

Pirtobrutinib (LOXO-305), A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor In Previously Treated CLL/SLL: Results From The Phase 1/2 BRUIN Study

Catherine C. Coombs¹, John M. Pagel², Nirav N. Shah³, Nicole Lamanna⁴, Ewa Lech-Maranda⁵, Toby A. Eyre⁶, Jennifer A. Woyach⁷, William G. Wierda⁸, Chan Y. Cheah⁹, Lindsey E. Roeker¹⁰, Manish R. Patel¹¹, Bitá Fakhri¹², Minal A. Barve¹³, Constantine S. Tam¹⁴, David Lewis¹⁵, James N. Gerson¹⁶, Alvaro J. Alencar¹⁷, Justin Taylor¹⁷, Omar Abdel-Wahab¹⁰, Paolo Ghia¹⁸, Stephen J. Schuster¹⁶, Jessica Chen¹⁹, Binoj Nair²⁰, Donald E. Tsai²⁰, Nora C. Ku²⁰, Matthew S. Davids²¹, Jennifer R. Brown²¹, Wojciech Jurczak²², Anthony R. Mato¹⁰

¹University of North Carolina at Chapel Hill, Chapel Hill, USA; ²Swedish Cancer Institute, Seattle, USA; ³Medical College of Wisconsin, Milwaukee, USA; ⁴Herbert Irving Comprehensive Cancer Center, Columbia University, New York, USA; ⁵Institute of Hematology and Transfusion Medicine, Warsaw, Poland; ⁶Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, UK; ⁷The Ohio State University Comprehensive Cancer Center, Columbus, USA; ⁸MD Anderson Cancer Center, Houston, USA; ⁹Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; ¹⁰Memorial Sloan Kettering Cancer Center, New York, USA; ¹¹Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, USA; ¹²University of California San Francisco, San Francisco, USA; ¹³Mary Crowley Cancer Research, Dallas, USA; ¹⁴Peter MacCallum Cancer Center, Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia; ¹⁵Plymouth Hospitals NHS Trust – Derriford Hospital, Plymouth, UK; ¹⁶Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA; ¹⁷University of Miami Miller School of Medicine, Miami, USA; ¹⁸Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; ¹⁹Eli Lilly and Company, Indianapolis, IN, USA; ²⁰Loxo Oncology at Lilly, Stamford, CT, USA; ²¹Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA; ²²Maria Skłodowska-Curie National Research Institute of Oncology, Krakow, Poland

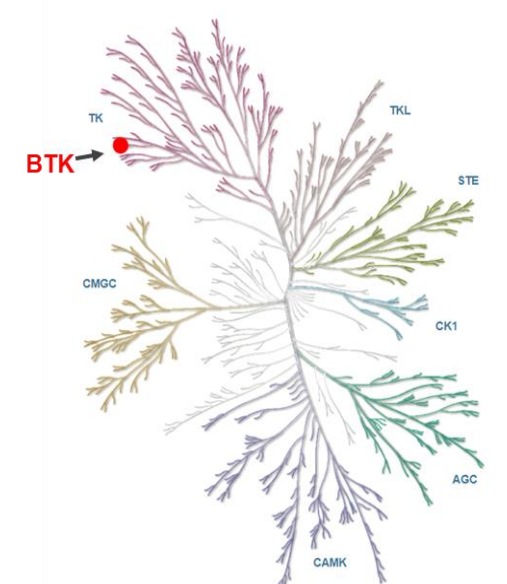
Poster # - CLL-039

Background

- Resistance and intolerance limit covalent BTK inhibitor outcomes in patients with advanced B-cell malignancies.¹⁻⁸
- Pirtobrutinib (LOXO-305) is a highly potent and selective non-covalent BTK inhibitor.⁹⁻¹¹

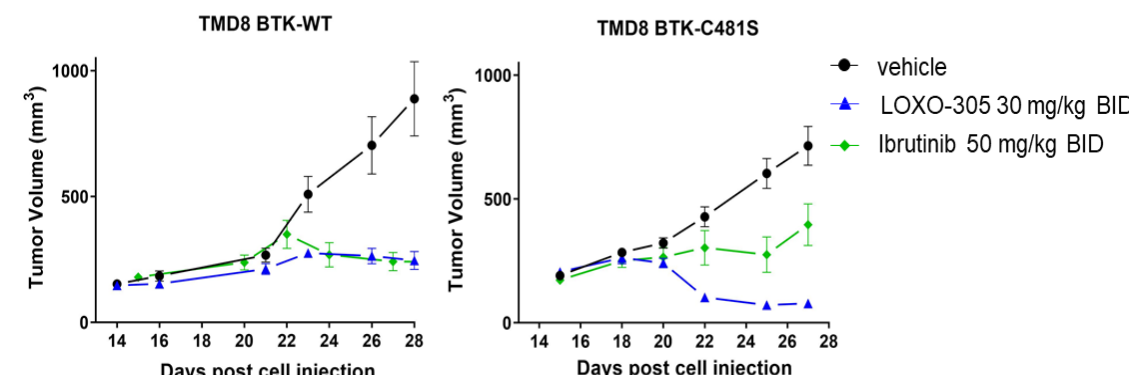
Kinome selectivity

Highly selective for BTK



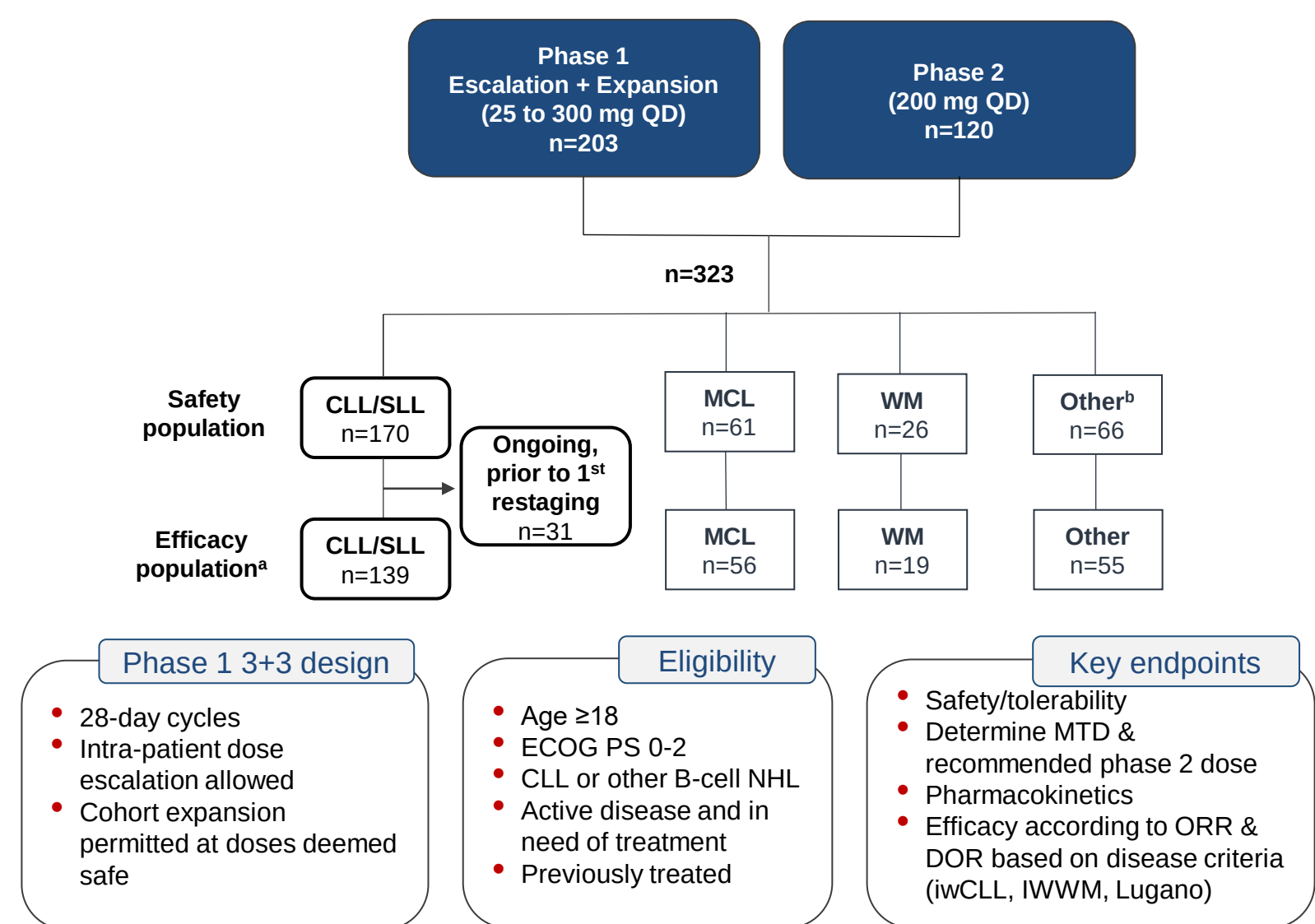
Xenograft models

In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



- The BRUIN trial investigates the clinical efficacy and safety of pirtobrutinib in previously treated advanced B-cell malignancies. Here, we present the safety and efficacy data of pirtobrutinib in the patients with previously treated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).^{11,12}

BRUIN Study Design



^aEfficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment.
^bOther includes DLBCL, FL, MZL, Richter's transformation, B-PLL, Hairy Cell Leukemia, and other transformation. All response data presented based on investigator assessment.

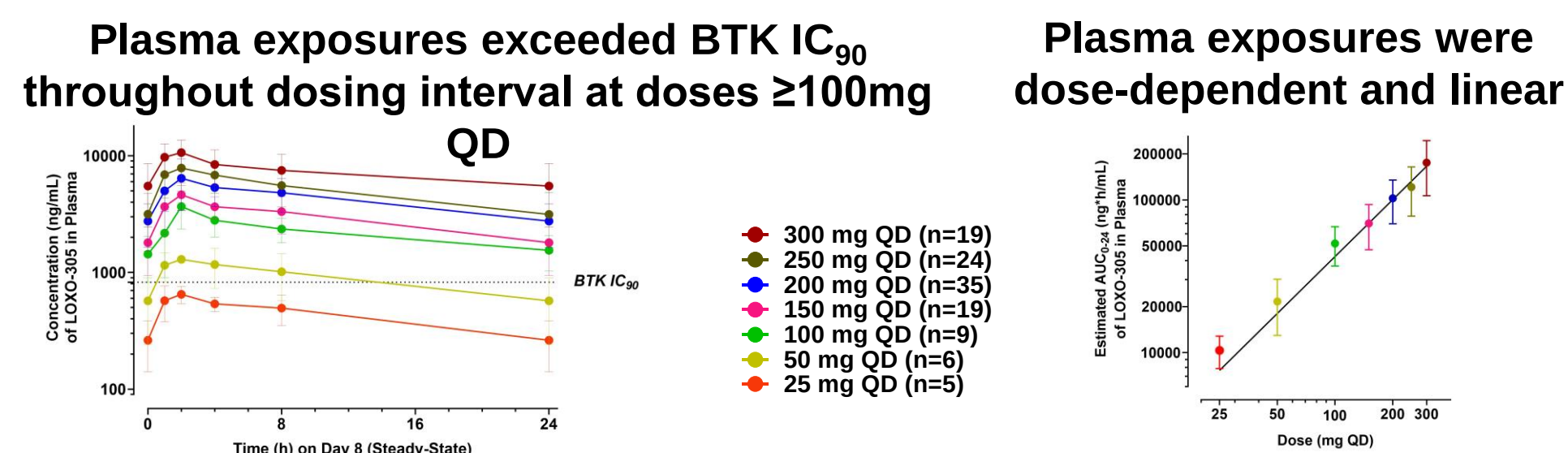
- Data cutoff date was 27 September 2020.
- ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL.

Table 1. Patient Characteristics

Characteristics	n=170	Baseline Molecular Characteristics ^d	
Median age, years (range)	69 (36-88)	Mutation status, n (%)	
Female, n (%)	61 (36)	BTK C481-mutant	25 (27)
Male, n (%)	109 (64)	BTK Wildtype	66 (73)
ECOG PS ^a , n (%)		PLCG2-mutant	4 (4)
0	87 (51)	High Risk Molecular Findings, n (%)	
1	69 (41)	17p deletion	20 (25)
2	13 (8)	TP53 mutation	27 (30)
Median number prior lines of systemic therapy (range)	3 (1-11)	17p13 deletion + TP53 mutant	18 (22)
BTK pre-treated	4 (1-11)	IGHV unmutated	71 (88)
Prior therapy, n (%)		11q deletion	15 (19)
BTK inhibitor	146 (86)		
Chemotherapy	140 (82)		
Anti-CD20 antibody	153 (90)		
BCL2 inhibitor	57 (34)		
PI3K inhibitor	36 (21)		
Lenalidomide	14 (8)		
Autologous stem cell transplant	0		
Allogeneic stem cell transplant	3 (2)		
CAR-T	10 (6)		
Reason discontinued any prior BTKi, n (%) ^b			
Progressive disease	98 (67)		
Toxicity/other ^c	48 (33)		

Total % may be different than the sum of the individual components due to rounding. ^aECOG PS is missing for 1 patient. ^bCalculated as percent of patients who received prior BTK inhibitor. ^cOther includes patients who completed treatment and those who discontinued voluntarily or due to physician's decision. ^dMolecular characteristics were determined centrally, in those patients with sufficient sample to pass assay quality control. 91 patients were tested for BTK and PLCG2, 81 patients for 17p13 deletion, 91 patients for TP53, 81 patients for 17p13 deletion + TP53, 81 patients for IGHV and 81 patients for 11q deletion.

Fig 1. Pirtobrutinib Pharmacokinetics



Horizontal line (left plot) represents the plasma level at which the unbound pirtobrutinib concentration corresponds to BTK-WT and BTK C481S IC₉₀ based on cellular assays. Concentration at 24 hours was inferred from the pre-dose concentrations.

Table 2. Pirtobrutinib Safety Profile

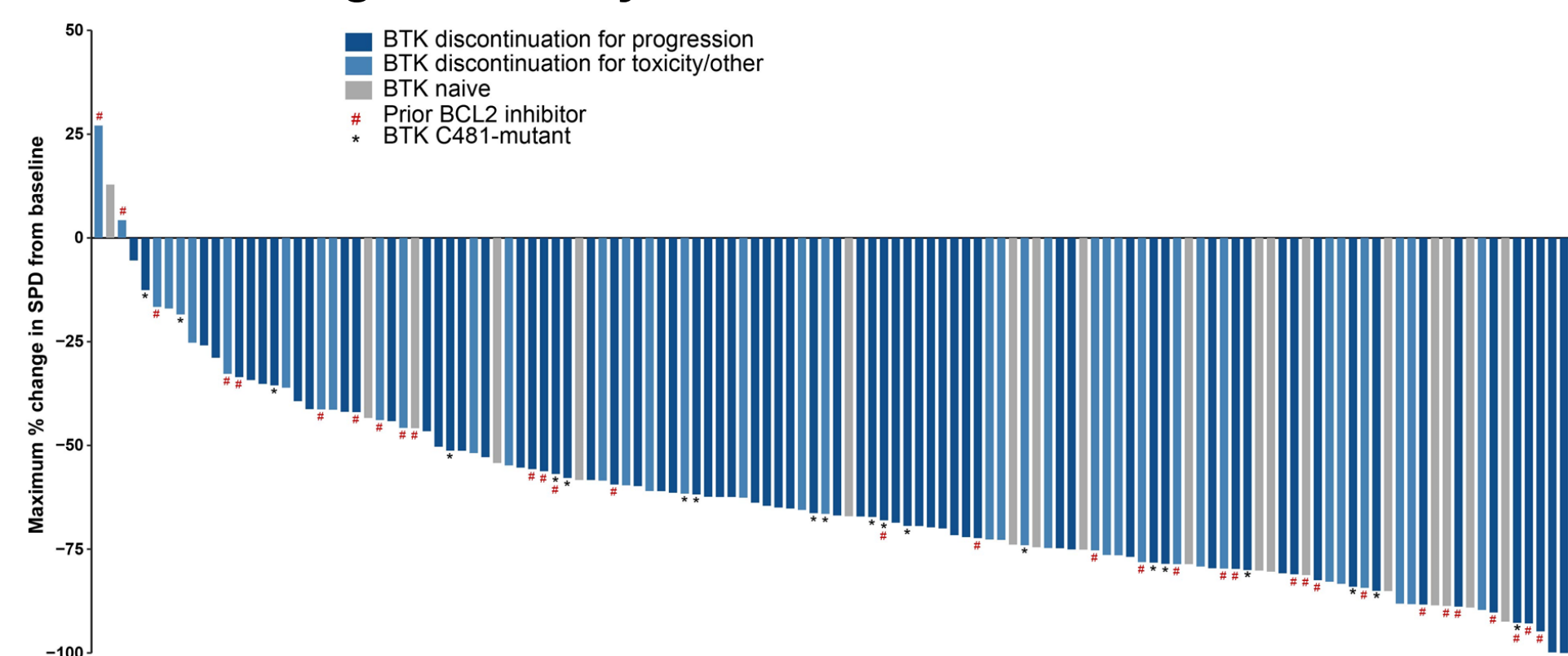
Adverse Event	All doses and patients (n=323)					Treatment-related AEs, n (%)	
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	40 (12%)	22 (7%)	3 (1%)	-	65 (20%)	2 (8%)	27 (8%)
Diarrhea	45 (14%)	10 (3%)	-	-	55 (17%)	-	28 (9%)
Contusion	37 (12%)	5 (2%)	-	-	42 (13%)	-	29 (9%)
AES of special interest ^b							
Bruising	48 (15%)	5 (2%)	-	-	53 (16%)	-	37 (12%)
Rash	30 (9%)	5 (2%)	-	-	35 (11%)	-	18 (6%)
Arthralgia	13 (4%)	3 (1%)	-	-	16 (5%)	-	5 (2%)
Hemorrhage	10 (3%)	4 (1%)	1 (<1%)	-	15 (5%)	-	5 (2%)
Hypertension	2 (<1%)	9 (3%)	4 (1%)	-	15 (5%)	-	4 (1%)
Atrial fibrillation/flutter	-	2 (<1%)	-	-	2 (<1%)	-	-

Total % may be different than the sum of the individual components due to rounding. ^aThe AEs listed are the most common that occurred at any grade in at least 10% of the patients, regardless of attribution. ^bAEs of special interest are those that were previously associated with covalent BTK inhibitors.

- No DLTs were reported and the MTD was not reached.
- 5 of 323 patients (1.5%) discontinued due to treatment-related AEs.
- 200mg QD was selected as recommended Phase 2 dose.

Results

Fig 2. Efficacy of Pirtobrutinib in CLL/SLL

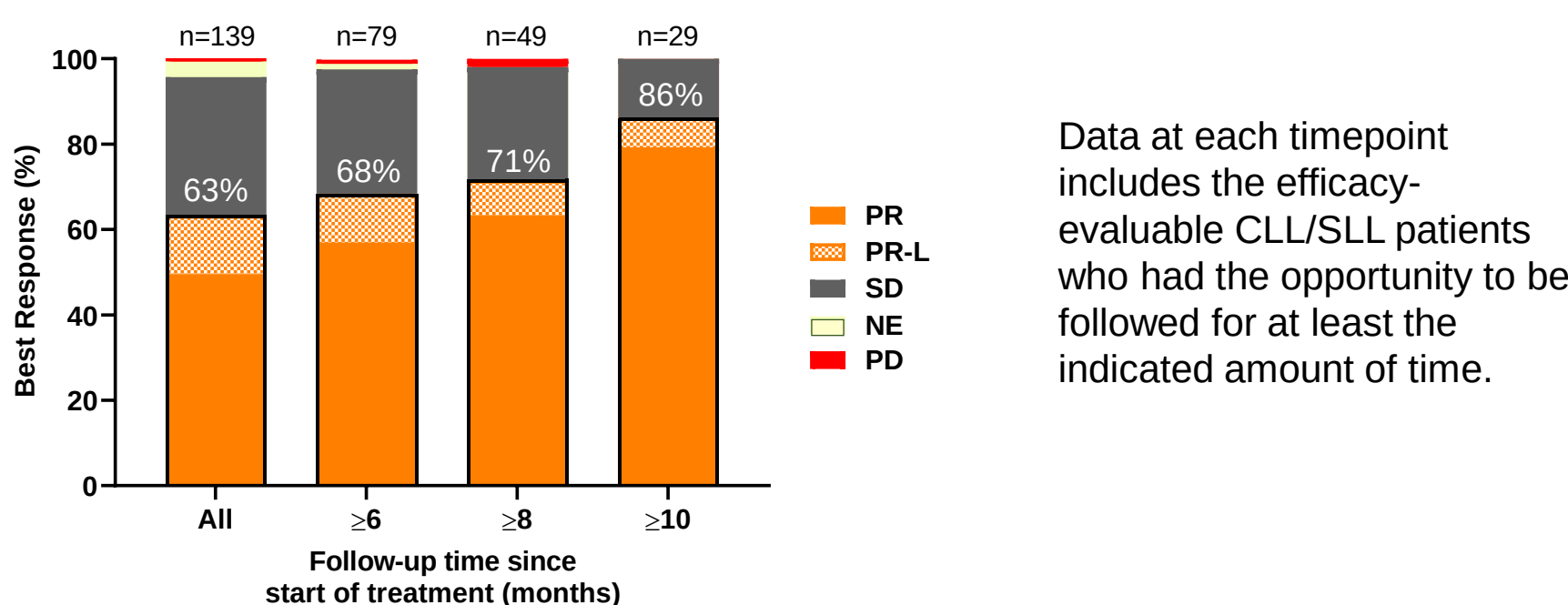


Data for 13 CLL/SLL patients are not shown in the waterfall plot due to 4 having no target lesions identified at baseline, 5 with no/incomplete post-baseline lesion measurements, and 4 discontinued prior to first post-baseline disease assessment.

Evaluable CLL/SLL Patients		n=139
Overall Response Rate ^b , % (95% CI)	63% (55 – 71%)	
Best response		
CR, n (%)	0	
PR, n (%)	69 (50%)	
PR-L, n (%)	19 (14%)	
SD, n (%)	45 (32%)	

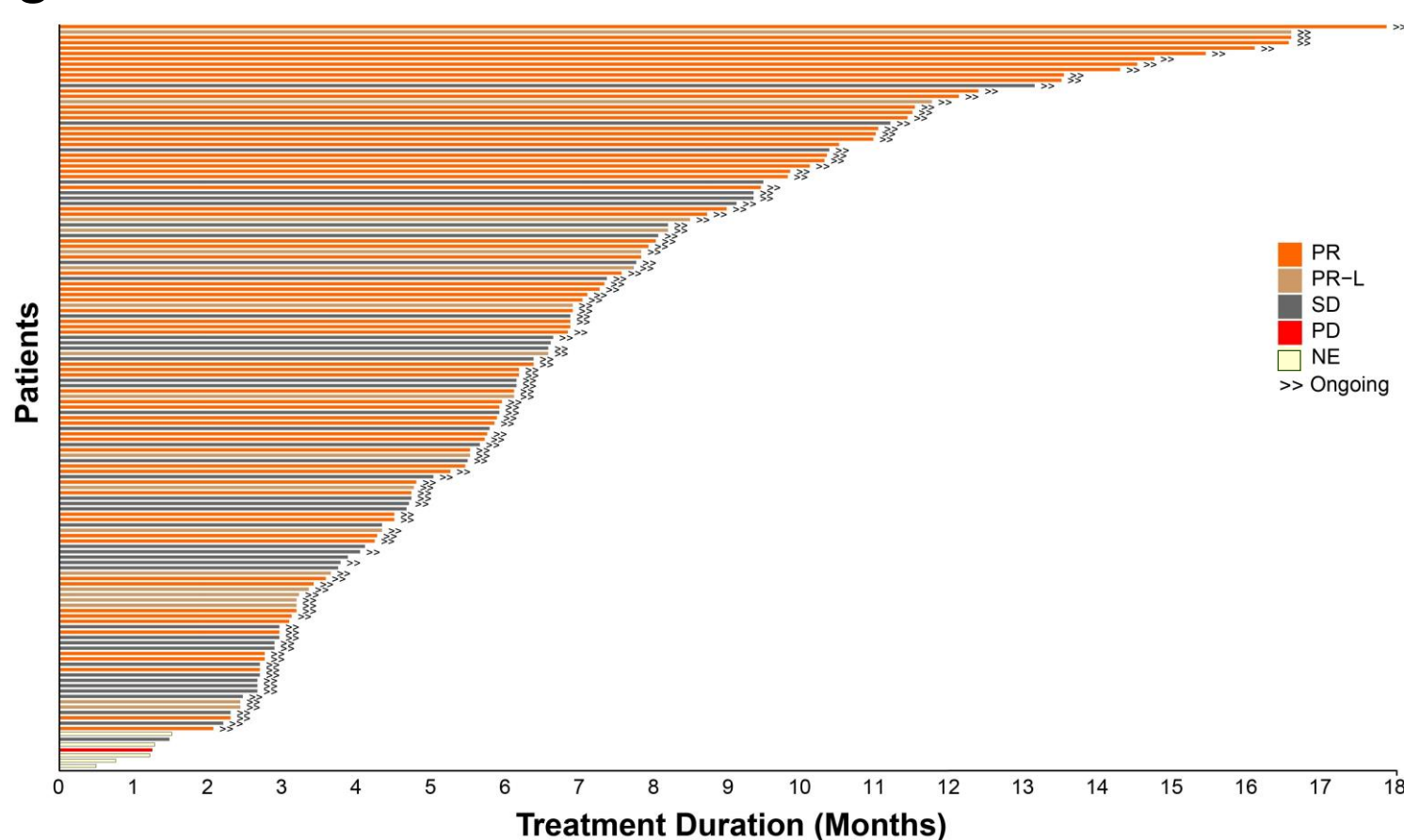
BTK Pre-Treated Evaluable CLL/SLL Patients		n=121
Overall Response Rate ^b , % (95% CI)	62% (53 – 71%)	
Best Response		
CR, n (%)	0	
PR, n (%)	57 (47%)	
PR-L, n (%)	18 (15%)	
SD, n (%)	41 (34%)	

Fig 3. ORR increases over time



Data at each timepoint includes the efficacy-evaluable CLL/SLL patients who had the opportunity to be followed for at least the indicated amount of time.

Fig 4. Pirtobrutinib Treatment Duration in CLL/SLL



- Median follow-up of 6 months (range, 0.6-17.8+) for the efficacy-evaluable patients.
- 94% (83 of 88) of responding patients are ongoing and in response. Only 5 responding patients discontinued (4 for PD, 1 patients in PR electively discontinued to undergo transplantation).

Fig 5. Pirtobrutinib Efficacy Regardless of BTK Experience and Other Prior Therapy

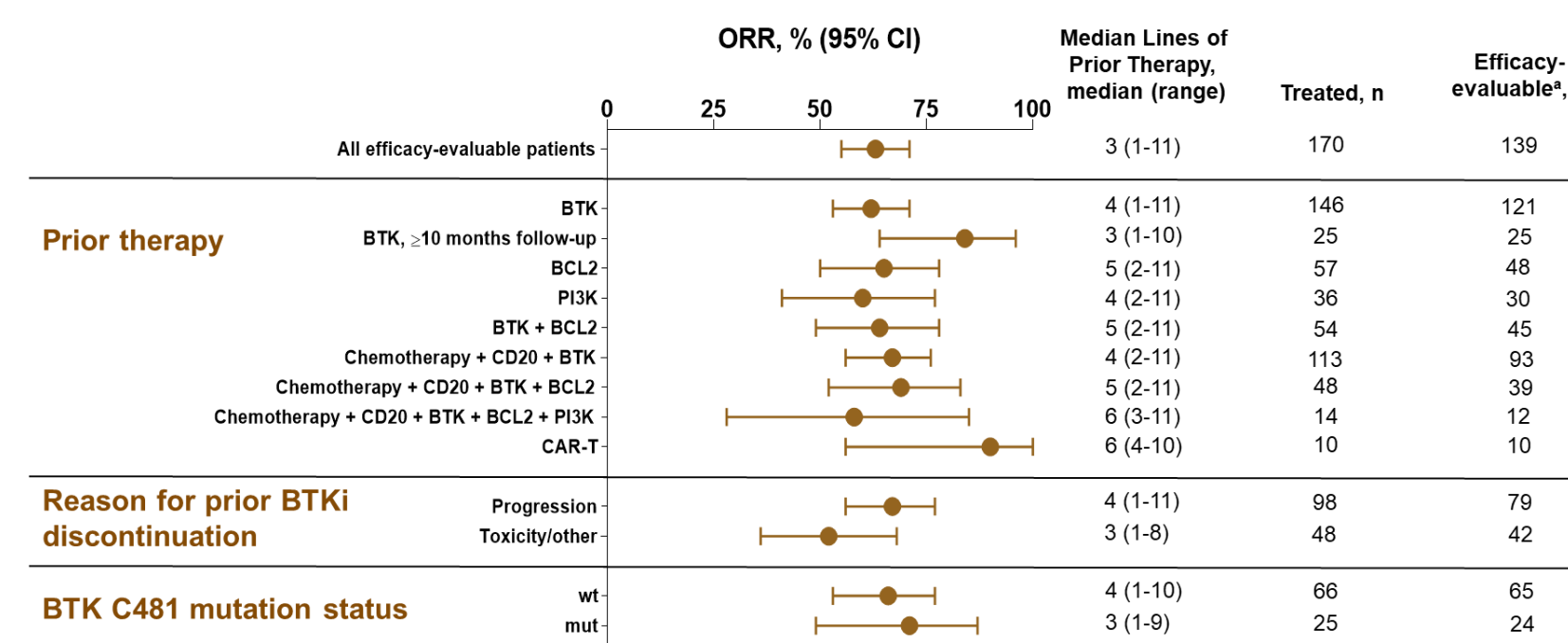
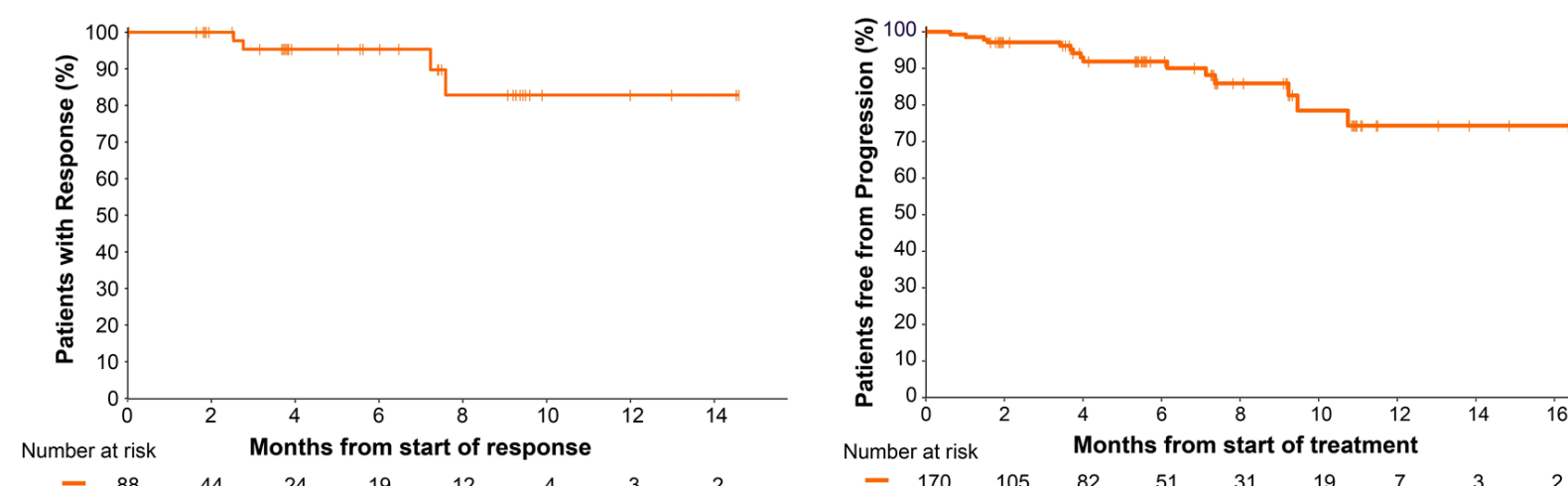


Fig 6. DOR and PFS in CLL/SLL



Conclusions

- Pirtobrutinib demonstrates promising efficacy in CLL/SLL patients previously treated with all classes of available therapy
 - Responses were observed across all dose levels
 - Efficacy was independent of BTK C481 mutation status, the reason for prior BTKi discontinuation (i.e., progression vs intolerance), or other classes of prior therapy received (including covalent BTK inhibitors, BCL2 inhibitors, and PI3K-delta inhibitors)
- Favorable safety and tolerability are consistent with the design of pirtobrutinib as a highly selective and non-covalent BTK inhibitor
 - No DLTs were observed and no MTD was identified
 - Notable covalent BTKi-associated toxicities were rarely observed
 - Longer follow-up is needed to better understand the pirtobrutinib safety profile associated with chronic administration
- Pirtobrutinib is well tolerated and exhibits promising efficacy in heavily pretreated CLL/SLL patients

References

¹Woyach et al. *J Clin Oncol*. 2017;35:1437-43. ²Lampson et al. *Expert Rev Hematol*. 2018;11:185-94. ³Burger et al. *Leukemia*. 2020;34:878-789. ⁴Byrd et al. *N Engl J Med*. 2016;374:323-32. ⁵Hershkovitz-Rokah et al. *Br J Haematol*. 2018;181:306-19. ⁶Woyach et al. *N Engl J Med*. 2014;370:2286-94. ⁷Woyach et al. *Blood*. 2019;134(Suppl 1):504. ⁸Xu et al. *Blood*. 2017;129:2519-5. ⁹Brandhuber et al. *Clin. Lymphoma Myeloma Leuk*. 2018;18:S216. ¹⁰Mato et al. *Blood*. 2019;134 (Suppl 1):501. ¹¹Mato, et al. *The Lancet*. 2021; 397:892-901. ¹²Wang, et al. *Blood* 2020 136(Suppl 1):8-10.

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