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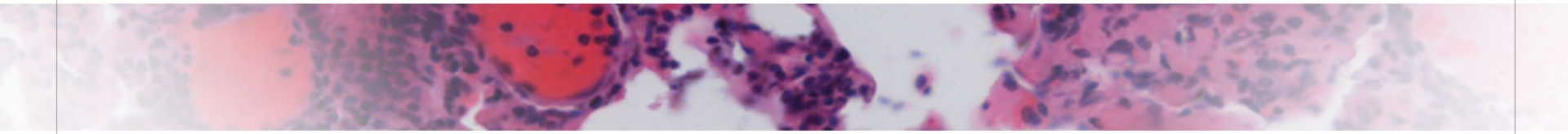

Sonrotoclax (BGB-11417) Monotherapy in Patients With R/R MCL Previously Treated With a BTK Inhibitor: Results From a Phase 1/2 Study

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Introduction

- Patients with MCL who have disease progression on or after treatment with BTK inhibitors, such as zanubrutinib and acalabrutinib, have few effective treatment options[1]
- Venetoclax, the first-generation BCL2 inhibitor, has shown some efficacy in a small study (N=20) of patients with R/R MCL after BTK inhibitor treatment,[2] but is not currently approved for MCL
- Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation[3,4]
- Presented here are results from the primary analysis of an ongoing phase 1/2 study to evaluate sonrotoclax monotherapy in patients with R/R MCL who have previously received anti-CD20–based therapy and treatment with at least 1 covalent or noncovalent BTK inhibitor

BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; MCL, mantle cell lymphoma; R/R, relapsed/refractory.

1.Eyre TA, et al. *Blood*. 2022;139(5):666-677; 2. Eyre TA, et al. *Haematologica*. 2019;104(2):e68-e71; 3. Guo Y, et al. *J Med Chem*. 2024;67(10):7836-7858; 4. Liu J, et al. *Blood*. 2024;143(18):1825-1836.

Sonrotoclax, a next-generation BCL2 inhibitor with a differentiated pharmacological profile

	Sonrotoclax	Venetoclax	Clinical implication for sonrotoclax
Potency (IC_{50})	0.014 nM[1]	0.20 nM[1]	14-fold more potent, which may lead to deeper target inhibition
Selectivity (vs BCL-xL)	2000×[1]	325×[1]	Improved (6-fold) selectivity may improve tolerability
Half-life in humans	≈5 hours[2]	26 hours[3]	No accumulation may improve tolerability Short half-life results in simplified TLS monitoring

BCL2, B-cell lymphoma 2; BCL-xL, B-cell lymphoma-extra large; IC_{50}, half-maximal inhibitory concentration; TLS, tumor lysis syndrome.

1. Liu J, et al. *Blood*. 2024;143(18):1825-1836; 2. Cheah CY, et al. ASH 2022. Abstract 962; 3. Venclexta (venetoclax). Prescribing information. AbbVie Inc; 2022.

BGB-11417-201 (NCT05471843) study design

Eligibility criteria

- Age ≥18 years
- Histologically-confirmed MCL per WHO 2016 classification
- ≥1 line of anti-CD20–based therapy and ≥1 BTK inhibitor
- ECOG PS of 0-2
- No prior BCL2 inhibitor treatment

Study design

Parts 1A + 1B dose escalation and safety expansion

Target dose 1:
160 mg QD (n=10)

Target dose 2:
320 mg QD (n=12)

Safety expansion: up to 2 cohorts at select sonrotoclax target dose levels n≤12 per cohort (including part 1A)

Part 1 endpoints

- Primary: DLTs (part 1A), TEAEs, SAEs, AEs leading to discontinuation, TLS events
- Secondary: preliminary antitumor activity

Part 2 efficacy expansion

Sonrotoclax at RP2D[a] until PD
n=103

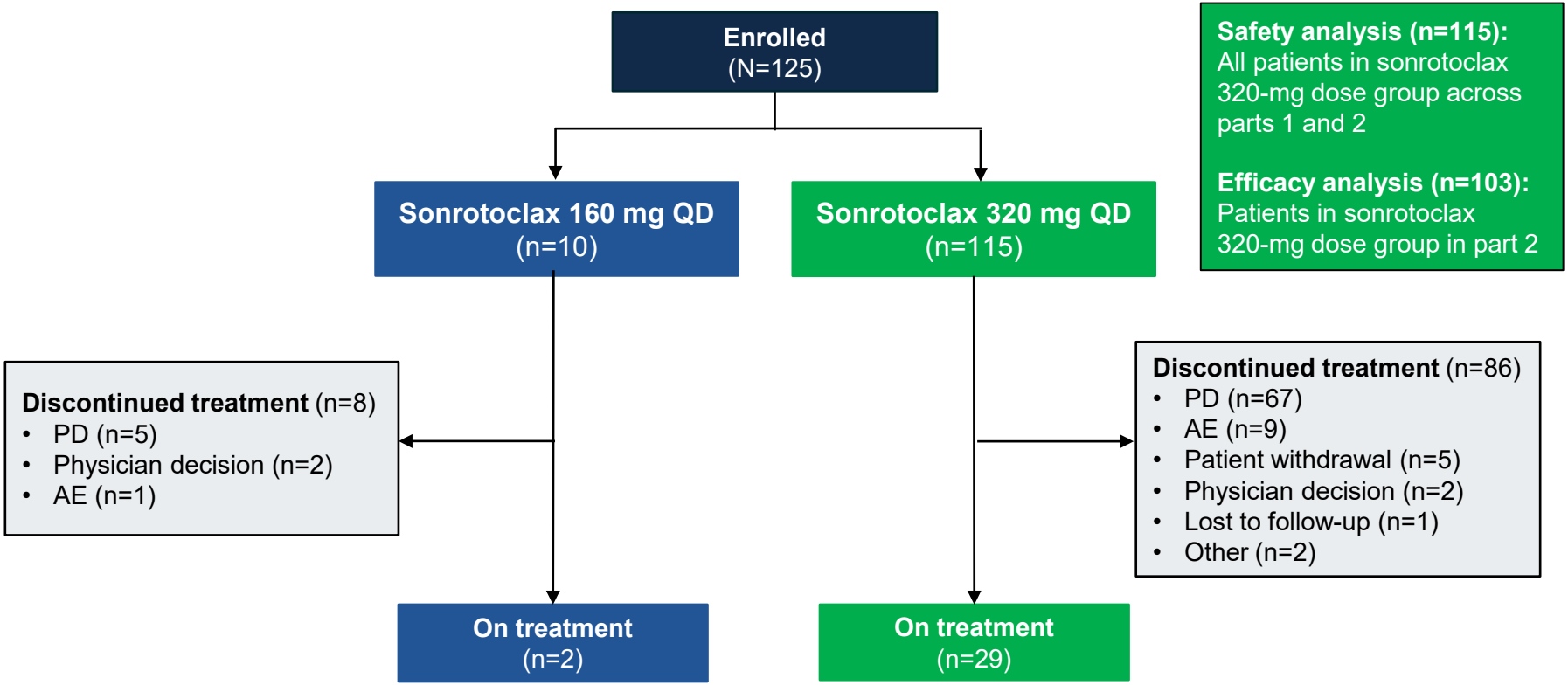
Part 2 endpoints

- Primary: ORR by IRC (Lugano 2014)
- Secondary: ORR by INV, DOR by IRC and INV, PFS by IRC and INV, TTR by IRC and INV, HR-QOL, OS, safety

- Sonrotoclax target doses were achieved after a ~4 week ramp-up that did not require hospitalization or 12- or 24-hour post-dose laboratory monitoring

[a]Determined by safety monitoring committee based on part 1 data; will not exceed maximum tolerated dose or maximum administered dose.
BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; DLT, dose limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR-QOL, health-related quality of life; INV, investigator; IRC, independent review committee MCL, mantle cell lymphoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QD, once daily; RP2D, recommended phase 2 dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; TTR, time-to-response.

Patient disposition



Data cutoff: July 18, 2025.
AE, adverse event; PD, progressive disease; QD, once daily.

Baseline patient demographics and disease characteristics

Parameters	Sonrotoclax 320 mg (n=115)
Age, median (range), years	68 (39-85)
≥65 years, n (%)	74 (64.3)
Male, n (%)	87 (75.7)
Race, n (%)	
Asian	45 (39.1)
Black or African American	3 (2.6)
White	61 (53.0)
Other/not reported	6 (5.2)
Ethnicity, n (%)	
Not Hispanic or Latino	87 (75.7)
Hispanic or Latino	25 (21.7)
ECOG performance status, n (%)	
0	34 (29.6)
1	74 (64.3)
2	7 (6.1)
Disease stage at study entry, n (%)	
III	11 (9.6)
IV	90 (78.3)
Disease status to last prior therapy, n (%)	
Refractory[a]	100 (87.0)
Relapsed[b]	14 (12.2)
MIPI, n (%)	
High	39 (33.9)
Intermediate	41 (35.7)

Parameters	Sonrotoclax 320 mg (n=115)
Bulky disease status, n (%)	
LDi ≥5 cm	46 (40.0)
LDi ≥10 cm	12 (10.4)
Bone marrow involvement at baseline, n (%)	58 (50.4)
Ki67 status, n/N with known status (%)	
Positive	92/98 (93.9)
≥30%	41/98 (41.8)
***TP53* mutation, n/N with known status (%)**	27/78 (34.6)
Prior lines of therapy, median (range)	3 (1-8)
≥3 prior lines, n (%)	68 (59.1)
Prior BTK inhibitor treatment, n (%)	115 (100)
≥2 prior BTK inhibitors	22 (19.1)
Prior ASCT, n (%)	17 (14.8)
Prior CAR-T therapy, n (%)	3 (2.6)
Reason for ending last line of anticancer therapy, n (%)	
Progressive disease	79 (68.7)
Treatment completed	17 (14.8)
Toxicity	12 (10.4)
Other	7 (6.1)

[a]Non-responsive to last line or progressive disease within 6 months after the last line end date. [b]Initial treatment response followed by progressive disease >6 months after the last line end date.
ASCT, autologous stem cell transplant; BTK, Bruton tyrosine kinase; CAR-T, chimeric antigen receptor T-cell; LDi, longest diameter; MIPI, Mantle Cell Lymphoma International Prognostic Index.

Safety summary

Sonrotoclax was well tolerated and adverse events were manageable

- Part 1: no DLTs, MTD was not reached; sonrotoclax RP2D was determined to be 320 mg QD

Sonrotoclax overall safety profile (N=115)

- Well tolerated; median RDI was 100%
- Most common serious TEAEs were infections
- For the 15 TEAEs leading to death, 11 were considered related to the disease under study; other deaths were due to pneumonia (n=1), pneumothorax (n=1), unknown (n=2)
- Most TEAEs leading to discontinuation were attributed to disease under study
- TEAEs led to temporary treatment interruption in 27%; supportive measures were used when needed and the events resolved

Patients, n (%)	Sonrotoclax 320 mg (n=115)
Any TEAE	111 (96.5)
Treatment-related	92 (80.0)
Grade ≥3 TEAE	60 (52.2)
Treatment-related	42 (36.5)
Serious TEAE	43 (37.4)
Treatment-related	20 (17.4)
Leading to death	15 (13.0)
Leading to treatment discontinuation	16 (13.9)
Leading to treatment modification	31 (27.0)
Dose interruption	31 (27.0)
Dose reduction	1 (0.9)

DLT, dose-limiting toxicity; MTD, maximum tolerated dose; QD, once daily; RDI, relative dose intensity; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

All grade TEAEs (≥10%) and grade ≥3 TEAEs

- Most common all grade TEAEs: hematologic toxicities, electrolyte abnormalities related to tumor cell apoptosis, and gastrointestinal disorders
- Most common grade ≥3 TEAEs: hematologic toxicities, infections
- TLS events were reported in 8 patients: 2 had clinical TLS and 6 had laboratory TLS
  - All events resolved without sequelae
  - No events resulted in death or treatment discontinuation

	Sonrotoclax 320 mg (n=115)	
Patients, n (%)	**Any grade**	**Grade ≥3**
Neutropenia[a]	41 (35.7)	22 (19.1)
Thrombocytopenia[b]	28 (24.3)	11 (9.6)
Anemia[c]	28 (24.3)	9 (7.8)
White blood cell count decreased	25 (21.7)	3 (2.6)
Hyperuricemia	22 (19.1)	0
Hypokalemia	20 (17.4)	0
Pneumonia	18 (15.7)	12 (10.4)
Diarrhea	16 (13.9)	5 (4.3)
AST increased	14 (12.2)	1 (0.9)
ALT increased	12 (10.4)	0
Constipation	12 (10.4)	0
Lymphopenia[d]	12 (10.4)	7 (6.1)
Select TEAEs by category/AE/SOC		
Infections (SOC)	45 (39.1)	19 (16.5)
Febrile neutropenia	2 (1.7)	2 (1.7)
TLS (AE)	8 (7.0)	8 (7.0)

[a]Includes preferred terms *neutrophil count decreased*, *neutropenia*, and *febrile neutropenia*. [b]Includes preferred terms *thrombocytopenia* and *platelet count decreased*.
[c]Includes preferred terms *anemia* and *hemoglobin decreased*. [d]Includes preferred terms *lymphocyte count decreased* and *lymphopenia*.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOC, system organ class; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome.

Efficacy for sonrotoclax at RP2D 320 mg QD

Very promising efficacy in heavily pretreated patients

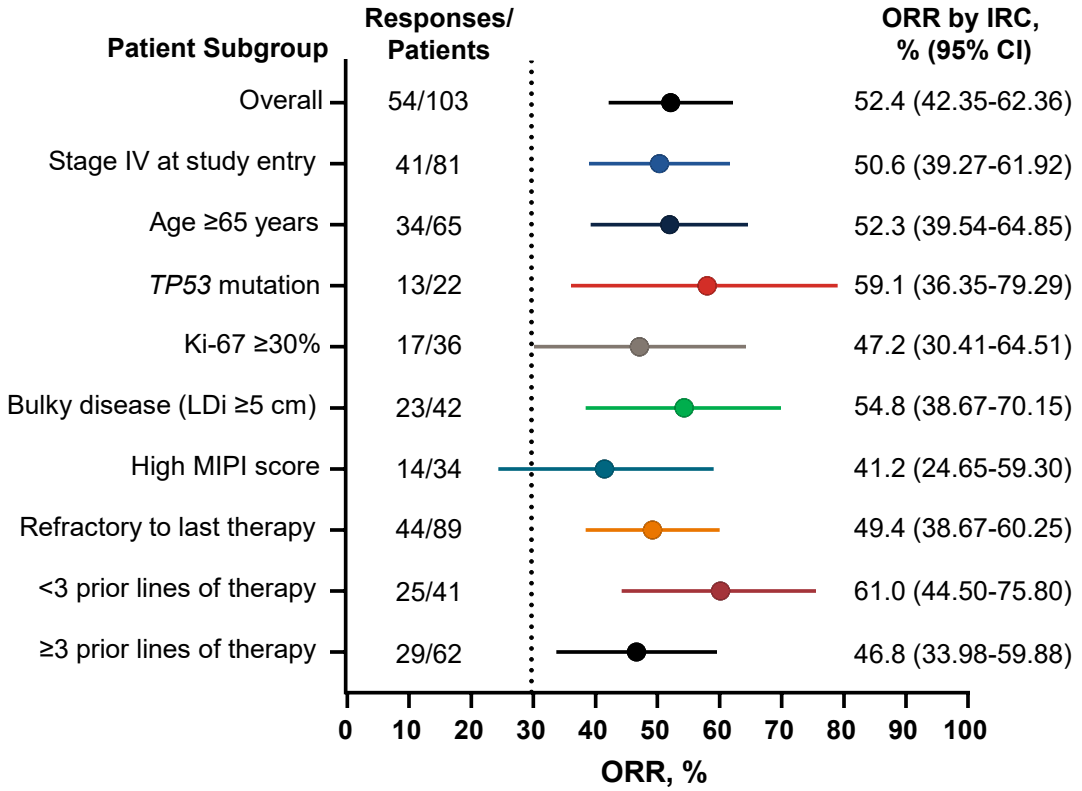
	Part 2: Sonrotoclax 320 mg (n=103)	
Parameters	**IRC-assessed**	**INV-assessed**
ORR, n (%)	54 (52.4)	49 (47.6)
95% CI, %	42.4-62.4	37.6-57.6
1-sided *P* value	<.0001	N/A
CR rate, n (%)	16 (15.5)	23 (22.3)
95% CI, %	9.1-24.0	14.7-31.6
TTR, median (range), months	1.9 (1.6-6.2)	1.9 (1.6-4.0)

- **Primary endpoint was met:** relative to the historical control ORR of 30%, IRC-assessed ORR of 52.4% represents a clinically meaningful improvement
- ORR by IRC for patients with <3 prior lines of therapy: 61.0% (95% CI, 44.5%-75.8%)
- Median study follow-up: 14.2 months (range, 0.3-24.9 months)

CR, complete response; INV, investigator; IRC, independent review committee; N/A, not applicable; ORR, overall response rate; QD, once daily; RP2D, recommended phase 2 dose; TTR, time to response.

IRC-assessed ORR benefit was consistent across patients with high-risk disease subtypes

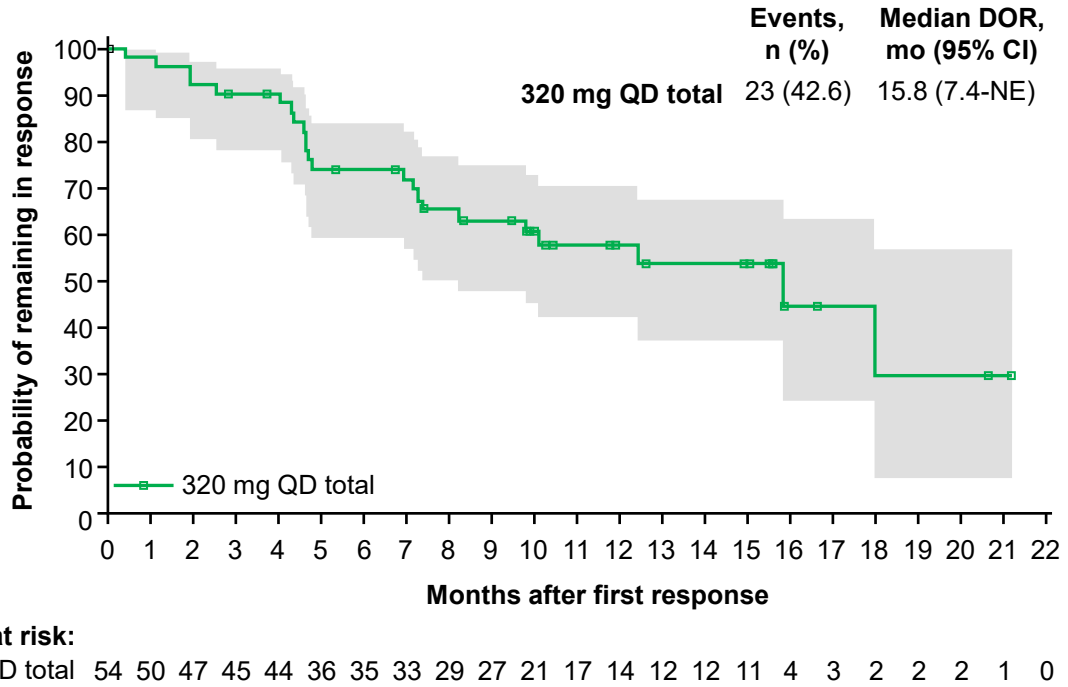
- Subgroups with ≥5 patients in part 2 showed a consistent superior ORR benefit relative to the historical control of 30%
- ORR by IRC for patients with *TP53* mutation: 59.1% (95% CI, 36.3%-79.3%)



Dotted line represents the historical control ORR of 30%.
IRC, independent review committee; LDi, longest diameter; MIPI, Mantle Cell Lymphoma International Prognostic Index; ORR, overall response rate.

Very promising efficacy in heavily pretreated patients with sonrotoclax 320 mg QD across multiple endpoints

- With a median study follow-up of 14.2 months, patients who received sonrotoclax 320 mg in part 2 demonstrated:
  - Median DOR by IRC was 15.8 months (95% CI, 7.4 months-NE); 63% of patients who responded remained in remission after 9 months
  - Median PFS by IRC was 6.5 months (95% CI, 4.0-10.4 months)
  - Median OS was not reached (95% CI, 14.8 months-NE)



DOR, duration of response; IRC, independent review committee; NE, not estimable; OS, overall survival; PFS, progression-free survival; QD, once daily; RP2D, recommended phase 2 dose.

Conclusions

- Sonrotoclax monotherapy demonstrated clinically meaningful benefits in heavily pretreated patients with advanced MCL, including a 52.4% ORR by IRC and median DOR of 15.8 months
  - ORR benefit was consistent across patient subgroups, including those with negative prognostic factors such as *TP53* mutation (ORR by IRC, 59.1%)
- Treatment with sonrotoclax monotherapy was well tolerated, with no new safety signals identified
  - The most common grade ≥3 TEAEs were hematologic events and infections that were manageable
  - TLS rate was low, and events were mostly laboratory abnormalities

These results support sonrotoclax as a promising treatment option for patients with R/R MCL

- A phase 3, randomized placebo-controlled trial to evaluate sonrotoclax in combination with zanubrutinib in patients with R/R MCL (CELESTIAL-RRMCL; NCT06742996) is ongoing

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