Pirtobrutinib monotherapy in Bruton tyrosine kinase inhibitor-intolerant patients with B-cell malignancies: results of the phase I/II BRUIN trial

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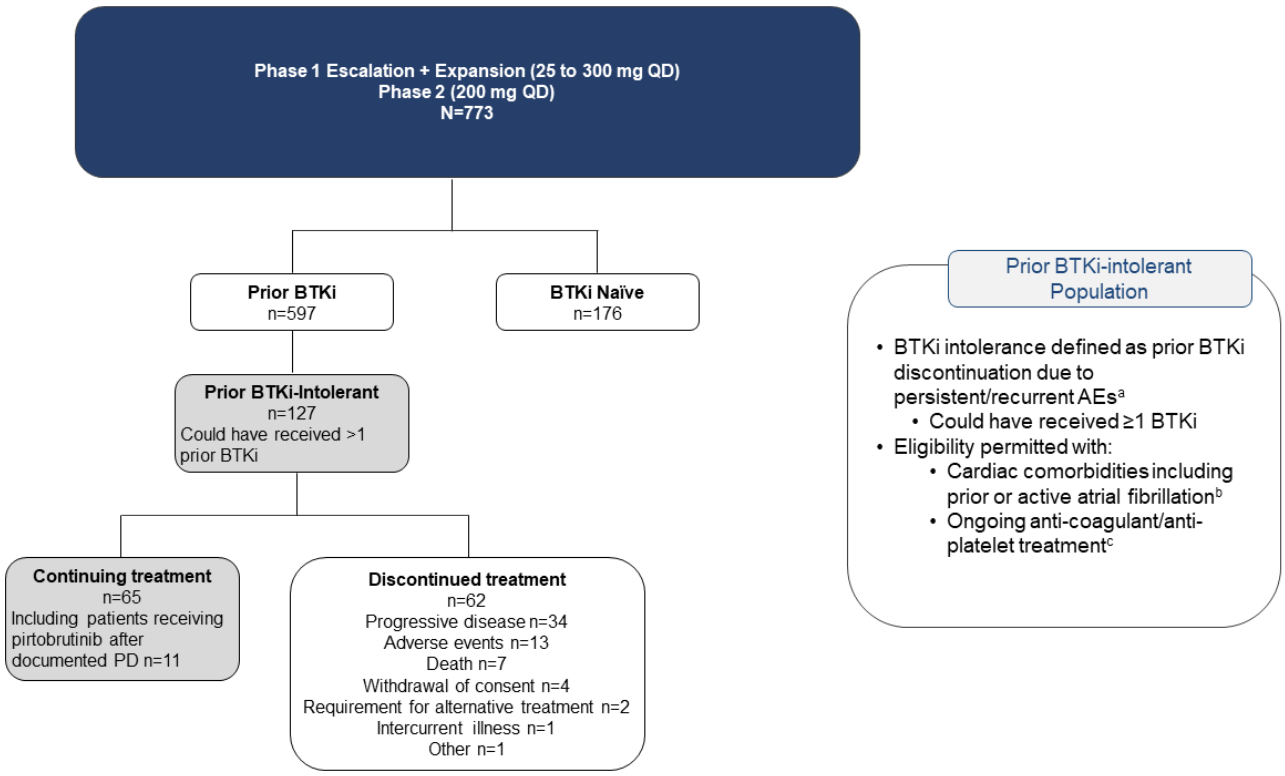
Supplemental Data

Supplemental Figure 1. Phase 1/2 BRUIN Study



A data cutoff date of 29 July 2022 was used for all analyses. [a]AEs were determined by the investigator. [b]Including due to prior BTKi. [c]Except warfarin.

Table S1: BTKi-intolerant patients discontinued at least one prior BTKi-containing regimen either as monotherapy or a combination regimen.

BTKi-intolerant (n=127)	**BTKi-containing regimen, n (%)**
Discontinued prior BTKi monotherapy regimens for toxicity	110 (86.6)
Discontinued prior BTKi-containing combination regimens for toxicity	19 (15.0)
Discontinued both prior BTKi monotherapy and prior BTKi-containing combination regimens for toxicity*	2 (1.6)
Number of different combination regimens, n	10
BTKi+anti-CD20 antibody	16 (12.6)
BTKi+BCL2i	5 (3.9)
BTKi+PI3Ki	2 (1.6)
BTKi+PD-1 antibody	2 (1.6)
BTKi+selinexor	1 (0.8)
BTKi+mTor/IMiD	1 (0.8)
BTKi+CAR-T cell therapy	1 (0.8)
BTKi+BR**	1 (0.8)
BTKi+proteasome inhibitor	1 (0.8)
BTKi+bispecific antibody	1 (0.8)

*2 patients who discontinued both monotherapy and combination regimens for toxicity are included in the counts for discontinuing monotherapy for toxicity and also for discontinuing combination therapy for toxicity. ** 1 patient received BTKi+BR and is not included with BTKi+anti-CD20 antibody. PI3K=phosphatidylinositol 3-kinase; PD-1=programmed cell death protein 1; mTor=mammalian target of rapamycin; IMiD=immunomodulatory imide drugs; CAR=chimeric antigen receptor; BR= bendamustine and rituximab.

Table S2

Characteristics	Overall Safety Population (n=773)
Disease types, n (%)	
CLL/SLL	317 (41.0)
MCL	166 (21.5)
WM	80 (10.3)
RT	82 (10.6)
Other	128 (16.6)
Age, median (range), years	68.0 (26-95)
<50	32 (4.1)
50-64	242 (31.3)
65-74	315 (40.8)
75-84	160 (20.7)
≥85	24 (3.1)
Male, n (%)	516 (66.8)
ECOG PS, n (%)	
0	385 (49.8)
1	343 (44.4)
2	45 (5.8)
Number of prior lines of systemic therapy, median (range)	3 (0-13)
Prior systemic therapy, n (%)	
BTKi	597 (77.2)
Anti-CD20 antibody	723 (93.5)
Chemotherapy	668 (86.4)
BCL2 inhibitor	228 (29.5)
PI3K agent	126 (16.3)
Immunomodulator	100 (12.9)
Stem cell transplant	75 (9.7)
Autologous	59 (7.6)
Allogeneic	21 (2.7)
CAR-T	55 (7.1)
Other systemic therapy	213 (27.6)
Number of prior lines of BTKi, n (%)	
1	478 (61.8)
2	99 (12.8)
≥3	20 (2.6)

Table S3: Recurrence with Pirtobrutinib Treatment of TEAEs that Previously Led to Discontinuation of Prior BTKi, within the Same Patient, among the Subgroup of Patients with Duration from last Prior BTKi to Start of Pirtobrutinib Treatment Less than or Equal to 18.8 months (median).

	No Recurrence n (%)	Low-grade n (%)	Grade ≥3 n (%)
Pain (n=3)	2 (66.7)	1 (33.3)	0
Fatigue (n=2)	2 (100.0)	0	0
Diarrhea (n=4)	4 (100.0)	0	0
Gastrointestinal disorders (n=4)	3 (75.0)	0	1 (25.0)
Bleeding/hemorrhage (n=5)	3 (60.0)	2 (40.0)	0
Arthralgias/myalgias (n=5)	1 (20.0)	4 (80.0)	0
Rash (n=6)	3 (50.0)	3 (50.0)	0
Neutropenia (n=9)	2 (22.2)	1 (11.1)	6 (66.7)
Infections (n=4)	2 (50.0)	1 (25.0)	1 (25.0)
Atrial fibrillation (n=15)	14 (93.3)	0	1 (6.7)
Cardiac disorders (n=21)	16 (76.2)	3 (14.3)	2 (9.5)

Table S3: Recurrence with Pirtobrutinib Treatment of TEAEs that Previously Led to Discontinuation of Prior BTKi, within the Same Patient, among the Subgroup of Patients with Duration from last Prior BTKi to Start of Pirtobrutinib Treatment Greater than 18.8 months (median).

	No Recurrence n (%)	Low-grade n (%)	Grade ≥3 n (%)
Pain (n=3)	3 (100.0)	0	0
Fatigue (n=4)	1 (25.0)	3 (75.0)	0
Diarrhea (n=2)	1 (50.0)	1 (50.0)	0
Gastrointestinal disorders (n=4)	0	4 (100.0)	0
Bleeding/hemorrhage (n=4)	3 (75.0)	1 (25.0)	0
Arthralgias/myalgias (n=5)	4 (80.0)	1 (20.0)	0
Rash (n=5)	3 (60.0)	2 (40.0)	0
Neutropenia (n=3)	1 (33.3)	0	2 (66.7)
Infections (n=9)	1 (11.1)	3 (33.3)	5 (55.6)
Atrial fibrillation (n=15)	14 (93.3)	0	1 (6.7)
Cardiac disorders (n=19)	14 (73.7)	4 (21.1)	1 (5.3)

Table S4: Pirtobrutinib Safety Profile

	Overall Safety Population (n=773)			
	Treatment-Emergent AEs, %		Treatment-related AEs, %	
AE	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	28.7	2.1	9.3	0.8
Neutropenia[a]	24.2	20.4	14.7	11.5
Diarrhea	24.2	0.9	9.3	0.4
Contusion	19.4	0.0	12.8	0.0
Cough	17.5	0.1	2.3	0.0
COVID-19	16.7	2.7	1.3	0.0
Nausea	16.2	0.1	4.7	0.1
Dyspnea	15.5	1.0	3.0	0.1
Anaemia	15.4	8.8	5.2	2.1
AEs of Clinical Interest[b]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[c]	55.6	21.3	12.0	3.1
Infections (excluding COVID-19)	47.2	15.9	10.7	2.8
Bruising[d]	23.7	0.0	15.1	0.0
Rash[e]	12.7	0.5	6.0	0.4
Arthralgia	14.4	0.6	3.5	0.0
Hemorrhage/hematoma[f]	11.4	1.8	4.0	0.6
Hypertension	9.2	2.3	3.4	0.6
Atrial fibrillation/flutter[g]	2.8	1.2	0.8	0.1

Median time on treatment for the overall population was 9.6 months. [a]Aggregate of preferred terms including neutropenia or neutrophil count decreased. [b]AEs of interest are those that were previously associated with cBTKi. [c]Aggregate of all preferred terms indicating infection and including COVID-19. [d]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [e]Aggregate of all preferred terms including rash. [f]Aggregate of all preferred terms including hemorrhage or hematoma. [g]Aggregate of atrial fibrillation and atrial flutter.

Table S5: Adverse events leading to discontinuation and fatal outcome.

Adverse event leading to discontinuation n=13		
Preferred Term	**Grade**	**Relationship to pirtobrutinib**
Anxiety	3	Not related
Abdominal Pain	2	Not related
Chronic Respiratory Failure	3	Not related
Myalgia	2	Related
Lymphocyte Count Decreased/ Platelet Count Decreased/Neutropenia	2/3/NA	Not related/related/Not related
Pneumonia	2	Not related
Neutropenia	3	Related
COVID-19 Pneumonia	5	Related
Hyponatremia	2	Not related
Rash maculo-papular	2	Related
Skin Necrosis	3	Related
Staphylococcal Sepsis	3	Related
Dyspnea/Pleural effusion	1/2	Not related/Not related
Adverse event with fatal outcome n=7		
Preferred Term	**Grade**	**Relationship to pirtobrutinib**
Pneumonia Fungal	5	Not related
Septic Shock	5	Not related
COVID-19 Pneumonia	5	Not related
COVID-19	5	Not related
Splenic Rupture	5	Not related
COVID-19	5	Not related
Legionella Infection	5	Not related

Table S6: Best Overall Response and Overall Response Rate Based on Investigator Assessments in CLL Subgroups.

	Time since End of Last Prior BTKi Discontinued for Toxicity to First Dose of Pirtobrutinib Treatment Less than or Equal to 18.8 months <Median> (N = 34)	**Time since End of Last Prior BTKi Discontinued for Toxicity to First Dose of Pirtobrutinib Treatment Greater than 18.8 months <Median> (N = 44)**
Overall Response Rate (95% CI)	70.6 (52.5, 84.9)	81.8 (67.3, 91.8)
Best Overall Response, n (%)		
Partial Response	24 (70.6)	34 (77.3)
PR with lymphocytosis	0	2 (4.5)
Stable Disease	7 (20.6)	5 (11.4)
Progressive Disease	2 (5.9)	1 (2.3)
Not Evaluable	1 (2.9)	2 (4.5)