A First-in-Human Phase 1 Trial of NX-5948, an Oral BTK Degrader, in Patients with Relapsed and Refractory B-Cell Malignancies

Kim Linton, Graham P. Cofrans, Dimaw El-Sharkawi, Rogier Mora, Francesco Forconi, May Tan, Strimand Nandakumar, Erinn Mendenh, Katherine L. Jameson, Sarah G. Injak, and Janette Doorly

1. The University of Manchester, Manchester, UK; 2. Cellerix University Hospitals NHS Trust, Dubai, UAE; 3. Royal Marsden NHS Foundation Trust, Sutton, UK; 4. NCI-UICC LiverCancer Center, University Medical Center Utrecht, The Netherlands; 5. University Hospital Southampton NHS Trust, Southampton, UK; 6. Nurix Therapeutics, Inc., San Francisco, CA, USA.

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 inhibitors have been shown to be safe and effective in a variety of B-cell lymphomas.1
• Mutations in the BTK protein that prevent inhibitors from binding can cause resistance to approved BTK inhibitors.2
• BTK degradation may offer an alternative method of interrupting B-cell receptor signaling and overcoming such resistance.
• Chimeric targeting molecules catalyze ubiquitination and proteasomal degradation of target proteins and are comprised of a ubiquitin ligase-binding element (“harness”), a linker, and a target-binding element (“hook”).3 NX-5948 is a target protein degrader that contains a BTK hook linked to a cereblon binding domain.
• Some CRBN-binding drugs, such as lenalidomide and pomalidomide, possess activity against many B-cell malignancies; however, they are not efficacious in all cases.
• Additionally, NX-5948 penetrates the central nervous system (CNS) and has demonstrated activity in a model of brain malignancies, supporting research in B-cell malignancies, including CNS lymphomas.

NX-5948: Mechanism of action

- Two-part, first-in-human Phase 1a trial of NX-5948 in relapsed or refractory tumors
- Dose level 1: 5 mg twice daily (BID) for 7 days
- Dose level 2: 28 mg BID for 7 days
- Dose level 3: 50 mg BID for 7 days
- Dose level 4: 100 mg BID for 7 days
- Dose level 5: 200 mg BID for 7 days

Key eligibility criteria

- Abbreviated inclusion criteria
  - Phase 1a and Phase 1b
    - Age ≥ 18 years
    - Histological diagnosis confirmed
    - Radiologically, measurable disease per response criteria specific to the malignancy
    - Evaluateable disease is allowed
    - ECOG performance status of 0 or 1
    - Prior CAR-T therapy is allowed within 100 days (Phase 1a) or 30 days (Phase 1b) of study start
    - Prior treatment within 30 days of study start
    - Chemotherapy within 4 weeks
    - Monoclonal antibody within 4 weeks
    - Radiotherapy within 2 weeks
    - Surgery within 2 weeks
    - Prior CAR-T therapy is allowed within 100 days (Phase 1a) and must have evidence of B-cell recovery
    - Systemic steroids within 14 days (20 mg/day prednisone or equivalent is allowed; 40 mg/day is not allowed)

Study objectives and endpoints

- Phase 1a objectives
  - Characterize PK profile
  - Evaluate MTD and RP2D
  - Changes from baseline in safety parameters
  - Changes from baseline in safety parameters

- Phase 1b objectives
  - Characterize PK profile
  - Further characterize PD profile

- Endpoints
  - Incidence of TEAEs
  - Incidence of all deaths
  - Change from baseline in safety parameters
  - Change from baseline in safety parameters

Target population

- Phase 1a dose escalation
  - Adult patients with histologically confirmed relapsed/refractory B-cell malignancies
  - Patients required to have any of the following: CLL, SLL, DLBCL, FL, MCL, or WM
  - Patients require regular (≥ 2) or prior therapy (≤ 1) for patients with WM, and for whom no other therapies are known to provide clinical benefit

- Phase 1b cohort expansion
  - Adult patients with histologically documented relapsed/refractory B-cell malignancies
  - Must meet criteria for phase 1a treatment
  - Patients must have received and received at least 2 prior systemic therapies (≥ 1 therapy for patients with WM) and for whom no other therapies are known to provide clinical benefit

- CLL/SLL without BTKi or DORi
  - Patients who have stopped BTKi due to side effects must have subsequent progression

- DLBCL or MCL cohort
  - Patients with disease progression on an existing BTKi and an anti-CD20 mAb-based regimen, including Richter-transformed DLBCL, high-grade B-cell lymphomas, and B-cell malignancies

- FL, MCL, or WM cohort
  - Patients with disease progression on an existing BTKi or an anti-CD20 mAb-based regimen

Reference