

REFERENCES

1. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395(10241):1907-1918.
2. He W, Chen L, Chen L, et al. COVID-19 in persons with haematological cancers. *Leukemia*. 2020;34(6):1637-1645.
3. Passamonti F, Cattaneo C, Arcaini L, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *Lancet Haematol*. 2020;7(10):e737-e745.
4. Abbasi J. Prolonged SARS-CoV-2 infection in a CAR T-cell therapy recipient. *JAMA*. 2021;325(10):924.
5. Marshall JC, Murthy S, Diaz J, et al. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192-e197.
6. Veyer D, Kernéis S, Poulet G, et al. Highly sensitive quantification of plasma SARS-CoV-2 RNA sheds light on its potential clinical value. *Clin Infect Dis*. 2020. <https://doi.org/10.1093/cid/ciaa1196>

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



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: <https://www.esmo.org/guidelines/gynaecological-cancers/newly-diagnosed-and-relapsed-epithelial-ovarian-carcinoma/eupdate-newly-diagnosed-epithelial-ovarian-carcinoma-treatment-recommendations>

FRONT-LINE CHEMOTHERAPY FOR EPITHELIAL OVARIAN CANCER (FIGO STAGE II-IV)

The text has been updated for targeted therapy and ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scores summarised in a new table (Table 3).

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.

The PRIMA/ENGOT-OV26 trial 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). 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 showed 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, population (HR 0.68, 95% CI 0.49-0.94, $P = 0.020$). Niraparib has been approved by both the 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 2 years, as well as completing 15 months of bevacizumab therapy in both arms of the trial.⁴ The study included all patients who had no residual disease after surgery and 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

Table 3. 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 in patients with <i>BRCA</i> -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 <i>BRCA</i> -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 patients with 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 ^{3,e} 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 immature	QoL: no benefit observed QoL: no benefit observed	3 (Form 2b) 3 (Form 2b)
Olaparib plus bevacizumab	Maintenance treatment of patients with 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 versus placebo patients with advanced high-grade serious or endometrioid ovarian, fallopian tube or peritoneal cancer treated with standard first-line treatment ovarian cancer (approved by the FDA and the EMA only for HRD ^d and/or <i>BRCA</i> MUT) PAOLA-1/ENGOT-ov25 ⁴ Phase III NCT02477644	Placebo plus bevacizumab HRD+ <i>BRCA</i> -MUT PFS control: 17.7 months HRD+ <i>BRCA</i> -WT PFS control: 16.6 months <i>BRCA</i> 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 QoL: no benefit observed 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 Drug Administration; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; HR, hazard ratio; HRD, homologous recombination deficiency; HRP, homologous recombination proficient; MUT, mutation; 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 on the myChoice HRD Plus assay (Myriad Genetic Laboratories).

^e HRP data derived from prespecified exploratory analysis are not eligible for ESMO-MCBS scoring: PFS control: 5.4 months; gain: 2.7 months, HR (95% CI): 0.68 (0.49-0.94).

Myriad myChoice assay as an HRD score of ≥ 42) 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 the FDA as maintenance therapy in combination with bevacizumab in *BRCA*-mutated and HRD-positive 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% was 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 (HR 0.57, 95% CI 0.43-0.76, $P < 0.001$; using the Myriad myChoice cut-off value of 33) and 32% in the ITT population (HR 0.68, 95% CI 0.56-0.83, $P < 0.001$). The median PFS in the ITT population was 23.5 months 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 affect overall survival, thus underscoring the importance of uncensored evaluation of overall survival 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 as acute myeloid leukaemia/myelodysplasia is recognised. Long-term outcome data (survival) are not yet available; these 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 *BRCA1* and *BRCA2* mutation (germline/somatic) at diagnosis. [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: 2 years for olaparib [ESMO-MCBS v1.1 score: 4] and 3 years for niraparib [ESMO-MCBS v1.1 score: 3] (Table 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, E]. 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].

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REFERENCES

- Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24(suppl 6):vi24-vi32.
- Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med.* 2018;379(26):2495-2505.
- González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med.* 2019;381(25):2391-2402.
- 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(25):2416-2428.
- 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(25):2403-2415.
- Banerjee S, Moore K, Colombo N, et al. Maintenance olaparib for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): 5-year (y) follow-up (f/u) from SOLO1. *Ann Oncol.* 2020;31(suppl 4):abstr 811MO.
- Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale Version 1.1. *Ann Oncol.* 2017;28:2340-2366.

Response to the letter to the Editor: TMB cut-offs fail to predict benefit of PD-1 blockade in gastroesophageal adenocarcinoma in KEYNOTE-061



The letter from Foote et al.¹ critiques the KEYNOTE-061 tumor mutational burden (TMB) data reported by Shitara et al.² along two primary lines. The first is that removal of patients with microsatellite instability-high (MSI-H) status from analysis qualitatively changes the conclusions at the pre-specified cut-off [175 mutations/exome (mut/exome) using whole exome sequencing (WES) or 10 mut/Mb using FoundationOne[®] CDx] such that actionable benefit is 'lost'. The second is that results may be biased or confounded because patients with unknown MSI-H and microsatellite stable (MSS) status were combined.

Claiming the impact of TMB has been lost when MSI-H cases are removed is ill-supported by review of Table 2 (MSI-H included) and Table 4 (MSI-H excluded). Apart from progression-free survival (PFS), pembrolizumab's advantage over paclitaxel in the high TMB subgroup in Table 2 is maintained in Table 4. Improvements in objective response rate (ORR), median overall survival (OS), and the OS hazard ratio (HR) favoring pembrolizumab versus paclitaxel provided in Table 4 persist and are similar qualitatively to those of Table 2. Likewise, the OS Kaplan-Meier curves in Figure 4, although less separated than those of Figure 3, show a similar trend favoring pembrolizumab for patients with high TMB. Perhaps the statement by Foote et al. refers to the inclusion of 1.0 in the confidence limit of the OS HR of the high TMB group in Table 4, but not Table 2. We would only note that *post-hoc* repurposing of confidence limits as tests of statistical significance may not be appropriate. Confidence limits gauge precision and, along with the point estimates in Tables 2 and 4, constitute a descriptive analysis

Table 1. Comparison of MSI-H status by WES and PCR^a

MSI status by NGS	MSI status by PCR		
	MSI-H	Non MSI-H	Missing
MSI-H	12	0	0
MSS	2	198	6

CPS, combined positive score; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NGS, next generation sequencing; TMB, tumor mutational burden; WES, whole exome sequencing.

^a Includes 204 patients in the pembrolizumab arm with evaluable TMB that were not MSI-H. Supplementary Table S3 includes 203 patients in the pembrolizumab arm as 1 patient has a missing CPS score.

of clinical utility, wherein the data in these two tables are largely congruent.

Pooling patients with unknown MSI-H status, as determined during the trial by PCR assay, with the MSS group was raised as a concern in relation to testing of continuous TMB score. If some patients were MSI-H, it might bias/confound conclusion of an association between TMB score and clinical outcome with pembrolizumab as shown in Supplementary Table S3. Our evaluation of this dataset however, included exploratory comparison of MSI-H status as predicted bioinformatically using our WES data pipeline³ to the MSI-H status obtained by PCR in KEYNOTE-061. Table 1 (pembrolizumab arm) shows there are six patients with missing PCR MSI-H status, all predicted to be MSS using the WES data. Given the high negative percent agreement, using WES as reference and PCR as comparator, pooling the MSI-H unknown by PCR with the MSS is justified and unlikely to bias conclusions. Furthermore, testing of continuous TMB versus clinical outcome, rather than an academic exercise, is a more powerful way to confirm an association with TMB that is independent of any predictive value of programmed death-ligand 1.

Data from the KEYNOTE-061 trial presented here, support an association between TMB and clinical outcome of treatment with pembrolizumab in gastric cancer. Moreover, comparative estimates of clinical utility in this large, randomized trial at a pre-specified TMB cut-off support actionable clinical benefit of pembrolizumab via that cut-off, an observation not solely attributable to the MSI-H subset. This exploratory analysis warrants further evaluation in independent studies.

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