Melflufen or pomalidomide plus dexamethasone for patients with multiple myeloma refractory to lenalidomide (OCEAN): a randomised, head-to-head, open-label, phase 3 study

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Summary

Background Melphalan flufenamide (melflufen), an alkylating peptide-drug conjugate, plus dexamethasone showed clinical activity and manageable safety in the phase 2 HORIZON study. We aimed to determine whether melflufen plus dexamethasone would provide a progression-free survival benefit compared with pomalidomide plus dexamethasone in patients with previously treated multiple myeloma.

Methods In this randomised, open-label, head-to-head, phase 3 study (OCEAN), adult patients (aged ≥18 years) were recruited from 108 university hospitals, specialist hospitals, and community-based centres in 21 countries across Europe, North America, and Asia. Eligible patients had an ECOG performance status of 0–2; must have had relapsed or refractory multiple myeloma, refractory to lenalidomide (within 18 months of randomisation) and to the last line of therapy; and have received two to four previous lines of therapy (including lenalidomide and a proteasome inhibitor). Patients were randomly assigned (1:1), stratified by age, number of previous lines of therapy, and International Staging System score, to either 28-day cycles of melflufen and dexamethasone (melflufen group) or pomalidomide and dexamethasone (pomalidomide group). All patients received dexamethasone 40 mg orally on days 1, 8, 15, and 22 of each

cycle. In the melflufen group, patients received melflufen 40 mg intravenously over 30 min on day 1 of each cycle and in the pomalidomide group, patients received pomalidomide 4 mg orally daily on days 1 to 21 of each cycle. The primary endpoint was progression-free survival assessed by an independent review committee in the intention-to-treat (ITT) population. Safety was assessed in patients who received at least one dose of study medication. This study is registered with ClinicalTrials.gov, NCT03151811, and is ongoing.

Findings Between June 12, 2017, and Sept 3, 2020, 246 patients were randomly assigned to the melflufen group (median age 68 years [IQR 60–72]; 107 [43%] were female) and 249 to the pomalidomide group (median age 68 years [IQR 61–72]; 109 [44%] were female). 474 patients received at least one dose of study drug (melflufen group n=228; pomalidomide group n=246; safety population). Data cutoff was Feb 3, 2021. Median progression-free survival was 6·8 months (95% CI 5·0–8·5; 165 [67%] of 246 patients had an event) in the melflufen group and 4·9 months (4·2–5·7; 190 [76%] of 249 patients had an event) in the pomalidomide group (hazard ratio [HR] 0·79, [95% CI 0·64–0·98]; p=0·032), at a median follow-up of 15·5 months (IQR 9·4–22·8) in the melflufen group and 16·3 months (10·1–23·2) in the pomalidomide group. Median overall survival was 19·8 months (95% CI 15·1–25·6) at a median follow-up of 19·8 months (IQR 12·0–25·0) in the melflufen group and 25·0 months (95% CI 18·1–31·9) in the pomalidomide group at a median follow-up of 18·6 months (IQR 11·8–23·7; HR 1·10 [95% CI 0·85–1·44]; p=0·47). The most common grade 3 or 4 treatment-emergent adverse events were thrombocytopenia (143 [63%] of 228 in the melflufen group vs 26 [11%] of 246 in the pomalidomide group), neutropenia (123 [54%] vs 102 [41%]), and anaemia

(97 [43%] vs 44 [18%]). Serious treatment-emergent adverse events occurred in 95 (42%) patients in the melflufen group and 113 (46%) in the pomalidomide group, the most common of which were pneumonia (13 [6%] vs 21 [9%]), COVID-19 pneumonia (11 [5%] vs nine [4%]), and thrombocytopenia (nine [4%] vs three [1%]). 27 [12%] patients in the melflufen group and 32 [13%] in the pomalidomide group had fatal treatment-emergent adverse events. Fatal treatment-emergent adverse events were considered possibly treatment related in two patients in the melflufen group (one with acute myeloid leukaemia, one with pancytopenia and acute cardiac failure) and four patients in the pomalidomide group (two patients with pneumonia, one with myelodysplastic syndromes, one with COVID-19 pneumonia).

Interpretation Melflufen plus dexamethasone showed superior progression-free survival than pomalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma.

Introduction

The standard-of-care therapy in multiple myeloma is to use combinations of immunomodulatory agents, proteasome inhibitors, and anti-CD38 monoclonal antibodies.[1,2] As triplet and quadruplet therapies move into earlier lines of therapy, patients with relapsed or refractory multiple myeloma might develop disease refractory to multiple standard-of-care drug classes earlier, necessitating additional treatments with novel mechanisms of action.[1,2]

Melphalan flufenamide (known as melflufen) is a first- in-class peptide-drug conjugate that targets amino- peptidases and thereby rapidly releases alkylating agents inside tumour cells.[3–9] Due to its high lipophilicity and affinity for aminopeptidases, melflufen can passively enter tumour cells and release cytotoxic, hydrophilic alkylating agents (melphalan and desethyl-melflufen) that remain trapped within cells.[3,5] Melflufen uses a novel approach, whereby increased aminopeptidase activity is used to achieve selective release of alkylating agents inside tumour cells.[8,9]

Melflufen has shown activity and a safety profile characterised by primarily monitorable and clinically manageable haematological toxicities in patients with advanced relapsed or refractory multiple myeloma in previous studies.[10,11] Results from the phase 2 HORIZON study had supported the initial accelerated approval by the US Food and Drug Administration (FDA) in 2021 of melflufen and dexamethasone for the treatment of patients with triple-class refractory multiple myeloma who have received at least four previous lines of therapy.[7,10,11] In HORIZON (N=157), patients had received a

median of five previous lines of therapy, 76% had triple-class refractory disease, 69% had received a previous autologous haematopoietic stem-cell transplantation (HSCT), 35% had extra- medullary disease at baseline, and 38% had high-risk cytogenetics.1 Pomalidomide plus dexamethasone was approved in 2013 for patients with relapsed or refractory multiple myeloma on the basis of data from the MM-003 trial,12 which established this doublet as the standard-of- care for patients who have previously received at least two previous lines of therapy including lenalidomide and a proteasome inhibitor.
We aimed to assess melflufen plus dexamethasone versus pomalidomide plus dexamethasone using a randomised, controlled, open-label trial design.13

Research in context Evidence before this study
We searched PubMed for clinical trials published between
Jan 01, 2011, and Sept 30, 2021, with no language restrictions, using the search terms "relapsed/refractory multiple myeloma" and "RRMM". We identified 60 articles, many of which supported the approval of multiple drug classes and combinations in the relapsed or refractory multiple myeloma setting. The phase 3 MM-003 study established pomalidomide plus dexamethasone as the standard-of-care for patients with relapsed or refractory multiple myeloma who had received at least two previous therapies including lenalidomide and a proteasome inhibitor. Subsequent phase 3 studies
(ICARIA-MM, ELOQUENT-3, APOLLO) showed the benefit of triplet combination therapies that use pomalidomide and dexamethasone as the backbone, which has resulted in the use of pomalidomide in earlier lines of therapy. As new triplet and quadruplet combinations of antimyeloma drugs are introduced in earlier lines of therapy, patients with relapsed or refractory multiple myeloma often now have disease that is refractory to multiple drug classes, even after second-line therapy; additional drugs with novel mechanisms of action are needed. Melphalan flufenamide (melflufen) is a highly lipophilic peptide-drug conjugate that targets elevated aminopeptidase activity to selectively increase the release and concentration of cytotoxic alkylating agents (melphalan and desethyl-melflufen) inside tumour cells. In the phase 2 HORIZON study, melflufen plus dexamethasone showed clinically meaningful activity and a manageable safety profile in patients with heavily pre-treated relapsed or refractory multiple myeloma, including patients with triple-class refractory disease. Added value of this study
The OCEAN study compared melflufen plus dexamethasone versus pomalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma who had received two to four previous lines of therapy (including lenalidomide and a proteasome inhibitor) and whose disease was refractory to lenalidomide and the last line of therapy. Melflufen plus dexamethasone resulted in improved progression-free survival compared with pomalidomide plus dexamethasone, per independent review committee. Patients in the melflufen group had a numerically higher overall response rate with numerically more patients having a complete response or very good partial response with melflufen than with pomalidomide. There was no difference in overall survival between the treatment groups at this short follow-up. Post-hoc subgroup analyses suggest that outcomes might have been driven primarily by patients who had received previous high-dose melphalan followed by an autologous haematopoietic stem-cell transplantation. The safety profile of melflufen plus dexamethasone was in line with previous reports.
Implications of all the available evidence
Results from OCEAN provide evidence that melflufen, with its novel mechanism of action, plus dexamethasone, can improve progression-free survival for patients with lenalidomide- refractory relapsed or refractory multiple myeloma who have received two to four previous lines of therapy. The results also suggest that treatment with melflufen should be carefully tailored on the basis of a patient's previous medical history.

Methods

Study design and participants

OCEAN is a randomised, controlled, open-label, head-to- head, phase 3 study of melflufen plus dexamethasone versus pomalidomide plus dexamethasone. Patients were recruited from 108 sites (a mixture of university hospitals, specialist hospitals, and community-based centres) in 21 countries across Europe, North America, and Asia (appendix pp 2–6).

Patients were eligible if they were aged 18 years or older, with a previous diagnosis of multiple myeloma and documented disease progression; had received two to four previous lines of therapy, including lenalidomide and a proteasome inhibitor, either sequentially or in the same line; and had disease that was refractory (relapsed and refractory or refractory) to both the last line of therapy and to lenalidomide administered within 18 months before randomisation. Patients with disease refractory to lenalidomide must have progressed while on lenalidomide therapy or within 60 days of last dose, after at least two cycles of lenalidomide (≥10 mg) with at least 14 doses of lenalidomide per cycle. Additionally, patients must have had, or been willing to have, an acceptable central catheter. Patients with previous exposure to pomalidomide, known intolerance to immunomodulatory drugs or steroid therapy, primary refractory disease (ie, never responded with at least a minimal response to any previous therapy), or previous allogeneic HSCT with active graft-versus-host disease were excluded.

Eligible patients also needed to have an ECOG performance status of 0–2 and measurable disease (serum monoclonal protein ≥0·5 g/L, urine monoclonal protein ≥200 mg per 24 h, or serum free light chain
≥10 mg/dL and an abnormal serum immunoglobulin kappa to lambda free light chain ratio). Laboratory criteria required at screening and before initiating therapy on cycle 1 day 1 included absolute neutrophil count of $1{\cdot}0 \times 10^9$ cells per L or higher (growth factors not allowed 10 days before initiating therapy), platelet count of 75×10^9 cells per L or higher (transfusions were not allowed 10 days before initiating therapy), haemoglobin concentration of 8·0 g/dL or higher, bilirubin concentration of 1·5 times the upper limit of normal (ULN) or lower, aspartate aminotransferase and alanine aminotransferase of 3·0 × ULN or lower, and estimated creatinine clearance of 45 mL/min or higher

(Cockcroft-Gault formula). Contraception methods for female patients of childbearing potential and all men were required as part of a pregnancy prevention plan and a Risk Evaluation and Mitigation Strategies programme. Full eligibility criteria are in the appendix (pp 8–10).

The study complied with the ethical principles set forth in the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines.14 The protocol was reviewed and approved by national regulatory authorities and an independent ethics committee or institutional review board at each study centre before implementation. Patients provided written informed consent. The full protocol and statistical analysis plan are in the appendix (pp 55–227). A protocol amendment was made on May 30 2018, to expand the eligibility criteria for patients refractory to lenalidomide from being within 60 days of their last dose to within 18 months of randomisation.

Randomisation and masking

Patients were randomly assigned (1:1), stratified by age (≥75 years vs <75 years), number of previous lines of therapy (two vs three to four), and International Staging System score (I vs II or III), to either melflufen plus dexamethasone or pomalidomide plus dexamethasone. Randomisation was done with an Interactive Response Technology system (hosted by Oracle Health Sciences, Austin, TX, USA) that assigned patients a unique number at enrolment for identification throughout the study. Due to different routes of study drug administration, this was an open-label study. The independent review committee that assessed the primary outcome met in closed-meeting sessions and were masked to all treatment data and investigator-assessed response. Study investigators were unmasked to individual patient treatment assignment throughout the study but did not have access to aggregate data.

Procedures

All patients were treated in 28-day cycles. Patients in the melflufen group were given melflufen 40 mg as a centrally administered intravenous infusion for 30 min on day 1 of each cycle. Patients in the pomalidomide group were given pomalidomide 4 mg orally on days 1 to 21 of each cycle. Patients in both treatment groups received dexamethasone 40 mg orally (20 mg for patients aged ≥75 years) on days 1, 8, 15, and 22 of each cycle. Patients received treatment until documented disease progression per International Myeloma Working Group Uniform Response Criteria,15 unacceptable toxicity, or if the patient or treating physician determined it was not in the patient's best interest to continue.

End-of-treatment visits occurred approximately 30 days (plus or minus 3 days) after the last dose of melflufen or pomalidomide. Progression-free survival assessments occurred monthly until disease progression or initiation of subsequent therapy; thereafter, assessments for overall survival occurred every 3 months (plus or minus 1 week) for up to 24 months after disease progression. An independent data monitoring committee monitored the benefit–risk ratio of treatment at regular intervals throughout the study. Any patients with a grade 3 or 4 neutropenia or thrombocytopenia event that was ongoing at the end-of-treatment visit were followed up until resolution (grade ≤2) or initiation of subsequent therapy. Patients with serious adverse events were followed up until resolution or stabilisation with no expected resolution.

Dose modifications, including dose delays and multiple dose reductions for drug-related toxicity were permitted. The lowest permitted dose was 20 mg for melflufen or 1 mg for pomalidomide; treatment was discontinued in patients unable to tolerate melflufen 20 mg or pomalidomide 1 mg due to drug-related toxicity. Full details on dose modifications are in the appendix (pp 10–11). Disease status was assessed locally at screening and at every cycle to assess response using monoclonal protein determination: serum protein electrophoresis and serum protein immunofixation with quantitative immuno- globulins; urine protein electrophoresis and urine protein immunofixation (both done using the same 24-h urine sample); and serum free light chains and serum free light chain ratio. Bone marrow aspirates were obtained to quantify percentage myeloma cell involvement, and skeletal x-rays or low-dose bone CT scans were performed. Additional physical examination and imaging for suspected extramedullary disease was done at screening and at every cycle according to the International Myeloma Working Group Uniform Response Criteria.15 Previous medications and concomitant medications and blood products received within 21 days of initiating therapy until the end of study visit were recorded.

Protocol amendments were made on March 24, 2020, due to the COVID-19 pandemic, including allowing patients with good tolerability to forego onsite assessments on days 8 and 22 of each cycle, and use of local laboratory assessments. A complete list of protocol amendments is in the appendix (p 7). Treatment- emergent adverse events were defined as adverse events with onset date and time or increase in severity level after the initial dose of study drug and within 30 days after the last dose of study drug or at the time of initiating a new antimyeloma therapy, whichever was sooner. Events of special interest were defined as serious or non-serious events of specific concern for melflufen and included grouped terms using standardised Medical Dictionary for Regulatory Activities (MedDRA; version 23.0) queries for thrombocytopenia, neutropenia, anaemia, haemorrhage, infections, and second primary malign- ancies. Treatment-related adverse events were recorded by the investigator as possibly or probably related to either study drug. We used the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03) to grade adverse events.

Outcomes

The primary endpoint was progression-free survival, as assessed by an independent review committee according to the International Myeloma Working Group Uniform Response Criteria (appendix pp 11–12).15 Progression-free survival was defined as the time from randomisation to confirmed disease progression or death from any cause, whichever occurred first. The primary analysis of progression-free survival was right-censored according to FDA guidance16 where applicable. For example, patients with no post-baseline assessment, excluding death, were censored at the date of randomisation, patients who started a new antimyeloma therapy without disease progression on study were censored at the last disease assessment before initiating the new line of therapy, and patients alive and without

documented disease progression were censored at the last date of disease assessment.
Key secondary endpoints were overall response rate, overall survival, and safety in the melflufen and pomalidomide groups. Overall response rate was defined as the proportion of patients with a stringent complete response, complete response, very good partial response, or a partial response, as best confirmed response. Response and progression were assessed by an independent review committee, unless otherwise specified, using local laboratory assessments in accordance with International Myeloma Working Group Uniform Response Criteria.15 To fulfil complete response criteria, patients must have had a negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and less than 5% of clonal cells in their bone marrow. Additionally, patients who fulfilled stringent complete response criteria must have also had normalisation of their serum free light chain ratio and an absence of clonal cells in their bone marrow as determined by immunofluorescence or immunohistochemistry.15 Overall survival was defined as the time from the date of randomisation to death due to any cause. Patients still alive at end of study, or lost to follow up, were censored at last date known alive. On the basis of recommendations by regulatory authorities, the protocol was amended on April 29, 2021, to demote duration of response from a key secondary endpoint to a non-ranked secondary endpoint.
Safety endpoints were treatment duration, frequency and grade of treatment-emergent adverse events and adverse events of special interest, frequency of events leading to dose modifications (ie, delays, reductions, or permanent discontinuation), and time to dose modifications. Timepoints of specific interest for deaths were within 30 days or more than 30 days after the last dose of study drug.
Other secondary endpoints were duration of response (per protocol amendment), clinical benefit rate, time to first confirmed response in patients with a partial response or better, time to progression, duration of clinical benefit (time from first evidence of confirmed assessment of stringent complete response, complete response, very good partial response, partial response, or minimal response to first confirmed disease progression or to death due to any cause), best confirmed response (assessed using the International Myeloma Working Group Uniform Response Criteria), and investigator assessment of primary and secondary endpoints.
Exploratory endpoints were subgroups analyses of primary and secondary endpoints, pharmacokinetic parameters of melflufen, minimal residual disease for patients who achieved a complete response, and change from baseline in each scale of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3, each scale of the QLQ-MY20, each dimension of the EQ-5D, and the visual analogue scale (VAS) of the EQ-5D. Patient-reported outcomes were added as an exploratory endpoint as part of a protocol amendment on May 24, 2019. Assessments for other secondary endpoints and exploratory endpoints can be found in the appendix (pp 12–13). The secondary endpoints of clinical benefit rate, best confirmed response, time to first response, and investigator assessment of primary and secondary endpoints are reported here; duration of response, time to progression, and duration of clinical benefit will be reported in subsequent publications. For the exploratory endpoints, subgroup analyses of primary and secondary endpoints are reported here; pharmacokinetics, minimal residual disease, and patient-reported outcomes will be reported in subsequent publications.

Statistical analysis
We estimated that a sample size of 450 patients was necessary to obtain 339 events for the primary analysis of progression-free survival to power the study at 90% to detect a hazard ratio (HR) of 0·70 for the progression- free survival of the melflufen and pomalidomide groups, using a two-sided log-rank test (5% significance level). The sample size calculation assumed a 15% drop-out rate, 3·6 month median progression-free survival for the pomalidomide group, 24 month accrual time, total study time of 30 months, and exponential survival distribution. Because of a lower-than-expected event rate, 495 patients were enrolled to obtain the 339 events needed within a reasonable time frame. Given these prespecified assumptions and that the final sample size was within a 10% margin of error, the study would remain sufficiently powered to detect a difference if the observed HR were 0·80 without the need for a formal protocol amendment.
For the primary statistical analysis of progression-free survival, we used a log-rank test, stratified by the randomisation stratification factors, to determine the p value for the treatment comparison. We calculated HRs and 95% CIs using a two-sided 0·05 level Cox proportional hazards regression model,

stratified by randomisation stratification factors. In case of a non-significant test of superiority, we defined a non- inferiority fallback if the upper limit of the 95% CI for the HR was below 1·2 for progression-free survival of the melflufen group compared with the pomalidomide group.
We compared overall response rate, clinical benefit rate, and best confirmed response using a Cochran Mantel Haenszel test stratified by randomisation stratification factors; we calculated 95% CIs for each treatment group. We estimated and summarised overall survival using the same methods as for progression-free survival. We did not do any formal statistical analysis for the safety endpoints.
In exploratory analyses, we assessed progression-free survival and overall survival in various predefined subgroups (including randomisation stratification factors, previous autologous HSCT [yes vs no], age [<65 years vs
≥65 years; <75 years vs ≥75 years], sex [male vs female], body surface area, race [White vs all other races], geographical region [USA vs Europe vs rest of world], refractory to lenalidomide [last line vs earlier lines], refractory to alkylators [yes vs no], refractory to anti-CD38 monoclonal antibody [yes vs no], refractory to proteasome inhibitor and immunomodulatory drug but not anti-CD38 monoclonal antibody [yes vs no], extramedullary disease [yes vs no], maximum plasma cell involvement at baseline [<30% vs 30–59% vs ≥60%], baseline creatinine clearance [45–59 mL/min vs 60–89 mL/min vs ≥90 mL/min], baseline lactate dehydrogenase [<1·5 × ULN vs ≥1·5 × ULN], baseline albumin [<35 g/L vs ≥35 g/L], and cytogenetic risk group determined by fluorescent in-situ hybridisation [standard risk vs high risk vs unknown]) using an unstratified Cox proportional hazards regression model and an unstratified log-rank test to determine the p value for the treatment comparison within subgroups.
Post hoc, we did a univariable analysis of interaction to assess differences between groups within each subgroup, with variables (ie, subgroups) with a p value of less than 0·2 for overall survival incorporated into a multivariable Cox regression model to determine independent prognostic factors associated with overall survival. We also generated a stepwise Cox regression model using Akaike information criteria to test for the same variables identified in the univariable analysis. A HR of more than 1 represented a negative prognostic factor and we deemed a p value of less than 0·05 to be significant. Post hoc, we also explored whether patients with and without a previous autologous HSCT had disease refractory to previous alkylators to the same degree and performed a logistic regression model using the full intention-to-treat (ITT) population without taking randomisation into account; results are presented as an odds ratio (95% CI) with previous autologous HSCT as the reference group.
Time to subsequent therapy (defined as the time from the date of randomisation to initiation of first subsequent antimyeloma therapy) was also assessed in a post-hoc analysis. Patients without subsequent therapy were censored at date of death or date of last contact. For time-to-event endpoints, all patients were included in the analyses. If a patient had a missing assessment, they were censored at the time of their last known event-free assessment. Missing data were not estimated or carried forward for any other summaries or analyses. When historical dates were used, if only a partial date (eg, only year or month reported) was available and was required for a calculation, the date was imputed. No dates for events occurring after randomisation were imputed.
The ITT population included all patients who were randomly assigned to treatment and was the primary population for all efficacy analyses (all patients were assessed). To assess the effect of the COVID-19 pandemic on progression-free survival and overall survival, we did sensitivity analyses in the ITT population. The safety population included all patients who received at least one dose or a partial dose of melflufen, pomalidomide, or dexamethasone, and is the primary population for all safety analyses. We did an additional safety analysis of the ITT population to determine the number of deaths among those not treated as part of this study.
We did all statistical analyses with SAS (version 9.4) and R (version 4.0.2). This study is registered with ClinicalTrials.gov, NCT03151811.

Role of the funding source
The study was designed by the funder (Oncopeptides AB) together with key advisors in the multiple myeloma community. Study data were collected by site staff and study investigators. The funders compiled and main- tained the data collected by the investigators. Data were analysed by the study sponsor. All authors and the sponsor participated in the interpretation of the data and writing and reviewing of the manuscript.
Results

Between June 12, 2017, and Sept 3, 2020, 644 patients were screened, of whom 495 were randomly assigned to either the melflufen group (n=246) or pomalidomide group (n=249; ITT population). 474 patients received at least one dose of study drug (melflufen group n=228; pomalidomide group n=246; safety population). 21 patients who were randomly assigned to treatment did not receive any study treatment (melflufen group n=18; pomalidomide group n=3; figure 1).

As of data cutoff (Feb 3, 2021), 186 (76%) of 246 patients in the melflufen group and 200 (80%) of 249 patients in the pomalidomide group had discontinued treatment, and 42 (17%) in the melflufen group and 46 (18%) in the pomalidomide group remained on treatment (figure 1; appendix p 20). Overall, 126 (51%) patients in the melflufen group and 129 (52%) in the pomalidomide group were alive and ongoing in the study as of data cutoff.

At baseline, the median age was 68 years (IQR 60–72) in the melflufen group and 68 years (61–72) in the pomalidomide group, 493 patients (>99%) had disease that was refractory to previous lenalidomide, and 245 (50%) had undergone a previous autologous HSCT (table 1). Most patients were enrolled in Europe (356 [71%] of 495), followed by the rest of the world (113 [23%]), and the USA (25 [5%]).

In the ITT population, median progression-free survival was 6·8 months (95% CI 5·0–8·5; 165 [67%] of 246 patients had an event) in the melflufen group and 4·9 months (4·2–5·7; 190 [76%] of 249 patients had an event) in the pomalidomide group (HR 0·79 [95% CI 0·64–0·98]; log-rank p=0·032; figure 2) at a median follow-up of 15·5 months (IQR 9·4–22·8) in the melflufen group and 16·3 months (10·1–23·2) in the omalidomide group.

Overall response rate was 33% (95% CI 27–39; 80 of 246 patients had a partial response or better) in the melflufen group and 27% (22–33; 67 of 249 patients had a partial response or better) in the pomalidomide group (p=0·16). More patients in the melflufen group had a complete response (seven [3%] vs three [1%]), a very good partial response (23 [9%] vs 18 [7%]), or a partial response (50 [20%] vs 46 [18%]) than in the pomalidomide group (appendix p 21). Clinical benefit rate and best confirmed response are shown in the appendix (p 21). In the melflufen group, at a median follow-up of 19·8 months (IQR 12·0–25·0), median overall survival was 19·8 months (95% CI 15·1–25·6; 117 [48%] of 246 patients had died); and in the pomalidomide group, at a median follow-up of 18·6 months (IQR 11·8–23·7), median overall survival was 25·0 months (95% CI 18·1–31·9; 108 [43%] of 249 patients had died; HR 1·10 [95% CI 0·85–1·44]; log-rank p=0·47; figure 3). Progression-free survival and overall response rate were consistent when assessed by study investigators (appendix pp 15, 22). We did a sensitivity analysis to determine the effect of the 11 deaths attributed to COVID-19 (seven [3%] in the melflufen group and four [2%] in the pomalidomide group), and found minimal impact of the global pandemic on progression-free survival and overall survival (appendix p 14). Time to first confirmed response in the melflufen group was 2·1 months (IQR 1·1–3·7) and in the pomalidomide group was 2·0 months (1·1–2·9); and time to best confirmed response (a post-hoc analysis) in the melflufen group was 3·2 months (IQR 1·9–5·9) and in the pomalidomide group was 2·8 months (1·2–5·6).

In the safety population, the median duration of treatment was 5·8 months (IQR 2·8–11·1) in the melflufen group and 5·1 months (2·6–9·2) in the pomalidomide group. Patients received a median of five treatment cycles in each treatment group (melflufen: IQR 3–11; pomalidomide: IQR 3–10). The most common treatment-emergent adverse events by preferred term and treatment group are summarised in table 2 and the appendix (pp 23–31), and disaggregated by sex in the appendix (pp 32–35). The most common haematological grade 3 or 4 events in the melflufen and pomalidomide groups were neutropenia (123 [54%] of 228 vs 102 [41%] of 246), thrombocytopenia (143 [63%] vs 26 [11%]), and anaemia (97 [43%] vs 44 [18%]), and the most common grade 3 or 4 non-haematological event was pneumonia (ten [4%] vs 20 [8%]; table 2). The most common grade 3 or 4 treatment-related treatment-emergent adverse events in the melflufen and pomalidomide groups were thrombocytopenia (138 [61%] vs 22 [9%]), neutropenia (122 [54%] vs 97 [39%]), anaemia (87 [38%] vs 25 [10%]; appendix pp 36–37). Serious treatment-emergent adverse events occurred in 95 (42%) patients in the melflufen group and 113 (46%) patients in the pomalidomide group, the most common of which were pneumonia (13 [6%] vs 21 [9%]), COVID-19 pneumonia (11 [5%] vs nine [4%]), and thrombocytopenia (nine [4%] vs three [1%]), and were considered to be treatment related in 42

(18%) in the melflufen group and 52 (21%) in the pomalidomide group (appendix p 38). Treatment-emergent adverse events of special interest are summarised in the appendix (pp 39–40). Despite grade 3 or 4 thrombocytopenia being more common in the melflufen group (174 [76%] of 228) than in the
pomalidomide group (31 [13%] of 246), few grade 3 (two [1%] vs none) and no grade 4 bleeding events occurred concurrently. 30 (13%) grade 3 or 4 infections occurred in the melflufen group (concurrently with grade 3 or 4 neutropenia in seven [3%] patients) versus 53 (22%) in the pomalidomide group (concurrently with grade 3 or 4 neutropenia in 16 [7%] patients). In patients with an event, median time to onset of grade 3 or
4 thrombocytopenia by laboratory values was 51 days (IQR 22–106) in the melflufen group and 16 days (14–22) in the pomalidomide group; median time to onset of grade 3 or 4 neutropenia by laboratory values was 24 days (IQR 15–43) in the melflufen group and 22 days (21–23) in the pomalidomide group. Three (1%) patients in the melflufen group and six (2%) patients in the pomalidomide group developed second primary malignancies overall, including one (<1%) patient in the melflufen group who developed acute myeloid leukaemia and one (<1%) in the pomalidomide group who developed myelodysplastic syndromes, both of which were fatal. Safety data analysed per previous autologous HSCT status are shown in a post- hoc analysis in the appendix (pp 41–42). Treatment-emergent adverse events resulted in 137 [60%] patients in the melflufen group having at least one dose delay compared with 109 [44%] in the pomalidomide group, and 107 [47%] with dose reductions in the melflufen group compared with 37 [15%] in the pomalidomide group. Permanent treatment discon- tinuation due to a treatment-emergent adverse event occurred in 60 [26%] patients in the melflufen group compared with 54 [22%] in the pomalidomide group, due to both haematological and non-haematological treatment-emergent adverse events (appendix pp 43–44). Patients in both treatment groups received concomitant supportive care as necessary (appendix p 45). Among patients who received at least one melflufen (119 [52%] of 228) or pomalidomide (43 [17%] of 246) dose reduction for any reason, median time to first dose reduction was 106 days (IQR 57–184) in the melflufen group and 50 days (29–144) in the pomalidomide group. Among 119 patients who received melflufen and subsequently required a dose reduction, 56 (47%) required one dose reduction, 60 (50%) required two dose reductions, and three (3%) required three dose reductions; 87 (73%) of 119 patients went on to receive at least one additional dose of melflufen. Among the 54 patients who required a pomalidomide dose reduction, 36 (84%) required one dose reduction and seven (16%) required two dose reductions. The median duration of therapy after a dose reduction was 17·0 weeks (IQR 4·0–35·9) in the melflufen group and 9·1 weeks (3·0–23·0) in the pomalidomide group.

Adverse events leading to death occurred in 27 (12%) of
228 patients in the melflufen group and 32 (13%) of 246 patients in the pomalidomide group, most commonly COVID-19 pneumonia (seven [3%] vs four [2%]), pneumonia (three [1%] vs four [2%), and multiorgan dysfunction syndrome (two [1%] vs two [1%]; appendix pp 46–47). Treatment-emergent adverse events leading to death were considered possibly related to treatment with melflufen in two patients (one patient with acute myeloid eukaemia and in one with pancytopenia and acute cardiac failure) and pomalidomide in four patients (two patients with pneumonia, one with myelodysplastic syndromes, and one with COVID-19 pneumonia).

In the safety population, 106 (46%) patients in the melflufen group and 106 (43%) patients in the pomalidomide group died overall. 23 (10%) patients in the melflufen group and 33 (13%) in the pomalidomide group died within 30 days of receiving their last dose of study drug; 83 (36%) in the melflufen group and 73 (30%), in the pomalidomide group died 30 days after having received their last dose of study medication. Additionally, 13 patients who were randomly assigned but not treated died (assigned to melflufen group, 11 [61%] of 18; pomalidomide group, two [67%] of three; appendix p 48).

In an exploratory analysis of prespecified subgroups of clinical relevance in the ITT population, progression-free survival data favoured melflufen in most subgroups, including patients aged 75 years and older (HR 0·43 [95% CI 0·24–0·76]; p=0·0031) and patients without a previous autologous HSCT (HR 0·59 [0·44–0·79]; p=0·0004; appendix p 16). By contrast, overall survival data favoured pomalidomide in patients younger than 65 years (HR 1·71 [95% CI 1·09–2·69]; p=0·019) and those with a previous autologous HSCT (HR 1·61 [1·09–2·40]; p=0·017; appendix p 16). Age and previous

autologous HSCT remained significant prognostic factors on the basis of an interaction test (appendix p 16).

We looked closer at the exploratory analysis by HSCT subgroup (baseline characteristics by transplantation subgroup are in the appendix [pp 51–52]). Among patients who did not receive a previous autologous HSCT

(melflufen group n=121; pomalidomide group n=129), median progression-free survival was 9·3 months (95% CI 7·2–11·8; 81 [67%] of 121 patients had an event) in the melflufen group and 4·6 months (3·5–6·3; 101 [78%] of 129 patients had an event) in the pomalidomide group (HR 0·59 [95% CI 0·44–0·79]; log-rank p=0·0004) at a median follow-up of 16·4 months; and median overall survival was 21·6 months (95% CI 14·6–26·0; 56 [46%] of 121 patients had died) in the melflufen group and 16·5 months (10·3–25·3; 67 [52%] of 129 patients had died) in the pomalidomide group (HR 0·78 [95% CI 0·55–1·12]; log-rank p=0·18]) at a median follow-up of 18·3 months (appendix pp 17–18). Among patients who had received a previous autologous HSCT (melflufen group n=125; pomalidomide group n=120), median progression-free survival was 4·4 months (95% CI 3·8–5·3; 84 [67%] of 125 patients had an event) in the melflufen group and 5·2 months (95% CI 4·3–7·4; 89 [74%] of 120 patients had an event) in the pomalidomide group (HR 1·06 [0·79–1·43] at a median follow-up of 14·7 months; log-rank p=0·69), and median overall survival was 16·7 months (95% CI 14·8–32·0; 61 [49%] of 125 patients had died) in the melflufen group and 31·0 months (20·2–34·1; 41 [34%] of 120 patients had died) in the pomalidomide group (HR 1·61 [95% CI 1·09–2·40]; log-rank p=0·017]) at a median follow-up of 19·4 months (appendix pp 17–18). In post-hoc analyses, more patients who had not received a previous autologous HSCT had alkylator-refractory disease than did patients who had received a previous transplantation (90 [36%] of
250 vs 63 [26%] of 245; odds ratio 1·62 [95% CI 1·10–2·39]; p=0·014). Among patients who had not received a previous autologous HSCT, survival outcomes were consistent regardless of previous alkylator (cyclo- phosphamide or melphalan; excluding high-dose melphalan) exposure and refractory status (appendix pp 51–52). To further elucidate factors affecting overall survival, we did a post-hoc multivariable analysis using the subgroups identified in the univariable analysis as affecting treatment: previous autologous HSCT (yes vs no), age (≥65 years vs <65 years), number of previous lines of therapy (three or four vs two), creatinine clearance (≥90 mL/min vs <90 mL/min), sex (male vs female), and ECOG performance status (1–2 vs 0; appendix p 16 and 53). In this multivariable analysis, previous autologous HSCT status and ECOG performance status (1–2 vs 0) were the only factors identified as significantly affecting overall survival outcomes between treatment groups (appendix p 53). Additionally, in a post-hoc analysis among patients who received subsequent therapy (melflufen group n=140; pomalidomide group n=135), median time to subsequent therapy was 10·5 months (95% CI 8·3–12·4) with melflufen and 8·9 months (95% CI 7·4–11·1) with pomalidomide. Details of subsequent therapies received are in the appendix (p 54).

Discussion

We found that progression-free survival was significantly higher with melflufen plus dexamethasone than with pomalidomide plus dexamethasone, with an HR of 0·79 (0·64–0·88; p=0·032). The median progression-free survival of 4·9 months (95% CI 4·2–5·7) with pomalidomide and dexamethasone was consistent with results of previous randomised phase 3 clinical trials and a randomised phase 2 trial featuring the doublet as the active comparator (ranging from 4·0 months to 6·5 months).12,17–19 Preliminary overall survival data for the ITT population was no different between the melflufen and poma- lidomide groups, and additional follow-up is ongoing. Although immature and non-statistically significant, the worse overall survival with melflufen plus dexamethasone (HR 1·10) triggered the FDA to send out a safety alert on July 28, 2021. Due to the overall survival data, the FDA requested suspension of enrollment in OCEAN and other ongoing melflufen clinical trials, and encouraged health-care professionals to review patients' progress on melflufen and discuss the risks of continued administration with each patient in the context of other treatments. Given that the benefit in progression-free survival did not result in a similar benefit in overall survival, we did exploratory and post-hoc analyses to determine what factors were driving this difference. In exploratory subgroup analyses, among patients without a previous autologous HSCT, melflufen plus dexa- methasone showed significantly increased progression- free survival and numerically higher overall survival, albeit not significantly different compared with pomalidomide plus dexamethasone. A post-hoc analysis

suggested that having received an autologous HSCT—

and by extension, previous high-dose melphalan conditioning therapy—was a significant negative prognostic factor for survival. Because patients who had not received a previous autologous HSCT had similar outcomes regardless of whether their disease was refractory to alkylators (cyclophosphamide or melphalan [excluding high-dose melphalan]) or not, it is reasonable to hypothesise that the negative prognostic effect of previous autologous HSCT in the melflufen group might be driven by exposure to high-dose melphalan in this context. Previous studies suggest that a patient's haematopoietic reserve might be negatively affected by alkylators used for stem-cell harvest and myeloablation before an autologous HSCT.20–22 In this scenario, patients might have difficulties tolerating subsequent treatments that induce cytopenias and could be more prone to developing haematological toxicities as a result. Furthermore, patients who relapse soon after receiving an autologous HSCT might be less likely to respond to any treatment, particularly one in which alkylation is the primary mechanism of action.

The safety and tolerability of melflufen plus dexa- methasone in OCEAN was consistent with previous reports in which haematological treatment-emergent adverse events were the most common treatment- emergent adverse events and were generally manageable with dose modifications and supportive care, and second primary malignancies were infrequent. Despite higher frequencies of grade 3 or 4 thrombocytopenia and neutropenia with melflufen than with pomalidomide overall, the number of concurrent grade 3 or 4 bleeding with thrombocytopenia and infection events with neutropenia were low. The number of non-haematological treatment-emergent adverse events were similar across treatment groups, although patients in the pomalidomide group had more grade 3 or 4 infections. Despite frequent dose delays and reductions in the melflufen group, most patients continued therapy after a dose reduction, and few adverse events resulted in treatment discontinuation. The OCEAN study has limitations, including the open- label study design, which could have resulted in a higher proportion of patients choosing to withdraw early from the study due to treatment preference. However, only two patients in the melflufen group chose to withdraw from the study before initiating study therapy and a similar number of patients remained on treatment in each study group at the time of writing. More patients in the melflufen group than in the pomalidomide group were randomly assigned but not treated (18 patients vs three patients), and 11 (61%) of these 18 patients had died as of data cutoff; hence, had they remained on study, they might have affected study outcomes. Furthermore, response assessment was assessed by an independent review committee whose members were masked to all treatment data and who did their reviews in closed-meeting sessions to mitigate any effect of the open-label design on the interpretation of the data. Another limitation is that the comparison of primary and secondary endpoints in various subgroups, such as patients with and without an autologous HSCT, was an exploratory analysis. Although post-hoc analyses suggested that previous autologous HSCT status was a prognostic factor for overall survival, future studies that are adequately powered to assess the difference in these patient populations will be needed to determine the clinical value of this factor. Finally, the small number of patients enrolled in the USA and other countries outside of Europe precludes us from drawing meaningful conclusions regarding potential geographical differences in treatment outcomes.

In summary, we found that melflufen plus dexamethasone improves progression-free survival for patients with lenalidomide-refractory relapsed or refractory multiple myeloma. Whether the treatment combination is beneficial for those who have or have not received a previous autologous HSCT needs to be investigated further.

Contributors

The study sponsor, Oncopeptides AB, conceptualised and designed the study in collaboration with FHS, M-AD, MT, CB, JH, NAB, RH, M-VM, PGR, and PS. Patient data were collected by FHS, M-AD, SD, PR, DC, WL, LP, IS, TM, VD, JM, GS, YA, AL, VM, GM, LR, AML, AS, RH,
M-VM, PGR, and PS. Data were analysed by MT, CB, JH, and NAB. NAB and MT had access to and verified the underlying study data. All authors had access to the data, participated in the interpretation of the data, took part in drafting and revising the manuscript, and approved the final version of the manuscript before submission.

Declaration of interests

FHS reports institutional grant support from Celgene, GlaxoSmithKline, Janssen, Oncopeptides AB, and

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Data sharing

Oncopeptides commits to share clinical study data with qualified researchers to enable enhancement of public health. As such, Oncopeptides will share anonymised patient-level data on request or if required by law or regulation. Qualified scientific and medical researchers can request patient-level data for studies of Oncopeptides pharmaceutical substances listed on ClinicalTrials.gov and approved by health authorities in the USA and the EU. Patient-level data for studies of newly approved pharmaceutical substances or indications can be requested 9 months after US Food and Drug Administration and European Medicines Agency approval. Such requests are assessed at Oncopeptides' discretion, and the decisions depend on the scientific merit of the proposed request, data availability, and the purpose of the proposal. The applicants should be willing to submit both positive and egative findings to a scientific journal. If Oncopeptides agrees to share clinical data for research purposes, the applicant is required to sign an agreement for data sharing before data release to ensure that the patient data are de-identified. In case of any risk of reidentification on anonymised data despite measures to protect patient confidentiality, the data will not be shared. Patient informed consent will always be respected. If the anonymisation process will provide futile data, Oncopeptides will have the right to refuse the request. Oncopeptides will provide access to patient-level clinical trial analysis datasets in a secured environment upon execution of the data sharing agreement. Oncopeptides will also provide the protocol, statistical analysis plan, and the clinical study report synopsis if needed. For additional information or requests for access to Oncopeptides clinical trial data for research purposes, please contact us at medinfoglobal@oncopeptides.com.

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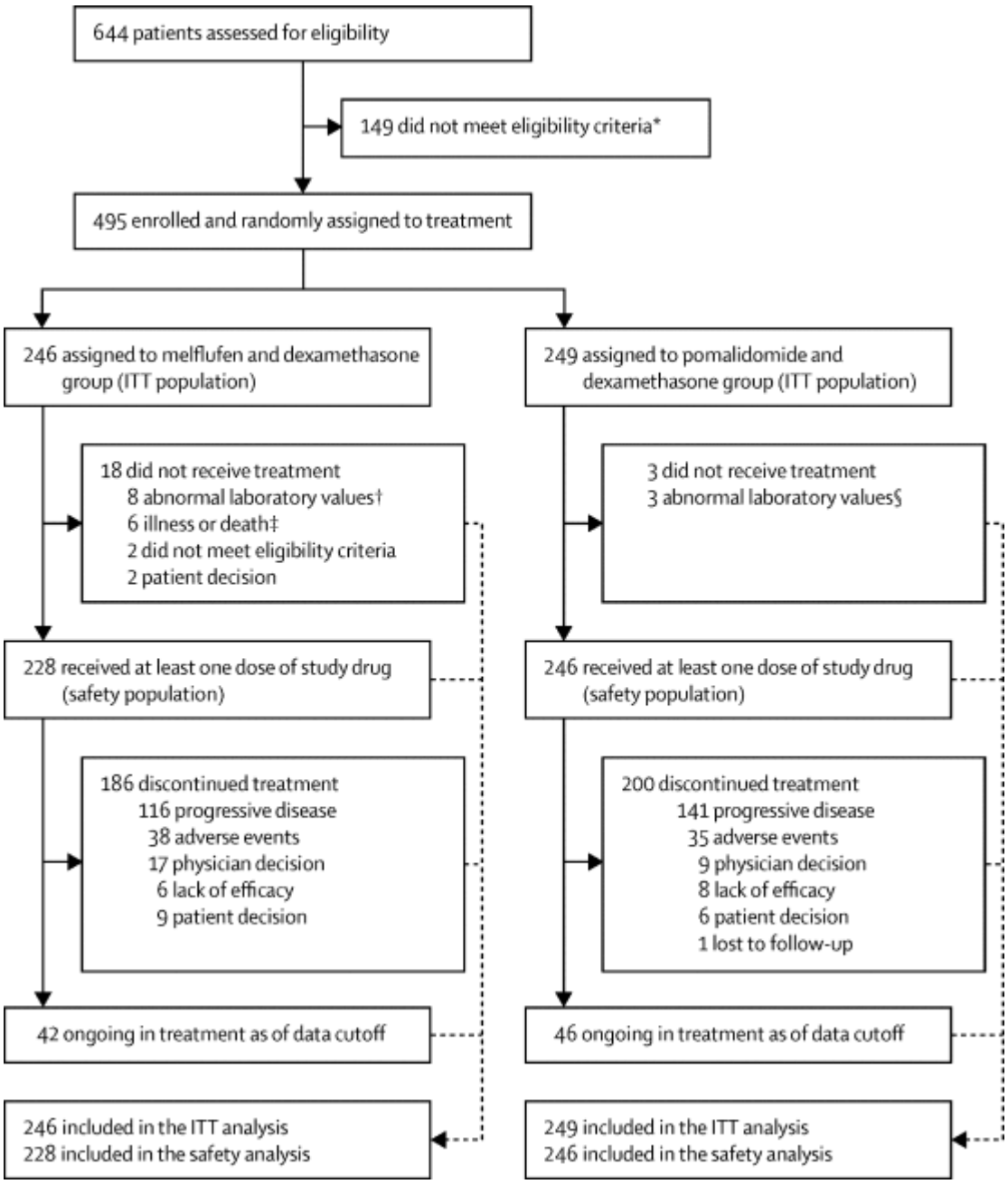

Figure 1: **Study profile**

ITT=intention-to-treat. Melflufen=melphalan flufenamide. *17 patients met one exclusion criterion, 120 patients did not meet one inclusion criterion, seven patients who met one or more exclusion criteria and/or did not meet one or more inclusion criteria, three patients died prior to randomisation, one patient withdrew due to investigator or sponsors' decision, and one patient withdrew consent (a full list of reasons for not meeting eligibility criteria can be found in appendix p 19). †One patient had low creatinine, six patients had low platelet counts, and one patient had a low platelet count and high creatinine. ‡One patient had the flu; one patient had hypercalcaemia-renal failure; one patient had a serious adverse event of pneumonia on the day of randomisation, never initiated treatment, and subsequently died 2 weeks later; one patient had disease progression; one patient needed radiation therapy and declined treatment; and one patient had a respiratory infection. §One patient had a low platelet count, one patient with a low platelet count and haemoglobin concentration, and one patient had a low platelet count and high creatinine.

	Melflufen group (n=246)	Pomalidomide group (n=249)
Age, years		
Median	68 (60–72)	68 (61–72)
<65	96 (39%)	85 (34%)
65–74	113 (46%)	125 (50%)
≥75	37 (15%)	39 (16%)
Sex		
Female	107 (43%)	109 (44%)
Male	139 (57%)	140 (56%)
Region		
USA	11 (4%)	15 (6%)
Europe	180 (73%)	176 (71%)
Rest of World	55 (22%)	58 (23%)
Race		
Asian	8 (3%)	13 (5%)
Black or African American	4 (2%)	4 (2%)
White	224 (91%)	222 (89%)
Other, unknown, or not reported	10 (4%)	10 (4%)
Time since diagnosis, years	4·0 (2·6–6·2)	3·9 (2·5–6·2)
ECOG performance status at baseline		
0	90 (37%)	92 (37%)
1	130 (53%)	136 (55%)
2	26 (11%)	21 (8%)
International Staging System score at study entry		
I	119 (48%)	124 (50%)
II	94 (38%)	94 (38%)
III	33 (13%)	31 (12%)
Creatinine clearance at baseline, mL/min	169 (69%)	180 (72%)
≥90	76 (31%)	69 (28%)
≥60 to <90	119 (48%)	112 (45%)
≥45 to <60	44 (18%)	58 (23%)
<45*	6 (2%)	10 (4%)
Cytogenetic risk group at diagnosis		
High risk†	83 (34%)	86 (35%)
Standard	128 (52%)	130 (52%)
Extramedullary disease at study entry	31 (13%)	31 (12%)

(Table 1 continues in next column)

	Melflufen group (n=246)	Pomalidomide group (n=249)
(Continued from previous column)		
Median number of previous lines of therapy	3 (2–3)	3 (2–3)
2	114 (46%)	111 (45%)
3 or 4	132 (54%)	138 (55%)
Previous autologous haematopoietic stem-cell transplantation		
Yes	125 (51%)	120 (48%)
No	121 (49%)	129 (52%)
Refractory to previous therapy		
Alkylator	78 (32%)	75 (30%)
Cyclophosphamide	63 (26%)	52 (21%)
Melphalan	15 (6%)	23 (9%)
High-dose melphalan	7 (3%)	10 (4%)
Proteasome inhibitor	163 (66%)	163 (65%)
Immunomodulatory agent	245 (>99%)	249 (100%)
Lenalidomide	245 (>99%)	248 (>99%)
Lenalidomide in last line	213 (87%)	217 (87%)
Anti-CD38 monoclonal antibody	48 (20%)	39 (16%)
Double refractory disease‡	162 (66%)	163 (65%)
Triple-class refractory disease§	39 (16%)	30 (12%)
Last line¶	245 (>99%)	247 (99%)

All data are n (%) or median (IQR) unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. Melflufen=melphalan flufenamide. *Per study inclusion criteria, these patients had creatinine clearance levels of ≥45 mL/min at the time of screening, but these decreased to <45 mL/min between screening and their baseline assessments. †High risk defined as t(4;14), t(14;16), t(14;20), del(17/p), gain(1q21), or gain 1q(+1q) by fluorescence in-situ hybridisation. ‡Double refractory disease was defined as refractory to both a previous immunomodulatory agent and a proteasome inhibitor, and not an anti-CD38 monoclonal antibody. §Triple-class refractory disease was defined as refractory to a previous immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. ¶Did not have at least a minimal response or progression on therapy within 60 days of the last dose of treatment.

Table 1: Baseline patient characteristics of the intention-to-treat population

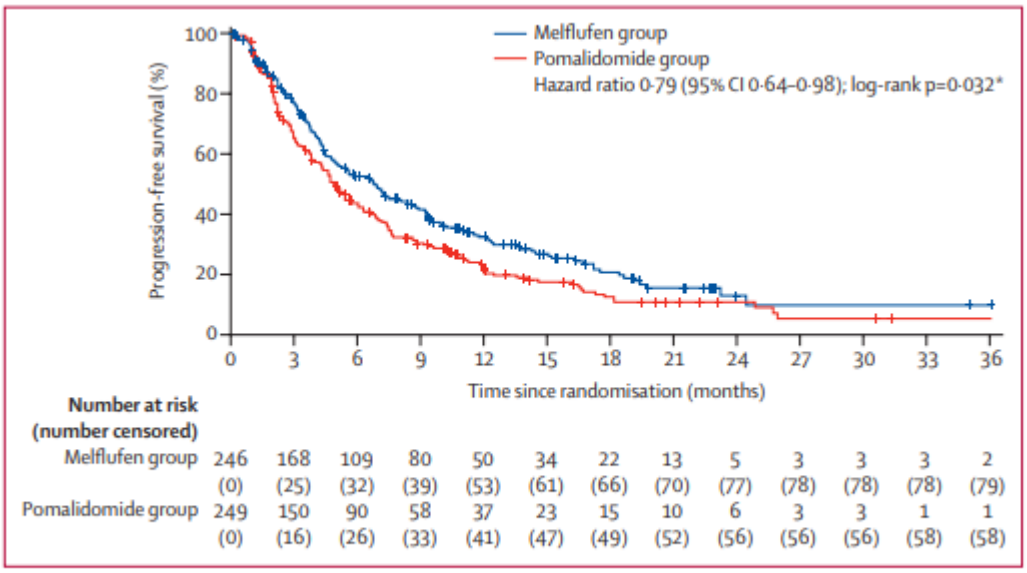

***Figure 2*: Progression-free survival, assessed by independent review committee**
Melflufen=melphalan flufenamide.

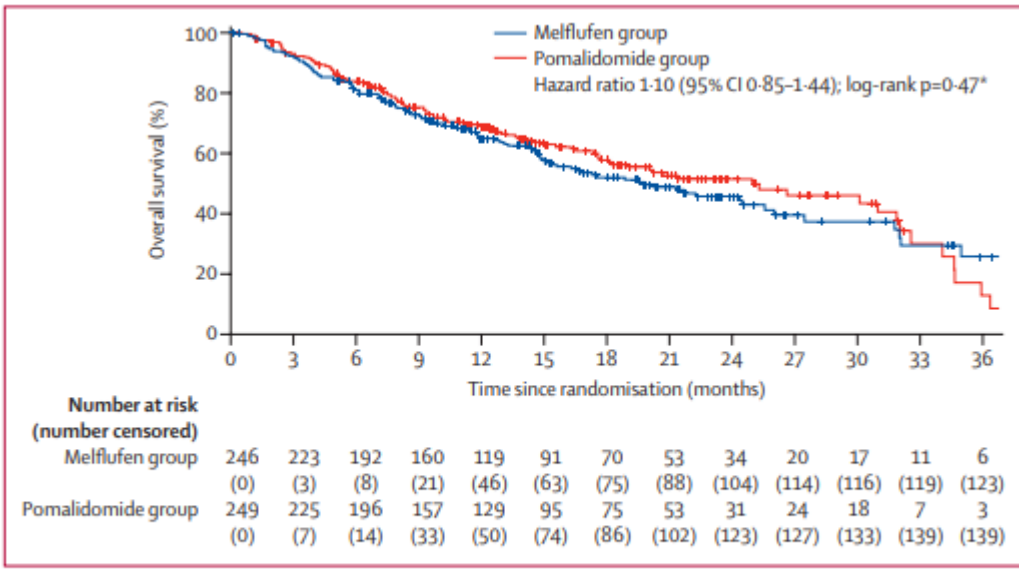

***Figure 3*: Overall survival assessed by independent review committee**
Melflufen=melphalan flufenamide.

	Melflufen group (n=228)				Pomalidomide group (n=246)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Haematological treatment-emergent adverse events								
Any haematological treatment-emergent adverse event	18 (8%)	75 (33%)	120 (53%)	2 (1%)	29 (12%)	89 (36%)	52 (21%)	0
Neutropenia	13 (6%)	64 (28%)	59 (26%)	1 (<1%)	11 (4%)	65 (26%)	37 (15%)	0
Anaemia	55 (24%)	92 (40%)	5 (2%)	0	48 (20%)	42 (17%)	2 (1%)	0
Thrombocytopenia	17 (7%)	72 (32%)	71 (31%)	0	22 (9%)	15 (6%)	11 (4%)	0
Neutrophil count decreased	2 (1%)	18 (8%)	10 (4%)	0	5 (2%)	15 (6%)	7 (3%)	0
Platelet count decreased	7 (3%)	18 (8%)	15 (7%)	0	5 (2%)	5 (2%)	1 (<1%)	0
Leukopenia	9 (4%)	13 (6%)	2 (1%)	0	4 (2%)	5 (2%)	2 (1%)	0
White blood cell count decreased	8 (4%)	7 (3%)	7 (3%)	0	4 (2%)	2 (1%)	0	0
Lymphopenia	2 (1%)	4 (2%)	4 (2%)	0	0	0	0	0
Pancytopenia	2 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0
Non-haematological treatment-emergent adverse events								
Any non-haematological treatment-emergent adverse event	100 (44%)	74 (32%)	5 (2%)	26 (11%)	96 (39%)	81 (33%)	15 (6%)	32 (13%)
Fatigue	32 (14%)	0	0	0	38 (15%)	2 (1%)	1 (<1%)	0
Asthenia	27 (12%)	4 (2%)	0	1 (<1%)	22 (9%)	6 (2%)	0	0
Pyrexia	30 (13%)	3 (1%)	0	0	13 (5%)	3 (1%)	0	0
Nausea	29 (13%)	1 (<1%)	0	0	16 (7%)	1 (<1%)	0	0
Diarrhoea	28 (12%)	3 (1%)	0	0	20 (8%)	1 (<1%)	0	0
Upper respiratory tract infection	26 (11%)	3 (1%)	0	0	24 (10%)	1 (<1%)	0	0
Pneumonia	7 (3%)	10 (4%)	0	3 (1%)	8 (3%)	19 (8%)	1 (<1%)	4 (2%)
Constipation	16 (7%)	0	0	0	29 (12%)	0	0	0
Bronchitis	10 (4%)	3 (1%)	0	0	21 (9%)	5 (2%)	0	0
COVID-19 pneumonia	0	4 (2%)	0	7 (3%)	1 (<1%)	4 (2%)	0	4 (2%)
Urinary tract infection	9 (4%)	0	0	2 (1%)	9 (4%)	7 (3%)	0	0
Lower respiratory tract infection	2 (1%)	2 (1%)	0	0	3 (1%)	3 (1%)	0	1 (<1%)
Pulmonary embolism	0	3 (1%)	0	1 (<1%)	0	2 (1%)	1 (<1%)	0
Renal failure	2 (1%)	0	0	2 (1%)	2 (1%)	5 (2%)	0	2 (1%)
Respiratory failure	0	1 (<1%)	1 (<1%)	2 (1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
General physical health deterioration	1 (<1%)	2 (1%)	0	0	1 (<1%)	1 (<1%)	0	3 (1%)
Abdominal mass	0	0	0	2 (1%)	0	0	0	0
Multiple organ dysfunction syndrome	0	0	0	2 (1%)	0	0	0	2 (1%)
Sepsis	1 (<1%)	1 (<1%)	0	0	1 (<1%)	3 (1%)	2 (1%)	1 (<1%)
Brain oedema	0	0	0	1 (<1%)	0	0	0	0
Cardiac arrest	0	0	0	1 (<1%)	0	0	0	2 (1%)
Cardiac failure acute	0	0	0	1 (<1%)	0	0	0	0
Cerebral haemorrhage	0	0	0	1 (<1%)	0	0	0	0
Escherichia sepsis	0	0	1 (<1%)	0	0	0	0	1 (<1%)
Myelodysplastic syndromes	1 (<1%)	0	0	0	0	0	0	1 (<1%)

	Melflufen group (n=228)				Pomalidomide group (n=246)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Oesophageal carcinoma	0	0	0	1 (<1%)	0	0	0	0
Pleural effusion	1 (<1%)	0	0	0	0	0	0	1 (<1%)
Post-procedural complication	0	0	0	1 (<1%)	0	0	0	0
Pulmonary oedema	0	0	0	1 (<1%)	0	0	0	1 (<1%)
Subdural haematoma	0	0	0	1 (<1%)	0	0	0	0
Sudden cardiac death	0	0	0	0	0	0	0	2 (1%)
Septic shock	0	0	0	0	0	0	1 (<1%)	1 (<1%)
Cerebrovascular insufficiency	0	0	0	0	0	0	0	1 (<1%)
Craniocerebral injury	0	0	0	0	0	0	0	1 (<1%)
Death for unknown reason	0	0	0	0	0	0	0	1 (<1%)
Respiratory arrest	0	0	0	0	0	0	0	1 (<1%)
Sudden death*	0	0	0	0	0	0	0	1 (<1%)

All data are n (%). Treatment-emergent adverse events of any grade, which were reported in at least 10% of patients in either treatment group or grade 3 or 4 treatment-emergent adverse events that were reported in at least 3% of patients, and all grade 5 treatment-emergent adverse events are shown. Treatment-emergent adverse events of any grade, which were reported in at least 10% of patients in either treatment group, or any grade 3, 4, or 5 treatment-emergent adverse events are in the appendix (p 23) in either treatment group, are listed in the safety population (by preferred term). *Patient died suddenly at home on cycle 18 day 15 of therapy, 22 days after the last dose of pomalidomide and 7 days after the last dose of dexamethasone. No autopsy was performed and the investigator considered the sudden death to be unrelated to study medication.

Table 2: Treatment-emergent adverse events in the safety population