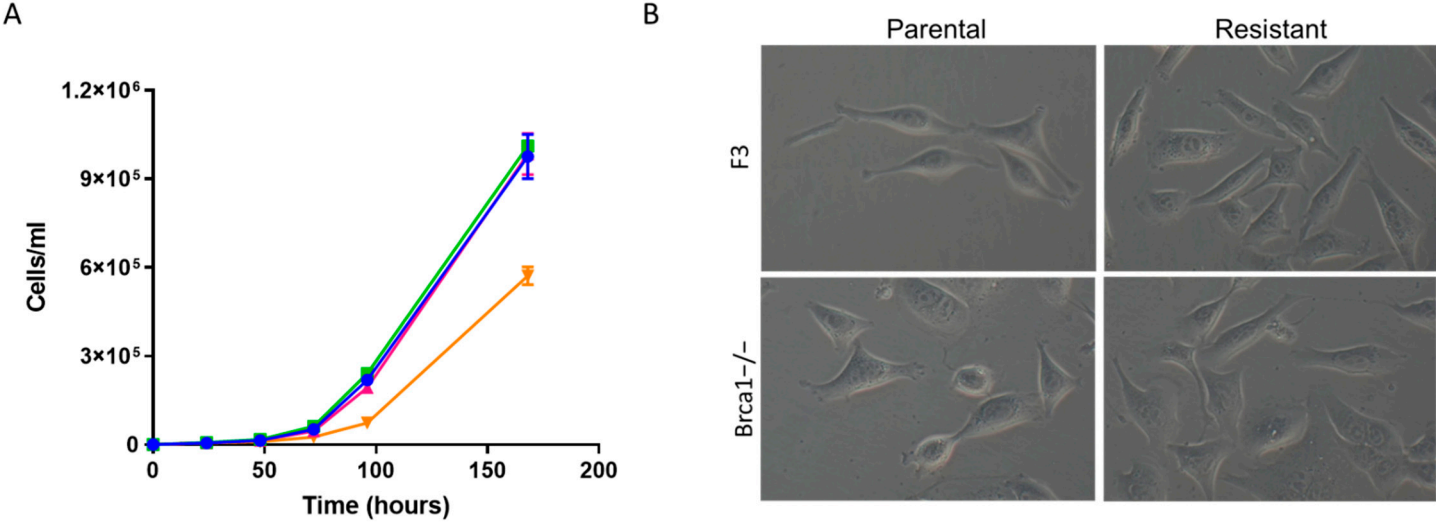


## Supplementary materials

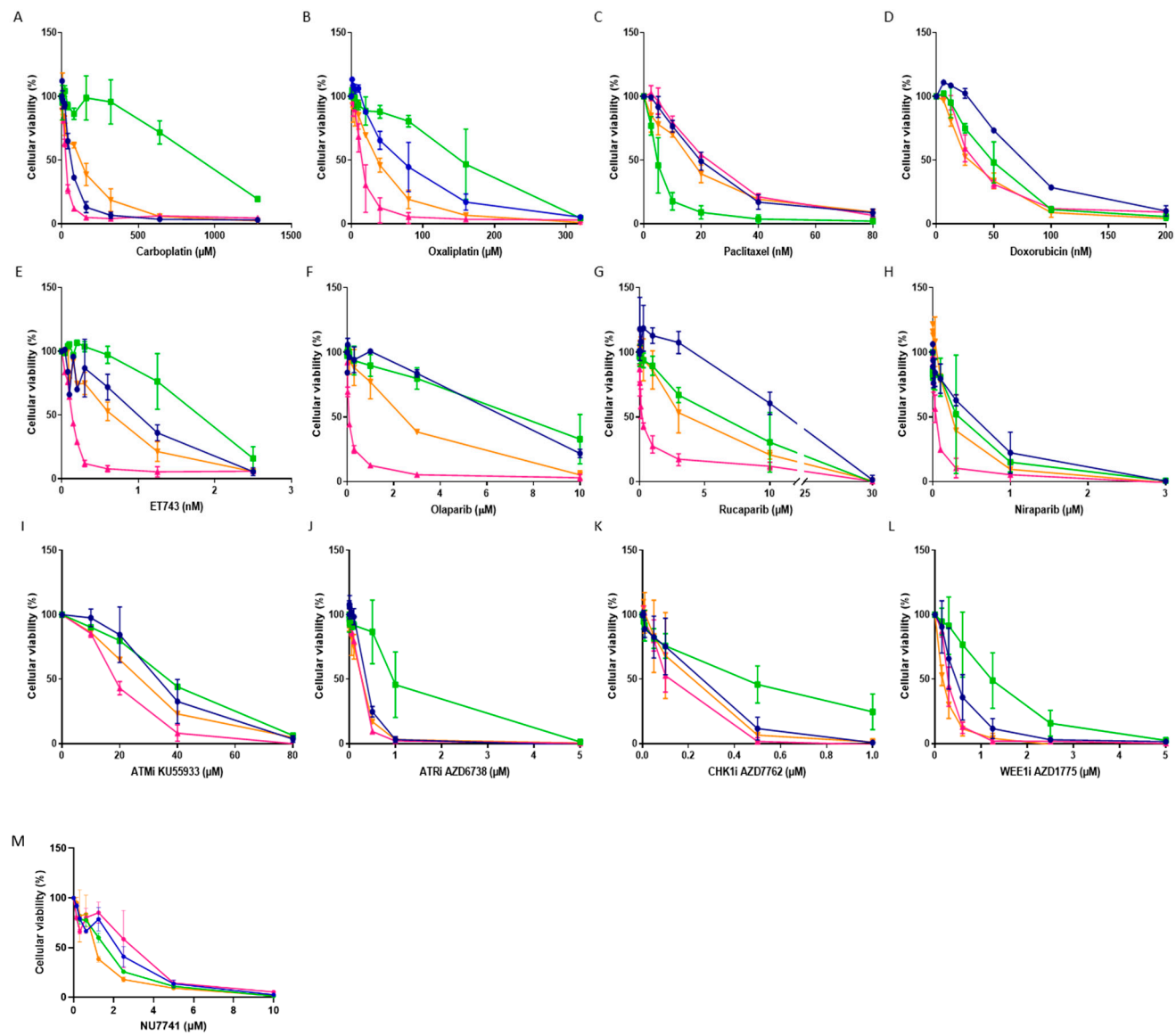
**Supplementary Table S1.** Primers used for Real Time-PCR.

GENE	PRIMER FORWARD	PRIMER REVERSE
<i>β-Actin</i>	GGCTGTATTCCCCTCCATCG	CCAGTTGGTAACAATGCCATGT
<i>ATP7A</i>	GAGCGTCAGATCCTGCCAG	GTAGAAGTACCAGCCGCCAC
<i>ATP7B</i>	GCTCTTTGTGTTTCATCGCCC	GCTTCTGTGGCTTGGAGTGA
<i>CTR1</i>	ACACCTGGAGAAATGGCTGG	TTTCGAAGCAGACCCCTCTCG
<i>CTR2</i>	AGGCCGTGCTTCTCTTTGAT	CTTTGCCAACCTTGATGCCC
<i>MDR1</i>	TGTCAGCTGGTATTTGGGCA	CAGTTCTGATGGCTGCTAAGAC
<i>LRR8D</i>	CTGCCTCTACACTCTCTTCTGGC	CGCAAAGTCGTTCTTGACATC
<i>REV7</i>	GGTGGTGGTGGTGATTTTGG	TCCACATGAGACAGGAGGGA
<i>TP53BP1</i>	TAGCCCGCTATCTGATGTGG	ACAGGGATGTCTTTGCTGGG
<i>SHLD1</i>	CAGGGAAGCAGCAACTCTCT	GTTCTCAGAGTCCCAGGAGC
<i>ERCC1</i>	CTGGGAATTCGGTGAGGTGA	AGTCTGGATGGAGGTTGTGG
<i>XPG</i>	GGGCCC GG CATGTCTATAAG	CCCAGTAGATAGGCCAAGTTGA
<i>XPF</i>	GAAGCTCTACCTGTGGCCAA	CGTCTGAATGGCAAGCATGG
<i>PRKDC</i>	TCACCACAACCCTGCTCATC	GCTCATGGGCTCACAGATCA
<i>LIG IV</i>	ACCACGAGAAGGCAAGGATG	GCAATCATGGCAAAGTCCCC
<i>XRCC6</i>	ATGGCCGTGACAGTGCTAAA	ACGGATACATCAAAGCCTCCTG

**Supplementary Figure S1. Resistant sublines characterization.** **A.** Growth curves of F3 (blue line), F3 ddpR (green line), Brca1-/- (pink line) and Brca1 -/- ddpR (orange line) cells at different times from seeding. Data are the mean  $\pm$  SD of six replicates. **B.** ID8 F3 and Brca1-/- parental and resistant cells. For each cell line a sample image was acquired with 40x magnification.

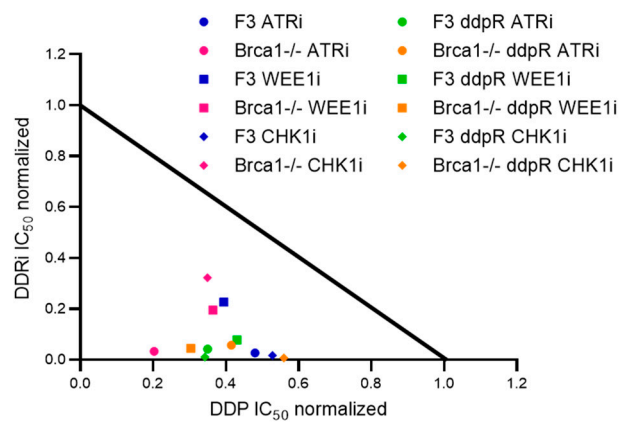


**Supplementary Figure S2. Pharmacological characterization of F3, F3 ddpR, Brca1<sup>-/-</sup> and Brca1<sup>-/-</sup> ddpR cells.** Dose response curves of carboplatin (A), oxaliplatin (B), paclitaxel (C), doxorubicin (D), Yondelis (ET-743) (E), olaparib (F), rucaparib (G), niraparib (H), ATMi (I), ATRi (J), Wee1i (K), Chk1i (L) and DNA PKi (M) in F3 (blue line), F3 ddpR (green line), Brca1<sup>-/-</sup> (pink line) and Brca1<sup>-/-</sup> ddpR (orange line) cells. Data are the mean  $\pm$  standard deviation (SD) of three or four independent experiments.

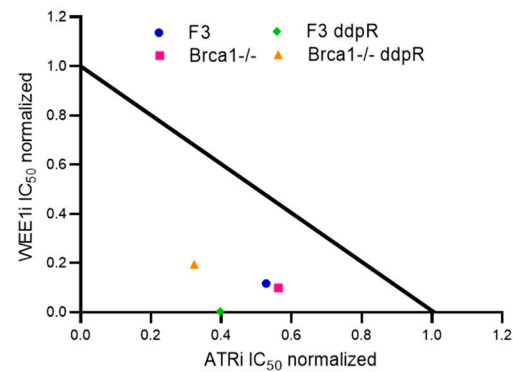


**Supplementary Figure S3. Combination of DDR inhibitors and cisplatin.** **A.** Normalized IC<sub>50</sub> isobolograms showing the synergistic effects of the combination of cisplatin with the inhibitors of ATR, Wee1 and Chk1. **B.** Normalized IC<sub>50</sub> isobolograms showing the synergistic effects of the combination of ATRi and WEE1i.

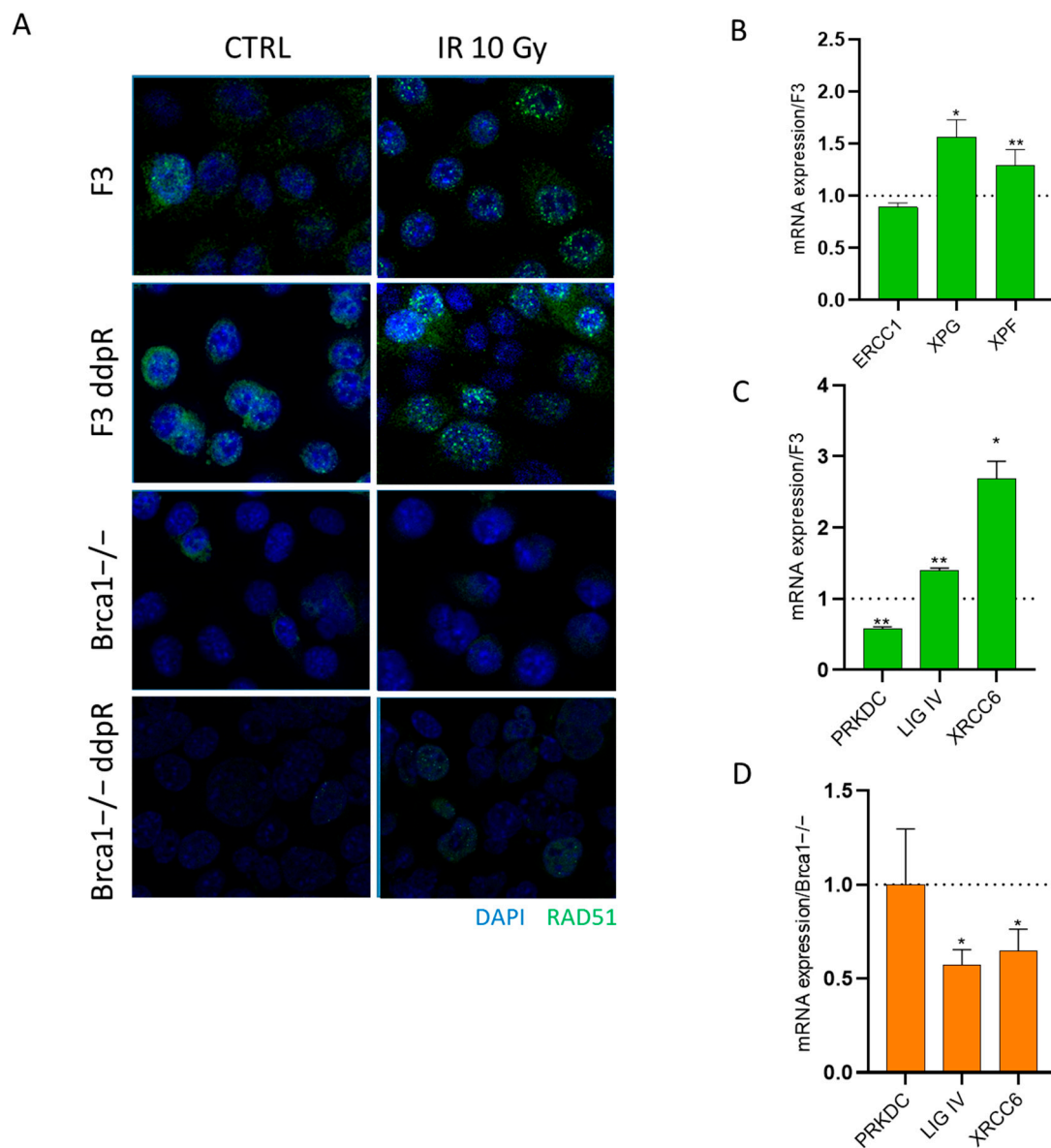
A



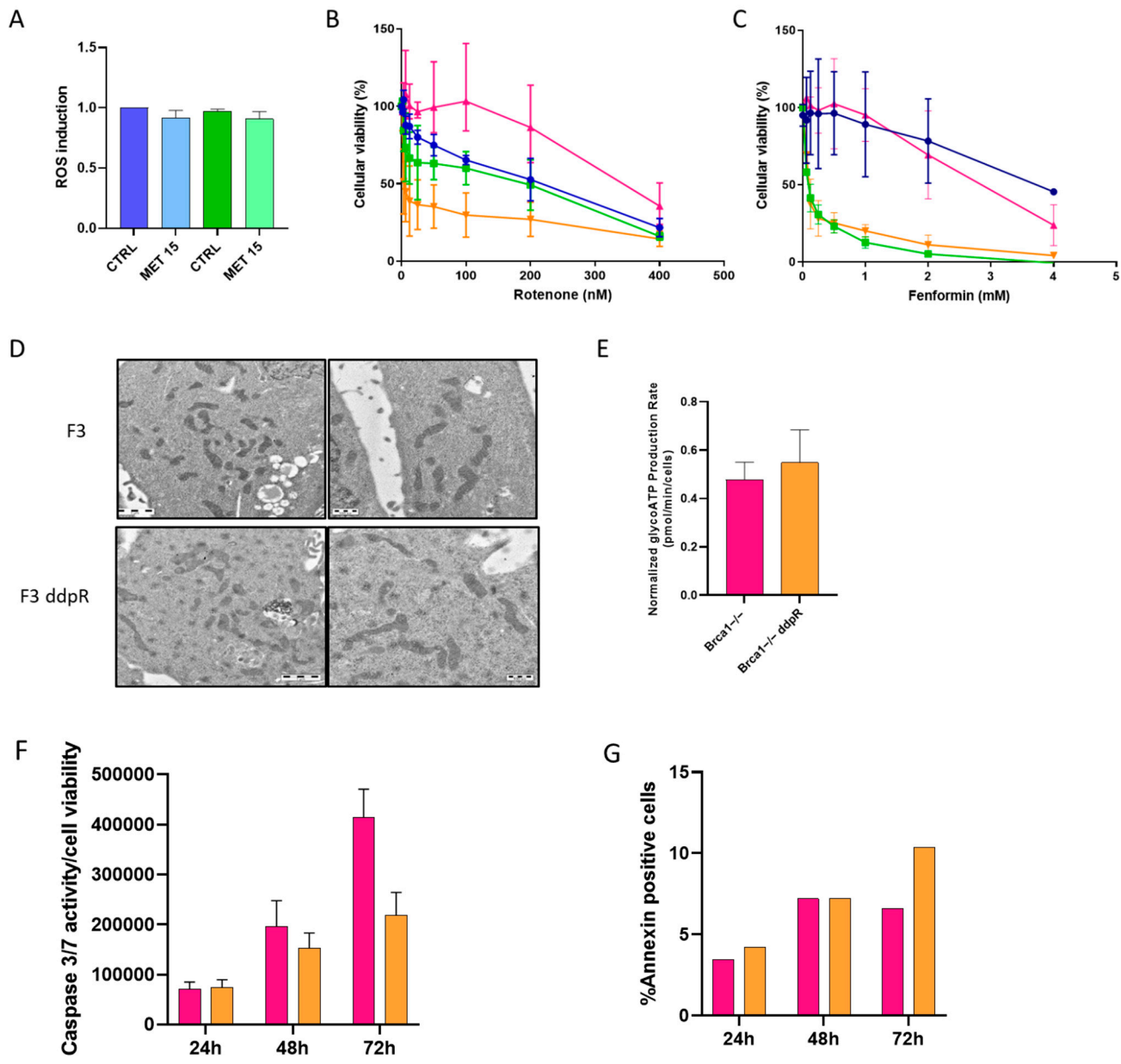
B



**Supplementary Figure S4. DNA repair in sensitive and resistant cells.** **A.** F3, F3 ddpR, Brca1<sup>-/-</sup> and Brca1<sup>-/-</sup> ddpR cells untreated (CTRL) or irradiated with IR 10Gy were stained with DAPI (nuclear staining, blue) and with anti-RAD51 antibody (green). Objective: 40×. **B.** mRNA levels of ERCC1, XPF and XPG in F3 ddpR cells. Values are the mean + SD of two independent experiments, run in triplicate and normalized on the actin gene. Data are expressed as fold-change over the parental cells (dotted line). **C.** mRNA levels of PRKDC, LIG IV and XRCC6 in F3 ddpR cells. Values are the mean + SD of two independent experiments, run in triplicate and normalized on the actin gene. Data are expressed as fold-change over the parental cells (dotted line). **D.** mRNA levels of PRKDC, LIG IV and XRCC6 in Brca1<sup>-/-</sup> ddpR cells. Values are the mean + SD of two independent experiments, run in triplicate and normalized on the actin gene. Data are expressed as fold-change over the parental cells (dotted line). Only statistically significant differences are reported. For statistical analyses unpaired t-test was used. \*= $p < 0.05$ ; \*\*= $p < 0.005$ .



**Supplementary Figure S5. Metabolic stress in F3 and Brca1-/- parental and ddpR sublines.** **A.** ROS induction in F3 (blue) and F3 ddpR (green) cells at basal levels and after 24h IC50 dose metformin treatment. Dose response curves of rotenone (**B**) and fenformin (**C**) in F3 (blue line), F3 ddpR (green line), Brca1-/- (pink line) and Brca1-/- ddpR (orange line) cells. Data are the mean  $\pm$  standard deviation (SD) of three or four independent experiments. **D.** Transmission electron microscopy of mitochondria in F3 and F3 ddpR cells. Scale bar: 1 $\mu$ m left panels, and 500nm right panels. **E.** Glycolytic ATP-production rate in Brca1-/- and Brca1-/- ddpR cells. **F.** Normalized caspase activity at basal level in Brca1-/- (pink) and Brca1-/- ddpR (orange) cells at 24, 48 and 72h after seeding. **G.** Quantification of annexin V positive cells at basal condition at 24, 48 and 72h after seeding in Brca1-/- (pink) and Brca1-/- ddpR (orange) sublines.



**Supplementary Figure S6. Uncropped versions of cropped western blots.** Uncropped version of gels showed in Figure 2A.

