

Supplementary Table 1. Relevant clinical trials of PARPi in OC.

Study	Phase	Patients (n)	Setting/Endpoint	Treatment arms	Median PFS, OS and PFS2 (if available) (months)		HR (95% CI), p-value
					Experimental arm	Control arm	
STUDY 19 (NCT00753545)	II	265	Maintenance after recurrence PS recurrent HGSO, primary peritoneal or fallopian tube Primary Endpoint: PFS	Olaparib 400mg twice daily Placebo	PFS All: 8.4	PFS All: 4.8	PFS: All: HR 0.35 (0.25 to 0.49), p<0.0001
					PFS BRCAm: 11.2	PFS BRCAm: 4.3	PFS BRCAm: HR 0.18 (0.10 to 0.31), p<0.0001
					PFS BRCAwt: 7.4	PFS BRCAwt: 5.5	PFS BRCAwt: HR 0.54 (0.34 to 0.85), p<0.0001
					OS All: 29.8	OS All: 27.8	OS All: HR 0.73 (0.55 to 0.95), p=0.021
					OS BRCAm: 34.9	OS BRCAm: 30.2	OS BRCAm: HR 0.62 (0.42 to 0.93), p=0.021

					OS <i>BRCAwt</i> : 24.5	OS <i>BRCAwt</i> : 26.6	OS <i>BRCAwt</i> : HR 0.84 (0.57 to 1.25), p=0.39
SOLO 3 (NCT02282020)	III	266	Treatment PS relapsed ovarian cancer who had received at least two prior lines of platinum-based chemotherapy <i>gBRCAm</i> Primary Endpoint: PFS	Olaparib 300mg twice daily Physician's choice single-agent non-platinum chemotherapy	PFS: 13.4	PFS: 9.2	PFS: HR 0.62 (0.43 to 0.91), p=0.013
					PFS2: 23.6	PFS2: 19.6	PFS2: HR 0.80 (0.56 to 1.15), p=0.229
					OS: 34.9	OS: 32.9	OS: HR 1.07 (0.76 to 1.49), p=0.714
SOLO 2 (NCT01874353)	III	295	Maintenance after recurrence PS recurrent HGSOC, HGEOC, primary peritoneal or fallopian tube <i>BRCAm</i> Primary Endpoint: PFS	Olaparib 300mg twice daily Placebo	PFS: 19.1	PFS: 5.5	PFS: HR 0.30 (0.22 to 0.41), p<0.0001
					PFS2: NR	PFS2: 18.4	PFS2: HR 0.50 (0.34 to 0.72), p<0.0002

					OS: 51.7	OS: 38.8	OS: HR 0.74 (0.54 to 1.0), p=0.054
SOLO 1 (NCT01844986)	III	451	First-line Maintenance PS after first-line platinum-based chemotherapy <i>BRCAm</i> Primary Endpoint: PFS	Olaparib 300mg twice daily Placebo	PFS: 56	PFS: 13.8	PFS: HR 0.33 (0.25 to 0.43) p<0.0001
					PFS2: NR	PFS2: 41.9	PFS2: HR 0.50 (0.35 to 0.72)
					OS: NR at 7y	OS: 75.2	OS: HR 0.55 (0.40 to 0.76), p=0.004
PAOLA-1 (NCT02477644)	III	391	First-line Maintenance PS HGSO, HGEOC, primary peritoneal or fallopian tube after first-line platinum-based	Olaparib 300mg twice daily + bevacizumab 15mg/kg every 3 weeks Placebo + Bevacizumab	PFS: All: 22.1	PFS All: 16.6	PFS All: HR 0.59 (0.49 to 0.72), p<0.001
					PFS <i>BRCAm</i> : 37.2	PFS <i>BRCAm</i> : 21.7	PFS <i>BRCAm</i> : HR 0.31 (0.20 to 0.47)

		chemotherapy and maintenance with bevacizumab Primary Endpoint: PFS		PFS HRD (including <i>BRCAm</i>): 37.2	PFS HRD (including <i>BRCAm</i>): 17.7	PFS HRD (including <i>BRCAm</i>): HR 0.33 (0.25 to 0.45)
				PFS HRD, <i>BRCAwt</i> : 28.1	PFS HRD, <i>BRCAwt</i> : 28.1	HRD, <i>BRCAwt</i> : HR 0.43 PFS (0.28 to 0.66)
				PFS <i>BRCAwt/HRD</i> negative/unknown: 16.9	PFS <i>BRCAwt/HRD</i> negative/unknown: 16	PFS <i>BRCAwt/HRD</i> negative/unknown: HR 0.92 (0.72 to 1.17)
				PFS2 All: 36.5	PFS2 All: 32.6	PFS2 All: HR 0.78 (0.64 to 0.95), p=0.0125
				OS All: 58.7% at 5y	OS All: 41.5% at 5y	OS All: HR 0.92 (0.76- 1.12)
				OS <i>BRCAm</i> : 52.3% at 5y	OS <i>BRCAm</i> : 48.4% at 5y	OS <i>BRCAm</i> : HR 0.60 (0.39 to 0.93)

					OS HRD (including <i>BRCAm</i>): 65.5% at 5y	OS HRD (including <i>BRCAm</i>): 48.4% at 5y	OS HRD (including <i>BRCAm</i>): HR 0.62 (0.45 to 0.85)
					OS HRD, <i>BRCAwt</i> : 54.7% at 5y	OS HRD, <i>BRCAwt</i> : 44.2% at 5y	OS HRD, <i>BRCAwt</i> : HR 0.71 (0.45 to 1.13)
					OS <i>BRCAwt/HRD</i> unknown: 30.6% at 5y	OS <i>BRCAwt/HRD</i> unknown: 34.9% at 5y	OS <i>BRCAwt/HRD</i> unknown: HR 1.14 (0.89 to 1.48)
					OS <i>BRCAwt/HRD</i> negative: 25.7% at 5y	OS <i>BRCAwt/HRD</i> negative: 32.3% at 5y	OS <i>BRCAwt/HRD</i> negative/unknown: HR 1.19 (0.88 to 1.63)
NOVA (NCT01847274)	II	555	Maintenance after recurrence PS recurrent HGSO, primary peritoneal or fallopian tube Primary Endpoint: PFS	Niraparib 300mg once daily Placebo	PFS <i>gBRCAm</i> : 21	PFS <i>gBRCAm</i> : 5.5	PFS <i>gBRCAm</i> : HR 0.27 (0.17 to 0.41), p<0.001
					PFS <i>BRCAwt HRD</i> : 12.9	PFS <i>BRCAwt HRD</i> : 3.8	<i>BRCAwt HRD</i> : HR 0.38 (0.24 to 0.59), p<0.001

					PFS All non- <i>gBRCAm</i> : 9.3	PFS All non- <i>gBRCAm</i> : 3.9	All non- <i>gBRCAm</i> : HR 0.45 (0.34 to 0.61), p<0.001
					--	--	PFS2 <i>gBRCAm</i> : 0.67 (0.48 to 0.95)
					--	--	PFS2 non- <i>gBRCAm</i> : 0.81 (0.62 to 1.05)
					OS <i>gBRCAm</i> : 45.9	OS <i>gBRCAm</i> : 43.2	OS <i>gBRCAm</i> : NS
					OS All non- <i>gBRCAm</i> : 38.5	OS All non- <i>gBRCAm</i> : 39.1	OS <i>gBRCAm</i> : NS
PRIMA (NCT02655016)	III	799	First-line maintenance PS cancer of ovary, primary peritoneal or fallopian tube	Niraparib 300mg once daily Placebo	PFS All: 13.8	PFS All: 8.2	PFS All: HR 0.62 (0.50 to 0.75), p<0.0001

			after first-line platinum-based chemotherapy stage III with residual disease after primary surgery or interval surgery or stage IV Primary endpoint: PFS		PFS HRD: 21.9	PFS HRD: 10.4	PFS HRD: HR 0.43 (0.31 to 0.59), p<0.0001
					PFS HRD/ <i>BRCAm</i> : 22.1	PFS HRD/ <i>BRCAm</i> : 10.9	PFS HRD/ <i>BRCAm</i> : HR 0.40 (0.27 to 0.62), p<0.0001
					PFS HRD/ <i>BRCAw</i> : 19.6	PFS HRD/ <i>BRCAw</i> : 8.2	PFS HRD/ <i>BRCAw</i> : HR 0.50 (0.31 to 0.83), p=0.006
					PFS HR-proficient: 8.1	PFS HR-proficient: 5.4	PFS HR-proficient: HR 0.62 (0.49 to 0.94), p=0.20
PRIME (NCT03709316)	III	381	First-line maintenance PS HGSO, HGEOC, primary peritoneal or fallopian tube	Niraparib 300mg once daily Placebo	PFS ITT: 24.8	PFS ITT: 8.3	PFS ITT: HR 0.45 (0.34 to 0.60), p<0.001

			after first-line platinum-based chemotherapy Primary endpoint: PFS		PFS <i>gBRCAm</i> : NR	PFS <i>gBRCAm</i> : 10.8	PFS <i>gBRCAm</i> : HR 0.40 (0.23 to 0.68), p<0.001
					PFS Non- <i>gBRCAm</i> : 19.3	PFS Non- <i>gBRCAm</i> : 8.3	PFS Non- <i>gBRCAm</i> : HR 0.48 (0.34 to 0.67), p<0.001
ARIEL 2 (part 1) (NCT01891344)	II	194	Maintenance after recurrence PS recurrent HGSO, HGEOC, primary peritoneal or fallopian tube Primary endpoint: PFS	Rucaparib 600mg twice daily	PFS <i>BRCAm</i> : 12.8	NA	PFS HR 0.27 (0.16 to 0.44), p<0.0001 (<i>BRCAm</i> vs wt)
					PFS <i>BRCA</i> wt LOH high: 5.7	NA	PFS <i>BRCAwt/LOH low</i> : HR 0.62 (0.42 to 0.90), p=0.011 (<i>BRCAwt/LOH high</i> vs <i>low</i>)
					PFS <i>BRCAwt</i> LOH low: 5.2	NA	NA
ARIEL 3 (NCT01968213)	III	564	Maintenance after recurrence	Rucaparib 600mg twice daily	PFS <i>BRCAm</i> : 16.6	PFS <i>BRCAm</i> : 5.4	PFS <i>BRCAm</i> : HR 0.23 (0.16 to 0.34), p<0.0001

			PS recurrent HGSOC, HGEOC, primary peritoneal or fallopian tube Primary Endpoint: PFS	Placebo			
					PFS HRD: 13.6	PFS HRD: 5.4	PFS HRD: HR 0.32 (0.24 to 0.42), p<0.0001
					PFS ITT: 10.8	PFS ITT: 5.4	PFS ITT: HR 0.36 (0.30 to 0.45), p<0.0001
					PFS2 BRCAm: 26.8	PFS2 BRCAm: 18.4	PFS2 BRCAm: HR 0.56 (0.38 to 0.83), p=0.004
					PFS2 HRD: 25.3	PFS2 HRD: 18.4	PFS2 HRD: HR 0.66 (0.49 to 0.87), p=0.0042
					PFS2 ITT: 21	PFS2 ITT: 16.5	PFS2 ITT: HR 0.66 (0.53 to 0.82), p=0.0002
					OS BRCAm: 45.9	OS BRCAm: 47.8	OS BRCAm: HR 0.832 (0.58 to 1.192)
					OS HRD: 40.5	OS HRD: 47.8	OS HRD: HR 1.005 (0.766 to 1.320)

					OS ITT: 36	OS ITT: 43.2	OS ITT: HR 0.995 (0.809 to 1.123)
ATHENA-MONO (NCT03522246)	III	538	First-line maintenance PS ovarian, fallopian tube or primary peritoneal cancer after first-line platinum-based chemotherapy Primary endpoint: PFS	Rucaparib 600mg twice daily Placebo	PFS HRD: 28.7	PFS HRD: 11.3	PFS HRD: HR 0.47 (0.31 to 0.72), p=0.0004
					PFS ITT: 20.2	PFS ITT: 9.2	PFS ITT: HR 0.52 (0.40 to 0.68), p<0.0001
					PFS non HRD: 12.1	PFS non HRD: 9.1	PFS non HRD: HR 0.65 (0.45 to 0.95)
ARIEL 4 (NCT02855944)	III	349	Treatment Relapsed ovarian cancer after two or more lines of chemotherapy <i>BRCAm</i> Primary endpoint: PFS	Rucaparib 600mg twice daily Chemotherapy	PFS: 7.4	PFS: 5.7	PFS: HR 0.67 (0.52 to 0.86), p=0.0017
					OS: 19.4	OS: 25.4	OS: HR 1.31 (0.99 to 1.72)

VELIA/GOG 3005 (NCT02470585)	III	1140	First-line maintenance/and or treatment PS HGSO, primary peritoneal or fallopian tube after first-line platinum-based chemotherapy Primary endpoint: PFS	Veliparib throughout (during chemotherapy and maintenance) (V1)	PFS ITT V1: 23.5	PFS ITT: 17.3	PFS ITT V1 vs C: HR 0.68 (0.56 to 0.83), p<0.001
				Veliparib during chemotherapy +placebo	PFS ITT V2: 15.2	PFS ITT: 17.3	PFS ITT V2 vs C: HR 1.07 (0.90 to 1.29)
				maintenance (V2)	PFS HRD V1: 31.9	PFS HRD: 20.5	PFS HRD V1 vs C: HR 0.57 (0.43 to 0.76), p<0.001
				Chemotherapy + Concomitant placebo + Placebo maintenance (C)	PFS HRD V2: 18.1	PFS HRD: 20.5	PFS HRD V2 vs C: HR 1.10 (0.86 to 1.41)
					PFS BRCAm V1: 34.7	PFS BRCAm: 22	PFS BRCAm V1 vs C: HR 0.44 (0.28 to 0.68), p<0.001
					PFS BRCAm V2: 21.1	PFS BRCAm: 22	PFS BRCAm V2 vs C: HR 1.22 (0.82 to 1.80)

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BRCAm, *BRCA* mutated; *gBRCAm*, germinal *BRCA* mutated; *BRCA* wt, *BRCA* wild type; HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer;

HR, hazard ratio; HR, homologous recombination; HRD, homologous recombination deficiency positive; ITT, intention to treat population; LOG, loss of heterozygosity; NA, not applicable; NR, not reached; NS, non-significant; OS, overall survival; PARP, poly ADP ribose polymerase; PFS, progression-free survival; PFS2, second progression-free survival; PS, platinum-sensitive.

Supplementary Table 2. Main resistance mechanisms PARP inhibitors.

Mechanism	Dependence on BRCA/HDR status	Cause of resistance	Evidence
Upregulation of drug efflux pumps	No	<i>ABCB1</i> overexpression	Clinical evidence
PARP signaling restoration	No	PARG loss	In vivo models
Reduced PARP1 trapping	Yes	Suppression of autoPARylation	In vivo models
Recovery of functional HR proteins and reactivation of HR	Yes	Secondary reversion mutations	Clinical evidence (most studied)
		<i>BRCA</i> hypomorphic isoforms	PDX
		Loss of <i>BRCA1</i> promoter demethylation	Clinical evidence
		Loss of resection inhibition: abnormal factors that participate in NHEJ	PDX, in vivo models

Stabilization of replication forks	Yes	Loss of factors such as PTIP CHD4, RADX, SLFN 11 and chromatin remodelers factors	In vivo models
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PARPi: poly ADP ribose polymerase inhibitor; HR: Homologous Recombination; PARG: PAR glycohydrolase; PDX: Patient Derived Xenografts; NHEJ: Non-homologous end joining repair.