Ongoing Clinical Trials of Noncovalent BTK Inhibitors in CLL/SLL

Trial	Phase	Status*	Population	Design
Pirtobrutinib				
BRUIN CLL-321 NCT 04666038	3	Recruiting	BTK-inhibitor–pretreated CLL/SLL	Pirtobrutinib vs investigator's choice of idelalisib + rituximab or bendamustine + rituximab
BRUIN CLL-322 NCT 04965493	3	Recruiting	Previously treated CLL/SLL	Pirtobrutinib + venetoclax + rituximab vs venetoclax + rituximab
BRUIN CLL-313 NCT 05023980	3	Recruiting	Treatment-naïve CLL/SLL	Pirtobrutinib vs bendamustine + rituximab
BRUIN CLL-3214 NCT 05250743	3	Recruiting	Previously treated or treatment-naïve CLL/SLL; excludes patients with prior exposure to a BTK inhibitor	Pirtobrutinib vs ibrutinib
Nemtabrutinib				
NCT 04728893	2	Recruiting	Hematologic malignancies including CLL/SLL	Nemtabrutinib
BELLWAVE -008 NCT 05624554	3	Recruiting	Previously untreated CLL/SLL without *TP53* aberrations	Nemtabrutinib vs investigator's choice of fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab

*As of February 2023.

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Woyach J, Flinn IW, Awan FT, et al. Efficacy and safety of nemtabrutinib, a wild-type and C481S-mutated Bruton tyrosine kinase inhibitor for B-cell malignancies: updated analysis of the open-label phase 1/2 dose-expansion Bellwave-001 Study. *Blood*. 2022;140(suppl 1):7004-7006.

Woyach JA, Flinn IW, Awan FT, et al. Efficacy and safety of nemtabrutinib, a wild-type and C481S-mutated Bruton tyrosine kinase inhibitor for B-cell malignancies: updated analysis of the open-label phase 1/2 dose-expansion Bellwave-001 Study. Abstract presented at: Annual Meeting of the American Society of Hematology; December 10-13, 2022; New Orleans, LA. Abstract 3114. https://ash.confex.com/ash/2022/webprogram/Paper163596.html

AXIS Medical Education

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The Emerging Landscape of BTK Inhibitors for Relapsed/Refractory CLL/SLL

A PATIENT/CLINICIAN DECISION SUPPORT AIDE

What Is Shared Decision-Making?

Shared decision-making (SDM) occurs when a healthcare provider and a patient work together to make a healthcare decision that is best for the patient. Optimal decision-making takes into account evidence-based information about available options; the provider's knowledge and experience; and the patient's values, goals, and preferences. Patients and their families/caregivers who are engaged in an SDM process are more likely to arrive at a treatment decision that works best for all those involved.

The AXIS 6 Ease ("Es") to SDM

ENSURE

Ensure you see and treat the patient as an individual not a disease.

ELEVATE

Elevate the patient-centric experience and improve satisfaction with care.

ENABLE

Enable a long-term personal connection with your patients.

ESTABLISH

Establish co created treatment plans that align medical evidence with patient preferences to foster adherence and optimize outcomes.

ELICIT

Elicit patient/caregiver preferences, values, and goals for therapy.

EVALUATE

Evaluate the risk/benefits and costs of treatment so that they are aligned with patient expectations.

Treatment Selection, Sequencing, and Oral Therapy Adherence

Selection of the appropriate BTK inhibitor is multifactorial and depends on:

- Side-effect profile
- Concomitant medications
- Cost
- Desired outcomes of therapy
- Patient comorbidities
- Potential drug-drug interactions
- Ease of administration
- Treatment sequencing after BTK inhibitor resistance/intolerance

Mechanism of Action and Differentiation Points: Covalent vs Noncovalent Bruton's Tyrosine Kinase (BTK) Inhibitors

	Covalent BTK Inhibitors	Noncovalent BTK Inhibitors
BTK inhibitor	Ibrutinib, Acalabrutinib, Zanubrutinib	Pirtobrutinib, Nemtabrutinib
Binding to BTK	Irreversible	Reversible
Requires cysteine for binding	Yes, covalently bound to cysteine 481 amino acid (C481)	No, does not require C481 to bind to the kinase domain
Causes of resistance	*C481* mutation *PLCγ2* mutation	BTK inhibition regardless of BTK mutation; preserve activity in the presence of a C481 acquired resistance mutation
Notable differences	• Require wild-type (WT) BTK for activity • Long-term efficacy can be limited by acquired resistance	• Potent against both WT and *C481*-mutant BTK • Highly selective for BTK: minimal activity against non-BTK kinases, greater than 300-fold selectivity for BTK vs 363 of 370 other kinases, reducing the potential for off-target toxicities • Longer half-life and increased BTK occupancy compared to covalent BTK inhibitors • Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover • Sustained BTK inhibition throughout the dosing interval

What Strategies Can We Use Against BTK Inhibitor Resistance in CLL?

Supported by Current Evidence	Limited Evidence	Not Appropriate
Venetoclax: Efficacious, but complicated administration and not appropriate for all patients **Noncovalent BTK inhibitors:** Initial evidence suggests potent efficacy against resistance mutations and in the setting of progressive disease	**PI3K inhibitors**: Limited benefit in this population and significant toxicity burden **Chemoimmunotherapy:** Limited benefit in this population, and most current patients have already received these regimens	**Covalent BTK inhibitor retreatment:** Only effective in the context of covalent BTK intolerance, not progression

Safety Profiles of Noncovalent BTK Inhibitors

	Pirtobrutinib	Nemtabrutinib
Common TRAEs	• Fatigue • Diarrhea • Neutropenia • Contusion	• Dysgeusia • Nausea • Hypertension • Diarrhea • Decreased platelet count • Fatigue • Decreased neutrophil count
TRAEs of special interest	• Bruising • Rash • Arthralgia • Hemorrhage • Hypertension • Atrial fibrillation/flutter	• Atrial fibrillation

TRAEs, treatment-related adverse events.

Key Efficacy Data of Non covalent BTK Inhibitors

	Pirtobrutinib	Nemtabrutinib
Trial	BRUIN	BELLWAVE-001
Design	Phase 1 escalation + expansion Phase 2 (200 mg QD)	Phase 1 escalation + expansion Phase 2 (65 mg QD)
Patient population	BTK-pretreated CLL/SLL Prior BTKi: n=247 Prior BTKi and BCL2i: n=100	R/R CLL/SLL with ≥2 prior therapies, including covalent BTKis All CLL/SLL: n=57 Cohort A with *C481* mutation: n=25 Cohort B without *C481* mutation: n=10
Key endpoints	Safety/tolerability MTD & RP2D Efficacy: ORR & DoR	Safety/tolerability RP2D Efficacy: ORR, DoR, PFS
ORR	Prior BTKi: 82% Prior BTK and BCL2i: 79%	Prior BTK and BCL2i: 58% *C481*-mutated BTK: 58% del(17p): 33%
mPFS	Prior BTKi: 19.6 months Prior BTKi and BCL2i: 16.8 months	Prior BTK and BCL2i: 10.1 months *C481*-mutated BTK: 26.3 months del(17p): 10.1 months
Notes	• Overcomes acquired resistance to covalent BTKi • Promising responses in heavily pretreated patients with CLL/SLL, irrespective of – BTK C481 mutation status – Reason for prior BTKi discontinuation – Other classes of previous therapy received	• Responses seen in very heavily pretreated patients and those progressing on prior covalent BTKi • Effective against BTK resistance mutations; demonstrated efficacy in patients with and without *C481* mutation

BTKi, Bruton's tyrosine kinase inhibitor; BCL2i, B-cell lymphoma 2 inhibitor, CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DoR, duration of response; MTD, maximum tolerated dose; mPFS, median progression-free survival; NE, not estimable; ORR, overall response rate; QD, once a day; PFS, progression-free survival; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.