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A Phase 1 Study With the Novel Bcl-2 Inhibitor BGB-11417 as Monotherapy or in Combination With Zanubrutinib in Patients With B-Cell Malignancies: Preliminary Data

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Introduction

BGB-11417 was developed as a potent and highly selective inhibitor of Bcl-2[1]

- The currently approved Bcl-2 inhibitor, **venetoclax**, is approved for the treatment of patients with **CLL/SLL** and AML[2]
- Treatment with venetoclax can be limited by common gastrointestinal toxicities, neutropenia, and the emergence of **specific BCL2 mutations around the BH3-binding groove**, resulting in resistance[3,4]
- **Antitumor activity of BGB-11417 appeared to be more potent** than venetoclax in human ALL, MCL, and DLBCL **in xenograft mouse models**[1]
- BGB-11417 has a favorable **pharmacokinetic profile with excellent bioavailability** and selectivity for Bcl-2 at a concentration of < 1 nM[1]
- Toxicology studies (data on file) have shown BGB-11417 to have a broad therapeutic index and **tolerable safety profile**

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Bcl-2, B-cell lymphoma 2; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma.

1. Hu N, et al. AACR 2020. Abstract 3077; 2. Venclexta (venetoclax) [package insert]. AbbVie and Genentech; 2021; 3. Davids MS, et al. *Clin Cancer Res.* 2018;24(18):4371-4379; 4. Blombery P, et al. *Cancer Discov.* 2019;9(3):342-353.

Introduction (2)

- The combination of venetoclax and the BTK inhibitor, ibrutinib, is tolerable and provides synergistic activity in patients with CLL[1-3] or MCL[4]
- **Zanubrutinib** is a next-generation BTK inhibitor that elicited excellent activity and favorable toxicity in patients with CLL/SLL[5] or MCL[6]; it is currently approved for the treatment of MCL, MZL, and WM (EMA)[7]
  - Early safety data show that combining zanubrutinib with venetoclax in patients with TN CLL/SLL appears to be tolerable.[8] Additionally, promising safety and efficacy were seen with the combination of zanubrutinib, obinutuzumab, and venetoclax in patients with CLL[9] or MCL[10]
- Here, we report preliminary results of the BGB-11417-101 trial (NCT04277637) in patients with NHL, WM, or CLL/SLL treated with BGB-11417 monotherapy or BGB-11417 in combination with zanubrutinib

BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; NHL, non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; TN, treatment-naive; WM, Waldenström macroglobulinemia.

1. Hillmen P, et al. *J Clin Oncol.* 2019;37(30):2722-2729; 2. Jain N, et al. *N Engl J Med.* 2019;380:2095-2103; 3. Siddiqi T, et al. EHA 2020. Abstract S158; 4. Tam CS, et al. *N Engl J Med.* 2018;378(13):1211-1223; 5. Hillmen P, et al. EHA 2021. Abstract LB1900; 6. Tam CS, et al. *Blood Adv.* 2021;5(12):2577-2585; 7. Brukinsa (zanubrutinib) [package insert]. BeiGene; 2021; 8. Tedeschi A, et al. *Blood.* 138(supp 1). Abstract 67; 9. Soumerai JD, et al. *Lancet Haematol.* 2021;8(12):e879-e890; 10. Kumar A, et al. *Blood.* 2021;138(suppl 1). Abstract 3540.

Study Design

Monotherapy Cohorts

Part 1: Dose escalation (BGB-11417 monotherapy)

Cohort	Population	Disease	Planned n
1A	R/R	NHL *(FL, DLBCL, MZL, or transformed NHL)*	15-30
1B	R/R *(low TLS risk)*	CLL/SLL	15-30
1C	R/R *(high TLS risk[a])*	CLL/SLL	3-6
1D	R/R	MCL	3-6
1E	R/R	WM	3-6

RP2D

RP2D per cohort will be decided based on SMC review of available safety and activity data

Part 2: Expansion (BGB-11417 monotherapy)

Cohort	Population	Disease	Planned n
2A	R/R *(food effect)*	Indolent NHL *(FL, MZL)*	10
2B	R/R *(food effect)*	Aggressive NHL *(DLBCL, transformed NHL)*	10
2C	R/R *(low TLS risk)*	CLL/SLL	20
2D	R/R *(high TLS risk[a])*	CLL/SLL	10
2E	R/R *(prior ven)*	CLL/SLL	10
2F	R/R	MCL	20
2G	R/R	WM	20

Combination Cohorts

Part 3: Dose finding (BGB-11417 + zanubrutinib combination)

Cohort	Population	Disease	Planned n
3A	R/R	CLL/SLL	15-30
3B	R/R	MCL	3-6

RP2D

RP2D per cohort will be decided based on SMC review of available safety and activity data

Part 2: Expansion (BGB-11417 + zanubrutinib combination)

Cohort	Population	Disease	Planned n
4A	R/R	CLL/SLL	30
4B	TN	CLL/SLL	20
4C	R/R	MCL	20

Blue text indicates cohorts presented here. [a]High TLS risk defined as the presence of any lymph node ≥ 10 cm or the presence of any lymph node ≥ 5 cm with concurrent absolute lymphocyte count ≥ 25 ×10^9/L.
CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SMC, safety monitoring committee; TLS, tumor lysis syndrome; TN, treatment-naive; ven, venetoclax; WM, Waldenström macroglobulinemia.

Dose Escalation and Target Dose Ramp-Up Schemas

- Cohorts of ≥ 3 patients were assigned to planned oral doses of BGB-11417: 40, 80, 160, 320, or 640 mg
- To protect against potential TLS, all patients received a dose ramp-up to the target dose level

  Cohort 1a, NHL, were the first patients to be treated. Venetoclax hasn't used a ramp-up in those populations given the low TLS risk outside CLL/MCL, given 11417's potential potency we built in a precautionary, brief, 3-day ramp-up.
- DLTs assessed from ramp-up through day 21 at the intended daily dose and evaluated by bayesian logistic regression model, were used to determine the MTD

Example ramp-up for 80 mg dose:

[a]Combination cohorts began zanubrutinib treatment 8-12 weeks before and during BGB-11417 ramp-up.
D, day; DLT, dose-limiting toxicity; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; QD, once daily; W, week; WM, Waldenström macroglobulinemia.

Patient and Disease Characteristics

Characteristic	BGB-11417 monotherapy (n = 34)	BGB-11417 + zanubrutinib combination (n = 44)	All patients (N = 78)
Age, median (range), years	72 (55-86)	61 (36-84)	65 (36-86)
ECOG PS, n (%)			
Unknown	1 (2.9)	1 (2.3)	2 (2.6)
0	14 (41.2)	27 (61.4)	41 (52.6)
1	16 (47.1)	15 (34.1)	31 (39.7)
2	3 (8.8)	1 (2.3)	4 (5.1)
Disease type, n (%)			
CLL	6 (17.6)	**34 (77.3)**	40 (51.3)
R/R DLBCL	**17 (50)**	N/A	17 (21.8)
R/R FL	**6 (17.6)**	N/A	6 (7.7)
R/R MZL	**3 (8.8)**	N/A	3 (3.8)
MCL	0	**10 (22.7)**	10 (12.8)
WM	2 (5.9)	N/A	2 (2.6)
TN, n (%)	0	14 (31.8)	14 (17.9)
R/R, n (%)	34 (100.0)	30 (68.2)	64 (82.1)
Prior lines of therapy, median (range)	2 (1-6)	1 (1-2)	1 (0-6)
Time from end of most recent systemic therapy to first dose, median (range), months	5.3 (0-49.7)	43.4 (1.6-194.4)	10.8 (0-194.4)

Data cutoff: February 4, 2022. CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory; TN, treatment-naive; WM, Waldenström macroglobulinemia.

Overall Adverse Events

AEs, n (%)	BGB-11417 monotherapy (n = 34[a])	BGB-11417 + zanubrutinib combination (n = 44[b,c])	All patients (N = 78)
Any AEs	32 (94.1)	34 (77.3)	66 (84.6)
Grade ≥ 3 AEs	14 (41.2)	7 (15.9)	21 (26.9)
Serious AEs	11 (32.4)	5 (11.4)	16 (20.5)
Leading to death	2 (5.9)[d]	1 (2.3)[e]	3 (3.8)
Leading to hold of BGB-11417	5 (14.7)[f]	1 (2.3)[g]	6 (7.7)
Leading to dose reduction of BGB-11417	0	0	0
Leading to discontinuation of BGB-11417	1 (2.9)[h]	0	1 (1.3)

Data cutoff: February 4, 2022. [a]All patients have relapsed/refractory disease; [b]Includes 20 patients who are still in zanubrutinib pretreatment phase and have not yet received BGB-11417; [c]Includes 14 patients who are treatment naive; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease of 2019; GGT, gamma-glutamyl transferase.

[d]Neither related to study drug; 1 death secondary to disease progression and 1 gastrointestinal hemorrhage subsequent to bowel surgery; [e]Cardiac arrest, not related to study drug;
[f]Thrombocytopenia, hemoptysis, and pyrexia; ALT, AST, and GGT levels increased; neutropenia, pyrexia, and febrile neutropenia; small intestinal obstruction; neutropenia; [g]Dose withheld due to COVID-19 infection;
[h]Gastrointestinal hemorrhage subsequent to bowel surgery.

DLTs in Dose-Escalation Cohorts

Monotherapy

- Dose escalation was completed for cohort 1A, with no MTD reached through 640 mg
  - 1 DLT at 160 mg (Grade 3 febrile neutropenia)
- Dose escalation continues for all other monotherapy dose-escalation cohorts
  - 1 DLT at 80 mg (Grade 4 neutropenia); patient with R/R CLL recovered and continued dosing

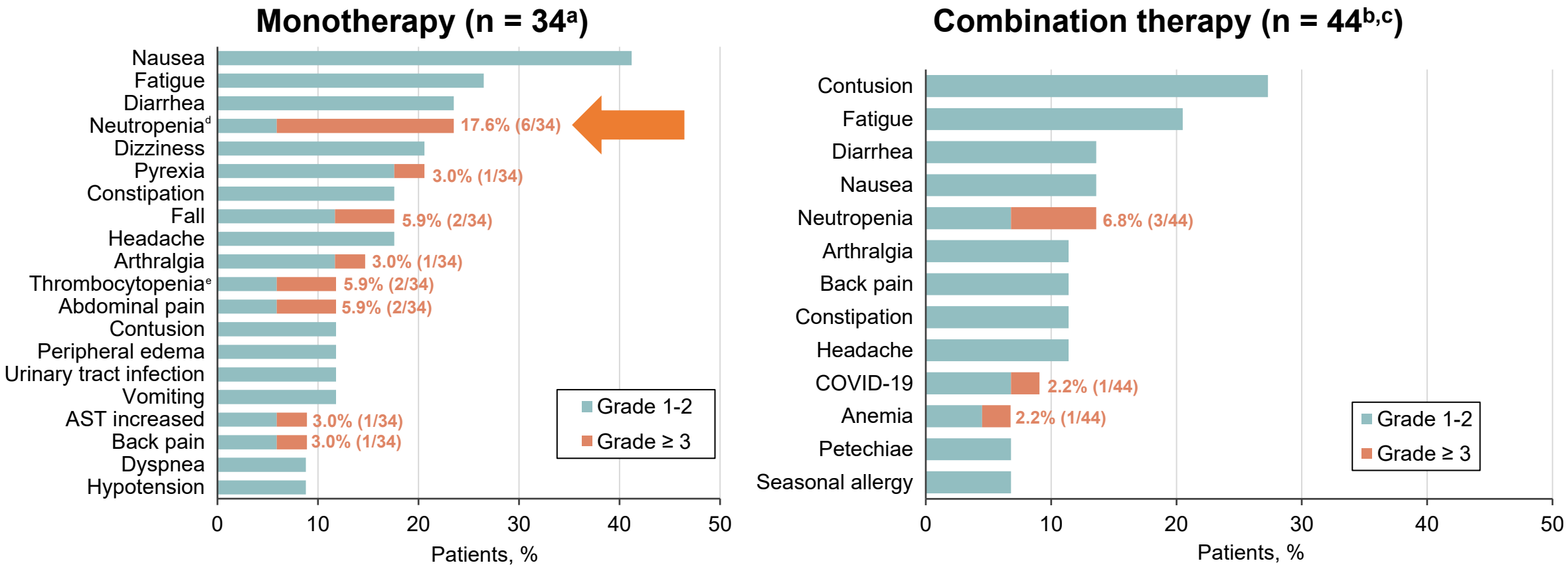
Combination Therapy

- Dose escalation continues for all cohorts, with no DLTs yet up to 160 mg (CLL) or 80 mg (MCL)
- Cohort 4B (TN CLL expansion) was opened at 160 mg; owing to tolerability and promising activity seen during dose escalation, additional dose levels may potentially be expanded

Cohort	40 mg[a]	80 mg	160 mg	320 mg	640 mg
			Monotherapy		
NHL (1A)	0/3	0/4	1/4	0/9	0/6
CLL (1B)	N/A	1/4	TBD	TBD	TBD
WM (1E)	N/A	TBD	TBD	TBD	TBD
			Combination		
CLL (3A)	0/4	0/3	0/3	TBD	TBD
MCL (3B)	N/A	0/3	TBD	TBD	TBD

Data cutoff: February 4, 2022. [a]Not tested in cohorts 1B, 1E, and 3B because this dose has been cleared in other cohorts by the time these cohorts were open.
CLL, chronic lymphocytic leukemia; DLT, dose-limiting toxicity; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; TN, treatment-naive; WM, Waldenström macroglobulinemia.

TEAEs Regardless of Causality in ≥ 3 Patients



Data cutoff: February 4, 2022. [a]All patients are relapsed/refractory; [b]Includes 20 patients who are are still in zanubrutinib pretreatment phase and have not yet received BGB-11417; [c]Includes 14 patients who were treatment naive; [d]Neutropenia: includes neutrophil count decreased and neutropenia; [e]Thrombocytopenia: includes platelet count decreased and thrombocytopenia.
AST, aspartate aminotransferase; COVID-19, coronavirus disease of 2019; TEAE, treatment-emergent adverse event.

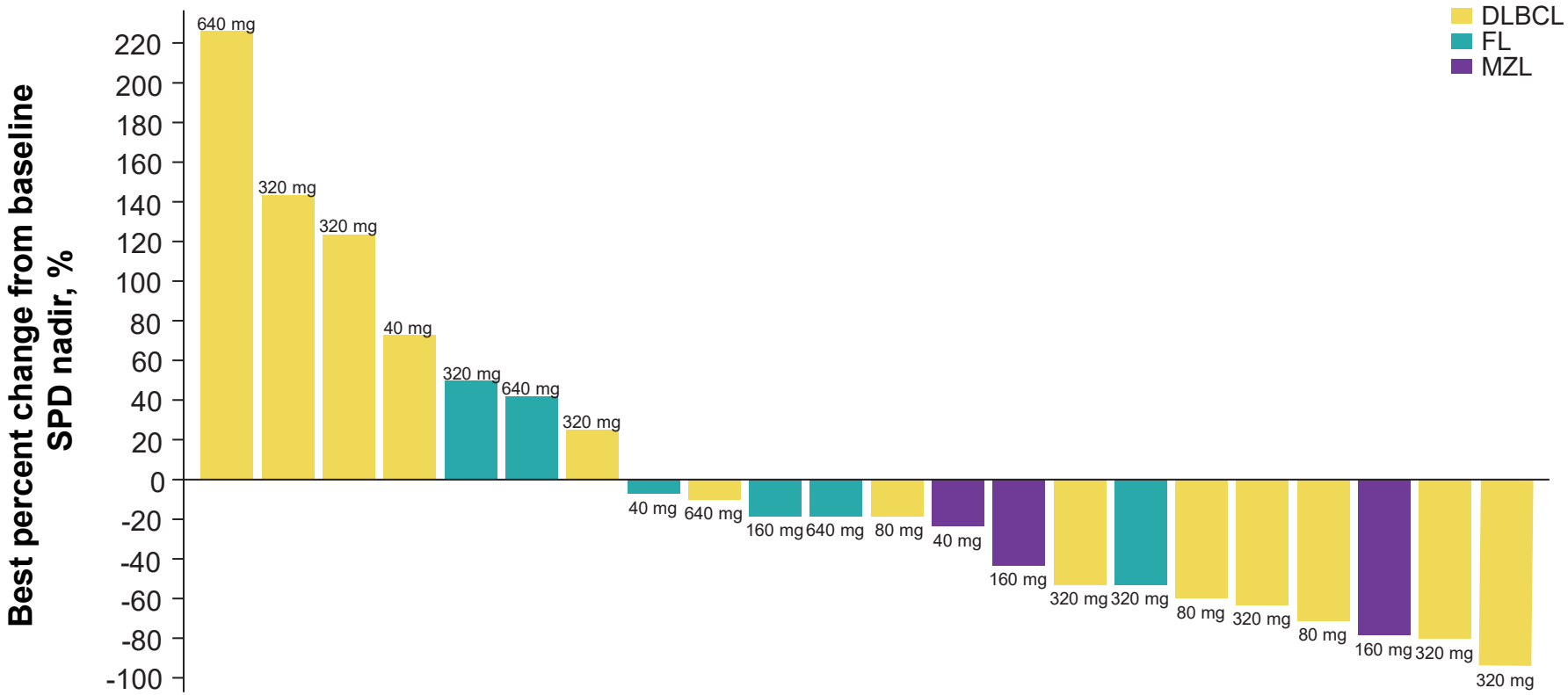
Bcl-2 Inhibitor Events of Interest

- One patient with CLL receiving monotherapy with high baseline TLS risk had a marked tumor flare on BTK inhibitor withdrawal and developed **laboratory TLS** in a late ramp-up
  - The patient experienced no sequelae from laboratory TLS and resolved by the next day; BGB-11417 did not need to be withheld
- **Neutropenia** was observed in 8 patients receiving monotherapy (n = 6, Grade ≥ 3; n = 5 received growth factor) and 6 patients receiving combination therapy (n = 3 Grade ≥ 3; n = 4 received growth factor). All cases resolved without dose reduction

Data cutoff: February 4, 2022. BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; TLS, tumor lysis syndrome.

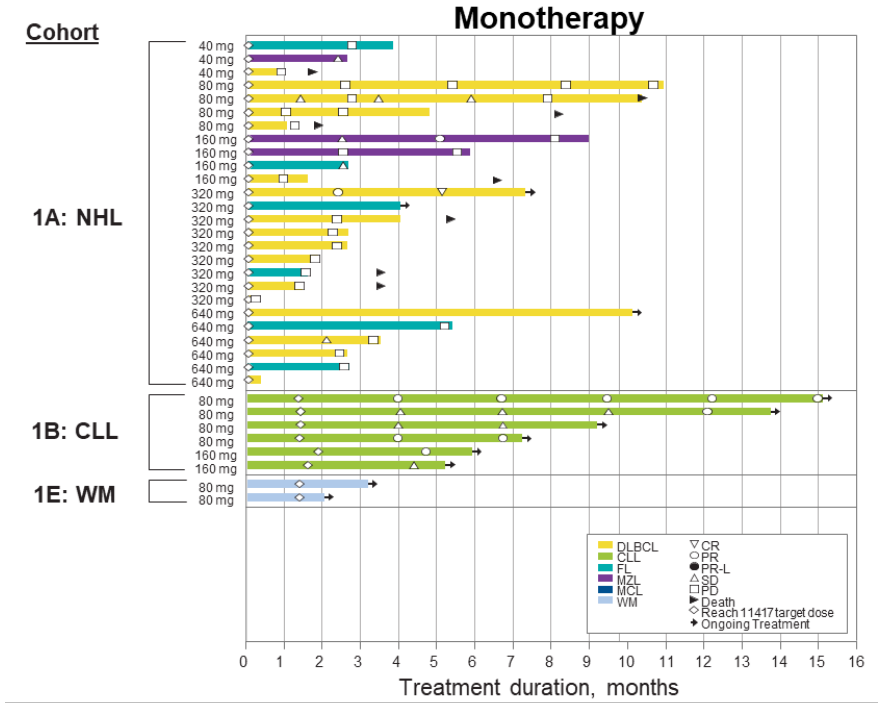
SPD Change in Patients with NHL

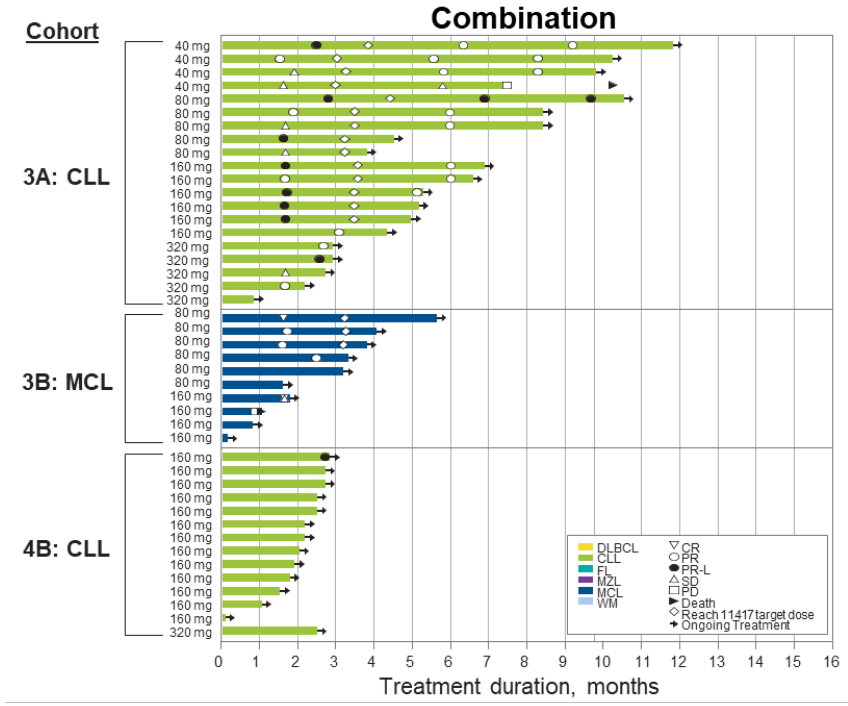
- Significant reductions in the SPD from baseline were seen in most patients



Data cutoff: February 4, 2022. DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; SPD, sum of product of perpendicular diameters.

Duration of Treatment and Best Response





Monotherapy

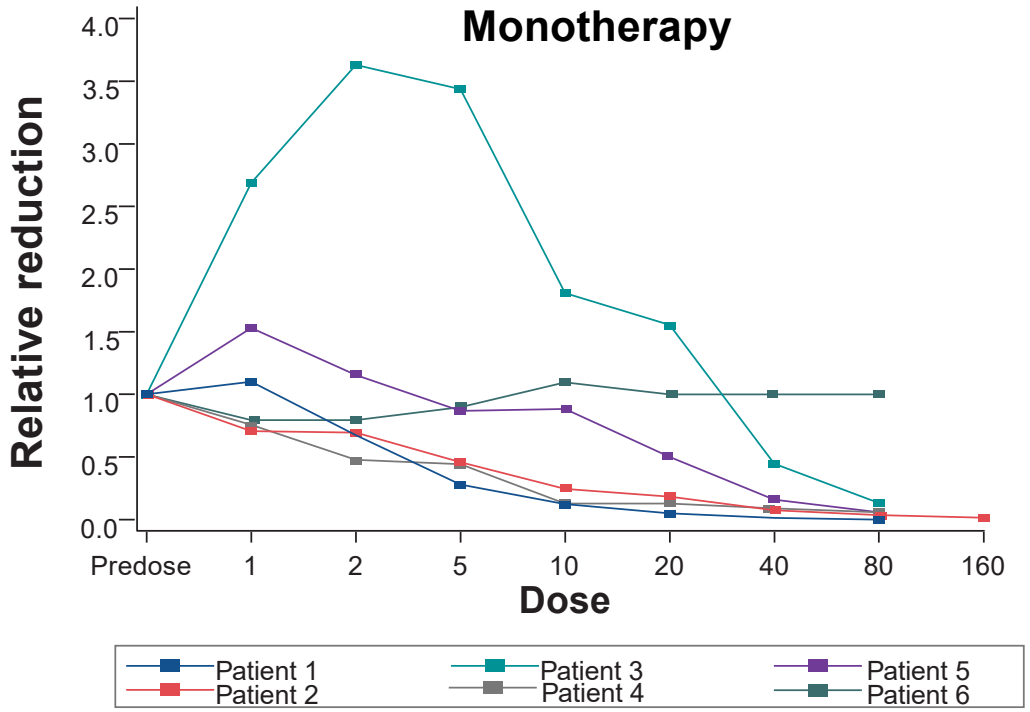
- NHL (R/R): 2 of 20 (10%) responded, 1 PR (160 mg) and 1 CR (320 mg)
- WM (R/R): limited follow-up; 1 of 2 (50%) with minor responses (80 mg)
- CLL/SLL (R/R): 4 of 6 (67%) achieved PR-L or better at either 80 or 160 mg

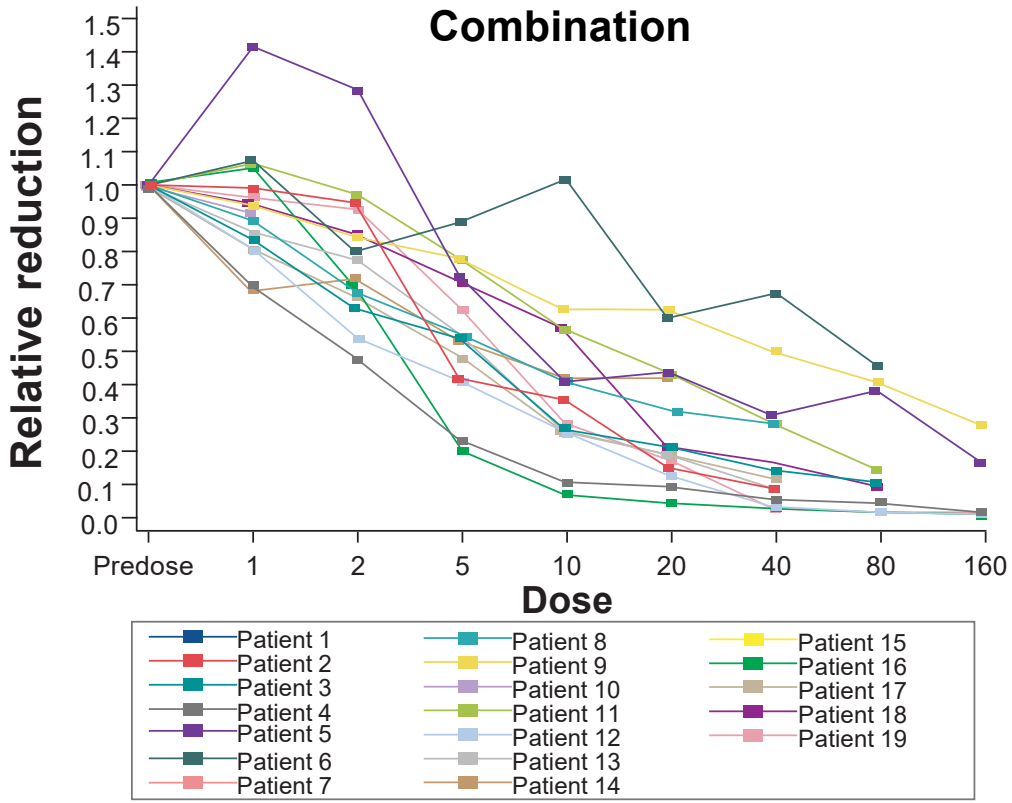
Combination therapy

- MCL (R/R): 5 of 10 (50%) have achieved PR or better so far at either 80 or 160 mg, including 1 CR at each dose level
- CLL/SLL (R/R): 16 of 20 (80%) achieved PR-L or better across all doses
- CLL/SLL (TN): limited follow-up, most still on zanubrutinib pretreatment

Data cutoff: February 4, 2022. CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive; WM, Waldenström macroglobulinemia.

Activity of BGB-11417





- Significant reduction in ALC was noted among all patients with CLL during ramp-up, with reduction in lymphocytes noted at dose levels as low as 1 mg

Data cutoff: February 4, 2022. [a]Figures represent reduction in ALC above the ULN (4 x 10^9/L) compared to pre–BGB-11417 baseline before next dose escalation (or after 1 week at target dose) per dose. Patients receive each BGB-11417 dose level for 1 week before escalating to the next dose. Combination patients were also receiving zanubrutinib during BGB-11417 ramp-up, beginning 8-12 weeks before the first BGB-11417 dose (Note: 1 patient with normal baseline ALC is excluded from monotherapy figure). ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukemia; ULN, upper limit of normal.

Conclusions

- These early phase 1 results suggest that BGB-11417 **is tolerable** in patients with CLL or NHL at the dose levels tested
  - Dose escalation concluded for monotherapy patients with NHL with only 1 DLT seen and no MTD reached; only 1 DLT was seen in monotherapy patients with CLL
  - Grade ≥ 3 AEs have been infrequent and manageable
  - Findings so far suggest that the combination of BGB-11417 and zanubrutinib is well tolerated, similar to BGB-11417 monotherapy
  - Risk of TLS appears limited and manageable: laboratory TLS has been seen in only 1 patient with high TLS-risk CLL receiving monotherapy
- Transient neutropenia was the most frequent Grade ≥ 3 AE
- Substantial decreases in ALC have been seen during ramp-up in patients with CLL, with promising early response rates in patients with R/R CLL

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