

## AN OPEN-LABEL, PHASE 1A/B STUDY OF AB248, A CD8 + SELECTIVE IL-2 MUTEIN FUSION PROTEIN, ALONE OR IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

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**Background** High-dose interleukin-2 (HD IL-2) induces durable clinical responses in patients with melanoma and RCC, but severe toxicity limits its therapeutic utility. Early clinical data from several not- $\alpha$  IL-2R $\beta$  agonists suggest better tolerability but lower response rates compared to historical HD IL-2.<sup>1-2</sup> In patients, these not- $\alpha$  IL-2R agonists demonstrate a NK cell bias, retain activity on Tregs, and exhibit limited CD8+ T cell expansion.<sup>3-5</sup>

AB248 is a CD8+ T cell-selective IL-2 with over 500-fold preference for CD8+ T cells over other immune cell types. AB248 has demonstrated a differentiated preclinical profile, with compelling anti-tumor activity when given alone and in combination with anti-PD1 in multiple murine models. Preclinical data suggests that AB248 may yield an improved therapeutic index compared to broadly acting IL-2R $\beta$  agonists by increasing CD8+ T cell activation while avoiding NK cell-driven toxicity and Treg-mediated immunosuppression.<sup>6</sup> Here we introduce the first-in-human study evaluating AB248 administered alone and in combination with pembrolizumab in subjects with advanced solid tumors who progressed after prior standard-of-care therapies.

**Methods** This open-label phase 1a/b study consisting of a dose-escalation and expansion phase aims to investigate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of AB248 alone or in combination with pembrolizumab. Subjects with locally advanced/metastatic tumors will be enrolled, including melanoma, RCC, NSCLC and SCCHN, which progressed on prior therapies (e.g. anti-PD(L)1), and first-line SCCHN during the expansion phase. Key eligibility criteria include age  $\geq 18$  years, ECOG  $\leq 1$ , measurable disease per RECIST v1.1, adequate end-organ function, and no autoimmune disease. The dose-escalation will follow the Bayesian Optimal Interval (BOIN) design and enroll subjects at multiple dose levels and schedules for both monotherapy and combination portions. Backfill cohorts for paired-tumor biopsies are included during dose-escalation. Upon identifying a suitable dose and schedule based on the totality of cumulative data, additional subjects will be enrolled in indication-specific expansion cohorts according to the Simon 2-stage design. The primary objectives for this study are to assess the safety and tolerability of AB248 alone or in combination with pembrolizumab. Secondary objectives include assessing PK, PD, immunogenicity, and antitumor activity. Exploratory objectives include evaluating the potential response-predictive and/or associated changes in immune cells, blood, and tissue biomarkers. Tumor assessments will be performed every 6 weeks for the first 30 weeks and every 8–9 weeks thereafter. Adverse events will be assessed by CTCAE v5.0, except CRS, assessed by ASTCT criteria. This study is currently enrolling.

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Trial Registration NCT05653882

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**Ethics Approval** This study has been approved by each participating site: Dana Farber Cancer Institute IRB approval #450613, Advarra IRB approval #00066518, Castle IRB approval #12092022. All participants gave their informed consent before taking part in the study.

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