ESMO 2016 Congress

7-11 October, 2016

Copenhagen, Denmark

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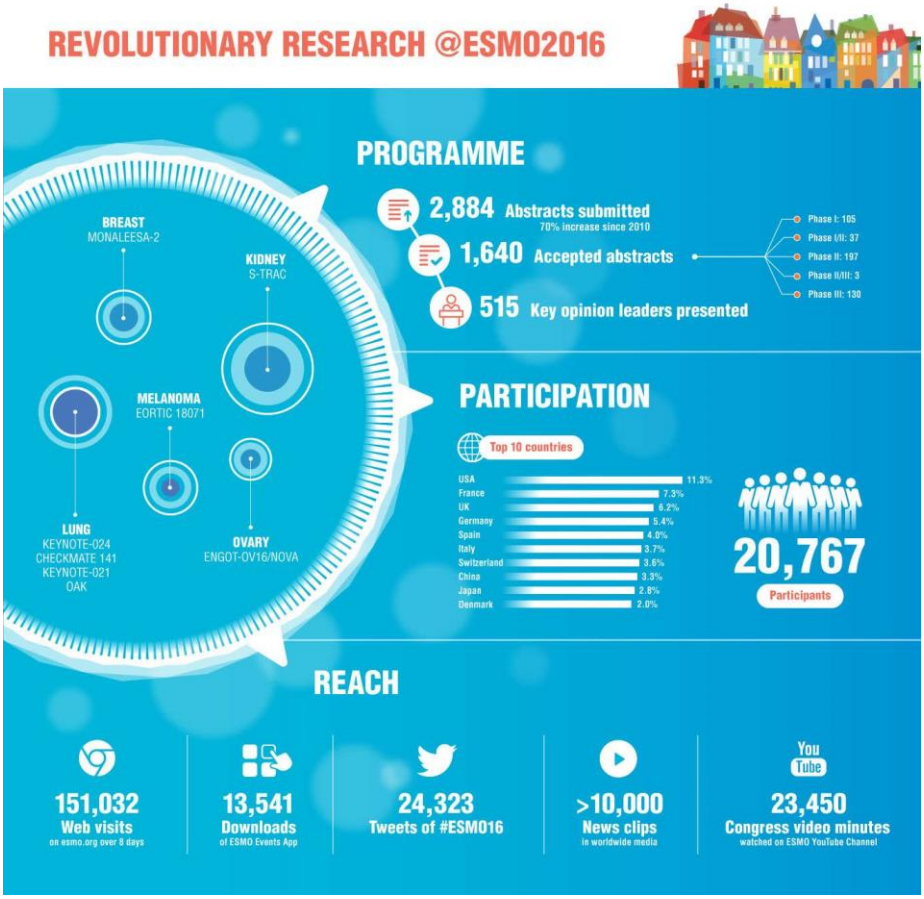
Summary

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 - nonPROSTATE

Sunitinib shows promise as adjuvant treatment in post-nephrectomy high-risk RCC

Lead author Alain Ravaud of the Hôpital Saint-André in Bordeaux, France discussed findings from the S-TRAC phase III study that randomised 309 treatment-naive patients with locoregional renal cell carcinoma (RCC) to receive sunitinib and 306 patients to receive placebo. The study included patients that had undergone nephrectomy that were at high-risk but with no evidence of metastasis upon central review of imaging done at baseline. Patients were started on 50 mg/day of sunitinib orally for 4 weeks on/2 weeks off or on placebo for the same schedule. Sunitinib dose reductions to a minimum of 37.5 mg/day were allowed. In the sunitinib cohort, the median number of cycles was 9 and relative dose intensity was 88.4%. Both treatment arms were well balanced at baseline for demographic and disease characteristics.

Sunitinib extended disease-free survival (DFS), the primary endpoint, to 6.8 years (95% confidence interval [CI] 5.8, NR) versus 5.6 years (95% CI 3.8, 6.6) years with placebo, by blinded independent review, hazard ratio [HR] 0.76; (p = 0.030). Fewer DFS events were seen with sunitinib; 113 DFS events occurred in 36.6% of patients versus 144 events in 47.1% of placebo patients.

Analyses of a subgroup of higher risk patients supported these findings; DFS in this subgroup was 6.2 years versus 4.0 years with placebo, HR 0.76 (p = 0.044). OS data were immature at data cut-off. The rate of serious adverse events (grade 3 or higher) was 63.4% in the sunitinib arm and 21.7% in the placebo arm. These results were published simultaneously online in *The New England Journal of Medicine (NEJM)*. NCT00375674. Ravaud *et al.* Abstract LBA11_PR; *NEJM* 2016; 375:2246-2254.

Practice point and future research opportunities

The recurrence rate following nephrectomy distinguishes RCC from other tumours that have a lower risk of recurrence. Approximately 16% of all cases of RCC are diagnosed with locoregional disease, and of these, up to 49% have a relapse with metastasis after nephrectomy, making a strong argument for adjuvant therapy. These are the first positive data in the adjuvant setting in loco-regional RCC and the result of this trial could change practice, if approved by health authorities, because there is currently no standard adjuvant treatment for clear-cell RCC. Sunitinib is a potential new option for adjuvant therapy in these patients, given the increase in DFS and the manageable safety profile.

An important caution is that the results apply to only the patient population represented in the trial: patients with clear-cell, high-risk RCC without metastases, and that sunitinib should be given at a starting dose of 50 mg with dose reductions to 37.5 mg/day, as in this study. A different regimen of adjuvant sunitinib was administered in the ASSURE trial, which showed no difference in DFS or OS. These contradictory findings generate uncertainty. Also, DFS is a useful surrogate endpoint, but does not necessarily translate to OS, which is the gold standard. There are a number of other trials ongoing in this area and additional positive data could tip the balance

towards recommending sunitinib as adjuvant therapy.

First-line cabozantinib improves PFS over sunitinib in mRCC

Toni Choueiri, director of the Lank Centre for Genitourinary Oncology at the Dana-Farber Cancer Institute in Boston, USA presented findings on behalf of colleagues from the phase II multicentre trial wherein 157 patients with untreated clear-cell metastatic renal cell carcinoma (mRCC) of intermediate or poor risk, and ECOG performance status 0 to 2, were randomised 1:1 to oral cabozantinib at 60 mg once daily or sunitinib at 50 mg once daily, 4 weeks on, 2 weeks off. The International mRCC Database Consortium Criteria (IMDC) intermediate risk was reported for 80.9% of patients, and 36.3% had bone metastases; these patients were equally distributed across treatment arms.

After a median follow up of 20.8 months patients treated with cabozantinib showed a 31% reduction in the rate of progression or death compared to those treated with sunitinib, adjusted hazard ratio HR [0.69]; 95% confidence interval [CI] 0.48, 0.98 (one-sided p = 0.012). The median progression-free survival (PFS) was 8.2 months, (95% CI 6.2, 8.8) compared to 5.6 months (95% CI 95% 3.4, 8.2), respectively (p = 0.012). The objective response rate was also significantly higher at 46% (95% CI 34, 57%) in the cabozantinib arm compared to 18% (95% CI 10-28%) in the sunitinib arm. Median overall survival was 26.4 months with cabozantinib compared to 23.5 months with sunitinib (adjusted HR 0.87, 95% CI 0.55, 1.4). At data cut-off, 13 (16.46%) cabozantinib patients versus 2 (2.56%) sunitinib patients remained on treatment.

Investigators observed a similar rate of adverse events (AEs) between the two arms of the study; the incidence of grade 3 or higher AEs was 70.5% in the cabozantinib arm and 72.2% in the sunitinib arm. The most common AEs for both treatments included diarrhoea, fatigue, hypertension, palmar-plantar erythrodysesthesia. Haematological events were higher with sunitinib; haematological events were reported in 2.6% of cabozantinib versus 22.2% of sunitinib patients. Treatment was terminated early due to toxicity by 16 patients in each arm. NCT01835158. Choueiri *et al.* Abstract LBA30_PR

Practice point and future research opportunities

In this trial, cabozantinib demonstrated a significant benefit in both PFS and ORR over standard sunitinib in poor-risk patients with untreated intermediate mRCC. Sunitinib targets the vascular endothelial growth factor receptor (VEGFR) but cabozantinib inhibits a broader range of activity, including VEGFR2, MET and AXL activity, and has demonstrated clinical benefit following anti-VEGFR therapy. Both MET and AXL seem to be associated with tumour progression, but more importantly, animal models showed that the development of resistance to VEGFR inhibitors like sunitinib can be mediated through AXL and MET. It is unknown whether these results are expandable to all mRCC patients, including patients with a good prognosis. The study did not include good-risk patients, but there is no biological or clinical rationale to think that cabozantinib would not be equally effective in that population. While more mature data and

additional studies using cabozantinib in the first line setting will be required, this study raises new expectations for the first-line treatment of mRCC.

For many years, sunitinib has been the most commonly used standard of care in first-line mRCC, and recently, cabozantinib demonstrated activity in second line for these patients, especially after sunitinib failure. Cabozantinib is currently approved for second or later lines of treatment in patients that have progressed on a VEGFR tyrosine kinase inhibitor, but these data show that cabozantinib has the potential to become a first-line standard treatment in mRCC.

Nivolumab in second line treatment of metastatic urothelial cancer

Lead author Matthew Galsky, Mount Sinai School of Medicine, New York, USA presented safety and efficacy findings on behalf of colleagues from the phase II CheckMate 275 trial. The investigators conducted this open-label, single-arm, phase II study in 270 patients with metastatic urothelial cancer who progressed despite first line platinum-based chemotherapy and who received nivolumab at 3 mg/kg i.v every 2 weeks until progression or unacceptable toxicity. The patients' median age was 66 years and 84.1% of patients had visceral metastases at baseline. Overall, 42.2% of patients had received one, and 29.3% of patients underwent 2 or more prior treatment regimens in the metastatic setting. The primary endpoint was objective response rate (ORR) by RECIST 1.1 confirmed by blinded independent review committee.

CheckMate 275 is the largest study of a PD-1 inhibitor in bladder cancer reported to date and showed a rapid response to nivolumab. The medium time to response was 1.9 (range: 1.8 to 5.9) months. The median duration of response has not yet been reached, but responses at a median follow-up of 7 months are ongoing in 76.9% of responders, and 24.4% of 265 patients remained on therapy. Median progression-free survival (PFS) in the overall cohort was 2 months (95% confidence interval [CI] 1.87, 2.63); median PFS was 1.87 in patients having less than 1% PD-L1 expression and increased to 3.55 months in patients with PD-L1 expression of 1% or greater.

Median overall survival (OS) was 8.74 months (95% CI 6.05, not estimable); median OS was 5.95 months in patients having less than 1% PD-L1 expression and 11.3 months in patients with PD-L1 expression of 1% or greater. Although higher PD-L1 expression was associated with a higher ORR of 19.6%, patients with low to no PD-L1 expression also responded well to nivolumab and demonstrated an ORR of 16.1%.

Biomarker analysis was done by immunohistochemistry to determine the association between response, urothelial cancer subtype (by The Cancer Genome Atlas), and immune gene signature expression. PD-L1 expression ≥1% and ≥5% was reported for 45.9% and 30.7% of patients, respectively. Biomarker analyses showed that the strongest nivolumab response was associated with basal 1 (ORR 69.5%), and luminal 2 (ORR 66.3%) subtypes. The basal 1 subtype also showed the strongest interferonγ gene signature expression.

A total of 18% of patients experienced grade 3/4 treatment-related adverse events (TRAEs); fatigue and diarrhoea were the most frequently reported and each occurred in 2% of patients. Grade 5 adverse events consisted of one death each due to cardiovascular disease,

pneumonitis, and acute respiratory failure. Treatment discontinuation due to a TRAE grade 3/4 was reported for 3 patients. Quality of life, as assessed using the Global Health Status Scale, improved from baseline and remained stable over the course of the trial. NCT02387996. Galsky *et al.* Abstract LBA31_PR

Practice point and future research opportunities

The majority of patients with metastatic urothelial cancer experience disease progression despite platinum-based chemotherapy and there are limited treatment options for these patients. Immune checkpoint blockade has become the most promising approach fin this setting. Nivolumab previously demonstrated impressive anti-tumour activity and prolonged overall survival across multiple tumour types. These data are being submitted to support registration of nivolumab as second-line treatment for patients with metastatic urothelial cancer that has progressed despite platinum-based chemotherapy, an indication for which breakthrough therapy designation was granted by the US Food and Drug Administration in June 2016 and the European Medicines Agency initiated review.

Anti-tumour activity with first-line pembrolizumab in advanced/metastatic urothelial cancer

Arjun Balar, NYU Langone Medical Centre in New York, USA presented findings from a preplanned interim analysis of the first 100 patients participating in the KEYNOTE-052 phase II trial of first-line pembrolizumab in cisplatin ineligible patients with metastatic urothelial cancer. KEYNOTE enrolled 374 adult patients with pathologically confirmed and measurable urothelial cancer, and ECOG performance status (PS) 0-2. The patients were cisplatin ineligible due to renal insufficiency in 45% of patients, and ECOG PS 2 plus renal insufficiency in 11% of patients. The patients' median age was 75 (range: 44 to 94) years, 87 (87%) patients had visceral metastases at baseline, and 46% of patients were ECOG PS 2/3. All patients received pembrolizumab at 200 mg every 3 weeks until progressive disease, unacceptable toxicity, or 24 months of treatment. The primary end point was RECIST v1.1 confirmed objective response rate (ORR) by independent review in all patients, and by combined positive score (CPS) in PD-L1–positive patients. The secondary objective was the determination of the CPS-high biomarker cut-point.

The ORR at a median follow-up of 8 months was 24.0% in the overall cohort (95% confidence interval [CI] 16.0, 33.6). Pembrolizumab treatment yielded a rapid response with a median time to response of 2 months (range: 0.1 to 13.4 months). Complete response (CR) was reported for 6 patients and partial response for 17 patients in the overall cohort. Stable disease was reported in 15 (15%) patients and 48 patients experienced progressive disease. The median duration of response (DOR) has not been reached (range: 1.4+ to 9.8+ months). The duration of response (DOR) rate ≥6 months was 83% by Kaplan-Meier estimate. The best change in tumour size was -30% from baseline, by RESIST 1.1, Central Review. A decrease in the target lesion was reported for 52% of patients. Four patients were non-evaluable and 10 patients were not

assessed for response.

When patients were stratified according to a CPS depicting of the level of PD-L1 expression on the tumour and surrounding immune cells, 33 patients with CPS <1 had an ORR of 18%, 33 patients with CPS ≥1% but <10 achieved an ORR of 15%, and 33 patients with CPS ≥10% expression levels achieved ORR 37%. The location of both the primary tumour and metastases were found to also affect pembrolizumab activity. Patients with a primary tumour in the upper tract had an ORR of 10% whereas patients with lower tract disease had an ORR of 28%. Regarding metastasis location, the ORR was 40% in 10 patients having lymph node involvement only, compared to ORR of 21% in 87 patients with visceral disease.

Pembrolizumab was well tolerated, with 67% of patients experiencing a drug-related adverse event (DRAE). The most common DRAE reported by 14% of patients was fatigue. A grade 3/4 DRAE occurred in 16% of patients and 5 patients discontinued therapy due to a DRAE. This trial is ongoing and pembrolizumab is being investigated as first-line treatment for advanced urothelial cancer in the phase III KEYNOTE-361 study. NCT02335424. Balar *et al.* Abstract LBA32_PR

Practice point and future research opportunities

Pembrolizumab administered in the first-line demonstrated substantial antitumour activity and favourable safety profile in cisplatin-ineligible patients with advanced/metastatic urothelial cancer. Cisplatin-based chemotherapy is the standard first-line treatment in advanced urothelial cancer but patients with impaired renal function, poor PS, and comorbidities, such as hearing loss, neuropathy, or heart failure are not eligible for this treatment. These patients are generally treated with a gemcitabine and carboplatin combination, which is associated with a 36% response rate; however, there is substantial toxicity and 21% of patients discontinue treatment due to toxicity,

Pembrolizumab treated patients demonstrated a 24% response rate that became greater as expression levels of PD-L1 on the tumour and surrounding immune cells increased. A PD-L1 high cut point of CPS ≥10% seems to identify patients most likely to respond well to pembrolizumab. This biomarker cut point is being validated in the study population in the ongoing trial.

RELATED INFORMATION

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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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