SEQUOIA Clinical Trial Fact Sheet

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Disclaimer: Any information on the products or the CLL disease contained herein is not intended to provide medical advice, and/or treatment guidance. The information within is not intended for promotional purposes.

BRUKINSA is not authorized in all countries for the treatment of CLL; HCPs should consult the approved prescribing information in their respective countries.

The SEQUOIA trial is a global pivotal study designed to evaluate the superiority of BRUKINSA® (zanubrutinib) compared to bendamustine plus rituximab (BR) in patients with treatment-naïve (first-line) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).[1,2]

A slow-growing, life-threatening, and incurable cancer of older adults, CLL is the most common leukemia in adults.[3-6] CLL and SLL are considered different manifestations of the same disease.[7] In the era of chemotherapy-based regimens, patients with del(17p)/TP53mut had the poorest prognosis, followed by patients with del(11q) and unmutated IGHV.[8-12]

THE SEQUOIA TRIAL (NCT03336333)[1,2,13]

Trial Design

- Randomized, multicenter, global Phase 3 trial – Cohort 3: the **largest prospective study of patients with del(17p)**.
- Patient characteristics were balanced between Arms A and B in cohort 1, with more than 50% with unmutated IGHV gene and 18% with del(11q) in each.

The SEQUOIA trial consisted of three cohorts, with a total enrollment of 589 patients to date.

Cohort 1 (n=479)	**Cohort 2*** (n=110)	**Cohort 3** *(enrollment ongoing)*
Patients without the deletion of chromosome 17p131.1 (del[17p])	Patients with del(17p)	Patients with del(17p) or pathogenic TP53 variant
Arm A (n=241): Patients randomized to receive BRUKINSA 160mg twice daily until progressive disease (PD) or unacceptable toxicity. **Arm B (n=238):** Patients randomized to receive BR for a maximum of 6 cycles.	**Arm C (n=110):** Non-randomized, all patients to receive BRUKINSA 160mg twice daily until disease progression, intolerable toxicity or end of study.	**Arm D:** Planned to enroll approximately 80 patients with TN CLL whose tumor exhibits del(17p) or TP53 mutations; patients will receive BRUKINSA treatment at 160 mg twice daily for three months, followed by combination treatment of BRUKINSA at the same dosing and venetoclax with a ramp-up dosing to 400 mg once daily for 12 to 24 cycles until progressive disease, unacceptable toxicity, or confirmed undetectable measurable residual disease (uMRD).

**BR not selected as a treatment due to unfavorable prognosis and poor response in patients with del(17p)[5]*

Primary endpoint:
Progression-free survival (PFS) as assessed by independent review committee (IRC) in Cohort 1 (Arm A vs Arm B)

Key secondary endpoints:
- IRC-assessed PFD in Arm C
- Investigator-assessed PFS
- IRC- and investigator-assessed overall response rate (ORR)
- Overall survival
- Safety

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Trial Results:

BRUKINSA met its primary endpoint, demonstrating a statistically significant improvement in PFS compared to BR; BRUKINSA superiority was demonstrated across most pre-specified patient subgroups, regardless of age, co-morbidities, mutation, or risk status.

Key Efficacy Findings*	**Cohort 1** **PFS** *(24 months)* BRUKINSA: 85.5% (95% CI: 80.1, 89.6) BR: 69.5% (95% CI: 62.4, 75.5) Hazard ratio (HR) of 0.42 (95% CI: 0.27, 0.63), p<0.0001	**Cohort 2** **PFS** 18 months: 88.6% as assessed by investigator[13] 24 months: 88.9% (95% CI: 81.3, 93.6)	**Cohort 3** **ORR** *(12 months, n=36)* 97.2%
Key Safety Findings	• Safety profile was consistent with prior studies and uniform between indications and treatment groups. • In a prespecified comparison, BRUKINSA demonstrated a **lower discontinuation rate** due to adverse events: 8% versus 14% in cohort 1. • In a prespecified comparison, similar rates of atrial fibrillation/flutter (3.3% for BRUKINSA vs 2.6% for BR) and hypertension (14.2% vs 10.6%) were reported. • Tumor lysis syndrome has been infrequently reported with BRUKINSA therapy in CLL, occurring mostly in patients with high tumor burden.		
Most Commonly Reported Grade ≥3 AEs	• Neutropenia (Arm A: 11%; Arm B: 51% Arm C: 15%) • Hypertension (Arm A: 6 % vs Arm B: 5%) • Low platelet count (Arm A: 2% vs Arm B: 7%)		

**Preliminary results of interim analyses; study is still enrolling and results not yet final*

About BRUKINSA:

BRUKINSA is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK) discovered by BeiGene scientists that is currently being evaluated globally in a broad clinical program as a monotherapy and in combination with other therapies to treat various B-cell malignancies. Because new BTK is continuously synthesized, BRUKINSA was specifically designed to deliver targeted and sustained inhibition of the BTK protein by optimizing bioavailability, half-life, and selectivity. With differentiated pharmacokinetics compared to other approved BTK inhibitors, BRUKINSA has been demonstrated to inhibit the proliferation of malignant B cells within a number of disease-relevant tissues.

BRUKINSA is supported by a broad clinical program which includes more than 4,500 subjects in 35 trials across 28 markets. To date, BRUKINSA has received more than 20 approvals covering more than 60 countries and regions, including the United States, China, the EU, Great Britain, Canada, Australia, and additional international markets. Currently, more than 40 additional regulatory submissions are in review around the world.

References:

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*BRUKINSA has been approved in the European Union/European Economic Area, United Kingdom, and Switzerland for the treatment of adults with WM.

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