

Pirtobrutinib (LOXO-305), A Next Generation Highly Selective Non-covalent BTK Inhibitor In Previously Treated Mantle Cell Lymphoma And Other Non-Hodgkin Lymphomas: Phase 1/2 BRUIN Study Results

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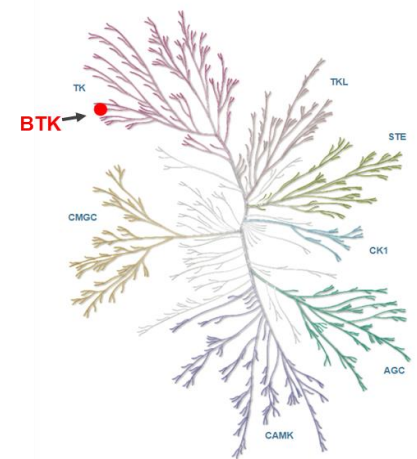
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Background

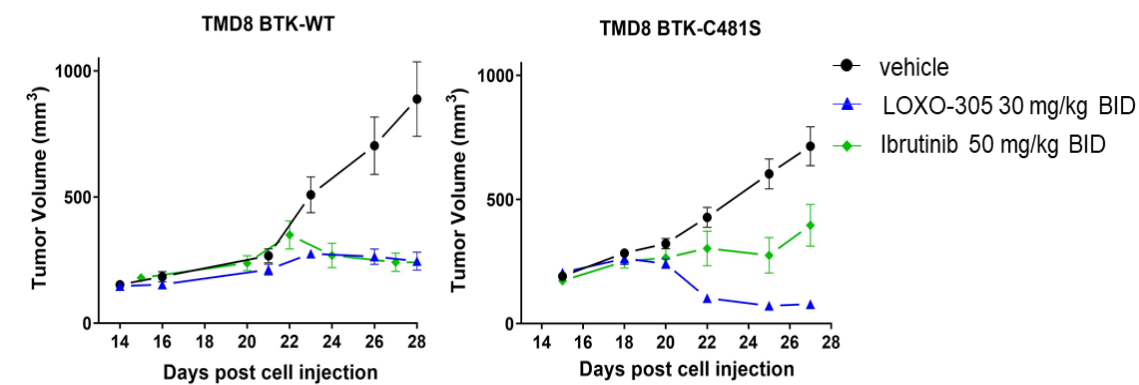
- Covalent BTK inhibitor resistance in MCL and other lymphomas is incompletely understood.1-5 Overall survival following covalent BTK inhibitor therapy is poor.1,2
- Pirtobrutinib (LOXO-305) is a highly potent and selective non-covalent BTK inhibitor.6-8
- Pirtobrutinib showed nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays,6-8 and >300-fold selectivity for BTK vs 370 other kinases.6

Kinome selectivity
Highly selective for BTK



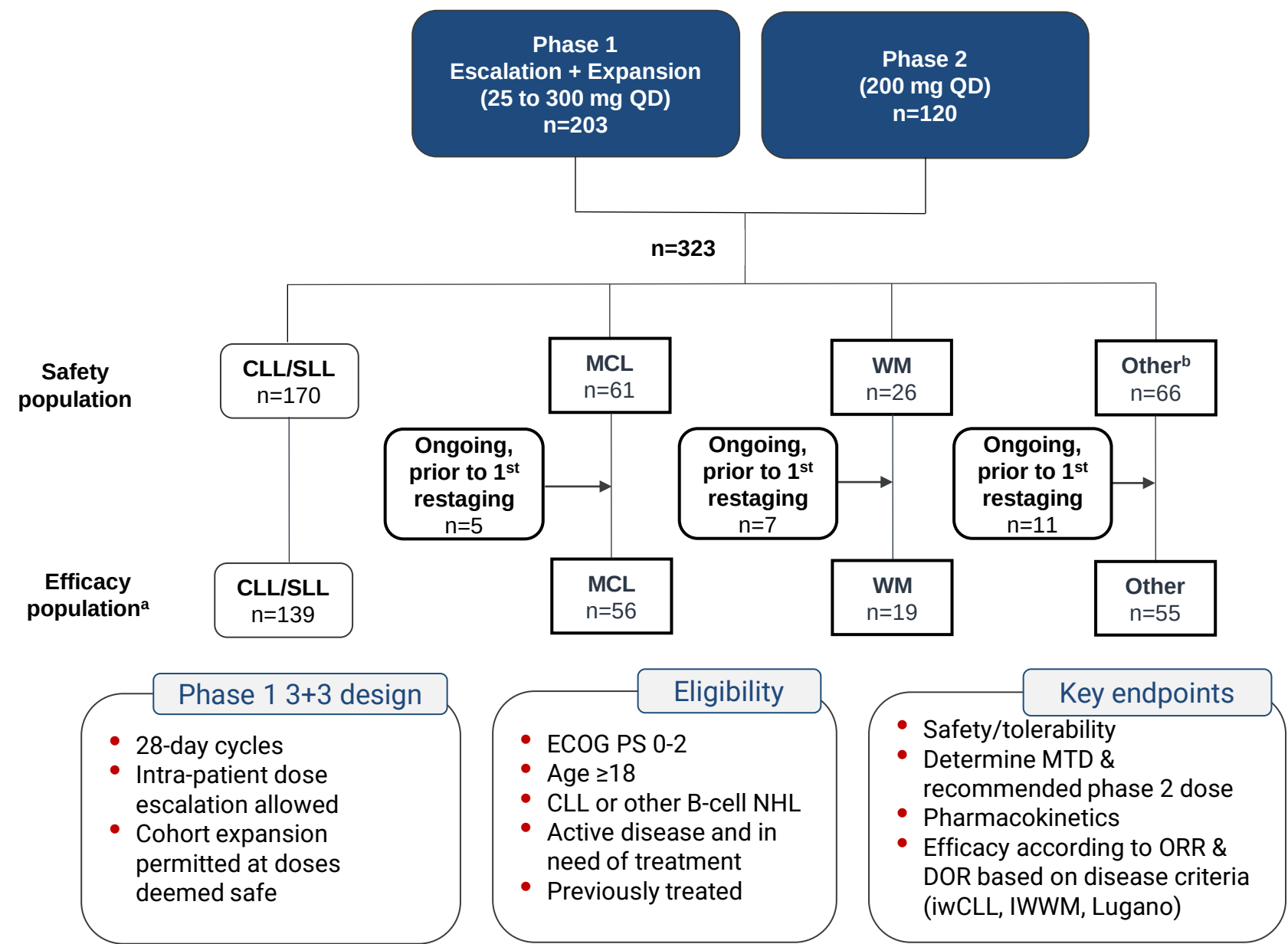
Xenograft models

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 safety and efficacy data of pirtobrutinib in patients with previously treated mantle cell lymphoma (MCL) or other non-Hodgkin lymphomas (NHL).7,8

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.

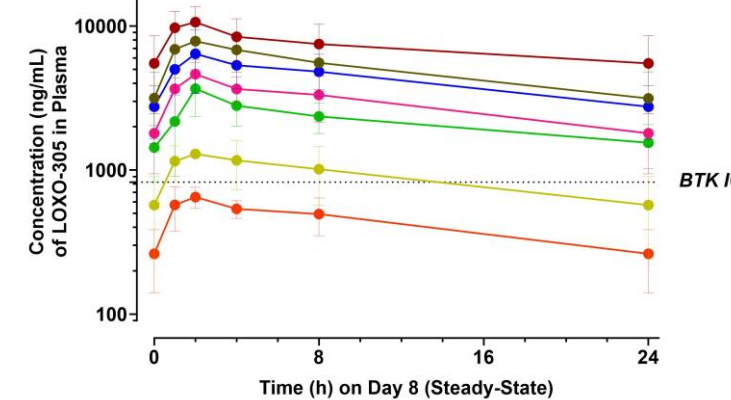
Table 1. Patient Characteristics

Characteristics	MCL (n=61)	WM (n=26)	Other ^a (n=66)
Median age (range), years	69 (50-87)	68 (42-84)	68 (27-86)
Female, n (%)	14 (23)	8 (31)	26 (39)
Male, n (%)	47 (77)	18 (69)	40 (61)
ECOG PS ^b , n (%)			
0	42 (69)	14 (54)	18 (27)
1	17 (28)	10 (39)	43 (65)
2	2 (3)	0	4 (6)
Median number prior lines of systemic therapy (range)	3 (1-8)	3 (2-11)	4 (2-10)
Prior therapy, n (%)			
BTK inhibitor	57 (93)	18 (69)	24 (37)
Chemotherapy	56 (92)	23 (89)	63 (96)
Anti-CD20 antibody	60 (98)	24 (92)	65 (99)
BCL2 inhibitor	9 (15)	3 (12)	12 (18)
PI3K inhibitor	1 (2)	1 (4)	13 (20)
Lenalidomide	12 (20)	1 (4)	18 (27)
CAR-T	3 (5)	0	9 (14)
Autologous stem cell transplant	15 (25)	0	7 (11)
Allogeneic stem cell transplant	3 (5)	0	2 (3)
Reason discontinued any prior BTKi ^c			
Progressive disease	44 (77)	12 (67)	19 (79)
Toxicity/other ^d	13 (23)	6 (33)	5 (21)

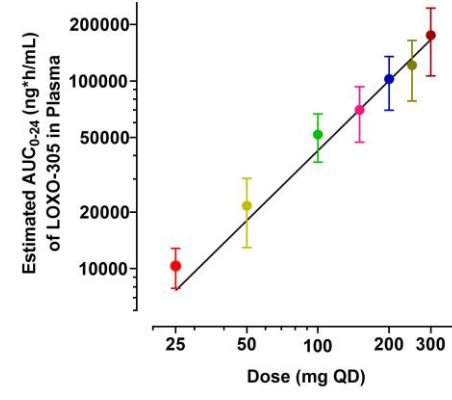
Total % may be different than the sum of the individual components due to rounding. ^aOther includes DLBCL (n=26), FL (n=12), MZL (n=13), Richter's Transformation (n=9), other transformation (n=3), B-PLL (n=2) and Hairy Cell Leukemia (n=1). ^bECOG PS is missing for 3 patients (2 WM, 1 Other). ^cCalculated as percent of patients who received prior BTK inhibitor. ^dOther includes patients who completed treatment and those who discontinued voluntarily or due to physician's decision.

Fig 1. Pirtobrutinib Pharmacokinetics

Plasma exposures exceeded BTK IC₉₀ throughout dosing interval at doses ≥100mg QD



Plasma exposures were dose-dependent and linear



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

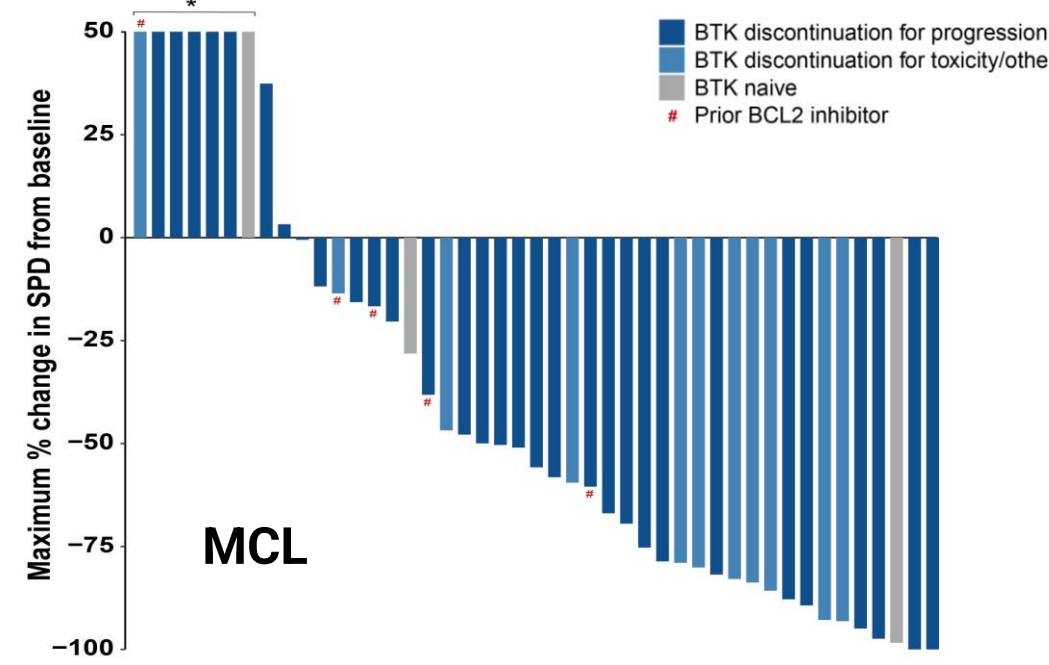
Adverse Event	All doses and patients (n=323)					Treatment-related AEs, n (%)	
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	40 (12%)	22 (7%)	3 (1%)	-	65 (20%)	2 (<1%)	27 (8%)
Diarrhea	45 (14%)	10 (3%)	-	-	55 (17%)	-	28 (9%)
Contusion	37 (12%)	5 (2%)	-	-	42 (13%)	-	29 (9%)
AEs 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. The AEs listed are the most common that occurred at any grade in at least 10% of the patients, regardless of attribution. AEs of special interest are those that were previously associated with covalent BTK inhibitors.

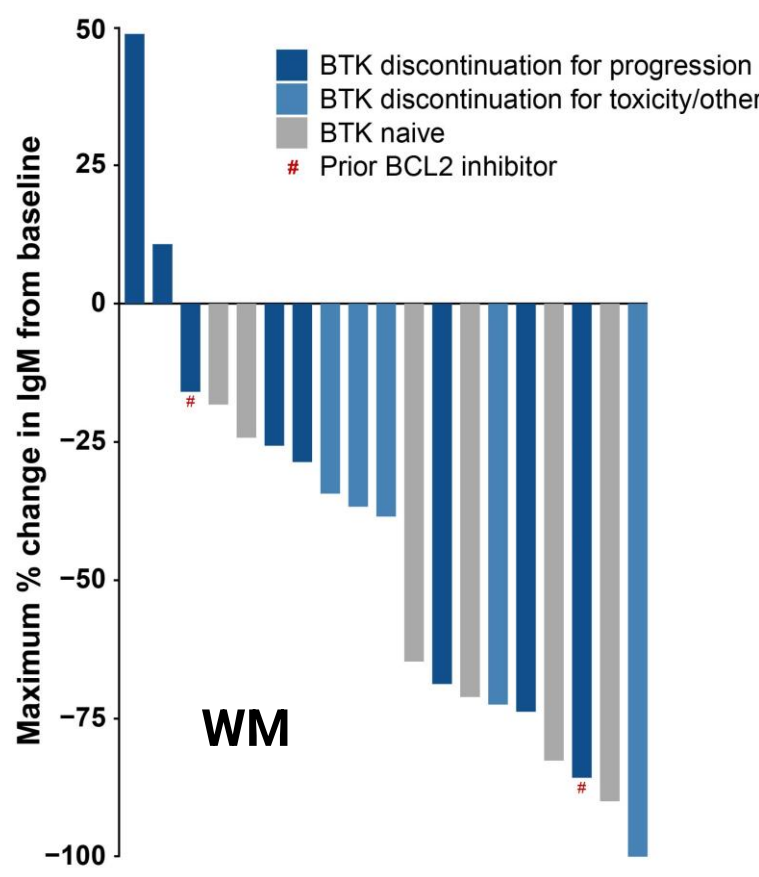
- No DLTs were reported and the MTD was not reached.
- 5 of 323 patients (1.5%) discontinued due to treatment-related AEs.
- 200mg QD was selected as recommended Phase 2 dose.

Results

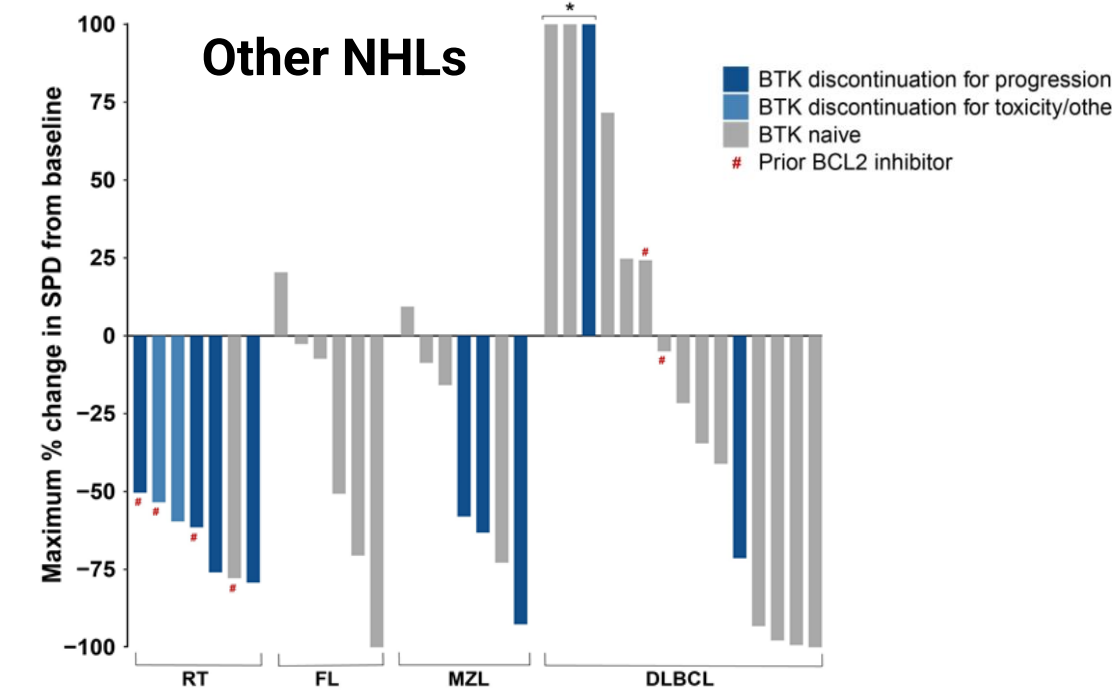
Fig 2. Efficacy of Pirtobrutinib in MCL, WM, and Other NHLs



Total % may be different than the sum of the individual components due to rounding. Data for 11 MCL patients are not shown in the waterfall plot due to 7 having no target lesions identified by CT at baseline (including 4 patients who achieved a best response of CR by PET), 1 with no/incomplete post-baseline lesion measurements, and 3 discontinued prior to first post-baseline disease assessment. ^aIndicates patients with >50% increase in SPD. ^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. ^bORR includes patients with a best response of CR and PR. Response status per Lugano criteria.

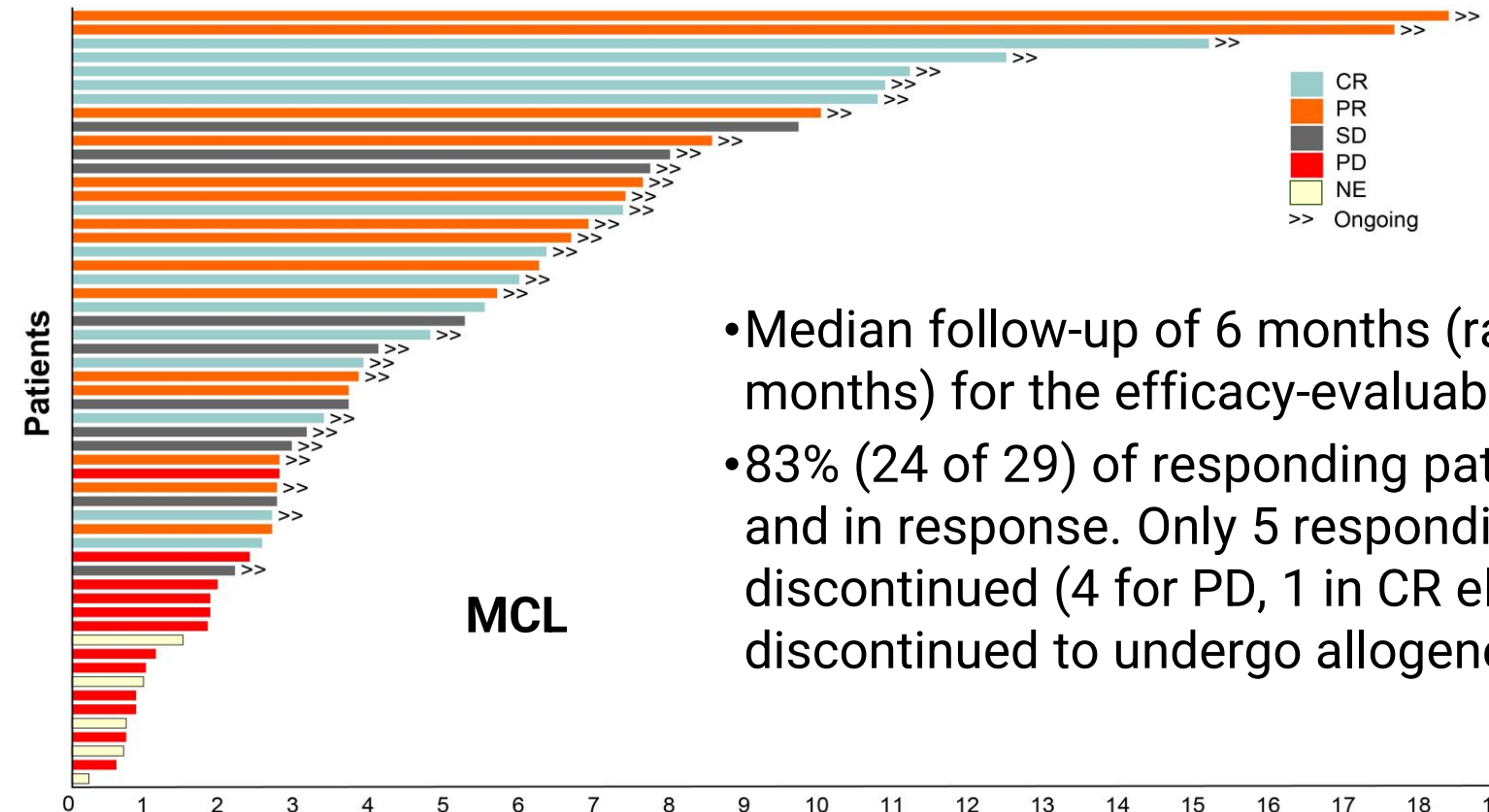


^aEfficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. ^bORR includes patients with a best response of CR, VGPR, PR, and MR. Response status per IWMM6 criteria.

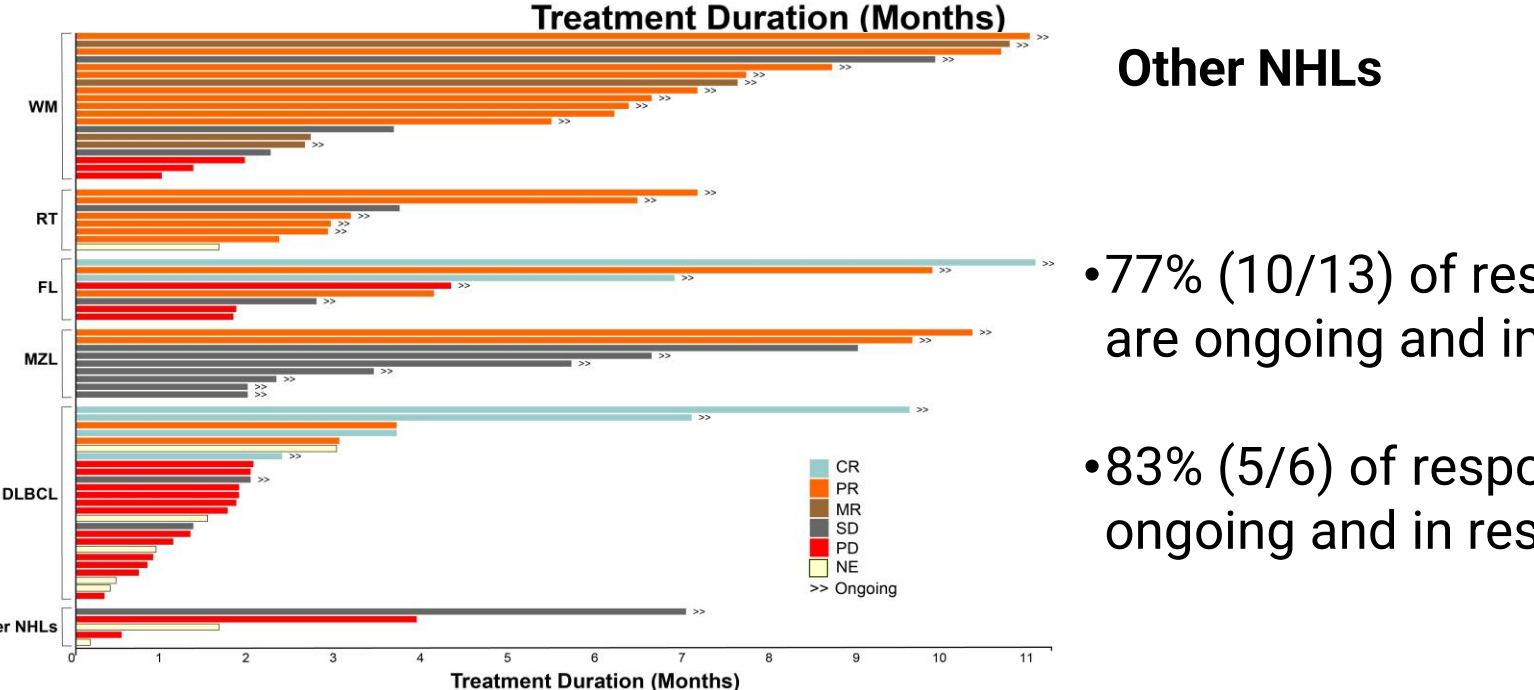


Data for 17 NHL patients are not shown in the waterfall plot due to 6 having no target lesions identified at baseline, 4 with no/incomplete post-baseline lesion measurements, and 7 discontinued prior to first post-baseline disease assessment. ^aIndicates patients with >100% increase in SPD. ^aEfficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. ^bORR includes patients with a best response of CR and PR. Responses were defined according to disease specific guidelines. As of data cutoff, no responses were observed in the efficacy evaluable patients with other tumor types not shown in the table above.

Fig 3. Pirtobrutinib Treatment Duration in MCL, and Other NHLs



- Median follow-up of 6 months (range, 0.7-18.3+ months) for the efficacy-evaluable patients
- 83% (24 of 29) of responding patients are ongoing and in response. Only 5 responding patients discontinued (4 for PD, 1 in CR electively discontinued to undergo allogeneic SCT)



- 77% (10/13) of responding WM patients are ongoing and in response
- 83% (5/6) of responding RT patients are ongoing and in response

Conclusions

- Pirtobrutinib demonstrates promising efficacy in MCL and other NHL patients previously treated with all classes of available therapy
 - Responses were observed across all dose levels
 - Efficacy was independent of prior therapy
 - Durable responses in BTK pre-treated MCL are particularly notable, given poor outcomes with existing therapeutic options
- 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 pre-treated patients with MCL and other NHLs

References

¹Cheah et al. *Ann. Oncol.* 2015;26:1175-79.; ²Martin et al. *Blood.* 2016;127:1559-63; ³Wang et al. *N. Engl. J. Med.* 2013;369:507-16; ⁴Dreyling et al. *Lancet.* 2016;387:770-8; ⁵Ondrisova L and Mraz M, *Front. Oncol.* 2020;10; ⁶Brandhuber et al. *Clin. Lymphoma Myeloma Leuk.* 2018;18:S216; ⁷Mato, et al. *The Lancet.* 2021; 397:892-901; ⁸Wang, et al. *Blood* 2020 136(Suppl 1):8-10.

Acknowledgements

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