ESMO 2016 Congress

7-11 October, 2016

Copenhagen, Denmark

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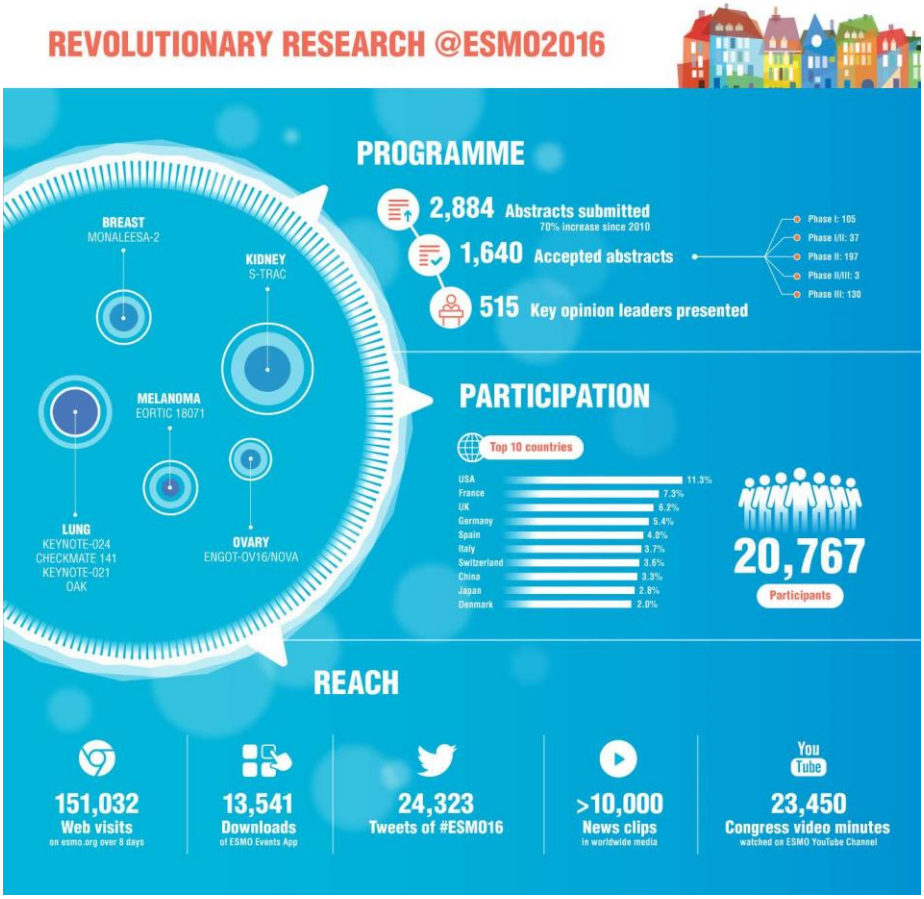
Summary

The European Society for Medical Oncology (ESMO) 2016 Congress, held October 7 to 11 in Copenhagen, Denmark, was a record-breaker on all levels. It was resounding success and in a dedicated infographic you can find the congress programme statistics. A primary emphasis in the scientific programme was placed on two areas: precision medicine and immunology and immunotherapy across multiple tumour types and how these advances change the treatment landscape in oncology. This report is an overview of key scientific presentations made during the Congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2016 scientific programme, as well as advances in oncology.



ESMO 2016 record breaking Congress

GYNAECOLOGICAL CANCER

Niraparib in second-line treatment for platinum sensitive recurrant ovarian cancer

Niraparib, a novel PARP inhibitor, significantly improved the outcome of patients with platinum-sensitive recurrent ovarian cancer and may provide a sorely needed treatment option in this setting. The current standard, platinum-based chemotherapy is limited by cumulative toxicity and a lack of additional benefit with time, which generally results in a treatment pause until the next relapse, according to Mansoor Raza Mirza, Rigshospitalet, Copenhagen University Hospital, Denmark and medical director of the Nordic Society of Gynaecological Oncology (NSGO). Professor Mirza and colleagues in the European Network of Gynaecological Oncology Trial groups (ENGOT) conducted the phase III ENGOT-OV16/NOVA trial to assess the efficacy and safety of niraparib as maintenance therapy in 553 patients with recurrent ovarian cancer that also were responsive to platinum-based chemotherapy. Baseline testing showed 203 patients had germline BRCA mutation and 350 did not; the patients were stratified by BRCA mutation status and randomised 2:1 to receive niraparib at 300 mg or placebo once daily.

The trial met its primary endpoint of progression-free survival (PFS), with niraparib considerably prolonging PFS compared to placebo across all patient cohorts. Median PFS with niraparib was 21.0 months compared to 5.5 months with placebo in patients with germline BRCA mutation, hazard ratio [HR] 0.27; 95% confidence interval [CI] 0.173, 0.410 ($p < 0.0001$). PFS was shorter but prolonged over placebo in patients without baseline BRCA mutation who demonstrated median PFS of 9.3 months versus 3.9 months with niraparib versus placebo, respectively, HR 0.45; 95% CI 0.338, 0.607 ($p < 0.0001$). Median PFS was12.9 versus 3.8 months in a subgroup of patients without BRAF mutation but with homologous recombination DNA repair deficiencies, HR 0.38; 95% CI 0.243, 0.586 ($p < 0.0001$). Significant improvements were also observed in all secondary endpoints. Compared to placebo, niraparib significantly prolonged the second PFS, time to first subsequent treatment, and chemotherapy-free interval in all 3 patient populations.

Grade 3/4 adverse event with niraparib included 28% of patients with thrombocytopenia, 25% had anaemia, and 11% of patients had neutropenia. These were resolved with dose adjustments and patients could continue their treatment. Patient-reported outcomes were similar with niraparib and placebo. Patients on niraparib maintained symptom control and had a quality of life comparable to those on placebo. These findings were published simultaneously online in *The New England Journal of Medicine (NEJM)*. NCT01847274. Mizra *et al.* Abstract LBA3_PR; *NEJM* 2016; 375:2154-2164.

Practice point and future research opportunities

The current options for maintenance therapy in the EU are bevacizumab, which can only be given once and improves PFS by just a few months, and the PARP inhibitor olaparib, which is only approved in patients with a germline BRCA mutation (about 10–15% of ovarian cancer patients). No maintenance therapy is approved outside the EU. The results from this study more than doubles the population of patients who may benefit from a PARP inhibitor; niraparib demonstrated large benefits in PFS in recurrent ovarian cancer. These landmark results could

change the way this disease is treated. That PARP inhibitors benefit patients with BRCA mutations has been demonstrated but niraparib seems to benefit patients with recurrent ovarian cancer who respond to platinum regardless of BRCA status.

This study was also the first trial to demonstrate that using homologous recombination deficiency to select patients for treatment is a useful strategy. Future studies are needed to define responder and non-responders to this treatment.

Low response rates halt CORAL study of abiraterone in patients with recurrent epithelial ovarian cancer

Susanna Banerjee, Royal Marsden NHS Foundation Trust, London, UK presented results from the CORAL phase II trial which evaluated the efficacy of abiraterone in patients with ovarian cancer. Dr. Banerjee and colleagues conducted the CORAL phase II trial in 42 patients with epithelial ovarian cancer who had progressed within 12 months of the last systemic therapy. The patients had a median age of 64 (range: 34 to 85) years, and 88% had high-grade serous histology. The patients had not received prior hormonal anticancer agents, but 47% had received 3 or more previous lines of therapy. The median time from diagnosis was 2.8 years. All patients were administered abiraterone acetate at 1,000 mg plus 5 mg prednisone daily until disease progression or end of study. Tissue and blood samples were obtained for determination of hormone receptor status; at baseline, 29 (69%) patients were positive for androgen receptor (AR) expression, 35 (83.3%) were positive for the oestrogen receptor (ER), and 25 (59.5%) patients were positive for the progesterone receptor (PgR). The primary endpoint of CORAL was the overall response rate (ORR) according to combined RECIST at 12 weeks, and the secondary endpoint was the clinical benefit rate (CBR) at 12 weeks.

CORAL, the first trial of abiraterone in ovarian cancer was halted early due to low response. At 12 weeks, the response rate was 2.4% in the overall study cohort and 3.4% in patients expressing the AR. However, one patient achieved complete response (CR). This patient was AR positive and had low-grade serous histology, achieved a CR that lasted for 47 weeks, and remains on abiraterone. A total of 11 patients showed clinical benefit at 12 weeks, which was prolonged to 24 weeks for 4 patients.

Treatment emergent adverse events (TEAEs) grade 3/4 included hypertension in 29% of patients, and hypokalaemia in 10%. Dose delays were required in 23% of patients lasting for an average of 7.6 days. Treatment discontinuation due to disease progression was reported for 78% of patients, 3 patients also choose to discontinue treatment, and 3 discontinuations occurred for other reasons. The investigators are assessing why some patients had clinical benefit by analysing their tumour and blood samples. EudraCT Number: 2013-000293-29 (17-01-2013). Banerjee *et al.* Abstract LBA33_PR

Practice point and future research opportunities

Abiraterone is a CYP17 inhibitor of androgen biosynthesis approved for the androgen deprivation treatment of prostate cancer; therefore, it should decrease androgen binding to the AR, which is reported to be expressed in up to 90% of epithelial ovarian cancer cases. Although the CORAL trial did not reach the desired level of activity, leading to early trial closure, some patients did respond, including one CR. There remains an urgent need to develop smarter treatment options for women with recurrent epithelial ovarian cancer

Further investigation of the role of the AR pathway in epithelial ovarian cancer may warrant further investigation.

Use of a novel oncologist-led BRCA1/2 germline mutation testing and counselling model for patients with ovarian cancer yields high marks for patient and clinician satisfaction

Giovanni Scambia, Gynaecology Oncology, Policlinico Universitario A. Gemelli Università Cattolica del Sacro Cuore, Rome, Italy, and colleague conducted ENGAGE, the first real-world study to evaluate whether an oncologist-led testing model first used at the Institute of Cancer Research and Royal Marsden Hospital, London, UK facilitates germline BRCA mutation (gBRCAm) testing and genetic counselling. ENGAGE is an ongoing prospective, observational study that was conducted across 11 sites in the US, 8 in Italy, and 7 sites in Spain, and enrolled 710 adult patients with epithelial ovarian, fallopian tube or primary peritoneal cancer. The analysis included baseline demographic, clinical and therapeutic data, and primary outcome data, including gBRCAm testing turnaround time, outcome of the BRCA test, and surveys completed by patients and oncogenetic counsellors regarding satisfaction with the model.

Professor Scambia reported findings from an interim analysis that comprised data from 444 patients with mean (standard deviation) age 63.7 (10.6) years. The median time since diagnosis was 0.8 years, 38% of participants were newly diagnosed, and 38% had family history of breast or ovarian cancer. Pre-BRCA test counselling was provided by oncologists (40%) or nurses (56%) in the US and by oncologists in Europe. Only one patient requested additional pre-test counselling. Mean (standard deviation) turnaround time from initial counselling to receipt of BRCA test results or oncogenetic counselling overall was 6.7 (SD 4.5) weeks. In the US, turnaround time was 5.1 (SD 3.7) weeks and 10.0 (SD 4.2) weeks in the EU. BRCA testing was performed in a central laboratory in 91% of cases. BRCA mutation was identified in 10% of patients. Mean patient-reported fulfilment of expectations and overall satisfaction with counselling were both >3.7/4 pre-/post-BRCA testing. Most patients, 92%, were satisfied to have the genetic test at an existing rather than a separate visit. Over 80% of oncologists reported that the BRCA-testing process worked well and that counselling patients on BRCA testing was an efficient use of their time. NCT02406235. Scambia *et al.* Abstract LBA34

Practice point and future research opportunities

Findings from this interim analysis support the novel testing model, which facilitated genetic counselling and provided the potential for quicker treatment decisions and better use of

resources. The model resulted in reduced turnaround times and high acceptance and satisfaction levels were reported by both patients and staff.

Single-agent selinexor shows promise in heavily pre-treated gynaecological cancers

Selinexor is a first-in-class inhibitor of XPO1, a nuclear export protein that is expressed in aggressive ovarian cancers and is also commonly expressed in patients with endometrial cancer. XPO1 has been linked to poorer patient outcomes. Ignace B. Vergote, Department of obstetrics and gynaecology and of gynaecologic oncology, Catholic University of Leuven in Belgium, and colleagues evaluated the safety and efficacy of selinexor in a phase II trial in 66 patients with ovarian cancer, 23 patients with endometrial cancer and 25 patients with cervical cancer. Patients in the respective groups, had received a median number of 6 (range: 1 to 11), 2 (range: 1 to 5), and 3 (range: 1 to 8) prior treatment regimens. All patients with ovarian cancer were refractory to platinum chemotherapy, and all patients with endometrial and cervical cancers had received at least one prior line of chemotherapy. Patients with ovarian cancer were randomly assigned to one of treatment schedules: selinexor at 50 mg/m^2 twice weekly, 35 mg/m^2 twice weekly, or 50 mg/m^2 every week in 4-week cycles. All other patients received selinexor 50 mg/m^2 twice weekly. The primary endpoint of the study was disease control rate (DCR) at week 12 and secondary endpoints included overall response rate (ORR), progression-free survival (PFS), duration of response (DoR), safety and tolerability.

At 12 weeks the DCR was 49% in patients with ovarian cancer across dosing schedules, and patients with endometrial cancer demonstrated a DCR of 45%: however, the DCR was 6% in patients with cervical cancer. The ORR was 14% among both patients with ovarian cancer, 15% among patients with endometrial cancer, and 4% in patients with cervical cancer. Across all parametres, selinexor demonstrated clinical benefit that was much lower in the cervical cancer cohort. Median PFS was 3 months among patients with ovarian and endometrial cancers, versus one month in patients with cervical cancer. Median overall survival was 7 months in patients with ovarian cancer, 8 months in patients with endometrial cancer and 5 months in patients with cervical cancer.

Analysis of the patients' blood samples for circulating tumour cells (CTCs) showed that patients with CTCs prior to treatment tended to have shorter PFS.

Common grade 1 and grade 2 drug-related adverse events (AEs) that occurred in all patients included nausea (56%), anorexia (47%), weight loss (44%) and fatigue (42%). Grade 3 drug-related AEs included thrombocytopenia (11%), fatigue (10%), anaemia (9%) and nausea (8%). One patient each experienced grade 4 cataract and hyponatremia. Based on these results, phase III trials are planned to evaluate selinexor in patients with ovarian and endometrial cancers. EduraCT No: 2013-003650-24; Clinical Trials NCT02025985. Vergote *et al.* Abstract 854O

Practice point and future research opportunities

Single-agent selinexor demonstrated interesting antitumour activity in heavily pretreated ovarian and endometrial cancers, but showed far less activity in patients with cervical cancer. It is surprising that the worst disease control rate was seen in patients with cervical cancer, despite the fact that this is an HPV–induced tumour, where a greater response than in the two other cohorts could have been expected. Selinexor offers promise as new treatment for heavily pretreated ovarian and endometrial cancers that warrants phase III confirmation.

Novel CHK1/2 inhibitor demonstrates activity in patients with sporadic high-grade serous ovarian cancer and germline BRCA mutation-associated ovarian cancer

Lead author Jung-Min Lee, Women's Malignancies Branch, National Cancer Institute, Rockville, USA and colleagues reasoned that LY2606368 could have clinical activity in high-grade serous ovarian cancer (HGSOC). LY2606368 is a second-generation inhibitor of checkpoint kinases 1/2 (CHK1/2), which are the primary cell cycle regulators in tumours with p53 dysfunction, including HGSOC. The study of LY2606368 enrolled 15 women with recurrent HGSOC plus negative BRCA testing or a negative family history of hereditary breast and ovarian cancer syndrome (cohort 1) and 7 women with a documented deleterious germline BRCA1/2 mutation (cohort 2). All patients had good end organ function, ECOG performance status 0-2, and disease that could be safely biopsied. The median age was 61 (range: 36 to 83) years. The median number of prior therapies was 5 (range: 1 to 13) in cohort 1 and 7 (range: 3 to 12) in cohort 2. All patients were treated with LY2606368 at 105 mg/m^2 i.v. every 14 days per 28-day cycle. Response was assessed every 2 cycles by RECIST v1.1, and safety by CTCAE v4.0 per cycle. The primary endpoint was overall response rate (ORR).

The ORR in 13 evaluable patients in cohort 1 was 38% with 5 patients achieving partial response (PR). The median duration of response (DoR) was 9 months (range: 3 plus to 9 plus months); 2 of the responding patients had platinum-sensitive and 3 had platinum-resistant disease. In cohort 2, stable disease lasting 4 or more months was attained by 4 of 6 evaluable patients (median DoR was 4.5 months), but there were no responses. Grade 3 or 4 treatment-emergent adverse events (AEs) included neutropenia in 91% of patients, thrombocytopenia in 27%, febrile neutropenia in 9%, and diarrhoea in 9% of patients. Grade 3 or 4 neutropenia occurring on day 8 resolved within 7 days in 13 patients and 13 patients received growth factor support due to febrile neutropenia or to avoid treatment delays. This study continues to enroll patients and paired tumour biopsy and blood samples are being collected to examine potential biomarkers of response. NCT02203513. Lee *et al.* Abstract 855O

Practice point and future research opportunities

In this study, the novel second-generation inhibitor of CHK½, LY2606368 administered as sole treatment in patients with BRCA wild-type high-grade serous ovarian cancer showed promising preliminary activity. Prophylactic use of G-CSF should be considered with this agent.

RELATED INFORMATION

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Save the date

ESMO 2017 Congress, Madrid, Spain, 8-12 September 2017.

Affiliations and Disclosure

Affiliation

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Disclosure

No conflicts of interest to disclose.

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