

# PLK1 inhibitor onvansertib potentiates the antitumor efficacy of trastuzumab deruxtecan (T-DXd) and reverses its resistance in therapy-resistant HER2-low breast cancer models

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## Background

### Trastuzumab deruxtecan (T-DXd, Enhertu)

- HER2-directed ADC with a topoisomerase I inhibitor (TOP1i) payload.
- Approved for HER2-low and HER2-ultralow metastatic breast cancer.
- Despite strong clinical activity, resistance limits durability of response<sup>1</sup>.

### Polo-like kinase 1 (PLK1)

- Key regulator of mitosis and cell-cycle progression.
- Overexpressed in breast cancer and linked to poor prognosis<sup>2,3</sup>.
- Implicated in resistance to taxanes, endocrine therapy (ET), and CDK4/6 inhibitors (CDK4/6i)<sup>4-7</sup>.

### Onvansertib

- Highly selective, oral PLK1 inhibitor in clinical development.
- Synergizes with TOP1 inhibitors (e.g., irinotecan) in preclinical models<sup>8,9</sup>.
- Demonstrated tolerability and promising clinical activity in combination with irinotecan-based regimens in KRAS-mutant metastatic colorectal cancer<sup>10</sup>.

**Hypothesis: PLK1 inhibition with onvansertib may enhance T-DXd efficacy and overcome resistance in HER2-low breast cancer models.**

## Patient-derived xenograft (PDX) models

PDX model	Subtype	HER2 status	PDX origin	Patient previously treated with	Genomic alterations	PDX resistance
HBCx-246	HR+	HER2-low	Local relapse	AC + paclitaxel, talazoparib Carbo + gemcitabine Abema + AI	BRCA1 mut. TP53 mut.	• Abema • Abema + Fulv • Talazoparib
HBCx-139 palbo+fulvR5	HR+	HER2-negative	Bone metastasis	FEC, taxanes, doxorubicin, Tam + triptorelin, AI, Fulv	PIK3CA mut. CCND1 amp.	• Palbo • Fulv • Palbo + Fulv
HBCx-131	HR+	HER2-low	Bone metastasis	Cyclophosphamide + Epirubicin + Docetaxel, AC, FUN, Tam, AI	CDKN2A/B mut. CCND1, FGFR1 amp.	Partial sensitivity to • Fulv • Palbo • Palbo + Fulv
HBCx-3	HR+	HER2-low	Primary tumor	Treatment-naive	TP53 mut. PTEN del.	• Palbo • Fulv • Palbo + Fulv
HBCx-134 palboR31	HR+	HER2-low	Bone metastasis	Alpelisib + AI, FEC + docetaxel	PIK3CA mut. CCND1 amp.	• Palbo • Alpelisib + Fulv
HBCx-169	HR+	HER2-low*	Local relapse	Palbo + AI + Enantone radiotherapy	CDKN2A/B mut. GATA3 mut.	• Palbo
HBCx-262	TNBC	HER2-low*	Primary tumor	AC + paclitaxel Carbo, Pembrolizumab	PIK3CA, TP53 mut. CDH1, PTEN, RB1 loss	• Trodelvy • Cisplatin
HBCx-264	TNBC	HER2-low*	Primary tumor	AC + paclitaxel Carbo, Pembrolizumab	FH, RB1 loss	Partial sensitivity to • Capecitabine

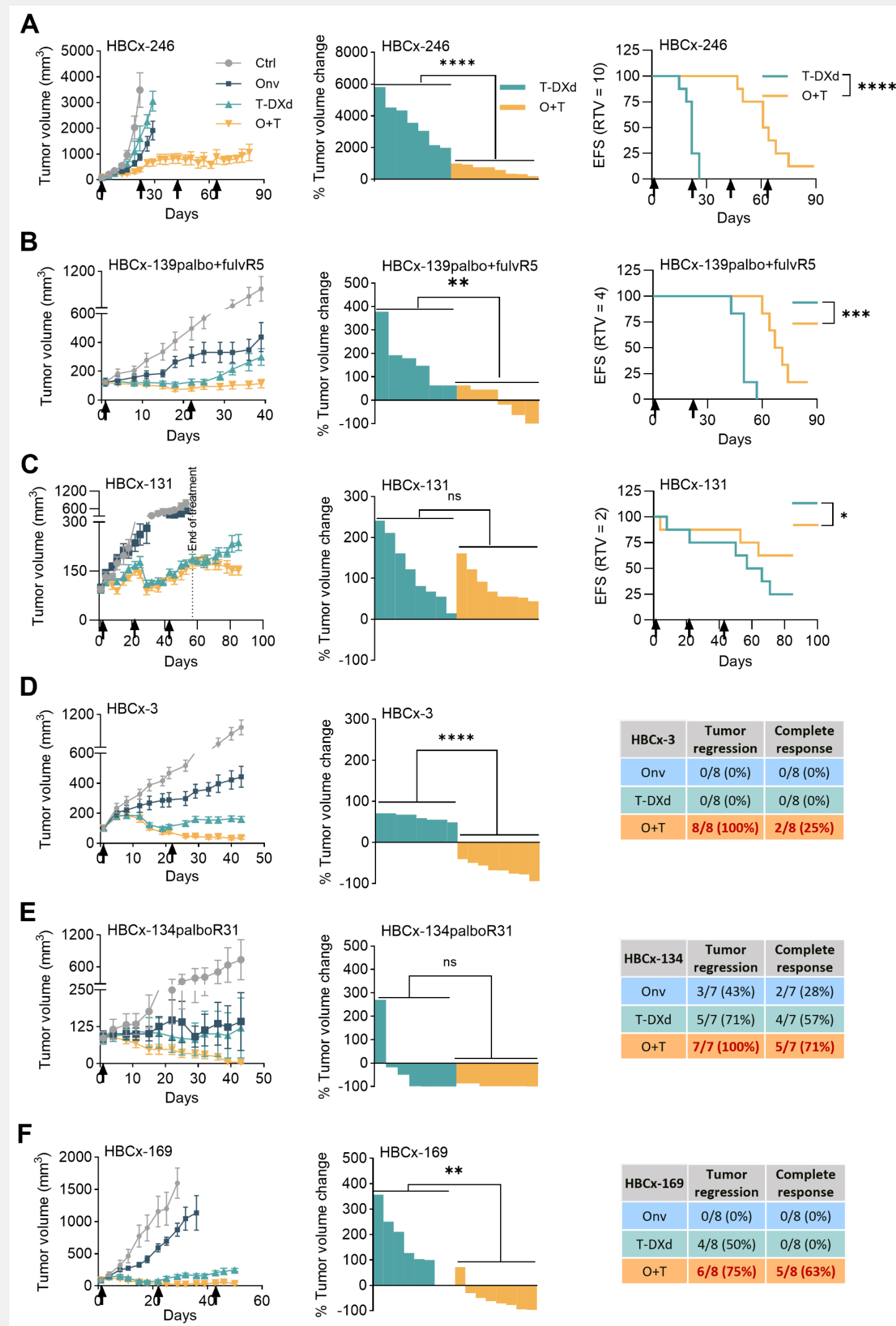
HER2 status of PDXs was confirmed using the HercepTest (Dako) HER2 immunohistochemistry (IHC) assay. \*HER2 IHC was performed using the A0485 anti-HER2 polyclonal antibody. **Abbreviations:** AC, Adriamycin (doxorubicin) + Cyclophosphamide; Abema, abemaciclib; FEC, 5-Fluorouracil + Epirubicin + Cyclophosphamide; FUN, 5-Fluorouracil + Uracil + Navelbine (vinorelbine); AI, aromatase inhibitor; Carbo, carboplatin; Palbo, palbociclib; Fulv, fulvestrant; Tam, tamoxifen; mut., mutation; amp., amplification; del., deletion.

### References

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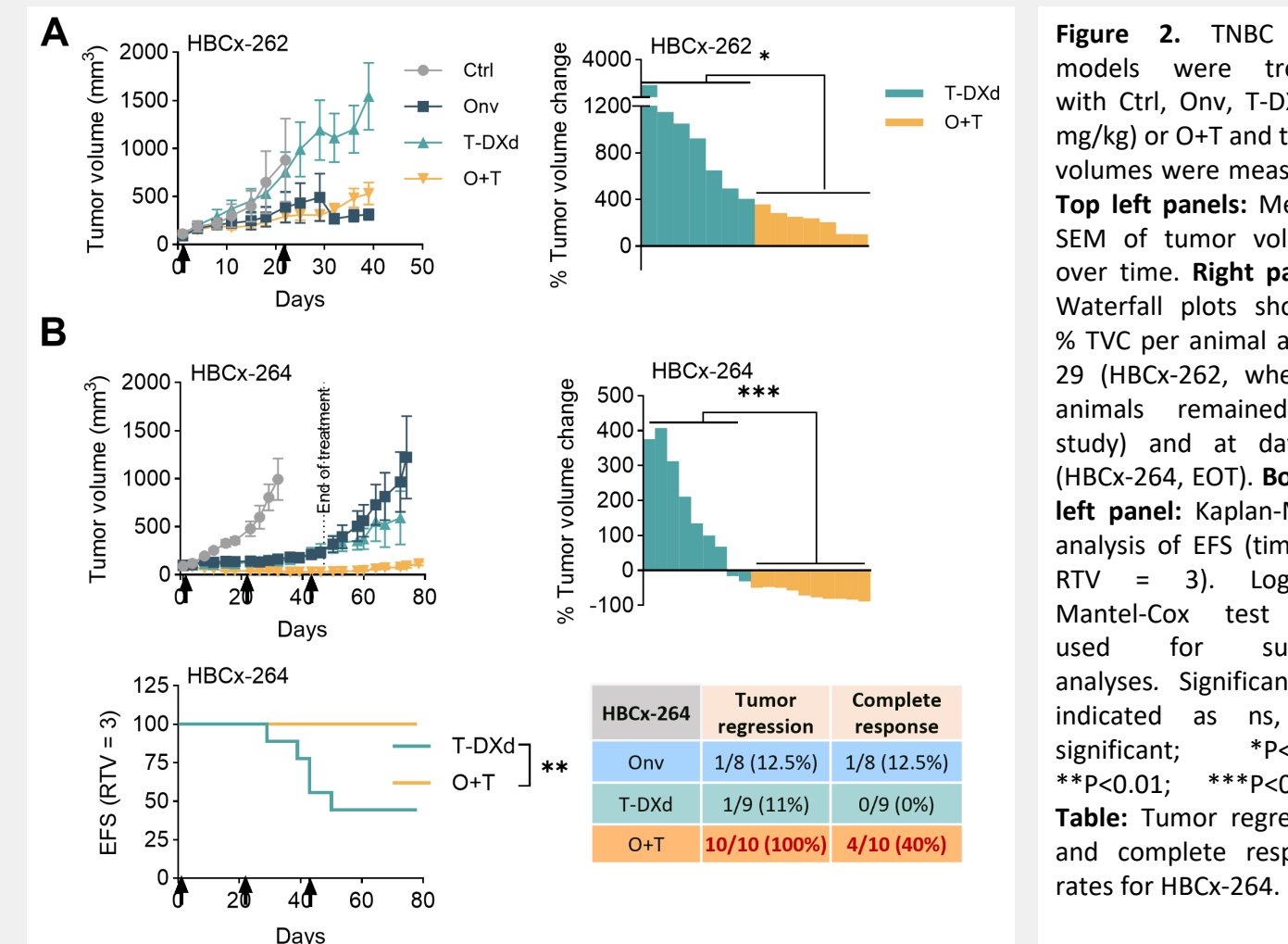
## Results

### Onvansertib + T-DXd reverses T-DXd resistance and induces tumor regression in ET/CDK4/6i-resistant HR+ breast cancer PDX models

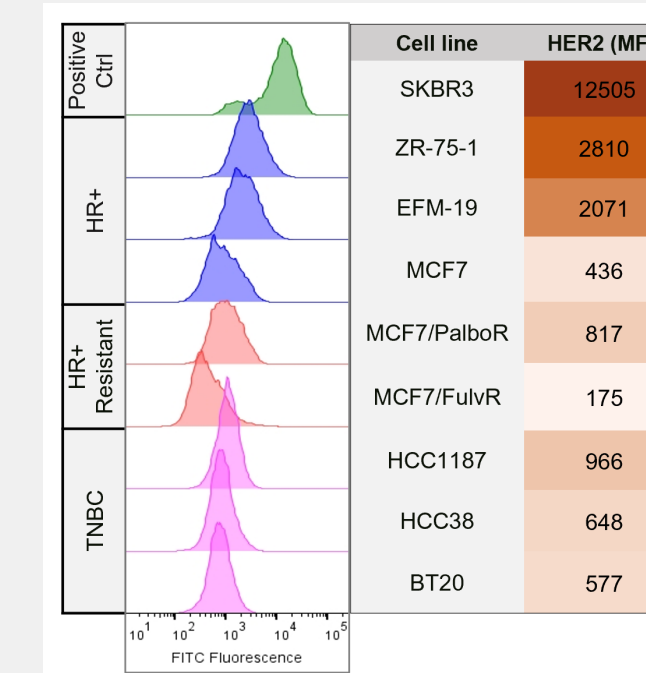


**Figure 1. (A-F)** HR+ PDX models were treated with vehicle (Ctrl), onvansertib (Onv; oral, 45mg/kg, 5x/week), T-DXd (4 mg/kg or 10 mg/kg, IV, every 21 days, black arrows) or Onv + T-DXd (O+T) and tumor volumes were measured twice weekly. The percent change in tumor volume (% TVC) was calculated as: %TVC = [(V<sub>t</sub> - V<sub>0</sub>) / V<sub>0</sub>] × 100, where V<sub>0</sub> is the tumor volume at treatment initiation and V<sub>t</sub> is the tumor volume at a given time point. Relative tumor volume (RTV) was calculated as V<sub>t</sub>/V<sub>0</sub>. **Left panels:** Mean ± SEM of tumor volumes over time (n=6-10 mice/group). **Middle panels:** Waterfall plots showing % TVC per animal at the end of treatment (EOT) on day 29 (HBCx-246), day 39 (HBCx-139), day 57 (HBCx-131), day 43 (HBCx-3 and HBCx-134) and day 50 (HBCx-169). Unpaired t-test was used to compare % TVC between O+T and T-DXd. **Right panels:** Kaplan-Meier analysis of event-free survival (EFS, time for RTV = 2-10). Log-rank Mantel-Cox test was used for survival analyses. Significance levels are indicated as ns, not significant; \*P<0.05; \*\*P<0.01; \*\*\*P<0.001; \*\*\*\*P<0.0001. **Right tables:** Tumor regression defined as % TVC ≤ -50% at any time point, and complete response as tumor volume <10 mm<sup>3</sup> in at least one measurement.

### Onvansertib and T-DXd combination elicits robust anti-tumor activity in TNBC PDX models

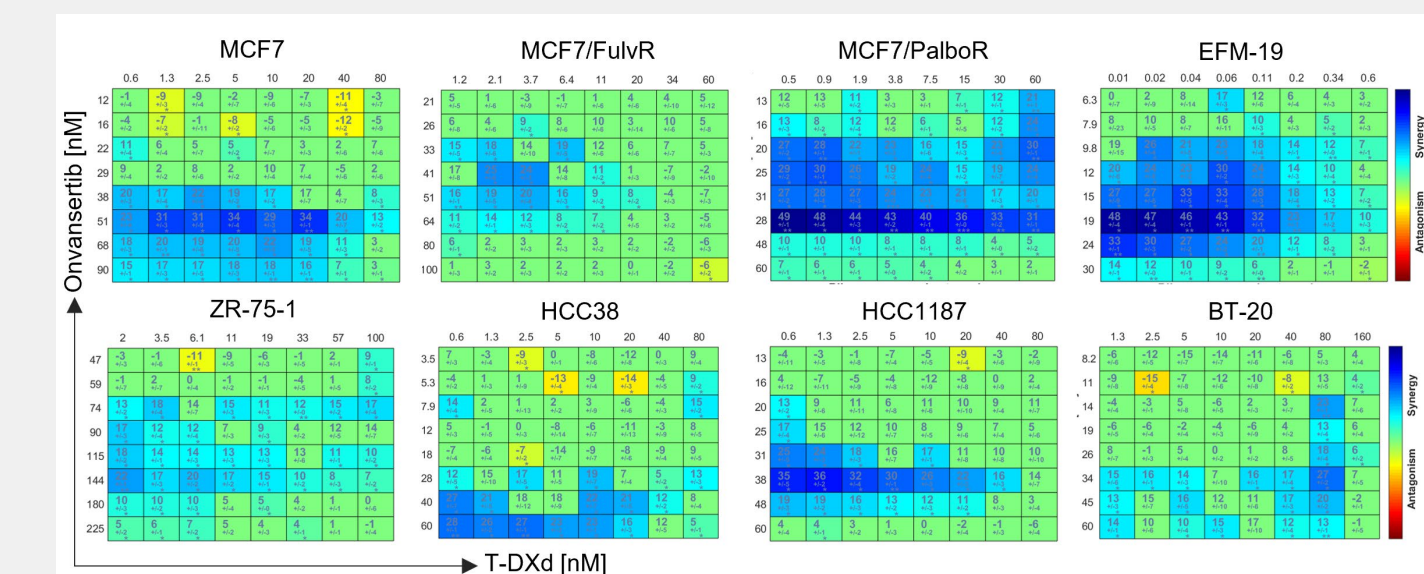


### Breast cancer cell line panel covering the HER2-low spectrum



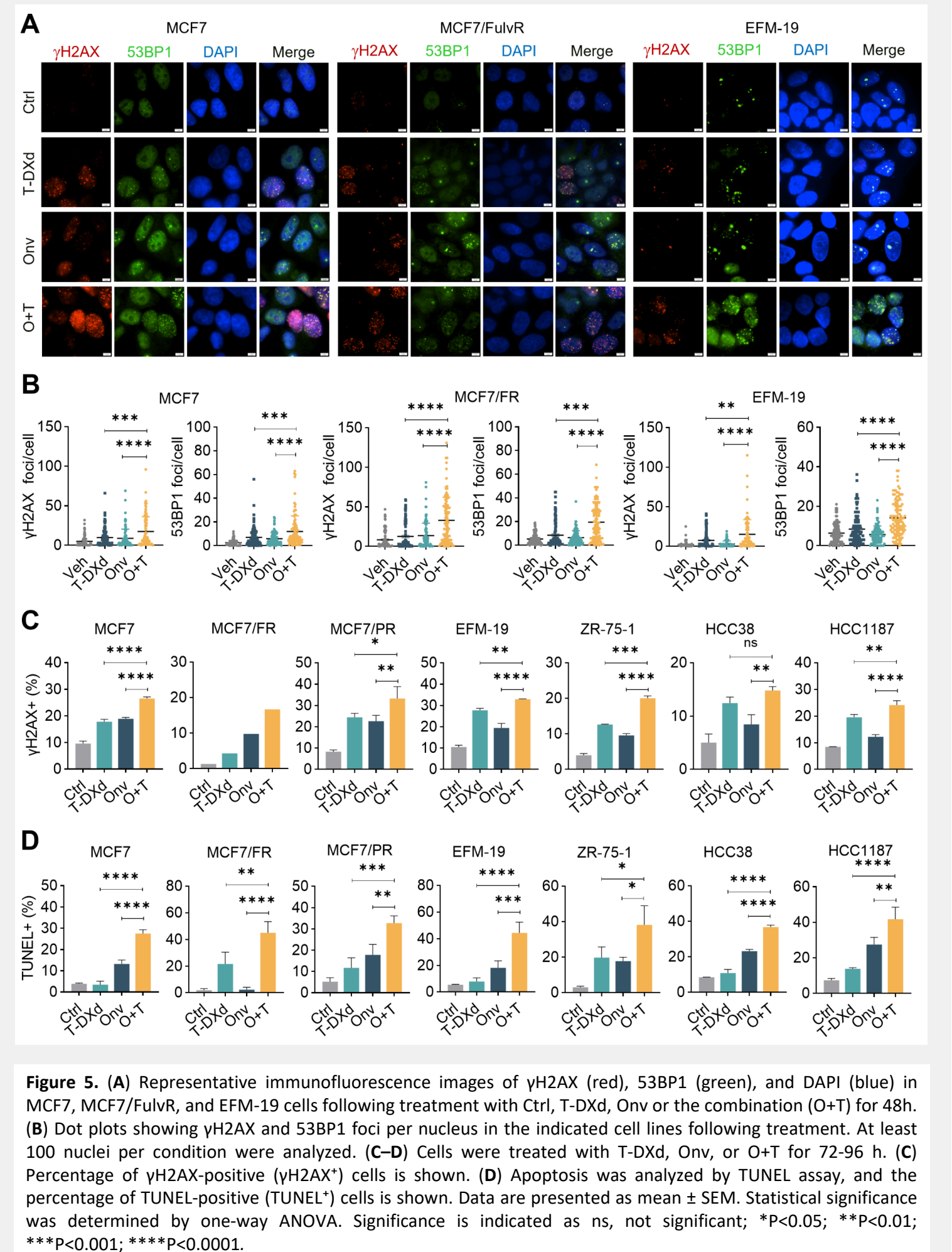
**Figure 3.** Representative flow cytometry histograms of surface HER2 expression in HR+, HR+ resistant [palbociclib-resistant (MCF7/PalboR), fulvestrant-resistant (MCF7/FulvR)], and TNBC breast cancer cell lines. SKBR3 served as a positive control. Mean fluorescence intensity (MFI; isotype-subtracted) values are shown in the table.

### Onvansertib + T-DXd is synergistic in HER2-low breast cancer cell lines



**Figure 4.** Cells were treated for 6-7 days with onvansertib, T-DXd, or the combination in a 9 × 9 dose matrix (n=3). Cell viability was assessed, and synergy was evaluated using the Bliss independence model. Heatmaps show Bliss synergy scores across the dose matrices, with blue indicating synergy.

### Onvansertib and T-DXd combination induces DNA damage and apoptosis in vitro



## Conclusions

- Onvansertib enhances T-DXd efficacy and overcomes its resistance across TNBC and HR+ breast cancer PDX models.
- The combination induces synergistic DNA damage and apoptosis.
- PLK1 inhibition offers a strategy to deepen and prolong T-DXd response in advanced HER2-low breast cancer resistant to first-line therapies.

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