Supplemental Information

Materials and Methods

PAR chain analysis. Cells were pre-treated for 5 hrs with DMSO or 10 μM Olaparib, then treated with MMS (1 mM) +/- Olaparib (10 μM) for 30 min. Cells were fixed with methanl:acetone (70:30) at -20˚C for 10 min, blocked (1% glycerol, 0.1% gelatin, 0.1% BSA, 4% goat serum, 0.4% sodium azide) for 1 hr. PAR chains were detected using anti-PAR antibody (Trevigen). Cells were imaged at 10X using Nikon 90i microscope and PAR intensity was measured using ImageJ software. Experiments were performed in triplicate.

RNA-seq analysis. RNA was isolated from untreated cycling cells using RNeasy kit (Qiagen). RNA-seq libraries were prepared using TruSeq Stranded Total RNA Library Prep Kit (Illumina) with RiboGold to remove mitochondrial and ribosomal RNA in biological duplicate. Libraries were sequenced on an Illumina HiSeq instrument using 50 cycle strand specific paired end reads in technical duplicate. Reads were trimmed of low quality and sequencing primer regions using Trimmomatic (Bolger et al. 2014). Reads were aligned to the hg19 UCSC annotation of the human genome using Tophat2 (Kim et al. 2013). Primer artifacts were removed and uniquely mapped reads were selected using Samtools (Li et al. 2009). GTF annotation file for known coding and non-coding genes was downloaded from the UCSC genome browser website (Rosenbloom et al. 2015). Raw gene feature counts were obtained using htseq-count using default parameters (Anders et al. 2015). Differentially expressed genes between the PARP resistant (SYr12, SYr13) and the control PARPi sensitive cell line (UWB1) were detected using the TweeDESeq software package (Esnaola et al. 2013). Differentially expressed genes were considered significant if the there was a 2-fold change between treatment and control samples and had an FDR ≤0.1. A Geneset enrichment analysis (GSEA) was done using the GSEA software available from the BROAD Institute (Subramanian et al. 2005). Genesets (MSigDB v4.0) enriched in the resistant cell lines with an FDR ≤ 0.25 were considered significant. Analyses were done using R 3.1.1.

RNA interference. siRNA transfections were performed using RNAi Max (ThermoScientific) using siRNAs at 4 μM final concentration. siRNAs were purchased from ThermoScientific.

siBRCA1: GAAGGAGCUUUCAUCAUUCtt
siBRCA1 (Silencer Select): CAGCUACCCUUCCAUCAUAtt
siBRCA2 (Silencer Select):GGAUUAUACAUAUUUCGCAtt
si53BP1 (Silencer Select): GAAGGACGGAGUACUAAUAtt
siPALB2 (Silencer Select): CUUAGAAGAGGACCUUAUUtt
siMRE11 (Silencer Select): GAUAGACAUUAGUCCGGUUtt
siXRCC2 (Silencer Select): UCAAGAAUUGUAACUAGCCgg
siXRCC3 (Silencer Select): CCGUCUACAUCUGCACGGAtt
siControl: Silencer Select (ThermoScientific, 4390844)

Knockdowns of targeted proteins were verified using anti-BRCA1 (Santa-Cruz), anti-BRCA1 (Millipore), anti-BRCA2 (Millipore), anti-53BP1 (Cell Signaling), anti-PALB2 (Novus) antibodies, and anti-MRE11 (Novus).

qPCR: Total RNA was extracted from cells using RNeasy Mini kit (Qiagen) according to

the manufacturer's instructions. Following extraction, total RNA was reverse transcribed using the High Capacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific). RT products were analyzed by real-time qPCR using SYBR Green (FastStart Universal SYBR Green Master, Roche) in a LightCycler 480 II (Roche). For each sample tested, the levels of indicated mRNA were normalized to the levels of *Actin* mRNA. The sequences of the PCR primers used in this study are:

Actin-forward: CCAACCGCGAGAAGATGA
Actin-reverse: CCAGAGGCGTACAGGGATAG
XRCC2-forward:GCGTCAATGGAGGAGAAAGT
XRCC2-reverse: AAGAACCAGGCGATAGTCATTTA
XRCC3-forward:ACCTTGTTGGAGTGTGTGAATA
XRCC3-reverse : GTCAAATTCACAGCGGAATGG

Viability assay. Cell viability assays were performed in 96 well format using CellTiter-Glo (Promega) according to manufacturers instructions following 6 days of inhibitor treatment. For long-term colony formation assays, cells were treated with the indicated inhibitors or vehicle for 14 days or 45 days, fixed with methanol, and stained with 0.1% Crystal Violet overnight.

Bliss Score. Analysis of viability data was used to identify potential synergistic effects between an ATR inhibitor (ATRi; 5 drug concentrations) and PARP inhibitor (PARPi; 9 concentrations) with Cisplatin (5 drug concentrations) within three different cell lines (UWB1+B1, UWB1, and SYr12). Viability data was collected in biological triplicate. Synergy scores were calculated using the Bliss independence metric (Bliss 1939). The Bliss model assumes that each drug in the combination act on different targets or sites and tests whether the observed single agent effects are modulated when used in combination. Synergy scores are calculated using the synergyfinder R package that calculates the difference between the observed and the expected effect (He 2016). Global synergy scores for each replicate drug combination were calculated as the average score of the associated synergy score matrix (e.g. ATRi vs PARPi yielded a 5x9 matrix of synergy scores whose average score represents an overall synergy score for ATRi with PARPi). An average synergy score across all replicates for each drug combination was used to determine the presence of synergistic (synergy score > 0) or antagonistic (synergy score < 0) effects. One sample t-tests were used to determine whether the average synergy scores were significantly different from independence (synergy score = 0). Drug combinations with p-value < 0.05 were considered significant.

Sequencing of the *BRCA1* gene. *BRCA1* sequencing for the deleted nucleotide in UWB1 (2549delC) (DelloRusso et al. 2007), as well as the deletion restoring the wild-type *BRCA1* open reading frame (2606_2628del23) (Swisher et al. 2008), was completed using the following primers:

Forward: 5'-TGTGCAGCATTTGAAAACCCCAAGG-3'
Reverse: 5'-CGGAGCAAATGACTGGCGCTT-3'

Immunofluorescence. Immunofluorescence analysis of RAD51 and BRCA2 was performed after 24 hrs of PARPi treatment (Olaparib, 10 μM) or 4 hrs after IR (10 Gy). Immunofluorescence analysis of p-RPA (S4/S8) was performed after 2 hrs of CPT treatment (1 μM). Cells were pre-extracted with 0.5% Triton X-100, methanol fixed, and blocked in 10% milk/2%BSA/0.1% Triton X-100. Subsequently, cells were incubated in

primary antibodies diluted in blocking buffer overnight at 4°C, and then in secondary antibodies (anti-Mouse Alexa-488 and anti-Rabbit Cy3, Jackson ImmunoResearch) at room temperature for 2 hrs. Cells were then counterstained with DAPI (10 μg/ml, Sigma), and were finally imaged at 60X or 20X using Nikon 90i microscope and quantified using ImageJ software.

Laser microirradiation. Prior to microirradiation, cells were cultured in 10 μM BrdU for 24 hrs, and treated with ATRi or DMSO for 10 min. Microirradiation was conducted using a Zeiss Observer.Z1 inverted microscope with a Palm microbeam laser microdissection workstation. At 1 hr after microirradiation, cells were pre-extracted with 0.1% Triton X-100, fixed with 3% paraformaldehyde/2% sucrose, and permeablized with 0.5% Triton X-100. Immunofluorescence analysis was performed as described above.

Homologous recombination (HR) reporter assay. U2OS cells with an integrated HR reporter plasmid (DR-GFP) were co-transfected with a plasmid expressing mCherry and a plasmid expressing I-SceI (Pierce et al. 1999). At 6 hr after transfection, cells were incubated with fresh media containing DMSO, ATMi (KU55933) or ATRi (VE-821 or AZ20) at 0.3, 3, or 10 μM. Cells were sorted for mCherry and GFP. The fractions of GFP-positive cells in the mCherry-positive cell populations were determined.

Cell cycle analysis. Cells were treated with DMSO or ATRi (VE-821) 10 μM or 0.3 μM for 8 hrs or 24 hrs, respectively. For cells treated with 10 μM, cells were pulsed with EdU for 30 min, processed using the Click-iT® EdU Alexa Fluor® 488 Flow Cytometry Assay Kit according to the manufacturers recommendations. For cells treated with 0.3 μM, cells were fixed in 70% Ethanol, treated with RNase (50 μg/ml) for 20 min, and stained with propidium iodide (10 μg/ml).

CRISPR knockout of *53BP1*. U2OS cells were transfected with a plasmid [pSpCas9(BB)-2A-GFP(px458), AddGene 48138] containing a guide RNA (gRNA) targeting the GAGCGCGAGGGACCTCCCGC sequence in the human *53BP1* gene. Single cells were sorted by GFP after 48 hrs, and colonies were grown and screened for 53BP1 knockout by Western blot.

Cell death analysis. Cells were treated with the indicated inhibitors for 7 days. Unfixed cells were processed using the Annexin V, Alexa Fluor 488 conjugated kit (ThermoFisher A13201) according to the manufacturer's instructions. Cells were sorted for propidium iodide (PI) and Annexin V staining using DMSO-treated cells as controls. PI or Annexin V positive cells (cells undergoing cell death) were counted.

Pulsed-field gel electrophoresis. Cells were treated with DMSO, HU (4 mM), or HU and ATRi (VE-821, 10 μM) for 5 hrs. Cells were harvested after trypsinization and 1% agarose plugs containing 500,000 cells were prepared with a CHEF-disposable plug mold (Bio-Rad). The cells were lysed by incubation of the plugs in 1 mg/ml proteinase K (ThermoFisher Scientific), 100 mM EDTA, 0.2% sodium deoxycholate, 1% sodium laurylsarcosine for 48 hrs at 37°C, and then washed three times for 1 hr with 10 mM Tris-HCl (pH 8.0), 100 mM EDTA. The plugs were loaded onto a 0.9% agarose gel, and electrophoresis was performed during 24 hr with a two-block pulse linear program (block 1: 0.1 s at 30 s, 5.8 V/cm, 14°C, angle 120°, TBE 0.5x, 12 hr; block 2: 0.1 s at 5 s, 3.6 V/cm, 14°C, angle 110°, TBE 0.5x, 12 hr) in a CHEF-DR III Pulsed Field Electrophoresis

System (BioRad). The DNA was stained with SYBR Gold (Molecular Probes) and visualized using a Typhoon 9200 scanner (Amersham Pharmacia Biotech).

Chromatin fractionation. Cells were treated with DMSO, HU (4 mM), or HU and ATRi (VE-821, 10 μM) for 5 hrs. Cells were washed, fixed with 1% paraformaldehyde for 15 min, and collected. Cells were treated with hypotonic buffer [10 mM HEPES pH7, 50 mM NaCl, 0.3 M Sucrose, 0.5% Triton X-100, Protease inhibitors (Sigma)] for 10 min on ice and pelleted at 1500xg for 5 min to collect the cytoplasmic fraction. Cells were treated with nuclear buffer [10 mM HEPES pH7, 200 mM NaCl, 1 mM EDTA, 0.5% NP-40, and Protease inhibitors (Sigma)] for 10 min on ice and pelleted at 13,000 rpm for 30 sec. The remaining chromatin fraction was resuspended in lysis buffer and sonicated.

iPOND. iPOND was performed as described previously (Sirbu et al. 2012; Dungrawala and Cortez 2015). Fifty million cells were labeled with 10 μM EdU for 30 min and treated as indicated with 4 mM HU and 10 μM ATRi (VE-821) for 5 hrs. Cells were crosslinked with 1 % formaldehyde for 20 min, quenched with 0.125 M glycine and washed three times with PBS. Cells were permeabilized with 0.25% Triton X-100 in PBS for 30 min at room temperature and washed once with 0.5 % BSA in PBS then with PBS. Click reaction was performed at room temperature for 2 hr with these following reagents: 20 μM biotine azide, 10 mM sodium ascorbate and 2 mM $CuSO_4$ in PBS. Cells were washed once with 0.5 % BSA in PBS then with PBS, and resuspended in lysis buffer (50 mM Tris-HCl, pH 8, and 1% SDS) supplemented with protease inhibitors. The lysed cells were sonicated with 550 Sonic Dismembrator (Fisher Scientific) for 3 min at 4°C followed by centrifugation at 13,000 rpm for 10 min. After removing an aliquot for input, biotinylated DNA was pulled down using streptavidin-MyOne C1 beads for 1hr. Following washes, beads were boiled for 30 min with SDS sample buffer to elute purified proteins. Captured proteins and input samples were resolved by electrophoresis using NuPAGE Novex 4-12% Bis-Tris gels and detected by with anti-H4 (Abcam) and anti-RAD51 (Santa Cruz) antibodies.

Supplemental Figure Legends

Fig. S1. ATR inhibitors have a unique ability to overcome the PARPi resistance of BRCA1-deficient cancer cells. (A) Viability assay of UWB1 (parental), UWB1+B1 (complemented with wild-type *BRCA1*), and all derived PARPi-resistant cell lines after 6 days of treatment with increasing doses of PARPi (Olaparib). **(B)** Viability assay of UWB1, UWB1+B1, and two derived PARPi-resistant cell lines (SYr12 and SYr13) after 6 days of treatment with increasing doses of ABT-888. n=3 replicates; error bars represent s.d. **(C)** Western blot of UWB1+B1, UWB1, and all derived resistant lines using the indicated antibodies. **(D)** qPCR from total RNA isolated from the indicated cell lines using primers to measure the levels of total BRCA1 mRNA or the BRCA1 Δ11q isoform relative to UWB1. Levels of ß-actin were used as a reference. **(E)** Western blot of the indicated cell lines using an antibody that recognizes total BRCA1 and the BRCA1 Δ11q isoform. **(F)** Levels of PAR chain formation in UWB1, UWB1+B1, and the resistant lines as measured by an anti-PAR antibody 30 min after treatments with DMSO, Methyl methanesulfonate (MMS, 1 mM), or MMS and PARPi (Olaparib,10 μM, 5 hr pre-incubation). Bars represent the median PAR intensity. **(G)** Western blot of UWB1+B1, UWB1, and all derived resistant lines using the indicated antibodies. **(H)** Pathways up regulated in resistant lines from Gene Set Enrichment Analysis (GSEA) of RNA-seq data resulting from comparing resistant lines (SYr12 and SYr13) and the parental UWB1 cell lines. **(I)** Viability assay of UWB1, UWB1+B1, and the PARPi-resistant cell lines SYr12 and SYr13 after 6 days of treatment with increasing doses of PARPi (Olaparib) in the absence or presence of ATRi (VE-821). Viability curves were used to calculate IC50 to Olaparib for each cell line (Fig. 1E). **(J)** The indicated cell lines were treated with increasing doses of ATRi (VE-821, 0 - 0.625 μM) in the absence or presence of PARPi (Olaparib, 2 μM). Color-coding denotes level of viability, green (100% viability) to red (0% cell viability) relative to DMSO treatment. (**K)** The indicated cell lines were treated with DMSO or the indicated doses of PARPi (Olaparib), AZ20, or PARPi and AZ20 for 6 days. Cell viability was measured. n=3 replicates; error bars represent s.d.; $P<0.05$ by Student *t*-test. **(L)** The indicated cell lines were treated with increasing doses of PARPi (0 - 25 μM) in combination with either increasing doses of ATRi (0 - 2.5 μM) or Cisplatin (0 - 1.25 μM) in triplicate. Bliss scores were calculated for each drug combination as well as an overall bliss score for each cell line. Bliss score >0, synergistic (red); Bliss score = 0, additive (white); Bliss score <0, antagonistic (blue).

Fig. S2. ATRi broadly overcomes acquired and preexistent PARPi resistance in multiple BRCA1-deficient cancer cell lines of distinct origins. Viability assay of the HCC1937 and HCC1937+B1 cell lines after 6 days of treatment with increasing doses of PARPi (Olaparib) in the absence or presence of ATRi (VE-821). n=3 replicates; error bars represent s.d.

Fig. S3. The HR function of BRCA1, but not PALB2-BRCA2, is partially bypassed in PARPi-resistant cancer cells. (A) UWB1, UWB1+B1, and all the PARPi-resistant cell lines were irradiated with IR (10 Gy), and fractions of RAD51 foci positive cells (> 5 foci per cell) were measured 4 hrs later. **(B)** Representative images of **A** are shown. **(C-D)** The indicated cell lines were transfected with siControl, siBRCA1, siBRCA2, or siPALB2, and cell lysates were prepared 48 hrs after knockdown. Levels of the indicated proteins were analyzed using specific antibodies. Tubulin serves as a loading control. **(E)** UWB1+B1, UWB1, or SYr12 were transfected with siControl or siBRCA1-Δ11q and total RNA or cell lysate was prepared 48 hrs after knockdown. qPCR was performed

using primers to measure the relative levels of the *BRCA1 Δ11q* isoform. Levels of *ß-actin* were used as a reference. Western blot of the indicated cell lines after knockdown with siControl or siBRCA1-Δ11q using an antibody that recognizes full-length BRCA1 and the truncated BRCA1 protein encoded by the *BRCA1 Δ11q* isoform. GAPDH was used as a loading control. **(F)** SYr12 were transfected with siControl or siBRCA1-Δ11q and treated with 4Gy IR 48 hrs after knockdown. Fractions of RAD51 foci positive cells (> 5 foci per cell) were measured 4 hrs later. **(G)** Western blot of the indicated cell lines using an antibody that recognizes full-length and truncated BRCA1 proteins. **(H-I)** The indicated cell lines were transfected with siControl, siBRCA1, siBRCA2, or siPALB2, and cell lysates were prepared 48 hrs after knockdown. Levels of the indicated proteins were analyzed using specific antibodies. Tubulin serves as a loading control.

Fig. S4. ATR functions in HR downstream of BRCA1 and remains indispensable when BRCA1 is bypassed. (A) Representative FACS data of the U2OS-DR-GFP cell line before or after I-SceI transfection in the absence or presence of ATMi (KU55933, 0.3 μM) or ATRi (VE-821, 0.3 μM; AZ20, 0.3 μM). Cells were co-transfected with a plasmid expressing I-SceI and a second plasmid expressing mCherry, which was used to sort for transfected cells. Fractions of mCherry-positive cells that were also GFP-positive were used to determine the efficiency of HR. **(B)** U2OS cells were treated with ATRi (VE-821, 10 μM; VE-822, 1 μM; AZ20, 1 μM) or ATMi (KU55933, 10 μM) in combination with Camptothecin (CPT, 1 μM) for 1 hr. Inhibition of ATR or ATM is assessed by loss of pChk1 and pChk2, respectively. **(C)** EdU incorporation profiles of U2OS cells treated with DMSO or ATRi (VE-821, 10 μM) for 8 hrs. **(D)** Cell-cycle profiles of UWB1 cells treated with DMSO or ATRi (VE-821, 0.313 μM) for 24 hrs. **(E-F)** Knockdown or knockout of BRCA1 and 53BP1 in U2OS cells was confirmed by Western blot. Tubulin or GAPDH serves as loading controls.

Fig. S5. ATRi blocks BRCA1-independent HR in PARPi-resistant cells by inhibiting PALB2-BRCA2 localization to DNA breaks. HCC1937+BRCA1 and HCC1937 cell lines were treated with PARPi (10 μM) or PARPi and ATRi (VE-821, 10 μM), and fractions of RAD51 foci positive cells (> 5 foci per cell) were measured 24 hrs later.

Fig. S6. ATRi reactivates degradation of stalled forks in PARPi-resistant cells. (A) DNA fiber analysis of stalled replication forks in SYr13. Newly synthesized DNA was sequentially labeled with CldU (50 μM, 30 min) and IdU (100 μM, 30 min). Cells were subsequently treated with HU (4 mM) for 5 hrs, and lengths of CldU and IdU-labeled DNA fibers were measured. IdU/CldU ratio was binned in increments of 0.2 and fit to a Gausian Curve using Prism software. At least n=100 fibers were measured for each condition; experiments were completed in triplicate. **(B)** DNA fiber analysis of stalled forks as in **A**, with each fiber plotted individually. The SYr9, SYr13, or SYr37 cells were untreated or treated with HU (4 mM), HU and ATRi (VE-821, 10 μM) for 5 hrs. Red bars represent the median IdU/CldU ratios. n=250 fibers for each condition; experiments were completed in triplicate. Significance was determined by Mann-Whitney test, * $p<0.05$, *** $p<0.001$, **** $p<0.0001$. **(C-D)** UWB1 and UWB1+B1 cells were transfected with siControl or siMRE11, treated with increasing doses of PARPi (Olaparib) for 6 days, and cell viability was measured in **D**. Partial knockdown of MRE11 is confirmed by Western blot in **C**. **(E)** The indicated PARPi-resistant cell lines were treated with HU (4 mM) for 5 hrs in the absence or presence of ATRi (VE-821, 10 μM). The levels of chromatin-bound RAD51 were analyzed with KU70 as a loading control. **(F)** SYr12 was transfected with siControl, siXRCC2, or siXRCC3 and total RNA was prepared 48 hrs after knockdown.

qPCR was performed using primers to measure the relative levels of XRCC2 and XRCC3. Levels of ß-actin were used as a reference.

Fig. S7. Models of how ATRi overcomes the PARPi resistance in BRCA-deficient cancer cells. (A) ATR regulates BRCA1-independent RAD51 loading to both DNA double-stranded breaks (DSBs) and stalled replication forks, which bypass the functions of BRCA1 in HR and fork protection, respectively. This model explains why ATR is indispensible for the PARPi resistance of BRCA1-deficient cancer cells. **(B)** Compared to BRCA1-proficient cells (e.g. UWB1+B1, HCC1937+B1), BRCA1-deficient cancer cells (e.g. UWB1, HCC1937) have reduced RAD51 loading activity. We propose that the PARPi sensitivity of BRCA1-deficient cells is determined by a threshold of RAD51 loading activity. If RAD51 loading activity is below the threshold, BRCA1-deficient cells (e.g. UWB1) are sensitive to PARPi. If RAD51 loading activity is above the threshold, BRCA1-dficient cells (e.g. HCC1937) are resistant to PARPi. When BRCA1-deficient cancer cells acquire PARPi resistance, RAD51 loading at stalled forks (and at DSBs in some cases) is elevated above the threshold (e.g. SYr12). Low concentrations of ATRi are sufficient to reduce RAD51 loading below the threshold in PARPi-resistant BRCA1-deficient cells (e.g. SYr12), but insufficient to do so in BRCA1-proficient cells (e.g. UWB1+B1). This model provides a possible explanation as to how ATRi preferentially sensitizes PARPi-resistant BRCA-deficient cells, as opposed to BRCA-proficient cells, to PARPi.

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