Efficacy of Pirtobrutinib in Covalent BTK-Inhibitor Pre-Treated Relapsed / Refractory Mantle Cell Lymphoma: Additional Patients and Extended Follow-up from the Phase 1/2 BRUIN Study

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Background

Outcomes in MCL are Extremely Poor Following Covalent BTK Inhibitor Progression

- Covalent Bruton tyrosine kinase inhibitors (cBTKi) have transformed the treatment landscape of mantle cell lymphoma (MCL)[1]
  - Covalent BTKi resistance in MCL and other lymphomas is incompletely understood[2-11]
- Overall survival (OS) following cBTKi therapy is poor[4, 6, 13,]
- There is an unmet need for efficacious post-cBTKi treatments, with no standard regimens defined

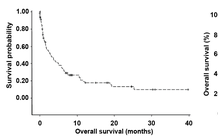


Fig 1[6]

Analysis of n = 114 global patients
Median OS = 2.9 months

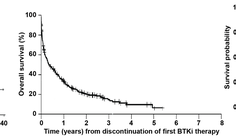


Fig 2[4]

Analysis of n = 238 European patients
Median OS = 4 months

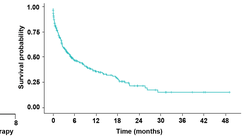
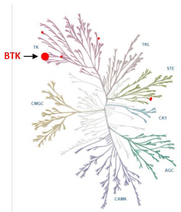


Fig 3[13]

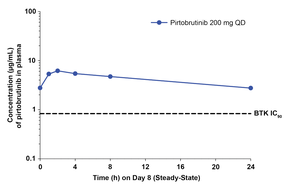
Analysis of n = 247 Japanese patients
Median OS = 5.6 months

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

Highly selective for BTK[14-15]

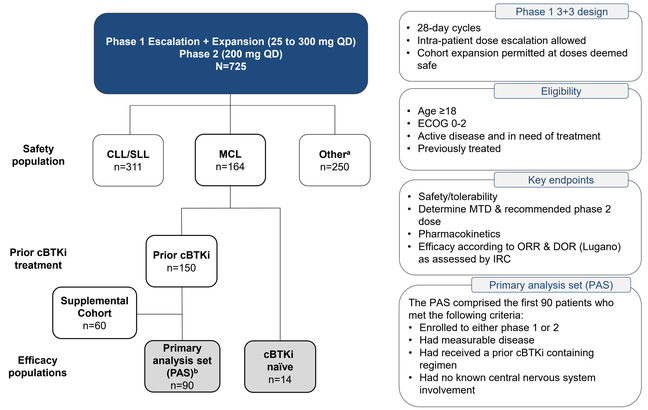


Plasma exposures exceeded BTK IC_{90} throughout dosing interval



- 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[14]

Phase 1/2 BRUIN Study Design



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 & recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR & DOR (Lugano) as assessed by IRC

Primary analysis set (PAS)

The PAS comprised the first 90 patients who met the following criteria:
- Enrolled to either phase 1 or 2
- Had measurable disease
- Had received a prior cBTKi containing regimen
- Had no known central nervous system involvement

Data cutoff date of 31 January 2022. [a]Other includes DLBCL, WM, FL, MZL, Richter's transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation. [b]To ensure adequate follow-up, a cut-off of 31 January 2022 was utilized which allowed the vast majority (>90%) of responders in the PAS to be followed for at least 9 months from onset of initial response to the data cut-off date.

Results

MCL Patient Characteristics

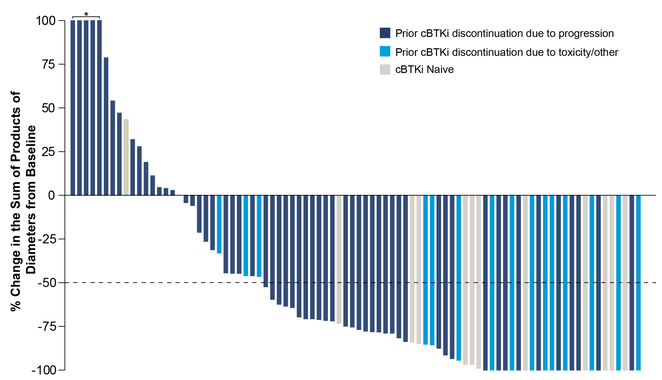
Characteristics	Prior cBTKi (n=90)	cBTKi Naïve (n=14)
Median age, years (range)	70 (46-87)	67 (60-86)
Male, n (%)	72 (80)	10 (71)
Histology, n (%)		
Classic	70 (78)	11 (79)
Pleomorphic/Blastoid	20 (22)	3 (21)
ECOG PS, n (%)		
0	61 (68)	5 (36)
1	28 (31)	8 (57)
2	1 (1)	1 (7)
sMIPI Score, n (%)		
Low risk (0-3)	20 (22)	3 (21)
Intermediate risk (4-5)	50 (56)	5 (36)
High risk (6-11)	20 (22)	6 (43)
Tumor Bulk (cm), n (%)		
<5 / ≥5	66 (73) / 24 (27)	9 (64) / 5 (36)
<10 / ≥10	87 (97) / 3 (3)	12 (86) / 2 (14)
Bone Marrow Involvement, n (%)		
Yes	46 (51)	4 (29)
No	44 (49)	10 (71)
Reason discontinued any prior cBTKi[a], n (%)		
Progressive disease	74 (82)	-
Toxicity/Other	16 (18)	-
Median number prior lines of systemic therapy (range)	3 (1-8)	2 (1-3)
Prior therapy, n (%)		
BTK inhibitor	90 (100)	0 (0)
Anti-CD20 antibody	86 (96)	14 (100)
Chemotherapy	79 (88)	14 (100)
Immunomodulator	19 (21)	1 (7)
Stem cell transplant	19 (21)	7 (50)
Autologous	17 (19)	7 (50)
Allogeneic	4 (4)	0 (0)
BCL2 inhibitor	14 (16)	0 (0)
CAR-T	4 (4)	0 (0)
PI3K inhibitor	3 (3)	1 (7)

Data cutoff date of 31 January 2022. [a]Calculated as percent of patients who received prior cBTKi.

Pirtobrutinib Efficacy in Patients with MCL

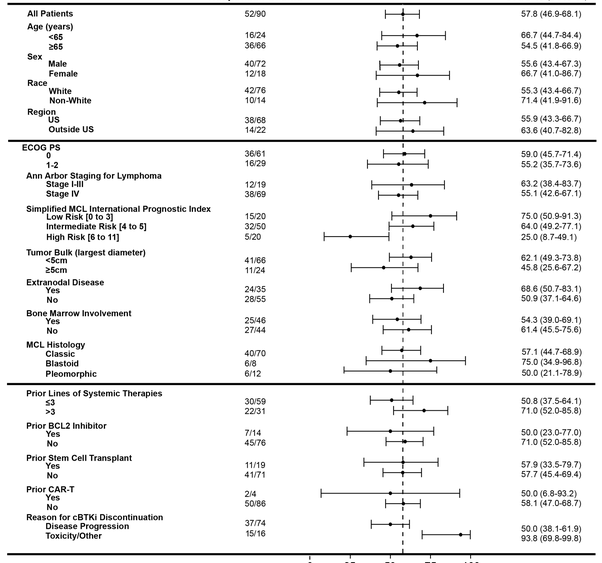
Prior cBTKi MCL Patients	n=90	cBTKi Naïve MCL Patients	n=14
Overall Response Rate[a], % (95% CI)	**57.8% (46.9-68.1)**	**Overall Response Rate[a], % (95% CI)**	**85.7% (57.2-98.2)**
Best Response[b]		**Best Response[c]**	
CR, n (%)	18 (20.0)	CR, n (%)	5 (35.7)
PR, n (%)	34 (37.8)	PR, n (%)	7 (50.0)
SD, n (%)	14 (15.6)	SD, n (%)	0 (0.0)
PD, n (%)	15 (16.7)	PD, n (%)	1 (7.1)

Data cutoff date of 31 January 2022. [a]ORR includes patients with a best response of CR and PR. [b]9 cBTKi pre-treated MCL patients were not evaluable. [c]1 cBTKi naïve patient was not evaluable. Response status per Lugano 2014 criteria based on IRC assessment



Data cutoff date of 31 January 2022. Data for 18 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..

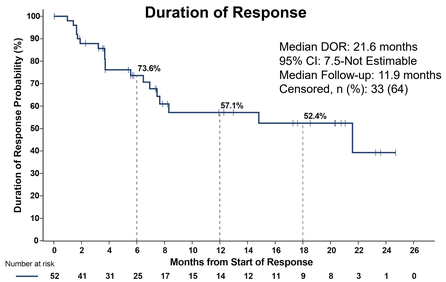
Overall Response Rate in Prior cBTKi MCL Subgroups



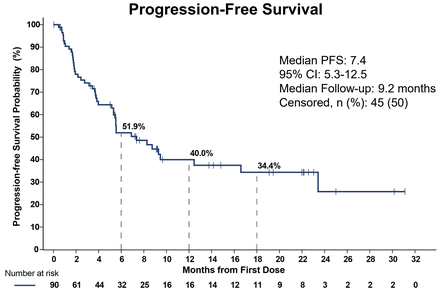
Data cutoff date of 31 January 2022. Data reported in the forest plot is overall response rate by prespecified patient characteristic subgroups. Two-sided 95% CI was calculated using the exact binomial distribution.

Pirtobrutinib Duration of Response, Progression-Free Survival and Overall Survival in Prior cBTKi MCL

Duration of Response

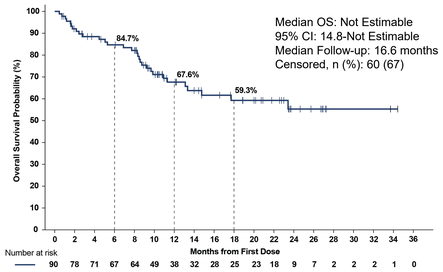


Progression-Free Survival



Data cutoff date of 31 January 2022. Response status per Lugano 2014 criteria based on IRC assessment.

Overall Survival



Pirtobrutinib Safety Profile

	All Doses and Patients (N=725)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	26.3%	1.7%	9.1%	0.8%
Diarrhea	22.1%	0.8%	8.6%	0.3%
Neutropenia[a]	21.7%	18.6%	13.0%	10.5%
Contusion	19.0%	0.0%	12.6%	0.0%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.2%	0.0%	14.9%	0.0%
Rash[d]	12.3%	0.4%	5.5%	0.3%
Arthralgia	13.0%	0.4%	3.2%	0.0%
Hemorrhage/Hematoma[e]	10.2%	1.7%	3.4%	0.4%
Hypertension	9.5%	2.8%	3.2%	0.6%
Atrial fibrillation/flutter[f, g]	2.6%	1.0%	0.7%	0.1%

Median time on treatment for the overall population was 8 months
Discontinuations due to TRAEs occurred in 2% (n=15) of overall patients
Dose reductions due to TRAEs occurred in 5% (n=38) of overall patients
Overall and MCL safety profiles were consistent[h]

Data cutoff date of 31 January 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with cBTKi. [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 19 total atrial fibrillation/flutter TEAEs, 6 occurred in patients with a prior medical history of atrial fibrillation. [h]MCL safety population data can be found via QR code.

Conclusions

- With more than a year of additional data, pirtobrutinib continues to demonstrate promising and durable efficacy in heavily pre-treated relapsed/refractory MCL patients who have been treated with a prior cBTKi
  - Consistently high overall response rates were observed regardless of number of prior lines of systemic therapy, and classes of prior therapy received
- Pirtobrutinib was well-tolerated with low-rates of discontinuation due to drug-related toxicity
  - Low rates of cBTKi-associated AEs were observed with pirtobrutinib
- A randomized, global, Phase 3 trial comparing pirtobrutinib with investigator's choice of cBTKi in pretreated BTKi naïve MCL is ongoing (BRUIN MCL-321; NCT04662255)

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Abbreviations: AE, adverse event; B-PLL, B cell prolymphocytic leukemia; cBTKi, covalent Bruton tyrosine kinase inhibitors; CI, confidence interval; CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; h, hours; IC90, concentration of drug required for 90% inhibition; IRC, independent review committee; MCL, mantle cell lymphoma; mg, milligram; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; nM, nanomolar; ORR, overall response rate; OS, overall survival; PCNSL, primary central nervous system lymphoma; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; SD, stable disease; SLL, small lymphocytic lymphoma; sMIPI, simplified MCL International Prognostic Index; SPD, sum of product diameters; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; WM, Waldenström Macroglobulinemia

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