Monotherapy With Second-Generation BCL2 Inhibitor Sonrotoclax (BGB-11417) is Well Tolerated with High Response Rates in Patients with Relapsed/Refractory Marginal Zone Lymphoma: Data from an Ongoing Phase 1 Study

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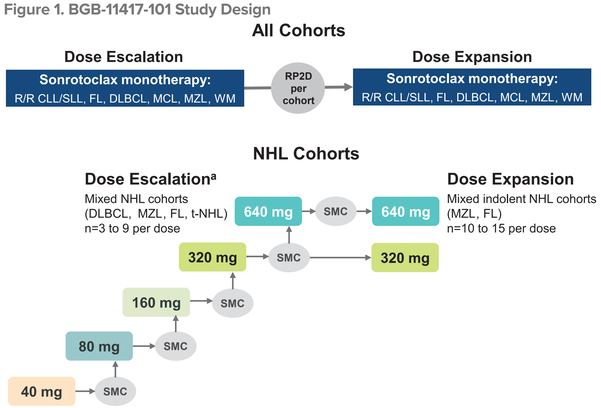
INTRODUCTION

- 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

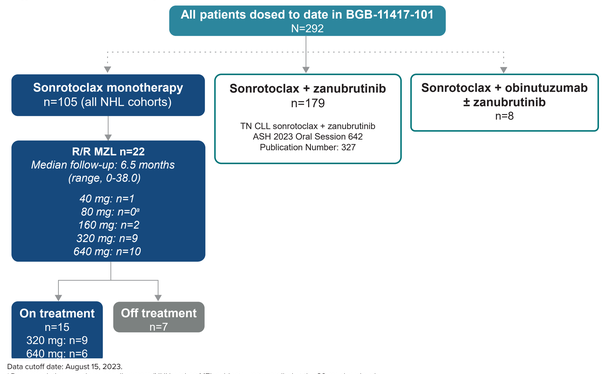
- BGB-11417-101 (NCT04277637) is a first-in-human, phase 1, multicenter study in patients with B-cell malignancies that is evaluating 3 different treatment options (**Figure 1**)
- Key study objectives include determining the safety and tolerability of sonrotoclax monotherapy, including the ramp up dosing, 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.

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.

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
- **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

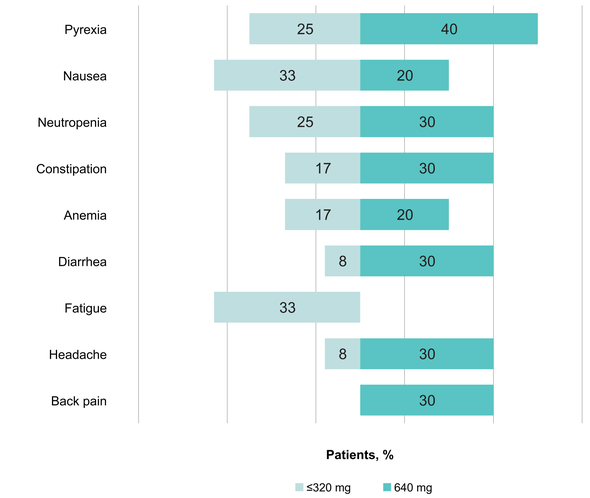


Table 3. Response Rates[a]

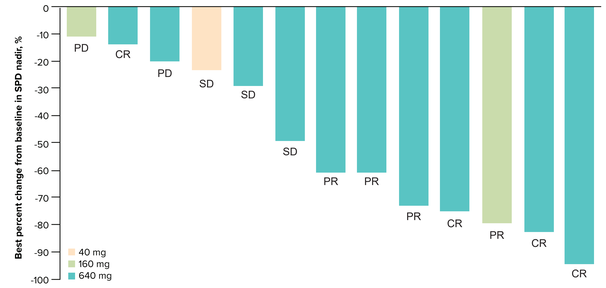
	40 mg (n=1)	160 mg (n=2)	320 mg[b] (n=9)	640 mg (n=10)	All patients with MZL (N=22)
Median follow-up (range), months	38.0 (N/A)	27.7 (27.4-28.1)	1.22 (0-3.4)	8.67 (3.5-15.4)	6.5 (0-38.0)
Efficacy-evaluable patients, n	1	2	–	10	13
ORR, n (%)	0	1 (50)	–	7 (70)	8 (62)
CR, n (%)	0	0	–	4 (40)	4 (31)
PR, n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

CONCLUSIONS

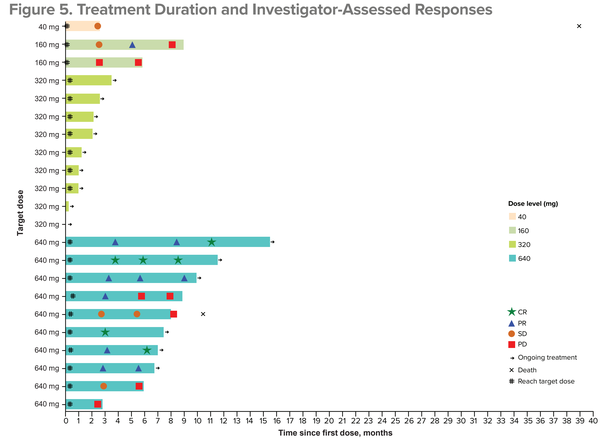
- Sonrotoclax doses as high as 640 mg QD are well tolerated; 640 mg was the highest dose assessed, and the MTD was not reached
- Sonrotoclax demonstrated promising single-agent activity in patients with R/R MZL
  - An ORR of 70% (including a CR rate of 40%) was observed at the dose of 640 mg; efficacy 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

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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