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Sonrotoclax (BGB-11417) Monotherapy in Patients With Relapsed/ Refractory Marginal Zone Lymphoma: An Ongoing Phase 1 Study

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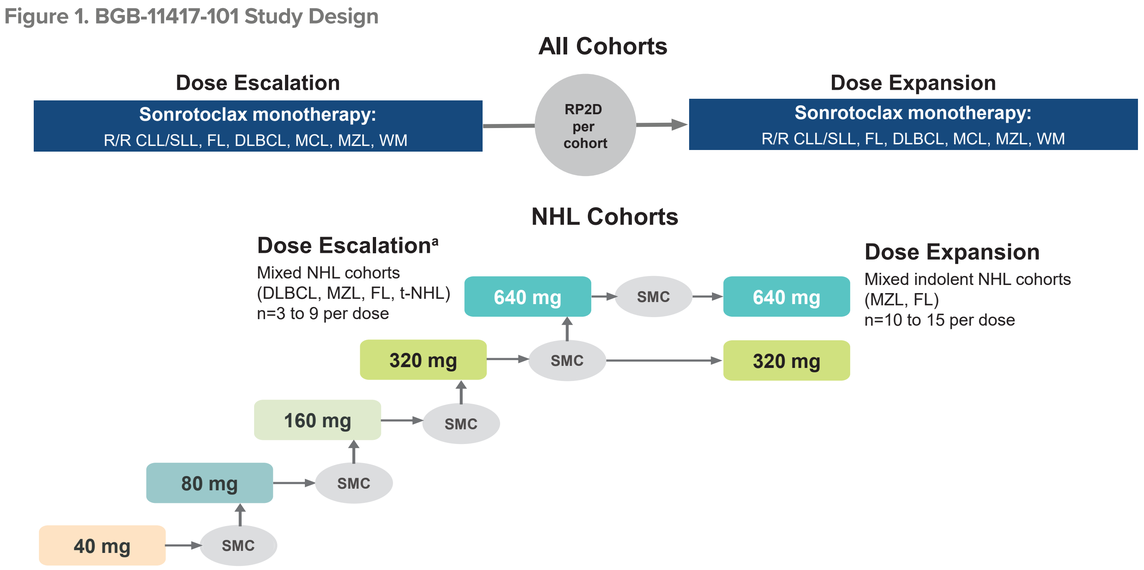
INTRODUCTION

- Marginal zone lymphomas (MZLs) are the third most common type of B-cell non-Hodgkin lymphoma (NHL), after diffuse large B-cell lymphoma and follicular lymphoma
- Approximately 20% of patients with MZL experience relapse or disease progression within 2 years and have a median overall survival of only 3-5 years[1]
- Though not approved for MZL, the B-cell lymphoma 2 (BCL2) inhibitor venetoclax has demonstrated activity in a small number of patients with relapsed/refractory (R/R) MZL[2]
- Sonrotoclax is a BH3 mimetic which binds and inhibits BCL2 with higher potency and a shorter half life than venetoclax based on preclinical data[3]

METHODS

- BGB-11417-101 (NCT04277637) is a first-in-human, phase 1, multicenter study in patients with B-cell malignancies that is evaluating 3 different treatment options (**Figure 1**)
- Key study objectives include determining the safety and tolerability of sonrotoclax monotherapy, including the ramp up dosing, and defining the maximum tolerated dose/maximum assessed dose and the RP2D of sonrotoclax monotherapy for the selected B-cell malignancy dose finding cohorts
- Sonrotoclax was administered orally
- Responses were assessed using Lugano 2014 criteria[4]
- As prophylaxis for tumor lysis syndrome (TLS), patients with NHL had a 3-day ramp-up to reach the target dose and received hydration and antihyperuricemics; patients with NHL and circulating cells used a 6-day ramp-up

Figure 1. BGB-11417-101 Study Design

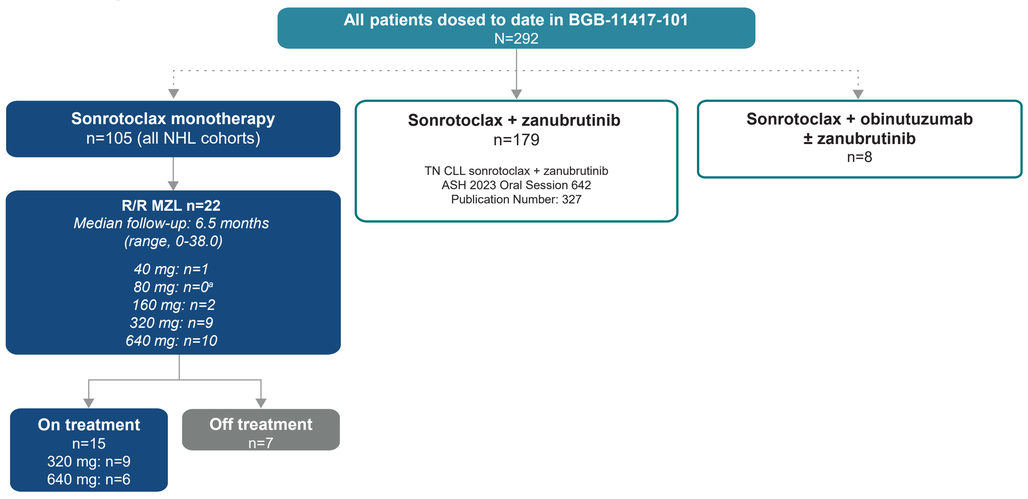


[a] The SMC reviewed dose-level cohort data before dose escalation.
SMC, safety monitoring committee; t-NHL, transformed non-Hodgkin lymphoma.

RESULTS

- Here, data from 22 patients with R/R MZL treated with sonrotoclax monotherapy are presented
- Dose escalation in a mixed NHL cohort reached the highest dose of 640 mg with no MTD reached; only 1 dose-limiting toxicity of febrile neutropenia was noted in the 160 mg cohort
- Dose expansion started with the 640 mg dose; the 320 mg dose was later expanded to include an additional 10 patients based on efficacy signal seen in the MZL subset

Figure 2. Patient Disposition



Data cutoff date: August 15, 2023.
[a] Dose escalation was done per all comers (NHL) and no MZL subjects were enrolled at the 80 mg dose level.

Table 1. Baseline Patient Characteristics

Characteristic	640 mg (n=10)	All patients with MZL (N=22)
Age, median (range), years	72.5 (54-77)	74.5 (54-85)
Male sex, n (%)	5 (50.0)	10 (45.5)
ECOG PS		
0	6 (60.0)	12 (54.5)
1	2 (20.0)	8 (36.4)
2	2 (20.0)	2 (9.1)
Prior therapy		
No. of prior lines of therapy, median (range)	1.5 (1-3)	2 (1-6)
Time from last systemic therapy to first dose, median (range), months	11.5 (0.2-158.1)	11.5 (0.1-158.1)
Prior BTKi, n	4 (40.0)	10 (45.5)
BTKi as last prior therapy, n	3 (30.0)	8 (36.4)
Prior BTKi duration, median (range), months	17.8 (7.9-41.8)	22.8 (12.1-42.6)
Prior rituximab use, n (%)	10 (100)	22 (100)
Prior CHOP-like regimens, n (%)	5 (50.0)	16 (72.7)
Prior bendamustine, n (%)	6 (60.0)	10 (45.5)

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone.

Table 2. Adverse Event Summary

Patients, n (%)	640 mg (n=10)	All patients with MZL (N=22)
Any AEs	10 (100)	21 (95.5)
Grade ≥3	6 (60.0)	10 (45.5)
Serious AEs	5 (50.0)	8 (36.4)
Leading to death[a]	1 (10.0)	1 (4.5)
Leading to discontinuation of sonrotoclax	1 (10.0)	1 (4.5)
Leading to dose interruption of sonrotoclax	2 (20.0)	3 (13.6)
Leading to dose reduction of sonrotoclax	0	0

[a] Patient with lymphopenia and low immunoglobulin levels at baseline developed PML and died 8 months after starting treatment with 640 mg sonrotoclax. Assessed as unrelated to sonrotoclax per investigator. Prior treatments included rituximab, bendamustine and a phosphoinositide-3-kinase inhibitor.
PML, progressive multifocal leukoencephalopathy.

CONCLUSIONS

- Sonrotoclax doses as high as 640 mg QD are well tolerated; 640 mg was the highest dose assessed, and the MTD was not reached
- Sonrotoclax demonstrated promising single-agent activity in patients with R/R MZL
  - An ORR of 70% (including a CR rate of 40%) was observed at the dose of 640 mg; efficacy data from the 320 mg expansion dose level is forthcoming
  - Responses at 640 mg are durable with 6 of 10 patients continuing on treatment at a median follow-up of 8.7 months
- No clinical TLS was observed. Only 2 transitory laboratory TLS were seen in patients with high baseline levels of circulating cells, including a patient with a very large spleen that significantly decreased in size with first dose. Lab TLS cases resolved quickly without need for dose modification

- **TLS:**
  - No clinical TLS
  - Two patients experienced laboratory TLS
    - In 2 cases with high baseline absolute lymphocyte count (43 x 10^9/L and 348 x 10^9/L), patients experienced transitory increase in phosphate and urate levels that resolved within 24 hours without dose modification; patients also experienced significant reduction in spleen size
- **Neutropenia:**
  - G-CSF used in 2 patients: 160 mg (grade 3; resolved after 2 days) and 640 mg (grade 3; same day recovery)
  - The patient in the 160 mg group experienced sonrotoclax-related grade 3 febrile neutropenia which resolved after 2 days without dose modification during ramp-up Day 1 on 40 mg of sonrotoclax

Figure 3. TEAEs in ≥3 Total Patients: 640 mg vs All Other Doses

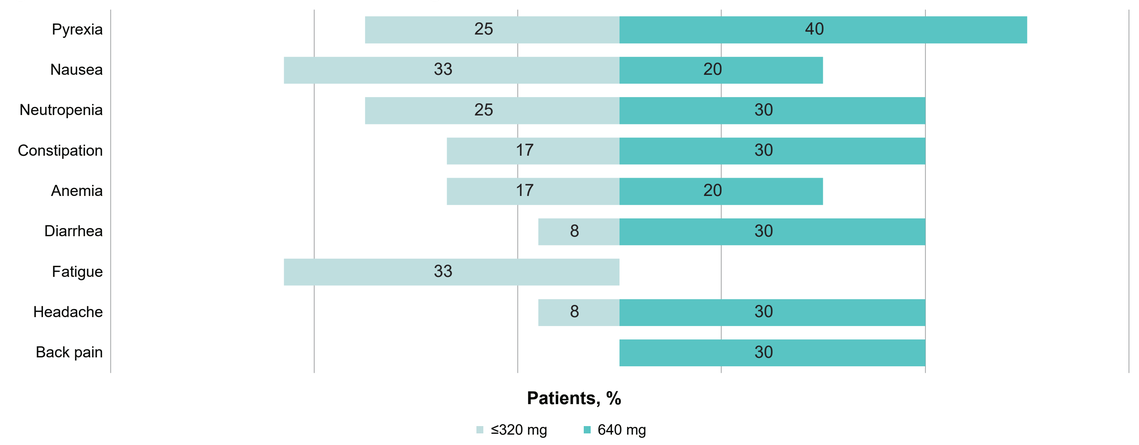
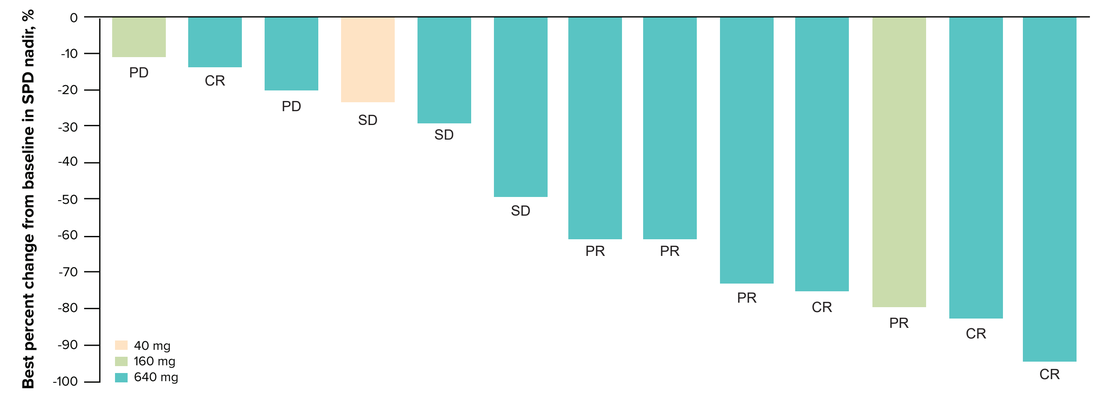


Table 3. Response Rates[a]

	40 mg (n=1)	160 mg (n=2)	320 mg[b] (n=9)	640 mg (n=10)	All patients with MZL (N=22)
Median follow-up (range), months	38.0 (N/A)	27.7 (27.4-28.1)	1.22 (0-3.4)	8.67 (3.5-15.4)	6.5 (0-38.0)
Efficacy-evaluable patients, n	1	2	–	10	13
ORR, n (%)	0	1 (50)	–	7 (70)	8 (62)
CR, n (%)	0	0	–	4 (40)	4 (31)
PR, n (%)	0	1 (50)	–	3 (30)	4 (31)
SD, n (%)	1 (100)	0	–	2 (20)	3 (23)
PD, n (%)	0	1 (50)	–	1 (10)	2 (15)

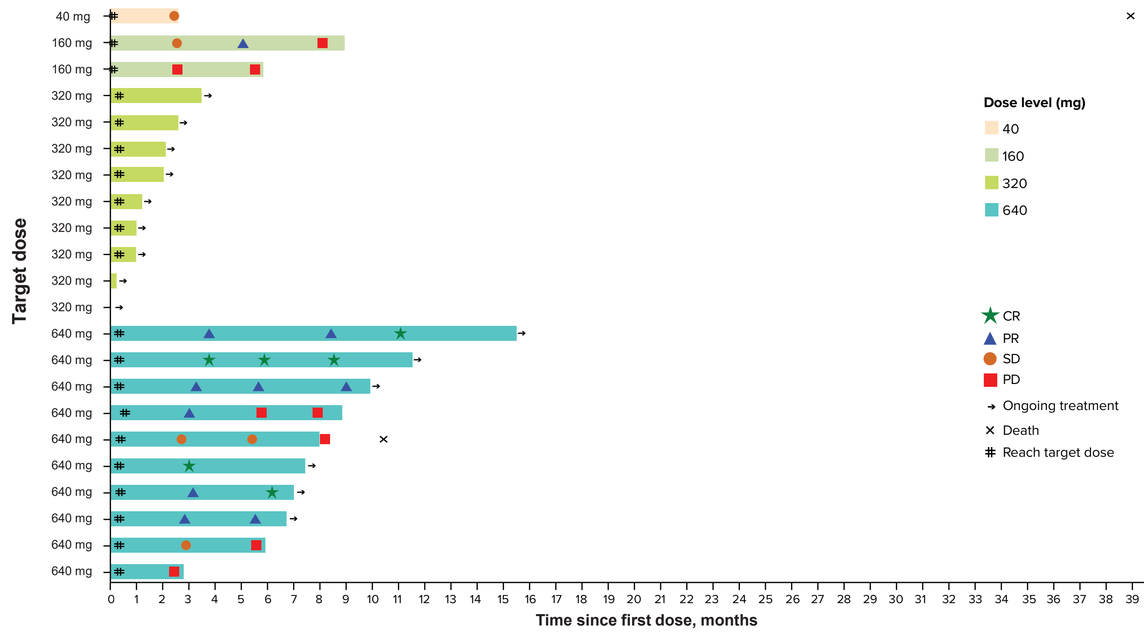
[a] PET/CT-based response assessed by investigator; CT imaging alone for subsequent response assessments for patients with non-FDG-avid disease at baseline.
[b] No patients in the 320 mg group were efficacy evaluable due to short follow-up.

Figure 4. SPD Change From Baseline in Patients With Measurable Disease



SPD, sum of perpendicular diameter.

Figure 5. Treatment Duration and Investigator-Assessed Responses



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DISCLOSURES

JK: Honoraria: BeiGene; Speakers bureau: Beigene; Travel, Accommodations, Expenses: Menarini Stemline, Beigene; **AT:** Consultancy: AbbVie, Beigene, Janssen, AstraZeneca, Lilly; Speakers bureau: Beigene, Janssen, AbbVie. **CC:** Consultancy: Roche, Janssen, MSD, Gilead, AstraZeneca, Lilly, TG therapeutics, Beigene, Novartis, BMS; Research funding: BMS, Roche, Abbvie; Honoraria; Roche, Janssen, MSD, Gilead, AstraZeneca, Lilly, TG therapeutics, Beigene, Novartis, BMS; Membership on an entity's Board of Directors or Advisory Committees: Roche, Janssen, MSD, Gilead, AstraZeneca, Lilly, TG therapeutics, Beigene, Novartis, BMS; **SO:** Research Funding: Abbvie, AstraZeneca, Beigene, Gilead, Janssen, Merck, Novartis, Pharmacyclics, Roche, Takeda; Honoraria: Abbvie, AstraZeneca, Beigene, Gilead, Janssen, Merck, Novartis, Pharmacyclics, Roche, Takeda; Membership on an entity's Board of Directors or advisory committee: Abbvie, Antengene, AstraZeneca, Beigene, CSL Behring, Gilead, Janssen, Merck, Novartis, Takeda. **EV:** Research Funding: Janssen Cilag; **LM:** Research Funding: Instituto de Investigación Carlos III, Ministerio de Ciencia e Investigación, Spain; **JH, YF, DS:** Employment: BeiGene. **MA:** Research Funding: National Health and Medical Research Council; Honoraria: Roche, Novartis, Takeda, Kite, AstraZeneca, Beigene, Abbvie, Janssen; Patents and royalties: The Walter and Eliza Hall Institute receives royalties in relation to venetoclax to which I am entitled to a share.

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