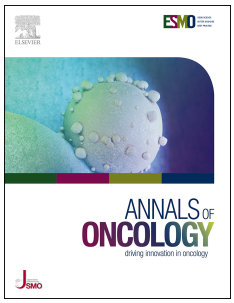


Efficacy of subsequent chemotherapy for patients with *BRCA*1/2-mutated recurrent epithelial ovarian cancer progressing on olaparib versus placebo maintenance: post-hoc analyses of the SOLO2/ENGOT Ov-21 trial

J.S. Frenel, J.W. Kim, N. Aryal, R. Asher, D. Berton, L. Vidal, P. Pautier, J.A. Ledermann, R.T. Penson, A.M. Oza, J. Korach, T. Huzarski, S. Pignata, N. Colombo, T.W. Park-Simon, K. Tamura, G.S. Sonke, A.E. Freimund, C.K. Lee, E. Pujade-Lauraine

PII: S0923-7534(22)01740-9

DOI: https://doi.org/10.1016/j.annonc.2022.06.011

Reference: ANNONC 1017

To appear in: *Annals of Oncology*

Received Date: 13 February 2022

Revised Date: 16 June 2022

Accepted Date: 20 June 2022

Please cite this article as: Frenel JS, Kim JW, Aryal N, Asher R, Berton D, Vidal L, Pautier P, Ledermann JA, Penson RT, Oza AM, Korach J, Huzarski T, Pignata S, Colombo N, Park-Simon TW, Tamura K, Sonke GS, Freimund AE, Lee CK, Pujade-Lauraine E, Efficacy of subsequent chemotherapy for patients with *BRCA*1/2-mutated recurrent epithelial ovarian cancer progressing on olaparib versus placebo maintenance: post-hoc analyses of the SOLO2/ENGOT Ov-21 trial, *Annals of Oncology* (2022), doi: https://doi.org/10.1016/j.annonc.2022.06.011.

Original Article

Efficacy of subsequent chemotherapy for patients with *BRCA*1/2-mutated recurrent epithelial ovarian cancer progressing on olaparib versus placebo maintenance: post-hoc analyses of the SOLO2/ENGOT Ov-21 trial

J. S. Frenel[1], J. W. Kim[2], N. Aryal[3], R. Asher[3], D. Berton[1], L. Vidal[4], P. Pautier[5], J. A. Ledermann[6], R. T. Penson[7], A. M. Oza[8], J. Korach[9], T. Huzarski[10], S. Pignata[11], N. Colombo[12], T. W. Park-Simon[13], K. Tamura[14], G. S. Sonke[15], A. E. Freimund[16], C. K. Lee[3], and E. Pujade-Lauraine[17]

[1]*GINECO, GINEGEPS & Institut de Cancerologie de l'Ouest, Centre René Gauducheau, Saint-Herblain, France;*

[2]*Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea, Republic of (South);*

[3]*NHMRC CTC Centre, University of Sydney, Camperdown, Sydney, Australia;*

[4]*GEICO & H Clínic de Barcelona, Barcelona, Spain;*

[5]*GINECO & Gustave Roussy Cancer Center, Villejuif, France;*

[6]*NCRI & University College London, London, United Kingdom;*

[7]*Massachusetts General Hospital, Boston, MA;*

[8]*Princess Margaret Cancer Centre, Toronto, ON;*

[9]*ISGO & Chaim Sheba Medical Center, Tel Aviv University, Tel Aviv, Israel;*

[10]*Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland;*

[11]*MITO & Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale Napoli, Naples, Italy;*

[12]*MaNGO & European Institute of Oncology IRCCS and University of Milan-Bicocca, Milano, Italy;*

[13]*AGO & Medical School, Dept. Gynecologic Oncology, Hannover, Hannover, Germany;*

[14]*Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan;*

[15]*DGOG & Netherlands Cancer Institute, Amsterdam, Netherlands;*

[16]*Peter MacCallum Cancer Centre, Melbourne, Australia;*

[17]*ARCAGY-GINECO, Paris, France.*

Corresponding author:

Dr Jean-Sebastien Frenel, Medical Oncology Department, Institut de Cancerologie de L'Ouest, 11 boulevard Jacques Monod, 44800, Saint-Herblain, France.

+33 2 40 67 99 00

jean-sebastien.frenel@ico.unicancer.fr

Highlights

- Progression on olaparib may diminish the efficacy of platinum-based subsequent chemotherapy for recurrent ovarian cancer.
- The disease progression patterns are similar in patients receiving either olaparib or placebo.
- Characterization of the mechanisms of resistance is crucial for the development of new treatments for these patients.

Abstract

Background. In the SOLO2 trial (ENGOT Ov-21; NCT01874353), maintenance olaparib in patients with platinum-sensitive relapsed ovarian cancer (PSROC) and *BRCA* mutation significantly improved progression-free survival (PFS) and prolonged overall survival (OS). Following disease progression on olaparib, efficacy of subsequent chemotherapy remains unknown.

Patients and Methods. We conducted post-hoc hypothesis-generating analysis of SOLO-2 data to determine the efficacy of different chemotherapy regimens following RECIST disease progression in patients who received olaparib or placebo. We evaluated time to second progression (TTSP) calculated from the date of RECIST progression to next progression/death.

Results. The study population comprised 147 patients who received chemotherapy as their first subsequent treatment after RECIST progression. Of these, 69 (47%) and 78 (53%) were originally randomized to placebo and olaparib arms, respectively. In the placebo-treated cohort, 27/69 and 42/69 received non-platinum and platinum-based chemotherapy, respectively, compared with 24/78 and 54/78, respectively, in the olaparib-treated cohort. Among patients treated with chemotherapy (*N* = 147), TTSP was significantly longer in the placebo than olaparib arm: 12.1 vs. 6.9 months (hazard ratio [HR] 2.17; 95% CI 1.47–3.19). Similar result was obtained on multivariable analysis adjusting for prognostic factors at RECIST progression (HR 2.13; 95% CI 1.41–3.22). Among patients treated with platinum-based chemotherapy (*N* = 96), TTSP was significantly longer in the placebo arm: 14.3 vs. 7.0 months (HR 2.89; 95% CI 1.73–4.82). Conversely, among patients treated with non-platinum-based chemotherapy (*N* = 51), the TTSP was comparable in the placebo and olaparib arms: 8.3 vs. 6.0 months (HR 1.58; 95% CI 0.86–2.90).

Conclusion. Following progression from maintenance olaparib in the recurrent setting, the efficacy of platinum-based subsequent chemotherapy seems to be reduced in *BRCA1/2* mutated patients with PSROC compared to patients not previously receiving PARPi. The optimal strategy for patients who relapse after PARP inhibitors is an area of ongoing research.

Keywords: PARP inhibitor resistance, *BRCA* mutation, relapsing ovarian cancer

Introduction

Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) have radically changed the treatment landscape for breast cancer gene (*BRCA*)-mutated ovarian cancers. SOLO2/ENGOT-ov21 (NCT01874353) is a randomized Phase III maintenance therapy study evaluating olaparib versus placebo in women with *BRCA1/2*-mutated platinum-sensitive relapsing ovarian cancer (PSROC), following response to platinum chemotherapy. In this trial, olaparib demonstrated a significant improvement of progression-free survival (PFS) (hazard ratio [HR]: 0.30, [95% confidence interval [CI]: 0.22–0·41], $P < 0.0001$) and prolongation of overall survival (OS) (HR: 0.74; 95% CI: 0.54–1.00, $P = 0.054$).[1, 2] Olaparib has been approved globally as maintenance therapy following response to platinum-based chemotherapy in patients with PSROC. Two other PARPi, niraparib and rucaparib, have also been approved in the same relapse setting.[3, 4]

In the first-line setting, PARPi are also being used as maintenance treatment following response to platinum-based chemotherapy. SOLO-1 trial demonstrated an unprecedented PFS benefit of maintenance olaparib in *BRCA*-mutated patients.[1, 5] Four other international randomized first-line clinical trials (PAOLA-1, PRIMA, VELIA and ATHENA) have also reported the efficacy of PARPi, administered either alone or in combination therapy, in both *BRCA*-mutated and wild-type tumors.[6-9]

A significant proportion of patients develop resistance to PARPi. The optimal treatment at relapse following PARPi exposure in routine practice is still unclear. Presently, chemotherapy is the mainstay of treatment after progression following PARPi therapy. The regimen could be platinum containing or non-platinum agents, depending on the platinum-free intervals. However, PARPi shares similar resistant mechanisms as chemotherapy, particularly, platinum like restoration of homologous recombination achieved by means of secondary *BRCA* mutations.[10, 11] The response rate of patients undergoing subsequent chemotherapy following PARPi was reported only in small series, ranging from 9.5% in patients with platinum-free interval of less than 6 months to 22.2% in patients with platinum-free interval of more than 12 months.[12, 13]

Here, we present the results of a post-hoc analysis of the SOLO-2 trial that sought to investigate the efficacy of different chemotherapy regimens following RECIST disease progression in patients who received either olaparib maintenance or placebo.

Methods

In the SOLO2/ENGOT-ov21 (NCT01874353) trial, patients were randomly assigned using a 2:1 design to receive either olaparib (300 mg tablets, twice daily) or placebo until RECIST-defined progressive disease, unacceptable toxicity, or when the patient was deemed to no longer derive any benefit from treatment.

In this analysis, only patients with RECIST disease progression who underwent post-progression treatment were included. Patients who had non-RECIST progression were excluded. Post-progression treatments following randomized therapy were prospectively recorded during SOLO-2 trial follow-up until the next disease progression. Patients were also assessed every 12 weeks (CT scan and CA125) for a second progression. A patient's progression status was defined according to local clinical practice and may involve any of the following: radiological progression, CA-125 progression, symptomatic progression or death. We classified post-progression chemotherapy as platinum containing vs. non-platinum-based agents. We further evaluated non-chemotherapy-based regimens. We also further analyzed the outcomes of patients who continued the study treatment beyond RECIST progression, as permitted by the protocol. At the time of disease progression, we also examined the patterns of progression (target vs. no-target vs. new lesions), their localization, and the number of organs involved.

The main efficacy criterion in patients receiving chemotherapy was the time to second progression (TTSP) defined as the time between RECIST first progression (using investigator assessment) and second progression or death. Multivariable analyses were performed to adjust for disease burden and other clinical factors. We defined low disease burden if the difference in the sum of target lesions at progression versus the sum of target lesions at baseline is less than 50%, and there was no new target lesion and CA125 was <70 U/ml at the time of progression. If none of the above criterion was met, disease burden was considered as high. We also performed the following sensitivity analyses: time between first subsequent treatment (TFST) and second progression, and time between the start dates of first and second subsequent treatments in chemotherapy-receiving patients.

Categorical variables were expressed as frequency and percentage and between-group differences were assessed using the Chi-squared test. TTSP and TFST were estimated using Kaplan-Meier curves and between-group differences assessed using the log-rank test. The Cox proportional hazard model was applied to assess the risk of second progression from the first RECIST progression for patients in both randomized groups. The median time from first progression to end of study was estimated using reverse Kaplan-Meier. The average time between first and second subsequent treatments was calculated using censored linear

regression. SAS (Version 9.4; SAS Institute Inc., USA) and R software were employed for statistical analyses.

Results

Population and treatment delivered following RECIST progression

Of the 295 SOLO2 trial patients, 186 had documented RECIST first progression at the time of analysis. Among these, 161 patients received subsequent therapy (86 and 75 patients assigned to the olaparib and placebo arms, respectively). Median follow-up from randomization in the SOLO-2 trial of the population who received subsequent therapy was 25.1 months (4.7–34.7) including 25.4 months (11.1–34.7) and 24.7 (4.7–33.5) months in the olaparib and placebo arms, respectively. The remaining 25 patients continued the investigational treatment, consisting of either olaparib (*N* = 14), placebo (*N* = 2), beyond RECIST progression or did not receive any further treatment (*N* = 9). **Figure 1** shows the patient disposition of this cohort.

Chemotherapy was the first subsequent treatment following RECIST progression in 147/161 (91.3%) patients (**Supplementary table 1)**. The remaining patients (*N* = 14; 8.7%) received various therapies including PARPi monotherapy, bevacizumab monotherapy, or endocrine therapy.

Of the 147 patients having received chemotherapy, 78 (53%) and 69 (47%) were in the olaparib and placebo arms, respectively. Platinum-based chemotherapy was used in 69.2% (54/78) and 60.8% (42/69) of patients in the olaparib and placebo arms, respectively.

The characteristics of patients included in this analysis were similar in terms of baseline factors at the time of entry into SOLO-2 trial, except for a higher proportion of patients with complete response following platinum-based chemotherapy in the placebo arm compared with the olaparib arm (41% vs. 23%) (*P* = 0.02) (**Table 1**).

Efficacy of chemotherapy as first subsequent therapy

The median follow-up of patients who received post-progression chemotherapy (*N*=147) was 17.8 months (range: 1.2–26.9); the median follow-up of patients in the olaparib and placebo arms was 15.3 (1.2–26.9) and 17.4 (1.6–24.2) months, respectively. Median TTSP was significantly longer in patients who were treated with chemotherapy following progression on placebo than on olaparib (12.1 vs. 6.9 months) (hazard ratio [HR] 2.17; 95% confidence interval [CI] 1.47–3.19) (**Figure 2)**. When further evaluated the patients according to tissue *BRCA 1* or *2* status **(Supplementary Figure 1)**, those randomized to olaparib with *BRCA 1* had the poorest prognosis with median TTSP of 6.5 months versus 10.0 months for those with *BRCA 2* mutation.

In multivariable analysis (**Supplementary table 2**), after adjusting for performance status at first disease progression, disease burden at first progression, randomized treatment group, number of prior platinum therapy lines, platinum-free interval, response to previous platinum chemotherapy at enrollment, as well as responses to randomized treatment, the HR was 2.13 (95% CI 1.41–3.22, $P < 0.001$).

Sensitivity analysis based on TFST to second progression showed median values of 4.8 vs. 9.5 months (HR 2.97; 95% CI 1.98–4.47). Sensitivity analysis based on time between the first and second subsequent treatments showed average times of 16.1 vs. 10.6 months in the placebo and olaparib cohorts, respectively.

Within the subgroup of patients ($N = 96$, 65%) who received platinum-based post-progression chemotherapy, 54 and 42 were previously randomly assigned to either olaparib or placebo arm, respectively. The characteristics of these two patient groups at entry into the SOLO2 trial were well balanced, except for a trend toward a more complete response to chemotherapy in placebo-treated patients: 45% vs. 26% ($P = 0.05$) **Table 1**. Of note, the proportion of patients in the 6-12 months' category of platinum sensitivity prior to entering SOLO-2 was similar in the olaparib (52%) and placebo treated (48%) cohorts of patients. Median TTSP on platinum-based chemotherapy was significantly longer for patients who had received placebo compared to those treated with olaparib: 14.3 vs 7 months (HR 2.89; 95% CI [1.73, 4.82]) (**Figure 2)**. Stratification by the platinum-free interval at trial entry showed a similar trend **(Supplementary figure 2).**

Of note, 18/42 (42.8%) patients in the placebo arm received a PARPI following platinum-based chemotherapy. Out of these 18 patients, 15 were unblinded after progression on placebo. We conducted additional analyses by excluding these patients to assess the potential impact of PARPi maintenance on the TTSP. The median TTSP was still longer for patients who received placebo (14.6 vs 7 months) (HR 2.33; 95% CI 1.27–4.28).

Similar analyses were conducted for patients treated with non-platinum-based chemotherapy. This group comprised of 51 patients (34.7%), with 24 and 27 patients randomly assigned to receive either olaparib or placebo, respectively. Characteristics of these two groups were well balanced at entry into the SOLO2 trial (**Table 1)**. The median TTSP did not significantly differ between the two groups (6.0 vs. 8.3 months in olaparib and placebo arms, respectively) (HR: 1.58; 95% CI 0.86–2.90).

Outcome with continuing Olaparib beyond RECIST progression

As permitted according to the study protocol, 14 patients continued with olaparib beyond RECIST disease progression. Their median TTSP was 10.1 months, involving 10 patients without a second progression documented during follow-up.

Patterns of disease progression

We conducted analyses of the 186 patients exhibiting RECIST progression. The disease progression patterns were similar in patients receiving either olaparib or placebo. The number of progressing RECIST target lesions was similar in olaparib or placebo groups (one progressing target lesion: 68% vs. 64%; two progressing lesions: 32% vs. 36%, respectively). Likewise, the progression site did not differ between the two groups, with the peritoneum (32% vs. 48%) and lymph node (31% vs. 29%) being the most common progressing lesion sites in the two groups. Details are shown in **Supplementary table 3.**

Discussion

This hypothesis-generating exploratory analysis suggests that PARPi maintenance therapy may reduce the efficacy of subsequent platinum-based chemotherapy. There was a 7.3-month difference in TTSP in favor of the placebo over olaparib cohort of the SOLO-2 trial. This difference remained significant in multivariable analysis and also in the sensitivity analyses excluding patients who received maintenance PARPi following platinum-based chemotherapy.

Maintenance PARPi treatment for recurrent ovarian cancer has been shown to confer durable clinical benefits that delay subsequent therapy requirements and persist throughout the course of subsequent treatments. Assessment of these post-progression endpoints in patients with ovarian cancer is classically based on TFST, time to second subsequent treatment (TSST), and PFS2. In the SOLO2 trial, olaparib maintenance was associated with improvement in TFST (27.9 vs. 7.1 months; HR: 0.28; 95% CI: 0.21–0.38; *P* = 0.0001), TSST (NR vs. 18.2 months; HR: 0.42; 95% CI: 0.26–0.53; *P* = 0.0001), PFS2 (NR vs. 18.4 months; HR: 0.50; 95% CI: 0.34–0.72; *P* = 0.0002) and OS (51.1 vs. 38.8 months; HR 0.74; 95% CI: 0.54–1.00; *P* = 0.054).[1] Similar benefits of rucaparib were reported in the *BRCA*-mutated subpopulation of the ARIEL-3 trial: TFST (18.9 vs. 7.2 months; HR: 0.28: 95% CI: 0.20–0.41; *P* = 0.0001), TSST (28.8 vs. 17.7 months; HR: 0.53; 95% CI: 0.36–0.80; *P* = 0.0022), and PFS2 (26.8 vs. 18.4 months; HR: 0.56; 95% CI: 0.38–0.83; *P* = 0.0040).[14] In addition, in *BRCA*-mutated patients in the NOVA study, niraparib significantly prolonged both TFST (21.6 vs. 8.4 months; HR: 0.31; 95% CI: 0.21–0.48; *P* < 0.0001) and PFS2 (HR: 0.67; 95% CI: 0.479–0.948).[15]

The TTSP from first RECIST progression, an endpoint used in our analysis, has not been widely utilized in PARPi ovarian cancer trials, either in the relapse or in the adjuvant setting. This endpoint differs from PFS2 since the time interval was calculated from the date of first RECIST progression to the date of second progression, whereas PFS2 is typically calculated from date of randomization to date of second progression. PFS2 encompasses both PFS duration and TTSP. In contrast to PFS2, TTSP provides a different insight into the efficacy of subsequent therapies, given that it does not include the impact of initial PARPi maintenance therapy. However, our analysis only evaluated those patients who had progressed on randomized therapies and excluded those who showed no disease progression. Nevertheless, the decreased TTSP observed in this study for platinum-based treated patients who had earlier progressed under olaparib did not represent a reversal of the benefits of olaparib maintenance. Indeed, both PFS and PFS2 in SOLO-2 remained significantly prolonged in the olaparib arm compared with placebo. However, we recognize that the duration of PFS decreases with each

chemotherapy line; PARPi maintenance most likely confirms this observation, which may thus be considered as a proper treatment line.[16]

We herein provide the first benchmark of *BRCA*-mutated relapsing ovarian cancer patients progressing on PARPi in a clinical trial setting, involving patients undergoing subsequent chemotherapy. PARPi maintenance did not affect the ability of patients to receive subsequent treatment lines. Of the 186 patients who had RECIST progression, only nine (6%) did not receive subsequent treatment (six and three patients in the olaparib and placebo arms, respectively). We did not notice any significant difference in the proportions of patients who received platinum-based and non-platinum-based regimens as subsequent chemotherapy among patients treated with olaparib (69%/31%) and placebo (61%/39%), respectively, suggesting similar distribution of platinum-sensitive disease among the relapsed patients. A similar distribution of platinum-based and non-platinum-based chemotherapy as post-progression treatment in the placebo and rucaparib arms was also observed in the ARIEL3 trial, even though the proportion of platinum-based chemotherapy regimens was lower. This difference is likely attributable to the smaller proportion of *BRCA*-mutated patients (35%) who were less likely to be platinum-sensitive.[14] A recent MITO study showed that among *BRCA*-mutated patients treated with maintenance olaparib for platinum-sensitive ovarian cancer, only 22% (platinum-free interval [PFI] > 12 months) and 11% (PFI: 6–12 months) responded to subsequent therapy, suggesting that resistance to platinum represents a real clinical challenge following PARP inhibition.[12]

Resistance to platinum-based chemotherapy is also a strong predictor of the resistance to PARPi treatment.[17] The current practice is to select patients for further platinum-based chemotherapy, if the platinum-free interval is ≥6 months, including in those who had received PARPi and developed disease progression. However, our data (Supplementary 3) showed that there was no difference in platinum chemotherapy outcome according to platinum-free interval following progression after olaparib. We hypothesized that similarity in the resistance mechanisms between platinum chemotherapy and olaparib explains this finding. This observation is in line with the statement from the sixth ovarian cancer consensus conference that discourage the only use of the interval from last platinum treatment as the only clinical trial eligibility criteria for patients with recurrent ovarian cancer. A number of different strategies are currently available to tackle the resistance to PARPi. The OReO/ENGOT-OV38 randomized Phase III trial (NCT03106987) evaluated the efficacy of PARPi re-challenge in both *BRCA*m and non-mutated ovarian cancer patients who had previously received a PARP inhibitor for at least 6 months.[18] Patients were recruited to this study only if they had showed a partial or complete response to platinum-based chemotherapy; these patients were then randomly assigned to receive either olaparib or placebo until disease progression. Re-challenge with

maintenance olaparib provided a statistically significant but clinically modest improvement in PFS compared with placebo, regardless of *BRCA* mutation status: *BRCA* mutant (median PFS: 4.3 vs. 2.8 months; HR 0.57; 95% CI: 0.37–0.87; *P* = 0.022); *BRCA* wild-type (median PFS: 5.3 vs. 2.8 months; HR 0.43, 95% CI: 0.26–0.7; *P* = 0.0023). Some patients derived clinically relevant long-term benefit from re-challenge of olaparib with treatment duration up to 36.9 months.

Resistance to PARPi occurs through three mechanisms: drug target-related resistance, restoration of homologous recombination, and restoration of replication fork stability.[19] The type of initial *BRCA* mutation may impact further sensitivity to chemotherapy after patients had received PARPi in maintenance as suggested by the shorter TTSP in BRCA1m compared to BRCA2m. BRCA1m tumors might more susceptible to resistance mechanisms than their BRCA2m counterparts. However, the numbers within each subgroup is small and hence the data should only be interpreted as hypothesis generating.

Current approaches to overcome resistance are focused on combining PARPi with another agent inhibiting the DNA damage response, immune checkpoint inhibition, or other targeted therapies. There is a mechanistic rationale for combining PARPi with agents targeting other DDR pathways so as to promote synthetic lethality. These include the WEE1, ATR, and CHK1 pathways. The EFFORT study has shown interesting results with a clinical benefit rate of 89% and a median PFS of 6.8 months with olaparib plus adavosertib (WEE1 inhibitor) in a platinum-resistant setting.[20] The CAPRI study has investigated the efficacy of the combination of ceralasertib (ATR inhibitor) plus olaparib in the same setting. The overall response rate and median PFS were 46% and 7.5 months, respectively.[21]

Some limitations of our study should be considered while interpreting the results. This was a post-hoc analysis primarily focused on patients with RECIST progression and this patient subset may represent those with more aggressive disease. In particular, patients who progressed on olaparib will have molecular features that were likely to be different from those who progressed on placebo. Multivariable analyses which we performed would not be able to account for all possible confounders. Further, only those who progressed were included in the current analysis and information of those who progressed later will need to be studied as well. Moreover, even if the proportion of 6-12 and >12 months platinum-free interval was similar in the 2 cohorts, a slight difference in terms of disease status at the inclusion in the SOLO-2 trial (partial response versus complete response) may suggest a difference of chemo-sensitivity in the cohorts. However, the relatively modest 7-month TTSP for patients treated with chemotherapy following progression after olaparib maintenance raises questions concerning

the best treatment strategy, particularly for those who relapse early following PARPi maintenance. Lastly, similar analyses are necessary with respect to PARPi maintenance in the first-line setting, given that the duration of PARPi exposure (2 years in first-line vs treatment until disease progression in SOLO-2) may clearly influence the mechanism of acquisition of resistance, as well as the efficacy of subsequent therapy lines at relapse.

Conclusion

Maintenance PARPi have significantly improved outcome for PSROC. In patients with *BRCA1/2* mutation, olaparib is associated with significant prolongation of PFS, and also numerical improvement of OS. As these agents are currently being widely used, overcoming resistance to PARPi in ovarian cancer patients constitutes a major challenge. Following disease progression on maintenance PARPi therapy, the efficacy of subsequent platinum-based therapy lines is diminished, as shown in this post-hoc hypothesis-generating analysis of SOLO2 trial. Despite the potential for diminished efficacy of subsequent platinum chemotherapy following progression on olaparib, PARPi should still be offered to all eligible patients as maintenance therapy. Better characterization of the underlying mechanisms of resistance is crucial for the development of new treatment strategies, which is currently being prospectively assessed in these patients.

Acknowledgements

The authors thank the patients and their families, the international centers that participated in this trial, the investigators and their study team.

The authors would like to thank Enago (www.enago.com) for the English language review

Funding

SOLO2 was sponsored by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. No grant number is applicable.

Disclosure

JSF reports personal fees from Roche Genentech, personal fees and non-financial support from SeattleGenetics, personal fees and non-financial support from Novartis, personal fees and non-financial support from Pfizer, personal fees and non-financial support from Lilly, personal fees and non-financial support from Novartis, personal fees and non-financial support from GSK, personal fees and non-financial support from Clovis oncoloy, personal fees and non-financial support from Astra Zeneca, personal

fees and non-financial support from Daiichi Sankyo, personal fees and non-financial support from Gilead, personal fees and non-financial support from MSD, personal fees and non-financial support from Pierre Fabre, personal fees and non-financial support from Amgen, outside the submitted work. JWK has no conflict of interest. NA has no conflict of interest. RA has no conflict of interest. DB has no conflict of interest. LV has no conflict of interest. PP reports non-financial support from GSK, Astra-Zeneca, Clovis Oncology outside the submitted work. JAL reports personal fees from Pfizer, AstraZeneca, GSK, MSD, Clovis Oncology, Eisai, Bristol Myers Squibb, Artios Pharma, VBL Therapeutics, Neopharm, outside the submitted work. RTP reports personal fees from AbbVie , AstraZeneca, Eisai, Genentech / Roche, GSK Inc, Merck & Co, Sutro Biopharma, Vascular Biogenics Ltd, outside the submitted work. AMO has nothing to disclose. JK has no conflict of interest. TH has no conflict of interest. SP reports personal fees from , AZ, MSD; ROCHE, Clovis, GSK, Pfizer, Pharmamar, outside the submitted work. NC reports personal fees from Astra-Zeneca, Esai, Genentech, GSK, Merck, Pfizer, Regeneron pharmaceutical, outside the submitted work. TWPS reports personal fee from Astra Zeneca, Tesaro, GSK, outside the submitted work. KT has no conflict of interest. GSS has received grant from Agendia, AstraZeneca, Merck, Novartis, Roche, Seagen, outside the submitted work. AEF has no conflict of interest CKL reports personal fee from Astrazeneca, Amgen, Takeda, Boehringer Ingelheim, Pfizer, Yuhan, Merck KGA, Roche, MSD, outside the submitted work. EPL reports grants and personal fees from AstraZeneca, Merck, GSK, Roche, Incyte, ARCAGY Research, outside the submitted work.

References

1. Poveda A, Floquet A, Ledermann JA et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology 2021; 22: 620-631.
2. Pujade-Lauraine E, Ledermann JA, Selle F et al. 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. The Lancet Oncology 2017; 18: 1274-1284.
3. Mirza MR, Monk BJ, Herrstedt J et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med 2016; 375: 2154-2164.
4. Coleman RL, Oza AM, Lorusso D et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 390: 1949-1961.
5. Moore K, Colombo N, Scambia G et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2018; 379: 2495-2505.
6. Ray-Coquard I, Pautier P, Pignata S et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med 2019; 381: 2416-2428.
7. Gonzalez-Martin A, Pothuri B, Vergote I et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2019; 381: 2391-2402.
8. Coleman RL, Fleming GF, Brady MF et al. Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. N Engl J Med 2019; 381: 2403-2415.

9. Monk BJ, Parkinson C, Lim MC et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA–MONO/GOG-3020/ENGOT-ov45). Journal of Clinical Oncology 0: JCO.22.01003.
10. Patch AM, Christie EL, Etemadmoghadam D et al. Corrigendum: Whole-genome characterization of chemoresistant ovarian cancer. Nature 2015; 527: 398.
11. Lin KK, Harrell MI, Oza AM et al. BRCA Reversion Mutations in Circulating Tumor DNA Predict Primary and Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma. Cancer Discov 2019; 9: 210-219.
12. Cecere SC, Giannone G, Salutari V et al. Olaparib as maintenance therapy in patients with BRCA 1-2 mutated recurrent platinum sensitive ovarian cancer: Real world data and post progression outcome. Gynecol Oncol 2020; 156: 38-44.
13. Ang JE, Gourley C, Powell CB et al. Efficacy of chemotherapy in BRCA1/2 mutation carrier ovarian cancer in the setting of PARP inhibitor resistance: a multi-institutional study. Clin Cancer Res 2013; 19: 5485-5493.
14. Ledermann JA, Oza AM, Lorusso D et al. Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): post-progression outcomes and updated safety results from a randomised, placebo-controlled, phase 3 trial. The Lancet Oncology 2020; 21: 710-722.
15. Matulonis U, Herrstedt J, Oza A et al. Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase III trial of niraparib in recurrent ovarian cancer. Gynecologic Oncology 2021; 162: S24-S25.
16. Hanker LC, Loibl S, Burchardi N et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol 2012; 23: 2605-2612.
17. Johnson N, Johnson SF, Yao W et al. Stabilization of mutant BRCA1 protein confers PARP inhibitor and platinum resistance. Proc Natl Acad Sci U S A 2013; 110: 17041-17046.
18. Pujade-Lauraine E, Selle F, Scambia G et al. LBA33 Maintenance olaparib rechallenge in patients (pts) with ovarian carcinoma (OC) previously treated with a PARP inhibitor (PARPi): Phase IIIb OReO/ENGOT Ov-38 trial. Annals of Oncology 2021; 32: S1308-S1309.
19. Dias MP, Moser SC, Ganesan S, Jonkers J. Understanding and overcoming resistance to PARP inhibitors in cancer therapy. Nat Rev Clin Oncol 2021; 18: 773-791.
20. Westin SN, Coleman RL, Fellman BM et al. EFFORT: EFFicacy Of adavosertib in parp ResisTance: A randomized two-arm non-comparative phase II study of adavosertib with or without olaparib in women with PARP-resistant ovarian cancer. Journal of Clinical Oncology 2021; 39: 5505-5505.
21. Shah PD, Wethington SL, Pagan C et al. Combination ATR and PARP Inhibitor (CAPRI): A phase 2 study of ceralasertib plus olaparib in patients with recurrent, platinum-resistant epithelial ovarian cancer. Gynecol Oncol 2021; 163: 246-253.

Figure Legends

Figure 1. Flow-chart of the study. O: olaparib; P: platinum; PARPi: PARP inhibitor

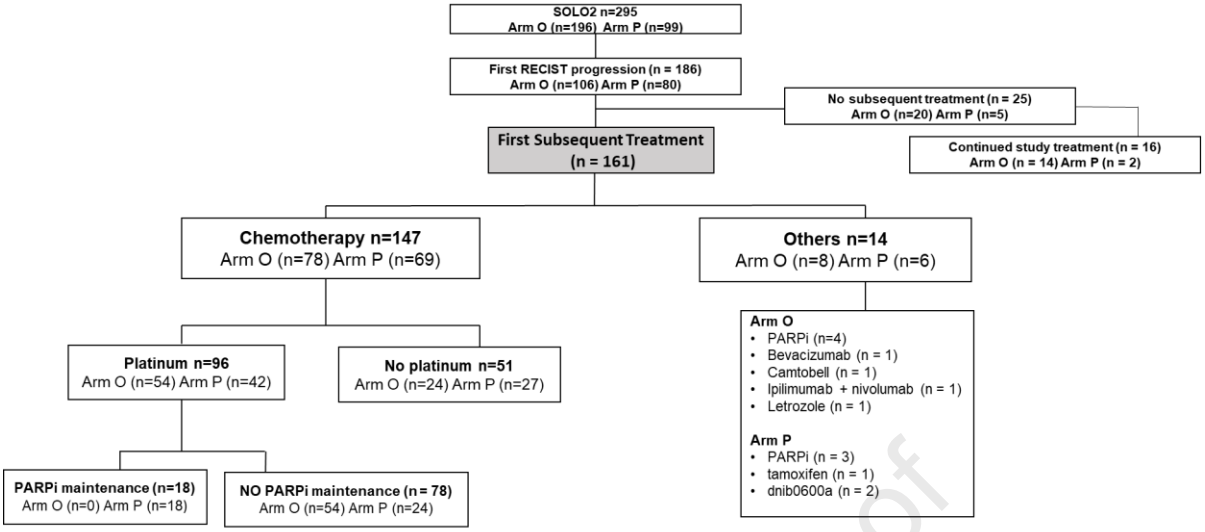
Figure 2. Time to second progression according to subsequent therapy type

Supplementary figure 1. Time to the second progression in patients treated with chemotherapy (*N* = 147) stratified by Myriad *BRCA1* or *BRCA2* mutation at entry in the SOLO2 trial

Supplementary figure 2. Time to the second progression in patients treated with platinum-based chemotherapy (*N* = 96) stratified by the previous platinum-free interval at entry in the SOLO2 trial

Table 1. Characteristics of patients who received chemotherapy as subsequent therapy regimen, with comparison between olaparib- vs. placebo-treated patients

Characteristics	Overall population (n=147)			Platinum-based cohort (n=96)			Non platinum-based cohort (n=51)			SOLO2 population (n=295)	
	olaparib N = 78	placebo N = 69	*p* value	olaparib N = 54	placebo N = 42	*p* value	olaparib N = 24	placebo N = 27	*p* value	olaparib N = 196	placebo N = 99
Mean (SD) age, years	57 (40 -83)	56 (39 -75)	0.41	57 (40-83)	57 (40-75)	0.58	56 (45-68)	55 (39-70)	0.65	56 (51–63)	56 (49–63)
ECOG, n (%)											
Normal activity	62 (81%)	54 (78%)	0.61	46 (87%)	31 (74%)	0.11	16 (67%)	23 (85%)	0.12	162 (84%)	77 (78%)
Restricted activity	15 (19%)	15 (22%)		7 (13%)	11 (26%)		8 (33%)	4 (15%)		32 (16%)	22 (22%)
Missing	1			1						2	0
Primary Tumor Location, n (%)											
Ovary	65 (83%)	59 (86%)	0.86	45 (83%)	36 (86%)	0.67	20 (83%)	23 (85%)	0.55	164 (84%)	86 (87%)
Fallopian	5 (6%)	3 (4%)		5 (9%)	2 (5%)		0 (0%)	1 (4%)		13 (7%)	4 (4%)
Other	8 (10%)	7 (10%)		4 (7%)	4 (10%)		4 (17%)	3 (11%)		19(9%)	9 (9%)
Histology, n (%)											
Serous	75 (96%)	63 (91%)	0.37	53 (98%)	38 (90%)	0.22	22 (92%)	25 (93%)	0.90	183 (93%)	86 (87%)
Endometrioid	3 (4%)	5 (7%)		1 (2%)	3 (7%)		2 (8%)	2 (7%)		9 (5%)	8 (8%)
Others	0 (0%)	1 (1%)		0 (0%)	1 (2%)		0 (0%)	0 (0%)		4 (2%)	5 (5%)
Myriad *BRCA* status, n (%)											
BRCA1	53 (71%)	43 (63%)	0.43	36 (69%)	24 (59%)	0.28	17 (74%)	19 (70%)	0.78	132 (69%)	61 (64%)
BRCA2	22 (29%)	25 (37%)		16 (31%)	17 (41%)		6 (26%)	8 (30%)		58 (31%)	35 (36%)
Missing	3	1		2	1		1	126		6	3
Previous platinum free interval, n (%)											
6-12 months	40 (51%)	33 (48%)	0.68	28 (52%)	20 (48%)	0.68	12 (50%)	14 (52%)	0.89	79 (40%)	40 (40%)
>12 months	38 (49%)	36 (52%)		26 (48%)	22 (52%)		12(50%)	13 (48%)		117 (60%)	59 (60%)
Previous platinum based regiment, n (%)											
2	41 (53%)	37 (54%)	0.15	30 (56%)	23 (55%)	0.49	11 (46%)	14 (52%)	0.25	110 (56%)	62 (63%)
3	28 (36%)	17 (25%)		18 (33%)	11 (26%)		10 (42%)	6 (22%)		60 (31%)	20 (20%)
>3	9 (12%)	15 (22%)		6 (11%)	8 (19%)		3 (13%)	7 (26%)		25 (13%)	17 (17%)
Disease status at inclusion in the SOLO2 trial, n (%)											
Partial reponse	60 (77%)	41 (59%)	**0.02**	40 (74%)	23 (55%)	**0.05**	20 (83%)	18 (67%)	0.17	91 (46%)	47 (47%)
Complete response	18 (23%)	28 (41%)		14 (26%)	19 (45%)		4 (17%)	9 (33%)		105 (54%)	52 (53%)
Prior use of bevacisumab, n (%)											
Yes	14 (18%)	18 (26%)	0.23	12 (22%)	14 (33%)	0.22	2 (8%)	4 (15%)	0.47	33(17%)	20(20%)
No	64 (82%)	51 (74%)		42 (88%)	28 (77%)		22 (92%)	23 (85%)		163(83%)	79(80%)



25 patients had a PARPi as part of maintenance or treatment of their subsequent therapy: Arm P= 21, Arm O= 4 pts

Figure 1.

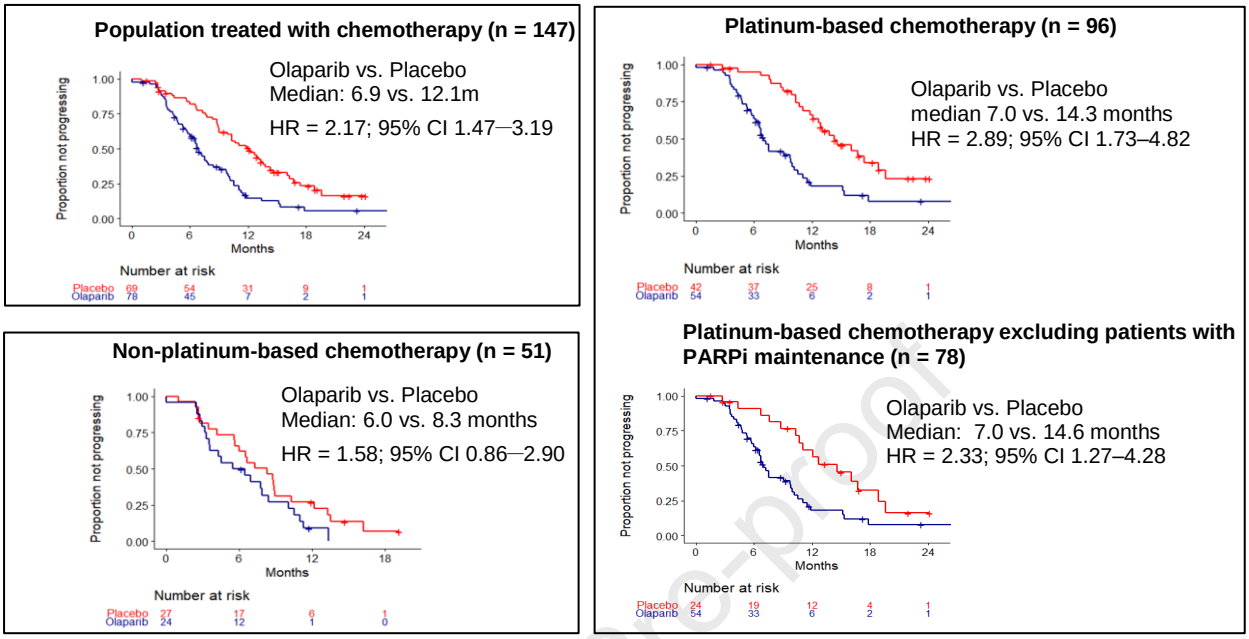


Figure 2.