

P113

Sonrotoclax Plus Dexamethasone is Tolerable and Demonstrates Antimyeloma Activity in Patients With Relapsed/Refractory Multiple Myeloma Harboring t(11;14)

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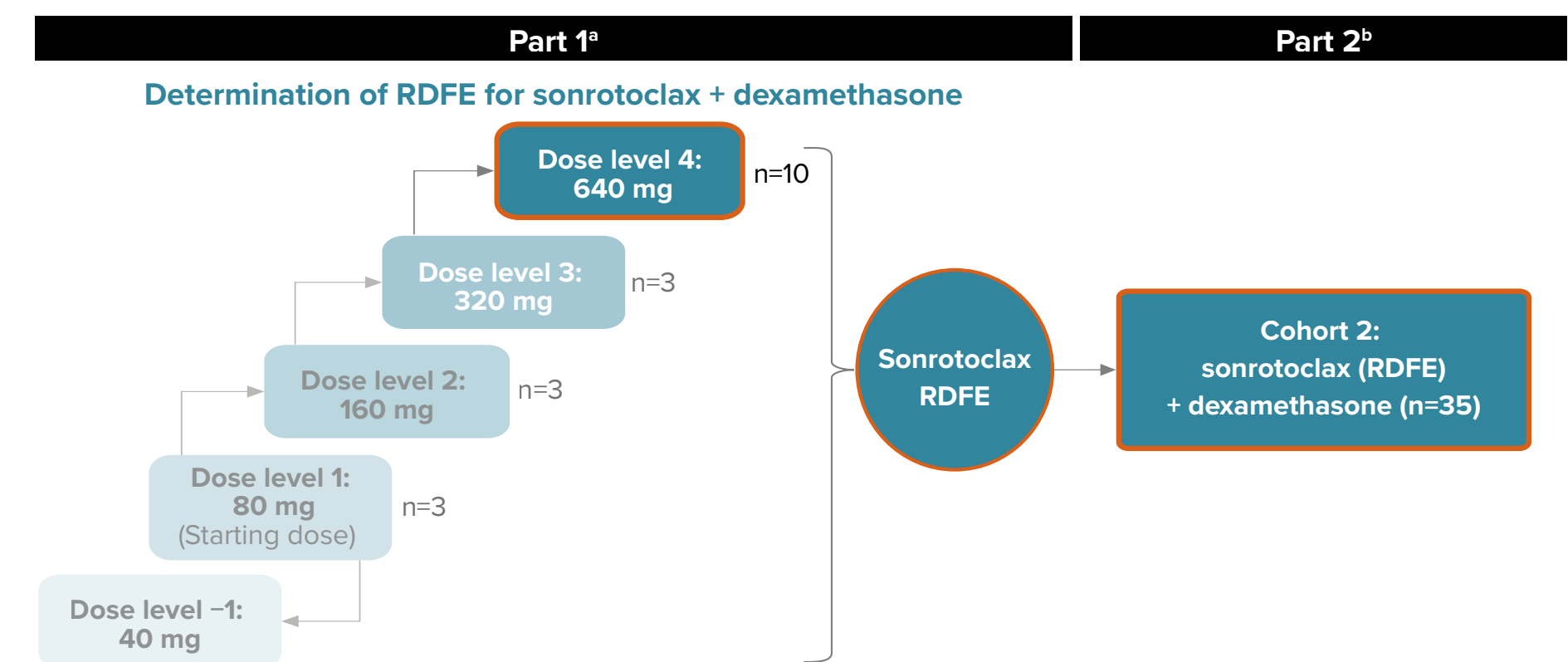
INTRODUCTION

- Multiple myeloma (MM) with t(11;14), found in approximately 15%-20% of patients at first diagnosis, has high expression of B-cell lymphoma 2 (BCL2) and is a unique disease subset with distinct features^{1,2}
- BCL2 is an attractive therapeutic target in MM with t(11;14) because MM cells are BCL2 primed and have been particularly responsive to oral BCL2 inhibitors, such as venetoclax, a first-generation BCL2 inhibitor²
- Combining a BCL2 inhibitor with dexamethasone or a proteasome inhibitor (PI) can improve clinical outcomes compared with monotherapy^{2,3}
- Although BCL2 inhibitors have shown clinical activity in patients with MM, no BCL2-targeted therapies are currently approved for MM^{2,4}
- Sonrotoclax (BGB-11417) is a more selective and a more pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no accumulation⁵
- Previously presented data from the dose-escalation period of the BGB-11417-105 (NCT04973605) study indicate sonrotoclax + dexamethasone was tolerable, with no DLTs reported⁶
- Updated safety and efficacy data are presented for patients treated with 640 mg sonrotoclax plus dexamethasone in the BGB-11417-105 study in patients with t(11;14)-positive relapsed/refractory (R/R) MM

METHODS

- BGB-11417-105 is an ongoing, open-label, multicenter, phase 1b/2, dose-escalation study of sonrotoclax as the backbone for different combination therapies, including combination with dexamethasone or dexamethasone plus carfilzomib, daratumumab, or pomalidomide in patients with R/R MM harboring t(11;14) (**Figure 1**)
- Eligible patients have R/R MM with centrally confirmed t(11;14) and had received a minimum of 3 (dose-finding cohort) or 1 (dose-expansion cohort) prior lines of therapy
- Study objectives include safety, tolerability, recommended dose for expansion (RDfE, part 1), and the antitumor activity of sonrotoclax combination therapy in patients with t(11;14)-positive R/R MM
- Sonrotoclax was administered orally once daily in cohorts at escalating doses, and 40 mg dexamethasone was administered weekly;⁶ data at the sonrotoclax RDfE (640 mg) are presented here

Figure 1. Study Design in Patients Harboring t(11;14) R/R MM



^a Dose escalation guided by mTP2 and safety monitoring committee recommendation. ^b Cohort 2 started after doublet RDfE was determined. mTP2, modified toxicity probability interval; RDfE, recommended dose for expansion.

RESULTS

- As of March 25, 2024, a total of 32 patients were treated at the RDfE of 640 mg sonrotoclax + dexamethasone (part 1, n=10; part 2, n=22) with a median follow-up of 4.6 months (range, 0.1-19 months)
 - There are 22 patients (69%) with ongoing study treatment and 10 patients (31%) have discontinued treatment due to disease progression (n=6), AE (n=2; hematuria, pancreatic cancer), patient withdrawal (n=1; due to pill burden after 1 dose), and physician decision (n=1; worsening not meeting PD criteria)
- The median number of prior lines of therapy was 3 (range, 1-12) and 66% of patients had ≥3 prior lines (**Table 1**)
 - All patients had prior PI and immunomodulatory drug (IMiD) exposure and most had prior anti-CD38 therapy (72%)
 - Many patients were refractory to PI (56%), IMiDs, (72%), anti-CD38 therapy (56%), and ≥1 PI + IMiD + anti-CD38 (47%)

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Sonrotoclax 640 mg + Dexamethasone 40 mg (N=32)
Age, median (range), years	69 (48-80)
Male sex, n (%)	15 (46.9)
ECOG PS, n (%)	
0	14 (43.8)
1	16 (50.0)
2	2 (6.3)
R-ISS stage at initial diagnosis, n (%)	
I	5 (15.6)
II	17 (53.1)
III	4 (12.5)
Unknown	6 (18.8)
Time from most recent R/R episode to first dose, median (range), months	1.9 (0.4-93.8)
Cytogenetic risk, n (%)	
High ^a	9 (28.1)
Not high	22 (68.8)
Unknown	1 (3.1)
Prior therapy	
No. of lines of prior systemic therapy, median (range)	3 (1-12)
No. of prior lines of systemic therapy, n (%)	
1	6 (18.8)
2	5 (15.6)
≥3	21 (65.6)
Prior exposure, n (%)	
PI	32 (100)
IMiD	32 (100)
Anti-CD38 antibody	23 (71.9)
≥1 PI + ≥1 IMiD + ≥1 anti-CD38 antibody	23 (71.9)
Refractory status, n (%)	
PI	18 (56.3)
IMiD	23 (71.9)
Anti-CD38 antibody	18 (56.3)
≥1 PI + ≥1 IMiD + ≥1 anti-CD38 antibody	15 (46.9)
Prior autologous transplant, n (%)	20 (62.5)

^a High-risk group consisted of patients with genetic subtype t(4;14), 1p deletion, del(17p13), and 1q21 amplification. ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drugs; PI, proteasome inhibitor; R-ISS, Revised International Staging System.

- An overall summary of TEAEs is shown in **Table 2**
 - Two patients died on study; neither death was considered related to study therapy (1 TEAE of metastatic pancreatic cancer [new diagnosis] and 1 non-TEAE of liver failure due to hepatocellular carcinoma 5 months after discontinuing study drug due to PD)
- Serious TEAEs occurred in 6 patients (19%) and grade ≥3 TEAEs occurred in 10 patients (31%)

Table 2. Overall Safety Summary

Patients, n (%)	Sonrotoclax 640 mg + Dexamethasone 40 mg (N=32)
Any TEAE ^a	28 (87.5)
Grade ≥3	10 (31.3)
Serious	6 (18.8)
Leading to death	1 (3.1)
TEAE leading to dose modification	
Dose interruption	7 (21.9)
Sonrotoclax	6 (18.8)
Dexamethasone	5 (15.6)
Dose reduction	10 (31.3)
Sonrotoclax	0
Dexamethasone	10 (31.3)
Treatment discontinuation	3 (9.4)
Sonrotoclax ^b	2 (6.3)
Dexamethasone ^c	3 (9.4)

^a AEs were graded per CTCAE v5.0. ^b n=1 each; hematuria, metastatic pancreatic cancer. ^c n=1 each; hematuria, metastatic pancreatic cancer, agitation.

- The most common any-grade TEAEs were fatigue and insomnia (each 28%), diarrhea (22%), and constipation and nausea (each 16%) (**Table 3**)
- Hematologic TEAEs occurred in 4 patients (13%) (thrombocytopenia [grade 3], platelet count decreased [grades 1 and 3], and neutrophil count decreased [grade 3]) (**Table 4**)
- No patients experienced a DLT (assessed during the first 21 days of part 1)

Table 3. Most Common TEAEs^a

Patients, n (%)	Sonrotoclax 640 mg + Dexamethasone 40 mg (N=32)	
Fatigue	9 (28.1)	2 (6.3)
Insomnia	9 (28.1)	1 (3.1)
Diarrhea	7 (21.9)	0
Constipation	5 (15.6)	0
Nausea	5 (15.6)	0
Abdominal distension	3 (9.4)	0
Arthralgia	3 (9.4)	0
Decreased appetite	3 (9.4)	0
Dizziness	3 (9.4)	0
Dyspnea	3 (9.4)	0
Gastroesophageal reflux disease	3 (9.4)	0
Headache	3 (9.4)	0
Acute kidney injury ^b	2 (6.3)	2 (6.3)
Retinal detachment	2 (6.3)	2 (6.3)

^a TEAEs of any grade in ≥3 patients or grade ≥3 in ≥2 patients. ^b Neither acute kidney injury was considered related to sonrotoclax by the investigator (1 in context of fatigue that was considered related to disease and 1 in context of urinary tract infection).

Table 4. Hematologic and Infection TEAEs

Patients, n (%)	Sonrotoclax 640 mg + Dexamethasone 40 mg (N=32)
Any hematologic TEAE	4 (12.5)
Platelet count decreased	2 (6.3)
Neutrophil count decreased	1 (3.1)
Thrombocytopenia	1 (3.1)
Any infection ^a	7 (21.9)
COVID-19	2 (6.3)
Upper respiratory tract infection	2 (6.3)
Influenza	1 (3.1)
Lower respiratory tract infection	1 (3.1)
Pneumonia parainfluenza viral	1 (3.1)
Sinusitis	1 (3.1)
Tooth infection	1 (3.1)
Urinary tract infection	1 (3.1)
Vascular device infection	1 (3.1)
Viral infection	1 (3.1)

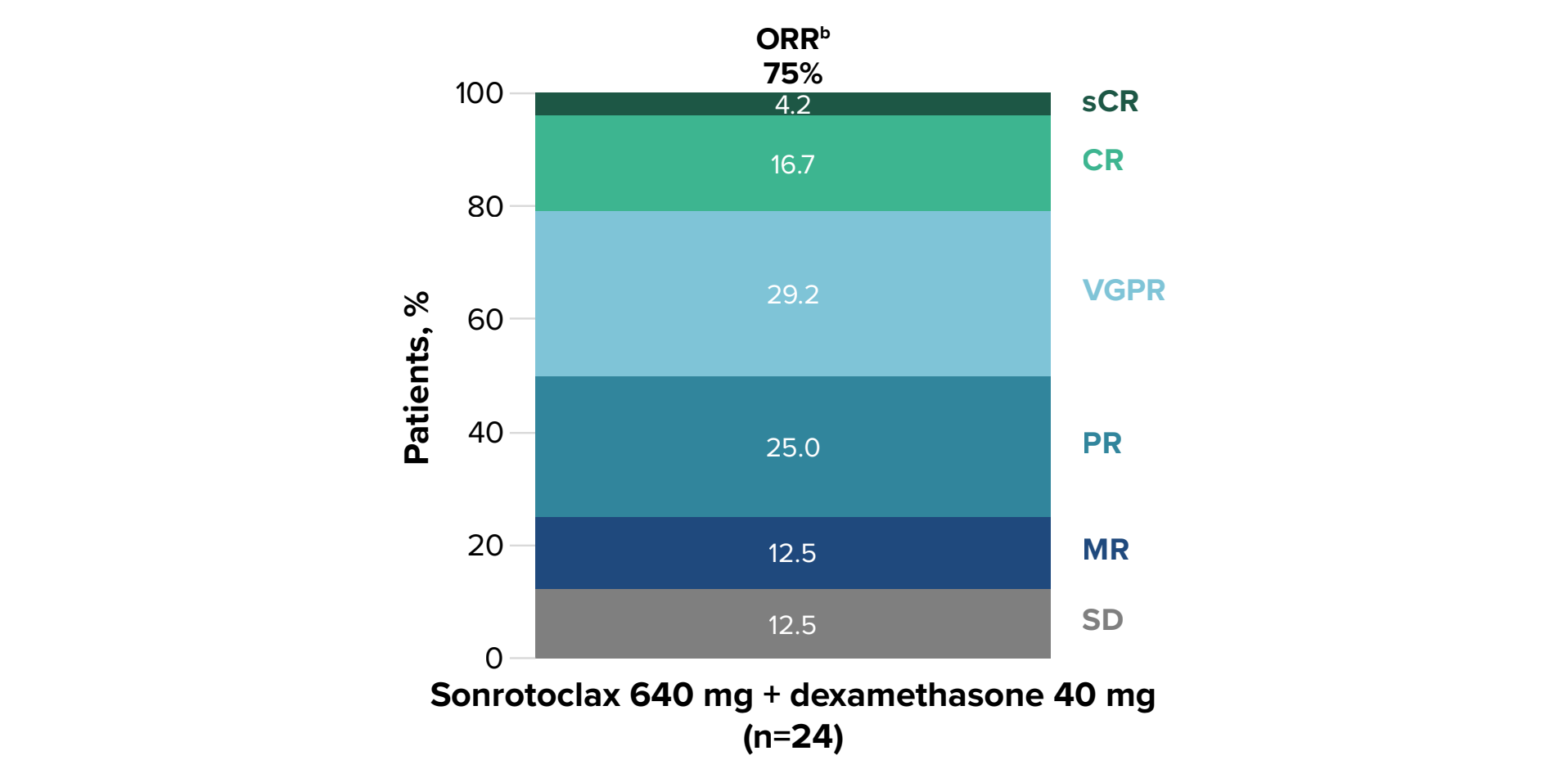
^a Preferred terms in system organ class *infections and infestations*.

CONCLUSIONS

- These results indicate that sonrotoclax plus dexamethasone is well tolerated in a heavily pretreated population
 - No DLTs were observed during dose-escalation and low rates of hematologic toxicities and infections continued to be observed during dose-expansion
- Sonrotoclax + dexamethasone combination treatment provided deep and durable responses in this R/R population
 - Most patients achieved a positive response, with an ORR of 75% (95% CI, 53-90) and VGPR or better rate of 50% (95% CI, 29-71), with 4% of patients achieving sCR and 17% achieving CR
- The study is ongoing and other combination treatments with sonrotoclax are being investigated

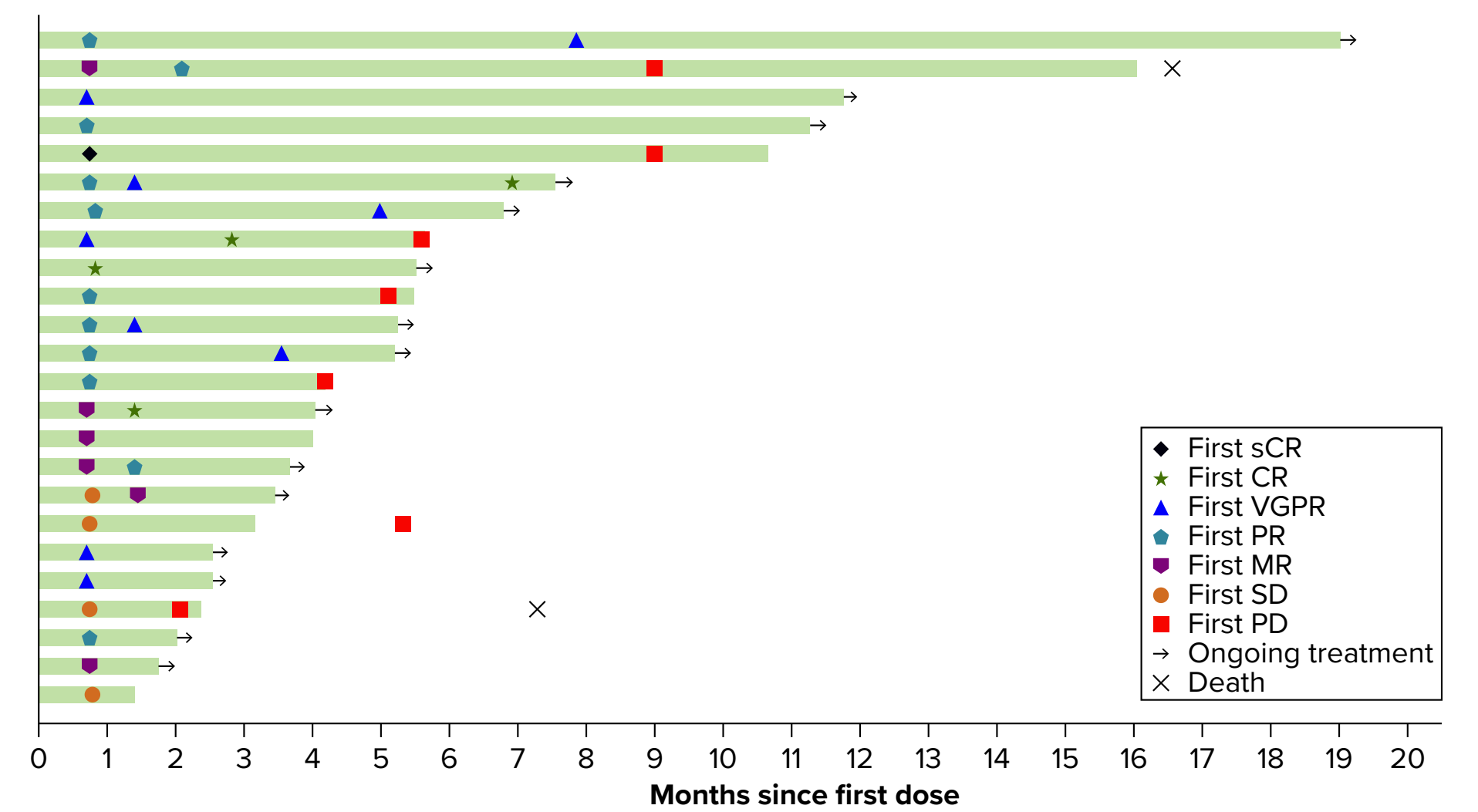
- Among 24 efficacy-evaluable patients, the ORR was 75% (n=18; 95% CI, 53-90), VGPR or better rate was 50% (n=12; 95% CI, 29-71), and CR or stringent CR (sCR) rate was 21% (CR, n=4; sCR, n=1; 95% CI, 7-42) (**Figure 2**)
- Of 5 patients with CR/sCR, 2 achieved minimal residual disease negativity based on a threshold of 10⁻⁵ using a flow cytometry assay
- The median time to response was 0.7 months and median duration of response (DOR) was 8 months (95% CI, 4 to not estimable; **Figure 3**)
 - Ten patients improved upon their first response, the longest DOR was 18 months, and 2 patients had more than 1 year on treatment

Figure 2. Best Overall Response by Investigator^a



^a Responses were assessed by the investigator per the IMWG 2016 response criteria.⁷ ^b ORR was defined as best overall response of PR or better. MR, minor response; sCR, stringent complete response; VGPR, very good partial response.

Figure 3. Treatment Duration, First Response, and Improved Response^a



^a Responses were assessed by the investigator per IMWG 2016 response criteria.⁷ Only changes to improved response or PD are shown per IMWG. MR, minor response; sCR, stringent complete response; VGPR, very good partial response.

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