Poster #
MCL-133

Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results from the Phase 1/2 BRUIN Study

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BACKGROUND

- Outcomes in MCL are extremely poor following covalent BTK inhibitor progression
  - Covalent BTK inhibitor resistance in MCL and other lymphomas is incompletely understood[1-10]
  - BTK C481-mutations are uncommon; bypass alterations and epigenetic changes implicated in some patients[7]
  - Overall survival following covalent BTK inhibitor therapy is poor[3,4,11]

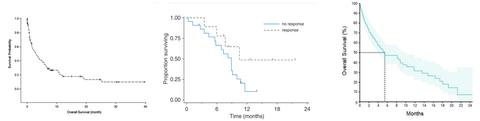


Fig 1[4]
Analysis of n = 114 global patients
Median OS = 2.9 months

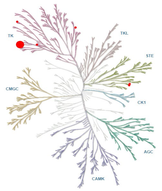
Fig 2[3]
Analysis of n = 31 US patients
Median OS = 8.4 months

Fig 3[11]
Analysis of n = 108 Japanese patients
Median OS = 5.46 months

- Pirtobrutinib is a highly potent and selective non-covalent (reversible) BTK inhibitor

Kinome selectivity[12]

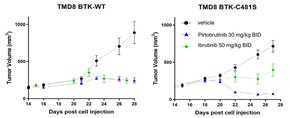
Highly selective for BTK



BID, twice-daily; BTK, Bruton tyrosine kinase.
Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

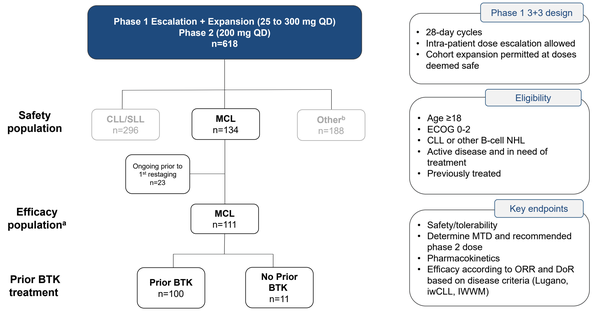
Xenograft models

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



- Nanomolar potency against WT and C481-mutant BTK in cell and enzyme assays[13]
- >300-fold selectivity for BTK vs 370 other kinases[13]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[13]

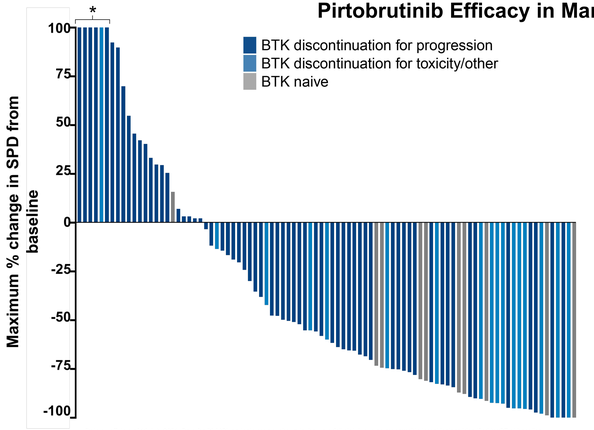
STUDY DESIGN



Data cutoff date of 16 July 2021.
[a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]Other includes DLBCL, WM, FL, MZL, Richter's transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

KEY RESULTS

Pirtobrutinib Efficacy in Mantle Cell Lymphoma



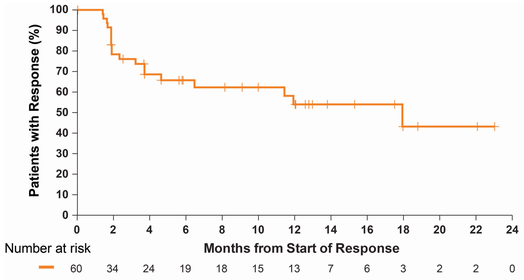
Data cutoff date of 16 July 2021. Data for 20 MCL patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up.
*Indicates patients with >100% increase in SPD.

BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	**51% (41-61)**
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	**82% (48-98)**
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

[a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR and PR. Response status per Lugano 2014 criteria based on investigator assessment. Total % may be different than the sum of the individual components due to rounding.

- Efficacy also seen in patients with prior:
  - Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
  - CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

Pirtobrutinib Duration of Response in Mantle Cell Lymphoma



- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

RESULTS

Patient Characteristics

Characteristics	MCL (n=134)
Median age (range), years	70 (46, 88)
Female / Male, n (%)	30 (22) / 104 (78)
Histology	
Classic	108 (81)
Pleomorphic/Blastoid	26 (19)
ECOG PS, n (%)	
0	82 (61)
1	50 (37)
2	2 (2)
Median number prior lines of systemic therapy (range)	3 (1, 9)
Prior therapy, n (%)	
BTK inhibitor	120 (90)
Anti-CD20 antibody	130 (97)
Chemotherapy	122 (91)
Stem cell transplant[b]	30 (22)
IMiD	23 (17)
BCL2 inhibitor	20 (15)
Proteasome inhibitor	17 (13)
CAR-T	7 (5)
PI3K inhibitor	5 (4)
Reason discontinued prior BTKi[a]	
Progressive disease	100 (83)
Toxicity/Other	20 (17)

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding.
[a]Calculated as percent of patients who received prior BTK inhibitor. [b]3 patients had both auto and allo stem cell transplants.

Pirtobrutinib Safety Profile

All Doses and Patients (n=618)	Treatment-Emergent AEs, (≥15%), %					Treatment-Related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding.
[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]Represents 6 events (all grade 3), including 2 cases of post-operative bleeding, 1 case each of GI hemorrhage in the setting of sepsis, NSAID use, chronic peptic ulcer disease, and one case of subarachnoid hemorrhage in setting of traumatic bike accident. [h]Of 10 total afib/aflutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation, 2 in patients presenting with concurrent systemic infection, and 2 in patients with both.

- No DLTs reported and MTD not reached
- 96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
- 1% (n=6) of patients permanently discontinued due to treatment-related AEs

CONCLUSIONS

- Pirtobrutinib demonstrates promising efficacy in MCL patients previously treated with BTK inhibitors, a population with extremely poor outcomes
- Favorable safety and tolerability are consistent with the design of pirtobrutinib as a highly selective and non-covalent (reversible) BTK inhibitor
- A randomized, global, phase 3 trial comparing pirtobrutinib with investigator's choice of covalent BTK inhibitors in BTK naïve relapsed MCL is ongoing (BRUIN MCL-321; NCT04662255)

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