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 Tumor Malignancies

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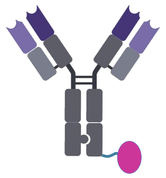
Background

- High-dose IL-2 demonstrates modest activity in melanoma and RCC, but its use is limited by severe toxicity.
- AB248 is a novel IL-2 fusion protein of an attenuated IL-2 mutein linked to an antibody targeting CD8β that features >500-fold selectivity for CD8+ T cells and demonstrates strong anti-tumor activity both alone and with anti-PD1 in preclinical models.
- In addition to achieving CD8+ T cell expansion and activation, AB248 avoids NK cell toxicity and Treg-mediated immunosuppression.
- NCT05653882 is a phase 1A/B study investigating the safety, pharmacokinetics, pharmacodynamics and anti-tumor activity of AB248 alone or with pembrolizumab in locally advanced/metastatic solid tumor malignancies, including melanoma, having previously progressed through PD-1/PD-L1 checkpoint blockade.

AB248 Background

AB248 Molecular Design

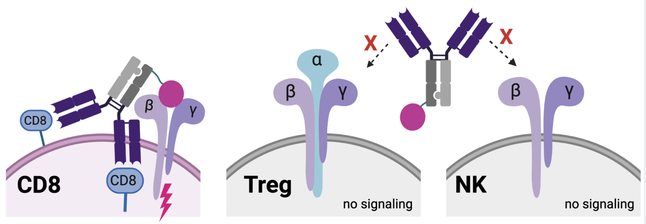


Anti-CD8 — Enables specific binding to CD8⁺ T cells without affecting CD8 co-receptor function

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

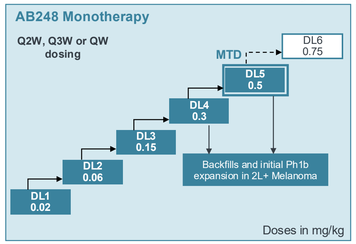
AB248 selectively provides an IL-2 signal to CD8⁺ T cells

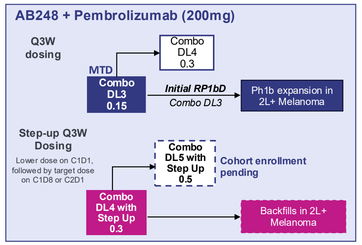


AB248 binds to CD8 on CD8⁺ T cells and provides an IL-2 signal in *cis*. The attenuated IL-2 mutein ensures minimal signaling on other IL-2Rβγ⁺ cell types like Treg and NK cells at physiologically relevant concentrations.

Phase 1 Clinical Trial Design and Patient Population

- Key eligibility criteria include age ≥18 years, ECOG ≤1, measurable disease per RECIST v1.1, adequate end-organ function and absence of autoimmune disease.
- Dose escalation was conducted via a Bayesian Optimal Interval (BOIN) design.
- Upon identification of recommended phase 2 doses, additional patients were enrolled in indication-specific cohorts in the expansion component of the study via Simon 2-stage design.





Patient Population	AB248 Monotherapy (n =61)	AB248 + Pembro (n=47)	AB248 + Pembro, with step dosing (n=21)
Age at screening, years Median (range)	64.0 (29–83)	67.0 (27.0–87.0)	64.0 (55–85)
Sex, n (%) Male Female	41 (67.2) 20 (32.8)	25 (53.2) 22 (46.8)	15 (71.4) 6 (28.6)
Ethnicity, n (%) Hispanic or Latino Not Hispanic or Latino No reported/Unknown	7 (11.5) 52 (85.2) 2 (3.3)	6 (12.8) 38 (80.9) 3 (6.4)	8 (38.1) 12 (57.1) 1 (4.8)
Stage at screening, n (%) IIIB IV Other/Unknown	8 (13.1) 40 (65.6) 13 (21.3)	8 (17.0) 35 (74.5) 4 (8.5)	3 (14.3) 15 (4.8) 3 (14.3)
Baseline ECOG, n (%) Missing 0 1	5 (8.2) 26 (42.6) 30 (49.2)	1 (2.1) 18 (38.3) 28 (59.6)	1 (4.8) 5 (23.8) 15 (71.4)
Primary tumor type Melanoma (cut./muc./acr.) RCC NSCLC Other	18 (29.5) 7 (11.5) 19 (31.1) 17 (27.9)	22 (46.8) 8 (17.0) 12 (25.5) 5 (10.6)	9 (42.9) 4 (19.0) 7 (33.3) 1 (4.8)
Number of prior therapies Median (range)	3 (1–7)	3 (1–5)	3 (1–5)
Prior Lines with ICI Median (range)	2 (1–6)	2 (0–4)	2 (1–4)

Phase 1 Safety and Tolerability

- AB248 demonstrated a generally manageable safety profile as monotherapy and in combination with pembrolizumab, with the most common TEAEs predominantly Gr 1-2.
- Gr ≥3 AEs in >5% of pts. were elevated liver enzymes and anemia.
- Gr ≥3 liver enzyme elevations (12.4% of all pts.) occurred generally in cycle 1 and were transient and reversible. Median onset/time to resolution: 8 and 4 days.
- Gr ≥3 anemia (9.3% of all pts.) occurred in pts. with baseline anemia and was treatment-related in 4.6% of cases.
- Gr ≥3 CRS (3.1% of all pts.) was uncommon and occurred exclusively in pts. with elevated baseline CRP (40-219 mg/mL).
- Treatment-related AEs leading to discontinuation occurred in 7 pts.
- Dose escalation in combination evaluated DL3 and DL4:
  - In the initial DL4 escalation cohort, DLTs were reported in 3 of 9 pts; 2 DLTs were in NSCLC pts. with very high baseline CRP (93.1 and 219 mg/L).
  - Step-up dosing was subsequently implemented with all step-up cohorts targeting DL4 cleared.
  - MTD with step-up dosing was not reached, supporting further evaluation of dose optimization, incl. evaluation of a higher dose.

Most Common Treatment Emergent AEs Reported in ≥15% Participants

No. of pts with AE (%)	AB248 Monotherapy (n =61)		AB248 + Pembro (n=47)		AB248 + Pembro (step dosing, n=21)	
	Any Gr.	Gr ≥3	Any Gr.	Gr ≥3	Any Gr	Gr ≥3
Fatigue	34 (55.7)	2 (3.3)	21 (44.7)	1 (2.1)	9 (42.9)	0
Rash^	32 (52.5)	1 (1.6)	20 (42.6)	2 (4.3)	10 (47.6)	0
Nausea	30 (49.2)	0	18 (38.3)	0	7 (33.3)	0
Chills	24 (39.3)	0	13 (27.7)	0	5 (23.8)	0
Vomiting	22 (36.1)	0	13 (27.7)	0	6 (28.6)	0
Pyrexia	23 (37.7)	1 (1.6)	13 (27.7)	1 (2.1)	5 (23.8)	0
Diarrhea	22 (36.1)	3 (4.9)	14 (29.8)	3 (6.4)	3 (14.3)	0
Liver enzymes^	16 (26.2)	8 (13.1)	15 (31.9)	6 (12.8)	6 (28.6)	2 (9.5)
AST increased	14 (23.0)	5 (8.2)	13 (27.7)	2 (4.3)	6 (28.6)	1 (4.8)
ALT increased	11 (18.0)	4 (6.6)	13 (27.7)	5 (10.6)	5 (23.8)	2 (9.5)
Anemia	15 (24.6)	7 (11.5)	10 (21.3)	3 (6.4)	4 (19.0)	2 (9.5)
Arthralgia	14 (23.0)	0	11 (23.4)	0	3 (14.3)	0
CRS	13 (21.3)	2 (3.3)	7 (14.9)	1 (2.1)	5 (23.8)	1 (4.8)
Edema periph.	15 (24.6)	0	6 (12.8)	1 (2.1)	3 (14.3)	0
Constipation	13 (21.3)	0	6 (12.8)	0	3 (14.3)	0
Headache	13 (21.3)	0	6 (12.8)	0	1 (4.7)	0
Dizziness	9 (14.8)	0	9 (19.1)	0	2 (9.5)	0
Hypokalemia	10 (16.4)	3 (4.9)	7 (14.9)	0	3 (14.3)	1 (4.8)
Decr. appetite	8 (13.1)	0	12 (25.5)	1 (2.1)	2 (9.5)	0
Any TRAE	56 (91.8)	22 (36.1)	39 (83.0)	11 (23.4)	17 (81.0)	6 (28.6)
Dose Hold / Rel.	17 (27.9) / 7 (11.5)		13 (27.7) / 8 (17.0)		8 (38.1) / 5 (23.8)	
Dose Red./ Rel.	4 (6.6) / 4 (6.6)		3 (6.4) / 1 (2.1)		0 / 0	
Discontin. / Rel.	8 (13.1) / 4 (6.6)		8 (17.0) / 3 (6.4)		1 (4.8) / 0	
DLT	5 (8.2)		7 (14.9)		2 (9.5)	

^ Liver enzymes and rash are composite terms encompassing all possible ways these AEs were coded in the database; Data snapshot: Dec 10, 2025

Phase 1 Anti-Tumor Activity in Melanoma

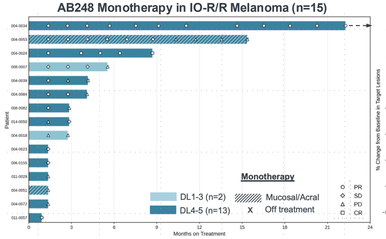
AB248 Monotherapy:

- Confirmed ORR was 13% (2/15) across DL1-DL6, 15% (2/13) in the DL4-DL5 target dose range, and 18% (2/11) among cutaneous melanoma pts. in the target dose range.
- Both responders received prior IO doublets and achieved max tumor reductions of 78.8% and 87.2%.
- A single patient remains on treatment for >2 years.
- One heavily pretreated mucosal melanoma patient (5 prior lines incl. 2 prior IO doublets) achieved SD for 10 mos. with tumor reduction of up to 15.8%.

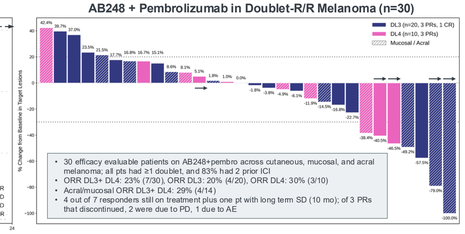
AB248 + Pembrolizumab:

- 30 pts. with doublet-refractory melanoma were efficacy-evaluable across the DL3 and DL4 combination cohorts.
- 7 of 30 pts. achieved a confirmed objective response, representing a confirmed ORR of 23% (95% CI, 9.9-42.3).
- Durable responses were observed at both dose levels:
  - 4 of 20 pts. treated at DL3 (20%)
  - 3 of 10 pts at DL4 (30%)
- Anti-tumor activity was observed across melanoma subtypes, including difficult-to-treat mucosal and acral types.
  - Among 14 efficacy-evaluable pts. with mucosal or acral melanoma, 4 responses were observed, including a PR in a pt. with acral melanoma and a CR in a pt. with mucosal melanoma.

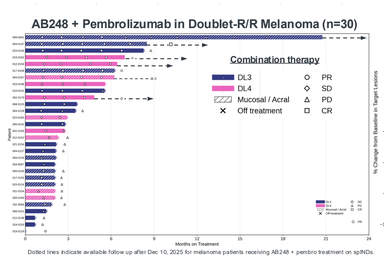
AB248 Monotherapy in IO-R/R Melanoma (n=15)

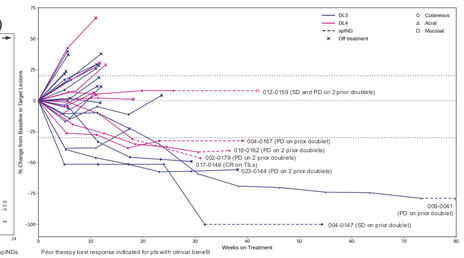


AB248 + Pembrolizumab in Doublet-R/R Melanoma (n=30)



AB248 + Pembrolizumab in Doublet-R/R Melanoma (n=30)



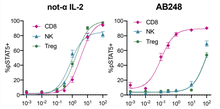


Dotted lines indicate available follow up after Dec 10, 2025 for melanoma patients receiving AB248 + pembro treatment on spINDs.

Prior therapy best response indicated for pts with clinical benefit

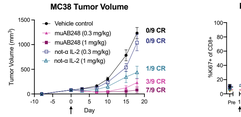
AB248 Preclinical/Translational Data

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



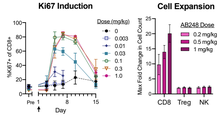
Human peripheral blood immune cells were stimulated with either not-α IL-2 or AB248, followed by measurement of pSTAT5 levels using flow cytometry. The graph illustrates the proportion of each cell type expressing pSTAT5 (n = 10 donors).

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



MC38 tumor-bearing mice were treated IV every 8 days following tumor injection; shown is tumor volume and durable complete responses (CR). No weight loss was observed with muAB248; not-α IL-2 at 1 mg/kg demonstrated approximately 7% weight loss compared to controls.

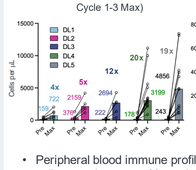
AB248 promotes selective CD8⁺ T cell expansion in non-human primates: 10-20X



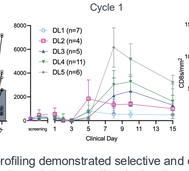
Cynomolgus monkeys were dosed with AB248 intravenously then immune cell counts were assessed in peripheral blood. Shown is Ki67 expression by CD8+ T cells and fold expansion in absolute cell count of CD8+ T cells, NK cells, and Tregs over baseline.

AB248 Pharmacodynamics

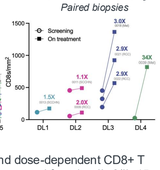
Absolute CD8 Counts
Cycle 1-3 Max



CD8+ T Cell Kinetics
Cycle 1



Tumor CD8 Density
Paired biopsies

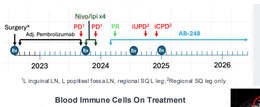


- Peripheral blood immune profiling demonstrated selective and dose-dependent CD8+ T cell expansion, up to 20x, substantially exceeding the levels reported for other IL-2/IL-15-based therapies. Expansion of Tregs and NK cells was up to 2.0x and 3.0x respectively.
- Dose-dependent increases in absolute CD8 counts were observed (>2,000 cells/µL), significantly exceeding even healthy donor counts (300-500 cells/µL).
- High CD8 T cell counts were maintained throughout treatment. AB248 induced dose-dependent increase in intratumoral CD8s based on obtained paired tumor biopsies.

Patient Vignette

Acral Melanoma (009-0041):

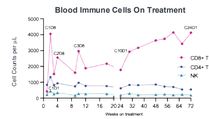
- Initially diagnosed as stage III in May '22, right toe amputation + adjuvant pembro
- Multiple new metastatic lesions in September '23
- Multiple new sites of PD in December '23 following 4 cycles of Nivolumab/Ipilimumab
- Commenced AB248 DL3 + Pembrolizumab in March '24, remains on treatment

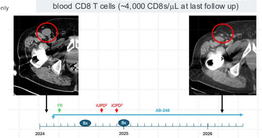


¹L inguinal LN, L popliteal fossa LN, regional SQ L leg; ²Regional SQ leg only

- Sustained response observed in inguinal RECIST targets throughout 26+ cycles of therapy.
- Intermittent waxing and waning of nodules both clinically and by imaging. Treatment continued per protocol despite fluctuation in size of nodules, given ongoing clinical benefit.
- Treatment induced sustained and selective increases in blood CD8 T cells (~4,000 CD8s/µL at last follow up)

Blood Immune Cells On Treatment





Summary and Acknowledgements

- AB248 demonstrates robust and dose-dependent pharmacologic activity including preferential CD8+ T cell expansion of approximately 20-fold at DL4 and DL5.
- A well tolerated safety profile at target dose levels administered with step-up dosing includes mostly Gr1-2 AEs.
- AB248 monotherapy demonstrates anti-tumor activity in ICI-refractory melanoma with deep and durable responses in the DL4-DL5 target dose range.
- In combination with Pembrolizumab, robust anti-tumor activity was observed across IO-refractory melanoma pts. (incl. mucosal and acral melanoma) with 7/30 responses observed among IO doublet R/R melanoma pts., including 3/10 PRs at DL4.
- AB248's favorable safety profile, differentiated PD and anti-cancer activity merit further investigation.
- In addition to further DL4/DL5 expansion in combination with anti-PD-1, AB248 is currently being evaluated in combination with the T-cell engager Tarlatamab in a multi-national SCLC clinical trial.
- The Sponsor wishes to thank all patients, families and investigators who made this clinical trial possible. Funding for this study was provided by Asher Biotherapeutics, Inc. with Pembrolizumab provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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