SEQUOIA – Arms A & B [NCT03336333]

An open label, randomized study of zanubrutinib vs bendamustine + rituximab in participants with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma, including participants without del(17p) [Cohort 1 shown here] and participants with del(17p) [Cohort 2 and 3], as measured by PFS. The data outlined in this Quick Reference guide is from Cohort 1.

STUDY DESIGN

PHASE **3**

STUDY SITES **Global**

INTERVENTION **Zanubrutinib vs bendamustine + rituximab**

PRIMARY ENDPOINT **PFS by IRC**

KEY SECONDARY ENDPOINTS **ORR and DoR by investigator and IRC, OS, safety**

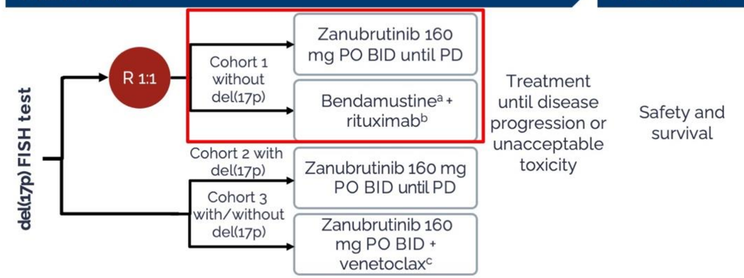
INCLUSION

- Treatment-naïve CLL/SLL requiring treatment
- ≥65 years of age or <65 years of age and unsuitable for FCR treatment
- Measurable disease by CT/MRI
- No current / past history of Richter's transformation
- ECOG PS ≤2

Stratification:

- Age (<65 vs ≥65 years)
- Binet stage (C vs A or B)
- IGHV mutational status (mutated vs unmutated)
- Geographic region (NA vs EU vs APAC)

TREATMENT



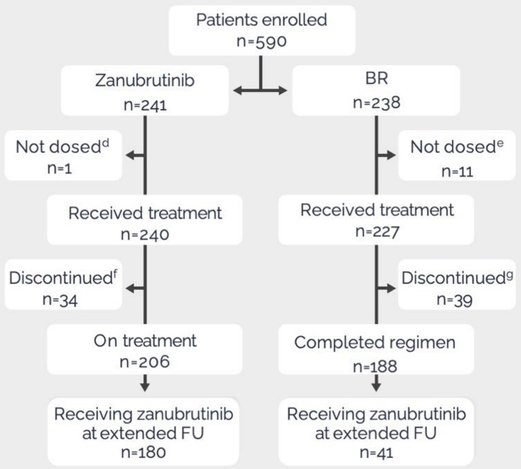
FOLLOW-UP

Treatment until disease progression or unacceptable toxicity

Safety and survival

[a]90 mg/m2 D1 and D2 for 6 cycles, [b]375 mg/m2 D0 or D1 C1 and 500 mg/m2 D1 C 2-6, [c]ramp-up cycle (C 4-11) then 400 mg PO daily C 12-24

PATIENT DISPOSITION



Data cutoff: 31 October, 2022
Median follow-up: 43.7 months

[d]1 due to investigator discretion; [e]6 patient withdrawal, 2 investigator discretion, 2 AE, 1 other; [f]1 PD, 20 AE, 1 investigator discretion, 2 patient withdrawal; [g]1 PD, 31 AE, 3 investigator discretion, 1 patient withdrawal, 3 other

PATIENT CHARACTERISTICS

Characteristics	Zanu (n=241)	BR (n=238)
Median age, years	70	70
≥65	81%	81%
Male	64%	61%
Geographical region		
North America	14%	12%
Europe	72%	72%
Asia-Pacific	14%	16%
CLL cancer type	92%	92%
Binet stage C	29%	29%
Bulky disease ≥5 cm	29%	31%
Cytopenia at baseline	42%	46%
β-2-microglobulin >3.5 mg/L	58%	57%
Time from initial diagnosis, months	31.28	28.67
Unmutated IGHV gene	53%	52%
Del mutation		
11q	18%	19%
13q	56%	54%
No FISH abnormalities	23%	25%
TP53 mutation	6%	6%
Complex karyotype with ≥3 abnormalities	14%	14%

EFFICACY DATA OVERVIEW [n=479; ITT population analysis]

Primary Endpoint

Median PFS not reached vs 42-months
(HR=0.30)

Secondary Endpoints

	Zanu (n=241)	BR (n=238)
CR/CRi rate	17.4%	21.8%
Median OS	NE	NE

- At interim analysis (median FU 26.2 months), the primary endpoint was met, and PFS difference met prespecified criteria for superiority – at the extended follow up, median PFS was still not reached in the zanubrutinib arm vs 42.2 months in the BR arm.
- Estimated 42-month PFS rates with zanubrutinib and BR were 82.4% and 50.0% (CI, 0.21-0.43, p<0.0001)
- PFS was improved with zanubrutinib vs BR in patients with mutated IGHV (HR 0.35; 95% CI 0.19-0.64) and unmutated IGHV (HR 0.23; 95% CI 0.14-0.37)
- Median OS was not reached; the estimated 42-month OS rates were 89.4% and 88.3% (B+R)

SAFETY DATA OVERVIEW [n=467; safety population analysis]

Summary of AEs
(DCO 07 May, 2021; median FU 26.2 months)

AE	Zanu (n=241)		BR (n=238)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	94%	53%	96%	80%
Serious AE	37%	30%	49%	44%
Common AE (>15%)				
Contusion	19%	0%	4%	0%
URTI	17%	1%	12%	1%
Diarrhea	14%	1%	14%	2%
Arthralgia	14%	1%	9%	<1%
Neutropenia	16%	12%	57%	51%
Rash	11%	0%	20%	3%

AEs of Interest
[Any grade, zanu vs BR; DCO 31 October, 2022; extended FU 42.2 months]

	Zanu	BR
Neutropenia	16.7%	56.8%
Infection	72.9%	62.6%
Atrial fibrillation / flutter	5.0%	2.6%
Bleeding	48.8%	12.3%
Thrombocytopenia	6.3%	18.1%
Other malignancies	18.8%	12.3%

CONCLUSIONS

The SEQUOIA extended follow-up showed that the efficacy of zanubrutinib was maintained in previously untreated patients with CLL/SLL without del(17p) and PFS rates were similar in patients with and without del(17p). Zanubrutinib was well tolerated over this extended treatment period and aligned with the known profile of BTK inhibitors; atrial fibrillation events remained low.

Munir T et al. Poster presented at EHA 2023; Abstract number: P639
Tam et al. Lancet Oncology. 2022. 22;S1460-2045

SEQUOIA – Arm D [NCT03336333]

Zanubrutinib

CLL/SLL

An open label, randomized study of zanubrutinib vs bendamustine + rituximab in participants with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma as measured by PFS. The data outlined in this Quick Reference guide is from Cohort 3 which is an investigational arm of the study assessing the combination of zanubrutinib + venetoclax in patients with and without del(17p) mutations.

STUDY DESIGN

PHASE **3**

STUDY SITES **Global**

INTERVENTION **Cohort 3: Zanubrutinib + venetoclax**

PRIMARY ENDPOINT **ORR by investigator**

KEY SECONDARY ENDPOINTS **PFS by investigator, uMRD4 rate (<10^{-4} sensitivity), safety**

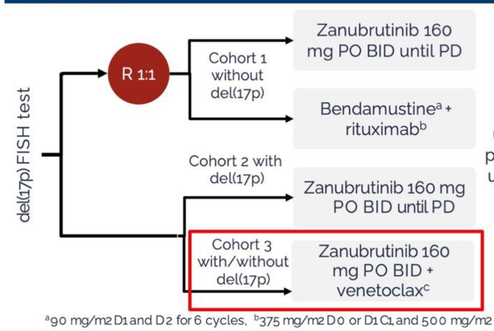
INCLUSION

- Treatment-naïve CLL/SLL requiring treatment
- ≥65 years of age or <65 years of age and unsuitable for FCR treatment
- Measurable disease by CT/MRI
- No current / past history of Richter's transformation
- ECOG PS ≤2

Stratification:

- Age (<65 vs ≥65 years)
- Binet stage (C vs A or B)
- IGHV mutational status (mutated vs unmutated)
- Geographic region (NA vs EU vs APAC)

TREATMENT



Treatment until disease progression or unacceptable toxicity

FOLLOW-UP

Safety and survival

[a]90 mg/m2 D1 and D2 for 6 cycles, [b]375 mg/m2 D0 or D1 C1 and 500 mg/m2 D1 C 2-6, [c]ramp-up cycle (C 4-11) then 400 mg PO daily C 12-24

PATIENT DISPOSITION

Patients with del(17p) and/or TP53 mutation[a] (n=66)
Enrolled between November 2019 and June 2022

Off study prior to V initiation (n=3)
- Death (n=2)[b]
- Withdrawal by patient (n=1)

Initiated Zanu + V (n=63)

Off study (n=3)
- Death (n=2)[c]
- Lost to follow-up (n=1)

Study follow-up (n=5)
- Long-term survival follow-up (n=2)
- Post-treatment efficacy follow-up (n=3)

On treatment (n=55)
- Z+V (n=8)
- Z mono after discontinuing V (n=47)

Data cutoff: 31 January, 2024
Median follow-up: 31.6 (0.4-50.5) months

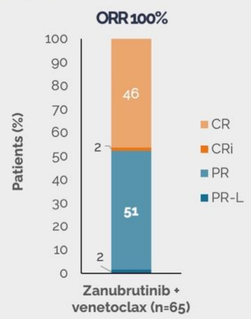
[a]Based on central assessment; [b]2 death due to AE; [c]1 AE, 1PD

PATIENT CHARACTERISTICS

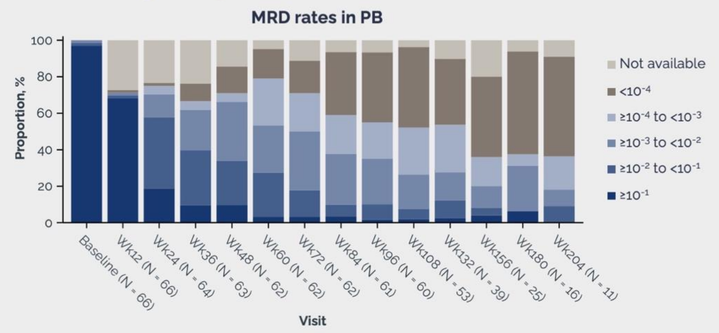
Characteristics	Zanu + V (n=66)
Median age, years	66
Male	55%
ECOG PS	
1	48%
2	3%
SLL	5%
Bulky disease	
Any target lesion LDi ≥5 cm	44%
Any target lesion LDi ≥10 cm	8%
Genotype status	
Del(17p)+ and/or *TP53* mut	64%
Del(17p)+ and/or *TP53* wt	26%
Del(17p)- and/or *TP53* mut	11%
Complex karyotype	
≥3 abnormalities	50%
≥5 abnormalities	36%
Del(17p) % of abnormal nuclei, median (range)	60.5 (1-98)

EFFICACY DATA OVERVIEW [n=65; Cohort 3 Patients with del(17p) mutations]

Primary Endpoint



Secondary Endpoints

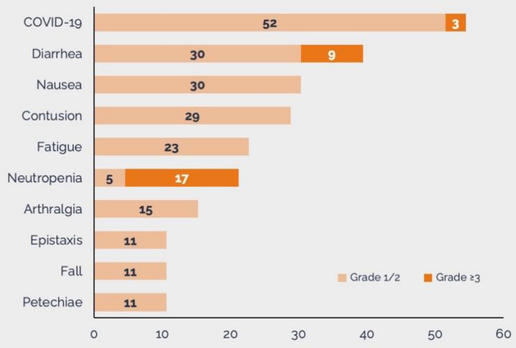


- In 65 response-evaluable patients[d] with del(17p) and/or TP53 Mutation, ORR[e,f] was 100% and the CR+CRi rate was 48%
- Rates of uMRD in PB increased with longer treatment duration
  - Best uMRD rate: 59% (39/66) in ≥1 PB sample; 37% (13/35) in ≥1 BM sample[g]
- Median PFS was not reached

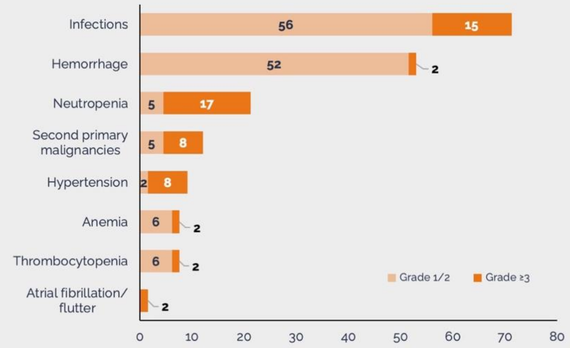
[d]Received ≥1 dose of zanubrutinib with ≥1 post-baseline disease assessment. The 1 patient that was not response-evaluable died during cycle 1. [e]Responses assessed by investigator per modified iwCLL criteria for CLL and Lugano criteria for SLL. [f]ORR was defined as PR-L or better. [g]BM biopsy and aspirate were required to confirm a suspected CR/CRi and additional BM aspirate uMRD sample collection was dependent on PB uMRD status; BM collection timing varied by patient. On treatment BM aspirate samples have been collected in 35 patients to date.

SAFETY DATA OVERVIEW [n=66; safety population analysis]

TEAEs in >10% of Patients



TEAEs of Special Interest



CONCLUSIONS

Preliminary results indicate that zanubrutinib combined with venetoclax shows favorable safety and tolerability in high-risk treatment-naïve CLL/SLL patients with del(17p) and/or TP53 mutation, with low rates of atrial fibrillation/flutter (2%) and hypertension (9%). The combination therapy demonstrated promising efficacy, achieving a 100% ORR and a high rate of uMRD. With a median follow-up of 31.6 months, the PFS estimates at 12 and 24 months were high at 95% and 94% respectively. The study is ongoing, and results for patients meeting MRD-guided early stopping criteria will be reported as data matures. Additionally, the phase 3 CELESTIAL-TNCLL trial (BGB-11417-301) is evaluating the combination of zanubrutinib and sonrotoclax, a potent next-generation BCL2 inhibitor, as a fixed-duration therapy in treatment-naïve CLL patients.

Ma S, et al. Oral Presentation at EHA 2024;S160.

1024--MRC-094

ASPEN [NCT03053440]

Zanubrutinib

An open-label, randomized study to compare the efficacy and safety of zanubrutinib and ibrutinib in participants with Waldenström's Macroglobulinemia who require therapy. The data outlined in this Quick Reference Guide are from Cohort 1.

STUDY DESIGN

PHASE **3**

STUDY SITES **Global**

INTERVENTION **Zanubrutinib vs ibrutinib**

PRIMARY ENDPOINT **CR / VGPR**

KEY SECONDARY ENDPOINTS **MRR (≥PR), PFS, OS, DoR, symptom resolution, safety**

INCLUSION

- WM histologic diagnosis
- Meeting ≥1 criterion for tx initiation
- Measurable disease
- Considered unsuitable for standard chemoimmunotherapy if treatment naïve
- No prior BTKi

Stratification:
Cohort 1:
- CXCR4 mutational status ($CXCR4^{WHIM}$ vs $CXCR4^{WT}$)
- Number of prior lines of therapy (0 vs 1-3 vs >3)

Cohort 2:
- $MYD88^{WT}$ WM patients

TREATMENT

Cohort 1 → R 1:1 → Zanubrutinib 160 mg PO BID

Cohort 1 → R 1:1 → Ibrutinib 420 mg PO QD

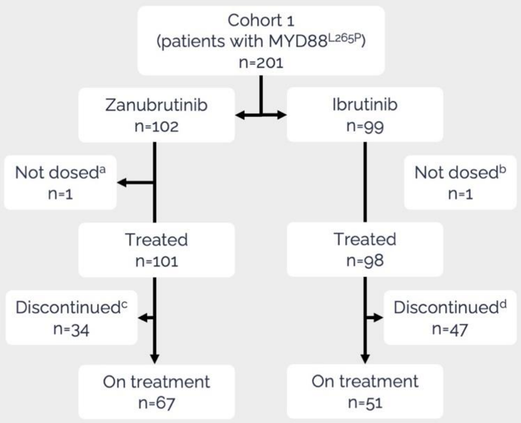
Cohort 2 → Zanubrutinib 160 mg PO BID

Treatment until unacceptable toxicity or disease progression

FOLLOW-UP

Safety and survival

PATIENT DISPOSITION



Data cutoff: 31 October, 2021 (long-term follow-up)
Median follow-up: 44.4 months

[a]1 AE; [b]1PD; [c]14 PD, 9 AE, 6 patient decision, 2 HCP decision, 3 other; [d]20 AE, 13 PD, 7 HCP decision, 2 patient decision, 5 other

PATIENT CHARACTERISTICS

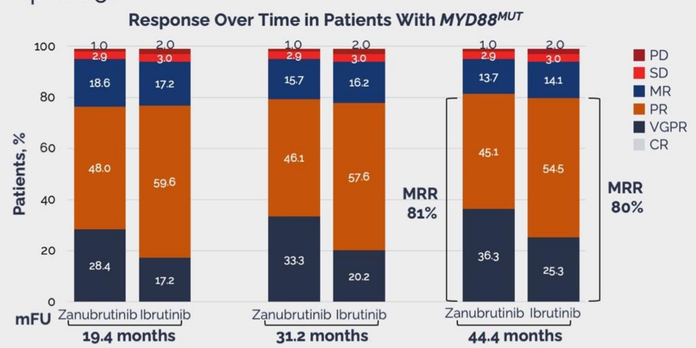
Characteristics[e]	Zanu (n=102)	Ibru (n=99)
Median age, years	70	70
Male	67.6%	65.7%
Prior lines of therapy		
0	18.6%	18.2%
1-3	74.5%	74.7%
>3	6.9%	7.1%
Genotype by NGS		
$CXCR4^{WT}$	63.7%	72.7%
$CXCR4^{MUT}$	32.4%	20.2%
Unknown	3.9%	7.1%
IPSS WM		
Low	16.7%	13.1%
Intermediate	37.3%	42.4%
High	46.1%	44.4%
Hemoglobulin ≤110 g/L	65.7%	53.5%
Median baseline IgM (g/L, central lab)	31.8	34.2
Median bone marrow involvement	60.0%	60.0%
Extramedullary disease by investigator	61.8%	66.7%

[e]Treatment arms were generally balanced except for patients aged >75 years, patients with $CXCR4^{MUT}$ by NGS, and patients with hemoglobin ≤110 g/L, which were higher on the zanubrutinib arm.

EFFICACY DATA OVERVIEW [n=201]

Primary Endpoint (DCO 31 August, 2019; median follow-up: 19.4 months)
CR / VGPR 28% vs 19%[f]
(p=0.09)

Response Over Time in Patients With *MYD88^MUT*



[f]The primary hypothesis of superiority in CR/VGPR rate (by IRC) was not met.

Secondary Endpoints (DCO 31 October, 2021)

	Zanu (n=102)	Ibru (n=99)
Estimated 42-month PFS	78.3%	69.7%
Events, n (%)	20 (19.6)	30 (30.3)
	HR (95% CI): 0.63 (0.36-1.12)	
Estimated 42-month PFS	87.5%	85.2%
Events, n (%)	12 (11.8)	17 (17.2)
	HR (95% CI): 0.75 (0.36-1.59)	

SAFETY DATA OVERVIEW [n=199]

Summary of AEs (DCO 31 August, 2019)

AE	Zanu (n=101)	Ibru (n=98)
Patients with ≥ 1 AE	99.0%	100%
Grade ≥ 3	74.3%	72.4%
Serious AE	56.4%	50.0%
AE leading to death	3.0%	5.1%
AE leading to treatment discontinuation	8.9%	20.4%
AE leading to dose reduction	15.8%	26.5%
AE leading to dose held	62.4%	63.3%
COVID-19 related AE	4.0%	4.1%

AEs of Interest
[Any grade, zanu vs ibru]

	Zanu	Ibru
Infection	79.2%	79.6%
Bleeding	55.4%	62.2%
Diarrhea	22.8%	34.7%
Hypertension	14.9%	25.5%
AF / flutter	7.9%	23.5%
Anemia	17.8%	22.4%
Neutropenia	34.7%	20.4%

CONCLUSIONS

The ASPEN trial revealed that zanubrutinib, with exploratory long-term follow-up, continued to demonstrate clinically meaningful efficacy in WM patients. A consistent trend of deeper, earlier, and more durable CR + VGPR rates vs ibrutinib responses was observed over time. Zanubrutinib provided faster and deeper responses in patients with $CXCR4^{MUT}$, and PFS and OS continued to favor zanubrutinib. Safety advantages of zanubrutinib remained consistent with less off-target activity compared with ibrutinib.

Dimopolous MA et al. J Clin Oncol 2023;41:5099-5106
Tam CS et al. Blood. 2020;136(18):2038-2050

BGB-3111-215 [NCT04116437]

An exploratory Phase 2, open-label, multicenter, single-arm study investigating zanubrutinib in patients with previously treated B-cell malignancies intolerant of previous Bruton tyrosine-kinase inhibitors.

STUDY DESIGN

PHASE	**2**
STUDY SITES	**USA**
INTERVENTION	**Zanubrutinib**
PRIMARY ENDPOINT	**Investigator-assessed recurrence and change in severity of ibrutinib and/or acalabrutinib intolerance events[a]**
KEY SECONDARY ENDPOINTS	**Investigator-assessed ORR, DCR, PFS and HRQoL**

INCLUSION

- Previously treated CLL/SLL, WM, MCL, or MZL patient intolerant of ibrutinib and/or acalabrutinib[b]
- Indication for treatment per iwCLL prior to ibrutinib
- Ibrutinib- and/or acalabrutinib intolerant in opinion of investigator[c]
- Ibrutinib- and/or acalabrutinib-related toxicities resolved to Gr ≤1 or baseline
- ECOG PS ≤2
- ANC ≥1000/mm^3 and platelet count ≥50,000/mm^3
- No documented PD during ibrutinib and/or acalabrutinib treatment[d]
- No clinically significant cardiovascular disease

TREATMENT

Cohort 1: Intolerant to ibrutinib

Cohort 2: Intolerant to acalabrutinib alone or to acalabrutinib and ibrutinib

Screening at ≤14 days

Zanubrutinib 160 mg PO BID or 320 mg PO QD

Treatment until PD, unacceptable toxicity, treatment consent withdrawal, or study termination

FOLLOW-UP

Safety follow-up for 30 days after the end of treatment

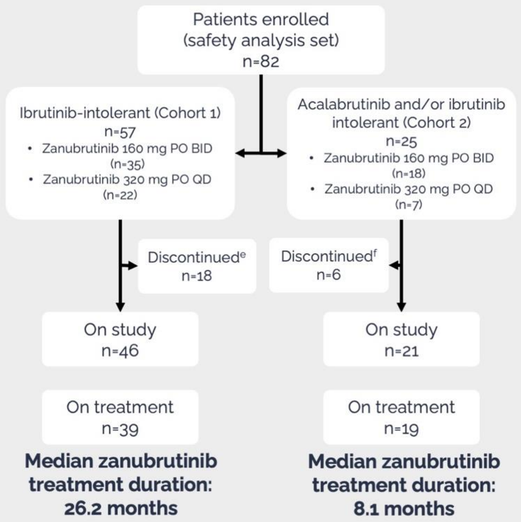
[a]TEAEs of interest: arthralgia, atrial fibrillation, diarrhea, fatigue, hemorrhage, hypertension, muscle spasms, myalgia, rash.

[b]There is a ≥7-day washout period for any anticancer therapy and a ≥4-week washout period for immunotherapy, taken alone or as part of a chemoimmunotherapy regimen.

[c]Intolerance is defined as an unacceptable toxicity where, in the opinion of the investigator, treatment should be discontinued in spite of optimal supportive care as a result of: Grade ≥2 non-hematologic toxicities for >7 days; Grade ≥3 non-hematologic toxicity of any duration; Grade 3 neutropenia with infection or fever; or Grade 4 hematologic toxicity that persists until ibrutinib therapy is discontinued due to toxicity NOT until progression.

[d]A disease flare meeting PD criteria while the patient is off ibrutinib and/or acalabrutinib treatment is not considered to be true PD.

PATIENT DISPOSITION



[e]5 AE, 6 PD, 3 withdrawal by patient, 4 other
[f]2 AE, 2 withdrawal by patient, 1 PD, 1 other

PATIENT CHARACTERISTICS

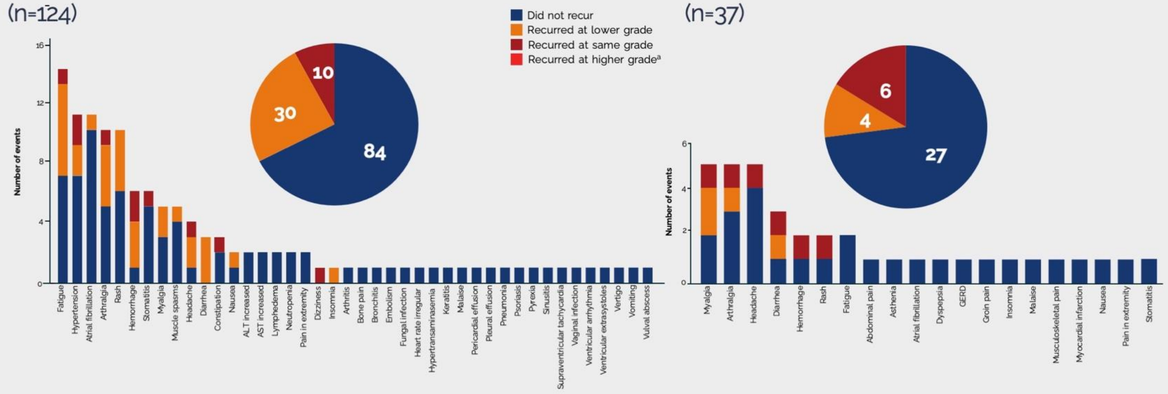
Characteristics	Ibru intolerant (n=57)	Acala intolerant[g] (n=25)
Indication		
CLL	66.7%	60.0%
SLL	10.5%	8.0%
MCL	3.5%	8.0%
MZL	3.5%	8.0%
WM	15.8%	16.0%
Median age, years	71.0	74.0
Male	52.6%	60.0%
ECOG PS 0-1	100%	92.0%
Median prior anticancer therapy regimens	1	2
Median prior BTKi exposure, months		
Ibrutinib	10.6	6.2
Acalabrutinib	-	5.1

[g]Includes patients intolerant to ibrutinib in addition to acalabrutinib

EFFICACY DATA OVERVIEW [n=84; DCO 03 January, 2023 (median follow-up: 25.2 months)]

Primary Endpoint: Recurrence and change in severity of ibrutinib or acalabrutinib intolerance events (DCO 03 January, 2023; median follow-up: 25.2 months)

Ibrutinib intolerance events (n=124)



Acalabrutinib intolerance events (n=37)

- ORR was 73.2% in ibrutinib intolerant patients and 65.0% in acalabrutinib and/or ibrutinib intolerant patients
- Among the 76 efficacy-evaluable patients receiving zanubrutinib, ≥95% of patients across cohorts had controlled disease and ≥65% achieved a PR, thereby maintaining or improving response

SAFETY DATA OVERVIEW [n=82; safety population analysis]

Summary of AEs

AE	Ibru intolerant (n=57)	Acala intolerant (n=25)
Patients with ≥1 AE	96.5%	92.0%
Grade ≥3 AE	50.9%	32.0%
Serious AE	26.3%	16.0%
AE Leading to treatment discontinuation	8.8%	8.0%
AE Leading to dose interruption or reduction	71.9%	60.0%
AE Leading to death	1.8%	0%

Most Common AEs (≥10%)

[Any grade, ibru intolerant vs acala intolerant]

	Ibru intolerant	Acala intolerant
Fatigue	31.6%	24.0%
Contusion	24.6%	16.0%
Arthralgia	21.1%	20.0%
Diarrhea	17.5%	28.0%
Myalgia	17.5%	20.0%
Cough	10.5%	24.0%
Hypertension	8.8%	20.0%

CONCLUSIONS

BGB-3111-215 may provide potential treatment options for patients intolerant of previous BTK inhibitors. These longer-term results suggest that exposure to zanubrutinib has the potential to offer sustained clinical benefit for patients intolerant to ibrutinib and/or acalabrutinib.

Shadman M et al. Lancet Haematol 2023;10:e35-e45
Shadman M et al. Poster presented at EHA 2023;abstract P683

BGB-3111-LTE1 [NCT04170283]

Zanubrutinib

An open-label, multicenter long-term extension study to evaluate the long-term safety of zanubrutinib regimens in participants with B-cell malignancies who participated in a BeiGene parent study for zanubrutinib. Presented here is the analysis from the ibrutinib arm of ASPEN.

STUDY DESIGN

PHASE **3**

STUDY SITES **USA**

INTERVENTION **Zanubrutinib**

PRIMARY ENDPOINT **Safety**

KEY SECONDARY ENDPOINTS **PFS, DoR, OS**

INCLUSION

- Currently participating/participated in a BeiGene parent study
- Intent to continue or start zanubrutinib after any of the following:
  - At time of final analysis or study closure
  - At time of PD, and investigator, patient and medical monitor agree it is patients' best interest
  - At an alternative timepoint for an alternative reason
- Currently on zanubrutinib treatment
- Zanubrutinib-naïve patient

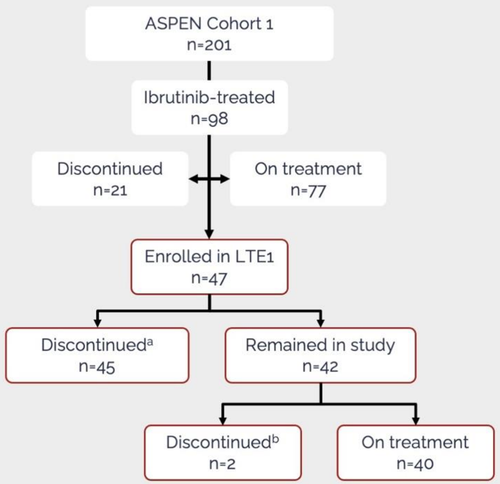
TREATMENT

Zanubrutinib 160 mg PO BID (or last dose level received)

FOLLOW-UP

Up to 5 years

PATIENT DISPOSITION



Data cutoff: 23 June, 2023
Median zanubrutinib treatment duration: 15.3 months

[a]3 death, 1 lost to follow-up, 1 withdrawal; [b]including 5 who left the study plus 2 who remained, 3 other, 2 AE, 1 PD, 1 withdrawal

PATIENT CHARACTERISTICS

Characteristics	Zanu (N=47)
Median age, years	73
Age group	
<65 years	17%
≥65 and <75 years	45%
≥75 years	38%
ECOG PS	
0	57%
1	36%
2	2%

SAFETY DATA OVERVIEW [n=47]

Primary Endpoint
Overall Safety Summary

AE	ASPEN: Ibru N=47	LTE1: Zanu N=47
Any TEAE	100%	81%
Treatment-related	89%	36%
Grade ≥3		23%
Serious	47%	13%
Treatment-related	32%	-
Leading to treatment discontinuation	6%	4%
Leading to dose reduction	23%	-
Leading to dose interruption	64%	23%
Fatal AE	-	4%

TEAEs of interest
[Any grade, all patients]

Infections	47%
Hemorrhage	13%
Secondary primary malignancy	11%
Neutropenia	11%
Anemia	9%
Hypertension	2%
Atrial fibrillation/flutter	2%
Thrombocytopenia	2%

- Majority of ibrutinib-emergent AEs did not recur or worsen with zanubrutinib
- Those that did worsen included infections (n=3; all COVID-19), anemia (n=1), and neutropenia (n=1)
- No ongoing hypertension worsened in severity and no new or recurrent episodes of hypertension occurred after patients switched from ibrutinib to zanubrutinib

EFFICACY DATA OVERVIEW [n=199]

ORR: 96%

Overall Response Assessment

n (%)	ASPEN Last Assessment	LTE1
CR	0	2 (4)
VGPR	13 (28)	17 (36)
PR	27 (57)	23 (49)
MR	3 (6)	3 (6)
IgM flare	1 (2)	NA
PD	2 (4)	NA
Discontinued prior to assessment	NA	1 (2)

- Best overall response was unchanged from last response in ASPEN in 72% of patients and improved in 21%
- IgM was stable or decreased in majority of evaluable patients

CONCLUSIONS

The majority of ibrutinib-emergent AEs did no recur or worsen with zanubrutinib treatment, despite advanced and increasing age. WM disease response was maintained or improved in efficacy-evaluable patients. While limited by sample size and non-randomized/ad hoc analysis, data suggest that patients who are tolerating ibrutinib may switch to zanubrutinib without compromising, and may improve upon, safety or efficacy. Long-term follow-up is ongoing.

Garcia-Sanz R, et al. Poster Presentation at ASH 2023; poster number 3043

BGB-11417-101: R/R CLL [NCT04277637]

Sonrotoclax

CLL/SLL

A Phase 1a/1b, open-label, dose escalation and expansion study investigating sonrotoclax in monotherapy and in combination with zanubrutinib and obinutuzumab in patients with mature B-cell malignancies.

STUDY DESIGN

PHASE	**1a/1b**
STUDY SITES	**Global**
INTERVENTION	**Sonrotoclax monotherapy, ± zanubrutinib, and ± obinutuzumab**
PRIMARY ENDPOINT	**Safety per CTCAE v5.0, MTD, and RP2D**
KEY SECONDARY ENDPOINTS	**PK/PD, ORR by investigator**

INCLUSION

Confirmed diagnosis of:
- R/R MZL: ≥2L, extranodal, splenic, or nodal
- R/R FL: ≥2L, grade 1-3a
- R/R DLBCL: ≥3L
- Transformed indolent B-cell NHL
- **CLL/SLL:** TN or R/R
- R/R MCL: ≥2L
- R/R WM
- ECOG PS 0-2
- No prior therapy ≥2 months with, or progression on, a BCL2 inhibitor

TREATMENT

Part 1: Dose Escalation Sonrotoclax Monotherapy → *R/R NHL, R/R CLL/SLL, R/R MCL, R/R WM*

RP2D

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

Part 2: Dose Expansion Sonrotoclax Monotherapy → *R/R aggressive and indolent NHL, R/R CLL/SLL, R/R MCL, R/R WM*

Part 3: Dose Finding Sonrotoclax + Zanubrutinib → ***R/R CLL/SLL**, R/R MCL*

RP2D

Part 4: Dose Expansion Sonrotoclax + Zanubrutinib → *TN CLL/SLL, **R/R CLL/SLL**, R/R MCL*

TREATMENT SCHEDULE

Sonrotoclax + zanubrutinib dose finding[a] (weekly ramp-up) — R/R CLL/SLL → **Sonrotoclax + zanubrutinib expansion (daily or weekly ramp-up)** — R/R CLL/SLL

- 640 mg
- 320 mg
- 160 mg
- 80 mg
- 40 mg

320 mg selected for expansion → 320 mg

Data cutoff: February 4, 2024
Median follow-up: 19.3 months

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

PATIENT CHARACTERISTICS

Characteristic	All R/R CLL/SLL (N=47)
Median age, years	65
Male	75%
ECOG PS 0-1	96%
Risk status, n/tested[b]	
del(17p)	11/42=26%
del(17p) and/or TP53 mutation	25/47=53%
Unmutated IGHV, n/tested	13/19=68%
Median no. prior lines of therapy	1
Prior BTKi[c]	15%
Median duration of BTKi, months	34.2

[b]TP53 mutations defined as >0.1% variant allele frequency. [c]BTK inhibitor was the last prior therapy for 7 patients: all discontinued due to toxicity.

SAFETY DATA OVERVIEW [N=47]

Primary Endpoint
Overall Safety Summary

AE	All Patients (N=47)
Any TEAE	94%
Grade ≥3	51%
Serious	28%
Led to zanu discontinuation	4%
Led to zanu dose reduction	2%
Treated with sonro	94%
TEAEs leading to sonro discontinuation	2%
TEAEs leading to sonro dose reduction	0

TEAEs in ≥20% of patients
[Any grade, all patients]

Contusion	32%
Neutropenia	27%
COVID-19	28%
Diarrhea	28%
Fatigue	26%
Nausea	23%
URTI	23%
Cough	21%

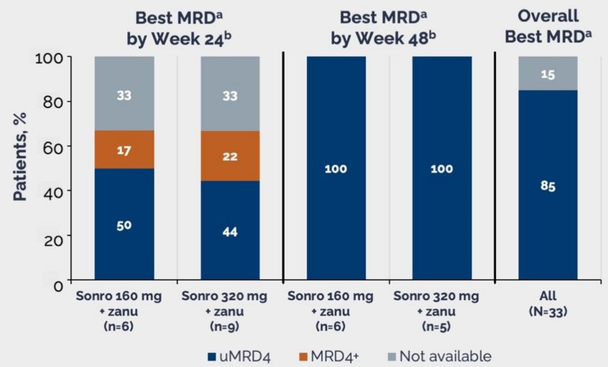
- No DLTs occurred and MTD was not reached; the 320 mg sonrotoclax + zanubrutinib cohort was expanded as RP2D
- Sonrotoclax + zanubrutinib was well tolerated, with very low rates of treatment discontinuation and dose reductions; no deaths were observed
- TEAEs observed with sonrotoclax + zanubrutinib were mostly low grade and transient
  - No TLS, atrial fibrillation, or febrile neutropenia

EFFICACY DATA OVERVIEW [n=35; efficacy evaluable population]

All Patients:
97% ORR with 57% CR/CRi
320 mg Cohort (n=11):
100% ORR with 73% CR/CRi

- Of 33 MRD-evaluable patients, 28 (85%) had uMRD at time of data cutoff
- All patients in the 160 mg, 320 mg and 640 mg cohorts who reached week 48 achieved uMRD

uMRD in Peripheral Blood



[a]Measured by an ERIC-approved flow cytometry method with 10^{-4} sensitivity. uMRD4 defined as $<10^{-4}$ CLL cells of total WBCs. MRD4+ defined as $\geq 10^{-4}$ CLL cells of total WBCs. MRD is best reported within a 2-week window following the W24/W48D1 MRD assessments. [b]Week 24 or 48 of treatment at target dose, following zanu monotherapy and sonro ramp-up to target dose.

CONCLUSIONS

Sonrotoclax + zanubrutinib combination treatment had a generally tolerable safety profile in patients with R/R CLL/SLL at all dose levels tested up to 640 mg. 46/47 of patients remain on study treatment with a median follow-up of 19.3 months. Initial efficacy was reported in this R/R CLL/SLL population, including patients with high-risk features. Follow up is ongoing with this combination therapy.

Opat S, et al. Oral Presentation at EHA 2024;S156.

1024--MRC-094

BGB-11417-101: TN CLL [NCT04277637]

Sonrotoclax

CLL/SLL

A Phase 1a/1b, open-label, dose escalation and expansion study investigating sonrotoclax in monotherapy and in combination with zanubrutinib and obinutuzumab in patients with mature B-cell malignancies.

STUDY DESIGN

PHASE	**1a/1b**
STUDY SITES	**Global**
INTERVENTION	**Sonrotoclax monotherapy, ± zanubrutinib, and ± obinutuzumab**
PRIMARY ENDPOINT	**Safety per CTCAE v5.0, MTD, and RP2D**
KEY SECONDARY ENDPOINTS	**PK/PD, ORR by investigator**

INCLUSION

Confirmed diagnosis of:

- R/R MZL: ≥2L, extranodal, splenic, or nodal
- R/R FL: ≥2L, grade 1-3a
- R/R DLBCL: ≥3L
- Transformed indolent B-cell NHL
- **CLL/SLL**: TN or R/R
- R/R MCL: ≥2L
- R/R WM
- ECOG PS 0-2
- No prior therapy ≥2 months with, or progression on, a BCL2 inhibitor

TREATMENT

Part 1: Dose Escalation
Sonrotoclax Monotherapy

R/R NHL, R/R CLL/SLL, R/R MCL, R/R WM

RP2D

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

Part 2: Dose Expansion
Sonrotoclax Monotherapy

R/R aggressive and indolent NHL, R/R CLL/SLL, R/R MCL, R/R WM

Part 3: Dose Finding
Sonrotoclax + Zanubrutinib

*R/R CLL/SLL, R/R MCL, **TN CLL/SLL***

RP2D

Part 4: Dose Expansion
Sonrotoclax + Zanubrutinib

***TN CLL/SLL**, R/R CLL/SLL, R/R MCL*

TREATMENT SCHEDULE

Sonrotoclax + zanubrutinib dose finding (weekly ramp-up)
TN CLL/SLL

→

Sonrotoclax + zanubrutinib expansion (daily or weekly ramp-up)
TN CLL/SLL

640 mg
320 mg
160 mg
80 mg
40 mg

160 mg and 320 mg selected for expansion

320 mg
160 mg

Data cutoff: August 15, 2023
Median follow-up: 9.7 months

PATIENT CHARACTERISTICS

Characteristic	Sonro 160 mg (n=51)	Sonro 320 mg (n=56)	All Patients (N=107)
Median age, years	63	61	62
Male	73%	79%	76%
Disease type			
CLL	96%	93%	94%
SLL	4%	7%	6%
Risk status[a]			
del(17p)	12%	11%	12%
del(17p) and/or TP53 mutation	24%	27%	26%
Unmutated IGHV	70%	55%	62%
Tumor bulk at baseline			
High[b]	39%	25%	32%
Not high	61%	75%	68%

[a]TP53 mutations defined as >10% variant allele frequency. [b]Nodes ≥10 cm or nodes >5 cm and ALC >25×10⁹/L.

SAFETY DATA OVERVIEW [N=47]

Primary Endpoint

Overall Safety Summary

AE	160 mg (n=51)	320 mg (n=56)	All Patients (N=107)
Any AE	92%	88%	90%
Grade ≥3	43%	38%	40%
Serious	14%	14%	14%
Led to zanu discontinuation	2%	0	1%
Led to zanu dose reduction	2%	4%	3%
Treated with sonro	80%	95%	88%
Leading to hold of sonro	27%	19%	22%
Leading to sonro discontinuation	2%	0	1%
Leading to sonro dose reduction	5%	6%	5%

TEAEs in ≥15% of patients

[Any grade, 160 mg vs 320 mg]

	160 mg	320 mg
Contusion	35%	36%
Neutropenia	31%	32%
COVID-19	31%	11%
Headache	24%	16%
Diarrhea	24%	20%
Fatigue	24%	9%
Petechiae	16%	5%
Nausea	14%	20%
Back pain	12%	16%
URTI	10%	23%

- Sonrotoclax in combination with zanubrutinib is well tolerated and generally favorable, with very low rates of treatment discontinuation and dose reductions
- AEs observed with sonrotoclax + zanubrutinib combination therapy were mostly Grades 1 and 2

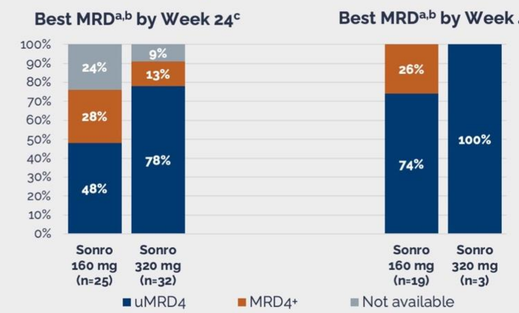
EFFICACY DATA OVERVIEW [n=75; efficacy evaluable population]

All Patients:

100% ORR with 32% CR

- At Week 48, ORR was 100% at both dose levels, with a CR rate of 42% and 33% for 160 mg and 320 mg, respectively
- High uMRD achieved at both dose levels – trend for higher uMRD rates with 320 mg

uMRD in Peripheral Blood



[a]MRD was measured by ERIC flow cytometry with 10^{-4} sensitivity. uMRD4 is defined as the number of CLL cells of total nucleated cells $<10^{-4}$. MRD4+ is defined as the number of CLL cells of total nucleated cells $>10^{-4}$; [b]MRD is best reported within a 2-week window following W24D1 and W48D1 MRD assessment timepoints, respectively; [c]W24 or 48 represents 24 or 48 weeks at target dose, following zanubrutinib monotherapy and sonrotoclax ramp-up to target dose.

CONCLUSIONS

Sonrotoclax 160 or 320 mg in combination with zanubrutinib 320 mg QD was safe and generally well tolerated in patients with TN CLL. 106/107 patients remain on treatment. Preliminary efficacy was demonstrated with ORR of 100% and no PFS events observed at data cut-off. Based on these data, 320 mg was selected for the Phase 3 study in combination with zanubrutinib in TN CLL.

Tam CS, et al. Oral Presentation at ASH 2023; abstract number 327.

1024--MRC-094

BGB-11417-101: WM [NCT04277637]

Sonrotoclax WM

A Phase 1a/1b, open-label, dose escalation and expansion study investigating sonrotoclax in monotherapy and in combination with zanubrutinib and obinutuzumab in patients with mature B-cell malignancies.

STUDY DESIGN

PHASE	**1a/1b**
STUDY SITES	**Global**
INTERVENTION	**Sonrotoclax monotherapy, ± zanubrutinib, and ± obinutuzumab**
PRIMARY ENDPOINT	**Safety per CTCAE v5.0, MTD, and RP2D**
KEY SECONDARY ENDPOINTS	**PK/PD, ORR by investigator**

INCLUSION

Confirmed diagnosis of:
- R/R MZL: ≥2L, extranodal, splenic, or nodal
- R/R FL: ≥2L, grade 1-3a
- R/R DLBCL: ≥3L
- Transformed indolent B-cell NHL
- CLL/SLL: TN or R/R
- R/R MCL: ≥2L
- **R/R WM**

- ECOG PS 0-2
- No prior therapy ≥2 months with, or progression on, a BCL2 inhibitor

TREATMENT

Part 1: Dose Escalation Sonrotoclax Monotherapy
*R/R NHL, R/R CLL/SLL, R/R MCL, **R/R WM***

→ **RP2D** → **Part 2: Dose Expansion** Sonrotoclax Monotherapy
R/R aggressive and indolent NHL, R/R CLL/SLL, R/R MCL, R/R WM

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

Part 3: Dose Finding Sonrotoclax + Zanubrutinib
R/R CLL/SLL, R/R MCL, TN CLL/SLL

→ **RP2D** → **Part 4: Dose Expansion** Sonrotoclax + Zanubrutinib
TN CLL/SLL, R/R CLL/SLL, R/R MCL

PATIENT DISPOSITION

Patients with R/R WM
N=20

- **Safety population/all enrolled (n=20)**
  - **Efficacy-evaluable population (n=19)**
  - **On active treatment (n=14)**
  - **Off treatment (n=6)**
    - Progressive disease (n=4)
    - AE of multifocal neurological syndrome (n=1)
    - COVID-19 (n=1)

Data cutoff: February 4, 2024
Median follow-up (all patients): 12.3 months

PATIENT CHARACTERISTICS

Characteristic	All Patients (N=20)
Median age, years	69
Male	80%
ECOG PS 0-1	95%
MYD88 mutation	100%
CXCR4 mutation	27%
Median no. prior lines of therapy	2.5
Prior BTK inhibitor	60%
BTK inhibitor as last therapy	45%

SAFETY DATA OVERVIEW [N=20]

Primary Endpoint

Overall Safety Summary

AE	80 mg (n=6)	160 mg (n=8)	320 mg (n=5)	640 mg (n=1)	All (n=20)
Any AE	83%	100%	100%	0	90%
Grade ≥3	50%	38%	20%	0	35%
Serious	50%	25%	20%	0	30%
Deaths	17%	13%	0	0	10%
Led to sonro discontinuation	17%	13%	0	0	10%
Led to sonro dose interruption	33%	38%	0	0	25%

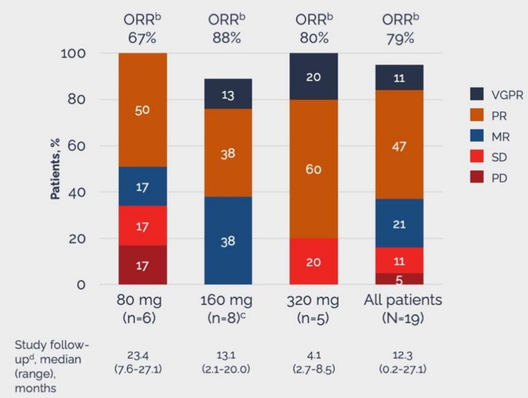
TEAEs in ≥15% of patients
[Any grade, all patients]

Anemia	35%
COVID-19	30%
Pyrexia	25%
Pruritus	20%
Neutropenia	20%
Nausea	20%
Rash	15%
Headache	15%
Contusion	15%
Fatigue	15%
Thrombocytopenia	15%

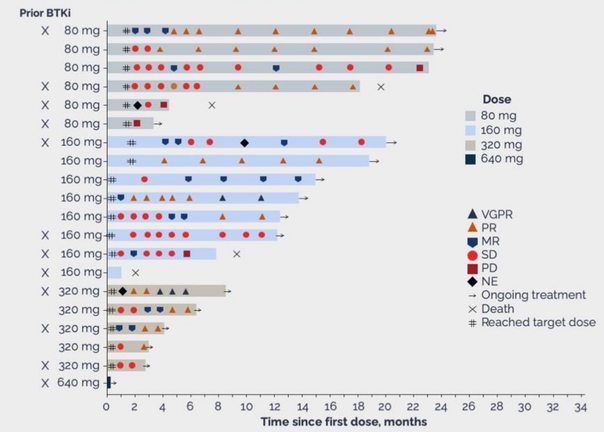
- No laboratory or clinical TLS was seen regardless of target dose
- No dose reductions were reported at any dose level and dose escalation is ongoing at 640 mg, with no MTD reached at the time of data cut-off

EFFICACY DATA OVERVIEW [n=19; efficacy evaluable population]

All Patients: 79% ORR with 11% VGPR



Treatment Duration



[a]Responses were assessed per modified Owens 2013 criteria. [b]ORR defined as MR or better. [c]One patient died due to COVID-19 before a post-baseline response assessment. [d]For all patients as treated (N=20).

CONCLUSIONS

Sonrotoclax monotherapy was generally well tolerated in patients with R/R WM; the MTD was not reached, and no laboratory or clinical TLS events were observed. Preliminary antitumor activity was demonstrated in a heavily pretreated population of patients. Further evaluation of sonrotoclax monotherapy in patients in R/R WM is ongoing in a pivotal Phase 2 study (BGB-11417-203).

Cheah C, et al. Poster Presentation at EHA 2024;P1110.

1024--MRC-094

BGB-11417-101: MZL [NCT04277637]

Sonrotoclax

MZL

A Phase 1a/1b, open-label, dose escalation and expansion study investigating sonrotoclax in monotherapy and in combination with zanubrutinib and obinutuzumab in patients with mature B-cell malignancies.

STUDY DESIGN

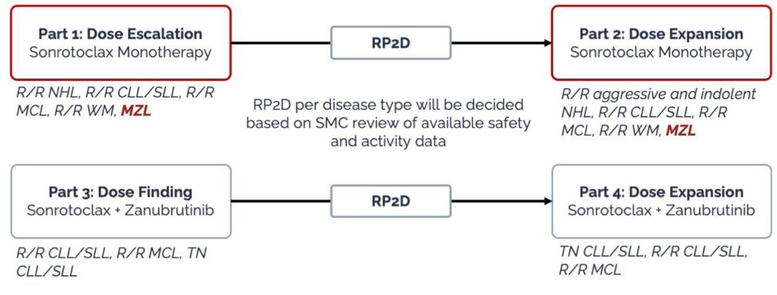
PHASE	**1a/1b**
STUDY SITES	**Global**
INTERVENTION	**Sonrotoclax monotherapy, +/- zanubrutinib, +/- obinutuzumab**
PRIMARY ENDPOINT	**Safety per CTCAE v5.0, MTD, and RP2D**
KEY SECONDARY ENDPOINTS	**PK/PD, ORR by investigator**

INCLUSION

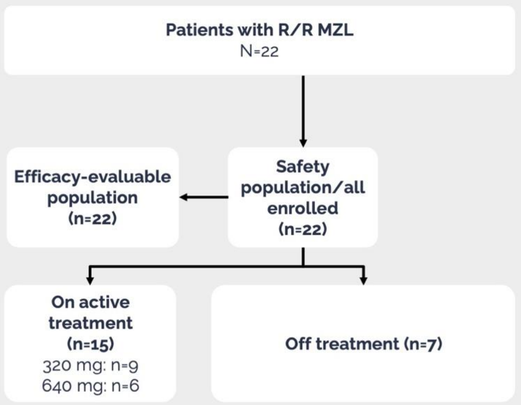
Confirmed diagnosis of:
- **R/R MZL**: ≥2L, extranodal, splenic, or nodal
- R/R FL: ≥2L, grade 1-3a
- R/R DLBCL: ≥3L
- Transformed indolent B-cell NHL
- CLL/SLL: TN or R/R
- R/R MCL: ≥2L
- R/R WM

- ECOG PS 0-2
- No prior therapy ≥2 months with, or progression on, a BCL2 inhibitor

TREATMENT



PATIENT DISPOSITION



Data cutoff: August 15, 2023
Median follow-up (all patients): 6.5 months

PATIENT CHARACTERISTICS

Characteristic	640 mg (n=10)	All Patients (N=20)
Median age, years	73	75
Male	50%	45%
ECOG PS 0-1	80%	91%
Median no. prior lines of therapy	1.5	2.0
Prior BTK inhibitor	40%	45%
BTK inhibitor as last therapy	30%	36%
Prior rituximab	100%	100%
Prior CHOP-like regimens	50%	73%
Prior bendamustine	60%	45%

SAFETY DATA OVERVIEW [N=22]

Primary Endpoint

Overall Safety Summary

AE	640 mg (n=10)	All (N=22)
Any AE	100%	95%
Grade ≥3	60%	45%
Serious	50%	36%
Leading to death	10%	5%
Led to sonro discontinuation	10%	5%
Led to sonro dose interruption	20%	14%

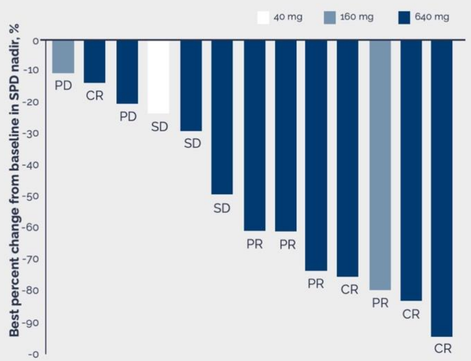
- Dose expansion started with the 640 mg dose; the 320 mg dose was later expanded to include an additional 10 patients based on efficacy signal seen in the MZL subset
- No clinical TLS was observed; 2 patients experienced laboratory TLS
- G-CSF used for neutropenia in 2 patients

TEAEs in ≥15% of patients
[Any grade, ≤320 mg and 640 mg]

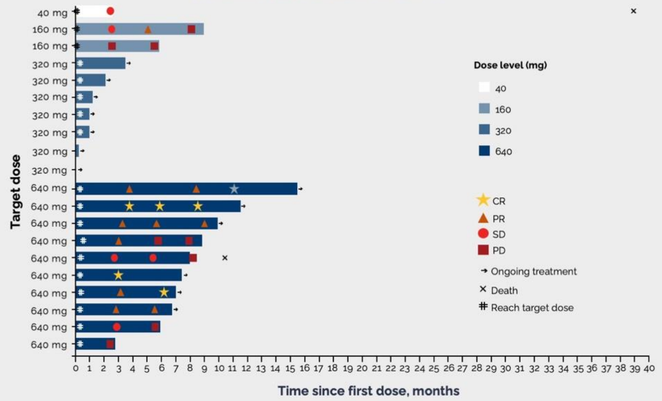
	≤320 mg	640 mg
Pyrexia	25%	40%
Nausea	33%	20%
Neutropenia	25%	30%
Constipation	17%	30%
Anemia	17%	20%
Diarrhea	8%	30%
Fatigue	33%	0
Headache	8%	30%
Back pain	0	30%

EFFICACY DATA OVERVIEW [n=19; efficacy evaluable population]

All Patients: 62% ORR



Treatment Duration



CONCLUSIONS

Sonrotoclax was generally well tolerated in patients with R/R MZL; 640 mg was the highest dose assessed, and the MTD was not reached. Sonrotoclax demonstrated single-agent activity, with an ORR of 70% with 640 mg dose; efficacy data from the 320 mg expansion dose level is forthcoming.

Tedeschi et al. Poster presented at ASH 2023; poster number: 3032.

BGB-11417-101: MCL [NCT04277637]

Sonrotoclax

MCL

A Phase 1a/1b, open-label, dose escalation and expansion study investigating sonrotoclax in monotherapy and in combination with zanubrutinib and obinutuzumab in patients with mature B-cell malignancies.

STUDY DESIGN

PHASE	**1a/1b**
STUDY SITES	**Global**
INTERVENTION	**Sonrotoclax monotherapy, ± zanubrutinib, and ± obinutuzumab**
PRIMARY ENDPOINT	**Safety per CTCAE v5.0, MTD, and RP2D**
KEY SECONDARY ENDPOINTS	**PK/PD, ORR by investigator**

INCLUSION

Confirmed diagnosis of:
- R/R MZL: ≥2L, extranodal, splenic, or nodal
- R/R FL: ≥2L, grade 1-3a
- R/R DLBCL: ≥3L
- Transformed indolent B-cell NHL
- CLL/SLL: TN or R/R
- **R/R MCL**: ≥2L
- R/R WM

- ECOG PS 0-2
- No prior therapy ≥2 months with, or progression on, a BCL2 inhibitor

TREATMENT

Part 1: Dose Escalation Sonrotoclax Monotherapy → **RP2D** → **Part 2: Dose Expansion** Sonrotoclax Monotherapy

R/R NHL, R/R CLL/SLL, R/R MCL, R/R WM, MZL

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

R/R aggressive and indolent NHL, R/R CLL/SLL, R/R MCL, R/R WM, MZL

Part 3: Dose Finding Sonrotoclax + Zanubrutinib → **RP2D** → **Part 4: Dose Expansion** Sonrotoclax + Zanubrutinib

*R/R CLL/SLL, **R/R MCL**, TN CLL/SLL*

*TN CLL/SLL, R/R CLL/SLL, **R/R MCL***

PATIENT DISPOSITION

Patients with R/R MCL
N=40

Safety population/all enrolled (N=40)

Efficacy-evaluable population (n=32)

On treatment (n=27)
80 mg: n=5
160 mg: n=6
320 mg: n=12
640 mg: n=4

Off treatment (n=13)
- PD (n=5)
- AE (n=4)
- Patient withdrawal (n=1)

Data cutoff: February 4, 2024
Median follow-up (all patients): 12.5 months

PATIENT CHARACTERISTICS

Characteristic	All Patients (N=40)
Median age, years	69
Male	65%
ECOG PS 0-1	98%
Tumor bulk	
LDi <10 and ≥5 cm	30%
LDi ≥10 cm	15%
Ki67 proliferation index	
<30%	33%
≥30%	25%
Median no. prior lines of therapy	1
Prior BTK inhibitor	8%
BTK inhibitor as last therapy	8%
Prior cellular therapies	28%

SAFETY DATA OVERVIEW [N=40]

Primary Endpoint

Overall Safety Summary

AE	All (N=40)
Any AE	93%
Grade ≥3	45%
Serious	23%
Leading to death	8%
Led to zanu discontinuation	15%
Led to zanu dose reduction	5%
Treated with sonro	88%
Led to sonro discontinuation	13%
Led to sonro dose reduction	0
Led to death	3%

TEAEs in ≥15% of patients
[Any grade, all patients]

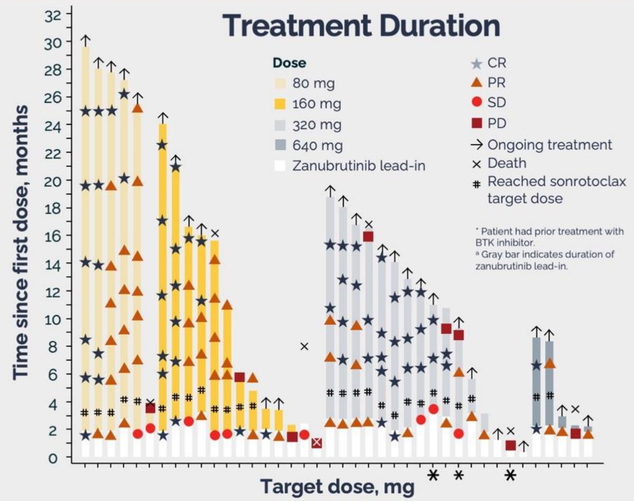
Contusion	30%
Neutropenia	28%
Diarrhea	28%
Thrombocytopenia	23%
COVID-19	23%
Fatigue	20%
Anemia	15%
Headache	15%

- Toxicity was generally the same amongst all tested dose levels with no new safety signals identified and sonrotoclax 160-mg and 320-mg dose levels were chosen for expansion cohorts
- No atrial fibrillation was observed
- No laboratory or clinical TLS seen regardless of target dose and dose escalation was completed with no MTD reached

EFFICACY DATA OVERVIEW [n=32; efficacy evaluable population]

All Patients:
81% ORR
63% CR

- ORRs were 73% and 92% in the 160- and 320-mg cohorts, respectively, and CR rates were 46% and 83%, respectively
- Of 3 response-evaluable patients with prior BTK inhibitor treatment, 2 responded: 1 achieved PR and 1 achieved CR



CONCLUSIONS

Sonrotoclax in combination with zanubrutinib was generally well tolerated in patients with R/R MCL. The MTD was not reached up to the highest assessed dose of 640 mg. Sonrotoclax plus zanubrutinib demonstrated responses in this patient population, with an ORR of 92% in the 320 mg cohort. The 320 mg cohort was selected as RP2D for development in future pivotal studies.

Tam C, et al. Poster Presentation at EHA 2024;P1112.

1024--MRC-094

CELESTIAL-TN CLL [BGB-11417-301, NCT06073821]

A Phase 3, randomized, open-label study comparing the efficacy of sonrotoclax + zanubrutinib versus venetoclax + obinutuzumab in patients with TN CLL.

Trial in Progress

PHASE	**3**
STUDY SITES	**Global**
INTERVENTION	**Sonrotoclax + zanubrutinib or venetoclax + obinutuzumab**
PRIMARY ENDPOINT	**PFS (IRC; iwCLL 2018)**
KEY SECONDARY ENDPOINTS	**CRR (IRC and INV), uMRD4 rates (BM and PB), OS, PFS (INV), ORR (IRC and INV), DoR (IRC and INV), PROs, safety and tolerability**

INCLUSION

- Age ≥18 years
- Confirmed CLL diagnosis, no previous treatment
- Measurable disease by CT/MRI
- ECOG PS of 0-2
- Adequate BM and organ function
- No history of, or currently suspected, Richter's transformation

TREATMENT

R 1:1

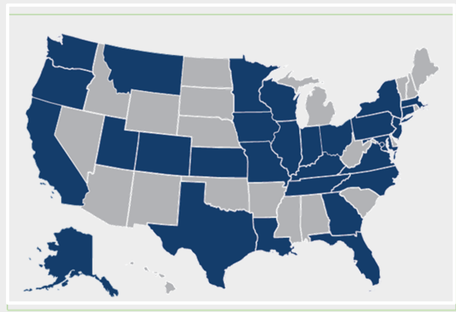
- Zanubrutinib lead-in (3 cycles) followed by: **Sonrotoclax + zanubrutinib** (12 cycles) (n~320)
- **Venetoclax** (12 cycles) + **obinutuzumab** (6 cycles) (n~320)

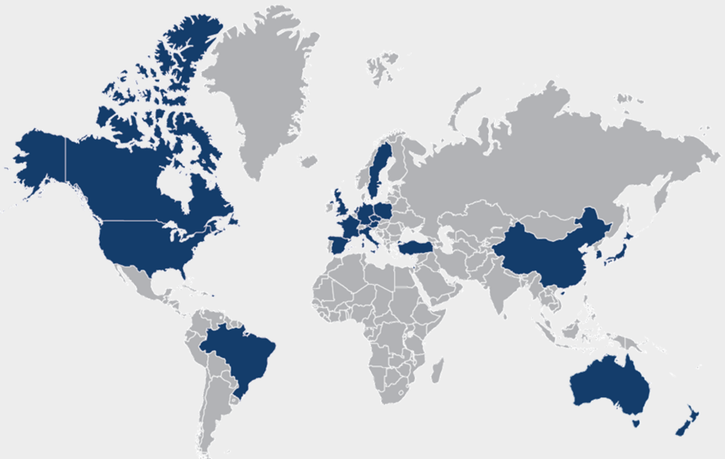
Randomization stratified by:

- Age (<65 vs ≥65 years)
- IGHV status
- Del(17p)/*TP53* mutation status

STUDY STATUS

Planned Study Sites





- Enrollment for CELESTIAL-TNCLL began in December 2023, and the study is currently recruiting
- Approximately 251 study sites in 19 countries are planned, with an estimated enrollment of 640 patients. In the Americas, there are approximately 55 sites in the US, 6 in Brazil and 16 in Canada

Shadman M, et al. Poster Presentation at ASCO 2024;abstract TPS7087.

CaDAnCe-101: TN CLL [BGB-16673-101, NCT05006716]

BGB-16673

CLL/SLL

A Phase 1/2, open-label, dose escalation and expansion study evaluating BGB-16673 in adults with R/R B-cell malignancies.

STUDY DESIGN

PHASE **1/2**

STUDY SITES **Global**

INTERVENTION **BGB-16673**

PRIMARY ENDPOINT **Safety and tolerability, MTD, and RP2D**

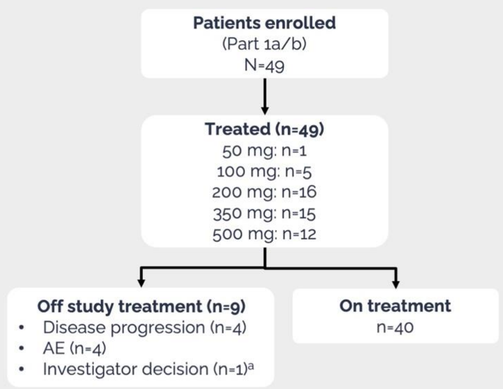
KEY SECONDARY ENDPOINTS **PK/PD, preliminary antitumor activity**

INCLUSION

- Received ≥2 prior therapies (≥1 prior therapy for RT)
- Received a cBTKi if approved for their disease
- ECOG PS 0-2
- Adequate end-organ function
- No current of history of central nervous system involvement by B-cell malignancy

TREATMENT

PATIENT DISPOSITION



Data cutoff: February 14, 2024
Median follow-up: 4.6 months

[a]Patient had ongoing low-grade arthralgia that did not otherwise meet the criteria for discontinuation.

PATIENT CHARACTERISTICS

Characteristic	All Patients (N=49)
Median age, years	70
Male	63%
ECOG PS	
1	39%
2	2%
CLL/SLL risk characteristics	
Binet stage	50%
Unmutated IGHV	82%
del(17p) or TP53 mutation	60%
Complex karyotype	47%
Mutation status	
BTK mutation	32%
PLCG2 mutation	13%
Median no. prior lines	4
Prior cBTK inhibitor	92%
Prior BCL2 inhibitor	86%
Discontinued BTK inhibitor due to PD	89%

SAFETY DATA OVERVIEW [N=49]

Primary Endpoint

Overall Safety Summary

AE	All Patients (N=49)
Any TEAE	96%
Grade ≥3	55%
Serious	43%
Leading to death	6%
Leading to treatment discontinuation	12%
Leading to treatment modification	37%
Dose interruption	37%
Dose reduction	6%
Any TRAE	61%
Grade ≥3	27%
Serious	12%
Leading to death	0
Leading to treatment discontinuation	2%

TEAEs in ≥15% of patients
[Any grade and Grade ≥3]

	Any grade	Grade ≥3
Fatigue	33%	2%
Contusion	29%	0
Anemia	22%	2%
Diarrhea	22%	0
Neutropenia/ neutrophil count decrease	22%	20%
Pneumonia	16%	12%

- One DLT was reported (Grade 3 maculopapular rash)
- None of the 3 TEAES that led to death were considered related to treatment by investigator
  - No cases of atrial fibrillation or grade ≥3 hypertension were reported

EFFICACY DATA OVERVIEW [n=43; efficacy evaluable population]

All Patients:
72% ORR

- ORR was similar in patients who had prior cBTK + BCL2 inhibitors (70%), del(17p) or TP53 mutation (68%), complex karyotype (67%)
- Responses have been observed in patients with C481S, T474I, and/or L528S BTK mutations, as well as patients with PLCG2 mutations

Overall Response Rate

	All Patients (N=43)
Best overall response	
CR	5%
PR	51%
PR-L	16%
SD	16%
PD	5%
ORR	72%
DCR	88%
Median time to first response, months	2.8

CONCLUSIONS

Results from this ongoing study showed a generally well tolerated safety profile for BGB-16673 in heavily pretreated patients with CLL. Preliminary antitumor activity was demonstrated, including in patients with BTK inhibitor-resistant mutations. These data support promising clinical activity of BGB-16673 for the treatment of patients with CLL/SLL.

Parrondo R, et al. Oral Presentation at EHA 2024;S157.

1024--MRC-094

CaDAnCe-101: FL, MZL, WM [BGB-16673-101, NCT05006716]

BGB-16673

FL/ MZL/ WM

A Phase 1/2, open-label, dose escalation and expansion study evaluating BGB-16673 in adults with R/R B-cell malignancies.

STUDY DESIGN

PHASE **1/2**

STUDY SITES **Global**

INTERVENTION **BGB-16673**

PRIMARY ENDPOINT **Safety and tolerability, MTD, and RP2D**

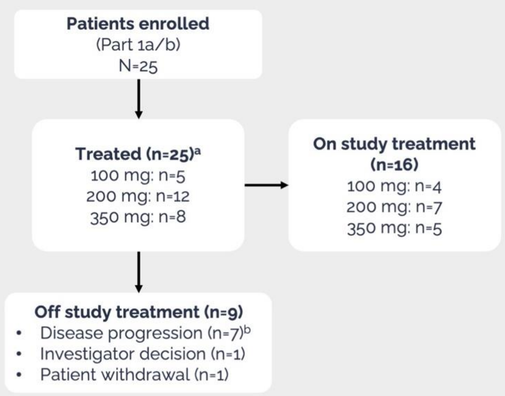
KEY SECONDARY ENDPOINTS **PK/PD, preliminary antitumor activity**

INCLUSION

- Received ≥2 prior therapies (≥1 prior therapy for RT)
- Received a cBTKi if approved for their disease
- ECOG PS 0-2
- Adequate end-organ function
- No current or history of central nervous system involvement by B-cell malignancy

TREATMENT

PATIENT DISPOSITION



Data cutoff: February 14, 2024
Median follow-up: 5.85 months

[a]Dose per day until disease progression or unacceptable toxicity. [b]Includes 1 patient who discontinued treatment due to an AE in the context of disease progression.

PATIENT CHARACTERISTICS

Characteristic	All Patients (N=25)
Median age, years	72
Male	60%
ECOG PS 0-1	96%
Disease type	
WM	52%
FL	28%
MZL	20%
Ann Arbor stage III/IV (FL/MZL)	75%
IWWM stage (WM)[c]	
Low risk	23%
Intermediate risk	38%
High risk	31%
Median no. prior lines of therapy[d,e]	4
Prior covalent BTKi	64%
Prior noncovalent BTKi	16%
Discontinued BTKi due to PD	82%
Prior BCL2i	24%

[c]One patient had unknown risk. [d]Must include prior anti-CD20 in patients with FL, WM, and MZL in the US and EU, and cBTKi in patients with WM in the US and EU, and in patients with MZL in the US. [e]One patient had prior treatment with noncovalent BTK inhibitor without prior covalent BTK inhibitor.

SAFETY DATA OVERVIEW [N=25]

Primary Endpoint

Overall Safety Summary

AE	All Patients (N=25)
Any TEAE	**96%**
Grade ≥3	52%
Serious	32%
Leading to death	4%
Leading to treatment discontinuation	4%
Leading to treatment modification	20%
Dose interruption	20%
Dose reduction	0
Any TRAE	72%
Grade ≥3	24%
Serious	0
Leading to death	0
Leading to treatment discontinuation	0

TEAEs in ≥15% of patients

[Any grade and Grade ≥3]

	Any grade	Grade ≥3
Contusion	32%	0
Neutropenia/ neutrophil count decrease	24%	20%
URTI	24%	4%
Amylase increase	24%	0
Fatigue	24%	0
Lipase increase	20%	4%
Anemia	16%	8%
Diarrhea	16%	0

- No cases of atrial fibrillation and 1 case of grade ≥3 hypertension were reported
- No patients experienced DLT during the DLT window (first 4 weeks of Part 1a)
- Discontinuations due to TEAEs were low (1 of 25 patients)

EFFICACY DATA OVERVIEW [n=24; efficacy evaluable population]

All Patients:

75% ORR

- Both patients with detected BTK mutations responded (WM; 200 mg; 1 PR, 1 VGPR)
- All patients with WM had a numerical reduction from baseline in immunoglobulin M

Overall Response Rate

	WM (n=12)	FL (n=7)	MZL (n=5)
Best overall response			
CR	0	14%	0
VGPR	17%	0	0
PR	75%	43%	60%
SD	8%	29%	20%
PD	0	14%	20%
ORR	92%	57%	60%
DCR	100%	86%	80%
Median time to first response, months	0.95	2.71	2.83

CONCLUSIONS

Updated data from this ongoing, first-in-human study show that the novel BTK degrader BGB-16673 appears to have a safe and generally tolerable profile, with no DLTs in patients with MZL, WM, or FL. Preliminary antitumor activity was shown with a relatively short time to response, including those with BTKi resistant-disease.

Cheah C, et al. Poster Presentation at EHA 2024;P1119.

1024--MRC-094