

M9657, a tumor-targeted CD137 agonist, induced significant antitumor immunity in combination with anti-PD-1 antibody

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CONCLUSIONS

- The combination of M9657 with anti-PD-(L)1 could overcome primary ICI therapy resistance and improve the antitumor efficacy and patient outcomes of current anti-PD-(L)1 therapy in the clinic.

RESULTS CONTINUED

Figure 4. The combination of M9657 and pembrolizumab significantly stimulate cytokine release in ex vivo functional assay

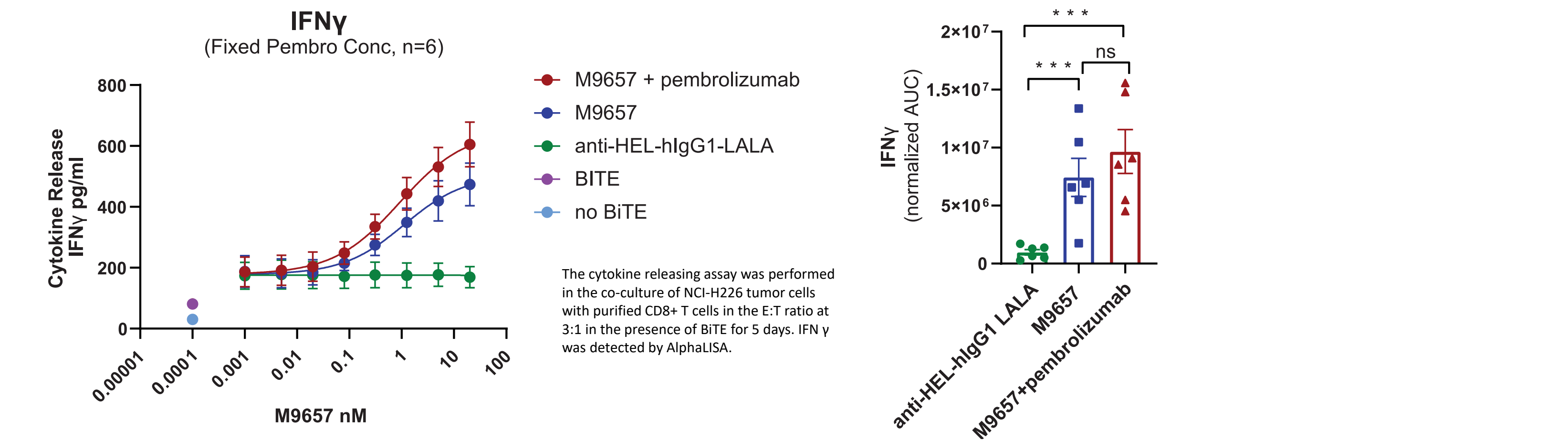


Figure 5. Combination treatment of FS122m and anti-mPD-1 enhanced antitumor efficacy and prolonged survival relative to monotherapies in syngeneic tumor models

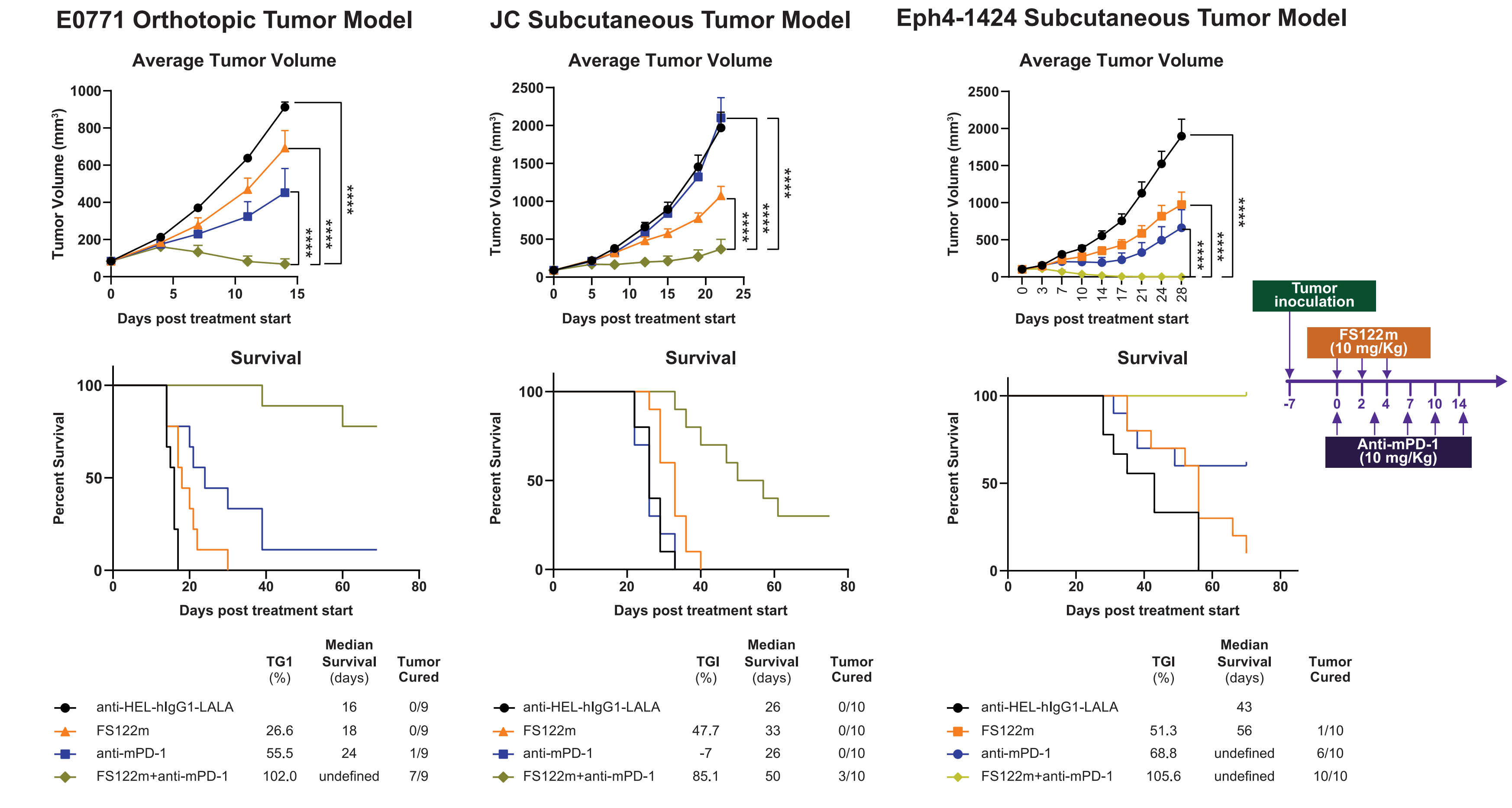
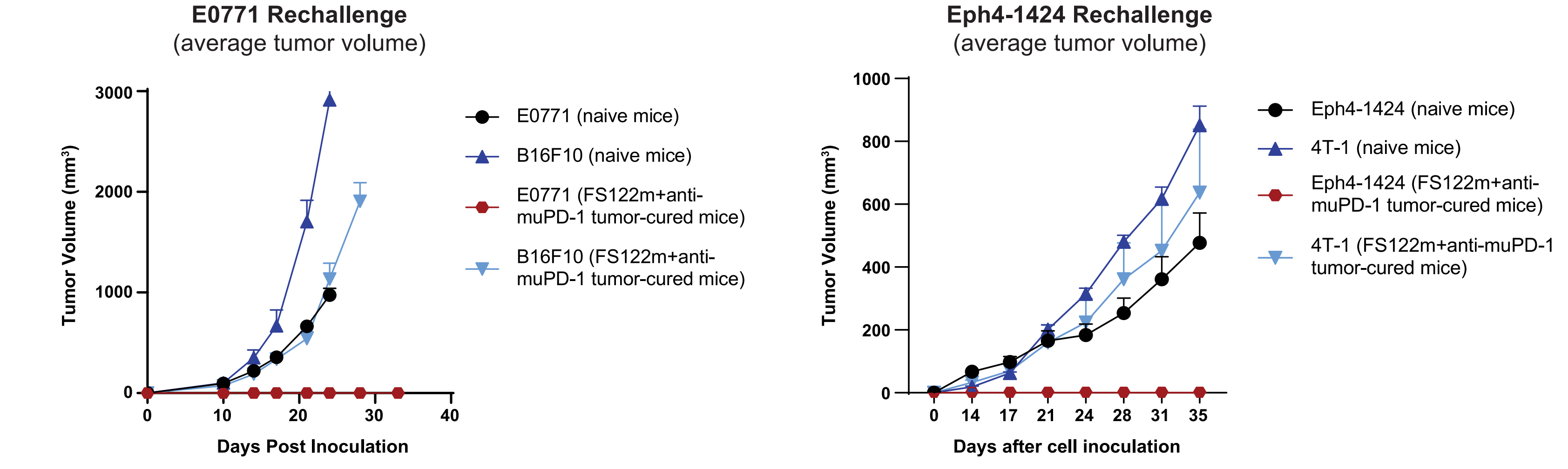


Figure 6. Rechallenge study demonstrated the generation of tumor antigen-specific antitumor immunity and long-term immune protectivity.



RESULTS

- The combination of M9657 and pembrolizumab displayed dose-dependent immune agonism potency and significantly enhanced tumor cell cytotoxicity and CD8+ T cell cytokine release relative to single agent treatments (Figure 2, 3 & 4).
- In various syngeneic tumor models, the combination of FS122m with anti-mPD-1 significantly increased antitumor efficacy relative to monotherapies, with more complete tumor regression and prolonged median survival (Figure 5).
- Tumor-cured mice after combination treatment exhibited resistance to the primary tumor rechallenge, indicating the generation of tumor antigen-specific antitumor immunity and long-term immune protectivity (Figure 6).

Figure 2. The combination of M9657 and pembrolizumab displayed enhanced immune agonism potency in luciferase cellular assay

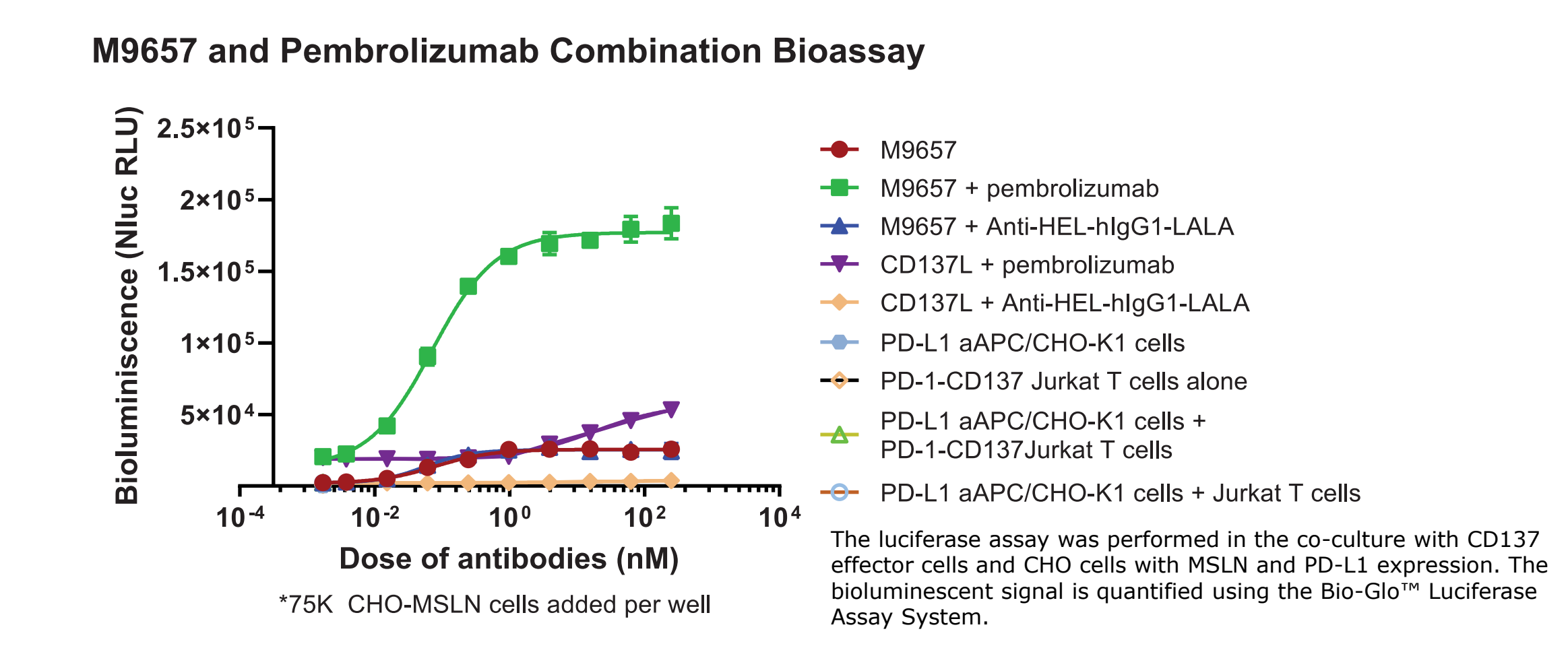
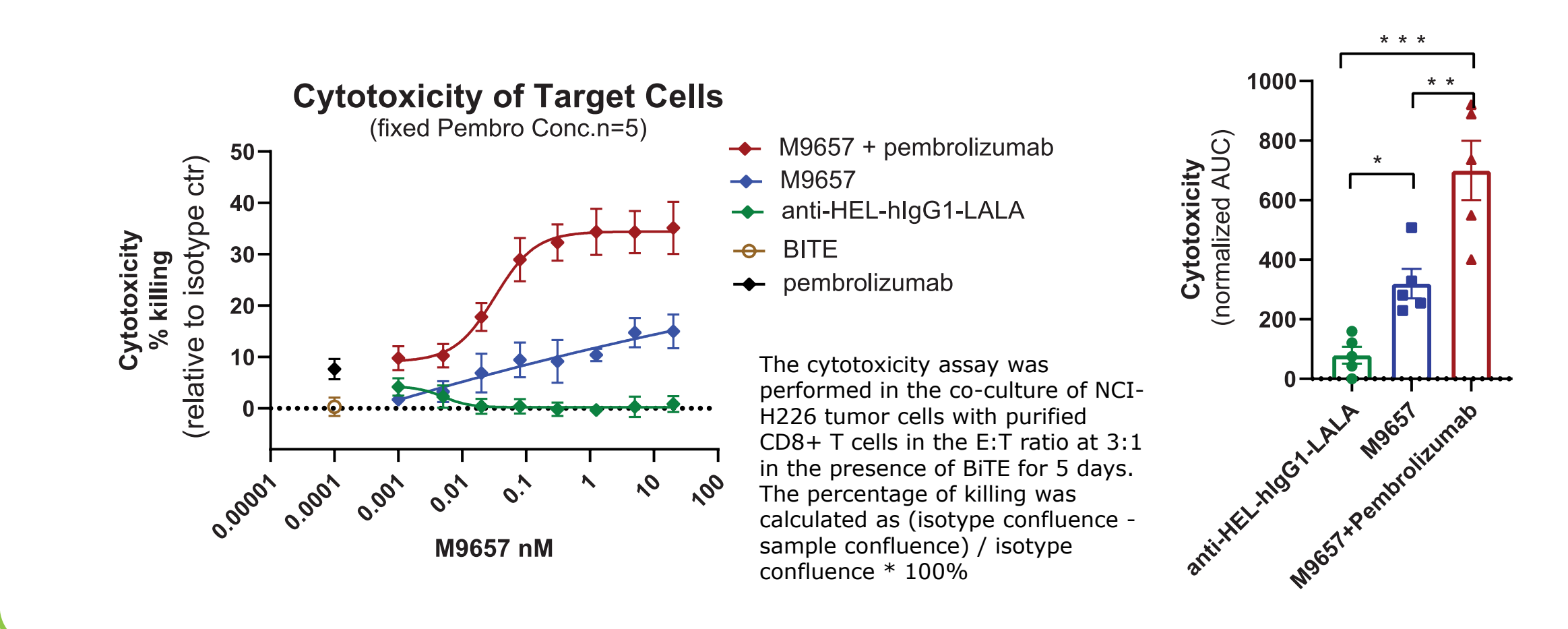


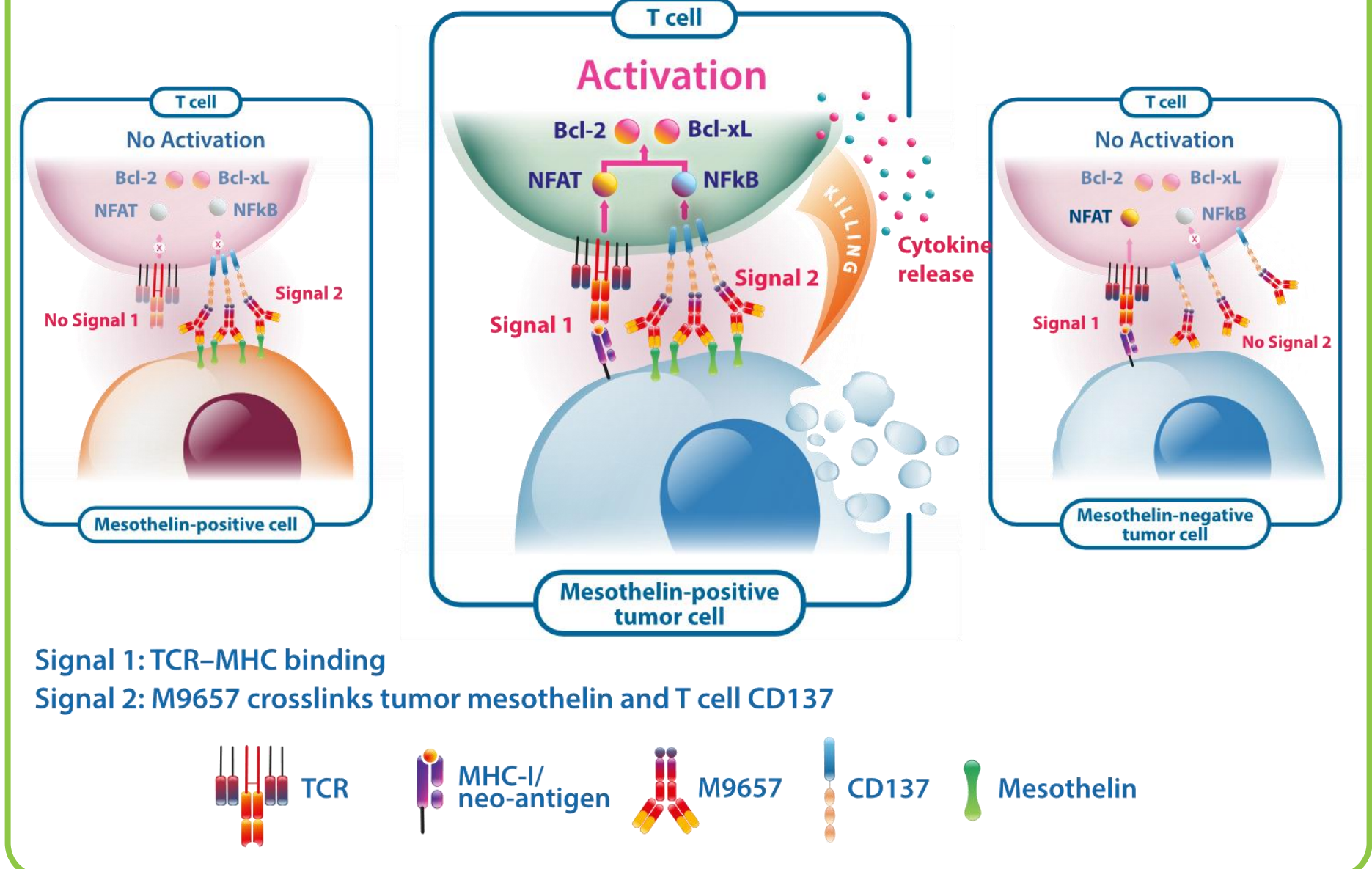
Figure 3. The combination of M9657 and pembrolizumab significantly enhanced tumor cell cytotoxicity in ex vivo functional assay



BACKGROUND

- M9657, a first-in-class tumor-targeted conditional immune agonist, was developed to boost antitumor immune responses in the tumor microenvironment (TME) by targeting CD137¹ (Figure 1).
- The immune agonism potency of M9657 was validated through in vitro assays and in vivo efficacy studies in syngeneic tumor models using the surrogate antibody FS122m.
- Combining CD137 agonists and anti-PD-(L)-1 antibodies presents a novel therapeutic strategy to overcome immune checkpoint inhibitor (ICI) resistance and enhance antitumor activity via complementary mechanisms². Anti-PD-(L)-1 antibodies can reverse the suppressive immune signals, and CD137 agonists can boost T cell activation, improving antigen presentation and cytokine release.

Figure 1. Schematic of M9657 mechanism of action



METHODS

- The antitumor immunity of M9657 + pembrolizumab (anti-PD-1 antibody) combination therapy was assessed using in-vitro luciferase and ex vivo functional assays.
- In vivo antitumor efficacy was investigated with the M9657 surrogate (FS122m) and anti-mouse PD-1 antibody (anti-mPD-1) in syngeneic tumor models expressing Mesothelin (MSLN).