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

P898

Binod Dhakal,[1] Malin Hultcrantz,[2] Susan Bal,[3] Hun Chuah,[4] Jonathan L. Kaufman,[5] Dickran Kazandjian,[6] Nitya Nathwani,[7] Gordon Royle,[8] Douglas W. Sborov,[9] Christopher P. Venner,[10] Huan Cheng,[11] Adam Idoine,[11] Amit Agarwal,[11] Hang Quach[12]

[1]Medical College of Wisconsin, Milwaukee, WI, USA; [2]Memorial Sloan Kettering Cancer Centre, New York, NY, USA; [3]University of Alabama at Birmingham, Birmingham, AL, USA; [4]Royal Perth Hospital, Perth, WA, Australia; [5]Emory University, Atlanta, GA, USA; [6]University of Miami, Miami, FL, USA; [7]City of Hope, Duarte, CA, USA; [8]Middlemore Hospital, Auckland, New Zealand; [9]Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT, USA; [10]BC Cancer Centre, Vancouver, BC, Canada; [11]BeiGene USA, Inc, San Mateo, CA, USA; [12]St Vincent's Health Australia, University of Melbourne, Melbourne, VIC, Australia

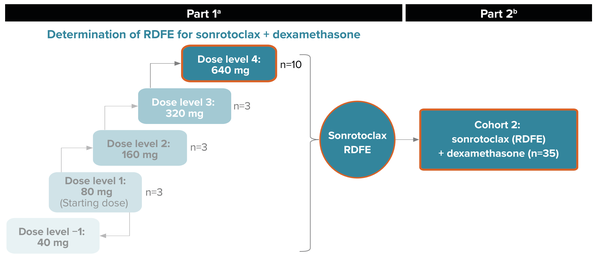
INTRODUCTION

- 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 inhibitor[2]
- 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 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 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 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.

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 immunomodulary 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	
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)
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	
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	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, proteosome 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] 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.

- 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)	
	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).

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)

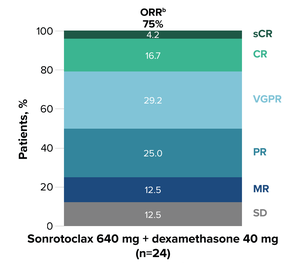
[a] Preferred terms in system organ class *infections and infestations*.

- 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

CONCLUSIONS

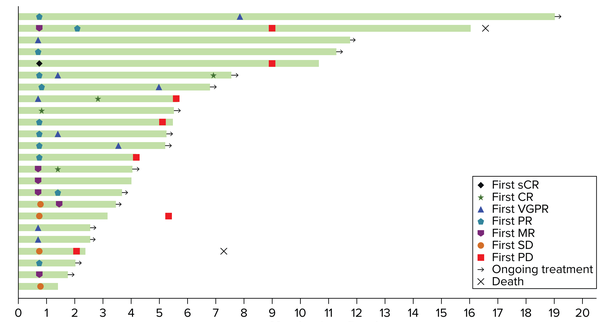
- These results indicate that sonrotoclax plus dexamethasone is well tolerated in a heavily pretreated population
  - No DLTs were observed during dose-escalation and low rates of hematologic toxicities and infections continued to be observed during dose-expansion
- Sonrotoclax + dexamethasone combination 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

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.

REFERENCES

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

DISCLOSURES

BD: Consultancy, Honoraria, and Speakers Bureaus: Janssen, Karyopharm, GSK, Arcellx, Sanofi, Genentech, Pfizer. **MH:** Consultancy: Bristol Myers Squibb, Johnson & Johnson; Research Funding: GSK, AbbVie, BeiGene, Daiichi Sankyo. **SB:** Consultancy/Honoraria: AbbVie, Adaptive Biotechnologies, Bristol Myers Squibb, Janssen, and MJH Lifesciences; Research Funding: Bristol Myers Squibb, BeiGene, Fate Therapeutics, AbbVie, Amyloid Foundation. **HC:** Consultancy: AbbVie; Research Funding: Thermo Fisher Scientific; Travel, accommodations, expenses: AbbVie. **JLK:** Consultancy: Bristol Myers Squibb, Celgene, AbbVie, Incyte, Sanofi, Sebia; Research Funding: Celgene, Janssen, Sutro Biopharma, Amgen, AbbVie/Genentech, Bristol Myers Squibb, Novartis, GSK, Heidelberg Pharma, Takeda; Travel, accommodations, expenses: Sanofi, Bristol Myers Squibb. **DK:** Current Employment: Karyopharm Therapeutics, MJH Life Sciences, Arcellx; Consultancy and Honoraria: AlphaSights, Aperture Medical Technology, LLC, Aptitude Health, Arcellx, Bridger Consulting Group, Bristol Myers Squibb, Curio Science, Sanofi; Ended employment in the past 24 months: MMRF, Plexus Communications. **DWS:** Consultancy and/or Research Funding: GSK, Janssen, Sanofi, AbbVie, BMS, Pfizer, Bioline, Arcellx, Gilead, Amgen, Cantex, RocheX. **CPV:** Honoraria: Janssen, Sanofi, Pfizer, Amgen, Forus. **HC, AA, AI:** Employment: BeiGene and holds stock with BeiGene. **HQ:** Consultancy, Honoraria, and/or Research Funding: GSK, BMS, Amgen, Antengene, Sanofi, Karyopharm, AbbVie, Roche. **NN, GR:** No disclosures.

ACKNOWLEDGMENTS

The authors thank the investigators, site support staff, and especially the patients for participating in this study. The authors would also like to thank Xin Wang (BeiGene) for assistance in development of this presentation and Rocco Crescenzo (BeiGene) for contributions to the study and development of the abstract. This study was sponsored by BeiGene Ltd. Medical writing support was provided by Angela R. Eder, PhD, of Nucleus Global, an Inizio company, and supported by BeiGene.

Presented at the EHA2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain