Daratumumab in combination with lenalidomide and dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma (GEN503): final results of an open-label, phase 1/2 study

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Running head: DARA-LEN-DEX phase 1/2 RRRM study: final results (48 characters with spaces [limit 50, abbreviations permitted, sentence case])

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DISCLOSURES

TP received research funding from Roche, Novartis, Janssen, and Celgene and served on advisory committees for Janssen, Celgene, and Genmab. FG received honoraria from Janssen and Celgene and served on an advisory committee for Celgene. MCM received research funding from Celgene and served on advisory committees for Celgene, Janssen, Amgen, Bristol-Myers Squibb, and Takeda. PM received honoraria from and served on advisory boards for Celgene, Takeda, and Janssen. JC received honoraria from Amgen, Celgene, Janssen, Novartis, and Takeda. AP received research funding from Janssen, Amgen, Celgene, and Takeda and served on

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ABSTRACT

Daratumumab has antitumor activity as a monotherapy and in combination with standards of care in all lines of treatment in patients with multiple myeloma. The final results of a 2-part, phase 1/2 study of daratumumab plus lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma are presented. In Part 1, no dose-limiting toxicities occurred in 13 patients who received daratumumab 2 to 16 mg/kg intravenously (weekly, cycles 1-2; every 2 weeks, cycles 3-6; every 4 weeks thereafter) plus lenalidomide (25 mg/day orally, days 1-21) and dexamethasone (40 mg/week). In Part 2, 32 patients received daratumumab 16 mg/kg plus lenalidomide and dexamethasone. Adverse events (>25%) in Part 2 included neutropenia, diarrhea, cough, muscle spasms, fatigue, thrombocytopenia, nausea, pyrexia, nasopharyngitis, hypertension, bronchitis, and upper respiratory tract infection. Second primary malignancies occurred in 1 and 4 patients in Parts 1 and 2, respectively. In Part 1 (39.9-month median follow-up), overall response rates were 100% (daratumumab 2 and 4 mg/kg), 75% (8 mg/kg), and 67% (16 mg/kg). In Part 2 (32.5-month median follow-up), overall response rate was 81%, with 10 (31.3%) stringent complete responses, and median duration of response was not reached (95% confidence interval [CI], 26.5 months-not estimable [NE]). Median progression-free survival (95% CI, 16.6 months-NE) and overall survival (95% CI, 32.2-NE) were not reached, with 2-year progression-free survival and overall survival rates of 69% and 78%, respectively. Extended treatment with daratumumab plus lenalidomide and dexamethasone had favorable safety and induced deep responses that were maintained for over 2 years. ClinicalTrials.gov: NCT01615029.

INTRODUCTION

In 2015, four new agents were incorporated into treatment regimens for relapsed and/or refractory (RR) multiple myeloma (MM) in the United States.[1] Among them is daratumumab, a human IgG1κ antibody that targets CD38, a protein expressed at high levels on the myeloma cell surface.[2,3] Engagement of CD38 by daratumumab promotes myeloma cell death via apoptosis, complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and modulation of CD38's enzymatic activities.[4-8] Additional antimyeloma effects appear to result from the ability of daratumumab to bind CD38 on immune suppressor cells, facilitating the expansion and activation of cytotoxic T cells and elevation in T-cell clonality.[9] Based on the results of the daratumumab monotherapy studies GEN501 and SIRIUS, and the daratumumab combination therapy studies POLLUX and CASTOR, daratumumab is approved in the United States, European Union, and many other countries for use as a monotherapy and in combination with the standard-of-care regimens lenalidomide/dexamethasone and bortezomib/dexamethasone in patients with RRMM.[10-14] Additionally, based on the results of the daratumumab combination therapy study EQUULEUS, daratumumab is approved in the United States for use in combination with the standard-of-care regimen pomalidomide/dexamethasone in patients with RRMM previously treated with lenalidomide and a proteasome inhibitor.[15,16] In the front line, daratumumab added to the standard-of-care regimen, bortezomib, melphalan, and prednisone (VMP), halved the risk of progression or death versus VMP in the phase 3 ALCYONE study of transplant-ineligible, newly diagnosed MM patients.[17]

Immunomodulatory drugs (IMiDs), including lenalidomide, appear to induce CD38 upregulation, providing a rationale for the use of a daratumumab/lenalidomide combination in treating MM.[18] In vitro, daratumumab and lenalidomide have synergistic antimyeloma activity, which is mediated by the activation of effector cells.[19]

GEN503 was a two-part, phase 1/2 study of daratumumab in combination with lenalidomide and dexamethasone in patients with RRMM.[20] As previously reported, at the primary analysis, which was conducted at a median follow-up of 15.6 months, the overall response rate (ORR) in Part 2 (daratumumab 16 mg/kg in combination with lenalidomide and dexamethasone) was 81.3%, including stringent complete responses (sCRs) in 25% of patients, complete responses (CRs) in 9% of patients, and very good partial responses (VGPRs) in 28% of patients. The 18-month progression-free survival (PFS) rate was 72%, and the 18-month overall survival (OS) rate was 90%. The regimen was well tolerated, with a safety profile consistent with those of lenalidomide/dexamethasone alone or daratumumab alone.[20]

This updated analysis of the GEN503 study is based on a median follow up of approximately 3 years.

METHODS

Patients and Study Design

The methods for this study are described in detail in a previous report.[20] Briefly, GEN503 was a phase 1/2, open-label, multicenter study. Part 1 was a standard 3+3 dose-escalation study in which patients received 1 of 4 doses of daratumumab ranging from 2 to 16 mg/kg. In Part 1,

eligible participants included MM patients ≥18 years of age, with measurable serum or urine M-protein levels, with Eastern Cooperative Oncology Group performance statuses of ≤2, and whose diseases had relapsed after 2 to 4 prior lines of therapy. Part 2 was a cohort expansion study in which patients were treated with the recommended phase 2 dose of daratumumab (16 mg/kg), selected based on the results of Part 1. Patients in Part 2 had received ≥1 prior line of therapy, had achieved at least a partial response (PR) to ≥1 regimen, and had documented evidence of progressive disease, as defined by International Myeloma Working Group criteria, during or after receiving their last regimen. Patients exposed to, but not refractory to, lenalidomide were permitted in the study.

Daratumumab was administered weekly for 8 weeks, every 2 weeks for 16 weeks, and, finally, every 4 weeks until disease progression or unacceptable toxicity. Patients also received lenalidomide orally at a dose of 25 mg daily on days 1 to 21 of each 28-day treatment cycle, as well as dexamethasone at a dose of 40 mg weekly. To evaluate the safety of shortened infusions, including the incidence of infusion-related reactions, one-third of the patients in Part 2 received an accelerated first infusion of 500 mL over 3 hours (rather than 1,000 mL over 6 hours).

This study was approved by institutional review boards or ethics committees at all participating institutions, was conducted in accordance with the Declaration of Helsinki, and is registered with ClinicalTrials.gov (NCT01615029).

Endpoints, Assessments, and Statistical Analyses

The primary endpoint was safety. Adverse events (AEs) were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[21] After the primary analysis, data collection was limited to serious AEs, disease assessments, and second primary malignancies. Secondary endpoints included objective response rate, time to progression, time to response, duration of response, PFS, OS, and the pharmacokinetics and immunogenicity of daratumumab. Responses were evaluated using International Myeloma Working Group Uniform Response Criteria for myeloma.[22] PFS, OS, time to progression, and duration of response were analyzed using the Kaplan-Meier method.

RESULTS

Patients and Treatment

The GEN503 study was initiated on June 12, 2012. The clinical cutoff date for this analysis was February 14, 2017, approximately 2.5 years after the last patient received their first dose of daratumumab. Thirteen patients were enrolled in Part 1 of the study and received 1 of 4 doses of daratumumab (2 mg/kg [n = 3], 4 mg/kg [n = 3], 8 mg/kg [n = 4], and 16 mg/kg [n = 3]) in combination with lenalidomide and dexamethasone. These patients had received a median (range) of 3 (2-4) prior therapies. All 13 patients had received a prior IMiD, and 10 (76.9%) patients had received prior lenalidomide (**Table 1**). At a median (range) duration of follow-up of 39.9 (4.0-49.5) months, patients in Part 1 had received a median (range) of 38 (4-53) treatment cycles. Eight patients discontinued treatment due to disease progression (4 patients) or AEs (4 patients, including 2 patients since the clinical cutoff for the primary analysis). The remaining 5 patients continue to receive treatment.

Thirty-two patients were enrolled in Part 2 and received 16 mg/kg daratumumab in combination with lenalidomide and dexamethasone. These patients had received a median (range) of 2 (1-3) prior therapies. Twenty-three (71.9%) patients had received a prior IMiD, and 11 (34.4%) had received prior lenalidomide (**Table 1**). At a median (range) duration of follow-up of 32.5 (5.1-34.7) months, patients in Part 2 had received a median (range) of 31 (1-39) treatment cycles. Since the primary analysis, an additional 6 patients discontinued treatment due to disease progression (5 patient) or AEs (1 patient). Sixteen patients remain on therapy.

The study will end once all 21 patients continuing to receive treatment in Parts 1 and 2 have discontinued study treatment, or, for patients still benefitting from treatment, when they can transition to the commercially marketed drug. All patients will be followed for 3 years after receiving their last dose of lenalidomide or from the end of the study, whichever comes first, in order to collect data on second primary malignancies.

Safety

No dose-limiting toxicities were observed in Part 1, as previously reported.[20] At a median (range) duration of follow-up of 39.9 (4.0-49.5) months, the most common (≥25%) treatment-emergent AEs (TEAEs) observed in Part 2 were neutropenia (90.6%), diarrhea (56.3%), cough (50.0%), muscle spasms (46.9%), fatigue (40.6%), thrombocytopenia, nausea, and pyrexia (34.4% each), nasopharyngitis and hypertension (31.3% each), bronchitis and upper respiratory tract infection (28.1% each), and anemia, leukopenia, rhinitis, peripheral edema, back pain, and insomnia (25.0% each; **Table 2**). Since the primary analysis, additional patients reported neutropenia, diarrhea, fatigue, muscle spasms, and cough, and 1 additional patient reported at least 1 grade ≥3

TEAE. Grade ≥3 neutropenia was reported in 84.4% of patients (including 2 patients since the primary analysis) and was, by far, the most frequently reported grade ≥3 TEAE. No new infusion-related reactions were reported with longer follow-up. Additionally, among patients who had at least 1 sample collected after their first daratumumab administration (13 patients in Part 1 and 26 patients in Part 2), none tested positive for anti-daratumumab antibodies, consistent with the previous report.[20]

One patient in Part 1 who was treated with 8 mg/kg daratumumab acquired a second primary malignancy of Epstein-Barr virus associated lymphoma. Four patients in Part 2 acquired second primary malignancies: 3 patients acquired cutaneous squamous cell carcinomas and 1 patient acquired a gastric adenocarcinoma. All 3 patients who acquired cutaneous squamous cell carcinomas continued study treatment after their lesions were treated. A second primary malignancy of myelodysplastic syndrome was reported in 1 additional patient in Part 2 after the clinical cutoff. Four patients in Part 1 died during the study, including 3 deaths after the primary analysis: 1 patient who received 4 mg/kg daratumumab, 2 patients who received 8 mg/kg, and 1 patient who received 16 mg/kg. The cause of death was disease progression, except for 1 patient who received 8 mg/kg and died within 30 days of the last dose and whose cause of death was unknown. Nine patients in Part 2 died during the study, including 6 patients after the primary analysis: 6 patients died due to disease progression, 2 due to AEs (septic shock and viral pneumonia), and 1 due to respiratory insufficiency resulting from polymorphic posttransplant lymphoproliferative disorder (association with Epstein-Barr virus unknown).

Since the primary analysis, 1 additional patient in the 4 mg/kg group of Part 1 received a red blood cell transfusion. One additional patient in Part 2 received red blood cell and platelet transfusions due to grade 3 anemia and thrombocytopenia, both of which the investigator deemed possibly or probably related to daratumumab and lenalidomide. The total number of transfusions increased in Part 2, with an additional 7 red blood cell transfusions and 2 platelet transfusions since the primary analysis.

Efficacy

In Part 1, the ORR was 100.0% for patients who received 2 mg/kg or 4 mg/kg daratumumab, 75.0% for patients who received 8 mg/kg daratumumab, and 66.7% for patients who received 16 mg/kg daratumumab (**Table 3**). One patient in the 2 mg/kg group, 2 patients in the 4 mg/kg group, and 2 patients in the 8 mg/kg group achieved sCRs. Although no patients in the 16 mg/kg group achieved sCRs, 1 patient in this group had a response that deepened from a VGPR to a CR since the primary analysis. **Figure 1A** shows the timing and depth of response for each patient in Part 1 who achieved PR or better. Seven of the 11 patients who responded remained progression free and alive. All 7 of these patients remained progression free for at least 28 months.

In Part 2, the ORR was 81.3% (**Table 3**). For best responses, 10 (31.3%) patients achieved sCR (compared with 8 patients in the primary analysis), 4 (12.5%) achieved CR (compared with 3 patients in the primary analysis), 8 (25.0%) achieved VGPR, and 4 (12.5%) achieved PR. Fourteen (43.8%) patients achieved CR or better, and 22 (68.8%) achieved VGPR or better. One (3.1%) patient had a minimal response, 5 (15.6%) had stable disease, and no patients had progressive disease. Since the primary analysis, the ORR has not changed but the number of

patients who achieved CR (4 versus 3 patients) or sCR (10 versus 8 patients) increased. Thus, with prolonged treatment, responses deepened over time. The median (range) duration of response was not reached (95% confidence interval [CI], 26.5 months-not estimable [NE]). **Figure 1B** shows the timing and depth of response for each patient in Part 2 who achieved PR or better. Nineteen of the 26 responders remained progression free. Median PFS was not reached (95% CI, 16.62 months-NE), and the 2-year PFS rate was 68.9% (95% CI, 48.5-82.5; **Figure 2A**). Median OS was not reached (95% CI, 32.2 months-NE), and the 2-year OS rate was 78.1% (95% CI, 59.5-88.9; **Figure 2B**).

DISCUSSION

Daratumumab in combination with lenalidomide and dexamethasone continued to be well tolerated and displayed notable efficacy in patients with RRMM. Responses to this regimen deepened over time and were maintained for more than 2 years. In Part 2 of the study, a remarkable number of patients (31%) achieved sCR.

The results of this study are consistent with those of POLLUX, a phase 3 study of daratumumab in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with RRMM who received ≥1 prior line of therapy.[12] In POLLUX, this triplet regimen significantly improved PFS and produced a higher ORR compared with the control regimen. It also produced a higher minimal residual disease–negative rate compared with the control regimen, demonstrating that daratumumab in combination with lenalidomide and dexamethasone can drive responses even deeper than sCR. Additionally, as seen in the current study, responses in POLLUX continued to deepen over time.[12,23] The safety profile observed in

the current study is also consistent with that observed in POLLUX; no new safety signals were identified.

The synergy between daratumumab and lenalidomide/dexamethasone may result from the fact that daratumumab has, in addition to its immune-mediated activities, immunomodulatory effects that include the depletion of immunosuppressive cell populations and the expansion of cytotoxic and helper T cells.[9] In POLLUX, the addition of daratumumab to lenalidomide and dexamethasone was associated with substantial increases in T-cell clonality and T-cell fraction (number of T cells per nucleated cell) and reductions in T-cell richness (number of clones with unique TCRβ rearrangements).[24] Additionally, in GEN503, changes in T cells towards a cytolytic, granzyme B+ phenotype indicate an adaptive immune response in patients treated with daratumumab in combination with lenalidomide and dexamethasone and may contribute to the depth of response in these patients.[25]

Our data compare favorably with those obtained in other clinical trials of lenalidomide and dexamethasone–containing triplet regimens in RRMM. In a phase 1b study of a humanized CD38 monoclonal antibody, isatuximab, in combination with lenalidomide and dexamethasone, the ORR was 56% and the median PFS was 8.5 months.[26] In ASPIRE, a phase 3 study of carfilzomib in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone, the ORR was 87%, with 14 % of patients achieving sCR, and the median PFS was 26.3 months.[27] In TOURMALINE-MM1, a phase 3 study of ixazomib versus placebo, both in combination with lenalidomide and dexamethasone, the ORR was 78%, with 48% of patients achieving VGPR or better and 2% of patients achieving sCR, and the median PFS was

20.6 months.[28] In ELOQUENT-2, a phase 3 study of elotuzumab in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone, the ORR was 79%, with 33% of patients achieving VGPR or better, the median PFS was 19.4 months, and the 2-year OS rate was 73%.[29]

The most common grade ≥3 AE in Part 2 of the GEN503 study was neutropenia, which is a known lenalidomide-associated toxicity. The rate of grade ≥3 neutropenia observed in this study exceeded those reported previously for lenalidomide and dexamethasone alone (29.5%-41.2%).[30,31] The higher rate of grade ≥3 neutropenia observed in this study may have resulted from a longer duration of lenalidomide exposure, or from the daratumumab-mediated depletion of CD38-expressing hematopoietic stem cells.[32] However, treatment interruptions, lenalidomide dose reductions, and growth factor administration were successful in managing this AE.

In conclusion, long-term treatment with the daratumumab, lenalidomide, and dexamethasone combination induced deep and durable responses and was associated with a manageable safety profile.

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Table 1. Baseline Characteristics of Patients in GEN503

	Part 1 (N = 13)	Part 2 (N = 32)
Median (range) age, y	62.0 (48-76)	59.5 (41-76)
Female/male sex, %	23/77	31/69
ECOG score, n (%)		
0	8 (61.5)	19 (59.4)
1	5 (38.5)	12 (37.5)
2	0 (0.0)	1 (3.1)
Median (range) time since diagnosis, y	3.8 (0.9-14.0)	3.2 (0.9-12.7)
Median (range) number of prior therapies	3.0 (2-4)	2.0 (1-3)
≥2 prior therapies, n (%)	13 (100.0)	17 (53.1)
Prior ASCT, n (%)	9 (69.2)	25 (78.1)
Prior IMiD, n (%)	13 (100.0)	23 (71.9)
Prior lenalidomide	10 (76.9)	11 (34.4)
Prior thalidomide	7 (53.8)	14 (43.8)
Prior PI, n (%)	12 (92.3)	29 (90.6)
Prior bortezomib	12 (92.3)	28 (87.5)
Prior PI + IMiD, n (%)[*]	12 (92.3)	21 (65.6)
Prior bortezomib + lenalidomide[*]	9 (69.2)	9 (28.1)
Prior steroids	12 (92.3)	32 (100)
Prior chemotherapy, n (%)[**]	13 (100.0)	32 (100.0)
Alkylating agents	13 (100.0)	29 (90.6)
Anthracyclines	8 (61.5)	15 (46.9)
Prior PI + IMiD + alkylating agents[*, **]	12 (92.3)	19 (59.4)
Refractory to last line of therapy, n (%)	5 (38.5)	7 (21.9)
Refractory to therapy containing, n (%)		
Lenalidomide	4 (30.8)	1 (3.1)
Bortezomib	6 (46.2)	5 (15.6)
Alkylating agents	3 (23.1)	3 (9.4)
PI only	2 (15.4)	5 (15.6)
IMiD only	2 (15.4)	1 (3.1)

ECOG, Eastern Cooperative Oncology Group; ASCT, autologous stem cell transplantation; IMiD, immunomodulatory drug; PI, proteasome inhibitor.

[*]Patients may have received these drugs in separate treatment regimens.

[**]Includes alkylating agents or ASCT.

Table 2. Most Common (≥25%) AEs in Part 2 (N = 32)

Event, n (%)	All grades	Grade 3 or 4
Neutropenia	29 (90.6)	27 (84.4)
Diarrhea	18 (56.3)	1 (3.1)
Cough	16 (50.0)	0 (0.0)
Muscle spasms	15 (46.9)	0 (0.0)
Fatigue	13 (40.6)	0 (0.0)
Thrombocytopenia	11 (34.4)	5 (15.6)
Nausea	11 (34.4)	0 (0.0)
Pyrexia	11 (34.4)	0 (0.0)
Hypertension	10 (31.3)	3 (9.4)
Nasopharyngitis	10 (31.3)	0 (0.0)
Bronchitis	9 (28.1)	1 (3.1)
Upper respiratory tract infection	9 (28.1)	1 (3.1)
Anemia	8 (25.0)	5 (15.6)
Leukopenia	8 (25.0)	4 (12.5)
Rhinitis	8 (25.0)	0 (0.0)
Peripheral edema	8 (25.0)	0 (0.0)
Back pain	8 (25.0)	0 (0.0)
Insomnia	8 (25.0)	0 (0.0)

AE, adverse event.

Table 3. Summary of Best Responses

	Part 1				Part 2
Response, n (%)	**2 mg/kg DARA (n = 3)**	**4 mg/kg DARA (n = 3)**	**8 mg/kg DARA (n = 4)**	**16 mg/kg DARA (n = 3)**	**16 mg/kg DARA (n = 32)**
sCR	1 (33.3)	2 (66.7)	2 (50.0)	0 (0.0)	10 (31.3)
CR	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	4 (12.5)
VGPR	1 (33.3)	1 (33.3)	0 (0.0)	1 (33.3)	8 (25.0)
PR	1 (33.3)	0 (0.0)	1 (25.0)	0 (0.0)	4 (12.5)
MR	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (3.1)
SD	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	5 (15.6)
PD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ORR[*]	3 (100.0)	3 (100.0)	3 (75.0)	2 (66.7)	26 (81.3)
VGPR or better[**]	2 (66.7)	3 (100.0)	2 (50.0)	2 (66.7)	22 (68.8)
CR or better[***]	1 (33.3)	2 (66.7)	2 (50.0)	1 (33.3)	14 (43.8)

DARA, daratumumab; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; ORR, overall response rate.

[*]sCR+CR+VGPR+PR.

[**]sCR+CR+VGPR.

[***]sCR+CR.

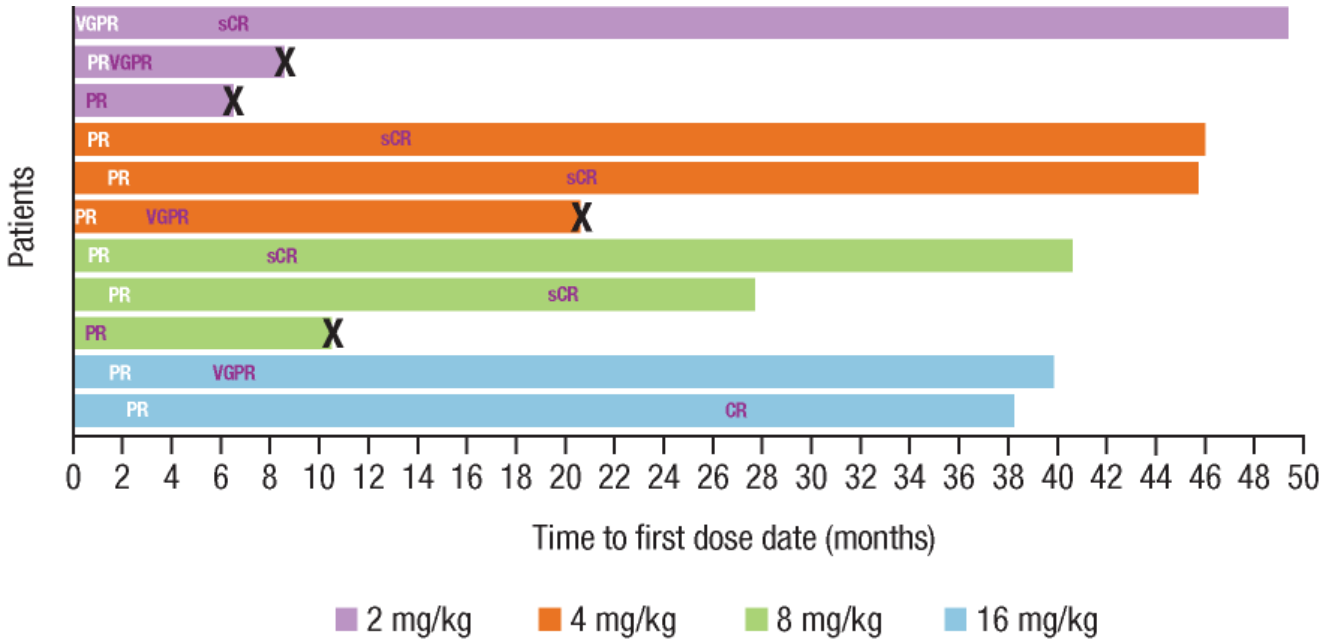
FIGURE LEGENDS

Figure 1. Swim lane plots of responders in Part 1 (A) and Part 2 (B). Unfilled ovals indicate the first response and filled ovals indicate the best response. “X” indicates disease progression. VGPR, very good partial response; sCR, stringent complete response; PR, partial response; CR, complete response.

Figure 2. Progression-free survival (A) and overall survival (B) of patients in Part 2. At a median duration of follow-up of 32.5 months, median PFS was not reached (95% CI, 16.62 months-NE), and the 24-month PFS rate was 68.9% (95% CI, 48.5-82.5). Median OS was not reached (95% CI, 32.2 months-NE), and the 24-month OS rate was 78.1% (95% CI, 59.5-88.9). PFS, progression-free survival; OS, overall survival; CI, confidence interval; NE, not estimable.

Figure 1. Swim lane plots of responders in Part 1 (A) and Part 2 (B).

A.



B.

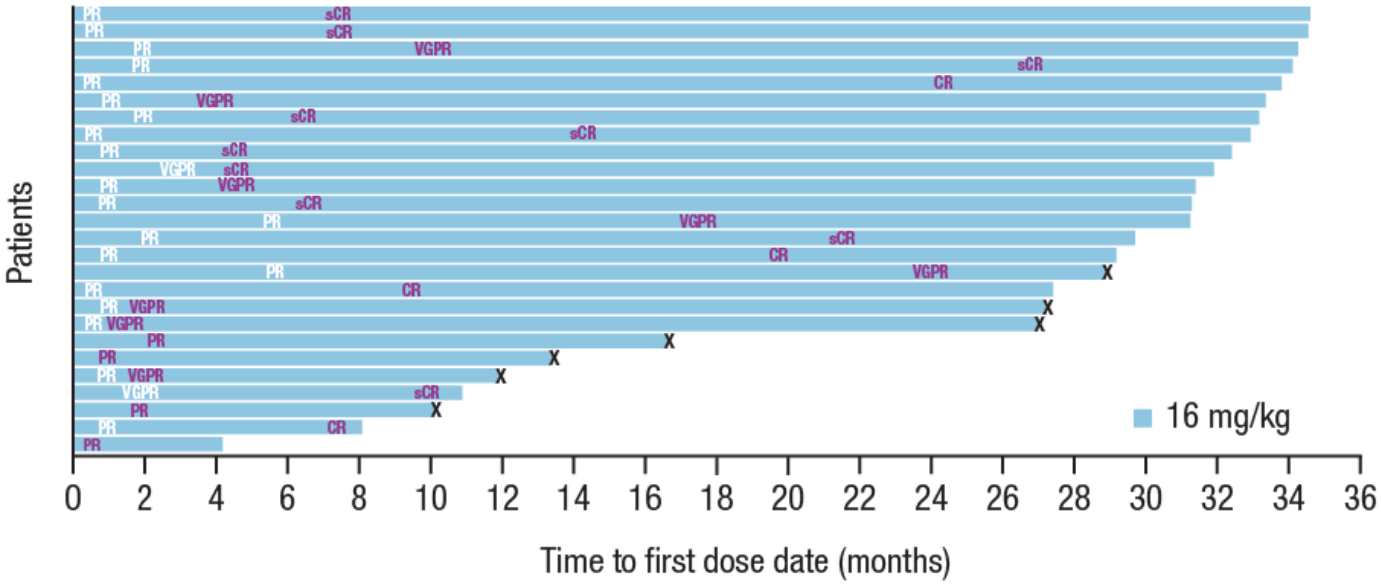
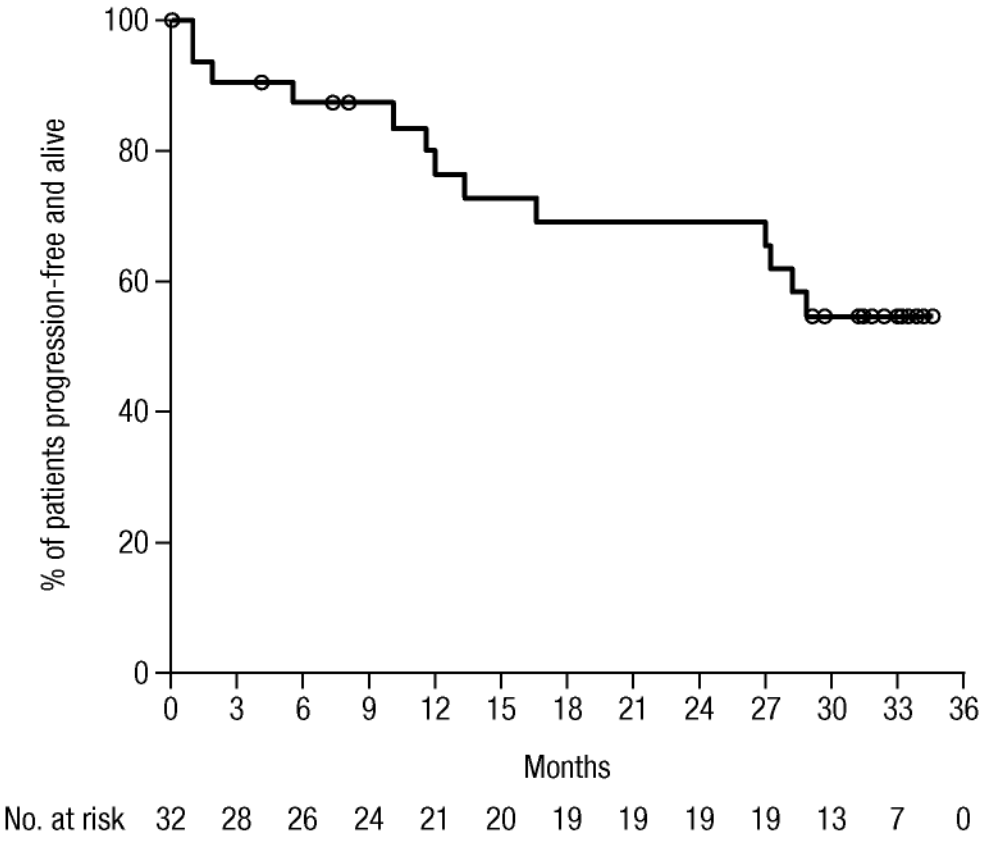
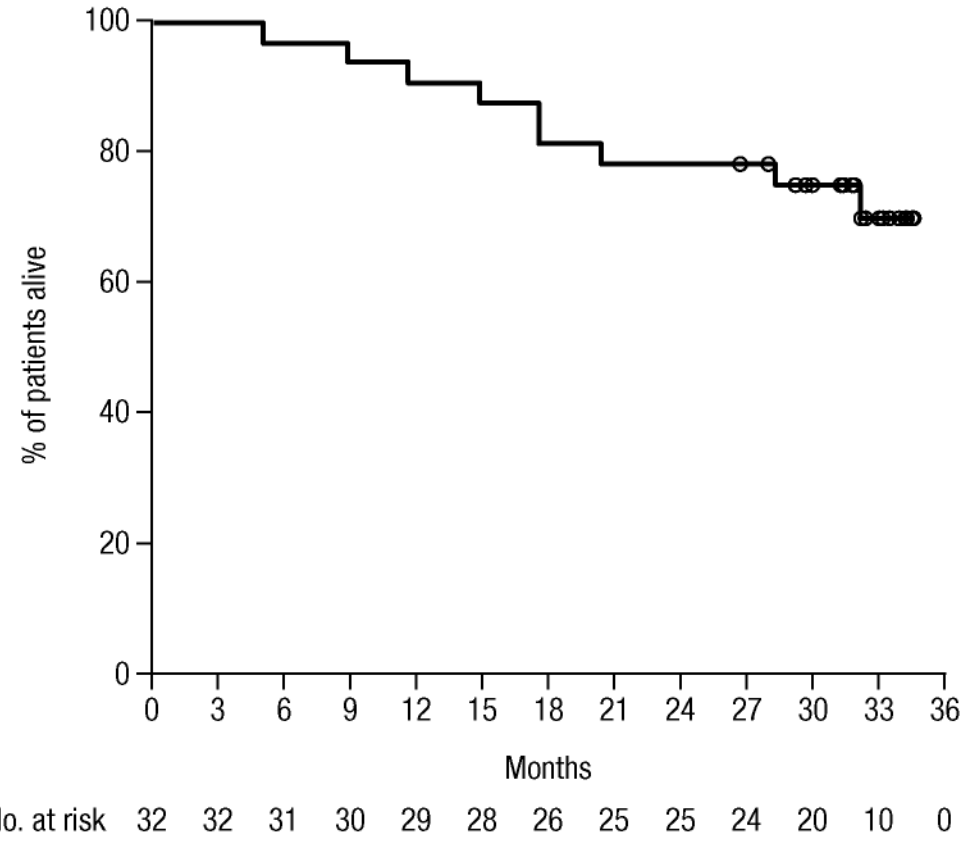


Figure 2. Progression-free survival (A) and overall survival (B) of patients in Part 2.

A.



B.


100
80
60
40
20
0
% of patients alive
0 3 6 9 12 15 18 21 24 27 30 33 36
Months
No. at risk 32 32 31 30 29 28 26 25 25 24 20 10 0