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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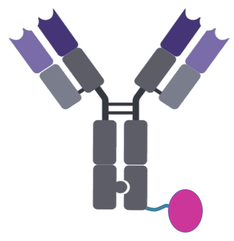
Introduction

High-dose interleukin-2 (HD IL-2) induces durable clinical responses in a subset of patients with melanoma and RCC, but severe toxicity limits its therapeutic utility. Early clinical data from several not-α IL-2Rβγ agonists suggest better tolerability but lower objective response rates compared to historical HD IL-2.[1-2] In patients, these not-α IL-2R agonists demonstrate a NK cell bias, retain activity on Tregs, and exhibit limited CD8+ T cell expansion.[3-5]

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 and in combination with anti-PD1 in multiple murine tumor models. Preclinical data suggests that AB248 may yield an improved therapeutic index compared to broadly acting IL-2Rβγ agonists by increasing CD8+ T cell activation while avoiding NK cell-driven toxicity and Treg-mediated immunosuppression.[6]
Here we introduce the first-in-human study evaluating AB248 administered alone or in combination with pembrolizumab in subjects with advanced solid tumors who progressed after prior standard-of-care therapies.

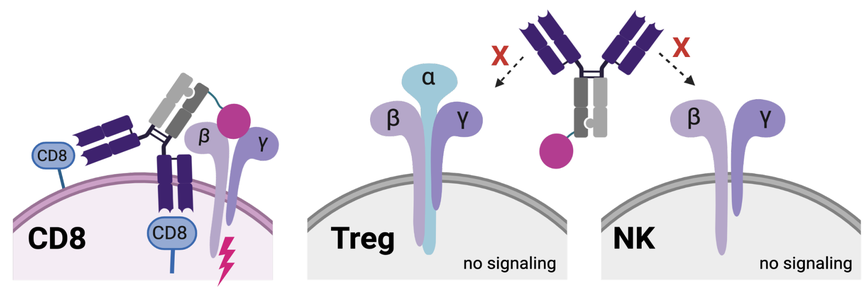
AB248 Overview

Figure 1: AB248's molecular design



Anti-CD8	Enables specific binding to CD8+ T cells without affecting CD8 co-receptor function
Engineered Bispecific Fc	Ensures fusion with a single IL-2 mutein per molecule; enables half-life extension
Attenuated IL-2 mutein	Attenuates the binding to IL-2R, enabling avidity-driven activity on targeted cells

Figure 2: AB248 selectively provides an IL-2 signal to CD8+ T cells

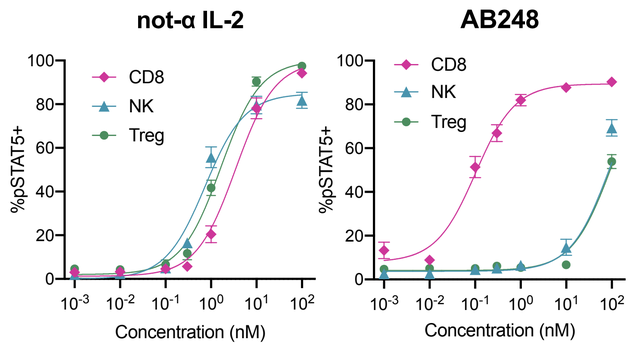


AB248 binds to CD8 on CD8+ T cells and provides an IL-2 signal in *cis*. The attenuated IL-2 mutein ensures minimal signaling on other IL-2Rβγ+ cell types like Treg and NK cells at physiologically relevant concentrations.

Non-Clinical AB248 Data

Human

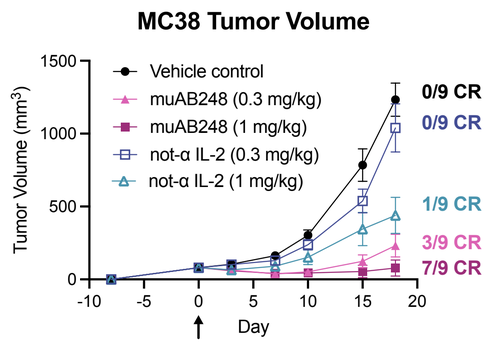
Figure 3: AB248 induces CD8+ T cell-selective IL-2 signaling with over 500-fold preference



Human peripheral blood immune cells were stimulated with a representative not-α IL-2 or AB248 and pSTAT5 was measured by flow cytometry. Shown is the fraction of the indicated cell types staining positive for pSTAT5. (n = 10 donors)

Mouse

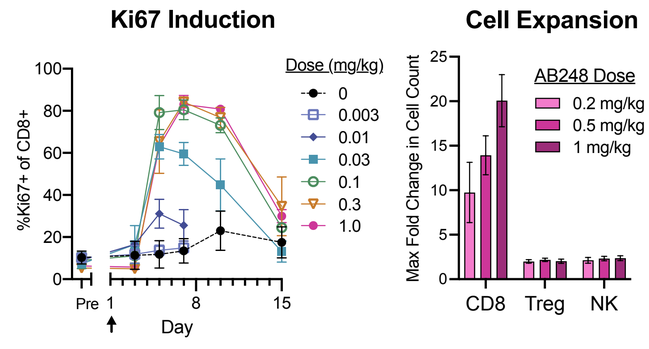
Figure 4: AB248's murine surrogate drives potent anti-tumor activity in mice and outperforms not-α IL-2



MC38 tumor-bearing mice were treated intravenously once 8 days after tumor injection; shown is tumor volume and the number of durable complete responses (CR). No body weight loss was observed with muAB248; not-α IL-2 at 1 mg/kg induced approximately 7% weight loss compared to controls.

Primate

Figure 5: AB248 promotes selective CD8+ T cell expansion in non-human primates



Cynomolgus monkeys were dosed with AB248 intravenously then immune cell counts were assessed in peripheral blood. Shown is Ki67 expression by CD8+ T cells and fold expansion in absolute cell count of CD8+ T cells, NK cells, and Tregs over baseline.

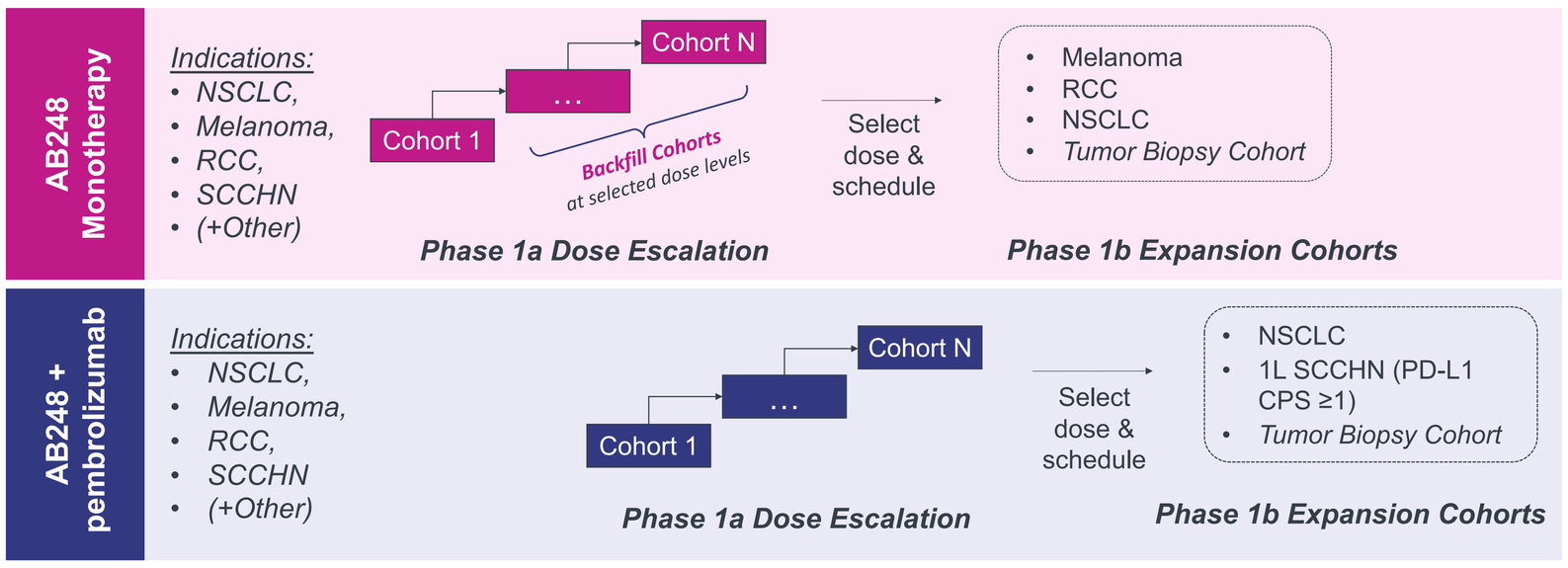
Methods

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.

Tumor assessments will be performed every 6 weeks for the first 30 weeks and every 9 weeks thereafter. Adverse events will be assessed by CTCAE v5.0 (and ASTCT criteria for cytokine release syndrome). The study is currently open for enrollment in the dose escalation phase at multiple sites in the US.

AB248-101 Study Design

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.



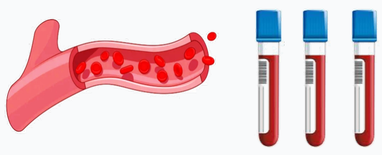
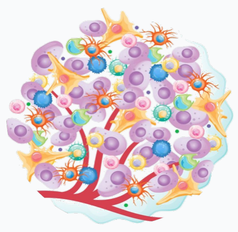
Study Objectives

- **Primary:** To assess the safety and tolerability of AB248 alone or in combination with pembrolizumab
- **Secondary:** To assess pharmacokinetics, pharmacodynamics immunogenicity, and preliminary anti-tumor activity of AB248 alone or in combination with pembrolizumab
- **Exploratory:** To evaluate the potential response-predictive and/or treatment-associated changes in immune cells, blood, and tissue biomarkers.

Study Details

- **Protocol Number:** AB248-101
- **Status:** Recruiting; enrollment is ongoing
- **ClinicalTrials.gov identifier:** NCT05653882

Key Translational Assessments

Blood	Tumor
	
Assessment of peripheral blood immune cell pharmacodynamics	Characterization of intra-tumoral immune changes via paired biopsies

Key Eligibility Criteria

Key Inclusion Criteria

- ✓ Age ≥18 years of age at the time consent is signed
- ✓ Adequate organ function per laboratory testing
- ✓ Pregnancy prevention requirements
- ✓ Measurable disease per RECIST 1.1 as assessed by the Investigator
- ✓ ECOG 0-1
- ✓ Incurable, locally advanced or metastatic tumor of the type being evaluated in individual cohorts
- ✓ Histologic documentation
- ✓ *Paired-biopsy cohorts:* Has lesions that are deemed safely accessible and will provide core or excisional biopsies at both screening and on-treatment time point for biomarker analyses

Key Exclusion Criteria

- ✗ Diagnosis of immunodeficiency
- ✗ History of a previous, additional malignancy, unless potentially curative treatment has been completed, with no evidence of malignancy for 5 years
- ✗ Known active CNS metastases and/or carcinomatous meningitis.
- ✗ Active autoimmune disease
- ✗ Active infection requiring systemic therapy
- ✗ Severe hypersensitivity reaction (Grade ≥3) to prior treatment with pembrolizumab, another monoclonal antibody, or has history of hypersensitivity to components of the study treatments or any of their excipients
- ✗ Received prior systemic anticancer therapy including investigational agents within 4 weeks (or, if shorter, within 5 half-lives for kinase inhibitors) prior to first dose of study treatment
- ✗ Received prior radiotherapy within 2 weeks of start of study treatment or has had a history of radiation pneumonitis
- ✗ Receiving chronic systemic steroid therapy or other form of immunosuppressive therapy within 7 days prior the first dose of study treatment, except for daily 10 mg prednisone or equivalent
- ✗ Received previous treatment with another agent targeting the IL-2, IL-7, or IL-15 receptors

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Acknowledgements

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