Onvansertib Enhances the Anti-tumor Efficacy of Trastuzumab Deruxtecan in Endocrine Therapy- and CDK4/6 Inhibitor-resistant HR+/HER2- Breast Cancer Patient-derived Xenograft Models

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Background

Trastuzumab deruxtecan (T-DXd):

- HER2-directed antibody-drug conjugate with a topoisomerase I (Top1) inhibitor payload.
- Approved for HER2-low [immunohistochemistry (IHC) Score 1+ or 2+/in situ hybridization-negative] metastatic breast cancer (mBC) patients who have received prior chemotherapy.
- Improved progression-free survival (PFS) in hormone receptor positive (HR+) HER2-low or ultralow mBC patients given prior endocrine therapy (ET) [1].
- Combination therapeutic strategies may be able to extend the clinical benefit of T-DXd in HR+ mBC.

Polo-like kinase 1 (PLK1):

- Serine/threonine protein kinase.
- Key regulator of mitosis and cell cycle progression.
- Overexpressed in breast cancer, associated with poor prognosis [2,3].
- Has been shown to mediate resistance to ET and CDK4/6 inhibitors in HR+ breast cancer [4,5,6].

Onvansertib:

- An orally bioavailable, highly selective inhibitor of PLK1, currently in clinical development.
- The combination of onvansertib and irinotecan, a Top1 inhibitor, has shown efficacy in colorectal cancer (CRC) preclinical models [7,8].
- Onvansertib in combination with irinotecan containing chemotherapy regimen FOLFIRI/bevacizumab showed promising efficacy in KRAS-mutant mCRC patients [9].

We investigated the potential of onvansertib to increase the efficacy of T-DXd in HR+/HER2- breast cancer patient-derived xenograft (PDX) models resistant to CDK4/6 inhibitors and ET.

PDX Models

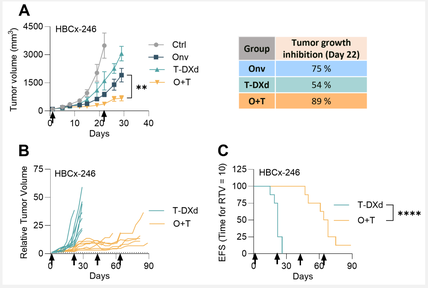
Overview of the HR+ Breast Cancer PDX Models

PDX Model	HBCx-246	HBCx-139palbo+fulvR5	HBCx-3	HBCx-134palboR31
PDX Origin	Local relapse	Bone met	Primary tumor	Bone met
HER2 status*	negative	negative	low	ultralow
Genomic alterations	*BRCA1* double mut. *TP53* mut.	*PIK3CA* mut. *CCND1* amp.	*TP53* mut. *PTEN* del.	*PIK3CA* mut. *CCND1* amp.
Resistant to	• Abemaciclib • Abemaciclib + Fulvestrant • Talazoparib	• Palbociclib • Fulvestrant • Palbociclib + Fulvestrant	• Palbociclib • Fulvestrant • Palbociclib + Fulvestrant	• Palbociclib • Alpelisib + Fulvestrant

* IHC staining of HER2 was performed using A0485 anti-HER2 polyclonal antibody. HER2 status confirmation with Ventana 4B5 anti-HER2 monoclonal antibody is ongoing.

Results

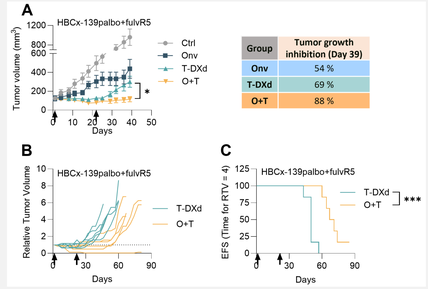
Onvansertib and T-DXd combination induces robust and durable anti-tumor activity in a HR+ breast cancer PDX model resistant to abemaciclib and fulvestrant



Group	Tumor growth inhibition (Day 22)
Onv	75 %
T-DXd	54 %
O+T	89 %

Figure 1. (A-C) HBCx-246 PDX model was treated with vehicle (Ctrl), onvansertib (Onv; oral, 45mg/kg, 5 times/week for 29 days), T-DXd (IV, 4 mg/kg, on days 1, 22, 43 and 64, indicated by black arrows) or Onv+T-DXd (O+T) and tumor volumes were measured twice a week. Relative tumor volume (RTV) was calculated as RTV = (tumor volume on measured day)/(tumor volume on day 0). Tumor growth inhibition on day 22 was calculated as 100% x (Vcontrol-Vtreated)/Vcontrol). (**A**) Mean ± SEM of tumor volumes overtime. Unpaired t-test was used to compare tumor volumes between O+T and the most effective monotherapy (Onv) on day 29. (**B**) Individual RTV over time. (**C**) Kaplan-Meier analysis of event-free survival (EFS, time for RTV = 10). Log-rank Mantel–Cox test was employed for survival analyses. Significance levels are indicated as *** p < 0.01* and ***** p < 0.0001*.

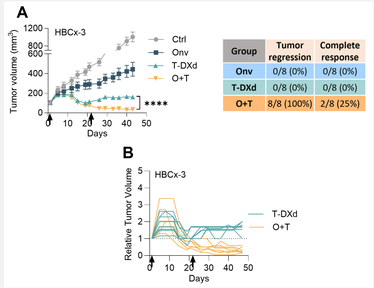
Onvansertib and T-DXd combination exhibits robust anti-tumor activity and delays tumor relapse in a HR+ breast cancer PDX model resistant to palbocilcib and fulvestrant



Group	Tumor growth inhibition (Day 39)
Onv	54 %
T-DXd	69 %
O+T	88 %

Figure 2. (A-C) HBCx-139palbo+fulvR5 PDX model was treated with vehicle (Ctrl), Onv (oral, 45mg/kg, 5 times/week for 39 days), T-DXd (IV, 10 mg/kg, on days 1 and 22, indicated by black arrows) or O+T and tumor volumes were measured twice a week. Tumor growth inhibition on day 39 was calculated as 100% x (Vcontrol - Vtreated)/Vcontrol). (**A**) Mean ± SEM of tumor volumes overtime. Unpaired t-test was used to compare tumor volumes between O+T and T-DXd on day 39. (**B**) Individual RTV over time. (**C**) Kaplan-Meier analysis of EFS (time for RTV = 4). Log-rank Mantel–Cox test was employed for survival analyses. Significance levels are indicated as **p < 0.05* and ****p < 0.001*.

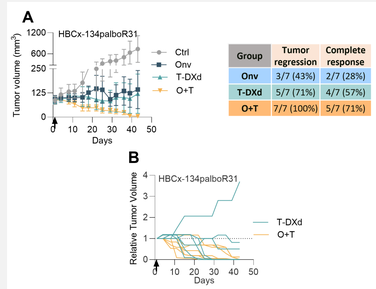
Onvansertib and T-DXd combination induces tumor regression in a HR+ breast cancer PDX model resistant to palbocilcib and fulvestrant



Group	Tumor regression	Complete response
Onv	0/8 (0%)	0/8 (0%)
T-DXd	0/8 (0%)	0/8 (0%)
O+T	8/8 (100%)	2/8 (25%)

Figure 3. (A-B) HBCx-3 PDX model was treated with vehicle (Ctrl), Onv (oral, 45mg/kg, 5 times/week for 43 days), T-DXd (IV, 4 mg/kg, on days 1 and 22 , indicated by black arrows) or O+T and tumor volumes were measured twice a week. RTV was calculated as RTV = (tumor volume on measured day)/(tumor volume on day 0). Tumor regression is reported if RTV < 0.5 in at least one tumor measurement and a complete response is indicated when tumor volume is less than 10 mm^3 in at least one measurement. (**A**) Mean ± SEM of tumor volumes overtime. Unpaired t-test was used to compare tumor volumes between O+T and T-DXd on day 43. (**B**) Individual RTV over time. Significance levels are indicated as *****p < 0.0001*.

Onvansertib and T-DXd combination exhibits robust anti-tumor activity in a HR+ breast cancer PDX model resistant to palbocilcib and alpelisib + fulvestrant



Group	Tumor regression	Complete response
Onv	3/7 (43%)	2/7 (28%)
T-DXd	5/7 (71%)	4/7 (57%)
O+T	7/7 (100%)	5/7 (71%)

Figure 4. (A-B) HBCx-134palboR31 PDX model was treated with vehicle (Ctrl), Onv (oral, 45mg/kg, 5 times/week for 43 days), T-DXd (IV, 4 mg/kg, on day 1 , indicated by black arrow) or O+T and tumor volumes were measured twice a week. RTV was calculated as RTV = (tumor volume on measured day)/(tumor volume on day 0). Tumor regression is reported if RTV < 0.5 in at least one tumor measurement and a complete response is indicated when tumor volume is less than 10 mm^3 in at least one measurement. (**A**) Mean ± SEM of tumor volumes overtime. (**B**) Individual RTV over time.

Onvansertib and T-DXd combination is well tolerated *in vivo*

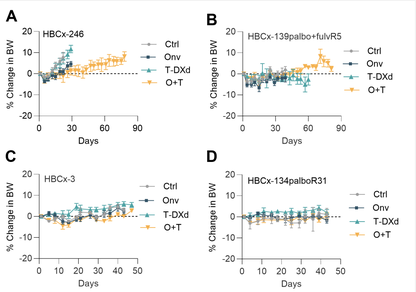


Figure 5. (A-D) Percentage change in body weight (BW) of mice treated with vehicle (Ctrl), Onv, T-DXd or O+T as indicated in Figures 1-4. (**A**) HBCx-246 (**B**) HBCx-139palbo+fulvR5 (**C**) HBCx-3 and (**D**) HBCx-134palboR31 PDX models.

Conclusions

Onvansertib and T-DXd combination was well tolerated and:

- Overcame T-DXd resistance and delayed tumor progression in an abemaciclib- and ET-resistant HR+ breast cancer PDX model.
- Displayed enhanced anti-tumor activity compared to single agents across the 3 ET- and palbociclib-resistant HR+ breast cancer PDX models.
- Displayed robust anti-tumor activity in an alpelisib-resistant HR+ breast cancer PDX model.

Combining T-DXd with onvansertib extends its benefit, overcomes T-DXd resistance and represents a promising therapeutic strategy for HR+ breast cancer patients resistant to first-line therapies.

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