PLK1 Inhibitor Onvansertib Extends the Response and Overcomes Resistance to Paclitaxel in Palbociclib-resistant HR+ Breast Cancer Patient-derived Xenografts

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Background

Paclitaxel in hormone receptor positive (HR+) metastatic breast cancer:

- Commonly used after patients progress on endocrine therapy + CDK4/6 inhibitors.
- Response rates range between 20-40%[1,2].
- Most patients progress due to intrinsic or acquired resistance.
- Therapeutic strategies to overcome paclitaxel resistance and extend its clinical benefit are urgently needed.

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[3,4].
- Has been shown to mediate resistance to CDK4/6 inhibitor palbociclib in HR+ breast cancer[5].

Onvansertib:

- An oral small molecule, selective inhibitor of PLK1, currently in clinical development.
- Showed potent anti-tumor activity in combination with paclitaxel in ovarian cancer and TNBC preclinical models[6,7].
- A phase 1b/2 clinical trial is ongoing to evaluate the safety and efficacy of onvansertib plus paclitaxel in advanced TNBC (NCT05383196).

This study aimed at evaluating the efficacy of onvansertib in combination with paclitaxel in HR+ breast cancer preclinical models.

Results

Mutational status and IC_{50} values of onvansertib and paclitaxel in ER+ breast cancer cell lines

Cell line	Mutational Status			IC_{50} (nM)	
	PIK3CA	PTEN	p53	Onvansertib	Paclitaxel
MCF7	Mut (E545K)	WT	WT	68	5.7
T-47D	Mut (H1047R)	WT	Mut (L194F)	211	8.0
EFM-19	Mut (H1047L)	WT	Mut (H193R)	20	4.5
CAMA-1	WT	Loss	Mut (R280T)	58	10
ZR-75-1	WT	Loss	WT	109	7
HCC1428	WT	WT	Mut (R273H)	Resistant	14
MCF7/S0.5 (Parental)	Mut (E545K)	WT	WT	70	13
MCF7/164R-7 (Fulvestrant-resistant)	Mut (E545K)	WT	WT	65	15

PIK3CA, PTEN and p53 mutational status of selected ER+ breast cancer cell lines. The cell lines were treated with varying doses of onvansertib or paclitaxel for 6-7 days and cell viability was assessed using CellTiter-Glow® assay. IC_{50} values are shown.

Onvansertib and paclitaxel are synergistic in ER+ breast cancer cell lines

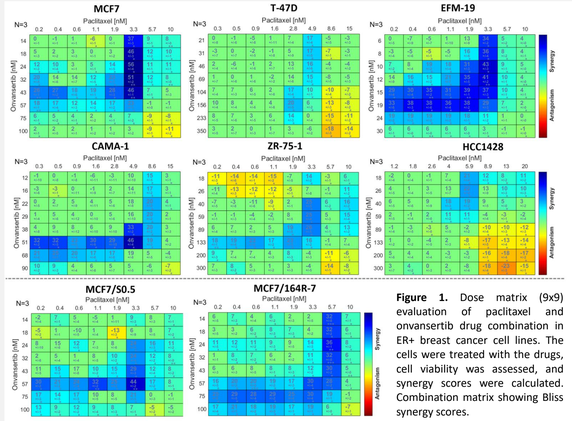


Figure 1. Dose matrix (9x9) evaluation of paclitaxel and onvansertib drug combination in ER+ breast cancer cell lines. The cells were treated with the drugs, cell viability was assessed, and synergy scores were calculated. Combination matrix showing Bliss synergy scores.

Onvansertib and paclitaxel combination induces G2/M arrest and apoptosis *in vitro*

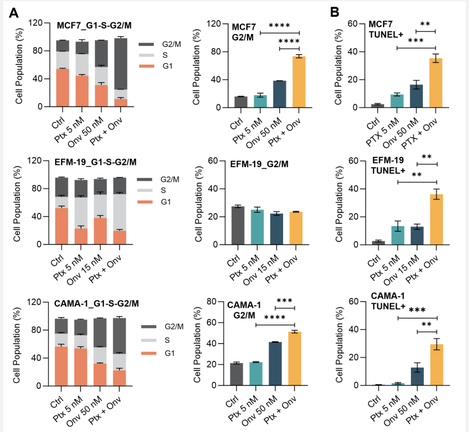


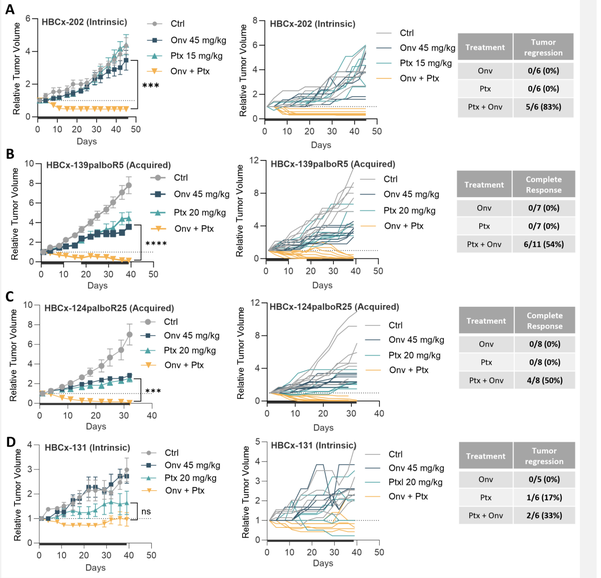
Figure 2. Effect of paclitaxel (Ptx) and onvansertib (Onv) single agents and combination on cell cycle and apoptosis. **(A)** The percentage of cells in G1, S and G2/M phases are plotted. **(B)** % of cells undergoing apoptotic DNA fragmentation as analyzed by TUNEL assay. Results are presented as mean ± SEM. One-way ANOVA was used to compare the means. **p<0.01,***p<0.001, **** p<0.0001 .

Results

Overview of the PDX models

PDX Model	HBCx-202	HBCx-139 palboR5	HBCx-124 palboR25	HBCx-131	HBCx-137 palboR26	HBCx-86	BC-52
PDX IHC	ER+	ER+	ER+ PR+	ER+ PR+	ER+ PR-	ER+	ER+
PDX Origin	Bone met	Bone met	Bone met	Bone met	Bone met	Primary breast tumor	Primary breast tumor
Mutations	-	PIK3CA		CDKN2A/B Del	GATA3 Mut	PIK3CA, RB1	TP53, PTEN
Gene amplification/ gain	CCND1	PAK1, CCND1, CCNB1, CCNE2	CCND1, FGFR1, MYC, CCNE2, AURKA	CCND1, FGFR1	CCND1, FGFR1&2, PAK1, TERT, CCNE2	CCND1, FGFR1	NA
Resistance to Palbociclib	Intrinsic	Acquired	Acquired	Intrinsic	Acquired	Intrinsic	Intrinsic

Onvansertib and paclitaxel combination exhibits robust anti-tumor activity in palbociclib-resistant ER+ breast cancer PDX models



Treatment	Tumor regression
Onv	0/6 (0%)
Ptx	0/6 (0%)
Ptx + Onv	5/6 (83%)

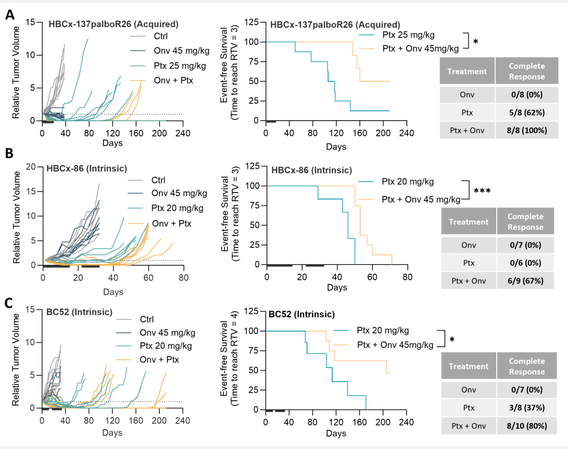
Treatment	Complete Response
Onv	0/7 (0%)
Ptx	0/7 (0%)
Ptx + Onv	6/11 (54%)

Treatment	Complete Response
Onv	0/8 (0%)
Ptx	0/8 (0%)
Ptx + Onv	4/8 (50%)

Treatment	Tumor regression
Onv	0/5 (0%)
Ptx	1/6 (17%)
Ptx + Onv	2/6 (33%)

Figure 3. HBCx-202 (**A**), HBCx-139palboR5 (**B**), HBCx-124palboR25 (**C**) and HBCx-131 (**D**) PDX models were treated with vehicle (Ctrl), onvansertib (Onv), paclitaxel (Ptx) or combination of Ptx and Onv for the indicated duration (▬). Tumors were measured, and relative tumor volume (RTV) was calculated as RTV = (tumor volume on measured day)/(tumor volume on day 0). Individual RTV over time is also shown. Tumor regression is reported if RTV < 0.5 in at least 1 tumor measurement. Complete response is defined as at least 1 tumor measurement < 10 mm^3. Unpaired t-test was used to compare relative tumor volume at last measurement , ***p<0.001, ****p<0.0001.

Onvansertib prolongs the benefit of paclitaxel in palbociclib-resistant ER+ breast cancer PDX models



Treatment	Complete Response
Onv	0/8 (0%)
Ptx	5/8 (62%)
Ptx + Onv	8/8 (100%)

Treatment	Complete Response
Onv	0/7 (0%)
Ptx	0/6 (0%)
Ptx + Onv	6/9 (67%)

Treatment	Complete Response
Onv	0/7 (0%)
Ptx	3/8 (37%)
Ptx + Onv	8/10 (80%)

Figure 4. HBCx-137palboR26 (**A**), HBCx-86 (**B**) and BC52 (**C**) PDX models were treated, and tumor volumes were measured as indicated in **Figure 3**. Individual RTVs over time are shown. Kaplan-Meier survival curve for event-free survival (time to reach RTV 3 or 4) was calculated. Log-rank Mantel Cox test was used for survival analyses, *p<0.05, ***p<0.001.

Conclusions

- Onvansertib in combination with paclitaxel synergistically inhibited the viability of ER+ breast cancer cell lines. Compared to monotherapies, the combination induced pronounced G2/M arrest and apoptosis.
- In all the palbociclib-resistant HR+ breast cancer PDX models tested (n=7), the combination of onvansertib and paclitaxel exhibited robust anti-tumor activity:
  - In the 4 models that showed no to minimal sensitivity to monotherapies, the combination induced tumor regression in 3 models and tumor stasis in 1 model.
  - In the 3 models sensitive to paclitaxel, the combination induced tumor regression with a higher rate of complete response than monotherapy, and response to the combination was more durable.

The PLK1 inhibitor onvansertib enhances the efficacy and duration of response of paclitaxel in HR+ breast cancer preclinical models. The combination represents a promising therapeutic strategy for HR+ breast cancer patients after progression on endocrine therapy and CDK4/6 inhibitors.

References

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