Olaparib maintenance for first-line treatment of ovarian cancer- Will SOLO1 reset the standard of care?

Abstract

Maintenance therapy with PARP inhibitors has heralded a new era in the management of recurrent epithelial ovarian cancer. The greatest effect is seen in women with *BRCA1/2* tumours but those without this mutation also benefit. However, in most patients, the drugs eventually fail to prevent progression, so alternative strategies are needed. The SOLO1 trial randomised women with *BRCA1/2* mutated advanced ovarian cancer to olaparib or placebo maintenance after first-line chemotherapy. Olaparib significantly improved progression-free survival to a degree that has not been seen in other first-line trials in ovarian cancer. This landmark trial is likely to change practice for this group of women. Here we focus on the SOLO1 results in the context of the current management of advanced ovarian cancer.

Key Words: ovarian cancer, PARP inhibitor, olaparib, SOLO1, BRCA mutation

Introduction

Most women with newly diagnosed advanced ovarian, primary peritoneal or fallopian-tube cancer (subsequently referred to as ovarian cancer) will relapse within three years after standard treatment with surgery and platinum-based chemotherapy [1]. The benefit of oral poly adenosine diphosphate–ribose polymerase (PARP) inhibitors as maintenance therapy in relapsed disease has been well established [2-6]. Olaparib, niraparib and rucaparib all delay progression following platinum-based chemotherapy in high grade ovarian cancer with benefit seen in all groups of patients, but the greatest benefit is observed in those with a *BRCA1* or *BRCA2* (*BRCA1/2*) mutation, either germline or somatic [2-5]. The median progression free survival (PFS) from randomisation ranges from 11.2-21 months for *BRCA*1/2 mutant populations and 7.4-10.8 months for *BRCA1/2* wild-type/all comer populations [2-6]. To date, no benefit has been observed in overall survival (OS), but with long-term follow up in Study 19, 11% of patients remained on olaparib for over six years without evidence of tumour progression [7]. Despite impressive prolongation in PFS, disease relapse remains almost inevitable, even within the *BRCA1/2* mutant population. The consistent clinical benefit seen using different PARP inhibitors in recurrent ovarian cancer raises the question whether the strategy of maintenance therapy post chemotherapy could be applied to the first-line setting. The SOLO1 trial with olaparib is the first study to evaluate PARP inhibitor maintenance therapy in this setting, to determine whether a greater benefit can be derived with the early introduction of PARP inhibition in the *BRCA1/2* mutant population [8].

SOLO1 Trial design and summary of result and toxicity

SOLO1 is an international, randomised, double-blind, phase 3 trial conducted in 391 patients with newly diagnosed advanced high-grade serous or endometrioid ovarian, primary peritoneal or fallopian-tube cancer and with a mutation in *BRCA1*, *BRCA2*, or both (Figure 1) [8]. Eligible patients were diagnosed with FIGO stage III or IV disease and had a complete or partial clinical response after platinum-based chemotherapy. Patients with stage III disease had undergone an attempt at cytoreductive surgery before commencing chemotherapy (up front) or after the start but before the end of chemotherapy (interval debulking surgery), and patients with stage IV disease had undergone either biopsy or up front or interval cytoreductive surgery. Eligible patients had a deleterious or suspected deleterious germline or somatic *BRCA1/2* mutation, as determined by local or central testing.

391 patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily, n = 260) or placebo (n=131). Trial intervention was continued until investigator-assessed disease progression. Patients who had no evidence of disease at two years discontinued treatment, but patients who had a partial response at two years were permitted to continue receiving the treatment. Crossover between trial groups was not permitted. The primary end point was investigator assessed progression-free survival. Enrolment was allowed up to eight weeks following the completion of chemotherapy.

The trial was considered positive after a median follow-up of 41 months; all patients had been followed for at least 36 months. The risk of investigator assessed disease progression or death (data maturity 51%) was 70% lower with olaparib than with placebo (60% versus 27%; hazard ratio (HR) 0.30; 95% CI, 0.23 to 0.41; p<0.001). In the analysis of PFS (as assessed by blinded independent central review (BICR), data maturity, 38%), the Kaplan–Meier estimate of the rate of freedom from disease progression and death at 3 years was 69% in the olaparib group, as compared with 35% in the placebo group (HR 0.28; 95% CI, 0.20 to 0.39; p<0.001) [8]. These results are consistent with the benefit of olaparib with regard to progression-free survival as assessed by investigators [8].

Adverse events were consistent with the known toxic effects of olaparib seen in similar patients undergoing maintenance treatment for recurrent ovarian cancer [3,6]. 98% and 92% of patient receiving olaparib and placebo respectively experienced at least one adverse events with the most common being nausea (77% olaparib versus 38% placebo), fatigue/asthenia (63% olaparib versus 42% placebo), vomiting (40% olaparib versus 15% placebo) and anaemia (39% olaparib versus 10% placebo). Serious adverse events occurred in 21% of olaparib treated patients and 12% of those receiving placebo, with anaemia the most common (7% olaparib versus 0% placebo). There were no treatment related deaths. Adverse events resulted in dose reduction and treatment discontinuation in 28% and 12% of olaparib treated patients and 3% and 2% of those on placebo respectively. Neither trial group had a clinically significant change in health-related quality of life [8].

BRCA1/2 **mutations and PARP inhibition**

Inherited mutations in *BRCA1* and *BRCA2* genes are responsible for the majority of familial ovarian cancer syndromes. BRCA1 and BRCA2 are essential components of the highly conserved homologous-recombination repair pathway, which is responsible for the error-free repair of DNA double-strand breaks and therefore critical for maintaining genomic stability [9]. Germline mutations in *BRCA1/2* account for approximately 13-15% of all high grade ovarian cancers [10,11] with an additional 5-7% of patients harbouring somatic *BRCA1/2* mutations [10,11]. The finding that single-agent PARP inhibition selectively killed *BRCA1/2* deficient cells was a key discovery in exploiting synthetic lethal approaches in oncology [12,13]. PARP inhibitors trap PARP protein onto DNA at sites of single-strand DNA breaks. When this trapped PARP is encountered by the DNA replication machinery it leads to stalling of the replication fork, collapse and the generation of a double strand break, which cannot be repaired in cells with defective homologous recombination, such as *BRCA1/2* mutated cells [14]. In addition to the familial ovarian cancer syndromes, a number of sporadic ovarian cancers are also defective in homologous-recombination repair and share the deficient phenotype associated with *BRCA1/2* [15,16]. Initial indications for PARP inhibition were limited to tumours characterized by either a germline or somatic *BRCA1/2* mutation, with olaparib receiving the first license from the EMA as maintenance treatment of recurrent *BRCA1/2* mutated epithelial ovarian cancer [17]. Emerging data, supports an extended scope for PARP inhibitor use and this has been reflected with the recent approval by the FDA and EMA for, niraparib, olaparib tablets and rucaparib as maintenance therapy for all patients, treated with two or more prior chemotherapy regimens who have responded to platinum therapy, regardless of *BRCA1/2* status [17-22]. Olaparib and rucaparib have additional licences as monotherapy for recurrent *BRCA1/2* mutant ovarian cancer [17,19,21,22]. Response rates of between 31% and 41% in *BRCA1/2* mutation carriers and up to 24% in *BRCA* wild-type patients have been demonstrated with olaparib monotherapy [23,24]. Similarly, within Study 10 and ARIEL2 trials, there was an overall response rate of 53.8% (95% CI 43.8–63.5) with rucaparib monotherapy in *BRCA1/2* mutated patients following at least two lines of prior therapy [25]. However, to date all studies had been performed in patients with recurrent disease and the SOLO1 study was the first to evaluate the role of PARP inhibition in the first line setting when treatment has curative potential.

First line therapy in advanced ovarian cancer

The SOLO1 trial should be considered a landmark study. It the first trial to demonstrate meaningful PFS improvement in the first line setting for patients with advanced ovarian cancer. Progression free survival can be viewed as an indicator of the effectiveness of first line therapy, with little improvement observed over the past two decades. Carboplatin and paclitaxel has been the standard of care since the introduction of paclitaxel in the 1990s. Progression free survival is affected by the amount of residual disease, quality of cytoreductive surgery and BRCA status [26-28]. Maintenance chemotherapy, high-dose chemotherapy and weekly dose-scheduling have not reduced recurrence rates [29,30]. The addition of bevacizumab to chemotherapy followed by maintenance bevacizumab improves PFS by around four months, with the greatest benefit observed with more advanced disease [31,32]. However, a recent analysis of the GOG-

218 data, suggested that *BRCA1/2* mutant patients (and those with other homologous recombination repair mutations) did not confer a statistically significant prolongation in PFS with extended bevacizumab use [28]. Whilst *BRCA1/2* mutation carriers with advanced disease have superior PFS and OS compared to *BRCA1/2* wild-type patients [28,33,34], relapses still occur in the majority of patients within three years of diagnosis, with a high rate of first line therapy failure.

Within the SOLO1 trial, the placebo arm had a median PFS of 13.8 months. This was measured from the completion of chemotherapy, with randomisation approximately 6.5 months from diagnosis, giving a median PFS from diagnosis of around 20.3 months. This is consistent with results reported in studies of carboplatin and paclitaxel in patients with newly diagnosed ovarian cancer and a *BRCA1/2* mutation [28,35]. Whilst the median PFS has not yet been reached for the olaparib arm, a sensitivity analysis of investigator-assessed PFS was performed to evaluate for possible attrition bias. This demonstrated a median PFS of approximately 36 months more in the olaparib group than in the placebo group. Furthermore, the Kaplan–Meier estimate of the rate of freedom from disease progression and from death at four years was 53% with olaparib compared to 11% with placebo. This clinically meaningful prolongation in PFS was observed despite the median duration of olaparib treatment of 24.6 months. Many patients in this study were able to stop trial intervention at two years and live progression free for several months without treatment. In keeping with this, the median time to the first subsequent therapy or death was 51.8 months in the olaparib group and 15.1 months in the placebo group (HR 0.30; 95% CI, 0.22 to 0.40) [8].

Patients with newly diagnosed ovarian cancer are the only patients with ovarian cancer treated with curative intent. Whilst the OS data from SOLO1 are immature, the fact that more than half of the patients treated with olaparib were free from progression at four years raises the very real potential that this intervention may result in long-term durable benefit or even cure in a sub-set of patients.

Patient population in SOLO1 – Does it compare to clinical practice?

The patient population of SOLO1 was well matched, as expected, between the two groups. The majority had no evidence of disease following chemotherapy (82%), were ECOG performance status zero (78%) and had a CA-125 level within the normal range (95%). Whilst this population is of better prognosis than that observed in everyday clinical practice, benefits for olaparib were observed in all subgroups including those patients with features which predict poorer prognosis including those with residual disease (HR 0.44; 95%CI 0.25–0.77), stage IV disease (HR 0.49; 95%CI 0.25-0.94), and ECOG performance status 1 (HR 0.38; 95%CI 0.21-0.68) [8]. The data from the sub-group analysis supports the use of olaparib in all sub-groups and suggests that this will translate into clinical benefit for all patients, including those with clinical features more typical for the non-trial patient population.

Olaparib maintenance in *BRCA1/2* mutant ovarian cancer: first or second line?

The impressive results from SOLO1 follow on from those reported in SOLO2 [6] Here, patients with advanced recurrent high-grade ovarian cancer and a *BRCA1/2* mutation were randomised to olaparib or placebo maintenance following a response to platinum-based chemotherapy with a significant improvement in PFS observed with olaparib; 19.1 months versus 5.5 months on placebo (HR 0.30; 95%CI 0.22-0.41) [6]. This raises the question as to whether patients with *BRCA1/2* mutant ovarian cancer should be treated with olaparib maintenance in the first line or relapsed setting. Within SOLO2, 58% of patients entered after second line platinum chemotherapy. The median PFS with olaparib was 19.1 months, with 43% of patients free from progression at 24 months [6]. In comparison 74% of patients on olaparib were free from progression at two-years within SOLO1. Furthermore, the absolute longer PFS with olaparib than with placebo seen in the sensitivity analysis in SOLO1 is substantially greater than that seen with SOLO2 (and with other PARP inhibitors in relapsed disease trials) [2,5,6]. Together these results suggest that olaparib maintenance in *BRCA1/2* patients has the greatest benefit in the first line setting. Furthermore, some patients (e.g. those who develop platinum resistance) are not eligible to receive olaparib as a second-line therapy and therefore the earlier introduction of these drugs will offer the opportunity for a greater number of patients to benefit and may even delay the onset of platinum resistance in this group.

There was a theoretical concern that treatment with PARP inhibitors may reduce response rate and duration of response to subsequent lines of therapies. This has not been borne out in the PARP maintenance studies performed in the relapsed setting, as evident by the prolonged time to second disease progression observed with both olaparib and niraparib compared to placebo [5,6]. In keeping with this, there was improvement in all efficacy endpoints with olaparib in SOLO1 (Table 1) suggesting that olaparib does not reduce the patients' ability to benefit from subsequent therapy. A significant increase in second progression free survival was observed with olaparib (Kaplan–Meier estimate of the rate of freedom from second disease progression or death at 3 years 75% with olaparib versus 60% with placebo; HR 0.50; 95% CI, 0.35 to 0.72; $p<0.001$). The median second PFS was 41.9 months in the placebo group, this may be partially explained by the observation that 35% of these patients subsequently received treatment with a PARP inhibitor.

Late toxicity

An additional concern with early PARP inhibitor use is whether long-term use of agents that interfere with repair of double-stranded DNA breaks result in the development of the myelodysplastic syndrome (MDS) and acute leukaemia (AML). Within SOLO1 the incidence of AML reported was 1% in patients who received olaparib, which is consistent with the incidence of the MDS or AML reported in the SOLO2 trial (2%) and

other trials of PARP inhibitors [2-6]. To date, these data do not support the concern that earlier introduction of PARP inhibitors is detrimental but longer-term follow-up is essential to answer this question.

Conclusions

The significant difference in PFS seen in SOLO1, with the median PFS not yet reached and the estimation from the PFS2 results suggesting that it is likely to be longer 48 months provides hope that for these women there will be long-term remission and even possible cure. This group of women includes up to 22 % of patients with high grade ovarian cancer, harbouring either a germline or somatic mutation in *BRCA1/2.* Whilst the OS data are not mature, the impressive data seen to date suggests that olaparib should be included in daily practice as maintenance therapy in this patient population. Interestingly, this is the first trial with a PARP inhibitor where a planned discontinuation of drug occurred after 24 months in patients without disease progression.

Ongoing and future trials will explore the role of PARP inhibition in patients regardless of *BRCA* status. This includes GOG 3005, which is examining the concomitant and maintenance use of veliparib in the primary setting in patients with high-grade serous ovarian cancer (ClinicalTrials.gov identifier: NCT02470585) and the PRIMA study (NCT02655016) comparing maintenance niraparib or placebo therapy in patients with suboptimal stage III or stage IV disease following surgery and chemotherapy. The PAOLA-1 study is evaluating the addition of olaparib or placebo maintenance to bevacizumab following first-line therapy (NCT02477644). This study is testing the hypothesis that bevacizumab increases the activity of PARP inhibitor, possibly due to increasing the degree of homologous deficiency in the tumour [36]. A phase 2 study combing olaparib and the VEGF receptor inhibitor cediranib supports this approach with the greatest benefit observed in the *BRCA* wildtype group [37].

Finally, there is increasing interest in the combination of PARP inhibitors with checkpoint inhibitors such as anti-PD1/PDL1 and anti-CTLA4 antibodies. Single agent therapy with checkpoint inhibitors has demonstrated only modest activity in the treatment of recurrent ovarian cancer to date [38] and it is hypothesised that checkpoint inhibitor benefit is improved by combining with a PARP inhibitor. This rationale is based on two hypotheses; firstly, tumours with a *BRCA1/2* mutation or an HRR defect have a higher mutational burden and therefore an elevated neo-antigen load, which is thought to elicit an increased anti-tumour immune response [39,40]. Secondly, PARP inhibitor treatment up regulates PD-L1 expression in vivo and in vitro [41] and in the absence of a functional BRCA pathway, there is activation of the innate immune response via the STING/TKB1/IRF3 response [42], which might influence the antitumor effect of a PARP inhibitor and checkpoint inhibitor combination. A number of phase 3 trials combing PARP inhibitor with checkpoint inhibition in the first line setting are underway. This includes; ATHENA (NCT03522246), combining rucaparib with nivolumab in the maintenance setting, DUO-O (NCT03737643) concomitant

durvalumab and bevacizumab with chemotherapy followed by durvalumab, bevacizumab and olaparib maintenance and FIRST (NCT03602859) concomitant TSR-042 (anti-PD1 antibody) with chemotherapy followed by maintenance TSR-042 and niraparib. However, these trials were designed before the results of SOLO1 appeared and although there is stratification for the presence of a *BRCA* mutation, an alteration of the design may be required, so that patients with a *BRCA* mutation do not miss the opportunity of receiving first-line maintenance olaparib.

Whilst it remains to be seen whether the dramatic improvement in PFS translate to an overall survival benefit or even an improved cure rate, the results from SOLO1 strongly supports the use of olaparib maintenance therapy in patients with *BRCA* mutant ovarian cancer. It is therefore imperative that BRCA testing is performed in all patients with advanced ovarian cancer in a timely manner to allow them to benefit from this therapy, if appropriate. Ongoing studies will establish whether a similar benefit for first-line maintenance PARP inhibitor treatment is seen in *BRCA1/2* wild-type patients and whether the response can be augmented with combination therapy.

Executive Summary

Advanced ovarian cancer

- Despite curative intent, combined-modality treatment with surgery and platinum-based chemotherapy has poor cure rates, with 5-year survival ranging from 28% for FIGO stage 3 to 19% with FIGO stage 4.
- Approximately 20% of all high grade ovarian cancers harbour a germline or somatic *BRCA1/2* mutation

First-line therapy for advanced ovarian cancer

- Limited improvement in first-line PFS over two decades since the introduction of carboplatin and paclitaxel.
- The majority of patients with advanced disease will recur within three years of diagnosis.

SOLO1 trial design

- Patients with advanced high-grade serous or endometrioid ovarian cancer with a mutation in *BRCA1/2*, and who had a complete or partial clinical response after platinum-based chemotherapy, randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily, n = 260) or placebo (n=131).
- Trial intervention was continued until disease progression. Patients who had no evidence of disease at two years discontinued treatment, but patients who had a partial response at two years continue receiving treatment. The primary end point was investigator assessed progression-free survival.

Results

- After median follow-up of 41 months, the risk of investigator assessed disease progression or death (data maturity 51%) was 70% lower with olaparib than with placebo (60% versus 27%; HR 0.30; 95% CI, 0.23 to 0.41, p<0.001)
- PFS (as assessed by BICR, data maturity, 38%), estimated rate of freedom from disease progression/ death at 3 years 69% olaparib versus 35% placebo (HR 0.28; 95% CI, 0.20 to 0.39, p<0.001).
- Adverse events were consistent with the known toxic effects of olaparib. Serious adverse events occurred in 21% of olaparib and 12% of placebo treated patients. AML occurred in 1% of the olaparib group and in none in the placebo group, new primary cancers occurred in 2% in both groups.

Impact and implications

- Olaparib maintenance should become the new standard of care for women with *BRCA1/2* mutant, advanced ovarian cancer following a response to first line platinum-based chemotherapy
- Early testing for BRCA status is required

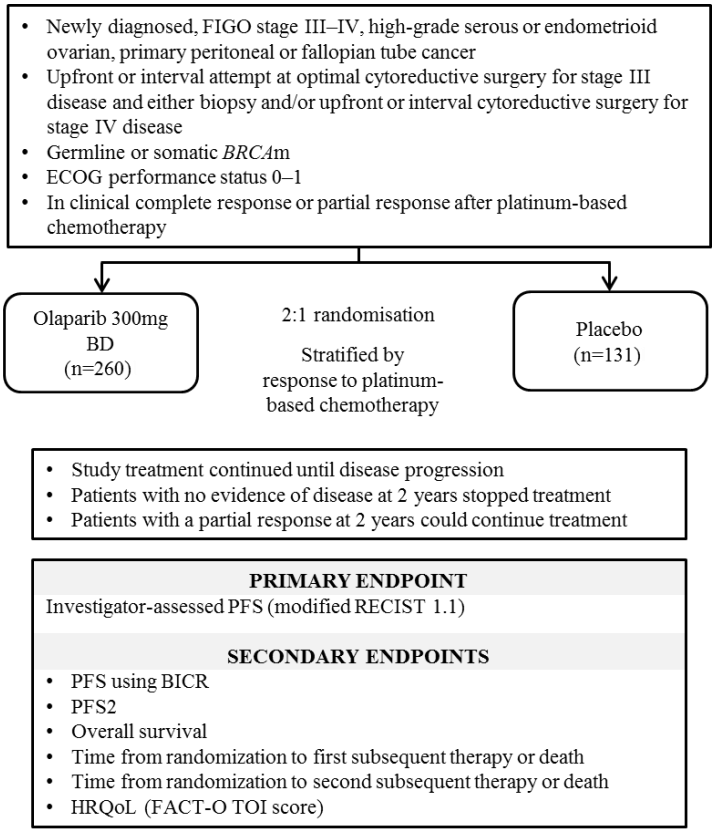
Unanswered questions

- Will the dramatic improvement in progression-free survival translate to an overall survival benefit or even an improved cure rate?
- Is there a similar benefit for first-line maintenance PARP inhibitor treatment in patients whose tumours are *BRCA1/2* wild-type?
- Does long-term use of PARP inhibitors that interfere with repair of double-stranded DNA breaks result in the development of the myelodysplastic syndrome and acute leukemia? To date, across published studies, accumulating evidence suggests that the risk is fairly low (<2%), but longer-term follow-up is essential.

Figure and Tables

Figure 1: SOLO1 trial design

FIGO, International Federation of Gynecology and Obstetrics; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumours; PFS, Progression Free Survival; BICR, blinded independent central review; PFS2, time to second progression or death; HRQoL, health-related quality of life; FACT-O, Functional Assessment of Cancer Therapy – Ovarian Cancer; TOI, Trial Outcome Index



Efficacy End Points	Olaparib N =260	Placebo N = 131	Hazard Ratio 95% CI
Median PFS* (months)	Not reached	13.8	0.30 (0.23-0.41)
Median time to first subsequent therapy or death (months)	51.8	15.1	0.30 (0.22-0.40)
Median PFS2 (months)	Not reached	41.9	0.50 (0.35-0.72)
Median time to second subsequent therapy or death (months)	Not reached	40.7	0.45 (0.32-0.63)

Table 1: Summary of efficacy end points**.** * investigator assessed, PFS2, median second Progression Free Survival- time to second progression or death, CI – confidence interval.

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** First trial demonstrating PFS benefit of maintenance olaparib

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* Key paper showing BRCA/PARP synthetic lethality

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