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A Phase 1 Study With the Novel B-Cell Lymphoma 2 (Bcl-2) Inhibitor BGB-11417 as Monotherapy or in Combination With Zanubrutinib in Patients With CLL/SLL: Preliminary Data

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12-December-2022 (4:30PM – 6:00PM)
642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Drugs in Development and COVID-19

INTRODUCTION

- Bcl-2 inhibition is an established mechanism for treating B-cell malignancies such as CLL/SLL[1-2]
- BGB-11417 has shown more potent and selective Bcl-2 inhibition and better activity against BCL2 mutations than venetoclax in vitro[2]
- The combination of Bcl-2 and BTK inhibitors has proven tolerable with potent activity in CLL and MCL[3-6]
- The combination of ibrutinib with venetoclax in patients with CLL/SLL appears to be effective, but the safety profile is concerning[7] there remains a need to develop a safe and efficacious BTKi + Bcl-2i
- Zanubrutinib has demonstrated superior efficacy and safety, especially cardiovascular safety, in head-to-head studies with ibrutinib[8,9]
- Here, we present the preliminary data from a phase 1 study with BGB-11417 as monotherapy or combination therapy with zanubrutinib in patients with CLL/SLL

BGB-11417 Is More Potent and Selective Than Venetoclax

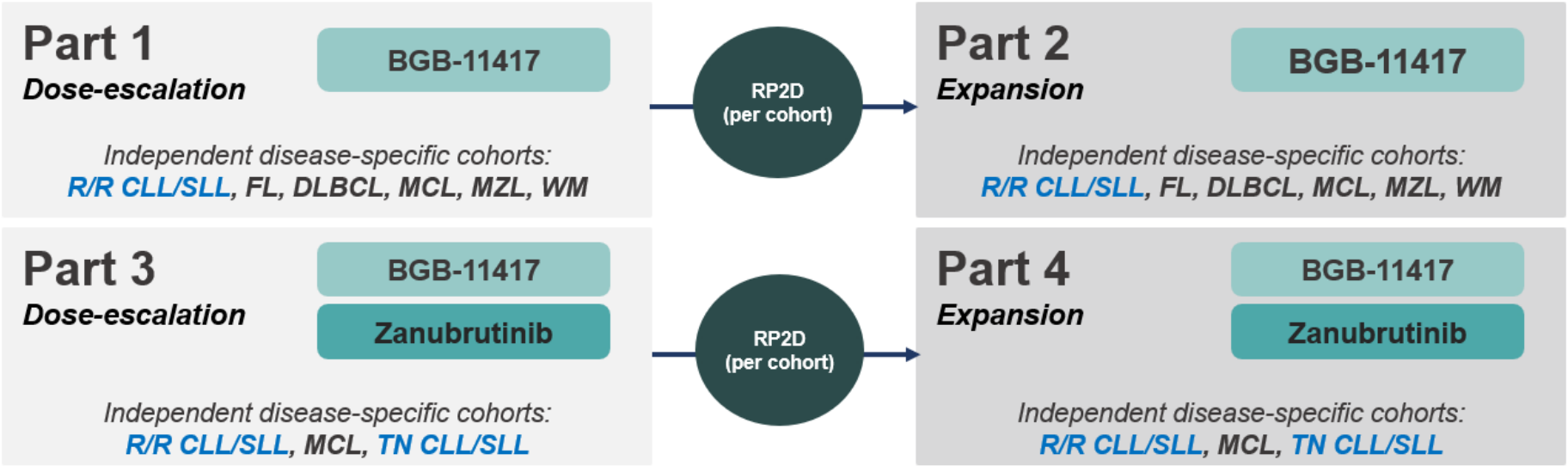
		Bcl-2 IC_{50} nM	Bcl-2 G101V IC_{50} nM
Highly potent[2,a]	BGB-11417	0.014 ± 0.0021	0.59 ± 0.08
	Venetoclax	0.20 ± 0.015	34 ± 3.8
	Ratio (BGB-11417:venetoclax)	**1:14**	**1:57**

		Bcl-2	BCLxL	BCL-w	MCL1	BCLA1
Highly selective[2,b]	BGB-11417	1	1/2000	1/129,000	<1/714,000	<1/714,000
	Venetoclax	1	1/325	1/13,700	<1/50,000	<1/50,000
	Ratio (BGB-11417:venetoclax)	-	**1:6**	**1:9**	-	-

[a]Biochemical assays based on the time-resolved fluorescence resonance energy transfer methodology. [b]Relative selectivity compared to BCL2.

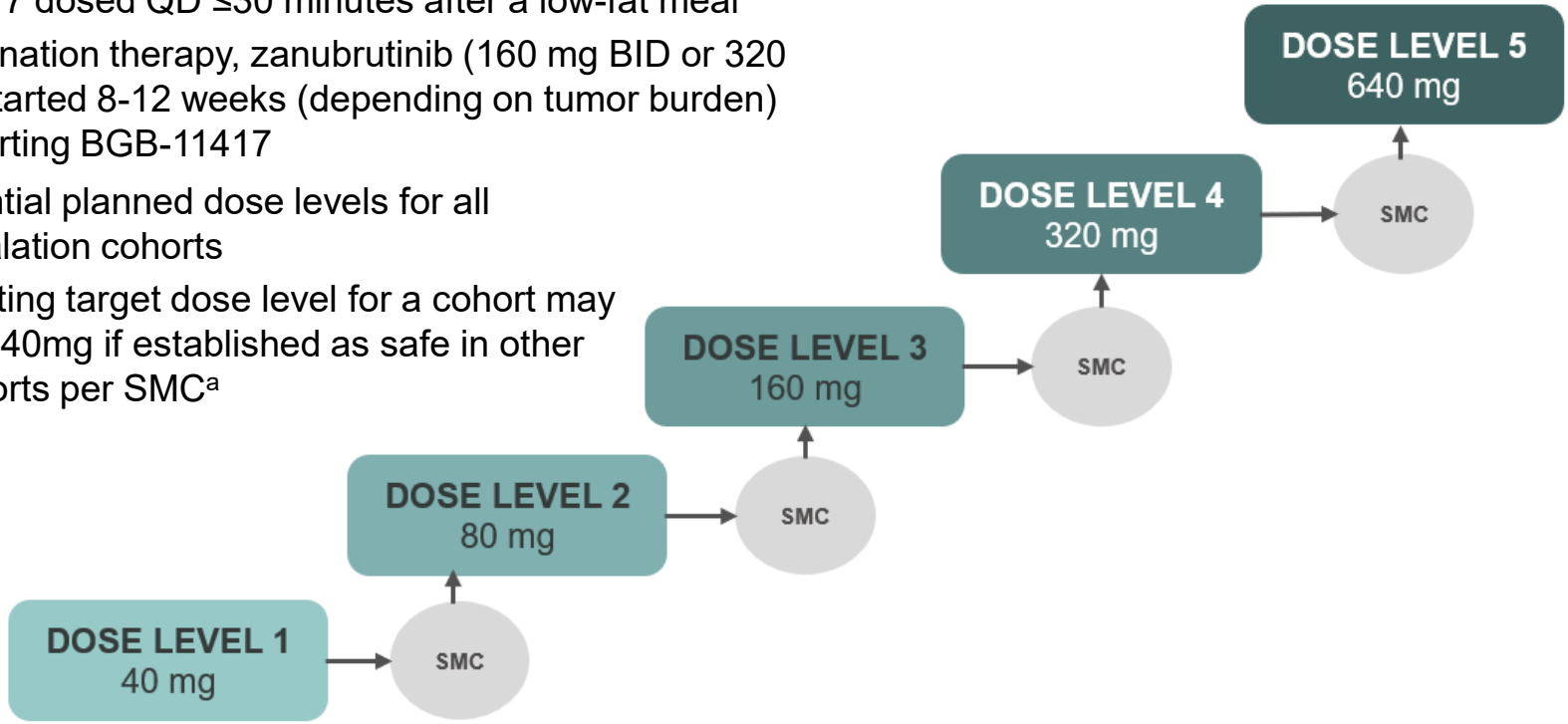
Study Design

- BGB-11417 is a first-in-human, phase 1, multicenter study in patients with B-cell malignancies (NCT04277637)
- **Blue:** CLL/SLL cohort data focused on in this presentation



Dosing and Dose Escalation

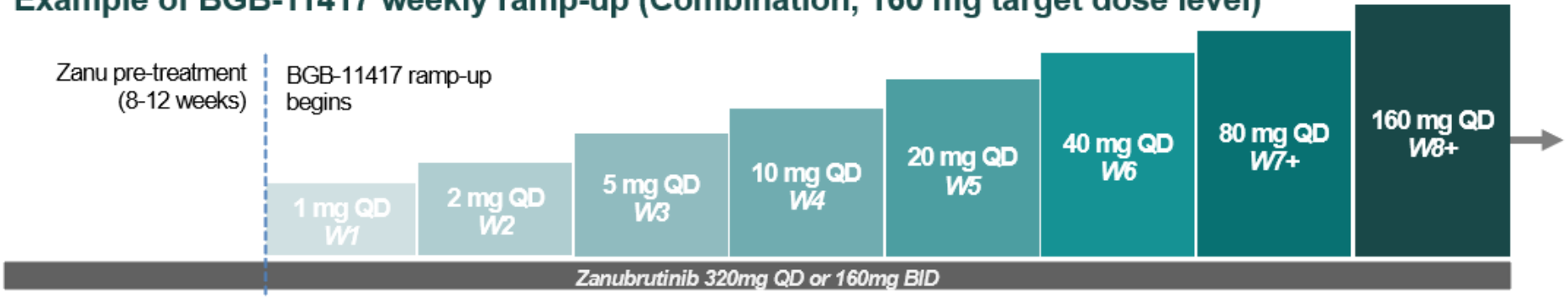
- BGB-11417 dosed QD ≤30 minutes after a low-fat meal
- For combination therapy, zanubrutinib (160 mg BID or 320 mg QD) started 8-12 weeks (depending on tumor burden) before starting BGB-11417
- Five potential planned dose levels for all dose-escalation cohorts
  - Starting target dose level for a cohort may be >40mg if established as safe in other cohorts per SMC[a]



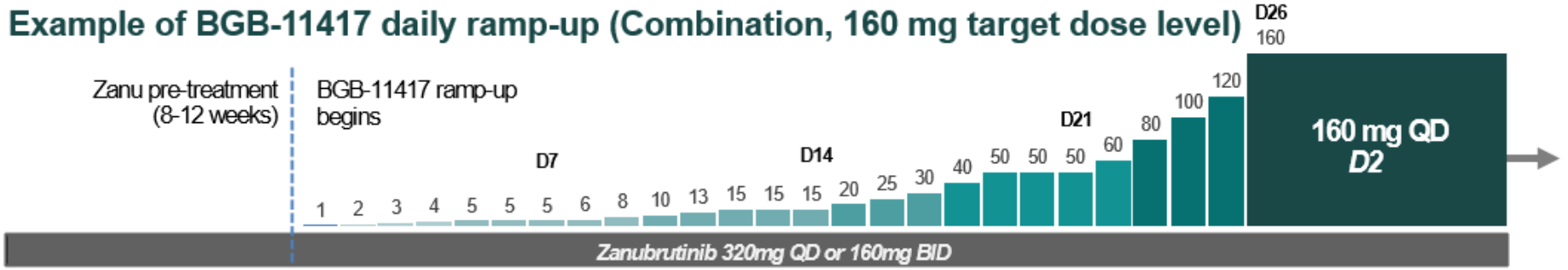
[a]Safety monitoring committee (SMC) Review of dose-level cohort data before dose escalation.

Dose Ramp-Up Schedules

Example of BGB-11417 weekly ramp-up (Combination, 160 mg target dose level)

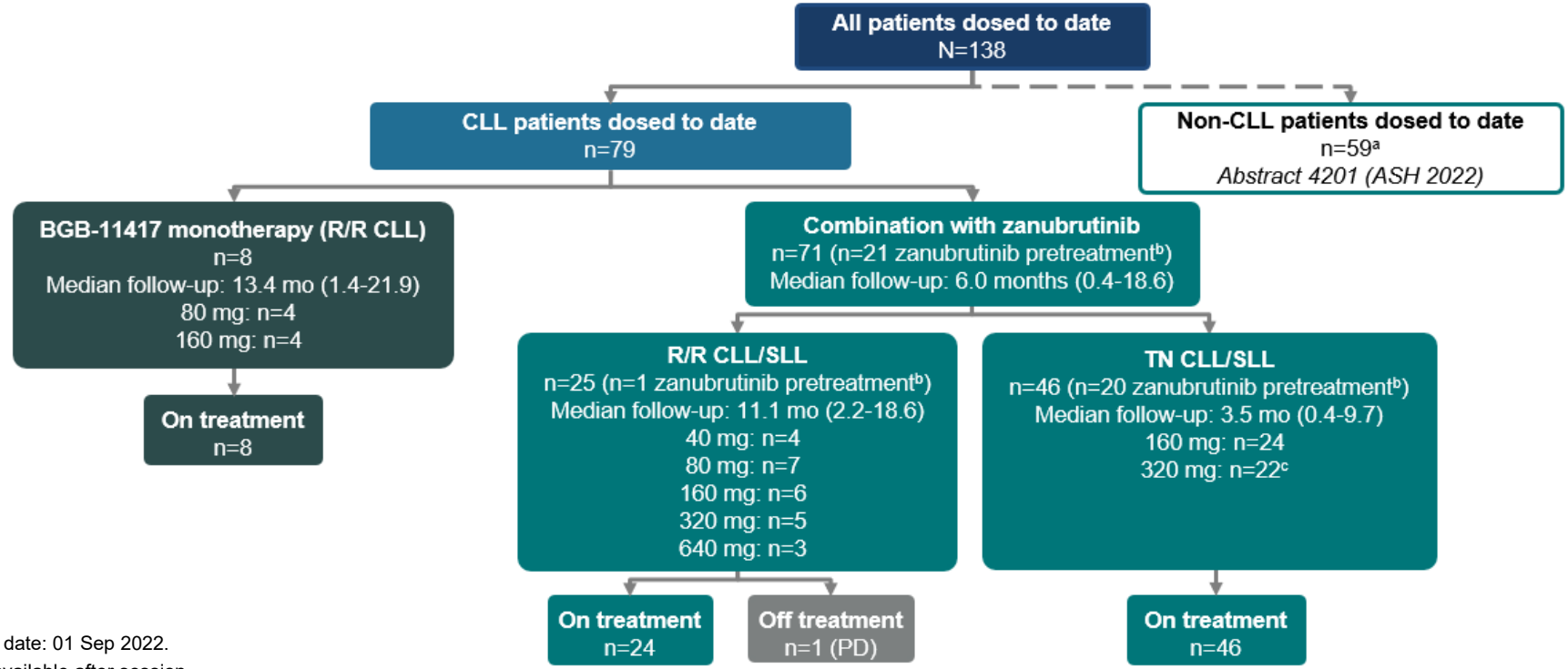


Example of BGB-11417 daily ramp-up (Combination, 160 mg target dose level)



- TLS prophylaxis included hydration, started 24-48 hrs prior to first dose. Allopurinol started 2-3 days prior to first dose and rasburicase as indicated. Hospitalization for observation was initially required for each new ramp-up dose level for first 3 dose levels but the requirement has been removed per SMC

Patient Disposition



Data cutoff date: 01 Sep 2022.

[a]Poster is available after session.

[b]Patients who are still in the zanubrutinib pretreatment phase and have not yet received BGB-11417.

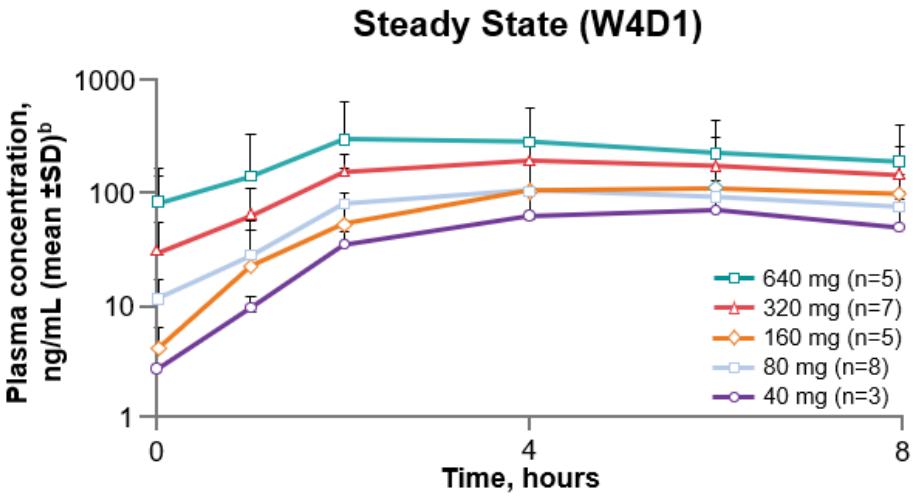
[c]All patients were assigned to a weekly ramp-up schedule except for n=4 TN patients (320mg dose level).

Patient Characteristics

Characteristic	BGB-11417 monotherapy (n=8)	BGB-11417 + zanubrutinib (n=71)	All patients (N=79)
Median age, (range), years	68.5 (55-84)	61 (35-84)	62 (35-84)
Sex, n (%)			
Male	6 (75)	56 (78.9)	62 (78.5)
Female	2 (25)	15 (21.1)	17 (21.5)
ECOG PS, n (%)			
0	3 (37.5)	49 (69)	52 (65.8)
1	5 (62.5)	21 (29.6)	26 (32.9)
2	0	1 (1.4)	1 (1.3)
Disease type, n (%)			
CLL	(100)	70 (99)	78 (99)
SLL	0	1 (1)	1 (1)
R/R, n (%)	8 (100)	25 (35.2)	33 (41.8)
No. of prior lines of therapy, median (range)	2 (1-3)	1 (1-2)	1 (1-3)
Time from end of most recent systemic therapy to first dose, median (range), months	0.4 (0.0-10.2)	57.0 (1.6-194.4)	45.4 (0.0-194.4)
TN, n (%)	0	46 (64.8)	46 (58.2)
Risk status, n (%)			
del(17p)	2 (25)	11 (15.5)	13 (16.5)
TP53^{mut}	3 (37.5)	15 (21.1)	18 (22.8)

Steady State Pharmacokinetics[a]

- **Preliminary steady state PK data from patients with NHL or CLL who received BGB-11417 monotherapy at 40 to 640 mg target doses QD for 3 weeks**
  - Dose-dependent PK from 40-640 mg
  - Fast absorption (median T_{max} ~4 hours)
  - Short half-life (median $T_{½}$ ~5 hours)
  - No significant accumulation at steady state
  - Similar PK with and without zanubrutinib (data not shown)



[a]PK data were pooled from all study cohorts, not just CLL. [b]Mean ±SD steady state BGB-11417 plasma concentration profile for 40-640 mg QD in patients with NHL and CLL who received BGB-11417 monotherapy (combination PK not shown here).

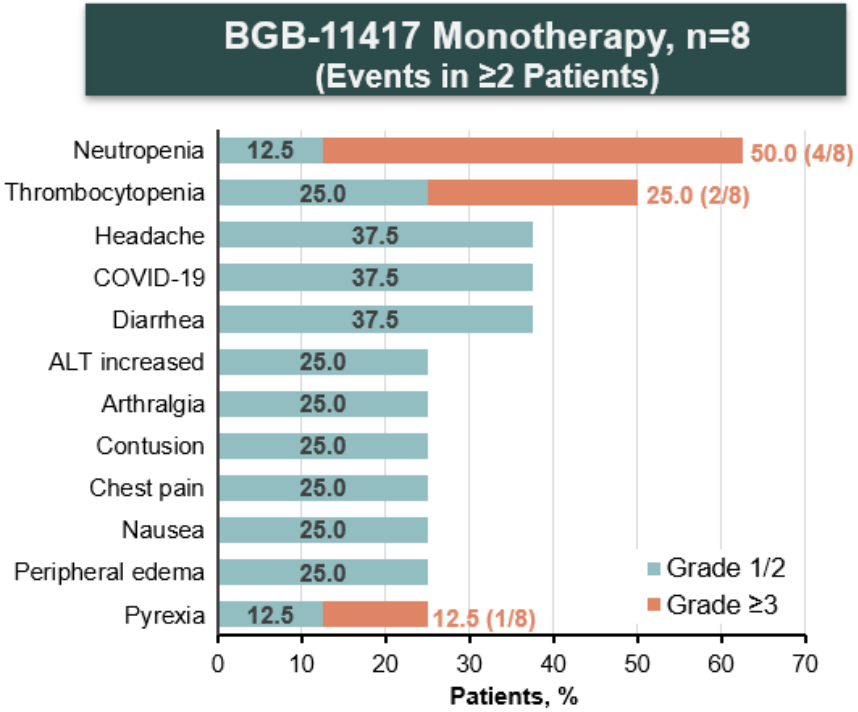
Summary of Adverse Events and DLTs

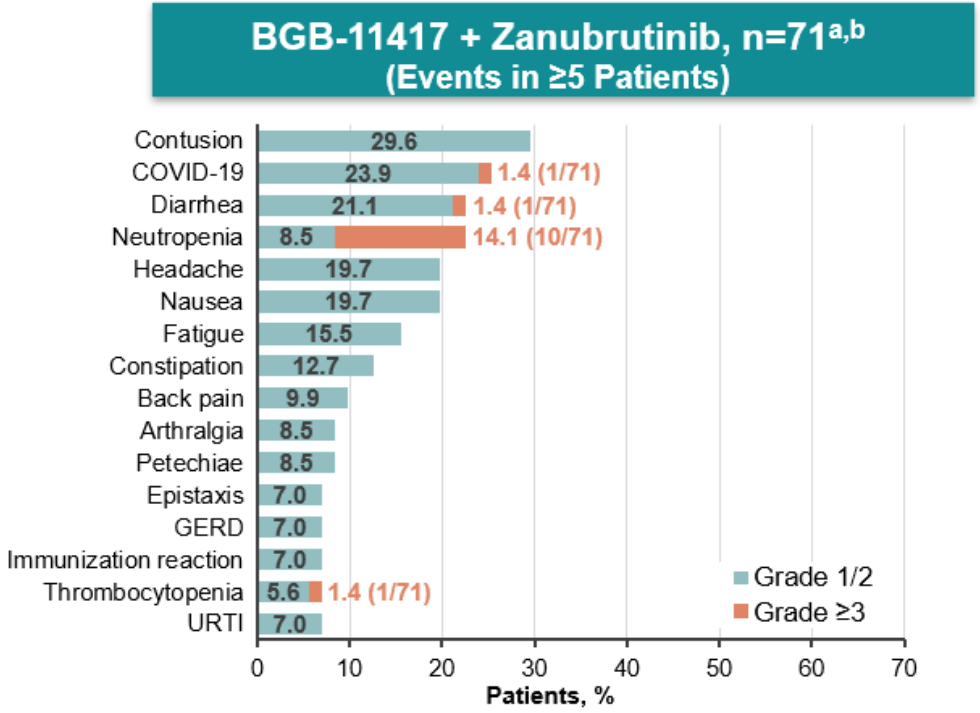
TEAE, n, %	BGB-11417 monotherapy (n=8)	BGB-11417 + zanubrutinib (N=71)	All patients with CLL (N=79)
Any AEs	8 (100)	61 (86)	69 (87)
Grade ≥3	5 (63)	20 (28)	25 (32)
Serious AEs	2 (25)	7 (10)	9 (11)
Leading to death	0	0	0
Treated with BGB-11417	**8**	**50**	**58**
Leading to hold of BGB-11417	5 (62.5)	14 (28)	19 (33)
Leading to dose reduction of BGB-11417	0	1 (2)	1 (2)
Leading to discontinuation of BGB-11417	0	0	0

- Only 1 DLT of febrile neutropenia noted among patients with CLL with BGB-11417 monotherapy at 80 mg; no DLTs were observed to date with the combination therapy at any dose level
- Toxicity does not seem dose dependent
- These AEs are consistent with BGB-11417 NHL data (see poster),[10] which tested through 640 mg with no MTD reached

TEAE, treatment-emergent adverse event.

Most Frequent Adverse Events





[a]Includes 21 patients who are still in zanubrutinib pretreatment phase and have not yet received BGB-11417. [b]Includes 46 patients who are TN.

Selected TEAEs

TLS:

- No clinical TLS and only one lab TLS observed
  - Lab TLS patient had high tumor burden receiving monotherapy[a]
  - The pre-dose urate was elevated the phosphate rose post-dose
- No TLS was observed with daily ramp-up (TN combination at 320mg; n=3)

GI toxicity: diarrhea was mostly grade 1

- Monotherapy grade ≥2: 12.5%; combination grade ≥2: 5.6% and grade 3: n=1

Neutropenia:

- G-CSF use[b]: monotherapy 4/8 (50%) patients; combination 10/71 (14.1%) patients
- Only 3/78 (3.8%) patients used more than one course of G-CSF to treat neutropenia

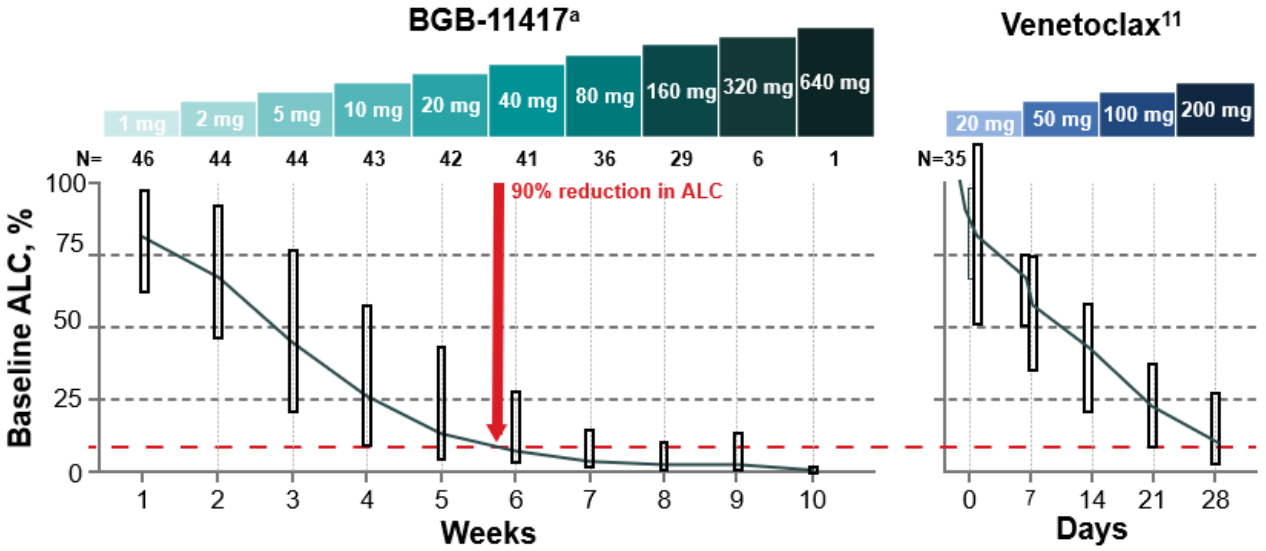
[a]High tumor burden is any node ≥10 cm or a node ≥5 and <10 cm with an ALC ≥25x10^9/L. If a patient is not classified as "high" they are classified as "low." [b]Includes all patients reporting G-CSF use during treatment, regardless of whether used for neutropenia or otherwise.

Reduction in Absolute Lymphocyte Count

- Absolute lymphocyte count dropped by ~90% after weekly ramp-up to 40 mg (BGB-11417 at 40 mg ≈ venetoclax at 200 mg [1:5])

Equivalent ALC Reduction (%) by Dose After Weekly Ramp-Up

BGB-11417 dose	Venetoclax dose
1 - 2 mg	~20 mg
40 mg	~200 mg
80 mg	~400 mg



Only data from patients with an ALC >5x10^9/L at baseline are included. Box plots represent median and 10th-90th percentiles.
[a]Minimum ALC among 1 week of each dose level was used for calculation. N represents the number of patients who completed weekly dosing at dose level underneath. ALC data were pooled from both monotherapy (n=7) and combination therapy (n=39) cohorts because no difference was observed.

Overall Response Rate

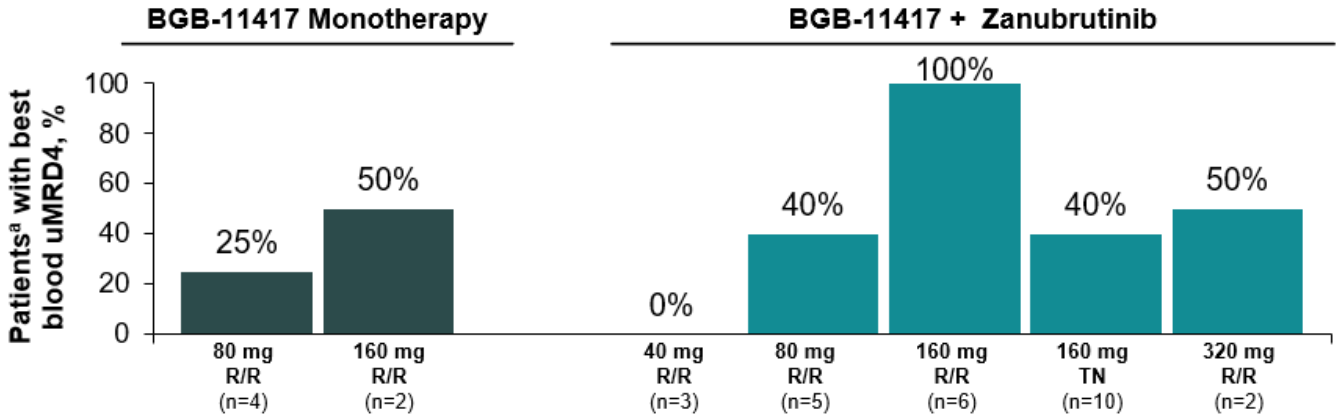
- Amongst R/R CLL/SLL patients on combination who had at least 3 post-baseline response assessments (n=15) ORR=93.3% and CR=40%. No TN patients have reached this timepoint

Response, n (%)	R/R BGB-11417 (n=8)	R/R BGB-11417 + zanubrutinib (n=25)	TN BGB-11417 + zanubrutinib (n=46)
Treated with BGB-11417	**8**	**24**	**26**
Efficacy evaluable	**6**	**20**[a]	**11**[a]
ORR, n (%)	4 (67)	19 (95)	11 (100)
CR	2 (33)[b]	6 (30)[c]	2 (18)[d]
PR	2 (33)[e]	13 (65)[f]	9 (82)[g]
SD	2 (33)	1 (5)	0
PD	0	0	0
Median follow-up, months (range)	13.4 (1.4-21.9)	11.1 (2.2-18.6)	3.5 (0.4-9.7)

[a]n=2 (R/R) and n=11 (TN) have responded after zanubrutinib pretreatment but have not yet had response assessment on combination treatment: they are not included here. [b]40 mg: n=1; 80 mg: n=1. [c]40 mg: n=1; 80 mg: n=2; 160 mg: n=3. [d]160 mg: n=2. [e]40 mg: n=1; 80 mg: n=1. [f]40 mg: n=2; 80 mg: n=3; 160 mg: n=3 ; 320 mg: n=5. [g]160 mg: n=9.
CR, complete response; ORR, overall response rate; PR, partial response; SD, stable disease.

Blood Minimal Residual Disease

- Blood MRD negativity was observed at **≥80 mg** after **6 months** (mono and combo in R/R CLL/SLL)
- **uMRD rate increased with longer follow-up and higher dose** (160 mg and 320 mg are immature)



	80 mg R/R (n=4)	160 mg R/R (n=2)	40 mg R/R (n=3)	80 mg R/R (n=5)	160 mg R/R (n=6)	160 mg TN (n=10)	320 mg R/R (n=2)
Median treatment duration months, range	**20.2** (15.9-23.8)	**14.3** (13.9-14.7)	**17.1** (16.4-17.8)	**15.0** (10.7-16.3)	**12.1** (9.8-13.7)	**8.2** (5.7-8.6)	**9.3** (9.0-9.5)
Median time to blood uMRD4[b], months, range	**12.2** (12.2-12.2)	**7.4** (7.4-7.4)	**0**	**9.5** (6.7-12.2)	**8.1** (4.6-10.4)	**6.6** (4.9-6.9)	**7.1** (7.1-7.1)

Data cutoff date: 29 October 2022.

MRD was measured by ERIC flow cytometry with 10^{-4} sensitivity. [a]In MRD-evaluable population, which was defined as patients who tested at least 1 postbaseline MRD sample. [b]From BGB-11417 first dose to first blood uMRD4; uMRD4 is defined as CLL cells out of total nucleated cells less than 10^{-4}.

CONCLUSIONS

- BGB-11417, alone or in combination with zanubrutinib, was well tolerated
  - Dose escalation continues to 640 mg with only one DLT; MTD not achieved
  - Grade ≥3 neutropenia and grade ≥2 diarrhea were uncommon and manageable
  - Only one laboratory TLS was seen; TLS was mitigated by the prophylactic measures and ramp-up schedule
- Promising efficacy is seen in monotherapy and in combination with zanubrutinib in R/R and in TN CLL/SLL
- Based on ALC reduction, BGB-11417 may be ~5X as potent as venetoclax by dose
- MRD data are preliminary but appear promising
- A venetoclax-treated CLL/SLL cohort is recruiting

REFERENCES

1. Kapoor et al. *Cell Death Dis* 2020;11(11):941.
2. Hu et al. AACR 2020. Abstract 3077.
3. Soumerai, et al. *Lancet Haematol*. 2021;8(12):e879-e890.
4. Hillmen et al. *J Clin Oncol* 2019;37(30):2722-2729.
5. Jain et al. *N Engl J Med* 2019;380(22):2095-2103.
6. Wierda J Clin Oncol 39:3853-3865. 2021.
7. Kater et al. *NEJM Evidence*. 2022;1(7).
8. Brown, et al. *Clinical Lymphoma Myeloma and Leukemia*. 2022/10/01/ 2022;22:S266.
9. Tam, et al. ASCO 2022. Abstract 7521.
10. Soumerai, et al. ASH 2022. Abstract 4201.
11. Roberts et al. *N Engl J Med* 2016;374(4):311-322.

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