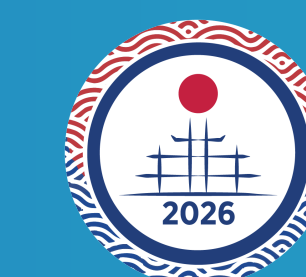


#P3.145: Nelmastobart enhances immune-mediated tumor-killing activity when combined with cisplatin-pemetrexed therapy and osimertinib-based first-line chemotherapy



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Abstract

Background:

Butyrophilin 1A1 (BTN1A1) is a novel immune checkpoint molecule involved in T-cell regulation within the tumor microenvironment. In non-small cell lung cancer (NSCLC), platinum-based chemotherapy, including cisplatin and pemetrexed, remains the standard first-line treatment, while osimertinib is a standard first-line targeted therapy for patients with EGFR-mutant NSCLC. However, therapeutic resistance and systemic toxicity limit clinical outcomes. Here, we investigated whether BTN1A1 blockade using Nelmastobart could enhance the efficacy of both cisplatin-pemetrexed and osimertinib-based first-line chemotherapies, while maintaining an acceptable safety profile.

Methods:

RFP-labeled lung cancer cell line and organoids were established in a three-dimensional (3D) culture system and subsequently co-cultured with human peripheral blood mononuclear cells (PBMCs). A549 cancer cells were treated with Nelmastobart, cisplatin, pemetrexed, or their combinations. Organoids were treated with Nelmastobart, osimertinib, or their combinations. Anti-tumor activity was quantitatively assessed based on organoid size reduction and attenuation of RFP fluorescence intensity. For in vivo safety evaluation, zebrafish embryos were exposed to Nelmastobart, cisplatin, pemetrexed, and their respective combinations at clinically relevant concentrations. Developmental toxicity endpoints included survival rate, morphological abnormalities (craniofacial defects, axial curvature), pericardial edema, cardiac function, and organogenesis.

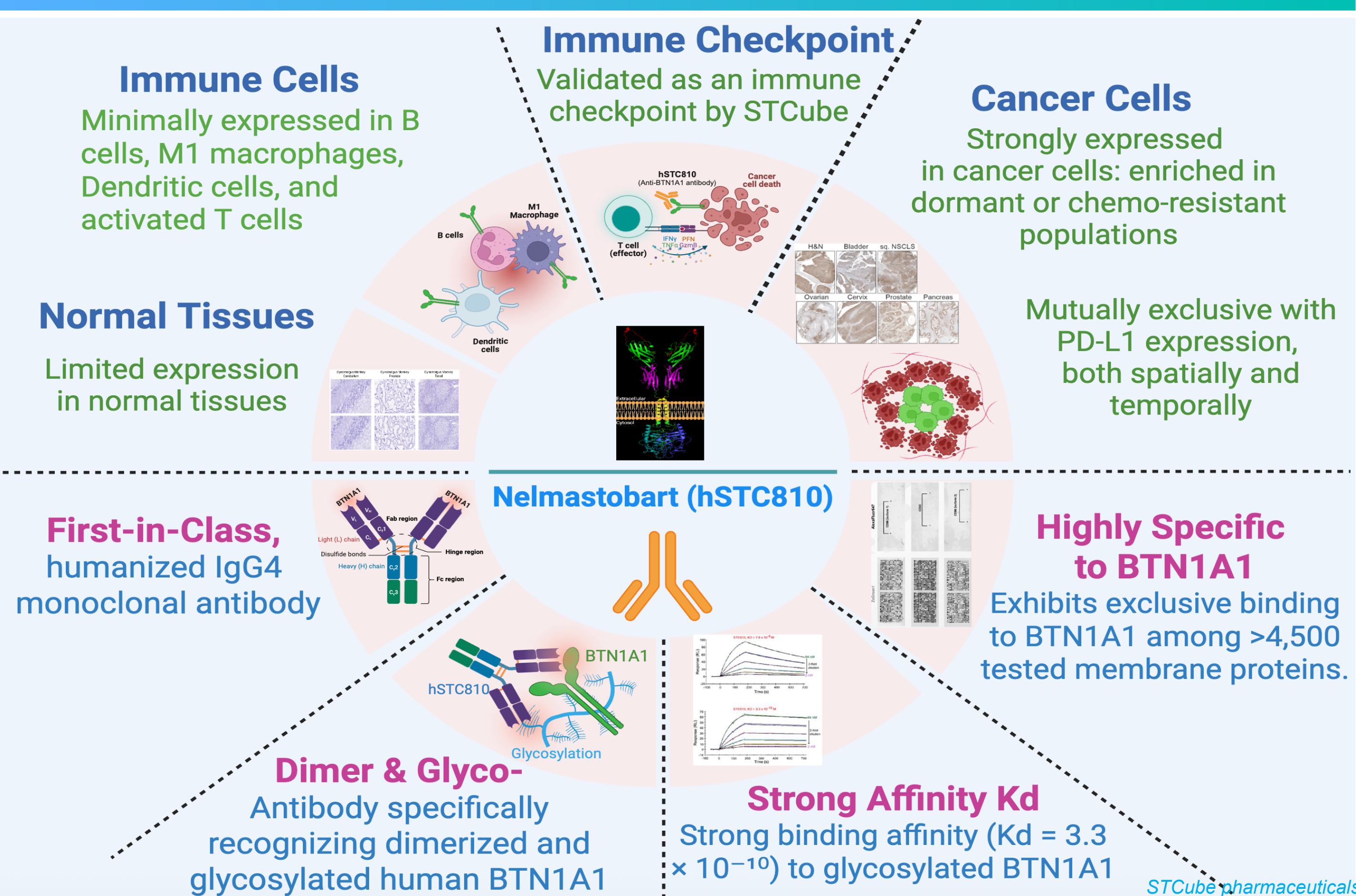
Results:

Combination of Nelmastobart with cisplatin and pemetrexed significantly enhanced PBMC-mediated cytotoxicity, resulting in marked spheroid shrinkage and substantial loss of RFP signal compared to either agent alone. Similarly, the combination of Nelmastobart with osimertinib demonstrated a synergistic anti-tumor effect in organoids, suggesting that BTN1A1 blockade enhances tumor susceptibility to immune-mediated killing across treatment lines. Zebrafish toxicity assays revealed no significant developmental abnormalities in embryos treated with Nelmastobart alone or in combination with either cisplatin or pemetrexed. Importantly, no additive or synergistic toxicity was observed in combination groups, indicating a favorable safety profile.

Conclusion:

BTN1A1 blockade with Nelmastobart markedly enhances the efficacy of both cisplatin-pemetrexed and osimertinib-based first-line chemotherapies by augmenting immune-mediated tumor killing in NSCLC preclinical models. The absence of increased developmental toxicity in zebrafish supports a favorable therapeutic window. These findings provide a strong rationale for clinical development of BTN1A1-targeted immunotherapy in combination with standard-of-care chemotherapeutics across treatment lines in NSCLC.

Hallmarks of BTN1A1 and Nelmastobart (hSTC810)



Osimertinib + PD-L1 Blockade vs Docetaxel + Nelmastobart Blockade

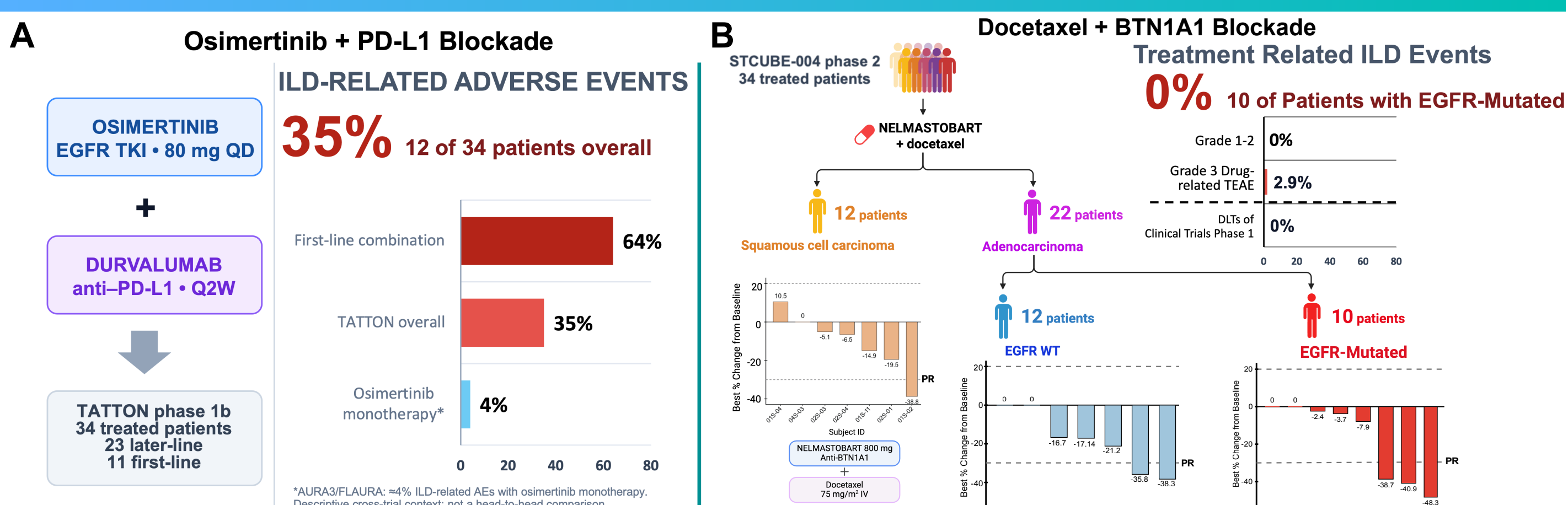


Figure. Safety signal associated with osimertinib plus durvalumab and Nelmastobart

- (A) Among 34 treated patients with osimertinib plus durvalumab, 12 (35%) experienced an interstitial lung disease (ILD)-related adverse event, including ILD, pneumonitis, or lung disorder. The incidence was particularly high in the first-line combination cohort, in which 7 of 11 patients (64%) developed an ILD-related adverse event, leading to early termination of cohort enrollment and discontinuation of durvalumab administration.
- (B) Among 34 treated patients, 12 had squamous cell carcinoma and 22 had adenocarcinoma; within the adenocarcinoma cohort, 12 patients were EGFR wild type and 10 had EGFR-mutant disease. Waterfall plots show best percentage change from baseline in target lesions, including partial responses in both EGFR wild-type and EGFR-mutated subgroups. Notably, no ILD-related adverse events were observed among the 10 EGFR-mutated patients. Treatment-related adverse events were predominantly grade 1-2, with 2.1% grade 3 drug-related TEAEs

Result

Synergistic Tumor Suppression by Nelmastobart and Osimertinib in patient-derived lung organoids with EGFR exon 19 deletion (del)

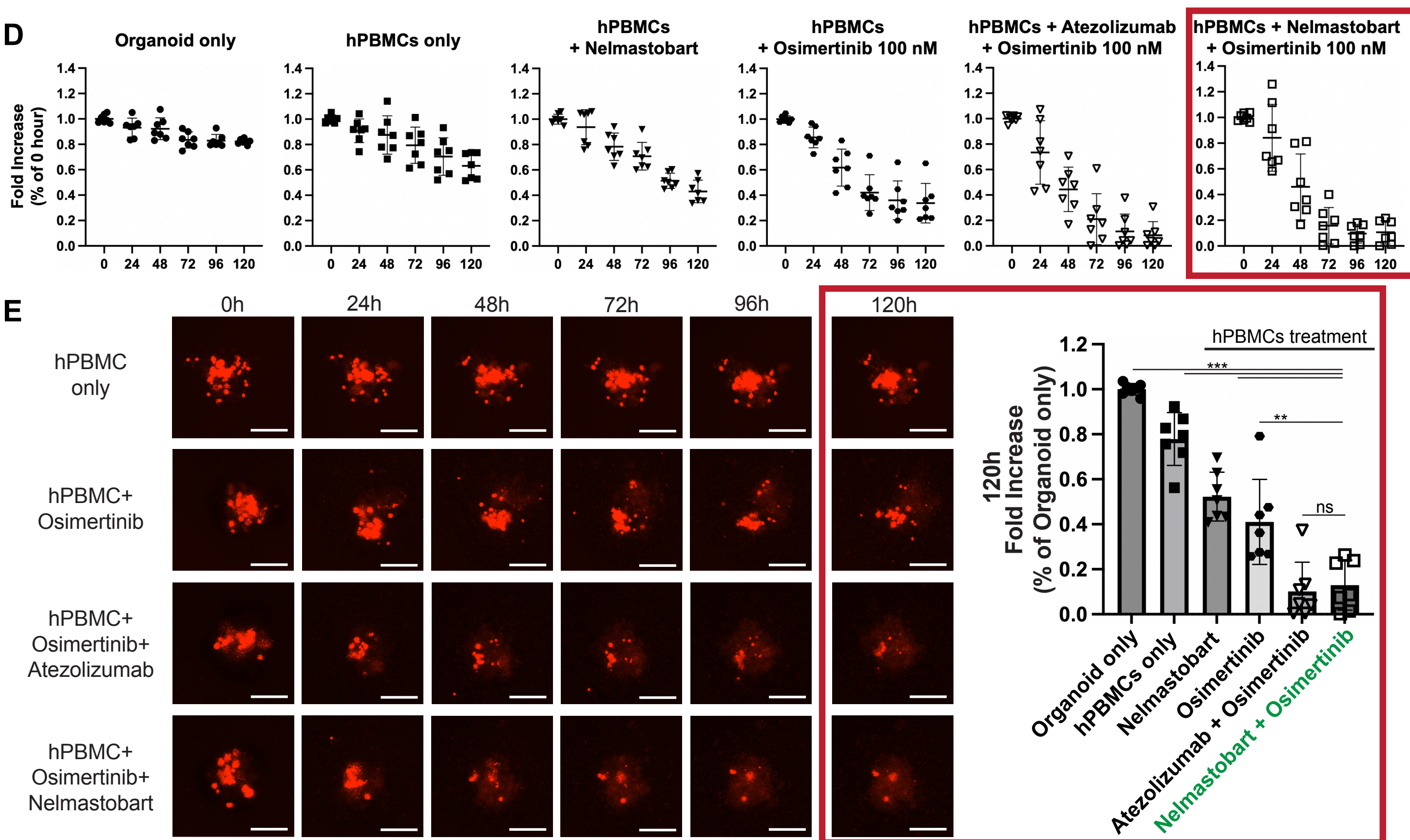
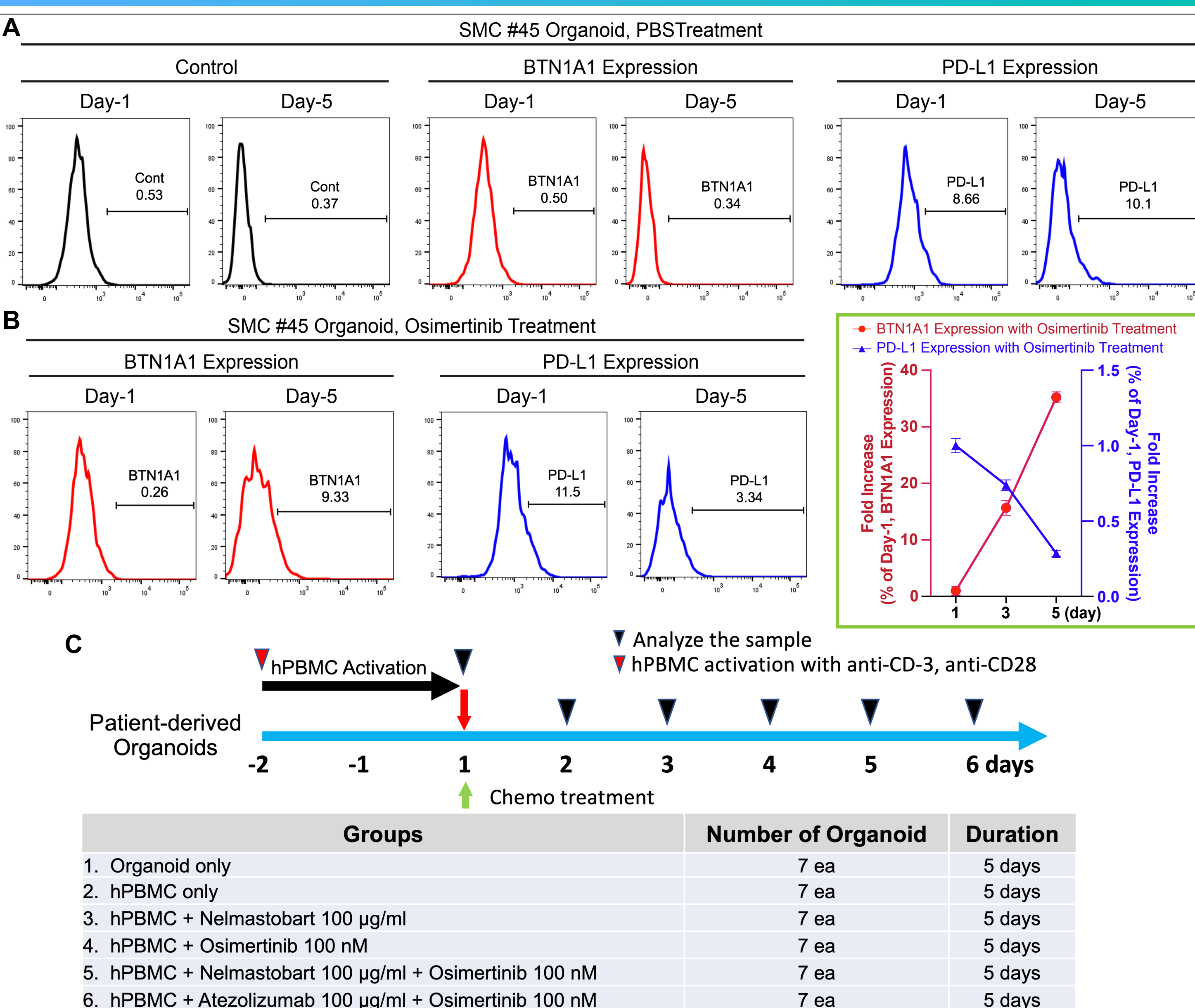


Figure A-E. Enhanced tumor suppression of Nelmastobart combined with osimertinib in EGFR exon 19-deleted patient-derived lung cancer organoids.

- (A, B) Flow cytometric analysis of BTN1A1 and PD-L1 expression in SMC #45 patient-derived lung cancer organoids treated with PBS (A) or osimertinib (B) on Days 1 and 5. Osimertinib induced dynamic modulation of immune checkpoint expression, including increased BTN1A1 expression at Day 5.
- (C) Experimental design of the organoid-hPBMC co-culture assay. Anti-CD3/anti-CD28-activated hPBMCs were co-cultured with organoids and treated with Nelmastobart, Atezolizumab (100 µg/mL), osimertinib (100 nM), or the indicated combinations for 5 days.
- (D) Longitudinal quantification of organoid growth by Incucyte live-cell imaging over 120 h. Combined Nelmastobart and osimertinib treatment produced greater growth inhibition than either monotherapy.
- (E) Representative fluorescence images and quantitative analysis of organoid growth at 120 h. Nelmastobart plus osimertinib markedly suppressed organoid growth, with an antitumor effect comparable to that of Atezolizumab plus osimertinib. Data are presented as mean $\pm$ SD (n = 7 organoids/group). ns, not significant; **P < 0.01; ***P < 0.001.

Synergistic Tumor Suppression by Nelmastobart, Pemetrexed, and Cisplatin in A549 Spheroid

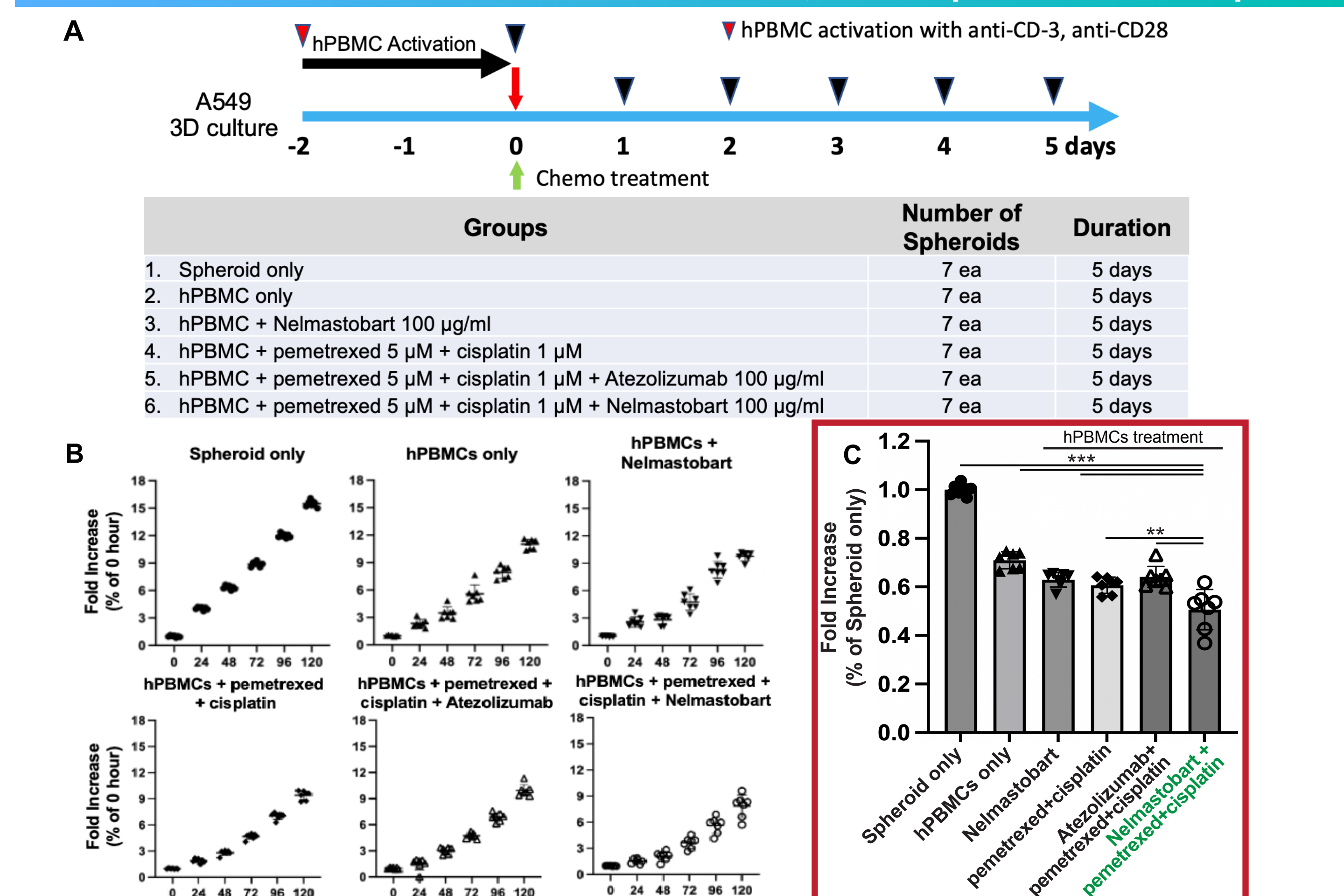


Figure A-C. Enhanced tumor suppression by Nelmastobart combined with pemetrexed and cisplatin in A549 spheroids.

- (A) Experimental design of the spheroid-hPBMC co-culture assay. Activated hPBMCs were co-cultured with spheroid and treated with Nelmastobart, Atezolizumab (100 µg/mL), pemetrexed (5 µM), cisplatin (1 µM) or the indicated combinations for 5 days.
- (B) Longitudinal quantification of spheroid growth by Incucyte live-cell imaging over 120 h. Combined Nelmastobart, pemetrexed, and cisplatin treatment produced greater growth inhibition than either monotherapy and Atezolizumab combination therapy.
- (C) Quantitative analysis of spheroid growth at 120 h (n = 7). ns, not significant; **P < 0.01; ***P < 0.001.

Synergistic Tumor Suppression by Nelmastobart, Pemetrexed, and Cisplatin in Zebrafish Xenograft Model

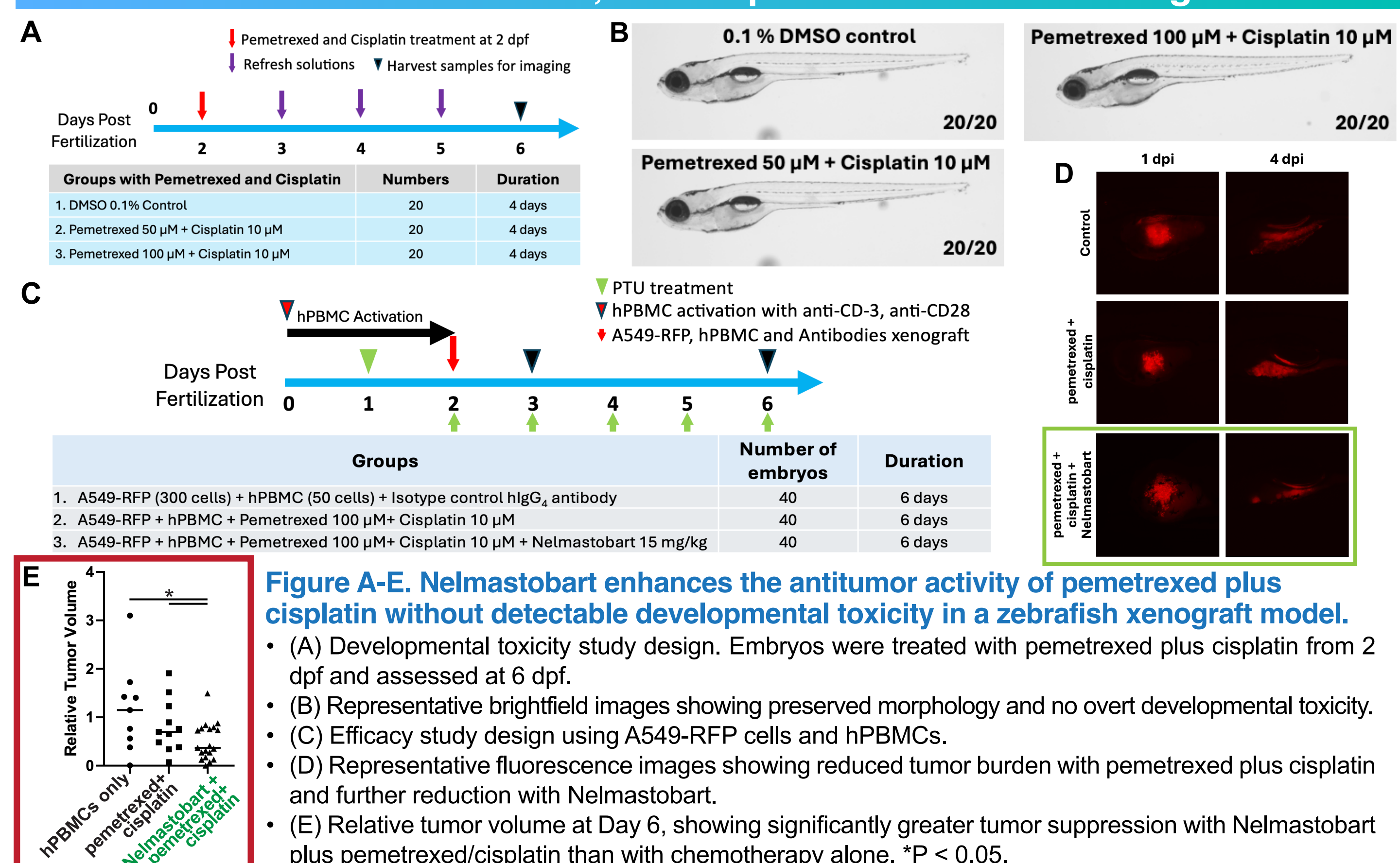


Figure A-E. Nelmastobart enhances the antitumor activity of pemetrexed plus cisplatin without detectable developmental toxicity in a zebrafish xenograft model.

- (A) Developmental toxicity study design. Embryos were treated with pemetrexed plus cisplatin from 2 dpf and assessed at 6 dpf.
- (B) Representative brightfield images showing preserved morphology and no overt developmental toxicity.
- (C) Efficacy study design using A549-RFP cells and hPBMCs.
- (D) Representative fluorescence images showing reduced tumor burden with pemetrexed plus cisplatin and further reduction with Nelmastobart.
- (E) Relative tumor volume at Day 6, showing significantly greater tumor suppression with Nelmastobart plus pemetrexed/cisplatin than with chemotherapy alone. *P < 0.05.

Conclusion: BTN1A1- A Key Therapeutic Target Enhanced in NSCLC

- Nelmastobart enhanced immune-mediated tumor suppression when combined with either cisplatin-pemetrexed or osimertinib in NSCLC preclinical models.
- The combination with osimertinib showed strong antitumor activity in EGFR-mutated patient-derived lung cancer organoids, supporting its potential application in EGFR-mutated NSCLC.
- The antitumor effect of Nelmastobart combined with pemetrexed and cisplatin was further confirmed in a zebrafish xenograft model, demonstrating efficacy in a whole-organism setting.
- Collectively, these findings support further clinical development of Nelmastobart in combination with standard-of-care therapies for both EGFR-mutated and non-EGFR-mutated NSCLC.