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Introduction

EP300 is a high-value therapeutic target in hematologic malignancies
EP300 is a histone acetyltransferase and transcriptional coactivator essential for tumor cell proliferation and survival in multiple myeloma (MM), and broad range of hematologic malignancies.

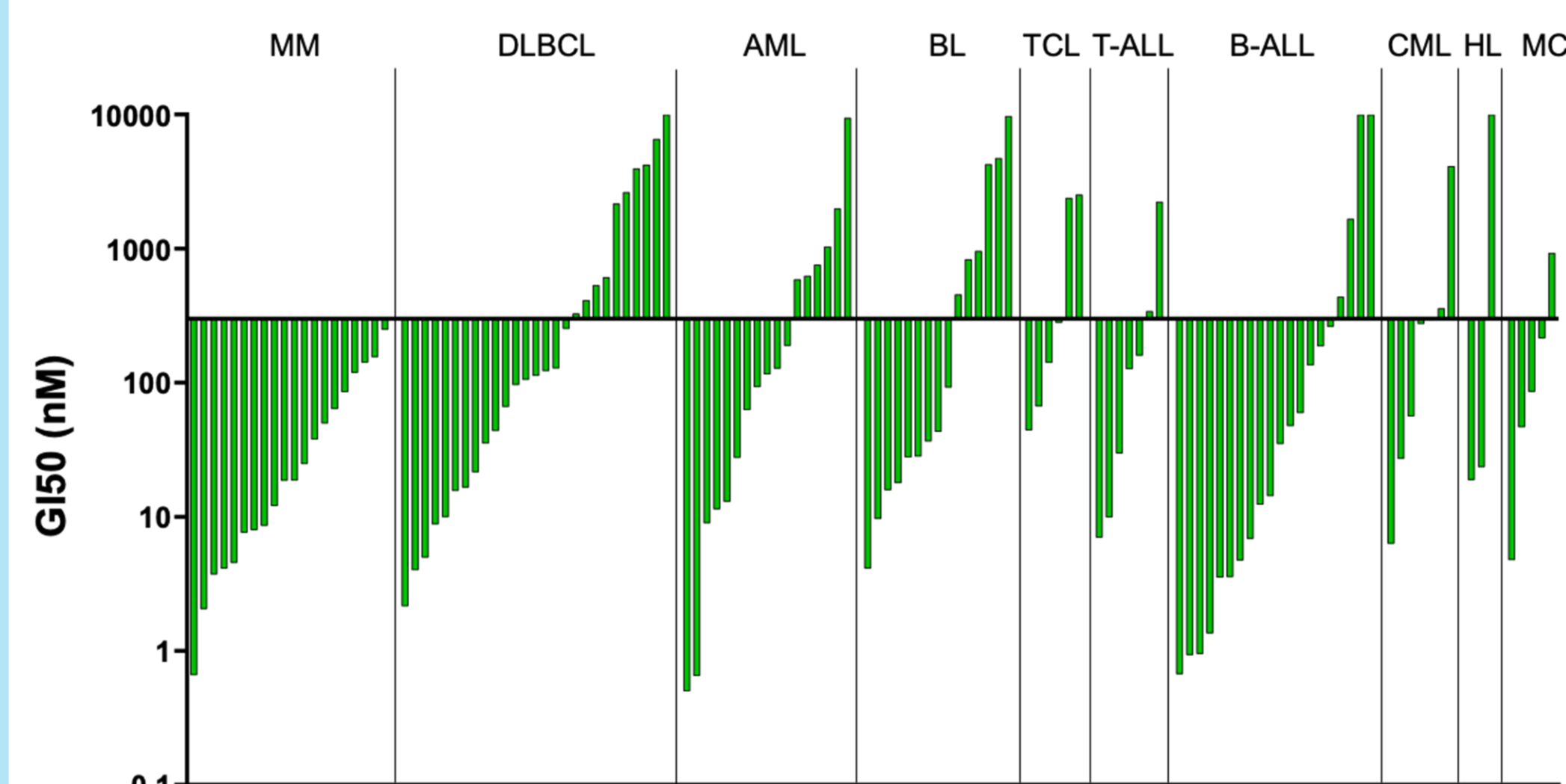
Dual targeting of EP300/CBP can cause toxicities

Pharmacological targeting of EP300 is hampered by high structural homology with its paralog CBP. Dual EP300/CBP inhibitor (CCS1477) causes dose-limiting thrombocytopenia, restricting its therapeutic utility.

Selective EP300 degradation offers a superior approach

We developed heterobifunctional degraders with exquisite EP300 selectivity that achieve rapid, sustained EP300 degradation *in vivo* while sparing CBP, broadening the therapeutic window of such agents over dual targeting.

EP300 degradation shows anti-proliferative activity in a broad range of hematological malignancies



(~ 70% of All Tested Cell Lines are Sensitive)

Figure 1. Hematologic cancer cell lines were treated with a selective dEP300 for 10 days and viability was assessed using the CellTiter-Glo assay.

Systemic exposure drives potent and sustained selective EP300 degradation in MM.1S xenograft

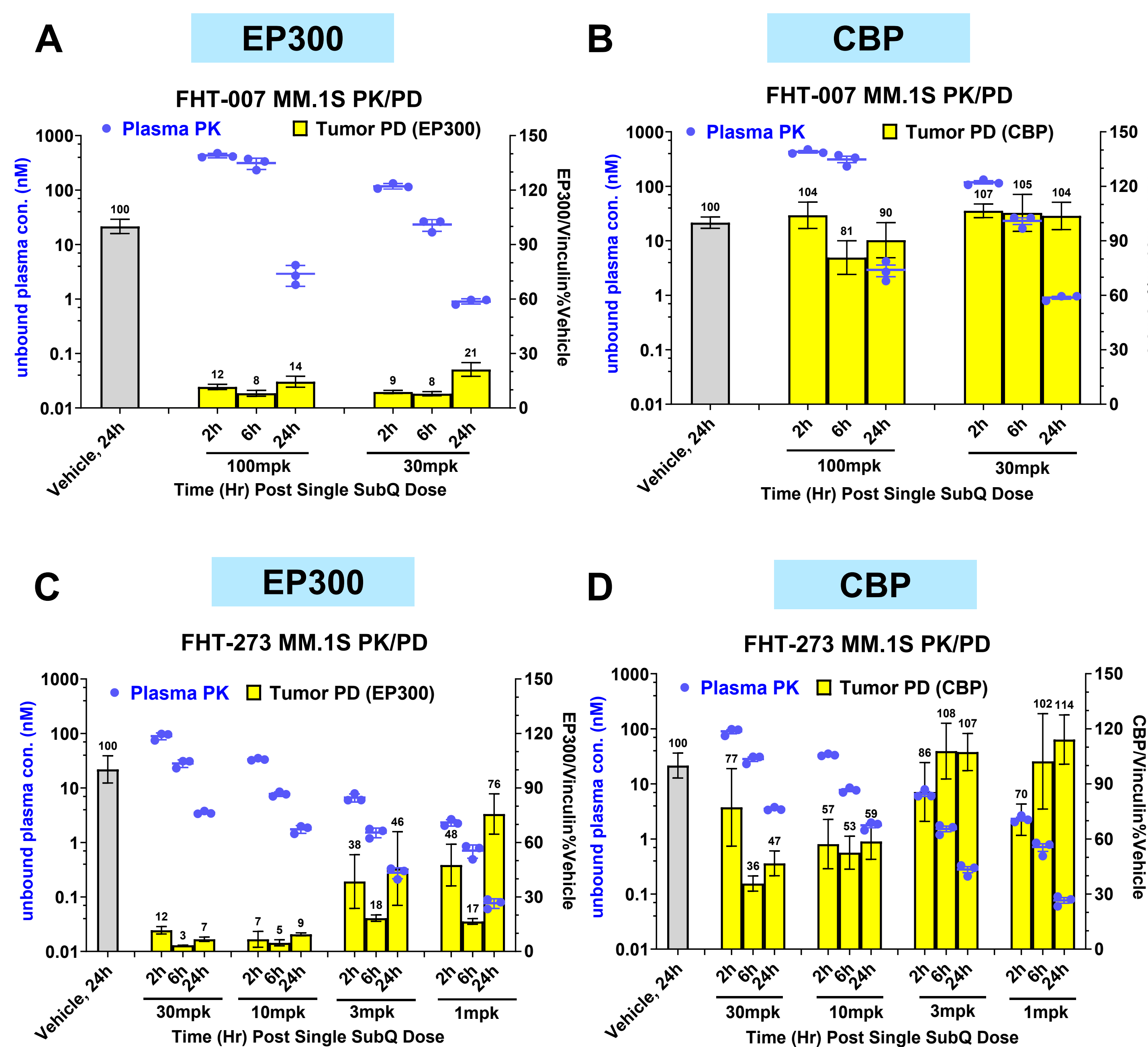


Figure 2. Plasma PK and tumor PD following a single subcutaneous dose in MM.1S xenograft-bearing mice. (A–B) FHT-007. (C–D) FHT-273. Unbound plasma concentration (nM, left y-axis) and tumor EP300/CBP levels (% remaining vs. vehicle, right y-axis) are shown.

FHT-007 overcomes acquired pomalidomide resistance and induces tumor regression in the MM.1S_PomR xenograft

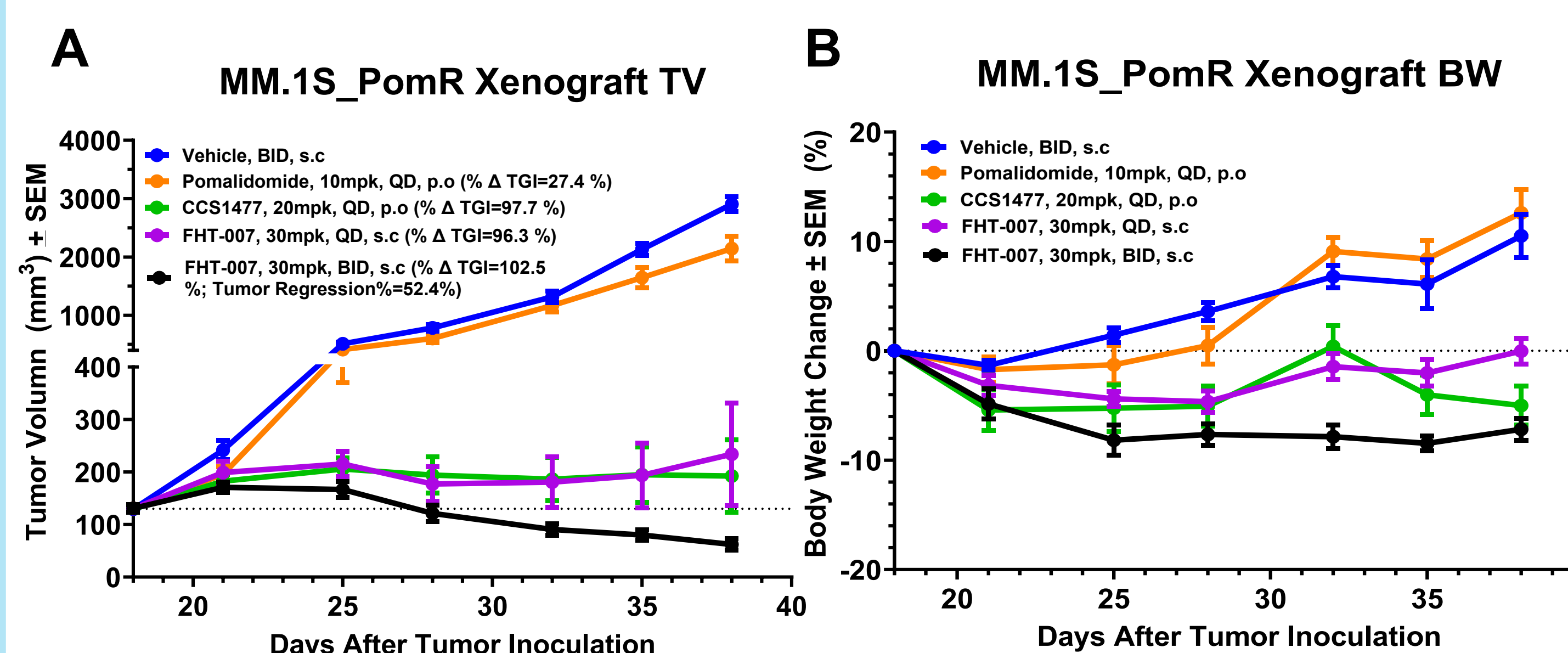


Figure 3. (A–B) Tumor volume and body weight change (%) in MM.1S_PomR xenograft-bearing mice treated with FHT-007, CCS1477 (dual bromodomain inhibitor), pomalidomide, or vehicle. MM1S_PomR cells were established by gradual pomalidomide exposure over 6 months *in vitro*.

RESULTS

Selective EP300 degradation drives deeper tumor regression and preserved platelet counts vs EP300/CBP dual inhibition in MM

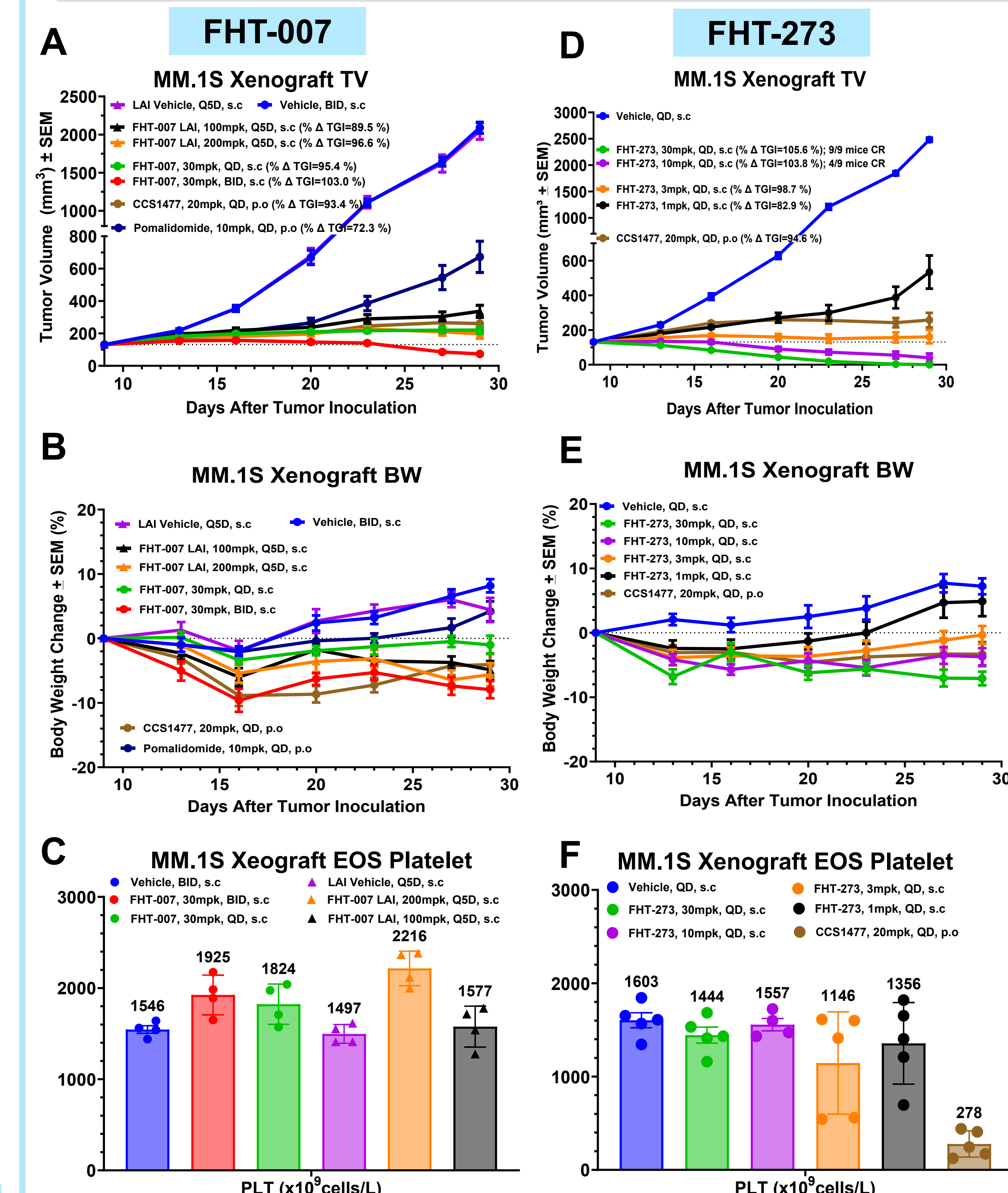


Figure 4. (A–C) MM.1S xenograft tumor volume, body weight change (%), and end-of-study platelet counts (PLT, $\times 10^9$ cells/L) for FHT-007 immediate release or long acting-injectable (LAI) formulation, CCS1477 (dual bromodomain inhibitor), pomalidomide, or vehicle. (D–F) Same readouts for FHT-273, CCS1477, or vehicle in a separate study.

FHT-273 demonstrates superior safety over a dual degrader

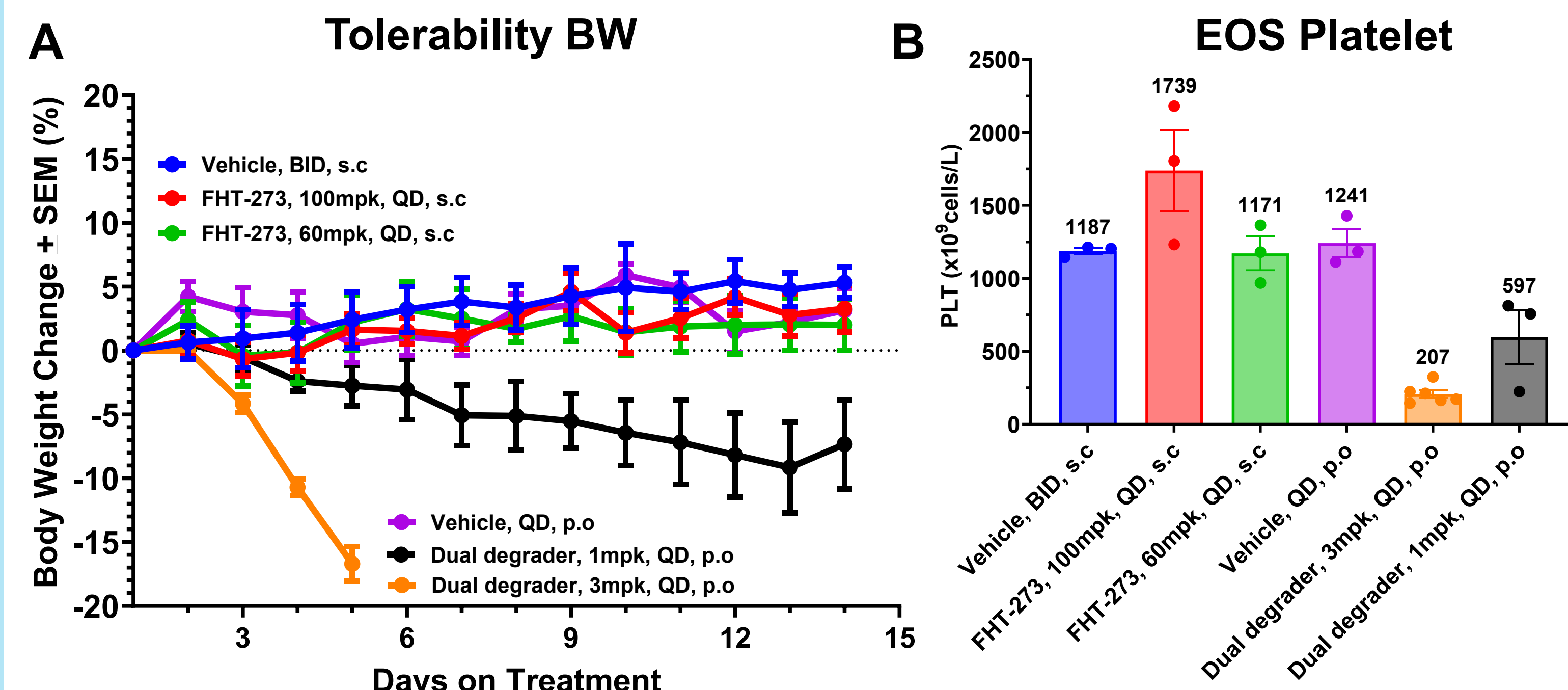


Figure 1. 14-day tolerability study in BALB/c mice. (A) Body weight change (%). FHT-273 was well tolerated at 3–10x above efficacious doses; the dual degrader caused severe weight loss requiring early euthanasia. (B) End-of-study platelet counts. The dual degrader caused marked thrombocytopenia.

CONCLUSIONS

- Selective EP300 degraders achieve potent and sustained target degradation *in vivo*, while sparing CBP
- Dose-dependent exposure and antitumor efficacy across immediate release and long acting-injectable formulations
- Superior safety profile with no thrombocytopenia or anemia at 3–10x above efficacious doses
- Tumor regression in a Pomalidomide-resistant MM model
- Selective EP300 degradation offers a differentiated approach with a wider therapeutic window vs dual targeting