MCL-155

# Pirtobrutinib in Covalent BTK-Inhibitor Pre-Treated Mantle Cell Lymphoma: Updated Results and Subgroup Analysis from the Phase 1/2 BRUIN Study with 2 Years of Survival Follow-up


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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]
  - –Resistance to cBTKi in MCL and other lymphomas is incompletely understood[2-11]
- Overall survival (OS) following cBTKi therapy is poor[6,12]
- There is an unmet need for efficacious post-cBTKi treatments, with no standard regimens defined

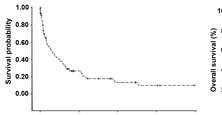



**Figure 1[6]**

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

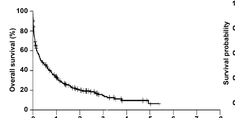



**Figure 2[4]**

Analysis of n = 238
European patients
Median OS = 4.0 months

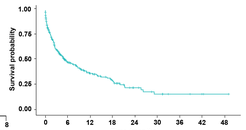
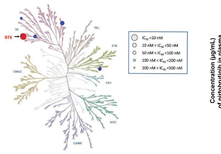



**Figure 3[13]**

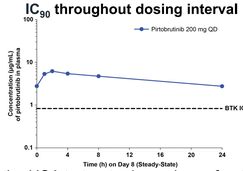
Analysis of n = 247
Japanese patients
Median OS = 5.6 months

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

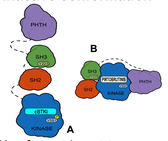
**Highly selective for BTK[13-14]**




**Plasma exposures exceeded BTK $IC_{90}$ throughout dosing interval**




**Pirtobrutinib may stabilize/ maintain BTK in a closed inactive conformation**




- Pirtobrutinib is approved in the USA to treat relapsed or refractory MCL after at least two lines of systemic therapy, including prior BTK inhibitor[15]
- Inhibits both WT and C481-mutant BTK with equal low nM potency[16]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[16]

## Phase 1/2 BRUIN Study Design

**Phase 1 Escalation + Expansion**
**(25 to 300 mg QD)**
**Phase 2 (200 mg QD)**
**N=773**

**Safety Population**

- **CLL/SLL** n=317
- **MCL** n=166
  - **Prior cBTKi** n=152
    - **Supplemental cohort** n=62
    - **Efficacy Populations**
      - **Primary analysis set (PAS)[b]** n= 90
      - **cBTKi naïve** n=14
- **Other[a]** n = 290

**Phase 1 3+3 design**

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

**Eligibility**

- Age ≥18
- ECOG PS 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 (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

[a]Other includes DLBCL, WM, FL, MZL, Richter's transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformations. [b]To ensure adequate follow-up, a data cut-off of 29 July 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.


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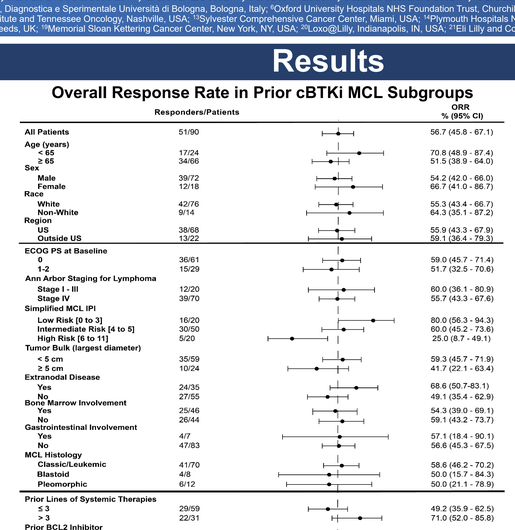
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## Results

### MCL Patient Characteristics

| Characteristics | Prior cBTKi (n=90) | cBTKi Naïve (n=14) |
|---|---|---|
| **Median age**, years (range) | 70.0 (46.0-87.0) | 67.0 (60.0-86.0) |
| **Male**, n (%) | 72 (80.0) | 10 (71.4) |
| **Histology**, n (%) | | |
| Classic | 70 (77.8) | 11 (78.6) |
| Pleomorphic/Blastoid | 20 (22.2) | 3 (21.4) |
| **ECOG PS**, n (%) | | |
| 0 | 61 (67.8) | 5 (35.7) |
| 1 | 28 (31.1) | 8 (57.1) |
| 2 | 1 (1.1) | 1 (7.1) |
| **sMIPI Score**, n (%) | | |
| Low risk (0-3) | 20 (22.2) | 3 (21.4) |
| Intermediate risk (4-5) | 50 (55.6) | 5 (35.7) |
| High risk (6-11) | 20 (22.2) | 6 (42.9) |
| **Tumor bulk (cm)**, n (%) | | |
| <5[a] / ≥5 | 66 (73.3) / 24 (26.7) | 9 (64.3) / 5 (35.7) |
| **Bone marrow involvement**, n (%) | | |
| Yes | 46 (51.1) | 4 (28.6) |
| No | 44 (48.9) | 10 (71.4) |
| **Median number of prior lines of systemic therapy**, n (range) | 3 (1-8) | 2 (1-3) |
| **Reason discontinued any prior cBTKi[b]**, n (%) | | |
| Progressive disease | 74 (82.2) | - |
| Toxicity / Other | 16 (17.8) | - |
| **Prior therapy**, n (%) | | |
| BTK inhibitor | 90 (100.0) | 0 (0.0) |
| Anti-CD20 antibody | 86 (95.6) | 14 (100.0) |
| Chemotherapy | 79 (87.8) | 14 (100.0) |
| Immunomodulator | 19 (21.1) | 1 (7.1) |
| Stem cell transplant | 19 (21.1) | 7 (50.0) |
| Autologous | 17 (18.9) | 7 (50.0) |
| Allogeneic | 4 (4.4) | 0 (0.0) |
| BCL2 inhibitor | 14 (15.6) | 0 (0.0) |
| CAR-T | 4 (4.4) | 0 (0.0) |
| PI3K inhibitor | 3 (3.3) | 1 (7.1) |
| ***TP53* status**, n (%) | | |
| Yes | 17 (18.9) | 3 (21.4) |
| No | 19 (21.1) | 4 (28.5) |
| Missing | 54 (60.0) | 7 (50.0) |
| **Ki-67 index**, n (%) | | |
| <30% | 9 (10.0) | 2 (14.3) |
| ≥30% | 25 (27.8) | 6 (42.9) |
| Missing | 56 (62.2) | 6 (42.9) |

### Overall Response Rate in Prior cBTKi MCL Subgroups

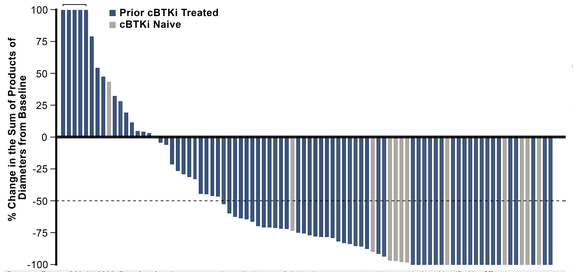



Data cutoff date of 29 Jul 2022. Data reported in the forest plot is overall response rate by prespecified patient characteristic subgroups. Two-sided 95% CI was calculated using the exact binomial distribution.

### Pirtobrutinib Efficacy in Patients with MCL Based on IRC Assessment

| Prior cBTKi MCL Patients | n=90 | cBTKi-Naïve MCL Patients | n=14 |
|---|---|---|---|
| **Overall Response Rate[a], % (95% CI)** | **56.7% (45.8-67.1)** | **Overall Response Rate[a], % (95% CI)** | **85.7% (57.2-98.2)** |
| **Best Response[b]** | | **Best Response[c]** | |
| CR, n (%) | 17 (18.9) | CR, n (%) | 6 (42.9) |
| PR, n (%) | 34 (37.8) | PR, n (%) | 6 (42.9) |
| SD, n (%) | 16 (17.8) | SD, n (%) | 0 (0.0) |
| PD, n (%) | 14 (15.6) | PD, n (%) | 1 (7.1) |

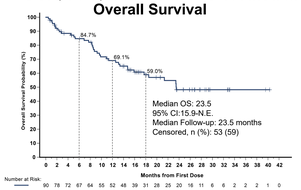
[a]ORR includes patients with a best response of CR and PR. [b]9 cBTKi pre-treated MCL patients were not evaluable. [c]1 cBTKi naïve patient was not evaluable. Response status per Lugano 2014 criteria based on IRC assessment.



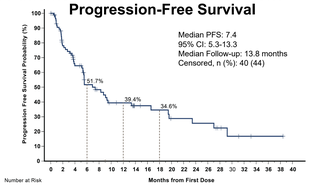

Data cutoff date of 29 Jul 2022. Data for 18 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD

### DoR, PFS, and OS in Pre-Treated MCL Patients Based on IRC Assessment

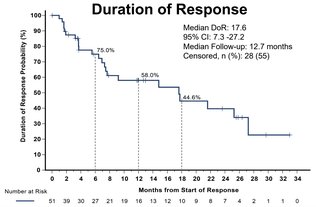
**Overall Survival**




**Progression-Free Survival**




**Duration of Response**




- cBTKi-naïve cohort, median DoR, PFS, and OS (95% CI) were not reached
  - –18-month DoR rate was 100% (95% CI: 100%)
  - –18-month PFS rate was 92.3% (95% CI: 56.6-98.9%)
  - –18-month OS rate was 92.3% (95% CI: 56.6-98.9%)

Data cutoff date of 29 Jul 2022. Response status per Lugano 2014 criteria based on IRC assessment.

### DoR, PFS, and OS in High-Risk Subgroups Based on IRC Assessment

**DoR in MCL by Ki-67 index**




**DoR in MCL by *TP53* status**




| Ki-67 | DoR Median (95% CI) | PFS Median (95% CI) | OS Median (95% CI) |
|---|---|---|---|
| <30% | 17.6 (1.6-N.E.) | 19.5 (0.9-N.E.) | N.E. (6.9-N.E.) |
| ≥30% | 21.6 (1.7-N.E.) | 5.2 (1.9-23.4) | N.E (14.7-N.E.) |

| *TP53* | DoR Median (95% CI) | PFS Median (95% CI) | OS Median (95% CI) |
|---|---|---|---|
| Negative | 14.8 (1.9-N.E.) | 7.4 (3.8-23.4) | N.E (6.9-N.E.) |
| Positive | 17.6 (1.7-N.E.) | 5.2 (1.7-19.5) | 15.9 (8.3-N.E.) |

Data cutoff date of 29 Jul 2022. Response status per Lugano 2014 criteria based on IRC assessment.

### Pirtobrutinib Safety Profile

| | MCL Patients (n=166)[a] | | | |
|---|---|---|---|---|
| | Treatment-Emergent AEs, (≥15%), % | | Treatment-Related AEs, % | |
| Adverse Event (AEs) | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Fatigue | 31.3 | 3.0 | 21.1 | 2.4 |
| Diarrhea | 22.3 | 0.0 | 12.0 | 0.0 |
| Dyspnea | 16.3 | 1.2 | 9.0 | 0.6 |
| AEs of special interest[b] | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Bruising[c] | 16.3 | 0.0 | 11.4 | 0.0 |
| Rash[d] | 8.4 | 0.6 | 5.4 | 0.0 |
| Arthralgia | 9.0 | 1.2 | 2.4 | 0.0 |
| Hemorrhage/Hematoma[e] | 10.2 | 2.4 | 4.2 | 0.6 |
| Hypertension | 3.6 | 0.0 | 1.8 | 0.0 |
| Atrial fibrillation/flutter[f,g] | 3.6 | 1.8 | 0.6 | 0.0 |

**Median time on treatment for the MCL population was 5 months**
**Discontinuations due to TRAEs occurred in 3% (n=5) of MCL patients**
**Dose reductions due to TRAEs occurred in 6% (n=10) of MCL patients**

Data cutoff date of 29 July 2022. [a]MCL patients who received ≥1 dose of pirtobrutinib by 29 July 2022. [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 6 total atrial fibrillation and atrial flutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation. In the MCL cohort, Treatment-related AEs causing discontinuation included weight decrease/alopecia/fatigue (1), neutropenia (1), platelet count decreased (1), pneumonitis (1), and cholecystitis (1).

## Conclusions

- Pirtobrutinib is approved in the USA to treat relapsed or refractory MCL after at least two lines of systemic therapy including prior BTK inhibitor treatment[16]
- With a median survival follow-up time of ~2 years, 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 in patients with high-risk disease features including blastoid/pleomorphic variants, elevated Ki-67 index, and *TP53* mutations
- 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; BCL-2, B-cell leukemia/lymphoma-2; BTK, Bruton tyrosine kinase; CART, chimeric antigens receptor-T; cBTKi, covalent Bruton tyrosine kinase inhibitors; CI, confidence interval; CLL, chronic lymphocytic leukemia; CR, complete response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; h, hours; $IC_{90}$, concentration of drug required for 90% inhibition; IPI, International Prognostic Index; IRC, independent review committee; MCL, mantle cell lymphoma; mg, milligram; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PHTH, pleckstrin homology and Tec homology; PI3K, phosphoinositide 3-kinase; PR, partial response; QD, once daily; SD, stable disease; SH, Src homology; SLL, small lymphocytic lymphoma; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

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