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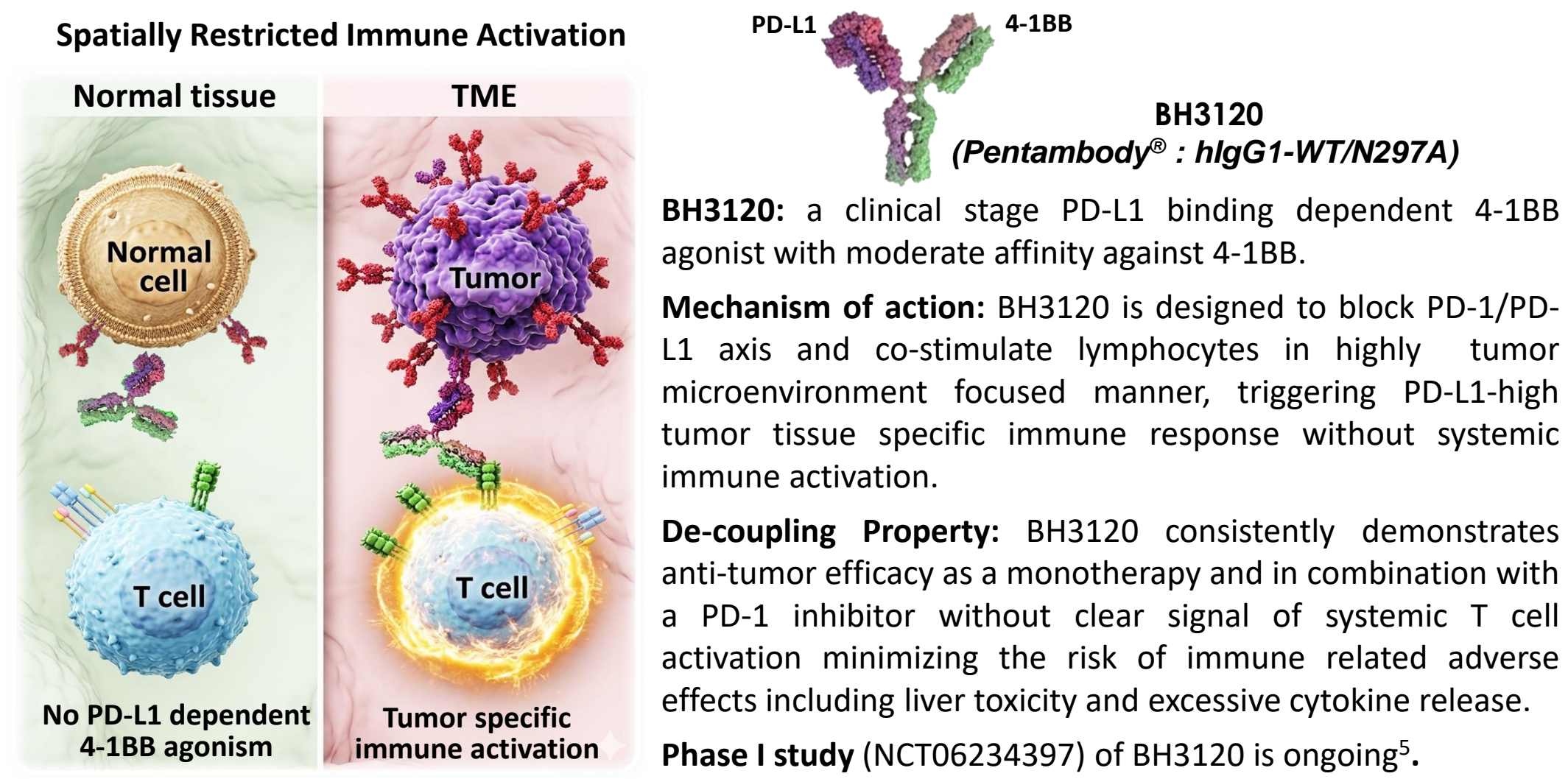
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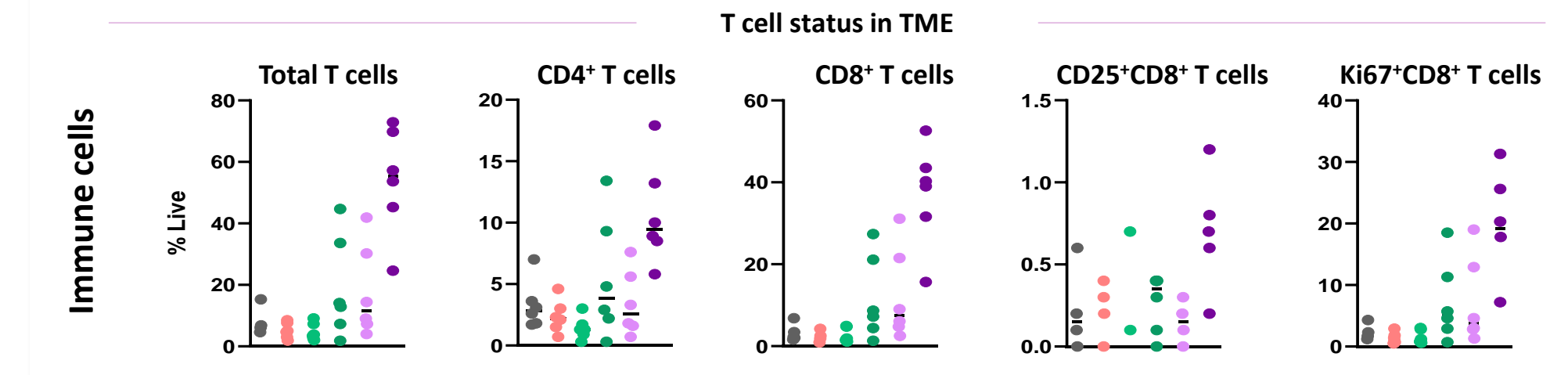
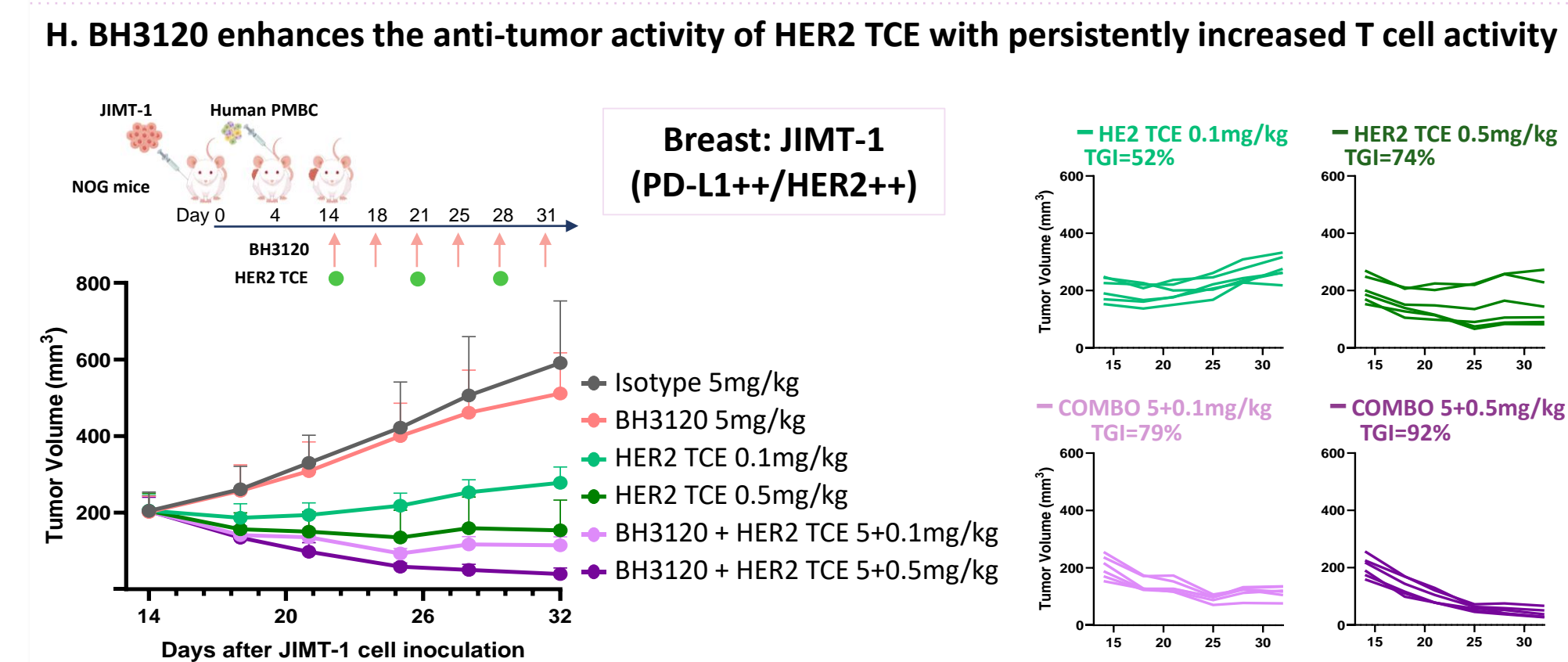
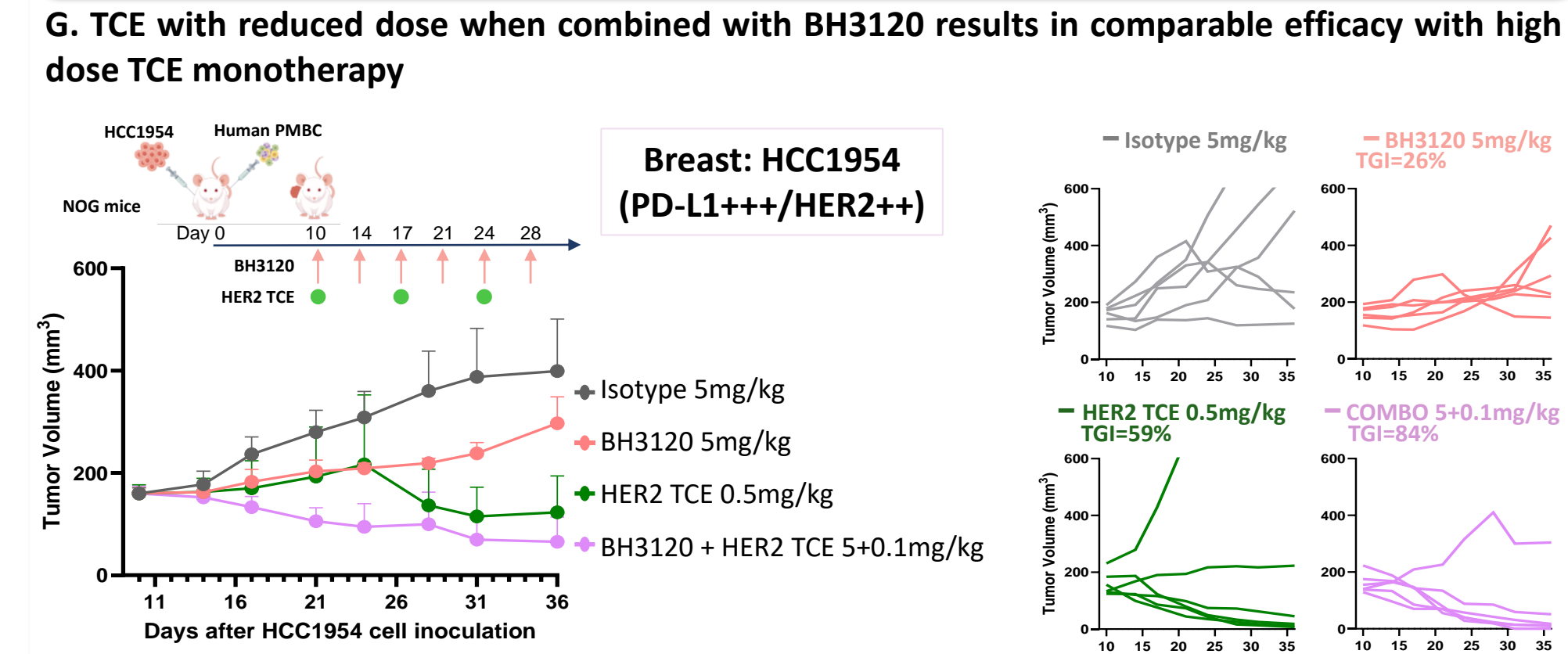
Abstract

In the tumor microenvironment (TME), T cell activation often leads to upregulation of immune checkpoints such as PD-1 and PD-L1. This adaptive resistance mechanism, combined with insufficient co-stimulatory signals, creates an immunosuppressive milieu that compromises T cell cytotoxicity and contributes to resistance against T cell-targeted immunotherapies^{1,3}. Activation of T cells with CD3 stimulation alone is often associated with cytokine related safety concerns and limited efficacy in solid tumors. To overcome the limitation with CD3 T cell engagers, different combination strategies have been discussed and co-stimulatory signals have been suggested as potential combination partner of T cell stimulators^{2,3}. BH3120 is a clinical stage bispecific antibody designed to induce 4-1BB co-stimulation in PD-L1 positive tumor tissue localized manner, inducing immune activation in TME with minimal irAEs including liver toxicity⁴. The therapeutic potential of BH3120 in combination with CD3 T cell engagers were tested resulting in enhanced T cell activation and specific lysis of tumor cells *in vitro*. Furthermore, this combination regimen shows synergistic tumor growth inhibition across different animal models without significant safety concerns. These findings support BH3120 as a rational combination partner for T cell-engaging therapies, offering a promising strategy to overcome adaptive immune resistance while minimizing systemic toxicities.

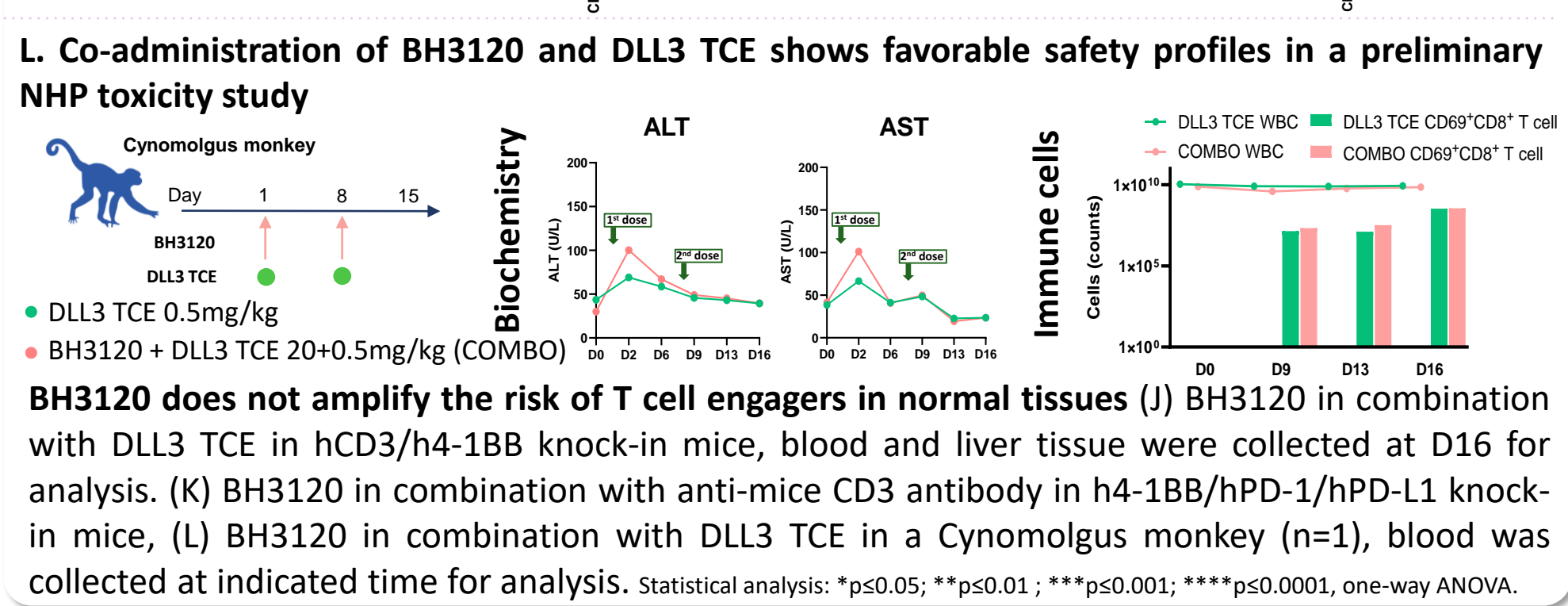
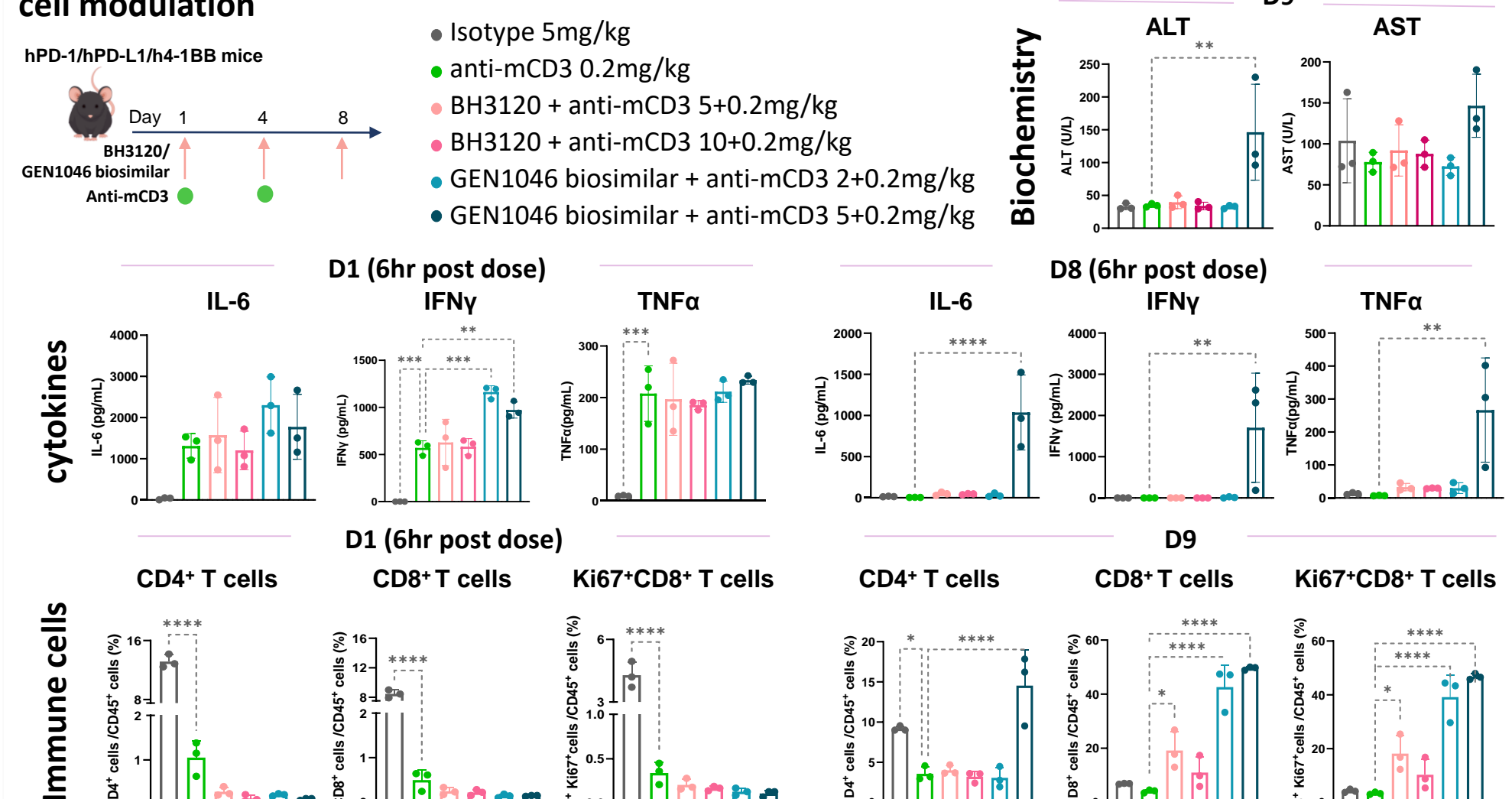
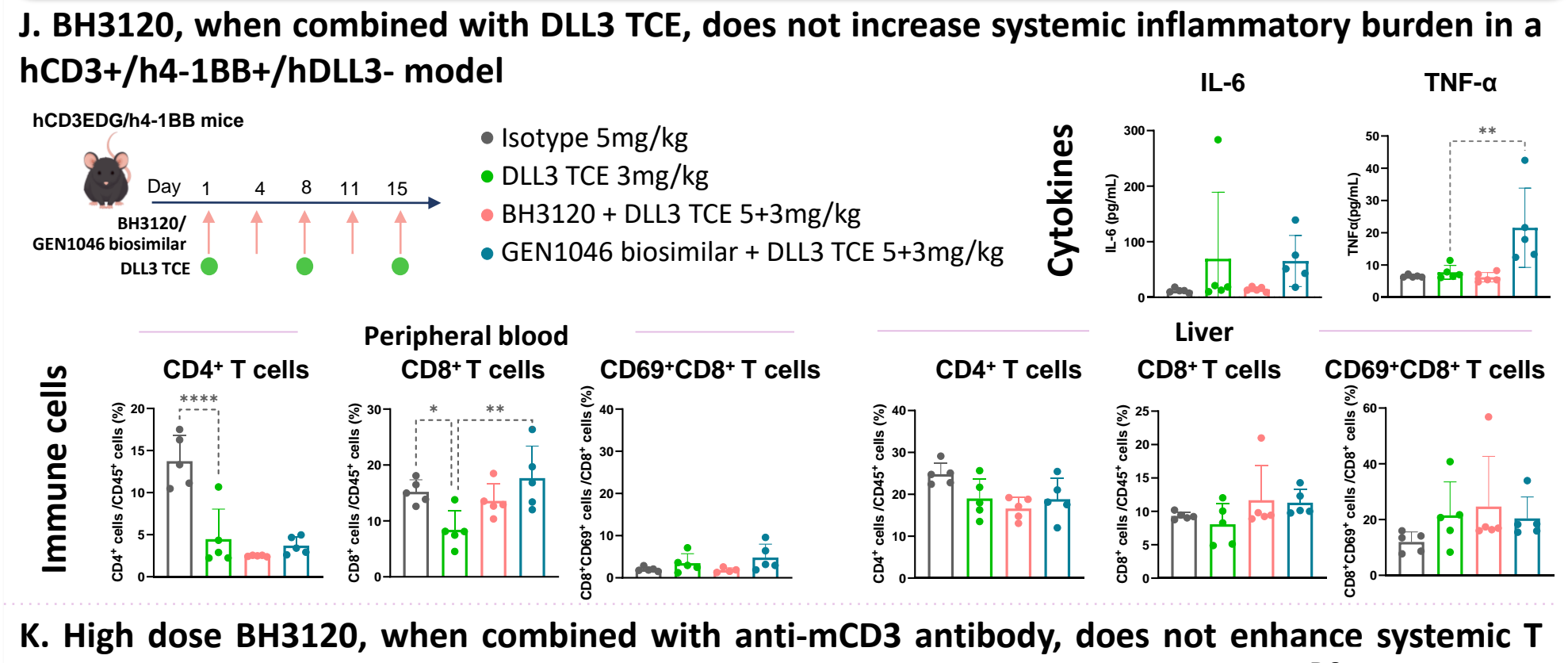
Characteristics of BH3120



The Combination Induces Persistent T cell Activities in TME

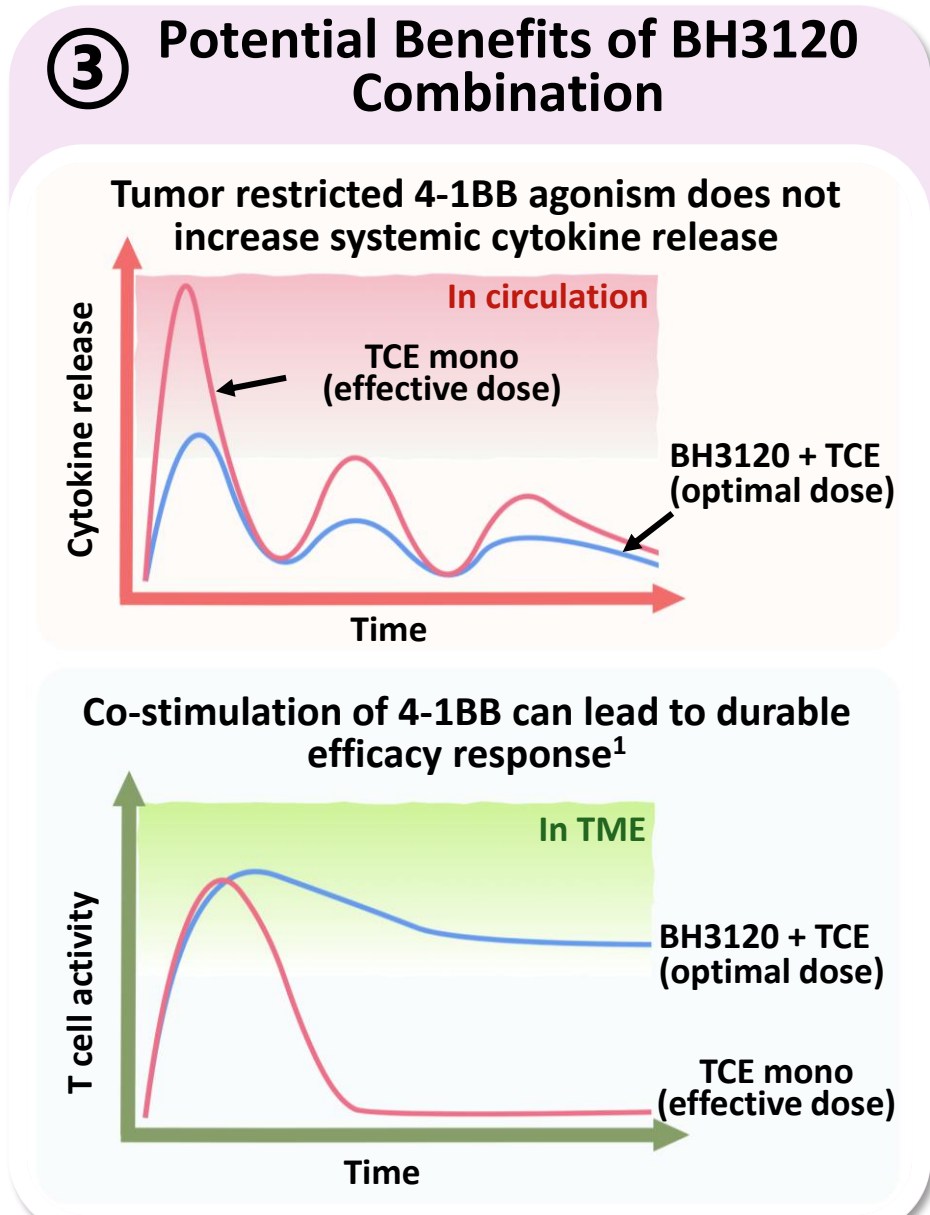
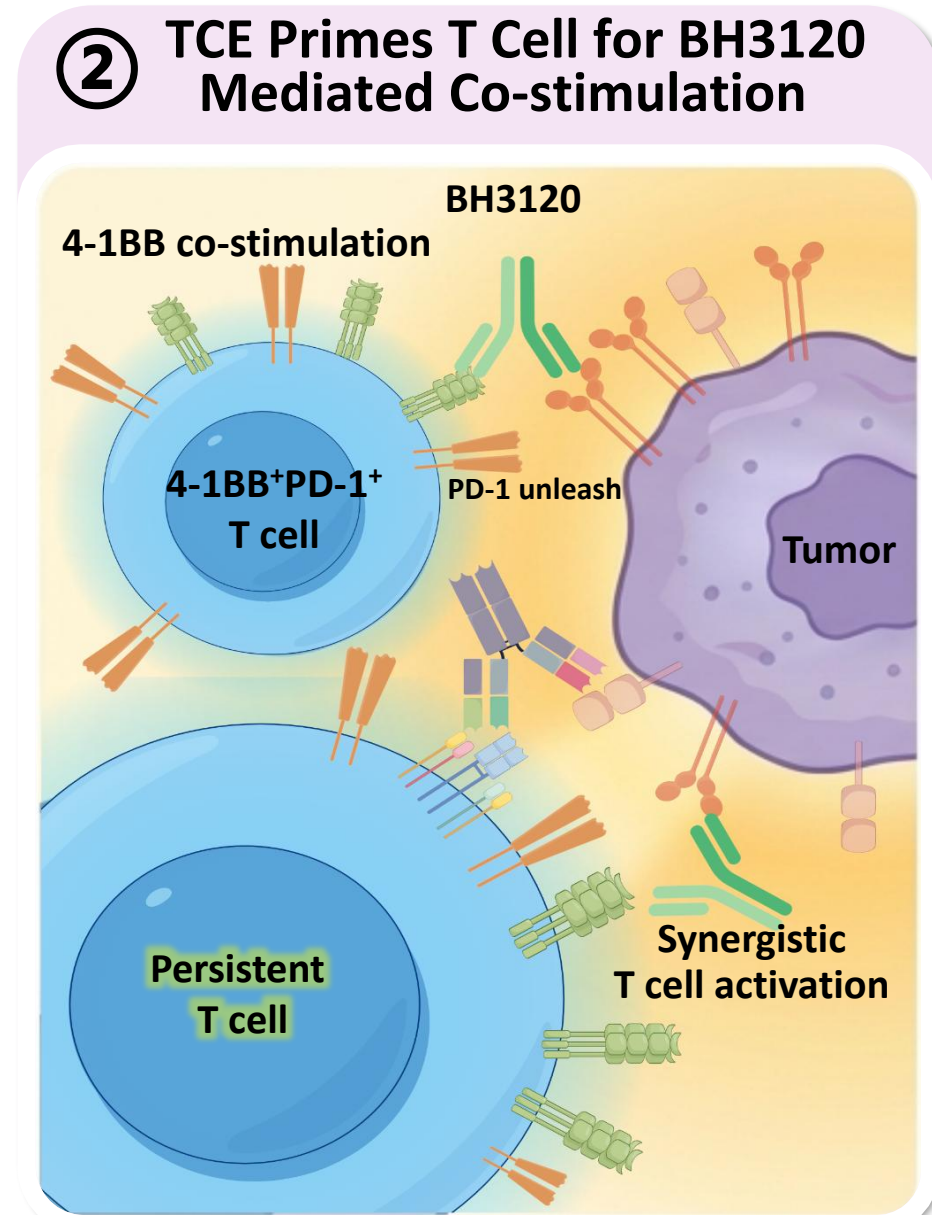
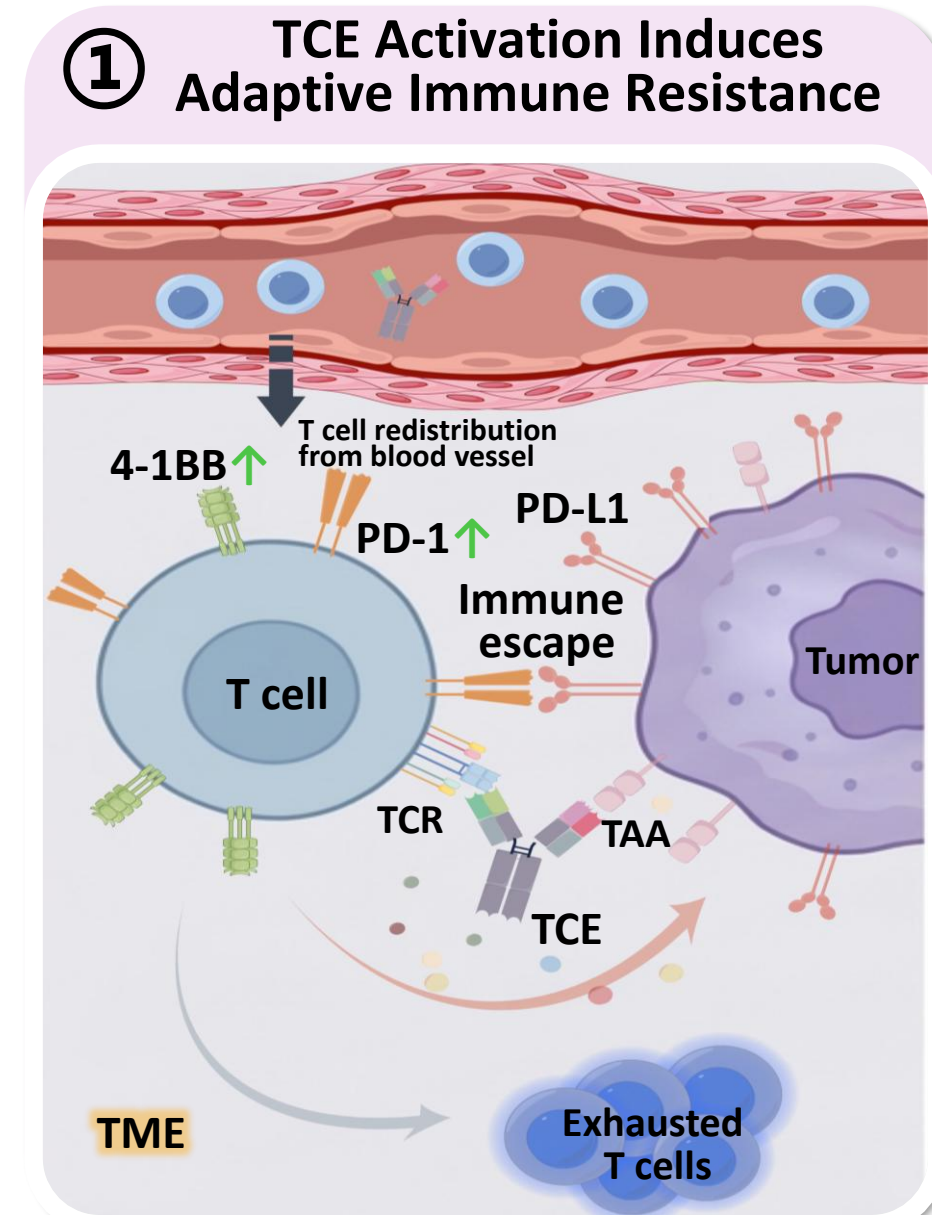


BH3120 together with TCEs Shows Favorable Safety Profiles

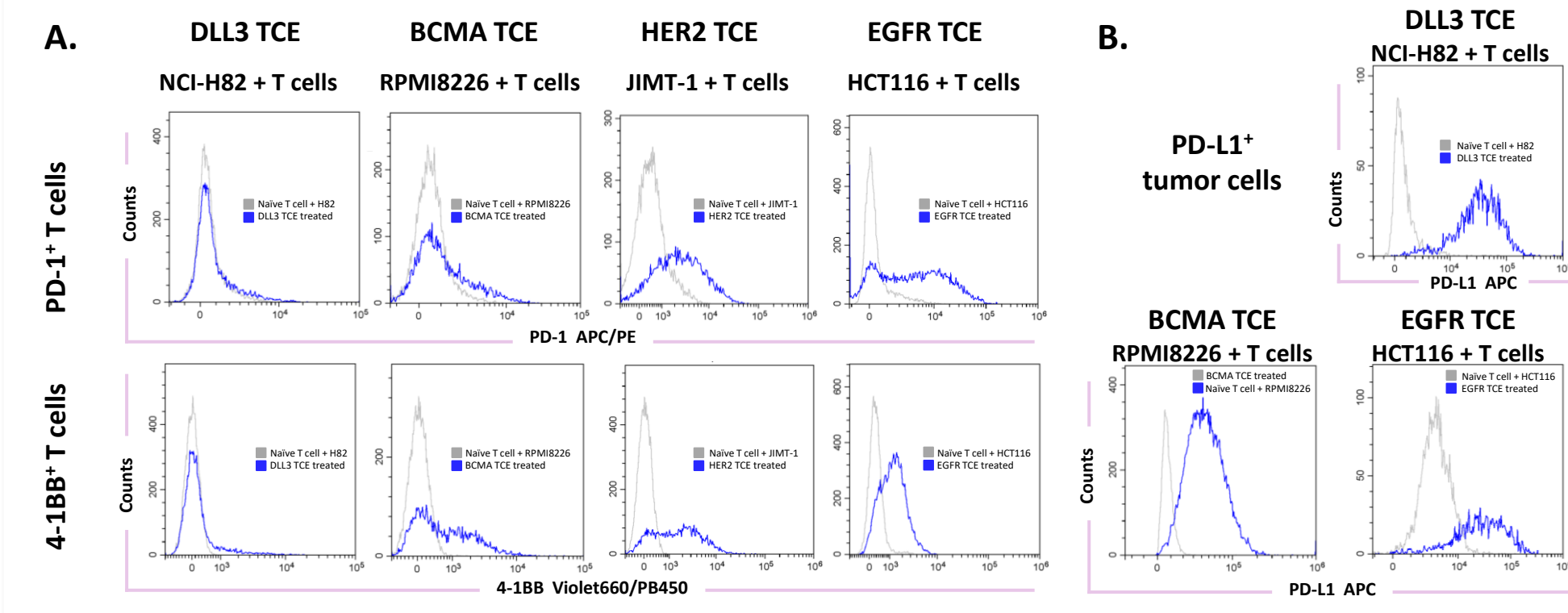


BH3120 and TCEs: Potential Mechanism of Combination

	Early cycles (C1~C2)	Following cycles (C3+)
Unmet Needs of CD3 TCEs		
Problem	Overstimulation of systemic T cells resulting in CRS	T cell exhaustion and depletion ↑ Antitumor efficacy ↓
Suggestion	Optimal TCE regimen Combined with Conditional PD-L1x4-1BB BsAb	Combination with Tumor localized PD-L1x4-1BB BsAb
Expectation	Burden of systemic T cell over stimulation reduced, while T cell functionality maintained	Persistent survival and expansion of T cells inducing durable antitumor efficacy

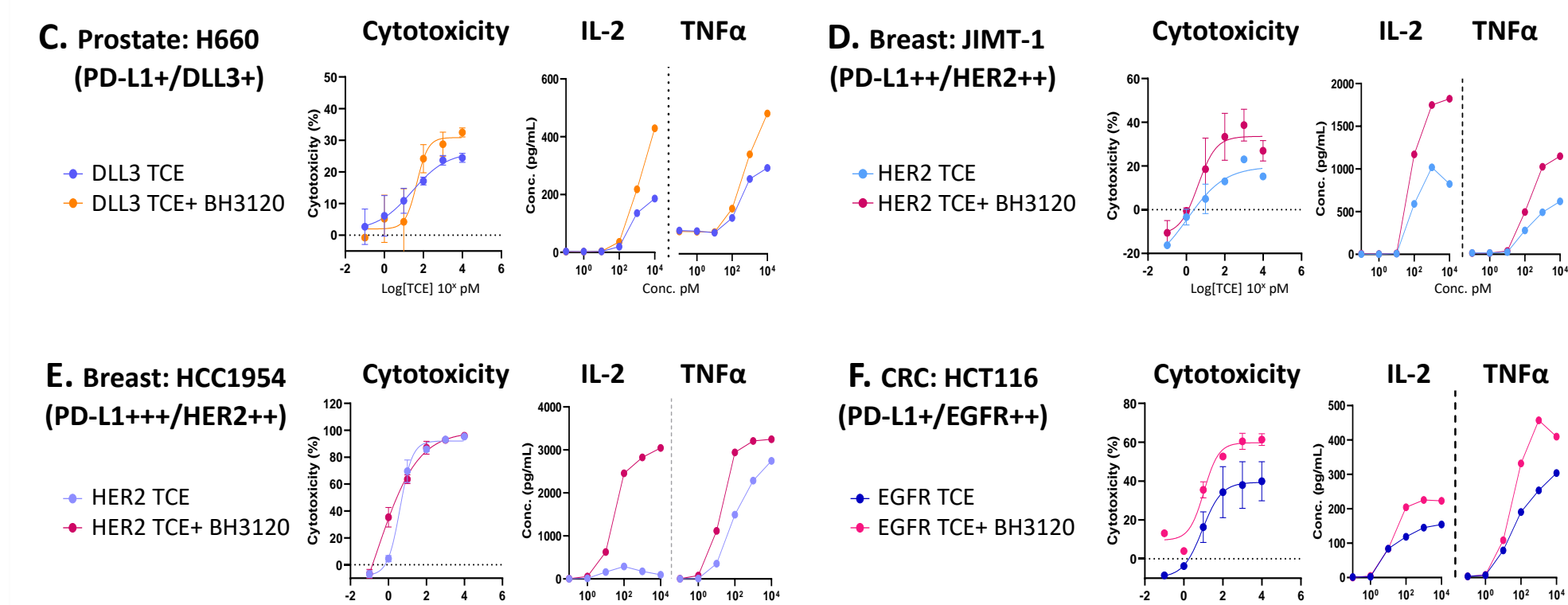


Modulation of TME by TCEs: A Foundation for BH3120 Combination



TCEs Induce T cell activation and Modulate Tumor microenvironment. Human CD3 T cells co-cultured with tumor cells with or without TCEs (100 pM) were incubated for 2 days and assessed by flow cytometry. (A) Stimulation by TCE induces PD-1 and 4-1BB expression on T cells, (B) TCEs also trigger an adaptive immune resistance with PD-L1 on the surface of tumor cells. PD-1, PD-L1, and 4-1BB were induced consistently and the induction level varied depending on the targets and relevant tumor cells tested. DLL3 TCE and BCMA TCE are biosimilars of Taltamab and Teclistamab, respectively.

BH3120 Synergizes with TCEs to Amplify T-cell Activation and Cytotoxicity across Tumor Cell Lines



BH3120 in combination with TCEs displays cytokine modulation and cytotoxicity superior to those of TCE alone. Human PMBC was co-cultured with PD-L1/DLL3 expressing tumor cell, (C) NCI-H660, PD-L1/HER2 expressing tumor cells, (D) JIMT-1 and (E) HCC1954, and PD-L1/EGFR expressing tumor cell, (F) HCT116. Different concentrations of TCEs and the combination with BH3120 (50nM) were incubated for 2 days. Tumor cytotoxicity was measured with CCK-8. Cytokine in supernatant was assessed by flow cytometry with Human Th1/Th2 Cytokine CBA Kit.

Conclusion

- BH3120, a PD-L1/4-1BB bispecific antibody, is currently under clinical investigation both as a monotherapy and in combination with a PD-1 inhibitor. Non-clinical and early clinical studies have indicated consistently favorable safety profiles supporting the de-coupling concept and suggesting further opportunities for different combination regimens.
- Activation of T cells by T cell engagers (TCEs) results in up-regulation of immunosuppressive signals including PD-1/PD-L1 in tumor tissues. In the meantime, the costimulatory receptor, 4-1BB is induced on the surface of activated T cells. BH3120 as a PD-L1 inhibitor and spatially restricted 4-1BB signal amplifier may provide profound and sustained TCE mediated antitumor activity and overcome immune resistance in TME while minimizing the risk of stacking toxicity systemically.
- Non-clinical evaluation of BH3120 as the combination partner of TCEs demonstrate the synergistic effects in multiple *in vitro* and *in vivo* models, and suggest the potential combinability of BH3120 with different T cell engagers. In preliminary toxicity studies, BH3120 combination did not induce additional immune activation signals in normal tissues.
- Taken together, given the immunosuppressive TME and lack of sufficient costimulatory signals, combining optimal dose of TCEs with BH3120 may offer alternative dosing strategies with durable efficacy and improved safety. Further studies with different dosing scenarios are encouraged to better understand the mechanism of the combination.