

Supplementary Data

An investigation of PARP inhibitor resistance through the analysis of serially collected circulating tumor DNA in patients with *BRCA*-mutated ovarian cancer

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Supplementary Methods

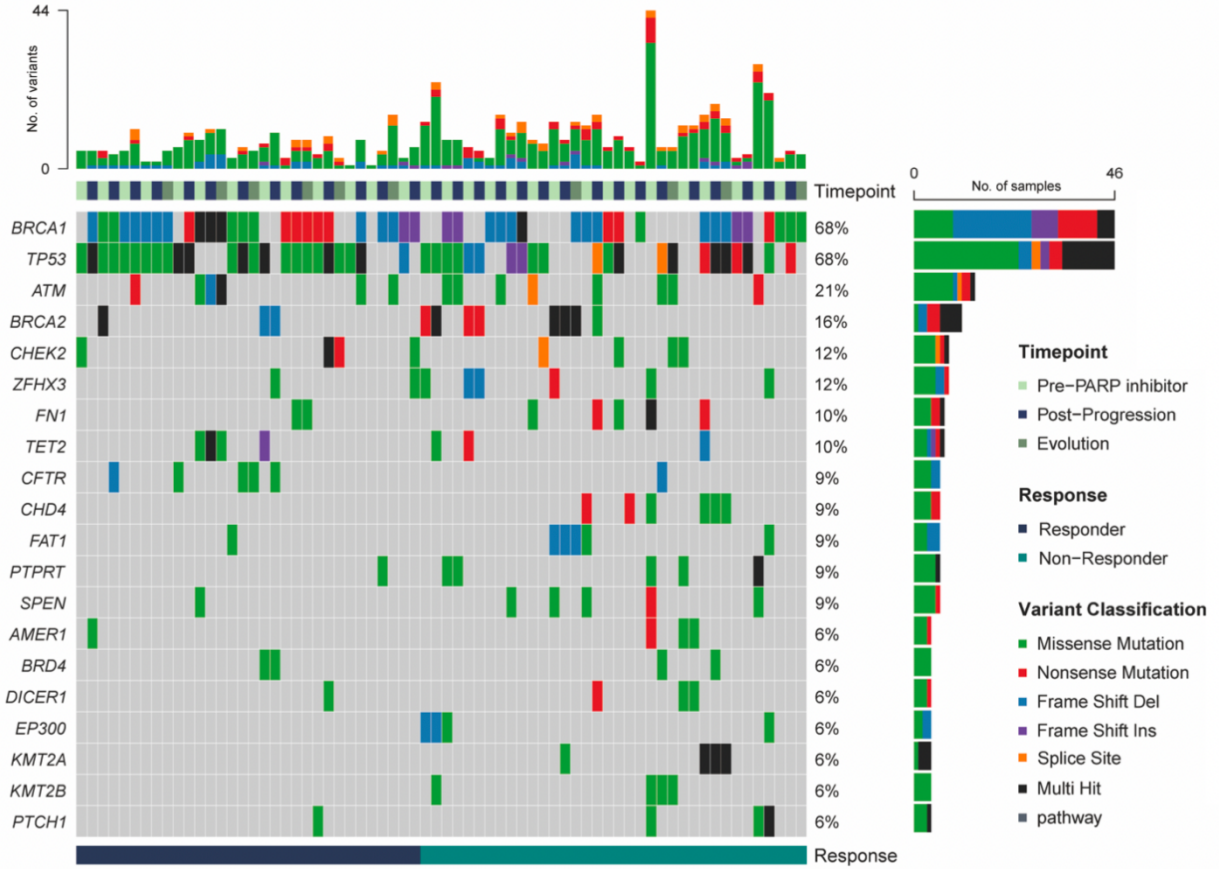
Resistance mechanisms	Genes
BRCA independent HR restoration	<i>TP53BP1</i> ¹ , <i>C11orf30</i> (<i>EMSY</i>) ² , <i>KMT2C</i> ^{3,4} , <i>KMT2A</i> ^{5,6} , <i>SLX4</i> ⁷ , <i>CTCF</i> ⁸⁻¹⁰ , <i>SMC3</i> ¹¹
Replication fork stabilization	<i>SUZ12</i> ¹² , <i>MRE11</i> ¹³ , <i>BLM</i> ¹⁴ , <i>CHD4</i> ^{15,16} , <i>ZFHX3</i> ¹⁷ , <i>TET2</i> ¹⁸ , <i>MED12</i> ¹⁹ , <i>MUC1</i> ²⁰ , <i>SMARCA4</i> ²¹ , <i>EPHA7</i> ²² , <i>ATRX</i> ^{23,24} , <i>WRN</i> ²⁵
Upregulation of pro-survival pathway	- <i>PI3K-AKT-mTOR</i> : <i>PIK3CA</i> , <i>PIK3CB</i> , <i>PIK3C2B</i> , <i>PIK3C2G</i> , <i>PIK3CD</i> , <i>PIK3R1</i> ²⁶ , <i>MTOR</i> ²⁷ , <i>RXRA</i> ²⁸ , <i>SETD2</i> ²⁹⁻³¹ , <i>PTPRS</i> ³² - <i>WNT</i> : <i>IRF2</i> ³³ , <i>AXINI</i> ³⁴ , <i>TCF7L2</i> ³⁵ , <i>AMER1</i> , <i>PDGFRB</i> ³⁶ , <i>PDGFRA</i> ³⁷ - <i>Oncogene</i> : <i>KRAS</i> ^{38,39} , <i>RET</i> , <i>MET</i> , <i>BRD4</i> ^{40,41}
Loss of target	<i>PARP1</i>
Increased drug efflux	<i>CYP1B1</i> ⁴² , <i>NUP93</i> ⁴³ , <i>TAP2</i> ⁴⁴ , <i>PTCH1</i> ⁴⁵

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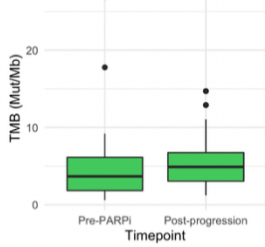
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Fig. S1. Analysis of ctDNA in matched samples. A Mutational profile grouped by time point for patients with matched samples. **B** Changes in TMB based on pre-PARPi and post-progression ctDNA. **C** Frequency of acquired resistance mechanisms stratified by PARPi duration.

A



B



C

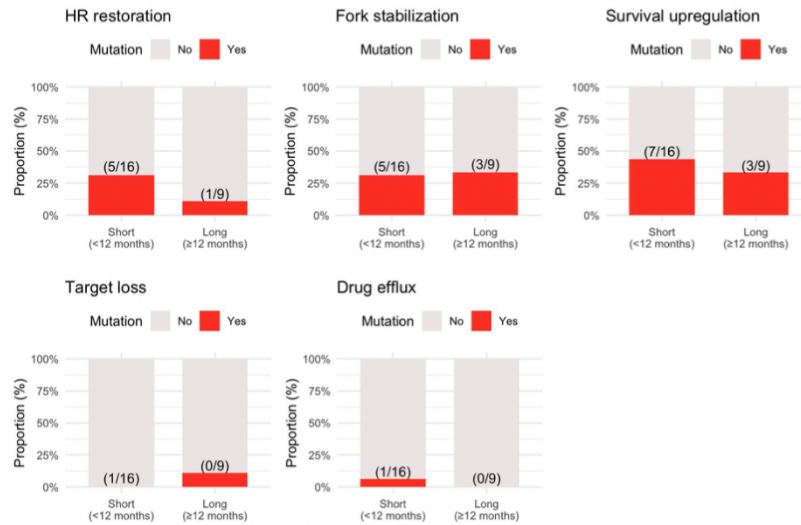


Fig. S2. BRCA reversion mutation identified in 3 patients.

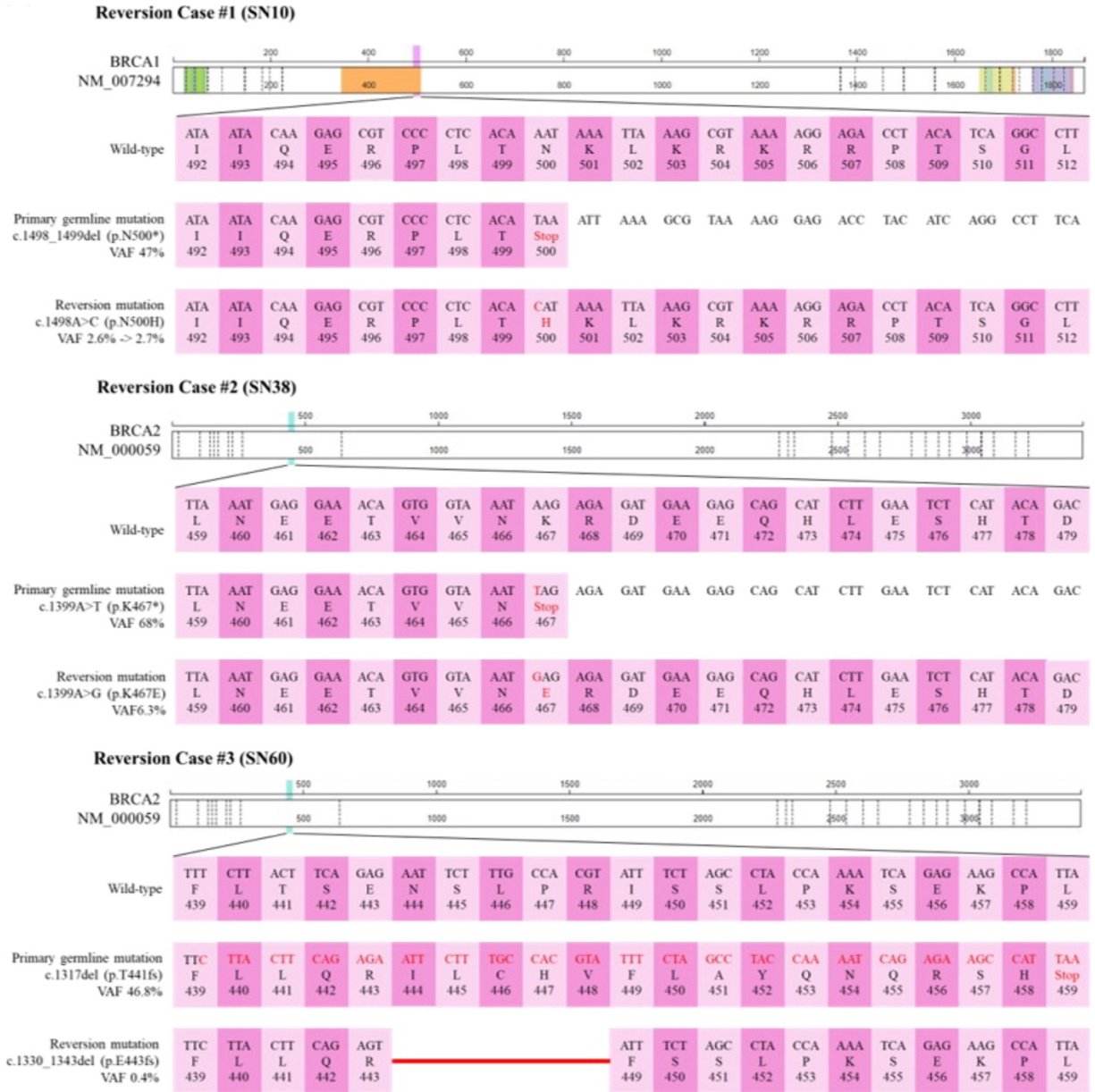


Fig. S4. Copy number alteration based on ctDNA. PIK3CA amplification based on **A pre-PARPi and **B** post-PARPi ctDNA**

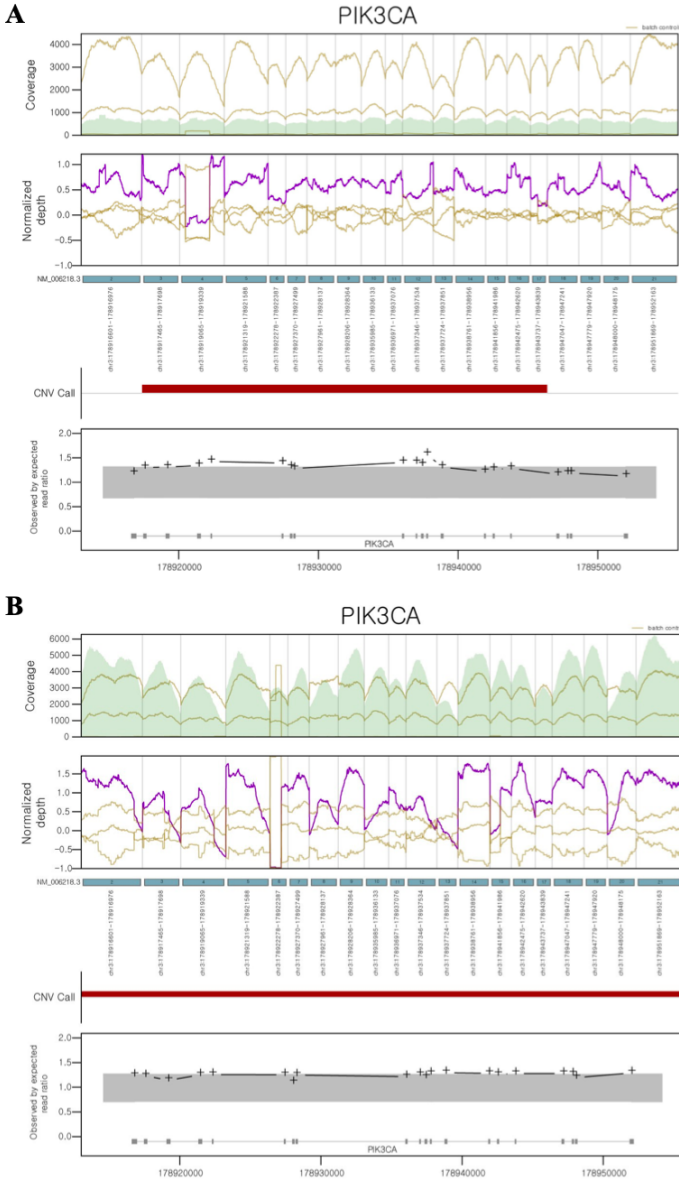


Fig. S5. Response to subsequent platinum-based therapy for each resistance mechanism.

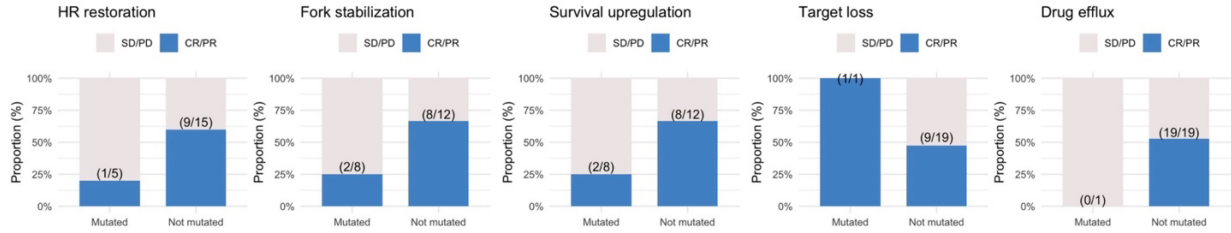


Table S1. Demographics

Variables	Patients (n=54)
Age (median, range)	55 (43 – 79)
Histology (n, %)	
Serous	52 (96.3%)
Mixed (serous and endometrioid)	2 (3.7%)
FIGO stage (n, %)	
I	4 (7.4%)
II	1 (1.9%)
III	22 (40.7%)
IV	27 (50.0%)
BRCA (n, %)	
germline	39 (72.2%)
somatic	15 (27.8%)
PARP inhibitor type (n, %)	
Olaparib	39 (72.2%)
Niraparib	15 (27.8%)
PARP inhibitor setting (n, %)	
Maintenance	44 (81.5%)
Salvage	10 (18.5%)

Table S2. Post-specific resistance mechanisms, including genes assessed and the proportion of patients with post-specific alterations.

	Resistant mechanism based on post-specific mutation	Gene mutations identified in TMB500 panel	Proportion of patients involved
HR dependent	BRCA reversion		3.4% (1 out of 29)
	Non-BRCA reversion		None
	BRCA independent HR restoration	-TP53BP1, C11orf30 (EMSY), KMT2C, KMT2A, SLX4, CTCF, SMC3	28% (8 out of 29)
HR independent	Replication fork stabilization	SUZ12, MRE11, BLM, CHD4, ZFH3, TET2, MED12, MUC1, SMARCA4, EPHA7, ATRX, WRN	34% (10 out of 29)
	Upregulation of pro-survival pathway	-PI3K-AKT-mTOR: PIK3CA, PIK3CB, PIK3C2B, PIK3C2G, PIK3CD, PIK3R1, MTOR, RXRA, SETD2, PTPRS -WNT: IRF2, AXIN1, TCF7L2, AMER1, PDGFRB, PDGFRA -Oncogene: KRAS,, RET, MET, BRD4	41% (12 out of 29)
	Loss of target	PARP1	7% (2 out of 29)
	Increased drug efflux	CYP1B1, NUP93, TAP2, PTCH1	3% (1 out of 29)