A First-in-Human Phase 1 Trial of NX-1607, a First-in-Class Oral CBL-B Inhibitor, in Patients with Advanced Solid Tumors

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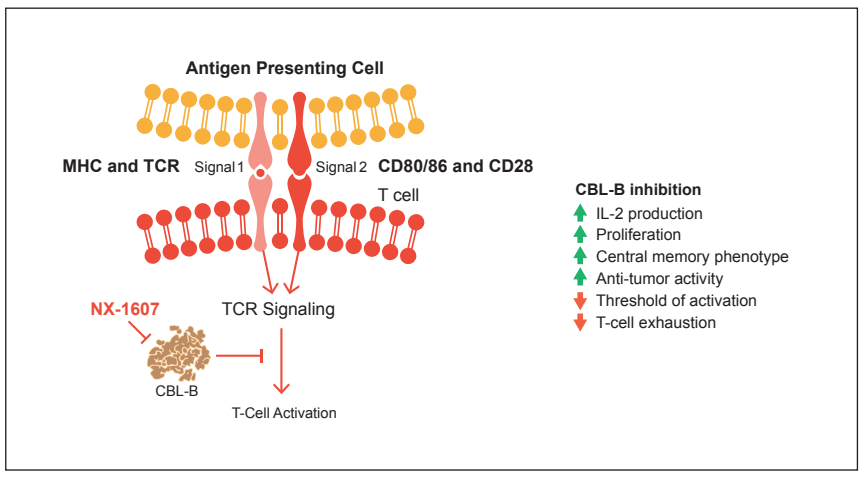
Background

- The proto-oncogene CBL-B encodes an E3 ubiquitin ligase expressed in immune cell lineages, that regulates T-cell activation. It imposes the requirement for co-stimulation to mount a productive immune response upon T-cell receptor engagement.
- CBL-B-deficient mice demonstrate enhanced signal-dependent T-cell activation and robust T-cell dependent anti-tumor activity.[1,2] In addition, CD4+ T-cells deficient in CBL-B demonstrate resistance to inhibition by regulatory T-cells.[3]
- Inhibiting CBL-B with a small molecule is expected to enhance T-cell response, increase response to sub-optimal priming, and restore response in exhausted T-cells. Thus, CBL-B is a promising immune-oncology target and may overcome challenges seen with other T-cell–directed therapies.
- NX-1607 is an oral small-molecule inhibitor of CBL-B that has demonstrated anti-tumor activity and long-term survival in murine models as both a single agent and in combination with PD-1 antibodies.[4,5] Further, NX-1607 elicits dose-dependent increases in cytokine secretion and proliferation in T-cell receptor-stimulated primary human T-cells with enhanced tumor antigen-specific T-cell and NK cell anti-tumor responses.[4,5] Thus, NX-1607 may be effective as a single agent or it may significantly enhance efficacy of other anti-tumor agents.

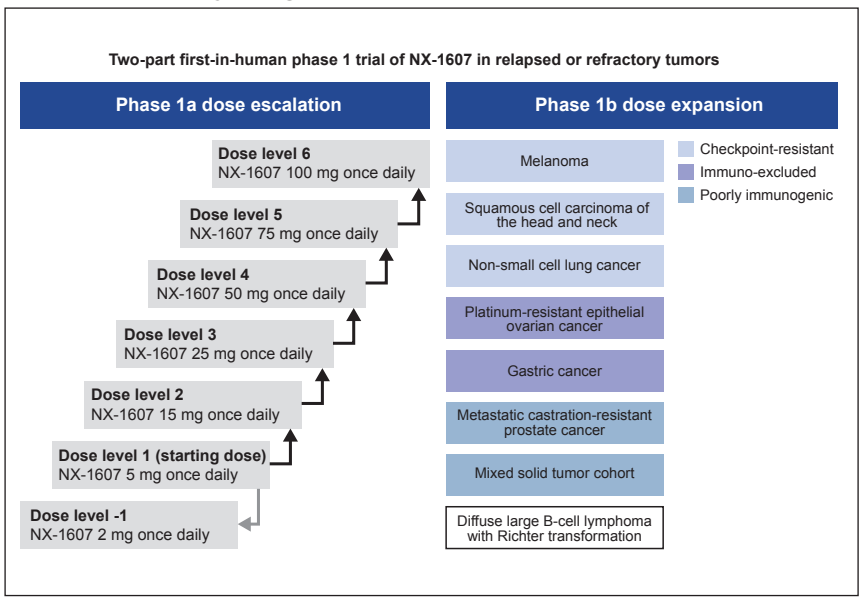
NX-1607: Proposed mechanism of action



Methods

- NX-1607-101 is a first-in-human, two-part, multicenter, open-label, Phase 1 trial evaluating NX-1607 in patients with tumors that are checkpoint inhibitor-resistant, immune-excluded, or are poorly immunogenic:
  - Phase 1a (dose escalation) will proceed using an accelerated modified Fibonacci dose escalation design that transitions to a standard 3 + 3 design based on protocol-specific criteria.
  - Phase 1b (dose expansion) will use a Simon 2-stage design and include up to 8 expansion cohorts.
- NX-1607 will be given orally once daily at doses ranging from 5 to 100 mg during Phase 1a, and at the recommended Phase 1b dose during Phase 1b.
- Eligible tumor types include platinum-resistant EOC, gastric cancer, HNSCC, metastatic melanoma, NSCLC, mCRPC, MPM, TNBC, locally advanced or metastatic urothelial cancer, cervical cancer, MSS CRC, and DLBCL-RT.
- The main objectives are to establish the safety and tolerability of NX-1607, characterize PD/PK, and determine the recommended Phase 1b dose.

NX-1607-101: Study design



Key eligibility criteria

Overview of inclusion criteria

Phase 1a and Phase 1b

- Age ≥18 years
- Histological or cytological evidence of malignancy
- Measurable disease per disease-specific response criteria
- Metastatic or unresectable disease, and received or are not candidates for standard treatment options
- ECOG performance status of 0 or 1
- Prior treatment with immune checkpoint inhibitors or CAR-T cells with washout is permitted
- Minimum of 3 weeks or 5 half-lives since last dose of systemic cancer therapy (unless otherwise specified) or minimum of 2 weeks since last radiotherapy, or minimum of 6 weeks since last systemic therapy with nitrosoureas, antibody-drug conjugate, or radio-immuno-conjugate therapy.
- Adequate organ/bone marrow function, as defined per protocol laboratory parameters

Phase 1a only

- Advanced or refractory solid tumors in phase 1a target indication(s) with protocol-specified prior lines of therapy

Phase 1b only

- Advanced or refractory malignancy, per the intended expansion cohort (i.e., phase 1b target indications)
- Accessible tumor for biopsy and must consent to on-study biopsies

Study objectives and endpoints

Phase	Objectives	Endpoints
Primary (1a)	• **Evaluate safety and tolerability** • **Evaluate MTD and/or RP1bD**	• **Incidence of TEAEs** • **Incidence of irAEs** • **Incidence of all deaths** • **Changes from baseline in safety parameters** • **Incidence of DLTs**
Secondary (1a)	• Characterize PK profile • Characterize PD profile • Characterize PK/PD relationship • Assess preliminary anti-tumor activity	• NX-1607 PK parameters in plasma • Changes from baseline in proximal biomarkers in circulating immune cells • ORR per RECIST v1.1, or mRECIST for MPM, or PCWG3 for mCRPC • DOR, DCR, PFS, OS
Primary (1b)	• **Evaluate anti-tumor activity of NX-1607 at the RP1bD in expansion cohorts**	• **ORR per RECIST v1.1, or mRECIST for MPM, or PCWG3 for mCRPC**
Secondary (1b)	• Evaluate safety and tolerability • Further evaluate preliminary anti-tumor activity • Further characterize PK profile • Further characterize PD profile • Further characterize PK/PD relationship	• Incidence of TEAEs • Incidence of irAEs • Incidence of all deaths • Changes from baseline in safety parameters • DOR, DCR, PFS, OS, time to progression • mCRPC cohort only: rPFS, time to radiographic progression, time to PSA progression, time to skeletal event • NX-1607 PK parameters in plasma • Changes from baseline in proximal biomarkers in circulating immune cells • Changes from baseline in distal biomarkers in the tumor micro-environment
Exploratory (1a, 1b)	• Explore biomarkers of CBL-B inhibition and various mechanisms of response/ resistance	• CBL-B signaling pathway analysis which may include, but is not limited to, plasma cytokine levels, immunophenotyping, and gene expression changes, and mutation analysis

Evaluations

- **Efficacy**
  - A secondary objective in Phase 1a, and primary objective in Phase 1b, is to make a preliminary assessment of the efficacy of NX-1607 (i.e., anti-tumor activity of NX-1607).
  - Tumor response will be assessed based on RECIST v1.1, modified RECIST for MPM, PCWG3 for mCRPC, or Revised Response Criteria for Malignant Lymphoma for DLBCL-RT.
  - Disease assessments will be performed at Screening, every 9 weeks (±7 days) (i.e., every 3 cycles) for patients who remain on treatment through Week 27 (end of Cycle 9) and every 12 weeks (±7 days) (i.e., every 4 cycles) thereafter and at time of clinical suspicion of disease progression.
- **Safety**
  - Safety will be determined from evaluation of DLTs, AEs, clinical laboratory assessments, vital signs assessments, physical examinations, and electrocardiograms.
  - At the occurrence of a significant safety event (e.g., DLT, study drug-related serious AEs, or study drug-related Grade 3 or greater AEs), PD and PK blood samples should be collected when possible.
  - Clinical examinations, including vital signs, will be performed at Screening and at every clinic visit before administration of NX-1607.
  - All patients will be evaluable for safety.

Sample size and statistics

Phase 1a dose escalation

- 6–60 evaluable patients, dependent on the number of dose levels investigated.

Phase 1b dose expansion

- Up to approximately 276 evaluable patients in up to 8 expansion cohorts:
  - **Stage 1:** 112 evaluable patients in first 6 cohorts (metastatic melanoma, platinum-resistant EOC, gastric cancer, HNSCC, NSCLC, mCRPC). Up to an additional 108 evaluable patients if all cohorts continue to Stage 2.
  - **Mixed solid tumor cohort:** 40 evaluable patients. Tumors include MPM, TNBC, urothelial cancer, cervical cancer, or MSS CRC.
  - **DLBCL-RT cohort:** 16 evaluable patients.

Current status

- Up to 336 patients will be enrolled at approximately 20 sites in the UK and US and treated until disease progression or unacceptable toxicity.
- Dose escalation is ongoing.
- Clinical trial information: NCT05107674.
- Study contact: nx1607101@nurixtx.com

Abbreviations

AEs, adverse events
CAR-T, Chimeric Antigen Receptor T-cell
CBL-B, Casitas B-lineage lymphoma B
CD, cluster of differentiation
DCR, disease control rate
DLBCL-RT, diffuse large B-cell lymphoma with Richter transformation
DLTs, dose-limiting toxicities
DOR, duration of response
ECOG, Eastern Cooperative Oncology Group
EOC, epithelial ovarian cancer
HNSCC, head and neck squamous cell carcinoma
IL-2, interleukin-2
irAEs, immune-related adverse events
mCRPC, metastatic castration-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
PCWG3, Prostate Cancer Working Group 3
PD, pharmacodynamics
PD-1, programmed cell death protein-1
(r)PFS, (radiographic) progression-free survival
PK, pharmacokinetics
PSA, prostate-specific antigen
(m)RECIST, (modified) Response Evaluation Criteria in Solid Tumours
RP1bD, recommended phase 1b dose
TCR, T-cell receptor
TEAEs, treatment-emergent adverse events
TNBC, triple-negative breast cancer

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