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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Study objectives and endpoints

Phase 1a: Objectives and Endpoints

Primary (1a) • Evaluate safety and tolerability Evaluate mT0 and mFU1P10 • Incidence of TEAEs • Incidence of infusion-related reactions • Changes from baseline in safety parameters • Incidence of AEs

Secondary (1a) • Characteristic PK profile • Characteristic PD profile • Characteristic T-cell response relationship • Assess preliminary anti-tumor activity • mCRPC cohort only: rPFS, time to radiographic progression, mRECIST, for MPM, PCWG3 for mCRPC • ORR per RECIST v1.1, or mRECIST for MPM, or PCWG3 for mCRPC

Phase 1b: Objectives and Endpoints

Primary (1b) • Evaluate antitumor activity of NX-1607 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 TCRP/RP0 relationship • rPFS, time to radiographic progression, mRECIST, for MPM, PCWG3 for mCRPC

Expansory (1a,b) • Explore biomarkers of CBL-B inhibition and various mechanisms of resolution of safety response • CBL-B signaling pathway analysis which may include, but is not limited to, plasma cytokines levels, immunophenotyping, and gene expression changes, and mutation analysis

Background

The proto-oncogene CBL-B encodes an E3 ubiquitin ligase expressed in immune cell lineages, that regulates NF-κB cell activation. It suppresses NF-κB cell activation. It promotes the requirement for complementation to produce a productive immune response upon T-cell receptor engagement.

The CBL-B-deficient cell line demonstrates enhanced signal-dependent T-cell activation and robust T-cell expansion. 4 In addition, CBL-B-deficient cell line demonstrates CBL-B-mediated cell expansion by inhibition by regulatory T-cols. 5

Inhibiting CBL-B with a small molecule is expected to enhance T-cell responses, increase responses to suboptimal priming, and restore responses in exhausted T-cells. Thus, CBL-B is a promising immunity-targeting and may overcome challenges seen with T-cell derived therapies.

Nexin-1607 is a new small-molecule inhibitor of CBL-B that has demonstrated anti-tumor activity and long-term survival in preclinical models as both a single agent and in combination with PD-1 antibodies. 6 Further, Nexin-1607 elicits dose-dependent increases in cytokine secretion and proliferation in tumor-immune-eliminated primary human T-cells with enhanced tumor antigen-specific T-cell and NK-cell anti-tumor responses. 7,8 Thus, Nexin-1607 may be effective as a single agent or it may significantly enhance efficacy of other anti-tumor agents.

Methods

NX-1607-101 is a first-in-human, two-part, multicenter, open-label, Phase 1 trial evaluating Nexin-1607 in patients with tumors that are checkpoint inhibitor-resistant, immune-escaped, and are poorly immunogenic.

Phase 1a: dose escalation

– Phase 1a (dose escalation) will proceed using an accelerated modified Fibonacci dose escalation design with a 0.7 to 3.0-fold dose gap design based on preclinical data.
– Phase 1b (dose expansion) will use a Simon 2-stage design and include up to 8 expansion cohorts.

Phase 1b: dose expansion

– Nexin-1607 will be given orally once daily at doses ranging from 5 to 150 mg during Phase 1a, and at the recommended Phase 1b dose during Phase 1b.
– Eligible tumor types include platinum-resistant GC, gastric cancer; HNSCC, metastatic melanoma, NSCLC, mCRPC, MPM, TH50. Finally advanced or metastatic uveal melanocarcinoma, cervical cancer, MMS CRC, and DLBCL-RT.

The main objectives are to establish the safety and tolerability of Nexin-1607, characterize PK/PD, and determine the recommended Phase 1b dose.

Key eligibility criteria

Overview of inclusion criteria

Phase 1a and Phase 1b

– ≥18 years
– No previous or current diagnosis of malignancy
– No evidence of active infection
– No clinically significant or unstable cardiac disease or condition
– No history of any condition that may affect study participation
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Phase 1a only

– Advanced or refractory solid tumors in phase 1a target indications (at least one phase 1a target indication) is required
– Accessible tumor for biopsy and residual tumor to be evaluable

Phase 1b only

– Advanced or refractory malignancy, or the intended expansion cohort (i.e., phase 1b target indications)
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A first-in-class oral CBL-B inhibitor, NX-1607, is an oral small-molecule inhibitor of CBL-B that has demonstrated anti-tumor activity and long-term survival in preclinical models as both a single agent and in combination with PD-1 antibodies.

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