Received: 20 July 2021 | Revised: 18 October 2021 | Accepted: 25 October 2021

DOI: 10.1111/ejh.13719

ORIGINAL ARTICLE

European Journal of Haematology WILEY

Pomalidomide plus dexamethasone for patients with relapsed or refractory multiple myeloma: Final results of the non-interventional study POSEIDON and comparison with the pivotal phase 3 clinical trials

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Funding information
This study was financially supported by Celgene Europe B.V. None of the funders had any role in study design, data collection and analysis, interpretation of results, decision to publish or preparation of the manuscript.

Abstract

Background: Prognosis of patients with multiple myeloma (MM) who have relapsed on or become refractory to immunomodulators and bortezomib is poor, and treatment options are limited. While pomalidomide plus low-dose dexamethasone (POM/DEX) has demonstrated efficacy in clinical trials, real-world evidence is scarce.

Patients and Methods: POSEIDON was a prospective non-interventional study designed to evaluate effectiveness, safety and quality of life (QoL) of POM/DEX in patients with relapsed or refractory MM (R/RMM) pretreated with at least two prior therapy lines including both lenalidomide and bortezomib in real world in Germany. Patients received POM/DEX according to physicians' choice. Data were analyzed descriptively.

Results: Between 2014 and 2017, 151 patients were enrolled, 144 patients with a median of three prior therapy lines qualified for effectiveness analysis. Median age was 73.2 years. Median progression-free and overall survival were 6.3 months [95% confidence interval (CI) 5.2, 8.6] and 12.9 months [95% CI 10.6, 15.1]. Most frequent grade 3/4 adverse events were leukopenia (8.2%), pneumonia (7.5%) and anemia (5.5%). QoL was maintained after start of POM/DEX.

Conclusion: The results of POSEIDON support the effectiveness and safety of POM/DEX in R/RMM patients pretreated with lenalidomide and bortezomib and highlight the clinical value of the POM/DEX regimen in the real-world setting.

Registered at clinicaltrials.gov (NCT02075996).

KEYWORDS
dexamethasone, Germany, non-interventional study, pomalidomide, relapsed or refractory multiple myeloma, routine clinical practice

1 | INTRODUCTION

Treatment of multiple myeloma (MM) has changed substantially during the past decade.[1–3] The introduction of immunomodulatory drugs (IMiDs®) and proteasome inhibitors (PIs) has resulted in significantly improved outcome of MM patients.[2] However, although current treatments are very effective, most MM patients will eventually become refractory to treatment or relapse[3–6] and treatment of advanced-stage patients whose disease progressed after several treatment lines remains challenging. Durations of remission have been inversely related to the number of treatment regimens, probably due to acquired drug resistance.[4] The prognosis of patients who relapse after or become refractory to PIs such as bortezomib and IMiD agents such as lenalidomide has been assessed to be poor with a median overall survival (OS) of 9 months.[7] Pomalidomide (Imnovid®) (POM) is a third-generation IMiD agent with antitumor and immune stimulating properties distinct from those of lenalidomide.[8–10] It has been shown to exhibit synergistic responses when used in combination with dexamethasone (DEX)[11] and demonstrated efficacy in lenalidomide-refractory patients in clinical trials.[11–14] Based on the pivotal phase III (MM-003) trial by San Miguel et al.,[12] in which the combination of pomalidomide and low-dose dexamethasone (POM/DEX) resulted in significantly longer survival and a greater number of clinical responses compared to DEX alone, it received approval in 2013 for the treatment of patients with relapsed and refractory MM who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.[15] Efficacy and safety of this combination regimen were further confirmed in a large phase IIIb trial (MM-010) by Dimopoulos et al.[14]

As published data from clinical trials may not reflect clinical outcomes in real world due to well-known significant differences in multiple aspects, including patient and disease characteristics, treatment-related factors and trial design,[16] the assessment of effectiveness and tolerability of POM/DEX in routine clinical practice in a more heterogenous population of patients with relapsed or refractory MM (R/RMM) is of key importance. Thus, the current POSEIDON study aimed to evaluate effectiveness and safety of POM/DEX therapy in Germany in a real-world setting.

2 | METHODS

2.1 | Study design and setting

POSEIDON (NCT02075996) was a prospective, non-interventional study (NIS) approved by the responsible ethics committees and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before study entry. Patients were enrolled between 2014 and 2017 at 43 study sites across Germany including hemato-oncologists in hospitals and outpatient clinics, and independent oncology practices. Patients were recruited into two cohorts (I/II) stratified by last prior treatment line. Patients of cohort I had received lenalidomide in the last preceding treatment prior to enrolment, whereas patients of cohort II had received any other prior therapy directly before enrolment, including lenalidomide in earlier treatment lines.

2.2 | Patients and treatment

Eligible patients were aged ≥18 years, diagnosed with R/RMM and with decision for treatment with POM/DEX in routine clinical practice. Patients must have received at least two prior therapy lines including both lenalidomide and bortezomib, and patients must have progressed on the last therapy. Further, patients had to fulfill the conditions of the pregnancy prevention program.[15]

Indication for treatment and decision for therapy with POM/DEX was the responsibility of the treating physician and independent from the decision to include the patient into the study. The treatment observation period comprised patients´ course of POM/DEX treatment until disease progression (PD), death or discontinuation of therapy, however, for a maximum of 12 months. Patients were followed up for assessment of the further course of disease and overall survival according to clinical routine until a maximum of 36 months after end of the treatment observation period of the last patient.

2.3 | Study objectives

The primary objective was to assess progression-free survival (PFS), defined as the time from first administration of POM until disease progression or death, whichever came first. Secondary effectiveness objectives included the overall response rate (ORR), according to the International Myeloma Working Group (IMWG) response criteria for MM,[17] time to treatment discontinuation (TTD), defined as the time from the first intake of POM until end of POM treatment, time to next treatment (TTNT), defined as the time from first intake of POM until start of a subsequent treatment with any substance other than POM, and OS, defined as the time from first intake of POM until death due to any cause. Effectiveness analyses were performed for predefined subgroups including patients with refractory MM (i.e., patients who had progressed on therapy or within 60 days after completing the last therapy) and patients with relapsed MM (i.e., patients who had progressed later than 60 days after completing the last therapy). Within the subgroup of patients with refractory MM, further subgroup analyses were performed for patients being primary refractory to lenalidomide (i.e., patients who never achieved a minor response (MR) or better with prior lenalidomide therapy) and patients not being primary refractory to lenalidomide. Moreover, analyses were stratified according to patients´ cytogenetic risk profile which was determined based on chromosomal aberrations. Patients who had at least one documented "high-risk" aberration according to the IMWG definition by Sonneveld et al.,[18] i.e., gain 1q, gain 1q21, del(13), del(13q), del(13q14), del(17p),

del(17p13), hypodiploidy (non-hyperdiploidy), t(4;14), t(14;16) and t(14;20), were assigned to high-risk cytogenetic profile. If none or only "standard risk" aberrations were documented, patients were assigned to standard risk profile. Further study objectives included the safety profile of POM (see Section 2.4), relative dose intensities and patient-reported changes in quality of life (QoL, Section 2.5).

2.4 | Adverse events

Any treatment-emergent adverse events (AEs) were recorded from day of first administration of the study treatment until 30 days after the last dose of POM/DEX treatment or end of the 12-months treatment observation period, whatever came first. AEs were graded in accordance with the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE version 4.03).

2.5 | Health-related quality of life

To assess patient's health-related QoL, the EORTC QLQ-C30, with focus on questions 29 and 30, and the EORTC QLQ-MY20 questionnaires were used. Domain scores of the respective questionnaires were averaged and transformed linearly to scores ranging from 0–100. Higher scores in the global health status/functional scales correspond to higher perceived QoL/healthy level of functioning, while higher scores in the symptom scale correspond to a higher level of perceived symptoms. Patients were asked to complete the questionnaires at baseline and every two months thereafter until study treatment discontinuation or latest at end of the 12-month treatment observation period.

2.6 | Statistical analysis

All enrolled patients having received at least one dose of POM and at least two prior therapies (including lenalidomide and bortezomib) were included in the full analysis set (FAS). The FAS was used to assess patient and disease characteristics and to analyze effectiveness objectives and QoL. Patients in the FAS for whom data on at least one further post-baseline variable under study treatment were available were included in the safety analysis set (SAF) used for evaluation of safety (AE analysis), exposure and treatment data. All variables were analyzed in a descriptive manner. Continuous variables were listed as number of observations, mean, standard deviation, median, 25%- and 75%-quartile and minimum–maximum. Categorical variables were presented as absolute and relative frequencies within single categories including an individual "missing" category. Subgroup analyses were considered exploratory.

The Kaplan–Meier method[19] was used to estimate time-to-event endpoints (PFS, OS and TTNT). The follow-up time (i.e., the treatment observation period plus the follow-up period) was estimated with the reverse Kaplan–Meier method[20] and additionally calculated and displayed with descriptive statistics for surviving patients only. Multivariate logistic regression and Cox regression analyses were performed to identify potential factors (age at inclusion, cohort, number of prior therapies, time from diagnosis until start of study treatment), which might have an impact on PFS, OS, TTNT or ORR. All statistical analyses were performed using SAS Version 9.4.

3 | RESULTS

3.1 | Patient, treatment and tumor characteristics at baseline

Between February 2014 and March 2017, 151 patients in 43 study centers across Germany were enrolled, of whom 79 patients were stratified by prior treatment into cohort I (lenalidomide treatment directly before inclusion) and 72 patients into cohort II (any other prior treatment directly before inclusion). Two patients had been assigned to the corresponding cohort but had no documented treatment start. In total, 144 patients (76 patients of cohort I and 68 patients of cohort II) were included in the FAS (Figure 1).

Detailed demographics and clinical characteristics are depicted in Table 1. Data are displayed for patients in total as well as stratified by cohort I/ II and by refractory and relapsed MM; 96 patients were diagnosed with refractory MM (66.7%). Relapsed MM was diagnosed in 40 (27.8%) patients. Eight patients were neither assigned to relapsed nor refractory MM as for them no progress was documented after the last prior treatment and before start of the study treatment. Median age (range) at inclusion was 73.2 years (44.6–86.0) with a median time from initial diagnosis (ID) until start of POM treatment of 4.9 years (0.4–24.2) and a median number of prior therapy lines of 3.0 (2.0–8.0). Most patients presented with an Eastern Cooperative Oncology (ECOG) status of 0 or 1 (61.1%). At the beginning of POM/DEX treatment, most patients had Durie and Salmon stage III (72.9%) and International Staging System (ISS) stage II (29.9%) or III (23.6%). ISS was unknown for 31.3% of patients. The cytogenetic risk group could be determined for 71 patients. Of these, 24 (16.7%) patients were classified into high risk and 47 (32.6%) into standard risk.

3.2 | Treatment with pomalidomide

The median number (range) of POM treatment cycles was 5.0 (1.0–12.0). The most common reason for end of POM/DEX treatment of 144 patients qualifying for effectiveness analyses was PD, among 57 (39.6%) patients. Further reasons for discontinuation documented among ≥10% of patients were inacceptable toxicity in 27 (18.8%) patients, death in 21 (14.6%) patients and physician´s decision in 15 (10.4%) patients.

Treatment modifications with POM were reported in 120 (82.8%) of 145 patients qualifying for treatment data analysis, thereof 107 (73.8%) therapy breaks and 70 (48.3%) dose reductions. Among

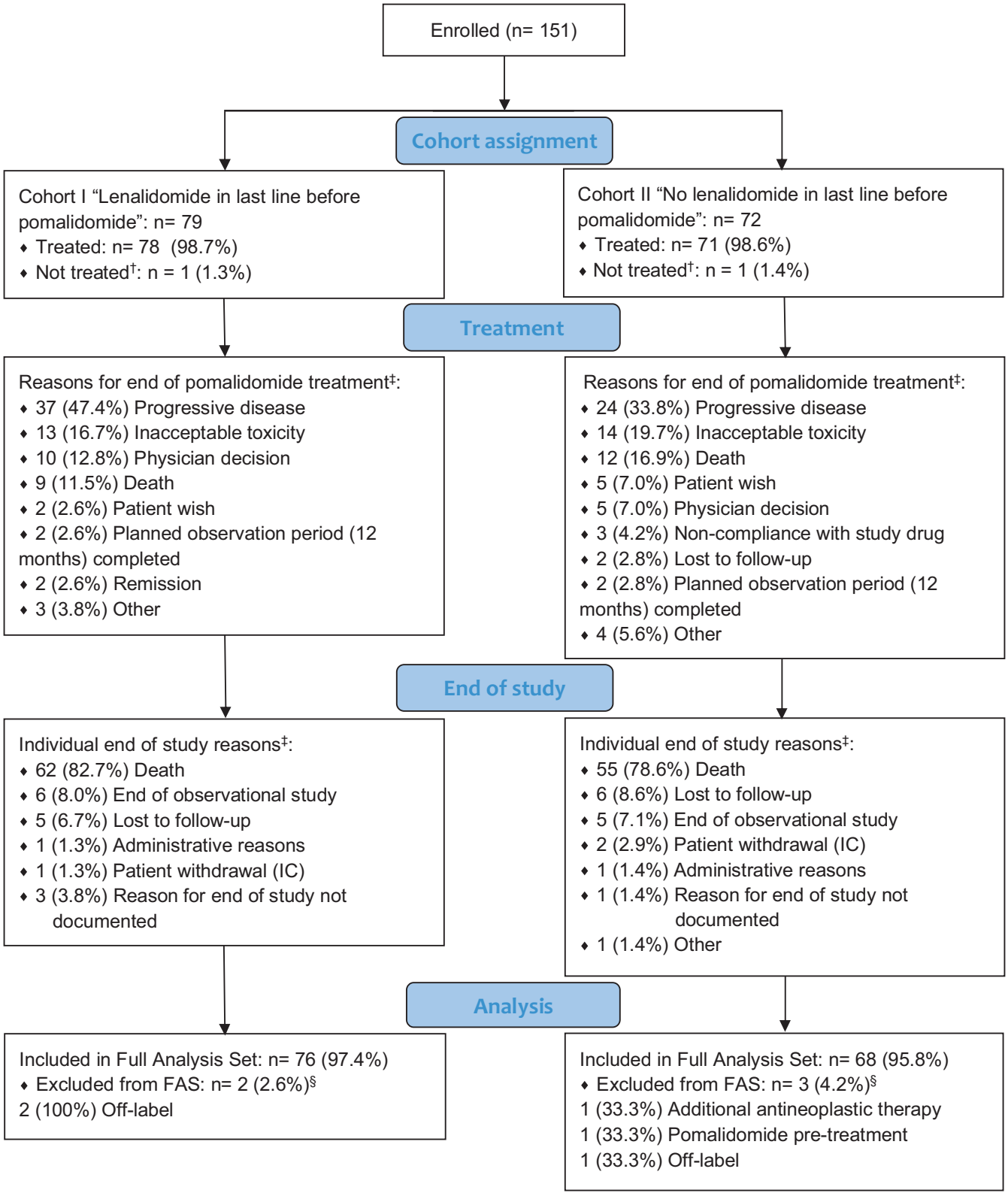


FIGURE 1 Consort diagram. †Patients assigned to the corresponding cohort but without documented treatment start date, ‡Includes only patients who received pomalidomide treatment, §The full analysis set (FAS) consists of all enrolled patients having received at least one dose of pomalidomide. Patients fulfilling at least one off-label criteria (not having received at least two prior therapies, not having received both lenalidomide and bortezomib in previous therapy lines) were excluded from the FAS. Planned observation period (12 months) completed: for these patients no further pomalidomide treatment or incomplete information on pomalidomide treatment was documented in the follow up, and therefore, no reason for end of pomalidomide treatment in the follow up is available

the reasons for treatment modifications, 37.2% were treatment related. Other reasons documented were patient´s wish (17.9%), noncompliance (6.9%) and reasons not further specified (64.8%). Median (range) relative dose intensities of POM were 80.6% (16.7–122.6), 82.7% (33.9–122.6) and 80.6% (16.7–101.0) for patients overall, in cohorts I and II, respectively.

3.3 | Patient survival and response to therapy

3.3.1 | Survival and response to therapy in the total patient population and stratified by cohorts

After a median follow-up of 43.5 months, for the total population, median PFS and OS were 6.3 months [95% confidence interval (CI) 5.2,8.6] and 12.9 months [95% CI 10.6,15.1], respectively (Figure 2A,B).

Median PFS of the cohorts (cohort I: 5.5 months [95% CI 3.8, 9.2]; cohort II: 6.4 months [95% CI 5.3, 8.7]) and median OS (cohort I: 14.1 months [95% CI 10.6, 18.7]); cohort II: 11.7 months [95% CI 8.7, 15.9]) were comparable (Figure 2C,D). Total ORR (complete response [CR]/very good partial response [VGPR]/partial response [PR]) for the total population was 31.9% [95% CI 24.9, 40.0] and 27.6% [95% CI 18.8, 38.6] for cohort I vs. 36.8% [95% CI 26.3, 48.7] for cohort II. 6.3% of patients in the total population ($n = 9$), 2.6% ($n = 2$) in cohort I and 10.3% ($n = 7$) in cohort II achieved CR/VGPR. For 30 (20.8%) patients, no response assessment was documented (Table 2). Median TTD (range) was 4.4 months (0–45.1) for the total population, 4.4 months (0.1–35.7) for cohort I and 4.7 months (0.0–45.1) for cohort II. Median TTNT was 7.7 months [95% CI 6.2–9.6] in total and 7.6 months [95% CI 4.6–11.9] for cohort I compared to 8.3 months [95% CI 6.2–9.2] for cohort II. Multivariate logistic regression analysis for ORR and Cox regression analyses for PFS and OS did not indicate statistically significant impacts of age, lenalidomide in last prior treatment, number of prior therapies and time from diagnosis to start of treatment on the respective effectiveness outcomes in the total patient population.

3.3.2 | Survival and response to therapy stratified by subgroups

Refractory vs. relapsed MM

For patients with refractory MM, median PFS was 5.5 months [95% CI 3.8, 7.4], for patients with relapsed MM, 8.8 months [95% CI 5.2, 12.1]. Median OS of patients with refractory MM vs. relapsed MM was 10.6 [95% CI 7.6, 13.8] and 23.3 months [95% CI 12.9–39.0], respectively (Figure 2E,F). The ORR among patients with refractory MM was 28.1% [95% CI 20.1, 37.9] compared to 40.0% [26.3, 55.4] among patients with relapsed MM (Table 2). Median TTD (range) and TTNT [95% CI] were 4.4 (0.0–45.1) and 6.5 months [95% CI 4.7, 8.6] among patients with refractory MM as compared to 4.7 (0.1–29.6) and 8.9 months [95% CI 6.7, 13.1] among patients with relapsed MM, respectively.

Primary refractory to lenalidomide vs. not primary refractory to lenalidomide

Of the 96 patients diagnosed with refractory MM, 42 (43.8%) patients were classified as not primary refractory to lenalidomide, while 39 (40.6%) patients were classified as primary refractory to lenalidomide. For 15 (15.6%) patients, response to prior lenalidomide therapy was not available. Median PFS was 4.6 [95% CI 3.2, 6.7] for patients not primary refractory to lenalidomide and 5.5 months [95% CI 3.0, 8.8] for patients primary refractory to lenalidomide, while OS was 10.6 [95% CI 6.1, 14.1] and 8.0 months [95% CI 5.1, 14.9], respectively (Figure S1). ORRs of patients not primary refractory to lenalidomide vs. patients primary refractory to lenalidomide were 28.6% [95% CI 17.1, 43.7] vs. 20.5% [95% CI 10.5, 35.8] (Table S1). TTD and TTNT of patients not primary refractory to lenalidomide vs. patients primary refractory to lenalidomide were 4.4 (0.2–31.3) and 6.0 months [95% CI 2.9, 8.4] vs. 3.5 (0.0–28.9) and 5.4 months [95% CI 4.1, 9.7], respectively.

Cytogenetic risk group

Considering patients´ cytogenetic risk profile, median PFS and OS of high-risk patients vs. standard risk patients were 5.9 [95% CI 3.2, 7.3] vs. 5.5 months [95% CI 3.8, 8.8] and 11.2 [95% CI 6.4, 18.3] vs. 11.4 months [95% CI 6.9, 15.9], respectively (Figure S1). ORRs of high- and standard-risk patients were 20.8% [95% CI 8.8, 40.9] and 34.0% [95% CI 22.1, 48.4] (Table S1). Median TTD (range) and median TTNT of high-risk vs. standard-risk patients were as follows: TTD: 4.7 (0.2–17.3) vs. 4.3 months (0.0–31.3) and TTNT: 6.5 [95% CI 3.8, 9.2] vs. 6.7 months [95% CI 3.7, 9.6].

3.4 | Quality of life

At baseline, the questionnaire return rate was 85.4%. Based on patient-reported outcomes, QoL maintained stable in POM/DEX treated patients. As shown in boxplots in Figure 3, Global Health Status/QoL was not significantly affected and functional scales (body image, future perspective) as well as symptom scales (disease symptoms, side effects) displayed hardly any changes over time. The greatest change from baseline of −15.2 (±29.5) points was observed after 10 months in the mean (SD) subscale score for body image. Details on changes of questionnaire scores from baseline are depicted in Table S2.

3.5 | Adverse events

Of all patients in the SAF ($n = 145$), 138 (95.2%) experienced at least one AE (Table 3). The most common AEs (≥10%) were anemia (21.4%), fatigue (17.9%), leukopenia (16.6%), pneumonia (13.8%), diarrhoea (11.7%) and thrombocytopenia (11.0%). The most common

TABLE 1 Patient demographics and clinical characteristics at the time of enrolment (FAS: *N* = 144)

	Total (*N* = 144)	Cohort I (*N* = 76)	Cohort II (*N* = 68)	Refractory MM (*N* = 96)	Relapsed MM (*N* = 40)
Patient characteristics					
Age at inclusion [years] (median, range)	73.2 (44.6–86.0)	73.0 (46.6–84.9)	73.6 (44.6–86.0)	72.8 (44.6–84.1)	74.5 (52.6–86.0)
Sex					
Female	63 (43.8)	37 (48.7)	26 (38.2)	41 (42.7)	19 (47.5)
Male	81 (56.3)	39 (51.3)	42 (61.8)	55 (57.3)	21 (52.5)
Time from ID [years] (median, range)	4.9 (0.4–24.2)	4.5 (0.7–12.6)	6.1 (0.4–24.2)	4.8 (0.4–18.2)	5.7 (1.4–16.7)
Performance status					
ECOG 0–1	88 (61.1)	45 (59.2)	43 (63.2)	60 (62.5)	23 (57.5)
ECOG 2–3	29 (20.1)	17 (22.4)	12 (17.6)	19 (19.8)	9 (22.5)
Missing	27 (18.8)	14 (18.4)	13 (19.1)	17 (17.7)	8 (20.0)
Creatinine clearance					
≥60 ml/min	80 (55.6)	47 (61.8)	33 (48.5)	58 (60.4)	20 (50.0)
<60 ml/min	92 (63.9)	47 (61.8)	45 (66.2)	61 (63.5)	24 (60.0)
Missing	1 (0.7)	1 (1.3)	0 (0.0)	0 (0.0)	1 (2.5)
Treatment characteristics					
Number of prior therapy lines (median, range)	3.0 (2.0–8.0)	2.0 (2.0–7.0)	4.0 (2.0–8.0)	3.0 (2.0–8.0)	3.0 (2.0–6.0)
2	53 (36.8)	47 (61.8)	6 (8.8)	33 (34.4)	18 (45.0)
3	34 (23.6)	14 (18.4)	20 (29.4)	21 (21.9)	11 (27.5)
4	30 (20.8)	9 (11.8)	21 (30.9)	24 (25.0)	5 (12.5)
≥5	27 (18.8)	6 (7.9)	21 (30.9)	18 (18.8)	6 (15)
Prior therapies					
Autologous SCT	51 (35.4)	23 (30.3)	28 (41.2)	31 (32.3)	15 (37.5)
Bortezomib	144 (100)	76 (100)	68 (100)	96 (100)	40 (100)
Dexamethasone	141 (97.9)	73 (96.1)	68 (100.0)	93 (96.9)	40 (100.0)
Lenalidomide	144 (100)	76 (100)	68 (100)	96 (100)	40 (100)
Thalidomide	16 (11.1)	7 (9.2)	9 (13.2)	10 (10.4)	6 (15.0)
Primary refractory[a]	n.a.	n.a.	n.a.	14 (14.6)	n.a.
Primary refractory to lenalidomide[b]	n.a.	n.a.	n.a.	39 (40.6)	n.a.
Tumor characteristics					
ISS[c]					
I	22 (15.3)	12 (15.8)	10 (14.7)	13 (13.5)	8 (20.0)
II	43 (29.9)	25 (32.9)	18 (26.5)	33 (34.4)	7 (17.5)
III	34 (23.6)	18 (23.7)	16 (23.5)	21 (21.9)	12 (30.0)
Unknown	45 (31.3)	21 (27.6)	24 (35.3)	29 (30.2)	13 (32.5)
Durie and Salmon[d]					
I	7 (4.9)	3 (3.9)	4 (5.9)	6 (6.3)	1 (2.5)
II	29 (20.1)	19 (25.0)	10 (14.7)	17 (17.7)	12 (30.0)
III	105 (72.9)	53 (69.7)	52 (76.5)	70 (72.9)	27 (67.5)
Unknown	3 (2.1)	1 (1.3)	2 (2.9)	3 (3.1)	–
A	16 (11.1)	5 (6.6)	11 (16.2)	10 (10.4)	4 (10.0)
B	120 (83.3)	69 (90.8)	51 (75.0)	81 (84.4)	33 (82.5)
Unknown	5 (3.5)	1 (1.3)	4 (5.9)	2 (2.1)	3 (7.5)

TABLE 1 (Continued)

	Total (*N* = 144)	Cohort I (*N* = 76)	Cohort II (*N* = 68)	Refractory MM (*N* = 96)	Relapsed MM (*N* = 40)
Cytogenetic risk group[e]					
High risk	24 (16.7)	10 (13.2)	14 (20.6)	18 (18.8)	5 (12.5)
Standard risk	47 (32.6)	29 (38.2)	18 (26.5)	33 (34.4)	12 (30.0)
Missing	73 (50.7)	37 (48.7)	36 (52.9)	45 (46.9)	23 (57.5)

Note: Data displayed with descriptive statistics (median (range) or frequencies (%) for the full analysis set (FAS, *n* = 144). Cohort I: lenalidomide in last line prior to pomalidomide treatment, Cohort II: no lenalidomide in last line prior to pomalidomide treatment; refractory MM = PD on or within 60 days after last prior therapy, relapsed MM = PD >60 days after last prior therapy; for eight patients an assignment to refractory or relapsed MM was not possible.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ID, initial diagnosis; MM, multiple myeloma; PD, progressive disease; SCT, stem cell transplantation.

[a]Patients with refractory MM who never achieved a minor response or better with any prior therapy.

[b]Patients with refractory MM who never achieved a minor response or better with any prior lenalidomide therapy.

[c]ISS, International Staging System.[34] ISS staging at the time of start with pomalidomide therapy.

[d]Staging according to the Durie and Salmon Staging system[35] at the time of start with pomalidomide therapy.

[e]Coded by medical experts, patients were classified into cytogenetic risk groups depending on their documented chromosomal aberrations (see Section 2.6).

AEs grade 3/4 (>5%) were leukopenia (8.3%), pneumonia (7.6%) and anemia (5.5%).

Treatment-related AEs (any grade) occurred in 92 (63.4%) patients. Treatment-related grade 3 and 4 AEs were reported in 44 (30.3%) and 8 (5.5%) patients, respectively. Most common treatment-related grade 3/4 AEs were hematological disorders and infections with leukopenia reported in 12 (8.3%) patients and pneumonia in 11 (7.6%) patients. Serious treatment-related AEs were documented in 23 (15.9%) patients. One patient (0.7%) was reported with a fatal treatment-related AE (pneumonia) occurring during POM/DEX safety follow-up period.

4 | DISCUSSION

In patients with refractory or relapsed and refractory MM, clinical trials have demonstrated efficacy of the third-generation IMiD agent POM in combination with DEX.[12,14] However, those results might have limited generalizability as they may not reflect outcome in an unselected, mostly older and more comorbid patient population encountered in clinical practice. Therefore, the POSEIDON study evaluated effectiveness and tolerability of POM/DEX in patients with R/RMM pretreated with lenalidomide and bortezomib in a real-world setting.

Overall, the results of POSEIDON support the efficacy and safety outcomes of published phase III clinical trials.[12,14] Median PFS in the present study was markedly longer than in the registrational MM-003[12] and MM-010 trials[14] with 6.3 [95% CI 5.2–8.6] vs. 4.0 [95% CI 3.6–4.7] and 4.6 months [95% CI 3.9–4.9], respectively, while median OS and ORR were comparable between studies (OS: 12.9 months [95% CI 10.6–15.1] vs. 12.7 months [95% CI 10.4–15.5] and 11.9 months [95% CI 10.6–13.4], respectively; ORR: 31.9% [95% CI 24.9–40.0] vs. 31% [95% CI not reported] and 32.6% [95% CI 29.0–36.2], respectively). The longer PFS obtained in POSEIDON may be attributable to a variety of factors. Thereof, the patients with relapsed myeloma (*N* = 40, 27.8%) included in POSEIDON with a median PFS of 8.8 months [95% CI 5.2, 12.1]) that were not eligible for the phase III clinical trials might play a role. However, PFS of patients with relapsed compared to refractory MM was comparable in the present study, while interestingly OS tended to be longer in patients with relapsed MM. Of note, differences between these groups should be interpreted with caution due to small and differing group sizes. Another factor which might explain the difference in PFS is the lower number of prior therapies patients had received in POSEIDON (median 3 therapies) as compared to those in the MM-003 and MM-010 trials (both median 5 therapies). Noteworthy, patients in the POSEIDON study were markedly older as compared to patients in the MM-003 and MM-010 trials (median age 73 years vs. 64 and 66 years). Further, patients in POSEIDON were likely to be in a poorer health status as reflected by the lower proportion of patients with ECOG 0–1 in POSEIDON (61.1% as compared to 82.0% (MM-003) and 90.0% (MM-010)) as well as by the higher number of patients with renal impairment (63.9% with eGFR <60 ml/min as compared to 31.0 (MM-003) and 34.8% (MM-010)), i.e., patient and disease characteristics generally related with poorer prognosis.[16] Notwithstanding the above, it is interesting to note that patients' age did not have an influence on PFS, OS or response rates in the POSEIDON study and neither on the efficacy and safety benefits of POM/DEX over DEX alone in the pivotal MM-003 study.[12]

To the best of our knowledge, this is the first prospective study investigating the effectiveness of POM/DEX in a real-world setting. However, several retrospective, mostly smaller studies from different countries, in which patients with R/RMM or patients with relapsed and refractory MM who had been treated with POM with or without DEX were analyzed, have been published during the last years.[21–27] With respect to the results on PFS, the POSEIDON study compares favorably with reported median PFS of 5.2 months each from two smaller studies from the UK[21,22] and the median

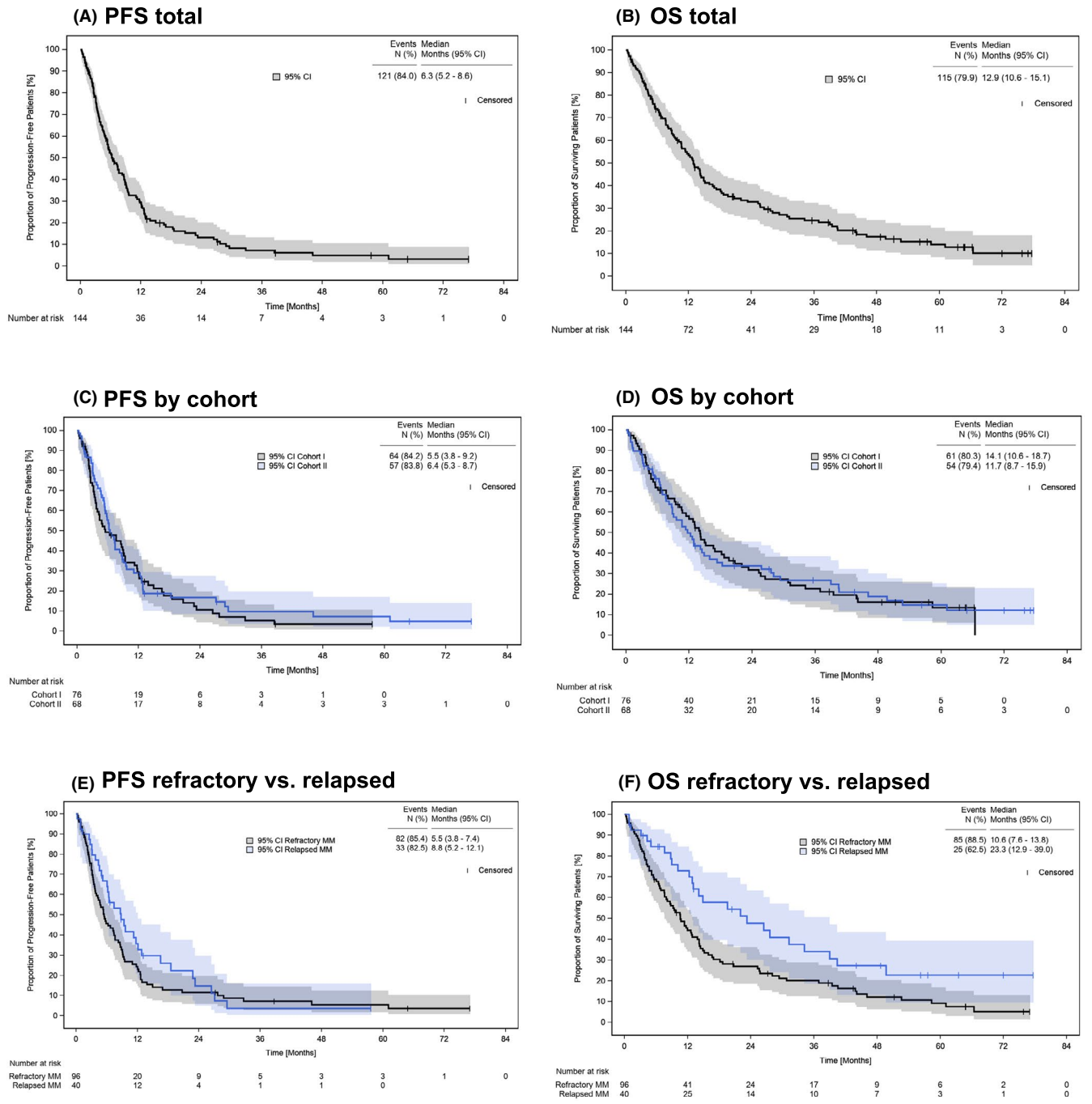


FIGURE 2 Progression-free survival (PFS) and overall survival (OS) of study patients. (A) PFS of the total patient population (FAS), (B) OS of the total patient population (FAS), (C) PFS stratified by cohorts. Cohort I represents patients with lenalidomide in last line prior to pomalidomide treatment and cohort II represents patients with no lenalidomide treatment in last line prior to pomalidomide treatment, (D) OS stratified by cohorts (i.e., cohort I and cohort II as described in C), (E) PFS stratified by refractory vs. relapsed MM. Refractory MM = PD on or within 60 days after last prior therapy; relapsed MM = PD >60 days after last prior therapy; (F) OS stratified by refractory vs. relapsed MM. For eight patients, an assignment to refractory or relapsed MM was not possible. FAS, full analysis set; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival

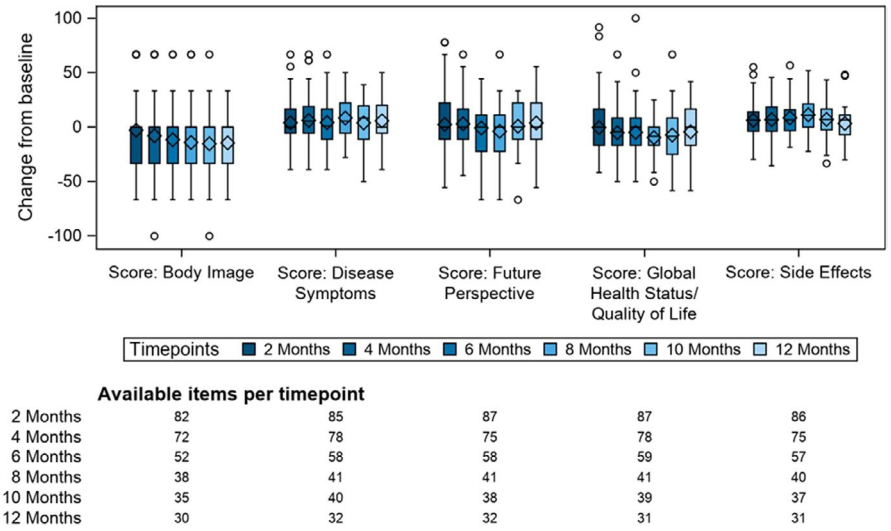
PFS of 3.5 months reported from an Australian study.[23] In two smaller studies from Poland[24] and Italy,[27] longer median PFS of 10.0 months and 9.4 months, respectively, were demonstrated. With respect to treatment response, either similar[23,25] or markedly higher response rates ranging from ORRs of 41%–53% have been reported.[21,22,24,26,27] Except for the study of Mele et al.,[26] patients were younger in all the referenced studies with median age ranging from 59 to 66 years. Although the overall high variability in study design, patient baseline characteristics, number of patients with relapsed vs. refractory patients, prior therapies and investigated treatments hinders comparability between the studies, it remains noteworthy that effectiveness and tolerability of POM in each of

TABLE 2 Responses under pomalidomide treatment (FAS: $n = 144$)

	Total ($N = 144$)	Cohort I ($N = 76$)	Cohort II ($N = 68$)	Refractory MM ($N = 96$)	Relapsed MM ($N = 40$)
Overall response rate *n* (%) [95% CI]	46 (31.9) [24.9, 40.0]	21 (27.6) [18.8, 38.6]	25 (36.8) [26.3, 48.7]	27 (28.1) [20.1, 37.9]	16 (40.0) [26.3, 55.4]
Complete response	2 (1.4)	2 (2.6)	0 (0.0)	0 (0.0)	2 (5.0)
Very good partial response	7 (4.9)	0 (0.0)	7 (10.3)	5 (5.2)	2 (5.0)
Partial response	37 (25.7)	19 (25.0)	18 (26.5)	22 (22.9)	12 (30.0)
Minor response	12 (8.3)	7 (9.2)	5 (7.4)	9 (9.4)	3 (7.5)
Stable disease	37 (25.7)	23 (30.3)	14 (20.6)	28 (29.2)	8 (20.0)
Progressive disease	10 (6.9)	7 (9.2)	3 (4.4)	8 (8.3)	1 (2.5)
Unknown	9 (6.3)	4 (5.3)	5 (7.4)	6 (6.3)	2 (5.0)
No assessment available	30 (20.8)	14 (18.4)	16 (23.5)	18 (18.8)	10 (25.0)

Note: Data displayed with frequencies (%) and with 95% confidence intervals (CIs) for overall response rate (ORR). Analyses based on the full analysis set (FAS, $n = 144$); Cohort I: Lenalidomide in last line prior to pomalidomide treatment, Cohort II: No lenalidomide in last line prior to pomalidomide treatment; refractory MM = PD on or within 60 days after last prior therapy; relapsed MM = PD >60 days after last prior therapy; for eight patients an assignment to refractory or relapsed MM was not possible. ORR is defined as the proportion of patients responding to the treatment (i.e., patients with complete, very good partial and partial response) during the treatment observation period, assessed in accordance with the International Myeloma Working Group (IMWG) criteria.[17] Response information was available for 114 patients (79.2% of the analysis population). Patients without response information ($n = 30$ (20.8%)) are considered non-responders.

Abbreviations: MM, multiple myeloma; PD, progressive disease.



Available items per timepoint

2 Months	82	85	87	87	86
4 Months	72	78	75	78	75
6 Months	52	58	58	59	57
8 Months	38	41	41	41	40
10 Months	35	40	38	39	37
12 Months	30	32	32	31	31

FIGURE 3 Changes from baseline in patient-reported quality of life (QoL) questionnaire scores. Boxplots of changes from baseline in EORTC QLQ-C30 (global health status/QoL score only) and QLQ-MY20 questionnaire scores. Higher scores in the global health status/QoL and functional scales (body image, future perspective) correspond to higher perceived QoL/healthy level of functioning, while higher scores in the symptom scales (disease symptoms, side effects) correspond to higher level of perceived symptoms severity based on the questionnaire results. Box: lower to upper quartile, horizontal line inside box: median, diamond inside box: mean, whisker: minimum/maximum value within lower quartile minus 1.5× IQR/upper quartile plus 1.5× IQR, respectively, circles: outliers outside of lower quartile minus 1.5× IQR/upper quartile plus 1.5× IQR, respectively (IQR, interquartile range)

different real-world settings was demonstrated to be comparable to published results from clinical trials.

Taking into account the influence of the last prior therapy on POM outcome in the present study, the comparable median PFS and OS between the two cohorts (prior lenalidomide therapy vs. any other prior therapy) as well as the results of the regression analysis did not indicate an impact of prior lenalidomide therapy on POM/DEX treatment outcome. Accordingly, PFS and OS of the subgroups of patients' primary refractory to lenalidomide vs. patients not primary refractory to lenalidomide were comparable. These results are consistent with data from clinical trials, which strongly support the sequential use of these treatment regimens.[12,28,29]

It is well known that adverse cytogenetic abnormalities are associated with poorer outcomes and that risk stratification in MM is

TABLE 3 Adverse events (AEs) occurring in >5% (any grade) of the safety population (SAF: *N* = 145)

Adverse event, *n* (%)	Any grade	Grade 3	Grade 4	Grade 5
Any event	138 (95.2)	84 (57.9)	22 (15.2%)	27 (18.6%)
Anaemia	31 (21.4)	8 (5.5)		
Fatigue	26 (17.9)	2 (1.4)		
Leukopenia	24 (16.6)	11 (7.6)	1 (0.7)	
Pneumonia	20 (13.8)	10 (6.9)	1 (0.7)	4 (2.8)
Diarrhoea	17 (11.7)	1 (0.7)		
Thrombocytopenia	16 (11.0)	4 (2.8)	3 (2.1)	
Dizziness	14 (9.7)			
Rash	13 (9.0)			
Bronchitis	12 (8.3)	2 (1.4)		
Malignant neoplasm progression	12 (8.3)	2 (1.4)		6 (4.1)
Nasopharyngitis	11 (7.6)			
Cough	10 (6.9)			
Dyspnoea	10 (6.9)	6 (4.1)		
Polyneuropathy	10 (6.9)	2 (1.4)		
Pyrexia	10 (6.9)	1 (0.7)		
Constipation	9 (6.2)	1 (0.7)		
Muscle spasms	9 (6.2)			
Dyspnea exertional	8 (5.5)	1 (0.7)		
Neutropenia	8 (5.5)	6 (4.1)	1 (0.7)	

Note: Data displayed with descriptive statistics (frequencies (%) for the safety analysis set (SAF, *n* = 145).

important to predict survival as well as to define treatment strategies.[18] Interestingly, in the present study, PFS and OS between patients who were rated as having a high-risk cytogenetic profile and patients with standard risk as defined by Sonneveld et al. (IMWG) were comparable. Despite limited interpretability due to the low number of available risk stratifications (71 patients)—which unfortunately have often found to be low in both clinical trials and analyses of routine practice[16]—these results are consistent with data from the MM-003 trial, in which benefits of POM/DEX therapy on PFS and OS were observed regardless of the patients' cytogenetic risk group.[30]

With regard to the patient-reported assessment of QoL, there were hardly any changes on QoL over time observed in the POSEIDON study. This may indicate that the POM/DEX treatment regimen does not adversely affect patients QoL, which was also suggested from the MM-003 trial, in which POM/DEX even led to improved QoL compared to DEX alone,[31] although the analyzed questionnaire domains and the survey periods in the MM-003 differed slightly from those analyzed in the present study. Control and maintenance of treatment-related impacts on QoL have been rated as particularly important in patients with R/RMM who have received many lines of therapies increasing the risk of cumulative toxicities and side effects.[32]

The POM/DEX regimen was well tolerated in the POSEIDON study. Consistent with clinical trials and other real-world studies, hematologic AEs were among the most frequently reported events, whereas the rates of the present study compare favorably with those reported from the MM-03 and MM-010 studies.[12,14]

Interpreting the outlined results, one must bear in mind certain limitations of the study. First, the NIS setting of the POSEIDON study limits direct comparisons of the obtained effectiveness and safety data to efficacy and safety data reported in clinical trials due to the very different study settings and heterogeneity of the study populations. Likewise, the referenced real-world studies differed from the POSEIDON study with respect to various factors as already mentioned before. Differences in subgroups should be interpreted with caution as no randomization was performed, and small group sizes limit their interpretability. As patients were recruited into the two cohorts (I/II) by prior treatment line with the aim to have equal proportions in both cohorts, the distribution of patients in the two cohorts does not reflect the distribution of patients having received lenalidomide or not as prior therapy before POM treatment in real world. Another limitation is that the enrolment period had to be prolonged from two to three years due to low recruitment, which may have affected the composition of the study cohort, among other factors. Notwithstanding the outlined limitations, the results of the POSEIDON study may complement the evidence gained from clinical trials by providing insights into treatment effectiveness of POM/DEX in an unselected patient population of R/RMM patients and may thus contribute to treatment decision-making in routine clinical practice, especially for patients who may not tolerate newly developed pomalidomide-based triplet regimens[33] such as frail patients.[29]

Furthermore, the comprehensive cohort and prospective study design renders the POSEIDON study a valuable addition to the results published from previous real-world studies.

5 | CONCLUSION

The results of the POSEIDON study support previous analyses from clinical trials and real-world studies demonstrating that the POM/DEX regimen is an effective and save treatment for patients with R/RMM who relapsed after or become refractory to currently available treatment options, thereof lenalidomide. As such, the POSEIDON study contributes to the limited evidence on POM effectiveness in routine clinical practice.

5.1 | Note on the impact of COVID-19

The COVID-19 pandemic has had no impact on the conduct of the study. Last-patient-last-visit took place on 11 December 2020. In the time period between the first COVID-19 case in Germany (27 January 2020) and date of LPLV, there were 14 patients in long-term follow-up. No follow-up visits had been delayed or cancelled due to the COVID-19 pandemic. Both the safety follow-up and the onsite monitoring had been completed before the outbreak of the COVID-19 pandemic. All study objectives were addressed and evaluated as planned and defined in the study protocol. No protocol amendments were required due to the COVID-19 pandemic.

ACKNOWLEDGEMENTS

The authors thank all patients, physicians and study teams participating in this study. We thank Horst Henning (iOMEDICO) for support with the data management, Dr. Mirja Grafetstätter (iOMEDICO) for preparation of the manuscript, Julia Falkenstein (iOMEDICO), Dr. Christian Johansson (iOMEDICO) and Dr. Sandra Woerner (iOMEDICO) for critical review of the manuscript. The study was financially supported by Celgene Europe B.V.

CONFLICT OF INTERESTS

Tobias Dechow, Ali Aldaoud, Matthias Groschek, Richard Hansen, Ulrike Söling, Sina Grebhardt, Hans Ulrich Siebenbach, Corinne Vannier, Karin Potthoff: No conflict of interest. Timo Behlendorf: ADVISORY BOARDS: Novartis, Chugai, AbbVie. HONORARIA and SUPPORT for meetings/events: Celgene/BMS, Amgen. Wolfgang Knauf: HONORARIA/ADVISORY BOARDS/TRAVEL: AbbVie, Amgen, Celgene, Janssen, Roche; HONORARIA/ADVISORY BOARDS: AstraZeneca, BeiGene, BMS, GSK, Sanofi, Takeda. Henning Eschenburg: HONORARIA: Workshop for oncologists in cooperation with Roche AG.

AUTHOR CONTRIBUTIONS

T. Dechow, S. Grebhardt, C. Vannier and K. Potthoff were involved in conceptualization and design. T. Dechow, A. Aldaoud, T. Behlendorf, W. Knauf, H. Eschenburg, M. Groschek, R. Hansen and U. Söling collected the data. H. U. Siebenbach performed statistical analyses. C. Vannier, H. U. Siebenbach and K. Potthoff were involved in analysis and interpretation of the data. All authors critically reviewed the paper and gave their approval for the final version of the manuscript to be published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this work are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Dechow T, Aldaoud A, Behlendorf T, et al. Pomalidomide plus dexamethasone for patients with relapsed or refractory multiple myeloma: Final results of the non-interventional study POSEIDON and comparison with the pivotal phase 3 clinical trials. *Eur J Haematol*. 2022;108:133–144. https://doi.org/10.1111/ejh.13719