Updates on Therapy for Gynecologic Cancers

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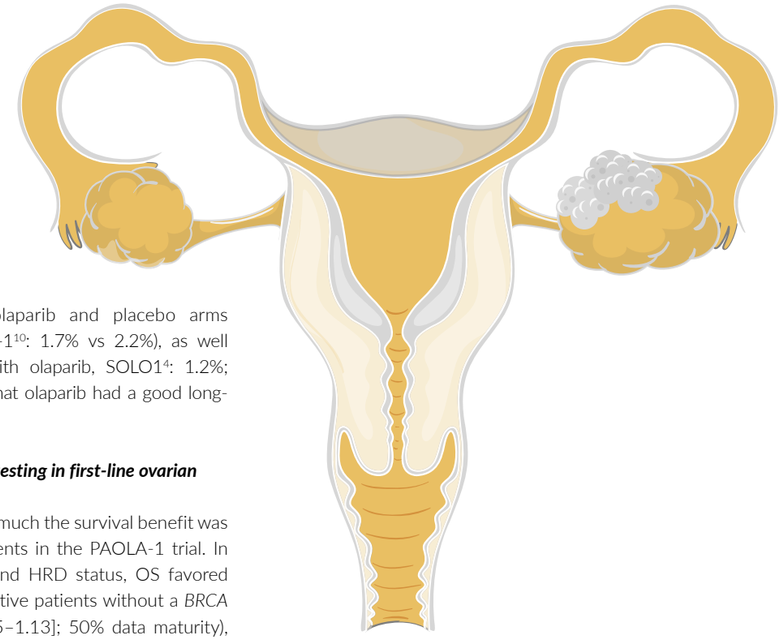

SOLO1 and PAOLA-1: Clinically meaningful OS benefit with first-line maintenance olaparib in *BRCA*- or HRD-mutated advanced ovarian cancer

Bevacizumab in combination with carboplatin and paclitaxel was approved for the first-line treatment of patients with advanced ovarian cancer,[1] despite the lack of overall survival (OS) advantage over chemotherapy alone in the ICON7 and GOG-0218 trials.[2,3] Recently, poly (adenoside phosphate-ribose [ADP]-ribose) polymerase (PARP) inhibitors, such as olaparib, niraparib and rucaparib, expanded the treatment landscape, with improvements in PFS when used as maintenance therapy in the first-line setting but unclear long-term benefit.[4-8] At the ESMO Congress 2022, the long-awaited OS data from the placebo-controlled, phase III studies SOLO1[9] (olaparib) and PAOLA-1[10] (olaparib plus bevacizumab) werepresented. Both trials included patients with newly diagnosed advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III or IV), high-grade serous or endometrioid ovarian cancer, primary peritoneal or fallopian tube cancer; while SOLO1 was restricted to patients with *BRCA*-mutated tumors, PAOLA-1 followed an all-comers design. SOLO-1 had a prespecified, 7-year post-last-patient-in descriptive OS analysis and a planned final analysis at ~60% data maturity, with statistical significance at p<0.0001 (two-sided).[9] In PAOLA-1, a hierarchical strategy was applied, with sequential testing for progression-free survival (PFS), PFS2 and OS, and the final OS analysis was planned at 3 years after the primary PFS report or 60% data maturity, with statistical significance at p<0.05.[10]

At the 5-year PFS update of SOLO1, maintenance olaparib for up to 2 years resulted in a 67%-reduction in the risk of disease progression or death versus placebo (HR: 0.33 [95% CI: 0.25–0.43]).[11] At this 7-year OS analysis, olaparib demonstrated a statistically non-significant but clinically meaningful improvement in OS compared with placebo (median, not reached vs 75.32 months, HR: 0.55 [95% CI: 0.40–0.76]; p=0.0004), with 7-year rates of 67.0% and 46.5%, respectively.[9] The OS benefit of olaparib versus placebo became more evident over time, despite the high rate of patients who received subsequent PARP inhibitor treatment in the placebo arm (44.3% vs 14.6% in the olaparib arm). In terms of time to first subsequent therapy (TFST), a plateau was reached in the placebo arm, while only a slight drop from the 5-year analysis was observed in the olaparib arm, with 5-year rates of 22.5% and 51.2% and 7-year rates of 20.6% and 45.3%, respectively. The median TFST was 4 times longer with olaparib than placebo (64.0 months vs 15.1 months, HR: 0.37 [95% CI: 0.28–0.48]).

In PAOLA-1, patients received maintenance olaparib versus placebo for up to 2 years on top of bevacizumab after first-line platinum-taxane chemotherapy plus bevacizumab.[10] With a 5-year median follow-up and 55.3% data maturity, there were no OS differences between the two treatment arms in the intention-to-treat (ITT) population (HR: 0.92; p=0.4118). However, olaparib provided a clinically meaningful OS benefit compared with placebo among patients with homologous recombination deficiency (HRD)-positive tumors (HR: 0.62 [95% CI: 0.45–0.85]); 5-year OS rates were 65.5% and 48.4%, respectively. In this subgroup, 50.8% of patients in the placebo arm received a PARP inhibitor during any subsequent therapy versus 17.3% in the olaparib arm. The updated PFS analysis showed a 26.9%-difference in the 5-year PFS rates (46.1% vs 19.2%) and a 59%-reduction in the risk of disease progression or death with olaparib versus placebo within the HRD-positive population (HR: 0.41 [95% CI: 0.32–0.54]). Of note, the benefit of bevacizumab addition to PARP inhibitor therapy is also being evaluated in the phase III ENGOT-ov57 trial on niraparib.[12]

With regards to long-term side effects of PARP inhibitors, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and aplastic anemia (AA) were adverse events (AEs) of special interest. With this long follow-ups, only minor differences were observed between the olaparib and placebo arms (SOLO1[9]: 1.5% vs 0.8%; PAOLA-1[10]: 1.7% vs 2.2%), as well as from the primary analyses (with olaparib, SOLO1[4]: 1.2%; PAOLA-1[5]: 1.1%), demonstrating that olaparib had a good long-term safety profile.

The importance of BRCA and HRD testing in first-line ovarian cancer

The question can be raised of how much the survival benefit was driven by the *BRCA*-mutated patients in the PAOLA-1 trial. In the subgroup analysis by *BRCA* and HRD status, OS favored olaparib over placebo in HRD-positive patients without a *BRCA* mutation (HR: 0.71 [95% CI: 0.45–1.13]; 50% data maturity), with comparable results for the *BRCA*-mutated subgroup (HR: 0.60 [95% CI: 0.39–0.93]; 36% data maturity).[10] Thus, BRCA testing alone might miss patients who may potentially benefit from PARP inhibition and HRD assessment with a validated test could be valuable in clinical practice. So far, only the MyChoice CDx test from Myriad Genetics can be regarded as a validated test and was predictive in the PAOLA-1 trial; patients with HRD-negative or unknown status did not show PFS advantage (HR: 0.92).[5,10] In the PRIMA trial, however, it was not predictive of response to PARP inhibition as HR-proficient patients also derived PFS benefit from niraparib therapy (HR: 0.68 [95% CI: 0.49–0.94]).[13] Similarly, rucaparib showed PFS improvement in HRD-negative patients in the ATHENA-MONO trial (HR: 0.60 [95% CI: 0.40–0.89]), in which the FoundationOne CDx assay was used for HRD status determination.[8] Of note, the Geneva test from the ENGOT HRD Initiative, which has been presented at the ESGO Congress 2022, represents a great opportunity for a validated, decentralized test from an academic initiative that is associated with low costs.

ARIEL4: Rucaparib did not improve OS versus chemotherapy in patients with relapsed ovarian cancer

In the phase III ARIEL4 trial, patients with recurrent ovarian cancer harboring *BRCA* mutations were randomized 2:1 to receive rucaparib or chemotherapy with either paclitaxel or a platinum-based regimen, depending on their platinum-sensitivity status.[14] Crossover to rucaparib was permitted upon progressive disease. Despite the PFS benefit of rucaparib versus chemotherapy in the ITT (HR: 0.67 [95% CI: 0.52–0.86]; p=0.0017),[14] OS favored chemotherapy in the final analysis (HR: 1.313 [95% CI: 0.999–1.725]).[15] Notably, in the platinum-resistant subgroup (rucaparib, n=120; chemotherapy, n=59), the median duration of treatment in the rucaparib arm was 5.6 months but 91.1% of patients in the chemotherapy arm crossed over, with 27 of those receiving treatment for ≥6 months (median duration of crossover to rucaparib: 9.4 months). When patients who crossed over were excluded from the OS analysis (ITT), there was a positive signal for rucaparib versus placebo (median, 19.4 months vs 9.1 months; HR: 0.423 [95% CI: 0.276–0.650]). Thus, crossover and long post-progression survival could explain the discrepancy between analyses. For the time being, chemotherapy is still the preferred option for relapsed patients.

ENGOT-cx9: Second-line cemiplimab improved OS in patients with recurrent cervical cancer, regardless of PD-L1 expression

In this phase III trial, 608 patients with recurrent cervical cancer after first-line platinum-based chemotherapy were randomized 1:1 to receive either the immune checkpoint inhibitor cemiplimab or single-agent chemotherapy.[16] At the second interim analysis, the trial met its primary endpoint of OS[16] and similar results were observed at this final analysis at a median follow-up of 30.2 months, with a median OS in the overall population of 11.7 months with cemiplimab versus 8.5 months with chemotherapy (HR: 0.656 [95% CI: 0.545–0.790]; one-sided p<0.00001).[17] The OS improvement was observed among patients with squamous cell carcinoma (HR: 0.690 [95% CI: 0.560–0.850]; p=0.0023) and those with adenocarcinoma (HR: 0.545 [95% CI: 0.365–0.814]).

In addition, programmed death-ligand 1 (PD-L1) testing was available for 42% of patients in the previous analysis[16] and 60% of patients in the current analysis.[17] The overall PD-L1 positivity was 64% and cemiplimab prolonged OS versus chemotherapy irrespective of PD-L1 status (tumor cell PD-L1 expression <1%; HR: 0.650), indicating that PD-L1 is not a predictive biomarker.[17] Interestingly, patients with tumor PD-L1 expression <1% showed no benefit of cemiplimab in the previous analysis (HR: 0.98).[16]

Notably, PD-L1 was a predictive biomarker in the phase III KEYNOTE-826 trial in patients with persistent, recurrent or metastatic cervical cancer.[18] The addition of pembrolizumab to first-line chemotherapy, with or without bevacizumab, prolonged PFS and OS in patients with a PD-L1 combined positive score (CPS) ≥1 (HR: 0.62 and 0.64, respectively; p<0.001 for both) but not in those with CPS <1 (n=69; HR: 0.94 and 1.00).

Based on these data, PD-L1 as a biomarker should be used with care and should not drive treatment decision-making.

Encouraging results with immunotherapy in gynecologic CCC

Clinical evidence of immunotherapy activity in ovarian clear cell cancer (OCCC) was provided in subgroup analyses of four clinical trials, namely NINJA,[19] KEYNOTE-100,[20] IMAGYN50[21] and NRG GY003.[22] The AGO-OVAR 2.29 trial of atezolizumab combination treatment in recurrent ovarian cancer will likely contribute data on CCC patients.[23] In advanced endometrial CCC, lenvatinib plus pembrolizumab improved PFS (HR: 0.47) and OS (HR: 0.33) versus treatment of physician's choice (TPC) chemotherapy in the KEYNOTE-775 trial.[24]

In the phase II PEACOCC trial, patients with advanced recurrent clear cell gynecological cancer (CCGC) (85% with ovarian cancer) received pembrolizumab monotherapy for up to 2 years.[25] The primary endpoint of PFS at 12 weeks was 43.8% and the median OS was 71 weeks. Importantly, the response rate in this patient population was 25%, with a 1-year duration of response rate of 47.7% Furthermore, preliminary results from the INOVA trial in relapsed or persistent OCCC showed an overall response rate (ORR) of 38.5% with the combination of the immune checkpoint inhibitor sintilimab and bevacizumab, hinting towards a benefit of the addition of antiangiogenic therapy.[26]

Overall, it is a reasonable approach to rely on histology if disease-based treatment is not possible. Related to this, basket trials such as BOUQUET investigate molecular-directed therapies in rare gynecologic tumors.[27]

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