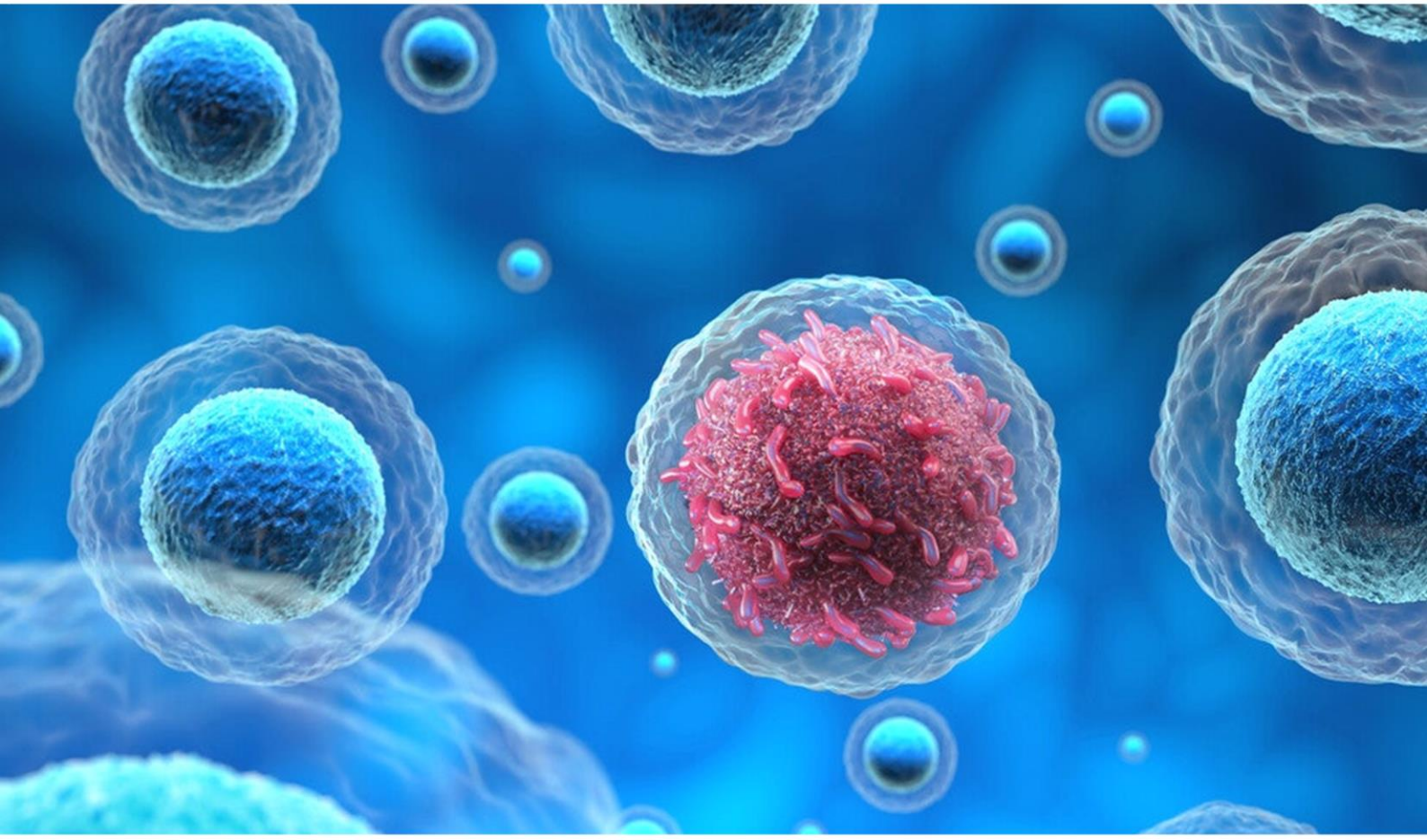
Role of Olaparib in BRCAm Ovarian Cancer



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Background and Objective of the Survey

Olaparib, a PARP inhibitor, has emerged as a cornerstone in the management of BRCA-mutated ovarian cancer, revolutionizing treatment paradigms and significantly improving outcomes for patients. By targeting the specific genetic vulnerabilities associated with BRCA mutations, olaparib disrupts DNA repair mechanisms in cancer cells, leading to their demise through synthetic lethality. Clinical trials, such as SOLO1 and SOLO2, have underscored olaparib's efficacy as maintenance therapy following platinum-based chemotherapy, demonstrating substantial improvements in progression-free survival for patients with newly diagnosed or relapsed BRCA-mutated ovarian cancer.

The introduction of olaparib maintenance therapy has reshaped treatment strategies, providing a valuable option for prolonging periods of remission and delaying disease progression. Its well-tolerated safety profile and manageable side effects have further solidified its role as a preferred therapeutic agent in this setting. Ongoing research continues to explore olaparib's potential in combination therapies and its utility across different stages of ovarian cancer management. Overall, olaparib represents a significant advancement in precision medicine, offering targeted treatment tailored to the genetic characteristics of BRCA-mutated ovarian cancer, ultimately improving patient outcomes and quality of life.

The objective of the survey is:

To evaluate the role of Olaparib in BRCAm ovarian cancer

Methodology of the Survey

A survey was conducted to evaluate the role of Olaparib in BRCAm ovarian cancer. A total of 75 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Pharmacodynamic properties of olaparib
- Pharmacokinetic properties of olaparib
- Olaparib in special populations
- Therapeutic efficacy of olaparib
- Tolerability of Olaparib
- Future perspectives

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

With an incidence of 8.1 cases/100,000 inhabitants/year, ovarian cancer (OC) is the eighth most common cancer among women worldwide. It accounts for more deaths than any other malignancy of the female reproductive system, bearing a mortality rate of 5.4 deaths/100,000 inhabitants/year. Most OC cases are diagnosed as metastatic (57%), with a 5-year survival rate of only 30.8%. Platinum-based chemotherapy (CHT) represents the first choice in the metastatic setting of OC. However, despite initial benefits, over 2 out of 3 patients will relapse within the first 2 years. Poly-(ADP-ribose)-polymerase (PARP) inhibitors (PARPis) are a class of antitumor agents whose mechanism of action relies on the exploitation of the defective DNA repair pathways in Breast Cancer (BRCA) mutant and Homologous Recombination (HR) repair genes deficient (HRD) cells, a group of crucial genes for double-stranded breaks (DSBs) and interstrand crosslinks (ICLs) repairing pathways, a process notably known as “synthetic lethality”. Of note, half of all OCs are associated with HRD, and 22% of cases bear a germline or somatic mutation of BRCA1 and BRCA2, thus indicating the use of PARPis as a possible target therapy for OC. Olaparib, a potent inhibitor of human PARP-1, PARP-2, and PARP-3, is historically the first PARPi developed and approved for the clinical use of metastatic OC. Currently, olaparib is approved in USA and EU for the maintenance treatment of women with high-grade (HG) epithelial ovarian, fallopian tube, or primary peritoneal cancer, if BRCA1/2-mutated (germline or somatic) in the first line, or platinum-sensitive relapsed OC (PS-ROC), after any response (complete or partial) to platinum-based CHT. In combination with bevacizumab, olaparib is approved in case of HRD after any response to platinum-based CHT.

Pharmacodynamic properties of olaparib[1]

In vitro, olaparib inhibits PARP-1, -2, and -3 with IC50 5, 1, and 4 nM, respectively. It also has weak activity against PARP-5a (tankyrase 1 [TNKS1]) with IC50 1,500 nM.

TABLE 1. Pharmacokinetics and pharmacodynamics of olaparib.

	Dose (mg)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)	IC50 (nM)	Metabolism	Cytocrome metabolism
Olaparib	300/12 h	7,700	1.5	11.9	PARP1: 5, PARP2: 1, PARP3: 4, PARP5a: 1500	Liver (42% recovered in feces), kidney (44% recovered in urine)	CYP 3A4/5 with 3 metabolites: M12 (ring opened hydroxy-cyclopropyl), M15 (mono-oxygenated), M18 (dehydrogenated piperazine)
	400/12 h	9,300	2				

CYP3A4/5, cytochrome P 3A4/5; PARP1/2/3, Poly (ADP-ribose) polymerase 1/2/3.

Similarly to other PARPis, olaparib acts through the mechanism of "synthetic lethality," as it inhibits PARP enzymes, causing the accumulation of DNA damage. In the case of HRD, this inhibition leads to apoptosis. Moreover, olaparib causes cytotoxic and pro-apoptotic PARP-DNA trapping. In pre-clinical models, these effects seemed additive or synergistic with the cytotoxicity exerted on DNA by chemotherapeutic agents, with even more contribution to DNA fragmentation and cell apoptosis than olaparib alone. Among resistance mechanisms, BRCA reversion mutations that restore the HR function are the main findings in olaparib-resistant cells. Moreover, the occurrence of somatic mutations which restore the open reading frame of HRR genes, defects in non-homologous end-joining, increased drug efflux [e.g., with mutations of P-glycoprotein (P-gp)], or loss of 53BP1, have been found.

Pharmacokinetic properties of olaparib[1]

At the daily dosage of 600 mg tablets divided into two administrations (BID), olaparib's mean maximum plasma concentration (Cmax) is 7,700 ng/mL, reached in a median time (Tmax) of 1.5 h, and the half-life is 14.9 h. Olaparib is available as capsules or tablets. The two formulations are not equivalent: as evidenced by different studies, the 300 mg tablets had a 13% higher mean relative exposure at the steady state than the 400 mg capsules. In the case of

400 mg BID, Cmax is around 9,300 ng/mL, and Tmax is around 2 h. Cytochromes P450 (CYP)3A4 and -5 mainly metabolize olaparib, forming three principal metabolites: M12 (ring opened hydroxy-cyclopropyl) M15 (mono-oxygenated), and M18 (dehydrogenated piperazine), with the potency to inhibit the growth of BRCA1-mutant cells and PARP-1 30-fold, 30-fold and 4-fold lower than olaparib, respectively. The use of potent inhibitors of CYP3A, such as clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal, and grapefruit, increases the Cmax of olaparib of 42% [90% confidence interval (CI), 33%–52%] and the median area under the curve (AUC) of 170% (90% CI, 144%–197%). Thus, co-administration is not recommended unless the dose of olaparib is reduced to 100 mg or 150 mg BID if a potent or moderate inhibitor is used, respectively. Olaparib also weakly inhibits CYP3A4 *in vitro* and CYP3A *in vivo*, thus possibly increasing the exposure to CYP3A substrates, which could be important for drugs with a narrow therapeutic window, such as simvastatin, cisapride, ciclosporin, ergotamine alkaloids, fentanyl, pimozide, sirolimus, tacrolimus e quetiapine. Furthermore, it has been demonstrated that the use of potent inducers of CYP3A, such as apalutamide, carbamazepine, enzalutamide, fosphenytoin, lumacaftor, lumacaftor-ivacaftor, mitotane, phenobarbital, phenytoin, primidone, rifampin (rifampicin) and St. John's wort might substantially decrease olaparib efficacy, reducing its median Cmax of 71% (90% CI, 76%–67%) and the median AUC of 87% (90% CI, 89%–84%); thus the co-administration should be avoided. The efficacy of hormonal contraceptives might be reduced, as olaparib slightly induces CYP1A2 and 2B6 *in vitro*. The liver metabolizes olaparib: after the drug administration, 44% is recovered in urine (of which 15% is unaltered, M15 representing the main metabolite) and 42% in feces (6% unaltered, M12 and M15 being among the most abundant metabolites)

Olaparib in special populations[1]

Renal and liver impairment

In patients with renal impairment, olaparib pharmacokinetic properties are altered, significantly increasing AUC and Cmax. Therefore, a higher exposure might eventually increase toxicity. In clinical studies, no relevant increase in exposure to olaparib was found in case of mild renal impairment. In the phase I trial, patients received olaparib if they had normal renal function or mild to moderate renal impairment. In patients with moderate reduction of renal function, exposure to olaparib could increase up to 44%; therefore, dose adjustments (e.g., 200 mg twice daily) should be used. In case of severe renal dysfunction, without specific evidence, it is not safe to recommend olaparib.

On the contrary, hepatic dysfunction did not alter olaparib pharmacokinetics, therefore not requiring dose adjustments, except in patients with severe liver impairment, for which no dedicated studies exist; hence, olaparib should not be recommended.

Older patients

Although most OCs develop after age 65, only around 1 out of 3 patients is aged ≥65 in the major clinical trials of olaparib. In an ancillary analysis of ≥65 patients included in olaparib trials, no differences in adverse events (AEs), even those of severe grade, were detected between the older and the younger patients. The discontinuation rate of the two groups stood around 44.7%–64.7% of patients but was not significantly different between the age subgroups. We recently performed a meta-analysis, showing no differences in efficacy between older and younger patients, both with single agents and in combination with bevacizumab. Moreover, no increased risk of hematologic toxicity emerged in ≥65 women. However, only SOLO1, SOLO2, and PAOLA-1 trials published data explicitly focusing on older patients. Therefore, even if the evidence did not limit the use of full-dose olaparib in the old population, considering the high median age at diagnosis of mOC and the aging population in the next years, trials explicitly focusing on the elder age subgroups should be designed.

Therapeutic efficacy of olaparib[1]

Advanced BRCA mutant OC after 3 or more lines of chemotherapy

In December 2014, the FDA approved olaparib for treating women with deleterious or suspected deleterious gBRCAm advanced OC who have been previously treated with three or more lines of chemotherapy, based on the results of the phase II trial Study 42. The study treated 298 germline BRCA mutant (gBRCAm) cancers, of whom 193 (65%) had OC, with olaparib. They had received at least three lines of CHT, with 39 patients defined as platinum-sensitive (PS), 81 platinum-resistant (PRes), and 14 platinum-refractory (PRef) if the time from completion of last platinum CHT to study start was >6 months, <6 months or <2 months and progressive disease (PD) was the best response to last platinum, respectively. There was no prespecified primary endpoint, but the overall response rate (ORR) and median duration of response (mDoR) were collected first. The overall ORR was 34%. The PS subgroup reached the highest ORR (46%) while in the PRes group, ORR was 30%. The lowest ORR was reached by the PRef subgroup (14%). mPFS was 6.7 months, ranging from 5.5 to 9.4 months in the PRes and the PS groups, respectively.

TABLE 2. Summary of studies employing Olaparib as maintenance in advanced OC.

Study name (NCT)—year	**Phase**	**Target population (*number of pts*)**	**Olaparib dosage**	**Comparative arm**	**Results**
Study 42	II	gBRCAm tumors (*n* = 298) 3 or more prior lines of CHT (*n* = 137) PS (*n* = 39) PRes (*n* = 81) PRef (*n* = 14)	400 mg BID	—	Overall
					ORR 34% (95% CI, 26%–42%)
					2 CRs (2%)
					44 PRs (32%)
					mDoR 7.9 months (95% CI, 5.6–9.6 months)
					mPFS 6.7 months (95% CI, 5.5–7.6 months)
					PS
					ORR 46% (95% CI, 30%–63%) mDoR 8.2 months (95% CI, 5.6–13.5 months)
					PFS 9.4 months (95% CI, 6.7–11.4 months)
					PRes
					ORR 30% (95% CI, 20%–41%) mDoR 8.0 months (95% CI, 4.8–14.8 months)
					PRef
					ORR 14% (95% CI, 2%–43%) mDoR 6.4 months (95% CI, 5.4–7.4 months)

					PFS 5.5 months (95% CI, 4.2–6.7 months)
Study 19 - 2012	II	PS-ROC (*n* = 265)	400 mg BID	PBO	Overall
		O group (*n* = 136)			PFS 8.4 months vs. 4.8 months (HR 0.35; 95% CI, 0.25–0.49; *p* < 0.001)
		PBO group (*n* = 129)			OS 29.8 months v. 27.8 months (HR 0.88; *p* = 0.44)
		g/sBRCAm (screened *n* = 254)			BRCAm
		O (*n* = 74, 56%)			PFS 11.2 months vs. 4.3 months (HR 0.18; 95% CI, 0.10–0.31; *p* < 0.0001)
		PBO (*n* = 62, 50%)			OS 34.9 months vs. 31.9 months (HR 0.73; *p* = 0.19)
SOLO2/ENGOT-Ov21—2013 ;	III	PS-ROC g/sBRCAm (*n* = 294)	300 mg BID	PBO	PFS 19.1 mos vs. 5.5 months (HR 0.30; 95% CI, 0.22–0.41; *p* < 0.0001)
		O group (*n* = 195)			
		PBO (*n* = 99)			
OPINION - 2018	IIIb	PS-ROC gBRCAwt (*n* = 279)	300 mg BID	-	Overall PFS 9.1 mos tBRCAm PFS 16.4 months

		Biomarker status tBRCAm (*n* = 27)			HRD + including BRCAm PFS 11.1 mos
		tBRCAwt (*n* = 232)			HRD + excluding BRCAm PFS 9.7 months
		HRD+ (*n* = 94)			HRD- PFS 7.3 months
SOLO1/GOG 3004 - 2013	III	First-line advanced g/sBRCAm OC after CR or PR to CHT (*n* = 391)	300 mg BID	PBO	PFS 56 months vs. 13.8 months (HR 0.30; 95% CI, 0.23–0.41; *p* < 0.001)
		O group (*n* = 260)			PFS2 NR vs. 41.9 months (HR 0.50; 95% CI, 0.35–0.72; *p* < 0.001) mOS NR vs. 75.2 months (HR 0.55; 95% CI, 0.40–0.76; *p* = 0.0004)
		PBO group (*n* = 131)			
PAOLA-1/ENGOT-ov25 - 2015	III	First-line advanced OC after CR or PR to CHT (*n* = 806)	300 mg BID plus bevacizumab 15 mg/kg q3w for 15 months	PBO + B	Overall HR for PFS 0.60 (95% CI, 0.49–0.74)
		O + B (*n* = 537)			HiR group
		PBO + B (*n* = 269)			Overall
		HiR group (74%)			PFS 20.3 months vs. 14.7 months (HR 0.60; 95% CI, 0.49–0.74)
					BRCAm

		LoR group (26%)			PFS US vs. 19.4 months (HR 0.37; 95% CI, 0.23–0.59)
					HRD+ (including BRCAm)
					PFS US vs. 16.0 months (HR 0.39; 95% CI, 0.28–0.54)
					HRD-PFS 15.6 vs. 13.8 months (HR 0.93; 95% CI, 0.68–1.30)
					LoR group
					Overall
					PFS US vs. 22.9 months (HR 0.46; 95% CI, 0.30–0.72)
					BRCAm
					PFS 29.2 months vs. 22.9 months (HR0.11; 95% CI, 0.03–0.31)
					HRD+
					PFS NR vs. 22.1 mos (HR 0.15; 95% CI, 0.07–0.30)

B, bevacizumab; BID, twice a day; BRCA, breast cancer gene; BRCAm, mutated BRCA; BRCAwt, BRCA, wild-type; CHT, chemotherapy; CI, confidence interval; CR, complete response; EP, endpoint; g/s/tBRCAm, germline/somatic/tumor-associated BRCA mutation;

HiR, higher risk [subgroup]; HR, hazard ratio; HRD, homologous recombination deficiency [genes]; LoR, lower risk [subgroup]; mos, months; NR, not reached; O, olaparib [arm]; OC, ovarian cancer; OS, overall survival; PBO, placebo [arm]; PFS, progression-free survival; PR, partial response; PRes, platinum resistant; PRef, platinum refractory; PS, platinum sensitive; PS-ROC, platinum sensitive - recurrent ovarian cancer; q3w, once every 3 weeks; US, unstable; vs., *versus*.

Maintenance treatment of recurrent ovarian cancer after complete or partial response to platinum-based chemotherapy

Olaparib is currently indicated for the maintenance treatment of adult patients with recurrent OC in complete or partial response to platinum-based CHT after FDA approval in August 2017 based on Study 19, SOLO2, and OPINION trials.

Study 19 was a randomized, phase II study to evaluate maintenance therapy with olaparib in patients with PS-ROC after receiving two or more platinum-based regimens. A pre-planned retrospective analysis of the BRCAm population was later performed and included. The primary endpoint was PFS—by overall population and by BRCA status. 265 patients were enrolled to receive olaparib (*n* = 136) or placebo (PBO—*n* = 129). A significantly longer PFS was observed with olaparib than PBO: mPFS in the overall population was 8.4 *versus* 4.8 months. In the BRCAm population, the benefit of olaparib over PBO was even more remarkable, with mPFS of 11.2 *versus* 4.3 months, if compared with BRCA wild type (BRCAwt) population, reaching an mPFS of 7.4 *versus* 5.5 months. No significant differences in terms of overall survival (OS) emerged. Of note, although the authors did not pre-plan the analysis, efficacy data seemed consistent with the hypothesis that olaparib is effective irrespectively of germline or somatic mutation of BRCA.

In the randomized, double-blind, phase III study SOLO2/ENGOT-Ov21, evaluating olaparib maintenance in PS-ROC with somatic or germline BRCAm, 294 patients were randomized to olaparib (*n* = 195) or PBO (*n* = 99). The study met its primary endpoint, as PFS was significantly longer in the olaparib subgroup: indeed, mPFS was 19.1 *versus* 5.5 months. The OS data, although immature, showed no detrimental survival for patients receiving Olaparib.

279 patients with gBRCAwt, PS-ROC were enrolled in the phase IIIb OPINION trial to receive olaparib. At screening, 264 (94.6%) patients presented gBRCAwt. Retrospective analyses of somatic BRCA mutations also resulted in 37 (13.3%) patients bearing a BRCA mutation, 27 of which had a sBRCAm (9.7%) and 6 (2.2%) with a gBRCAm. Furthermore, among the 232 (83.2%) non-tBRCAm patients - namely, patients not bearing deleterious or suspected

deleterious sBRCAm, 94 resulted in HRD (33.7%). 165 (59.1%), 84 (30.1%). PFS was the primary endpoint, while mPFS according to biomarker status (e.g., HRD and tBRCAm), and the number of prior lines of treatment, were secondary endpoints. The overall mPFS was 9.2 months. In the tBRCAm subgroup, mPFS was 16.4 months mPFS was 11.1 months in the HRD group including BRCAm, 9.7 months in the HRD excluding BRCAm, and 7.3 months in the HR proficient (HRP) subgroup. Although the study lacked a PBO comparator group that could quantify the magnitude of olaparib benefit in terms of PFS, it demonstrated the activity of maintenance olaparib in the context of PS-ROC, regardless of HRD or BRCA status.

First-line maintenance treatment of either BRCAm or HRD-positive advanced ovarian cancer

Olaparib is also indicated, in combination with bevacizumab, for the maintenance treatment of women with advanced OC after CR or PR to first-line platinum-based CHT, bearing HRD and/or BRCA mutation. FDA approved in December 2018, based on the pivotal results of the randomized, phase III clinical trial SOLO1/GOG 3004, employing olaparib (n = 260) *versus* PBO (n = 131). The primary endpoint was PFS, while the second-interval PFS (PFS2) and OS were secondary endpoints. 5-year PFS rate was 60% in the olaparib and 27% in the PBO group, mPFS was 56 months in the olaparib *versus* 13.8 months in the PBO group. PFS2 rate was 75% in the olaparib and 60% in the PBO group, and mPFS2 was NR in the olaparib and 41.9 months in the PBO group. The OS analysis was recently updated after a 7-year follow-up, showing that 67.0% of patients in the olaparib group were still alive compared with 46.5% in the PBO group.

Furthermore, in the phase III PAOLA-1/ENGOT-ov25 trial, 806 patients with advanced newly diagnosed advanced OC, with CR or PR to platinum-based CHT, were randomized to receive olaparib plus bevacizumab (n = 537) or PBO plus bevacizumab (n = 269). In this analysis, patients were divided into a higher-risk subgroup (HiR—74%) in case of surgery performed on a FIGO stage III disease with residual disease or neoadjuvant chemotherapy administered or FIGO stage IV disease, and a lower-risk subgroup (LoR—26%), with radical surgery performed on a FIGO stage III disease. BRCA status was assessed only on tumor samples; thus, germline BRCA status was unknown. After a median follow-up of 22.9 months, PFS favored the olaparib plus bevacizumab group in both risk subgroups, thus confirming the benefit of olaparib as in SOLO1, and showing, in addition, the efficacy of the combination with bevacizumab. In fact, based on the PAOLA-1 results, the combination was approved by FDA in May 2020. In the HiR subgroup, mPFS was 20.3 *versus* 14.7 months. In the LoR subgroup,

HR for PFS was 0.46 in the olaparib plus bevacizumab group. At the same time, the mPFS was inestimable in the olaparib plus bevacizumab group *versus* 22.9 months in the PBO group. Among the HiR BRCAm patients, mPFS was inestimable for the olaparib plus bevacizumab group *versus* 19.4 months in the PBO group, while in the lower-risk mBRCA patients, mPFS was 29.2 *versus* 22.9 months. In HRD patients mPFS was not estimable *versus* 16.0 months in the HiR subgroup, while in the LoR subgroup, mPFS was NR vs 22.1 months. Considering the HiR HRP patients, mPFS was 15.6 *versus* 13.8 months. No benefit in terms of PFS among LoR HRP patients derived from olaparib plus bevacizumab. PAOLA-1 was more representative of advanced OC patients than SOLO1, as patients' selection was not based on BRCA status. The PFS benefit observed with olaparib plus bevacizumab in patients with tBRCAm tumors in the PAOLA-1 appears consistent with the SOLO-1 results, supporting the efficacy of olaparib in BRCAm tumors regardless of somatic or germline mutation origin.

Tolerability of olaparib[1]

Hematological toxicities are common class effects of PARPis, representing the most common cause of dose modification, interruption, and discontinuation. They tend to occur early after treatment start and to recover after a few months. Anemia, usually the most common among haematologic AEs, might be related to PARP2 inhibition that affects the differentiation of erythroid progenitors, reducing erythrocytes' life expectancy in mice, even if erythropoietin plasma concentrations are increased, thus suggesting that supplementation might not be the best therapeutic option to manage anemia in these patients. On the contrary, transfusions are generally recommended for symptomatic anemia and hemoglobin values less than 7 g/dL. A baseline blood count should be obtained before starting olaparib and monitored monthly, at least during the first year of treatment. Olaparib should not be restarted if hematologic toxicity results > G1 (e.g., haemoglobin<10 g/dL, neutrophils <1,500/mm^3, platelets <75,000/mm^3) from previous therapy. A bone marrow analysis is recommended if severe hematologic toxicity lasts over 4 months. As the fundamental mechanism of PARP inhibition is interfering with DNA repair pathways, another severe class effect, although rare, is the onset of secondary malignancies, namely, myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), with an incidence of 0.5%–1.4%, usually after long-term treatment. The true incidence of SPMs after PARPis is difficult to estimate, as almost all patients also received other DNA-damaging drugs, such as platinum-based CH. The risk of developing new second primary malignancies (SPMs), reported in 0.7%–2% of patients in the SOLO2, OPINION, SOLO1, and PAOLA-1—especially breast, thyroid, and rectal cancers, was not found to be increased in the olaparib

group in a recent meta-analysis of 23 randomized clinical trials, thus suggesting no additional close monitoring of patients treated with PARPis. Among 8,857 patients included in the analysis, 51 SPMs were reported in the PARPis (0.9%) and 24 in the PBO group (0.7%). PARPis exposure was not associated with an increased risk of developing SPM *versus* PBO ($p = 0.62$) after up to 78 months of follow-up.

Gastrointestinal toxicities are also very commonly associated with PARPis, and patients should be aware of the high incidence of nausea to prevent its occurrence prophylactically. To lessen symptoms, daily prokinetic and antihistamine drugs can be administered. Persistent nausea or vomiting can be managed using various antiemetic drugs, such as metoclopramide, prochlorperazine, phenothiazine, dexamethasone, olanzapine, haloperidol, or lorazepam. The neurokinin-1 receptor antagonist, aprepitant, should be avoided with olaparib since it strongly inhibits CYP3A4, thus affecting olaparib plasma concentrations. Fatigue and asthenia also seem to be a class effect and can be managed using non-pharmacological approaches, such as exercise, massage therapy, and cognitive and behavioral therapy. The use of psychostimulants such as methylphenidate and ginseng is currently being investigated. Of note, it is confirmed by several animal studies that olaparib is embryo-toxic and teratogenic and, thus, should be avoided during pregnancy. In addition, fertile women should avoid pregnancy during treatment and at least 6 months after olaparib stops and thus be counseled about birth control. Breastfeeding is also contraindicated during treatment and until 2–4 weeks after the last dose of olapari. Analyzing the tolerability of olaparib as maintenance therapy in advanced OC, we found a median duration of treatment ranging from 5.6 to 22.6 months, while if considering the PBO arms, from 5.6 to 19.8 months. Almost every patient experienced any grade AEs, ranging from 95.6% to 99% of patients receiving olaparib and from 90.6% to 96% of patients in the PBO arms. Focusing on the olaparib arms, nausea was the most commonly reported all-grade AEs, ranging from 60% to 75.9%, followed by fatigue/asthenia (48.5%–64%), vomiting (22%–44%), diarrhea (14.3%–35%) while, among the haematologic toxicity, anemia was by far the most commonly reported, ranging from 16.9% to 43.6%. However, if considering only ≥ G3 AEs, reported by 29%–57% of patients treated with olaparib *versus* 19%–51% of patients receiving PBO, hematological toxicities were the most frequent, with ≥G3 anemia as the most common by far, ranging from 5.1% to 22%. Neutropenia ranged from 0% to 9%, and thrombocytopenia from 1% to 2.2%. ≥G3 fatigue ranged from 3.2% to 7.3%, and abdominal pain from 0% to 8%, while nausea, vomiting, and diarrhea were experienced only by less than 5% of patients. Anaemia was the most frequent AE that led to treatment discontinuation, which occurred in 2.2%–25% of patients receiving olaparib *versus* 0.7%–6% of the PBO group. AEs

were managed with dose interruptions (27.9%–60% *versus* 8.6%–26%) or reductions (22%–41% *versus* 3%–7%) rather than discontinuation.

Considering the safety data from olaparib studies, we found that, in Study 42, the median treatment duration was 168 days 43% of dose interruptions were reported, 22% of dose reductions and 5% of patients discontinued treatment. 98% of patients experienced AEs of any grade, while 55% experienced ≥ G3 AEs. The most common any-grade AEs were nausea (60%), fatigue (55%), vomiting (44%), anemia (34%), abdominal pain (29%), and diarrhea (30%), while the most common ≥ G3 AEs were anemia (20%), abdominal pain (8%), fatigue (7%) and dyspnea (4%). In Study 19, the median treatment duration was 206.5 days with olaparib and 141 days with PBO. 95.6% and 90.6% of patients developed any-grade AEs in the olaparib and PBO groups, respectively. Among patients in the olaparib group, the most common AEs were nausea (68.4%), fatigue (48.5%), vomiting (31.6%), diarrhea (22.8%), abdominal pain (17.6%), anemia (16.9%). ≥G3 AEs occurred in 35.3% of patients treated with olaparib *versus* 20.3% of patients receiving PBO, most commonly fatigue (6.6%), anemia (5.1%), nausea/vomiting/diarrhea (each 2.2%), and abdominal pain (1.5%). In the olaparib group, 27.9% and 22.8% of patients experienced dose interruption or reductions (vs 8.6% and 4.7% of the PBO group). Three patients in the olaparib group permanently discontinued treatment *versus* one treatment interruption with PBO. No deaths were recorded. In the SOLO2/ENGOT-Ov21 trial, the median treatment duration was 19.4 months with olaparib and 5.6 months with PBO. 98.5% of patients in the olaparib group and 94.9% in the PBO group experienced any grades AEs, with 36.9% and 18.2% experiencing ≥ G3 AEs, respectively. The most common all-grade toxicities were nausea (75.9% vs 33.3%), fatigue/asthenia (65.6% vs 39.4%), anemia (43.6% vs 8.1%), vomiting (37.4% vs 19.2%), and diarrhea (32.8% vs 20.2%). However, anemia was the most common ≥ G3 AE (19.5% vs 2.0%), while the incidences of ≥G3 neutropenia (5.1% vs 4.0%) and thrombocytopenia (both 1.0%) were not significantly increased in the olaparib subgroup. SOLO2 had a higher incidence of anemia than Study 19, which could be explained by more prolonged exposure to olaparib for patients in this study. Of note, one patient (0.5%) of the olaparib group experienced AML, resulting in death. The long-term incidence of AML, MDS, and chronic myelomonocytic leukemia (CMML) was 2.1% with olaparib and 4.0% with PBO. 45.1% and 18.2% of patients in the olaparib and PBO groups required dose interruptions, while 25.1% and 3.0% required dose reductions due to AEs, respectively. 10.8% of patients in the olaparib and 2.0% in the PBO group discontinued treatment because of toxicity, mainly anemia (3.1%) and neutropenia (1.0%).

All grades and ≥G3 AEs were reported in 95.7% and 29.0% of patients in the OPINION trial, respectively. Nausea (48.4%), fatigue/asthenia (44.1%), anemia (39.1%), and diarrhea (14.3%) were the most common AEs of all grades, while anemia (13.6%) and fatigue/asthenia (3.2%) were the most common ≥ G3 AEs. Dose interruption, dose reduction, and treatment discontinuation were applied to 47.0%, 22.6%, and 7.5% of patients. The median treatment duration was 9.4 months. Anaemia (1.8%), decreased platelet count, depression, fatigue/asthenia, and thrombocytopenia (0.7% each) were the most common AEs leading to treatment discontinuation. MDS and SPMs (mainly rectal and breast cancer) were reported in 0.7% of patients each. 98% of olaparib and 92% of PBO patients of the SOLO1 trial experienced AEs of any grade, among which ≥ G3 AEs were reported in 40% and 19% of patients. Nausea (78% and 38%), fatigue/asthenia (64% and 42%), vomiting (40% and 15%), anemia (40% and 10%), and diarrhea (35%) were the most common all-grade AEs. The most frequent ≥ G3 AE was anemia, which occurred in 22% of olaparib and 2% of PBO patients. Dose interruptions occurred in 52% of olaparib vs 17% of PBO patients, while dose reductions occurred in 29% vs 3%. Discontinuations were less frequent with olaparib (12%) than with PBO (3%). One (1%) fatal AML occurred over 30 days after olaparib discontinuation. Of note, 2% of olaparib patients developed SPMs (breast, oral cavity, and thyroid), and 2% of PBO patients developed SPMs (breast cancer). Finally, in the PAOLA-1 trial, the median duration of treatment was 16.6 months for olaparib plus bevacizumab and 13.4 months for PBO in the HiR group, while for the LoR group, 22.6 vs19.8 months 99% and 96% of patients experienced AEs, with olaparib plus bevacizumab and PBO plus bevacizumab, respectively. 57% of patients experienced severe AEs with olaparib plus bevacizumab vs 51% in the PBO/bevacizumab arm, showing no significant safety differences among all subgroups. Fatigue or asthenia (53% vs 22%), nausea (53% vs 22%), hypertension (46% vs 60%), and anemia (41% vs 10%) were the most frequent all-grade AEs. Hypertension (19% vs 30%) and anemia (17% vs 1%) were the most frequently reported ≥ G3 AEs. Dose interruptions occurred in 53% vs 26% of HiR patients and 60% vs 21% of LoR patients, while discontinuation in 19% vs 6% in the HiR and 25% vs 5% in the LoR subgroups. One patient (0.3%) receiving olaparib/bevacizumab and 2 (1%) receiving PBO/bevacizumab experienced fatal AEs. A total of 6 patients (1%) in the olaparib/bevacizumab and 1 (<1%) in the PBO/bevacizumab group developed AML or MDS, while 7 patients (1%) and 3 (<1%) developed SPMs.

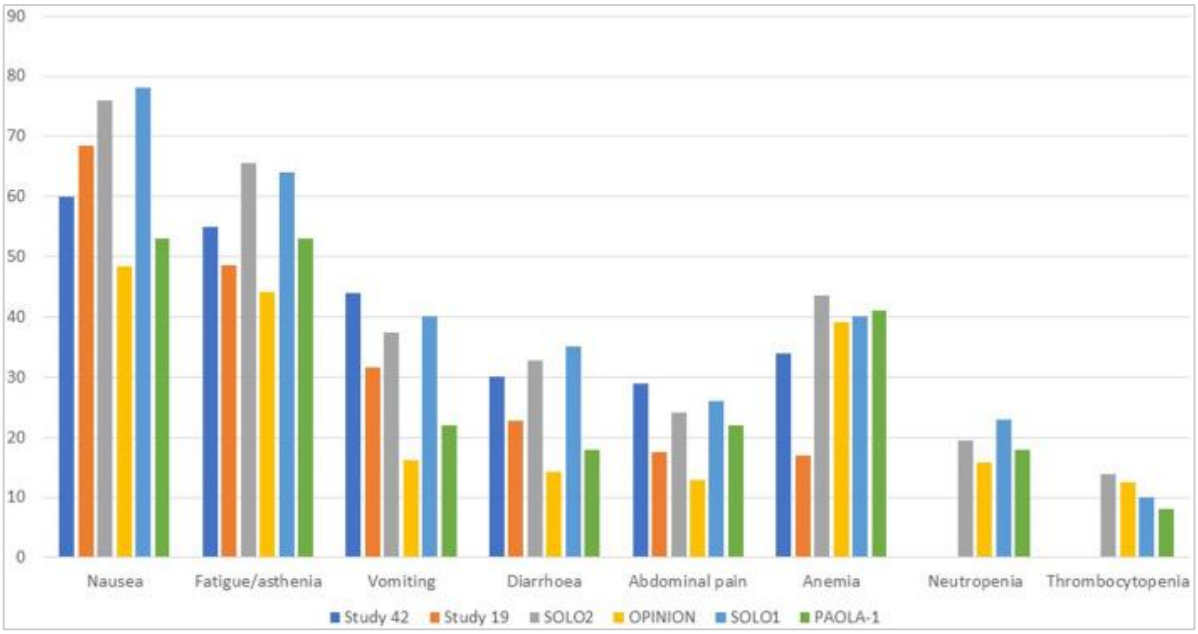

FIGURE 1. Most frequent all-grades adverse events during olaparib therapy.

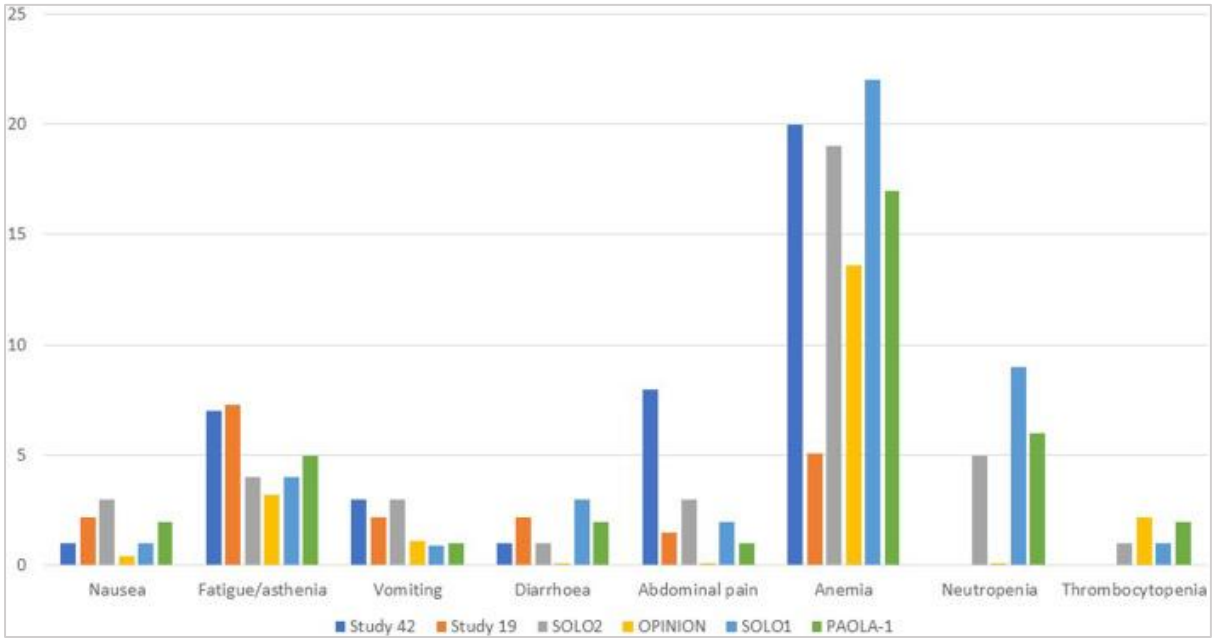

FIGURE 2. Most frequent ≥G3 adverse events during olaparib therapy.

TABLE 3. Adverse events of Olaparib in clinical trials according to CTCAE.

	Study 42		Study 19		SOLO2		OPINION		SOLO1		PAOLA-1	
AEs	**All grades (%)**	**≥G3 (%)**	**All grades (%)**	**≥G3 (%)**	**All grades (%)**	**≥G3 (%)**	**All grades (%)**	**≥G3 (%)**	**All grades (%)**	**≥G3 (%)**	**All grades (%)**	**≥G3 (%)**
Nausea	60	1	68.4	2.2	75.9	3	48.4	0.4	78	1	53	2
Fatigue	55	7	48.5	6.6	65.6	4	44.1	3.2	64	4	53	5
Vomiting	44	3	31.6	2.2	37.4	3	16.1	1.1	40	<1	22	1
Diarrhoea	30	1	22.8	2.2	32.8	1	14.3	14.3	35	3	18	2
Abdominal pain	29	8	17.6	1.5	23	3	12.9	12.9	25	2	19	1
Anemia	34	20	16.9	5.1	43.6	19	39.1	13.6	40	22	41	17
Neutropenia	NA	NA	NA	NA	19	5	15.8	1.8	11	9	18	6
TCP	NA	NA	NA	NA	14	1	12.5	2.2	11	1	8	2

AE(s), adverse event(s); G3, grade 3; NA, not available; TCP, thrombocytopenia.

Future perspectives[1]

PARPis have transformed the therapeutic landscape of advanced OC in the last decade, and olaparib was a pioneer drug in this field. We provided an overview of the clinical and pre-clinical characteristics of olaparib, synthesizing the results of trials that led to its approval in different settings and analyzing its safety profile. Olaparib resulted in effective maintenance therapy in the recurrent and newly diagnosed advanced OC setting in all patients' subgroups, regardless of BRCA status, with a generally good safety profile and quality of life. Some queries, however, remain unanswered and are currently being investigated by new ongoing trials, mainly the combination with different agents, and the use of olaparib in the platinum-resistant setting.

Combination studies are trying to meet the need for new therapeutic approaches, increasing the potential for new or augmented adverse events. An exciting strategy, currently under

investigation, is to combine PARPis with immune checkpoint inhibitors (ICIs), with a strong rationale behind this combination. In fact, PARPis upregulate Programmed death-ligand 1 (PD-L1) expression; they interact with the tumor microenvironment, being able to switch it towards an immune-responsive state and increase tumor-infiltrating lymphocytes. Moreover, through DNA damage, PARPis stimulate neo-antigen production, therefore augmenting the tumor mutational burden. PARPis also switch on the STING pathway that, on its hand, reinforces interferon-γ dependent immune cells. The combination of olaparib and the anti-PD-L1 durvalumab was tested in two ongoing phase II trials, reporting strong response rates. In the context of PS-ROC BRCAm OC, the MEDIOLA study reported an ORR of 71.9%, mOS NR, and mPFS of 11.1 months. Subsequently, the study randomized 63 BRCAwt patients to durvalumab plus olaparib with or without bevacizumab. The doublet cohort reached an ORR of 31.3%, and the triplet cohort of 77.4. A final mOS analysis presented at ESMO2022 showed an mOS of 23.3 months vs 31.9 months in the doublet and triplet cohorts, respectively. The same combination was administered in the phase II trial, with an ORR of 14% and an mPFS of 3.0 months. The phase Ib/II trial investigated the combination of olaparib with the anti-Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) tremelimumab. Only 3 patients were treated, all of them achieving a PR.

TABLE 4. Results of studies employing olaparib and ICIs.

Phase	**Target population (*number of patients*)**	**Combination**	**Results**
II	ROC (*n* = 35: 30 PR-ROC +5 PS-ROC)	Olaparib plus durvalumab (anti-PD-L1)	ORR 14% mPFS 3.0 months
	BRCAwt (*n* = 27) gBRCAmut (*n* = 6)		
	sBRCAmut (*n* = 2)		
II	PS-ROC gBRCAmut (*n* = 32)	Olaparib plus durvalumab	ORR 71.9% mPFS 11.1 mos
			mOS NR
	PS-ROC BRCAwt	Olaparib plus durvalumab	ORR 31.3% mPFS 5.5 months
			mOS 23.3 months

	PS-ROC BRCAwt	Olaparib plus bevacizumab plus durvalumab	ORR 77.4% mPFS 14.7 months
			mOS 31.9 months
Ib/II	gBRCAmut ROC (*n* = 3)	Olaparib plus tremelimumab (anti-CTLA4)	ORR 100%

BRCA, breast cancer associated gene; BRCAwt, BRCA, wild-type; CTLA4, cytotoxic T.lymphocyte-associated protein 4; gBRCAmut, germline mutated BRCA; mos, months; NR, not reached; ORR, overall response rate; PD-L1, programmed death-ligand 1; PFS, progression free survival; PR/PS-ROC, platinum-resistant/platinum-sensitive recurrent ovarian cancer; ROC, recurrent ovarian cancer; sBRCAmut, somatic mutated BRCA.

The rationale behind the combination of PARPis and anti-angiogenic drugs stands on two main mechanisms: PARP inhibition decreases angiogenesis; hypoxia and Vascular endothelial growth factor receptor 3 (VEGFR3) inhibition also induce the downregulation of HR proteins. PAOLA-1 already showed the efficacy and safety of the combination of olaparib and bevacizumab. A phase II trial combining cediranib with olaparib *versus* olaparib alone in PS-ROC showed a significantly better mPFS in the combination group (17.7 vs 9.0 months). NRG-GY004, a phase III randomized clinical trial, compared the efficacy of olaparib, with or without cediranib, *versus* platinum-based CHT in PS-ROC. However, in this study, olaparib/cediranib did not improve PFS *versus* chemotherapy regardless of BRCA status, but increased AEs.

OC with a "BRCAness" phenotype exhibits a higher sensitivity to both platinum and PARPis, than OC without a "BRCAness" phenotype. Hence, platinum sensitivity might represent a potential biomarker for olaparib sensitivity. In fact, the clinical benefit rate of olaparib fell from 69.2% in platinum-sensitive to 45.8% in platinum-resistant and 23.1% in platinum-refractory BRCA1/2-mutated OC. In BRCA1/2 wild-type OC, half of the platinum-sensitive patients responded to olaparib *versus* only 4% of the platinum-resistant women. However, a response to platinum does not always guarantee a response to olaparib. Indeed, differently from PARPis, platinum sensitivity results from defective nucleotide excision repair (NER). The platinum-induced DNA cross-links are highly deleterious and more cytotoxic than the SSBs caused by PARPis. In addition, the partial restoration of HR is insufficient to repair the cross-links caused by platinum salts. Therefore, such OCs retain platinum sensitivity but exhibit PARPis resistance. It has also been evidenced that an increased platinum-to-platinum interval during olaparib treatment is associated with a response to subsequent platinum treatment. As for the

platinum-resistant recurrent OC (PR-ROC) setting, patients relapsing within 12 months of platinum-based CHT usually have a poorer response to subsequent treatments. Several trials involving PR-ROC patients have not yet resulted in improved responses or benefits in terms of survival, thus justifying further experimental work and clinical trials with novel agents. The phase II BAROCCO trial compared weekly paclitaxel with the olaparib-cediranib combination in PR-ROC, not significantly impacting PFS). Clinical activity of the olaparib-cediranib combination was shown by the phase IIb CONCERTO trial, with 60 BRCAwt PR-ROC reaching an ORR of 15.3%, an mPFS of 5.1 months, and a mOS of 13.2 months. The same combination is also being investigated in the phase II OCTOVA trial . The GEICO1601-ROLANDO phase II trial will assess the efficacy of olaparib with pegylated liposomal doxorubicin (PLD) in PR-ROC, regardless of BRCA status, while the randomized phase II CLIO/BGOG-ov10 trial compared olaparib monotherapy vs physicians' CHT of choice (PLD, Topotecan, Paclitaxel or Gemcitabine) in 100 PR-ROC patients. Olaparib monotherapy showed higher efficacy than CHT in the PR-ROC setting, with an ORR of 17.9% vs 6.1% for olaparib *versus* CHT. Even in heavily pretreated PR-ROC, ORR was 22.9% for olaparib *versus* 0% for CHT. mPFS in PR-ROC was not significantly improved.

PARP1 has currently been identified as a more significant driver of synthetic lethality than PARP2. Therefore, a new generation of highly-selective PARP1-inhibitors is under development. AZD5305 is a first-in-class PARP1-inhibitor and trapper. Preliminary results of the phase I/IIa PETRA study in patients with BRCA1/2, PALB2, RAD51C/D mutations have been recently presented. Around half of 61 patients with OC (n = 19) had PR or SD to AZD5305. The drug's safety profile is of particular interest, as no discontinuations occurred. The most common AEs were nausea (34%), anemia (21.3%), neutropenia, and TCP (18%). 14.8% of patients experienced ≥ G3 AEs. This is in line with mouse models, in which the PARP1 selectivity was associated with a more manageable safety profile than common PARPis.

ABTRACTS

Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial[2]

Abstract

Background: Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, has previously shown efficacy in a phase 2 study when given in capsule formulation to all-comer patients with platinum-sensitive, relapsed high-grade serous ovarian cancer. We aimed to confirm these findings in patients with a BRCA1 or BRCA2 (BRCA1/2) mutation using a tablet formulation of olaparib.

Methods: This international, multicentre, double-blind, randomised, placebo-controlled, phase 3 trial evaluated olaparib tablet maintenance treatment in platinum-sensitive, relapsed ovarian cancer patients with a BRCA1/2 mutation who had received at least two lines of previous chemotherapy. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group performance status at baseline of 0-1 and histologically confirmed, relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer, including primary peritoneal or fallopian tube cancer. Patients were randomly assigned 2:1 to olaparib (300 mg in two 150 mg tablets, twice daily) or matching placebo tablets using an interactive voice and web response system. Randomisation was stratified by response to previous platinum chemotherapy (complete vs partial) and length of platinum-free interval (6-12 months vs ≥12 months) and treatment assignment was masked for patients, those giving the interventions, data collectors, and data analysers. The primary endpoint was investigator-assessed progression-free survival and we report the primary analysis from this ongoing study. The efficacy analyses were done on the intention-to-treat population; safety analyses included patients who received at least one dose of study treatment. This trial is registered with ClinicalTrials.gov, number , and is ongoing and no longer recruiting patients.

Findings: Between Sept 3, 2013, and Nov 21, 2014, we enrolled 295 eligible patients who were randomly assigned to receive olaparib (n=196) or placebo (n=99). One patient in the olaparib group was randomised in error and did not receive study treatment. Investigator-assessed median progression-free survival was significantly longer with olaparib (19·1 months [95% CI 16·3-25·7]) than with placebo (5·5 months [5·2-5·8]; hazard ratio [HR] 0·30 [95% CI 0·22-0·41], p<0·0001). The most common adverse events of grade 3 or worse severity were

anaemia (38 [19%] of 195 patients in the olaparib group vs two [2%] of 99 patients in the placebo group), fatigue or asthenia (eight [4%] vs two [2%]), and neutropenia (ten [5%] vs four [4%]). Serious adverse events were experienced by 35 (18%) patients in the olaparib group and eight (8%) patients in the placebo group. The most common in the olaparib group were anaemia (seven [4%] patients), abdominal pain (three [2%] patients), and intestinal obstruction (three [2%] patients). The most common in the placebo group were constipation (two [2%] patients) and intestinal obstruction (two [2%] patients). One (1%) patient in the olaparib group had a treatment-related adverse event (acute myeloid leukaemia) with an outcome of death.

Interpretation: Olaparib tablet maintenance treatment provided a significant progression-free survival improvement with no detrimental effect on quality of life in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation. Apart from anaemia, toxicities with olaparib were low grade and manageabl

Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial[3]

Abstract

Background: There is a high unmet need for treatment regimens that increase the chance of long-term remission and possibly cure for women with newly diagnosed advanced ovarian cancer. In the primary analysis of SOLO1/GOG 3004, the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib significantly improved progression-free survival versus placebo in patients with a BRCA mutation; median progression-free survival was not reached. Here, we report an updated, post-hoc analysis of progression-free survival from SOLO1, after 5 years of follow-up.

Methods: SOLO1 was a randomised, double-blind, placebo-controlled, phase 3 trial, done across 118 centres in 15 countries, that enrolled patients aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0-1 and with BRCA-mutated, newly diagnosed, advanced, high-grade serous or endometrioid ovarian cancer with a complete or partial clinical response after platinum-based chemotherapy. Patients were randomly assigned (2:1) via a web-based or interactive voice-response system to receive olaparib (300 mg twice

daily) or placebo tablets orally as maintenance monotherapy for up to 2 years; randomisation was by blocks and was stratified according to clinical response after platinum-based chemotherapy. Patients, treatment providers, and data assessors were masked to group assignment. The primary endpoint was investigator-assessed progression-free survival. Efficacy is reported in the intention-to-treat population and safety in patients who received at least one dose of treatment. The data cutoff for this updated, post-hoc analysis was March 5, 2020.

Findings: Between Sept 3, 2013, and March 6, 2015, 260 patients were randomly assigned to olaparib and 131 to placebo. The median treatment duration was 24·6 months (IQR 11·2-24·9) in the olaparib group and 13·9 months (8·0-24·8) in the placebo group; median follow-up was 4·8 years (2·8-5·3) in the olaparib group and 5·0 years (2·6-5·3) in the placebo group. In this post-hoc analysis, median progression-free survival was 56·0 months (95% CI 41·9-not reached) with olaparib versus 13·8 months (11·1-18·2) with placebo (hazard ratio 0·33 [95% CI 0·25-0·43]). The most common grade 3-4 adverse events were anaemia (57 [22%] of 260 patients receiving olaparib vs two [2%] of 130 receiving placebo) and neutropenia (22 [8%] vs six [5%]), and serious adverse events occurred in 55 (21%) of 260 patients in the olaparib group and 17 (13%) of 130 in the placebo group. No treatment-related adverse events that occurred during study treatment or up to 30 days after discontinuation were reported as leading to death. No additional cases of myelodysplastic syndrome or acute myeloid leukaemia were reported since the primary data cutoff, including after the 30-day safety follow-up period.

Interpretation: For patients with newly diagnosed advanced ovarian cancer and a BRCA mutation, after, to our knowledge, the longest follow-up for any randomised controlled trial of a PARP inhibitor in this setting, the benefit derived from 2 years' maintenance therapy with olaparib was sustained beyond the end of treatment, extending median progression-free survival past 4·5 years. These results support the use of maintenance olaparib as a standard of care in this setting.

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer[4]

Abstract

Background: Most women with newly diagnosed advanced ovarian cancer have a relapse within 3 years after standard treatment with surgery and platinum-based chemotherapy. The benefit of the oral poly(adenosine diphosphate-ribose) polymerase inhibitor olaparib in relapsed disease has been well established, but the benefit of olaparib as maintenance therapy in newly diagnosed disease is uncertain.

Methods: We conducted an international, randomized, double-blind, phase 3 trial to evaluate the efficacy of olaparib as maintenance therapy in patients with newly diagnosed advanced (International Federation of Gynecology and Obstetrics stage III or IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (or a combination thereof) with a mutation in BRCA1, BRCA2, or both (BRCA1/2) who had a complete or partial clinical response after platinum-based chemotherapy. The patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or placebo. The primary end point was progression-free survival.

Results: Of the 391 patients who underwent randomization, 260 were assigned to receive olaparib and 131 to receive placebo. A total of 388 patients had a centrally confirmed germline BRCA1/2 mutation, and 2 patients had a centrally confirmed somatic BRCA1/2 mutation. After a median follow-up of 41 months, the risk of disease progression or death was 70% lower with olaparib than with placebo (Kaplan-Meier estimate of the rate of freedom from disease progression and from death at 3 years, 60% vs. 27%; hazard ratio for disease progression or death, 0.30; 95% confidence interval, 0.23 to 0.41; $P<0.001$). Adverse events were consistent with the known toxic effects of olaparib.

Conclusions: The use of maintenance therapy with olaparib provided a substantial benefit with regard to progression-free survival among women with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation, with a 70% lower risk of disease progression or death with olaparib than with placebo.

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Survey Form

1. In your clinical practice, What % of ovarian cancer patients can afford diagnostic genetic testing?

a. 0-20%

b. 20-40%

c. 40 – 60%

d. More than 60%

2. In your clinical practice, when will you do diagnostic testing?

a. Post cytoreduction before starting 1st line

b. Post platinum treatment

c. Pre cytoreduction in biopsy

3. In your clinical practice, which diagnostic test do you first perform in your advanced ovarian cancer patients?

a. HRD only

b. g BRCA followed by s BRCA

c. s BRCA followed by g BRCA

d. s BRCA only

4. in your clinical practice, what % of ovarian cancer patients are BRCA positive?

a. 0-20%

b. 20-40%

c. 40 – 50%

d. More than 50%

5. in your clinical practice , what % of ovarian cancer patients are HRD positive?

a. 0-20%

b. 20-40%

c. 40 – 50%

d. More than 50%

e. No I don’t do HRD testing often

6. In case patients has not undergone diagnostic testing during first line, you would do before treatment with 2nd line?

a. Yes

b. No

7. Before 2nd line (if patient untested previously), which testing would you now prefer if patient responded well to platinum ?

a. HRD

b. g BRCA only

c. s BRCA followed by g BRCA

d. s BRCA only

8. What percentage of your patients who are platinum sensitive respond to maintainance first line PARPi?

a. 90-100%

b. 75-90%

c. 50-75%

d Less than 75%

9. In your clinical practice, in HRD positive ovarian cancer, what would be your treatment choice?

a. Olaparib + bevacizumab as per PAOLA-1 data

b. Rucaparib as per ATHENO-MONO trials

C Only Olaparib as per SOLO-1

10. In your clinical practice, do you consider maintainance bevacizumab post first line chemotherapy? (considerting genetic testing results unknown in first line treatment)

a. Yes

b No

11. In your clinical practice, in g/s BRCA positive ovarian cancer patients, which PARPi would you prefer?

a. Olaparib

b. Rucaparib

c. Olaparib plus bevacizumab

12. Based on results of SOLO-1, you would treat upfront maintainance with olaparib for how long?

a. ≤ 1 yr

b. ≤ 2 yr

c Beyond 2 yr also

13. Based on results of PAOLA-1 trial, would you consider olaparib + bevacizumab to s BRCA ONLY patients?

a. Yes would consider for s BRCA

b. I would consider only for HRD positive not for s BRCA

c. I would consider only for HRD positive and s BRCA both

14. In your clinical practice, what is average PFS for first line maintainance olaparib in real world?

a. 2 yr

b. 3 yr

c. 4 yr

d. 5 yr or more

15. Please rate safety of Olaparib as per your clinical experience?

a. Well tolerated and manageable safety profile

b. No I have concerns

Survey Findings

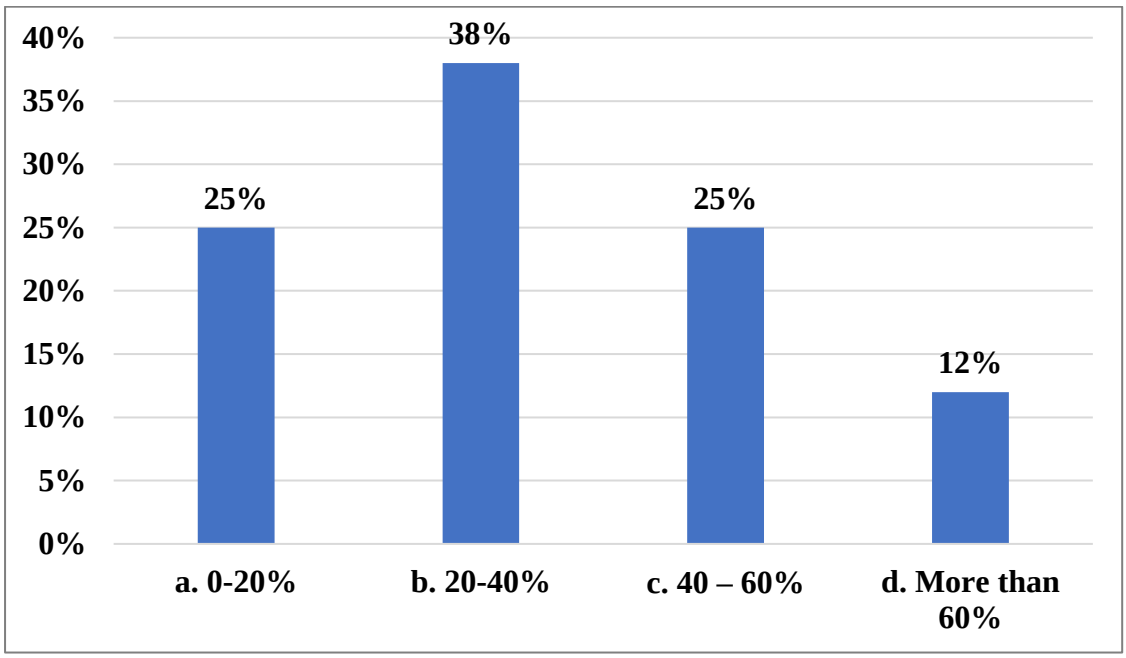
1. In your clinical practice, what % of ovarian cancer patients can afford diagnostic genetic testing?

a. 0-20%

b. 20-40%

c. 40 – 60%

d. More than 60%



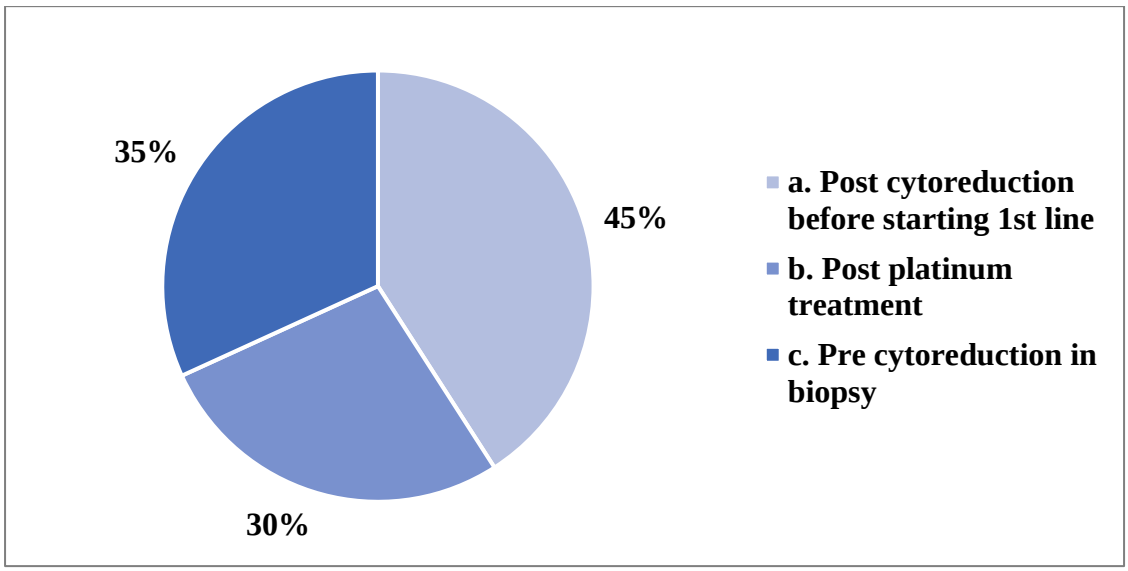
In the clinical practice of 38% of doctors, 20-40% of ovarian cancer patients can afford diagnostic genetic testing.

2. In your clinical practice, when will you do diagnostic testing?

a. Post cytoreduction before starting 1st line

b. Post platinum treatment

c. Pre cytoreduction in biopsy



According to 45% of doctors, they conduct diagnostic testing post cytoreduction before starting 1st line.

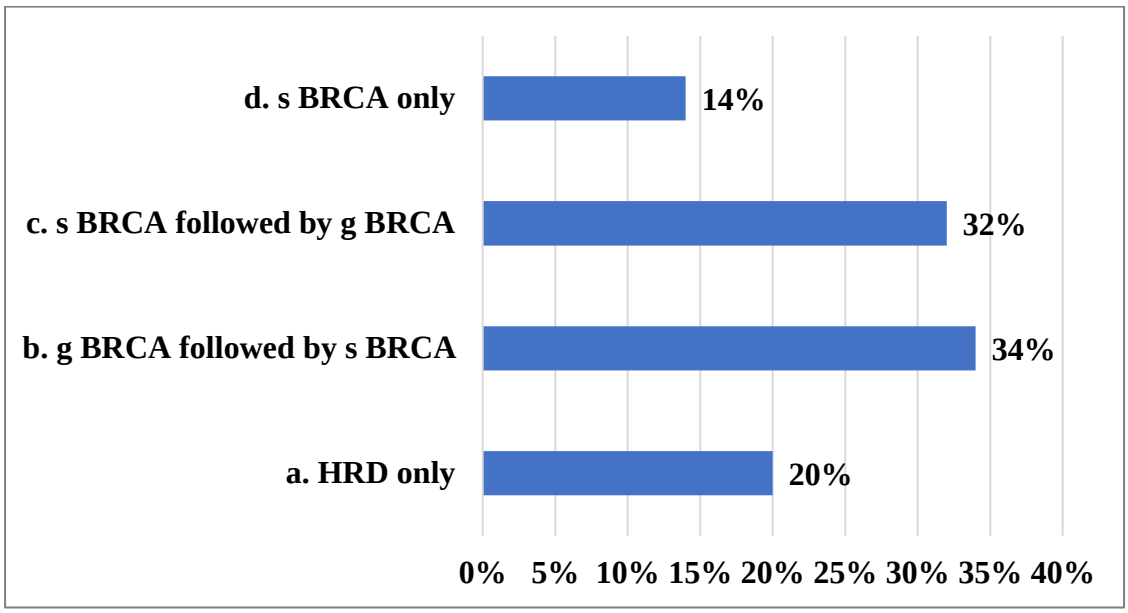
3. In your clinical practice, which diagnostic test do you first perform in your advanced ovarian cancer patients?

a. HRD only

b. g BRCA followed by s BRCA

c. s BRCA followed by g BRCA

d. s BRCA only



As per 34% of doctors, they first perform diagnostic test of g BRCA followed by s BRCA in their advanced ovarian cancer patients.

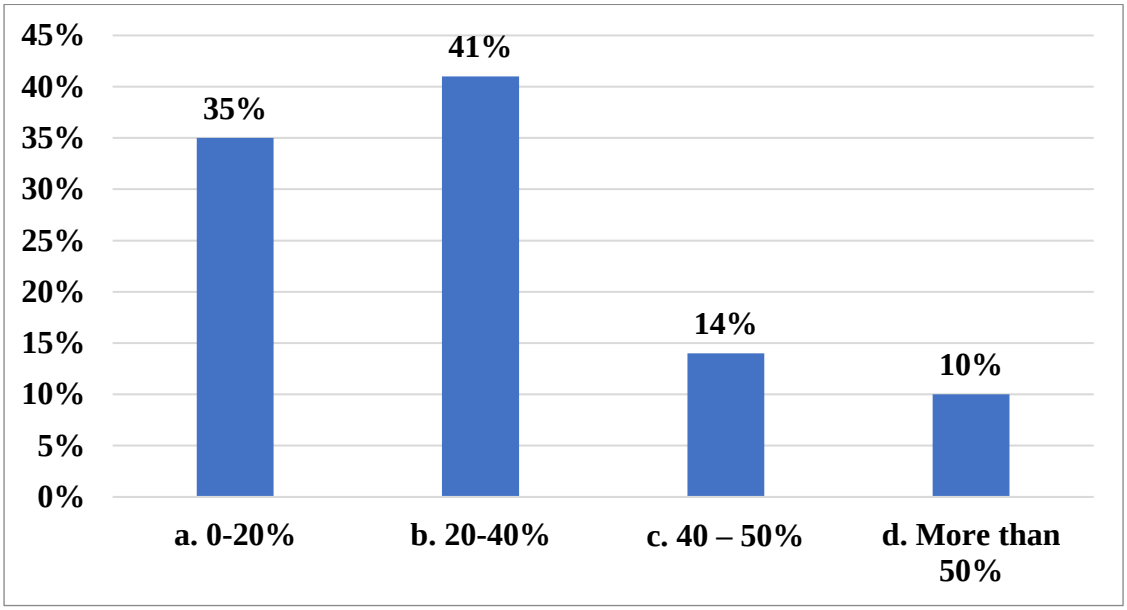
4. in your clinical practice, what % of ovarian cancer patients are BRCA positive?

a. 0-20%

b. 20-40%

c. 40 – 50%

d. More than 50%



According to 41%b of doctors, 20-40% of ovarian cancer patients are BRCA positive.

5. In your clinical practice, what % of ovarian cancer patients are HRD positive?

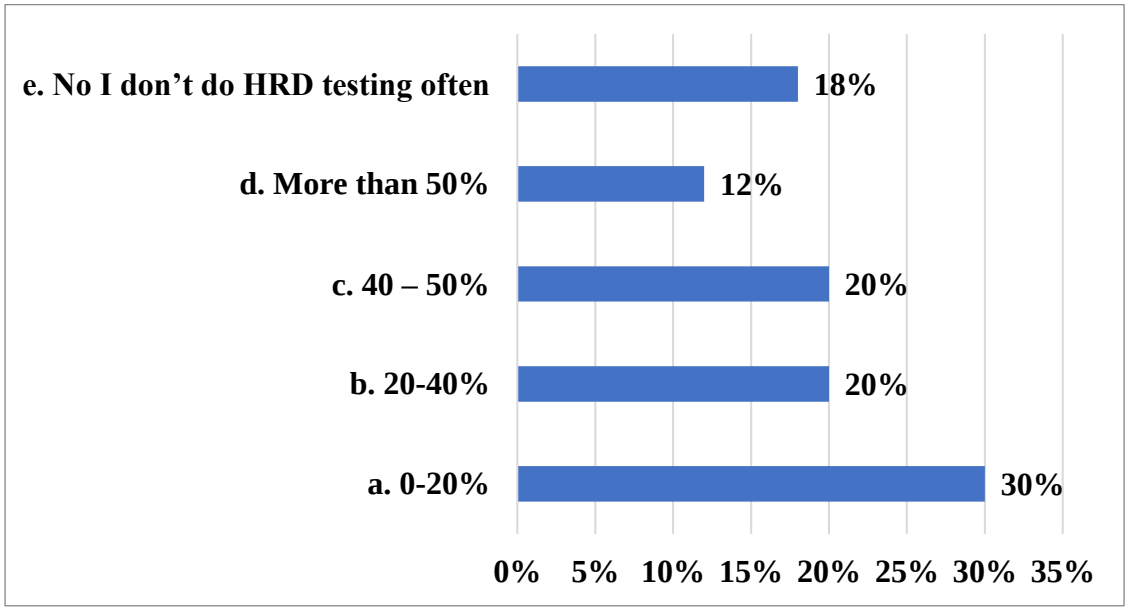
a. 0-20%

b. 20-40%

c. 40 – 50%

d. More than 50%

e. No I don’t do HRD testing often

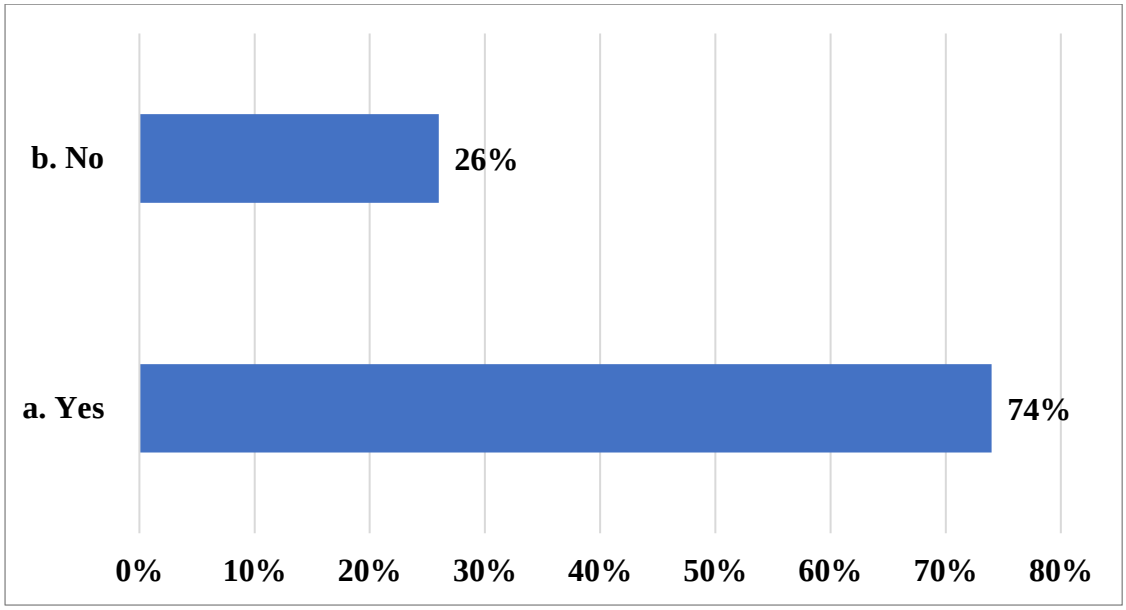


As per 30% of doctors, 0-20% of ovarian cancer patients are HRD positive.

6. In case patients has not undergone diagnostic testing during first line, you would do before treatment with 2nd line?

a. Yes

b. No



Majority of doctors, 74%, perform diagnostic testing with 2nd line in case patients have not undergone it during first line.

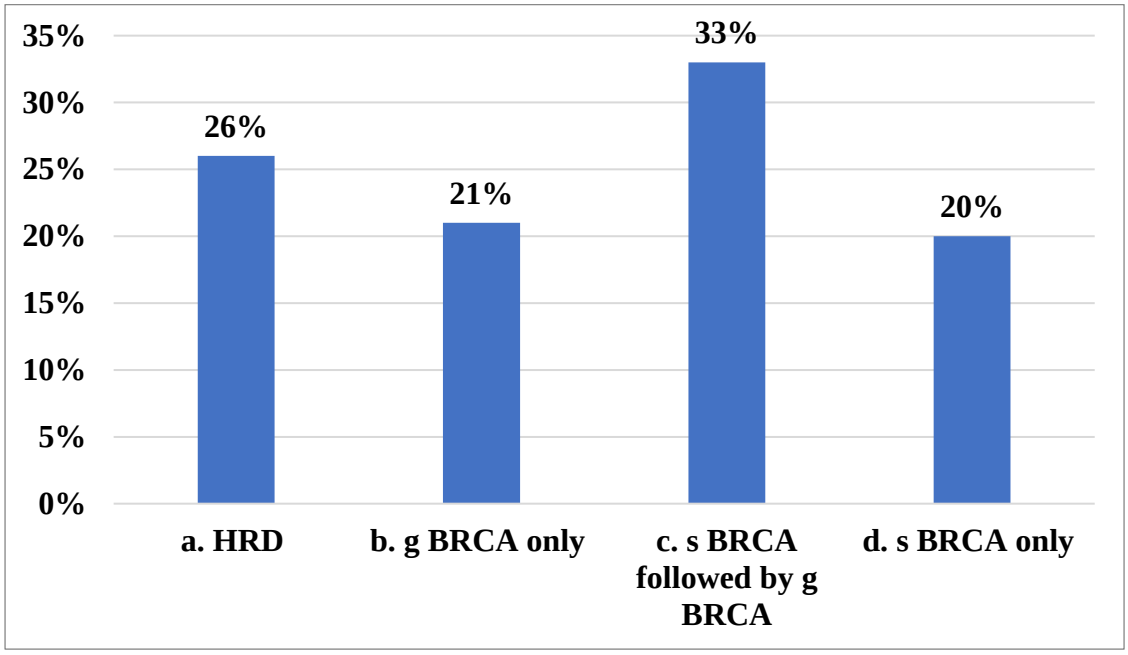
7. Before 2nd line (if patient untested previously), which testing would you now prefer if patient responded well to platinum?

a. HRD

b. g BRCA only

c. s BRCA followed by g BRCA

d. s BRCA only



Before 2nd line (if patient untested previously), 33% of doctors would prefer s BRCA followed by g BRCA if patient responded well to platinum.

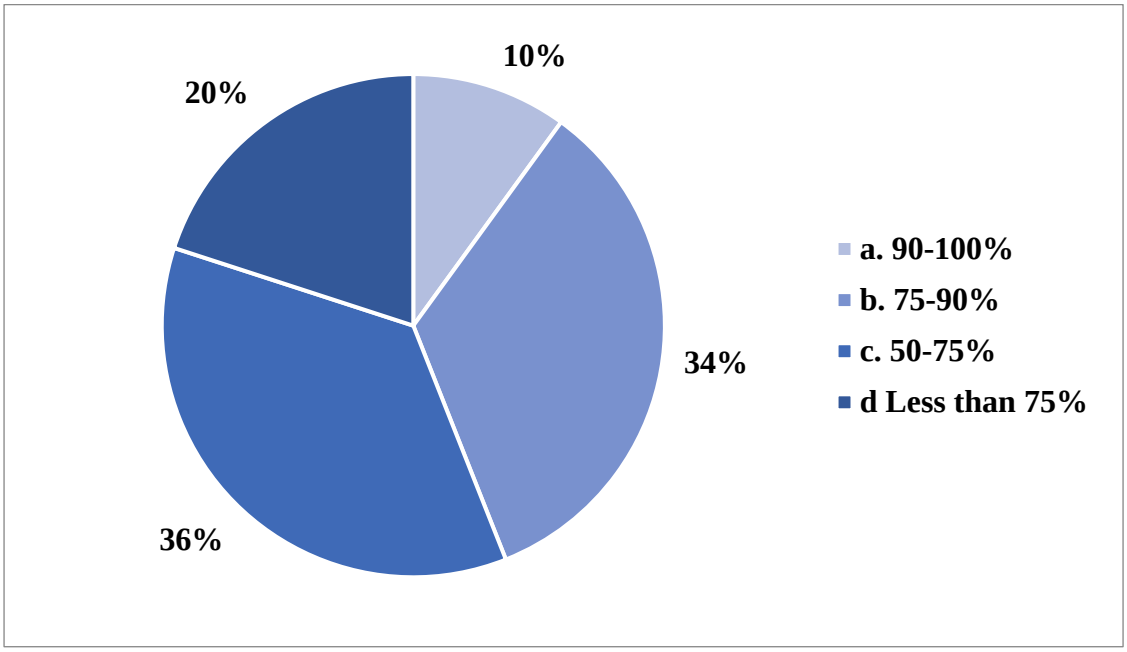
8. What percentage of your patients who are platinum sensitive respond to maintenance first line PARPi?

a. 90-100%

b. 75-90%

c. 50-75%

d Less than 75%



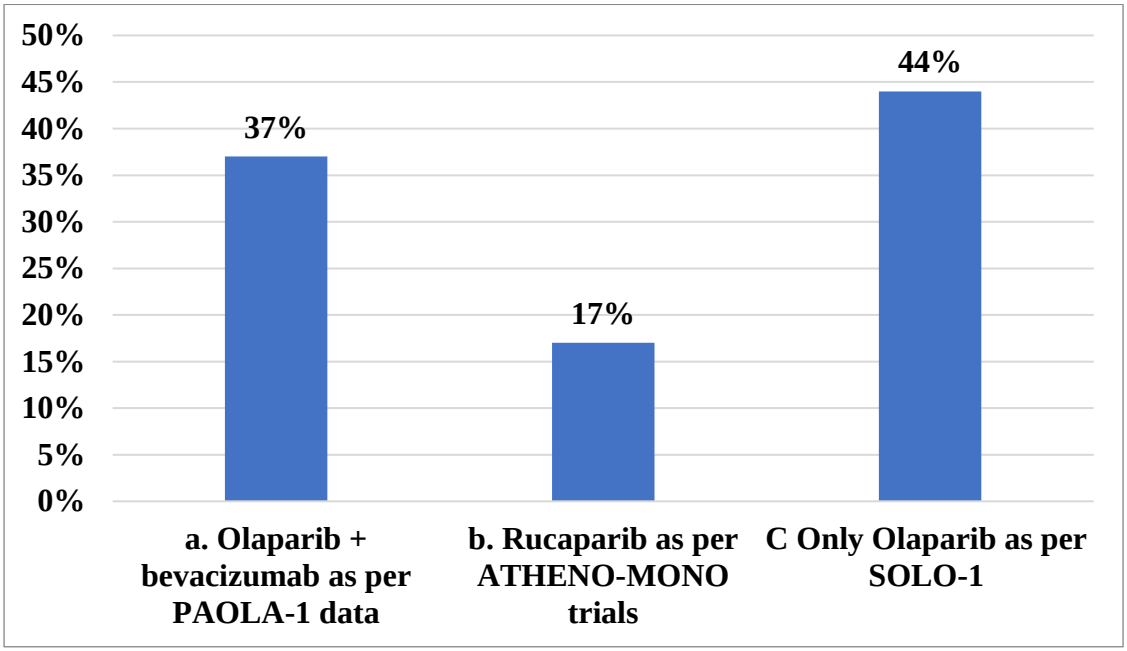
According to 46% of doctors, 50-75% of their patients who are platinum sensitive respond to maintenance first line PARPi.

9. In your clinical practice, in HRD positive ovarian cancer, what would be your treatment choice?

a. Olaparib + bevacizumab as per PAOLA-1 data

b. Rucaparib as per ATHENO-MONO trials

C Only Olaparib as per SOLO-1

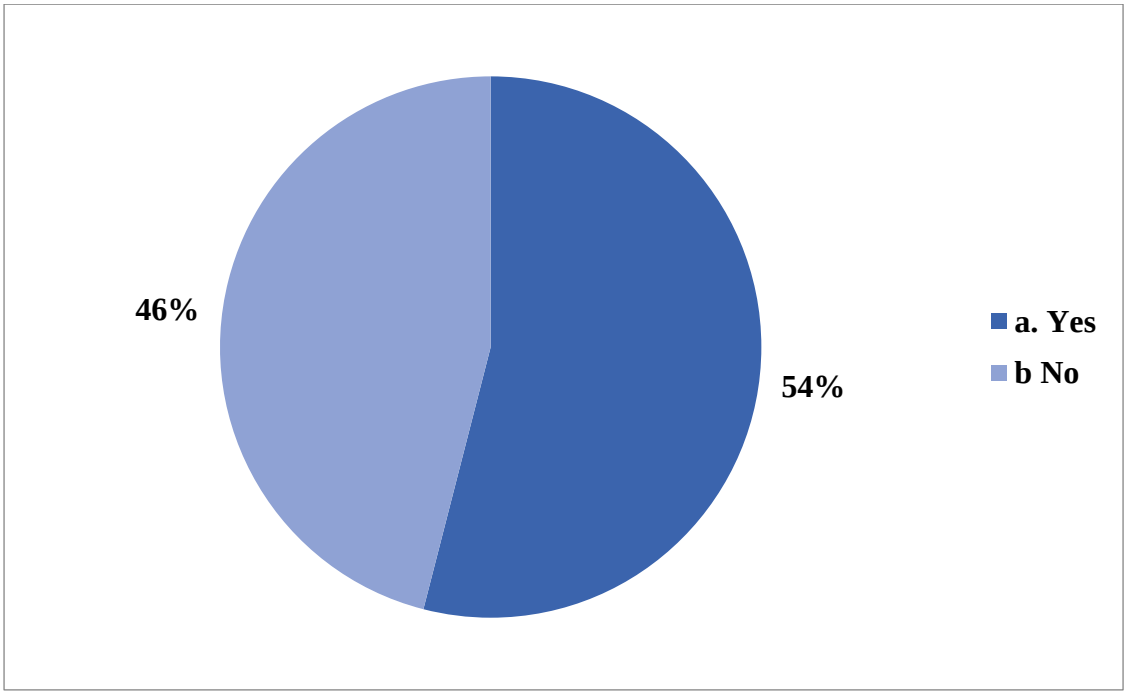


For 44% of doctors, in HRD positive ovarian cancer, their treatment choice would be Only Olaparib as per SOLO-1.

10. In your clinical practice, do you consider maintenance bevacizumab post first line chemotherapy? (considering genetic testing results unknown in first line treatment)

a. Yes

b No



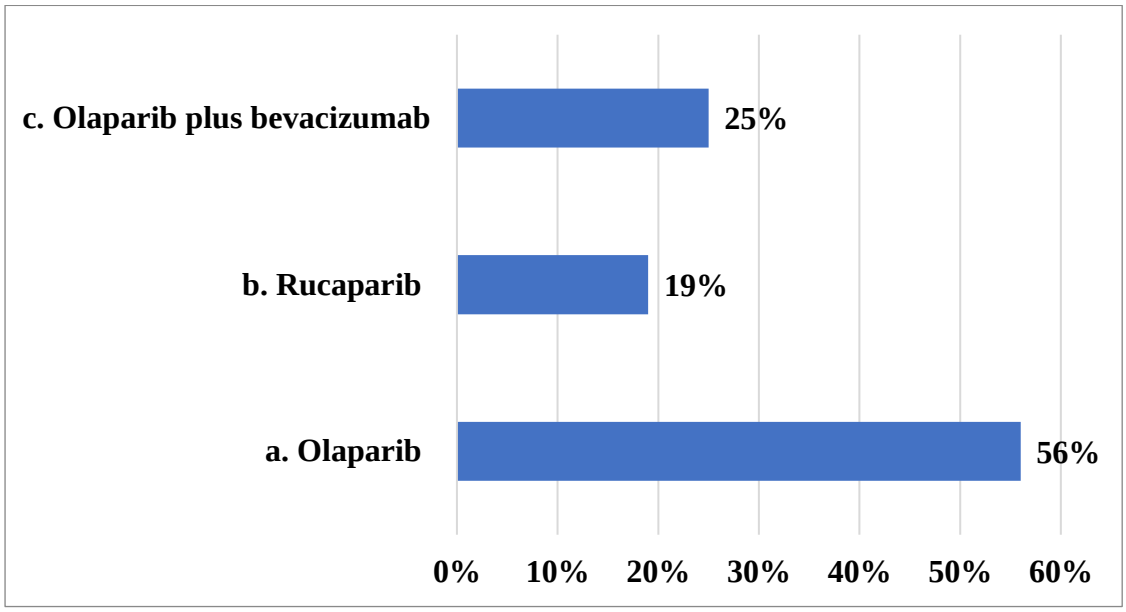
Majority of doctors agree that they consider maintenance bevacizumab post first line chemotherapy (considering genetic testing results unknown in first line treatment).

11. In your clinical practice, in g/s BRCA positive ovarian cancer patients, which PARPi would you prefer?

a. Olaparib

b. Rucaparib

c. Olaparib plus bevacizumab



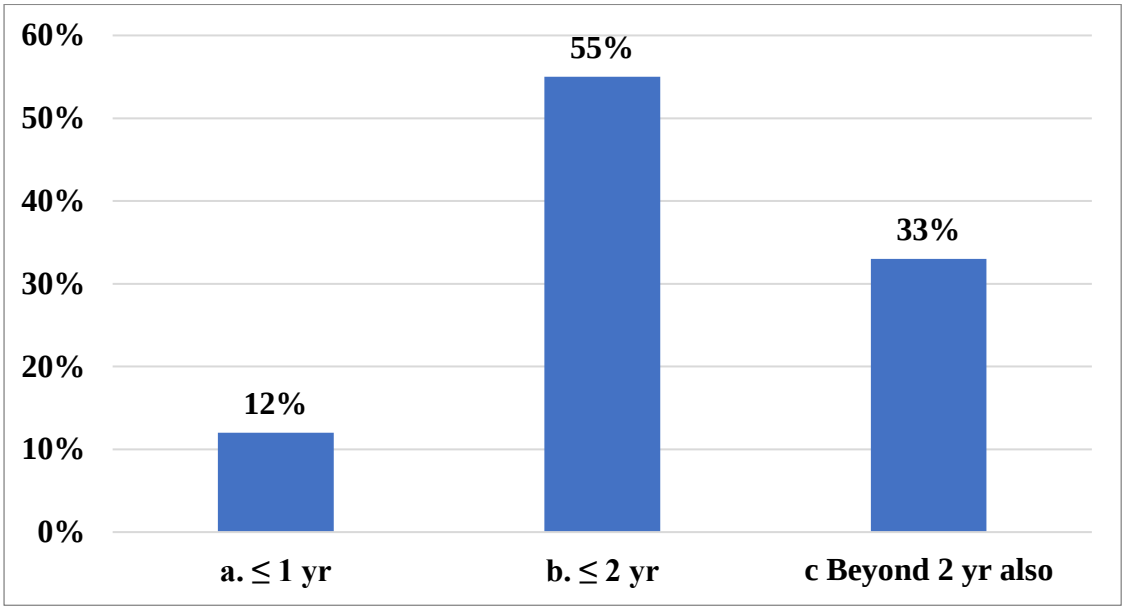
In the clinical practice of 56% of doctors, in g/s BRCA positive ovarian cancer patients, they prefer Olaparib PARPi.

12. Based on results of SOLO-1, you would treat upfront maintainance with olaparib for how long?

a. ≤ 1 yr

b. ≤ 2 yr

c Beyond 2 yr also



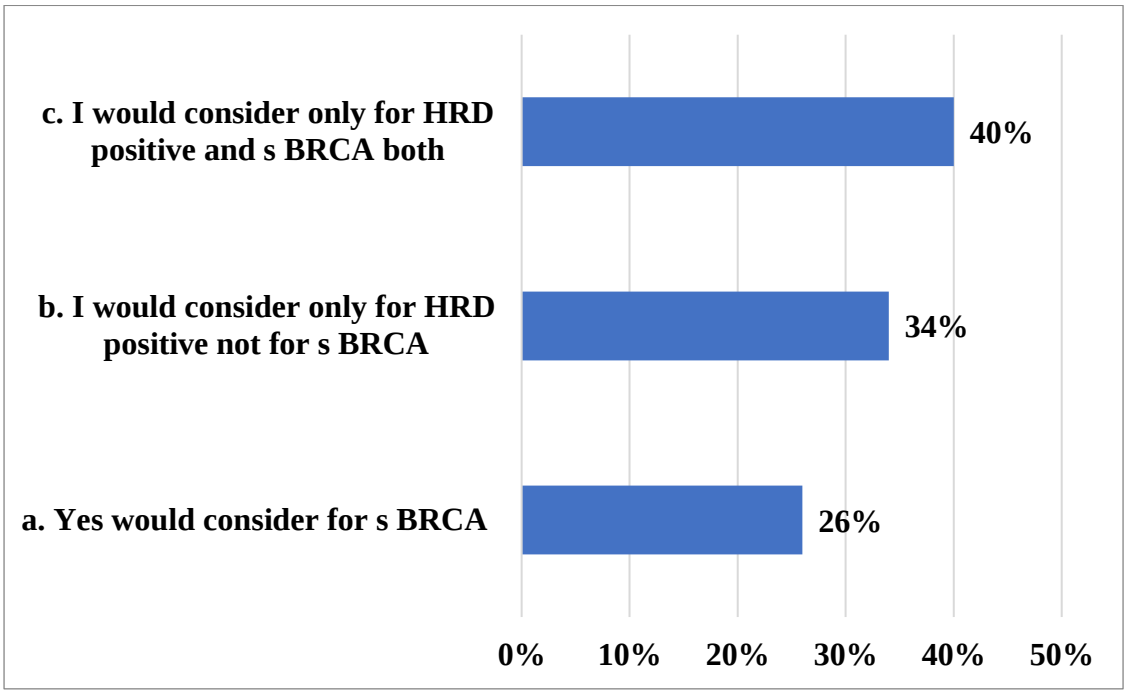
According to 55% of doctors, based on results of SOLO-1, they would treat upfront maintenance with olaparib for ≤ 2 yr.

13. Based on results of PAOLA-1 trial, would you consider olaparib + bevacizumab to s BRCA ONLY patients?

a. Yes would consider for s BRCA

b. I would consider only for HRD positive not for s BRCA

c. I would consider only for HRD positive and s BRCA both



40% of doctors would consider olaparib + bevacizumab for HRD positive and s BRCA both.

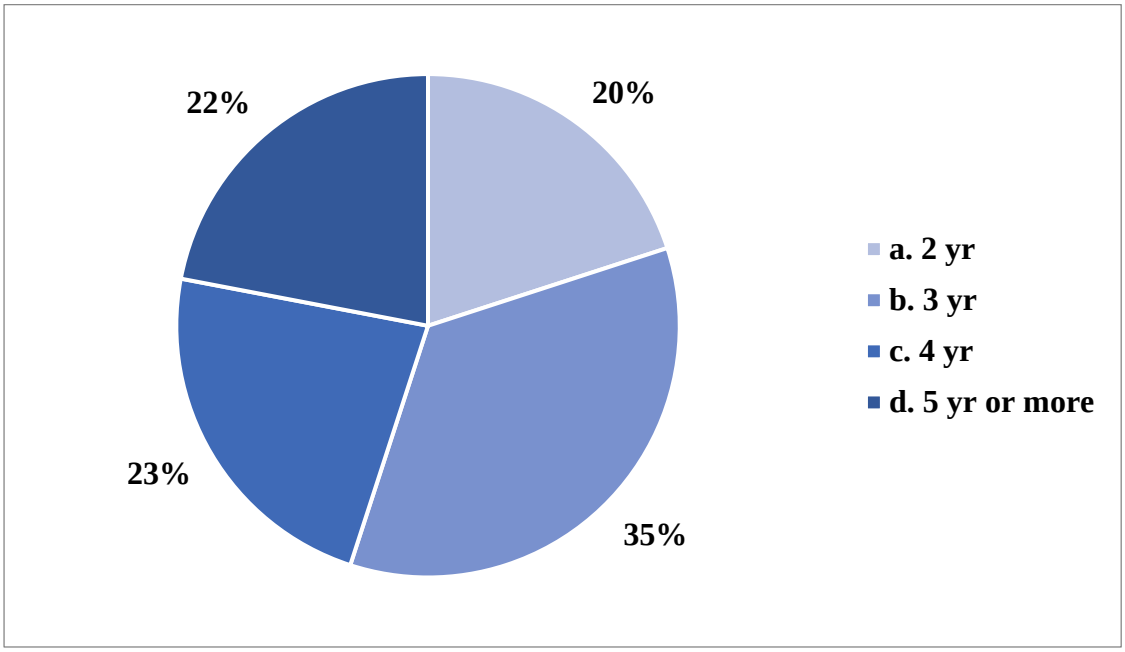
14. In your clinical practice, what is average PFS for first line maintenance olaparib in real world?

a. 2 yr

b. 3 yr

c. 4 yr

d. 5 yr or more

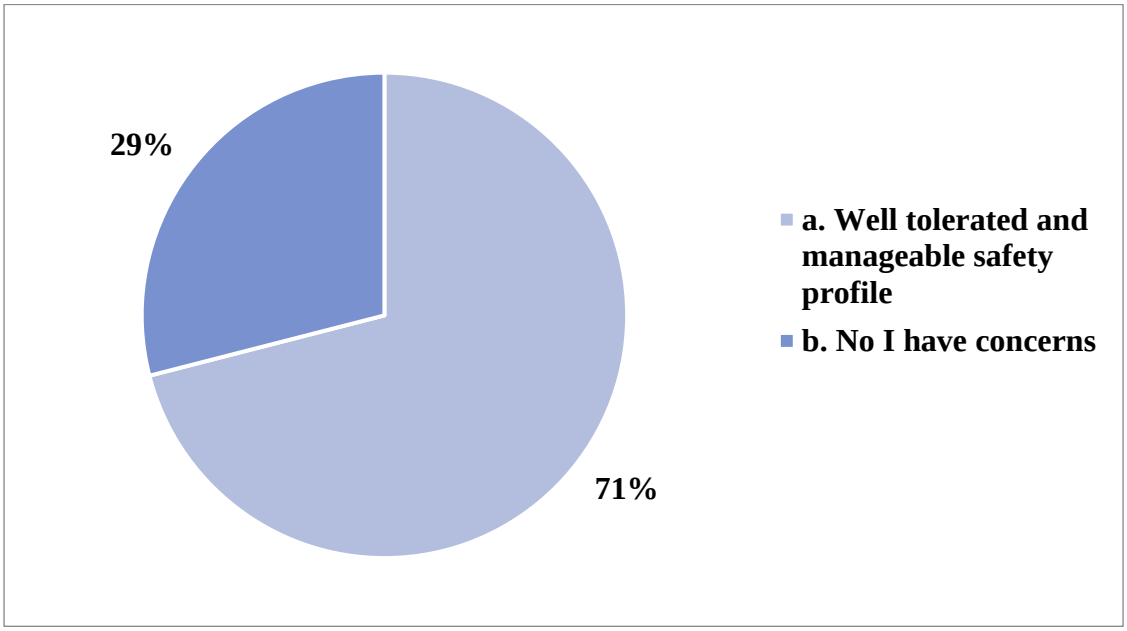


According to 35% of doctors, the average PFS for first line maintenance olaparib in real world is 3 yrs.

15. Please rate safety of Olaparib as per your clinical experience?

a. Well tolerated and manageable safety profile

b. No I have concerns



Majority of doctors, 71%, consider Olaparib is well tolerated and has manageable safety profile.

Summary

- In the clinical practice of 38% of doctors, 20-40% of ovarian cancer patients can afford diagnostic genetic testing.
- According to 45% of doctors, they conduct diagnostic testing post cytoreduction before starting 1st line.
- As per 34% of doctors, they first perform diagnostic test of g BRCA followed by s BRCA in their advanced ovarian cancer patients.
- According to 41%b of doctors, 20-40% of ovarian cancer patients are BRCA positive.
- As per 30% of doctors, 0-20% of ovarian cancer patients are HRD positive.
- Majority of doctors, 74%, perform diagnostic testing with 2nd line in case patients have not undergone it during first line.
- Before 2nd line (if patient untested previously), 33% of doctors would prefer s BRCA followed by g BRCA if patient responded well to platinum.
- According to 46% of doctors, 50-75% of their patients who are platinum sensitive respond to maintenance first line PARPi.
- For 44% of doctors, in HRD positive ovarian cancer, their treatment choice would be Only Olaparib as per SOLO-1.
- Majority of doctors agree that they consider maintenance bevacizumab post first line chemotherapy (considering genetic testing results unknown in first line treatment).
- In the clinical practice of 56% of doctors, in g/s BRCA positive ovarian cancer patients, they prefer Olaparib PARPi.
- According to 55% of doctors, based on results of SOLO-1, they would treat upfront maintenance with olaparib for ≤ 2 yr.
- 40% of doctors would consider olaparib + bevacizumab for HRD positive and s BRCA both.
- According to 35% of doctors, the average PFS for first line maintenance olaparib in real world is 3 yrs.
- Majority of doctors, 71%, consider Olaparib is well tolerated and has manageable safety profile.

Consultant Opinion

Market Opportunities:

- **Affordability and Accessibility**: Develop programs to make diagnostic genetic testing more affordable and accessible. Collaborate with insurance companies and healthcare providers to subsidize costs and provide financial assistance to patients.
- **Educational Campaigns**: Increase awareness among healthcare providers and patients about the importance of genetic testing for personalized treatment plans. Highlight the benefits of knowing BRCA and HRD status for effective treatment planning.

Value for Healthcare Professionals:

- **Training and Support**: Offer training programs and resources to educate healthcare professionals on the latest guidelines and best practices for genetic testing and the use of PARP inhibitors. This can improve diagnostic accuracy and treatment outcomes.
- **Clinical Data and Evidence**: Provide robust clinical data and case studies demonstrating the efficacy and safety of PARP inhibitors like Olaparib in different patient populations. This can help doctors make informed treatment decisions.

Adverse Effect Management:

- **Side Effect Monitoring**: Develop comprehensive guidelines for monitoring and managing the side effects of PARP inhibitors. Provide tools and resources to help doctors identify and address adverse effects early, ensuring patient adherence and safety.
- **Patient Education**: Create patient education materials that explain potential side effects and management strategies. Educating patients can improve compliance and reduce anxiety about treatment.

Market Positioning:

- **Highlighting Treatment Benefits**: Emphasize the benefits of PARP inhibitors, such as prolonged progression-free survival and manageable safety profiles, in marketing campaigns. Use real-world evidence to support these claims and differentiate from competitors.
- **Strategic Partnerships**: Partner with leading oncologists and cancer centers to endorse the use of PARP inhibitors and genetic testing, enhancing credibility and trust in these treatments.

Personalized Treatment Decisions:

- **Customized Treatment Plans**: Encourage doctors to personalize treatment plans based on genetic testing results. Provide decision-support tools that help tailor treatment regimens for individual patients, considering factors like BRCA and HRD status.
- **Regular Monitoring Protocols**: Advocate for regular monitoring protocols to assess treatment response and adjust therapy as needed. This ensures that patients receive the most effective and appropriate care.

Improving Patient Outcomes:

- **Comprehensive Care Plans**: Promote the use of comprehensive care plans that include genetic testing, personalized treatment with PARP inhibitors, and regular follow-ups. This holistic approach can improve overall patient outcomes.
- **Support Services**: Offer support services such as patient counseling, nutritional advice, and mental health support to address the broader needs of ovarian cancer patients. This can enhance their quality of life and treatment adherence.

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

Weston Medical Education Foundation of India

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