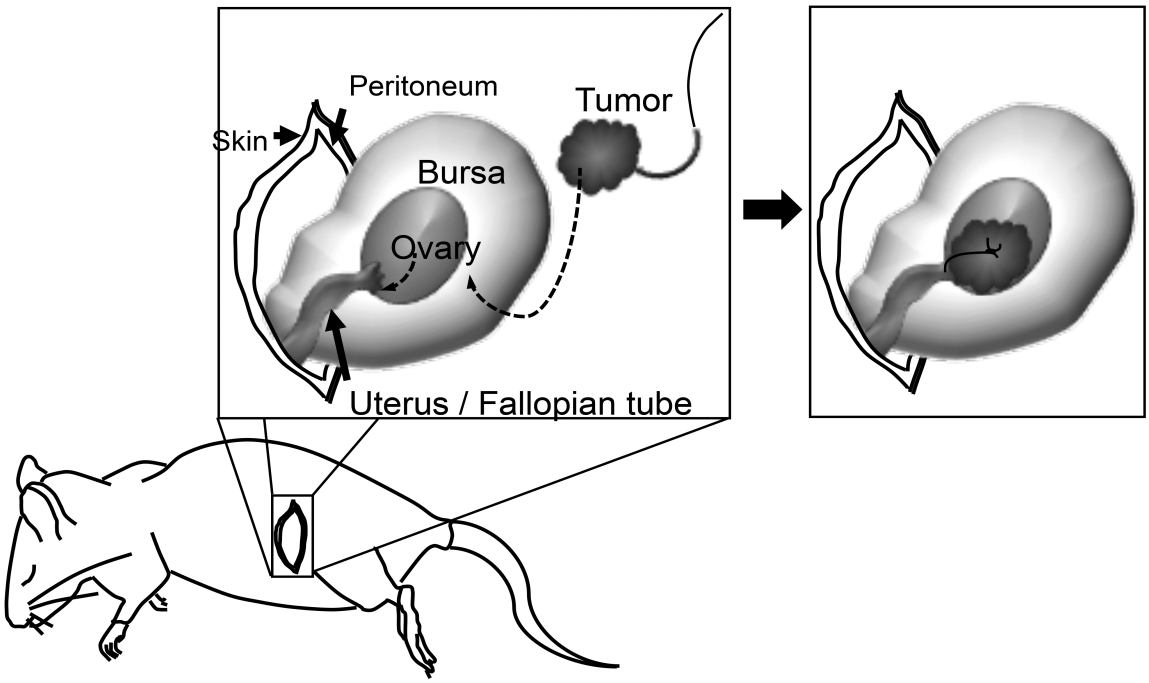
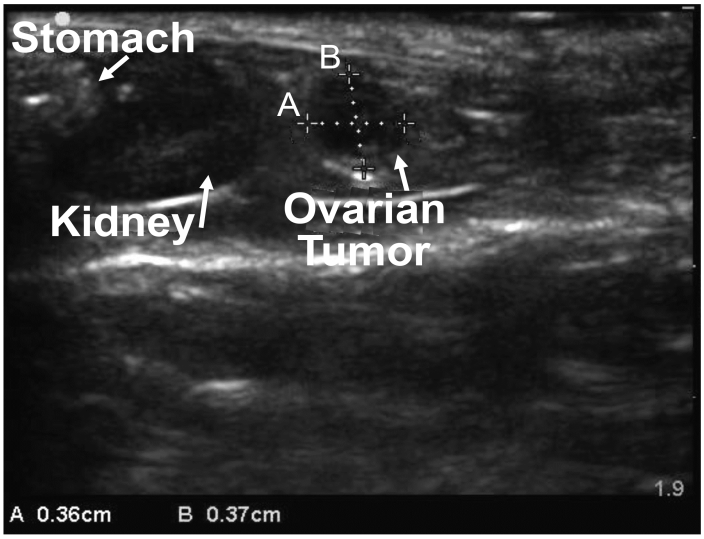
A


Peritoneum
Tumor
Skin
Bursa
Ovary
Uterus / Fallopian tube

B


Stomach
B
A
Kidney
Ovarian Tumor
1.9
A 0.36cm
B 0.37cm

Supplemental Figure 1. Orthotopic ovarian patient derived xenograft (PDX) Model: transplant procedure and tumor evaluation. (A) Diagram showing surgical tumor transplantation to mouse ovary. Under anesthesia, a small 1-2cm vertical incision is made through the skin over the left flank. The skin is undermined and the peritoneal cavity is then opened and a 1cm vertical incision is created. The left ovary, ovarian bursa and uterine horn are elevated and exteriorized. Once the left ovary is identified on the anterior side of the bursa, two to three tumor chunks (~2x2x2mm each) are sutured to the ovary/fallopian tube fimbria using 5.0 PDS suture. The tumor transplant is then internalized back into the peritoneal cavity, and ~50μL of matrigel is placed over the transplant. The peritoneal cavity is closed and the skin is re-approximated using dermabond (skin glue). (B) PDX tumor volume measurements by ultrasound are shown. Representative ultrasound image obtained with the SonoSite M-TURBO ultrasound using a HFL38x 13-6MHz linear transducer. Sagittal view highlighting landmark anatomy (stomach and kidney). Ovarian tumor length (*l*) and width (*w*, smaller of two measurements) is illustrated (B and A, respectively). Tumor volume was calculated using the following equation: $V=l*w^2/2$.

ABL1
AKT1
AKT2
AKT3
ALK
APC
ARAF
ARID1A
ARL11
ATM
ATR
AURKA
BAP1
BARD1
BLM
BRAF
BRCA1
BRCA2
BRIP1
CBX2
CCND1
CCND2
CCND3
CCNE1
CDH1
CDK12
CDK4
CDK6
CDKN1A
CDKN1B
CDKN1C
CDKN2A
CDKN2B

CEBPA
CHEK1
CHEK2
RP3-510D11.2
RP11-554I8.2
CREBBP
CRKL
CSF1R
CTNNB1
DAB2
DDR2
DICER1
DIRAS3
DLEC1
DPH1
EGFR
EIF5A2
EME1
EPHA3
ERBB2
ERBB3
ERBB4
ERCC3
ESR1
FANCA
FANCE
FANCM
FBXW7
FGF1
FGFR1
FGFR2
FGFR3
FLT3

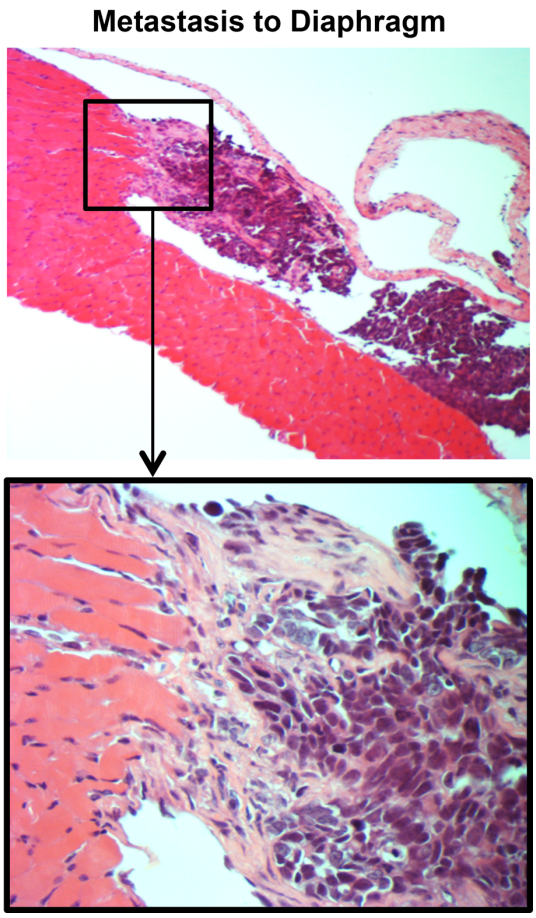
FOXL2
FRS2
GNA11
GNAQ
GNAS
HRAS
IGF1R
JAK1
JAK2
JAK3
JARID2
KDR
KIT
KMT2C
KRAS
MAP2K1
MAP2K2
MAP2K4
MAP3K4
MAPK1
MAPK3
MECOM
MET
MLH1
MPL
MRE11A
MSH2
MSH3
MSH6
MTOR
MUS81
MYC
NBN

NF1
NF2
NOTCH1
NOTCH2
NOTCH3
NRAS
OPCML
PALB2
PAX8
PDGFRA
PEG3
PIK3CA
PIK3R1
PLAGL1
PMS2
POLD1
POLD2
POLD3
POLD4
PPM1D
PPP2R1A
PRKCI
PTEN
RAB25
RAD50
RAD51
RAD51B
RAD51C
RAD51D
RAD52
RAD54B
RAD54L
RAF1

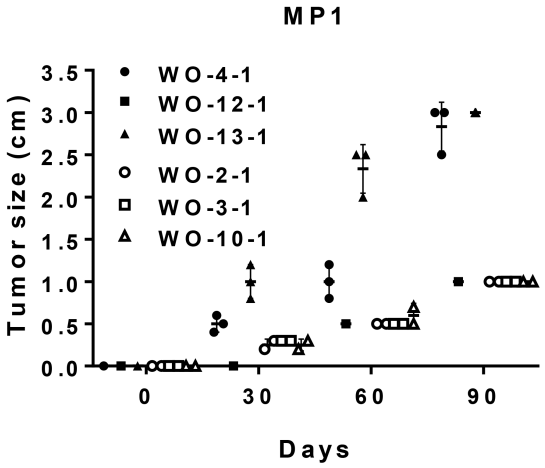
RASSF1
RB1
RPA1
RPA2
RPA3
RPA4
RPS6KA2
RSF1
SHFM1
SMAD2
SMAD4
SMARCA4
SMARCB1
SPARC
SRC
SSBP1
STK11
TERT
TOP3A
TOP3B
TP53
TP53BP1
WWOX
XRCC2
XRCC3

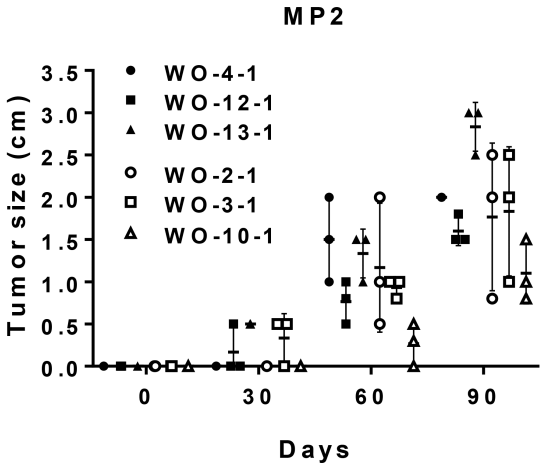
Key:
Whole Genes
Exons + UTR’s

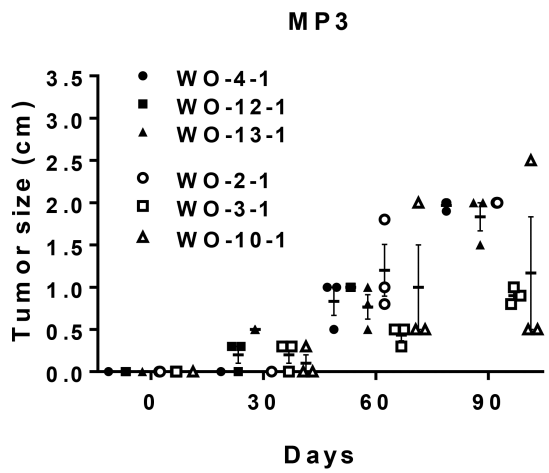
Supplemental Figure 2. DNA targeted sequence ovarian cancer gene panel. Custom capture panel including 157 genes, primarily genes targetable and involved in pathways implicated in ovarian and/or breast cancer susceptibility and tumorigenesis, such as HR, mismatch repair, or checkpoint inhibition. Whole genes were sequenced for the genes most frequently mutated (including *BRCA1* and *BRCA2*), while only exons and untranslated regions (UTR's) were analyzed in the remaining genes.



Supplemental Figure 3. Histology of PDX metastatic tumor to diaphragm. Metastatic tumor to diaphragm was obtained from a *BRCA2*^{MUT} PDX (WO-2-3, mouse passage 3). Magnifications are 10x (upper image) and 40x (lower image). Insert shows tumors invading diaphragm.


MP1
WO-4-1
WO-12-1
WO-13-1
WO-2-1
WO-3-1
WO-10-1
Tumor size (cm)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
30
60
90
Days


MP2
WO-4-1
WO-12-1
WO-13-1
WO-2-1
WO-3-1
WO-10-1
Tumor size (cm)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
30
60
90
Days


MP3
WO-4-1
WO-12-1
WO-13-1
WO-2-1
WO-3-1
WO-10-1
Tumor size (cm)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
30
60
90
Days

Supplemental Figure 4. PDX tumor size by palpation over time shown by dot plot for select PDX models comparing *BRCA*^{MUT} (WO2-1, WO3-1, WO-10-1) to *BRCA*^{WT} (WO-4-1, WO-12-1, WO-13-1) HGSOC over mouse passage 1 (MP1) to mouse passage 3 (MP3). The horizontal line is the mean of determinations with the SD. Each symbol represents tumor size of individual mouse. MP1; WO-4-1 (n=3), WO-12-1 (n=1), WO-13-1 (n=3), WO-2-1 (n=2), WO-3-1 (n=2), WO-10-1 (n=2), MP2 and MP3 ; n=3 each PDX.

PDX	PAX8				CK7				ER				BRCA1			
	P	MP1	MP2	MP3	P	MP1	MP2	MP3	P	MP1	MP2	MP3	P	MP1	MP2	MP3
WO-2 (BRCA2)	+++	+++	+++	+++	++	++	+	++	+++	+++	+++	+++				
WO-3 (BRCA1)	+++	+++	+++	+++	++	++	+++	+++	+++	+++	+++	+++	+	+	-	+
WO-4 (WT)	+++	+++	+++	+++	+++	+++	×	+++	+++	+++	++	+++	×	+++	+	++
WO-8 (BRCA1)	+++	+++	+++		×	++	++		++	+++	+++		×	+	+	
WO-10 (BRCA1)	+++	+++	+++	+++	++	++	++	++	+++	+++	+++	+++	+	-	-	-
WO-13 (WT)	+++	+++	+++	+++	+++	+++	+++	+++	-	-	-	-				
WO-16 (BRCA1)	+++	+++	+++		+++	++	+++		++	-	++		×	-	-	
WO-19 (WT)	+	++	++		+	++	++		+++	+++	+++		++	++	+++	
WO-20 (WT)	+++	+++	+++		+++	+++	+++		-	+	-		×	++	++	
WO-21 (BRCA1)	++	+++			+	+			++	+++			+	+		
WO-24 (WT)	+++	+++			+++	+++			-	-						

+++ strong nuclear (PAX8, ER, BRCA1) / cytoplasmic (CK7) staining

++ clear nuclear (PAX8, ER, BRCA1) / cytoplasmic (CK7) staining in multiple cells

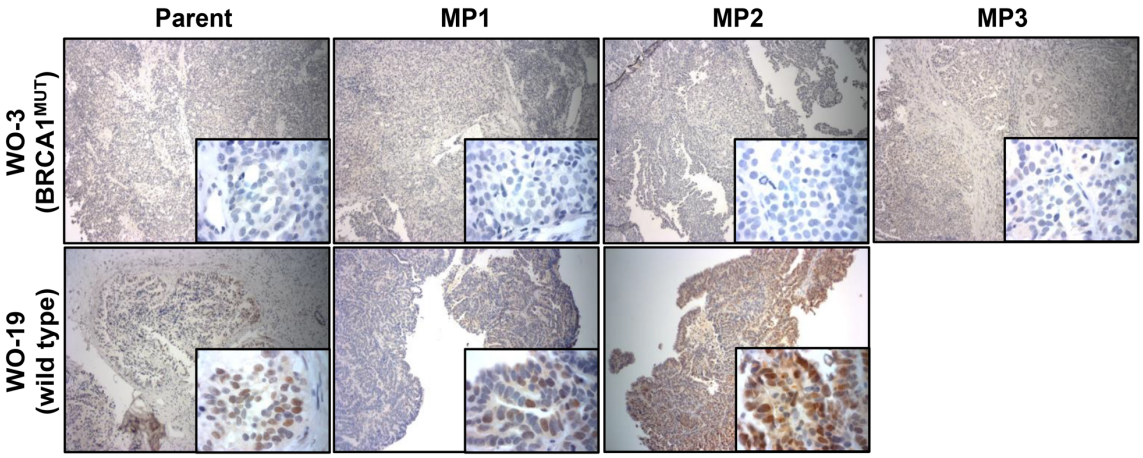
+ weak nuclear (PAX8, ER, BRCA1) / cytoplasmic (CK7) staining in a few cells

- none

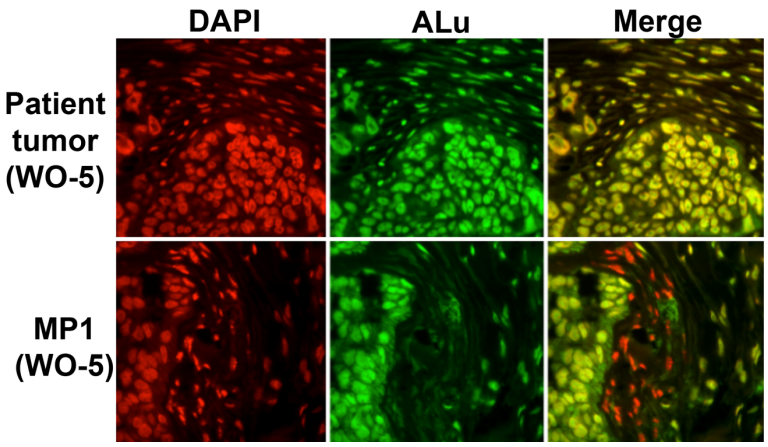
× Not enough cells

■ Not done

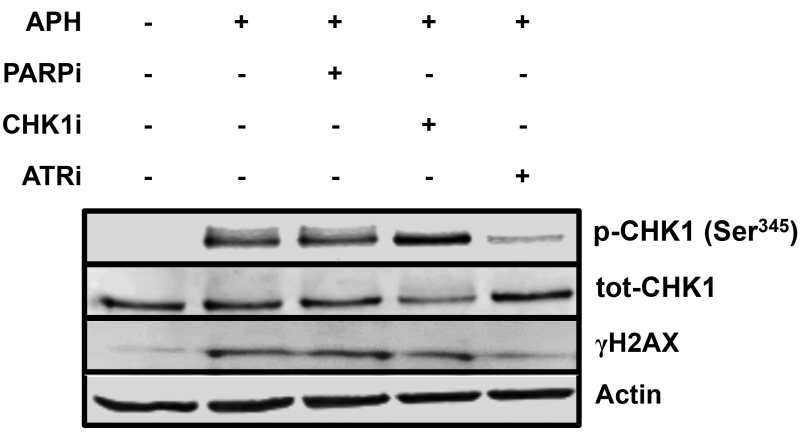
Supplemental Figure 5. Summary of IHC findings in *BRCA*^{MUT} and *BRCA*^{WT} parent tumors and PDXs. Parent (P) and PDX tumors mouse passage 1 (MP1) up to mouse passage 3 (MP3) were fixed, paraffin embedded, and stained for PAX8, CK7, ER, and BRCA1 proteins. Slides were assessed by a Gynecologic Oncology pathologist in a blinded manner using light microscopy and scored based on nuclear (PAX8, ER, BRCA1) or cytoplasmic (CK7) staining. Epithelial HGSOC markers, PAX8 and CK7, were positive in all patient tumors (n=11/11) and preserved over multiple mouse passages in all PDXs up to MP3. ER was expressed in 72.7% (n=8/11) of patient tumors (defined as >10% of nuclear staining). All *BRCA*^{MUT} patient tumors (n=6/6) and 40% (n=2/5) *BRCA*^{WT} patient tumors were ER+. ER status was preserved over MP1 to MP3 in 91% (n=10/11). IHC slides were evaluated from n=3 tumors for each model and representative staining is shown. Staining intensity was calculated by counting percentage of positive cells in 10 High power fields. +++ was defined as >50% positive; ++ was defined as 10-50% positive, + was defined as <10% and – was defined as no staining.



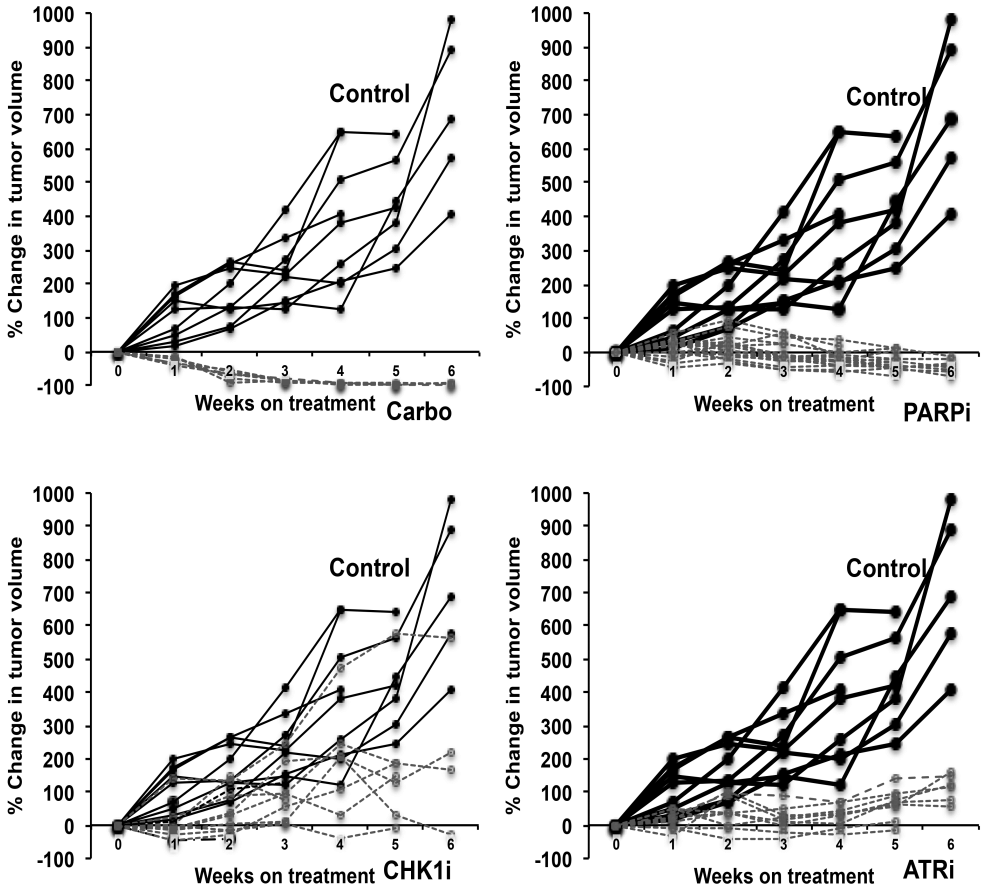
Supplemental Figure 6. BRCA1 protein in parent tumor from BRCA germline and wild-type patient and matched PDXs. Staining for BRCA1 protein in a *BRCA1*^{MUT} (WO-3-1) and *BRCA*^{WT} (WO-19-1) patient tumor is preserved in PDXs passaged up to mouse passage 3 (MP3). Magnifications are 10x (large box) and 100x (insert). IHC slides were evaluated from n=3 tumors for each model and representative staining is shown.



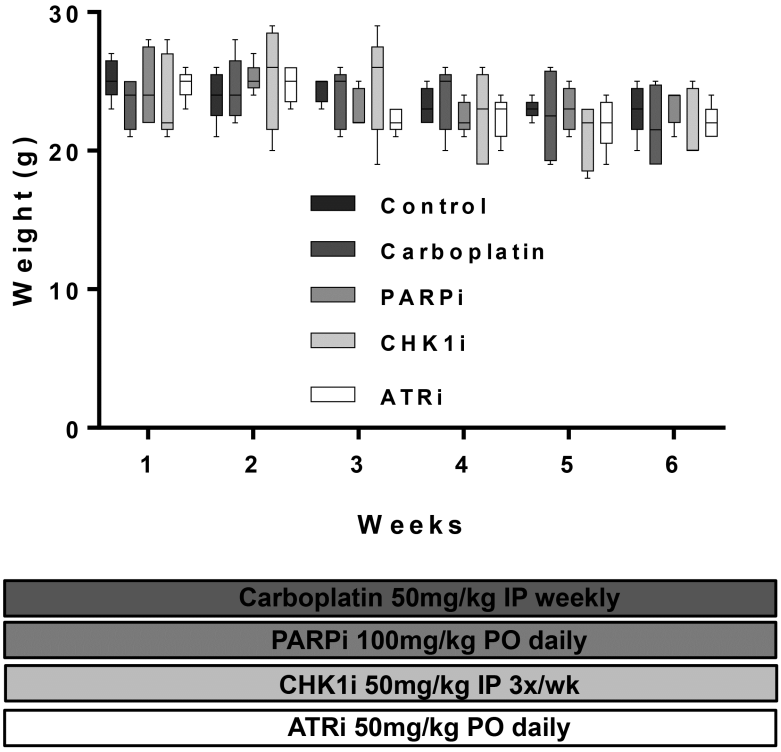
Supplemental Figure 7. Human cells are present in the PDX stroma. Human specific Alu staining confirmed human origin, and DAPI staining identified nuclei of a parent tumor and matched PDX MP1 tumor (red is DAPI, green nuclei is ALU, and right is merged image) Merged image represents co-localization of human cells present in the PDX stroma (WO-5) at an early mouse passage (MP-1). Magnification=40x. Staining was performed on at least 3 PDX tumors for each model and representative staining is shown.



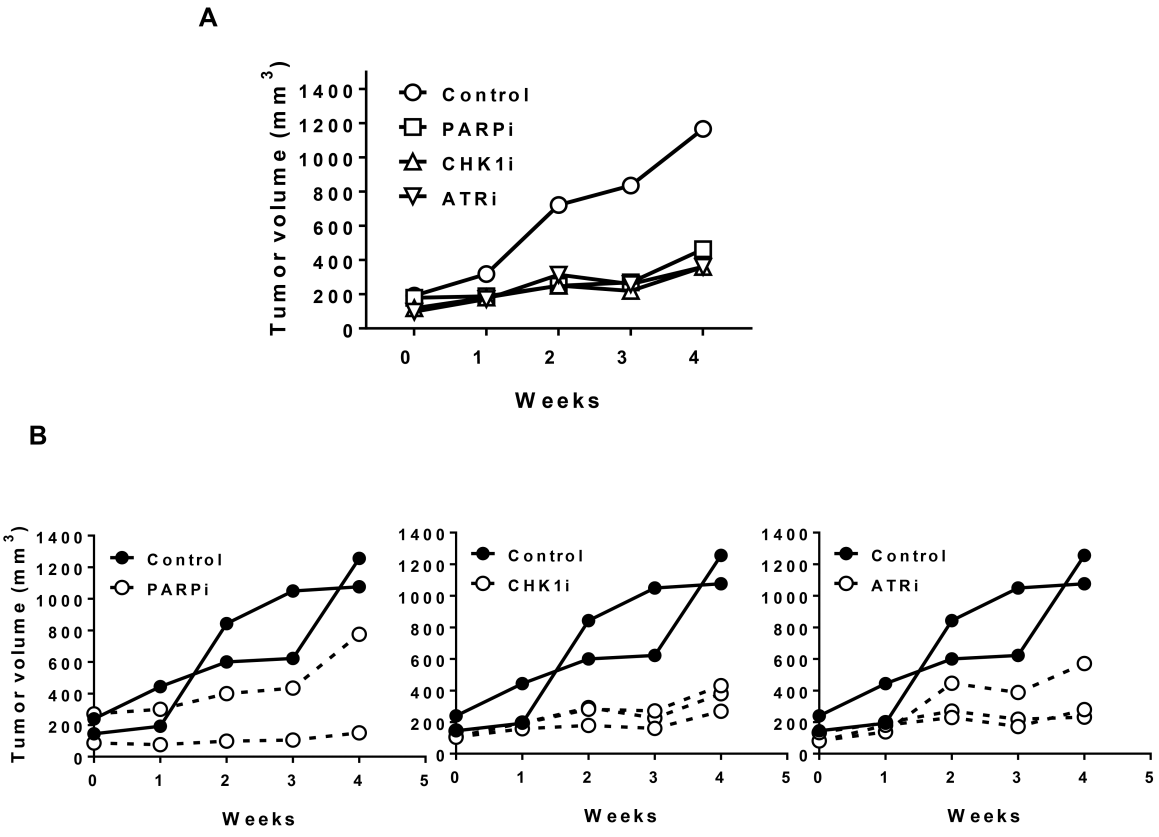
Supplemental Figure 8. Targeting the ATR axis. To exam direct effects of PARPi, CHK1i, and ATRi on ATR/CHK1 pathway, *BRCA2*^{MUT} (PEO1) and *BRCA2*^{REV} (PEO4) cells were treated with aphidicolin (APH) for 30 minutes prior to the addition of the indicated inhibitors (PARPi 1uM (AZD2281), CHK1i 1uM (MK8776), and ATRi 1uM (AZD6738)). Lysates were collected after 4h treatment. Western blot for the indicated total and phospho-proteins. Representative experiment of three independent experiments



Supplemental Figure 9. Individual PDX tumor volume change with carboplatin, PARPi, CHK1i, and ATRi monotherapy treatment. The percent change in tumor volume from the starting tumor volume was plotted over treatment duration for individual PDXs. All mice in the carboplatin group after 6 weeks of treatment had complete remission (n=6/6). In the PARPi group 68.8% (n=11/16) and 31.2% (n=5/16) of mice showed a partial remission (PR) and stable disease (SD), respectively, by RECIST1.1. There were no complete responses with PARPi alone. In the CHK1i group 25% (n=2/8) had SD and 75% (n=6/8) had PD. In the ATRi group 22.2% (n=2/9) and 77.8% (n=7/9) of mice had SD and PD, respectively. Each dot represents measurement of individual mouse. Control, n=9; PARPi n=16; Carboplatin, n=6; ATRi, n=9; CHK1i, n=8.



Supplemental Figure 10. Animal weights by treatment group. Weight (grams) of mice treated with vehicle (control), carboplatin, PARPi, CHK1i or ATRi for 6 weeks. All treatments were administered at the maximum tolerated doses. (Data is shown for experiment displayed in Figure 6C). The dot and whisker plot shows median, with box extending from the 25th to 75th percentile and the whiskers extending from minimum and maximum values of the data set. Control, n=9; PARPi n=16; Carboplatin, n=6; ATRi, n=9; CHK1i, n=8.



Supplemental Figure 11. Targeting the ATR-CHK1 axis in a BRCA1 mutant PDX model (WO21-1). (A) WO-21-1 PDXs were randomized into the following groups: vehicle control, PARPi (AZD2281) 100mg/kg by oral gavage daily, CHK1i (MK8776) 50mg/kg intraperitoneally every 3 days, and ATRi (AZD6738) 50mg/kg daily. Tumor volume was measured by weekly ultrasound. Each symbol represents mean of 2-3 determinations. (B) Tumor volume plotted over treatment duration for individual PDXs.

Each dot represents tumor volume of individual mouse. Control, n=2; PARPi n=2; ATRi, n=3; CHK1i, n=3.