ESMO 2016 Congress

7-11 October, 2016

Copenhagen, Denmark

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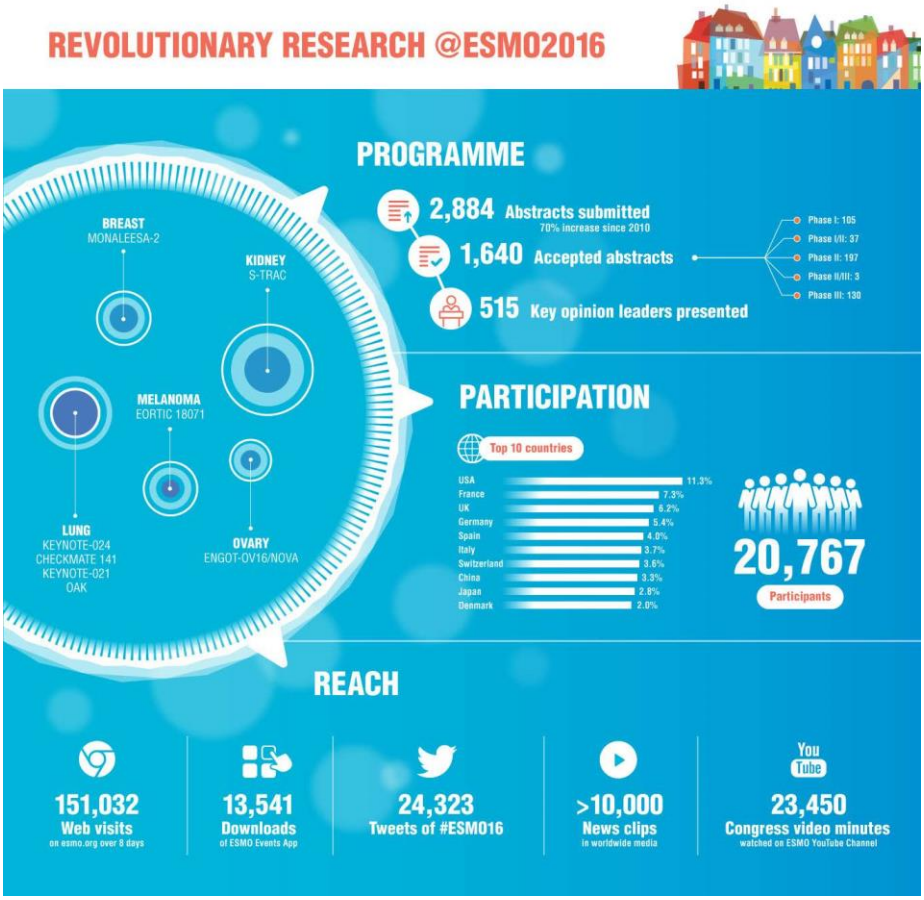
Summary

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

HEAD AND NECK CANCER

Patients with recurrent or metastatic HNSCC maintain function following nivolumab treatment

Kevin Harrington, Division of Radiotherapy and Imaging, Institute of Cancer Research, London, UK and The Royal Marsden NHS Foundation Trust presented the results of patient reported outcomes from the CheckMate 141 randomised, open label phase III trial. In this study, 361 patients with platinum refractory relapsed head and neck cancer received nivolumab or standard of care chemotherapy (physician's choice of methotrexate, docetaxel or cetuximab). Previously reported findings demonstrated that overall survival (OS) was improved by an average of 2.5 months with nivolumab over chemotherapy. The patient reported outcomes discussed at ESMO 2016 included functional capacity and physical symptoms following nivolumab or chemotherapy. The European Organisation for Research and Treatment of Cancer QoL Questionnaire (EORTC QLQ-C30), EORTC Head and Neck Cancer module (QLQ-H&N35), and EQ-5D were administered to 129 patients at baseline, 9 weeks, and at 6-week intervals thereafter. An overall score was calculated for global health from questions covering functional areas, such as the physical ability to perform daily activities, and emotional, cognitive, and social aspects of the patients' lives. A score change or difference of 10 points in the EORTC subscales was regarded as clinically relevant.

Patients receiving nivolumab maintained or improved function and symptom burden at 9 and 15 weeks compared to baseline. In contrast, patients receiving standard of care showed poorer scores across all parametres at both time-points compared to baseline. When the scores between the two arms were compared at 9 and 15 weeks, it emerged that nivolumab provided a clinically significant benefit over chemotherapy in most of the function and symptom areas: Time to deterioration was significantly delayed with nivolumab ($p < 0.05$, 2-tailed) compared to chemotherapy regarding global health, physical role, cognitive, and social functioning, and for physical symptoms including fatigue, dyspnoea, and insomnia, as reported on the EORTC QLQ-C30, as well as pain, sensory problems, and mouth opening problems as reported on the QLQ-H&N35. These findings have been published simultaneously in *The New England Journal of Medicine (NEJM).* NCT02105636. Harrington *et al.* Abstract LBA4; *NEJM* 2016; 375:1856-1867.

Practice point and future research opportunities

The historical median survival is 6 months or less in patients with platinum refractory relapsed head and neck cancer. Previously reported findings from this trial showed that nivolumab improved OS by an average of 2.5 months over physician's choice of standard of care chemotherapy. This study assessed symptoms and quality of life using several questionnaires, including one specifically designed for patients with head and neck cancer, which is important because these tumours have specific consequences. For example, a tumour mass in the neck is painful and may impair eating and speaking functions and is also visible and can lead to social isolation. Patient reported outcomes form this trial show that, while prolonging survival, nivolumab also enables patients to function at work and socially, and to experience less pain and fatigue than chemotherapy. These data suggest that the superior clinical activity of

nivolumab maintains patient-reported outcomes, but it is also likely that nivolumab is a gentler treatment that is associated with fewer side effects.

This is the first study to show that an immunotherapy is superior to classical treatment options for improving quality of life and symptoms, on top of prolonging survival. Nivolumab works in around one-third of patients with advanced head and neck cancer and biomarkers or biological criteria are needed to identify patients likely to benefit. When these patients are identified, it can be explained to them that nivolumab may help them to feel and function better in daily life.

Meta analysis confirms superiority of concomitant over induction chemotherapy in non-metastatic HNSCC

Jean Bourhis of the Département d'oncologie, Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland presented an update of the MACH-NC meta-analysis on behalf of first author Pierre Blanchard, Department of Radiation Therapy, Gustave Roussy Cancer Campus in Villejuif, France and the MACH-NC group, which confirmed that concomitant chemotherapy added to loco-regional treatment significantly prolongs overall survival (OS) in patients with head and neck squamous cell carcinoma (HNSCC). The investigators analysed individual patient data from 15 new trials in addition to updated patient data from 11 additional trials done between 1965 and 2010 in patients with non-metastatic HNSCC; induction chemotherapy plus radiotherapy was compared to radiotherapy plus concomitant (or alternating) chemotherapy in 2574 patients, and loco-regional treatment (LRT) was compared to LRT plus chemotherapy in 18,394 patients taking part in 94 trials with a median follow-up of 6.7 years. The investigators used a fixed effect model and treatment comparison was evaluated using the log-rank test, stratified by trial. The primary endpoint of the study was OS.

Overall, 29% of patients had stage III tumours and 63% had stage IV tumours. The oropharynx was the most frequently involved tumour site in 35% of patients. Adding chemotherapy to loco-regional therapy significantly improved OS over loco-regional therapy alone, hazard ratio [HR] 0.89; 95% confidence interval [CI] 0.86, 0.92 ($p < 0.0001$). When the chemotherapy was delivered was crucial for this benefit; adding induction chemotherapy did not prolong OS over loco-regional treatment alone, HR 0.97; 95% CI 0.91, 1.03.

The analysis specifically comparing concomitant to induction chemotherapy plus radiotherapy comprised data from 1214 patients participating in 8 trials showed that OS was significantly prolonged with concomitant over induction adjunct chemotherapy, HR 0.84; 95% CI 0.74, 0.95 ($p = 0.007$), and progression-free survival, HR 0.83; 95% CI 0.79, 0.87 ($p < 0.0001$), which translates to a 5- and 10-year absolute survival benefit of 6.5% and 3.4%.). An interaction test done on data from recent trials of concomitant chemotherapy revealed a trend towards decreased efficacy with increasing age and poorer performance status (PS), HR 1.00; 95% CI 0.81, 1.23 (p trend = 0.06) in patients aged 70 or more years, and HR 0.93; 95% CI 0.73, 1.19 (p trend = 0.07) for patients with performance status of 2 or greater. NCT0059731. Blanchard *et al.* Abstract 950O

Practice point and future research opportunities

Findings from this analysis suggest that patients with head and neck squamous cell carcinoma experienced prolonged OS when concomitant chemotherapy was administered with local regional treatment or radiotherapy. This updated meta-analysis, which has a larger cohort and longer patient follow-up, confirmed the superiority of adding concomitant chemotherapy as compared to induction chemotherapy. Patients with head and neck squamous cell carcinoma achieved prolonged overall survival when concomitant chemotherapy was administered with local regional treatment or radiotherapy, However, timing was important, as the survival benefit was not observed with the addition of induction chemotherapy.

Adding motolimod to chemotherapy plus cetuximab in patients with recurrent or metastatic HNSCC fails to improve survival

In order to test whether the efficacy of the EXTREME regimen consisting of platinum, 5-FU, and cetuximab could be enhanced with the addition of motolimod, Enzra Cohen, Translational Science, UCSD Moores Cancer Centre, La Jolla, USA and colleagues conducted the Active8 randomised phase II study. Motolimod is a Toll-like receptor 8 agonist that stimulates the innate immune system and increases antigen-specific T cell responses against EGFR. Motolimod plus cetuximab has been reported to enhance NK cell activity, decrease markers of T cell suppression, and reduce myeloid-derived suppressor cells in tumours. This trial enrolled patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC); 100 patients were randomly assigned to EXTREME plus motolimod and 95 to EXTREME plus placebo. Patients were stratified by ECOG performance status (PS) of 0 versus 1, prior systemic therapy for HNSCC, and choice of cisplatin or carboplatin. The patients had a median age of 58 years (range: 23 to 81), 38% of patients were ECOG PS 0 and 62% ECOG PS 1, and 65% of patients had previously received systemic treatment for HNSCC. At baseline 80% of patients were assigned to receive carboplatin.

The primary endpoint of progression-free survival (PFS) per independent central review was not met. In the intent to treat (ITT) population, the median PFS for EXTREME/motolimod was 185 compared to 181 days with control, hazard ratio [HR] 0.99 ($p = 0.266$). Median overall survival (OS) was 412 for motolimod versus 343 days for control, HR 0.95 ($p = 0.399$). However, findings from a subgroup analysis of patients having an injection site reaction (ISR) demonstrated that these patients had significantly improved PFS of 216 versus 181 days, HR 0.69 ($p = 0.005$), and OS was 570 versus 382 days, HR 0.56 ($p = 0.015$), respectively with EXTREME/motolimod versus controls. Adverse events occurring more frequently with EXTREME/motolimod included ISR, pyrexia, chills, anaemia, influenza-like illness, and dermatitis acneiform. NCT01836029. Cohen *et al.* Abstract LBA37

Practice point and future research opportunities

Neither PFS nor OS were improved in the ITT population with the addition of motolimod to the EXTREME regimen. Significant survival benefits were observed in a subgroup experiencing immune-related injection site reaction that may warrant further investigation.

PFS and distant metastasis-free survival may serve as surrogate endpoints for OS following chemotherapy in loco-regionally advanced nasopharyngeal carcinoma

Federico Rotolo, Service de Biostatistique et d'Epidemiologie, CESP, Inserm U1018, Universite Paris Sud, and Gustave Roussy Cancer Campus, Villejuif, France and colleagues determined the association of progression-free survival (PFS) and distant metastasis-free survival (DMFS) to overall survival (OS) and evaluated their utility as surrogate endpoints in randomised trials of chemotherapy in loco-regionally advanced nasopharyngeal carcinomas (LANPC). The investigators reviewed individual patient data from 5,144 patients treated in 19 trials contained in the updated Meta-Analysis of Chemotherapy in Nasopharyngeal Carcinoma (MAC-NPC), plus one additional trial. Surrogacy was evaluated at the individual level using a rank correlation coefficient ρ and at the trial level using a correlation coefficient R^2 between treatment effects on the surrogate endpoint and OS.

The analysis revealed a strong association between PFS and OS at both the individual and trial level (ρ = 0.93; 95% confidence interval [CI] 0.93, 0.94) and (R^2 = 0.95; 95% CI 0.47, 1.00), respectively. DMFS also associated with OS on the individual-level (ρ = 0.98; 95% CI 0.98, 0.98): DMFS at trial level could not be computed after the regression was adjusted for measurement error; however, the unadjusted association was high between DMFS and OS (unadjusted R^2 = 0.96; 95% CI 0.94; 0.99).

The sensitivity analysis also showed a strong association between 2-year PFS and 5-year OS at the individual level (ρ = 0.89; 95% CI 0.88,0.90) and at the trial level (R^2 = 0.85, 95% CI 0.46, 1.00). A strong association was also demonstrated between 2-year DMFS and 5-year OS at the individual level (ρ = 0.95; 95% CI 0.94, 0.95) and at the trial level (R^2 = 0.78; 95% CI 0.33,1.00). Rotolo *et al.* Abstract 951O

Practice point and future research opportunities

Both PFS and DMFS showed strong associations with OS in this large meta-analysis, suggesting that both are valid surrogate endpoints for OS when assessing the treatment effect of chemotherapy in loco-regionally advanced nasopharyngeal carcinomas. An additional advantage is that PFS can be measured at an earlier time point.

Comprehensive genomic profiles of metastatic and relapsed salivary gland carcinomas are associated with tumour type and reveal new routes to targeted therapies

Lead author Laurie M. Gay, Pathology, Foundation Medicine, Inc., Cambridge, USA, and colleagues used comprehensive genomic profiling (CGP) to define tumour subtypes of salivary gland tumours, which have diverse histologic subtypes. The investigators also endeavoured to uncover clinically relevant genomic alterations (CRGA), to identify new routes to targeted

therapies for patients with relapsed and metastatic salivary gland carcinomas (SGC). Tumour samples were obtained from 300 consecutive patients with FFPE specimens, from which DNA was extracted. CGP was performed on hybridization-captured, adaptor ligation-based libraries (mean coverage depth >500X) for up to 315 cancer-related genes. The total mutational burden (TMB) was determined on 1.2 Mbp of sequenced DNA. CRGA were defined as genomic alterations targeted by drugs on the market or being evaluated in clinical trials.

Through this genomic testing, the investigators were able to identify specific subtypes of SGC. The most prevalent histologic subtype was acinic cell carcinoma (AiCC) which occurred in 73 patients, followed by adenocarcinoma NOS (Ac-NOS) in 54, muco-epidermoid (MEC) in 48, ductal carcinoma (DCA) in 42, carcinoma NOS (CA-NOS) in 32, adenoid cystic carcinoma (ACC) was identified in 28 patients, and 24 patients had carcinoma ex pleomorphic adenoma (CPA). Mammary associated secretory carcinomas (MASC) were grouped with AC-NOS; AciCC and MEC with ETV-NTRK fusions are likely MASC with unusual histologic presentations.

Non-specialised carcinomas, which includes MEC, DCA, AC-NOS, CA-NOS, and CPA, are frequently ERBB2 driven, but also harbour significant genomic alterations in RET, BRAF and NF1 genes. In these respective subtypes, the mutation frequency of TP53, the gene showing the greatest mutation frequency overall, was 42%, 54%, 53%, 59%, and 46%, respectively. TMB > 10 mutations per Mb was 13% in CA-NOS, 12% in CPA, 11% in DCA, 10% in MEC and 6% and less in the remaining disease subtypes: The investigators determined the opportunity for targeted therapies to be high in DCA, AC-NOS, CA-NOS, and CPA. Modest opportunity was determined for MEC and the opportunity for targeted therapy was low in specialised metastatic SGCs, ACC and AciCC, which had significantly fewer genomic alterations including targetable alterations, as well as less TMB than non-specialised carcinomas. Clinical outcomes following targeted therapies for mSGC were presented. Gay *et al.* Abstract 954PD

Practice point and future research opportunities

Salivary gland carcinomas have a broad diversity of histologic subtypes that have variable clinical aggressiveness and response to local and systemic therapies. Metastatic salivary gland carcinomas include specialised carcinomas, adenoid cystic carcinoma and acinic cell carcinoma, that have low frequencies of genomic alteration, low tumour mutation burden and offer few opportunities for targeted therapies. However, non-specialised salivary gland carcinomas offer more opportunities to use targeted therapies due to more genomic alterations that provide possible treatment targets for HER2, RET, BRAF, and mTOR inhibitors, and also have higher tumour mutation burden, making the use of immune checkpoint inhibitors a possibility.

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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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