497 A STUDY OF ALPN-202, A PD-L1-DEPENDENT CD28 COSTIMULATOR AND DUAL CHECKPOINT INHIBITOR, IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH ADVANCED MALIGNANCIES

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Background 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. This study is being conducted in collaboration with Merck & Co., Inc., Kenilworth, NJ, USA.

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Trial Registration NCT04920383

REFERENCES

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2. Moser, Justin C, et al. First-in-human dose escalation of ALPN-202, a conditional CD28 costimulator and dual checkpoint inhibitor, in advanced malignancies. 2021; 2547–2547.

Ethics Approval All required ethics committees have reviewed and approved the protocol. The first was WCG IRB, Approval number 20211877. All participants provided informed consent before study participation.

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