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A Study of ALPN-202, a PD-L1-dependent CD28 Costimulator and Dual Checkpoint Inhibitor, in Combination with Pembrolizumab in Patients with Advanced Malignancies (NEON-2)

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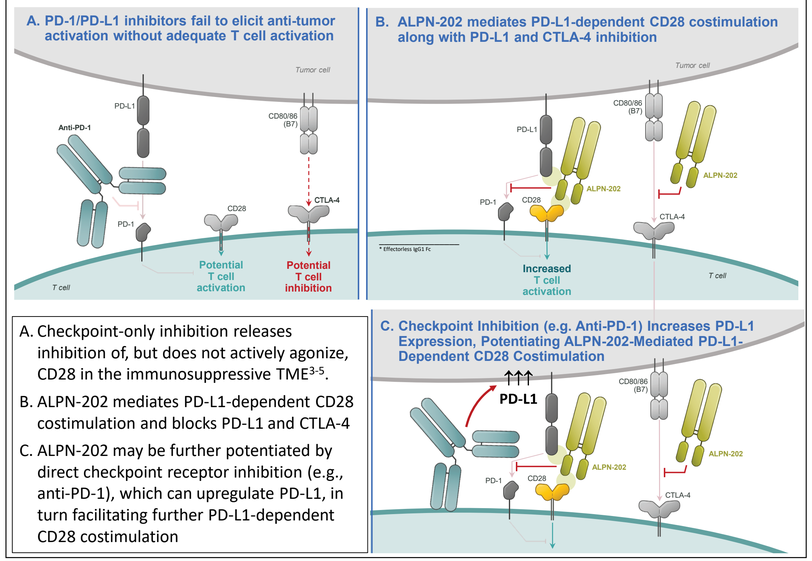
ABSTRACT

INTRODUCTION: Despite successes with checkpoint inhibition (CPI) in a wide range of tumors, most patients demonstrate primary or acquired resistance, thus driving the need for better IO therapy. Research has suggested that CPI therapy exerts much of its benefit via releasing the inhibition of CD28 signaling, which would only be expected to show clinical benefit in the presence of intra-tumoral engagement of CD28 by its ligands CD80/86. ALPN-202, a variant CD80 vIgD-Fc fusion protein, was engineered to provide tumor localizing PD-L1-dependent CD28 agonism, while inhibiting the PD-L1 and CTLA-4 checkpoints. It has demonstrated superiority to CPI-only therapies *in vitro* and in *in vivo* tumor models, while also demonstrating additional benefit in combination with targeted PD-1 axis blockade[1]. The benefit appeared to be at least additive in tumor models of poorly immunogenic tumors, suggesting the possibility of meaningful clinical benefit where CPI therapeutic efficacy is limited, i.e., "non-inflamed or cold" tumors. Single agent safety and tolerability of ALPN-202 has been demonstrated along with pharmacodynamic evidence of CD28 engagement with immune checkpoint inhibition[2].

METHODS: An open-label dose escalation and expansion study of ALPN-202 in combination with pembrolizumab in adults with advanced solid tumors or lymphoma was initiated in June 2021 (NCT04920383). Eligibility includes those tumors where single agent PD-(L)1 antagonists are SOC, or patients refractory or resistant to standard therapies (including approved CPIs), or those without available standard or curative therapy. The study is a standard 3+3 dose escalation design with two schedules of ALPN-202 in parallel, Q1W and Q3W. Pembrolizumab is given per label at 400 mg IV Q6W. Objectives include evaluation of safety and tolerability, identification of the recommended phase 2 dose, PK, PD, exploratory predictive biomarker analysis (i.e., PD-L1, CD28, CD80 and CD86, as well as immunophenotyping of immune cell populations on treatment) and preliminary anticancer activity of ALPN-202 in combination with pembrolizumab. Disease assessments are evaluated by RECIST v1.1 for solid tumors or by Lugano Classification for lymphoma. Efficacy endpoints include ORR, duration of response and disease control rate. Once the recommended phase 2 dose combination is identified, dose expansion cohorts will be initiated. Approximately 30-35 patients will be enrolled in each tumor type-specific expansion cohort, including histologies that have not been demonstrated to be CPI responsive, as well as those where CPIs are approved SOC.

RATIONALE



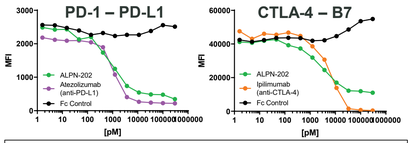
A. Checkpoint-only inhibition releases inhibition of, but does not actively agonize, CD28 in the immunosuppressive TME[3-5].

B. ALPN-202 mediates PD-L1-dependent CD28 costimulation and blocks PD-L1 and CTLA-4

C. ALPN-202 may be further potentiated by direct checkpoint receptor inhibition (e.g., anti-PD-1), which can upregulate PD-L1, in turn facilitating further PD-L1-dependent CD28 costimulation

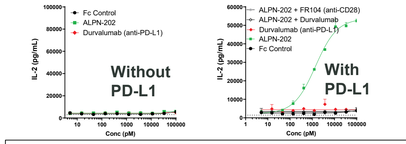
PRECLINICAL DEVELOPMENT

1. ALPN-202 Antagonizes PD-L1 and CTLA-4



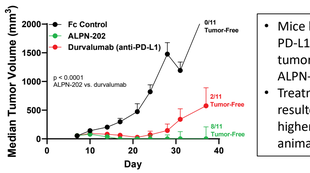
- ALPN-202, bound to human PD-L1- or CTLA-4-expressing CHO cells potently blocked the binding of fluorescently conjugated PD-1-Fc or CD80 (B7)-Fc, respectively.
- Thus, ALPN-202 binds both PD-L1 and CTLA-4 and blocks binding of their native counter-structures.

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



- 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.

3. PD-L1-Superior Monotherapy in Mouse Models

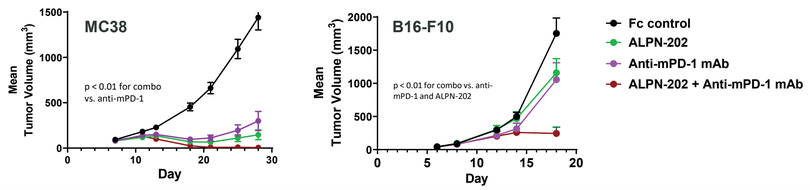


- Mice bearing human PD-L1-expressing MC38 tumors were treated with ALPN-202 or durvalumab
- Treatment with ALPN-202 resulted in significantly higher rates of tumor-free animals

4. Preclinically Well-Tolerated as Monotherapy

- 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 (cynomolgus monkey)
- No clinically-significant colitis or other immune-related AEs as previously reported with dual checkpoint blockade in cynomolgus monkeys[6]

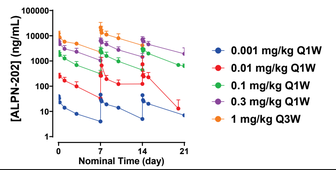
5. ALPN-202 Improves Efficacy of Anti-PD-1 Therapies in Combination Mouse Tumor Models



- Mice bearing human PD-L1-expressing MC38 or B16-F10 tumors were treated with ALPN-202, an anti-mouse PD-1 antibody, or a combination of the two.
- Treatment with ALPN-202 in combination with an anti-PD-1 antibody resulted in significantly superior antitumor responses

CLINICAL BACKGROUND

- In an ongoing monotherapy study (NEON-1; NCT04186637), ALPN-202 monotherapy has been well-tolerated, exhibiting dose-dependent PK/PD. No cytokine release syndrome has been observed[2].
- Peripheral immunological analyses demonstrate evidence of CD28 costimulation and relevant immune activation, including ↑ ICOS, ↑ Ki-67, ↑ TCM and ↓ Treg, supporting rationale for combination therapy[2].

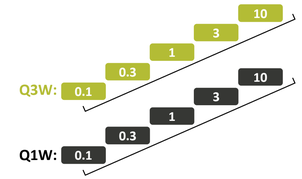


NEON-2 STUDY DESIGN

STUDY POPULATION

- Adults with advanced solid malignancies or lymphoma
- Eligible for a PD-(L)1 inhibitor; or refractory or resistant to standard therapy including CPIs
- Measurable disease
- ECOG: grade 0-1
- Adequate hematological, renal and hepatic function

Part A: Dose Escalation



- 3+3 cohorts
- ALPN-202 IV Q1W or Q3W (mg/kg)[7]
- All receive pembrolizumab 400 mg IV Q6W

Part B: Expansion Cohorts (TBD)

- Select CPI-refractory or resistant indications and/or populations TBD
- 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 and on-study (if accessible) tumor expression of PD-L1, CD28, CD80, CD86

SUMMARY/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 efficacy of ALPN-202 administered in combination with PD-1 inhibitors compared to either therapy alone, attributable to CPI-induced PD-L1 upregulation that potentiates ALPN-202-mediated CD28 costimulatory activity.
- ALPN-202 has been well tolerated to date in an ongoing monotherapy dose escalation and expansion study (NEON-1), with promising immune pharmacodynamics.
- NEON-2 (NCT04920383) is a dose escalation and expansion study of ALPN-202 administered in combination with pembrolizumab. Enrollment began in June 2021.

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This study is being conducted in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

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