The European Society for Medical Oncology 2016 Congress: Highlights and summary of selected abstracts in gynecologic cancers

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Introduction

The 2016 ESMO Congress held in Copenhagen, Denmark (07–11th October 2016) brought together over 20,000 attendees from 127 countries. The highlight of the meeting for the gynecological track was the presentation at a Presidential session of the ENGOT-OV16/NOVA niraparib maintenance study. Other sessions included the following: 4 oral abstract presentations, 6 poster-discussion presentations and 45 general posters; an educational session on difficult decisions in gynaecological oncology and a special symposium on personalized medicine in gynecological oncology. This report discusses the oral abstract sessions and selected poster presentations from the conference.

Ovarian Cancer

Targeting homologous recombination repair deficiency (HRD)

Results from the randomized phase III niraparib versus placebo ENGOT-OV16/NOVA trial

The results from the ENGOT-OV16/NOVA trial were presented by Mansoor Mirza during the presidential session (Abstract LBA3). This phase III trial was performed in collaboration with European Network of Gynaecological Oncological Trial groups (ENGOT). The ENGOT-OV16/NOVA trial evaluated the efficacy and safety of the PARP inhibitor niraparib as maintenance therapy in patients with recurrent ovarian cancer who respond to platinum-based chemotherapy (1). 533 patients were enrolled in two independent cohorts; those with a germline BRCA mutation (gBRCAmut, n=203) and those without (non-gBRCAmut). Within each cohort, patients were randomized (2:1) to receive once daily niraparib 300 mg or placebo. Three prospectively defined populations were assessed: 1) the gBRCAmut cohort; 2) the overall non-gBRCAmut cohort; 3) the non-gBRCAmut cohort whose tumors were retrospectively defined as deficient in the repair of DNA by homologous recombination (HRD) using the myChoice® HRD test. This test evaluates chromosomal damage within cells as a result of HRD and derives a score based on the amount of telomeric allelic inbalance (TAI), large-scale chromosomal transitions (LST) and loss of heterozygosity (LOH).

All patients enrolled had platinum-sensitive relapsed disease; defined as a complete or partial response to the penultimate platinum-based chemotherapy before study enrollment and disease progression more than six months after completion of the prior round of platinum chemotherapy. In the gBRCAmut group approximately 57% had received a total of two prior lines of chemotherapy. The primary end point was progression free survival (PFS) from time of trial entry (and not the date of prior platinum-based chemotherapy).

Patients receiving niraparib had a significantly longer median PFS,, regardless of BRCA mutation or HRD status including; 21.0 vs. 5.5 months in the gBRCAmut cohort (hazard

ratio [HR], 0.27; 95% confidence interval [CI], 0.17 to 0.41), and 9.3 months vs. 3.9 months in the non-gBRCAmut cohort (HR, 0.45; 95%CI 0.34 to 0.61; p<0.0001). Within and exploratory analysis of the non-gBRCAmut HRD positive subset, which included patients with somatic BRCA mutations, the median PFS was 12.9 vs. 3.8 months (HR, 0.38; 95% CI, 0.24 to 0.59). In the HRD negative cohort; niraparib also improved the median PFS (6.9 months vs. 3.8 months; HR 0.58; 95% CI, 0.36 to 0.92; p = 0.02). The median follow up is only 16.9 months, but significant improvements were also observed in all secondary endpoints. Compared to placebo, niraparib significantly prolonged the PFS2 (the time to second progression), time to first subsequent treatment, and chemotherapy-free interval in the gBRCAmut and non-gBRCAmut cohorts, as well as in the HRD subgroup.

At least one treatment related adverse event was observed in all patients treated with niraparib and 95.5% of patients on placebo. Common grade 3 or 4 adverse events with niraparib included thrombocytopenia (33.8%), anemia (25.3%), neutropenia (19.6%) and fatigue (8.2%), which were managed by dose interruption (69%) and dose reduction (67%). 14.7% of patients treated with niraparib discontinued treatment due to an adverse event.

The presentation was discussed by Sandro Pignata, highlighting the novel aspects of this study. To date, olaparib is the only PARP inhibitor to be licensed for use in ovarian cancer; as maintenance treatment of platinum-sensitive relapsed BRCA mutated (germline or somatic) by the European Medicine Agency (2) and as monotherapy for patients with germline BRCA mutated advanced ovarian cancer, who have been treated with three or more prior lines of chemotherapy by the FDA (3). This trial is the first to demonstrate prospectively a benefit for maintenance PARP inhibitors in all platinum-sensitive high-grade serous ovarian cancer (HGSOC) patients, regardless of BRCA status. Furthermore, it is the first study to investigate the selection of patients for treatment using HRD status, and it showed a differential effect across HRD positive and negative groups, although both had a significant improvement in median PFS with niraparib. The reasons for a benefit in HRD negative tumors is not well understood. It may be due to the precision of the assay or the use of historical (primary) tumor samples.

Clinical activity of rucaparib in patients with high-grade serous ovarian cancer and a BRCA mutation

Data from Study 10 (NCT1482715) and ARIEL2 (NCT01891344) were combined for an integrated efficacy and safety analysis and presented by Rebecca Kristeleit (Abstract 856O) in the oral abstract session. Study 10 was a first-in-human dose escalation oral rucaparib study with subsequent dose expansion in BRCA mutant cohorts, whereas ARIEL 2 was a single arm, phase II study of rucaparib in patients with platinum-sensitive relapsed ovarian cancer. The efficacy population included 106 patients with a diagnosis of ovarian cancer and a deleterious germline or somatic BRCA mutation, who had

received ≥ 2 prior chemotherapies including ≥ 2 platinum-based regimens, enrolled at the 600 mg BID dosing level and had received ≥ 1 dose of rucaparib. Seventy-five percent of patients had platinum-sensitive recurrence and 65% had received ≥ 3 prior therapies. The median PFS was 10.0 months (95% CI 7.3-12.5) and 50 patients were without evidence of disease progression or death at the time of data cut off. There was an overall response rate (ORR, confirmed complete and partial response) by RECIST criteria of 53.8%. Seventy-nine percent and 41% of patients were progression-free at 6 and 12 months respectively. Responses were highest in patients with a platinum free interval ≥ 6 months (65.8%) or two prior lines of therapy (68.3%).

The safety analysis included 377 ovarian cancer patients treated with at least one dose of 600 mg BID rucaparib. Overall, rucaparib had a manageable safety profile. Treatment related ≥ grade 3 adverse events were observed in 46.9% of patients; with 58.6% of patients requiring dose interruption and 44.3% dose reduction. Rucaparib was discontinued due treatment-related adverse events in 8.0% of patients. Common grade 3/4 adverse events were as expected; anemia (24.9%), thrombocytopenia (4.5%) and fatigue (10.9%). There are two ongoing phase III confirmatory trials; ARIEL 3 (NCT 01968213) in the maintenance setting in patients with relapsed high-grade ovarian cancer and ARIEL 4 (NCT02855944) in the treatment setting in which rucaparib is compared to standard chemotherapy.

The question now is where do these new PARP inhibitors fit in the ovarian cancer treatment landscape? Based on the above results, Clovis Oncology submitted a New Drug Application to the FDA in June 2016. Will rucaparib be approved as a single agent in patients with germline or somatic BRCA mutations who have received 2 lines of prior therapy? Compared to olaparib in this indication there was a higher ORR (54 vs. 36%) and PFS (10.0 vs 7.8 months) with rucaparib, however the olaparib treated patients had received more prior-therapies (4). Similarly, should niraparib be offered to all platinum sensitive ovarian cancer patients, regardless of BRCA or HRD status? Whilst these result are exciting and likely to change the treatment landscape for HGSOC patients, a number questions remain. It is not yet clear how best to optimize the use of PARP inhibitors e.g. as single agents, maintenance therapy or in combination with chemotherapy, targeted therapy or immunotherapies. Furthermore, it is unknown whether clinical differences exist between PARP inhibitors in terms of efficacy and/ or toxicity and as yet there are no direct comparative trials to evaluate these.

Novel targets for ovarian cancer

Four studies involving novel therapies for ovarian cancer were presented in the oral abstract and poster discussion sessions. Selinexor is a first-in-class oral selective inhibitor of XPO1, which controls the export of critical nuclear proteins including tumor suppressors (p53, BRCA pRB) and inhibition theoretically has the potential to impact both DNA repair and the cell cycle. Ignace Vergote et al (Abstract 854O) presented the

results of a phase II trial evaluating the efficacy and tolerability of selinexor in 114 patients with advanced gynecological cancers. Eligible patients had either platinum-resistant/refractory ovarian cancer or relapsed endometrial or cervical cancer following ≥ 1 line of therapy for advanced disease. Three randomized treatment schedules were evaluated (50 mg/m^2 bi-weekly (BIW); 35 mg/m^2 BIW and 50 mg/m^2 once-weekly in 28 day cycles) using a disease control rate (DCR) at 12 weeks as the primary end point. Patients were enrolled were heavily pre-treated; 66 ovarian cancer, 23 endometrial cancer and 25 cervical cancer. A DCR of 49%, 45% and 26% and ORR of 14%, 15% and 4% were seen in the ovarian, endometrial and cervical cohorts respectively with 15 patients remaining on study for > 6 months. Common grade 2 toxicity for all 3 cohorts included: nausea (37%), anorexia (27%), weight loss (18%) and fatigue (39%). Grade 3 or 4 adverse events included: thrombocytopenia (17%), fatigue (15%), anemia 10%) and nausea (9%). Toxicity was reduced with the weekly versus bi-weekly regimens, without any apparent difference in efficacy.

The results of this study with selinexor are interesting and there is a rationale for further studies in HGSOC, which is characterized by almost ubiquitous TP53 mutations and frequent aberrations in other tumor suppressor proteins such as BRCA and RB1 (5). However, in the context of p53 null tumors, the mechanism of action is unclear. Selinexor appeared reasonably well tolerated with evidence of clinical benefit in heavily pre-treated patients. Furthermore, there was a cohort of exceptional responders with four patients (3 ovarian cancer) on treatment for >12 months and it will be interesting to see the results of exploratory biomarker studies. Combination studies with selinexor are ongoing with phase III trials in ovarian and endometrial cancer planned.

LY2606368 is a small molecule inhibitor of cell cycle checkpoint kinases 1 (CHK1) and to a lesser extent CHK2. CHK1/2 control the cell cycle and play a particular role in regulating tumors with p53 dysfunction, such as HGSOC. Jung-Min Lee and colleagues presented the results of a phase II study of LY2606368 in sporadic HGSOC and gBRCAmut ovarian cancer (Abstract 855O). 24 patients with sporadic HGSOC and 7 with a gBRCAmut were enrolled. Patients were treated with 105mg/m^2 IV every 2 weeks and ORR was the primary end point. In the somatic HGSOC cohort the ORR was 35% with a median duration of response of six months and a disease control rate (DCR, response and stable disease) of 60% in the 20 (of 24) evaluable patients. No response was seen the six patients in the gBRCAmut cohort although there was a DCR of 67%. The most common adverse event was neutropenia (75% G3/4), although only 6% suffered from febrile neutropenia. Dose reductions were required in 3% of patients and 56% required G-CSF support. Non-hematological toxicity was rare. LY2606368 appears a promising therapy in sporadic HGSOC and responses were seen within a heavily pre-treated predominately platinum-resistant/ refractory population (72%). It is of interest that there were no responses within the gBRCAmut cohort, a possible explanation for this proposed by the discussant, (Charlie Gourley) is that inhibition of the cell cycle may be of less consequence in HRD cells than HR proficient cells and that BRCA mutant cells may require additional DNA damage to sensitize to CHK1/2 inhibition.

Abiraterone, a CYP17 inhibitor, irreversibly inhibits generation of adrenal steroids downstream of CYP17, has been successfully developed for the management of prostate cancer. The androgen receptor (AR) is reported to be expressed in up to 90% of epithelial ovarian cancers (6), although prior studies with anti-androgens have been disappointing. The results of a phase II study of abiraterone in patients with advanced ovarian cancer (CORAL), were presented by Susana Banerjee (LBA33). 43 patients who progressed within 12 months of last systemic treatment were treated with 1000mg abiraterone and 5mg prednisolone daily in 28-day cycles. The primary end-point was ORR at 12 weeks. The majority of patients enrolled had HGSOC (88%); there were also 3 cases of low-grade serous (LGSOC) and 2 cases of endometrioid ovarian cancer. Using an IHC cut-off of 10%, 69% of patients were deemed AR positive. Only one objective response was observed (2.4%) leading to early trial closure. There was a clinical benefit rate (ORR plus stable disease) of 26.6% at 12 weeks. Interestingly the observed response was seen in a patient with AR positive LGSOC, suggesting that although there is no role for abiraterone in patients with HGSOC, it may merit further evaluation in LGSOC.

Protein tyrosine kinase 7 (PTK7) plays a role in developmental biology and is overexpressed on ovarian cancer cells and cancer stem cells. PF-06647020 is an antibody-drug conjugate (ADC) comprised of a humanized monoclonal antibody directed against PTK7, linked to an auristatin microtubule inhibitor payload. Sachdev et al (LBA35) presented the results of phase 1 study of PF-06647020 in patients with advanced solid tumors including platinum resistant ovarian cancer. Of the 22 evaluable ovarian cancer patients the ORR was 27% with one CR. Stable disease was seen in 55% of patients. The drug was well tolerated with only 4% of patients requiring dose reductions. No clear correlation was observed between PTK7 level (on archival biopsies) and response. Further trials with PF-06647020 are under development.

Anti-angiogenesis in the setting of neo-adjuvant therapy for ovarian cancer

During the poster discussion session two studies evaluating angiogenesis inhibition in the neo-adjuvant setting were discussed. The safety outcomes of the CHIVA study, a randomized double blind phase II trial of nintedanib versus placebo with neo-adjuvant chemotherapy (NACT) for patients with advanced unresectable ovarian cancer (Ferron et al, 859PD) were reported. 188 patients, stratified by peritoneal cancer index, were randomized 2:1 to receive nintedanib or placebo with standard NACT. Only 64% of patients underwent interval-debulking surgery (IDS). The perioperative complication rate with nintedanib was comparable to placebo although there was a slightly higher incidence of bleeding (9 vs. 2 %) and transfusion (26 vs. 12%). Secondly, the IDS results from the ANTHALYA study, a randomized phase II study of NACT with or without bevacizumab, were reported (Rouzier et al, 860PD). The primary objective was to assess the superiority of complete response rate (CRR) at IDS compared to a reference rate of 45% from the EORTC study evaluating NACT versus primary surgery (7). In the

bevacizumab group (n = 58), IDS was performed in 69% patients with a CRR of 58.6% compared to an IDS rate of 60% with CRR of 51.4% in patients treated without bevacizumab (n = 37). However, IDS was performed after four cycles of chemotherapy in this trial compared to three cycles within the EORTC trial, making it difficult to make a direct comparison (7). As with the CHIVA study the number of patients proceeding to IDS was lower than with historical data, 65% overall. Combining the data from these studies it appears that the addition of angiogenesis inhibitors to NACT is safe without any significant increase in hemorrhage, transfusion or fistula formation. However, as yet there is insufficient evidence that the addition improves the CRR and PFS and overall survival data are not yet mature.

Endometrial cancer

Anti-angiogenesis in advanced endometrial cancer

The results of the single arm phase II study of pazopanib in metastatic and locally advanced hormone-resistant endometrial cancer were presented in the poster discussion session (Broom et al, 858PD). 60 patients, of whom 45 were evaluable, with heavily pre-treated endometrial cancer were enrolled and treated with pazopanib 800 mg od. Twenty-six of the evaluable patients (58%) had no progression at three months, with median PFS and OS of 5.3 and 9.5 months, respectively. There was a high incidence of toxicity with 38% of patients experience a serious adverse event, including 15% incidence of severe gastrointestinal toxicity, which included two gut perforations, one fatal gastrointestinal hemorrhage, one enterocutaneous fistula and one fatal enterovaginal fistula. 44% of patients required a dose reduction. The clinical activity observed in such a heavily pre-treated population is of interest and merits further evaluation albeit with caution in view of the high incidence of toxicity. It is worth noting that the majority of patients with gastrointestinal toxicity had peritoneal disease suggesting that pazopanib should be avoided in this subgroup.

Conclusion

Two strong themes emerged from the gynecological track at ESMO 2016. Firstly, the therapeutic landscape for PARP inhibitors is expanding beyond the treatment of gBRCAmut HGSOC. HRD assays may usefully identify patients likely to have the greatest response to PARP inhibitor treatment, but may not be sufficiently sensitive to separate out non-responders to PARP inhibitors from within the HRD negative group. The niraparib trial provides additional evidence that there is a clinical benefit for PARP inhibitor maintenance therapy in most patients with platinum sensitive recurrent disease. Secondly, there are number of novel therapies, including ADCs and small molecules which are showing promising preliminary activity in platinum-resistant ovarian cancer, where a minimal gain in outcome has been made in the past decade.

Details of all of the ESMO abstracts can be found at:

http://www.esmo.org/content/download/88721/1622334/file/ESMO-2016-abstracts-excl-LBA-and-press-programme.pdf

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