Robust Bruton’s tyrosine kinase (BTK) degradation with NX-5948, an oral BTK degrader, in a first-in-human phase 1a trial in patients with relapsed/refractory B cell malignancies

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Background

- Bruton’s tyrosine kinase (BTK) is a key component of the B cell receptor signaling pathway; chronic activation of BTK-mediated B cell receptor signaling is a hallmark of many B cell malignancies.
- BTK inhibition has been validated as an effective therapeutic strategy in patients with B cell malignancies; however, emerging patterns of resistance and intolerance limit the utility of covalent and/or non-covalent BTK inhibitors in later lines of treatment.
- Novel therapies that can overcome emerging resistance mutations may represent an alternative treatment option for patients who have developed resistance to BTK inhibitors or in B cell indicators where treatment with BTK inhibitors has been less effective.
- NX-5948 is a novel, orally administered, small molecule that induces BTK degradation via recruitment of the crosstalk E3 ubiquitin ligase complex, without inducing degradation of other crosstalk neo-substrates (Figure 1): – NX-5948 induces sub-nanomolar potency degradation of both wild-type and known mutant forms of BTK in vivo.
- Orally administered NX-5948 results in BTK degradation in circulating and splenic B cells, and exhibits potent tumor growth inhibition in TMD8 xenograft models that contain either wild-type BTK or BTK-resistant mutations.
- NX-5948 can cross the blood-brain barrier and degrade BTK intracranially, translating to preclinical efficacy in mouse brain lymphoma disease models.

Methods

- NX-5948-301 is a first-in-human, dose-escalation (Phase 1a) and cohort-expansion (Phase 1b) study designed to evaluate the safety, tolerability, and preliminary efficacy of NX-5948 in adult patients with relapsed and refractory B cell malignancies (Figure 2): – Phase 1a (dose escalation) will utilize a standard 3+3 dose-escalation design of 3 patients per dose level (starting dose 50 mg qd), in the absence of dose-limiting toxicities (DLTs).
- Phase 1b (dose expansion) will include up to 4 expansion cohorts. The recommended Phase 1b dose will be determined following assessment of pharmacokinetics (PK)/pharmacodynamics (PD), safety, and anti-tumor activity in Phase 1a.
- Eligible tumor types include chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenström macroglobulinemia (WM), including those with secondary central nervous system (CNS) involvement in any disease indication listed or primary CNS lymphoma (PCNSL).
- The primary objectives are to evaluate safety, determine the maximum tolerated dose and/or recommended Phase 1b dose (Phase 1a), and to evaluate the anti-tumor activity of NX-5948 in expansion cohorts (Phase 1b; Figure 3).

Results

- As of December 1, 2022, seven patients have been enrolled in Phase 1a and received NX-5948 at 50 mg (n=4) or 100 mg (n=3).

Table 1. Baseline demographics/disease characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall population (n=7)</th>
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<tbody>
<tr>
<td>Median age, years (range)</td>
<td>59.0 (46.0–79.0)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>7 (100)</td>
</tr>
</tbody>
</table>

Table 2. NX-5948 pharmacokinetics

<table>
<thead>
<tr>
<th>Cycle 1, Day 1</th>
<th>Dose</th>
<th>Cmax (nmol/L)</th>
<th>AUC0-last (μmol*h/L)</th>
<th>Tmax (hours)</th>
<th>C24 (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL</td>
<td>50 mg</td>
<td>2.4 (0.74)</td>
<td>32.1 (15.2)</td>
<td>3.0</td>
<td>12.8 (19.9)</td>
</tr>
<tr>
<td>MCL</td>
<td>1000 mg</td>
<td>12.3 (4.13)</td>
<td>99.6 (50.2)</td>
<td>2.0</td>
<td>12.4 (9.59)</td>
</tr>
</tbody>
</table>

Figure 5. NX-5948 pharmacodynamics

- Preliminary data suggest that NX-5948 exhibits dose-proportional pharmacokinetics (Figure 4; Table 2):
  - The half-life of ~12 hours supports daily dosing.
  - The Tmax of 2–3 hours suggests fast absorption.
  - Exposure (both AUC and C24) increase with dose.
- NX-5948 resulted in rapid, robust and sustained BTK degradation in all patients dosed, regardless of their absolute BTK starting level, tumor type, or dose level of NX-5948 (Figure 5).

Figure 3. Key study objectives and endpoints

- Primary objectives:
  - Evaluate safety and tolerability
  - Evaluate MTDR and/or recommended Ph1b dose
  - Evaluate anti-tumor activity

- Secondary objectives:
  - Characterization of PK and PD
  - Characterize preliminary anti-tumor activity

- Exploratory objectives:
  - OS, disease control, BTK inhibition, PK/PD, mechanism of response/resistance, impact on cognitive function

Summary/conclusion

- Preliminary findings suggest that NX-5948 exhibits dose-proportional pharmacokinetics.
- Exposure to NX-5948 results in rapid, robust and sustained BTK degradation, supporting daily dosing.
- Additional indications, including CLL, and additional dosing levels are currently being explored. Potential dose-expansion cohorts are expected to open in the second half of 2023.
- The study continues to enroll patients and further data will be shared at an upcoming meeting.

References/acknowledgements


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