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NEON-1: A First-in-Human Phase I Open-Label Study of ALPN-202, a Conditional CD28 Costimulator and Dual Checkpoint Inhibitor, in Advanced Malignancies

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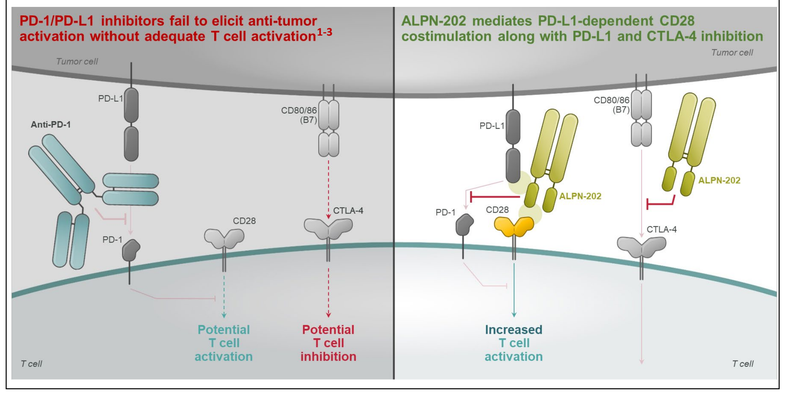
ABSTRACT

BACKGROUND: Checkpoint inhibitors (CPI) targeting the PD-1 and CTLA-4 pathways have demonstrated significant clinical benefit in multiple tumors, but the majority of patients exhibit or develop resistance, at least in part due to insufficient activation and/or excessive exhaustion of tumor-specific T cells. Strong preclinical rationale exists to combine CPIs with T cell costimulatory agonists, but such approaches have not yet translated into significantly improved clinical benefit. The majority of these approaches, though, have not targeted CD28, a critical T cell costimulator recently recognized as a key target of checkpoint inhibition. ALPN-202 is a variant CD80 vIgD-Fc fusion that mediates PD-L1-dependent CD28 costimulation and inhibits the PD-L1 and CTLA-4 checkpoints. As monotherapy, ALPN-202 has demonstrated superiority to CPI-only therapies in tumor models, while demonstrating a favorable safety profile in preclinical toxicology studies.

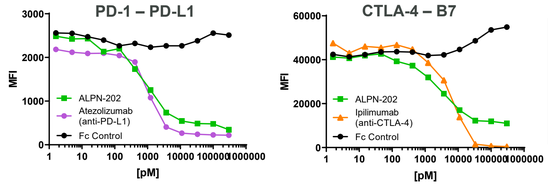
METHODS: This is a cohort-based, open-label dose escalation and expansion study in adults with advanced solid tumors or lymphoma (NCT04186637). The objectives of this study are to evaluate the safety, efficacy, pharmacokinetics, anti-drug antibodies, and pharmacodynamics of ALPN-202. Subjects who are refractory or resistant to standard therapy (including approved CPIs), or without available standard or curative therapy are eligible. ALPN-202 is administered by IV infusion. After two single-subject cohorts (0.001 mg/kg, 0.01 mg/kg), a standard 3+3 dose escalation (0.1-20 mg/kg) has been implemented with two dose schedules in parallel, Q1W and Q3W. Thereafter, expansion cohorts are planned to enroll subjects at a selected dose regimen(s) in selected indications. Biomarkers include tumor measurements of PD-L1, CD28, CD80 and CD86 to explore the possible relationship between baseline expression and outcomes. Other pharmacodynamic analyses include target saturation, inflammatory cytokines and immunophenotyping of circulating leukocytes. As of March 2021, the trial is continuing as planned; no DLTs have been observed through the 1 mg/kg weekly cohort.

RATIONALE



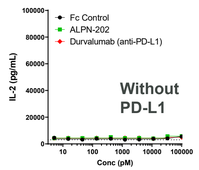
PRECLINICAL DEVELOPMENT

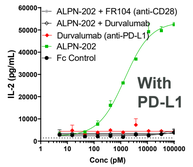
1. ALPN-202 Antagonizes PD-1 – PD-L1 and CTLA-4 – B7 Interactions



- ALPN-202, bound to human PD-L1- or CTLA-4-expressing CHO cells potently blocked the binding of fluorescently conjugated PD-1-Fc or CD80 (B7)-Fc, respectively.
- Thus, ALPN-202 binds both PD-L1 and CTLA-4 and blocks binding of their native counter-structures.

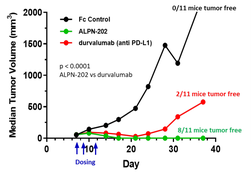
2. ALPN-202-Mediated CD28 Costimulation Requires PD-L1





- Pan T cells from healthy human donors were incubated with artificial antigen presenting cells (aAPC; K562) with or without surface expression of human PD-L1. Activity of test proteins was measured by IL-2 production.
- ALPN-202 co-stimulated T cells only in the presence of PD-L1-expressing aAPC. Activity was dependent on CD28 and PD-L1 since co-incubation with antibodies against CD28 or PD-L1 inhibited ALPN-202's activity.
- ALPN-202 therefore provides PD-L1-dependent CD28 costimulation to primary human T cells *in vitro*

3. PD-L1-Superior Efficacy in Mouse Models



- Mice bearing human PD-L1-expressing MC38 tumors were treated with ALPN-202 or durvalumab
- Treatment with ALPN-202 resulted in significantly higher rates of tumor-free animals

4. Well-Tolerated in Preclinical Safety Studies

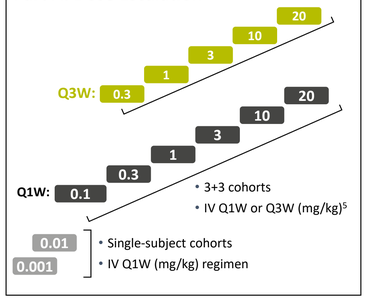
- Maximum tolerated dose not reached in rats or cynomolgus monkeys
- No evidence of cytokine release or systemic agonism at all dose levels up to 150 mg/kg (rat) or 200 mg/kg (monkey)
- No clinically-significant colitis or other immune-related AEs as previously reported with dual checkpoint blockade in cynomolgus monkeys[4]

NEON-1 (PHASE I) STUDY DESIGN

STUDY POPULATION

- Adults
- Advanced solid malignancies and lymphoma
- Refractory or resistant to standard therapy including CPIs
- Measurable disease
- ECOG: grade 0-2
- Adequate hematological, renal and hepatic function

Part A: Dose Escalation



Part B: Expansion Cohorts (TBD)

- Specific PD-1-refractory indications and/or populations (TBD among melanoma, non-small cell lung, head & neck, renal cell, neuroendocrine, uveal melanoma, colorectal and pancreatic cancers)
- Biomarker-selected when appropriate

STUDY ENDPOINTS

Safety:
- DLTs
- Adverse events
- Immunogenicity
- Cytokines

Efficacy:
- ORR, DOR
- DCR, PFS, OS

PK/PD:
- Target saturation
- Immuno-phenotyping
- *Ex vivo* costimulatory capacity
- Baseline tumor expression of PD-L1, CD28, CD80, CD86

CONCLUSIONS

- Current checkpoint inhibitor therapies may be limited by a lack of sufficient T cell costimulatory ligands (e.g., the CD28 ligands CD80 and/or CD86) in the tumor microenvironment
- ALPN-202 is a first-in-class conditional (i.e., PD-L1-dependent) CD28 costimulator, and dual checkpoint (PD-L1 and CTLA-4) inhibitor
- Preclinical studies demonstrate superior anti-tumor efficacy vs. checkpoint inhibition alone with excellent tolerability in GLP toxicology studies
- NEON-1 (NCT04186637) is the first-in-human trial of ALPN-202. Enrollment at 3 mg/kg Q1W began 01/2021; no DLTs were observed in prior cohorts

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