Letter to the Editor

Updated treatment recommendations for newly diagnosed epithelial ovarian carcinoma from the ESMO Clinical Practice Guidelines

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The following ESMO Clinical Practice Guideline has been recently updated with new treatment recommendations:

Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.[1]

EUPDATE

View the ESMO eUpdate here: [hyperlink to the eUpdate on the ESMO guidelines website to be inserted when available]

CHEMOTHERAPY IN NEWLY DIAGNOSED OVARIAN CANCER

Targeted therapy

Three phase III trials (SOLO-1, PAOLA-1/ENGOT-ov25 and PRIMA/ENGOT-OV26) in newly diagnosed high-grade epithelial ovarian cancers (including fallopian tube and peritoneal) have investigated maintenance therapy with the poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors olaparib or niraparib after surgery and chemotherapy (ChT).[2-4] In another trial (VELIA/GOG-3005), veliparib was given with ChT followed by maintenance.[5] All four trials have demonstrated significant improvements in progression-free survival (PFS).

SOLO1 assessed first-line maintenance monotherapy with olaparib given for 2 years in women with FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) stage III-IV ovarian cancer and a *BRCA* mutation with a partial or complete response to platinum-based ChT.[2] Primary results from SOLO1 showed that maintenance with olaparib significantly reduced the risk of disease progression by 70% [hazard ratio (HR) 0.30, 95% confidence

interval (CI) 0.23-0.41, *P*<0.001] compared with placebo.[2] Extended follow-up has demonstrated sustained long-term benefit, with 5-year follow-up showing a median PFS of 56 months with olaparib versus 14 months with placebo (HR 0.33, 95% CI 0.25-0.43). At 5 years, 48% of patients treated with olaparib remained progression-free compared with 21% in the placebo group.[6] Olaparib has been approved by both the European Medicines Agency (EMA) and Food and Drug Administration (FDA) as maintenance therapy in *BRCA*-mutated patients in first remission after platinum-based therapy.

PRIMA/ENGOT-OV26 evaluated niraparib as maintenance therapy for up to 3 years in patients with stage III-IV disease at high risk of treatment failure, with or without *BRCA* mutation.[3] Patients with stage III ovarian cancer and no residual disease after primary debulking surgery were excluded and 67% of patients had received neoadjuvant ChT. Patients were stratified according to homologous recombination repair deficiency (HRD) status of the tumour using the Myriad myChoice assay (defined as an HRD score of 42 or higher). The primary analysis was performed on the HRD population, followed hierarchically by the all-comer population. The study showed a significant improvement in PFS in the HRD population (HR 0.43, 95% CI 0.31-0.59, *P*<0.001) and in the overall population (HR 0.62, 95% CI 0.50-0.76, *P*<0.001). An exploratory subgroup analysis showed that the greatest benefit occurred in women with a *BRCA* mutation and a significant but lesser benefit in women who were *BRCA* wild type with HRD. There was also an increase of 2.7 months in the median PFS in the HRD-negative, sometimes termed homologous recombination proficient (HRP) population (HR 0.68, 95% CI 0.49-0.94, *P*=0.020). Niraparib has been approved by both EMA and FDA as maintenance therapy for unselected patients in first remission after platinum-based therapy.

In the PAOLA-1/ENGOT-ov25 trial, patients with stage III-IV ovarian cancer, with or without residual tumour after surgery, were treated with ChT and bevacizumab, and after ChT randomised to maintenance therapy with olaparib tablets or placebo for two years, as well as completing 15 months bevacizumab in both arms of the trial.[4] The study included all patients who had no residual disease after surgery and remained NED (no evidence of disease) or achieved a complete or partial response after ChT and bevacizumab. Randomisation to olaparib or placebo was stratified based on tumour *BRCA* mutation status and response to first-line treatment. The primary analysis in the all-comer intention-to-treat (ITT) population showed a significant benefit in PFS in patients receiving olaparib and bevacizumab with a median PFS of 22.1 months compared with 16.6 months with placebo and bevacizumab (HR 0.59, 95% CI 0.49-0.72, *P*<0.001). Exploratory subgroup analyses

showed the greatest benefit among women with a *BRCA* mutation (HR 0.31, 95% CI 0.20-0.47) followed by HRD-positive women (defined using the Myriad myChoice assay as an HRD score of 42 or higher) -including women with *BRCA* mutation (HR 0.33, 95% CI 0.25-0.45) and HRD-positive women with *BRCA* wild-type (HR 0.43, 95% CI 0.28-0.66). No benefit was observed in the HRD-negative/unknown population.[4] Olaparib has been approved by both the EMA and FDA as maintenance therapy in combination with bevacizumab in *BRCA* mutated and HRD patients in first remission after platinum-based therapy.

In the VELIA/GOG-3005 trial, standard ChT in stage III-IV ovarian cancer was compared with veliparib given during ChT and then as maintenance for up to 2 years, or with veliparib given only with ChT.[5] A hierarchical testing analysis showed the greatest reduction in the risk of progression or death of 56% among patients with a *BRCA* mutation (HR 0.44, 95% CI 0.28-0.68, *P*<0.001), followed by 43% in patients with HRD, using the Myriad Mychoice cut off value of 33 (HR 0.57, 95% CI 0.43-0.76, *P*<0.001) and 32% in the ITT population (HR 0.68, 95% CI 0.56-0.83, *P*<0.001). The median PFS in the ITT group was 23.5 and 17.3 months in the veliparib and control groups, respectively. Veliparib in first-line therapy has not been submitted for regulatory approval.

All trials have shown a benefit in median PFS for PARP inhibitor maintenance therapy in the first-line setting, with the greatest effect seen in women with a *BRCA* mutation.[2-6] It is unclear to what extent later use of PARP inhibitors in the placebo arm will have on the overall survival (OS), thus underscoring the importance of uncensored evaluation of OS as the studies mature.

Olaparib monotherapy maintenance after first-line treatment is licensed in women with a *BRCA* mutation. In many countries, it is also licensed together with bevacizumab in a broader population in tumours with HRD (*BRCA* mutation or *BRCA* wild type). Many countries have also approved niraparib as a single agent in women with stage III-IV ovarian cancer who have responded to first-line therapy, irrespective of biomarker status. The side-effects of oral PARP inhibitors are manageable in most patients but a slight increase in rare serious adverse events such Acute Myeloid Leukaemia/Myelodysplasia is recognised. Long-term outcome data (survival) are not yet available; this will aid decision-making about which subgroups of patients benefit more from first-line use of PARP inhibitors or their use at recurrence.

Recommendations

- All patients with high-grade ovarian cancer should be tested for a *BRCA* mutation at diagnosis. This should include tumour *BRCA* testing for somatic mutations [I, A].
- Patients with a *BRCA* mutation and a partial or complete response to front-line platinum-based ChT should receive maintenance treatment with a PARP inhibitor (two years for olaparib [ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4], three years for niraparib [ESMO-MCBS v1.1 score: 3]. The combination of olaparib and bevacizumab should be used when bevacizumab is added to front-line ChT [I, A; ESMO-MCBS v1.1 score: 3] though it is not clear that this provides superior results to the use of olaparib alone.
- Testing for genomic instability (HRD) is recommended. It identifies a subgroup of women who are *BRCA* wild type but derive greater benefit from a PARP inhibitor [I, A]. Patients with a positive HRD test and a partial or complete response to front-line platinum-based ChT, with or without bevacizumab, should receive maintenance treatment with a PARP inhibitor, either olaparib/bevacizumab (if started with ChT) or niraparib monotherapy [I, A; ESMO-MCBS v1.1 score: 3].
- Patients receiving bevacizumab with front-line ChT and who are HRD-negative do not have a PFS benefit from the addition of olaparib to maintenance bevacizumab [I, B]. This is not a licenced indication and consequently is not recommended.
- Niraparib monotherapy is licensed for all patients with stage III-IV ovarian cancer who have responded to ChT. Long-term outcome data are not available, a decision about using the drug as first-line or at recurrence in the HRD-negative population or in the absence of knowledge about HRD status, needs to be made on a case-by-case basis [I, C; ESMO-MCBS v1.1 score: 3]

Table 1. ESMO-MCBS table for new therapies/indications in newly diagnosed epithelial ovarian carcinoma[a]

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[b]
Olaparib	Maintenance therapy *BRCA*-mutated high grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer who are in response (complete or partial) following completion of platinum-based ChT	Olaparib maintenance monotherapy in patients with *BRCA* mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum-based chemotherapy[2] SOLO-1 Phase III NCT01844986	Placebo PFS control: 13.8 months	PFS gain: 30+[c] months >10% gain in PFS at 24 months with plateauing of curve	PFS HR: 0.30 (0.23-0.41)	QoL no benefit observed	4 (Form 2b)

Niraparib	Maintenance treatment for high grade ovarian, fallopian tube or peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based ChT	Niraparib maintenance treatment in patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy, HRD[d] and unselected and HRP[e,3] PRIMA/ENGOT-OV26/GOG-301 Phase III NCT02655016	Placebo HRD PFS control: 10.4 months Overall population PFS control: 8.2 months	HRD PFS gain: 11.5 months Overall population PFS gain 5.6 months	HRD PFS HR: 0.43 (0.31-0.59) Overall population PFS HR: 0.62 (0.50-0.76) OS: Not significant in the interim	QoL no benefit observed	3 (Form 2b) 3 (Form 2b)

Olaparib plus bevacizumab	Maintenance treatment of high grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based ChT- bevacizumab	Olaparib vs. placebo patients with advanced high grade serious or endometrioid ovarian, fallopian tube, or peritoneal cancer treated standard first-line treatment ovarian cancer (approved by FDA and EMA only for HRD[d] and/or *BRCA* MUT) PAOLA-1/ENGOT-ov25[4] Phase III NCT02477644	Placebo plus bevacizumab HRD+ BRCA-MUT PFS control: 17.7 months HRD+ *BRCA*-WT PFS control: 16.6 months *BRCA* MUT PFS control: 21.7 months	PFS gain: 19.5 months PFS gain: 11.5 months PFS gain: 15.5 months	PFS HR: 0.33 (0.25-0.45) PFS HR: 0.43 (0.28-0.66) PFS HR: 0.31 (0.20-0.47)	QoL no benefit observed	3 (Form 2b) 3 (Form 2b) 3 (Form 2b)

BRCA, breast cancer gene; ChT, chemotherapy; CI, confidence interval; EMA, European Medicines Agency; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDA, Food and Drugs Administration; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; HRP, homologous recombination proficient; MUT, mutation; NS, not significant; OS, overall survival; PFS, progression-free survival; QoL, quality of life; WT, wild type.

[a] EMA approvals since 1 January 2016 and FDA approvals since 1 January 2020.

[b] ESMO-MCBS version 1.1.[7] The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1).

[c] Updated data in abstract PFS Control 14 months, gain 42 months.[6]

[d] HRD positive was defined as a tumour *BRCA* mutation or an HRD score of 42 or higher on the myChoice HRD Plus assay (Myriad Genetic Laboratories).

[e] HRP data derived from pre–specified exploratory analysis are not eligible for ESMO-MCBS scoring: PFS control 5.4 months, gain 2.7 months HR 0.68 (0.49 -0.94).

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