CT-168

Comparison of Bleeding-Related Events in Patients Who Received Pirtobrutinib with and without Antithrombotic Agents

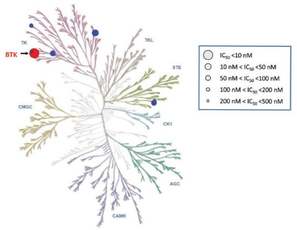
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Background

- Covalent Bruton tyrosine kinase inhibitors (cBTKi) have transformed the management of B-cell malignancies, including CLL and MCL[1-4]
- Bleeding events due to cBTKi are reported in a sizeable patient population
  - Risk of minor and major bleeding events has been observed in up to 66% and 6% of patients treated with ibrutinib, respectively[5]
  - Prescribers are cautious about concomitant antithrombotic use[5,6]
  - Mechanism underlying cBTKi-related bleeding is attributed to both on-target and platelet-relevant off-target activity[7]
- Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi that has demonstrated promising efficacy and safety in multiple B-cell malignancies[8,9]

Highly selective for BTK[8-9]



- Pirtobrutinib is approved in the USA to treat relapsed or refractory MCL after at least two lines of systemic therapy including prior BTKi treatment[10]
- Herein, we report bleeding/bruising events in patients from BRUIN who received pirtobrutinib with or without concomitant antithrombotic therapy

Study Design

BRUIN is a global, open-label, phase 1/2 study of pirtobrutinib (NCT03740529)

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

- With Concomitant Antithrombotic Therapy n=216
- Without Concomitant Antithrombotic Therapy n=557

Eligibility

Inclusion Criteria
- Age ≥18
- ECOG PS 0-2
- Active CLL/SLL, WM, or NHL and in need of treatment
- Ongoing treatment with select antithrombotic agents was permitted
  - Direct factor Xa inhibitors
  - Heparin anticoagulants
  - Platelet aggregation inhibitors

Exclusion Criteria
- Requirement of therapeutic anticoagulation with warfarin
- Clinically significant uncontrolled cardiovascular disease[a]
- Current treatment with strong CYP3A4 inhibitors or inducers

[a]Cardiovascular disease includes any of the following: unstable angina; history of myocardial infarction <6 months prior to treatment; previously documented LVEF of ≤45% within 12 months prior to treatment; Class 3 or 4 cardiac disease as defined by NYHA Functional Classification; and uncontrolled or symptomatic arrhythmias.
A data cutoff date of 29 July 2022 was used for all analyses.

Results

Patient Characteristics

Characteristics	Pirtobrutinib Monotherapy N=773	
	With Concomitant Antithrombotic (n=216)	Without Concomitant Antithrombotic (n=557)
Disease types, n (%)		
CLL / SLL	98 (45.4)	219 (39.3)
MCL	43 (19.9)	123 (22.1)
Other NHL	75 (34.7)	215 (38.6)
Age, median (IQR), years	71.5 (65.0–77.0)	67.0 (60.0–73.0)
<50	2 (0.9)	30 (5.4)
50-64	46 (21.3)	196 (35.2)
65-74	95 (44.0)	220 (39.5)
75-84	60 (27.8)	100 (18.0)
≥85	13 (6.0)	11 (2.0)
Male, n (%)	157 (72.7)	359 (64.5)
ECOG PS, n (%)		
0	100 (46.3)	285 (51.2)
1	102 (47.2)	241 (43.3)
2	14 (6.5)	31 (5.6)
Patients with history of thrombocytopenia, n (%)	11 (5.1)	34 (6.1)
Time on pirtobrutinib treatment, median (IQR), months	10.6 (4.0–19.9)	9.3 (3.1–17.3)
Number of prior lines of systemic therapy, median (range)	3 (1–12)	3 (0–13)
Prior systemic therapy, n (%)		
BTKi	166 (76.9)	431 (77.4)
Chemotherapy	178 (82.4)	490 (88.0)
anti-CD20 antibody	196 (90.7)	527 (94.6)
anti-CD20 antibody + chemotherapy	174 (80.6)	482 (86.5)
BCL2 inhibitor	59 (27.3)	169 (30.3)
PI3K agent	33 (15.3)	93 (16.7)
Immunomodulator	35 (16.2)	65 (11.7)
CAR-T	12 (5.6)	43 (7.7)
Stem cell transplant	15 (6.9)	60 (10.8)
Autologous	12 (5.6)	47 (8.4)
Allogeneic	3 (1.4)	18 (3.2)
Other systemic therapy	63 (29.2)	150 (26.9)

Concomitant Antithrombotic Therapy

Antithrombotic Agents	With Concomitant Antithrombotic (n=216) n (%)[a]
Platelet aggregation inhibitors excluding heparin	112 (51.9)
Acetylsalicylic acid	105 (48.6)
Clopidogrel	7 (3.2)
Ticagrelor	2 (0.9)
Dipyridamole	1 (0.5)
Prasugrel	1 (0.5)
Direct factor Xa inhibitors	79 (36.6)
Apixaban	56 (25.9)
Rivaroxaban	22 (10.2)
Edoxaban	4 (1.9)
Heparins	40 (18.5)
Enoxaparin	29 (13.4)
Heparin	15 (6.9)
Dalteparin	1 (0.5)
Sulodexide	1 (0.5)
Salicylic acid and derivatives	12 (5.6)
Acetylsalicylic acid	12 (5.6)
Enzymes	5 (2.3)
Alteplase	5 (2.3)

[a]Patients may have received more than one type/subtype of concomitant antithrombotic therapy.

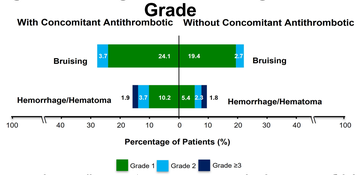
Abbreviations: BCL2, B-cell leukemia/lymphoma 2; BTK, Bruton tyrosine kinase; CAR-T, chimeric antigen receptor – T cell therapy; cBTKi, covalent Bruton tyrosine kinase inhibitor; CD20, cluster of differentiate 20; CLL, chronic lymphocytic leukemia; CYP3A4, cytochrome P450 3A4; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; LVEF, left ventricular ejection fraction; MCL, mantle cell lymphoma; NHL, Non-Hodgkin lymphoma; NYHA, New York Heart Association; PI3K, phosphoinositide 3-kinase; QD, once daily; SLL, small lymphocytic lymphoma; WM, Waldenstrom macroglobulinemia; Xa, xabans

Overview of Treatment-Emergent All-Grade Bleeding/Bruising Events[a]

	Pirtobrutinib Monotherapy N=773	
	With Concomitant Antithrombotic (n=216)	Without Concomitant Antithrombotic (n=557)
Number of events	157	296
Patients with events, n (%)	97 (44.9)	181 (32.5)
Median time to first onset, weeks (IQR)	8.1 (2.6–24.0)	4.1 (1.3–16.1)
Median duration, weeks (IQR)	2.1 (0.6–4.3)	4.0 (1.1–7.9)
Patients with serious events, n (%)	6 (2.8)	10 (1.8)
Patients with events requiring:		
Dose interruption, n (%)	8 (3.7)	14 (2.5)
Dose reduction, n (%)	0 (0)	1 (0.2)
Dose discontinuation, n (%)	0 (0)	0 (0)
Prolonged hospitalization, n (%)	5 (2.3)	9 (1.6)

[a]Bleeding/Bruising events included bruising, hemorrhage/hematoma, hematuria, gingival bleeding, hemoptysis, epistaxis, and other less common bleeding events

Treatment-Emergent Bruising and Hemorrhage/Hematoma Events by Grade



- Bruising and hemorrhage/hematoma were subclasses of bleeding/bruising
  - Bruising: aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise
  - Hemorrhage/hematoma: aggregate of all preferred terms including hematoma or hemorrhage

Summary of Treatment-Emergent Bleeding/Bruising Events

	Pirtobrutinib Monotherapy N=773			
	With Concomitant Antithrombotic (n=216)		Without Concomitant Antithrombotic (n=557)	
	All Grades n (%)	Grade ≥3[a] n (%)	All Grades n (%)	Grade ≥3 n (%)
Bleeding/Bruising Events[b]	97 (44.9)	6 (2.8)	181 (32.5)	11 (2.0)
Hematuria	12 (5.6)	0 (0)	15 (2.7)	0 (0)
Epistaxis	11 (5.1)	0 (0)	19 (3.4)	0 (0)
Gingival bleeding	3 (1.4)	0 (0)	2 (0.4)	0 (0)
Hemoptysis	3 (1.4)	0 (0)	1 (0.2)	0 (0)
Bruising	60 (27.8)	0 (0)	123 (22.1)	0 (0)
Contusion	49 (22.7)	0 (0)	101 (18.1)	0 (0)
Petechiae	8 (3.7)	0 (0)	27 (4.8)	0 (0)
Ecchymosis	4 (1.9)	0 (0)	6 (1.1)	0 (0)
Increased tendency to bruise	3 (1.4)	0 (0)	4 (0.7)	0 (0)
Hemorrhage/Hematoma	34 (15.7)	4 (1.9)	54 (9.7)	10 (1.8)
Hematoma	7 (3.2)	0 (0)	10 (1.8)	2 (0.4)
Conjunctival hemorrhage	4 (1.9)	0 (0)	6 (1.1)	0 (0)
Upper gastrointestinal hemorrhage	3 (1.4)	2 (0.9)	3 (0.5)	2 (0.4)
Vitreous hemorrhage	3 (1.4)	0 (0)	1 (0.2)	0 (0)

[a]No grade 4-5 bleeding/bruising events occurred in patients with concomitant antithrombotic therapy; [b]Patients may appear in more than one subcategory. Events occurring in ≥1% of patients are presented. Bruising and Hemorrhage/hematoma were subclasses of bleeding/bruising.

- Of the 6 (2.8%) patients who received antithrombotic therapy and had a grade 3 bleeding event, 2 (0.9%) were considered related to pirtobrutinib by investigators: upper gastrointestinal bleeding with anemia and a hemarthrosis from a knee injury (1 each)

Treatment-Emergent Bleeding/Bruising Events of Special Interest by Antithrombotic Agents

	Antithrombotic Agents									
	Direct Factor Xa Inhibitors (n=79)		Heparins (n=40)		Platelet Aggregation Inhibitors (excluding Heparin) (n=112)		Salicylic Acid and Derivatives (n=12)		Enzymes (n=5)	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Bleeding/Bruising[a]	37 (46.8)	2 (2.5)	22 (55)	1 (2.5)	49 (43.8)	4 (3.6)	4 (33.3)	1 (8.3)	3 (60)	0 (0)
Hematuria	4 (5.1)	0 (0)	2 (5)	0 (0)	7 (6.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Epistaxis	6 (7.6)	0 (0)	2 (5)	0 (0)	4 (3.6)	0 (0)	2 (16.7)	0 (0)	0 (0)	0 (0)
Gingival bleeding	3 (3.8)	0 (0)	1 (2.5)	0 (0)	2 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hemoptysis	1 (1.3)	0 (0)	2 (5)	0 (0)	2 (1.8)	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)
Bruising	22 (27.8)	0 (0)	12 (30)	0 (0)	32 (28.6)	0 (0)	3 (25.0)	0 (0)	2 (40)	0 (0)
Contusion	18 (22.8)	0 (0)	10 (25)	0 (0)	25 (22.3)	0 (0)	2 (16.7)	0 (0)	1 (20)	0 (0)
Petechiae	4 (5.1)	0 (0)	1 (2.5)	0 (0)	5 (4.5)	0 (0)	1 (8.3)	0 (0)	0 (0)	0 (0)
Ecchymosis	1 (1.3)	0 (0)	1 (2.5)	0 (0)	2 (1.8)	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)
Increased tendency to bruise	1 (1.3)	0 (0)	0 (0)	0 (0)	2 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hemorrhage/ Hematoma	13 (16.5)	0 (0)	10 (25)	1 (2.5)	18 (16.1)	4 (3.6)	2 (16.7)	1 (8.3)	1 (20)	0 (0)
Hematoma	2 (2.5)	0 (0)	5 (12.5)	0 (0)	3 (2.7)	0 (0)	1 (8.3)	0 (0)	0 (0)	0 (0)
Conjunctival hemorrhage	4 (5.1)	0 (0)	0 (0)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Upper gastrointestinal hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.7)	2 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)
Vitreous hemorrhage	1 (1.3)	0 (0)	1 (2.5)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a]Patients may appear in more than one subcategory. Bruising and Hemorrhage/hematoma were subclasses of bleeding/bruising.

Conclusions

- Patients who received concomitant antithrombotic therapy with pirtobrutinib had an increased rate of bleeding/bruising events (44.9%) relative to patients who received pirtobrutinib (32.5%) alone
- Grade 3 bleeding events were infrequent (<3%), and no grade 4-5 events occurred in patients who received concomitant antithrombotic therapy
- No dose reductions or treatment discontinuations due to bleeding/bruising events occurred in patients who received concomitant antithrombotic therapy, and hospitalization was uncommon (<3%)
- These data support the safe use of pirtobrutinib in patients requiring antithrombotic therapies, including combination antiplatelet and anticoagulant agents

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DISCLAIMER:
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REFERENCES
1. Byrd et al. *N Engl J Med* 2013;369:32–42.
2. Wang et al. *N Engl J Med* 2013;369:507–16.
3. Song et al. *Blood* 2022;139:3148–58.
4. Brown et al. *N Engl J Med* 2023;388:319–32.
5. Stephens & Byrd. *Blood* 2019;133:1298–307.
6. Chen et al. *Eur J Haematol* 2018. doi: 10.1111/ejh.13148.
7. von Hundelshausen & Siess. *Cancers (Basel)* 2021;13:1103.
8. Mato et al. *Lancet* 2021;397:892–901.
9. Brandhuber et al. *Clin Lymphoma Myeloma Leuk* 2018;18:5216.
10. Jaypirca [US Prescribing Information]. Indianapolis, IN: Eli Lilly and Company, 2023.

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