Activity of Chemotherapy Drugs in Patient-Derived Xenografts (PDXs) From Triple Negative Breast Cancer (TNBC) Patients

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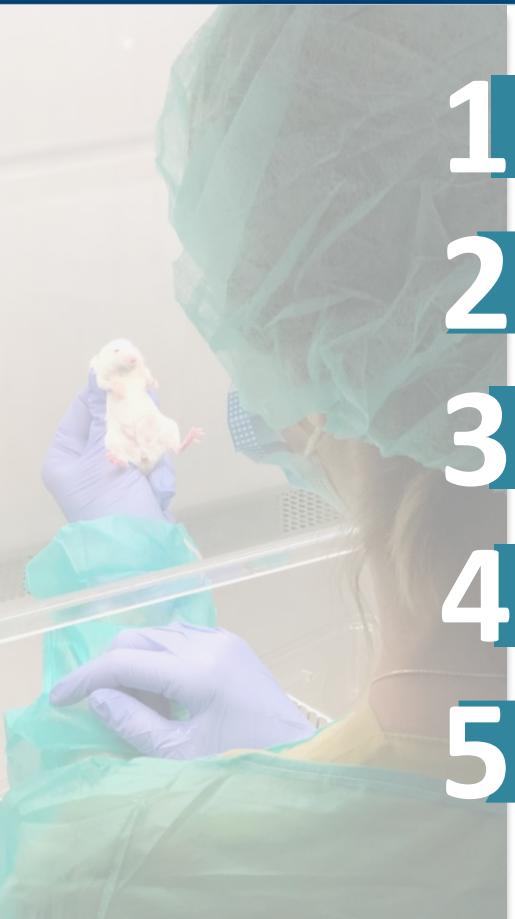


1. Background: Triple Negative Breast Cancer

10-20% Of diagnosed breast cancers are triple negative

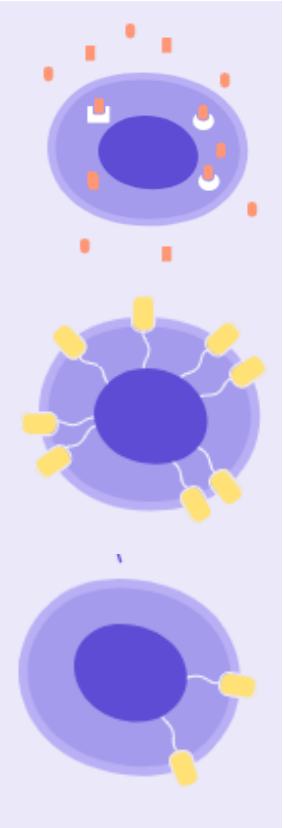
Triple negative breast cancer is characterized by having expression of estrogen receptors and progesterone receptors of less than 1% and by not having over expression of HER2.
Disproportionately affects an African/Hispanic descent, younger age (<50 years), overweight stage at diagnosis vs other subtype.

60-80% Of tumor in women carrying BRCA1 mutation

TNBC is the predominant subtype in germline BRCA1 mut carrier.

Chemotherapy Is currently the base of the treatment

Those commonly used include anthracyclines and taxanes. In addition, recent studies show that the addition of carboplatin to chemotherapy with anthracycline and/or taxanes improves the complete pathological response (pCR) in the neoadjuvant setting.



HR+ Breast cancer cells

HER2+ Breast cancer cells

TN Breast cancer cells

2. Objective

Generate new in vivo models of TNBC treatment naïve to evaluate efficacy of three chemotherapy agents: doxorubicin, carboplatin, docetaxel as single-agent regimens, and the combination of docetaxel and carboplatin

3. Methodology

PDXs models

- PDXs are generated from treatment-naïve TNBC diagnostic core-biopsies.
- Patients have been classified according to Symmans classification after neoadjuvant chemotherapy and depending on the absence or presence of deficiencies in homologous recombination repair pathways (HR), specifically the presence in BRCA and PALB2 germline mutation.
- Orthotopic injection of a small tissue sample from the patient's biopsy on NOD/SCIF KO IL-2r (NSG).

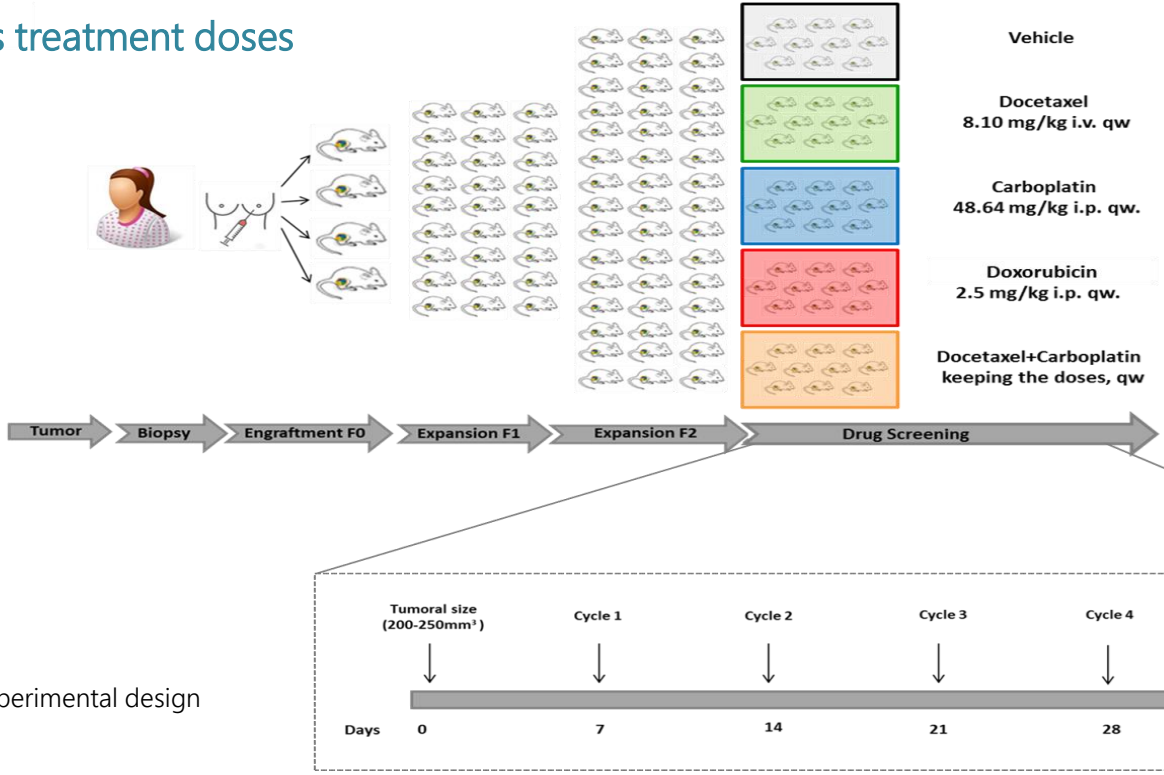
Table 1.Patient treated with docetaxel and carboplatin combination and tumor characteristics

Patient and disease features	***N=9 (%)***
Age (year)	
<50	4 (45%)
≥50	5 (55%)
Menopausal status	
Pre	4 (45%)
Post	5 (55%)
Clinical T-stage	
T1	1 (11%)
T2	5 (55%)
T3	2 (23%)
T4	1 (11%)
Clinical N-stage	
N0	2 (23%)
N1	6 (66%)
N2	1 (11%)
N3	0
Symmans Class	
pCR	3 (33%)
RCB-I	1 (11%)
RCB-II	3 (33%)
RCB-III	2 (23%)

Clinical response (MRI)	
Complete response	2 (23%)
Minor Response	5 (55%)
Partial response	1 (11%)
Progression disease	0 (0%)
Stable disease	1 (11%)
Ki 67 expression	
<50	1 (11)
≥50	8 (89%)
Histologic grade	
G1	0
G2	2 (23%)
G3	6 (66%)
No data	1 (11%)
Homolgous recombination mutation	
BRCA wt	5 (55%)
BRCA mut	3 (33%)
PALB2 mut	1 (11%)

3. Methodology

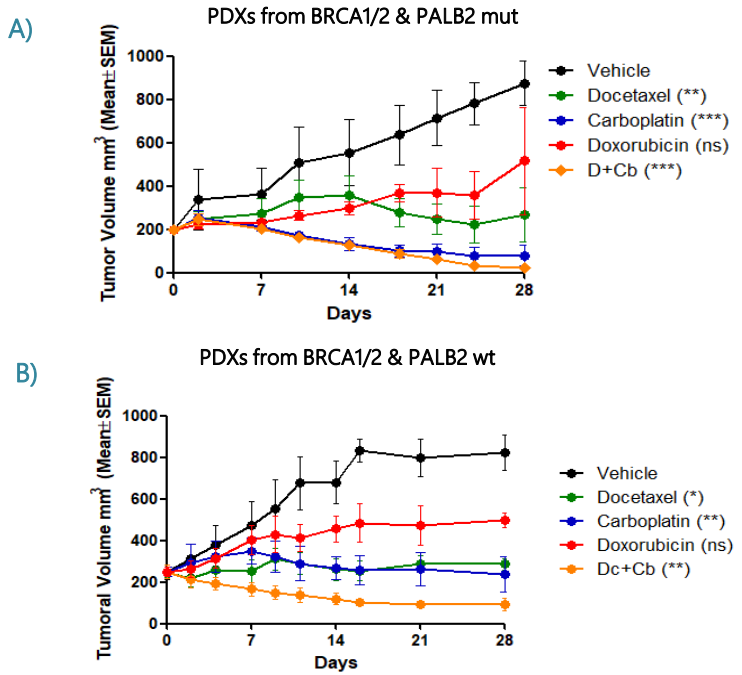
PDXs treatment doses



Engraftment rate (Px0)
45%

Figure 1. Experimental design

4. Results



Antitumor activity

- Low sensitivity to doxorubicin.
- Platinum-based neoadjuvant chemotherapy was highly effective in BRCA1/2 and PALB2 germline mutation carriers.
- Combined regimen achieved the best antitumor response in both cases.

Figure 2. Antitumor activity of drugs in PDX

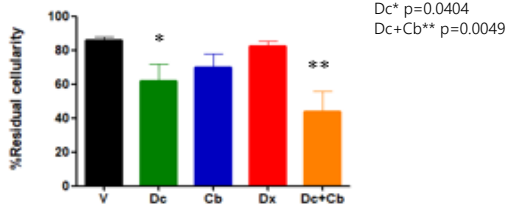
A) With germline mutations in the HR pathway (gHR) with significant differences between vehicle and pharmacological treatment: docetaxel (p=0.0427), carboplatin (p=0.041) and combination (p=0.0037)

B) B) Without gHR with significant differences between vehicle and docetaxel (p=0.0217), carboplatin (p=0.0005) and combination (p=0.0004).

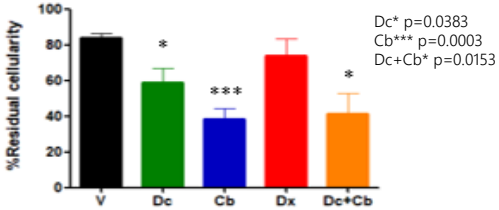
4. Results

Residual cellularity

PDXs from BRCA1/2 & PALB2 wt

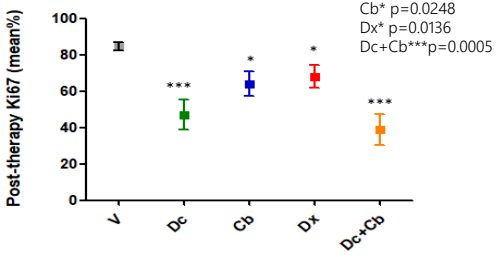


PDXs from BRCA1/2 & PALB2 mut

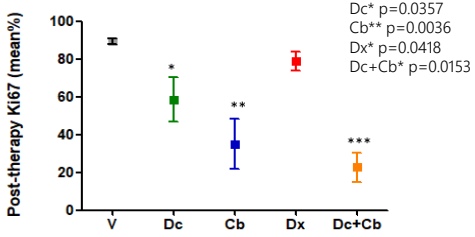


Proliferation rate

PDXs from BRCA1/2 & PALB2 wt



PDXs from BRCA1/2 & PALB2 mut



Combined regimen achieved the best reduction rate in %Ki67 and residual cellularity.

60-75% Of reduction in %Ki67

50% Of reduction in residual cellularity

PDXs from BRCA1/2 and PALB2 germline mutation carriers have higher response rate to carboplatin.

61% Of reduction in %Ki67

54% Of reduction in residual cellularity

Figure 3. Relationship of % residual cellularity and % of proliferation marker Ki67

5. Conclusions

We established PDXs models using tumor samples from patients with triple negative breast cancers naïve to chemotherapy. This tool is useful for testing new drugs.

The results of the study confirmed the sensitivity of PDXs with homologous recombination pathway deficiency to platinum agents.

Our findings suggest that the combination of docetaxel and carboplatin produces better results than monotherapy in the PDXs.

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Thank you