(S150) UPDATED EFFICACY AND SAFETY DATA FROM AN ONGOING PHASE 1A/B TRIAL OF THE BTK DEGRADER BEXOBRUTIDEG (NX-5948) IN PATIENTS WITH CLL ACROSS LINES OF THERAPY

Topic: 06. Chronic lymphocytic leukemia and related disorders - Clinical

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Background

Although BTK inhibition is a successful treatment for CLL/SLL, the emergence of BTK inhibitor (BTKi) resistance mutations and kinase-independent signaling via the scaffolding function of BTK result in a need for alternative treatments. Bexobrutideg (NX-5948) is a highly selective, orally administered small molecule degrader that causes the removal of wild-type and mutant forms of BTK through ubiquitination by the cereblon E3 ligase complex and subsequent proteasomal degradation.

Aims

We report new and updated efficacy and safety data with bexobrutideg in CLL/SLL from a Phase (Ph) 1a trial and select Ph1b cohorts including patients (pts) with different prior treatment profiles, in pts with relapsed/refractory (R/R) disease as well as pts in earlier lines of therapy (LoT).

Methods

NX-5948-301 (NCT05131022) is a Ph1, first-in-human trial of bexobrutideg in advanced B-cell malignancies. In CLL/SLL, bexobrutideg is being evaluated in R/R pts in the Ph1a dose-escalation part and then in Ph1b dose-expansion cohorts that include heavily pre-treated, earlier-line and treatment-naïve pts. Safety is presented for all pts with CLL/SLL. Efficacy is presented for all Ph1a dose-escalation pts and for selected Ph1b dose-expansion cohorts treated at the recommended Ph2 dose (RP2D) of 600 mg: Cohort 1 (C1; primarily BTKi and BCL2i exposed), C5 (BTKi-exposed and BCL2i-naïve), and C15 (BTKi-naïve, including treatment-naïve pts).

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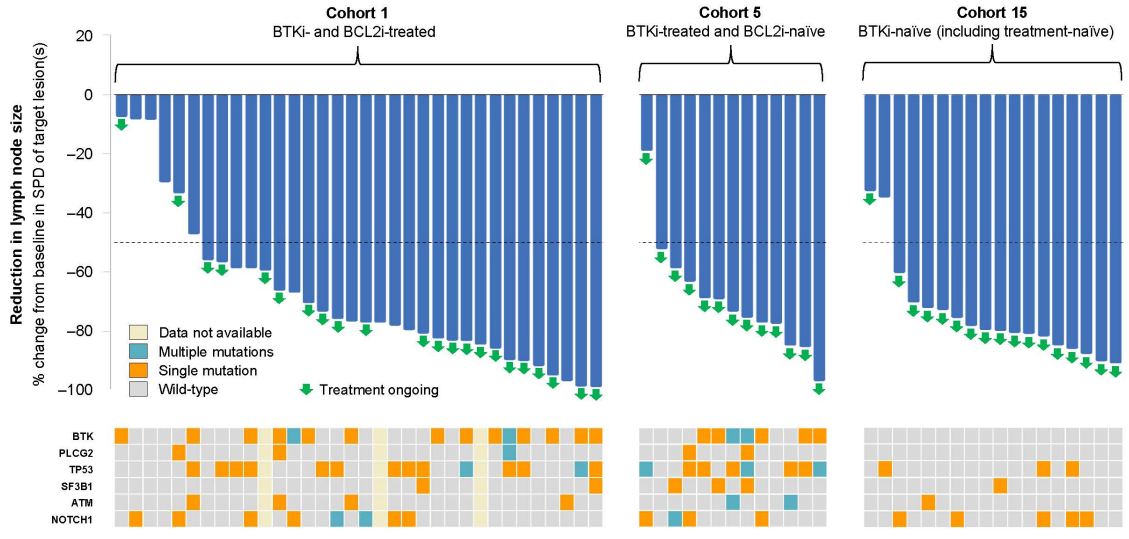
Results

As of 1 Jan 2026, 142 CLL/SLL pts have been enrolled (48 to Ph1a; 42 to Ph1b C1; 19 to Ph1b C5; and 20 to Ph1b C15 with 10 treatment-naive). Ph1a and Ph1b C1 had a median 4 and 5 prior LoT respectively, while Ph1b C5 and Ph1b C15 had a median 2 and 1 prior LoT, respectively.
Bexobrutideg continues to be well tolerated in pts treated across all doses (n=142), including in 86 pts treated at 600 mg. The safety profile in Ph1a and the Ph1b cohorts was maintained over the duration of treatment and across different prior LoT with most adverse events (AEs) being grade 1/2. The most common treatment-emergent AEs included purpura/contusion, neutropenia, and petechiae.
A high objective response rate (ORR) was observed across all cohorts irrespective of prior therapies: Ph1a 83.0% (22.4 months follow-up); Ph1b C1 (BTKi/BCL2i exposed) 83.3% at 600 mg (13.1 months follow-up); Ph1b C5 (BTKi-exposed/BCL2i naïve) 86.7% (5.3 months follow-up); Ph1b C15 (BTKi-naïve including treatment naïve) 84.2% (4.9 months follow-up). The high ORRs in Ph1b C5 and Ph1b C15 are notable, given the short duration of treatment and follow-up; deepening of responses would be anticipated with longer duration of treatment. Lymph node size decreases were observed regardless of prior treatments or mutational burden at baseline (see Figure). Median progression-free survival (mPFS) was 22.1 months in Ph1a (mPFS follow-up 19.8 months).

Summary/Conclusion

In this Ph1a/b trial, bexobrutideg demonstrated a favorable safety profile in pts with CLL/SLL with longer follow-up across doses and prior treatments. Durable responses were maintained in the Ph1a dose-escalation cohort, which has the longest follow-up to date. High response rates were observed across populations with different prior therapies, including in pts previously treated with BTKi and in BTKi-naïve pts, supporting further clinical development. Bexobrutideg is being evaluated in the Ph2 DAYBreak-201 study (NCT07221500) and a Ph3 DAYBreak-306 study investigating bexobrutideg vs pirtobrutinib is planned.

Figure. Lymph node reduction in select cohorts of Ph1b with different ranges of prior treatments and associated mutational burden levels at baseline



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