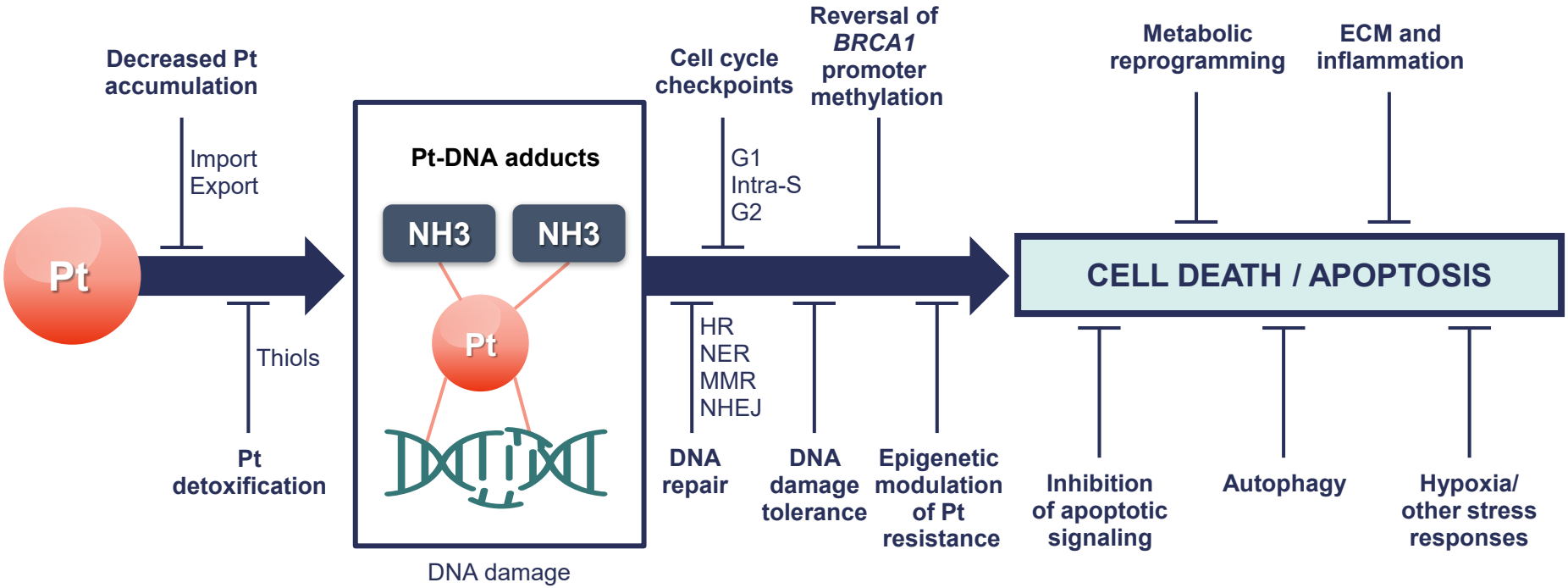
Post-PARP Inhibition Data in Platinum-Sensitive Recurrent Disease

Katherine Fuh, MD, PhD

University of California, San Francisco

Mechanisms of platinum resistance[1–4]



DNA, deoxyribonucleic acid; ECM, extracellular matrix; HR, homologous recombination; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining; Pt, platinum.

1. Damia G et al. *Cancers (Basel)*. 2019;11(1):119. 2. Lv P et al. *Biochim Biophys Acta Rev Cancer*. 2021;1876(1):188577. 3. Menghi F et al. *Sci Transl Med*. 2022;14(652):eabn1926. 4. Matei D et al. *Cancer Res*. 2012;72(9):2197-2205.

Mechanisms of PARPi resistance

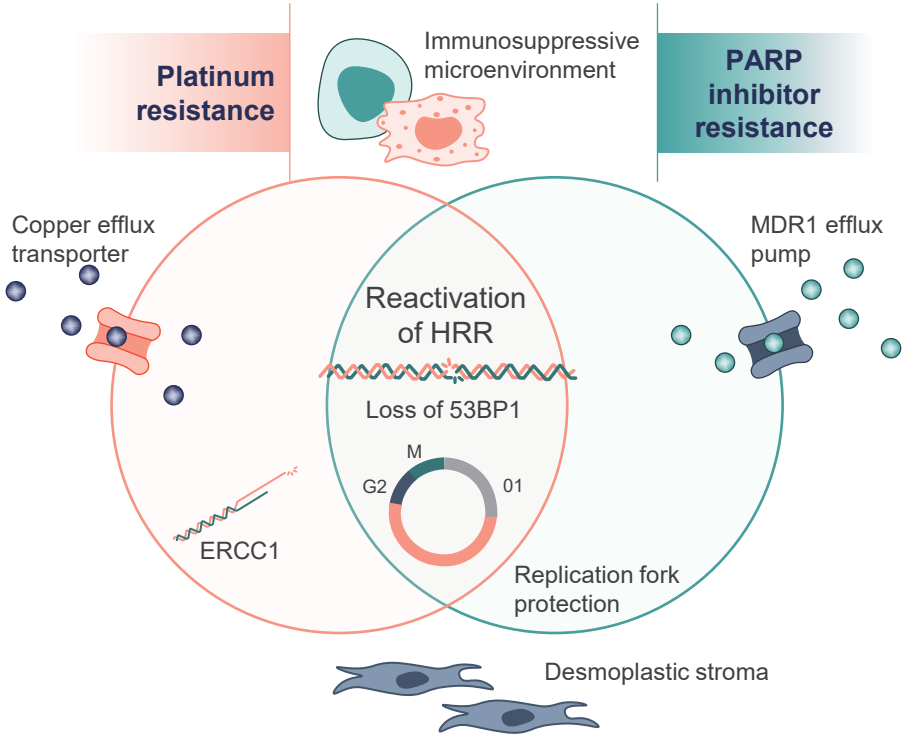
MECHANISM	SPECIFIC ALTERATIONS	
Altered PARP1	Mutations abolish PARP1 trapping or generate hypomorphic forms	
	PARP1 phosphorylation reduces binding to PARPi, increases catalytic activity	
Restoration of HR	*BRCA* reversion mutations or demethylation of *BRCA1* promoter restores functional BRCA proteins	Restoration of functional HR-associated proteins
	Protection of mutant BRCA from proteasomal degradation	
	Amplification of wild-type of hypomorphic *BRCA*	
	RAD51 reversion mutations	
	Loss of 53BP1	Restoration of end-resection
	Loss of REV7	
	Loss of DYNLL1	
	Increased histone methylation for repair protein recruitment	
	Protection of RAD51 from degradation	
	miR-622-mediated repression of alternative DNA repair pathways	

MECHANISM	SPECIFIC ALTERATIONS
Replication fork stability	Depletion of chromatin remodelers
	miR-493-5p-mediated repression of nuclease expression
PARPi efflux	Overexpressed MDR I efflux pump

53BP1, tumor suppressor p53-binding protein 1; *BRCA*, BRCA DNA repair associated gene; BRCA, breast and ovarian cancer susceptibility protein; HR, homologous recombination; MDR1, multidrug resistance mutation 1; miR, microRNA; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor.

Lee EK, Matulonis UA. *Cancers (Basel)*. 2020;12(8):2054.

Overlapping mechanisms of PARP inhibitor and platinum resistance[1,2]

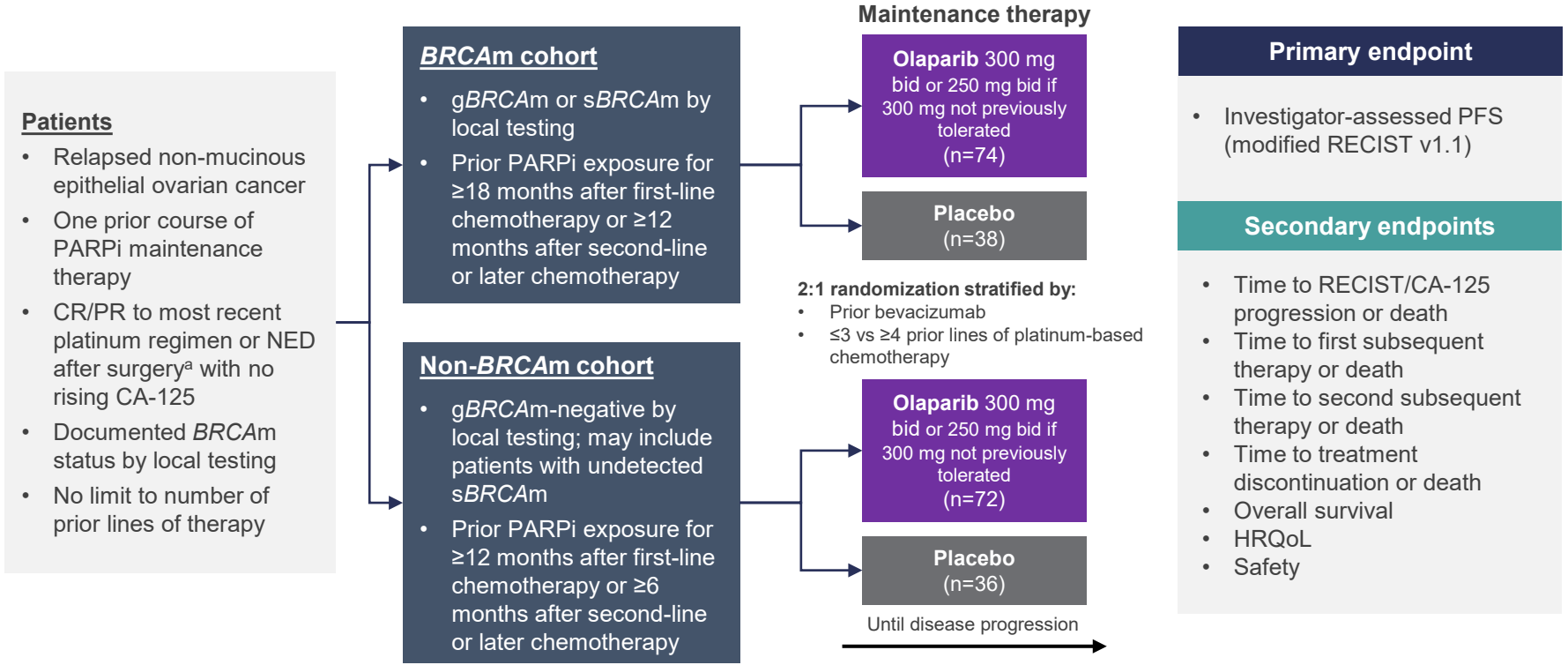


Mechanism	Proteins involved
PARP activity alteration Loss of PARG Increased stabilization of replication forks	RAS P13K/AKT PARP
Altered ion channel drug accumulation Upregulation of drug efflux pumps Intracellular drug inactivation	VRAC MRP 2
Restoration of BRCA function through secondary reversion mutation Modification of other proteins	BRCA1/2 53BP1 RIF1 Shieldin complex

53BP1, tumor suppressor p53-binding protein 1; *BRCA*, BRCA DNA repair associated gene; ERCC1, ERCC excision repair 1, endonuclease non-catalytic subunit; HR, homologous recombination; HRR, homologous recombination repair; MDR1, multidrug resistance mutation 1; PARG, poly (ADP-ribose) glycohydrolase; PARP, poly (ADP-ribose) polymerase; PARPi, poly (ADP-ribose) polymerase inhibitor.

1. McMullen M et al. *Cancers (Basel).* 2020;12(6):1607. 2. Flynn MJ, Ledermann JA. *Cancer Drug Resist.* 2022;5(2):424–435.

OReO/ENGOT-ov38: study design

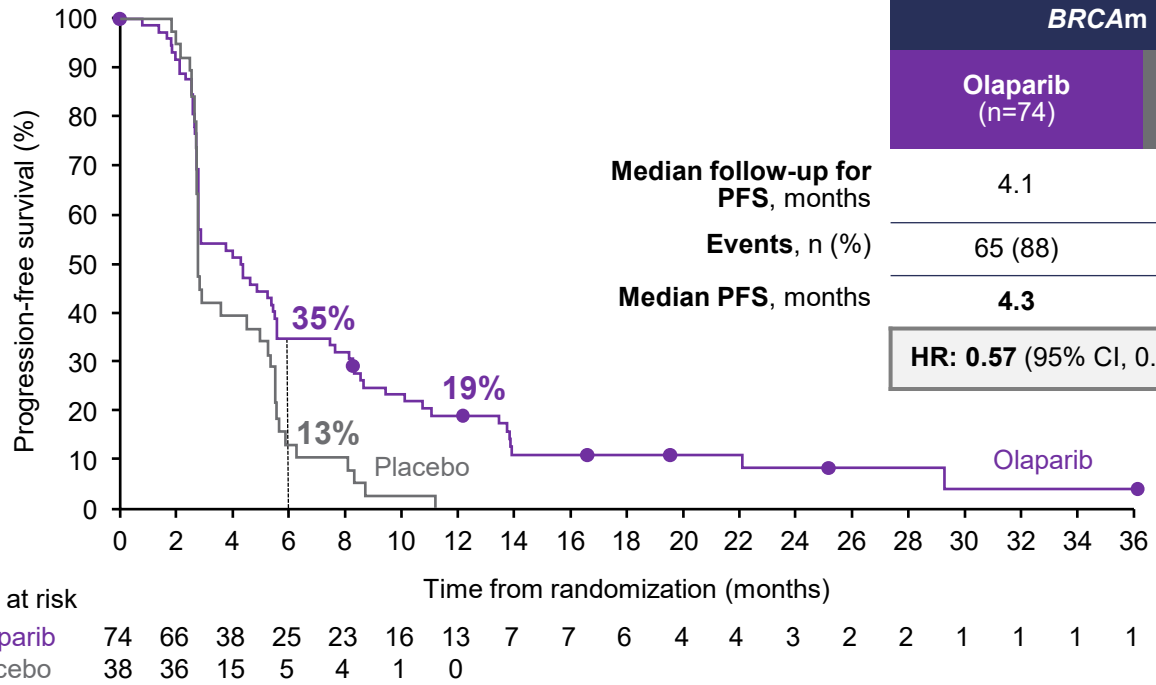


[a] NED was permitted if optimal cytoreductive surgery was conducted prior to chemotherapy.

bid, twice daily; *BRCA*, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; CA-125, cancer antigen 125; CR, complete response; g*BRCA*m, germline *BRCA* mutation; HRQoL, health-related quality of life; NED, no evidence of disease; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; s*BRCA*m, somatic *BRCA* mutation.

Pujade Lauraine E et al. ESMO Annual Meeting 2021; Abstract LBA33.

OReO/ENGOT-ov38: a statistically significant PFS benefit was observed with olaparib in the *BRCA*m cohort



	*BRCA*m cohort	
	Olaparib (n=74)	**Placebo** (n=38)
Median follow-up for PFS, months	4.1	2.8
Events, n (%)	65 (88)	38 (100)
Median PFS, months	**4.3**	**2.8**

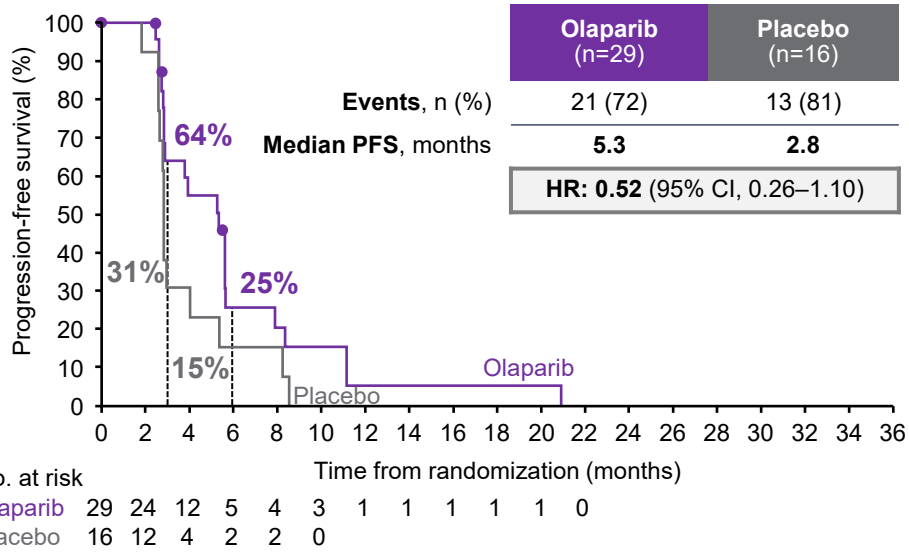
HR: 0.57 (95% CI, 0.37–0.87); *P*=0.022

BRCA, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Pujade Lauraine E et al. ESMO Annual Meeting 2021; Abstract LBA33.

OReO/ENGOT-ov38: in exploratory analyses, benefit in the non-*BRCA*m cohort appeared consistent irrespective of HRD status

Non-*BRCA*m cohort: HRD-positive

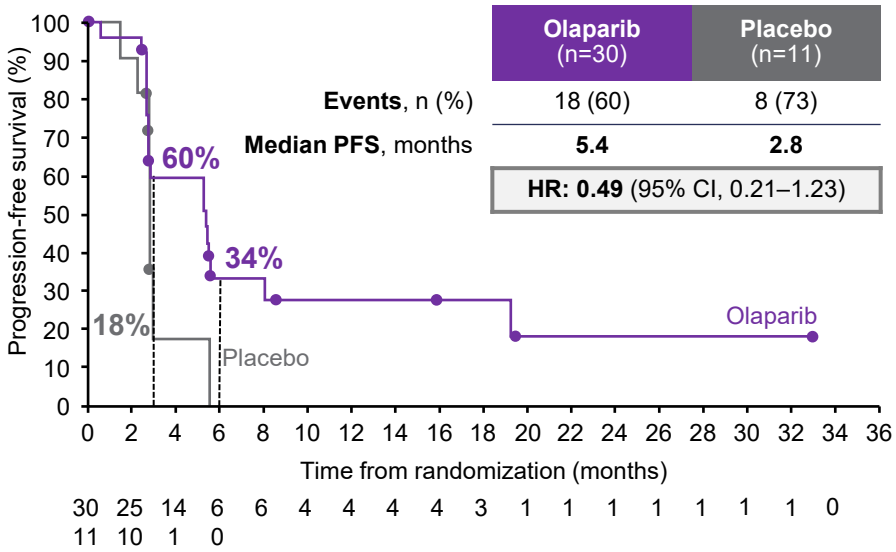


	Olaparib (n=29)	Placebo (n=16)
Events, n (%)	21 (72)	13 (81)
Median PFS, months	**5.3**	**2.8**
HR: 0.52 (95% CI, 0.26–1.10)		

No. at risk

Olaparib	29	24	12	5	4	3	1	1	1	1	1	0
Placebo	16	12	4	2	2	0						

Non-*BRCA*m cohort: HRD-negative



	Olaparib (n=30)	Placebo (n=11)
Events, n (%)	18 (60)	8 (73)
Median PFS, months	**5.4**	**2.8**
HR: 0.49 (95% CI, 0.21–1.23)		

Olaparib	30	25	14	6	6	4	4	4	4	3	1	1	1	1	1	1	1	0	
Placebo	11	10	1	0															

BRCA, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; PFS, progression-free survival.

Pujade Lauraine E et al. ESMO Annual Meeting 2021; Abstract LBA33.

SOLO2/ENGOT-ov21: maintenance olaparib in *BRCA*m recurrent PSOC

Patients

- Relapsed, high-grade serous or endometrioid ovarian cancer[a]
- *BRCA*m
- Received ≥2 previous lines of platinum-based chemotherapy
- Responded to most recent platinum regimen

Olaparib 300 mg bid

2:1 randomization

Stratified by:

- Response to previous chemotherapy[b]
- Length of platinum-free interval[c]

Placebo

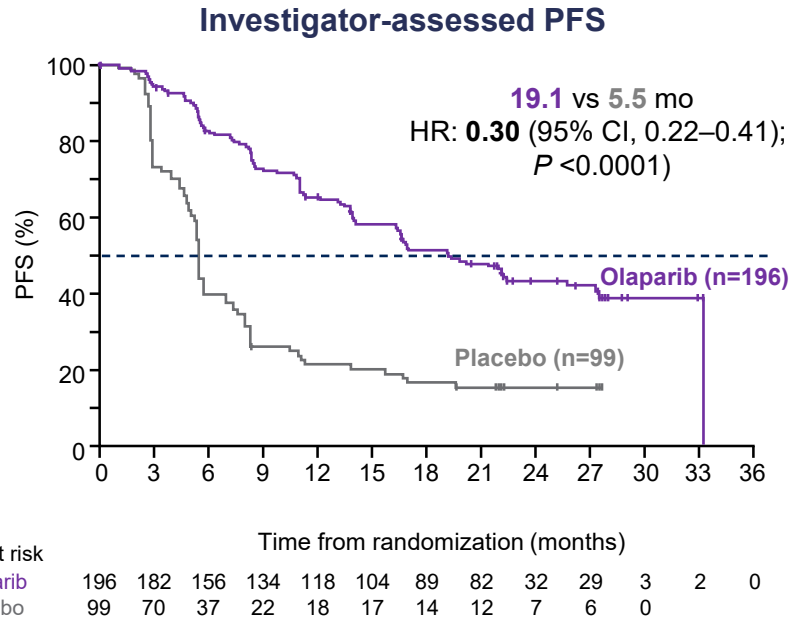
Study treatment continued until disease progression[d]

Primary Endpoint

- Investigator-assessed PFS

Secondary Endpoint

- OS, PFS2, TFST, TSST, TDT, HRQoL[e]

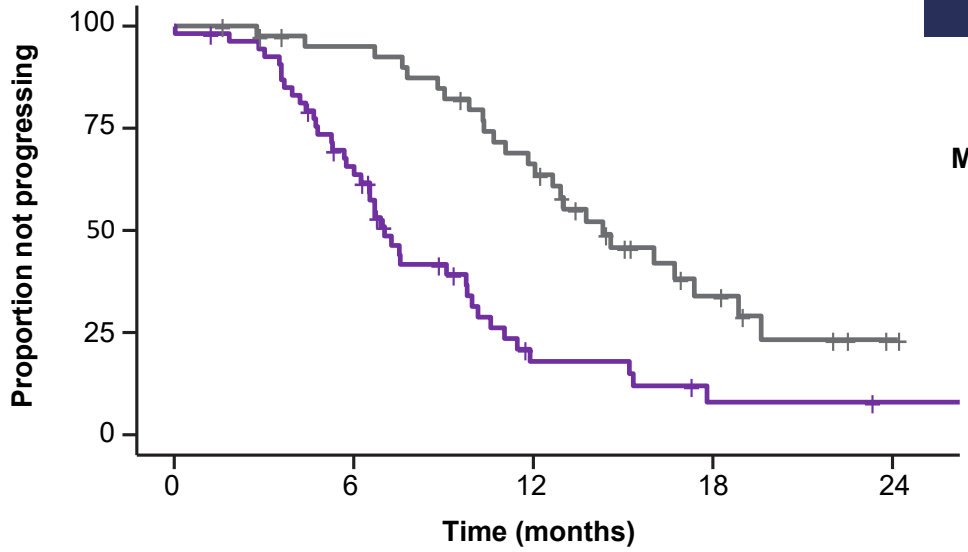


[a] Includes primary peritoneal or fallopian tube cancer. [b] Complete or partial response. [c] >6–12 or >12 months. [d] Or until discontinuation criteria were met, and treatment could continue beyond progression if the investigator deemed the patient to be experiencing benefit. [e] Assessed by the TOI of the FACT-O.

bid, twice daily; *BRCA* DNA repair associated gene; *BRCA*m, *BRCA* mutated; CI, confidence interval; FACT-O, Functional Assessment of Cancer Therapy – Ovarian; HR, hazard ratio; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PSOC, platinum-sensitive ovarian cancer; TDT, time to study treatment discontinuation or death; TFST, time to first subsequent therapy or death; TOI, trial outcome index; TSST, time to second subsequent therapy or death.

1. Poveda A et al. ASCO Annual Meeting 2020. Abstract 6002. 2. Lynparza Prescribing Information. AstraZeneca. Revised March 2022.

SOLO2/ENGOT-ov21 post hoc analyses: efficacy of platinum-based chemotherapy reduced in *BRCA1/2*m platinum-sensitive recurrent EOC with prior olaparib maintenance



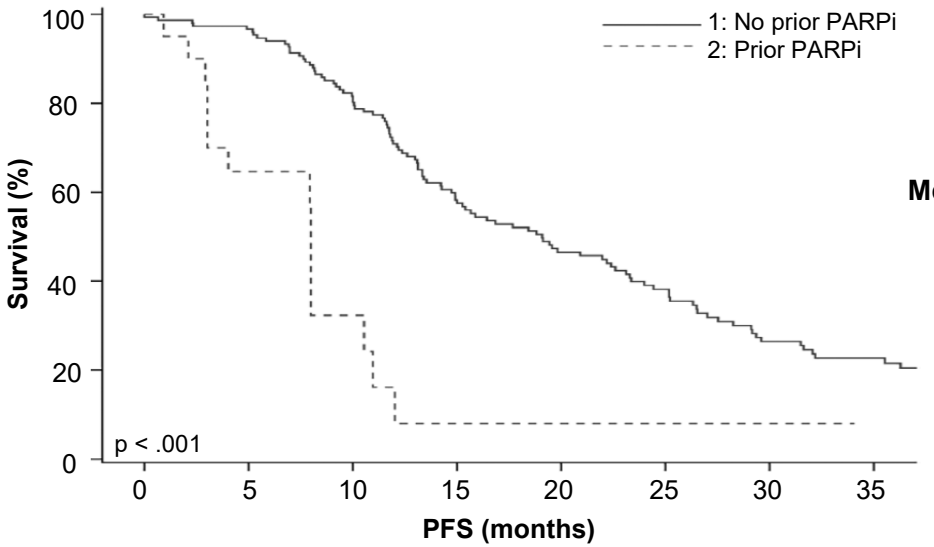
Platinum-based chemotherapy (n=96)		
	Olaparib (n=54)	Placebo (n=42)
Median PFS, months	**7.0**	**14.3**

HR: 2.89 (95% CI, 1.73–4.82)

BRCA, BRCA DNA repair associated gene; *BRCAm*, BRCA mutated; CI, confidence interval; ENGOT, European Network of Gynaecological Oncological Trial Groups; EOC, epithelial ovarian cancer; HR, hazard ratio.

Frenel JS et al. [published online June 27, 2022]. *Ann Oncol*. doi:10.1016/j.annonc.2022.06.011

Decreased response to 2L/3L platinum-based chemotherapy after prior PARPi in *BRCA*m EOC: results from a single-institution retrospective study



No. at risk

1: No prior PARP	150	145	115	76	58	43	29	21
2: Prior PARP[a]	20	10	4	1	1	1	1	0

	No prior PARPi (n=150)	Prior PARPi (n=20)
Events, n (%)	107 (71)	14 (70)
Median PFS, months (95% CI)	**19.1** (14.9–23.1)	**8.0** (3.0–10.5)

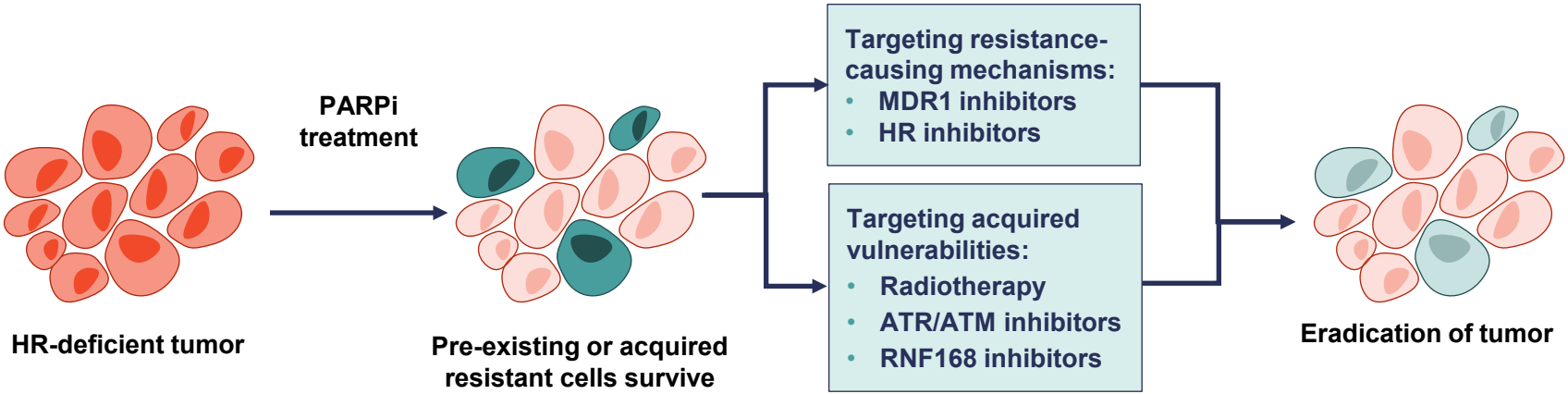
HR: 4.01 (95% CI, 2.25–7.16); *P*=<0.001

[a] PARPi utilized by these patients were olaparib (13), niraparib (4), rucaparib (1) or veliparib (2).

BRCA, BRCA DNA repair associated gene; *BRCA*m, *BRCA* mutated; EOC, epithelial ovarian cancer; PARP, poly (ADP-ribose) polymerase; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

Rose PG et al. *Anticancer Drugs.* 2021;32(10):1086–1092.

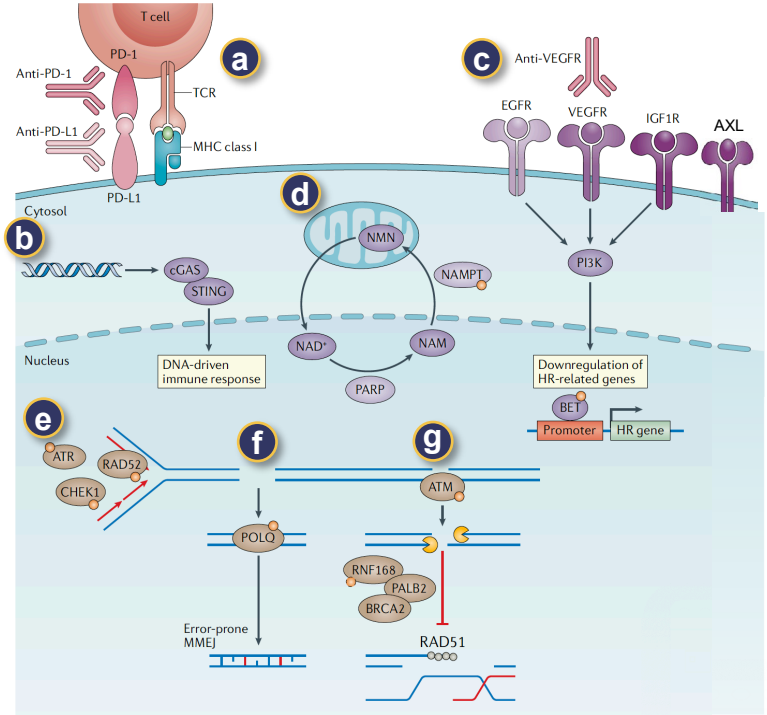
Targeting resistance and acquired vulnerabilities to overcome PARPi resistance



ATM, ATM serine/threonine kinase; ATR, ATR serine/threonine kinase; HR, homologous recombination; MDR1, multidrug resistance mutation 1; PARPi, poly (ADP-ribose) polymerase inhibitor; RNF168, ring finger protein 168.

Noordermeer SM, van Attikum H. *Trends Cell Biol.* 2019;29(10):820–834.

Targeting PARPi resistance



a) HR-deficient tumors usually have high genomic instability and are thought to present an increased number of neoantigens on their surfaces

b) PARPi have been shown to induce PD-L1 expression and upregulate cGAS-STING signaling, which might further boost recruitment and/or activation of CD8+ T cells

c) Inhibition of RTKs may inhibit reactivation of the HR pathway in tumors with acquired resistance to PARPi

d) Inhibition of NAD+ synthesis might further enhance the cytotoxicity of PARPi through indirect inhibition of PARylation

e) Suppressing restored replication fork protection in PARPi-resistant cells

f) Inhibiting MMEJ – inhibitors of POLQ

g) Targeting ATM or RNF168 to promote HR in the absence of BRCA1

ATM, ATM serine/threonine kinase; ATR, ATR serine/threonine kinase; BET, bromodomain and extraterminal domain; BRCA, BRCA DNA repair associated protein; CD, cluster of differentiation; cGAS, cyclic GMP-AMP synthase; CHEK1, checkpoint kinase 1; EGFR, endothelial growth factor receptor; HR, homologous recombination; IGF1R, insulin-like growth factor 1 receptor; MHC, major histocompatibility complex; MMEJ, microhomology-mediated end-joining; NAD, nicotinamide adenine dinucleotide; NAM, nicotinamide; NAMPT, nicotinamide phosphoribosyltransferase; NMN, nicotinamide mononucleotide; PALB2, partner and localizer of BRCA2; PARP, poly (ADP-ribose) polymerase; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-1, programmed death receptor 1; PD-L1, programmed death receptor-ligand 1; PI3K, phosphoinositide 3-kinase; POLQ, DNA polymerase theta; RNF168, ring finger protein 168; RTK, receptor tyrosine kinase; STING, stimulator of interferon genes; TCR, T-cell receptor; VEGFR, vascular endothelial growth factor receptor.

Dias MP et al. *Nat Rev Clin Oncol*. 2021;18(12):773–791.

DNA damage repair pathway alterations contribute to platinum and PARPi resistance

DNA damage repair pathway	Key pathway functions	Key genes	Effect of pathway alterations on therapeutic resistance
Homologous Recombination (HR)	**Repair of DSBs or stalled replication forks during S and G2 phases of cell cycle**	***BRCA1, BRCA2, RAD51, HSP90***	**Reactivation of HR pathway enables repair of DSBs and resolves replisome blocks, promoting cancer cell progression through the cell cycle despite the presence of cytotoxic DNA damage**
Non-Homologous End Joining (NHEJ)	Repair of DSBs during interphase	*53BP1*	Loss of 53BP1 re-wires NHEJ pathway, reactivating HR independent of BRCA1
Base Excision Repair (BER)	Repair of SSBs and DNA base lesions	*PARP-1, XRCC1, Pol β*	Functional BER pathway leads to loss of synthetic lethality and PARPi resistance
Nucleotide Excision Repair (NER)	Removes “bulky lesions” which distort the DNA double helix, including intra-strand crosslinks formed by platinum adducts	*ERCC1, XPF*	Upregulation of ERCC1 and XPF potentially restores NER function. NER pathway alteration potentially confers sensitivity to platinum, and not PARPi
Fanconi Anemia (FA)	Removes intra-strand DNA crosslinks, coordinates DNA replication by fine-tuning mitotic checkpoints and replication fork stabilization	*FANCC, FANCD2, FANCA*	Mutations in FA pathway genes may have a similar effect to *BRCA1* and *BRCA2* mutation, in promoting progression of cancer cell through the cell cycle, even in setting of DNA damage and replication stress
Mismatch Repair (MMR) Deficiency	Recognize, excise and resynthesize mismatched or unmatched DNA base pairs or insertion-deletion loops	*MLH1, MSH2*	MMR deficiency results in microsatellite instability, interfering with detection of cytotoxic DNA damage, allowing cancer cells to proliferate despite DNA damage

53BP1, tumor suppressor p53-binding protein 1; *BRCA*, BRCA DNA repair associated gene; DSB, double-strand break; ERCC1, ERCC excision repair 1, endonuclease non-catalytic subunit; FANCA, FA complementation group A; FANCC, FA complementation group C; FANCD2, FA complementation group D2; HSP90, heat shock protein 90; *MLH1*, MutL homolog 1; *MSH2*, MutS homolog 2; PARPi, poly (ADP-ribose) polymerase inhibitor; RAD51C, RAD51 paralog C; SSB, single-strand break.

McMullen M et al. *Cancers (Basel)*. 2020;12(6):1607.

Reactivation of HR repair

Resistance Mechanism	Function
***BRCA* (or HR gene) reversion mutation**	Restores open reading frame of gene, resulting in functional protein expression
Loss of *BRCA1* promoter methylation	Restores BRCA1 function
Upregulated HSP90	Promotes BRCA-independent RAD51 loading onto damaged DNA
***BRCA1* c-terminal domain mutation**	Upregulation of BRCA1, in absence of *BRCA1* reversion mutation
Loss 53BP1	Recruits Shieldin complex to inhibit DNA resection, initiating HR in a BRCA-independent manner

53BP1, tumor suppressor p53-binding protein 1; *BRCA*, BRCA DNA repair associated gene; HR, homologous recombination; HSP90, heat shock protein 90.

McMullen M et al. *Cancers (Basel)*. 2020;12(6):1607.

Select active trials targeting DNA damage repair pathways to overcome platinum and PARPi resistance

Study name/NCT #	Target	Study treatment	Study population	Study phase, design
COCOS, NCT02502266[1,2]	Angiogenesis/PARP	Cediranib + olaparib, or chemotherapy	Platinum resistant or refractory OC	II/III, RCT
EFFORT, NCT03579316[1,2]	WEE-1/PARP	Adavosertib + olaparib, or adavosertib monotherapy	Recurrent OC with progression on prior PARPi therapy	II, RCT
NCT02901899[1,2]	DNMT/PD-1	Guadecitabine + pembrolizumab	Recurrent PROC	II, open-label
NRG-GY029, NCT05295589[3,4]	PI3K/PARP	Copanlisib + olaparib vs chemotherapy	Recurrent PROC with progression on prior PARPi therapy	II, RCT
CAPRI, NCT03462342[4]	ATR/PARP	AZD6738 + olaparib	Recurrent OC (platinum-sensitive or platinum-resistant)	II, open-label
REVOCAN, NCT04826198[4]	DNA damage/PARP	AsiDNA + niraparib, olaparib or rucaparib	Recurrent PSOC with prior PARPi therapy	Ib/II, open-label
NIRVANA-R, NCT04734665[4]	Angiogenesis/PARP	Niraparib + bevacizumab maintenance	Recurrent PSOC with prior PARPi therapy	II, open-label
NCT04669002[4,5]	Top1/PARP	EP0057 + olaparib	Advanced OC including PROC and prior PARPi therapy	II, open-label
NCT05071937[6]	BET/PARP	ZEN003694 + talazoparib	Recurrent PSOC with progression on prior PARPi therapy	II, open-label
ComBET, NCT05327010[6]	BET/PARP	ZEN003694 + talazoparib	Advanced molecularly-selected solid tumors	II, open-label
ANLOLA, NCT04566952[6]	TK/PARP	Anlotinib + olaparib	Recurrent PSOC	II, open-label
NCT05407584[6,7]	CA125	Oregovomab + PLD	Recurrent OC with progression on prior PARPi therapy	II, open-label
NCT04267939[8]	ATR/PARP	Elimusertib + niraparib	Advanced solid tumors and EOC	I, open-label
NCT04703920[8,9]	HDAC/PARP	Talazoparib + belinostat	Metastatic breast cancer, metastatic castration resistant prostate cancer, and metastatic OC	I, open-label
NCT04586335[8]	PI3K/PARP	CYH33 + olaparib	DDR gene mutations and/or PIK3CA mutations; progression on prior PARPi therapy; recurrent PROC	I, open-label

ATR, ATR serine/threonine kinase; BET, bromodomain and extraterminal domain; DDR, DNA damage response; DNMT, DNA methyltransferase; EOC, epithelial ovarian cancer; HDAC, histone deacetylase; OC, ovarian cancer; Pac, paclitaxel; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; PD-1, programmed death receptor 1; PLD, pegylated liposomal doxorubicin; PROC, platinum-resistant ovarian cancer; PSOC, platinum-sensitive ovarian cancer; RCT, randomized controlled trial; TK, tyrosine kinase; Top1, topoisomerase-1.

1. McMullen M et al. *Cancers (Basel)*. 2020;12(6):1607. 2. ClinicalTrials.gov. NCT02502266, NCT03579316, NCT02901899. Accessed Sep 20, 2022. 3. NRG Oncology. NRG-GY029. Accessed Sep 27, 2022. 4. ClinicalTrials.gov. NCT05295589, NCT04734665, NCT04826198, NCT03462342, NCT04669002. Accessed Sep 27, 2022. 5. Duska, LR et al. *Gynecol Oncol*. 2021;160(3):688-695. 6. ClinicalTrials.gov. NCT05071937, NCT05327010, NCT04566952, NCT05407584. 7. Pietragalla A et al. *Expert Opin Investig Drugs*. 2021;30(2):103-110. 8. ClinicalTrials.gov. NCT04267939, NCT04703920. Accessed Sep 27, 2022. 9. Campbell P, Thomas CM. *J Oncol Pharm Pract*. 2017;23(2):143-147. 10. ClinicalTrials.gov. NCT04586335. Accessed Sep 27, 2022.

Summary

- There are overlapping mechanisms of resistance that develop against PARP inhibitors and platinum-based chemotherapy[1]
- Additional sequencing studies for PARP inhibitor resistance are needed[1]
- Retrospective and post hoc analysis data highlight that prior exposure to PARP inhibitors decreases response to 2L/3L platinum-based chemotherapy[2,3]
- Novel strategies to overcome PARP inhibitor resistance are under investigation[1]

2L, second line; 3L, third line; PARP, poly (ADP-ribose) polymerase.

1. McMullen M et al. *Cancers (Basel)*. 2020;12(6):1607. 2. Rose PG et al. *Anticancer Drugs*. 2021;32(10):1086–1092. 3. Frenel JS et al. [published online June 27, 2022]. *Ann Oncol*. doi:10.1016/j.annonc.2022.06.011