A first-in-human Phase 1 study of NL-201 in patients with relapsed or refractory cancer

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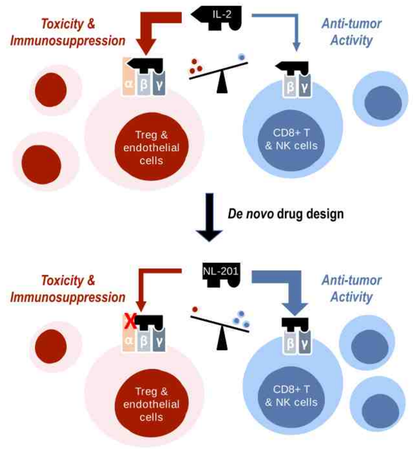
SITC 2021 WASHINGTON, D.C. NOV. 10–14 Join us in person or virtually

Abstract # 509

Background

- IL-2 was the first effective cancer immunotherapy;[1] however, conventional IL-2 treatment is commonly associated with numerous serious acute toxicities, including capillary leak syndrome, renal failure, and hypotension.[2] Therefore, IL-2 therapy is not feasible for all patients, indicating an unmet need for an IL-2 based regimen that is effective and well-tolerated.
  - The toxicity of IL-2 is mediated by its high-affinity interactions with the alpha chain of the IL-2 receptor (CD25), selectively expressed on off-target cells, including regulatory T cells (T_{reg}), and vascular endothelial cells. IL-2 stimulation of T_{reg} cells can contribute to immunosuppression in the tumor microenvironment (TME), and the interaction of IL-2 with vascular endothelial cells can lead to vascular leak syndrome.[3,4]

Figure 1. IL-2 Preferentially Stimulates Immunosuppressive T_{reg}



- Currently available cancer immunotherapies are often limited by various mechanisms of resistance[5]
  - Mechanisms of resistance are multifaceted and may include downregulation of the major histocompatibility complex class-I (MHC-I), resulting in immunologically "cold" tumors due to a decrease in T-cell activation and subsequent tumor detection and killing[6,7]

NL-201

- NL-201 is a selective and long-acting computationally designed alpha-independent agonist of the IL-2 and IL-15 receptors, which share IL-2Rβ and IL-2Rγ signaling subunits[8,9]
  - NL-201 was engineered to be IL-2Rα and IL-15Rα independent and have increased affinity for the IL-2Rβγ receptor, thereby widening the therapeutic index and eliminating the bias toward cells that cause immunosuppression and toxicity.[8,9] Preclinical studies have demonstrated that NL-201 induces significant antitumor activity at doses that are well tolerated in mice.[10]

Background (cont.)

NL-201

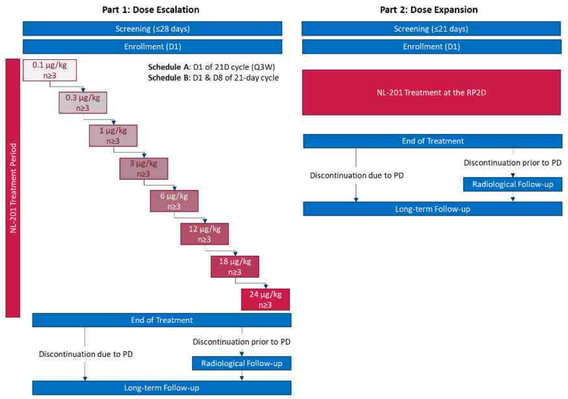
- NL-201 is being developed as a potent activator of CD8+ T cells and NK cells for cancer immunotherapy and has demonstrated robust therapeutic activity in numerous syngeneic mouse tumor models, including those refractory to immune checkpoint inhibitors[10,11]
- This first-in-human Phase 1 trial of NL-201 monotherapy is being conducted to assess the safety profile and recommended Phase 2 dose (RP2D) and treatment schedule in patients with advanced and/or refractory solid tumors

Study

Design

- NL201-101 is a multinational Phase 1 first-in-human, open-label, dose-escalation, and cohort expansion study consisting of two parts (Figure 2)
  - **Part 1 (dose escalation; n≤60):** adaptive monotherapy dose-escalation study in patients with advanced and/or refractory solid tumors to determine the safety profile, RP2D, and schedule of NL-201
    - Two schedules will be evaluated:
      - Schedule A: Administration on Day 1 of each 21-day cycle
      - Schedule B: Administration on Days 1 and 8 of each 21-day cycle
  - **Part 2 (dose expansion; n≤60):** Simon two-stage dose expansion cohort study in patients in with either renal cell carcinoma or melanoma (up to 30 patients per cohort) with exploratory paired biopsies to estimate the tolerability and anti-tumor activity of NL-201 as monotherapy in these indications

Figure 2. Study Design



D, day; PD, progressive disease; RP2D, recommended Phase 2 dose; Q3W, every three weeks.

Study (cont.)

- The maximum tolerated dose will be defined as the highest dose for which the probability of a patient experiencing a dose-limiting toxicity during Cycle 1 is ≤33%
- The RP2D and treatment schedule for Part 2 will be determined by evaluating pharmacokinetics (PK), pharmacodynamics (PD), and any cumulative toxicities over multiple cycles of NL-201

Assessments

- Safety assessments will include adverse events and laboratory parameters
- Tumor response to treatment will be assessed by radiographic evaluation by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and/or iRECIST after 6 and 12 weeks and every 12 weeks thereafter
- Blood samples will be collected to assess peripheral lymphocyte subsets and serum cytokine levels
- To assess the potential conversion from 'cold' to 'hot' TME (as observed in pre-clinical models, see poster #716), paired pre- and post-treatment tumor biopsies will be collected and assessed for transcriptional changes and immunohistochemistry
- PK, PD, immunogenicity, and exploratory tumor biopsy samples will be collected

Objectives

- Primary Objectives
  - Assess safety and toxicity profile of NL-201 in patients with advanced solid tumors
  - Define the RP2D and treatment schedule
- Secondary Objectives
  - Characterize the PK of NL-201
  - Estimate immunogenicity of NL-201
  - Estimate the anti-tumor activity of NL-201 per RECIST 1.1/iRECIST criteria, including best objective response, objective response rate, duration of response, and progression-free survival

Select Eligibility Criteria

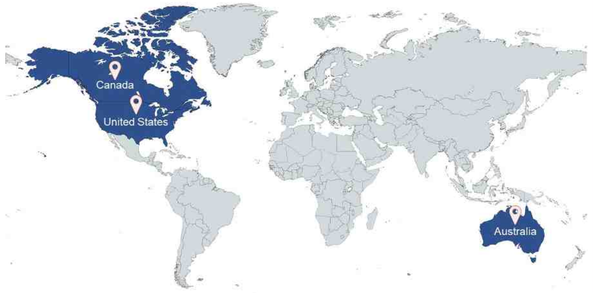
Inclusion Criteria	Exclusion Criteria
○ Adults (≥18 years old) providing written, informed consent ○ Measurable disease per RECIST 1.1. ○ Eastern Cooperative Oncology Group performance status of 0 or 1 ○ Adequate organ function ○ Part 1 Only ▪ Patients with measurable advanced solid tumors, other than prostate cancer, who have exhausted all approved non-IL-2-based lines of treatment, including checkpoint inhibitors if indicated ○ Part 2 Only ▪ Patients with pathologically proven diagnosis of the target disease indications, (1) malignant melanoma and (2) renal cell carcinoma, who have advanced disease and have failed at least one line of treatment, including checkpoint inhibitors	○ Prior treatment with IL-2-based therapy or CAR-T/allogeneic cellular therapy ○ Prior discontinuation of an immunotherapy due to development of clinically severe non-endocrine autoimmune disorder ○ History of primary brain cancer or active central nervous system metastases ○ History of potentially life-threatening autoimmune disease ○ History of solid organ or bone marrow transplant ○ History of hypersensitivity to PEG or PEGylated drugs

Study (cont.)

Status

- Enrollment is ongoing at sites in North America and Australia
- ClinicalTrials.gov Identifier: NCT04659629

Figure 3. Locations of Clinical Trial Sites



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Acknowledgements

This study is sponsored by Neoleukin Therapeutics, Inc. (Seattle, WA, USA). Medical writing assistance was provided by Meghan Sullivan, PhD, of MedVal Scientific Information Services, LLC (Princeton, NJ, USA) and was funded by Neoleukin Therapeutics, Inc.

Disclosures

AN: Research funding from NCI, EMD Serono, MedImmune, Healios Onc. Nutrition, Atterocor/Millendo, Amplimmune, ARMO BioSciences, Karyopharm Therapeutics, Incyte, Novartis, Regeneron, Merck, Bristol-Myers Squibb, Pfizer, CytomX Therapeutics, Neon Therapeutics, Calithera Biosciences, TopAlliance Biosciences, Eli Lilly, Kymab, PsiOxus, Arcus Biosciences, NeoImmuneTech, ImmuneOncia, Surface Oncology, Monopteros Therapeutics, BioNTech SE, Seven & Eight Biopharma, and SOTIO Biotech AG; advisory board of CytomX Therapeutics, Novartis, Genome & Company, OncoSec KEYNOTE-695, Kymab, STCube Pharmaceuticals, and Deka Biosciences; travel and accommodation expense from ARMO BioSciences
MKC: Consultant/advisor for BMS, Merck, InCyte, Moderna, ImmunoCore, and AstraZeneca
BCostello: Nothing to disclose
BCurti: Paid consultant for Merck (data safety monitoring board), advisory board for Clinigen and Nektar; research support from Clinigen and Galectin Therapeutics
EH: Institutional research funding from Neoleukin Therapeutics, Inc., ImCheck Therapeutics, Checkmate Pharmaceuticals, Nektar; consulting: for Cancer Support Community
AH: Research funding (paid to institution) from GSK, Merck, Pfizer, MedImmune/Genetech, Roche, Janssen, BMS, AstraZeneca, Astellas, Boeringher-Ingelheim, Bayer; Consulting/Advisory for GSK, Merck,` Eisai
GVL: Consultant/advisor for Aduro Biotech Inc, Amgen Inc, Array Biopharma Inc, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Evaxion Biotech A/S, Hexel AG, Highlight Therapeutics S.L., Merck Sharpe & Dohme, Novartis Pharma AG, OncoSec, Pierre Fabre, QBiotics Group Limited, Regeneron Pharmaceuticals Inc, SkylineDX B.V., Specialised Therapeutics Australia Pty Ltd.
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AW: Honoraria from BMS, Pfizer, Ipsen, Astellas; consulting for BMS, Ipsen, Astellas, Merck; research support from Merck