Background AB248 is a fusion of an affinity-attenuated IL-2 mutein and an antibody targeting CD8+ T cells designed to overcome the limitations of wild-type IL-2 and second-generation IL-2Rβγ agonists, “not-α” IL-2 and IL-15 variants. Like “not-α” IL-2, AB248’s IL-2 mutein does not bind IL-2Rα and thus avoids IL-2Rα-associated vascular leak syndrome (VLS) and preferential Treg activation in nonclinical models. Further, the IL-2 mutein in AB248 has reduced IL-2Rβ affinity, and its cis-targeting to CD8+ T cells enables AB248 to avoid the biased expansion of IL-2Rβγ high NK cells and IL2Rbg-mediated activation of Tregs associated with untargeted IL2Rbg agonists. Thus, AB248’s design enables robust IL-2 pharmacology on CD8+ T cells, key effectors with IL-2-based therapy1-2, while avoiding cell types that may promote toxicity or oppose anti-tumor activity. Here, the mechanisms by which AB248 achieves enhanced nonclinical activity and safety profiles over untargeted IL-2-based therapies are elucidated.

Methods In vitro activation and cytokine release assays were performed on human immune cells. Tumor immune profiling including scRNAseq was performed in mice treated with AB248’s surrogate, muAB248. Cynomolgus monkeys were dosed with AB248.

Results We previously showed that IL-2 and “not-α” IL-2 triggered antigen-independent cytokine release from PBMCs in vitro, which was mitigated by the depletion CD56+ cells, which are largely NK cells, and that AB248 avoided this non-selective cytokine release. Studies with sorted PBMC subsets further interrogated this observation and demonstrated the necessity of dual IL-2Rα and IL-2Rβγ affinity reduction as well as CD8+ T cell cis-targeting to avoid antigen-independent cytokine release. Strong anti-tumor activity was elicited by muAB248 in multiple murine models without body weight loss. In contrast, “not-α” IL-2 could not achieve meaningful activity without accompanying NK cell-dependent weight loss. Bypassing the NK cell sink was also important for optimal expansion of intratumoral CD8+ T cells. Comprehensive analysis following treatment with muAB248 demonstrated profound impacts to the tumor immune infiltrate, including activation of unique CD8+ T cell clusters by muAB248 compared to “not-α” IL-2, which may explain muAB248’s superior anti-tumor activity. In cynomolgus monkeys, repeated doses of AB248 that selectively expanded CD8+ T cells >20-fold were well tolerated, without evidence of cytokine release syndrome or VLS.

Conclusions AB248 exhibited strong anti-tumor activity in mice, profound pharmacodynamic effects in primates, and a favorable nonclinical safety profile. CD8+ T cell restriction was essential for optimal anti-tumor activity and safety in nonclinical models. Collectively, this data demonstrates AB248’s differentiation from broadly acting IL-2-based therapies and supports AB248’s clinical development.

REFERENCES