Società Italiana Ematologia Sperimentale
SIES

XVII CONGRESSO NAZIONALE SIES2022

ROMA

31 marzo, 1- 2 aprile

ERGIFE PALACE HOTEL

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DATI PRELIMINARI DI SICUREZZA ED EFFICACIA DA PAZIENTI (PTS) CON MALATTIE LINFOPROLIFERATIVE A CELLULE B RICADUTI/REFRATTARI (R/R) TRATTATI CON IL NUOVO INIBITORE DI BCL2 BGB-11417 IN MONOTERAPIA O IN COMBINAZIONE CON ZANUBRUTINIB

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Disclosures of Paolo Ghia

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other (Honoraria)
AbbVie	x		x				x
ArQule/MDS			x				x
AstraZeneca	x		x				x
BeiGene			x				x
Celgene/Juno/ BMS			x				x
Gilead	x						
Janssen	x		x				x
Roche			x				x
Sunesis	x						

Introduction

- BCL2 inhibitors have been shown to be safe and effective, and are approved for the treatment of patients with CLL/SLL or AML[1]
  - Venetoclax, the currently approved BCL2 inhibitor, is associated with common gastrointestinal toxicities, neutropenia, and the emergence of *BCL2* mutations causing resistance[2,3]
- BGB-11417 is a potent and highly selective inhibitor of BCL2[4] with:
  - Superior antitumor activity to venetoclax in human ALL, MCL, and DLBCL mouse xenograft models[4]
  - Favorable pharmacokinetic profile along with excellent bioavailability and selectivity for BCL2 (<1nM)[4]
  - Broad therapeutic index and tolerable safety profile[5]
- The combination of BCL2 inhibitor with BTK inhibitor is tolerable, with synergistic activity in patients with CLL[6-8] or MCL[9]
- Zanubrutinib, a next-generation BTK inhibitor with excellent activity and favorable toxicity in patients with CLL/SLL[10] or MCL[11], is currently approved for the treatment of MCL, MZL, and WM
- Here we report preliminary results of the **BGB-11417-101 trial** (NCT04277637) in patients with non-Hodgkin lymphomas or CLL/SLL treated with BGB-11417 monotherapy or in combination with zanubrutinib

AML, acute myeloid leukemia; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; WM Waldenström macroglobulinaemia.

1. VENCLEXTA (venetoclax). Prescribing information. AbbVie and Genentech; 2020. 2. Davids MS, et al. *Clin Cancer Res.* 2018;24(18):4371-4379. 3. Blombery P, et al. *Cancer Discov.* 2019;9(3):342-353. 4. Hu N, et al. AACR 2020. Abstract 3077. 5. BeiGene Inc. Data on File. 6. Hillmen P, et al. *J Clin Oncol.* 2019;37(30):2722-2729. 7. Jain N, et al. *N Engl J Med.* 2019;380:2095-2103. 8. Siddiqi T, et al. ASH 2020. Abstract S158. 9. Tam CS, et al. *N Engl J Med.* 2018;378:1211-1223. 10. Hillmen P, et al. EHA 2021. Abstract LB1900. 11. Tam CS, et al. *Blood Adv.* 2021;5(12):2577-2585.

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*)	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

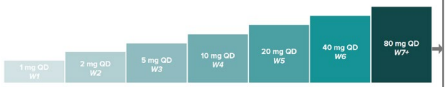
Part 4: EXPANSION (BGB-11417 + Zanubrutinib Combination)

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

Ramp-Up Scheme Examples:

Cohort 1A: NHL- 3-day ramp-up

Cohort 1B: CLL- Weekly ramp-up



As of data cutoff, 25 September 2021, Cohorts 1A, 1B , 3A, and 3B have opened and enrolled patients.
[a]High TLS risk was 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, chronic lymphocytic leukemia; D, day; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; QD, once daily; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; SMC, safety monitoring committee; TLS, tumor lysis syndrome; TN, treatment naive; ven, venetoclax; W, week; WM, Waldenström macroglobulinemia.

Patient Baseline Disease Characteristics

Characteristic	BGB-11417 Monotherapy (N=25)	BGB-11417 + Zanubrutinib Combination (N=11)	All Patients (N=36)
Age, median (range), year	72 (55-86)	60 (41-75)	68.5 (41-86)
ECOG PS, n (%)			
0	10 (40)	7 (63.6)	17 (47.2)
1	13 (52)	4 (36.4)	17 (47.2)
2	2 (8)	0	2 (5.6)
Disease types, n (%)			
CLL	6 (24)	10 (90.9)	16 (44.4)
DLBCL	12 (48)	—	12 (33.3)
FL	4 (16)	—	4 (11.1)
MZL	3 (12)	—	3 (8.3)
MCL	0	1 (9.1)	1 (2.8)
No. of prior lines of therapy, median (range)	2 (1-5)	1 (1-2)	1 (1-5)
Time from end of most recent systemic therapy to first dose median (range), months	7.7 (9-49.7)	45.5 (1.6-194.4)	11.4 (1.7-34.2)

[a]FL, DLBCL, tNHL, and MZL. [b]Includes "other" or "physician decision." [c]N=4 still in zanubrutinib pretreatment phase.
AE, adverse event; 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; NHL, non-Hodgkin lymphoma; PD, progressive disease; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; tNHL, transformed NHL.

Treatment-Emergent AEs and Dose-Limiting Toxicities

Overall Treatment-Emergent Adverse Events

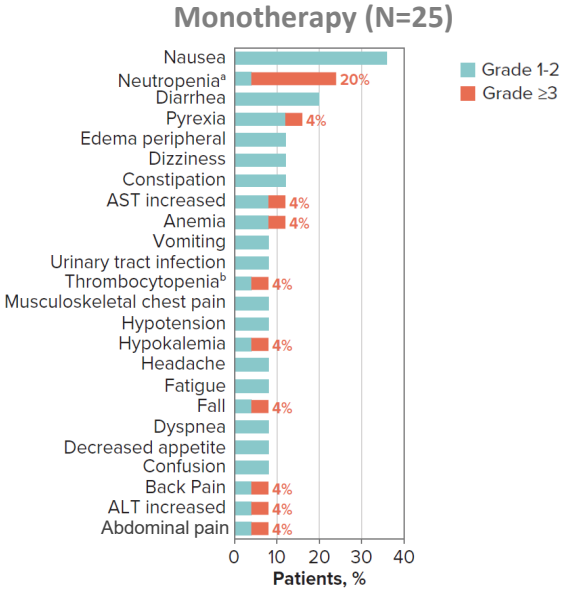
AEs, n (%)	BGB-11417 Monotherapy (N=25)	BGB-11417 + Zanubrutinib Combination (N=11)	All Patients (N=36)
Any AE	22 (88)	9 (82)	31 (86)
Grade ≥3 AEs	11 (44)	0	11 (30)
Serious AEs	9 (36)	0	9 (25)
Leading to death	2 (8)	0	2 (6)[a]
AEs leading to hold of BGB-11417	4 (16)	0	4 (11)[b]
AEs leading to dose reduction of BGB-11417	0	0	0
AEs leading to discontinuation of BGB-11417	1 (4)	0	1 (3)[c]

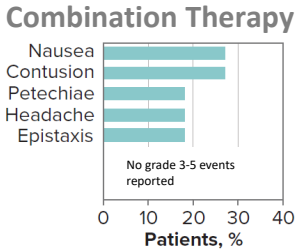
DLTs in Dose-Escalation Cohorts

Cohort	40 mg	80 mg	160 mg	320 mg	640 mg
Monotherapy					
NHL (1A)	0/3	0/4	1/4[d]	0/3	TBD
CLL (1B)	—	1/4[e]	TBD	TBD	TBD
Combination					
CLL (3A)	0/4	0/3	TBD	TBD	TBD

[a]Neither related to study drug; 1 death secondary to disease progression and 1 GI hemorrhage subsequent to bowel surgery. [b]ALT increased and GGT increased; neutropenia, pyrexia, and febrile neutropenia; GI hemorrhage and small intestinal obstruction; neutropenia. [c]GI hemorrhage subsequent to bowel surgery. [d]DLT of grade 3 febrile neutropenia. [e]DLT of grade 4 neutropenia.
AE, adverse event; ALT, alanine aminotransferase; CLL, chronic lymphocytic leukemia; DLT, dose limiting toxicity; GGT, gamma-glutamyl transferase; GI, gastrointestinal; NHL, non-Hodgkin lymphoma.

Treatment-Emergent AEs Regardless of Causality Occurring in ≥2 Patients





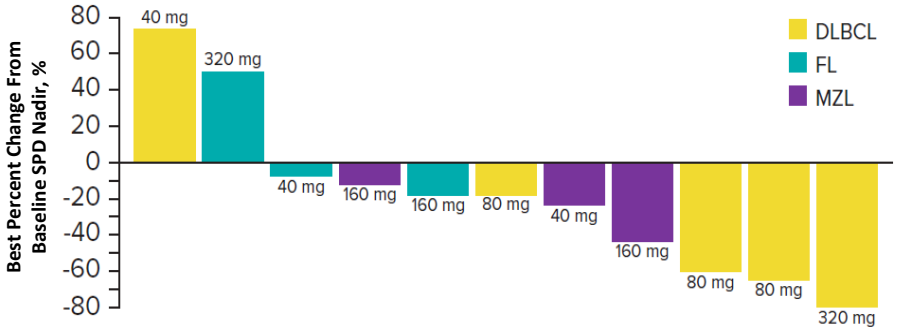
Laboratory TLS (Howard Criteria) was seen in 1 patient with CLL in the monotherapy group:

- An asynchronous rise in urate and phosphate
- The patient had a high-tumor burden after ibrutinib withdrawal flare
- Laboratory TLS was seen after first dose of 40 mg and 80 mg
- No change in management was required

[a]Neutropenia: combines "neutrophil count decreased" and "neutropenia." [b]Thrombocytopenia: combines "platelet count decreased" and "thrombocytopenia."
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase.

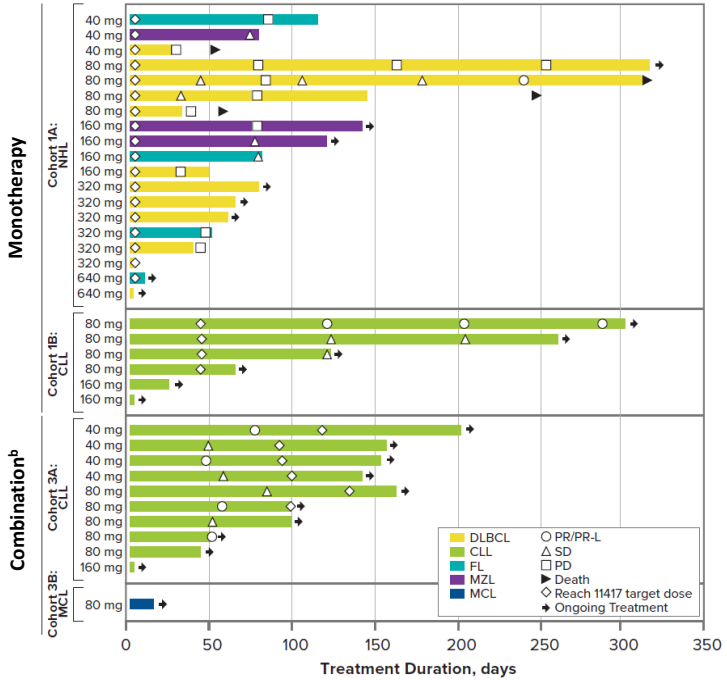
Early Efficacy Outcomes

Change in SPD among Patients with NHL[a]



- **NHL Monotherapy**: Decreases in sum of SPD have been seen at all dose levels tested in patients with NHL
- **CLL Monotherapy**: Treatment resulted in 1 of 4 patients responding at the 80-mg dose level
- **CLL Combination**: Treatment resulted in 4 of 10 patients responding with partial response with lymphocytosis or better (n=2 at both 40 mg and 80 mg)

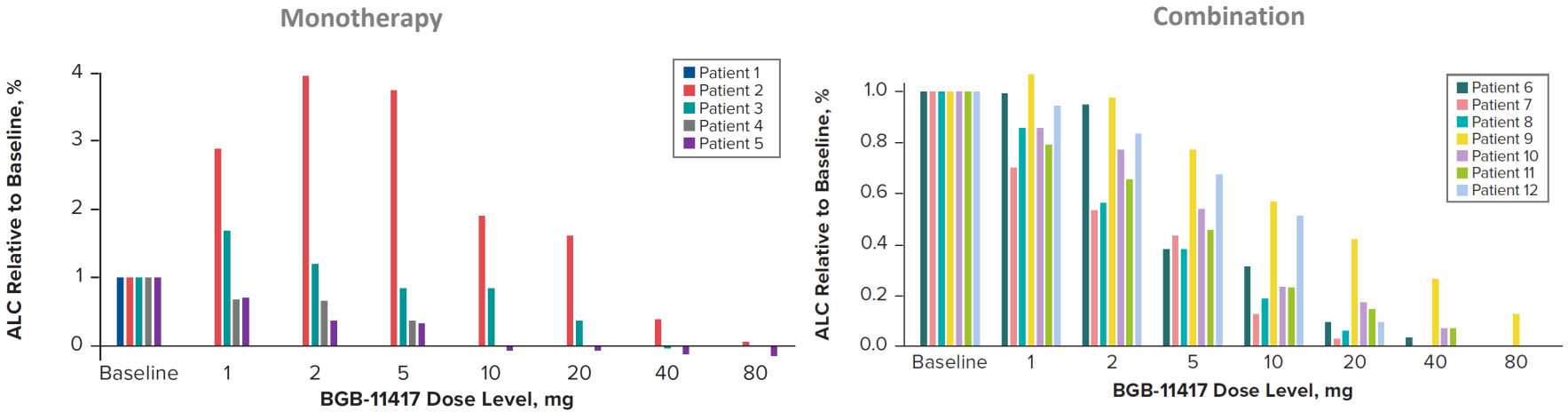
Duration of Treatment and Best Response



[a]Includes all patients from Cohort 1A that had a post baseline CT scan as of data cutoff (n=11). [b]Duration of treatment includes 8-12 weeks of zanubrutinib monotherapy prior to initiation of BGB-11417+zanubrutinib combination

CLL, chronic lymphocytic leukemia; 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, PR with lymphocytosis; SD, stable disease; SPD, sum of product of perpendicular diameters.

Activity of BGB-11417: Reduction in ALC Over Ramp-Up in Patients with CLL[a]



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

[a]Figures represent reduction in ALC above the ULN ($4x10^9$/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. Patients on combination therapy 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 was excluded from the monotherapy figure).
ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukemia.

Conclusions

- These early phase 1 results suggest that BGB-11417 is tolerable in patients with CLL or NHL at the dose levels tested
  - Only 1 DLT (febrile neutropenia) was seen across the 4 dose levels tested in NHL, and 1 DLT was seen in a CLL cohort
  - Grade ≥3 AEs have been infrequent and manageable, with none seen so far in combination cohorts
- Risk of TLS appears limited and manageable: laboratory findings suggesting TLS was seen in 1 patient with CLL who had high TLS risk
- Transient neutropenia has been the most frequent grade ≥3 AE
- Substantial decreases in ALC have been seen during ramp-up for CLL patients
- Evaluation of patients with MCL, treatment-naive CLL, or WM is planned for future cohorts

Acknowledgments

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