A First-in-Human Phase 1 Trial of NX-1607, a First-in-Class Oral CBL-B Inhibitor, in Patients with Advanced Malignancies Including Diffuse Large B-Cell Lymphoma

Poster #3093

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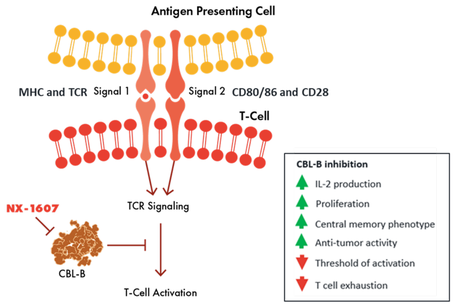
Background

- Effective treatment for recurrent DLBCL is a high unmet medical need despite the advances of novel modalities such as cell- and immune-mediated therapies.
- T-cell dysfunction and emerging resistance to T-cell-mediated therapies such as CAR-T and T-cell engagers suggest a potential role for novel therapies that can both enhance T-cell function to overcome a suppressive TME and prevent tumor escape associated with low tumor antigen expression.
- CBL-B is an E3 ubiquitin ligase expressed in immune cells that regulates T-cell activation. CBL-B inhibition reduces T-cell exhaustion and increases cytokine production upon TCR stimulation, overcoming suppressive TME signals.[1–3] Furthermore, lack of CBL-B allows T-cell activation despite low target antigen expression on tumor cells,[4] potentially reversing the tumor escape mechanism of resistance.
- NX-1607 is an oral small-molecule inhibitor of CBL-B that enhances innate and adaptive immune responses (Figure 1):
  - NX-1607 has demonstrated anti-tumor activity and long-term survival in murine models as a single agent and in combination with PD-1 antibodies.[2,5]
  - Furthermore, NX-1607 elicits dose-dependent increases in cytokine secretion and proliferation in TCR-stimulated primary human T cells with enhanced tumor antigen-specific T-cell and NK-cell anti-tumor responses.[2,5]
  - NX-1607 may, as a single agent, enhance the efficacy of endogenous T-cell- and NK-cell-mediated anti-tumor activity, thus supplementing and rescuing CAR-T or NK cell therapies in patients with hematologic malignancies that have developed resistance.

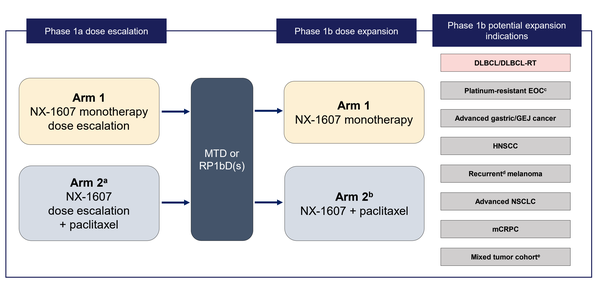
Figure 1. NX-1607: Proposed mechanism of action



Methods

- NX-1607-101 is a first-in-human, multicenter, open-label, Phase 1a/1b dose-escalation/expansion trial evaluating the safety, tolerability, PK/PD, and preliminary anti-tumor activity of NX-1607 in patients with advanced malignancies, including DLBCL (Figure 2).

Figure 2. Study design (ClinicalTrials.gov NCT05107674)



[a]Starting dose for NX-1607 in Arm 2 will be ≥1 dose level below the highest previously cleared monotherapy dose level and dosing regimen. [b]Combination indications for Arm 2 may include platinum-resistant EOC, gastric cancer, HNSCC, NSCLC, TNBC, urothelial cancer, cervical cancer. [c]Including primary peritoneal and fallopian tube carcinoma. [d]Includes metastatic or unresectable disease. [e]Includes MPM, TNBC, locally advanced/metastatic urothelial cancer, cervical cancer, MSS CRC- or DLBCL/DLBCL-RT.

Phase 1a accelerated and 3+3 dose-escalation design

Arm 1 NX-1607 monotherapy

- Modified Fibonacci dose-escalation design of 1 patient per NX-1607 dose level until first observation of grade ≥2 AE starting with Dose Level 1 (5 mg QD).
- Following occurrence of grade ≥2 AE during Cycle 1 with no clear alternative explanation for causality, escalation will change to a 3+3 dose escalation.

Phase 1a dose-escalation

Primary Objectives
- Safety and tolerability
- MTD and/or RP1bD

Primary Endpoints
- TEAEs, including grade ≥3 TEAEs, SAEs, discontinuations, deaths due to TEAEs, irAEs
- Deaths
- DLTs

Secondary Objectives
- PK/PD of NX-1607
- Preliminary anti-tumor activity
- Tumor markers of response

Secondary Endpoints
- NX-1607 PK parameters in plasma
- Changes in biomarkers in circulating immune cells
- ORR

Possible Phase 1b dose-expansion

Primary Objective: Antitumor activity at the RP1bD(s)

Primary Endpoint: ORR

Secondary Objectives
- Safety and tolerability
- Preliminary anti-tumor activity
- PK/PD of NX-1607

Secondary Endpoints
- TEAEs; irAEs; deaths
- Changes from baseline in safety parameters
- DOR, DCR, PFS, OS, TTP
- NX-1607 PK parameters in plasma
- Changes in biomarkers in the blood and within tumor tissue
- Changes in tumor tissue biopsies of immune cell infiltration or other histological features

Phase 1a/1b exploratory

Exploratory Objectives
- Biomarkers of CBL-B inhibition and mechanisms of response/resistance:
  - Changes in immune profiles in circulation post-exposure
  - Characterizing systemic immune signatures
  - Gene expression & mutation analysis
  - NX-1607 metabolites

Exploratory Endpoints
- CBL-B signaling pathway analysis:
  - Changes in biomarkers in the blood and within tumor tissue
  - Changes in circulating blood tumor-specific biomarkers (e.g., CEA)

Patient cohorts and inclusion criteria

General

Inclusion criteria
- Age ≥18 years
- Measurable metastatic or unresectable disease
- Received or not candidates for standard treatment options
- ECOG performance status 0 or 1
- Phase 1b only: accessible tumor or lymph node (DLBCL only) for biopsy

Exclusion criteria
- Active untreated brain metastases
- Treatment with CPI within 3 weeks
- Prior radiotherapy within 2 weeks
- CAR-T therapy within 30 days
- Stem cell transplant within 100 days
- History of uveitis
- Inability to swallow capsules
- Major surgery planned within 4 weeks

Denotes hematology-oncology indication

[a]Clearly demarcated lesions/nodes with long axis >1.5 cm and short axis >1.0 cm or 1 clearly demarcated lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm AND baseline FDG PET scans must demonstrate positive lesion compatible with CT (or MRI) defined anatomical tumor sites

Indication-specific

HNSCC • Previously received a PD-1 or PD-L1 inhibitor in advanced setting if eligible	**MPM** • ≥1 prior therapy including platinum-based chemotherapy or CPI
EOC • Platinum-resistant but documented disease progression within 6 months • Platinum-refractory provided refractory in second line or later	**Urothelial cancer** • Previously received a PD-1 or PD-L1 inhibitor and/or platinum chemotherapy • CA-125 ≥2 x ULN
DLBCL/DLBCL-RT • DLBCL-RT: ≥ 1 lines standard therapy; must have responded to treatment • Non-RT DLBCL: ≥2 lines standard therapy • ≥1 measurable site and ≥ 2 lesions[a] • No progressive multifocal leukoencephalopathy	**MSS CRC** • ≥2 prior lines including irinotecan, fluoropyrimidine, and/or oxaliplatin • Prior EGFR inhibitor if known *Ras* wild type
mCRPC • ≥2 prior lines in advanced setting including androgen receptor-directed therapy and taxane-based chemotherapy • Radiographic progression by bone scan	**Melanoma** • Prior CPI if tumors express PD-L1 • Prior BRAF inhibitor if tumor is *BRAF* mutation positive
Cervical cancer • ≥1 prior lines including platinum-based chemotherapy • Prior CPI if tumor expresses PD-L1	**TNBC** • ≥2 prior lines for metastatic disease • Including PARP inhibitor for gBRCAm, HER2-TNBC
NSCLC • Prior therapy as applicable including anti-PD-1 or PD-L1	**Gastric or GEJ adenocarcinoma** • ≥2 prior lines including platinum- and fluoropyrimidine-containing chemotherapy and HER2-targeted therapy if appropriate

Sample size and statistics

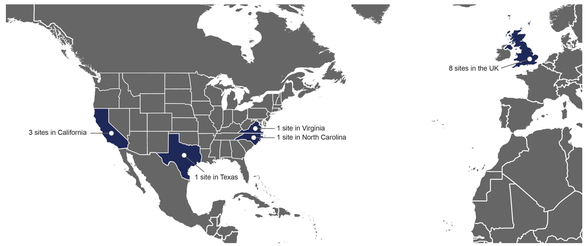
- Up to 303 patients will be enrolled at approximately 20 sites in the United States and United Kingdom and treated until disease progression or unacceptable toxicity.
  - Phase 1a dose escalation:
    - Up to 109 evaluable patients in monotherapy dose-escalation stage, dependent on number of dose levels investigated.
  - Phase 1b dose expansion:
    - Up to 194 patients in the monotherapy dose-expansion phase.

Biomarker analyses

- Biomarkers of CBL-B signaling pathway and target engagement may include:
  - Evaluation of immune cell infiltration into tumor.
  - Assessment of immune profiles in circulation following exposure.
  - Characterization of systemic immune signatures.
  - Analysis of gene expression & mutational landscape.

Current status

- Dose escalation is ongoing at 14 locations in the United States and United Kingdom.



References

1. Gosling J, et al. Cancer Res 2019;79(13Suppl):2696.
2. Rountree R, et al. Cancer Res 2021;81(13Suppl):1595.
3. Galotta M, et al. J Immunother Cancer 2022;10(Suppl 2):A348.
4. Stromnes IM, et al. J Clin Invest 2010;120;3722–34.
5. Nurix Therapeutics. Inhibitors of the E3 ubiquitin ligase CBL-B promote potent T and NK cell mediated anti-tumor response. 17th Annual Drug Discovery Chemistry, Apr 19, 2022. San Diego, CA, USA.
6. Fourie Zirkelbach J, et al. J Clin Oncol 2022;40:3489−500.

Abbreviations

AE, adverse event; **BID**, twice daily; **CAR-T**, chimeric antigen receptor T-cell; **CBL-B**, Casitas B-lineage lymphoma B; **CD**, cluster of differentiation; **CPI**, checkpoint inhibitor; **DCR**, disease control rate; **DLBCL**, diffuse large B-cell lymphoma; **DLBCL-RT**, diffuse large B-cell lymphoma with Richter transformation; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **EOC**, epithelial ovarian cancer; **HNSCC**, head and neck squamous cell carcinoma; **IL-2**, interleukin-2; **irAE**, immune-related adverse event; **mCRPC**, metastatic castrate-resistant prostate cancer; **MHC**, major histocompatibility complex; **MPM**, malignant pleural mesothelioma; **MSS CRC**, microsatellite stable colorectal cancer; **MTD**, maximum tolerated dose; **NSCLC**, non-small-cell lung cancer; **ORR**, objective response rate; **OS**, overall survival; **PD**, pharmacodynamics; **PD-1**, programmed cell death protein-1; **PK**, pharmacokinetics; **QD**, once daily; **RP1bD**, recommended Phase 1b dose; **TCR**, T-cell receptor; **TEAE**, treatment-emergent adverse event; **TME**, tumor microenvironment; **TNBC**, triple-negative breast cancer

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For information about this clinical trial please follow the QR code

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