Combination Treatment With Novel BCL2 Inhibitor Sonrotoclax (BGB-11417) and Zanubrutinib Induces High Rate of Complete Remission for Patients With Relapsed/Refractory Mantle Cell Lymphoma

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Constantine S. Tam,[1] Stephen Opat,[2] Marc Hoffmann,[3] Jacob Soumerai,[4] Masa Lasica,[5] Narendranath Epperla,[6] Jing-Zhou Hou,[7] Ramón García-Sanz,[8] Johannes Schetelig,[9] Robert Weinkove,[10,11] Yiqian Fang,[12] Sheel Patel,[13] Wei Ding,[13] Haiyi Guo,[14] Raul Cordoba[15]

[1]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [2]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [3]University of Kansas Cancer Center, Fairway, KS, USA; [4]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; [5]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [6]The James Cancer Hospital and Solove Research Institute at Ohio State University, Columbus, OH, USA; [7]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [8]Hospital Universitario de Salamanca, Salamanca, Spain; [9]Universitätsklinikum Carl Gustav Carus, TU Dresden, Dresden, Germany; [10]Te Rerenga Ora Blood and Cancer Centre, Te Whatu Ora Health New Zealand Capital Coast & Hutt Valley, Wellington, New Zealand; [11]Cancer Immunotherapy Programme, Malaghan Institute of Medical Research, Wellington, New Zealand; [12]BeiGene (Beijing) Co, Ltd, Beijing, China; [13]BeiGene USA, Inc, San Mateo, CA, USA; [14]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [15]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

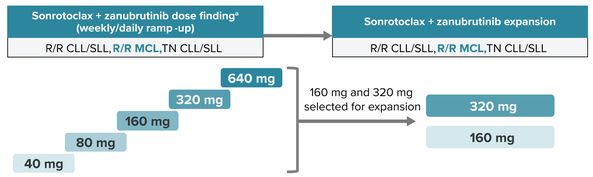
INTRODUCTION

- Mantle cell lymphoma (MCL) is an incurable and commonly aggressive disease[1]
- Despite high response rates with frontline therapy, many patients experience relapsed/refractory (R/R) disease and require novel therapies to improve clinical outcomes[1]
- Combining BCL2 and BTK inhibition with venetoclax + ibrutinib has shown efficacy in patients with R/R MCL; however, this treatment was associated with high rates of toxicity and a need for a safer and potent combination still remains[2]
- Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax with a shorter half-life and no accumulation[3]
- Zanubrutinib is a next-generation BTK inhibitor approved in multiple (5) indications, including R/R MCL[4]
- Zanubrutinib was designed to provide complete and sustained BTK occupancy for efficacy across multiple B-cell malignancies with fewer off-target AEs compared with other BTK inhibitors[5,6]
- Here, safety and efficacy data are presented for patients with R/R MCL treated with sonrotoclax + zanubrutinib in the ongoing BGB-11417-101 study

METHODS

- BGB-11417-101 (NCT04277637) is a first-in-human, phase 1, open-label, multicenter, dose-escalation and -expansion study in patients with B-cell malignancies (**Figure 1**)
- Eligible patients had R/R MCL (disease that relapsed after or was refractory to ≥1 prior systemic therapy) and required treatment in the opinion of the investigator
- The primary objectives of the study were to assess safety/tolerability, evaluate the ramp-up dosing schedule, define the MTD, and determine the RP2D of sonrotoclax in combination with zanubrutinib in patients with B-cell malignancies including R/R MCL
- Responses were assessed per Lugano 2014 criteria[7]
- Zanubrutinib was administered orally (320 mg QD or 160 mg BID) 8 to 12 weeks prior to sonrotoclax treatment
- Sonrotoclax was administered orally, QD, following a daily or weekly ramp-up schedule to mitigate potential risk of TLS

Figure 1. BGB-11417-101 Study Design

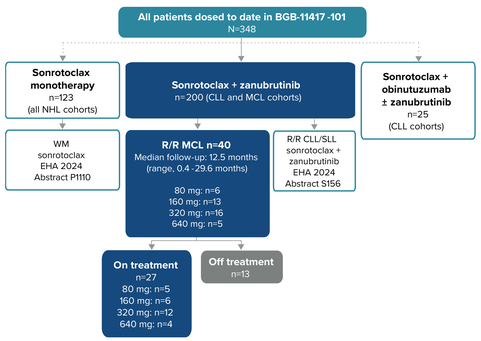


[a] The safety monitoring committee reviewed dose-level cohort data before dose escalation.

RESULTS

- As of February 4, 2024, a total of 40 patients with R/R MCL had received sonrotoclax + zanubrutinib and 27 remained on study treatment (**Figure 2**)
  - Ten patients (25%) discontinued sonrotoclax + zanubrutinib due to PD (n=5), patient withdrawal (n=1), and AEs (n=4), only 1 of which was treatment related (pneumonia)
  - Four patients discontinued zanubrutinib, 3 (160 mg, n=2; 320 mg, n=1) due to PD during lead-in; one patient discontinued from zanubrutinib only due to diarrhea
- The sonrotoclax 160- and 320-mg dose levels were chosen for expansion cohorts

Figure 2. Patient Disposition



- Across dose cohorts, the median age was 68.5 years, and the median number of prior treatments was 1 (**Table 1**)
  - Three patients received prior BTK inhibitor therapy and all had it as their last prior therapy; 2 patients discontinued due to toxicity

Table 1. Baseline Patient Characteristics

Characteristic	Sonro 80 mg + zanu (n=6)	Sonro 160 mg + zanu (n=13)	Sonro 320 mg + zanu (n=16)	Sonro 640 mg + zanu (n=5)	All (N=40)
Study follow-up, median (range), months	27.5 (3.9-29.6)	16.0 (1.0-25.7)	12.5 (0.4-18.8)	3.5 (2.2-8.6)	12.5 (0.4-29.6)
Age, median (range), years	60.0 (46-84)	69.0 (45-81)	69.0 (45-85)	71.0 (68-80)	68.5 (45-85)
Male sex, n (%)	5 (83)	11 (85)	7 (44)	3 (60)	26 (65)
ECOG PS					
0	3 (50)	8 (62)	4 (25)	3 (60)	18 (45)
1	2 (33)	5 (38)	12 (75)	2 (40)	21 (53)
Tumor bulk, n (%)					
LDi <10 and ≥5 cm	3 (50)	4 (31)	3 (19)	2 (40)	12 (30)
LDi ≥10 cm	1 (17)	2 (15)	3 (19)	0	6 (15)
Ki67 proliferation index, n (%)					
<30%	3 (50)	4 (31)	6 (38)	0	13 (33)
≥30%	2 (33)	2 (15)	4 (25)	2 (40)	10 (25)
Prior therapy					
No. of lines of prior systemic therapy, median (range)	1 (1-1)	1 (1-4)	1 (1-3)	1 (1-1)	1 (1-4)
No. of lines of prior systemic therapy, n (%)					
1	6 (100)	10 (77)	11 (69)	5 (100)	32 (80)
2	0	2 (15)	1 (6)	0	3 (8)
≥3	0	1 (8)	4 (25)	0	5 (13)
Prior BTK inhibitor, n (%)	0	0	3 (19)	0	3 (8)
BTK inhibitor as last prior therapy, n (%)	0	0	3 (19)	0	3 (8)
Prior BTK inhibitor duration, median (range), months	–	–	4.8 (0.3-25.0)	–	4.8 (0.3-25.0)
Prior cellular therapies (transplant or CAR-T), n (%)	2 (33)	3 (23)	6 (38)	0	11 (28)

CAR-T, chimeric antigen receptor T-cell; LDi, longest diameter; PS, performance status; sonro, sonrotoclax; zanu, zanubrutinib.

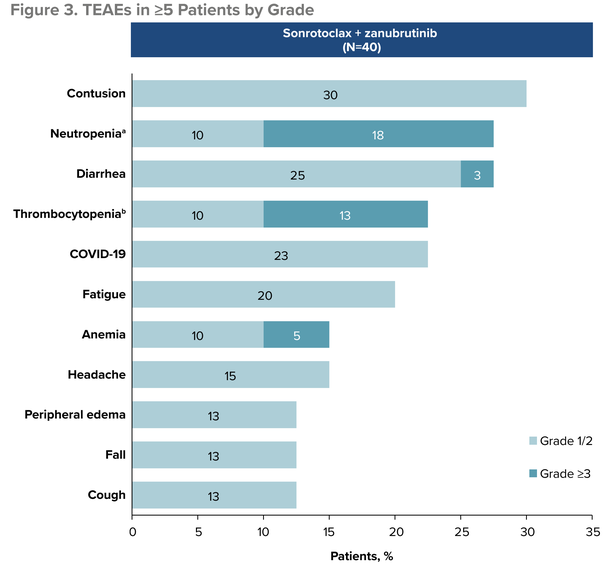
- An overall summary of TEAEs in patients with R/R MCL is shown in **Table 2**
- Toxicity was generally the same among all tested dose levels with no new safety signals identified; sonrotoclax 160-mg and 320-mg dose levels were chosen for expansion cohorts
- The most common any-grade TEAEs were contusion (30%), neutropenia (28%), and diarrhea (28%) (**Figure 3**)
- The most common grade ≥3 TEAE was neutropenia (18%)
  - Neutropenia was manageable, with no dose reductions and only 1 dose hold due to a concurrent COVID-19 infection; 6 patients used G-CSF with a median treatment duration of 3.5 days
- No laboratory or clinical TLS was seen regardless of target dose
- Dose escalation was completed with no MTD reached

Table 2. TEAE Summary

Patients, n (%)	Sonro 80 mg + zanu (n=6)	Sonro 160 mg + zanu (n=13)	Sonro 320 mg + zanu (n=16)	Sonro 640 mg + zanu (n=5)	All (N=40)
Any TEAE	4 (67)	13 (100)	15 (94)	5 (100)	37 (93)
Grade ≥3	4 (67)	6 (46)	7 (44)	1 (20)	18 (45)
Serious TEAEs	3 (50)	4 (31)	2 (13)	0	9 (23)
Leading to death	1 (17)	1 (8)	1 (6)	0	3 (8)[a]
Leading to zanu discontinuation	1 (17)	3 (23)	2 (13)	0	6 (15)[b]
Leading to zanu dose reduction	1 (17)	1 (8)	0	0	2 (5)[c]
Treated with sonro, n (%)	6 (100)	11 (85)	13 (81)	5 (100)	35 (88)
Leading to sonro discontinuation	0	3 (23)	2 (13)	0	5 (13)[d]
Leading to sonro dose reduction	0	0	0	0	0
Leading to death	0	1 (8)	0	0	1 (3)[e]

[a] Pleural effusion (due to PD), abdominal sepsis, and pneumonia. [b] Lymph node pain (due to PD), diarrhea, MDS, abdominal sepsis, pneumonia, and bruising. [c] COVID-19 (temporary). [d] Diarrhea, abdominal sepsis, MDS, pneumonia and lymph node pain secondary to PD. [e] Pneumonia. MDS, myelodysplastic syndrome; sonro, sonrotoclax; zanu, zanubrutinib.

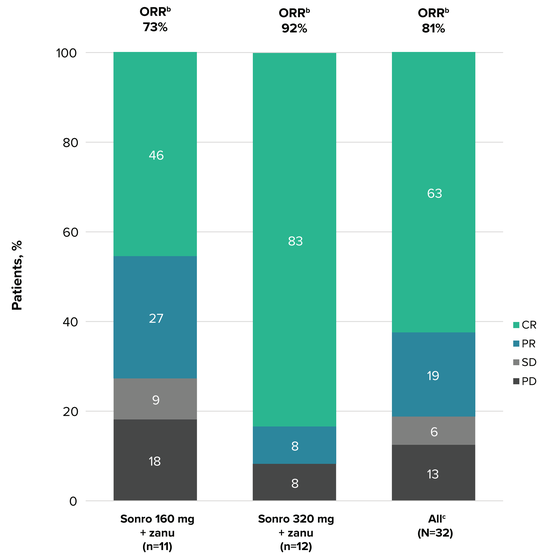
Figure 3. TEAEs in ≥5 Patients by Grade



[a] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [b] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

- With a median study follow-up of 12.5 months, ORRs were 73% and 92% in the 160- and 320-mg cohorts, respectively, and CR rates were 46% and 83%, respectively (**Figure 4**)
- Of 3 response-evaluable patients with prior BTK inhibitor treatment, 2 responded: 1 achieved PR and 1 achieved CR (**Figure 5**)

Figure 4. Response Rates[a]

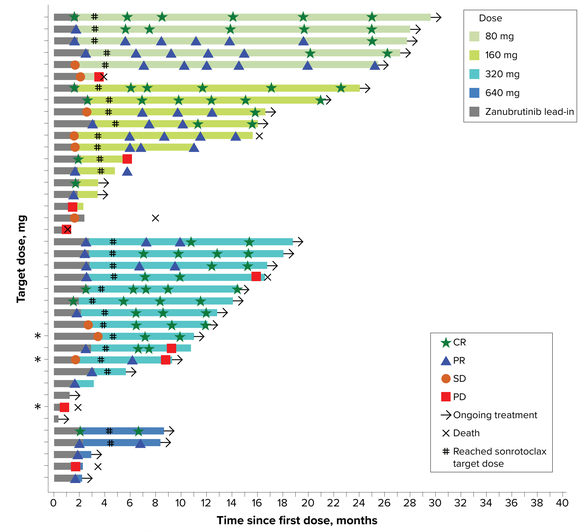


[a] Responses were assessed per Lugano 2014 criteria.[7] [b] ORR was defined as PR or better. [c] For all dose levels. [d] For all patients as treated (N=40). sonro, sonrotoclax; zanu, zanubrutinib.

CONCLUSIONS

- Sonrotoclax in combination with zanubrutinib was generally well tolerated
  - The maximum tolerated dose was not reached up to the highest assessed dose of 640 mg
  - No atrial fibrillation or TLS (laboratory or clinical) events were observed
- Sonrotoclax + zanubrutinib combination therapy demonstrated deep responses in patients with R/R MCL, including an ORR of 92% and CR rate of 83% in the 320-mg cohort
- The 320-mg dose was selected as RP2D for development in future pivotal studies

Figure 5. Treatment Duration and Investigator-Assessed Responses[a]



[*] Patient had prior treatment with BTK inhibitor.
[a] Gray bar indicates duration of zanubrutinib lead-in.

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DISCLOSURES

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