Selinexor, daratumumab, bortezomib and dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma: results of the phase II, non-randomized, multicenter GEM-SELIBORDARA study

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Abstract

The treatment landscape for multiple myeloma has significantly evolved in the last decade. Notwithstanding, a large proportion of patients continue to relapse and novel combinations continue to be needed. In this phase II study, selinexor, a first-in-class inhibitor of exportin-1 was evaluated in combination with standard daratumumab-bortezomib-dexamethasone (DVd), for the treatment of relapsed and refractory multiple myeloma (RRMM). The aim of the trial was to assess the efficacy and safety of the combination of selinexor with DVd (S-DVd).

A total of 57 patients were enrolled in the two parts of the study. Part 1 enrolled a heavily pretreated population with at least three prior lines (PL) of therapy and part 2 enrolled an early relapse population with at least one PL of therapy. The primary endpoint was complete response (CR) rate in part 2 and overall response rate (ORR) in part 1. In the latter, 24 patients were treated with a median of three PL. Overall response rate (ORR) was 50% with two CR. Median progression-free survival (PFS) was 7 months. In part 2, 33 patients were enrolled, with a median of one PL. ORR was 82% and CR or better was 33%. Median PFS was 24 months. In lenalidomide-refractory patients, a median PFS of 22.1 months was observed. Thrombocytopenia was the most common hematological adverse event (69%; grade 3-4: 34%) and nausea, the most frequent non-hematological adverse event (38%; grade 3-4: 6%). Sixty-two percent of the patients required dose modifications. In summary, although the primary endpoint of the study was not met, the combination of S-DVd showed encouraging clinical efficacy with a generally manageable safety profile representing a potential option for the treatment of RRMM patients.

Introduction

The translation of innovative drugs from bench to patient has allowed continued improvement in survival in multiple myeloma (MM) patients.[1] Despite this benefit, many patients with MM will eventually relapse and become multi-drug resistant highlighting the need of developing new drugs and combinations based on drugs with novel mechanisms of action.

Selinexor is a first-in-class oral inhibitor of a nuclear export protein called exportin 1 (XPO-1). By blocking this protein, most tumor suppressor proteins remain in the nucleus, resulting in cell cycle arrest and death of malignant plasma cells.[2,3] Selinexor showed anti-MM activity in preclinical studies leading to the development of several clinical trials evaluating selinexor in combination with different antimyeloma drugs.[4] Currently, selinexor is approved in different settings and combinations. Selinexor in combination with dexamethasone (Sd) is approved for penta-refractory MM adult patients who have received at least four prior lines (PL) of therapies, based on the positive results of the STORM trial.[5] In addition, selinexor is approved in combination with bortezomib and dexamethasone (SVd) for relapsed and refractory MM (RRMM) patients who have already received at least one PL of treatment based on efficacy and safety results of the BOSTON trial.[6]

Current treatment guidelines for RRMM patient, particularly in those lenalidomide (len)-refractory, recommended the use of proteasome inhibitors (PI)-based combinations together with anti-CD38 monoclonal antibodies, such as daratumumab or isatuximab.[7,8] Mechanisms of action of daratumumab include induction of apoptosis, immune-mediated actions and immunomodulatory functions, resulting in deep responses and prolonged survival when combined with immunomodulatory drugs (IMID), or PI, allowing even its combination in quadruplets with an acceptable toxicity in the upfront setting.[9,10] One of the approved combinations for RRMM after one PL is daratumumab plus bortezomib and dexamethasone (DVd), based on results of the phase III CASTOR trial, where an improvement in the progression-free survival (PFS) as compared with bortezomib and dexamethasone (Vd) was demonstrated.[11] Based on this background, we hypothesize that the addition of selinexor may improve the efficacy of DVd in a well tolerated manner. Here we present the results of a phase II clinical trial conducted by the Spanish myeloma group (GEM/PETHEMA) to investigate the efficacy and safety of the quadruplet selinexor plus DVd (S-DVd) in RRMM patients.

Methods

Trial design

An open-label, non-randomized, multicenter, phase II study to evaluate the efficacy and safety of S-DVd in RRMM patients (GEM-SELIBORDARA trial). The study was designed by GEM/PETHEMA and carried out in 14 Spanish hospitals from July 2018 to March 2021. The cut-off date was February 6, 2023. The study had two different parts. In part 1, eligible patients had to have received at least three PL of therapy, including a PI (bortezomib) and any IMID and to be refractory to the last line of therapy or double refractory as per IMWG definition.[12] In part 2, eligible patients had received at least one PL. Prior treatment with PI was allowed if prior response, no grade ≥3 related-toxicity, and a washout of at least 6 months. Prior therapy with selinexor or anti-CD38 monoclonal antibodies was not permitted (see protocol in the *Online Supplementary Appendix*).

Patients received DVd (with intarvenous daratumumab) at the approved dose and schedule, in combination with selinexor days 1, 8, 15 and 22 (100 mg in part 1 and 60 mg in part 2) (Table 1). Treatment was given until disease progression or unacceptable toxicity. Recommended supportive treatment to minimize nausea was 5-HT3 receptor antagonists (*Online Supplementary Appendix*).

All patients provided written informed consent. The protocol was approved by the Spanish Health Authorities and a central ethical committee. The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice (ICHGCP). The trial was registered at *clinicaltrials gov. Identifier: NCT03589222*.

Endpoints and assessments

The primary endpoint of the trial was to evaluate the efficacy of the combination S-DVd in terms of overall response rate (part 1) and complete response rate (CR) or better in part 2, according to IMWG criteria.[13] Additional study endpoints are included in *Online Supplementary Appendix*.

Table 1. Treatment schedule in the clinical trial GEM-Selibordara.

PART 1	PART 2
Daratumumab (16 mg/kg IV/SC) weekly C1 and C2, C3-C6 Q2W, C7+ Q4W Bortezomib (1.3 mg/m^2 SC): d1, 8, 15 & 22 (C1-C8), d1 & 15 (C9+). Dexamethasone 40 mg d1, 8, 15 & 22	
Selinexor 100 mg d1, 8, 15 & 22	Selinexor 60 mg d1, 8, 15 & 22
4-week duration cycles	5-week duration cycles
Treatment was continued until disease progression or unacceptable toxicity	

IV: intravenously; SC: subcutaneously, C: cycle; Q2W: every 2 weeks; Q4W: every 4 weeks; d: day.

Statistical analysis

The sample size was estimated based on the primary endpoint of the study. For part 1, the hypothesis was that we would be able to increase the ORR from 30% with daratumumab monotherapy[14] and 45% with SVd in patients refractory to bortezomib[15] to 70% with the quadruplet combination of SDVd. With 57 patients we would obtain statistical power of approximately 90% with a one-sided α error of 0.05. For part 2, the primary endpoint was CR rate. The CR rate reported with the SVd in patients with RRMM after one to three PL was 13%. Our hypothesis was that by adding daratumumab the CR rate could increase up to 35%. With 52 patients we would obtain a statistical power of approximately 90% to reject the null hypothesis, with a predefined α error of 0.05 (one-sided). Considering a percentage of withdrawals of 10%, the final sample size would be 57 patients. The response rate was determined using an intent-to-treat (ITT) analysis. The statistical analysis done is detailed in the *Online Supplementary Appendix*.

Results

Efficacy in part 1

Twenty-four patients were included in part 1 (Figure 1). Median age was 66 years (range, 44-76). Seventeen percent of the patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 2. Eight (35%) patients had an International Staging System (ISS) staging score III, three (16%) a R-ISS staing score III, and five of 21

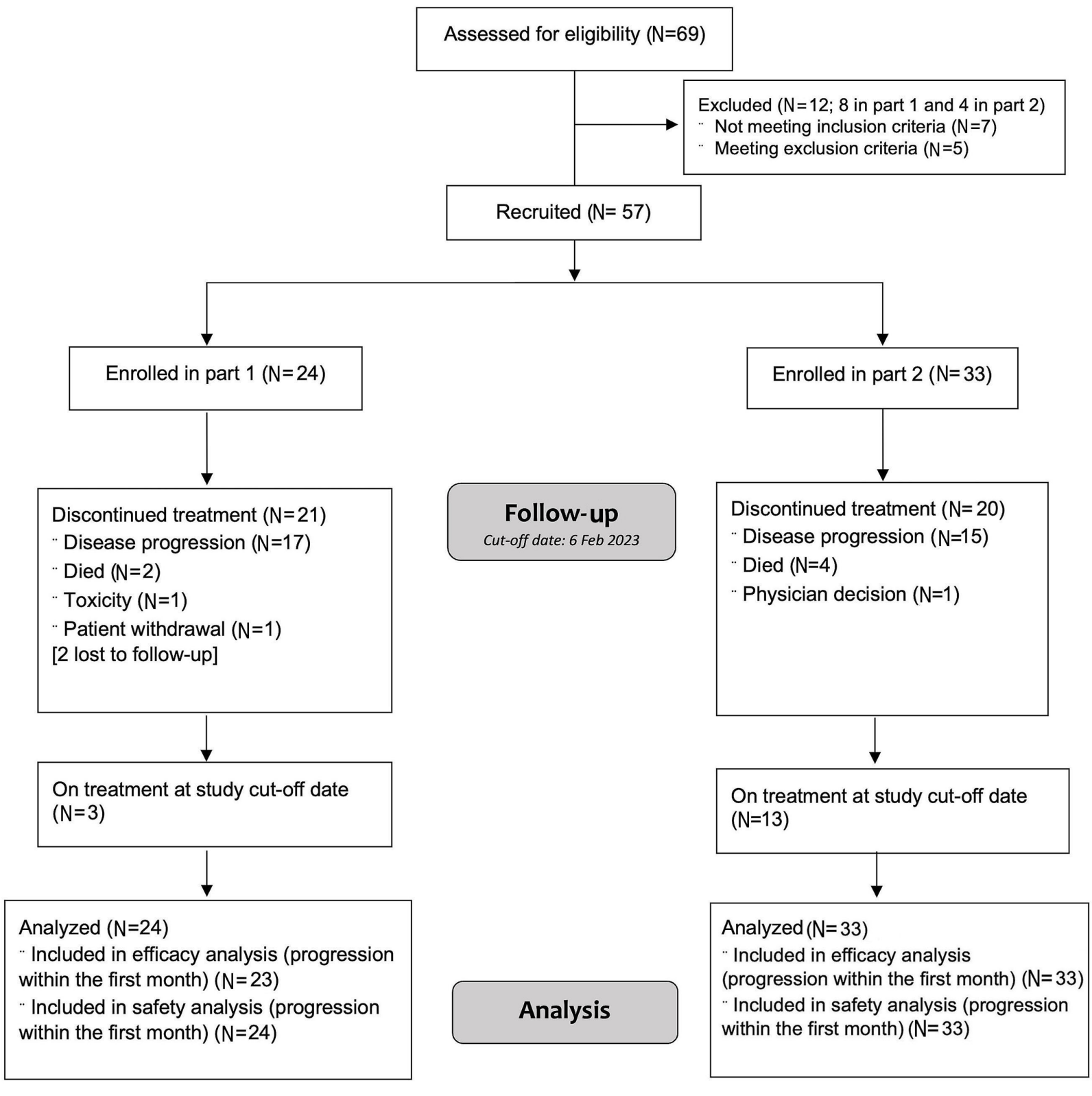


Figure 1. Consort flow diagram.

Table 2. Patient baseline characteristics.

	Part 1 N=24	Part 2 N=33
Age in years, median (range)	66 (44-76)	69 (33-81)
>75, N (%)	2 (8.3)	9 (27.3)
Male, N (%)	13 (54.2)	20 (60.6)
ECOG, N (%)		
0	12 (50.0)	16 (48.5)
1	8 (33.3)	16 (48.5)
2	4 (16.7)	1 (3.0)
MM subtype, N (%)		
IgG	13 (54.2)	21 (63.6)
IgA	6 (25.0)	8 (24.2)
IgD	0	1 (3.0)
Bence-Jones	5 (20.8)	3 (9.1)
ISS, N (%)		
I	4 (17.4)	5 (18.5)
II	11 (47.8)	15 (55.6)
III	8 (34.8)	7 (25.9)
Unknown	1	6
R-ISS, N (%)		
I	0	2 (8.0)
II	16 (84.2)	19 (76.0)
III	3 (15.8)	4 (16.0)
Unknown	5	8
High LDH, N (%)	4 (28.6)	4 (14.8)
HRCA positive/studied, N/N (%)	5/19 (26.3)	5/26 (19.2)
del(17p)	5/21 (23.8)	4/26 (15.4)
t(4;14)	0/20	1/26 (3.7)
t(14;16)	0/19	0/26
1q gain	13/20 (65.0)	18/29 (62.1)
1p loss	1/19 (5.0)	2/24 (8.3)
Extramedullary disease, N (%)	3 (12.5)	3 (9.1)
Median number of PL (range)	3 (2-3)	1 (1-3)
1 (%)	-	20 (60.6)
2 (%)	7 (29.2)	5 (15.1)
3 (%)	17 (70.8)	8 (24.2)
Prior IMID, N (%)		
Yes	24 (100)	27 (81.8)
No	0	4 (18.2)
Type of prior IMID, N (%)		
Thalidomide	13 (54.2)	15 (45.5)
Len	24 (100)	23 (71.8)
Pomalidomide	9 (37.5)	6 (18.7)
Prior PI, N (%)		
Yes	24 (100)	30 (90.9)
No	0	3 (9.1)
Type of prior PI, N (%)		
Bortezomib	24 (100)	30 (90.9)
Carfilzomib	11 (45.8)	4 (12.1)
Ixazomib	0 (0)	0 (0)
Refractory to the last line of therapy, N (%)	24 (100)	12 (36.4)
Refractory to len, N (%)	23 (95.8)	15 (45.5)
Refractory to PI, N (%)	17 (70.8)	5 (15.1)
Double refractory len/PI, N (%)	17 (70.8)	4 (12.1)
Prior ASCT, N (%)	7 (29.2)	15 (45.5)

MM: multiple myeloma; ISS: International Staging System; R-ISS: revised International Staging System; LDH: lactate dehydrogenase; HRCA: high-risk cytogenetic abnormalities; IMID: immunomodulatory drugs; ECOG: Eastern Cooperative Oncology Group; PL: prior line; PI: proteasome inhibitor; len: lenalidomide; ASCT: autologous stem cell transplantation.

patients had del(17p). The median number of PL was three (range, 2-3). Twenty-three (96%) patients were refractory to len and 17 (71%), double refractory. All patients were exposed to both PI and IMID and refractory to the last line of treatment (Table 2).

In the ITT population, CR or better was achieved in two patients (8%). ORR was 50% (Figure 2). Median time to response was 1.8 months (range, 1.3-7.3) and median DoR was 13.5 (range, 2.8-48.2). No differences in responses according to PL of therapy were detected (Figure 3A).

At the time of data cutoff, 21 (87.5%) patients had discontinued treatment (Figure 1). The main reason for treatment discontinuation was disease progression (17 patients). One patient discontinued due to adverse events (AE) and another patient withdrawn informed consent after one cycle. After a median follow-up of 39.7 months (range, 12.2-51.0), 22 (91.7%) progressed or died with a median PFS of 7.2 months (95% confidence interval [CI]: 3.6-10.8) (Figure 4A). Fourteen (58.3%) patients died, and median OS was 28.5 months (95% CI: 0.0-57.9) (Figure 4B). No differences were observed in PFS or OS according to number of PL.

Efficacy in part 2

In part 2, 33 patients were included, with a median age of 69 years (range, 33-81). Forty-eight percent had an ECOG of 0 or 1. Seven (26%) patients had an ISS III, four (16%) R-ISS III, and five (19%) patients had high-risk cytogenetic abnormalities. Median number of PL was one (range, 1-3). Twenty-seven (82%) were previously exposed to IMID; and 30 (91%) to PI. Fifteen patients (45%) were refractory to len, and 12 (36%) were refractory to the last line of treatment (Table 2).

Regarding efficacy of the ITT population, 11 patients (33%) achieved CR. Measurable residual disease (MRD) negativity was reported in nine patients (27%). ORR was 82% (Figure 2). Median time to response was 1.8 months (range, 1.2-4.1) and median DOR was 22.4 (range, 3.3-30.8). Best responses were achieved after a median of three cycles (range, 1-13). Numerically higher CR rates were found in patients after one PL or two PL as compared to three PL (45%, 40%, 0%, respectively) (*P*=not significant [NS]) (Figure 3A). CR rates were consistent among several subgroups analyzed including len-refractory (27% *vs*. 39%; *P*=NS), R-ISS III or HR-CA.

At the time of the data cutoff and with a median follow-up of 27.0 months (range, 19.7-32.5), 19 (57.6%) patients had progressed or died and the median PFS was 25.1 months (95% CI: 16.0-34.2) (Figure 4A). Eleven (33.3%) patients died, and median OS was not reached i.e., not estimable (NE) (95%

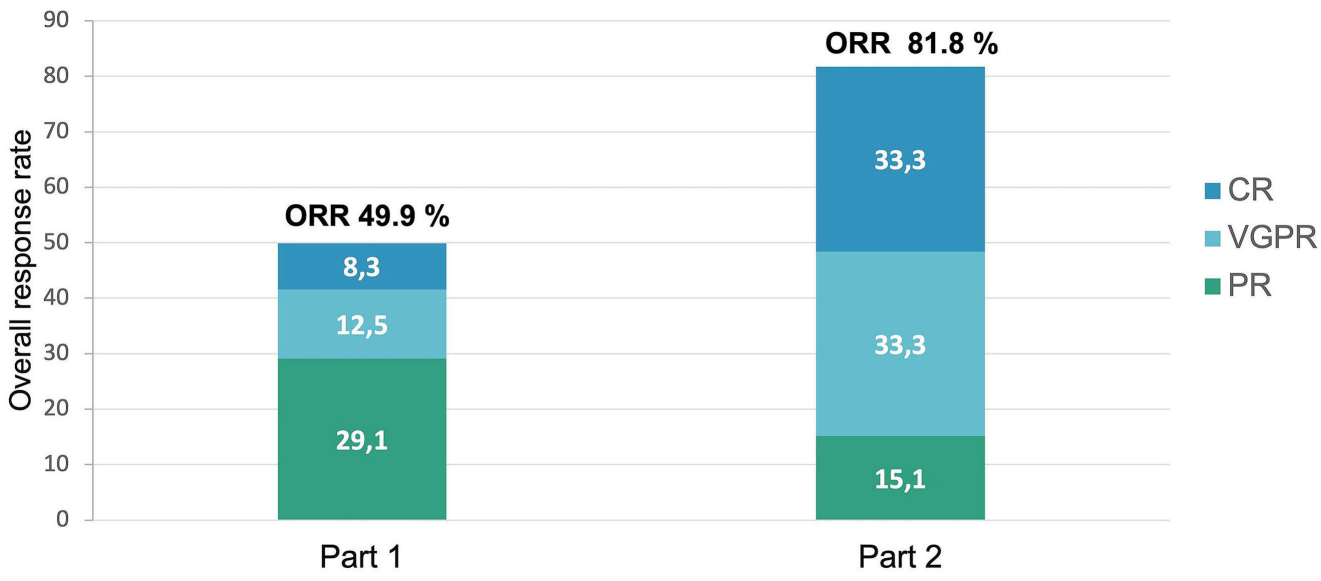
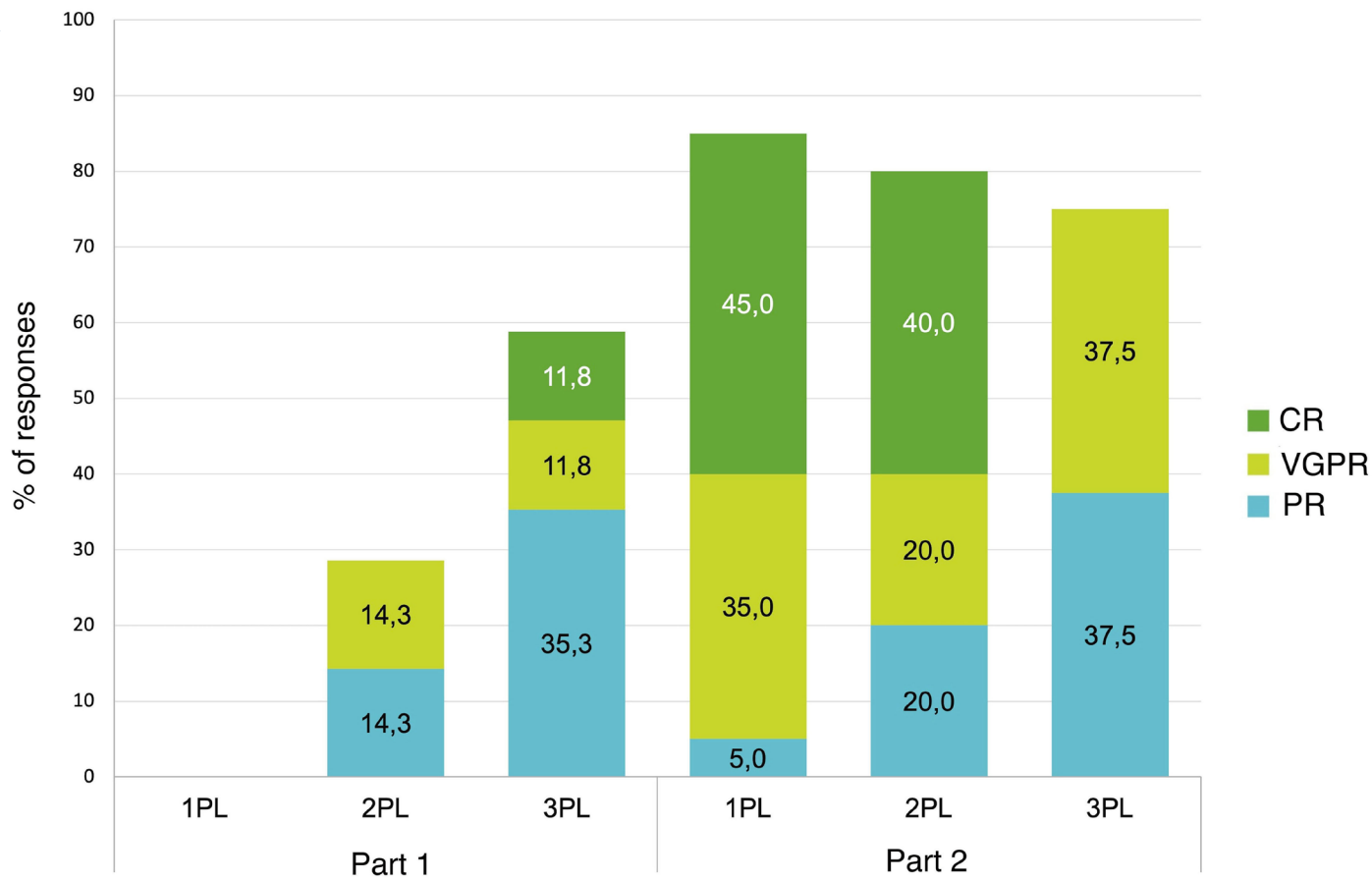


Figure 2. Response rates in part 1 and part 2 of the study. ITT: intention-to-treat; ORR: overall response rate; CR: complete response; VGPR: very good partial response; PR: partial response.

A



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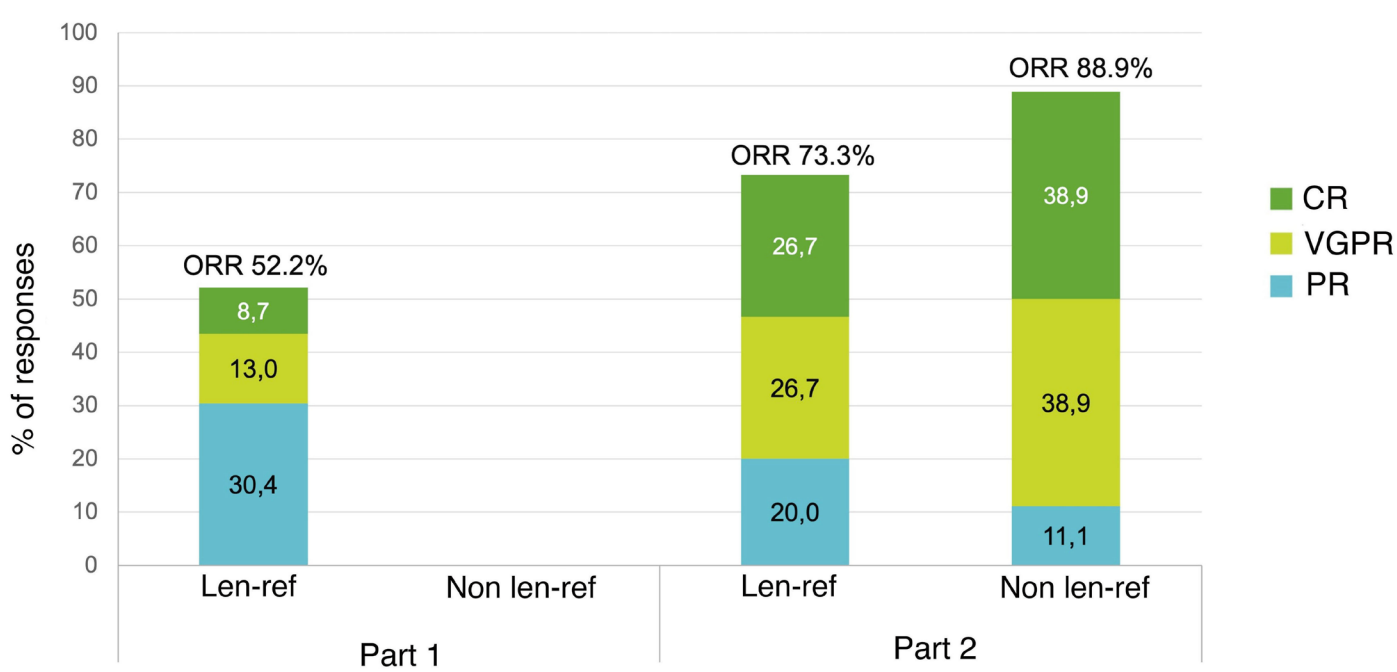

Figure 3. Detail of responses in the study. Panel (A) represents response rate in the intention-to-treat (ITT) population in part 1 and 2 of the study according to the number of prior lines (PL) of treatment. Panel (B) represents responses according to refractoriness to lenalidomide (len) (note: only 1 patient in part 1 was not refractory to len (len-ref), best response in this patient was minor response). ORR: overall response rate; CR: complete response; VGPR: very good partial response; PR: partial response.

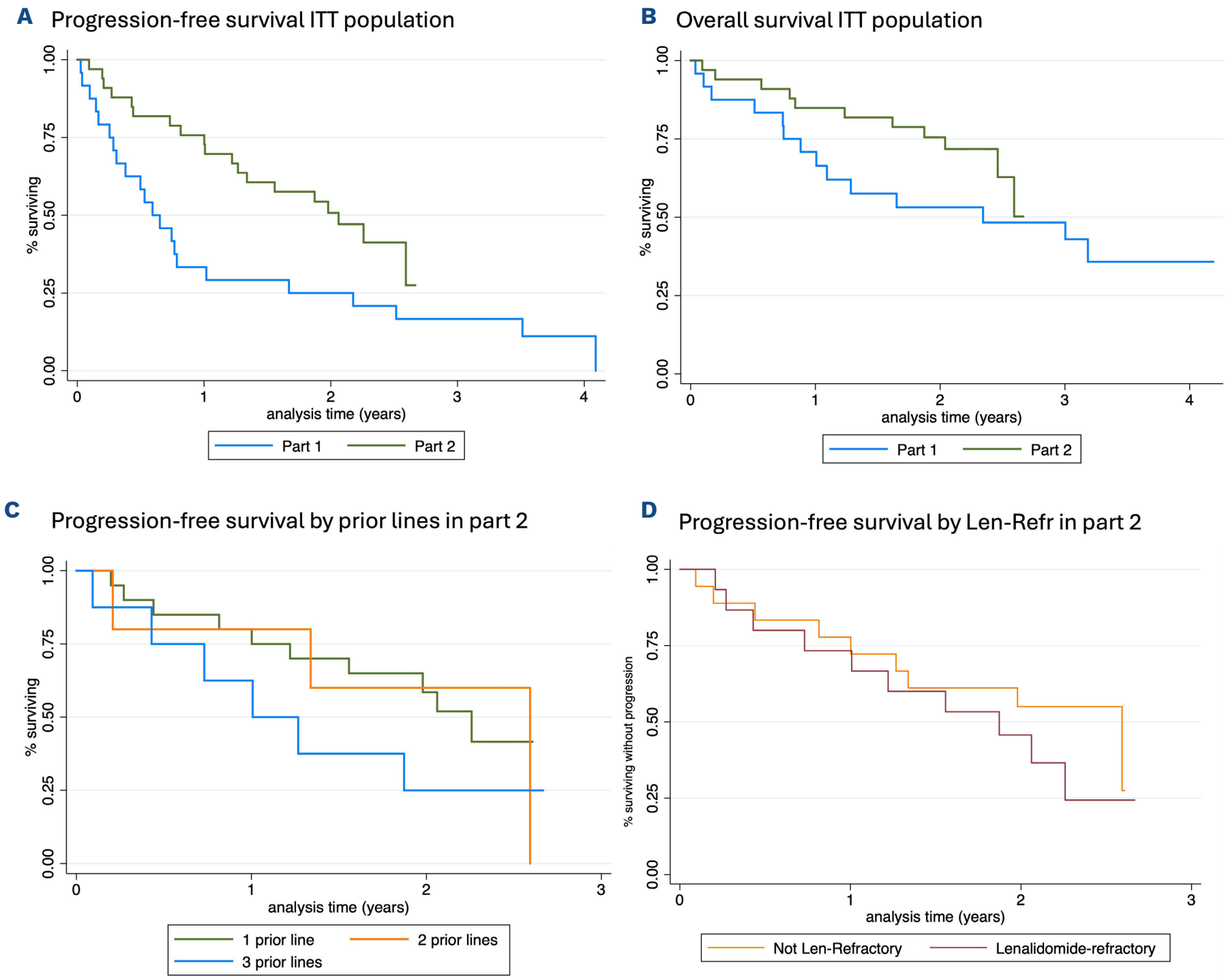

Figure 4. Kaplan-Meier survival curves in part 1 and 2 of the study. Panel (A) shows progression-free survival for (PFS) the intention-to-treat (ITT) population in part 1 and part 2. Panel (B) shows overall survival for the ITT population in part 1 and part 2. Panel (C) shows PFS for patients according to number of prior lines (PL) of therapy; Panel (D) shows PFS according to lenalidomide refractoriness (len-ref) in part 2 of the trial.

CI: NE-NE), with a 2-year OS rate of 71.7% (Figure 4B). In the *post hoc* subgroup analysis, median PFS for those relapsing after one PL, two PL and three PL were 27.5 months (95% CI: 22.3-32.7), 31.6 months (95% CI: NE-NE), and 12.3 months (95% CI 3.2-21.3), respectively (Figure 4C). Median OS for these patients according to PL of treatment was not reached (95% CI: NE-NE), 31.6 months (95% CI: NE-NE) (*P*=0.8), and 22.8 months (95% CI: 15.7-29.9) (*P*=0.1), respectively. Notably, PFS (22.8 months *vs*. 31.6 months, hazard ratio [HR] =1.5; 95% CI: 0.6-3.7; *P*=0.4) and OS (30.0 months *vs*. not reached, HR=1.4; 95% CI: 0.4-4.8; *P*=0.6) were comparable between patients refractory and not refractory to len, respectively (Figure 4D). Importantly, no differences were found across other subgroups like ISS staging score, R-ISS or the presence of high-risk cytogenetic abnormalities but this comparison is limited due to small sample size.

Safety

Hematological AE were the most frequently reported AE in both parts of the study, overall, 47 (82.4%) of patients had at least one hematological AE. Thrombocytopenia was the most common AE present in 70.2% of patients (grade 3-4 in 45.6%) followed by neutropenia in 38.6% of the patients (grade 3-4 in 29.8%). Infection was the most frequent non-hematological AE and occurred in 42 (73.6%) of patients (grade 3-4 in 31.6%). Regarding gastrointestinal AE, diarrhea was reported in 38.6% (grade 3-4: 3.5%) and nausea or vomiting in 35.1% (grade 3-4: 8.8%). Peripheral neuropathy occurred in ten (17.5%) patients, without any grade 3 or 4 events. No differences in safety have been observed between part 1 or 2 of the study. There was a trend toward a higher percentage of patients with thrombocytopenia (83.3% *vs*. 60.6%, respectively; *P*=0.06) and

neutropenia (50.0% *vs*. 30.3%; *P*=0.1) in part 1. Similar rates of infection were observed, with seven cases with grade 3-4 infection in part 1 and nine in part 2, with two fatal cases occurred in the study (1 patient in each part due to septic shock) (Table 3). Overall, one patient in part 1 discontinued the treatment due to toxicity (severe cytopenias persisting beyond the cycle 1).

Median number of cycles received in part 1 of the study was 7 (range, 1-47) and 17 (range, 1-27) in part 2. Cumulative doses of selinexor, daratumumab, bortezomib and dexamethasone delivered are depicted in Table 4, and no statistically significant differences among these cumulative doses administered between part 1 and part 2 of the study were found. Regarding dose modifications, selinexor was the drug most frequently modified and was reduced in 30 (52.7%) patients, (10 dose reductions in part 1 and 20

Table 3. Incidence of most common treatment-related adverse events.

	Incidence of AE in the ITT population N=57		Incidence of AE in part 1 N=24		Incidence of AE in part 2 N=33		*P*
	All grade	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3	
Hematological AE, N (%)	47 (82.4)	34 (59.6)	22 (91.6)	16 (66.7)	25 (75.8)	18 (54.5)	0.1
Thrombocytopenia	40 (70.2)	26 (45.6)	20 (83.3)	13 (54.2)	20 (60.6)	13 (39.4)	0.06
Neutropenia	22 (38.6)	17 (29.8)	12 (50.0)	10 (41.7)	10 (30.3)	7 (21.2)	0.1
Anemia	17 (29.8)	7 (12.3)	8 (33.3)	5 (20.8)	9 (27.3)	2 (6.1)	0.6
Non-Hematological AE, N (%)							
Infection	42 (73.6)	18 (31.6)	17 (70.8)	8 (33.3)	25 (75.8)	10 (30.3)	0.9
Asthenia or fatigue	25 (43.9)	8 (14.0)	9 (37.5)	2 (8.3)	16 (48.5)	6 (18.2)	0.4
Diarrhea	22 (38.6)	2 (3.5)	8 (33.3	1 (4.2)	14 (42.4)	1 (3.0)	0.5
Nausea or vomiting	20 (35.1)	5 (8.8)	7 (29.2)	2 (8.3)	13 (39.4)	3 (9.1)	0.4
Peripheral neuropathy	10 (17.5)	0 (0)	3 (12.5)	0 (0)	7 (21.2)	0 (0)	0.4
Loss of apetite	3 (5.3)	0 (0)	2 (8.3)	0 (0)	1 (3.0)	0 (0)	0.4

ITT: intention-to-treat population; AE: adverse events.

Table 4. Cycles, cumulative doses of selinexor, daratumumab, bortezomib and dexamethasone (S-DVd) and dose modifications in GEM Selibordara trial.

	Whole series N=57	Part 1 N=24	Part 2 N=33	*P*
Cycles administered, median (range)	12 (1-47)	7 (1-47)	17 (1 - 27)	0.1
Cumulative doses				
Selinexor mg, median (IQR)	2,140 (630-3,860)	1,750 (405-3,950)	2,400 (630-3,850)	0.6
Daratumumab mg, mean (SD)	25,422 (16,847)	22,655 (21,313)	27,434 (12,660)	0.3
Bortezomib mg/m^2, mean (SD)	47.1 (33.3)	42.9 (42.5)	50.1 (25.3)	0.5
Dexamethasone mg, median (IQR)	1,600 (540-2,850)	740 (220-2,815)	2,080 (1,020-2,850)	0.1
Dose modifications				
Selinexor, N (%)				
No dose modification	19 (33.3)	9 (37.5)	10 (30.3)	0.2
Dose reduction	30 (52.7)	10 (41.7)	20 (60.6)	
Withdrawn	8 (14.0)	5 (20.8)	3 (9.1)	
Daratumumab, N (%)				
No dose modification	57 (100)	24 (100)	33 (100)	0.2
Withdrawn	0 (0)	0 (0)	0 (0)	
Bortezomib, N (%)				
No dose modification	38 (66.7)	16 (66.7)	22 (66.7)	0.3
Dose reduction	15 (26.3)	5 (20.9)	10 (30.3)	
Withdrawn	4 (7.0)	3 (12.5)	1 (3)	
Dexamethasone, N (%)				
No dose modification	45 (78.9)	17 (70.8)	28 (84.8)	0.2
Dose reduction	10 (17.5)	5 (20.8)	5 (15.2)	
Withdrawn	2 (3.5)	2 (8.3)	0 (0)	

Part 1: weekly selinexor dose 100 mg in 4-week cycles. Part 2: weekly selinexor dose 60 mg in 5-week cycles. IQR: interquartile range. SD: standard deviation.

in part 2; *P*=0.2) and discontinued in eight (14%) patients (5 in part 1 and 3 in part 2; *P*= 0.2). Bortezomib was the second drug most commonly modified and was reduced in 15 (26.3%) and withdrawn in four (7.0%) (3 in part 1 and 1 in part 2; *P*=0.3), patients. Dexamethasone was reduced in ten (17.5%) patients (5 in each part) and withdrawn in two (3.5%) patients belonging to part 1 of the study. No patient discontinued daratumumab permanently. Only one patient discontinued daratumumab treatment temporarily due to a grade 4 cytopenia and restarted therapy after recovery (Table 4).

Discussion

The addition of selinexor to DVd (S-DVd) resulted in encouraging clinical efficacy with a safety profile generally consistent with known safety profile of selinexor. Higher efficacy was observed when S-DVd was administrated in earlier lines of treatment and, also in len-refractory patients. The primary endpoint of the study was CR rate. If we analyze the ITT population, as a whole, the CR rate was 22%, although, it is important to acknowledge that 22 of 57 patients enrolled were heavily pretreated and 52% previously exposed to bortezomib. Thus, although the trial did not meet its primary endpoint potentially due to the changes in the study design and mixed patient populations, the CR rate in part 2 here presented seems encouraging.

In part 1, the population included was consistent with the population enrolled in the pivotal studies that the led to the approval of daratumumab monotherapy (mostly double refractory and daratumumab-naïve).[16,17] In this trial, increased efficacy was observed with the addition of selinexor plus bortezomib to daratumumab (median PFS 7,2 months as compared with the 3.7 months PFS reported for daratumumab single agent). However, the major interest of our trial regards part 2 since the clinical characteristics of the patients were closer to those treated with DVd in the phase III CASTOR trial (almost half [49%] of patients received only 1 PL of therapy, and one third were refractory to last line of treatment).[18,19] In this context, the addition of selinexor to the backbone DVd in the present trial may have led to a deepening in the responses as compared to CASTOR in terms of MRD-negative rate in the ITT population (27% *vs*. 15%,[20] respectively), translating into potentially longer PFS for S-DVd compared to the DVd-treated population in the CASTOR trial (median PFS of 25.1 *vs*. 16.7 months, respectively, or 18 months for patients with one or more PL in the CASTOR trial).[19,21]

Furthermore, 45% of the S-DVd-treated patients were len-refractory, whereas only 24% in the DVd arm of the CASTOR trial, and interestingly, in these subsets the PFS also appeared to be longer with S-DVd *versus* DVd (median PFS of 22.8 *vs*. 7.8 months).[21] As previously mentioned, len-refractory patients remained a difficult to treat population and carfilzomib + anti-CD38 monclonal antibodies (MoAb) are becoming standard of care in this setting based on positive results of the phase III CANDOR and IKEMA studies, respectively. These studies were also conducted in a similar RRMM population after one to three PL of therapy, apparently obtaining a similar ORR (84-87%) and CR rates (29-40%) as in part 2 of GEM Selibordara trial, but with a slightly underrepresented population of len-refractory patients in both CANDOR and IKEMA studies (33%).[22–25] Still, PFS was longer in both IKEMA and CANDOR trial as compared to the trial here presented. The safety profile is different, and the intravenous formulation of carfilzomib has its drawbacks. In this sense, the availability of regimens such as S-DVd could be an alternative for patients with cardiovascular comorbidities, when there is a preference for subcutaneous and oral administration or in places where the combination of anti-CD38 plus carfilzomib and dexamethasone is not yet available.

In addition, it is worth mentioning that in the phase III BOSTON trial the SVd combination was investigated for patients with RRMM after one PL based.[6] In this scenario, the addition of daratumumab to SVd may also appear to improve the depth of responses compared to SVd alone (CR or better: 33% *vs*. 17%; MRD negativity: 82% *vs*. 17%), and, as a result, also to prolong PFS (median PFS: 25.1 months *vs*. 13.9 months), despite a high proportion of prior bortezomib-exposed patients in part 2 of GEM Selibordara (91%) as compared to the BOSTON trial (69%). Moreover, focusing on len-refractory patients, deeper responses were also seen in the current trial as compared to the BOSTON study (ORR: 73% *vs*. 68%, and CR or better: 27% *vs*. 9%,), as well as longer PFS (median 22.8 *vs*. 10.2 months), suggesting a potential role of this quadruplet combination in this setting.

Regarding safety, incidence of treatment related AE were generally consistent with other studies with regimens containing selinexor, daratumumab, bortezomib and dexamethasone, such as SVd and DVd. A similar incidence of hematological AE such as thrombocytopenia or anemia was observed, although a higher incidence of neutropenia was reported in this trial compared to the BOSTON trial, likely related to the addition of daratumumab, but overall grades 3-4 were similar.[6,11] With regard to non-hematological AE, infections were the most frequently observed with S-DVd, although it is true that not only respiratory infections have been considered, which in the BOSTON and CASTOR studies reached an incidence of 48-68%. Asthenia or fatigue were similar to that reported in the BOSTON trial. Regarding gastrointestinal toxicity, it was consistent with what was reported with SVd in the BOSTON trial, and, of note, loss of appetite was observed in only 5.3% of participants, probably due to the prophylactic measures implemented in the GEM Selibordara protocol. Importantly the discontinuation rate due to AE was lower although a significant proportion of patients did require dose modifications to

manage treatment related AE.

Our study has several limitations. First, it is a phase II non-randomized trial, with a limited number of patients, and, some of the prior comparisons are limited by different confounders such as differences in study design, methods, or patient's characteristics. Indeed, the weekly bortezomib schedule may explain the lower incidence of peripheral neuropathy seen in the GEM-Selibordara trial (21%, grade 3-4: 0%) as compared to the CASTOR trial (50%, grade 3-4: 4.5%).[11] Regarding selinexor dosing, in the part 2 the schedule and dose was adjusted (60 mg every week in a 5-week cycle) to improve tolerability. As a result, there were fewer discontinuations as compared to part 1, suggesting that 60 mg weekly of selinexor might be the optimal dose for the combination with DVd in a well balanced manner between efficacy and toxicity.[26]

In summary, encouraging efficacy and generally manageable safety were observed in this phase II multicenter trial evaluating S-DVd in RRMM patients, including in patients who were len-refractory, suggesting this combination could be an attractive option for len-refractory but daratumumab-sensitive patients if cardiovascular comorbidities are a concern or oral formulations are preferred.

Disclosures

VG-C discloses consulting for or advisory role at Janssen; speakers' bureau at Janssen, GlaxoSmithKline, Pfizer, Bristol Myers Squibb/Celgene, travel and accommodation expenses from Janssen and GlaxoSmithKline. PR-O discloses honoraria derived from consulting or advisory board role at Celgene-BMS, Janssen, Roche, Abbvie, Pfizer, GSK, Sanofi and H3Biomedicine; steering committee membership at Celgene-BMS, Regeneron and Janssen; speaker's bureau at Janssen, Celgene-BMS, GSK, Sanofi and Abbvie; travel grant from Pfizer. FA discloses honoraria for lectures and advisory board from Janssen, BMS-Celgene, Amgen, GSK, Sanofi and Takeda. AO discloses honoraria from consultant activities for Amgen, Celgene, BMS, GSK, Janssen and Sanofi. JM-L discloses honoraria from consulting activities for Astellas Pharma, BMS, F.Hoffman-La Roche, Janssen, Novartis and Sanofi; research grant from BMS. MVM discloses honoraria derived from lectures and advisory role at Amgen, Celgene, BMS, GSK, Janssen, Pfizer, Regeneron, Sanofi and Takeda. M-TH discloses consulting or advisory role at Janssen, Sanofi/Aventis, Celgene/Bristol Myers Squibb and GlaxoSmithKline; speakers' bureau at Janssen, Celgene/Bristol Myers Squibb and GlaxoSmithKline; research funding from Celgene/Bristol Myers Squibb (Inst). M-TC discloses honoraria from Janssen. NP discloses honoraria from Amgen, Celgene, Janssen, Takeda and The Binding Site; consulting or advisory role at Amgen, Celgene, Janssen and Takeda; speakers' bureau of Celgene; research funding from Celgene, Janssen, Amgen and Takeda; travel and accommodation expenses from Amgen, Celgene, Janssen and Takeda. BP discloses honoraria for lectures and advisory boards from Adaptive, Amgen, BMS-Celgene, Gilead, GSK, Janssen, Oncopeptides, Roche, Sanofi and Takeda; unrestricted grants from Beigene, BMS-Celgene, EngMab, GSK, Roche, Sanofi and Takeda; consultancy for BMS-Celgene, Janssen and Sanofi. JB discloses honoraria for lectures and advisory boards from Janssen, BMS-Celgene, Amgen, Takeda and Oncopeptides. JJL discloses consulting or advisory role at Celgene, Amgen, Janssen-Cilag and Sanofi; travel and accommodation expenses from Celgene and Pfizer. JSM discloses consulting activies at Abbvie, Amgen, BMS, Celgene, F.Hoffman-La Roche, GSK, HaemaLogiX, KaryoPharm, Merck, Novartis, Pfizer, Regeneron, Sanofi-Aventis, Takeda and SecuraBio. MVM discloses honoraria for lectures and advisory boards from Janssen, Celgene, Takeda, Amgen, GSK, Abbvie, Pfizer, Regeneron, Roche, Sanofi and Oncopeptides. The remaining authors have no conflicts of interest to disclose.

Contributions

MVM and JSM designed the study and wrote the protocol. VG-C and PR-O made the statistical analysis and wrote the manuscript. All authors contributed to enrolling patients in the clinical trial and provided data. All author reviewed and approved the manuscript.

Data-sharing statement

The Spanish Myeloma Group is open to the possibility of sharing the data used in this study for research projects as long as they do not interfere with the present or future objectives of the clinical trial. The interest and feasibility of any clinical or biological research proposal based on the data from this study must be approved by the board of directors of the Spanish Myeloma Group. In such a case, the data, deposited in REDCap, will be presented in anonymized CSV format. This availability is subject to the laws and provisions in force that regulate the development of clinical trials both in Spain and in the European Union. Data are available on request from the corresponding author.

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