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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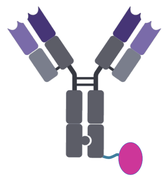
Introduction

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 data.[1-2] In patients, these not-α IL-2s demonstrate a profound NK cell bias, while retaining activity on Tregs, and exhibiting limited CD8+ T cell expansion.[3-5]

AB248 is a CD8+ T cell selective IL-2 that demonstrates more than 500-fold selectivity for CD8+ T cells over other immune cell types. AB248 has demonstrated a highly differentiated preclinical profile, with compelling anti-tumor activity and less toxicity when given alone and in combination with anti-PD1 in multiple murine tumor models. These data suggest that AB248 may have an improved therapeutic index compared to broad-acting IL-2Rβγ agonists by increasing CD8+ T cell expansion and activation, avoiding NK cell-driven toxicity and Treg-mediated immunosuppression.[6] Here we introduce the first-in-human study which aims to investigate AB248 when administered alone or in combination with pembrolizumab in subjects with advanced solid tumors who failed prior standard of care therapies.

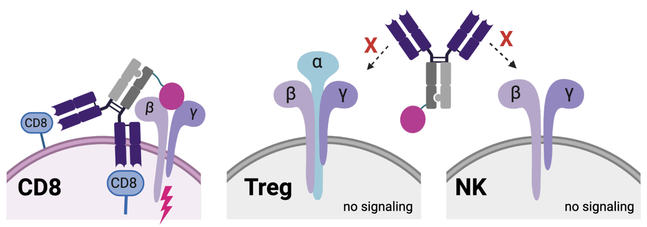
AB248 Overview

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.

Acknowledgements

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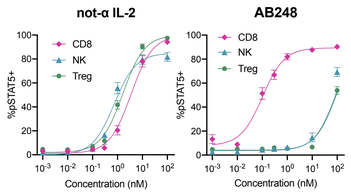
Non-Clinical AB248 Data

Human

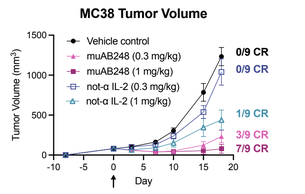
Figure 3: AB248 induces CD8+ T cell-selective IL-2 signaling with over 500-fold preference



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

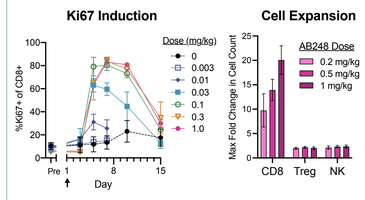
Figure 4: AB248's murine surrogate drives potent anti-tumor activity in mice and outperforms not-α IL-2



MC38 tumor-bearing mice were treated as indicated intravenously once 8 days following 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 demonstrated 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, administered at a fixed dose of 200mg Q3W, in subjects with locally advanced/metastatic tumors, including melanoma, renal cell carcinoma, NSCLC and SCCHN, who failed prior therapies, including prior anti-PD(L)1, as well as in first-line SCCHN during the expansion phase.

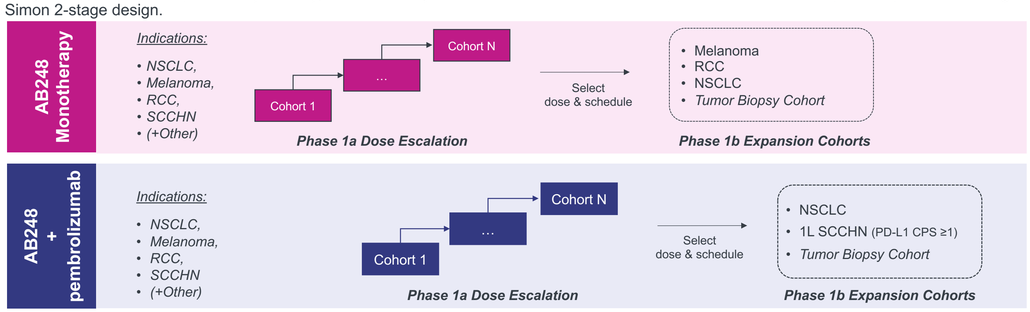
Assessments will be performed every 6 weeks for the first 30 weeks and every 9 weeks thereafter. Adverse events will be assessed by CTCAE v5.0 (and ASTCT criteria for cytokine release syndrome). The study is currently open for enrollment in the dose escalation phase at multiple sites in the US.

Study Objectives

- **Primary:** To assess the safety and tolerability of AB248 alone or in combination with pembrolizumab
- **Secondary:** To assess the preliminary antitumor effect, pharmacokinetic, pharmacodynamic and immunogenicity relationship of AB248 alone or in combination with pembrolizumab
- **Exploratory:** To evaluate the potential response-predictive and/or associated changes in immune cells, blood, and tissue biomarkers.

AB248-101 Study Design

The dose escalation phase will follow the Bayesian Optimal Interval (BOIN) design and enroll subjects at multiple dose levels and schedules for the AB248 monotherapy and pembrolizumab combination portion. Upon identifying suitable dose and schedule based on the totality of cumulative data including safety, PK, PD and preliminary efficacy, additional subjects will be enrolled in indication specific cohorts in the expansion phase according to the Simon 2-stage design.



Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
✓ Age ≥18 years of age at the time consent is signed	✗ Diagnosis of immunodeficiency
✓ Adequate organ function per laboratory testing	✗ History of a previous, additional malignancy, unless potentially curative treatment has been completed, with no evidence of malignancy for 5 years
✓ Pregnancy prevention requirements	✗ Known active CNS metastases and/or carcinomatous meningitis.
✓ Measurable disease per RECIST 1.1 as assessed by the Investigator	✗ Active autoimmune disease
✓ ECOG 0-1	✗ Active infection requiring systemic therapy
✓ Histologic documentation of incurable, locally advanced or metastatic tumor of the type being evaluated in individual cohorts	✗ 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
	✗ 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
	✗ Prior radiotherapy within 2 weeks of start of study treatment or has had a history of radiation pneumonitis
	✗ 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
	✗ Previous treatment with another agent targeting the IL-2, IL-7, or IL-15 receptors

Key Translational Assessments

Blood	Tumor
	
Assessment of peripheral blood immune cell pharmacodynamics	Characterization of intratumoral immune changes via paired biopsies

Study Details

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

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