TPS2683: Davoceticept (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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Background:

- Most patients treated with checkpoint inhibitors (CPI) experience primary or acquired resistance.
- Davoceticept (ALPN-202), a variant CD80 vIgD-Fc fusion protein, was engineered to provide tumor localizing PD-L1-dependent CD28 agonism, while inhibiting PD-L1 and CTLA-4.
- Davoceticept demonstrated superiority to CPI-only therapies in both in vitro and in vivo tumor models, while also demonstrating additional benefit in combination with targeted PD-1 axis blockade[1], attributable to anti-PD-1-induced upregulation of PD-L1, enabling PD-L1-dependent CD28 costimulation via davoceticept.

Methods:

- NEON-2 is an open-label dose escalation and expansion study of davoceticept combined with pembrolizumab in adults with advanced solid malignancies. The study started in June 2021
- Objectives: safety, tolerability, RP2D, PK, PD, exploratory predictive biomarker analysis (including tumor expression of PD-L1, CD28, CD80 and CD86, as well as immunophenotyping of immune cell populations on treatment), and preliminary anticancer activity via RECIST v1.1 for solid tumors or Lugano for lymphoma.
- Tumor-specific expansion cohorts of ~ 30 to 35 patients are planned, including histologies that have not been demonstrated to be CPI responsive, as well as those where CPIs are approved SOC.
- This study is being conducted in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

- Therapeutic subversion of PD-L1 into a CD28 costimulatory ligand may improve clinical outcomes during PD-1 inhibition.
- NEON-2 is a study of davoceticept in combination with pembrolizumab in advanced malignancies.
- To date, the 0.1 mg/kg cohorts have completed without DLT.

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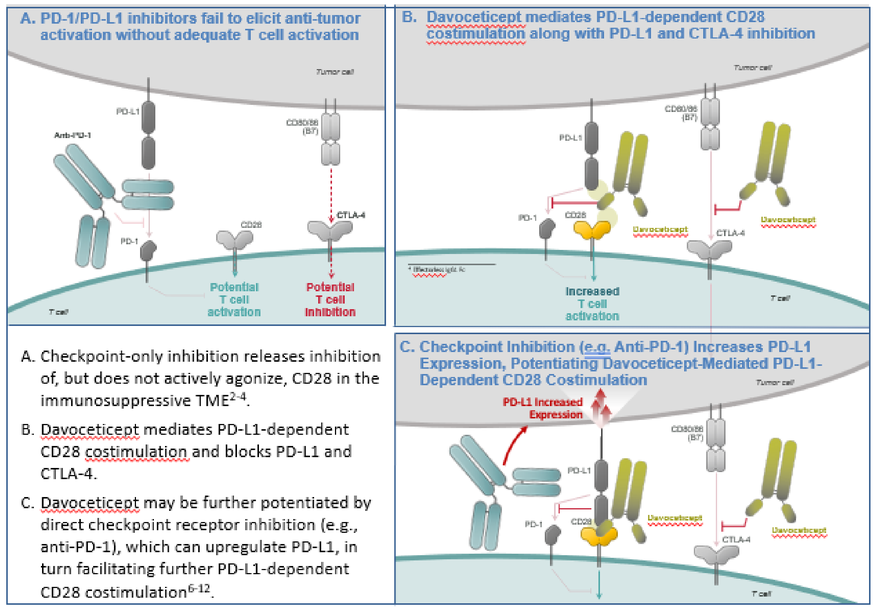
Rationale:

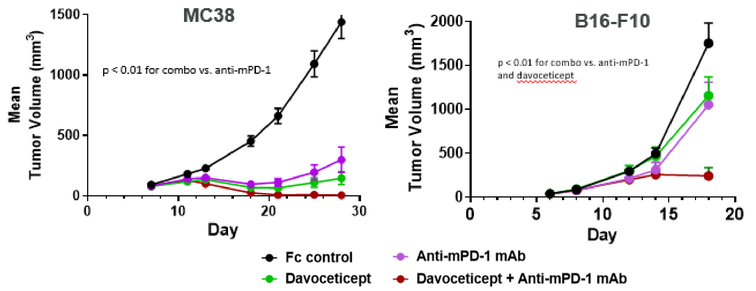


A. Checkpoint-only inhibition releases inhibition of, but does not actively agonize, CD28 in the immunosuppressive TME[2-4].

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

C. Davoceticept 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[6-12].

Davoceticept Improves Efficacy of Anti-PD-1 Therapies in Combination Mouse Tumor Models



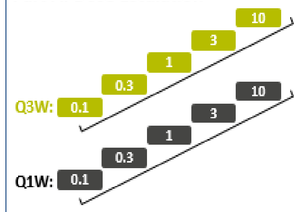
- Mice bearing hPD-L1-expressing MC38 or B16-F10 tumors were treated with davoceticept, an anti-mouse PD-1 antibody, or combo of the two.
- Treatment with davoceticept in combination with an anti-PD-1 antibody resulted in significantly superior antitumor responses.

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
- Davoceticept IV Q1W or Q3W (mg/kg)[5]
- 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

References:

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