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Long-Term Safety with ≥12 Months of Pirtobrutinib in Relapsed/Refractory B-Cell Malignancies

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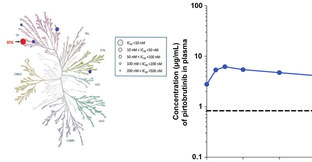
Background

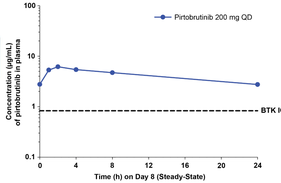
- While Bruton tyrosine kinase inhibitors (BTKi) can induce sustained remissions, ongoing response requires continuous treatment and thus long-term safety/tolerability is critical for adherence, maintaining dose intensity, and delivering maximum efficacy
- Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi was approved by US-FDA in January 2023 for relapsed or refractory mantle cell lymphoma (MCL) after at least 2 lines of systemic therapy including prior BTKi treatment[1]
- Pirtobrutinib is well tolerated and demonstrates promising efficacy in poor-prognosis B-cell malignancy patients following prior therapy, including prior covalent BTKi[2]
- However, the long-term safety and tolerability of pirtobrutinib has not yet been reported
- Here we report the clinical safety in patients with long-term (≥12 months) pirtobrutinib treatment from the phase 1/2 BRUIN trial

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

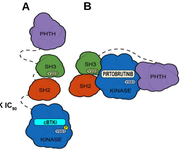
Highly Selective for BTK[2,3]



Plasma Exposures Exceeded BTK IC_{90} Throughout Dosing Interval



Pirtobrutinib may stabilize/ maintain BTK in a closed inactive conformation



- Inhibits both WT and C481-mutant BTK with equal low nM potency[4]
- 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[4]

Study Design

Phase 1/2 BRUIN Study

Phase 1 Escalation + Expansion (25 to 300 mg QD)

Phase 2 (200 mg QD)

Overall Safety Population N=773

≥ 12 months treatment N=326

- Patients with R/R B-cell malignancies who received ≥12 months of pirtobrutinib at the time of data cutoff (29 July 2022) were included in this *post-hoc* analysis.
- Median time to onset, dose reduction, discontinuation, and exposure adjusted incidence rates were determined for TEAEs that occurred in ≥15% of patients and select AE of special interest associated with BTKi. Distributions for times to first occurrence of AEs were summarized using the Kaplan-Meier methodology.

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
- Eligibility permitted with:
  - Cardiac comorbidities including prior atrial fibrillation[a]
  - Ongoing anti-coagulation/anti-platelet treatment[b]

Key endpoints

- Safety/tolerability
- Determine MTD and recommended Phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DoR as assessed by Investigator

Data cutoff date of 29 July 2022. BTKi, Bruton tyrosine kinase inhibitors; TEAE, treatment emergent adverse event. [a]Including due to prior BTKi. [b]Except warfarin

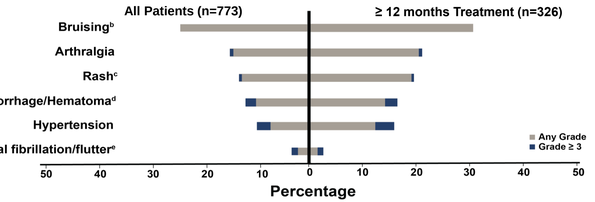
Results

Patient Characteristics

Characteristics	≥12 Months Treatment N=326	All Patients N=773
Disease types, n (%)		
CLL/SLL	211 (64.7)	317 (41)
MCL	42 (12.9)	166 (21.5)
WM	41 (12.6)	80 (10.3)
RT	6 (1.8)	82 (10.6)
FL/MZL	19 (5.8)	79 (10.2)
Others	7 (2.1)	49 (6.3)
Median age, years (range)	69 (33-88)	68 (26-95)
Male, n (%)	213 (65.3)	516 (66.8)
ECOG PS, n (%)		
0	186 (57.1)	385 (49.8)
1	126 (38.7)	343 (44.4)
2	14 (4.3)	45 (5.8)
Median number prior lines of systemic therapy, n (range)	3 (1-13)	3 (0-13)
Prior therapy, n (%)		
Anti-CD20 antibody	297 (91.1)	723 (93.5)
Chemotherapy	282 (86.5)	668 (86.4)
BTK inhibitor	253 (77.6)	597 (77.2)
BCL2	75 (23.0)	228 (29.5)
PI3K inhibitor	46 (14.1)	126 (16.3)
Immunomodulator	32 (9.8)	100 (12.9)
Prior Stem Cell Transplant	26 (8.0)	75 (9.7)
Autologous	20 (6.1)	59 (7.6)
Allogeneic	8 (2.5)	21 (2.7)
Prior CART	12 (3.7)	55 (7.1)
Other systemic therapy	79 (24.2)	213 (27.6)
Reason discontinued any prior BTK inhibitor[a], n (%)		
Progressive disease	184 (72.7)	468 (78.4)
Toxicity/Other	69 (27.3)	129 (21.6)

Data cutoff date of 29 July 2022. [a]In the event more than one reason was noted for discontinuation, disease progression took priority.

Selected AEs of Special Interest[a] in the Overall Safety Population and in Patients with ≥12 Months Treatment

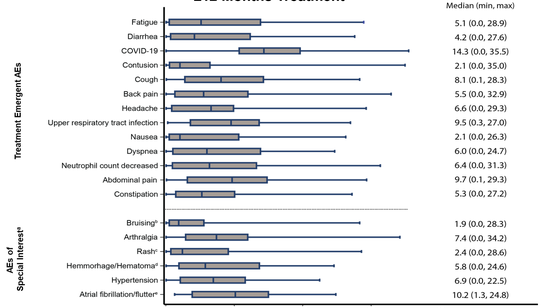


[a]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [b]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [c]Aggregate of all preferred terms including rash. [d]Aggregate of atrial fibrillation and atrial flutter.

Among the 326 patients who received ≥12 months treatment:

- Most TEAEs and AEs of special interest were low grade and did not lead to dose reduction or discontinuation
- 42% of the patients with treatment-emergent hypertension had a pre-existing medical history of hypertension
- In total, across all TEAEs, dose reduction or discontinuation occurred in 23 (7%) and 11 (3%) patients, respectively
- **With additional treatment, the rates of selected AEs of special interest did not show clinically meaningful increases, particularly Grade ≥3**

Time to First Occurrence of TEAEs and AEs of Special Interest in Patients with ≥12 Months Treatment



[a]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [b]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [c]Aggregate of all preferred terms including rash. [d]Aggregate of all preferred terms including hematoma or hemorrhage. [e]Aggregate of atrial fibrillation and atrial flutter.

- **The median times for first occurrence of most common and select TEAEs were generally within the first 12 months of treatment initiation**

Pirtobrutinib Safety Profile in Patients with ≥12 Months Treatment and in the Overall Safety Population

Treatment Emergent AEs (≥15%)	≥12 Months Treatment (N=326)				All Patients (N=773)			
	Any Grade TEAE (%)	Grade ≥3 TEAE (%)	Leading to Dose Reduction (%)	Leading to Drug Discontinuation (%)	Any Grade TEAE (%)	Grade ≥3 TEAE (%)	Leading to Dose Reduction (%)	Leading to Drug Discontinuation (%)
Fatigue	32.2	1.2	0	0	28.7	2.1	0.4	0.3
Diarrhea	30.7	1.2	0.3	0	24.2	0.9	0.3	0
Neutropenia[a]	29.8	23.9	3.1	0.6	25.0	20.3	2.1	0.5
Covid-19	28.5	4.3	0.3	0	16.7	2.7	0.1	0.4
Contusion	25.8	0	0.3	0	19.4	0	0.1	0
Cough	24.5	0	0	0	17.5	0.1	0.1	0
Back Pain	20.9	0.9	0	0	12.7	0.5	0	0
Headache	18.4	0.6	0	0	13.1	0.5	0.1	0
Upper Respiratory Tract Infection	18.1	0	0	0	9.8	0.1	0	0
Nausea	17.5	0.3	0	0	16.2	0.1	0.1	0.1
Dyspnea	17.2	0.6	0.3	0	15.5	1.0	0.1	0.1
Abdominal Pain	16.3	0.9	0	0	13.1	1.0	0	0.1
Constipation	16.3	0	0	0	13.6	0.3	0	0
AEs of Special Interest[b]	**Any Grade TEAE (%)**	**Grade ≥3 TEAE (%)**	**Leading to Dose Reduction (%)**	**Leading to Drug Discontinuation (%)**	**Any Grade TEAE (%)**	**Grade ≥3 TEAE (%)**	**Leading to Dose Reduction (%)**	**Leading to Drug Discontinuation (%)**
Bruising[c]	30.7	0	0.3	0	23.7	0	0.1	0
Arthralgia	21.2	0.6	0	0	14.4	0.6	0	0
Rash[d]	19.6	0.3	0	0	12.7	0.5	0.3	0.1
Hemorrhage/ Hematoma[e]	16.6	2.1	0	0	11.4	1.8	0	0
Hypertension	16.0	3.4	0.3	0	9.2	2.3	0.1	0
Atrial fibrillation/ flutter[f]	2.8	0.9	0	0	2.8	1.2	0	0

Data cutoff date of 29 July 2022. [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.

Treatment Related Modifications Were Similar between Patients with ≥12 Months Treatment Compared to the Overall Safety Population

	≥12 Months Treatment (N = 326)	All Patients (N = 773)
Median time on treatment, months (IQR)	19.4 (16.0, 25.4)	9.6 (3.5, 18.1)
Discontinuations due to TRAEs, n (%)	4 (1.2%)	20 (2.6%)
Dose reductions due to TRAEs, n (%)	18 (5.5%)	35 (4.5%)

Data cutoff date of 29 July 2022. TRAEs, treatment related adverse events.

Among the 326 patients who received ≥12 months treatment:

- Median time on treatment was 19.4 months, with 231 (71%) patients remaining on pirtobrutinib at data cutoff
- Four (1%) patients discontinued due to a TRAE (platelet count decreased, Covid-19 pneumonia, neutropenia, pneumonitis)
- One patient experienced a fatal TRAE (Covid-19 pneumonia)
- Treatment discontinuation and dose reduction rates were similar between the overall safety population and for patients who received ≥12 months treatment

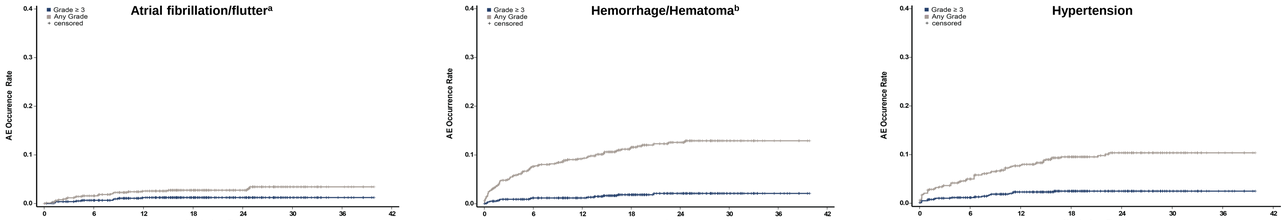
Exposure Adjusted Incidence Rates[a] for AEs of Special Interest

AEs of Special Interest[b]	≥12 Months Treatment (N=326)		All Patients (N=773)	
	TEAE Incidence Rate	TRAE Incidence Rate	TEAE Incidence Rate	TRAE Incidence Rate
Bruising[c]	1.99	1.21	2.69	1.55
Arthralgia	1.16	0.23	1.41	0.31
Rash[d]	1.27	0.44	1.11	0.55
Hemorrhage/ Hematoma[e]	0.87	0.30	1.07	0.36
Hypertension	0.85	0.23	0.87	0.30
Atrial fibrillation/ flutter[f]	0.13	0.04	0.25	0.07

Data cutoff date of 29 July 2022. [a]Exposure-adjusted incidence rate is calculated as the first occurrence of each adverse event of interest per 100 person-months of pirtobrutinib exposure. [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.

- **Prolonged treatment with pirtobrutinib did not lead to an increase in exposure adjusted incidence rates of majority of treatment emergent or treatment-related AEs of special interest**

Cumulative AE Occurrence Rate Over Time for Selected AEs of Interest in the Overall Safety Population



Data cutoff date of 29 July 2022. [a]Aggregate of atrial fibrillation and atrial flutter. [b]Aggregate of all preferred terms including hematoma or hemorrhage.

- **The AE occurrence rate (Grade ≥3) of atrial fibrillation/flutter, hemorrhage/hematoma and hypertension was low and does not suggest a temporal relationship to pirtobrutinib exposure**

Conclusions

- **In this post-hoc safety analysis in patients (N = 326) who received pirtobrutinib for ≥12 months:**
  - With continued therapy, low incidence of grade ≥3 AEs and few dose modifications were observed
  - The safety and tolerability profile observed was similar to previously published safety analyses on all patients enrolled regardless of follow-up
- **Prolonged pirtobrutinib therapy continues to demonstrate a safety profile amenable to long-term administration at the recommended dose without evidence of new or worsening toxicity signals**

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