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

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Introduction

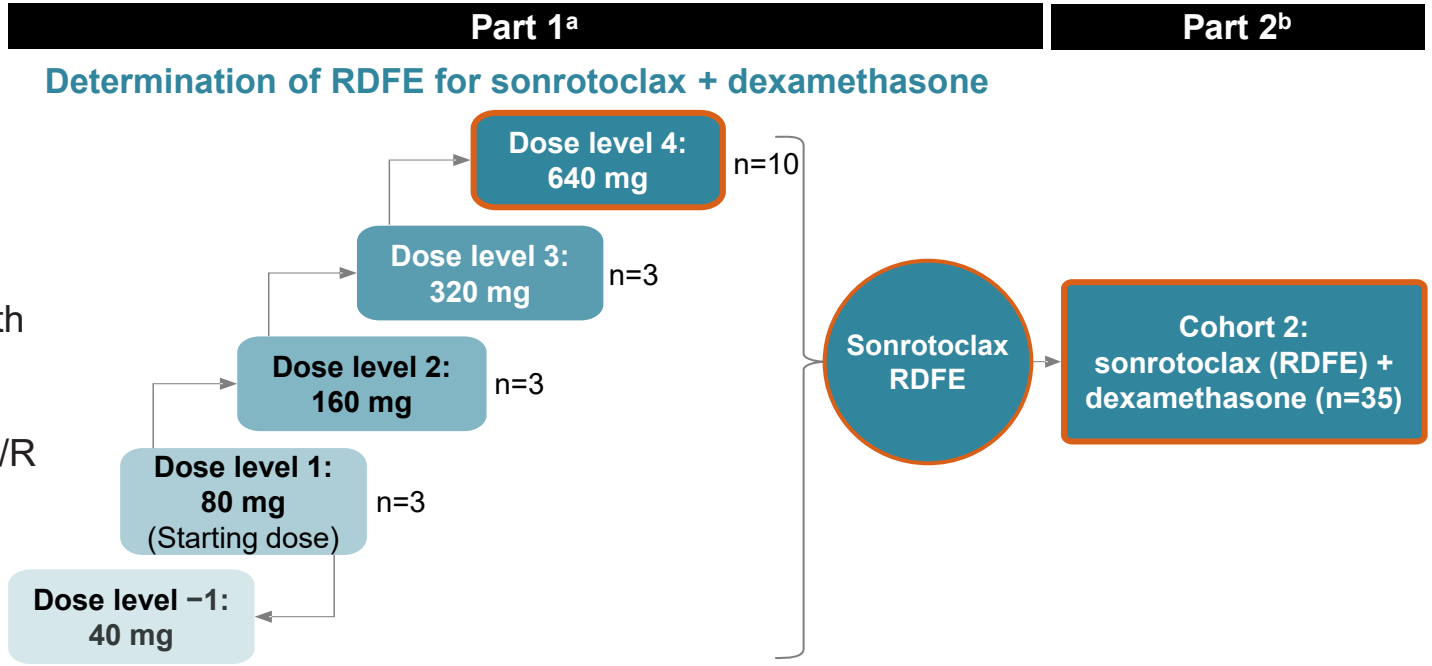
- MM with t(11:14), found in approximately 15%-20% of patients at first diagnosis, has high expression of BCL2 and is a unique disease subset with distinct features[1,2]
- BCL2 is an attractive therapeutic target in MM with t(11;14) because MM cells are BCL2 primed and have been particularly responsive to oral BCL2 inhibitors, such as venetoclax, a first-generation BCL2 inhibitor[2]
- Combining a BCL2 inhibitor with dexamethasone or a 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 accumulation[5]
- Previously presented data from the dose-escalation period of the BGB-11417-105 (NCT04973605) study indicate sonrotoclax + dexamethasone was tolerable, with no DLTs reported[6]
- 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 R/R MM with a median follow-up of 4.6 months

PI, proteasome inhibitor.

1. Bal S, et al. *Am J Cancer Res.* 2022;12:2950-2965; 2. Inam S, et al. *Expert Rev Hematol.* 2021;14:323-327; 3. Kaufman JL, et al. *Am J Hematol.* 2020;96:418-427;
4. International Myeloma Foundation. https://www.myeloma.org/multiple-myeloma-drugs; 5. Hu N, et al. AACR 2020. Abstract 3077; 6. Quach H, et al. ASH 2023. Abstract 1011.

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

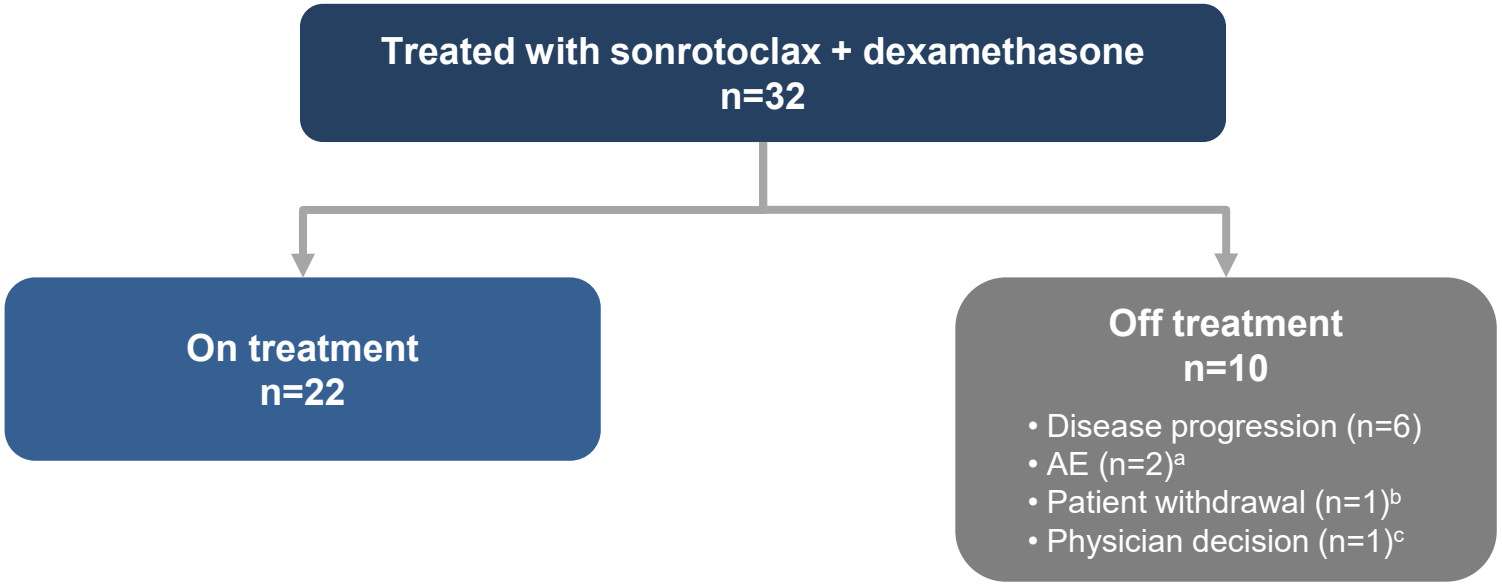
- BGB-11417-105 is an ongoing, open-label, multicenter, phase 1b/2, dose-escalation study of sonrotoclax as the backbone for different combination therapies, including combination with dexamethasone or combinations with SOC agents in patients with R/R MM harboring t(11;14)
- Combined data from patients treated with 640 mg in part 1 and 2 are presented



[a] Dose escalation guided by mTPI-2 and safety monitoring committee recommendation. [b] Cohort 2 started after doublet RDFE was determined.
mTPI-2, modified toxicity probability interval; RDFE, recommended dose for expansion; SOC, standard of care.

Patient Disposition

- 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)



[a] Hematuria, pancreatic cancer. [b] Due to pill burden after 1 dose. [c] Worsening not meeting PD criteria.
RDFE, recommended dose for expansion.

Baseline Demographics and Disease Characteristics

Patients	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)
Cytogenic risk, n (%)	
High[a]	9 (28.1)
Not high	22 (68.8)
Unknown	1 (3.1)

Patients	Sonrotoclax 640 mg + Dexamethasone 40 mg (N=32)
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.

Overall Safety Summary

- 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%)
- No patients experienced a DLT (assessed during the first 21 days of part 1)

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] Adverse events were graded per CTCAE v5.0. [b] n=1 each; hematuria, metastatic pancreatic cancer. [c] n=1 each; hematuria, metastatic pancreatic cancer, agitation.

Most Common TEAEs[a]

- The most common any-grade TEAEs were fatigue and insomnia (each 28%), diarrhea (22%), and constipation and nausea (each 16%)

	Sonrotoclax 640 mg + Dexamethasone 40 mg (N=32)	
Patients, n (%)	Any Grade	Grade ≥3
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).

Hematologic and Infection TEAEs

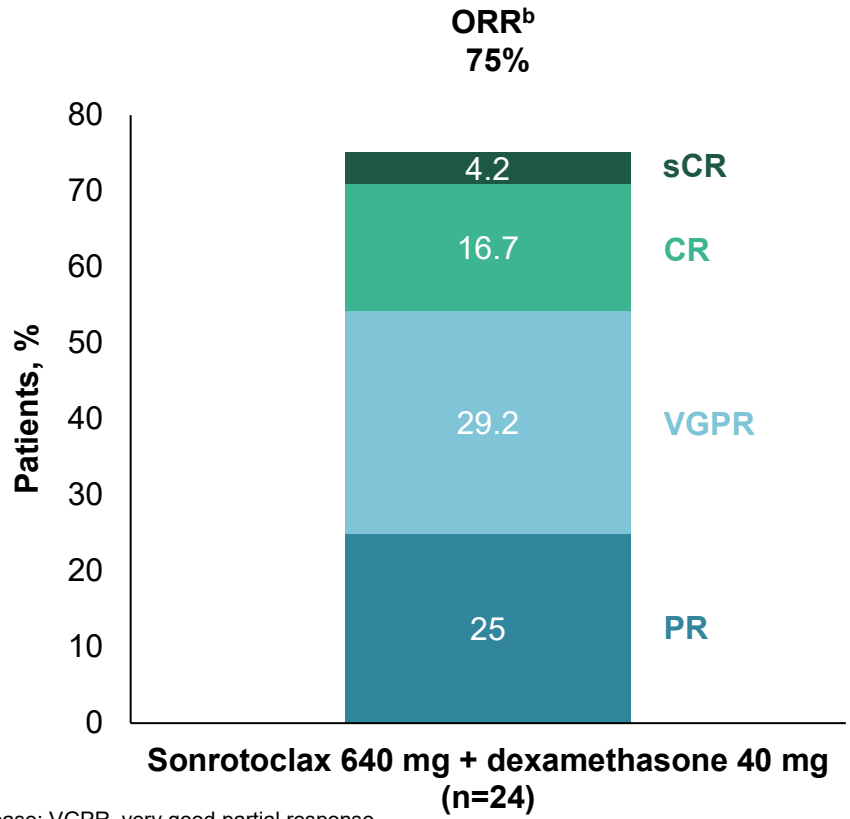
- Hematologic TEAEs occurred in 4 patients (13%)
  - Thrombocytopenia (grade 3)
  - Platelet count decreased (grades 1 and 3)
  - Neutrophil count decreased (grade 3)
- Low rates of grade ≥3 hematologic and infection TEAEs occurred

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.*

BOR by Investigator[a]

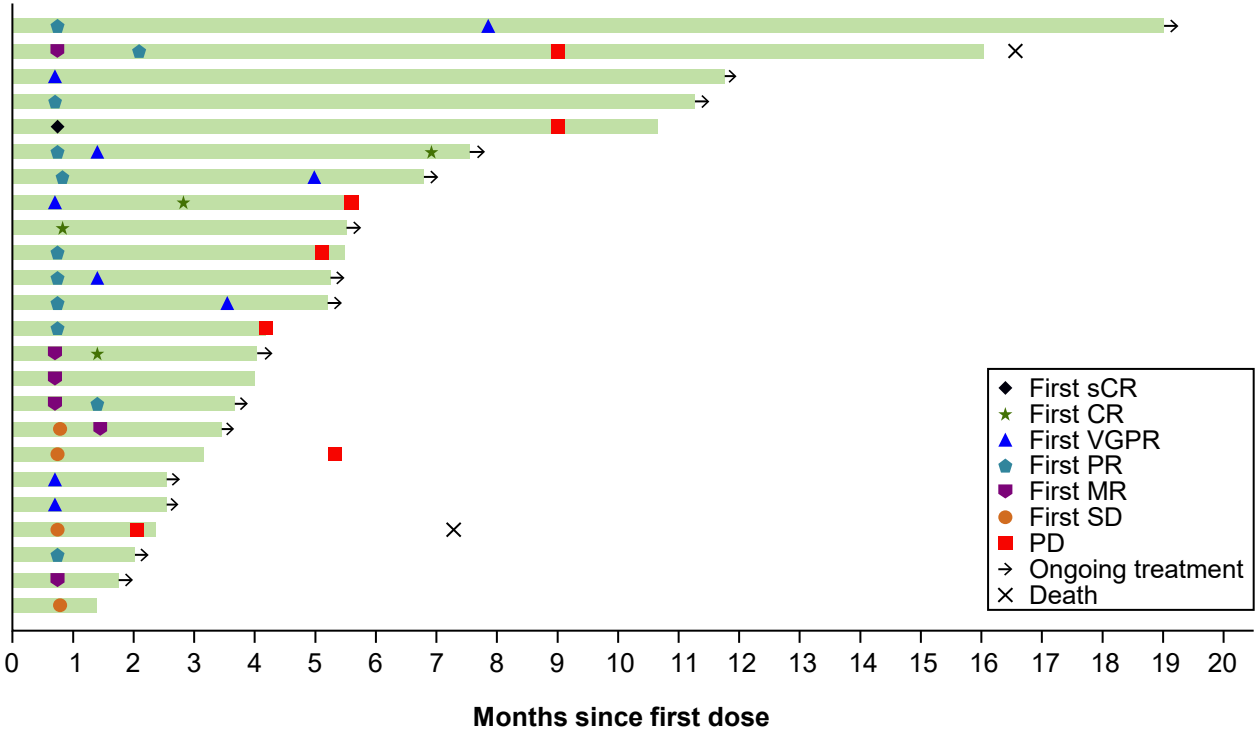
- Among 24 efficacy-evaluable patients, the ORR was 75% (n=18; 95% CI, 53-90)
  - VGPR or better rate was 50% (n=12; 95% CI, 29-71)
  - CR or sCR rate was 21% (4 CR, 1 sCR; 95% CI, 7-42)
  - Three patients (13%) achieved a BOR of MR and 3 (13%) achieved SD
- Of 5 patients with CR/sCR, 2 achieved MRD negativity based on a threshold of 10^{-5} using a flow cytometry assay



[a] Responses were assessed by the investigator per the IMWG 2016 response criteria.[1]
[b] ORR was defined as best overall response of PR or better.
BOR, best overall response; MR, minor response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.
1. Kumar S, et al. *Lancet Oncol*. 2016;17:e328-e346.

Rapid and Durable Responses[a]

- The median time to response was 0.7 months and median DOR was 8 months (95% CI, 4 to NE)
- Ten patients improved upon their first response, longest DOR was 18 months, and 2 patients had more than 1 year on treatment



[a] Responses were assessed by the investigator per the IMWG 2016 response criteria.[1] Only changes to improved response or PD are shown per IMWG.
MR, minor response; NE, not estimable; sCR, stringent complete response; VGPR, very good partial response.

1. Kumar S, et al. *Lancet Oncol*. 2016;17:e328-e346.

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

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