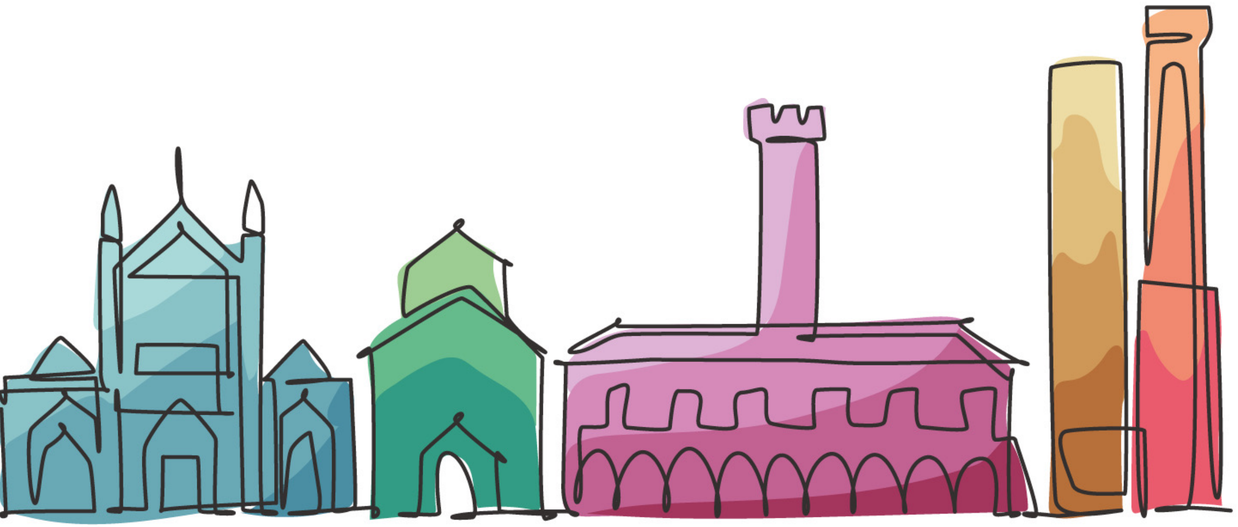
PRECEPTORSHIP



Un confronto sulla gestione delle malattie linfoproliferative al Sant'Orsola di Bologna

Bologna, NH DE LA GARE, 18 settembre 2025

Malattia di Waldenström e il Linfoma della Zona Marginale...dietro l'angolo

Beatrice Casadei
IRCSS, AOU di Bologna

Disclosures of Beatrice Casadei

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Kite-Gilead					x	x	
Novartis					x		
Celgene-BMS						x	
Abbvie					x	x	
Janssen					x	x	
Lilly					x		
Beigene						x	
Roche					x	x	
Incyte					x		
Takeda						x	

Waldenstrom Macroglobulinemia, around the corner….

Treatment Naive

	BTKi	BCL2i
Combo	BR+Acala	Ven+R
	BR+Zanu	Ven+R vs Ibru+R
	Zanu+Sonrotoclax	Ven+R vs DRC

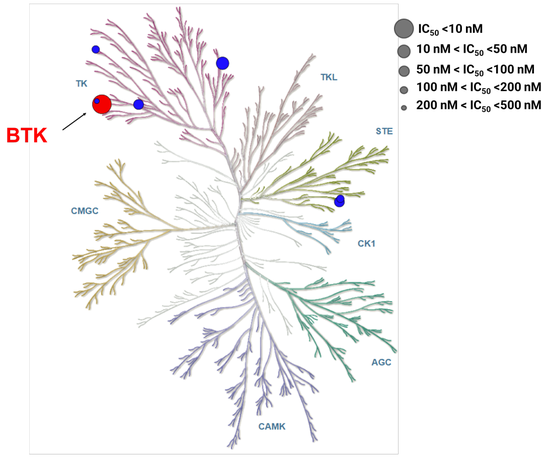
→ Ongoing or completed but data missing

Ricaduto/Refrattario

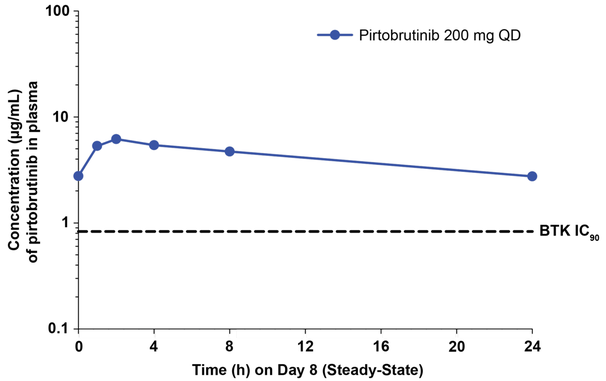
	BTKi	BTK degrader	BCL2i	ADC	BsAbs
Single Agent	Pirtobrutinib	BGB-16673 NX-5948 ABBV-101	Sonrotoclax	Lonca	Epco
Combo	Pirto+Ven	\	Zanu+Sonrot	\	\

RR Waldenstrom Macroglobulinemia: Pirtobrutinib (ncBTKi)

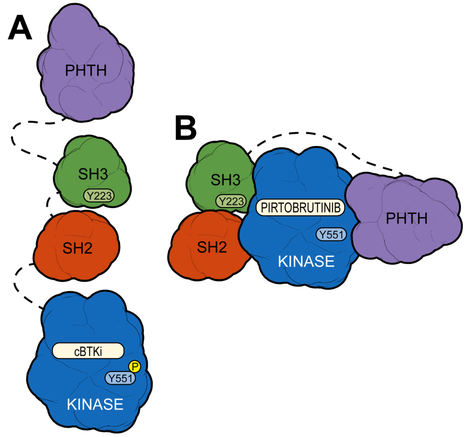
Highly selective for BTK[4-5]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



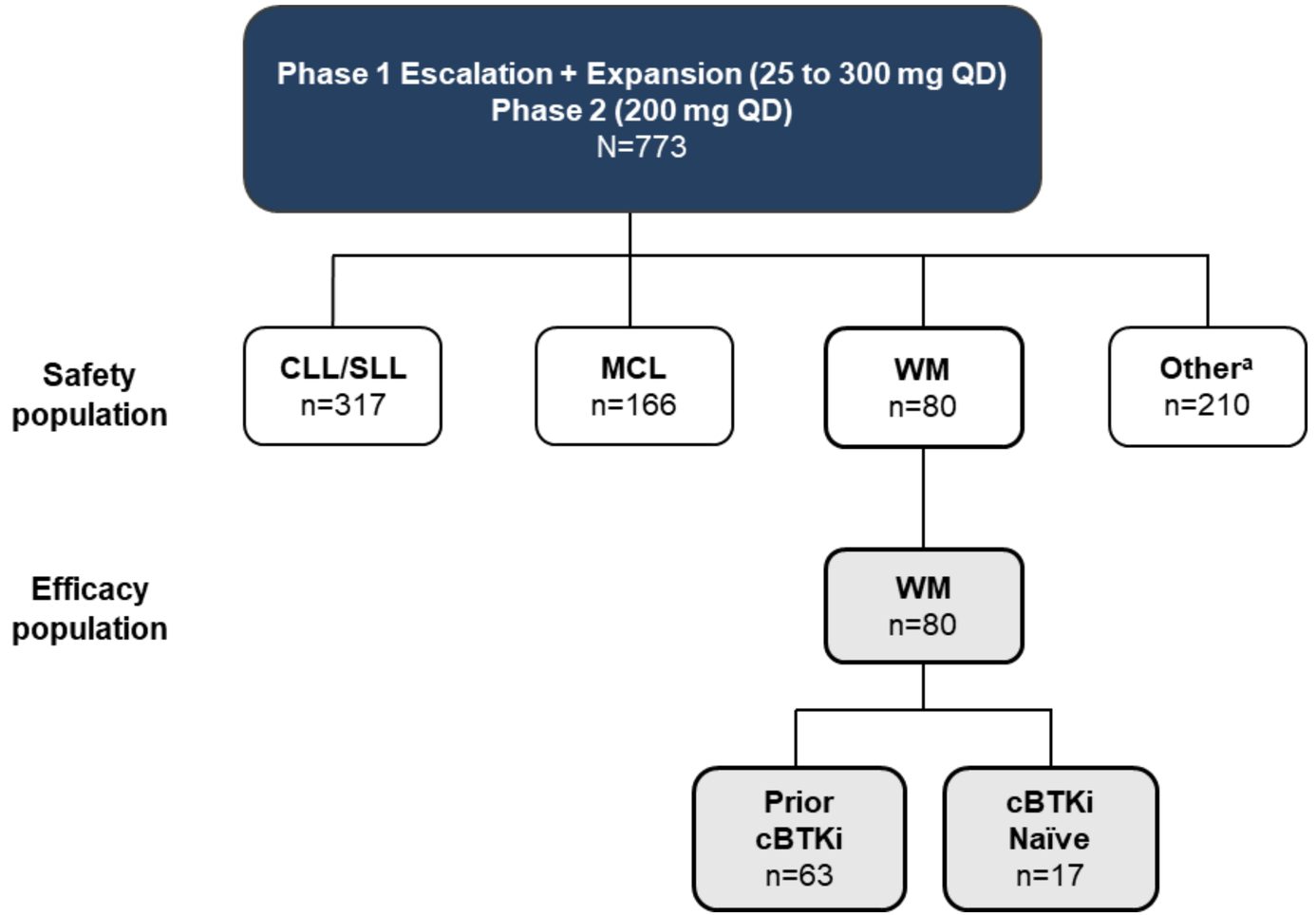
Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[6]



- Inhibits both WT and C481-mutant BTK with equal low nM potency[6]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[6]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[6]

1. Mato et al, *Lancet*, 2021:397:892-901. 2. Brandhuber et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and recommended Phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DoR (IWWM6/Modified IWWM6) as assessed by Investigator

cBTKi=covalent Bruton tyrosine kinase inhibitor. Data cutoff date of 29 July 2022. [a]Other includes DLBCL, Richter transformation, FL, MZL, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.
Data from Palomba ML, et al. Presented at ASH Annual Meeting 2022. Abstract 229.

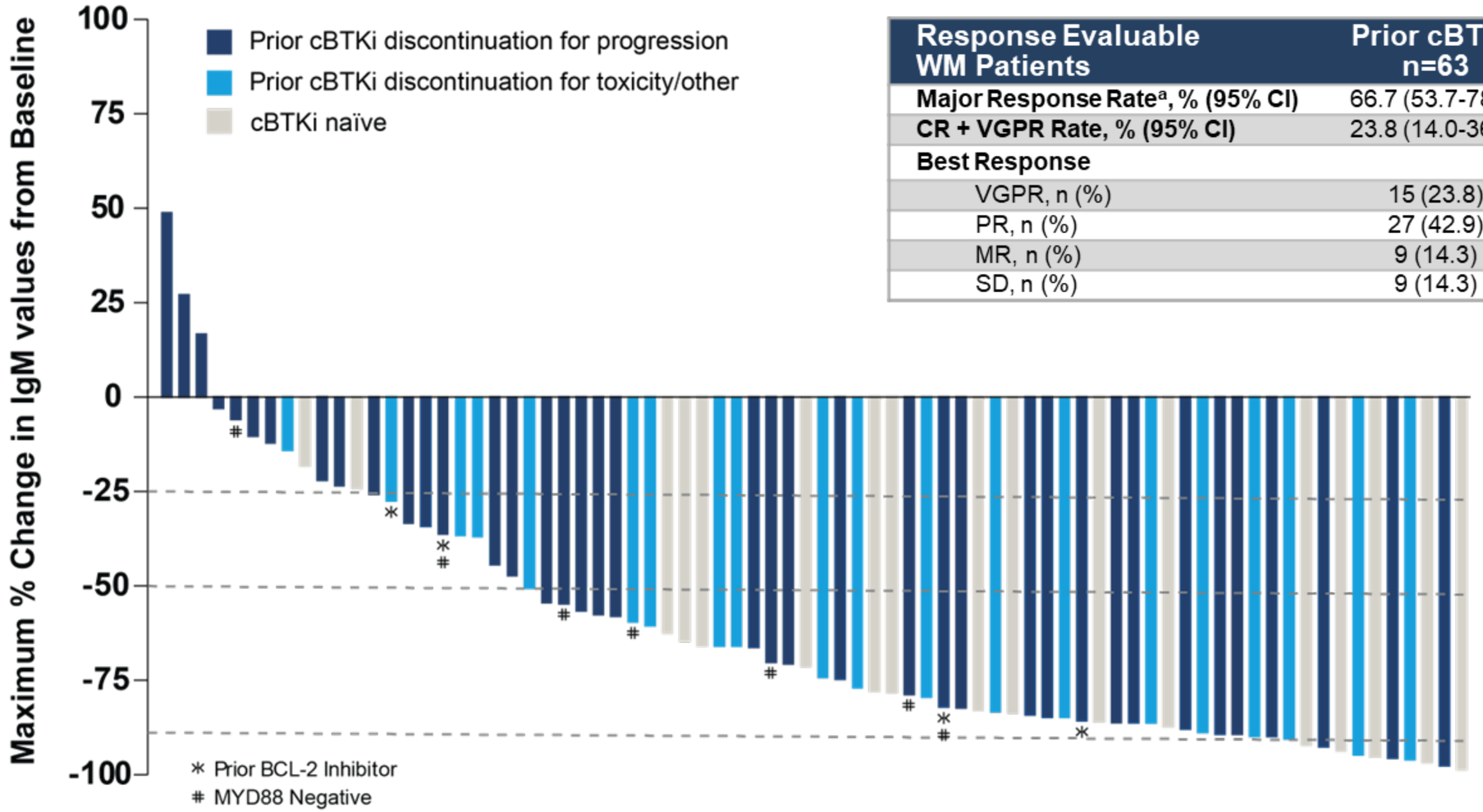
WM Patient Characteristics

Characteristics	Prior cBTKi n=63	cBTKi Naïve n=17
Median age (range), years	69 (42-84)	68 (47-83)
Male, n (%)	42 (67)	10 (59)
ECOG PS, n (%)		
0	34 (54)	9 (53)
1	28 (44)	8 (47)
2	1 (2)	0 (0)
Median number prior lines of systemic therapy (range)	3 (1-11)	2 (1-4)
Prior therapy, n (%)		
cBTK inhibitor	63 (100)	0 (0)
Chemotherapy	52 (83)	17 (100)
Anti-CD20 antibody	58 (92)	16 (94)
CIT + BTK inhibitor	50 (79)	0 (0)
PI3K inhibitor	3 (5)	0 (0)
Immunomodulator	6 (10)	2 (12)
BCL2 inhibitor	4 (6)	0 (0)
Autologous stem cell transplant	4 (6)	0 (0)
Other systemic therapy	31 (49)	6 (35)
Reason discontinued any prior BTK inhibitor[a,b], n (%)		
Progressive disease	41 (65)	-
Toxicity/Other	21 (33)	-

	Prior cBTKi n=63	cBTKi Naïve n=17
WM IPSS score, n (%)		
Low	13 (21)	1 (6)
Intermediate	38 (60)	14 (82)
High	10 (16)	2 (12)
Missing	2 (3)	0 (0)
IgM, median (min, max)	2.46 (0.1, 8.0)	2.59 (0.6, 6.1)
≤7 g/dL, n (%)	61 (97)	17 (100)
>7 g/dL, n (%)	2 (3)	0 (0)
β-2 Microglobulin, median, (min, max)	4.00 (1.6, 95.3)	3.36 (2.4, 11.8)
≤3 mg/L, n (%)	20 (32)	3 (18)
>3 mg/L, n (%)	41 (65)	14 (82)
Missing, n (%)	2 (3)	0 (0)
Peripheral blood cytopenias, n (%)		
Hemoglobin ≤11.5 g/dL	42 (68)	12 (71)
Platelet count ≤100 × 10^9/L	11 (18)	3 (18)
MYD88 genotype[c], n (%)		
Negative	7 (11)	0 (0)
Positive	52 (83)	9 (53)
Missing	4 (6)	8 (47)
CXCR4 genotype[c], n (%)		
Negative	11 (18)	0 (0)
Positive	9 (14)	0 (0)
Missing	43 (68)	17 (100)
Extramedullary disease, n (%)		
Lymphadenopathy	37 (59)	10 (59)
Splenomegaly	18 (29)	3 (18)

cBTKi=covalent Bruton tyrosine kinase inhibitor; CIT=Chemoimmunotherapy; IPSS=International Prognostic Scoring System. Data cutoff date of 29 July 2022. Total % may be different than the sum of the individual components due to rounding. [a]In the event more than one reason was noted for discontinuation, disease progression took priority. [b]One patient had unknown reason for prior BTKi discontinuation. [c]Molecular characteristics were determined locally and are presented based on data availability. Data from Palomba ML, et al. Presented at ASH Annual Meeting 2022. Abstract 229.

Pirtobrutinib Efficacy in WM Patients

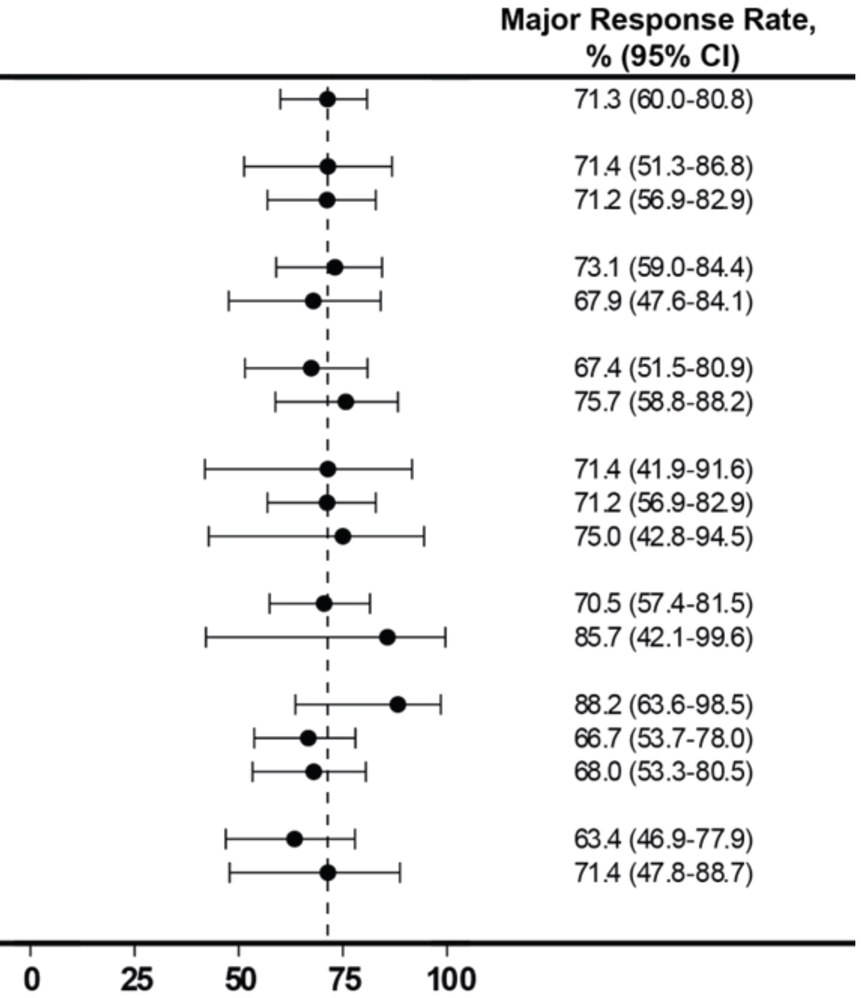


Response Evaluable WM Patients	Prior cBTKi n=63	cBTKi Naïve n=17
Major Response Rate[a], % (95% CI)	66.7 (53.7-78.0)	88.2 (63.6-98.5)
CR + VGPR Rate, % (95% CI)	23.8 (14.0-36.2)	29.4 (10.3-56.0)
Best Response		
VGPR, n (%)	15 (23.8)	5 (29.4)
PR, n (%)	27 (42.9)	10 (58.8)
MR, n (%)	9 (14.3)	0 (0)
SD, n (%)	9 (14.3)	2 (11.8)

Data cutoff date of 29 July 2022. Data for 4 patients are not shown in the waterfall plot due to missing IgM values at baseline or response assessment. Response as assessed by investigator based on Modified IWWM6 (Owen's) criteria. Under modified IWWM6 criteria, a PR is upgraded to VGPR if corresponding IgM is in normal range or has at least 90% reduction from baseline. [a]Major response includes subjects with a best response of CR, VGPR, or PR. Total % may be different than the sum of the individual components due to rounding. Data from Palomba ML, et al. Presented at ASH Annual Meeting 2022. Abstract 229.

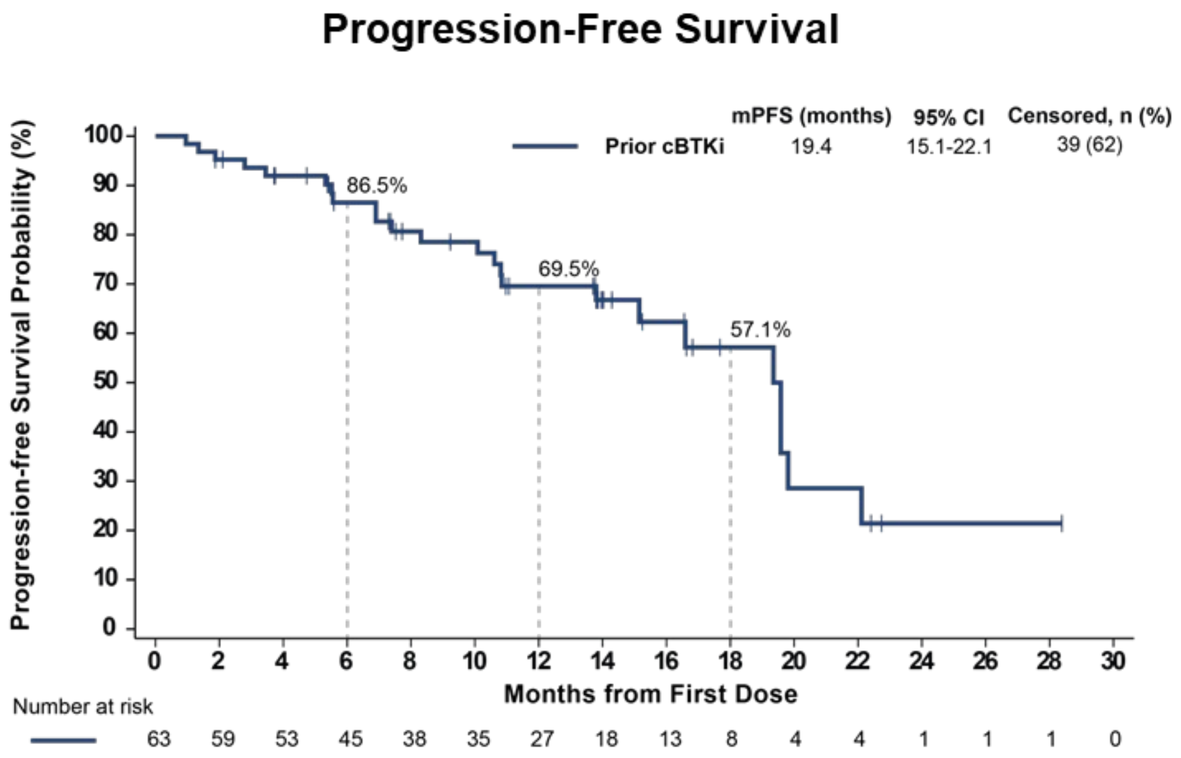
Major Response Rate in WM Subgroups

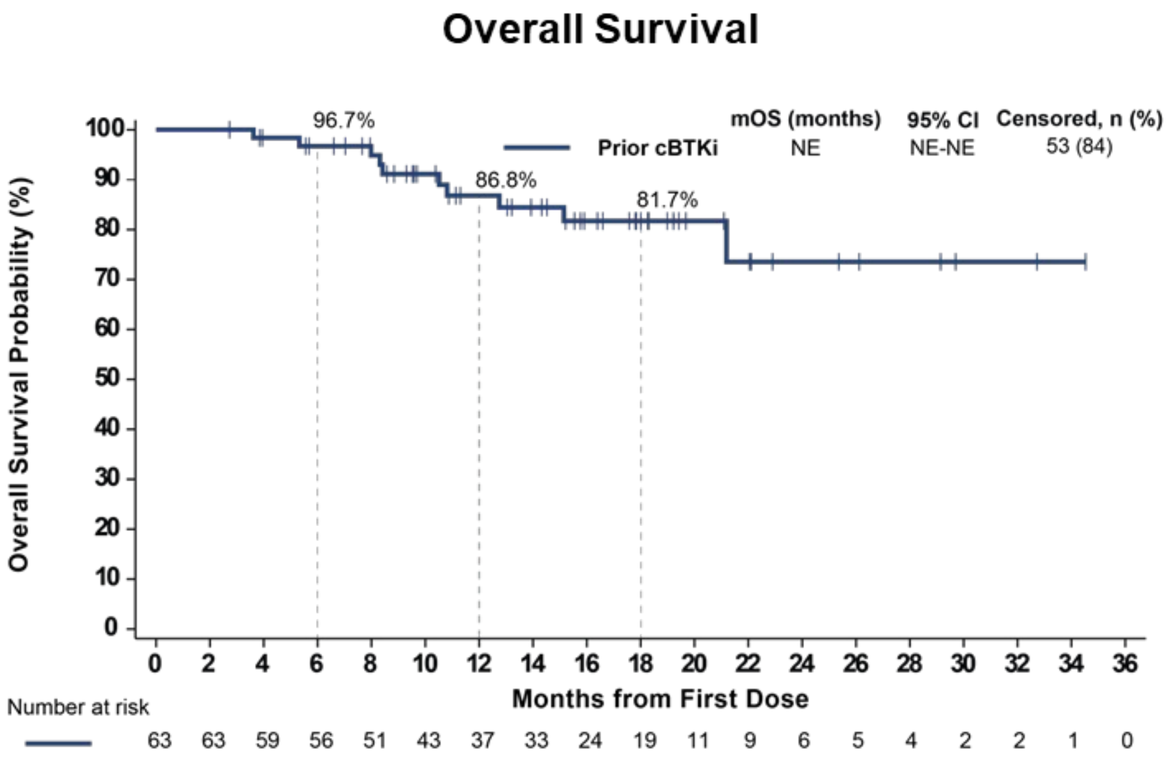
	Responders/ Patients	Major Response Rate, % (95% CI)
All Patients	57/80	71.3 (60.0-80.8)
Age at Enrollment		
< 65	20/28	71.4 (51.3-86.8)
≥ 65	37/52	71.2 (56.9-82.9)
Sex		
Male	38/52	73.1 (59.0-84.4)
Female	19/28	67.9 (47.6-84.1)
ECOG PS		
0	29/43	67.4 (51.5-80.9)
1/2	28/37	75.7 (58.8-88.2)
IPSS Category		
Low Risk	10/14	71.4 (41.9-91.6)
Intermediate Risk	37/52	71.2 (56.9-82.9)
High Risk	9/12	75.0 (42.8-94.5)
MYD88 Genotype		
Positive	43/61	70.5 (57.4-81.5)
Negative	6/7	85.7 (42.1-99.6)
Prior Therapy		
cBTKi naïve	15/17	88.2 (63.6-98.5)
cBTKi pretreated	42/63	66.7 (53.7-78.0)
CIT + cBTKi	34/50	68.0 (53.3-80.5)
Reason for Discontinuation from any Prior cBTKi		
Disease Progression	26/41	63.4 (46.9-77.9)
Toxicity/Other	15/21	71.4 (47.8-88.7)



Data cutoff date of 29 July 2022. Response as assessed by investigator based on modified IWWM6 criteria.
Data from Palomba ML, et al. Presented at ASH Annual Meeting 2022. Abstract 229.

Progression-Free Survival and Overall Survival in Prior cBTKi Patients





- The median follow-up for PFS and OS in patients who received prior cBTKi was 19.4 and NR months, respectively
- All population, median followup 22.3 mo, median PFS 22 mo; PFS rate at 18 mo: 61.4%
- 55.6% (35/63) of patients who received prior cBTKi remain on pirtobrutinib

Data cutoff date of 29 July 2022. Response as assessed by investigator based on modified IWWM6 criteria.
Data from Palomba ML, et al. Presented at ASH Annual Meeting 2022. Abstract 229.

Pirtobrutinib Safety Profile in WM

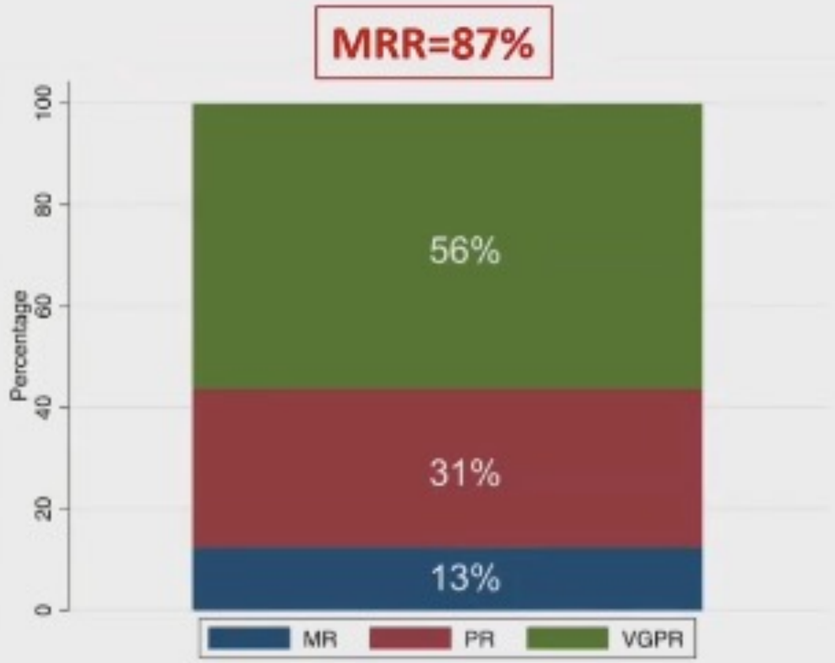
	WM patients (n=80)			
	Treatment-emergent AEs, (≥15%)		Treatment-related AEs	
Adverse Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	22.5%	3.8%	11.3%	1.3%
Covid-19	21.3%	0.0%	1.3%	0.0%
Headache	21.3%	0.0%	6.3%	0.0%
Fatigue	20.0%	0.0%	7.5%	0.0%
Anemia	18.8%	11.3%	5.0%	2.5%
Neutropenia[a]	18.8%	16.3%	12.5%	10.0%
Constipation	15.0%	0.0%	2.5%	0.0%
Contusion	15.0%	0.0%	11.3%	0.0%
AEs of special interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	20.0%	0.0%	15.0%	0.0%
Rash[d]	17.5%	1.3%	12.5%	1.3%
Arthralgia	10.0%	0.0%	2.5%	0.0%
Hemorrhage/Hematoma[e]	17.5%	1.3%	8.8%	1.3%
Hypertension	11.3%	3.8%	8.8%	2.5%
Atrial fibrillation/flutter[f]	1.3%	1.3%	0.0%	0.0%

Median time on treatment for the WM safety population was 13.1 months
Discontinuations due to TRAEs occurred in 5.0% (n=4) of WM patients
Dose reductions due to TRAEs occurred in 2.5% (n=2) of WM patients

Data cutoff date of 29 July 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. dAggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. Data from Palomba ML, et al. Presented at ASH Annual Meeting 2022. Abstract 229.

RR WM: Pirtobrutinib + Venetoclax

PIRTOBRUTINIB AND VENETOCLAX IN RELAPSED/REFRACTORY WM PATIENTS



Major RR by CXCR4 WT vs. Mut: 90% vs. 83%
Major RR by prior BTK-I Exp vs. Non-Exp: 86% vs. 89%

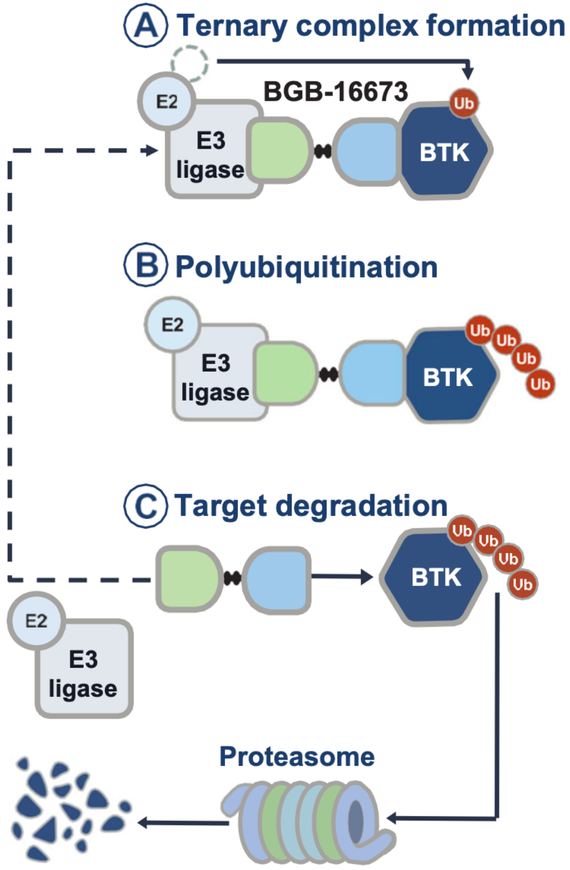
N=16

- The median follow-up was 6 months (95% CI, 3-12)
- The PFS rate at 6 months 84% (95% CI 49-96%)

Castillo et al, IWWM-12, 2024

RR WM - BGB-16673 (BTK degrader)

- BTK inhibitors are effective in WM but are associated with toxicities and/or resistance development[1,2]
- BGB-16673 is an orally available protein degrader that blocks BTK signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression[3]
- In preclinical models, BGB-16673 showed CNS penetration and degraded both wild-type and mutant BTK resistant to cBTK (C481S, C481F, C481Y, L528W, T474I) and ncBTK inhibitors (V416L, M437R, T474I, L528W)[3,4]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[5]
- Here, updated safety and efficacy results are presented in patients with R/R WM in phase 1 of CaDAnCe-101



Frustaci AM et al, EHA 2025

CaDAnCe-101: Phase 1/2, Open-Label, Dose-Escalation/Expansion Study in R/R B-Cell Malignancies

CaDAnCe-101 (BGB-16673-101, NCT05006716)

Key eligibility criteria for WM

- Met IWWM-7 criteria for treatment
- ≥2 prior therapies, includ. anti-CD20 monoclonal antibody & cBTK inhibitor (US & EU only)
- ECOG PS 0-2
- Adequate organ function

Key objectives: part 1

- **Primary:** safety[c] & tolerability, MTD, & RDFE
- **Secondary:** PK, PD, & preliminary antitumor activity[d]

Part 1: Monotherapy dose finding[a]

Part 1a: Dose escalation
Selected R/R B-cell malignancies
(MZL, FL, MCL, CLL/SLL, **WM**, DLBCL, RT)
n≤72
Oral, QD, 28-day cycle[b]
Doses: 50 mg, 100 mg, 200 mg, 350 mg, 500 mg, 600 mg

Part 1b: Safety expansion
Selected R/R B-cell malignancies
(MZL, MCL, CLL/SLL, **WM**)
n≤120

Part 1c: Additional safety expansion
Selected R/R B-cell malignancies
(MZL, **WM**, RT, DLBCL, FL)
n≤100

Part 1d: Additional safety expansion
R/R CLL/SLL
n≤30

Part 1e: Additional safety expansion
Selected R/R B-cell malignancies (Japan only)
(MZL, FL, MCL, CLL/SLL, WM)
n=6-9

Part 1f: Monotherapy safety expansion
Selected BTK inhibitor–naive B-cell malignancies
(MZL, MCL, CLL/SLL, WM, RT)
n≤40

Determination of BGB-16673 RDFE

Phase 2

- **Cohort 1:** Post BTK inhibitor, R/R CLL/SLL
- **Cohort 2:** Post BTK inhibitor, R/R MCL
- **Cohort 3:** Post BTK inhibitor, R/R WM
- **Cohort 4:** Post BTK inhibitor, R/R MZL
- **Cohort 5:** R/R FL
- **Cohort 6:** R/R non-GCB DLBCL
- **Cohort 7:** Post BTK inhibitor, R/R RT

[a]Data from gray portions of the figure are not included in this presentation. [b]Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. [c]Safety was assessed according to CTCAE v5.0. [d]Responses were assessed per IWWM-6, modified Owen 2013 criteria after 4 weeks.

Frustaci AM et al, EHA 2025

Patient's Characteristics

	Total (N=36)
Age, median (range), years	72.0 (49-81)
Male, n (%)	22 (61.1)
ECOG PS, n (%)	
0	17 (47.2)
1	17 (47.2)
2	2 (5.6)
Hemoglobin, median (range), g/L	102 (60-146)
Hemoglobin ≤110 g/L, n/N with known status (%)	25/34 (73.5)
Neutrophils, median (range), 10^9/L	2.6 (0.2-7.4)
Neutrophils ≤1.5×10^9/L, n/N with known status (%)	11/33 (33.3)
Platelets, median (range), 10^9/L	153.5 (14.0-455.0)
IgM, median (range), g/L	35.1 (0.3-92.6)

	Total (N=36)
Mutation status, n/N with known status (%)[a]	
MYD88 mutation present	31/35 (88.6)
CXCR4 mutation present	19/35 (54.3)
BTK mutation present	11/31 (35.5)
TP53 mutation present	16/31 (51.6)
No. of prior lines of therapy, median (range)	3 (1-11)
Prior therapy, n (%)	
cBTK inhibitor	36 (100)
Anti-CD20 antibody	36 (100)
Chemotherapy	34 (94.4)
Proteasome inhibitor	11 (30.6)
BCL2 inhibitor	9 (25.0)
ncBTK inhibitor[b]	7 (19.4)
Discontinued prior BTK inhibitor due to PD, n (%)	30 (83.3)

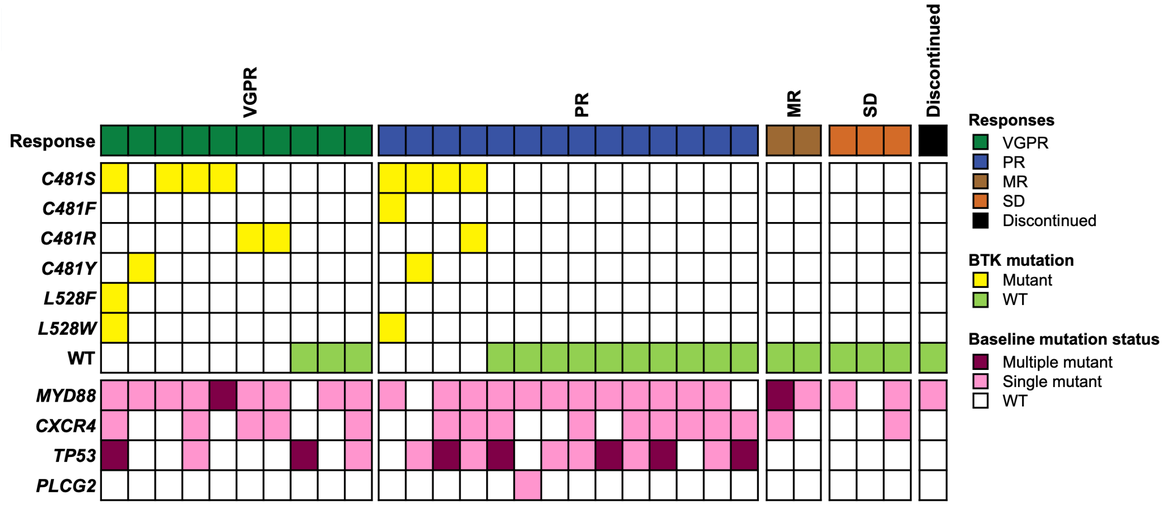
Data cutoff: March 3, 2025.
[a]Confirmed by central laboratory. [b]All seven patients with ncBTK inhibitor exposure were also exposed to a cBTK inhibitor.

Frustaci AM et al, EHA 2025

BGB-16673 - Response Rates

	Total (N=32)[a]
Best overall response, n (%)	
VGPR	10 (31.3)
PR	14 (43.8)
MR	3 (9.4)
SD	3 (9.4)
PD	1 (3.1)
Discontinued prior to first assessment	1 (3.1)
ORR, n (%)[b]	27 (84.4)
Major response rate, n (%)[c]	24 (75.0)
Time to first response, median (range), months[d]	1.0 (0.9-3.7)

Mutation status, n/N tested (%)	ORR (N=32)[a]
BTK	
Mutated	11/11 (100)
Unmutated	15/19 (78.9)
Unknown	1/2 (50.0)
MYD88	
Mutated	25/28 (89.3)
Unmutated	2/3 (66.7)
Unknown	0/1 (0)
CXCR4	
Mutated	16/17 (94.1)
Unmutated	11/14 (78.6)
Unknown	0/1 (0)
TP53	
Mutated	15/15 (100)
Unmutated	11/15 (73.3)
Unknown	1/2 (50.0)



[a]Efficacy-evaluable population; 4 patients were too early in treatment course to be response-evaluable. [b]Includes best overall response of MR or better. [c]Includes best overall response of PR or VGPR.
[d]In patients with a best overall response better than SD.

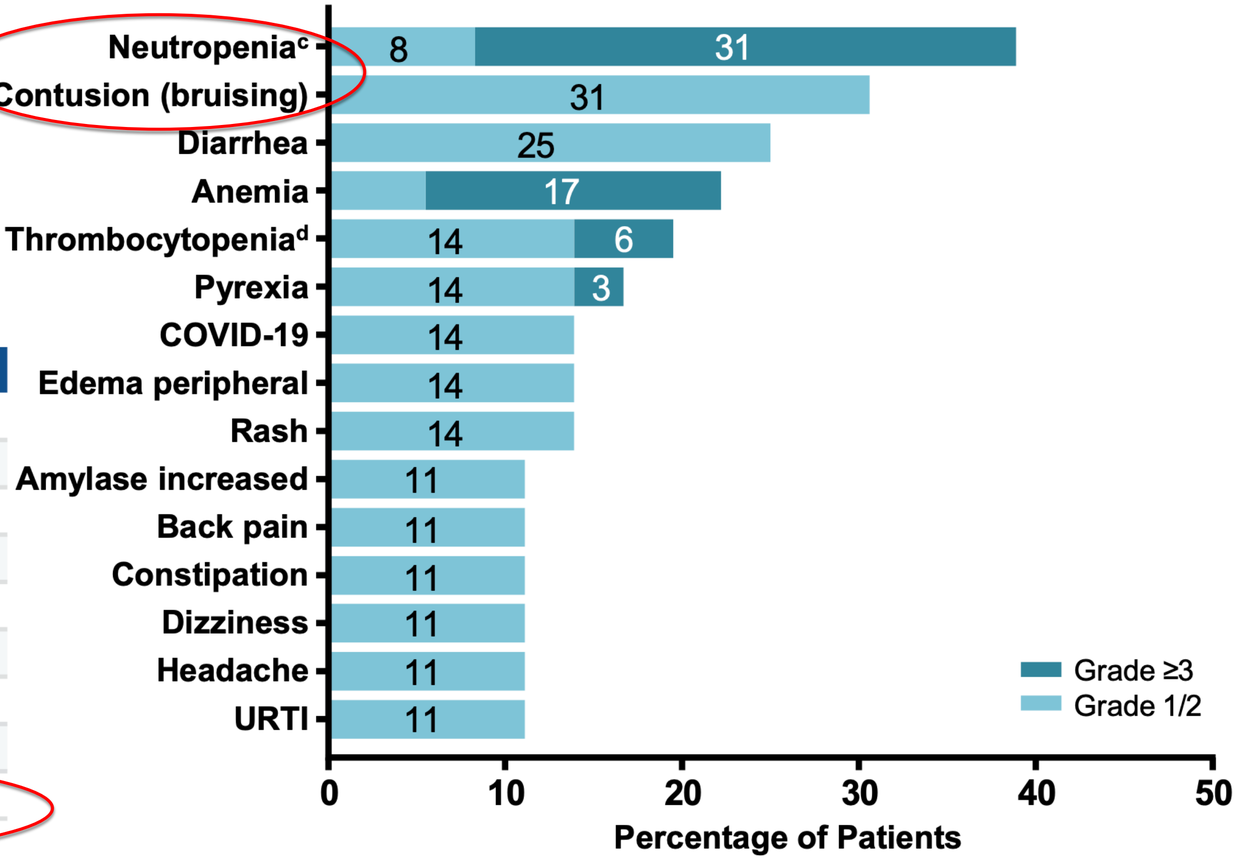
- Response rates were observed at all dose levels and in pts with prior CIT (25/30), cBTKi (27/32) or ncBTKi (4/4)
- Responses occurred regardless of baseline mutations (BTKi-resistant mutations, TP53 and CXCR4)
- Rapid decline in IgM with
- With a median follow-up of 8.2 mo, mPFS was NR

Frustaci AM et al, EHA 2025

BGB-16673 - Safety and TRAEs in ≥ 10% of Patients

- Most common TEAEs were neutropenia in 39% and contusion (bruising) in 31% of patients
- No atrial fibrillation, major hemorrhage[a], febrile neutropenia, or pancreatitis

Patients, n (%)	Total (N=36)
Any TEAE	32 (88.9)
Any treatment-related	25 (69.4)
Grade ≥3	22 (61.1)
Treatment-related grade ≥3	14 (38.9)
Serious	12 (33.3)
Treatment-related serious	4 (11.1)
Leading to death[b]	1 (2.8)
Treatment-related leading to death	0
Leading to treatment discontinuation	2 (5.6)

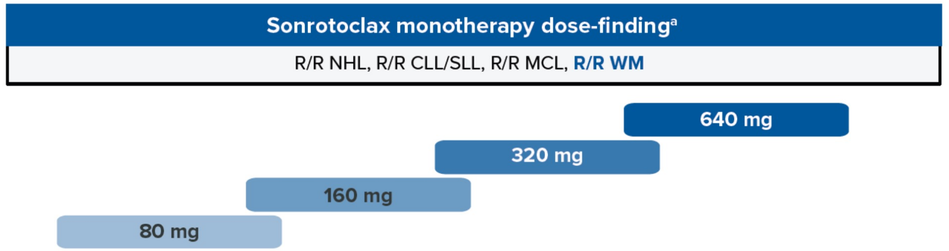


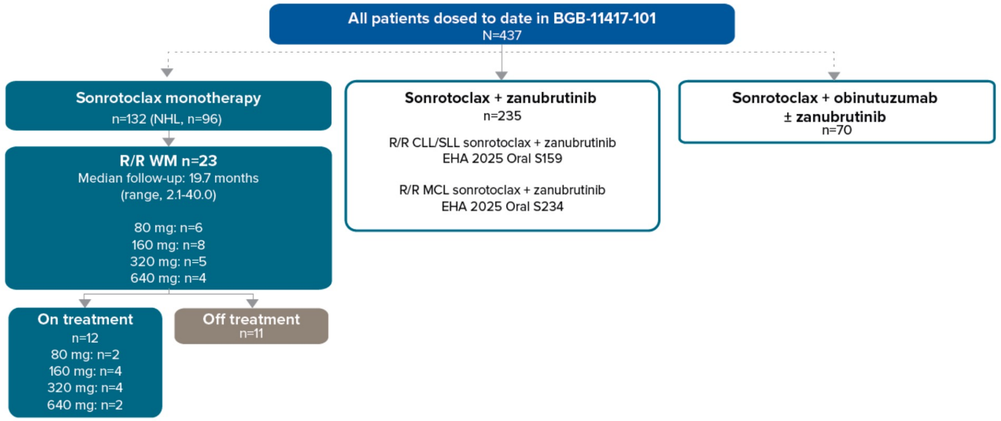
Data cutoff: March 3, 2025. Median follow-up: 8.2 months (range, 0.6-30.6 months).
[a]Grade ≥3, serious, or any central nervous system bleeding. [b]Septic shock (200-mg dose level), note in the context of PD. [c]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*.
[d]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

Frustaci AM et al, EHA 2025

Ph 1/1b Trial BGB-11417-101 – RR WM Cohort

- BGB-11417-101 (NCT04277637) is an ongoing, phase 1/1b, open-label, multicenter, dose-escalation and -expansion study of sonrotoclax as mono- or combination therapy in patients with various B-cell malignancies
- For the R/R WM cohort, eligible patients have WM that relapsed after or was refractory to at least one prior systemic therapy and requires treatment per International Workshop on Waldenstrom's Macroglobulinemia-7 criteria
- Sonrotoclax monotherapy is administered orally QD, with ramp-up to the intended target dose to prevent TLS, until disease progression or unacceptable toxicity
- The primary study objectives are to assess safety/tolerability, define MTD, and determine RP2D of sonrotoclax monotherapy; a secondary objective is to assess ORR, defined as MR or better per modified Owens 2013 criteria



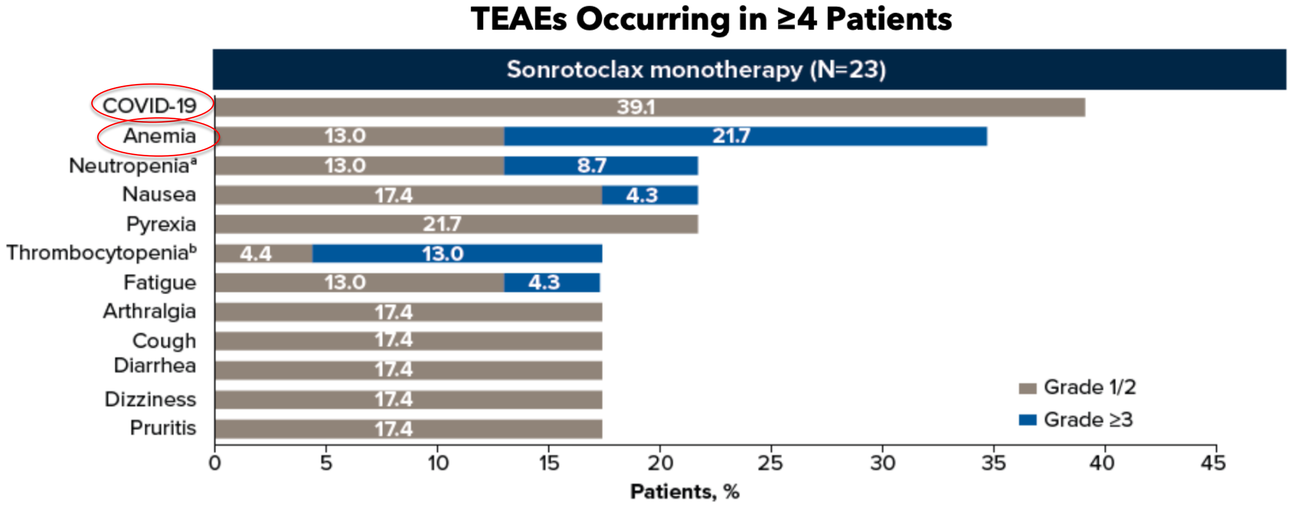


Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation

Cheah CY et al, EHA 2025

Ph 1/1b Trial BGB-11417-101 – Pts Characteristics and Safety

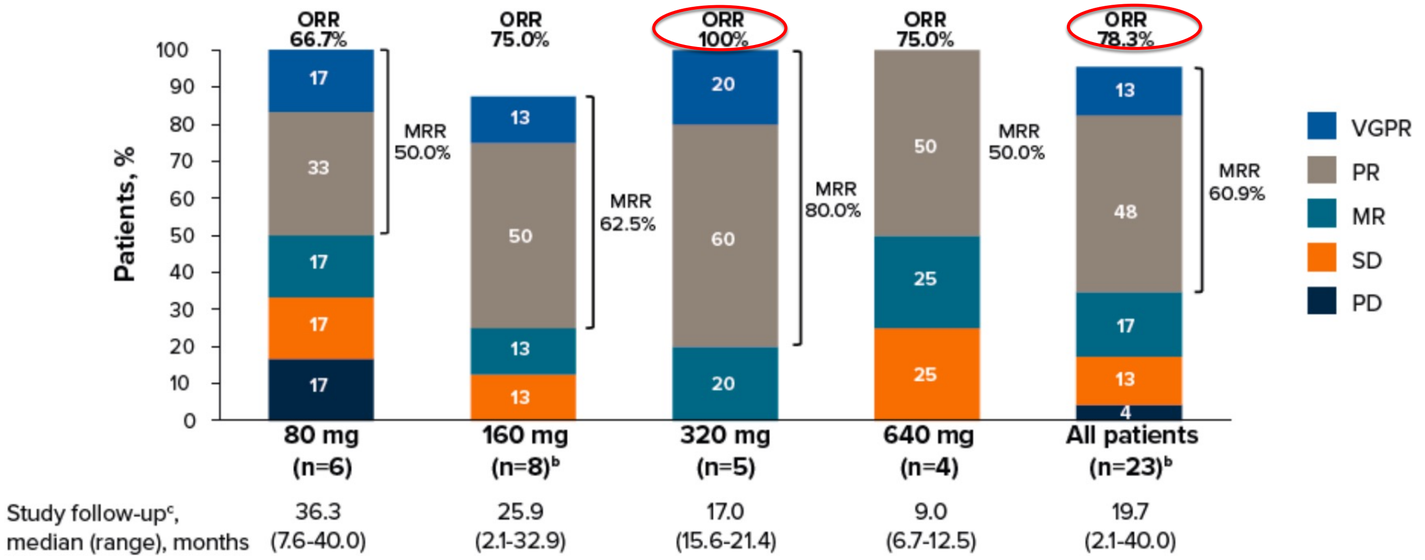
Characteristic	80 mg (n=6)	160 mg (n=8)	320 mg (n=5)	640 mg (n=4)	All (N=23)
Study follow-up time, median (range), months	36.3 (7.6-40.0)	25.9 (2.1-32.9)	17.0 (15.6-21.4)	9.0 (6.7-12.5)	19.7 (2.1-40)
Age, median (range), years	65.5 (48-79)	69.5 (61-87)	65.0 (61-77)	73.0 (68-84)	69.0 (48-87)
Male, n (%)	6 (100)	5 (62.5)	4 (80.0)	4 (100)	19 (82.6)
ECOG PS, n (%)					
0	3 (50.0)	2 (25.0)	1 (20.0)	2 (50.0)	8 (34.8)
1	3 (50.0)	5 (62.5)	4 (80.0)	2 (50.0)	14 (60.9)
2	0	1 (12.5)	0	0	1 (4.3)
MYD88 mutation, n/tested (%)	5/5 (100)	7/8 (87.5)	5/5 (100)	4/4 (100)	21/22 (95.4)
CXCR4 mutation, n/tested (%)	1/5 (20.0)	2/8 (25.0)	3/5 (60.0)	3/4 (75.0)	9/22 (40.9)
Prior therapy					
No. of lines of prior systemic therapy, median (range)	3.0 (1-8)	2.5 (1-9)	1.0 (1-8)	2.0 (1-3)	3.0 (1-9)
No. of prior lines of systemic therapy, n (%)					
1	1 (16.7)	3 (37.5)	3 (60.0)	2 (50.0)	9 (39.1)
2	1 (16.7)	1 (12.5)	0	0	2 (8.7)
≥3	4 (66.7)	4 (50.0)	2 (40.0)	2 (50.0)	12 (52.2)
Prior BTK inhibitor, n (%)	4 (66.7)	4 (50.0)	3 (60.0)	3 (75.0)	14 (60.9)
BTK inhibitor as last therapy, n (%)	3 (50.0)	3 (37.5)	1 (20.0)	2 (50.0)	9 (39.1)
Prior BTK inhibitor duration, median (range), months	58.0 (28.5-85.4)	53.7 (19.4-66.5)	33.1 (1.1-46.0)	37.0 (21.5-68.5)	49.5 (1.1-85.4)

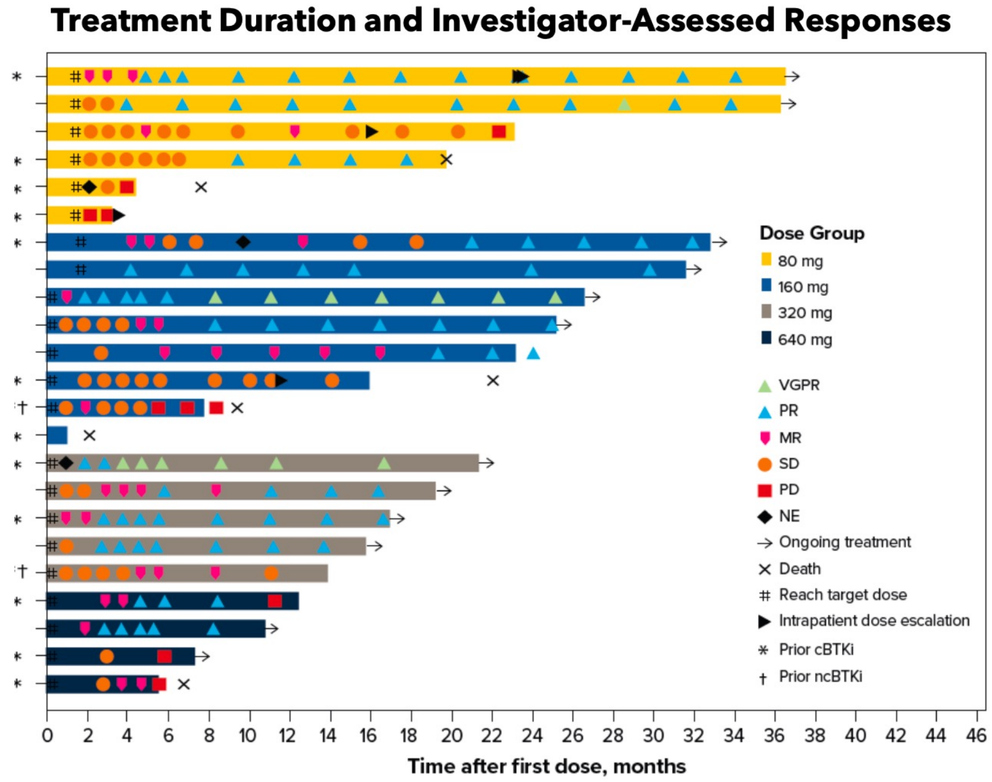


- 6 patients died while on study due to PD (n=4) and AEs (n=2) of COVID-19 and pneumonia;
- No cases of laboratory or clinical TLS occurred up to the highest dose tested (640 mg);
- No cases of atrial or ventricular fibrillation were reported;
- Sonrotoclax 320 mg was declared the RP2D, and no MTD was reached.

Cheah CY et al, EHA 2025

Ph 1/1b Trial BGB-11417-101 – Response Rates

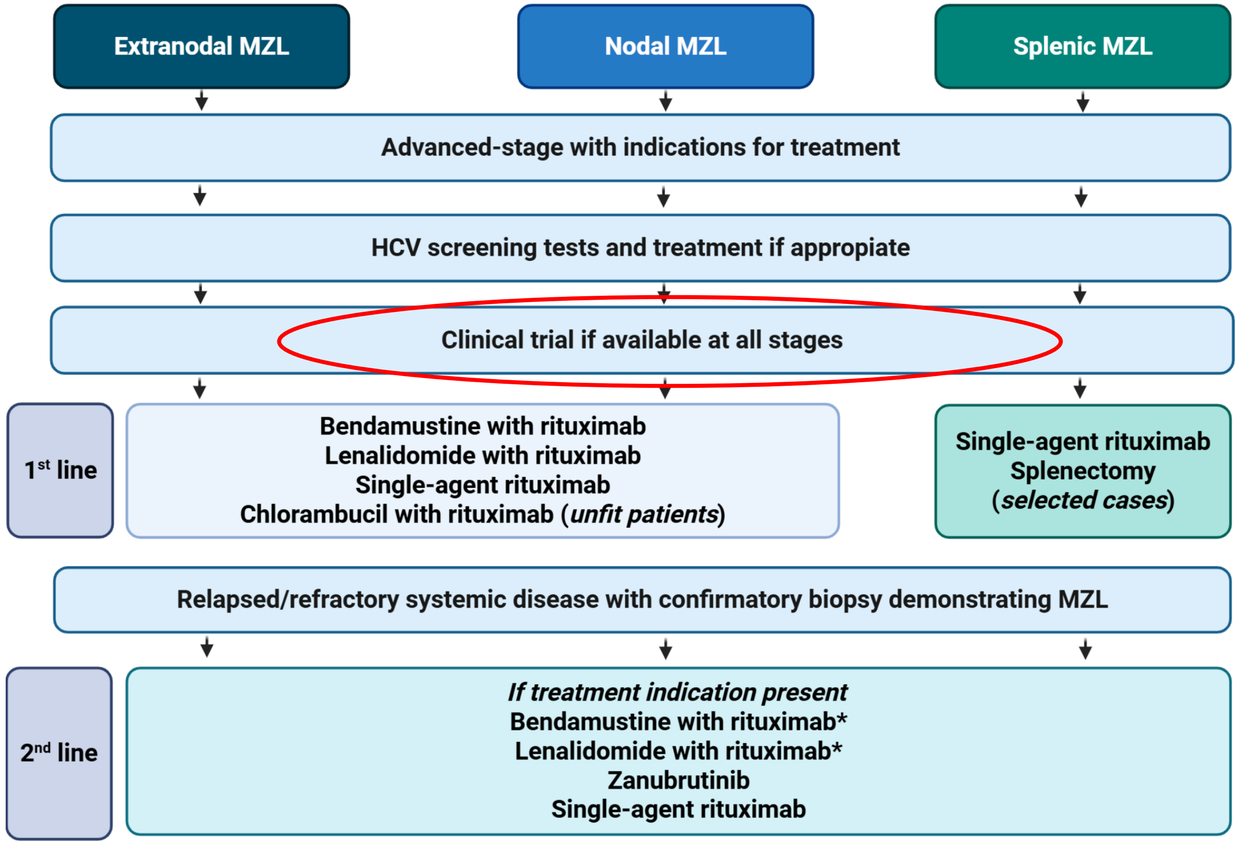




- Median time to response: 4.4 mo in all pts, 2.8 mo in 320 mg cohort
- Among 9 patients with a BTK inhibitor as their last therapy, an ORR of 66.7% (MR, n=1; PR, n=4; VGPR, n=1) was achieved
- Median DoR and median PFS were NR

Cheah CY et al, EHA 2025

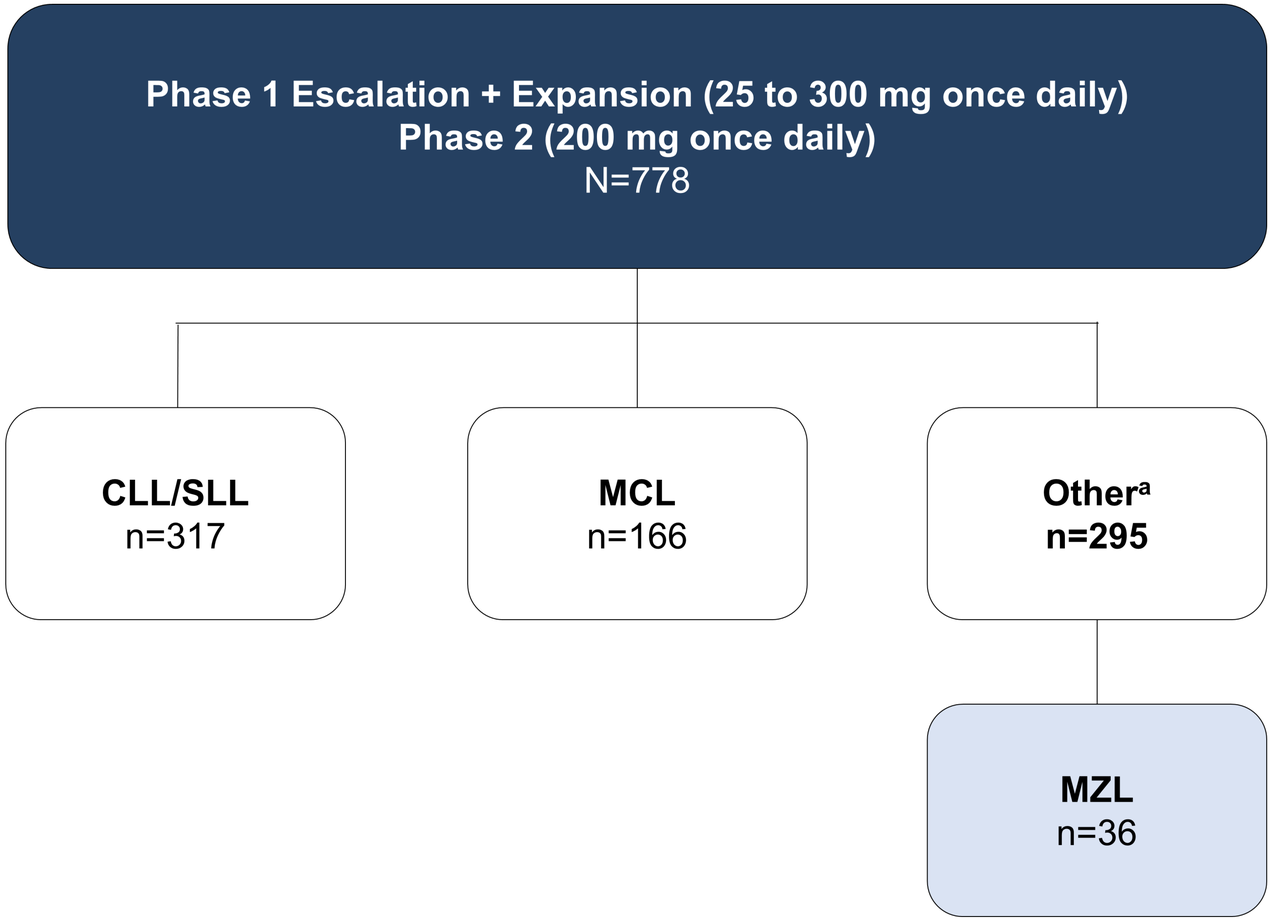
Marginal Zone Lymphomas, around the corner….



	BTKi	BTK degrader	BCL2i	ADC	BsAbs	CAR T
Single Agent	Pirto Nemta	BGB-16673 NX-5948 ABBV-101	Sonrotoclax	Lonca	Odro (ELM-2, RR)	Axicel (ZUMA5)
Combo	Zanu+Obi vs R2	\	Zanu+Sonrot	\	Mosu+Lena (TN)	\

Modified from Alderuccio P et al, Blood 2025

Phase 1/2 BRUIN Study Design



Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key Endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to Lugano criteria, DoR, PFS, and OS)

Data cutoff date of 05 May 2023 (NCT03740529). [a]Other includes DLBCL, RT, WM, FL, MZL, B-PLL, HCL, PCNSL, and other transformations.

Patel, et al.; ASH 2023

MZL Patient Characteristics

Characteristics	n=36
Median age, years (range)	68 (22-83)
Male, n (%)	16 (44)
Female, n (%)	20 (56)
ECOG PS, n (%)	
0	18 (50)
1	17 (47)
2	1 (3)
MZL Subtype, n (%)	
Nodal	17 (47)
Splenic	13 (36)
Extranodal*	6 (17)
Tumor Bulk (cm), n (%)	
≥5	4 (11)
<5	23 (64)
No measurable lymph node	9 (25)
Elevated LDH, n (%)	
Yes	15 (42)
No	21 (58)
Baseline Hemoglobin >12g/dL	
Yes	29 (81)
No	7 (19)
Involved Nodal Sites, n (%)	
≤4	20 (56)
>4	16 (44)

Characteristics	n=36
Ann Arbor Staging, n (%)	
Stage I/II	1 (3)
Stage III/IV	29 (81)
Missing	6 (17)
MALT-IPI Risk Group, n (%)	
Low Risk (0)	1 (3)
Intermediate Risk (1)	10 (28)
High Risk (≥2)	19 (53)
Missing	6 (17)
Median Number of Prior Lines of Systemic Therapy, (range)	3 (2-10)
Prior Therapy, n (%)	
cBTK inhibitor	26 (72)
Anti-CD20 antibody	36 (100)
Chemotherapy + Anti-CD20 antibody	31 (86)
PI3K inhibitor	6 (17)
Lenalidomide	8 (22)
BCL2 inhibitor	1 (3)
Autologous stem cell transplant	1 (3)
Other Systemic Therapy[a]	4 (11)
Reason for Discontinuation of any Prior cBTKi[b], n (%)	
Progressive disease	20 (77)
Toxicity/Other	6 (23)

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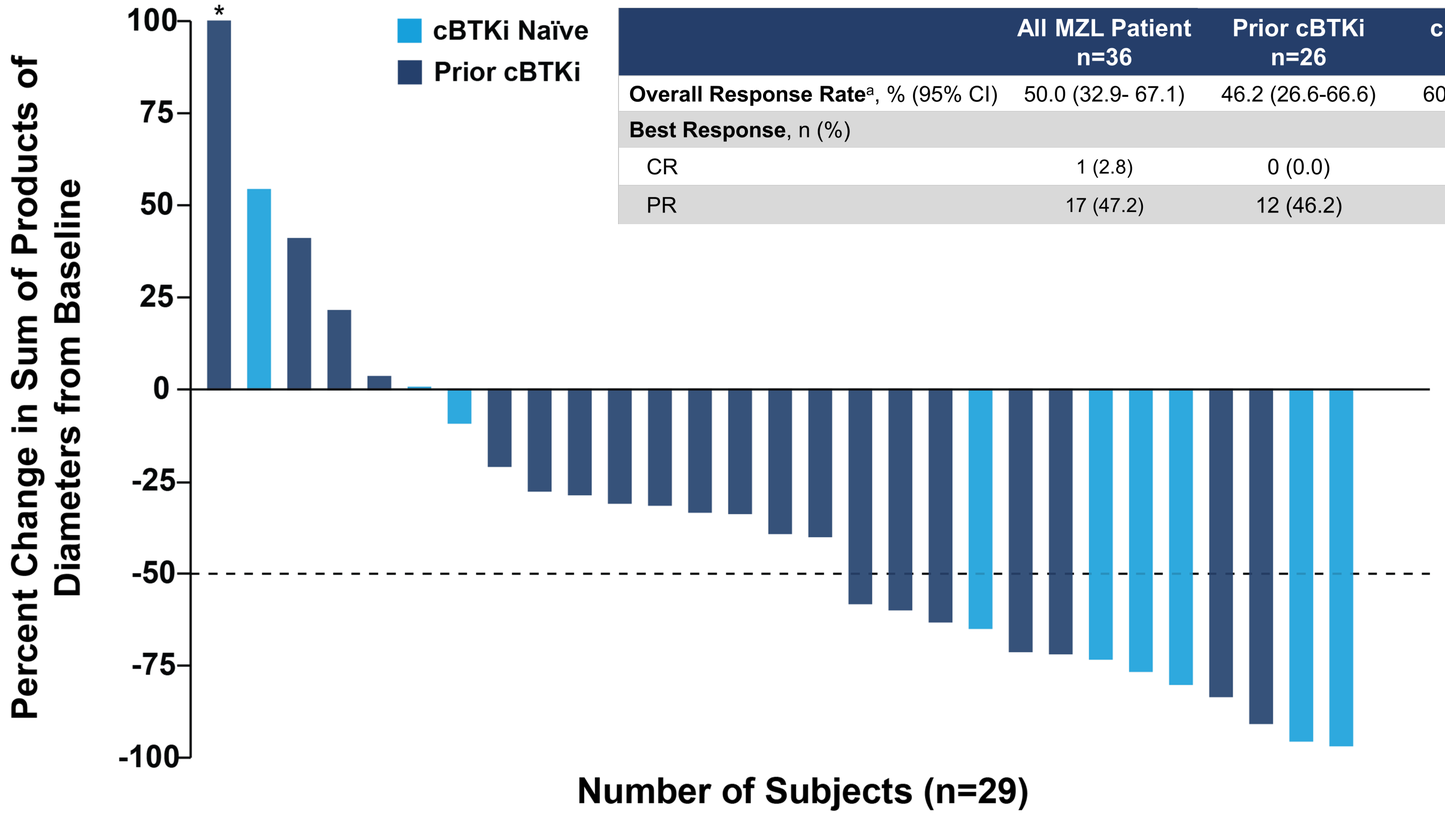
Pirtobrutinib Efficacy in MZL



	All MZL Patient n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Overall Response Rate[a], % (95% CI)	50.0 (32.9- 67.1)	46.2 (26.6-66.6)	60.0 (26.2-87.8)
Best Response, n (%)			
CR	1 (2.8)	0 (0.0)	1 (10.0)
PR	17 (47.2)	12 (46.2)	5 (50.0)

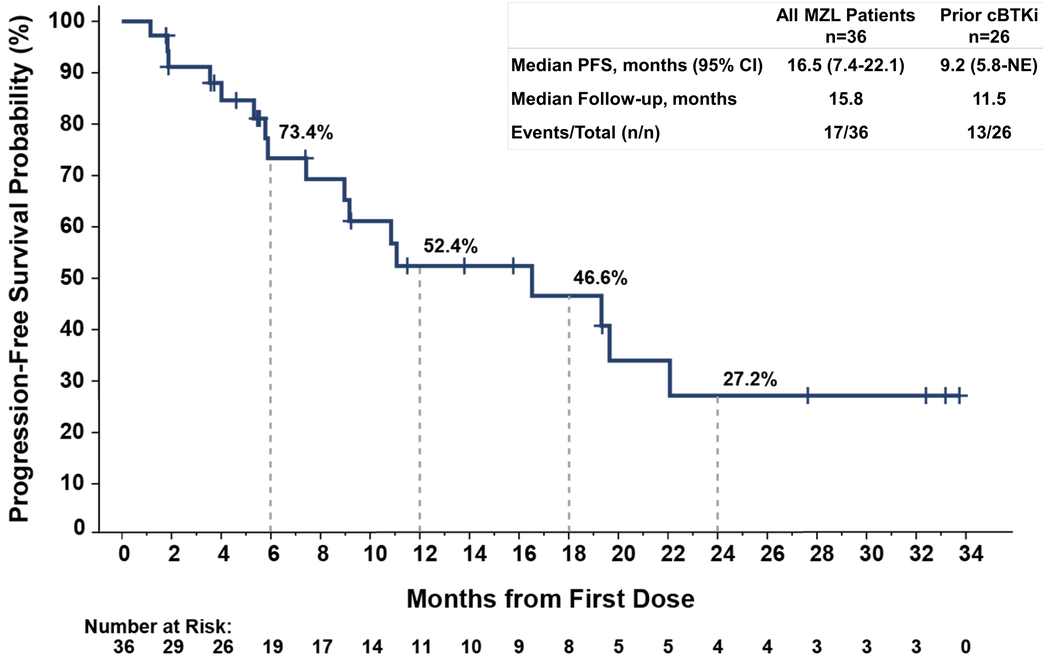
- Median time-to-response was 1.9 months (range, 1.6-19.3)

Data for 7 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patient with a > 100% increase in sum of products of diameter, with the corresponding change from baseline of 181.6%. [a]ORR is the number of patients with best response of CR or PR divided by the total number of patients; No patients with a best response of not evaluable (NE) are included in the denominator.

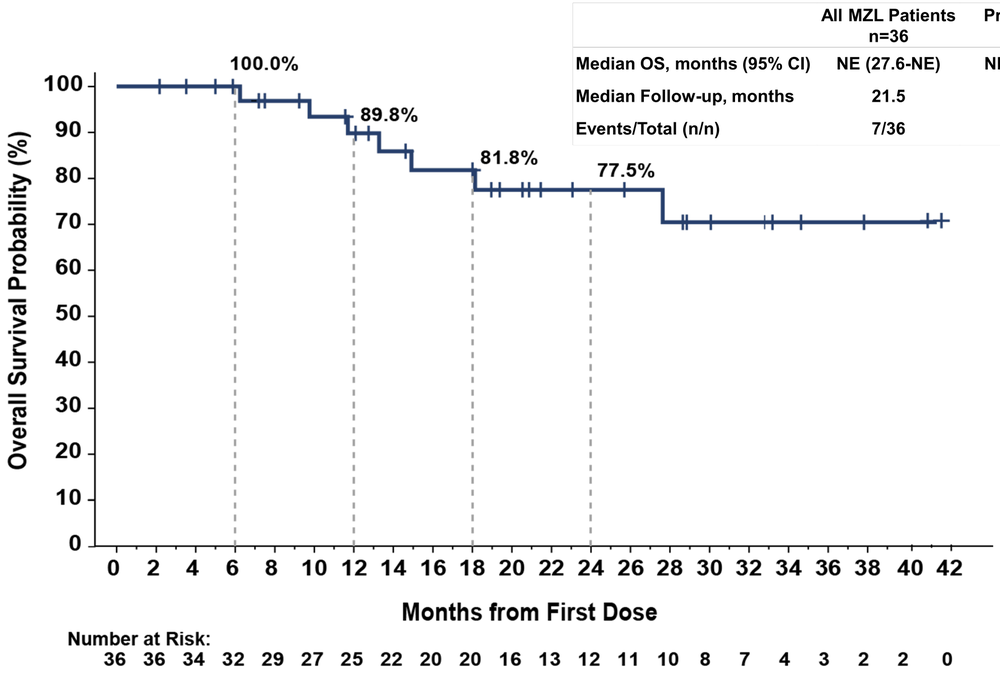
Patel, et al.; ASH 2023

Pirtobrutinib Progression-Free and Overall Survival

	All MZL Patients n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Median PFS, months (95% CI)	16.5 (7.4-22.1)	9.2 (5.8-NE)	NE (1.9-NE)
Median Follow-up, months	15.8	11.5	32.4
Events/Total (n/n)	17/36	13/26	4/10



	All MZL Patients n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Median OS, months (95% CI)	NE (27.6-NE)	NE (NE-NE)	NE (11.7-NE)
Median Follow-up, months	21.5	19.0	33.2
Events/Total (n/n)	7/36	3/26	4/10



Patel, et al.; ASH 2023

Pirtobrutinib Safety Profile

	Treatment Emergent AEs in Patients with MZL (n=36)			
	All-Cause AEs, (≥15%) %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Diarrhea	36.1	5.6	16.7	2.8
Fatigue	33.3	0	11.1	0
Neutropenia[a]	30.6	27.8	13.9	13.9
Anemia	25.0	13.9	8.3	5.6
Dyspnea	25.0	0	2.8	0
Nausea	22.2	0	2.8	0
Platelet Count Decrease	22.2	11.1	11.1	2.8
Arthralgia	16.7	0	2.8	0
Abdominal Pain	16.7	0	0	0
AEs of Interest[b]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infection[c]	61.1	13.9	5.6	0
Bruising[d]	30.6	0	25.0	0
Rash[e]	25.0	0	19.4	0
Hemorrhage[f]	13.9	0	2.8	0
Hypertension	5.6	2.8	2.8	2.8
Atrial Fibrillation/Flutter[g]	0	0	0	0

Median time on treatment for patients with MZL was 9 months
Pirtobrutinib discontinuations due to treatment-related AEs occurred in 5.6% (n=2) of all patients
Dose reductions due to treatment-related AEs occurred in 11.1% (n=4) of all patients

Patel, et al.; ASH 2023

Study Design of ELM-2 Ph 2 Trial

- Phase 2, open-label, multicohort, multicenter study of odronextamab monotherapy in patients with R/R B-NHL (NCT03888105)

Key eligibility criteria

- ≥18 years old
- MZL (extranodal, splenic, or nodal subtype)*
- ECOG PS 0 or 1
- Refractory to, or relapsed after, ≥2 prior lines of systemic therapy

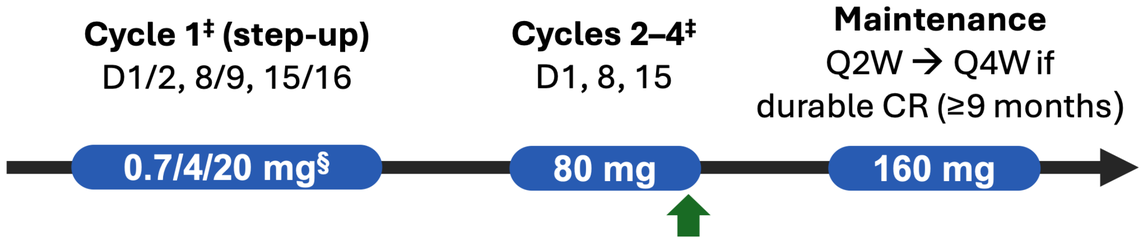
Primary endpoint

- ORR† by ICR

Secondary endpoints

- ORR† by local investigator
- DOR,† PFS,† and OS
- Safety and tolerability
- Patient-reported outcomes

Odronextamab IV administration



Measures taken to facilitate diverse, inclusive enrollment:

- Diverse trial sites
- Translated consents
- Extended screening windows
- Broad eligibility criteria
- Investigator training

Anti-infection prophylaxis including IVIg supplementation and antivirals was recommended, and PJP prophylaxis was mandated

Kim TM et al, Oral at ASH 2024

ELM-2 Patient's Characteristic

Patient and disease characteristics		Overall (n=42)*	Extranodal (n=21)	Nodal (n=15)	Splenic (n=5)
Median age (range), years		63.5 (34–82)	59.0 (34–82)	66.0 (38–80)	73.0 (52–80)
Male, %		45.2	42.9	46.7	40.0
Ann Arbor stage III/IV, %		83.3	76.2	93.3	80.0
Bulky disease, %		9.5	14.3	0	20.0
Race, %	*White / Asian / Black or African American / Not reported*	47.6 / 38.1 / 4.8 / 9.5	33.3 / 57.1 / 4.8 / 4.8	60.0 / 26.7 / 6.7 / 6.7	80.0 / 0 / 0 / 20.0
ECOG PS, %	*0 / 1*	45.2 / 54.8	42.9 / 57.1	46.7 / 53.3	40.0 / 60.0
IPI score, %	*3 / 4–5*	19.0 / 9.5	23.8 / 0	13.3 / 20.0	20.0 / 20.0
Median number of prior lines of therapy (range)		2 (1–8)	2 (1–8)	2 (1–4)	2 (2–4)
Number of prior lines,† %	*≥2 / ≥3 / ≥4 / ≥5*	83.3 / 31.0 / 19.0 / 2.4	76.2 / 38.1 / 19.0 / 4.8	93.3 / 20.0 / 13.3 / 0	100 / 40.0 / 40.0 / 0
Primary refractory, %		33.3	38.1	33.3	20.0
Refractory to last line of therapy, %		64.3	57.1	80.0	60.0
Refractory to anti-CD20 antibody in any line, %		47.6	52.4	53.3	20.0
Double refractory to alkylator/anti-CD20 antibody in any line, %		33.3	42.9	33.3	0
Prior BTKi, %		28.6	19.0	33.3	60.0
Prior bendamustine, %		33.3	33.3	40.0	20.0
Prior ASCT, %		7.1	9.5	6.7	0
POD24, %		50.0	57.1	60.0	0

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ELM-2 Results

Best overall response, %*	Overall (n=35)	Extranodal (n=19)	Nodal (n=12)	Splenic (n=3)
Objective response rate (ORR)	77.1 (95% CI 59.9–89.6)	78.9 (95% CI 54.4–93.9)	75.0 (95% CI 42.8–94.5)	100 (95% CI 29.2–100)
Complete response	77.1 (95% CI 59.9–89.6)	78.9 (95% CI 54.4–93.9)	75.0 (95% CI 42.8–94.5)	100 (95% CI 29.2–100)
Partial response	0	0	0	0
Stable disease	8.6	10.5	8.3	0
Progressive disease	0	0	0	0
Not evaluable	14.3	10.5	16.7	0

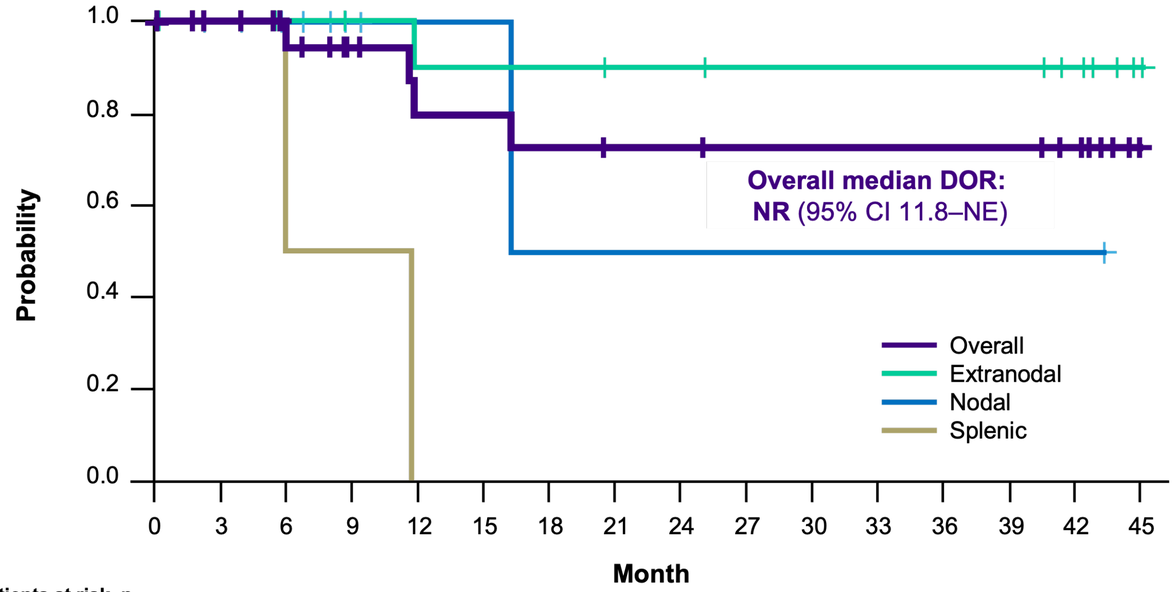
12-month PFS rate (95% CI):

Overall	Extranodal	Nodal	Splenic
87.5 (65.9–95.8)	93.3 (61.3–99.0)	88.9 (43.3–98.4)	50.0 (0.6–91.0)

12-month OS rate (95% CI):

Overall	Extranodal	Nodal	Splenic
92.2 (71.8–98.0)	93.3 (61.3–99.0)	100 (100–100)	50.0 (0.6–91.0)

Duration of response (investigator assessed)*



Patients at risk, n

Overall	27	22	18	14	11	11	10	9	9	8	8	8	8	8	6	0
Extranodal	15	12	1 1	10	9	9	9	8	8	7	7	7	7	7	5	0
Nodal	9	8	6	3	2	2	1	1	1	1	1	1	1	1	1	0
Splenic	3	2	1	1	0											

	Overall	Extranodal	Nodal	Splenic
12-mo DOR (95% CI)	80.2 (49.6–93.3)	90.0 (47.3–98.5)	100 (100–100)	0.0 (NE–NE)

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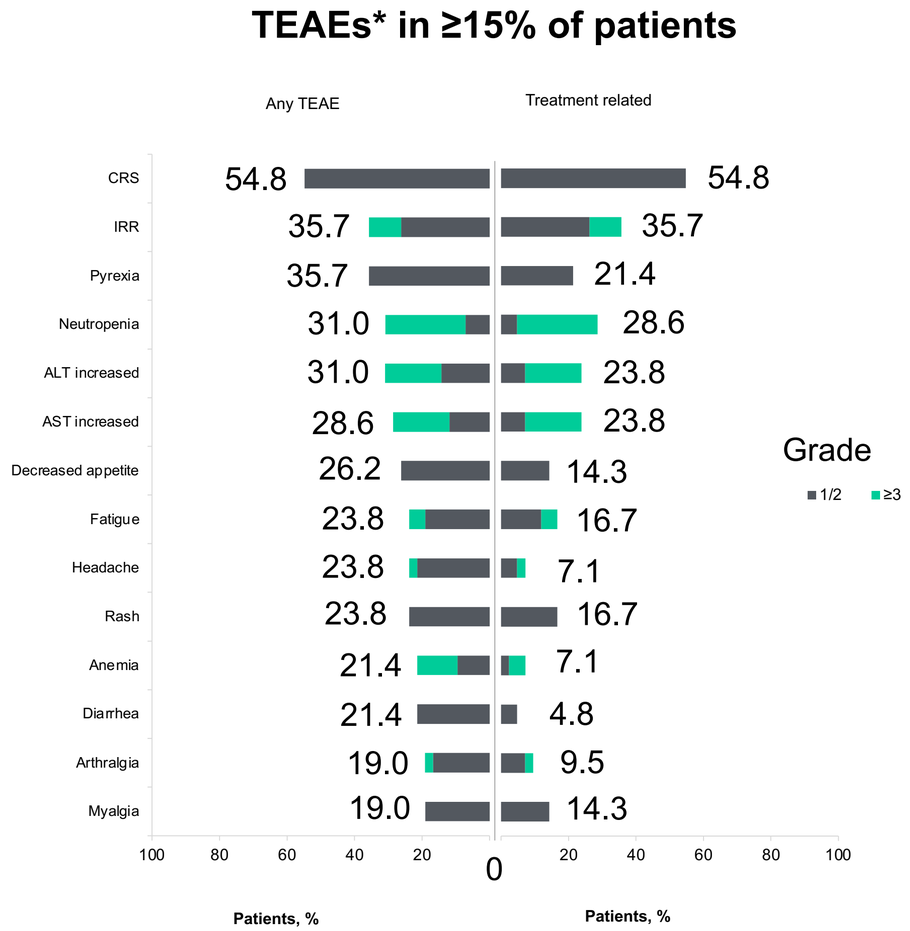
Odronextamab demonstrated generally manageable safety consistent with that reported in 3L+ R/R FL

n (%)	Overall (n=42)	
	Any event	Treatment related
Any TEAE	42 (100.0)	42 (100.0)
Grade ≥3 TEAE	35 (83.3)	31 (73.8)
Serious TEAE	27 (64.3)	17 (40.5)
TEAE leading to dose interruption/delay	35 (83.3)	33 (78.6)
TEAE leading to dose reduction	4 (9.5)	3 (7.1)
TEAE leading to discontinuation	4 (9.5)	1 (2.4)
TEAE leading to death	0	0

- Safety profile was generally consistent across MZL subtypes, with CRS, IRR, and pyrexia among the most frequent TEAEs
- Treatment-related TEAEs leading to discontinuation: CRS (n=1)
- Overall safety consistent with that in 3L+ R/R FL in ELM-2[2]



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AEs of interest: CRS and ICANS

	0.7/4/20 mg			
	Overall **(n=23)**	Extranodal (n=10)	Nodal (n=9)	Splenic (n=4)
CRS (any grade), n (%)	13 (56.5)	5 (50.0)	5 (55.6)	3 (75.0)
Grade 1	8 (34.8)	5 (50.0)	2 (22.2)	1 (25.0)
Grade 2	5 (21.7)	0	3 (33.3)	2 (50.0)
Grade 3	0	0	0	0
Grade ≥4	0	0	0	0
Median time to onset CRS (range), hours	4.0 (–6.0–64.0)	4.0 (–6.0–18.7)	3.6 (0.0–64.0)	3.0* (3.0–3.0)
Median CRS duration (range), hours	6.2 (1.0–29.0)	5.5 (1.4–29.0)	6.0 (1.0–16.8)	6.7* (6.7–6.7)
Systemic steroid for CRS management, n (%)	8 (34.8)	2 (20.0)	3 (33.3)	3 (75.0)
Tocilizumab for CRS management, n (%)	7 (30.4)	2 (20.0)	3 (33.3)	2 (50.0)

- 0.7/4/20 mg step-up regimen:
  - CRS events all Grade 1/2 and generally confined to Cycle 1
  - CRS events resolved within a median of 6.2 hours (range 1.0–29.0) with supportive measures
- No ICANS events reported

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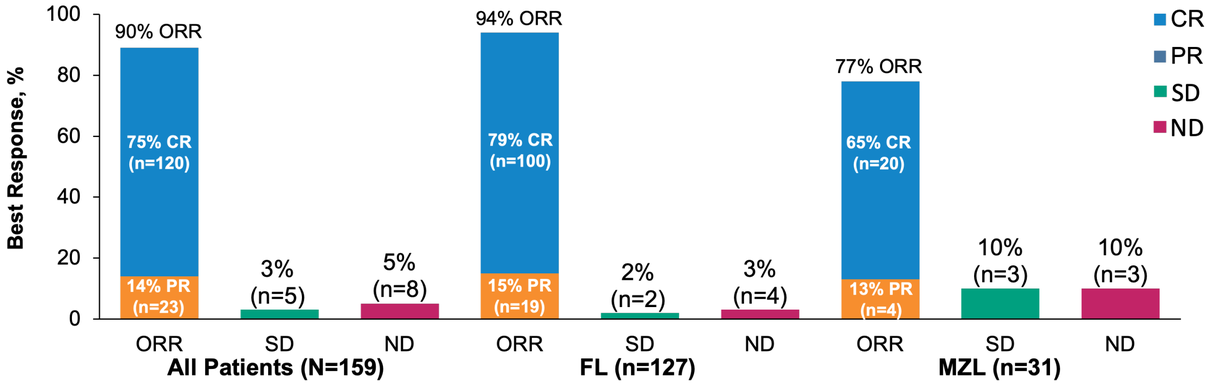
AEs of interest: Infections

Patients with any infection TEAE, n (%)	All safety-evaluable patients			
	Overall (n=42)	Extranodal (n=21)	Nodal (n=15)	Splenic (n=5)
Any grade	29 (69.0)	17 (81.0)	9 (60.0)	3 (60.0)
Grade 1	4 (9.5)	3 (14.3)	1 (6.7)	0
Grade 2	15 (35.7)	8 (38.1)	5 (33.3)	2 (40.0)
Grade 3	9 (21.4)	5 (23.8)	3 (20.0)	1 (20.0)
Grade 4	1 (2.4)	1 (4.8)	0	0
Grade 5	0	0	0	0

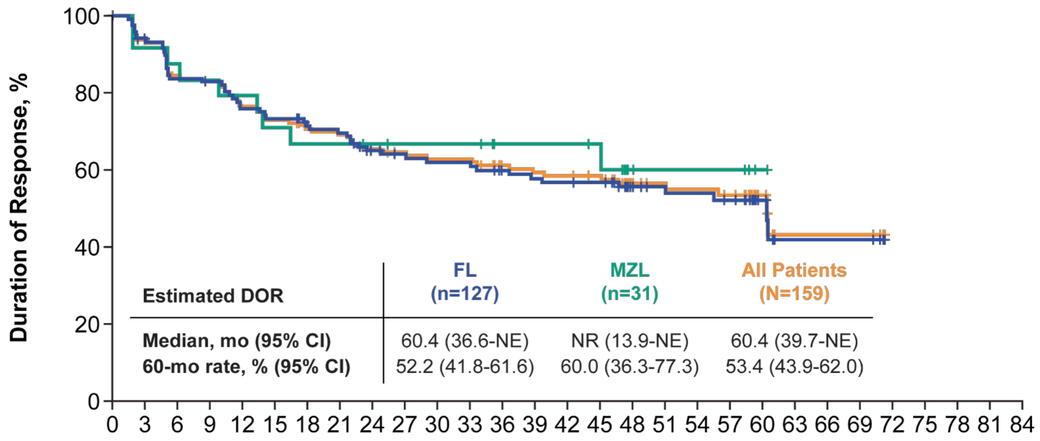
- Most frequent infections: COVID-19* (19.0%), cytomegalovirus reactivation† (11.9%), upper respiratory tract infection† (9.5%), and herpes zoster† (9.5%)
- Infection incidence was broadly similar across extranodal, nodal, and splenic subtypes
- No treatment discontinuations due to treatment-related infections
- No Grade 5 infections
- COVID-19* infection was reported in eight patients overall (Grade 3/4, n=2; no Grade 5)

Data cut-off date: August 15, 2024.
*Incidence of COVID-19 equates to incidence of coronavirus infection (HLT), as all preferred-term infection events reported under this HLT were COVID-19 related; †Preferred term description per NCI-CTCAE v5.0.
CMV surveillance was done by PCR testing in blood during screening, at Week 6, Week 12, Week 24, and at other timepoints when clinically indicated.
AEs, adverse events; HLT, high-level term; MZL, marginal zone lymphoma; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

ZUMA-5: Ph 2 Trial of Axicel in 3L+ MZL



Duration of response

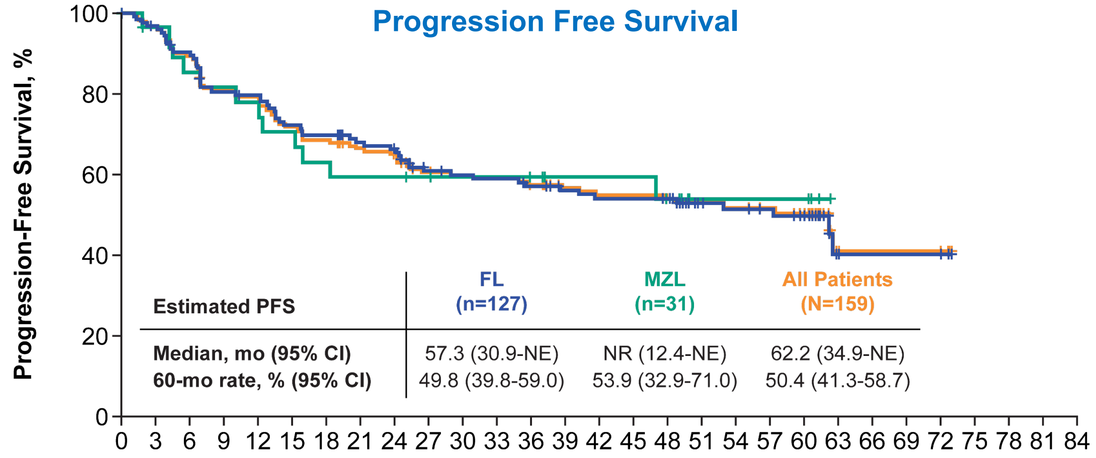


Estimated DOR	FL (n=127)	MZL (n=31)	All Patients (N=159)
Median, mo (95% CI)	60.4 (36.6-NE)	NR (13.9-NE)	60.4 (39.7-NE)
60-mo rate, % (95% CI)	52.2 (41.8-61.6)	60.0 (36.3-77.3)	53.4 (43.9-62.0)

No. at risk

FL	119	109	97	95	87	84	78	76	66	63	61	61	56	54	53	52	37	33	32	30	12	6	6	6	0
MZL	24	22	21	20	19	17	16	16	15	14	14	14	11	11	11	10	5	4	4	4	1	0			
All patients	143	131	118	115	106	101	94	92	81	77	75	75	67	65	64	62	42	37	36	34	13	6	6	6	0

Progression Free Survival



Estimated PFS	FL (n=127)	MZL (n=31)	All Patients (N=159)
Median, mo (95% CI)	57.3 (30.9-NE)	NR (12.4-NE)	62.2 (34.9-NE)
60-mo rate, % (95% CI)	49.8 (39.8-59.0)	53.9 (32.9-71.0)	50.4 (41.3-58.7)

No. at risk

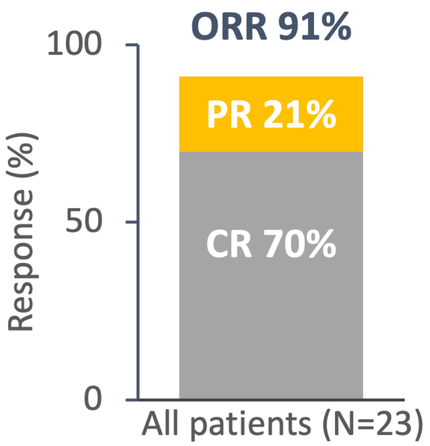
FL	127	120	111	98	96	87	84	78	75	65	63	62	59	55	53	53	52	36	34	32	29	7	6	6	6	0
MZL	31	26	23	22	21	19	17	16	16	15	14	14	13	11	11	11	9	4	4	4	4	0				
All patients	159	146	134	120	117	106	101	94	91	80	77	76	72	66	64	64	61	40	38	36	33	7	6	6	6	0

Neelapu SS, abs#864 ASH 2024

ADC – Ph 2 Trial of Lonca in RR MZL

23 patients enrolled
- Median age was 65 years (range 45–82)
- 100% had ECOG PS 0–1
- 83% had stage III/IV disease
- 48% had POD24
- 61% had relapsed disease
- 39% were refractory
- Median no. of prior LoT was 2 (range 1–4)

Response rates



Additional efficacy findings

93% of CRs currently maintained

64% of POD24 patients achieved CR

1 patient received prior CAR-T and achieved CR

67% 18-mo DoCR

92% 12-mo PFS

Lonca was generally well tolerated

%	Any Grade	Grade 3–4
Maculopapular rash	65	4
Increased AST	65	0
Increased ALT	61	9
Increased ALP	48	13
Neutropenia	43	17
Local oedema	43	0
Photosensitivity	30	4
Anaemia	30	4

- 1 patient discontinued treatment†
- 3 patients required Lonca dose reductions
- No treatment-related deaths occurred

Lossos I et al, Poster at ASH 2024

BTK Degrader:

	FL (n=17)	MZL (n=29)
Age, median (range), years	70 (52-86)	75 (33-88)
Male, n (%)	13 (76.5)	13 (44.8)
ECOG PS, n (%)		
0		
1		
Ann Arbor stage III/IV at study entry, n/N (%)[a]		
Tumor bulk, n (%)		
Longest diameter ≥5 cm		
No. of prior lines of therapy, median (range)		
Prior therapy, n (%)		
cBTK inhibitor		
ncBTK inhibitor		
BCL2 inhibitor	0	7 (24.1)
Anti-CD20-based therapy	17 (100)	29 (100)
Chemotherapy	16 (94.1)	28 (96.6)
Discontinued prior BTK inhibitor due to PD, n/N (%)	3/3 (100)	21/25 (84.0)[b]

Patients, n (%)	FL (n=12)	MZL (n=20)
Best overall response, n (%)		
CR	1 (8.3)	2 (10.0)
PR	4 (33.3)	8 (40.0)
SD	3 (25.0)	5 (25.0)
PD	3 (25.0)	3 (15.0)
ORR, n (%)[a]	5 (41.7)	10 (50.0)
Disease control rate, n (%)[b]	8 (66.7)	15 (75.0)
Time to first response, median (range), months[c]	2.6 (2.3-3.3)	2.9 (2.6-9.9)
Duration of response, median (95% CI), months[c]	9.5 (5.7-NE)	10.8 (2.8-NE)

	FL (n=17)		MZL (n=29)	
Patients, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
URTI	4 (23.5)	1 (5.9)	4 (13.8)	0
Fatigue	3 (17.6)	0	7 (24.1)	0
		0	6 (20.7)	0
		0	4 (13.8)	0
		1 (5.9)	3 (10.3)	0
		2 (11.8)	8 (27.6)	6 (20.7)
		0	4 (13.8)	0
		0	3 (10.3)	0
		0	3 (10.3)	1 (3.4)
		0	3 (10.3)	1 (3.4)
		0	3 (10.3)	0
		0	4 (13.8)	0
Asthenia	0	0	4 (13.8)	1 (3.4)
Petechiae	0	0	4 (13.8)	0
Decreased appetite	0	0	3 (10.3)	0
Hematoma	0	0	3 (10.3)	0

Zinzani PL et al, ICML 2024