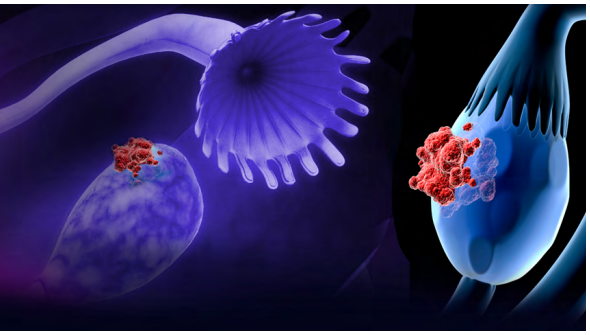
ESMO 2023 Conference Review™ Focus on Ovarian Cancer



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20-24 October, 2023

In this review:

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Abbreviations used in this review:

AE = adverse event; **CCRT** = concurrent chemoradiotherapy; **CPS** = combined positive score; **CR** = complete response; **DFS** = disease-free survival; **DOR** = duration of response; **(d/p)MMR** = (deficient/proficient) mismatch repair; **ER** = oestrogen receptor; **HPV** = human papillomavirus; **HRD** = homologous recombination deficiency; **HRP** = homologous recombination proficiency; **ICI** = immune checkpoint inhibitor; **ITT** = intention-to-treat; **LACC** = locally advanced cervical cancer; **MSI-H** = microsatellite instability-high; **NACT** = neoadjuvant chemotherapy; **OR** = odds ratio; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression-free survival.

Welcome to our review of the 2023 ESMO Congress held in Madrid, Spain.

This year more than 33,000 professionals from around the world gathered both in-person and online at the ESMO annual congress in Madrid to explore the latest clinical discoveries and advances in gynaecological cancer research. The quality of the presentations was very high and a number of practice-changing studies were reported at ESMO 2023. Over 2545 abstracts were presented, and I have selected twelve which were particularly noteworthy and interesting for our Australian community to discuss, but there were many more. Highlights include the KEYNOTE-A18 trial, which supports pembrolizumab + concurrent chemoradiotherapy as a new standard of care in patients with high-risk locally advanced cervical cancer, and the INTERLACE trial which showed that 6 weeks of weekly induction chemotherapy with weekly carboplatin and paclitaxel followed by chemoradiotherapy could also be considered a new standard of care in patients with locally advanced cervical cancer. How we combine KEYNOTE–A18 with INTERLACE will be challenging. There were also important studies presented in endometrial cancer and ovarian cancer. I have also included ICON8B which was presented a few weeks earlier at ESGO, as it may also change practice.

I hope you enjoy these abstracts and the others shared in this review, and I look forward to reading your thoughts and comments.

Kind Regards,

Professor Michael Friedlander
michael.friedlander@researchreview.com.au

ESMO 2023 Conference Review™ Focus on Ovarian Cancer

Expert commentary by Professor Michael Friedlander

Michael Friedlander is conjoint Professor of Medicine at the University of NSW and a senior medical oncologist at the Prince of Wales Hospital and Royal Hospital for Women. He has a broad range of research interests with a focus on clinical trials for women with breast and gynaecologic cancers as well as incorporating patient-reported outcomes as endpoints into clinical trials and to inform clinical practice.

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Pembrolizumab plus chemoradiotherapy for high-risk locally advanced cervical cancer: A randomized, double-blind, phase III ENGOT-cx11/GOG-3047/KEYNOTE-A18 study

Speaker: Domenica Lorusso (Rome, Italy)

Summary/comment: The KEYNOTE-A18 trial investigated the combination of pembrolizumab and concurrent chemoradiotherapy (CCRT) versus CCRT alone in 1060 patients with locally advanced cervical cancer (LACC) and demonstrated significant improvements in PFS (the study's co-primary endpoint) for patients who received pembrolizumab and CCRT versus placebo and CCRT (HR 0.70; 95% CI 0.55—0.89; p=0.0020). The median PFS was not reached and the 24-month PFS was 68% versus 57% in the control arm. The median follow-up was 19.9 months. OS results are immature, but a favourable trend was reported for the pembrolizumab arm. The combination of pembrolizumab and CCRT had a manageable and acceptable safety profile.

The median age of participants was 42 years and 85% had squamous cell cervical cancers. Importantly, 50% were non-Caucasian, making it more representative of the global population. 95% had a PD-L1 CPS >1. 44% were stages 1B2-2B and 56% stage 3-4A (FIGO 2014 staging). I will remind you that in 2018 the FIGO staging system changed and now defines regional lymph node metastasis -pathological and/or radiological, as stage 3C, which will cause stage shift. The vast majority (85%) were node-positive, with 20% having both pelvic and para-aortic node involvement. Very importantly, patients received high-quality contemporary external beam radiotherapy and brachytherapy – all plans were centrally reviewed. The Forest Plots suggest the greatest benefit was observed in the patients with Stage 3-4A disease (HR 0.58) with a HR of 0.9 in stages 1B-2A. We need to wait for longer follow-up and more details.

The findings are very different to the phase 3 CALLA trial of the PD-L1 inhibitor durvalumab in a similar patient population reported last year, which was a negative trial (Int J Gynecologic Cancer. 2022;32[Suppl 3]:A2–A3). It is unclear why the KEYNOTE-A18 study was positive while CALLA was negative, and one of the possible reasons is that there is a difference between PD-1 versus PD-L1 inhibitors in cervical cancer, which is a viral-induced malignancy. However, this may be a simplistic comment as the response rates in HPV-associated head and neck cancers are the same with durvalumab and pembrolizumab, but the patient numbers are relatively small.

It is now clear that ICIs play an important role in the treatment of cervical cancer and there are approvals for two PD-1 inhibitors (pembrolizumab and cemiplimab) in the first- and second-line settings for metastatic, recurrent or persistent cervical cancer. KEYNOTE A-18 now shows benefit in combination with CCRT in patients with LACC. The challenge ahead is to identify which patients are most likely to benefit from an ICI and I encourage all to read an elegant study by Rodrigues et al. (Nat Commun. 2023;14(1):3698). The elephant in the room is, how will this treatment be affordable in countries which have the highest incidence of cervical cancer? The other challenge is, what will you recommend to the next new patient with LACC you see in clinic?

Abstract LBA38
Abstract

A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer

Speaker: Mary McCormack (London, UK)

Summary: The GCIG INTERLACE trial investigated whether a short course of weekly induction chemotherapy before standard chemoradiation improved survival outcomes in LACC. Eligible patients (n=500; median age 46 years) were randomly assigned 1:1 to undergo induction chemotherapy (carboplatin/paclitaxel) followed by chemoradiation (cisplatin), or chemoradiation alone. Patient characteristics were balanced between treatment arms. The median time between induction chemotherapy and chemoradiation was 7 days. At 64 months follow-up, patients in the combination arm showed higher 5-year PFS (59% vs. 48%; p=0.013) and 5-year OS (80% vs. 72%; p=0.04) versus chemoradiation alone. Grade ≥3 AEs occurred in 59% of those in the combination arm and 48% in the chemoradiation arm. The authors concluded that induction chemotherapy followed by chemoradiation should be considered a new standard of care for patients with LACC.

Comment: This presentation has attracted a lot of media attention as well as a lot of interest at ESMO. I must be honest that I did not expect that INTERLACE would be a positive trial based on previous trials of NACT in cervical cancer. There was a hint from the Cochrane meta-analysis and systematic review of all trials a few years ago that dose-dense neoadjuvant chemotherapy regimens may be associated with a survival benefit, while 3-weekly regimens were associated with a survival detriment. This could explain why INTERLACE was positive as they used weekly carboplatin and paclitaxel for 6 weeks followed by chemoradiation in week 7. The patient population was not as high-risk as in other trials, with 57% of patients being node-negative. The majority of patients (76%) were enrolled in the UK although it was an international trial - 20% were from Mexico and a small number from India and Brazil. Radiation quality was good, and all centres had radiotherapy quality assurance. The bottom line was that there was a significant survival benefit as well as a PFS benefit which cannot be ignored. The findings can be readily translated into clinical practice in almost all parts of the world as well, which is a huge advantage. So, what will you recommend to the next patient you see with a locally advanced cervical cancer in your clinic, the INTERLACE protocol or KEYNOTE A-18 protocol? It also begs the question of whether a combination of the two would be even better, but I doubt we will ever find out.

Abstract LBA8
Abstract

innovaTV 301/ENGOT-cx12/GOG-3057

Speaker: Ignace Vergote (Leuven, Belgium)

Summary: This was a global, randomised, open-label, phase 3 study of tisotumab vedotin versus investigator's choice of chemotherapy in the second- or third-line setting of recurrent/metastatic cervical cancer. A total of 502 patients (median age 50 years) were randomly allocated to receive either tisotumab vedotin (n=253) or chemotherapy (n=249; topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed). Compared to chemotherapy, patients administered tisotumab vedotin showed significantly improved OS (primary endpoint; 11.5 vs. 9.5 months), overall response rate (17.8% vs. 5.2%; OR 4.0; p<0.0001) and PFS (HR 0.67; p<0.0001), with a 30% decreased risk of death (HR 0.70; p=0.0038). A lower rate of grade ≥3 AEs occurred in the tisotumab vedotin arm (29.2% vs. 45.2%).

Comment: This study was included in the Presidential Plenary at ESMO as the results of the trial showed that treating patients with metastatic cervical cancer in the second- and third-line setting with an antibody-drug conjugate - tisotumab vedotin - was superior to physician's choice of chemotherapy, which we know is usually ineffective. The low activity of chemotherapy was confirmed in this trial as chemotherapy had a 5% response rate compared to 18% treated with tisotumab vedotin. 60% of patients had one prior line of chemotherapy and 40% had two prior lines. 65% had prior bevacizumab and 28% an ICI. The median OS was 11.5 versus 9.5 months and median PFS 4.2 versus 2.9 months. These are numerically small differences although they are statistically significant.

The findings are very similar to the EMPOWER trial of cemiplimab versus chemotherapy whereby the median OS was 12 versus 8.5 months, and the response rates were almost the same as in the tisotumab vedotin versus chemotherapy trial. The patient population in EMPOWER was also very similar, with the exception that no patient had prior treatment with an ICI. EMPOWER looked at patient-reported outcomes and importantly, found that there were clinically important benefits with regards to pain and role functioning; this is essential in palliative therapy, and I look forward to a similar analysis for the INNOVA trial. It remains to be seen whether tisotumab vedotin will be approved in Australia, but this is just the beginning for antibody-drug conjugates in cervical cancer. It's likely that they will have a role, particularly in patients who have been treated with platinum-based chemotherapy in combination with bevacizumab and an ICI.

Abstract LBA9
Abstract

Phase III double-blind randomized placebo controlled trial of atezolizumab in combination with carboplatin and paclitaxel in women with advanced/recurrent endometrial carcinoma

Speaker: Nicoletta Colombo (Milan, Italy)

Summary: In the AtTEnd trial, 551 eligible patients across 10 countries with advanced/recurrent endometrial carcinoma were randomised 2:1 to be administered either carboplatin/paclitaxel chemotherapy + atezolizumab, or placebo followed by atezolizumab or placebo until progression. In the ITT population, 22.8% had dMMR tumours, 64.1% endometrioid carcinoma and 67.2% recurrent disease. PFS was significantly improved with the addition of atezolizumab in the dMMR cohort versus placebo (median PFS not reached vs. 6.9 months, respectively; HR 0.36; p=0.0005). This improvement was also seen in the all-comer population (10.1 vs. 8.9 months; HR 0.74; p=0.0219). The OS data were immature, yet interim analyses revealed a trend in favour of atezolizumab, even though immunotherapy was commenced by 24.3% of patients in the placebo arm. Rates of grade ≥3 AEs were similar between treatment arms.

Comment: There can be no doubt that the combination of carboplatin and paclitaxel with an ICI is now standard of care in patients with advanced/recurrent endometrial cancer who have tumours deficient in DNA mismatch repair (dMMR), irrespective of whether you use a PD-1 or PD-L1 inhibitor. AtTend is the third kid off the block and confirms the positive findings reported in RUBY and GY018. Although there are some differences in the patient population and eligibility criteria as well as trial design between them e.g., in AtTend, atezolizumab was continued indefinitely until progression, and we can debate whether this is needed beyond 2 years. AtTend also differed in that it included 20% of Asian patients and pleasingly, 15 Australian sites also participated. Furthermore, they included a number of translational endpoints including PD-L1 positivity and *ARID1A* loss. Although they showed a benefit of the combination in the all-comer population, which included both MMR-deficient and proficient cancers, the reality is that the benefit is largely confined to the dMMR population, and it is back to the drawing board for the MMR-proficient subset. We await with interest the results of LEAP 001 comparing carboplatin and paclitaxel versus lenvatinib and pembrolizumab in the pMMR population.

Finally, similar to other trials, the responses to atezolizumab were durable – the PFS curves separate rapidly after chemotherapy, clearly demonstrating the benefit of maintenance atezolizumab. The median PFS was not reached in the experimental arm and was 6.9 months with chemotherapy alone. The OS was superior in the experimental arm despite 40% of patients in the placebo arm crossing over to an ICI. The median OS was not reached in the experimental arm and was 25.7 months in the placebo arm. All patients with dMMR advanced/recurrent endometrial carcinoma should ideally be offered chemotherapy and an ICI. Trials in progress will determine whether chemotherapy is required for all patients with dMMR endometrial cancers or whether only a subset require an ICI alone.

Abstract LBA40
Abstract

Durvalumab (durva) plus carboplatin/paclitaxel (CP) followed by maintenance (mtx) durva ± olaparib (ola) as a first-line (1L) treatment for newly diagnosed advanced or recurrent endometrial cancer (EC)

Speaker: Shannon Westin (Houston, USA)

Summary: This session reported on results from the phase 3 DUO-E/GOG-3041/ENGOT-EN10 trial, in which 718 patients with newly diagnosed advanced/recurrent endometrial cancer were randomised 1:1:1 to receive chemotherapy (carboplatin/paclitaxel) + durvalumab + olaparib, chemotherapy + durvalumab, or chemotherapy alone. Patients administered chemotherapy + durvalumab + olaparib had significantly longer PFS versus chemotherapy alone (median PFS 15.1 vs. 9.6 months, respectively; HR 0.55; p<0.0001;) there was also a trend towards a benefit in OS (HR 0.59; p=0.003), although the data were not yet mature (27.7%). Subgroup analyses revealed that both dMMR and pMMR patients showed improved PFS with chemotherapy + durvalumab + olaparib, and with chemotherapy + durvalumab versus chemotherapy alone. PFS was enhanced further with maintenance olaparib in pMMR patients.

Comment: DUO-E included patients with newly diagnosed stage 3-4 recurrent endometrial cancer and was very similar to those enrolled in RUBY, GY018 and AtTend, although with some differences. About 30% of participants were Asian and 50% had recurrent disease. The trial met its primary objective and in the ITT population, it demonstrated that durvalumab plus chemotherapy followed by olaparib and durvalumab reduced the risk of disease progression or death by 45% compared to the control of chemotherapy (median PFS 15.1 vs. 9.6 months), while chemotherapy + durvalumab followed by durvalumab and placebo reduced the risk of disease progression or death by 29% compared to chemotherapy alone (10.2 vs. 9.6 months). Pre-specified exploratory analyses showed no added benefit of olaparib to durvalumab in the dMMMR subset with a similar PFS and with over 60% of patients progression free at 18 months versus 31% in the chemotherapy-only arm. pMMR patients comprised 80% of the population enrolled, and there was a significant benefit of durvalumab and olaparib (median PFS 15 vs. 9.7 months and HR of 0.57).

The obvious question is, who are the patients with pMMR tumours that derive benefit from the combination of durvalumab and olaparib, and can they be identified? They most likely include the subgroup with mutations in *HRR* (HR 0.3 in the Forest Plot) as well as the subgroup with PD-L1-positive tumours (based on a TAP score of >1%). They didn't specifically look at the subset with *TP53* mutations, but there are data to suggest that they may also benefit. There was also a benefit of durvalumab alone versus chemotherapy in the pMMR group, but the difference was more striking and clinically important with durvalumab + olaparib. There was more toxicity associated with the durvalumab and olaparib arms as one would expect. OS is immature, although the trends suggest a benefit of the experimental arms. DUO-E is an important next step – we can be pretty confident that there is no added benefit of olaparib to durvalumab in the patients with dMMR tumours, but there appears to be a role for the combination in pMMR patients; however, additional work is required to select this subset. Hopefully additional translational studies will be carried out including HRD testing.

Abstract LBA41
Abstract

Updated response data and analysis of progression free survival by mechanism of mismatch repair loss in endometrial cancer (EC) patients (pts) treated with pembrolizumab plus carboplatin/paclitaxel (CP) as compared to CP plus placebo (PBO) in the NRG GY018 trial

Speaker: Ramez Eskander (La Jolla, USA)

Summary: These researchers investigated the relationship between the mechanism of MMR deficiency and clinical outcomes with pembrolizumab + chemotherapy (carboplatin/paclitaxel) in patients with dMMR endometrial cancer. Eligible patients (n=819) were randomly assigned 1:1 to receive either pembrolizumab + chemotherapy, or placebo + chemotherapy, followed by maintenance pembrolizumab or placebo for up to 2 years. In both dMMR and pMMR patient populations, respectively, the addition of pembrolizumab was associated with improved ORR ([81.5% vs. 70.7%; OR 1.83] and [70.7% vs. 58.1%; OR 1.74]), improved CR ([32% vs. 15%] and [15% vs. 8%]) and improved DOR ([28.7 vs. 6.2 months; HR 0.22; p<0.0001] and [9.2 vs. 6.2 months; HR 0.47; p<0.0001]). There were 223 patients with central-dMMR, 72% of whom had *MLH1* promoter hypermethylation and 13% had MMR protein loss secondary to gene mutation; 12-month PFS was comparable between these two mechanisms of MMR loss (75% vs. 85%). The median PFS and OS were not reached.

Comment: This was an important presentation as it addresses the question of whether patients with dMMR due to *MLH1* promoter hypermethylation have an inferior response to an ICI compared to patients with other causes of dMMR. There are a number of relatively small phase 2 trials in the recurrent setting that suggest that this is the case, although there have been contradictory findings in the GARNET trial. A very recent paper (Gynecol Oncol. 2023;177:132-41) reporting on the outcomes of over 1600 patients with dMMR endometrial cancer found that patients with promoter hypermethylation of *MLH1* had an inferior OS to those with *MLH1*-mutated cancers, and this was also evident in the subset (145 vs. 23) treated with pembrolizumab, which makes the findings of GY018 so interesting. The investigators of GY018 found that the mechanism of MMR loss was not a predictor of PFS or response to pembrolizumab combined with chemotherapy. The *MLH1* promoter-hypermethylated subset make up the majority of patients with dMMR endometrial cancers, and may be better treated with combination therapy rather than an immune checkpoint inhibitor alone. The response rates are much higher in this subset than we would expect from an ICI alone. I expect that there will be similar analyses in the other first-line trials, and we should have more data in the near future to support treatment recommendations for the subset of patients with promoter hypermethylation of *MLH1*. We will also need to drill down further to identify the subset with hypermethylation of *MLH1* who respond to a single agent ICI and those who may benefit from the addition of chemotherapy or combined immune checkpoint blockade.

Abstract LBA43
Abstract

Dostarlimab + chemotherapy for the treatment of primary advanced or recurrent endometrial cancer (pA/rEC)

Speaker: Mansoor Raza Mirza (Copenhagen, Denmark)

Summary: In the ENGOT-EN6-NSGO/GOG-3031/RUBY trial, patients with primary/advanced recurrent endometrial cancer showed significantly improved PFS with dostarlimab + carboplatin/paclitaxel versus carboplatin/paclitaxel alone, in both the overall population (HR 0.64) and those with dMMR/MSI-H (HR 0.28). This session shared the exploratory PFS and OS outcomes according to patient molecular subgroup. Among 400 evaluable patients, 1.3% had *POLε* alterations, 22.8% dMMR/MSI-H, 22.0% *TP53* alterations and 54.0% had 'no specific molecular profile'. At the time of data cut-off, no patients in the *POLε* alterations subgroup had progressed. Dostarlimab + carboplatin/paclitaxel was associated with improved PFS and OS versus carboplatin/paclitaxel in the remaining subgroups; the largest benefit was observed in dMMR/MSI-H patients (PFS HR 0.13; OS HR 0.4) and those with *TP53* mutations (PFS HR 0.55; OS HR 0.41).

Comment: This is a breakdown of the PFS based on the molecular classification of endometrial cancer; it is interesting and raises important points. As expected, the patients with dMMR/MSI-H have the best outcome with the combination of dostarlimab and chemotherapy. It was very interesting to note just how few patients with metastatic disease have *POLε* mutations (1.3%), so they are clearly not contributing to the benefit observed in the pMMR subset – not surprisingly they had an excellent prognosis irrespective of what treatment they got. The *TP53* subset also appeared to derive greater benefit from dostarlimab + chemotherapy, which is really interesting and suggests that we should consider combination therapy in them – this needs to be confirmed in the two other randomised trials discussed above. The benefit is less clear and questionable in the 'no specific molecular profile' subgroup. This is a very heterogeneous group and includes ER-negative, aggressive histologies including clear cell, mesonephric–like adenocarcinoma, gastric type adenocarcinomas which are ER-negative as well, *CTTNNB1* mutations, *PTEN* mutations, *L1CAM* expression, etc., and I hope that someday we will see a combined analysis of all of the trials to drill down further into this large group of patients.

Abstract 740M0
Abstract

Neoadjuvant immune checkpoint blockade in mismatch repair deficient endometrial cancer

Speaker: Marco de Bruyn (Groningen, The Netherlands)

Summary: Recent data have indicated that dMMR cancers may be treated more effectively with neoadjuvant immune checkpoint blockade than adjuvant treatment. This phase 1 feasibility study explored the use of neoadjuvant pembrolizumab in ten patients (stage 1-2 n=4; stage 3 n=6) with dMMR endometrial cancer. All patients received two 3-weekly cycles of pembrolizumab monotherapy, followed by standard-of-care resection and adjuvant treatment. A total of five patients showed a pathological response, defined as <90% of viable cancer cells. Eight patients had measurable disease on MRI, three of whom showed a partial radiologic response. No recurrences have been recorded to date; the median DFS is 17 months and the longest DFS is 26 months. Nine of ten patients displayed a treatment-induced immunological response, with increased lymphoid infiltrates, clonal T cell expansion and diverse T cell phenotypes. Neoadjuvant pembrolizumab had a favourable safety profile.

Comment: It was only a matter of time until we would see results of neoadjuvant ICIs in patients with dMMR endometrial cancer, and not unexpectedly, there was a high response observed with just two cycles of pembrolizumab. There are a number of trials in progress investigating this approach and we will know a lot more in the next few years.

Abstract 742M0
Abstract

ICON8B: GCIG phase III randomised trial comparing weekly dose-dense chemotherapy + bevacizumab to three-weekly chemotherapy + bevacizumab in first-line high-risk stage III-IV epithelial ovarian cancer treatment

Speaker: Andrew Clamp (Manchester, UK)

Summary: This session was presented at the 2023 ESGO (European Society of Gynaecological Oncology) Congress 2 weeks before ESMO. Andrew Clamp shared the primary progression-free survival analysis from ICON8B, a phase 3 trial enrolling patients with high-risk stage 3-4 epithelial ovarian cancer. Eligible patients (n=707) were randomly assigned 1:1:1 to either B1 (three-weekly carboplatin/paclitaxel + bevacizumab), B2 (three-weekly carboplatin with weekly dose-dense paclitaxel) or B3 (three-weekly carboplatin with weekly dose-dense paclitaxel + bevacizumab). Recruitment was discontinued in the B2 arm due to a lack of PFS. The median follow-up was 59.0 months. Compared to patients in the B1 arm, those in B3 showed improved PFS (22.2 vs. 16.7 months, respectively; HR 0.75; p=0.002) and OS (51.1 vs. 40.9 months; HR 0.77; p=0.020). Grade ≥3 toxicities occurred in 45% and 58% of patients in the B1 and B3 arms, and 49% and 61% completed 18 cycles of bevacizumab.

Comment: Just when you thought that dose-dense weekly paclitaxel in a Caucasian population was of historical interest given the results of ICON8, out of left field comes ICON8B. The trial demonstrates that dose-dense paclitaxel in combination with bevacizumab (7.5mg/kg) and 3-weekly carboplatin (AUC 5) in patients with high-risk stage 3 (residual disease >1 cm), stage 3 requiring NACT and all stage 4 was associated with a significant improvement in PFS. The trial included 578 patients, the majority with high-grade serous cancers who had NACT followed by interval surgery. The median PFS was 16.7 months in the 3-weekly arm versus 22.2 months in the dose-dense arm (HR 0.75). The greatest benefit was observed in the subset of patients receiving NACT compared to primary surgery. Given the increasing proportion of patients in Australia now being treated with NACT (≈70%), the findings of ICON8B cannot be ignored and there is good case for recommending this approach in the clinic on Monday. Survival data are immature, but the trend favours dose-dense treatment with a median OS of 51.1 versus 40.9 months. The toxicity was as expected, with similar AEs apart from more anaemia in the dose-dense arm. Translational studies are planned, and it will be important to determine whether there are differences in the HRP versus HRD population.

Abstract

Efficacy and safety of senaparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer (FLAMES study)

Speaker: Xiaohua Wu (Shanghai, China)

Summary: The efficacy and safety of the novel, high-potency PARP inhibitor senaparib was evaluated in this randomised, double-blind, placebo-controlled, phase 3 trial of Chinese patients with newly diagnosed advanced ovarian cancer. Eligible patients (n=404) were randomly assigned to either senaparib (n=270) or placebo (n=133). PFS was significantly improved with senaparib (HR 0.43; p<0.0001), regardless of *BRCA* alteration status (HR 0.43; p<0.01). It was noted that no new safety concerns were identified and senaparib was well-tolerated; patients who received senaparib had a higher rate of grade ≥3 AEs (66.3% vs. 20.3%), with a higher rate of dose reductions (63.3% vs. 6.0%) and discontinuations (4.4% vs. 0%).

Comment: Senaparib is a PARP 1 and 2 inhibitor and likely very similar to the currently approved PARP inhibitors in ovarian cancer. The FLAMES trial randomised 404 patients with stage 3 or 4 high-grade serous or endometrioid ovarian cancer to either senaparib or placebo after response to first-line chemotherapy. The results are much the same as has been reported with olaparib, niraparib and rucaparib with a HR of 0.43 in the *BRCA*-mutated population treated with senaparib. They did not report on the results of HRD testing, but the HR in the *BRCA* wild-type population, which is a mix of HRD and HRP, was 0.43, which is better than expected and suggests a benefit independent of biomarker status. These findings are consistent with the PRIME trial conducted in a similar population of Chinese patients with advanced ovarian cancer, which reported that niraparib significantly prolonged PFS versus placebo in patients without a *BRCA* mutation (PFS 19.3 vs. 8.3 months; HR 0.48; 95% CI 0.34—0.67). PRIME used the BGI HRD assay and there was no difference in benefit observed between HRD and HRP subsets, and in the HRP population niraparib was associated with a HR of 0.41 (median PFS 16.8 vs. 5.5 months).

So, we have two randomised, double-blind, placebo-controlled trials in a Chinese population using two different PARP inhibitors that demonstrate significant benefit in the HRP population (niraparib) and the *BRCA* wild-type population (FLAMES). Is the biology of high-grade serous cancer different in different ethnic populations? It's interesting that only 23% of patients were classified as HRP using the BGI assay and were 67% as HRD. Both of these studies highlight the need to explore whether there are ethnic differences in the molecular subtypes of high-grade serous cancers.

Abstract LBA36
Abstract

Atezolizumab (atezo) combined with platinum-based chemotherapy (CT) and maintenance niraparib for recurrent ovarian cancer (rOC) with a platinum-free interval (TFIp) >6 months

Speaker: Antonio Gonzalez Martin (Madrid, Spain)

Summary: Antonio Martin presented the primary analysis of the double-blind, placebo-controlled ENGOT-Ov41/GEICO 69-O/ANITA trial; this is the first reported phase 3 trial of atezolizumab + platinum-based chemotherapy and maintenance niraparib (PARP inhibitor) for late-relapsing recurrent ovarian cancer. Eligible patients (n=417) were randomly assigned to either a carboplatin doublet (paclitaxel, gemcitabine or pegylated liposomal doxorubicin) + atezolizumab or placebo, followed by maintenance niraparib + atezolizumab or placebo. At a median follow-up of 36 months, there were no between-group differences in PFS or ORR.

Comment: ANITA joins a growing list of negative trials that have investigated the potential role of ICIs in both the first-line setting as well as in recurrent ovarian cancer (including platinum-sensitive and platinum-resistant). Despite a strong rationale and potential synergy when combining a PARP inhibitor with an ICI due to STING pathway activation and creation of neoantigens, there was no difference in median PFS between the niraparib arm and the niraparib and atezolizumab arm. DUO-O has been reported recently – the HR in the t*BRCA* wild-type arm with the triplet (durvalumab, olaparib, bevacizumab) was very similar to PAOLA 1 with olaparib and bevacizumab, although there was a 3-month increase in PFS (20.9 vs. 17.4 months) in the HRP arm with the triplet, which is not earth-shattering, although statistically significant. There are at least four or five other trials that have been carried out investigating the potential role of ICIs either in combination with a PARP inhibitor or an angiogenesis inhibitor or both, and will read out in the near future. Based on what we have observed to date it seems unlikely that any of them will change the standard of care, although I would be very pleased to be proved wrong. It is possible that a subset of patients may benefit but we need robust translational studies embedded in these trials to determine who they are.

Abstract LBA37
Abstract

Efficacy of gemcitabine (gem) based therapy in ovarian clear cell carcinoma (OCCC)

Speaker: Jerold Loh (Singapore, Singapore)

Summary: Following the results of in-vitro testing, these researchers predicted that gemcitabine-based therapy would be more effective than non-gemcitabine therapy in the treatment of ovarian clear cell carcinoma, particularly in patients with *ARID1A* alterations. A retrospective analysis was performed on 90 patients (median age 53 years) with advanced/relapsed disease; patients had undergone a median of one prior line of treatment, 74.4% had undergone ≥2 lines and 52.2% of these had included gemcitabine-based therapy. Five patients were administered gemcitabine monotherapy, 18 platinum-gemcitabine, 12 platinum-gemcitabine with bevacizumab and 50% harboured *ARID1A* alterations. The disease control rate to gemcitabine across all treatment lines was 61.1%. Gemcitabine was associated with a significantly improved disease control rate versus non-gemcitabine therapy (OR 6.5; p=0.004), and this was more pronounced in those with *ARID1A* alterations versus wild-type (OR 28.0 vs. 4.2, respectively). Multivariate analysis showed that disease control rate was significantly improved with earlier use of gemcitabine (OR 4.1; p=0.04) and addition of bevacizumab (OR 7.2; p=0.02). In patients with *ARID1A* alterations, PFS was significantly improved with second-line gemcitabine versus non-gemcitabine therapy (296 vs. 70 days; HR 4.3; p=0.04). There were no significant differences in OS.

Comment: Have a read of the abstract and check out the poster if you can, as it is very interesting. This is not the first time this observation has been made and there is good preclinical work supporting the findings (Gynecol Oncol. 2019;155[3]:489-98). This begs the question of whether we should be considering a randomised trial of platinum gemcitabine and bevacizumab versus platinum and paclitaxel and bevacizumab in the first-line setting in this group of patients, who historically do badly with our standard therapies.

Abstract 794P
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