Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed / Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study

Presented at: ASH Annual Meeting

Date: December 10, 2022

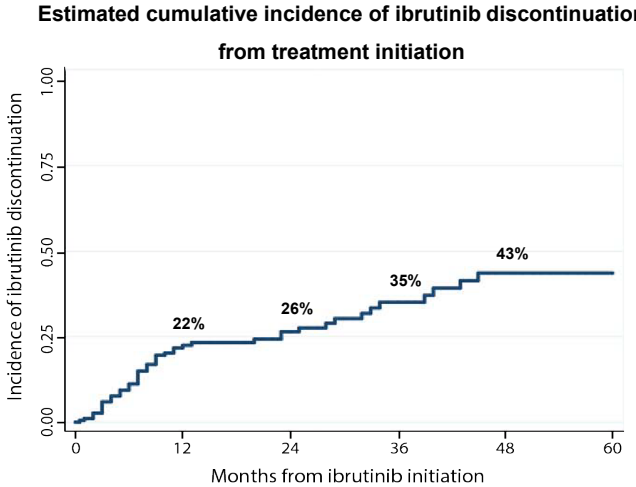
Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed / Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study

M Lia Palomba[1], Manish R. Patel[2], Toby A. Eyre[3], Wojciech Jurczak[4], David Lewis[5], Thomas Gastinne[6], Shuo Ma[7], Jonathon B. Cohen[8], Krish Patel[9], Jennifer R. Brown[10], Lydia Scarfò[11], Talha Munir[12], Ewa Lech-Maranda[13], Marc S. Hoffmann[14], Chaitra S. Ujjani[15], Bita Fakhri[16], Michael Wang[17], Koji Izutsu[18], Hirokazu Nagai[19], Constantine S. Tam[20], Joanna M. Rhodes[21], Julie Vose[22], Matthew McKinney[23], James N. Gerson[24], Minal A. Barve[25], Bryone Kuss[26], Youngil Koh[27], John F. Seymour[20], Wei Gao[28], Amy S. Ruppert[28], Richard A. Walgren[29], Donald E. Tsai[29], Binoj Nair[29], Katherine Bao[29], Anthony R. Mato[1], Chan Y. Cheah[30]

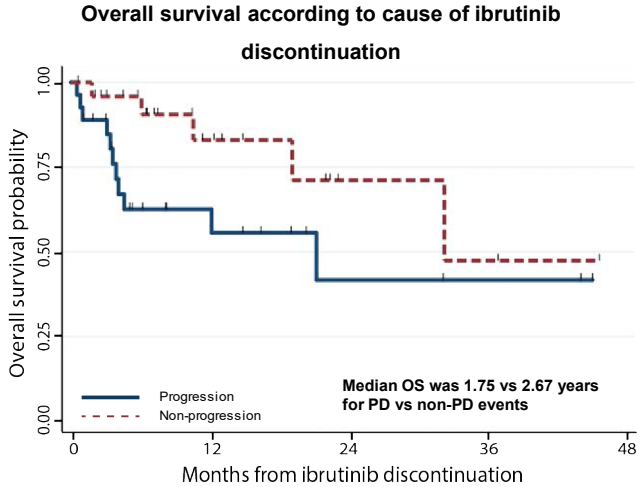
[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]Florida Cancer Specialists, Sarah Cannon Research Institute, Sarasota, USA; [3]Churchill Cancer Center, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; [4]Maria Sklodowska-Curie National Institute of Oncology, Krakow, Poland; [5]Plymouth Hospitals NHS Trust - Derriford Hospital, Plymouth, UK; [6]Centre Hospitalier Universitaire de Nantes, Nantes, France; [7]Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, USA; [8]Winship Cancer Institute, Emory University, Atlanta, USA; [9]Swedish Cancer Institute, Seattle, USA; [10]Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA; [11]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [12]Department of Haematology, St. James's University Hospital, Leeds, UK; [13]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [14]The University of Kansas Cancer Center, Kansas City, USA; [15]Fred Hutchinson Cancer Center, University of Washington, Seattle, USA; [16]University of California San Francisco Medical Center, San Francisco, USA; [17]University of Texas, MD Anderson Cancer Center, Houston, USA; [18]National Cancer Center Hospital, Tokyo, Japan; [19]National Hospital Organization Nagoya Medical Center, Nagoya, Japan; [20]Peter MacCallum Cancer Centre, Royal Melbourne Hospital & University of Melbourne, Melbourne, Australia; [21]Northwell Health Cancer Institute, New Hyde Park, USA; [22]University of Nebraska Medical Center, Omaha, USA; [23]Duke Cancer Institute, Durham, USA; [24]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA; [25]Mary Crowley Cancer Research Center, Dallas, USA; [26]Flinders University Medical Centre, Bedford Park, Australia; [27]Seoul National University Hospital, Seoul, South Korea; [28]Eli Lilly and Company, Indianapolis, USA; [29]Loxo@Lilly, Indianapolis, USA; [30]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia

Limited Therapeutic Options and Poor Outcomes after cBTKi Treatment Represent a Major Unmet Medical Need in Waldenström macroglobulinemia

- Covalent BTK inhibitors are increasingly the mainstay of treatment for Waldenström macroglobulinemia (WM)
- However, patients discontinue these agents due to both progression and intolerance; mechanisms of acquired resistance are incompletely understood[1-6]
- Patients with relapsed/refractory WM have limited treatment options following CIT and covalent BTK inhibitor therapy[7]



Data from Figure 1, Gustine JN, et al.[7]

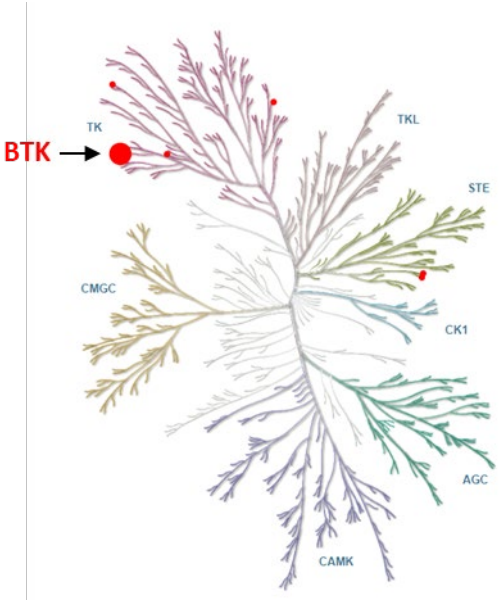


Data from Figure 2, Gustine JN, et al.[7]

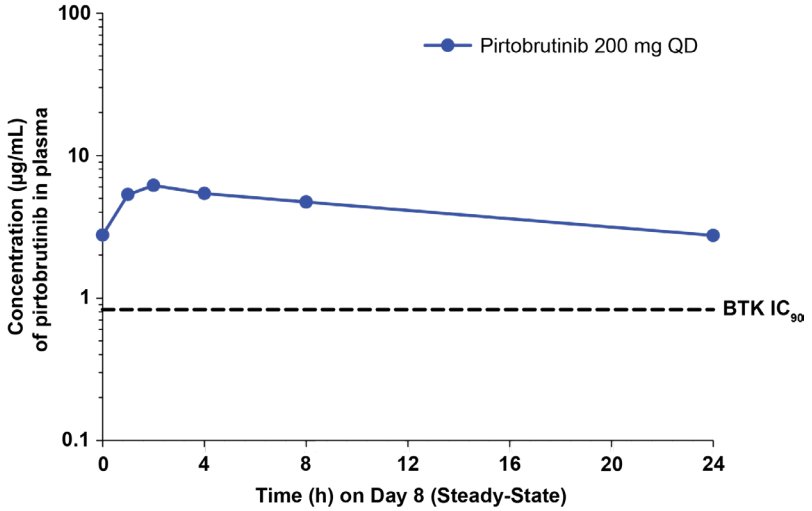
[1]Gertz. *Am J Hematol.* 2021; 96: 258– 269. [2]Ababneh et al. *Clin Hem Intl.* 2022;4:21-29. [3]Tam et al. *Blood.* 2020;136:2038-50. [4]Dimopoulos et al. *N Engl J Med.* 2018; 378:2399-2410. [5]Xu et al. *Blood.* 2017;129(18): 2519–2525. [6]Treon et al. *JCO.* 2020;38(11). [7]Gustine et al. *Am J Hematol.* 2018;93:511-517.

Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

Highly Selective for BTK[1,2]



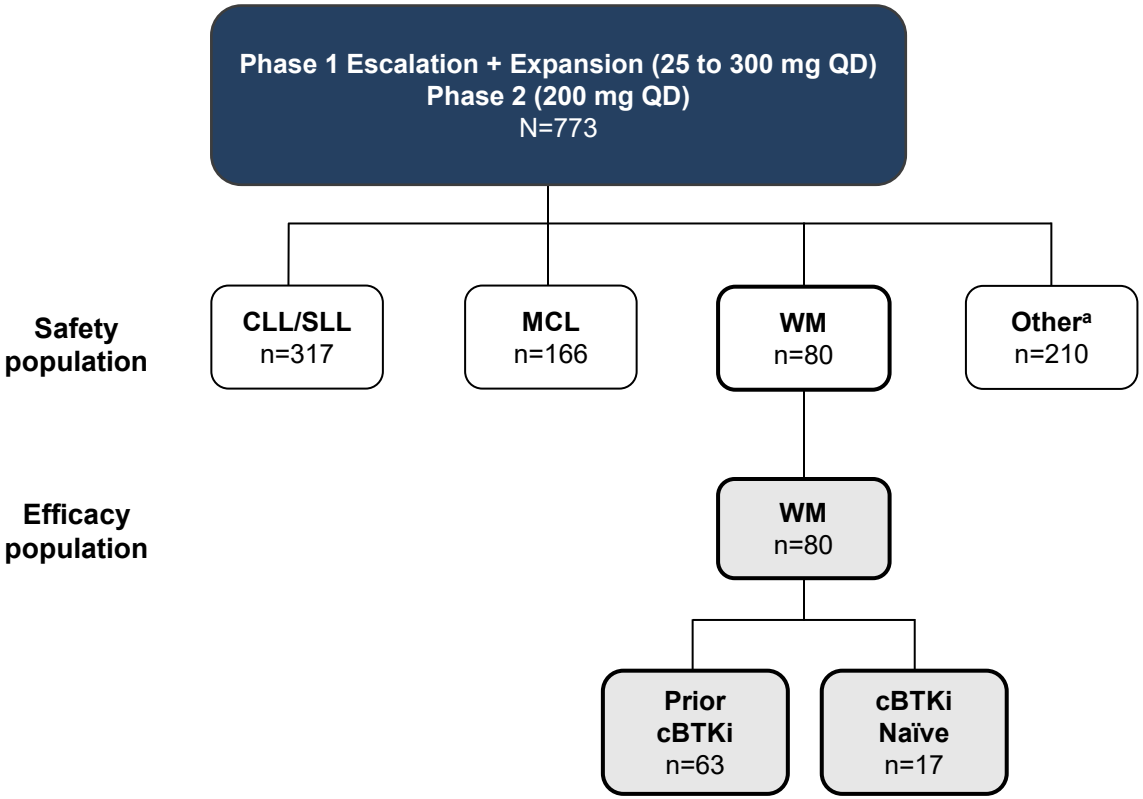
Plasma Exposures Exceeded BTK IC_{90} Throughout Dosing Interval



- Inhibits both wildtype and C481-mutant BTK with equal low nM potency, and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover
- Pirtobrutinib is well tolerated and demonstrates promising efficacy in poor-prognosis B-cell malignancy patients following prior therapy, including prior cBTKi[1]

cBTKi, covalent Bruton tyrosine kinase inhibitor. [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.

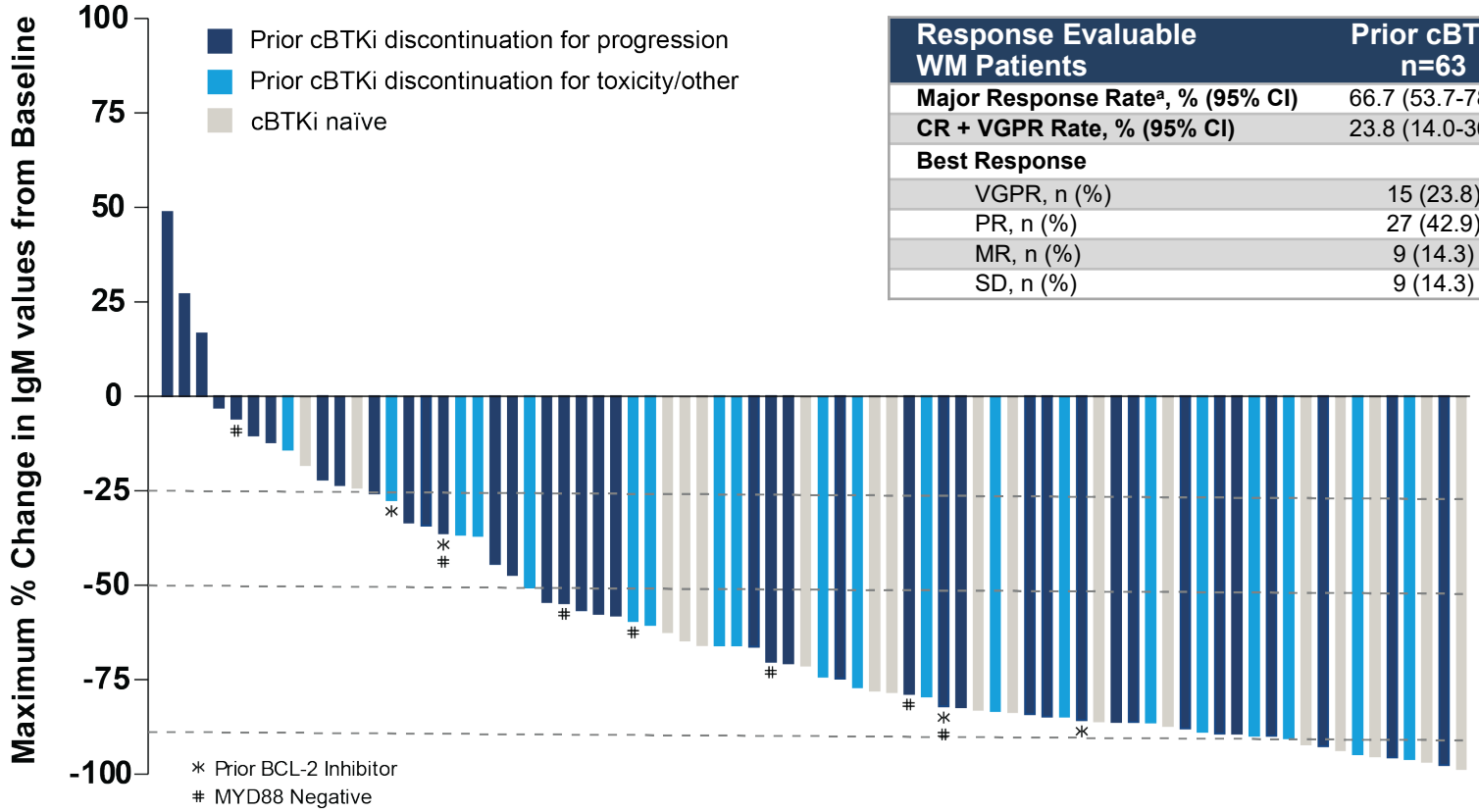
WM Patient Characteristics

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.

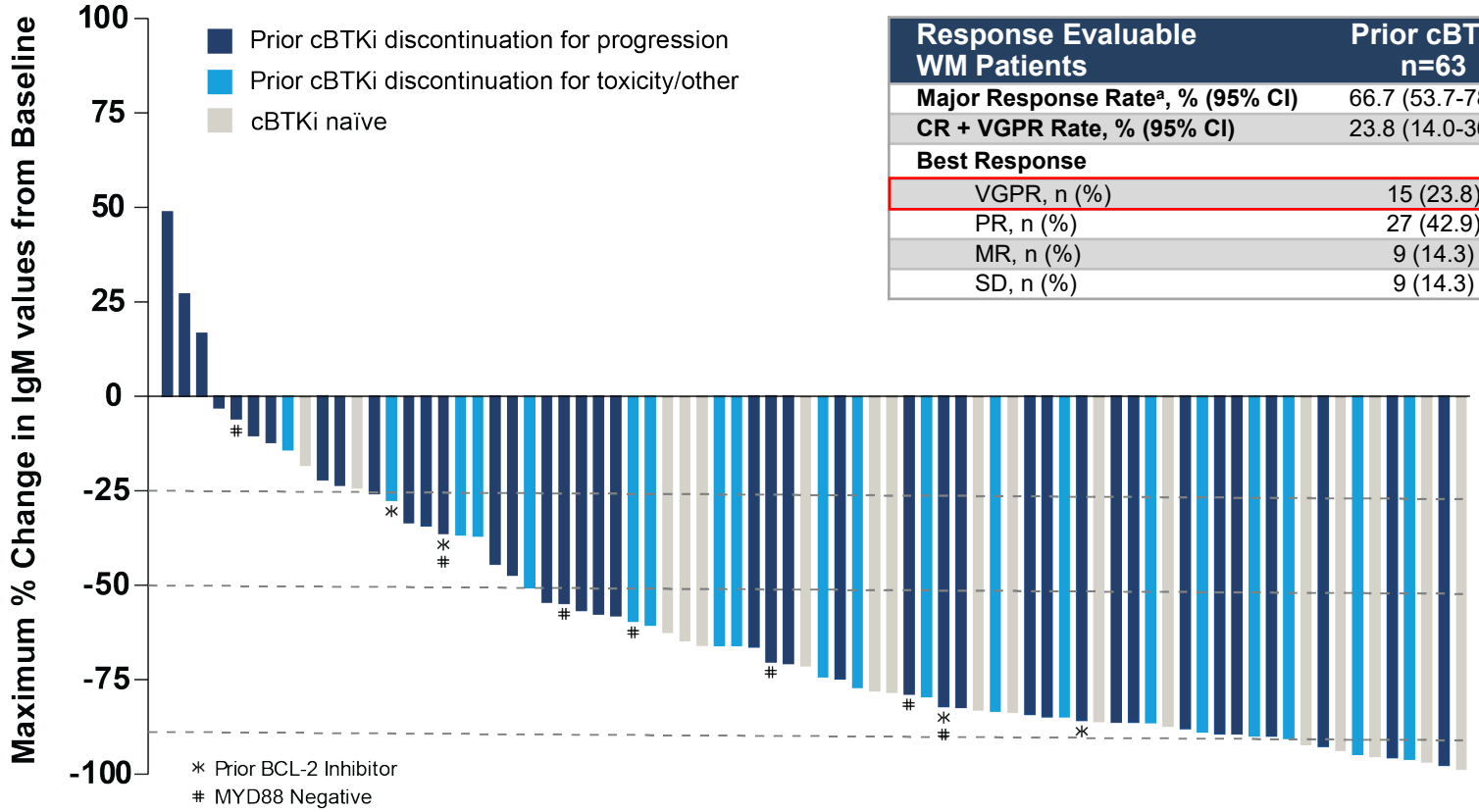
Pirtobrutinib Efficacy in WM Patients



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.

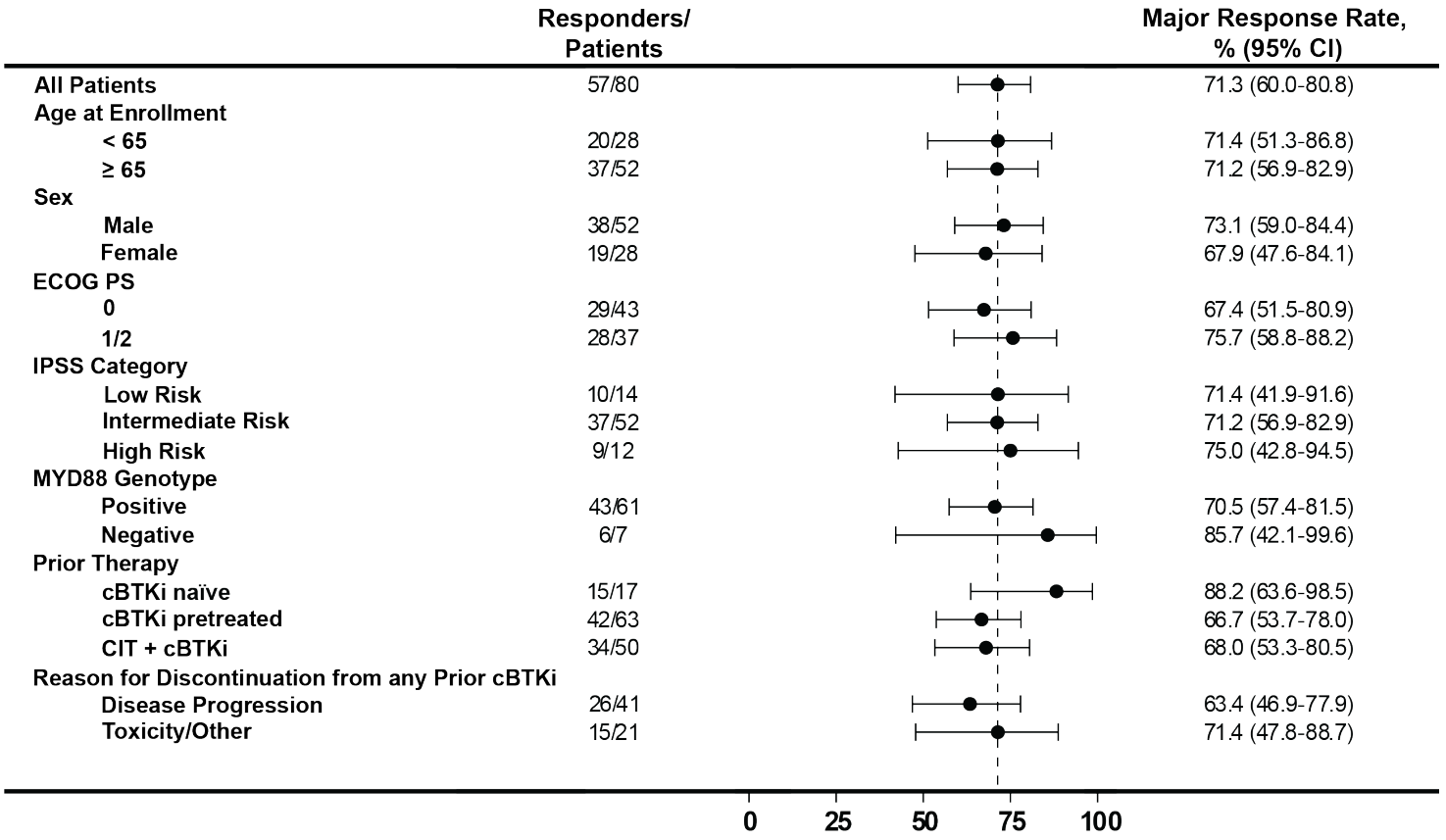
Pirtobrutinib Efficacy in WM Patients



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.

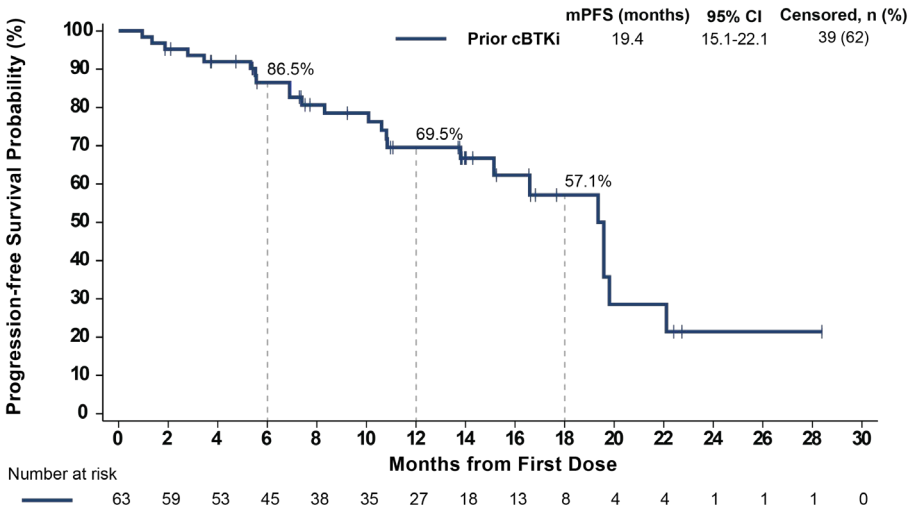
Major Response Rate in WM Subgroups



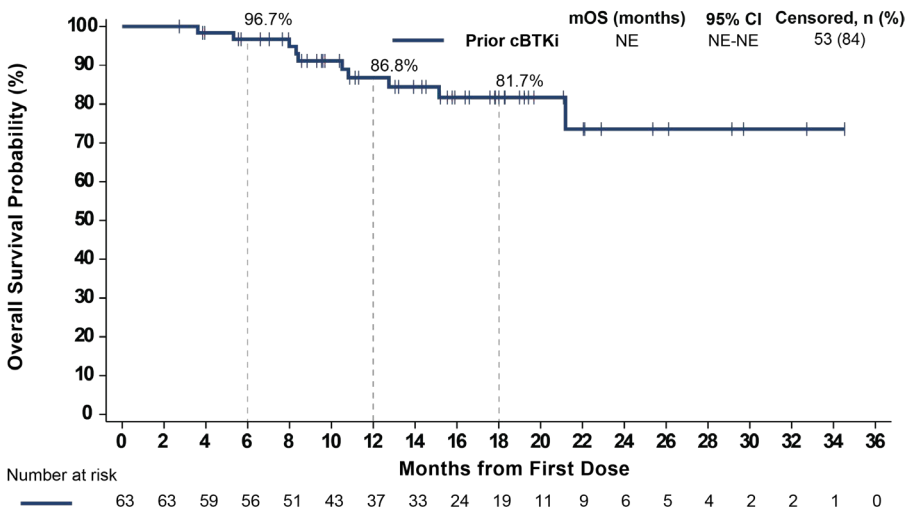
Data cutoff date of 29 July 2022. Response as assessed by investigator based on modified IWWM6 criteria.

Progression-Free Survival and Overall Survival in Prior cBTKi Patients

Progression-Free Survival



Overall Survival



- The median follow-up for PFS and OS in patients who received prior cBTKi was 14 and 16 months, respectively
- 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.

Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

Median time on treatment for the overall safety population was 9.6 months
Discontinuations due to treatment-related AEs occurred in 2.6% (n=20) of all patients
Dose reductions due to treatment-related AEs occurred in 4.5% (n=35) of all patients
Overall and WM safety profiles are generally consistent[h]

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. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of the 22 total afib/aflutter TEAEs in the overall safety population, 7 occurred in patients with a prior medical history of atrial fibrillation. [h]WM safety population data can be found via QR code. Constipation is more commonly seen as a TEAE in the WM population than in all patients.

Conclusions

- Pirtobrutinib demonstrated promising efficacy in this cohort of heavily pretreated relapsed/refractory WM patients, including among patients who received prior CIT and cBTKi
  - Major response rate among prior CIT + cBTKi patients was 68%
- The depth of response observed, as identified by the favorable VGPR rate, is notable in the subset of patients with prior cBTKi therapy
  - Major response rate and VGPR rate among prior cBTKi patients was 67% and 24%, respectively
- Pirtobrutinib continues to be well-tolerated with low rates of Grade ≥3 AEs and discontinuation due to drug-related toxicity
  - Low rates of cBTKi-associated AEs were observed with pirtobrutinib

Acknowledgements

- Loxo@Lilly would like to thank the BRUIN clinical trial participants and their caregivers, without whom this work would not be possible
- Loxo@Lilly would like to thank the BRUIN trial investigators and study staff
- Medical writing support was provided by Hannah M. Messersmith, PhD, of Eli Lilly and Company

Scan or click the QR code or use this URL (https://lillyscience.lilly.com/congress/ash2022) for a list of all Lilly content presented at the congress.

Data Available via QR Code: WM Safety Profile

	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

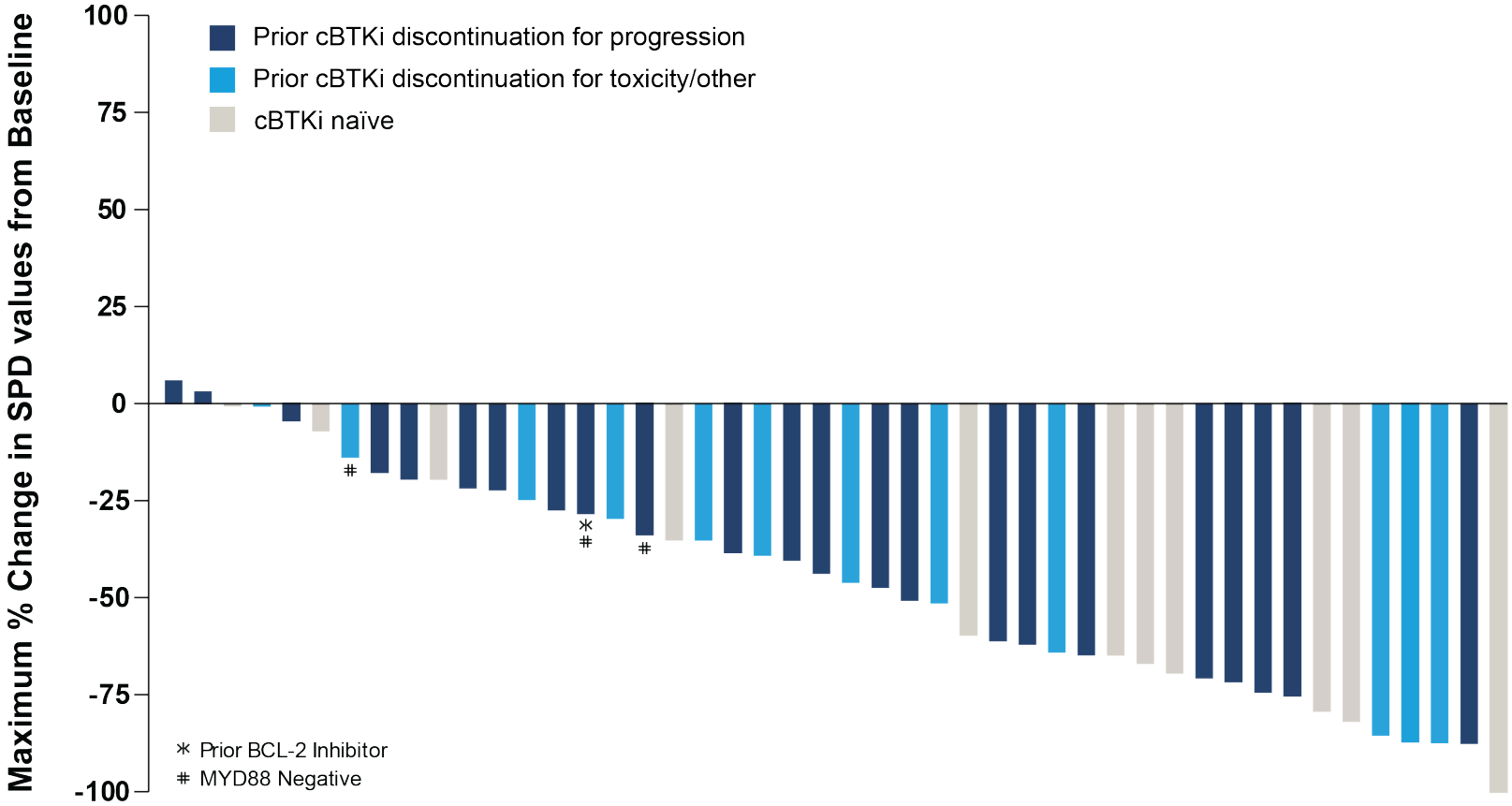
Data cutoff date of 29 July 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter.

Data Available via QR Code: Pirtobrutinib Efficacy in WM Patients

Response Evaluable WM Patients	Prior cBTKi n=63		cBTKi Naïve n=17	
	IWWM6 criteria	Modified IWWM6 criteria	IWWM6 criteria	Modified IWWM6 criteria
Major Response Rate[a], % (95% CI)	66.7 (53.7-78.0)	66.7 (53.7-78.0)	88.2 (63.6-98.5)	88.2 (63.6-98.5)
CR + VGPR Rate, % (95% CI)	1.6 (0-8.5)	23.8 (14.0-36.2)	11.8 (1.5-36.4)	29.4 (10.3-56.0)
Best Response				
VGPR, n (%)	1 (1.6)	15 (23.8)	2 (11.8)	5 (29.4)
PR, n (%)	41 (65.1)	27 (42.9)	13 (76.5)	10 (58.8)
MR, n (%)	9 (14.3)	9 (14.3)	0 (0)	0 (0)
SD, n (%)	9 (14.3)	9 (14.3)	2 (11.8)	2 (11.8)

Response as assessed by investigator based on IWWM6 (Owen's) and Modified IWWM6 criteria. For PR based on IWWM6 criteria, if corresponding IgM is in normal range or has 90% reduction from baseline, it is updated to VGPR using modified IWWM6 criteria. [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 Available via QR Code: Nodal Response in WM Patients Receiving Pirtobrutinib



Data cutoff date of 29 July 2022. Waterfall plot for 46 patients who have SPD values at baseline and at response assessment are shown.