ESMO 2016 Congress

7-11 October, 2016

Copenhagen, Denmark

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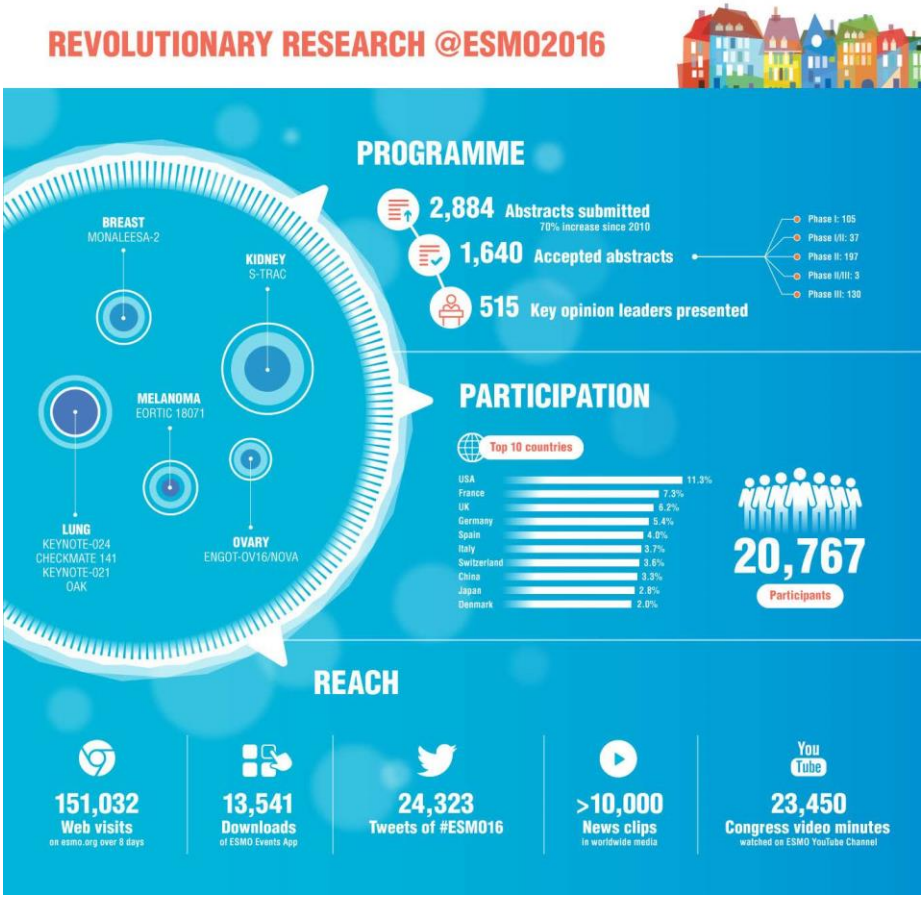
Summary

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

GENITOURINARY TUMOURS - PROSTATE

Custirsen provides no additional survival benefit to cabazitaxel/prednisone in metastatic prostate cancer

Karim Fizazi, head of the Department of Cancer Medicine at the Institut Gustave Roussy, Villejuif, France expressed disappointment with the results from the AFFINITY trial of custirsen in metastatic, castration-resistant prostate cancer but noted that custirsen remains a viable candidate currently under evaluation in non-small cell lung cancer, as failure in one tumour type does not predict the outcome in other indications. Custirsen blocks production of the protein clusterin, which is upregulated in tumour cells following treatment interventions such as chemotherapy, hormone ablation, and radiation therapy and is overexpressed in a number of cancers, including prostate, lung, breast and bladder. Clusterin promotes carcinogenesis and tumour growth, and may contribute to treatment resistance.

Professor Fizazi and colleagues conducted the phase III AFFINITY trial in 635 patients with metastatic, castration-resistant prostate cancer, who had previously been treated with docetaxel. The patients were randomised 1:1 to 21-day cycles of custirsen at 25 mg/m2 i.v. plus cabazitaxel/prednisone or cabazitaxel/prednisone plus placebo, until disease progression, unacceptable toxicity, or ten cycles.

Median overall survival (OS) at 14.2 months in the custirsen arm compared to 13.4 months in the placebo arm ($p = 0.529$). Findings from an analysis of 62% of patients who met the criteria for poor prognosis supported this result, and demonstrated median OS of 11.1 with custirsen and 10.9 months with placebo.

Similar numbers of patients, 28.9% in the custirsen arm and 25% in the placebo arm, discontinued the study due to progressive disease. Discontinuation due to adverse events was also similar; 21.9% of patients receiving custirsen and 18.9% of patients on placebo halted treatment. The incidence of adverse events grade 3 and higher was similar between arms with the most frequently reported being neutropenia, anaemia, fatigue, asthenia, bone pain, and febrile neutropenia. NCT01578655. Fizazi *et al.* Abstract LBA9_PR

Practice point and future research opportunities

Treatment failure is the major barrier to extending survival in patients with advanced cancer. Custirsen was designed to block clusterin, a cytoprotective protein that is upregulated by chemotherapy and other treatment in cancer cells. Although the outcome of this trial was negative, the evaluation of custirsen in prostate cancer was conducted on the basis of solid preclinical and clinical evidence supporting anti-tumour activity. A previous phase II trial of custirsen combined with chemotherapy in men with metastatic castration-resistant prostate cancer suggested inhibition of clusterin may lead to improved clinical outcome, and an earlier phase III trial of custirsen in combination with docetaxel suggested patients with more aggressive cancers may benefit from the combination. An ongoing trial of custirsen may contribute to evidence.

Phase II findings show alisertib has benefit in patients with neuroendocrine prostate cancer

Himisha Beltran, Division of Hematology and Medical Oncology at Weill Cornell Medicine in New York, USA presented phase II findings demonstrating that aurora kinase A inhibition with alisertib may benefit a subset of patients with neuroendocrine prostate cancer (NEPC). NEPC is an aggressive subtype of castration resistant prostate cancer that is androgen independent, and preclinical studies demonstrated that NEPC signalling supporting tumour growth could be suppressed with alisertib, which targets Aurora A and blocks the interaction between Aurora A and N-myc.

Dr. Beltran and colleagues enrolled 59 patients with metastatic prostate cancer in this multicentre, phase II trial to receive alisertib at 50 mg twice daily for 7 days of a 21-day cycle. Of these, 41 (70%) patients had at least one additional pathologic criteria, including NEPC morphology, greater than 50% neuroendocrine marker by immunohistochemistry, new liver metastases but without prostate specific antigen (PSA) progression, and/or greater than 3 to 5 times elevated serum NSE/CgA concentration. The patients' median age was 67 (range: 45 to 87) years, median PSA was 1.13 ng/ml (range: 0.01 to 514.2), and the patients had received prior therapy with docetaxel, platinum and abiraterone/enzalutamide. The metastatic sites were bone in 78%, lymph node in 73%, liver in 61% and lung in 37% of patients.

Among the evaluable 56 patients, median overall survival (OS) was 38 weeks and the 6-month progression-free survival (PFS) rate was 11.1% overall, but rose to 16.3% in the cohort of patients with pathologically defined NEPC. Among the 17 patients with scans taken at cycle 3, median PFS was 20 weeks and 6-month PFS was 35.8%. An exception response was seen in 2 patients, one of which demonstrated complete resolution of liver metastasis, and a third patient achieved stable disease lasting 39 months at follow-up. No new toxicity signals were raised and grade 3/4 toxicities occurred in 5 (9%) patients. NCT01799278. Beltran *et al.* Abstract LBA29

Practice point and future research opportunities

Alisertib is being explored across a broad range of haematological malignancies and solid tumours, including phase III trials in refractory T- and B-cell lymphoma. These findings suggest that alisertib may be beneficial in some patients with neuroendocrine prostate cancer. The authors are continuing genetic analyses and the results may allow the integration of clinical, pathologic, and molecular features that may help to improve patient selection and enhance outcome following alisertib.

Meta-analysis supports metastasis-free survival as a surrogate for OS in localised prostate cancer

Wanling Xie, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, USA presented finding from a meta-analysis on behalf of colleagues in the

Intermediate Clinical Endpoints in CaP (ICECaP) Working Group that attempted to identify surrogate end points that correlate with overall survival in localised prostate cancer clinical trials. The investigators analysed data from 12,712 men included in 19 mature randomised clinical trials conducted between 1987 and 2010. Of those, 90% of patients were from radiotherapy-based studies, 30% had intermediate-risk disease, and 57% had high-risk disease.

Metastasis-free survival (MFS) was defined as the time from randomisation to the first evidence of distant metastatic disease, excluding pelvic lymph nodes, or death from any cause, and overall survival (OS) as the time from randomisation to death from any cause. At a median follow-up of 9.9 years, there were 5733 MFS events and 5350 OS events. There were 2154 time to metastasis (TTM) events and 1460 disease-specific survival (DSS) events, which did not include non-prostate cancer-related deaths. Linear regression showed the 5-year MFS associated with 10-year OS, 0.71 (95% confidence interval [CI] 0.50, 0.80) and with 8-year OS 0.83 (95% CI 0.71, 0.88), log hazard ratio [HR] 0.92 (95% CI 0.81, 0.95). Analysis of whether TTM could serve as a surrogate for DSS revealed that 5-year TTM associated with 10-year DSS, 0.78 (95% CI 0.60, 0.85) and with 8-year DSS 0.86 (95% CI 0.75, 0.90), log HR 0.89 (95% CI 0.72,0.93). Xie *et al.* Abstract 717O

Practice point and future research opportunities

Results from this meta-analysis suggest that metastasis-free survival may be used as a surrogate endpoint for OS in clinical trials evaluating patients with localised prostate cancer, and that the time to metastasis may serve as a surrogate end-point of disease-specific survival. Both metastasis-free survival and time to metastasis usually can be measured earlier than overall or disease-specific survival.

Phase II findings show early evidence of anti-PD-1 activity in mCRPC

Julie N. Graff, Knight Cancer Institute, Oregon Health Science University, Portland, USA presented first results from first 14 patients treated with panitumumab added to enzalutamide in an ongoing phase II clinical trial. The study showed for the first time evidence of meaningful clinical activity for PD-1 blockade in men with metastatic prostate cancer that showed resistance to androgen deprivation. In the trial, men with metastatic castration resistant prostate cancer (CRPC) that progressed on the androgen receptor antagonist enzalutamide were treated with pembrolizumab at 200 mg i.v. every 3 weeks for 4 doses with continued enzalutamide. Men having chemotherapy for mCRPC were not enrolled. The primary endpoint of the ongoing trial is the proportion of men with a prostate specific antigen (PSA) response ≥ 50%. The secondary endpoints were objective disease response, PSA progression-free survival, and overall survival.

Following pembrolizumab/enzalutamide treatment, 4 patients experienced rapid, confirmed reductions in PSA≥ 50%, and achieved serum PSA levels less than 0.1 ng/ml. These patients remained progression-free at 9 to up to 54 weeks of treatment. Stable disease was seen in 6 patients, and 4 patients experienced progressive disease.

Subsequent imaging scans taken in 2 of the 4 responders with measurable disease in the liver and lymph nodes showed tumour shrinkage, and both achieved partial response that was

durable for 54 and 15 weeks of follow-up. Two responding patients experienced reduction of cancer-related pain that was sufficient to allow discontinuation of opiate pain medication. Biopsies had been taken at baseline, when possible, and protein expression was evaluated by immunohistochemistry. This analysis revealed the presence of CD3+, CD8+, and CD163+ leukocyte infiltrates, and PD-L1 expression in 2 of the responder's samples.

Significant immune-related adverse events were reported in 4 patients, including grade 2 myositis with muscle weakness and pain, grade 3 hypothyroidism, and grade 2 hypothyroidism. NCT02312557. Graff *et al.* Abstract 719O

Practice point and future research opportunities

Early results from this trial of pembrolizumab in metastatic prostate cancer demonstrate profound, ongoing responses to PD-1 inhibition with pembrolizumab plus enzalutamide in some men with mCRPC. Approved agents for mCRPC rarely produce PSA reduction to less than 0.2 ng/ml after enzalutamide has stopped working. Significant responses in liver metastases are also relatively uncommon with androgen receptor-targeting drugs or cytotoxic chemotherapies. These promising results represent the experience of the first 14 patients treated with pembrolizumab and must be viewed as preliminary. The ongoing study, which is continuing to follow these men and has enrolled additional participants, will provide more robust answers about the potential benefits of PD-1 inhibition for men with metastatic prostate cancer.

RELATED INFORMATION

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Save the date

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

Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

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