SUPPLEMENTARY MATERIALS AND METHODS

siRNA sequences

All siRNAs were purchased from Dharmacon.

Target	Sequence
Luciferase	5′-CUUACGCUGAGUACUUCGA-3′
BRCA1 #1	5′-GUGGGUGUUGGACAGUGUA-3′
BRCA1 #2	5′-GAAGGAGCUUUCAUCAUUC-3′
CDK12 #1	5′-GAGACUAGACAAUGAGAAA-3′
CDK12 #2	5′-GCUGAAUAACAGUGGGCAA-3′
BRCA2 #1	5’-GACUCUAGGUCAAGAUUUA-3’
BRCA2 #2	5’-GAAGAAUGCAGGUUUAAUA-3’
RAD51 #1	5’- GGGAUUUGUGAAGCCAAA-3’
RAD51 #2	5’- CCAACGAUGUGAAGAAAUU-3’
NNMT siRNA #1	5’-UGUGUAGCCAGCCUCUUUCUU-3’
NNMT siRNA #2	5’-AACUUUGCGAGAUCACCUCUU-3’
Non-Targeting siRNA #3	Target Sequence: 5’-AUGUAUUGGCCUGUAUUAG-3’
Non-Targeting siRNA #5	Target Sequence: 5’-UGGUUUACAUGUCGACUAA-3’

Non-targeting Control siRNA #3 (D-001210-03) and #5 (D-001210-05) are predesigned control siRNAs from Dharmacon.

Primers used for qRT-PCR

Target	Forward Sequence	Reverse Sequence
BRCA1	5'-GCCAAGGCAAGATCTAGAGG-3'	5'-GTTGCCAACACGAGCTGA-3'
NNMT	5'-TGATCATGGATGCGCTCAAG-3	5'-TTGCGAGATCACCTCAAACC-3'
GAPDH	5'-GAAGGTGAAGGTCGGAGTCA-3'	5'-AATGAAGGGGTCATTGATGG-3'

Primers used for qRT-PCR in Supplementary Fig. S4B

Target	Sequence
BRCA1 Primer #1	5'-GATTCTGCAAAAAAGGCTGCT-3'
BRCA1 Primer #2	5'-CAGATGCTGCTTCACCCTGA-3'
BRCA1 Primer #3	5'-TAGCAAGGAGCCAACATAACAGAT -3'
BRCA1 Primer #4	5'-CTTATTCCATTCTTTTCTCTCACACAG-3'
BRCA1 Primer #5	5'-TTCATTGGAACAGAAAGAAATGG-3'
BRCA1 Primer #6	5'-CAGATGGGACACTCTAAGATTTTC-3'
BRCA1 Primer #7	5'-GAGCCTACAAGAAAGTACGAG-3'
BRCA1 Primer #8	5'-ACTCCAAACCTGTGTCAAGCT-3'
BRCA1 Primer #9	5'-CTCATGCCAGCTCATTACAGC-3'
BRCA1 Primer #10	5'-TTTCTGTGCTGGGAGTCCGCC-3'
BRCA1 Primer #11	5'-TGATGACCCTGAATCTGATCC-3'
BRCA1 Primer #12	5'-CAGCAGTATCAGTAGTATGAGC-3'

BRCA1 Primer #1 and BRCA1 Primer #2, which specifically amplify BRCA1 Δ11q, and BRCA1 Primer #3 and BRCA1 Primer #4, which amplifies exon 11-containing transcripts, were previously described (1).

RNA-seq analysis

OVCAR-8 cells were transfected with luciferase (siLuc), CDK12 #1, or CDK12 #2 siRNAs. Forty-eight hours after transfection, RNA was isolated using miRNeasy mini kit (Qiagen). Three independent RNA samples were prepared for each of the transfected siRNAs. Libraries were prepared (Illumina TruSeq mRNA v2) and processed through Mayo Clinic's MAP-RSeq (v2.1.0) application (2), a comprehensive computational pipeline for the analysis of Illumina's paired end RNA-Sequencing reads. MAP-RSeq uses publicly available bioinformatics tools tailored by in-house developed methods. Within MAP-RSeq, TopHat2 (3) with the bowtie1 (4) option was called to align each sample's reads to the hg19 reference genome. The first 100,000 reads of each sample were used to estimate the mean and the standard deviation of the fragment length, which is required information for TopHat. The gene counts were generated by FeatureCounts (5) using Ensembl's hg19 gene definition file. The "-O" option within FeatureCounts was used to account for the expression derived from regions shared by multiple genomic features. RSeqQC (6) was used to create quality control metrics, including gene body coverage plots, to insure the results from each sample were reliable and could be collectively used for a differential expression analysis. Genes with an average of less than 25 reads per group were removed from the differential expression analysis. The R package (v3.3.1), edgeR (7) was used to identify which genes were differentially expressed across group comparisons. Statistically significant genes were defined by having a false discovery rate below 0.0001 and an absolute log2 fold change greater than 0.75.

Proteomics Sample Preparation and Methods.

Fresh frozen tumor tissue was obtained from Mayo Clinic Ovarian SPORE Biospecimen Core following approval of Mayo Clinic Institutional Review Board as described in the Materials and Methods Section. All patients had HGSOC that was chemoresistant, i.e., showed evidence of

disease progression while subjected to adjuvant therapy with carboplatin and paclitaxel or within six months from the end of treatment with at least five cycles of this chemotherapy. All patients had previously undergone primary debulking surgery leading to residual disease <1 cm in diameter ("optimal debulking").

Tissue proteins (225 µg protein/sample) were extracted and used for proteomic analysis by high resolution Hyper Reaction Monitoring with SWATH (HRM-SWATH) at BIOGNOSYS (https://www.biognosys.com/) following a procedure described previously (8) (9). Briefly, HRM-SWATH was acquired on 40 samples. A pooled reference sample was included in each shotgun proteomic experiment to enable cross-experiment comparison in the entire set of samples. The shotgun mass spectrometric data were analyzed using the MaxQuant 1.5.5.1 software (maxquant.org) and the false discovery rate on the peptide and protein level set to 1 %. A human UniProt.fasta database (Homo sapiens, 2015-08-28) was used for the search engine. An extended spectral library was generated for the patient samples using a high pH reversed-phase (HPRP) fractionation. The spectral library for tumor lysates corresponded to 12 shotgun measurements. Each fraction of each pool was measured once in shotgun proteomics mode. All measurements were used for the generation of the spectral library (protein inventory) and their relative abundances were quantified across all samples. The HRM measurements analyzed with Spectronaut 9.0 (www.spectronaut.org) were normalized using local regression normalization (10). The false discovery rate on the peptide level was set to 1 %, data were filtered using row-based extraction. Normalization of the peptide intensity data was performed to compensate for loading and instrument performance fluctuations. Because acquisition stability was high, only minor normalization adjustments were required.

REFERENCES

1. Wang Y, Bernhardy AJ, Cruz C, Krais JJ, Nacson J, Nicolas E*, et al.* The BRCA1-Delta11q Alternative Splice Isoform Bypasses Germline Mutations and Promotes Therapeutic Resistance to PARP Inhibition and Cisplatin. Cancer Res **2016**;76:2778-90
2. Kalari KR, Nair AA, Bhavsar JD, O'Brien DR, Davila JI, Bockol MA*, et al.* MAP-RSeq: Mayo Analysis Pipeline for RNA sequencing. BMC Bioinformatics **2014**;15:224
3. Kim D, Pertea G, Trapnell C, Pimentel H, Kelley R, Salzberg SL. TopHat2: accurate alignment of transcriptomes in the presence of insertions, deletions and gene fusions. Genome Biol **2013**;14:R36
4. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics **2009**;25:1754-60
5. Liao Y, Smyth GK, Shi W. featureCounts: an efficient general purpose program for assigning sequence reads to genomic features. Bioinformatics **2014**;30:923-30
6. Wang L, Wang S, Li W. RSeQC: quality control of RNA-seq experiments. Bioinformatics **2012**;28:2184-5
7. Robinson MD, McCarthy DJ, Smyth GK. edgeR: a Bioconductor package for differential expression analysis of digital gene expression data. Bioinformatics **2010**;26:139-40
8. Bruderer R, Bernhardt OM, Gandhi T, Miladinovic SM, Cheng LY, Messner S*, et al.* Extending the limits of quantitative proteome profiling with data-independent acquisition and application to acetaminophen-treated three-dimensional liver microtissues. Mol Cell Proteomics **2015**;14:1400-10
9. Bruderer R, Muntel J, Muller S, Bernhardt OM, Gandhi T, Cominetti O*, et al.* Analysis of 1508 Plasma Samples by Capillary-Flow Data-Independent Acquisition Profiles Proteomics of Weight Loss and Maintenance. Mol Cell Proteomics **2019**;18:1242-54
10. Callister SJ, Barry RC, Adkins JN, Johnson ET, Qian WJ, Webb-Robertson BJ*, et al.* Normalization approaches for removing systematic biases associated with mass spectrometry and label-free proteomics. J Proteome Res **2006**;5:277-86