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GYNAECOLOGIC MALIGNANCIES

KEYNOTE-826 trial met its dual primary endpoints

Survival benefit with first-line pembrolizumab plus chemotherapy in persistent, recurrent or metastatic cervical cancer

At Presidential Symposium I today, a statistically significant 33% improvement in overall survival (OS) was reported with first-line combination therapy with pembrolizumab versus placebo (24.4 months versus 16.5 months, respectively; hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.54–0.84; p<0.001) in 617 patients with recurrent or metastatic cervical cancer who did not previously receive systemic chemotherapy and were no longer candidates for curative treatments such as surgery and/or radiation (LBA2_PR). The pembrolizumab combination also led to significantly longer progression-free survival (PFS) (10.4 months versus 8.2 months, respectively; HR 0.65; 95% CI 0.53–0.79; p<0.001) (Figure).

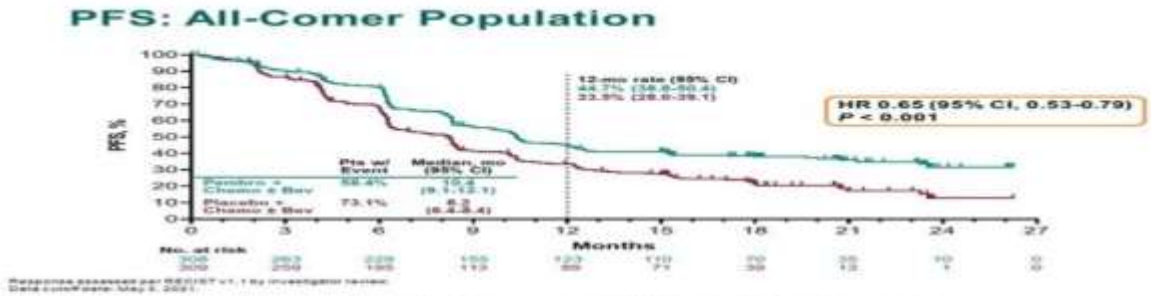

Figure. In the first-line setting, PFS was significantly longer with combination pembrolizumab therapy than with placebo (Abstract LBA2_PR, ESMO 2021)

This large randomised international phase III trial, with a well-designed control arm, provides a high level of evidence for the efficacy of pembrolizumab plus chemotherapy for prolonging

survival in the first-line setting – these data will change medical practice," says Prof. Isabelle Ray-Coquard from Centre Léon Bèrard, Université Claude Bernard Lyon I, Lyon, France. She continues, "The large survival improvements observed are clearly needed in this vulnerable population who currently are underserved. Cervical cancer has been the 'poor relation' in gynae-oncology and in oncology in general, but this study provides further support for immunotherapy as the new cornerstone of its treatment." Ray-Coquard thinks that the utility of this regimen could be explored further: "Whether immunotherapy could be used even earlier in cervical cancer, in localised disease, is an important follow-up question."

Across subgroups defined by PD-L1 combined positive score (CPS), Ray-Coquard points out that OS HRs were similar for pembrolizumab versus placebo in all comers (HR 0.67), those with PD-L1 CPS ≥1 (HR 0.64) and in those with PD-L1 CPS ≥10 (HR 0.61), but data on effects in patients with PD-L1 CPS 0 would help to complete the picture.

In KEYNOTE-826, patients received platinum-based chemotherapy (paclitaxel with cisplatin or carboplatin), with bevacizumab (63.6%) or without, at the investigators' discretion. The benefits of the pembrolizumab combination were seen regardless of bevacizumab use. "Understanding how best to combine bevacizumab with pembrolizumab in this setting should now be explored," says Ray-Coquard. "The trial was not randomised for bevacizumab and therefore further studies are needed. Whether we need chemotherapy at all, particularly in patients with PD-L1 CPS ≥10, is up for debate and requires clinical investigation."

There appeared to be no unexpected safety signals with the pembrolizumab combination. From the data presented, the adverse event profile, including neutropenia and anaemia, appeared manageable and consistent with previous studies. Despite this, and as a note of caution, Ray-Coquard adds, "Pembrolizumab treatment is of longer duration than chemotherapy alone and patients will need to be supported to understand the benefits of treatment over 2 years."

Ref.

Colombo N et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for persistent, recurrent, or metastatic cervical cancer: randomized, double-blind, phase 3 KEYNOTE-826 study. ESMO Congress 2021, Abstract LBA2

Simultaneous publication in The New England Journal of Medicine, DOI: 10.1056/NEJMoa2112435

PARP inhibitor re-treatment: the future of maintenance therapy for relapsed ovarian cancer?

A significant progression-free survival improvement after re-treatment with olaparib was reported in the OReO/ENGOT Ov-38 trial

Late-Breaking results from the phase III OReO/ENGOT Ov-38 trial (LBA33) demonstrated that re-treatment with olaparib significantly prolonged progression-free survival (PFS) compared with placebo in both BRCA1/2-mutated (4.3 months versus 2.8 months, respectively, hazard ratio [HR] 0.57; p=0.022) and non-BRCA1/2-mutated disease (5.3 months versus 2.8 months, respectively, HR 0.43; p=0.002).

More and more patients with epithelial ovarian cancer will receive a PARP inhibitor as upfront therapy following positive results in the SOLO1, PAOLA-1 and the PRIMA/ENGOT-OV26/GOG-3012 studies in which olaparib prolonged the time to recurrence in BRCA1/2-mutated disease and niraparib prolonged progression-free survival time, regardless of homologous-recombination status. However, conserving platinum sensitivity in patients with disease progression on or after PARP inhibitor maintenance remains an unresolved issue. OReO/ENGOT Ov-38 is the first phase III study to evaluate PARP inhibitor maintenance re-treatment in this setting, and the findings will undoubtedly help inform the most appropriate strategy.

In the OReO/ENGOT Ov-38 study, patients with platinum-sensitive, non-mucinous epithelial ovarian cancer and one prior line of PARP inhibitor maintenance therapy who were responsive to their most recent platinum-based chemotherapy were randomised 2:1 to olaparib (300 mg bid [or 250 mg bid if 300 mg not previously tolerated]) or placebo until disease progression. Of 220 patients enrolled, 112 had BRCA1/2-mutated disease and 108 had non-BRCA1/2-mutated disease. Patients were heavily pre-treated, with most patients in both the BRCA1/2-mutated (93%) and non-BRCA1/2-mutated (86%) arms having received ≥3 prior lines of chemotherapy. The median duration of prior PARP inhibitor therapy was longer for patients with BRCA1/2-mutated disease (18.3–21.2 months) than those with non-BRCA1/2-mutated disease (12.4–12.6 months).Among patients with BRCA1/2-mutated ovarian cancer, 6-month PFS rates were 35% with olaparib and 13% with placebo, while at 12 months, the respective rates were 19% and 0%. In the non-BRCA1/2-mutated cohort, respective PFS rates with olaparib and placebo were 30% and 7% at 6 months, and 14% and 0% at 12 months

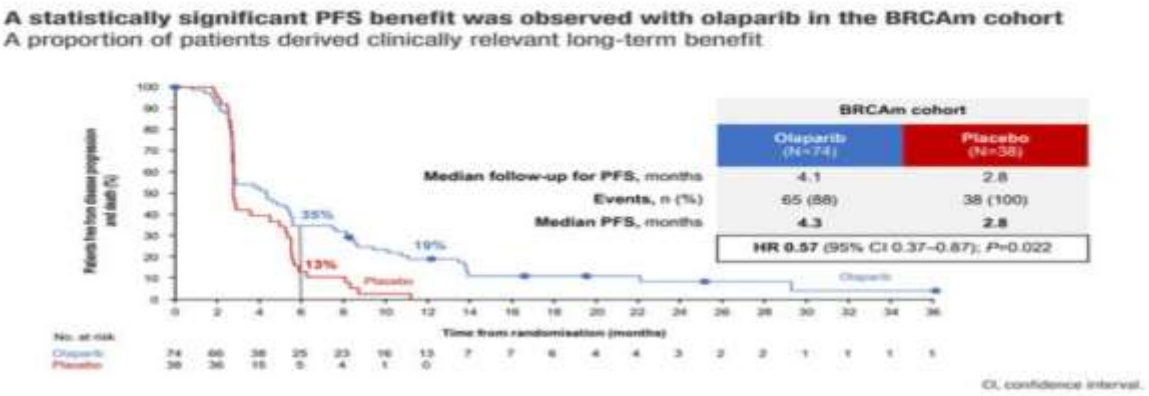

Figure. Significant PFS benefit following rechallenge with maintenance olaparib in patients with heavily pre-treated BRCA1/2-mutated ovarian cancer (Abstract LBA33, ESMO 2021)

Adverse events (AEs) were more common with olaparib than placebo. Among patients with BRCA1/2-mutated disease, grade ≥3 AEs occurred in 15% of olaparib-treated versus 5% of placebo-treated patients, while among non-BRCA1/2-mutated patients, these AEs occurred in 21% of olaparib-treated versus 8% of placebo-treated patients. Treatment discontinuation because of an AE also occurred more frequently in olaparib-treated patients (3% with BRCA1/2-mutated disease and 1% with non-BRCA1/2-mutated disease) than in placebo-treated patients (0% of patients)

Ref.

Pujade-Lauraine E. Maintenance olaparib rechallenge in patients (pts) with ovarian carcinoma (OC) previously treated with a PARP inhibitor (PARPi): Phase IIIb OReO/ENGOT Ov-38 trial. ESMO Congress 2021, Abstract LBA33

Women receiving immunotherapy may be at higher risk of adverse events than men

Prospective evidence from a multicentre study support the need for a more personalised immuno-oncology approach based on sex and gender differences

Results from an ongoing multicentre, observational, prospective study presented at the ESMO Congress 2021 show that cumulative grade ≥2 immune-related adverse events (irAEs) in patients receiving immune checkpoint inhibitors were reported more frequently in females (n=41) than in males (n=65) (Abstract 1795P).

The findings come as no surprise to Dr Berna Özdemir from Bern University Hospital (Inselspital), Switzerland, and member of the ESMO Gender Medicine Task Force. “They confirm indications from retrospective data, showing a higher incidence of these types of events in the female population,” she says. “Recognition and appropriate management of irAEs at an early stage is important in ensuring optimum patient treatment. The data from this study send a signal to oncologists that women receiving immunotherapy may benefit from personalised and closer follow-up,” advises Özdemir.

The likely drivers of the inter-sex disparities in irAEs are the well-documented biological differences in their immune system reactions, with women tending to have stronger immune responses than men, independent of age and ethnicity. However, differentiating the impact of sex from that of gender is fraught with difficulty, given the constant interplay between the two. In general, clinical trials have not been powered to investigate sex and gender differences. But as their role in side -effects, and probably response, to therapy becomes increasingly important, so does the need to revisit clinical trial designs to incorporate sex and gender. Among 106 patients included in the study to date – with a minimum follow-up of 12 months – the 6-month cumulative incidence of grade ≥2 irAEs in females was more than double that in males (61.4% versus 27.9%; p=0.005). The difference remained significant in multivariate analysis, adjusting for cancer type, ECOG performance status and setting (p=0.001). However, of the 106 irAEs of any type and grade reported, fewer were reported in females than in males (38.7% vs 61.3%). Patients living alone, particularly males, were at a higher risk of developing grade ≥2 irAEs compared with those not living alone.

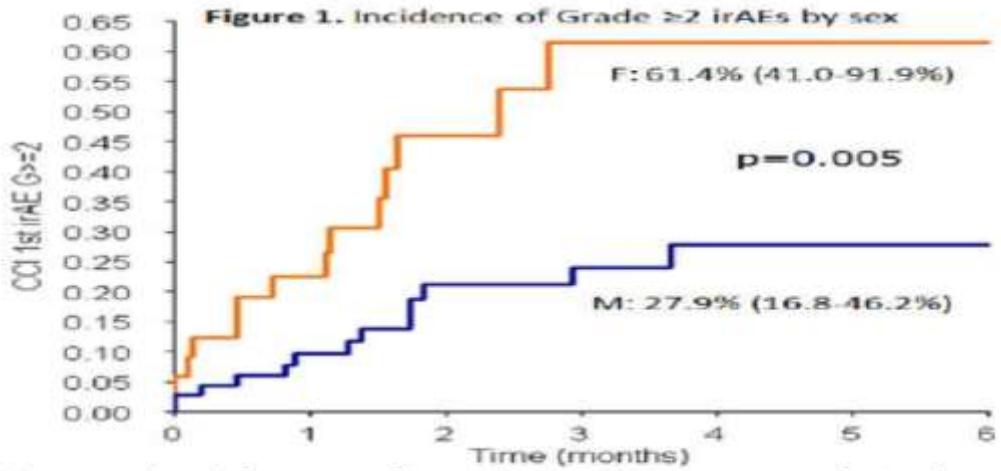

Figure. Incidence of grade ≥2 immune-related adverse events by sex (Abstract 1795P, ESMO 2021)

The study authors aim to use the final trial results to develop tools enabling the prediction of irAE risk based on sex and gender determinants. Özdemir thinks the initial results are encouraging for personalising immunotherapy. "The results are a more general indication that immunotherapy selection in the future should take account not only of the type of cancer but also the sex of the patient," she concludes. "Women may benefit more from other agents that modulate the immune system, alone or in combination with other therapies, whereas men appear to respond better than women to the current checkpoint inhibitors."

Ref.

Miceli R et al. Gender difference in side effects of immunotherapy: a possible clue to optimize cancer treatment. ESMO Congress 2021, Abstract 1795P