

ABSTRACT (TPS2687)

BACKGROUND:

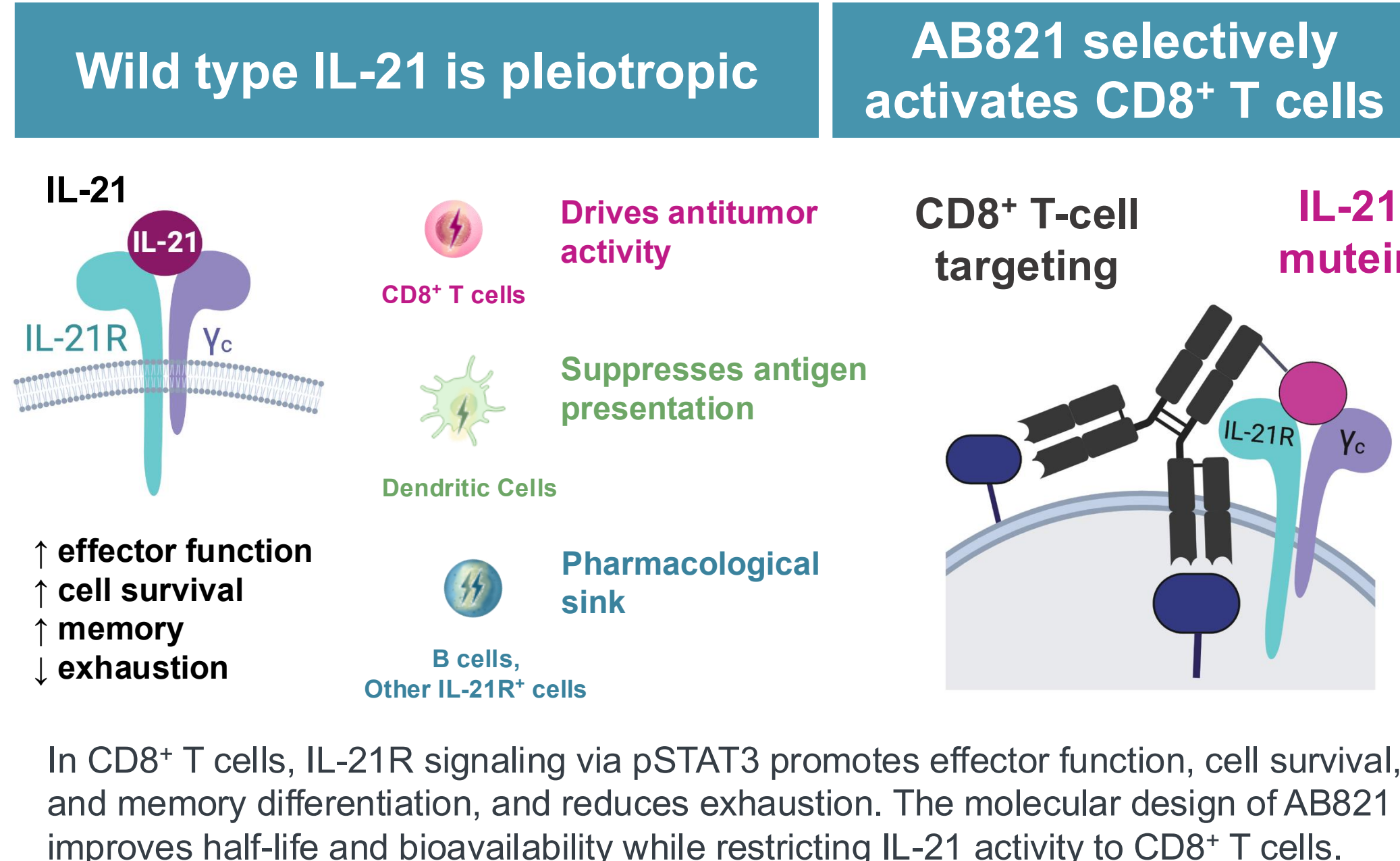
- IL-21 enhances proliferation, survival and function of CD8+ T cells. rhIL-21 was active in pre-clinical models but is limited by off-target effects and rapid clearance.
- AB821 is a fusion of a CD8-targeting antibody that binds to the CD8αβ heterodimer on CD8+ T cells and an IL-21 mutein containing mutations that attenuate affinity for the IL-21 receptor and improve IL-21's half-life and bioavailability.

PRE-CLINICAL DATA SUMMARY:

- AB821 promotes CD8+ T-effector cell cytotoxicity and CD8+ T-cell memory.
- AB821 demonstrates robust tumor growth inhibition and minimal toxicity in immune checkpoint inhibitor refractory tumor models.
- AB821 avoids activation of other IL-21R-expressing cell types, including CD4+ T cells, NK cells, B cells, dendritic cells, and monocytes, that can be "sinks" or contribute to off-target toxicity.

CLINICAL TRIAL METHODS:

- First-in-human phase 1 dose-escalation clinical trial to assess the safety, pharmacokinetics, pharmacodynamics and preliminary anti-tumor activity of AB821 monotherapy administered every 2 weeks (Q2W) in patients with recurrent locally advanced or metastatic melanoma and other immune-responsive solid tumors.
- Patients with melanoma are required to have previously been treated with an inhibitor of PD1/L1 while pts. with other cancer types are required to have received a previous systemic treatment regimen.
- The primary objective is to assess the safety and tolerability of AB821 and identify a recommended phase 2 dose for further evaluation.
- AB821 is administered IV Q2W for up to 2 years. Dose-escalation and/or de-escalation by a BF-BOIN design employing a target toxicity probability of 0.30 with up to 20 total pts. enrolled in backfill cohorts at the RP2D or lower to better assess safety and efficacy.



AB821 PRECLINICAL DATA

Figure 1: AB821 selectively activates pSTAT3 in CD8+ T cells

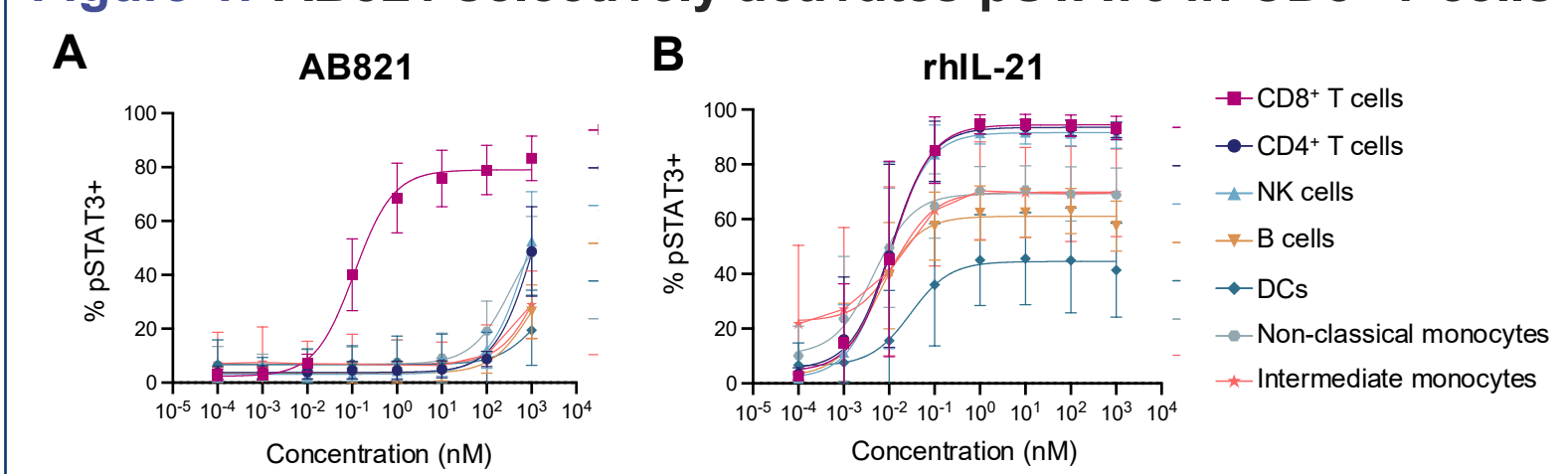


Figure 5: AB821 increases expression of GZMB in exhausted CD8+ T cells in a delayed MC38 tumor model

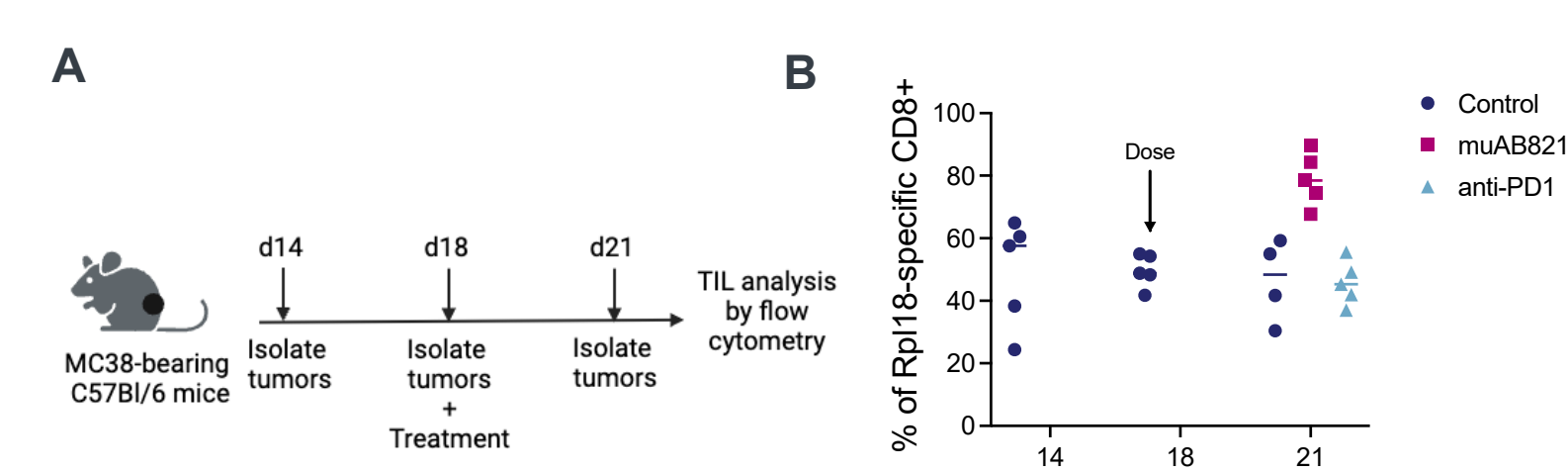


Figure 2: muAB821, the murine surrogate of AB821, has superior antitumor activity compared to wild type mouse IL-21

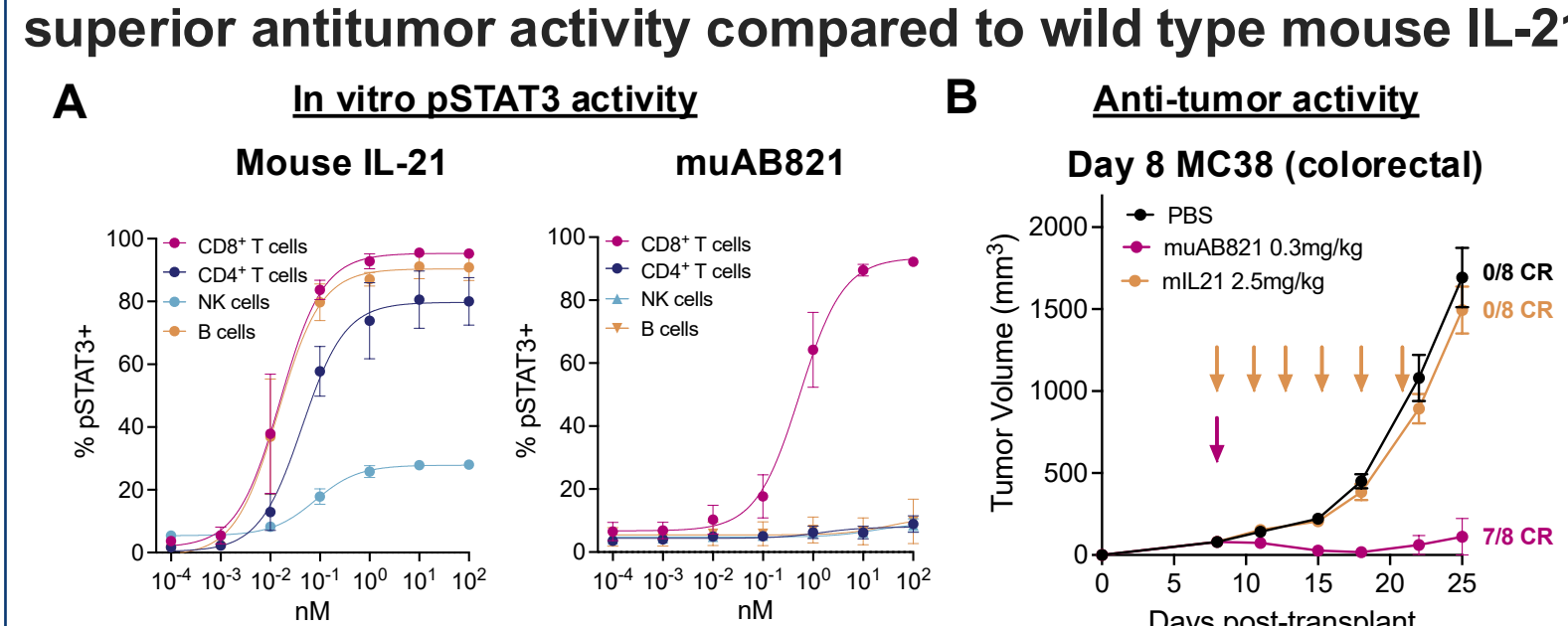


Figure 6: AB821 restores functionality to exhausted human CD8+ T cells

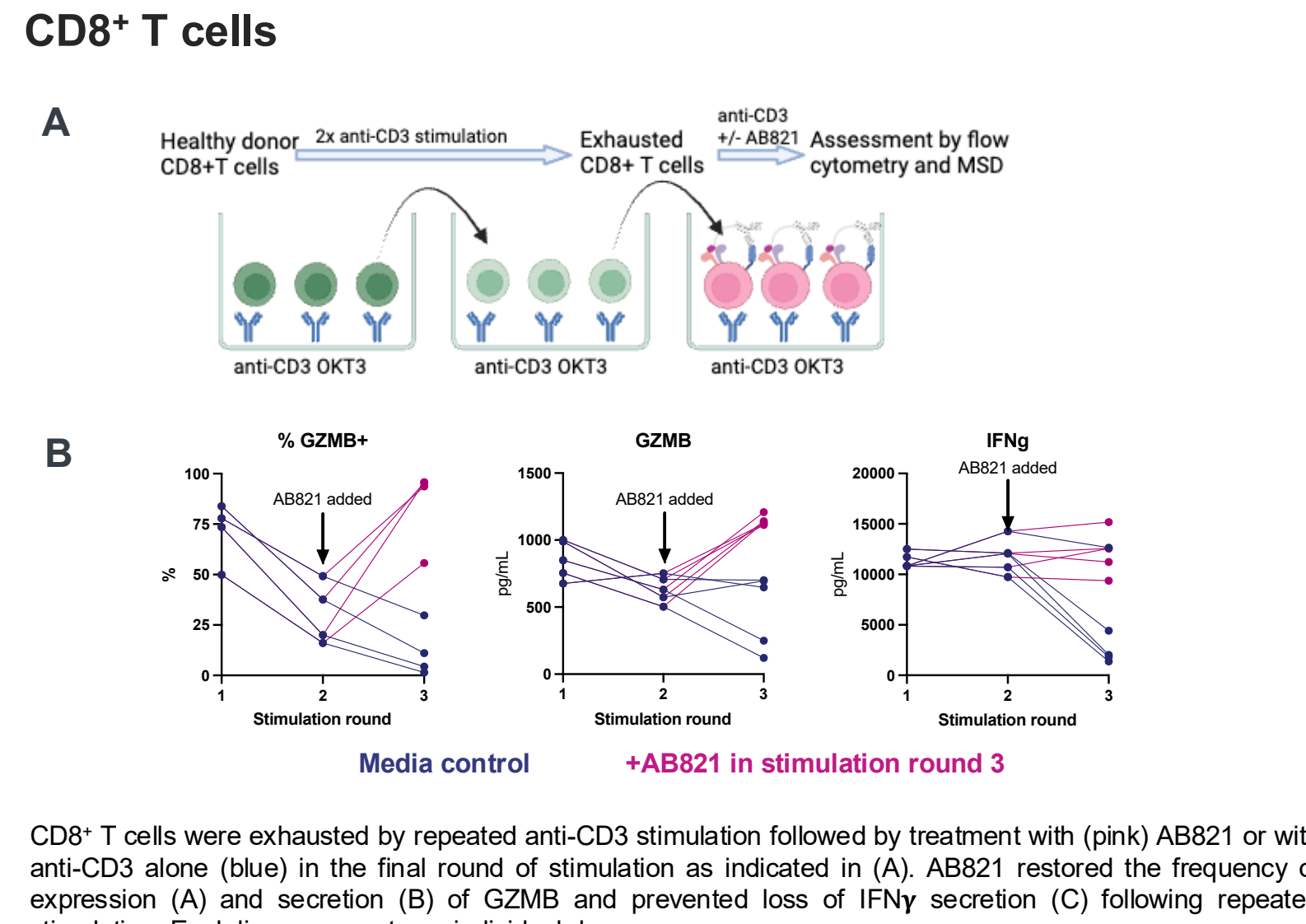


Figure 3: Potent antitumor activity of a potency-matched mouse surrogate of AB821 in anti-PD-1 refractory models

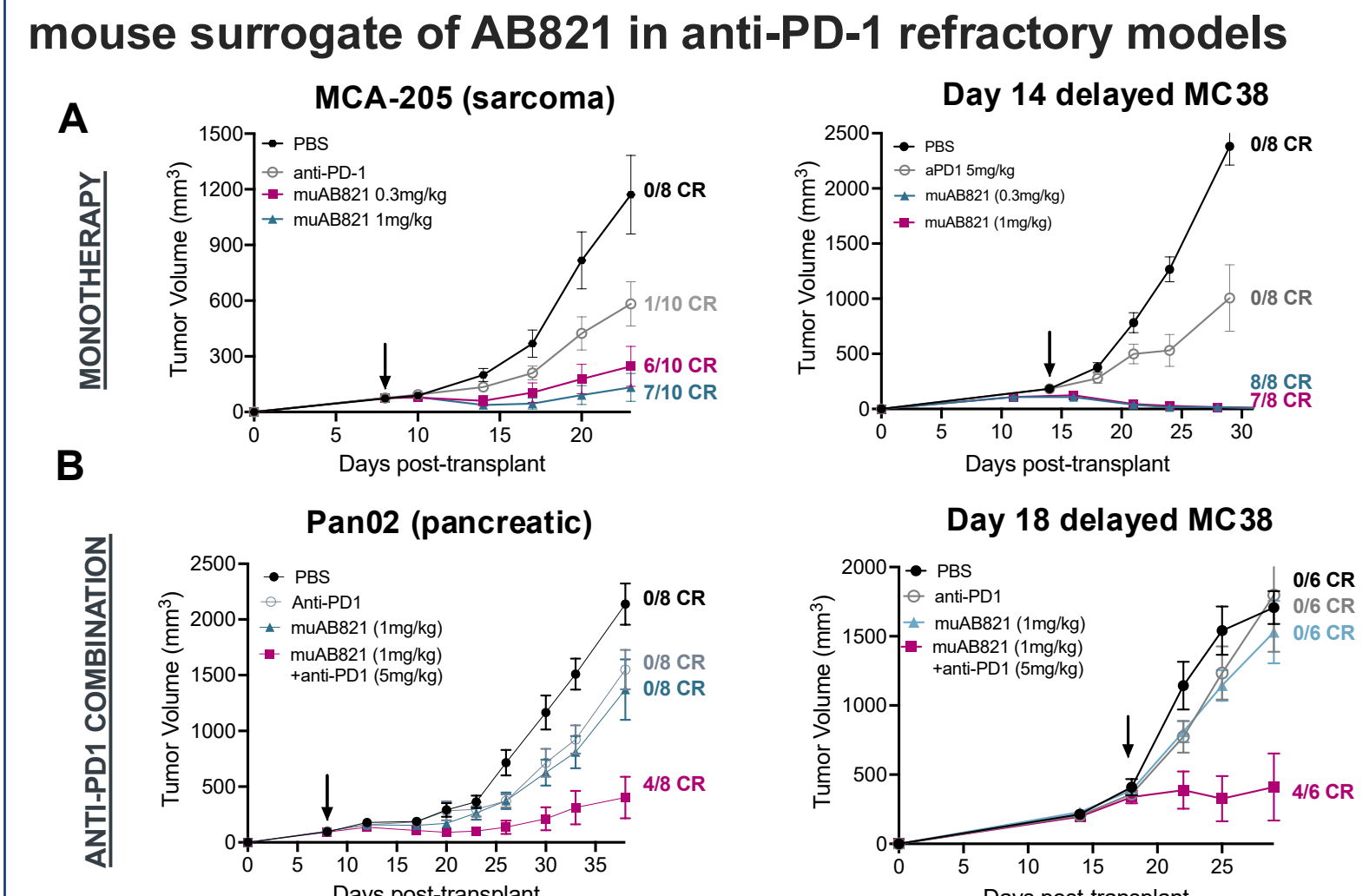
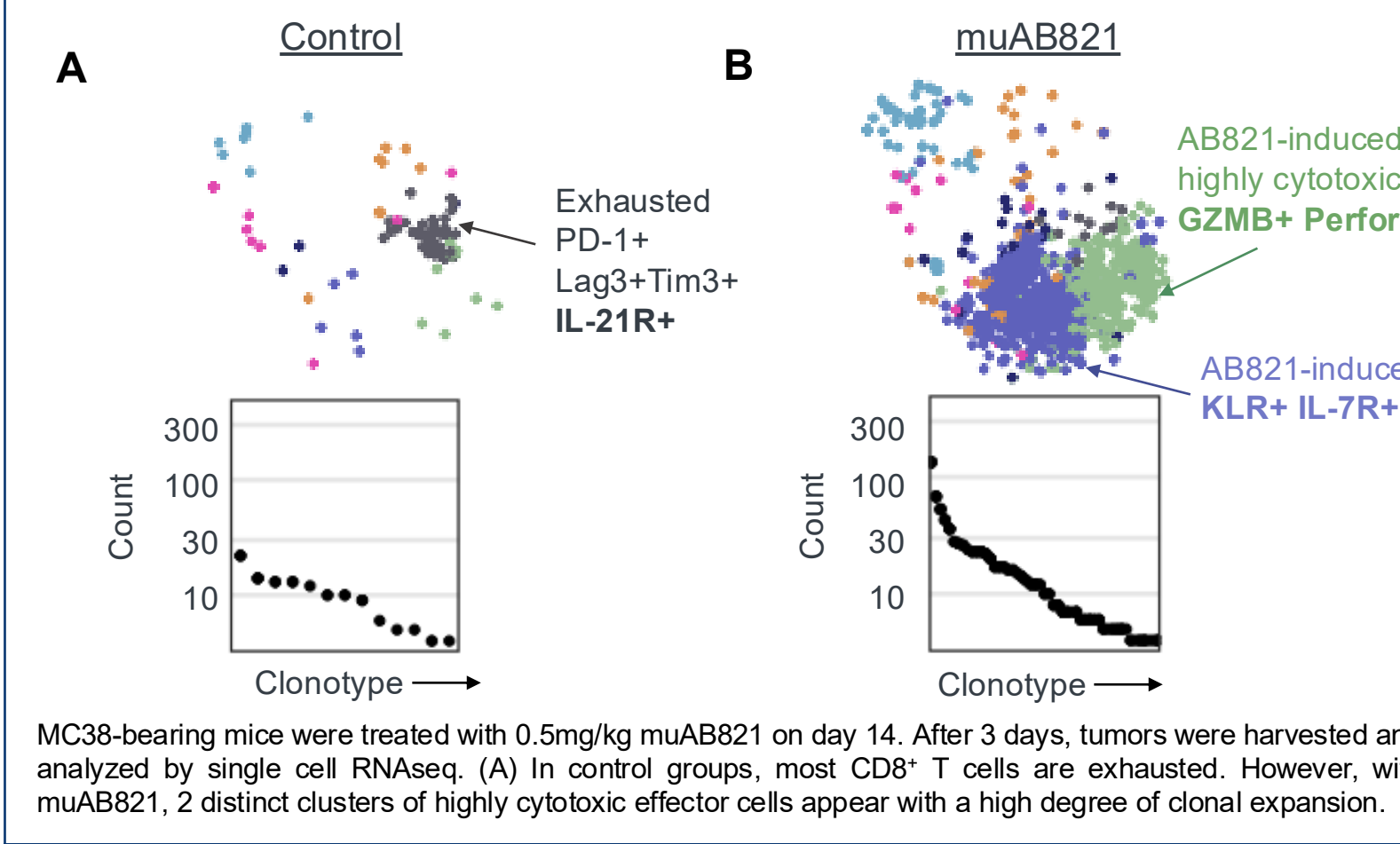


Figure 4: The exhausted CD8+ T cell population is replaced by distinct functional CD8+ T cell populations by AB821 treatment



AB821 PHASE 1 PK AND PD ASSAYS

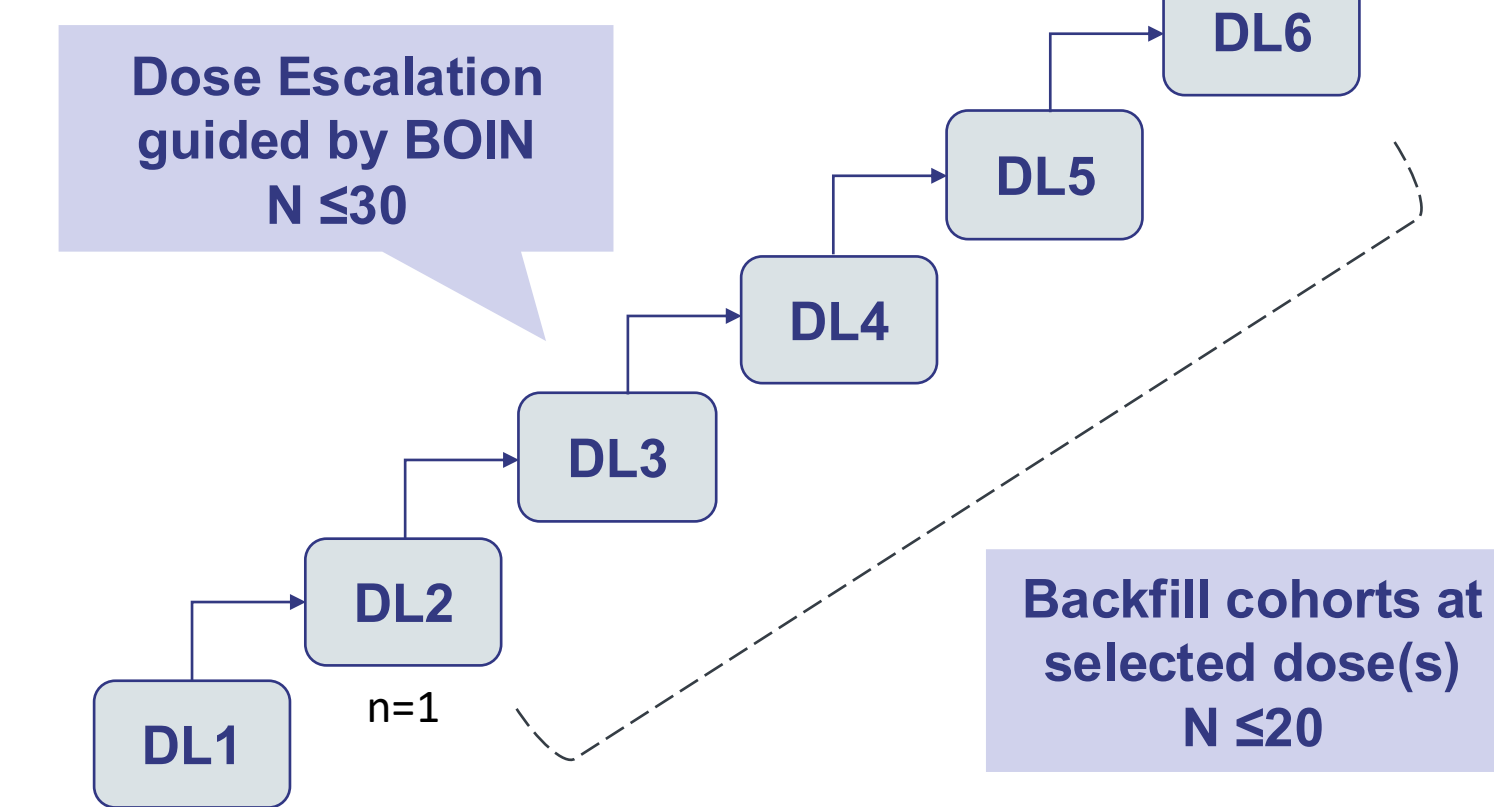
- Validated PK and anti-drug antibody (ADA) assays are used for batched serum analysis in phase 1 pts.
- Whole blood is collected for real-time flow cytometry profiling of immune cell subsets, including markers of proliferation (Ki67), cytotoxicity (Granzyme B), activation (HLA-DR), and markers relevant to tumor antigen-specific T cells and their functional state, including: PD1, TIM3, LAG3, 41BB, CD39, and IL7R.
- Serum assays are performed at Bioagilytix, blood flow cytometry at CellCarta Biosciences.
- Additional samples collected from all pts.: cryopreserved PBMCs, plasma, and if available, tumor biopsies.

NCT07027488 PHASE 1 DESIGN AND OBJECTIVES

- Dose-escalation with a BOIN backfill design employed to determine the MTD/MAD and select the recommended phase 2 dose (RP2D).
- Participants in dose-escalation cohorts are followed for dose-limiting toxicities for 28 days (completion of two 14-day cycles of treatment).
- Based on emerging safety, PK, and PD data, additional participants may be enrolled in backfill cohorts at or below dose levels previously cleared in the dose-limiting toxicity (DLT) assessment and determined to be safe and tolerable by the Data and Safety Monitoring Board (DSMB).

Phase 1A Dose Escalation and Backfill

- AB821 administered IV Q2W
- 28-day DLT window
- Participants with 2L+ melanoma + other solid tumors
- Up to 50 patients (Escalation: ≤30, Backfill: ≤20)



Primary Objective:

- Assess the safety and tolerability of AB821.

Secondary Objectives:

- Assess the pharmacokinetics (PK) of AB821 in serum.
- Assess the immunogenicity of AB821.
- Assess the preliminary antitumor effect of AB821 per RECIST v1.1.

Exploratory Objectives:

- Assess the pharmacodynamics of AB821 in tumor tissue.
- Evaluate exploratory biomarkers in blood and tumor tissues that may be predictive or associated with response to AB821.
- Assess the exposure-safety and exposure-response relationship for antitumor effects.

KEY INCLUSION / EXCLUSION CRITERIA

Inclusion Criteria include:

- ≥18 years at the time of consent
- ECOG PS of 0 or 1
- Adequate organ function including: ANC > 1500/uL; platelets > 100,000; Hgb. > 9 g/dL.; Cr. Cl. ≥ 50 mL/min; total bili ≤ 1.5x ULN OR direct bilirubin ≤ ULN for participants with total bilirubin > 1.5 x ULN; PT INR > 1.5 x ULN unless on anticoagulation; Albumin > 3 g/dL.
- Life expectancy of ≥12 weeks, per treating investigator's judgment.
- For Melanoma participants: Unresectable or metastatic melanoma that have progressed on or after PD-1/PD-L1 checkpoint blockade (alone or with anti-CTLA-4 or anti-LAG-3). Prior BRAF/MEK not required.
- For other tumor types: Must have a recurrent histologically or cytologically proven metastatic or locally advanced solid tumor (non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), Merkel-cell carcinoma, bladder cancer, or squamous cell carcinoma of the head and neck (SCCHN)), meeting each of the following:
 - Tumor not amenable to curative treatment with surgery or radiation.
 - Tumor for which immune checkpoint inhibitors form part of standard-of-care.
 - At least one prior line of systemic anticancer therapy in the recurrent or metastatic setting.
- Measurable disease per RECIST v1.1 as assessed by the local site investigator/radiology.

Exclusion Criteria include:

- Immunodeficiency.
- Prior stem cell, bone marrow, or organ transplant.
- Known history of HIV infection.
- History of HBV (defined as HBV surface antigen reactive) or active HCV.

CONCLUSIONS, ONGOING PROGRESS, AND ACKNOWLEDGEMENTS

- This ongoing phase 1 clinical trial of AB821, an investigational CD8 cis-targeted IL-21, is currently evaluating patients at dose level 4.
- Preliminary data from approximately 10 patients enrolled to date suggest promising PK, PD, tolerability, and clinical activity.
- Emerging findings are consistent with preclinical data, including evidence of cis targeting and pharmacodynamic effects on CD8+ T cells.
- An amendment evaluating AB821 in combination with AB248, a cis-targeted IL-2 (presented separately as abstract #2616), is in development.
- The Sponsors extend their appreciation to the patients, families, investigators and site staff members who are making this clinical trial possible. Funding for this study was provided by Asher Biotherapeutics, Inc. (Asher Bio) and Yale Cancer Center. ID and EG are employed by Asher Bio and MS is an advisor to Asher Bio.

