INTERIM DOSE ESCALATION OF DAVOCETICEPT, A CONDITIONAL CD28 COSTIMULATOR AND DUAL CHECKPOINT INHIBITOR, IN COMBINATION WITH PEMBROLIZUMAB IN ADVANCED MALIGNANCIES (NEON-2)

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Background PD-1/PD-L1 inhibitors (PD-(L)1i) have improved outcomes for many patients with advanced malignancies; however, most do not respond, or fail to achieve durable antitumor immunity. PD-1-mediated inhibition of T-cell effector function works primarily by inactivating the CD28 costimulatory signal. While PD-(L)1i can remove such inhibition, active CD28 costimulation is likely still required for optimal T-cell activation. Davoceticept is a variant CD80 vIgD-Fc fusion protein, engineered to provide PD-L1-dependent CD28 costimulation, while inhibiting PD-1 and CTLA-4. In NEON-1 (NCT04186637), davoceticept monotherapy was well-tolerated up to 10mg/kg, Q3W, and showed evidence of clinical activity in papillary renal cell carcinoma (RCC). A davoceticept + PD-1i approach is supported by preclinical models where combination treatment yielded tumor volume reductions beyond those seen with either monotherapy. Further, PD-1 inhibition may up-regulate PD-L1 in the tumor and sensitize it to PD-L1-dependent CD28 costimulation by davoceticept.

Methods NEON-2 is an open-label dose escalation and expansion study of davoceticept + pembrolizumab in adults with advanced solid tumors or lymphoma (NCT04920383). Eligibility includes tumors for which single agent PD-(L)1i are standard of care, are refractory/resistant to standard therapies, or have no standard or curative treatments available. The study employs a standard 3+3 dose-escalation design with 2 schedules of intravenous (IV) davoceticept: Q1W and Q3W. Pembrolizumab is given per label at 400mg IV Q6W. Study objectives include evaluation of safety and tolerability, identification of the recommended phase 2 dose(s) (RP2D), pharmacokinetic, pharmacodynamic, exploratory biomarker analyses, and preliminary efficacy.

Results As of June 2022, 19 subjects have been treated with davoceticept in dose escalation at 0.1 and 0.3mg/kg, Q1W and Q3W. Seven subjects experienced a total of 9 Grade 3+ treatment-related adverse events, including one Grade 5 cardiogenic shock in the 0.3mg/kg, Q3W cohort. Gr3+ immune-related adverse events were more common in subjects receiving 0.3 vs. 0.1mg/kg regimens of davoceticept, at 27.3% and 12.5%, respectively. Of 14 evaluable subjects, 1 confirmed partial response has been observed in a nivolumab-experienced subject with clear cell RCC. Additionally, tumor reductions have been noted in a second ongoing RCC subject, and in subjects with prostate cancer and serous peritoneal carcinoma. Fifty percent of evaluable subjects achieved a best response of stable disease.

Conclusions The davoceticept + pembrolizumab combination has demonstrated preliminary anti-tumor activity in clear cell RCC, potentially by reversing resistance to PD-(L)1i. Dose escalation efforts will resume at 0.1mg/kg, Q1W and Q3W. Tumor-specific expansion cohorts will open once the RP2D/schedule of the combination treatment is identified.

Trial Registration NCT04920383
Ethics Approval This study received ethics approval from the WCG IRB (Sarah Cannon; ID 20211877), Salus IRB (START Texas; ID START2021.28, START Midwest; ID STMW2021.18), and Mass General Brigham IRB (Massachusetts General Hospital; ID 2021P002079). All study subjects provided their informed consent to participate in this study.