ESMO 2016 Congress

7-11 October, 2016

Copenhagen, Denmark

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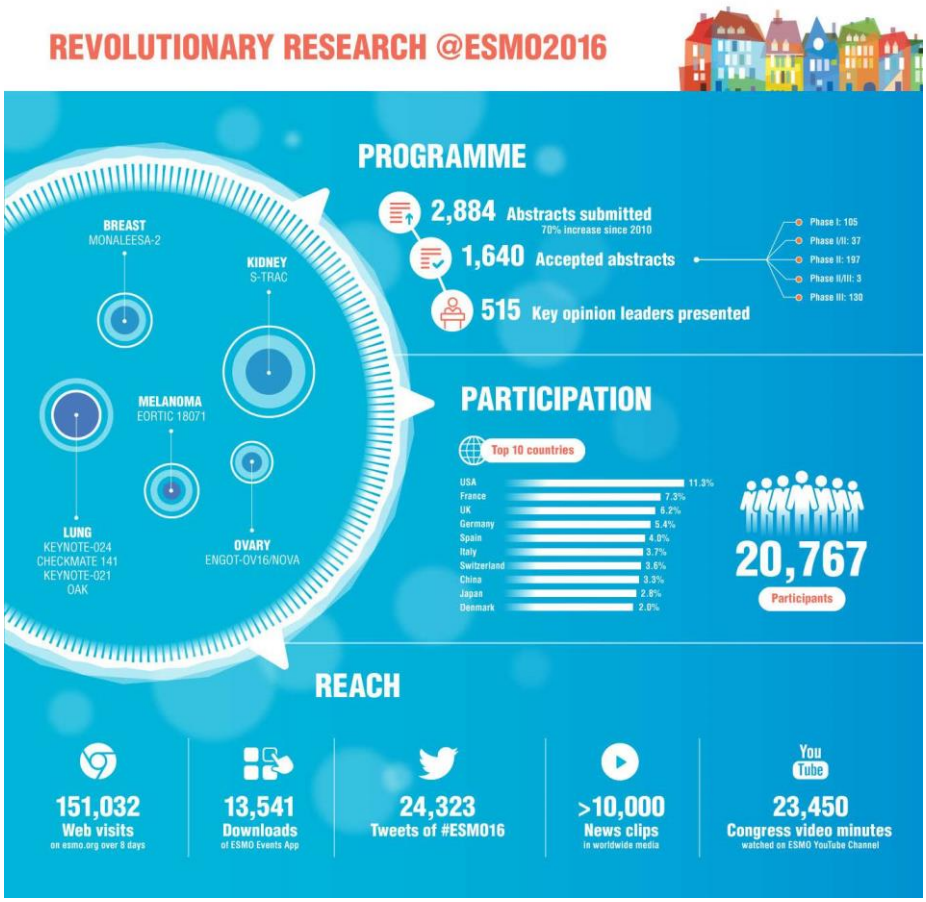
Summary

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

MELANOMA AND OTHER SKIN TUMOURS

Long-term results show adjuvant therapy with ipilimumab improves OS in high risk stage III melanoma

Alexander Eggermont, Institut Gustave Roussy, Villejuif, France presented long-term findings from the EORTC 18071 phase III trial evaluating ipilimumab as adjuvant therapy for patients with high-risk stage III melanoma. Beginning in 2008, the investigative team randomised 951 patients to ipilimumab at 10 mg/kg or placebo; 20%, 44%, and 36% of patients had stage IIIA, IIIB, or IIIC disease. The majority of patients (58%) had macroscopic lymph node involvement and the remaining patients had ulcerated primary melanoma. Results reported in 2015 showed that the trial met its primary endpoint of recurrence-free survival (RFS) after a median follow up of 2.3 years. Based upon these data, ipilimumab was approved by the US Food and Drug Administration (FDA) as adjuvant therapy for stage III melanoma.

At ESMO 2016, Professor Eggermont presented overall survival (OS) results from this trial after a median follow-up of 5.3 years that showed ipilimumab as adjuvant therapy significantly improved OS in these high-risk, stage III melanoma patients. Median OS was 86 months with ipilimumab versus not reached with placebo and the 5-year OS rates were 65.4% with ipilimumab compared to 54.4% with placebo, which represents a 28% reduction of the relative risk of death, hazard ratio [HR] 0.72 ($p = 0.001$). The 5-year RFS rates were 40.8% versus 30.3% with ipilimumab versus placebo, respectively, HR 0.76 ($p < 0.001$). The 5-year distant metastases-free survival rates were 48.3% with ipilimumab versus 38.9% with placebo, HR 0.76 ($p = 0.002$).

At the 5.3-year follow-up, immune-related grade 3-4 adverse events (AEs) included gastrointestinal events, reported in 16% of patients, hepatic in 11%, and endocrine AEs were reported in 8% of patients that resolved within 4 to 8 weeks, except the endocrine AEs, which took much longer to resolve or required permanent hormonal replacement therapies. Ipilimumab was discontinued due to an AE by 251 (53.3%) patients and 5 drug-related deaths occurred on study, as previously reported. These results were published simultaneously online in *The New England Journal of Medicine (NEJM)*. NCT00636168. Eggermont *et al.* Abstract LBA2_PR; *NEJM* 2016; 375:1845-1855.

Practice point and future research opportunities

Ipilimumab is an immune checkpoint inhibitor of cytotoxic T-lymphocyte antigen-4 (CTLA-4) that was approved in 2011 for first-line treatment of advanced melanoma in the US and Europe. This was the first trial to evaluate checkpoint blockade in the adjuvant setting in melanoma and the data reinforce ipilimumab as an important treatment option for these patients. The OS results reported at ESMO 2016 revealed clinically and statistically significant improvement with ipilimumab as adjuvant therapy in high-risk stage III melanoma patients.

These results also provide important scientific information: until now it was unknown whether ipilimumab, which works by stimulating the immune system against tumour antigens, or other immunotherapies could be effective in the adjuvant setting where there is microscopic residual disease that may or may not contain a sufficient amount of antigen to trigger a response. The risks and benefits of this option should now be discussed with patients; the toxicity is not negligible and patients need to be aware of the adverse event profile, and treatment should be reserved for experienced centres.

This trial represents an important milestone in the treatment of melanoma and the results open the door for other studies based on checkpoint blockade to try and improve cure rates in the adjuvant setting of melanoma, as well as other disease types. The results of several trials are anticipated, including EORTC 1325, which is investigating pembrolizumab, a PD-1 checkpoint blocking antibody, compared to placebo in the adjuvant setting.

Neoadjuvant ipilimumab plus nivolumab reduces pre-surgical tumour load in advanced melanoma

Christian Blank of the Netherlands Cancer Institute, Amsterdam, The Netherlands, and colleagues conducted the two-arm phase Ib OpACIN-neo trial in 18 patients with high-risk AJCC stage IIIB/C melanoma and palpable nodes. The patients' mean age was 54 years, WHO performance status was 0 for 8 patients in the adjuvant arm and for 10 patients in the neo-adjuvant arm, and the median number of lymph nodes involved was 2 (range: 1 to 4) and 1 (range: 1 to 5) in the respective arms. All patients received ipilimumab at 3 mg/kg plus nivolumab at 1 mg/kg; however, patients were randomised to receive either adjuvant 4 courses after surgery, or 2 courses each of split neo-adjuvant and adjuvant immunotherapy. The co-primary endpoints of the study were safety and feasibility, as measured by adverse events (AEs), adherence to timelines, and alteration in the magnitude or breadth of the neo antigen specific T cell response between pre- to post-adjuvant therapy. Secondary endpoints included relapse-free survival (RFS) by RESIST 1.1, and the rate and type of late adverse events.

Improved results were observed when combined ipilimumab and nivolumab were given pre- and post- surgery compared with only post-surgery administration. All 10 patients in the neo-adjuvant arm underwent lymph-node dissection at the pre-planned week 6 time-point. This regimen reduced the tumour burden by the scheduled surgery date without any delays in planned lymph node dissections. Tumour load was reduced after 6 weeks of ipilimumab plus nivolumab immunotherapy in 8 of 10 patients. Pathologic complete response (pCR) was achieved by 3 patients, and 5 patients showed minimal remaining micro-metastases, including one partial response (PR) with remaining metastasis of 0.5 mm. One patient showed stable disease and one patient experienced progressive disease (PD). The objective response rate (ORR) was 78%. So far, none of the responding patients within the neoadjuvant arm has relapsed.

No differences in surgery-associated AEs between adjuvant and neo-adjuvant immunotherapy were observed and no surgery-related AEs were attributed to the neoadjuvant immunotherapy.

Only 2 of 18 patients received all 4 courses of immunotherapy; 15 patients halted treatment due to toxicity grades 2 to 4, and one patient due to PD following 2 courses of adjuvant ipilimumab/nivolumab. All patients experienced an immunotherapy-related AE and 16 patients had a grade 3/4 AEs. The most commonly reported immunotherapy-related AES greater than grade 3 were diarrhoea in 4 patients, elevated lipase in 7, and colitis in 6 patients. Four patients reported elevated ALT, 3 patients each experienced rash and vomiting, headache, adrenal insufficiency, and fever each occurred in 2 patients and one case of hyperthyroidism was reported. At a median follow-up of 34 weeks, 7 of 8 patients had recovered from AEs and 12 patients have ongoing AEs; of these 8 require hormonal supplementation. The remaining 4 patients have low grade AEs of diarrhoea, elevated lipase, or hyperglycaemia. A phase II OpACIN-neo trial study is planned in collaboration with several melanoma institutes world-wide and will explore regimens that are adjusted to retain efficacy while reducing toxicity. NCT02437279. Blank *et al.* Abstract LBA39

Practice point and future research opportunities

The outcome of patients with high-risk stage III macroscopic/palpable melanoma is poor, with 5-year survival rates of just 20% to 59%. Adjuvant radiotherapy after lymph node dissection improves the local control but has no effect on RFS or OS. Immunotherapy initiated prior to surgery successfully reduced tumour burden and allowed on-schedule lymph node dissection in all patients with high-risk stage III melanoma in the neo-adjuvant arm. Neo-adjuvant ipilimumab plus nivolumab is feasible, results in on-time surgery, and induces a high frequency and depth of responses.

First-line dabrafenib/trametinib combination in melanoma supported by long-term results

Lead author Caroline Robert, Institut Gustave Roussy, Paris, France discussed the co-inhibition of BRAF and MEK pathways with dabrafenib and trametinib, which continued at 3 years to be superior to sole BRAF inhibition with vemurafenib in patients with unresectable metastatic melanoma. Dr. Robert presented an updated survival analysis from the phase III COMBI-v trial, which randomised 704 patients with advanced, treatment-naive, BRAF-mutated, stage III/IV melanoma 1:1 to dabrafenib at 150 mg twice daily plus trametinib at 2 mg daily or to the standard dose of vemurafenib at 960 mg twice daily. A total of 33 (9%) patients in the vemurafenib arm crossed over to the combination arm after the interim analysis. The primary endpoint of COMBI-v was overall survival (OS), while secondary endpoints were progression-free survival (PFS), overall response rate (ORR), duration of response (DOR), and safety.

The updated analysis occurred following 411 deaths and 16 months of additional follow-up since the 2-year data cut-off, which was July 2016. Patients receiving the combination had a 3-year OS rate of 45% (95% confidence interval [CI] 39.1, 49.8) compared with 32% (95% CI 26.1, 36.4) for vemurafenib monotherapy, hazard ratio 0.68. The 3-year PFS rates were 25% with dabrafenib plus trametinib and 11% with vemurafenib. The median duration of exposure was 12.2 months (95% CI 0.1, 47.3) with the combination versus 6.7 months (95% CI 0.1, 42.4) with vemurafenib.

Response was higher in the combination arm where the ORR was 67% versus 53% with monotherapy. Complete responses (CRs) were achieved by 68 (19%) versus 41 (12%) patients, partial responses (PR) by 48% versus 41%, and stable disease was observed in 24% versus 31% of patients receiving the combination versus vemurafenib, respectively. Progressive disease was reported for 6% and 11% of patients in the respective arms, and 8% of patients overall were not evaluable for response. The median DOR was 13.8 months with the combination versus 7.6 months with single-agent vemurafenib.

Subgroup analysis identified patients with baseline levels of lactate dehydrogenase (LDH) equal to or less than the upper limit of normal (ULN) who performed particularly well with combined therapy; 56% of these patients achieved 3-year OS with the combination versus 39% of patients on the vemurafenib arm. Median OS was not reached with combination treatment versus 21.6 months with vemurafenib. Three-year PFS rates in this subset were 33% versus 13%; median PFS was 17.5 versus 9.2 months (HR, 0.56) with the combination versus monotherapy, respectively.

In contrast, in the cohort of patients with LDH > ULN, 20% of patients achieved 3-year OS versus 14% of patients on vemurafenib, median OS was 10.8 versus 8.7 months with monotherapy (HR, 0.79). Median PFS in this subset at 3 years was 5.5 months versus 4 months (HR, 0.70) with dabrafenib/trametinib and vemurafenib, respectively. When the subset of patients with normal LDH was combined with patients having fewer than 3 sites of metastases, 3-year OS rates rose to 70% versus 46%, and PFS rates were 39% with the combination versus 15% with single-agent vemurafenib.

Dabrafenib/trametinib was found to have a manageable adverse event (AE) profile, with no new safety signals reported. Sixteen percent of patients discontinued treatment due to AEs with dabrafenib/trametinib versus 15% who received vemurafenib. The most commonly reported grade 3/4 AEs in the combination arm included hypertension (15%) and pyrexia (5%). NCT01597908. Robert *et al.* Abstract LBA40

Practice point and future research opportunities

These findings support the long-term use of dabrafenib plus trametinib as a standard first-line treatment for patients with BRAF, V600 negative–mutant metastatic melanoma. Improved outcomes with the combination over vemurafenib were demonstrated despite crossover. COMBI-v is the second trial to show superiority for the combination versus monotherapy in advanced melanoma; the phase III COMBI-d trial showed 3-year OS rates of 44% versus 32% with the combination versus dabrafenib alone, respectively. Patients with low LDH responded extremely well to the targeted treatment, which was especially effective in patients with low LDH and fewer that 3 metastatic sites.

Final OS data for KEYNOTE-002 with pembrolizumab in ipilimumab-refractory melanoma

Omid Hamid of the Melanoma & Skin Cancers Centre, The Angeles Clinic and Research Institute, Los Angeles, USA, presented final overall survival (OS) results on behalf of the KEYNOTE-002 investigators. Previously reported findings from KEYNOTE-002 demonstrated the superiority of pembrolizumab over investigator-choice chemotherapy in patients with advanced melanoma and confirmed progression after 2 or more doses of ipilimumab, hazard ratio [HR] 0.57 ($p < 0.0001$) for pembrolizumab at 2 mg/kg Q3W and HR 0.50 ($p < 0.0001$) for pembrolizumab at 10 mg/kg Q3W.

KEYNOTE-002 randomised 180 patients to pembrolizumab 2 mg/kg every 3 weeks, 181 patients to pembrolizumab at 10 mg/kg every 3 weeks, and 179 to investigator's choice of chemotherapeutic agents, including dacarbazine, temozolomide, carboplatin, paclitaxel, or the latter two in combination. Crossover to pembrolizumab was allowed upon progression in the chemotherapy arm.

As of November 16, 2015, median follow-up was 13.5 months and 368 deaths had occurred. The study found that both doses of pembrolizumab produced superior OS compared with chemotherapy. Median OS was 13.4 and 14.7 months at the respective pembrolizumab doses versus 11.0 months with chemotherapy. The OS rates at 18 months were 40% and 44% versus 36%, and 24-month OS rates were 36%, 38%, versus 30%, respectively with pembrolizumab at 2 mg/kg and 10mg/kg versus chemotherapy. The HR for OS was 0.86; 95% confidence interval [CI] 0.67, 1.10 for 2 mg/kg ($p = 0.1173$) and HR 0.74; 95% CI 0.57, 0.96 for 10 mg/kg ($p = 0.0106$), with no difference observed between doses, HR 0.87.

Crossover patients also demonstrated improved OS with pembrolizumab. Upon experiencing progression in the chemotherapy arm, 98 (55%) patients crossed over and were censored; the HR was 0.79; 95% CI 0.58,1.08 for 2 mg/kg ($p = .0683$) and HR 0.67; 0.49, 0.92 for 10 mg/kg ($p = 0.0068$), also showing no difference between doses, HR 0.87. In this cohort, the 24-month PFS rates were 16% for 2 mg/kg, 22% for 10 mg/kg versus <1% with chemotherapy. The objective response rates were 22%, and 28%, versus 4%; no disease progression at the time of the analysis was observed in 73%, 74%, and 13% of responders, respectively, in the 2 mg/kg and 10 mg/kg pembrolizumab versus chemotherapy cohorts.

In addition, grade 3 to 4 toxicities were less frequent with both doses of pembrolizumab at 13% and 17% versus 26% with chemotherapy, even though pembrolizumab exposure was more than triple at mean 232 days and 276 days versus 82 days with chemotherapy. NCT01704287, Hamid *et al.* Abstract 1107O

Practice point and future research opportunities

The KEYNOTE-002 study long term follow-up findings demonstrate that pembrolizumab prolonged OS over chemotherapy in population of patients with ipilimumab-refractory melnoma, although with a 55% crossover rate, the difference did not reach statistical significance for either

dose of pembrolizumab. Taken together with the significant PFS benefit, durable responses, and favourable safety profiles, these data support pembrolizumab in patients with ipilimumab-refractory melanoma.

Safety and efficacy of anti-PD-1 antibodies in elderly patients with metastatic melanoma

Rajat Rai of the Melanoma Institute Australia, University of Sydney in North Sydney, Australia noted that, even though melanoma incidence increases with age and anti-PD-1 antibodies are often the first option for elderly patients with metastatic melanoma, limited data exist on the safety and efficacy of anti-PD-1 antibodies in this age group. With colleagues, Dr. Rai reviewed data from all patients treated with PD-1/PD-L1 antibodies in clinical trials at 4 centres, including patient demographics, primary and metastatic melanoma characteristics, toxicity, response, and survival data. Efficacy and safety following anti-PD-1/L1 treatment was compared in patients aged >75 years with patients ≤75 years. The analysis comprised 283 patients with a median follow-up of 44.5 months. Pembrolizumab had been given to 208 patients and 71 received nivolumab.

The majority, (75%) of patients had American Joint Committee on Cancer (AJCC) stage M1c disease, 57% were ECOG performance status 0, 40% of patients had elevated LDH, 14% of patients received treatment for stable brain metastases. Prior treatment with ipilimumab had been received by 124 (43%) patients, and 63 (22%) received MAPK inhibitors. These prognostic factors were similar in the cohort of 35 (12%) patients older than 75 years old, and in the cohort of 159 (47%) patients aged ≤75years; overall, the patients in both arms had received similar rates of prior ipilimumab, but fewer patients in the older group had received MAPK inhibitors compared with younger patients (p = 0.04).

The objective response rates (ORRs) were similar in both arms; in patients >75 the ORR was 48% compared to 34% in patients ≤75 years. There was no difference in the incidence of immune-related adverse events in elderly versus younger patients (p > 0.05), and the rates of discontinuation for toxicity were equivalent at 0.05% in both groups (p > 0.05). Median progression-free survival (PFS) and overall survival (OS) were 8.7 months and 33.5 months, respectively in older patients compared to PFS of 4.6 months and OS of 48.1 months in younger patients (p = 0.48). Rai 3001 *et al.* Abstract 1113PD

Practice point and future research opportunities

In this retrospective analysis, immunotherapy with anti-PD-1/L1 antibodies in elderly patients aged 75 and older with metastatic melanoma was safe and effective. These results support the consideration of immunotherapy in elderly patients who demonstrated similar responses and toxicity profiles as those of patients with metastatic melanoma younger than 75 years.

Efficacy of anti-PD-1 therapy in patients with melanoma brain metastases

Lead author John J. Park, Medical Oncology, Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, Australia presented findings from a retrospective analysis of the efficacy of anti-PD-1 agents in patients with metastatic melanoma and brain metastases who were treated in 4 centres. The analysis included patient demographics, tumour characteristics, and treatment history including intracranial and extracranial response rates and progression-free survival (PFS). Response was determined by modified RECIST where up to 5 intracranial (IC) target lesions were used for intracranial assessment.

This interim analysis was done at a median follow-up of 8.5 months and included data from 39 patients; 77% of patients were male and 9 (23%) patients were to receive anti-PD-1 as first-line therapy. At the start of PD-1 inhibitor treatment, 56% patients had an elevated LDH. ECOG performance status of 0-1, 2 and >2 was reported in 64%, 26% and 10% of patients, respectively. The patients had a median of 4 intracranial lesions (range: 1 to 20) and 26 (67%) patients had received local therapy of radiotherapy or surgery for brain metastasis. BRAF mutation was detected in 23 (59%) patients, Dexamethasone at doses ranging from 0.5 to 8 mg was administered to 13 (33%) patients.

Following anti-PD-1 treatment the best intracranial response rate was 26%, which included 18 patients with symptomatic brain metastases and 13 patients receiving steroids. Of these 10 patients, 2 had not received prior radiotherapy, 3 were receiving concurrent radiotherapy, and 5 patients had received prior radiotherapy. Stable disease was achieved by 8 patients and 12 patients experienced progressive disease. The median intracranial PFS was 2.1 months (95% confidence interval [CI] 1.3, 2.9). The extracranial response rate was 17% and median PFS was 2.1 months (95% CI 1.9, 3.4). Analysis of the full patient cohort is ongoing. Park *et al.* Abstract 1114PD

Practice point and future research opportunities

This study provides data regarding the use of anti-PD-1 immunotherapy in patients with metastatic melanoma and untreated, symptomatic, or progressing brain metastasis, a patient population with a poor prognosis and limited data on the efficacy and safety of these agents in this cohort exist. Intracranial responses to anti-PD-1 agents were seen in patients with symptomatic brain metastases and in patients on corticosteroids. Data from the prospective trials evaluating anti-PD-1 therapy in patients with brain metastasis that are underway will also contribute to the understanding of the efficacy and safety of anti-PD-1 therapy in these patients.

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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