4%)	218 (87.6%)	433 (87.5%)
Type of measurable disease at Baseline ^b			
SPEP and UPEP	48 (19.5%)	57 (22.9%)	105 (21.2%)
SPEP only	140 (56.9%)	128 (51.4%)	268 (54.1%)
UPEP only	37 (15.0%)	36 (14.5%)	73 (14.7%)
sFLC only	21 (8.5%)	28 (11.2%)	49 (9.9%)
Baseline SPEP M-Spike (g/dL) ^b			
n	245	248	493
Mean (SD)	18.35 (14.877)	19.07 (16.495)	18.71 (15.700)
Median (Min, Max)	17.00 (0.0, 71.0)	17.00 (0.0, 68.8)	17.00 (0.0, 71.0)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide +Dexamethasone N=249	Overall N=495
Baseline UPEP M-Spike (mg/day) ^b			
n	241	247	488
Mean (SD)	588.3 (1604.36)	525.7 (1068.14)	556.6 (1358.60)
Median (Min, Max)	70.0 (0, 17016)	50.0 (0, 7991)	60.0 (0, 17016)
Cytogenetic risk group based on FISH at study entry			
High	83 (33.7%)	86 (34.5%)	169 (34.1%)
Standard	128 (52.0%)	130 (52.2%)	258 (52.1%)
Unknown	35 (14.2%)	33 (13.3%)	68 (13.7%)
Patients with two or more high-risk abnormalities, n (%)			
Yes	24 (9.8%)	25 (10.0%)	49 (9.9%)
No	201 (81.7%)	205 (82.3%)	406 (82.0%)
Missing	21	19	40
Patients with deletion 17p, n (%)	33 (13.4%)	37 (14.9%)	70 (14.1%)
Heavy-light chain combination at study entry			
IgA-Kappa	33 (13.4%)	29 (11.6%)	62 (12.5%)
IgA-Lambda	15 (6.1%)	18 (7.2%)	33 (6.7%)
IgA; IgG-Kappa	0	2 (0.8%)	2 (0.4%)
IgA; IgG; IgM-Kappa	1 (0.4%)	0	1 (0.2%)
IgA; IgG; IgM-Lambda	2 (0.8%)	0	2 (0.4%)
IgA; IgM-Kappa	1 (0.4%)	0	1 (0.2%)
IgA; IgM-Lambda	1 (0.4%)	0	1 (0.2%)
IgD-Kappa	1 (0.4%)	1 (0.4%)	2 (0.4%)
IgD-Lambda	1 (0.4%)	1 (0.4%)	2 (0.4%)
IgG-Biclonal	1 (0.4%)	0	1 (0.2%)
IgG-Kappa	99 (40.2%)	98 (39.4%)	197 (39.8%)
IgG-Lambda	48 (19.5%)	53 (21.3%)	101 (20.4%)
IgG; IgE-Kappa	0	1 (0.4%)	1 (0.2%)
IgG; IgM-Kappa	1 (0.4%)	0	1 (0.2%)
IgM-Kappa	4 (1.6%)	1 (0.4%)	5 (1.0%)
IgM-Lambda	1 (0.4%)	0	1 (0.2%)
None-Kappa	22 (8.9%)	25 (10.0%)	47 (9.5%)
None-Lambda	15 (6.1%)	20 (8.0%)	35 (7.1%)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide +Dexamethasone N=249	Overall N=495
Baseline Kappa/Lambda FLC ratio ^b			
N	245	249	494
Mean (SD)	270.804 (1186.2441)	185.769 (554.5585)	227.942 (923.5617)
Median (Min, Max)	9.833 (0.00, 14222.22)	6.02 (0.00, 5430.23)	8.03 (0.00, 14222.22)

FAS = Full Analysis Set; FISH = fluorescence in situ hybridization; FLC = free light chain; Ig = immunoglobulin;

Max = maximum; Min = minimum; (R-)ISS = (Revised-) International Staging System; SD = standard deviation;

sFLC = serum free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

Note: The Multiple Myeloma History CRF at Diagnosis CRF and the Multiple Myeloma History CRF at Study Entry CRF were used where "at Diagnosis" and "at Study Entry" were indicated, respectively.

^a Time since initial diagnosis was calculated relative to first dose of study drug.

^b Baseline labs were defined as the most recent assessment prior to administration of the first dose of study drug.

Source: [Table 14.1-8](#)

Prior treatment

The median number of prior regimens was 3.0 (Table 7). The most common prior regimens contained PIs and IMiDs (100%, each), alkylators (86.9%), mAbs (21.0%), and other (99.8%). Dexamethasone was counted as 'other' therapy and represents the majority of this category.

Table 6. Prior treatment for MM (FAS)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide + Dexamethasone N=249	Overall N=495
Patients with at least 1 prior radiotherapy, n (%)	60 (24.4%)	71 (28.5%)	131 (26.5%)
Patients with at least 1 prior autologous transplant, n (%)	125 (50.8%)	120 (48.2%)	245 (49.5%)
Mean (SD)	1.3 (0.46)	1.3 (0.47)	1.3 (0.47)
Median (Min, Max)	1.0 (1, 2)	1.0 (1, 3)	1.0 (1, 3)
Total number of prior autologous transplants per patient			
1	88 (35.8%)	86 (34.5%)	174 (35.2%)
2	37 (15.0%)	33 (13.3%)	70 (14.1%)
3	0	1 (0.4%)	1 (0.2%)
Time from autologous transplant to randomization, n			
<5 years	91	86	177
<2.5 years	43	35	78
2.5 to 5 years	48	51	99
>5 years	34	34	68
No autologous transplant	121	129	250
Time from front line transplant to relapse (years) ^a			
n	63	64	127
Mean (SD)	2.69 (2.660)	2.33 (1.815)	2.51 (2.272)
Median (Min, Max)	1.89 (0.1, 15.0)	1.82 (0.1, 9.0)	1.85 (0.1, 15.0)
<1 year	13 (20.6%)	15 (23.4%)	28 (22.0%)
1 to <1.5 years	8 (12.7%)	12 (18.8%)	20 (15.7%)
1.5 to 2 years	14 (22.2%)	10 (15.6%)	24 (18.9%)
>2 years	28 (44.4%)	27 (42.2%)	55 (43.3%)
Patients with at least 1 prior allogeneic transplant, n (%)	3 (1.2%)	0	3 (0.6%)
Number of prior regimens			
Mean (SD) number of prior regimens per patient	2.8 (0.80)	2.7 (0.76)	2.8 (0.78)
Median (Min, Max) number of prior regimens per patient	3.0 (2, 4)	3.0 (2, 4)	3.0 (2, 4)
Total number of prior regimens per patient			
2	114 (46.3%)	111 (44.6%)	225 (45.5%)
3	76 (30.9%)	90 (36.1%)	166 (33.5%)
4	56 (22.8%)	48 (19.3%)	104 (21.0%)
Patients exposed to standardized drug group/therapy in at least one prior regimen, n (%) ^b			
Alkylators	217 (88.2%)	213 (85.5%)	430 (86.9%)
Monoclonal antibodies	54 (22.0%)	50 (20.1%)	104 (21.0%)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide + Dexamethasone N=249	Overall N=495
IMiD	246 (100%)	249 (100%)	495 (100%)
PI	246 (100%)	249 (100%)	495 (100%)
Other ^c	246 (100%)	248 (99.6%)	494 (99.8%)
Dexamethasone	243 (98.8%)	245 (98.4%)	488 (98.6%)
Patients exposed to standardized drug group/therapy in most recent prior regimen, n (%) ^b			
Alkylators	27 (11.0%)	30 (12.0%)	57 (11.5%)
Monoclonal antibodies	42 (17.1%)	39 (15.7%)	81 (16.4%)
IMiD	215 (87.4%)	218 (87.6%)	433 (87.5%)
PI	95 (38.6%)	91 (36.5%)	186 (37.6%)
Other ^c	230 (93.5%)	231 (92.8%)	461 (93.1%)
Dexamethasone	216 (87.8%)	220 (88.4%)	436 (88.1%)
Patients refractory to standardized drug group/therapy in at least 1 prior regimen, n (%) ^b			
Alkylators	78 (31.7%)	75 (30.1%)	153 (30.9%)
Monoclonal antibodies	51 (20.7%)	49 (19.7%)	100 (20.2%)
IMiD	245 (99.6%)	249 (100%)	494 (99.8%)
PI	163 (66.3%)	163 (65.5%)	326 (65.9%)
Other ^c	237 (96.3%)	233 (93.6%)	470 (94.9%)
Dexamethasone	226 (91.9%)	225 (90.4%)	451 (91.1%)
Patients refractory to standardized drug group/therapy in most recent prior regimen, n (%) ^b			
Alkylators	10 (4.1%)	13 (5.2%)	23 (4.6%)
Monoclonal antibodies	41 (16.7%)	39 (15.7%)	80 (16.2%)
IMiD	214 (87.0%)	218 (87.6%)	432 (87.3%)
PI	76 (30.9%)	72 (28.9%)	148 (29.9%)
Other ^c	216 (87.8%)	214 (85.9%)	430 (86.9%)
Dexamethasone	203 (82.5%)	206 (82.7%)	409 (82.6%)
Best response for most recent prior regimen			
Stringent Complete Response	1 (0.4%)	1 (0.4%)	2 (0.4%)
Complete Response	19 (7.7%)	17 (6.8%)	36 (7.3%)
Very Good Partial Response	50 (20.3%)	54 (21.7%)	104 (21.0%)
Partial Response	91 (37.0%)	89 (35.7%)	180 (36.4%)
Minimal Response	18 (7.3%)	19 (7.6%)	37 (7.5%)
Stable Disease	35 (14.2%)	39 (15.7%)	74 (14.9%)
Progressive Disease	27 (11.0%)	21 (8.4%)	48 (9.7%)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide + Dexamethasone N=249	Overall N=495
Unknown	4 (1.6%)	7 (2.8%)	11 (2.2%)
Best response for second most recent prior regimen			
Stringent Complete Response	2 (0.8%)	4 (1.6%)	6 (1.2%)
Complete Response	32 (13.0%)	36 (14.5%)	68 (13.7%)
Very Good Partial Response	71 (28.9%)	76 (30.5%)	147 (29.7%)
Partial Response	83 (33.7%)	80 (32.1%)	163 (32.9%)
Minimal Response	13 (5.3%)	11 (4.4%)	24 (4.8%)
Stable Disease	30 (12.2%)	24 (9.6%)	54 (10.9%)
Progressive Disease	8 (3.3%)	10 (4.0%)	18 (3.6%)
Unknown	6 (2.4%)	7 (2.8%)	13 (2.6%)

FAS = Full Analysis Set; IMiD = immunomodulatory drug; Max = maximum; Min = minimum; PI = proteasome inhibitor; SD = standard deviation.

^a Front-line transplant occurred within the first regimen of therapy from start of first dose of antineoplastic therapy prior to, or on the date of last dose of therapy within the first regimen.

^b At each level of summarization (Standardized Drug Group, Therapy), patients reporting more than one medication were counted only once.

^c Dexamethasone was counted as an 'other' therapy and represents the majority of this category.

Refractory status

Almost all patients (>99%) had received at least 2 prior lines of therapy, were refractory to the most recent prior regimen, and refractory to lenalidomide (Table 7, Table 8). All 495 patients (100%) in the FAS were double-class exposed, defined as patients who had received an IMiD and PI, and 89 patients (18.0%) were triple-class exposed, defined as patients who had received an IMiD, a PI, and an anti-CD38 mAb. Of the 89 patients who were triple class exposed, 69 patients (14%) were triple class refractory.

Table 7. Refractory Status (FAS)

Refractory Status	Melflufen + Dexamethasone N=246 n (%)	Pomalidomide + Dexamethasone N=249 n (%)	Overall N=495 n (%)
Refractory to most recent prior regimen	245 (99.6%)	247 (99.2%)	492 (99.4%)
Refractory to lenalidomide in last line	213 (86.6%)	217 (87.1%)	430 (86.9%)
Refractory to lenalidomide within 18 months of randomization by dose *	245 (99.6%)	248 (99.6%)	493 (99.6%)
Refractory to 25 mg	159 (64.6%)	165 (66.3%)	324 (65.5%)
Refractory to <25 mg	81 (32.9%)	77 (30.9%)	158 (31.9%)
Refractory to dose unknown	5 (2.0%)	6 (2.4%)	11 (2.2%)
Refractory to prior alkylator	78 (31.7%)	75 (30.1%)	153 (30.9%)
Refractory or intolerant to prior IMiD	245 (99.6%)	249 (100%)	494 (99.8%)
Refractory to prior IMiD	245 (99.6%)	249 (100%)	494 (99.8%)
Refractory or intolerant to prior PI	177 (72.0%)	172 (69.1%)	349 (70.5%)
Refractory to prior PI	163 (66.3%)	163 (65.5%)	326 (65.9%)
Refractory and/or intolerant to prior anti-CD38 mAb	48 (19.5%)	39 (15.7%)	87 (17.6%)
Refractory to prior anti-CD38 mAb	48 (19.5%)	39 (15.7%)	87 (17.6%)
Received an IMiD and PI (double-class exposed)	246 (100%)	249 (100%)	495 (100%)
Number of patients with double-class refractory disease	162 (65.9%)	163 (65.5%)	325 (65.7%)
Received an IMiD, PI, and anti-CD38 mAb (triple-class exposed)	49 (19.9%)	40 (16.1%)	89 (18.0%)
Number of patients with triple-class refractory disease	39 (15.9%)	30 (12.0%)	69 (13.9%)
Patients refractory to at least 1 component of most recent prior regimen	245 (99.6%)	247 (99.2%)	492 (99.4%)

FAS = Full Analysis Set; IMiD = immunomodulatory drug; mAb = monoclonal antibody; PI = proteasome inhibitor.

* Number (%) of subjects who are refractory to lenalidomide 25 mg vs. lenalidomide < 25 mg (10 mg or 15 mg) during last (most recent) line of prior therapy or administered within 18 months prior to randomization.

Subsequent therapy

At this time, a total of 140 patients (56.9%) in the melflufen+dex group and 135 patients (54.2%) in the pom+dex group received subsequent therapy. In the melflufen+dex group, the most commonly received subsequent therapies were IMiDs (26.4%) and PIs (23.2%) followed by anti-CD38s (16.3%) and alkylators (8.1%; Table 9). In the pom+dex group, the most commonly received subsequent therapies were anti-CD38s (26.9%]) and PIs (26.1%) followed by alkylators (12.0%) and IMiDs (9.6%).

Table 8. Subsequent therapy (FAS)

	Melflufen+Dexamethasone N=246 n (%)	Pomalidomide+Dexamethasone N=249 n (%)
Any subsequent therapy	140 (56.9%)	135 (54.2%)
Alkylator	20 (8.1%)	30 (12.0%)
Cyclophosphamide	17 (6.9%)	15 (6.0%)
Melfhalan	0	10 (4.0%)
Melflufen	0	1 (0.4%)
Anti-CD38	40 (16.3%)	67 (26.9%)
Daratumumab	40 (16.3%)	65 (26.1%)
Isatuximab	0	2 (0.8%)
IMiD	65 (26.4%)	24 (9.6%)
Pomalidomide	50 (20.3%)	4 (1.6%)
Lenalidomide	12 (4.9%)	15 (6.0%)
Thalidomide	3 (1.2%)	3 (1.2%)
PI	57 (23.2%)	65 (26.1%)
Bortezomib	30 (12.2%)	38 (15.3%)
Carfilzomib	21 (8.5%)	24 (9.6%)
Ixazomib	6 (2.4%)	3 (1.2%)

FAS = Full Analysis Set; IMiD = immunomodulatory drug; PI = protease inhibitor.

Baseline data target indication

Demographics

Compared with the overall study population of Study OP-103, the population of patients who had no prior ASCT or had progressed >36 months after ASCT, i.e. the target indication, were slightly older (median 71 years vs 68 years in the full study population) and had had fewer prior treatment regimens (median 2 regimens, compared with median 3 regimens in the full study population).

As shown in the previous tables for the overall study population, almost all patients (>99%; and thereby also in this subgroup) had received at least 2 prior lines of therapy and were refractory to the most recent prior regimen. All patients of the target indication population were refractory to lenalidomide.

Demographic and disease characteristics for the target indication population are presented in Table 10.

Table 9. Demographic and Disease Characteristics in Patients who had no ASCT or Progressed >36 Months after an ASCT in Study OP-103 (Target Indication Analyses)

Parameter	<u>Melflufen+dex</u> N=145	<u>Pomalidomide+dex</u> N=148
Median years from diagnosis to start of study treatment (range)	3.5 (0.5-26.3)	3.6 (0.6-25.2)
Prior treatment regimens, median (range)	2 (2-4)	2 (2-4)
Age, median (range)	71 (46-91)	71 (47-87)
Patients <65 years of age, n (%)	41 (28.3)	30 (20.3)
Patients 65-74 years of age, n (%)	69 (47.6)	80 (54.1)
Patients ≥75 years of age, n (%)	35 (24.1)	38 (25.7)
Documented refractory status, n (%)		
Lenalidomide	145 (100)	148 (100)
Pomalidomide	0 (0)	0 (0)
Bortezomib	67 (46)	86 (58)
Carfilzomib	17 (12)	16 (11)
Daratumumab	21 (14)	20 (14)
Alkylator refractory	54 (37)	53 (36)
Melphalan exposed	53 (37)	54 (36)
Melphalan refractory	14 (10)	23 (16)
Previous stem cell transplant, n (%)	24 (17)	19 (13)
ECOG at baseline, n (%)		
0	54 (37)	45 (30)
1	74 (51)	89 (60)
2	17 (12)	14 (9)
3	0	0
International Staging System at Baseline, n (%)		
I	64 (44)	62 (42)
II	60 (41)	63 (43)
III	21 (14)	23 (16)
Missing/Unknown	0	0
High-risk <u>cytogenetics</u> ^a , n (%)	42 (29)	48 (32)
Extramedullary disease (EMD), n (%)	12 (8)	15 (10)

Abbreviations Dex dexamethasone; ECOG Eastern Cooperative Oncology Group

^a del(17p), t(4;14), t(14;16), gain (1q) and t(14;20)

Numbers analysed

The first patient initiated study treatment in Jun 2017. Due to a slower than expected enrolment rate, the event rate in the study was lower than projected and, therefore, enrolment was extended and more patients were randomized to the study than originally planned.

In total of 495 patients were included in the FAS: 246 patients were randomized to the melflufen+dex group and 249 patients to pom + dex.

In total 454 patients were included in the PP analysis set.

In total 293 patients represented a post-hoc defined subgroup of patients who had no prior ASCT or had progressed >36 months after ASCT, and comprised the target indication population.

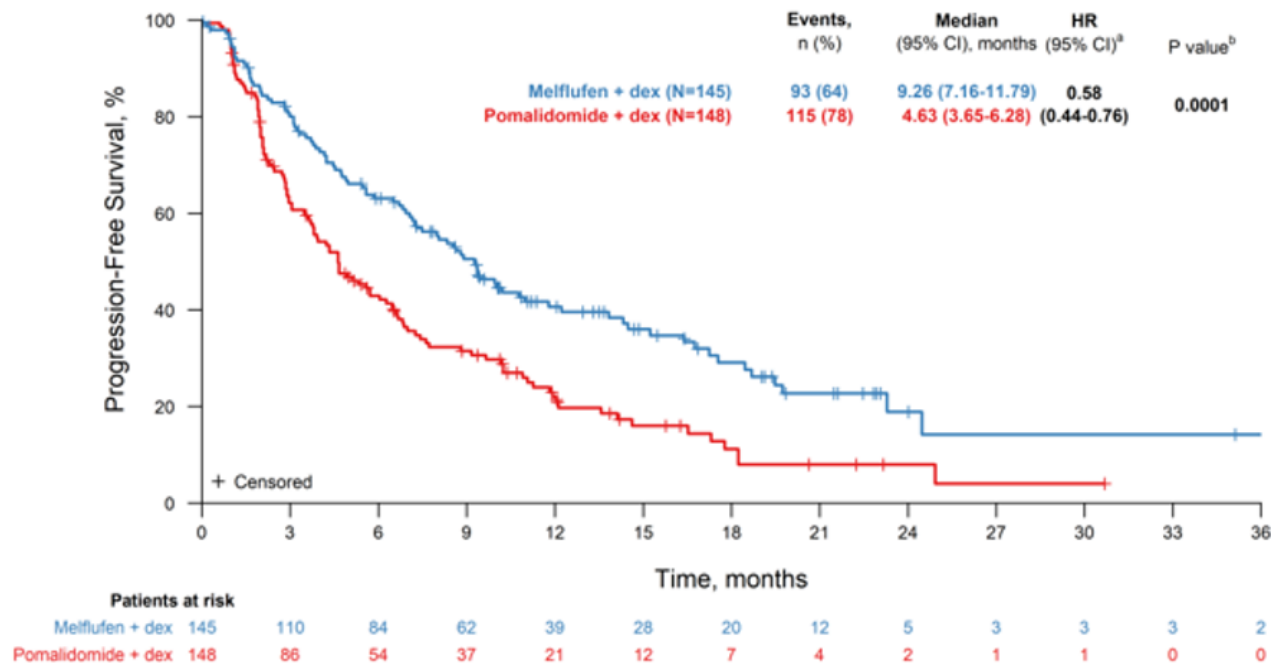
Outcomes and estimation

Data cut-off 3 Feb 2021

Primary endpoint – PFS

Overall study population - The primary endpoint PFS was met for the overall study population (FAS). The median IRC assessed PFS was 6.83 (95% CI 4.96, 8.54) in the melflufen + dex arm vs. 4.93 (95% CI 4.24, 5.72) in the pom + dex arm. The stratified HR was 0.792 (95% CI: 0.640, 0.981; $p=0.0319$). The median PFS follow-up duration was 15.5 months (95% CI: 13.3, 19.4) in the melflufen+dex group and 16.3 months (95% CI: 12.1, 21.3) in the pomalidomide+dex group.

Target indication – Patients treated with melflufen+dex and no prior ASCT or disease progression >36 months after ASCT had a median PFS of 9.26 months (95% CI 7.16-11.79) compared with for 4.63 months (95% CI: 3.65, 6.28) in the corresponding patients treated with pomalidomide+dex (HR 0.577; 95% CI: 0.438; 0.760; nominal $p=0.0001$). A Kaplan-Meier-plot of PFS in the target indication population is presented in Figure 4.



Abbreviations: CI confidence interval; Dex dexamethasone; HR hazard ratio; IRC Independent Review Committee; PFS progression-free survival.

^a Hazard ratio from an unstratified Cox regression model

^b..Unstratified log-rank test

Figure 4. Study OP-103: Kaplan-Meier plot of PFS based on IRC Assessment (Target Indication Analyses)

Subgroup analyses - FAS

A HR for PFS >1 was observed for the subgroups of patients with prior ASCT, refractory to anti-CD38 mAb, EMD at baseline, age <65, Creatinine clearance <45 ml/min or ≥90 ml/min and ≥1.5x ULN LDH (data not shown).

Subgroup analyses - target indication

PFS subgroup analyses in the target indication population show HR point estimates in favour of melflufen + dex in all subgroups, except for the small subgroup of patients with LDH ≥1.5 ULN (Figure 5).

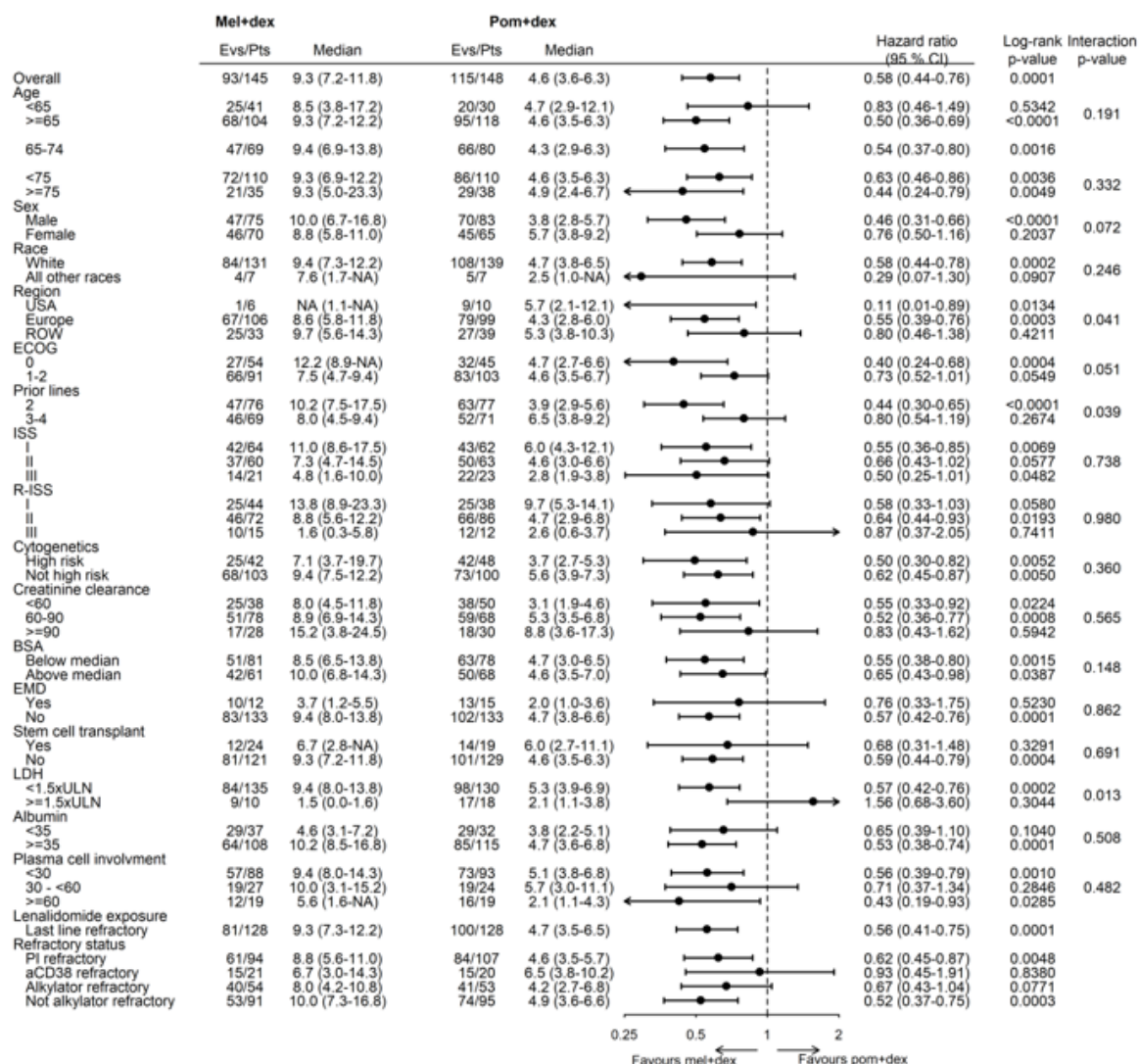


Figure 5. PFS – unstratified HR by subgroup (data cut-off 03-02-2021)

Sensitivity analyses

The results for PFS based on Investigator assessment of the FAS and IRC assessment of the Per Protocol analysis set were consistent with the PFS based on IRC assessment of the FAS.

Key secondary endpoints

ORR

Overall study population - Based on IRC assessment for the FAS, key secondary endpoint ORR was not met. In total 80 patients out of 246 in the melflufen+dex group had a best response of PR or better for an overall confirmed response rate of 32.5% (95% CI: 26.71%, 38.76%) and 67 out of 249 patients in the pomalidomide+dex group had an overall confirmed response rate of 26.9% (95% CI: 21.50%, 32.87%). This difference was not significant (stratified p=0.1422).

Target indication - The ORR in the target indication population was 42.1% (95% CI:33.9%, 50.5%) for melflufen+dex and 26.4% (95% CI:19.5%, 34.2%) for pomalidomide+dex (Table 11). Compared with the pomalidomide+dex treated patients, a numerical higher percentage of melflufen+dex treated patients achieved CR (4.8% vs 1.4%), VGPR (13.8% vs 6.8%) and PR (23.4% vs 18.2%).

Table 10. Overall Response Rate in patients who had no ASCT or progressed >36 months after an ASCT in Study OP-103 (Target Indication Analyses).

	Melflufen+dex N=145	Pomalidomide+dex N=148
Overall response rate (ORR)		
sCR+CR+VGPR+PR, n (%)	61 (42.1)	39 (26.4)
95% CI (%)	(33.9-50.5)	(19.5-34.2)
p-value (unstratified)	0.0046	
Stringent complete response (sCR)	0 (0.0)	0 (0.0)
Complete response (CR)	7 (4.8)	2 (1.4)
Very good partial response (VGPR)	20 (13.8)	10 (6.8)
Partial response (PR)	34 (23.4)	27 (18.2)

Abbreviations: ASCT Autologous stem cell transplant; CI Confidence interval; CR complete response; NE Not evaluable; PR partial response; sCR stringent complete response; VGPR very good partial response.

OS

Overall study population - The other key secondary endpoint OS was also not met for the FAS and suggested a detriment for the melflufen arm. The results of the OS analysis in the FAS as assessed by the Investigator at the time of the data cutoff (03 Feb 2021) indicated that melflufen+dex did not lead to longer OS, as would have been expected by the superior PFS, as shown by the HRs and p-values for the comparison between the melflufen+dex group and pom+dex group (stratified log-rank p-value: p=0.4667 and HR of 1.104 [95% CI: 0.846, 1.441]). Median OS was 19.75 months (15.08, 25.56) for melflufen + dex vs. 25.00 months (18.14, 31.87) for pom + dex.

An updated median OS with one additional year of follow up, submitted to CHMP in responses to questions at the time of the MAA, indicated similar results. The median OS was 20.24 months (95% CI: 15.84, 24.34) in the melflufen +dex arm vs. 23.98 months (95% CI: 19.06, 28.71) in the pomalidomide + dex arm, with a HR of 1.14 (95% CI: 0.912-1.434, nominal p=0.2438).

Final OS analysis results with data cut-off 03-02-2023 confirmed previous observations with a median OS of 20.24 months (95% CI: 15.84, 24.15) in the melflufen + dex arm vs. 23.98 months (95% CI: 18.92, 27.86) in the pomalidomide + dex arm. The HR was 1.09 (95% CI: 0.88, 1.35, log-rank p=0.3254).

Target indication - Using the follow-up data cut-off, median OS in the target indication population was nominally longer in the melflufen+dex group than the corresponding pomalidomide +dex group: 23.56 months (18.86, 27.96) vs 19.84 months (12.62, 26.48), with a HR of 0.833 (95% CI: 0.620, 1.120) and nominal p=0.2249.

At the final analysis, median OS in the target population was 23.56 months (95% CI: 18.86, 27.96) vs. 19.06 months (95% CI: 12.62, 26.48), with a HR of 0.88 (95% CI: 0.67, 1.16, nominal log-rank p=0.3606).

A Kaplan-Meier-plot of OS in the target indication population is presented in Figure 6 (final analysis).

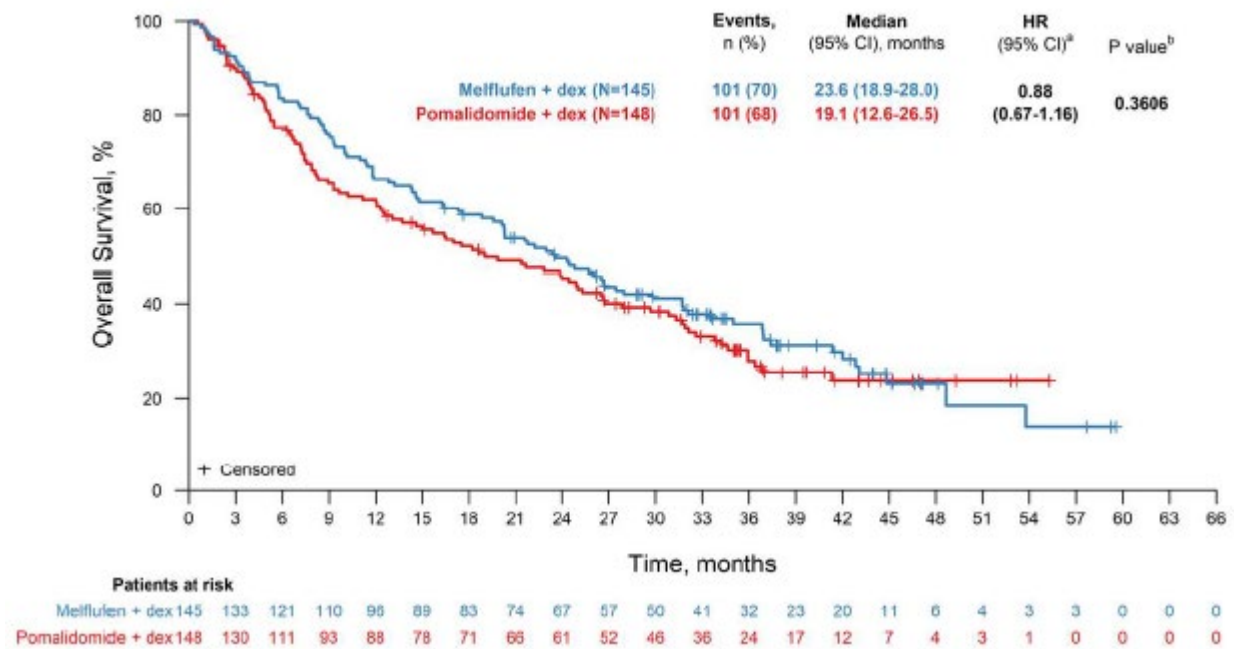


Figure 6. Study OP-103: Kaplan-Meier plot of OS based on IRC Assessment (Target Indication, Final Analyses)

OS subgroup analysis FAS – For multiple subgroups in the FAS, HR is above 1 suggesting a worse overall survival, including age <65, 3 or 4 prior lines of therapy, creatinine clearance ≥ 90 mL/min, low BSA, presence of EMD, prior ASCT, not refractory to alkylator, refractory to anti-CD38 mAb, females, BSA $\leq$ median, white race, ISS stage II or III, and standard or unknown risk status (Figure 7). For age <65 and prior ASCT, the 95% CI excludes 1.

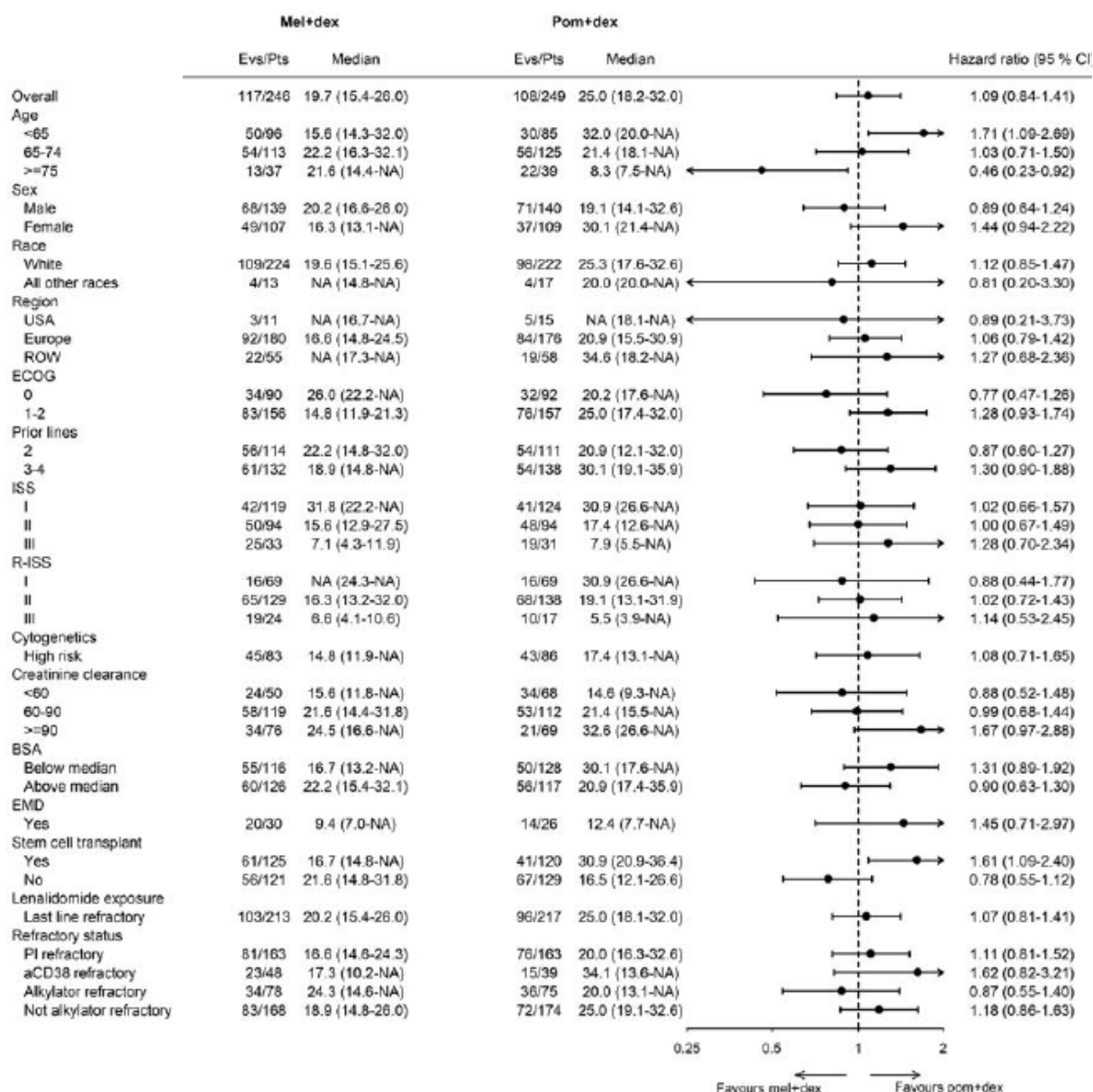


Figure 7. OS Subgroup Analysis – Overall Study Population

OS subgroup analysis target indication – Final OS subgroup analysis of patients who had no prior ASCT or had progressed >36 months after ASCT showed a trend for an OS benefit of melflufen + dex treatment in most of the subgroups. The OS HR point estimate was above 1 in small subgroups of patients including 3-4 prior lines, creatinine clearance ≥ 90 , LDH $\geq 1.5 \times \text{ULN}$, plasma cell involvement 30- <60 and aCD38 refractory patients , (Figure 8).

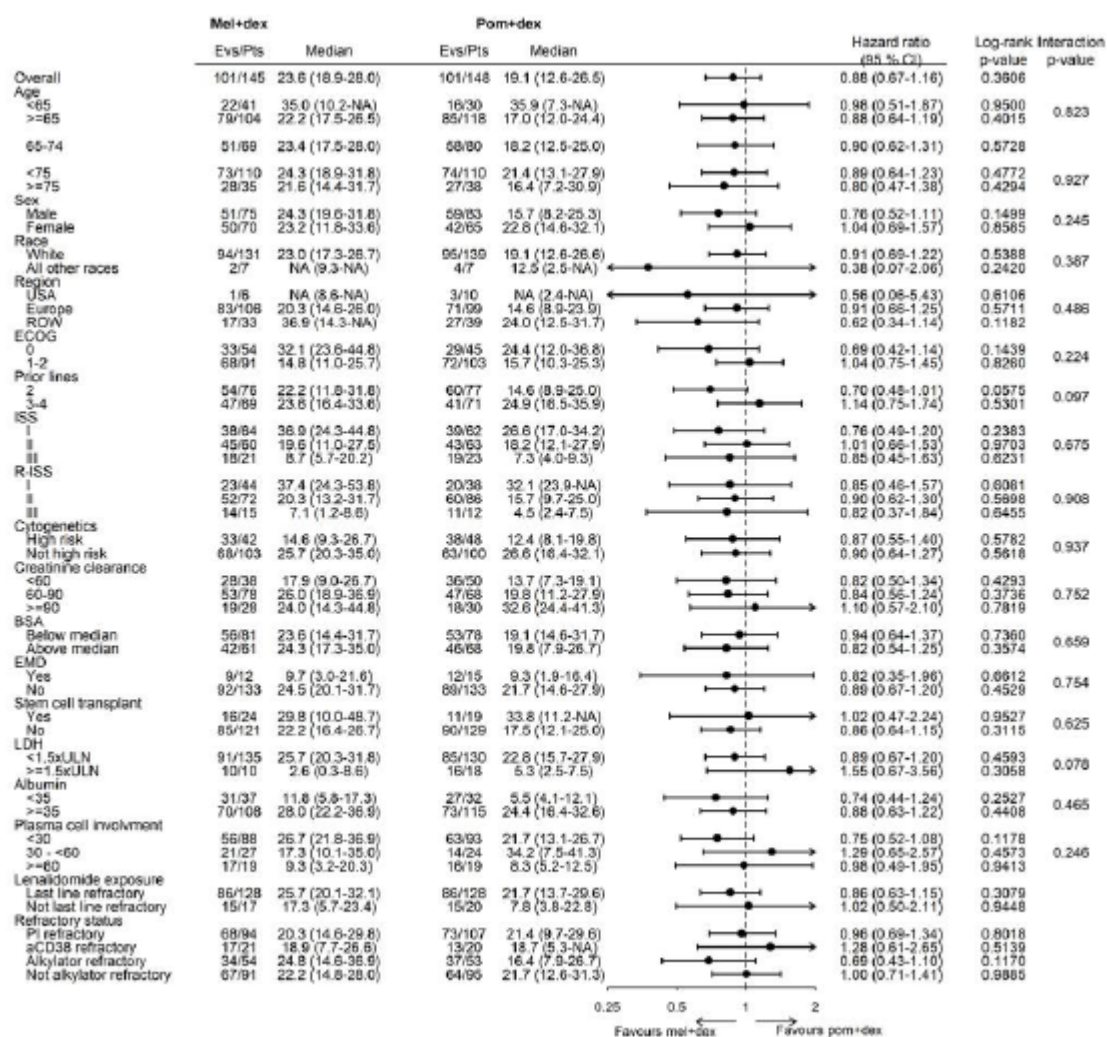


Figure 8. Overall survival – unstratified HRs by subgroup – target indication

Main other secondary endpoints (melufen+dex vs. pom+dex)

Duration of Response (DOR)

- Overall study population - The IRC based median DOR for the FAS was 11.17 months (95% CI: 8.48, 17.48) in the melufen+dex group and 11.07 months (95% CI: 7.62, 15.44) in the pom+dex group with a stratified HR of 1.061 (95% CI: 0.651, 1.728).
- Target population - In the target indication melufen+dex treated patients had a longer DOR than in the corresponding pomalidomide-treated patients (15.7 months [95% CI: 9.23, NE] vs. 11.1 months [95% CI: 7.36, 16.30] with a HR of 0.697 [95% CI: 0.40, 1.22]).

Time to response (TTR)

- Overall study population - The median TTR was also similar in both treatment arms for the target indication population, i.e. 2.14 months (min, max 0.95, 14.55) vs. 2.10 months (0.79, 8.38).

Clinical benefit rate (CBR)

- *Overall study population* - The CBR (i.e., proportion of patients with best response of MR or better) based on IRC assessment was 49.6% (95% CI: 43.18%, 56.02%) vs. 41.0% (95% CI: 34.80%, 47.35%), respectively.
- *Target population* – Data not presented.

Time to progression (TTP)

- *Overall study population* - The median TTP based on IRC assessment in the FAS was 7.16 months (95% CI: 5.59, 9.23) vs. 5.32 months (95% CI: 4.63, 6.67) with a stratified HR 0.800 (95% CI: 0.640, 1.000; p=0.0498).
- *Target population* - Data not presented.

Duration of clinical benefit (DOCB)

- *Overall study population* - The median DOCB was 9.23 months (95% CI: 7.46, 12.68) vs. 8.31 months (95% CI: 6.44, 10.38) with a stratified HR 0.895 [95% CI: 0.635, 1.261].
- *Target population* - Data not presented.

Exploratory endpoints

Proportion of patients with MRD (yes/no) for patients that achieve a CR

MRD was analysed in 8 patients (5 in the melflufen/dexamethasone arm and 3 in the pomalidomide/dexamethasone arm) who had achieved at least a CR. For technical reasons, 2 samples from patients in the melflufen arm were not assessable. MRD-negativity was achieved in one patient in the melflufen arm and not in any patient in the pomalidomide arm.

HRQoL

PRO measurements were collected on a subset of patients that began after protocol Amendment 4.1, comprising 32% of the trial population (PRO Analysis set). PRO data seem to suggest that patients treated with melflufen+dex were able to maintain HRQoL with no detriment, despite experiencing more adverse events during the clinical study. However, due to the exploratory nature, the limited size of the PRO Analysis set as well as small differences observed from baseline at each cycle and between treatment groups for all three measures, no firm conclusions can be drawn for the HRQoL endpoints.

Ancillary analyses

PFS-OS discrepancy

At the time of the MAA for melflufen, the discrepancy between the PFS and OS results in Study OP-103 and the divergent results of the subgroup OS analyses prompted further exploratory analyses. A multivariable analysis was performed to explore any signals of effect modification for different subgroups (age, ASCT, gender, creatinine clearance). A strong signal of effect modification was observed for the post-hoc defined subgroup of time-to-progression (TTP) post ASCT <36 months vs no ASCT or TTP post ASCT ≥36 months (HR: 2.02 (95% CI: 1.26-3.25); multivariable Cox-model after stepwise selection based on Akaike Information Criteria). In response to Day 180 list of outstanding issues, main efficacy results of Study OP-103 were presented by time to progression post ASCT (Table 12). Results seem to improve with larger time since ASCT or with no prior ASCT vs. the ITT. Further, for the primary endpoint of PFS as well as for ORR and OS, the results for patients with a time-to-progression post ASCT of <36 months consistently demonstrated reduced efficacy in this group. On the

contrary, consistent results on efficacy in favour of melflufen were seen for the subgroup with no ASCT or prior ASCT and TTP ≥ 36 months (Table 13).

Table 11. OS, PFS and ORR by time-to-progression post-ASCT in Study OP-103

Time-to-progression post-ASCT	OS (95% CI)			PFS (95% CI)			ORR (95% CI)		
	Mel OS	Pom OS	HR	Mel PFS	Pom PFS	HR	Mel%	Pom%	OR
<1 year n=31 (Mel) n=32 (Pom)	13.1 (5.9, NE)	20.9 (18.1, NE)	2.18 (1.01, 4.73)	4.4 (3.2, 6.9)	4.3 (3.3, 8.6)	1.21 (0.69, 2.12)	19.4 (7.5, 37.5)	25.0 (11.5, 43.4)	0.72 (0.22, 2.38)
1-2 years n=47 (Mel) n=51 (Pom)	14.8 (10.2, NE)	30.1 (19.1, NE)	2.07 (1.13, 3.79)	4.0 (3.5, 6.6)	5.6 (3.8, 8.5)	1.20 (0.74, 1.94)	17.0 / 7.6, 30.8)	23.5 (12.8, 37.5)	0.67 (0.25, 1.81)
2-3 years n=23 (Mel) n=18 (Pom)	19.7 (15.1, NE)	32.0 (30.9, NE)	1.27 (0.46, 3.53)	4.9 (3.7, 12.4)	6.9 (4.7, NE)	1.49 (0.70, 3.16)	21.7 (7.5, 43.7)	44.4 (21.5, 69.2)	0.35 (0.09, 1.35)
<3 years n=101 (Mel) n=101 (Pom)	15.6 (13.1-NE)	30.9 (20.2-NE)	1.86 (1.21-2.85)	4.3 (3.7, 5.3)	5.2 (4.3, 7.5)	1.28 (0.92, 1.77)	18.8 (11.7, 27.8)	27.7 (19.3, 37.5)	0.60 (0.31, 1.17)
≥ 3 years n=24 (Mel) n=19 (Pom)	35.0 (20.2, NE)	32.6 (NE, NE)	0.95 (0.33, 2.76)	6.7 (4.2, NE)	6.0 (4.3, NE)	0.68 (0.31, 1.48)	41.7 (22.1, 63.4)	21.1 (6.1, 45.6)	2.68 (0.68, 10.53)
Non-ASCT n=121 (Mel) n=129 (Pom)	21.6 (14.8, 31.8)	16.5 (12.1, 26.6)	0.78 (0.55, 1.12)	9.3 (7.3, 12.2)	4.6 (3.5, 6.5)	0.59 (0.44, 0.79)	42.1 (33.2, 51.5)	27.1 (19.7, 35.7)	1.96 (1.15, 3.32)
ITT n=246 (Mel) n=249 (Pom)	19.7 (15.4, 26.0)	25.0 (18.2, 32.0)	1.09 (0.84, 1.41)	6.8 (5.1, 8.6)	4.9 (4.3, 5.9)	0.77 (0.62, 0.95)	32.5 (26.7, 38.8)	26.9 (21.5, 32.9)	1.31 (0.89, 1.93)

Abbreviations: ASCT Autologous stem-cell transplant; CI Confidence interval; HR Hazard ratio; ITT intent-to-treat; Mel Melflufen; NE Not estimable; Pom Pomalidomide; OR Odds ratio; ORR Overall response rate; OS Overall survival; PFS Progression-free survival; TTP Time to progression. Median values are shown in months for OS and PFS.

Table 12. Efficacy Results Study OP-103 Based on Time-to-Progression < or ≥36 Months Post-ASCT (DCO 3 Feb 2022)

	Melflufen	Pomalidomide	
ITT	N=246	N=249	
Median PFS (95% CI), months	6.83 (4.96, 8.54)	4.93 (4.24, 5.72)	HR: 0.792 (0.640, 0.981)* HR: 0.770 (0.625, 0.949)
Median OS (95% CI), months	20.24 (15.84, 24.34)	23.98 (19.06, 28.71)	HR: 1.144 (0.912, 1.434)* HR: 1.132 (0.905, 1.416)
ORR (95% CI), %	32.5 (26.7, 38.8)	26.9 (21.5, 32.9)	P=0.1722
No ASCT or TTP≥36 months	N=145	N=148	
Median PFS (95% CI), months	9.26 (7.16, 11.79)	4.63 (3.65, 6.28)	HR: 0.577 (9.438, 0.760)
Median OS (95% CI), months	23.56 (18.86, 27.96)	19.84 (12.62, 26.48)	HR: 0.833 (0.620, 1.120)
ORR (95% CI), %	42.1 (33.9, 50.5)	26.4 (19.5, 34.2)	P=0.046
ASCT and TTP<36 months	N=101	N=101	
PFS	4.27 (3.68, 5.06)	5.16 (4.27, 7.39)	HR: 1.277 (0.920, 1.772)
OS (95% CI)	15.72 (11.89, 20.47)	28.71 (20.17, 34.07)	HR: 1.803 (1.274, 2.551)
ORR (95% CI)	18.8 (11.7, 27.8)	27.7 (19.3, 37.5)	P=0.1349

* Stratified HR

Melphalan/alkylator refractory patients

In alkylator-refractory patients of Study OP-103, the ORR and DOR in the target population were 29.6% and 14.7 months for melflufen + dex and 24.5% and 15.4 months for pom + dex. In patients refractory to melphalan, the ORR and DOR were 40.0% and 10.1 months for melflufen + dex and 25.9% and 15.4 months for pom + dex. A total of 17 patients in the ITT, 7 in the melflufen and 10 in the pomalidomide arm, were refractory to high-dose melphalan. The ORR in these patients was 28.6% and 20.0%, respectively.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial OP-103 (OCEAN)

Title: A Randomized, Controlled, Open-Label, Phase 3 Study of Melflufen/Dexamethasone Compared with Pomalidomide/Dexamethasone for Patients with Relapsed Refractory Multiple Myeloma who are Refractory to Lenalidomide	
Study identifier	Sponsor ID: OP-103 (OCEAN) EudraCT number: 2016-003517-95 NCT number: NCT03151811
Design	Phase 3 randomised, controlled, open-label study of melphalan flufenamide in combination with dexamethasone (Dex) in patients with RRMM who are refractory to lenalidomide.

	Duration of Main phase:		Until progressive disease (PD) or unacceptable toxicity
	Duration of Run-in phase:		Not applicable
	Duration of Follow-up phase:		Until death, or 24 months after subsequent therapy or PD
Hypothesis	Non-inferiority followed by superiority		
Treatments groups*	Melflufen + dex (n=145)		Melflufen 40 mg IV on Day 1 of every 28-Day cycle. Dex 40 mg orally once weekly on Days 1, 8, 15 and 22 of each 28-Day cycle for patients <75 years of age or 20 mg for patients ≥75 years
	Pomalidomide + dex (n=148)		Pomalidomide 4 mg capsules orally on Days 1 to 21 in each 28-Day cycle. Dex posology similar to melflufen arm.
Endpoints and definitions	Primary endpoint	Progression free survival (PFS)	The time in months from date of randomization to the earlier of confirmed PD or death due to any cause.
	Key secondary endpoint	Overall Response Rate (ORR)	The proportion of patients achieving a best confirmed response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR).
	Key secondary endpoint	Overall survival (OS)	The time in months from data of randomisation to death due to any cause.
Database lock	3 Feb 2021 (for OS 3 Feb 2023)		
Results and Analysis			
Analysis description	Secondary Analysis* - target indication population		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Melflufen + dex	Pomalidomide + dex
	Number of subject	n=145	n=148
	PFS	9.26 months	4.63 months
	95% CI	(7.16; 11.79)	(3.65; 6.28)
	ORR	42.1%	26.4%
	95% CI	(33.9; 50.5)	(19.5; 34.2)
	OS**	23.6 months	19.1 months
	95% CI	(18.9; 28.0)	(12.6; 26.5)
Effect estimate per comparison	Primary endpoint	Comparison groups	Melflufen + dex vs. pomalidomide + dex
		HR	0.577
		95% CI	(0.438; 0.760)
		P-value	Nominal p =0.0001

	Key secondary endpoint OS	Comparison groups	Melflufen + dex vs. pomalidomide + dex
		HR	0.88
		95% CI	(0.67; 1.16)
		P-value	Nominal p = 0.3606
Notes	*Results presented are based on the post-hoc defined target indication population. For results of the primary analysis in the overall study population, please refer to efficacy result section. ** Final analysis (data cut-off 3 Feb 2023).		

Clinical studies in special populations

Clinical efficacy has not been investigated for special populations in separate clinical studies. Subgroup analyses for OS in Study OP-103 have been presented in the *outcome and estimation* section above.

Supportive studies

Study OP-106 – HORIZON

Single arm, open-label Phase 2 study of melflufen in combination with dexamethasone (dex) in patients with RRMM who are refractory to Pomalidomide and/or an anti-CD38 mAb.

Phase 2 study OP-106 was the pivotal trial for the MAA of melflufen. This is a single arm study of melflufen in combination with dexamethasone (dex) in patients with RRMM who had received a minimum of 2 prior lines of therapy, including an IMiD and a PI, and were refractory to pomalidomide and/or an anti-CD38 mAb. The study design is discussed in detail in the EPAR for the MAA of melflufen.

Disposition - A total of 157 patients was included in the overall study population. The majority of the 157 patients in the overall FAS (n=113, 83.4%) had discontinued treatment and 26 patients (16.6%) were ongoing on treatment at the data cut-off (14 Jan 2020). The most common reason for treatment discontinuation was progressive disease (n=88, 56.1%), followed by adverse event (n=26, 16.6%).

Study population - Median age at enrolment was 65 years in the overall population, almost 60% of patients was male and most patients were Caucasian. Median time since initial diagnosis was 6.5 years. As expected in this advanced patient population, patients with ISS stage III disease, extramedullary disease, and high-risk cytogenetic features were well represented. Patients had received a median of 5 (range 2-12) prior therapies. A total of 154 patients (98.1%) was refractory to the most recent prior regimen, and 89% was refractory to lenalidomide. In total 119 patients (75.8%) were triple class refractory (TCR). In total 72 patients had received at least 2 prior lines of therapy; had disease refractory to lenalidomide and the last line of therapy; and did not receive a prior ASCT, or for patients with prior ASCT, had a time to progression at least 3 years since transplantation. Disease characteristics are summarised in Table 14.

Table 13. Disease characteristics for target population in OP-106.

	Indication, N=72
Age	68 (42-86)
Male	44 (61)
Weight	73.8 (35.0-129.0)
ISS	
I	28 (39)
II	23 (32)
III	18 (25)
Missing/Unknown	3 (4)
EMD	25 (35)
High risk	30 (42)
ECOG	
0	15 (21)
1	42 (58)
2	14 (19)
3	1 (1)
Time since diagnosis	7.4 (0.7-24.6)
Number of prior lines	5 (2-10)
ASCT status	
PD post ASCT <3 years	0 (0)
PD post ASCT ≥3 years	31 (43)
No ASCT	41 (57)
Alkylator refractory	36 (50)
Pomalidomide refractory	68 (94)
Bortezomib refractory	44 (61)
Carfilzomib refractory	32 (44)
Daratumumab refractory	49 (68)

Source data: ADSL 25FEB2022

Efficacy results

The primary efficacy analysis of Phase 2 Study OP-106 was based on investigator assessment with a data cut-off of 14 Jan 2020 and results are presented below. Thereafter, a comparison of efficacy results (data cut-off Oct 2021) with Phase 3 Study OP-103 efficacy results is provided.

Primary endpoint ORR - Based on Investigator assessment and data cutoff 14 Jan 2020, a total of 46 patients out of 157 had a best response of PR or better for an overall confirmed response rate of 29.3% (95% CI: 22.32%, 37.08%) in the overall study population.

ORR in the target indication population is 37.5% as shown in Table 15, with a median duration of response of 6.97 months. Median PFS is 4.40 months and median OS is 11.60 months.

Table 14. ORR for target population in Study OP-106

Indication N=72	
Best Overall Confirmed Response, n (%)	
sCR	0 (0.0)
CR	0 (0.0)
VGPR	11 (15.3)
PR	16 (22.2)
MR	7 (9.7)
SD	15 (20.8)
PD	18 (25.0)
NE	5 (6.9)
Overall Confirmed Response Rate	
sCR+CR+VGPR+PR, n (%)	27 (37.5)
[95% CI]	26.4-49.7

Source data: ADRESP 25FEB2022

Key secondary endpoint DOR – In total 46 patients (30 patients with events and 16 censored patients) achieved PR or better; the median DOR in the overall study population was 5.5 months (95% CI: 3.9, 7.6) based on investigator assessment.

Main other secondary endpoints (Investigator based)

- *PFS* - Median PFS in the overall study population was 4.24 months (95% CI: 3.42, 4.86) after a median follow up of 10.18 months.
- *OS* - The median OS was 11.63 months (95% CI: 9.30, 15.41) for the overall study population after a median OS follow-up of 14.00 months (95% CI: 10.78, 18.69).
- *CBR* - The clinical benefit rate (MR or higher) was 45.2% (95% CI: 37.3, 53.4) in the overall study population.
- *TTR* – The median time to response was 1.9 months.
- *TTP* - Median TTP in the overall study population was 4.4 months (95% CI: 3.8, 5.3).
- *TTNT* - Median time to next treatment or death was 5.8 months (95% CI: 4.8, 7.1). Median time to next treatment without death as event was 8.21 months (7.16, 10.84).
- *Duration of stable disease* - The median duration of SD was 3.8 months (95% CI: 3, 4.6).
- *Duration of disease stabilization* – The median duration of disease stabilization was 5.6 months (95% CI: 4.9, 6.8).
- *Duration of clinical benefit* - Of the 71 patients with investigator-assessed response of MR or better in the overall study population, median duration of clinical benefit was 6.7 months (95% CI: 4.3, 7.5).

In response to D120 list of outstanding issues at the time of the MAA, updated data from Study OP-106 were submitted with longer follow up, using a data cut-off of Oct 2021. A comparison of updated OP-106 efficacy data with OP-103 results is presented in Table 16.

Table 15. Comparison of Efficacy Parameters in Study OP-103 and Study OP-106

	OP-103/OCEAN		OP-106/ HORIZON
	IRC assessment		Investigator Assessment
	<u>Mel+Dex</u>	<u>Pom+dex</u>	<u>Mel+Dex</u>
	N=246	N=249	N=157
Efficacy parameters			
Median PFS, months	6.83	4.93	4.27
(95% CI)	(4.96, 8.54)	(4.24, 5.72)	(3.42, 4.90)
Median OS, months	19.75	25.00	11.79
(95% CI)	(15.08, 25.56)	(18.14, 31.87)	(9.53, 14.55)
ORR (≥ PR), (%)	32.5	26.9	33.8
(95% CI)	(26.71, 38.76)	(21.50, 32.87)	(26.41, 41.73)
Median DOR (≥ PR), months	11.17	11.07	6.70
(95% CI)	(8.48, 17.48)	(7.62, 15.44)	(4.40, 8.11)
Median TTR (≥ PR), months	2.1	2.0	2.1

Abbreviations: CI = confidence interval; Dex = dexamethasone; DOR = duration of response; IRC = Independent Review Committee; Mel = melflufen; n = number of patients in each category; N = total number of patients in the relevant analysis set; NE = not evaluable; ORR = overall response rate; OS = overall survival; Pom = pomalidomide; PFS = progression-free survival; PR = partial response; TTR = time to response.

In response to D195 list of outstanding issues at the time of the MAA, the Applicant presented post-hoc subgroup results for the 3L+ TCR study population by time to progression since stem cell transplantation (Table 17). This is based on exploratory analyses in study OP-103. The response rate as well as median DoR was numerically higher in patients without prior autologous stem cell transplantation (ASCT) or time to progression (TTP) ≥3 years compared to patients with more recent transplantation with TTP <36 months.

Table 16. Efficacy results in TCR 3L+ patients and with no prior ASCT or who have progressed more than 36 months from an ASCT and patient who have progressed within 36 months from an ASCT in OP-106 HORIZON study

<i>Population</i>	<i>TCR 3L+ (n=110)</i>	<i>No ASCT or progressed ≥36 months (n=52)</i>	<i>ASCT progressed <36 months (n=58)</i>
Overall response rate (ORR), 95% CI (%)	28 (25.5) <i>[17.6%, 34.6%]</i>	15 (28.8) <i>[17.1, 43.1]</i>	13 (22.4) <i>[12.5, 35.3]</i>
Median duration of response (DOR), 95% CI (months)	5.4 (3.5-8.1)	7.6 (3.0-12.3)	3.9 (3.1-7.4)
Median time to first response (range)	2.1 (1.0-15.3)	2.3 (1.0-10.5)	1.9 (1.0-15.3)
Median PFS, 95% CI (months)	3.7 (2.8-4.4)	4.2 (2.1-5.4)	3.4 (2.8-4.2)
Median OS, 95% CI (months)	9.5 (6.4-12.0)	11.2 (6.4-12.7)	8.6 (5.6-13.2)

Study OP-108 – LIGHTHOUSE

A randomized, controlled, open-label Phase 3 study of melflufen in combination with daratumumab compared with daratumumab in patients with relapsed or relapsed-refractory MM.

Study OP-108 was an open-label, randomized, international, multicentre Phase 3 trial which enrolled patients with RRMM who were either double refractory to an IMiD and a PI, or had at least 3 prior lines of therapy including exposure to both an IMiD and a PI. Patients were randomized (1:1) to Arm A (melflufen 30 mg [Day 1 in each 28-day cycle] + dex 40 mg [once weekly] + daratumumab 1800 mg [once weekly] or Arm B (daratumumab at the same dose levels as Arm A). For each arm, treatment

was given in 28-day cycles and may have been given in an outpatient treatment setting. After confirmed disease progression, patients in Arm B could have crossed over and received treatment with melflufen, dexamethasone and daratumumab and continued in the study. The primary objective of Study OP-108 was to show superiority of progression free-survival (PFS) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.

As part of compliance with the FDA request on 7 July 2021 to put the melflufen program on Partial Clinical Hold, enrollment in Study OP-108 was paused and eventually terminated without further enrolment. At the time the study was terminated, 54 patients (out of a planned 240), 27 patients in each arm, had been enrolled into the study. Of those patients 14 in Arm A and 15 in Arm B fell into the target indication (i.e., patients with a minimum 2 prior lines of therapy who had either no prior ASCT or who had progressed >36 months after an ASCT).

Some imbalances were observed between treatment groups. The median age in Arm A was 65 years (range 43 to 80) compared with 68 years (range 50 to 83) in Arm B. Patients in Arm A had a median 3 prior lines of treatment, compared with 4 in Arm B, and more patients were refractory to prior treatment (PIs and IMiDs) in Arm B than in Arm A. In Arm A only 1 patient (3.7%) had an ECOG 2 at baseline, compared with 6 patients (22.2%) in Arm B.

Median duration of study treatment was 30.8 weeks (median 7.0 treatment cycles) in Arm A vs 19.3 weeks in Arm B (median 5 treatment cycles), and median duration of melflufen treatment in Arm A was 28.9 weeks, with a median of 6.5 cycles.

Despite the small number of patients enrolled in Study OP-108 at the time of study termination (N=54), efficacy results suggested superiority of melflufen treatment in combination with daratumumab over daratumumab alone. There were fewer PFS events for the melflufen treatment arm compared with the control arm (11.1% vs 48.2%), and superiority in PFS in the FAS was demonstrated (HR 0.18; nominal p-value 0.0032). Early and continued separation between the PFS KM curves of the two groups was observed. The FAS ORR was higher in Arm A compared with Arm B (59.3% vs 29.6%; nominal p-value 0.030), and the FAS OS HR was 0.47 with a nominal p-value of 0.3721. The OS KM graphs, while based on few events, showed a benefit for melflufen treatment.

Results in the target indication population were consistent with the overall FAS. There were fewer PFS events in Arm A compared with Arm B (7.1% vs 73.3%), and early and continued separation between the KM curves of the two groups was observed. By contrast, in patients with disease progression <36 months after an ASCT (Arm A N=13; Arm B N=12) there was no difference between groups in PFS events (15.4% in Arm A vs 16.7% in Arm B) or ORR (53.8% vs 50.0%).

2.4.3. Discussion on clinical efficacy

With this application, an extension of indication (EoI) is requested for melflufen + dexamethasone (dex) in patients who have received at least 2 prior lines of therapy, and whose disease is refractory to lenalidomide and the last line of therapy, i.e. an earlier line of treatment compared to the current approved indication in triple class refractory patients (TCR) after at least 3 prior lines. Similar to the current approved indication, for patients with prior ASCT, the time to progression should be at least 3 years since transplantation.

The proposed posology is 40 mg of intravenous melflufen on Day 1 of each 28-day cycle and 40 mg (or 20 mg in patients $\geq$ 75 years) of oral dexamethasone (dex) on Days 1, 8, 15, and 22. This posology is similar to the approved posology supported by the dose-finding Phase 1/2a Study O-12-M1.

Design and conduct of clinical studies

Main clinical data for this EoI is derived from Phase 3 Study OP-103 (OCEAN), which has been presented previously as confirmatory trial for the marketing authorization application (MAA) for melflufen. Study OP-103 is a randomised, open-label study investigating melflufen + dex compared with pomalidomide + dex in patients with relapsed or refractory multiple myeloma (RRMM) following 2 to 4 lines of prior therapies, and refractory to lenalidomide and the last line of therapy. The study design as well as results for the overall study population and TCR subpopulation without recent autologous stem cell transplantation (ASCT), i.e. the current approved indication, were agreed during the MAA. Although results for the overall study population have been repeated in the efficacy result section above, the main clinical data for this application is derived from the population without prior ASCT or progression >36 months after ASCT. Similar to the MAA, some uncertainties remain considering that data for the new proposed target indication are again derived from the time to progression at least 36 months after ASCT/non-ASCT post-hoc defined subgroup (see discussion below). Nevertheless, as per MAA approval, the comparator arm, endpoints and statistical methods are considered acceptable.

Support is derived by data from the single arm open-label Phase 2 Study OP-106 (HORIZON), investigating melflufen + dex in patients with RRMM who had received a minimum of 2 prior lines of therapy, including an IMiD and a PI, and were refractory to (at least) pomalidomide and/or an anti-CD38 mAb. Results from this study were pivotal for the MAA of melflufen, and the study design is considered acceptable.

In addition, efficacy results from early terminated Study OP-108 (LIGHTHOUSE), a randomised Phase 3 study investigating Pepaxti in combination with daratumumab and dexamethasone vs. daratumumab alone have been presented as supportive clinical data. Melflufen was administered at 30 mg per cycle (instead of the currently approved 40 mg). Although subgroup results in a small subgroup of patients reflecting the target indication are interesting considering the preference for triple therapy in RRMM setting in clinical practice, due to the choice of the study arms, these data cannot be considered supportive to establish efficacy of combination treatment with melflufen + dex in the proposed target population and posology.

Efficacy data and additional analyses

Of the 495 patients included in Study OP-103, 293 patients (145 patients in the melflufen+dex arm and 148 patients in the pomalidomide+dex arm) had no prior ASCT or had progressed >36 months after ASCT. Compared with the overall study population, these patients were slightly older (median 71 years vs. 68 years in the full study population) and had had fewer prior treatment regimens (median 2 vs. 3, respectively). Since all patients in the study had at least 2 prior lines of treatment, 99% were refractory to the last regimen and 99% refractory to lenalidomide, this also applies to the subgroup of 293 patients without recent ASCT, which therefore adequately reflects the applied extended target indication.

The primary endpoint PFS was met for the overall study population, with a median of 6.83 months (95% CI 4.96, 8.54) in the melflufen + dex arm vs. 4.93 months (95% CI 4.24, 5.72) in the pomalidomide + dex arm. The stratified HR was 0.792 (95% CI: 0.640, 0.981; p=0.0319). During the MA evaluation, concerns regarding robustness of PFS data a.o. regarding handling of randomised but not-treated patients were alleviated based on additional sensitivity analyses. For the overall study population, the key secondary endpoint ORR was not met and for the second key secondary endpoint OS, a detriment could not be excluded, resulting in post-hoc selection of the approved target population without progression in less than 36 months after an ASCT.

In brief, despite the active comparator and the fact that study OP-103 was not powered to demonstrate a difference in OS, the OS HR of 1.104 and KM curves in the OP-103 ITT population warranted further investigation. The analyses indicated that the potential OS detriment was mostly driven by a lack of efficacy/reduced efficacy in patients with disease progression within 3 years after ASCT. While the 3 year cut-off is based on a post-hoc defined variable identified in a stepwise multivariable analysis, there is the biological rationale that patients who progress early after ASCT, which requires high dose melphalan, might be less responsive to another alkylator-based regimen. In addition, these patients may have an increased risk of myelotoxicity with loss of marrow reserve after recent transplantation, although a clear toxicity signal was not observed (see safety section). The cut-off of 36 months was based on the data in the trial and to some extent supported by expert data stating that the PFS cut-off for a transplant to be considered successful enough to consider a salvage ASCT is ≥ 36 months, although not the same situation as in the trial (EHA-ESMO guidelines, Dimopoulos et al. 2021). In addition, the treatment effect observed in the subgroup was larger than the all-randomised study population, providing additional support for the subgroup (EMA/CHMP/539146/2013; Guideline on the investigation of subgroups in confirmatory clinical trials). Subgroup analysis of OP-106 also suggested a larger effect in patients with no ASCT or prior ASCT and TTP ≥ 36 months, however interpretation was hampered by the lack of a control arm. Upon consultation, the SAG-O concluded that melflufen + low dose dex is associated with clinically relevant efficacy, with the exception of the subgroup of patients with relapse within 36 months following high-dose melphalan and autologous SCT. Hence, the indication was restricted to exclude these patients.

Presented results for the new target indication population, i.e. the time to progression *>36-months*-after ASCT post-hoc defined subgroup of patients who have received at least 2 prior lines of therapy, and whose disease is refractory to lenalidomide and the last line of therapy, indicated a median PFS improvement of 4.63 months with melflufen + dex treatment (median PFS **9.26 months** [95% CI 7.16-11.79] vs. 4.63 months [95% CI: 3.65, 6.28] in the pomalidomide+dex arm; HR 0.577; 95% CI: 0.438; 0.760; nominal $p=0.0001$). PFS results are better compared to the overall study population (6.83 months) and TCR subpopulation (6.6 months) for which melflufen is currently approved.

This is supported by key secondary endpoints ORR (**42.1%** with melflufen + dex vs. 26.4% with pomalidomide + dex; nominal $p=0.0046$; with median duration of response in favour of melflufen + dex of 15.7 vs. 11.1 months) and a trend in OS benefit (**23.6 months** vs. 19.1 months, respectively; HR 0.88 [95% CI: 0.67, 1.16; nominal log-rank $p=0.3606$], final analysis).

OS subgroup analysis for the target indication population showed a trend for an OS benefit of melflufen + dex treatment in most of the subgroups. The OS HR point estimate in the target indication population suggested better or similar OS with melflufen + dex compared to pomalidomide + dex in patients refractory to lenalidomide in last line or in earlier lines. The OS HR point estimate was above 1 for some small subgroups, including patients with 3-4 prior lines, creatinine clearance ≥ 90 , LDH $\geq 1.5 \times \text{ULN}$, plasma cell involvement 30- <60 and aCD38 refractory patients. Interpretation of these subgroups is hampered by the low number of patients involved.

Due to the exploratory nature, the limited size of the PRO Analysis set as well as small differences observed from baseline at each cycle and between treatment groups for all three measures, no firm conclusions can be drawn for the HRQoL endpoints.

Monoclonal antibodies (mAbs) daratumumab, isatuximab and elotuzumab all have been approved based on clinical data derived from a randomised trial with pomalidomide + dex as comparator. Despite the known limitations when comparing results across trials, the 4.6 month improvement seen with melflufen + dex compared to pomalidomide + dex in Study OP-103 is more or less in line with the approximately 5 month PFS improvement observed with these mAbs in a similar setting.

The observed PFS benefit, supported by an ORR and duration of response in favour of melflufen as well as a trend in OS benefit are considered clinically relevant for the requested target population. The restriction to patients with no prior ASCT or progression >36 months after ASCT, based on the same rationale as during the MAA, is acceptable for the new requested earlier line of treatment as well.

Supportive study OP-106 indicated efficacy of melflufen in the currently approved later line TCR setting, with an ORR of 28.8% and median duration of response of 7.6 months. The response rate in the post-hoc defined target population of this supportive study OP-106 (37.5%) was slightly lower when indirectly compared to the pivotal trial OP-103 (ORR 42.1%). No firm conclusions can be drawn based on the time dependent endpoints in this single arm trial OP-106, although median duration of response (6.97 months), PFS (4.4 months) and OS (11.6 months) seem lower compared to Study OP-103. This is not unexpected considering the more heavily pre-treated population (median 5 prior lines) compared to the pivotal trial (median 2 prior lines in target population).

2.4.4. Conclusions on the clinical efficacy

Clinical data in the target population (patients who had at least 2 prior lines of therapy, are refractory to lenalidomide and last line of therapy, and for patients with prior ASCT a time to progression of at least 3 years) is derived from randomised controlled Phase 3 study OP-103 + supportive data in single arm Phase 2 Study OP-106. The study designs and results for the overall study population and later line TCR population for these studies have already been discussed during the MAA for melflufen. Current pivotal clinical data reflects the proposed earlier line target population. The observed 4.6 months PFS improvement with melflufen + dex compared to pomalidomide + dex in Study OP-103, supported by an ORR and duration of response in favour of melflufen as well as a trend in OS benefit are considered clinically relevant for the requested target population. The restriction to patients with no prior ASCT or progression >36 months after ASCT is, based on the same rationale as during the MAA, acceptable for the new requested earlier line of treatment as well. Some concerns need to be addressed before final conclusions can be drawn, a.o. regarding OS subgroup analyses and results of the supportive study in the target indication population, but overall efficacy of melflufen seems to be established in earlier line RRMM treatment as well.

2.5. Clinical safety

Introduction

The current safety profile for melflufen as presented in the SmPC is based on pooled safety data from 491 patients in 4 clinical studies in RRMM (Studies O-12-M1 (n=75), OP-103 (n=228), OP-106 (n=157) and OP-107 (n=31)) in which patients received the recommended dose of melflufen. This has been assessed within the previous procedure (EMA/H/C/005681) and no new safety data are submitted within the current application in support of the safety profile.

As presented in section 4.8 of the SmPC, the most frequent adverse reactions are thrombocytopenia (83%), neutropenia (72%), anaemia (66%), nausea (21%), diarrhoea (19%) and pyrexia (19%). The most frequent serious adverse reactions are pneumonia (11%), thrombocytopenia (5%) and respiratory tract infection (4%).

The safety profile will be summarised based on the pooled safety data as well as for the OP-103 study, which forms the basis for the current SmPC. The safety profile for the newly applied, more broad target population excluding patients with post-ASCT progression <36 months will be briefly discussed as well.

Patient exposure

In the Safety Pool, 57.2% of patients were male, 89.8% were white, and mean (SD) age was 65.8 (9.2) years. More than 75% of patients were classified as ISS Stage I or II. Approximately two-thirds (67.2%) of patients had evidence of lytic bone disease and 17.5% had evidence of extramedullary disease. The mean (SD) number of prior lines of therapy was 3.9 (2.04). The incidence of refractoriness to at least one line of therapy was as follows: 72.3% for PIs, 95.1% for IMiDs, 39.7% for mAbs, 35.2% for alkylators. About 70% of the patients were double class refractory and 33.4% were TCR. Over half of the patients (54.2%) had received a prior transplant, most commonly an autologous transplant (53.6%).

The median duration of treatment was 20.1 weeks (range: 1-164 weeks) and the median number of treated cycles was 4 (range 1-40) for the Safety Pool. The starting dose of melflufen varied from 15 mg (n=4) to 55 mg (n=6). Most patients (n=464) received the recommended melflufen dose of 40 mg and 431 patients received a starting dose (first dose, first cycle) of melflufen 30 or 40 mg on Day 1 of all planned 28-day cycles in combination with dexamethasone in line with the recommended dose. Few patients received melflufen as single agent in study O-12-M1 and some patients received a starting dose other than 30 or 40 mg, or in 21-day cycles.

Of the 491 patients included in the Safety Pool, 408 (83.1%) had permanently discontinued treatment at the time of the data cut-off. The primary reasons for treatment discontinuation was progressive disease (246 patients, 50.1%), followed by AE (100 patients, 20.4%). A total of 284 patients (57.8%) had discontinued from the studies by data cut-off date, with the most common reason being death (245 patients, 49.9%).

Study OP-103 enrolled patients in earlier-stage RRMM (2-4 prior lines of treatment and refractory to both the last line and to lenalidomide) compared to the pooled safety population. In Study OP-103 the safety population consisted of 228 patients treated with melflufen + dexamethasone and 246 treated with pomalidomide + dexamethasone. Treatment duration with melflufen was longer in Study OP-103 than in the pooled safety population (median 25 weeks (range: 4-164) compared to 20 weeks (range: 1-189) and median 5 cycles started compared to 4 cycles, respectively), reflecting the patients' earlier disease stage. The study drug exposure in the melflufen + dexamethasone arm in Study OP-103 was comparable to the pomalidomide + dexamethasone arm exposure (median 25 weeks compared to 22 weeks, respectively and a median of 5 cycles started in both arms).

Adverse events

A summary of the safety profile is shown for the Safety Pool and OP-103 (Table 18). The overall summary of safety profile was comparable for the Safety Pool and the melflufen-arm in study OP-103.

OP-103

Within the melflufen arm, grade 3 or 4 TEAEs occurred frequently (89.9%), and were mostly treatment-related. The number of fatal TEAEs was 11.8% and only one event was considered treatment-related. Serious TEAEs occurred in 41.7% of patients and about half of these were considered treatment-related (18.4%). Dose reductions and dose interruptions occurred frequently. Overall, 26.3% of patients had at least one TEAE leading to drug discontinuation. Treatment-related grade 3 or 4 events as well as dose modifications, including discontinuations, were more common for the melflufen arm than for the pomalidomide arm. SAEs and fatal events were in the same order of magnitude.

Table 17 Overall summary of treatment-emergent events (Safety Pool and OP-103)

	Safety Pool (N=491)	OP-103 Melflufen+Dex (N=228)	OP-103 Pomalidomide+Dex (N=246)
Patients with at least 1 TEAE	489 (99.6%)	226 (99.1%)	241 (98.0%)
Patients with at least 1 treatment-related TEAE	476 (95.1%)	216 (94.7%)	209 (85.0%)
Patients with at least grade 3/4 TEAE	452 (92.1%)	205 (89.9%)	183 (74.4%)
Patients with at least 1 treatment-related grade 3/4 TEAE	425 (86.6%)	195 (85.5%)	157 (63.8%)
Patients with at least 1 serious TEAE	220 (44.8%)	95 (41.7%)	113 (45.9%)
Patients with at least 1 treatment-related serious TEAE	110 (22.4%)	42 (18.4%)	52 (21.1%)
Patients with at least 1 grade 5 TEAE	45 (9.2%)	27 (11.8%)	32 (13.0%)
Patients with at least 1 treatment-related fatal TEAE	7 (1.4%)	1 (0.4%)	4 (1.6%)
Patients with at least 1 TEAE associated with dose reduction	209 (42.6%)	115 (50.4%)	66 (26.8%)
Patients with at least 1 TEAE associated with dose delay/interruption	336 (68.4%)	153 (67.1%)	112 (45.5%)
Patients with at least 1 TEAE associated with drug withdrawn	139 (28.3%)	60 (26.3%)	56 (22.8%)

TEAE: Treatment emergent adverse event. Notes: If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term. Data as of 03 February 2021 are included for Study OP-103; Data as of 05 April 2021 are included for Study OP-107; Data as of 31 March 2020 are included for Study OP-106; Data as of 09 November 2017 are included for Study O-12-M1.

Within the Safety Pool, TEAEs were reported most commonly in the following MedDRA SOCs: Blood and lymphatic system disorders (87.4%), General disorders and administration site condition (55.4%), and Infections and infestations (51.7%). A similar pattern was seen in OP-103 for the melflufen arm; 87.7% of patients reported a TEAE in the SOC Blood and lymphatic system disorders, 50.0% in the SOC Infections and infestations and 41.2% in the SOC General disorders and administration site condition.

The most commonly reported TEAEs, experienced by over 50% of patients, in the Safety Pool and in study OP-103 were thrombocytopenia, anaemia, and neutropenia (Table 19). The most common non-haematologic TEAEs were fatigue, nausea, diarrhoea, asthenia, pyrexia and upper respiratory tract infection. Haematological events occurred more frequently (>10% difference) compared to the pomalidomide arm.

Table 18 Treatment emergent adverse events by preferred term reported by at least 10% of patients in de Safety Pool (Safety Pool and OP-103)

Preferred Term	Safety Pool (N=491) n (%)	OP-103 Melflufen + dex (N=228) n (%)	OP-103 Pomalidomide + dex (N=246) n (%)
Number of patients with at least 1 TEAE	489 (99.6)	226 (99.1)	241 (98.0)
Thrombocytopenia ^a	333 (67.8)	160 (70.2)	48 (19.5)
Anaemia ^a	321 (65.4)	152 (66.7)	92 (37.4)

Preferred Term	Safety Pool (N=491) n (%)	OP-103 Melflufen + dex (N=228) n (%)	OP-103 Pomalidomide + dex (N=246) n (%)
Neutropenia ^a	281 (57.2)	137 (60.1)	113 (45.9)
Fatigue	106 (21.6)	32 (14.0)	41 (16.7)
Nausea	105 (21.4)	30 (13.2)	17 (6.9)
Diarrhoea	95 (19.3)	31 (13.6)	21 (8.5)
Asthenia	93 (18.9)	32 (14.0)	28 (11.4)
Pyrexia	92 (18.7)	33 (14.5)	16 (6.5)
Neutrophil count decreased ^a	82 (16.7)	30 (13.2)	27 (11.0)
Platelet count decreased ^a	81 (16.5)	40 (17.5)	11 (4.5)
White blood cell count decreased ^a	79 (16.1)	22 (9.6)	6 (2.4)
Upper respiratory tract infection ^a	63 (12.8)	29 (12.7)	25 (10.2)
Pneumonia ^a	55 (11.2)	20 (8.8)	32 (13.0)
Cough	54 (11.0)	18 (7.9)	19 (7.7)
Constipation	52 (10.6)	16 (7.0)	29 (11.8)
Dyspnoea	52 (10.6)	21 (9.2)	24 (9.8)
Back pain	51 (10.4)	17 (7.5)	24 (9.8)

MedDRA Medical Dictionary for Regulatory Activities; TEAE: Treatment emergent adverse event; PT: Preferred term
^a The indicated PTs are included in the discussion of AESIs (Module 2.7.4, Section 2.7.4.1.1.3.4.2) grouped under standardized, customized, or modified MedDRA queries.

Notes: Preferred terms included in table based on the incidence within a given system organ class. If a patient experienced more than 1 episode of a TEAE, then the patient was counted only once within a PT. Preferred terms are reported using MedDRA version 19.1 or later.

Data as of 03 February 2021 are included for Study OP-103; Data as of 05 April 2021 are included for Study OP-107; Data as of 31 March 2020 are included for Study OP-106; Data as of 09 November 2017 are included for Study O-12-M1.

Grade 3 and 4 events

Safety Pool

The most common Grade 3 or 4 TEAEs in the Safety Pool were thrombocytopenia (60.7%), neutropenia (53.0%), and anaemia (41.1%). Clinically significant Grade 3/4 non-hematologic TEAEs were relatively infrequent (Table 20). Only the PT pneumonia (8.6%) was reported in >5% of the patients.

OP-103

Haematological events were also the most frequently reported ≥Grade 3 events in both treatment arms in study OP-103 and higher for the melflufen arm (79.4% vs 52.0% for melflufen + dexamethasone and pomalidomide + dexamethasone, respectively). The percentage of patients who had at least one Grade 3 non-hematological TEAE was similar for the melflufen + dexamethasone group compared with the pomalidomide + dexamethasone group (32.5% vs 32.9%) and the percentage of patients who had at least one Grade 4 non-haematological TEAE was slightly lower in the melflufen + dexamethasone group compared with the pomalidomide + dexamethasone group (2.2% vs 6.1%).

Table 19 Grade 3 or 4 TEAEs by preferred term reported by at least 5% of patients in the Safety Pool (Safety Pool and OP-103)

Preferred Term	Safety Pool (N=491) n (%)	OP-103 Melflufen + dex (N=228) n (%)	OP-103 Pomalidomide + dex (N=246) n (%)
Patients with at least 1 Grade 3/4 TEAE	452 (92.1)	205 (89.9)	183 (74.4)
Thrombocytopenia	298 (60.7)	143 (62.7)	26 (10.6)
Neutropenia	260 (53.0)	124 (54.4)	102 (41.5)
Anaemia	202 (41.1)	97 (42.5)	44 (17.9)
Neutrophil count decreased	73 (14.9)	28 (12.3)	22 (8.9)
Platelet count decreased	71 (14.5)	33 (14.5)	6 (2.4)
White blood cell count decreased	61 (12.4)	14 (6.1)	2 (0.8)
Pneumonia	42 (8.6)	10 (4.4)	21 (8.5)
Leukopenia	27 (5.5)	15 (6.6)	7 (2.8)

TEAE: Treatment emergent adverse event. Notes: If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term. Data as of 03 February 2021 are included for Study OP-103; Data as of 05 April 2021 are included for Study OP-107; Data as of 31 March 2020 are included for Study OP-106; Data as of 09 November 2017 are included for Study O-12-M1.

Treatment-related TEAEs

Treatment-related TEAEs reported by at least 10% of patients overall in the safety pool by PT are summarized in Table 21.

Safety Pool

Most patients (95.1%) experienced a treatment-related TEAE, and haematological events were also the most commonly treatment-related events. A total of 85.1% of patients experienced at least 1 Grade 3 or 4 treatment related TEAE, mainly thrombocytopenia (58.7%), neutropenia (52.1%), and anaemia (37.9%).

OP-103

Haematological TEAEs were also the most frequently observed treatment-related TEAEs in study OP-103, with higher frequencies observed in the melflufen arm compared to the pomalidomide arm. Frequencies of melflufen- or pomalidomide-related TEAEs were nearly identical to the treatment-related (any study drug) TEAEs.

Table 20 Treatment-related (any drug) TEAEs by preferred term reported by at least 10% of patients in the Safety Pool (Safety Pool and OP-103)

Preferred Term	Safety pool (N=491) n (%)	OP-103 Melflufen + dex (N=228) n (%)	OP-103 Pomalidomide + dex (N=246) n (%)
Patients with at least 1 treatment-related TEAE	467 (95.1)	216 (94.7)	209 (85.0)
Thrombocytopenia	325 (66.2)	157 (68.9)	40 (16.3)
Anaemia	288 (58.7)	132 (57.9)	59 (24.0)
Neutropenia	277 (56.4)	134 (58.8)	107 (43.5)
Nausea	87 (17.7)	24 (10.5)	7 (2.8)
Neutrophil count decreased	80 (16.3)	28 (12.3)	26 (10.6)
Platelet count decreased	78 (15.9)	39 (17.1)	9 (3.7)
White blood cell count decreased	78 (15.9)	21 (9.2)	6 (2.4)
Fatigue	74 (15.1)	20 (8.8)	24 (9.8)

Preferred Term	Safety pool (N=491) n (%)	OP-103 Melflufen + dex (N=228) n (%)	OP-103 Pomalidomide + dex (N=246) n (%)
Diarrhoea	52 (10.6)	13 (5.7)	11 (4.5)
Asthenia	50 (10.2)	18 (7.9)	16 (6.5)

TEAE: Treatment emergent adverse event.

Notes: If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term. Data as of 03 February 2021 are included for Study OP-103; Data as of 05 April 2021 are included for Study OP-107; Data as of 31 March 2020 are included for Study OP-106; Data as of 09 November 2017 are included for Study O-12-M1.

Serious adverse event/deaths/other significant events

Deaths

Safety Pool

In the Safety Pool, a total of 260 patients (53.0%) died during the studies, of which 23 patients (4.7%) died ≤30 days after the last dose of melflufen. The main cause of death was disease progression, a total of 45 patients (9.2%) experienced 56 fatal TEAEs (Table 22).

Table 21 Treatment-emergent AEs with fatal outcome occurring in >1 patient by preferred term (Safety pool)

Preferred Term	Total (N=491) n (%)
Patients with at least 1 TEAE with a fatal outcome ^a	45 (9.2)
COVID-19 pneumonia	7 (1.4)
Pneumonia	5 (1.0)
Respiratory failure	4 (0.8)
General physical health deterioration	3 (0.6)
Abdominal mass	2 (0.4)
Cardiac arrest	2 (0.4)
Escherichia sepsis	2 (0.4)
Multiple organ dysfunction syndrome	2 (0.4)
Neutropenia	2 (0.4)
Renal failure	2 (0.4)
Septic shock	2 (0.4)
Urinary tract infection	2 (0.4)

TEAE: Treatment emergent adverse event. a Adverse event reported as outcome FATAL.

If a patient experienced more than 1 episode of a TEAE, then the patient was counted only once within a preferred term. Preferred terms are reported using the Medical Dictionary for Regulatory Activities version 19.1 or later.

Note: Data as of 03 February 2021 are included for Study OP-103; Data as of 05 April 2021 are included for Study OP-107; Data as of 31 March 2020 are included for Study OP-106; Data as of 09 November 2017 are included for Study O-12-M1.

Nine events in 7 patients were considered (possibly) related to melflufen. These events included Escherichia sepsis, neutropenia, pneumonia, pneumonia influenzal, bacteraemia, cardiac failure, acute pancytopenia, and cardiac arrest.

OP-103

In study OP-103, 106 patients (46.5%) in the melflufen + dexamethasone group and 106 patients (43.1%) in the pomalidomide + dexamethasone group died during the study. Progressive disease was the primary cause of death in both treatment arms.

A total of 27 patients (11.8%) in the melflufen + dexamethasone group and 32 patients (13.0%) in the pomalidomide + dexamethasone group had a TEAE reported with a fatal outcome. All of the fatal TEAEs in the melflufen + dexamethasone group were considered by the Investigator to be unrelated to melflufen, with the exception of pancytopenia and cardiac failure acute in one patient, which were considered possibly related. All of the fatal TEAEs in the pomalidomide + dexamethasone group were considered by the Investigator to be unrelated to pomalidomide + dexamethasone, with the exception of COVID-19 pneumonia, myelodysplastic syndrome in one patient each, and pneumonia in two patients, which were considered possibly related.

SAEs

Safety Pool

Treatment emergent SAEs reported by at least 2% of patients in the Safety Pool are summarized in Table 23. A total of 220 patients (44.8%) experienced a total of 428 SAEs. Most SAEs were reported for less than 2% of patients; the only SAEs reported for more than 5% of patients was the MedDRA PT pneumonia (7.9%).

OP-103

Frequencies of overall patients with one SAE or one treatment-related SAE were comparable between treatment arms. Infections were the most common SAEs in both treatment arms. In the melflufen + dexamethasone group, the most frequently reported SAEs by PT were pneumonia (5.7% vs 8.5% in pomalidomide + dexamethasone group), thrombocytopenia (3.9% vs. 1.2% in pomalidomide + dexamethasone arm), and anemia (3.1% vs 2.0% in pomalidomide + dexamethasone group). SAEs in the MedDRA SOC Blood and lymphatic system disorders were more common in the melflufen + dexamethasone arm (9.2%) than in the pomalidomide + dexamethasone arm (4.5%).

Table 22 Treatment-emergent SAEs by PT reported by at least 2% of patients in the Safety pool.

Preferred Term	Safety pool (N=491) n (%)	OP-103 Melflufen + dex (N=228) n (%)	OP-103 Pomalidomide + dex (N=246) n (%)
Patients with at least 1 treatment-emergent SAE	220 (44.8)	95 (41.7)	113 (45.9)
Pneumonia	39 (7.9)	13 (5.7)	21 (8.5)
Thrombocytopenia	16 (3.3)	9 (3.9)	3 (1.2)
Febrile neutropenia	15 (3.1)	4 (1.8)	2 (0.8)
Anaemia	11 (2.2)	7 (3.1)	5 (2.0)
COVID-19 pneumonia	11 (2.2)	11 (4.8)	9 (3.7)
Neutropenia	11 (2.2)	4 (1.8)	3 (1.2)

SAE: Serious adverse event.

If a patient experienced more than 1 TEAE within a given preferred term, then the patient was counted only once for that preferred term. Preferred terms are reported using the Medical Dictionary for Regulatory Activities version 19.1 or later.

Note: Data as of 03 February 2021 are included for Study OP-103; Data as of 05 April 2021 are included for Study OP-107; Data as of 31 March 2020 are included for Study OP-106; Data as of 09 November 2017 are included for Study O-12-M1.

Adverse events of special interest

Adverse events of special interest (AESI) were identified by evaluating expected AEs for the drug class and the evolving safety profile for melflufen and determining the clinical significance of the reported AEs based on medical review of the type of event as well as its frequency, severity, and potential relatedness to melflufen. An overall summary of AESIs is provided in Table 24.

Table 23 Overall summary of adverse events of special interest (Safety Pool and OP-103)

AESI	Safety pool (N=491) n (%)	OP-103 Melflufen + dex (N=228) n (%)	OP-103 Pomalidomide + dex (N=246) n (%)
Thrombocytopenia	408 (83.1)	198 (86.8)	58 (23.6)
Neutropenia	354 (72.1)	161 (70.6)	135 (54.9)
Anaemia	323 (65.8)	153 (67.1)	93 (37.8)
Febrile Neutropenia	19 (3.9)	6 (2.6)	4 (1.6)
Infections	254 (51.7)	114 (50.0)	137 (55.7)
Infective pneumonia	108 (22.0)	38 (16.7)	60 (24.4)
Bleeding Events	101 (20.6)	36 (15.8)	16 (6.5)
Second Primary Malignancies	10 (2.0)	3 (1.3)	6 (2.4)
MDS/AML	4 (0.8)	1 (0.4)	1 (0.4)

AESI: Adverse event of special interest; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome.

AESIs were defined using Standardized or modified Standardized (broad scope) or Customized MedDRA queries or multiple preferred terms (see Module 2.7.4, Section 2.7.4.1.1.3.4.2).

Note: Data as of 03 February 2021 are included for Study OP-103; Data as of 05 April 2021 are included for Study OP-107; Data as of 31 March 2020 are included for Study OP-106; Data as of 09 November 2017 are included for Study O-12-M1.

Safety Pool

Thrombocytopenia and bleeding events

A total of 408 patients (83.1%) had at least 1 AESI of thrombocytopenia, whereof 363 patients (73.9%) experienced Grade 3 or 4 events of thrombocytopenia. The median time to onset of the first event was 43.0 days (range: 1-451 days). Of these patients, 71 (14.5%) experienced a concomitant bleeding event of any grade at least once; there was only one bleeding event of grade 4 and one bleeding events of grade 5 concomitant with a grade 3 or 4 thrombocytopenia. Bleeding events were observed in 101 patients (20.6%). Out of these, 11 (2.2%) experienced Grade 3 bleeding events, and 1 patient experienced a single Grade 4 bleeding event, an epistaxis, considered related to study drug. One Grade 5 SAE of subdural hematoma, considered unrelated to study drug, was reported.

Neutropenia, infections, infective pneumonia, and febrile neutropenia

A total of 354 patients (72.1%) had at least 1 AESI of neutropenia, whereof 325 patients (66.2%) experienced Grade 3 or 4 neutropenia. The median time to onset of the first event of Grade 3 or 4 neutropenia was 22 days. Of these patients with grade 3 or 4 neutropenia, 104 (21.2%) experienced a concomitant infection of any grade; two patients experienced three Grade 5 infections. A total of 254 patients (51.7%) had at least 1 AESI of infection, whereof 73 patients (14.9%) experienced Grade 3 infections. Five patients (1.0%) experienced Grade 4 infections and 20 patients (4.1%) experienced Grade 5 infections.

A total of 108 patients (22.0%) had at least 1 AESI of infective pneumonia. Thirty-seven (7.5%) of patients had infective pneumonia starting in a cycle concomitant with grade 3 or 4 neutropenia.

Nineteen patients (3.9%) had at least 1 AESI of febrile neutropenia. All febrile neutropenia AESIs except 1 Grade 2 event were Grade 3 or 4 in severity.

Anaemia

A total of 323 patients (65.8%) had at least 1 AESI of anaemia, 40.9% and 1.2% of patients, respectively, experienced Grade 3 or 4 anaemia.

Management of haematological events:

Most patients received supportive treatment; 68.4% received colony stimulating factors (57.8% filgrastim) and 57.6% of patients received blood substitutes and perfusion solutions (27.1% platelets and 43.2% red blood cells). Thrombocytopenia and neutropenia were also the most commonly reported PTs resulting in dose modifications (see section below on discontinuations of adverse events).

Second primary malignancies

Among the 491 patients in the Safety pool, 10 patients (2.0%) experienced SPMs. Of these 10 patients, a total of 4 patients (0.8%) with MDS were reported, including 3 patients with MDS and 1 patient with refractory cytopenia with multilineage dysplasia and ringed sideroblasts. All events were considered related to melflufen by the investigators. The remaining 6 patients experienced in total 9 other SPMs (4 events of squamous cell carcinoma, 3 of basal cell carcinoma, and 1 each of oesophageal carcinoma and malignant melanoma). All these events were considered not related to melflufen, with the exception of 1 event of squamous cell carcinoma. Two additional patients reported MDS/AML during the overall survival follow-up, but were not reported as AEs.

OP-103

The AESIs thrombocytopenia, anaemia, and neutropenia frequently occurred in both treatment arms with higher frequencies in the melflufen + dexamethasone arm (see Table 24). Bleeding events were more frequent in the melflufen + dexamethasone arm (15.8%) compared to the pomalidomide + dexamethasone arm (6.5%). Severe (Grade 3) bleeding events (AESI) in connection with AESIs of thrombocytopenia occurred only in the melflufen + dexamethasone arm but were uncommon (n=2 (0.9%) patients). There were no life-threatening (Grade 4) or fatal (Grade 5) bleedings in connection with thrombocytopenia.

The overall frequencies of patients with AESIs of infection were similar in both treatment arms, 50.0% and 55.7% in melflufen + dexamethasone and pomalidomide + dexamethasone, respectively. Grade 3 or 4 infections were more common in the pomalidomide + dexamethasone arm (21.5% vs 13.2%). The frequency of infections in connection with Grade 3 or 4 AESIs of neutropenia were similar in the 2 treatment arms (12.7% vs 15.0%) despite Grade 3 or 4 neutropenias being more frequent in the melflufen + dexamethasone arm (64.5% vs 49.2%). Febrile neutropenia occurred more frequently with melflufen + dexamethasone (2.6% vs. 1.6%).

Management of haematological events

Supportive care and concomitant medication use was higher in the melflufen+dex compared to pomalidomide+dex; immunostimulants (colony stimulating factors [ATC level 4]) (67.1 % vs 42.2%) and blood substitutes and perfusion solutions (51.6% vs 27.3%) including red blood cells (31.7% vs. 14.1% and platelets (23.2% vs. 4.0%).

Three and six patients in the melflufen + dexamethasone (1.3%) and pomalidomide + dexamethasone (2.4%) groups, respectively, reported an AESI of SPM and 1 patient in each treatment group (0.4%) reported a TEAE of MDS.

Laboratory findings

Clinical laboratory evaluations, including haematology and serum chemistry, confirm the safety profile of melflufen. Shifts in haematologic parameters are common and in line with the TEAE profile. The only exception being lymphocyte count decrease which is a common laboratory finding despite seldom being reported as a TEAE.

Shifts in chemistry parameters to Grade 3 or 4 were uncommon and there were no clinically relevant changes in serum chemistry parameters.

There were no clinically relevant changes for ECG or vital sign measurements.

Safety in special populations

Selected AESIs (thrombocytopenia, neutropenia, febrile neutropenia, infections, infective pneumonia, anaemia, bleeding events and MDS/AML) were summarised per subgroup (age, sex, race, BSA, baseline CrCl, and weight). An analysis of safety data by subgroup did not identify clinically meaningful differences, although there were some imbalances in the incidence of certain AEs. These could partly be explained by low numbers in some subgroups and there were no signs for a consistent increase in AESIs in certain subgroups except for patients with renal impairment. A larger effect of melflufen on thrombocyte levels was observed in patients with a lower GFR. Based on an additional renal impairment study and population PK analysis, a melflufen dose of 30 mg is recommended in patients with eGFR 30-45 mL/min/1.73 m² and close monitoring is warranted in case of renal impairment.

Discontinuation due to adverse events

Safety Pool

A total of 139 patients (28.3%) had at least 1 TEAE associated with withdrawal of study drug and 85 patients (17.3%) had at least 1 melflufen-related TEAE associated with drug withdrawn. The most common melflufen-related TEAE associated with drug withdrawn was thrombocytopenia (10.6%), followed by neutropenia (3.3%), anaemia (1.8%), and platelet count decreased (1.2%).

A total of 209 patients (42.6%) had at least 1 TEAE associated with a dose reduction, and 172 patients (35.0%) had at least 1 melflufen-related TEAE associated with dose reduction. The most common melflufen-related TEAE associated with dose reduction was thrombocytopenia (21.4%), followed by neutropenia (7.9%), platelet count decreased (6.5%), anaemia (3.3%), and neutrophil count decreased (2.0%). A total of 336 patients (68.4%) had at least 1 TEAE associated with a drug interruption, and 269 patients (54.8%) had at least 1 melflufen-related TEAE associated with drug interruption. The most common melflufen-related TEAE associated with drug interruption was thrombocytopenia (34.0%), followed by neutropenia (21.6%), anaemia (8.6%), platelet count decreased (8.4%), and neutrophil count decreased (4.7%).

OP-103

A comparable percentage of patients in the melflufen + dexamethasone group compared with the pomalidomide + dexamethasone group had a TEAE resulting in discontinuation of study drug (26.3% vs 22.8%, respectively). A total of 26.3% of patients in the melflufen + dexamethasone group had at

least one TEAE leading to discontinuation of melflufen and 22.0% of patients in the pomalidomide + dexamethasone group had at least one TEAE leading to discontinuation of pomalidomide. The most commonly reported melflufen-related TEAE resulting in permanent discontinuation of melflufen by PT was thrombocytopenia (7.9%) followed by neutropenia (2.2%). The most commonly reported pomalidomide-related TEAE resulting in permanent discontinuation of pomalidomide by PT was pneumonia (2.8%), followed by anaemia (2.0%).

A higher percentage of patients in the melflufen + dexamethasone group compared with the pomalidomide + dexamethasone group had a TEAE resulting in dose reductions of study drug (50.4% vs 26.8%, respectively). A total of 46.9% of patients in the melflufen + dexamethasone group had a TEAE resulting in dose reduction of melflufen and 15.0% of patients in the pomalidomide + dexamethasone group had a TEAE resulting in dose reduction of pomalidomide. The most commonly reported TEAEs associated with dose reduction of melflufen were thrombocytopenia (31.1%) and neutropenia (12.3%). The most commonly reported TEAE resulting in dose reduction of pomalidomide was neutropenia (7.7%) and thrombocytopenia (2.0%).

Also, a higher percentage of patients in the melflufen + dexamethasone group compared with the pomalidomide + dexamethasone group had a TEAE resulting in dose delay of any study drug (67.1% vs 45.5%, respectively). A total of 137 patients (60.1%) had a TEAE resulting in dose delay of melflufen and 109 patients (44.3%) had a TEAE resulting in dose delay of pomalidomide. The most commonly reported TEAEs associated with dose delay of melflufen were thrombocytopenia (35.1%) and neutropenia (20.2%). The most commonly reported TEAEs resulting in dose delay of pomalidomide were neutropenia (15.4%) and pneumonia (5.3%).

AEs by prior ASCT status

Safety Pool

A total of 204 patients (41.5%) in the Safety Pool had a prior ASCT with progression within 36 months post ASCT, and 287 (58.5%) had no prior ASCT or post-ASCT progression after >36 months. The melflufen exposure in patients with no prior ASCT or post-ASCT progression after >36 months is longer than in patients with an early progression after ASCT, with a median treatment duration of 24.9 vs 15.4 weeks and a median number of treatment cycles of 6 vs 3, respectively.

An overview of TEAEs by ASCT status based on frequencies and events per patient year is shown in Table 25. With the exception of TEAEs leading to drug withdrawal, the percentage of patients with TEAEs is similar between groups. On the other hand, when adjusted for exposure time, events per patient year were numerically lower for all presented type of TEAEs in patients with no prior ASCT or post-ASCT progression after >36 months compared to early progressors post-ASCT.

Table 24 Overview of TEAEs by frequency and number of events per patient year by ASCT status (Safety Pool)

	Post-ASCT progression ≤ 36 months (N = 204)		No ASCT or Post-ASCT progression >36 months (N = 287)	
Median study drug exposure	15.4 weeks		24.9 weeks	
	Frequency	Events / patient year	Frequency	Events / patient year
Any TEAE	99.5%	43.1	99.7%	30.8
Grade 3/4 TEAE	92.6%	19.1	90.2%	12.7
Serious TEAE	42.6%	2.1	46.3%	1.4
TEAEs leading to dose delay	64.2%	5.5	62.7%	3.7
TEAEs leading to dose reduction	35.3%	1.4	35.9%	1.0
TEAEs leading to drug withdrawal	32.4%	1.1	23.0%	0.5

TEAE: Treatment emergent adverse event; ASCT: Autologous stem cell transplant

A similar pattern was observed when comparing frequencies for TEAEs of special interest (AESIs) by ASCT subgroup with overall comparable frequencies of events between subgroups, except for a numerically higher frequency of thrombocytopenia in early progressors (89.2% vs 78.7%) (Table 25). The number of all selected AESIs per patient year was lower among patients with no ASCT or post-ASCT progression after >36 months compared to early progressors post-ASCT (Table 28).

Table 25 Overall summary of adverse events of special interest on all cycles by ASCT status (Safety Pool)

	ASCT ^a N=204	No ASCT ^a N=287
Thrombocytopenia	182 (89.2)	226 (78.7)
Neutropenia	148 (72.5)	206 (71.8)
Febrile Neutropenia	9 (4.4)	10 (3.5)
Infections	95 (46.6)	159 (55.4)
Infective Pneumonia	39 (19.1)	69 (24.0)
Anemia	140 (68.6)	183 (63.8)
Bleeding Events	47 (23.0)	54 (18.8)
Second Primary Malignancies	5 (2.5)	5 (1.7)
MDS/AML	3 (1.5)	1 (0.3)

Abbreviations: AML Acute myeloid leukemia; ASCT Autologous stem cell transplant; MDS Myelodysplastic syndrome.

a Last prior ASCT with progression within 36 months

b No ASCT or ASCT with progression after ≥36 months

Table 26 Most common (>0.6 events per patient year) AESIs by events per patient year (Safety Pool)

	Post-ASCT ≤36 months N=204 Events/patient year		No ASCT or Post-ASCT progression>36 months N=287 Events/patient year	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	10.0	6.9	6.9	4.5
Bleeding events	0.8	0.1	0.5	<0.1
Neutropenia	8.4	5.8	6.4	4.3
Infections	2.2	0.4	1.9	0.5

Anemia	5.4	2.5	3.3	1.2
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AESI: Adverse event of special interest; ASCT: autologous stem cell transplantation

OP-103

Median study drug exposure in the target indication population of Study OP-103 was 35.1 weeks compared to 16.0 weeks in patients in the melflufen + dexamethasone arm with an early progression after ASCT. A summary safety profile based on frequencies as well as events per patient year is shown in Table 28. Frequencies were in general comparable except for more discontinuations in the post-ASCT progression ≤ 36 months group. When comparing AESI for melflufen + dexamethasone arm in patients with ASCT and TTP 36 months versus patients with no ASCT or TTP >36 months, the main difference was an increase in grade 3/4 thrombocytopenia (85.7% vs 70.1%) in early progressors. Upon adjustment for exposure time, events per patient year were in general lower in the target indication population.

Table 27 Overview of TEAEs by frequency and number of events per patient year by ASCT status (Safety population OP-103)

	Safety Population (N=228)	Post-ASCT progression ≤ 36 months (N = 91)		Target indication population (N = 137)	
Median study drug exposure	25.1 weeks	16.0 weeks		35.1 weeks	
	Frequency	Frequency	Events / patient year	Frequency	Events / patient year
Any TEAE	99%	99%	31.8	99%	24.0
Grade 3/4 TEAE	90%	92%	16.6	88%	11.2
Serious TEAE	42%	38%	1.6	44%	1.1
TEAEs leading to melflufen dose reduction	47%	45%	1.7	48%	1.0
TEAEs leading to melflufen dose delay	60%	63%	4.3	58%	3.1
TEAEs leading to melflufen treatment discontinuation	26%	31%	0.9	23%	0.4
Fatal TEAE	12%	13%	0.3	11%	0.2

TEAE: Treatment emergent adverse event; ASCT: Autologous stem cell transplant

When comparing the target indication population with the corresponding pomalidomide + dexamethasone population, exposure to study drug is longer with melflufen than with pomalidomide (35 weeks vs. 22 weeks). Upon adjustment for exposure time, TEAEs, including TEAEs Grade 3/4 were still more common with melflufen in the target indication population (Table 29). This reflects the higher number of haematologic TEAEs, especially thrombocytopenia. Other events were more or less comparable.

Table 28 Overview of TEAEs by number of events per patient year in patients with no ASCT or Post-ASCT progression ≥ 36 months (Safety population OP-103)

	Melflufen+dex (N = 137)	Pomalidomide+dex (N = 147)
	Events / patient year	Events / patient year
Any TEAE	24.0	16.8
Grade 3/4 TEAE	11.2	5.7
Serious TEAE	1.1	1.8
TEAEs leading to dose modification	4.5	3.3
TEAEs leading to treatment discontinuation	0.4	0.7
Fatal TEAE	0.2	0.3

TEAE: Treatment emergent adverse event; ASCT: Autologous stem cell transplant

Peripheral administration

OP-109 PORT study

A Randomized, Two-period, Cross-over, Phase 2 Study, Comparing the Pharmacokinetics, and Assessing Safety and Tolerability of Peripheral and Central Intravenous Administration of Melflufen in Patients with Relapsed and Refractory Multiple Myeloma.

Study OP-109 was a randomized, 2-period, crossover, Phase 2 study designed to evaluate and compare PK and to assess safety, tolerability, and efficacy of melflufen in patients with RRMM when it is administered via peripheral or central IV infusion. The study was performed in 13 centers, the first subject enrolled on 04 August 2020 and the planned date for the last subject completed was 10 January 2022. The study was early terminated based on a FDA-request (04 November 2021). An interim CSR was submitted for the primary objectives of PK and safety analyses (DCO: 02 June 2021) and a supplemental CSR was submitted for efficacy data (secondary and exploratory objectives) including a safety update (DCO: 11 February 2021).

The study included adult patients with RRMM, defined as at least 2 prior lines of therapy and refractory to an immunomodulatory drug (IMiD) and a proteasome inhibitor (PI), including patients intolerant to an IMiD/PI after at least two 28-day cycles of therapy. Patients were randomized (1:1) to Arm A or Arm B (Figure 10). For each arm, treatment was given in 28-day cycles and could be given in an outpatient treatment setting. PK samples were collected at Day 1 of Cycles 1 and 2. Samples were drawn 5, 10, 15, 20, 25, and 30 minutes after the start of the infusion, and 5, 10, 15, 30, 60, 120, and 240 minutes after the end of the melflufen infusion.

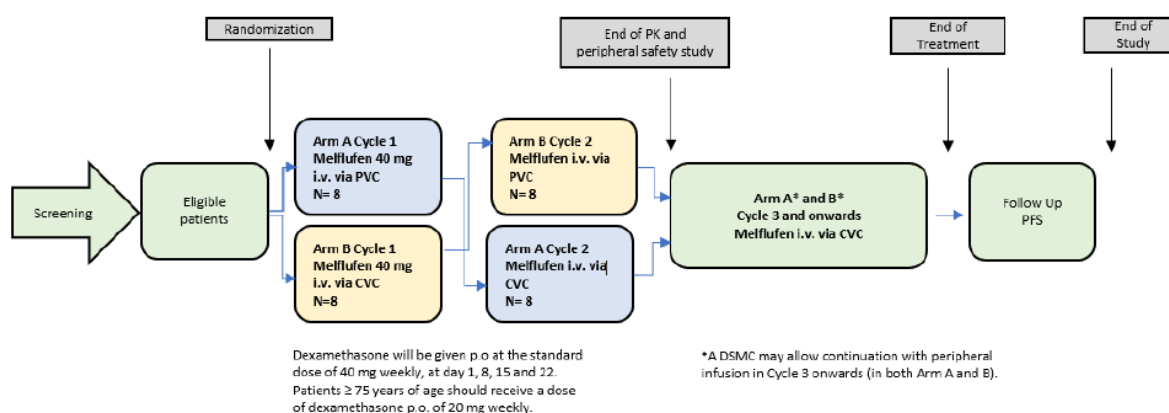


Figure 9 Study design OP-109

Note: 14 patients were allocated to Arm A and 13 to Arm B.

The primary objectives were:

- To evaluate and compare the PK variables maximum observed concentration (C_{max}), area under curve from 0 hours to the last measurable concentration (AUC(0-t)), and area under curve from 0 hours to infinity (AUC(0-∞)) of melphalan after central and peripheral IV infusion of melflufen
- To assess the local tolerability of peripheral IV administration of melflufen

Secondary objectives were:

- To evaluate and compare the PK variables C_{max}, AUC(0-t), and AUC(0-∞) of melflufen and desethyl-melflufen, and to evaluate the elimination half-life for melflufen, melphalan, and desethyl-melflufen after central and peripheral IV infusion of melflufen
- To assess safety and general tolerability of melflufen
- To evaluate efficacy: best response during the study, overall response rate (ORR), clinical benefit rate (CBR), duration of response (DOR), duration of clinical benefit (DOCB), time to response (TTR), time to progression (TTP), time to next treatment (TTNT), and progression-free survival (PFS)

A complete CSR was provided by the MAH. The description of results in the current AR is limited to the primary objectives as these concern the comparison between central and peripheral IC administration of melflufen.

Results:

The Safety Analysis Set (similar to Full Analysis Set) comprised 27 patients (14 patients in Arm A and 13 patients in Arm B).

Median age for the Full Analysis Set was 67.0 years (range 44 to 80 years); 13 patients (48.1%) were male; and all were Caucasian/White. Patients had received a median of 4 prior lines of therapy (range 2 to 10). At study entry, 9 patients (33.3%) had derived International Staging System (ISS) Stage I disease, 12 patients (44.4%) had derived ISS Stage II disease, and 5 patients (18.5%) had derived ISS Stage III disease. Derived ISS staging was missing in 1 patient. A total of 9 patients (33.3%) had received an autologous transplant. Cytogenetic testing at study entry revealed high-risk cytogenetics in 13 patients (48.1%). At Baseline, 8 patients (29.6%) had an ECOG status of 0, 18 patients (66.7%) had a score of 1, and 1 patient (3.7%) had a score of 2. Patients in Arm A were younger than patients in Arm B (median age: 60.5 versus 72.0 years). The sequence arms were similar for other demographic and baseline characteristics.

As of the data cut-off on 02 June 2021 (interim CSR), 15 patients (55.6%) had permanently discontinued treatment: 10 patients (66.7%) due to disease progression, 4 patients (26.7%) due to AEs, and 1 patient (6.7%) due to physician decision.

Primary endpoints

- **Pharmacokinetics**

The PK Analysis Set comprised patients who had adequate PK samples after their first 2 cycles of treatment and included 21 patients (13 patients in Arm A and 8 patients in Arm B). These data have been included in the popPK model in the initial MAA. There was no difference in pharmacokinetics of melphalan following central and peripheral IV infusion of melflufen.

- **Local tolerability of peripheral IV administration**

Median duration of treatment for patients in the overall Safety Analysis Set was 13 weeks (range 4.1 to 41.4 weeks), with a median of 3 cycles per patient (range 1 to 9). As of the data cut-off for the interim CSR, the maximum number of cycles per patient was 9 cycles (2 patients; 7.4%).

In Arm A, 14 patients received melflufen via PVC in Cycle 1, of whom 13 patients (92.9%) continued to Cycle 2 (CVC). In Arm B, 13 patients received melflufen via CVC in Cycle 1, of whom 8 patients (61.5%) continued to Cycle 2 (PVC).

The peripheral infusion site was inspected pre- and post-infusion for any local reaction (including but not limited to redness, swelling, and signs of phlebitis or extravasation) and graded using CTCAE 5.0, and visual infusion phlebitis (VIP) score. All signs of extravasations or phlebitis were to be photo documented at least daily until resolution. At the time of the data cut-off for the interim CSR, no local infusion-related reactions had been reported in this study.

Post marketing experience

There are no new post-marketing data available from the USA as melflufen has not been commercially available in the USA since October 2021.

Post-marketing surveillance data for Europe as of 2023-02-06, the data lock point (DLP) for the first Pepaxti PSUR, are very limited due to low exposure. At the time of the DLP it is calculated that 3 patients have received at least 1 dose of Pepaxti. There have been no spontaneous safety reports from these patients. In addition, melflufen corresponding to approximately 350 treatment cycles has been distributed for use in a Managed Access Program in Europe.

There were no new safety signals. Overall, the safety profile during post-marketing use is similar to what has been seen in clinical studies, with thrombocytopenia being the most frequently reported event.

2.5.1. Discussion on clinical safety

The pooled safety data of melflufen comprising 491 patients from 4 clinical studies forms the basis for the description of the safety profile in the currently approved SmPC. A total of 431 patients received melflufen at a starting dose of 30 or 40 mg in combination with dexamethasone for a 28 day treatment cycle, in line with the recommended dose. Main safety data within the Safety Pool are derived from study OP-106 (n=157, pivotal study for the currently approved indication) and study OP-103 (n=228) which is the pivotal study for this variation application. Safety data from study OP-103 has been presented and discussed in the previous initial application which was based on study OP-106

(EMA/H/C/005681). The discussion here briefly summarises the overall safety profile, and where relevant highlights differences based on the newly proposed indication.

Safety Pool

The safety database is limited in terms of exposure time, with a median treatment duration of 20 weeks and median number of 4 treatment cycles. Nevertheless, the lack of long-term safety data for the product was not considered of major concern given the long-term clinical experience with melphalan as antitumor agent. Treatment duration with melflufen was slightly longer in study OP-103 (median duration of 25 weeks and median of 5 cycles started) compared to the overall safety database, reflecting the patients' earlier disease stage in study OP-103 compared study OP-106. Exposure in the melflufen + dexamethasone arm was comparable to the pomalidomide + dexamethasone arm exposure (median duration of 22 weeks and median of 5 cycles started).

The safety profile is primarily characterised by haematological TEAEs consistent with the mechanism of action (alkylating agent) and resembles that of melphalan, the main metabolite of melflufen. The MAH is requested to present frequencies for grade 3/4 TEAEs within the Safety Pool and OP-103, where relevant, regardless of maximum grade (**OC**). Thrombocytopenia, anaemia, and neutropenia were each reported in over half of the patients. These events were also the most commonly reported $\geq$ grade 3 events, but SAEs were observed less frequently and highest for thrombocytopenia (3.3% by PT). Thrombocytopenia was also the main TEAE resulting in drug discontinuation (11.6% of patients). Haematological events were manageable in most cases with dose modifications and supportive treatments and regular monitoring of blood counts is required (section 4.2 and 4.4 SmPC). Patients with platelet count $<50 \times 10^9/L$ or baseline ANC count $<1 \times 10^9/L$ were excluded from the studies and treatment in these patients is not recommended (section 4.2 and 4.4 SmPC). Thrombocytopenia may lead to serious bleeding events. A total of 14.5% had a grade 3 or 4 thrombocytopenia and concomitant haemorrhage, most of these bleedings were grade 1 or 2 and severe bleedings were infrequent. The overall frequency of bleeding events was 20.6% and also mostly of low grade. An appropriate warning for the risk of bleeding is included in the SmPC (section 4.4) and the most common bleedings (PT Epistaxis and PT Haematoma) are included in section 4.8 of the SmPC.

Neutropenia can lead to infections and 21.2% of patients reported an AESI of infection and concomitant Grade 3 or 4 neutropenia. About half of the patients reported AESIs of infections, and infective pneumonia was the most commonly reported event. Pneumonia was also the most commonly reported SAE (7.9%). Some patients experienced infections with fatal outcome (section 4.8 SmPC), which is of concern. An appropriate warning for the risk of infections is included in the SmPC (section 4.4), as well as a recommendation for prophylactic concomitant treatment with antimicrobials (section 4.2 and 4.4 SmPC). Febrile neutropenia is another potentially serious consequence of neutropenia for the patient and reported as SAE in 3.1% of the patients. Supportive treatment with haematopoietic growth factors was allowed in the studies and frequently reported, its use is recommended in section 4.4. SmPC.

Non-haematological TEAEs frequently reported with melflufen were asthenia, nausea, diarrhoea, fatigue, pyrexia, and upper respiratory tract infection (range 12.8% to 21.6%). Gastrointestinal events were mostly grade 1 or 2 and well known for melphalan. A recommendation for prophylactic concomitant use of anti-emetics is included (section 4.2 SmPC). Asthenia and fatigue were mostly grade 1 or 2 and known adverse events for treatments of MM. The risk of secondary primary malignancies (SPMs) was identified as an AESI and 10 patients had at least one AESI of SPM. Four patients reported MDS/AML as AESI (section 4.4 and 4.8 SmPC).

Melphalan in combination with amongst others dexamethasone has been associated with an increased risk of thromboembolic complications. Pulmonary embolism and deep vein thrombosis were therefore added to section 4.8 and an appropriate warning was included in section 4.4 for melflufen.

Laboratory findings were in line with the reported AEs.

No clinical meaningful interactions were observed based on intrinsic or extrinsic factors, except that a larger effect of melflufen on thrombocyte levels was observed in patients with a lower GFR. Based on an additional renal impairment study and population PK analysis, a melflufen dose of 30 mg is recommended in patients with eGFR 30-45 mL/min/1.73 m² and close monitoring is warranted in case of renal impairment (section 4.4 SmPC).

OP-103

The safety profile in OP-103 resembles that seen before in study OP-106 in the later line setting and no new safety signals were identified. This also holds true compared to the overall Safety Pool. Frequencies of some non-haematological events were numerically lower, which may reflect the earlier line setting. As seen before, haematological and GI events were the most frequently observed events. More patients (10% difference) in the melflufen + dexamethasone arm had grade 3/4 TEAEs compared to pomalidomide + dexamethasone arm and more patients had a dose reduction or dose delay due to TEAEs, indicating an overall lower tolerability for melflufen + dexamethasone. This is mainly explained by the difference in haematological events which were more frequently observed in the melflufen + dexamethasone arm compared to the pomalidomide + dexamethasone arm (thrombocytopenia: 70.2% vs 19.5%; anaemia: 66.7% vs 37.4%; neutropenia: 60.1% vs 45.9%). On the other hand, SAEs (41.7% vs 45.9%), grade 5 TEAEs (11.8% vs 13.0%), and drug discontinuations (26.3% vs 22.0%) occurred at comparable rates. Infective pneumonia (24.4% vs 16.7%) and grade 3 or 4 infections (21.5% vs 13.2%) were more frequently reported for pomalidomide + dexamethasone. Most subjects in the melflufen + dexamethasone arm received supportive treatment with haematopoietic growth factors.

Of note, melflufen is administered via central venous administration which may be associated with an increased risk of thrombosis as well as infections. Results from study OP-109 comparing PK and safety of a single peripheral and central intravenous administration in a limited number of patients suggest that peripheral administration constitutes a suitable alternative. Results showed that there was no difference in pharmacokinetics of melphalan following central and peripheral IV infusion of melflufen. In addition, no local infusion-related reactions were observed. Peripheral administration is further supported by the experience obtained with melphalan. The information in section 4.2 of the SmPC is considered adequate.

Safety profile by prior ASCT status

Within the initial application, the potential detrimental effect observed for OS in Study OP-103 was extensively discussed from an efficacy and safety perspective. Briefly, the safety data indicated that overall tolerability of melflufen + dexamethasone is lower than for pomalidomide + dexamethasone, as shown by higher frequencies of treatment-related grade 3/4 events and dose modifications. On the other hand, frequencies of SAEs and fatal events were in the same order of magnitude, and it was considered unlikely that the OS detriment could be explained by a direct toxicological effect of melflufen. OS subgroup analyses indicated a differential effect based on prior ASCT and TTP and the indication was restricted to the subgroup of patients with no ASCT or TTP >36 months post-ASCT where no OS detriment was seen (see also efficacy discussion).

Given the restriction of the indication based on ASCT status, pooled safety data were previously also presented by prior ASCT status. Within the Safety Pool, almost 60% of the patients (n=287) had no prior ASCT or post-ASCT progression after >36 months. With the exception of TEAEs leading to drug withdrawal which occurred more frequently in patients with post-ASCT progression ≤36 months, the percentage of patients with TEAEs was comparable between groups for the overall summary of safety profile. Based on AESIs, the main difference was an increase in thrombocytopenia in patients with post-ASCT progression ≤36 months. As patients with early progression post-ASCT had a shorter median treatment duration (15.4 vs 24.9 weeks), the MAH also presented post-hoc safety data adjusted for exposure time, indicating a numerical improved tolerability in patients with no prior ASCT or post-ASCT progression after >36 months compared to early progressors based on the overall summary of safety profile. It appears reasonable to assume that pre-treatment with high dose of melphalan (200 mg/m²) negatively affects a patient's hematopoietic reserve and therefore these patients may be less likely to tolerate subsequent treatments that induce cytopenia and are more prone to develop haematological toxicity. Also for study OP-103, upon exposure adjustment overall safety data indicate a somewhat improved safety profile in the subgroup encompassing the **newly proposed target population (n=137)** compared to patients with early progression post-ASCT (n=91). Overall frequencies of events in the target population were in the same order of magnitude as observed in the ITT population of OP-103 for the melflufen arm. Upon adjustment for exposure time, TEAEs and TEAEs Grade 3/4 were still more common in the melflufen arm compared to the pomalidomide arm for the proposed target population, reflecting the higher number of haematologic TEAEs, especially thrombocytopenia. Other events like SAEs and fatal events were in the same order of magnitude upon adjustment for exposure time, or showed minor differences. It is of reassurance that there is no sign of an OS detriment in the newly proposed target population.

Overall, frequencies of adverse events were in the same order of magnitude for the overall population and by ASCT subgroup, with somewhat less discontinuations and thrombocytopenia in the newly proposed target population. These data support the use of overall safety pool for the safety information in the SmPC, enabling a more robust estimation of the safety profile based on higher patient numbers. Upon exposure adjustment, subgroup data per ASCT status suggest a better tolerability of melflufen + dexamethasone in the proposed target population compared to patients with early progression post-ASCT. These data are reassuring in that it is reasonable to exclude that the safety in the newly proposed target population is worse compared to the overall population.

Frequencies of adverse events in section 4.8 of the SmPC are based on the total safety pool which is considered acceptable.

2.5.2. Conclusions on clinical safety

Safety data are available from 491 patients, mostly from the recommended dose in combination with dexamethasone. No new safety signals were identified based on study OP-103 as the safety data was already presented within the initial application. The safety profile of melflufen appears non-negligible, although generally manageable with adequate monitoring and dose adjustment or discontinuation. The most important safety concerns are the haematological toxicities and the possible serious clinical consequences of infections and bleeds. These are understood to be related to the mechanism of action and well known for the active substance melphalan. Tolerability of melflufen was lower than for pomalidomide, however remains acceptable. Upon exposure adjustment, subgroup data per ASCT status suggest a better tolerability of melflufen + dexamethasone in the proposed target population compared to patients with early progression post-ASCT. These data are reassuring in that it is reasonable to exclude that the safety in the newly proposed target population is worse compared to the overall population.

Relevant safety information and recommendations are adequately presented in the SmPC based on the safety pool, enabling a more robust safety profile based on higher patient numbers.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version number 1.2 with this application. The (main) proposed RMP changes were the following:

- Update to remove severe renal impairment as “missing information” in sections SVII.3 and Part VI as the supplemental clinical study report for OP-107 (BRIDGE) that includes the final 4 patients with severe renal impairment has been submitted.
- Updated indication population in section SI due to extension of indication.
- To include peripheral administration.

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

Safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	none
Important potential risks	none
Missing information	none

Considering the data in the safety specification, the safety concerns listed above are appropriate.

Pharmacovigilance plan

The additional pharmacovigilance activity study OP-107 (BRIDGE) was removed from section III.2 of the RMP following the completion of the study and the submission of the supplemental CSR with data from with eGFR of ≥15 mL/min to <30 mL/min.

The removal of the study as is as additional pharmacovigilance activity is endorsed.

Risk minimisation measures

None.

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Elements for a public summary of the RMP

The elements for a public summary of the RMP do not require revision following the conclusion of the procedure.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Treatment of adult patients with multiple myeloma who have received at least two prior lines of therapies, whose disease is refractory to lenalidomide and the last line of therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation.

3.1.2. Available therapies and unmet medical need

Current treatment strategies in pre-treated relapsed/refractory (RR)MM patients focus on controlling disease progression and prolonging survival. These strategies include glucocorticoids (dexamethasone, prednisolone, methylprednisolone); chemotherapy (primarily alkylating agents, including high dose chemotherapy followed by autologous stem cell transplantation [ASCT]); proteasome inhibitors (PIs, such as bortezomib, carfilzomib and ixazomib); immunomodulatory agents (such as thalidomide,

lenalidomide and pomalidomide); monoclonal antibodies (such as daratumumab, isatuximab, elotuzumab and belantamab); the histone deacetylase inhibitor panobinostat; selective inhibitors of nuclear export (SINE) (selinexor); chimeric antigen receptor T-cells (CAR-T; idecabtagene vicleucel, and ciltacabtagene autoleucel); and the recently approved bispecific antibody teclistamab.

None of the approved medicinal products (mainly triple combinations) has provided a cure. Ultimately patients relapse and treatment options are exhausted. As such, patients exposed to lenalidomide and a PI, and refractory to lenalidomide have an unmet medical need. New effective and convenient treatment options are needed.

Melphalan flufenamide is a lipophilic derivative of melphalan aimed to enhance cell penetration and thus obtain higher intracellular concentrations than melphalan. Melphalan is formed from melphalan flufenamide upon intracellular hydrolysis by peptidases and is considered the main active substance of melflufen. Cross-linking of DNA is probably the most important factor for the cytotoxic effect. Melphalan itself is licensed for the treatment of multiple myeloma. In theory, this would allow treatment in third line RRMM patients as well. In clinical treatment guidelines, melphalan is recommended only in first line. In patients eligible for autologous stem cell transplantation (ASCT) it is used as part of the conditioning regimen, whereas in patients in-eligible for ASCT, melphalan could be used in combination with daratumumab, bortezomib and prednisone.

3.1.3. Main clinical studies

Main clinical data is derived from Phase 3 randomised controlled open-label Study OP-103 (OCEAN). This study compared the efficacy of melflufen + dexamethasone (dex) at the proposed dose vs. pomalidomide + dex at the approved dose in RRMM patients. Enrolled patients had documented disease progression with measurable disease, had received 2-4 prior lines of therapy, including lenalidomide and a PI, and were refractory to both the last line of therapy and to lenalidomide administered within 18 months prior to randomization. Of the 495 patients in Study OP-103, 145 patients in the melflufen+dex arm and 148 patients in the pomalidomide+dex arm had no prior ASCT or had progressed >36 months after ASCT, and comprised the applied target indication population.

The primary endpoint was PFS and key secondary endpoints ORR and OS (planned to be sequentially tested and alpha-controlled).

Supportive data is expected to be derived from Phase 2 Study OP-106 (HORIZON), a single arm study of melflufen in combination with dex in patients with RRMM who had received a minimum of 2 prior lines of therapy, including an IMiD and a PI, and who were refractory to pomalidomide and/or an anti-CD38 mAb.

Full clinical study reports for OP-103 and OP-106 were submitted to EMA during the MAA for melflufen in triple class refractory (TCR) RRMM patients after 3 prior treatment lines. Although the study design as well as results for the overall study population and TCR population were presented previously, data for the newly proposed target population in an earlier line (i.e. after 2 prior lines and refractory to lenalidomide and last line of therapy) are new in this EoI application. Potential reasons for the observed OS detriment in the overall study population of Study OP-103 and consequently post-hoc selection of the patients with no prior ASCT or had progressed >36 months after ASCT at the time of the MAA for melflufen are discussed in detail in the EPAR for the melflufen MAA and summarized below.

3.2. Favourable effects

Study OP-103

Overall study population - The primary endpoint median IRC assessed PFS was met for the overall study population with a median PFS of 6.83 months (95% CI 4.96, 8.54) in the melflufen + dex arm vs. 4.93 months (95% CI 4.24, 5.72) in the pomalidomide + dex arm. The stratified HR was 0.792 (95% CI: 0.640, 0.981; p=0.0319). The sensitivity analyses were in line with results from the primary PFS analysis. (Of note: key secondary endpoint ORR was not met and the second key secondary endpoint OS indicated an OS detriment for the overall study population.)

Target indication - Patients treated with melflufen+dex and no prior ASCT or disease progression >36 months after ASCT had an **PFS improvement of 4.63 months** as shown by a median PFS of **9.26 months** (95% CI 7.16-11.79) vs. **4.63 months** (95% CI: 3.65, 6.28) in the pomalidomide+dex arm (HR 0.577; 95% CI: 0.438; 0.760; nominal p =0.0001).

Key secondary endpoint **ORR** was **42.1%** (95% CI:33.9%, 50.5%) for melflufen+dex and **26.4%** (95% CI:19.5%, 34.2%; nominal p=0.0046) for pomalidomide+dex. Compared with the pomalidomide+dex treated patients, a numerical higher percentage of melflufen+dex treated patients achieved CR (4.8% vs 1.4%), VGPR (13.8% vs 6.8%) and PR (23.4% vs 18.2%). The **median duration of response** was **15.7 months** [95% CI: 9.23, NE] vs. **11.1 months** [95% CI: 7.36, 16.30] with a HR of 0.697 [95% CI: 0.40, 1.22]).

Key secondary endpoint **OS** showed a trend in favour of the melflufen+dex group **23.6 months** (18.89, 28.0) vs **19.1 months** (12.6, 26.5) with pomalidomide + dex, and a HR of 0.88 (95% CI: 0.67, 1.16; nominal p=0.3606, final analysis).

Study OP-106

Overall study population - The primary endpoint ORR based on Investigator (Inv) assessment in the overall study population was 29.3% (95% CI: 22.32%, 37.08%). Comparable results were obtained per Independent Review Committee (IRC). The median DoR was 5.5 months (95% CI: 3.9, 7.6) based on Inv and 6.7 months (95% CI: 4.2, 8.1) based on IRC assessment.

Exploratory updated results (data cut-off 12 Oct 2021) suggest an ORR of 33.8% (95% CI: 26.4%, 41.7%) and median DoR of 6.70 months (95% CI: 4.40, 8.11) for the overall population. Median Inv based PFS was 4.27 months (95% CI: 3.42, 4.90) and comparable results were seen per IRC. Median OS was 11.79 months (95% CI: 9.53, 14.55).

Target population - ORR in the target indication population (n=72) is 37.5% (26.4-49.7), with a median duration of response of 6.97 months (4.01-9.92). Median PFS is 4.40 (3.06-5.52) months and median OS is 11.60 (9.66-17.25) months.

3.3. Uncertainties and limitations about favourable effects

- In pivotal study OP-103, key secondary endpoint ORR was not met (32.5% vs. 26.9%, stratified p=0.1422) and the second key secondary endpoint OS indicated an OS detriment for the overall study population (HR 1.09, nominal p=0.3254). As agreed during the MAA of melflufen, the potential OS detriment was mostly driven by a lack of efficacy/reduced efficacy in patients with progression within 3 years after ASCT. Similar to the MAA, some uncertainties

for the new proposed target indication are again derived from the time to progression of at least *36-months after anASCT* / non ASCT post-hoc defined subgroup.

- There are no interpretable quality of life data. PRO endpoints were added via a protocol amendment during the study. As a consequence, the PRO data set was limited. Combined with the exploratory nature of the analysis, no firm conclusions can be drawn for this endpoint.
- Efficacy in primary refractory patients is unknown, as these patients were excluded from the pivotal trial. This is reflected in section 5.1 of the SmPC.

3.4. Unfavourable effects

The overall safety database consists of 491 patients of which 431 received the recommended dose in combination with dexamethasone. Median treatment duration was 20.1 weeks (range: 1-164 weeks).

Within the pivotal trial OP-103 of this variation application, 228 patients received the combination treatment with a median treatment duration of 25 weeks (range: 4-164). The safety profile of melflufen is primarily characterised by haematological TEAEs consistent with the mechanism of action (alkylating agent) and resembles that of melphalan, the main metabolite of melflufen. The most frequently reported haematological events in study OP-103 were thrombocytopenia (70.2%), anaemia (66.7%), and neutropenia (60.1%). These were also the most commonly reported $\geq$ grade 3 events, with incidences of roughly 40-60%. The events were mostly manageable with dose modifications and supportive treatment (67.1% received colony stimulating factors and 51.6% received blood substitutes and perfusion solutions). Thrombocytopenia was the most common adverse event leading to discontinuation of melflufen (7.9%). Bleeding events occurred in 15.8% of patients, severe (Grade 3) bleeding events (AESI) in connection with AESIs of thrombocytopenia were uncommon (n=2 (0.9%) patients). Half (50.0%) of patients had infections and 12.7% had an infection and concomitant Grade 3 or 4 neutropenia (including neutrophil count decreased). Infections were in general manageable with anti-infective treatment and dose modifications. Within the Safety Pool (n=491) some fatal TEAEs were reported in the SOC Infections and infestations. Febrile neutropenia occurred in 2.6% of patients in the Safety Pool.

Non-haematological TEAEs frequently (> 10%) reported with melflufen were pyrexia, asthenia, fatigue, diarrhoea, nausea, diarrhoea, and upper respiratory tract infection. These events were mostly grade 1 or 2. Gastrointestinal events are frequently observed and known for melphalan.

Overall, grade 3/4 TEAEs were reported in 89.9% of patients and SAEs were reported in 41.7% of patients. Pneumonia (5.7%) and thrombocytopenia (3.9%) were the most frequently reported SAEs. In the overall population, 46.5% of patients died during study. Most deaths were due to progressive disease, fatal TEAE rate was 11.8%. Furthermore, 26.3% reported a TEAE leading to discontinuation of melflufen. Melflufen dose reductions were observed in 46.9% of patients and 60.1% had a dose delay of melflufen.

The overall safety profile of melflufen was worse compared to the comparator arm, with more grade 3/4 events (89.9% vs. 74.4%) and dose reductions/delays, mainly due to the higher frequencies of haematological events. SAEs, fatal TEAEs, and drug discontinuations were in the same order of magnitude. The safety profile of the comparator arm (pomalidomide + dexamethasone) was in line with that described in the SmPC.

Overall frequencies of events in the target population were in the same order of magnitude as observed in the ITT population of OP-103, and safety data for the ITT are therefore presented in the

effect table. Upon exposure adjustment, subgroup data per ASCT status suggest a better tolerability of melflufen + dexamethasone in the proposed target population compared to patients with early progression post-ASCT.

The safety profile in OP-103 resembles that seen before in study OP-106 in the later line setting and no new safety signals were identified. Frequencies of some events were numerically lower, which may reflect the earlier line setting. This also holds true compared to the overall Safety Pool. The Safety Pool consisting of 491 patients treated with melflufen as single agent or in combination with dexamethasone has been previously submitted and was used for the safety profile in the SmPC. No new safety data has been submitted within the current variation application. The safety database reflects the safety profile as observed in OP-103 and allows a more robust estimate of the safety profile due to higher patient numbers.

3.5. Uncertainties and limitations about unfavourable effects

The median duration of exposure in the safety pool was 20 weeks and 25 weeks in the pivotal study OP-103, therefore long term safety data is limited. This is of relevance for AEs that might occur after long-term exposure, like secondary primary malignancies. This risk is, however, well known based on the long-standing use of melphalan and no additional risk minimization measures are needed. This is addressed in the RMP based on what is known for melphalan.

The risk of bleeding and infections is of particular importance in a patient population prone to these risks.

Overall, within the safety database of 491 patients, 431 patients received the recommended dose in combination with dexamethasone. With the understanding that the selection of type of treatment regimen is multifactorial, the observed safety profile may not be fully representative for clinical practice given the inclusion of a less frail patient population and a limited number of patients >75 age.

There appears to be no direct toxicological signal of melflufen that explains the observed OS detriment in the overall population in study OP-103. It is unlikely that the difference in tolerability is the main cause of OS detriment/the lower survival rate in patients with TTP ≤36 months post-ASCT. No OS detriment is seen in the newly proposed target population.

3.6. Effects Table

Table 2. Effects Table for melflufen in combination with dexamethasone for the treatment of adult patients with MM, who have received at least 2 prior lines of therapies, whose disease is refractory to lenalidomide and the last therapy and who had no ASCT or progressed >36 months after an ASCT. (target population Study OP-103, data cut-off: 3 Feb 2021)

Effect	Short description	Unit	Treatm ent	Control	Uncertainties / Strength of evidence	References
Favourable Effects*						
PFS (95% CI)	Time from randomisati on to PD or death due to any cause.	Months	9.3 months (7.2; 11.8)	4.6 months (3.6; 6.3)	HR 0.577 (0.438, 0.760) Supported by secondary endpoints. Post-hoc selection of target indication	Clin summary efficacy OP-103

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					population without recent ASCT agreed based on the same rationale as during the MAA.	
ORR (95% CI)	Proportion of patients achieving sCR, CR, CGPR or PR.	Percentage	42.1% (33.9; 50.5)	26.4% (19.5; 34.2)	Nominal p=0.0046 Endpoint not met for ITT.	Clin summary efficacy OP-103
OS** (95% CI)	Time from randomisation to death due to any cause.	Months	23.6 months (18.9; 28.0)	19.1 months (12.6; 26.5)	Potential OS detriment in ITT, mostly driven by a lack of efficacy/reduced efficacy in patients with progression within 3 years after ASCT.	Clin summary efficacy OP-103

Unfavourable Effects^						
Grade 3/4 TEAEs	Incidence of grade 3/4 TEAEs	%	89.9	74.4	Summary safety profile appears improved for target population compared to early progressors upon exposure adjustment	
Serious adverse events (SAEs)	Incidence of SAEs	%	41.7	45.9		
Grade 5 TEAEs	Incidence of grade 5 TEAEs	%	11.8	13.0		
TEAEs associated with drug discontinuation	Incidence of TEAEs associated with drug discontinuation	%	26.3	22.0		
Thrombocytopenia	Incidence of thrombocytopenia <i>Grade 3-4</i>	%	70.2 62.7	19.5 10.6		
Anaemia	Incidence of anaemia <i>Grade 3-4</i>	%	66.7 42.5	37.4 17.9		
Neutropenia	Incidence of neutropenia <i>Grade 3-4</i>	%	60.1 54.4	45.9 41.5		
Febrile neutropenia	Incidence of febrile neutropenia		2.6	1.6		
Infections	Incidence of infections <i>Grade 3-4</i>	%	50.0 13.2	55.7 21.5		

Abbreviations: ASCT: autologous stem cell transplantation, CI: confidence interval, CR: complete response, sCR: stringent complete response, ORR: overall response rate, OS: overall survival, PFS: progression free survival, PR: partial response, VGPR: very good partial response.

Notes: *Presented favourable effects is for the time to progression >36 months since/non-ASCT subgroup (i.e. target indication population); **Data-cut-off for OS analysis is 3 Feb 2023 (final

analysis); ^Unfavourable effects based on the total safety population of OP-103.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

An extension of indication is requested for melflufen + dexamethasone (dex) in patients who have received at least 2 prior treatment lines, and are refractory to lenalidomide and last line of therapy, i.e. an earlier line of treatment compared to the current approved indication. Similar to the current approved indication, for patients with prior ASCT, the time to progression should be at least 3 years from transplantation.

Pivotal study OP-103 data for the overall study population and TCR subpopulation have been presented during the MAA of melflufen. Despite the active comparator and the fact that study OP-103 was not powered to demonstrate a difference in overall survival, the OS HR of 1.104 and KM curves in the OP-103 ITT population warranted further investigation. The analyses indicated that the potential OS detriment was mostly driven by a lack of efficacy/reduced efficacy in patients with progression within 3 years after ASCT. Hence, the indication was restricted to exclude these patients. The restriction to patients with no prior ASCT or progression >36 months after ASCT is, based on the same rationale as during the MAA, acceptable for the new requested earlier line of treatment as well.

Results for the new target population without prior ASCT or progression >36 months after ASCT, at least 2 prior treatment lines and refractory on lenalidomide and last therapy indicate a PFS benefit of 4.6 months (HR 0.577; 95% CI: 0.438; 0.760; nominal p =0.0001). This improvement, supported by an ORR and duration of response in favour of melflufen as well as a trend in OS benefit, is considered clinically relevant for the new target indication population. Similar to the MAA, some uncertainties remain considering that data are again derived from the time to progression >36-months-since/non-ASCT subgroup. The clinical efficacy in terms of PFS is considered sufficiently large to at least conclude that melflufen is not inferior to pomalidomide + dex, which is considered acceptable in this substitution trial (i.e. melflufen instead of pomalidomide).

The PFS estimate in the melflufen + dex arm and the observed benefit compared to pomalidomide + dex are of clinical relevance in this line of RRMM treatment considering the results of other trials in this setting. Monoclonal antibodies (mAbs) daratumumab, isatuximab and elotuzumab all have been approved based on clinical data derived from a randomised trial with pomalidomide + dex as comparator. Despite the known limitations when comparing results across trials, the 4.6 month improvement seen with melflufen + dex compared to pomalidomide + dex in Study OP-103 is more or less in line with the approximately 5 month PFS improvement observed with these mAbs in a similar setting.

Results for intended supportive study OP-106 indicated efficacy of melflufen in the ITT and currently approved later line TCR setting, with an ORR of 28.8% and median duration of response of 7.6 months. Results for the target population were slightly better (ORR 37.5% with median duration of response of 6.97 months), though still lower when indirectly compared to the pivotal trial. This is not unexpected considering that patients in the supportive trial were more heavily pre-treated.

The safety profile is dominated by haematological adverse events of which thrombocytopenia and neutropenia are the most important as they carry potentially severe clinical consequences in patients prone to bleeding events and infections. Fatal events of infections concomitant with neutropenia have

been reported. Most frequently occurring SAEs were pneumonia and thrombocytopenia. Although the toxicity of melflufen is in line with what may be expected from a drug product with melphalan as the active substance in a setting where patients are heavily pre-treated and can be considered generally manageable with adequate monitoring and dose adjustment or discontinuation, it is not negligible and relevant safety information and recommendations are presented in the SmPC. Melflufen offers a different mechanism of action compared to other products used in clinical practice in a similar population and thus a somewhat different safety profile. Although there appears no indication of a direct toxicological effect of melflufen, it appears less tolerated in patients with ASCT $\leq$ 36 months compared to the newly proposed target population especially when based on exposure adjusted analyses.

3.7.2. Balance of benefits and risks

Clinical efficacy is considered demonstrated by a clinically relevant improvement in PFS supported by a trend in OS gain, in the requested earlier line setting restricted to patients with no prior ASCT or progression $\geq$ 36 months after ASCT.

Although the toxicity of melflufen is in line with what is expected in a setting where patients are pre-treated, and can be considered generally manageable with adequate monitoring, supportive management and dose modifications, it is not negligible. Still, it is considered acceptable in the target population with dismal prognosis and outweighed by the observed clinical benefit.

As such, the benefit risk balance is considered positive

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Pepaxti is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of patients with Multiple Myeloma who have received at least two prior lines of therapies for PEPAXTI, based on final results from study OP-103 OCEAN; this is a randomized, open-label phase III study in patients with relapsed or refractory multiple myeloma

following two to four lines of prior therapies and who were refractory to lenalidomide and the last line of therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the SmPC.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Pepaxti is not similar to Abecma, Carvykti, Blenrep, Darzalex, Farydak, Imnovid, Kyprolis, Ninlaro within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Pepaxti-H-C-5681-II-0002'