ESMO 2016 Congress

7-11 October, 2016

Copenhagen, Denmark

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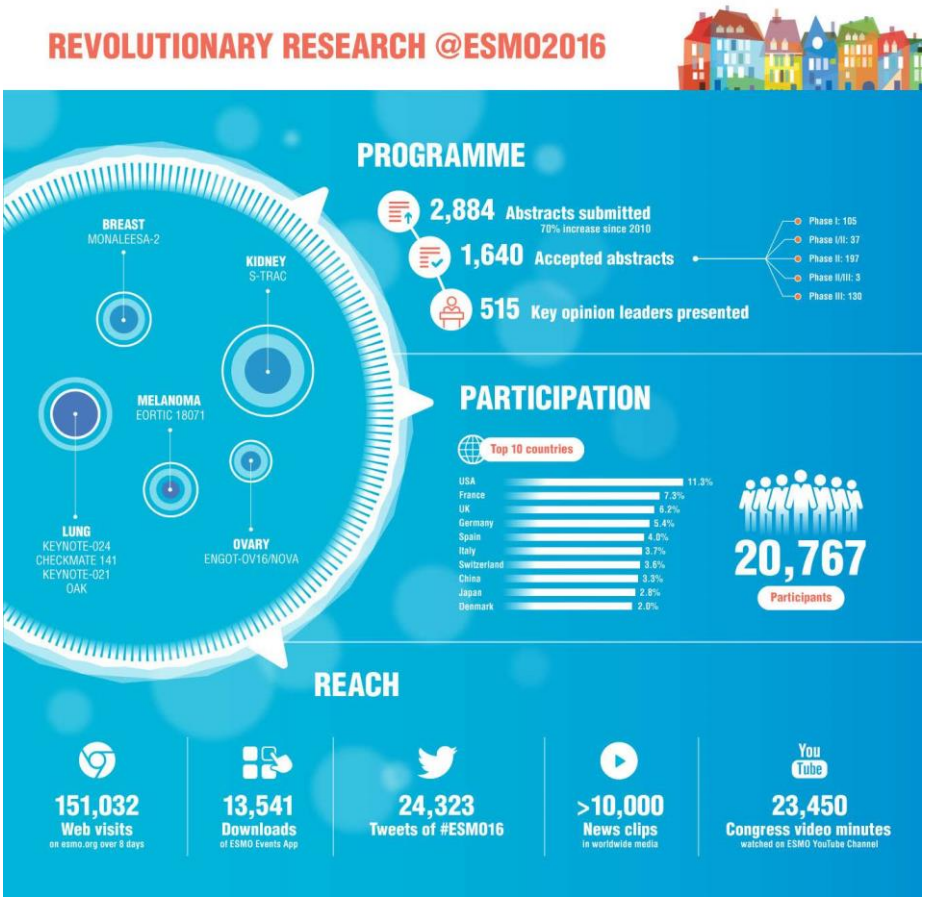
Summary

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

CENTRAL NERVOUS SYSTEM MALIGNANCIES

Molecular characterisation of risk factors in low-grade gliomas

Enrico Franceschi, Medical Oncology, Bellaria - Maggiore Hospitals, Azienda USL - IRCCS Institute of Neurological Sciences in Bologna, Italy, presented findings on behalf of the Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO) from a molecular characterisation of IDH1/2, 1p/19q codeletion, and MGMT methylation status in low grade gliomas (LGG). Data from all adult LGG patients in the database of the institution who received surgery and had sufficient tissue for biomarker characterisation were evaluated for outcome. IDH1/2 assessment was performed on FFPE samples by PCR, MGMT was assessed by methylation specific PCR, and 1p/19 codeletion by FISH.

The study comprised 198 consecutive patients with LGG, with a median age of 38 (range: 18 to 72) years. The majority, 109 (55.1%) patients were younger than 40 years of age. Biopsy was done in 26 (13.1%) patients, 119 (60.1%) patients underwent partial resection, and 53 (26.8%) patients had complete resection. Twenty-eight patients (14.1%) were considered low risk (<40 years with complete resection). IDH1/2 mutation was found in 79.8% of patients, 1p/19q codeletion was found in 41.4% of patients, and MGMT methylation was seen in 57.1% of patients. A subgroup of 28 patients was considered to be at low risk of recurrence that were aged < than 40 years and had undergone complete resection.

At a median follow-up of 74.0 months, an evaluation of patient outcome revealed that median survival in low risk patients was 211.0 months (95% confidence interval [CI] 190.4, 231.6) compared to 145.3 months (95%CI 108.5,182.2) in high-risk patients (p = 0.006). Median survival for patients with IDH1/2 mutation was 159 months (95%CI 103.3, 214.7) versus 87.9 months in patients with IDH1/2 wild type (95%CI 61.1, 114.6; p < 0.001). On multivariate analysis clinical risk (p = 0.006), IDH1/2 mutation (p < 0.001), and 1p/19q codeletion (p = 0.03) emerged as biomarkers that significantly correlated with overall survival; however, MGMT methylation was not statistically significant. Franceschi *et al.* Abstract 323O

Practice point and future research opportunities

This study demonstrated that molecular characterisation of low-grade glioma can be used to identify prognostic markers that define the outcome of this disease; clinical risk, IDH1/2 mutation, and 1p/19q codeletion significantly associated with survival. Moreover, clinical risk assessment continues to play an important role.

ANG1005, a novel peptide-paclitaxel conjugate that crosses the BBB demonstrates clinical benefit in patients with recurrent CNS metastasis from breast cancer

Lead author Shou-Ching Tang, Georgia Regents University Cancer Center, Augusta University, Augusta, USA, presented findings from an open label phase II clinical study testing the activity

of ANG1005, a novel taxane derivative comprised of 3 paclitaxel molecules covalently linked to Angiopep-2, a peptide designed to cross the blood-brain and blood cerebrospinal fluid barriers via the LRP-1 transport system. ANG1005 was designed to penetrate malignant cells in the central nervous system (CNS) and was evaluated in 72 patients with metastatic breast cancer and recurrent brain metastasis, including patients with blood/cerebrospinal fluid metastasis (BCBM) and newly diagnosed leptomeningeal carcinomatosis (LC). ANG1005 was administered i.v. at 600 mg/m^2 every 3 weeks and HER2-positive patients were allowed to continue trastuzumab with/without pertuzumab. Intracranial response was assessed by Gd-MRI using CNS RECIST 1.1, and extracranial response was evaluated per RECIST 1.1. The patients' median age was 47.5 (range: 26 to 76) years. A median of 6 (range: 1 to 29) prior therapies for breast cancer had been received by the patients, with 84% of patients receiving prior taxane treatment. Prior therapy for brain metastasis included cranial surgery and/or radiation for 87% of patients, and 19% patients received systemic therapies.

The analysis was done on 72 patients in the safety population and 58 patients with evaluable data in the efficacy population. The best intracranial response following ANG1005 treatment in the efficacy population included 8 (14%) patients with partial response (PR), 3 (5%) of which were confirmed. Stable disease was reported in 33 (57%) patients. Extracranial tumour responses included one (3%) complete response (CR), 2 (7%) PRs, and 24 (80%) patients achieved SD among the 30 evaluable patients, which included the 93% of patients that had received prior taxane therapy. The 6-month overall survival (OS) rate was 63.6 % (95% confidence interval [CI] 42.9, 78.5) for patients with LC. In contrast, the Kaplan-Meier estimated median OS was 34.6 weeks (95% CI 24.1, 40.9) from first ANG1005 treatment for LC patients. Following ANG1005 treatment, improved CNS clinical symptoms were reported, including in LC patients. Safety was similar to that of paclitaxel, with myelosuppression as the predominant toxicity. NCT02048059. Tang *et al.* Abstract 324O

Practice point and future research opportunities

Novel ANG1005, a taxane derivative plus paclitaxel that was designed to cross the blood brain and blood cerebrospinal fluid barriers demonstrated activity in previously treated breast cancer metastasis located both within and outside of the central nervous system. Patients with leptomeningeal carcinomatosis experienced clinical benefit of an estimated median OS of approximately 8 months, which doubled the historical median of about 4 months following therapy. The results from the planned randomised study are awaited.

Routine molecular subgrouping of medulloblastoma for clinical applications using low-cost, mass spectrometry-based DNA methylomics

Ed Schwalbe, Paediatric Neuro-Oncology, Northern Institute for Cancer Research University of Newcastle, Newcastle Upon Tyne, UK, and colleagues evaluated an array-independent, robust subgrouping assay suitable for routine quality-controlled subclassification, including scant, poor-quality, aged samples that they developed, with the intent of making subclassification of

medulloblastoma by DNA methylation patterns cost effective and feasible in the clinic to inform treatment decisions. DNA methylation patterns allow the categorisation of medulloblastoma into 4 molecular subgroups; in this study, the investigators tested the utility of the microarray on data from the PNET4 trial. Using a cross-validated classification model, a minimal, multiply-redundant, 17-locus signature was derived to assign subgroup from 220 MBs profiled using Illumina 450k DNA-methylation arrays. The investigators then adapted the MALDI-TOF Mass Spectrometry (MassARRAY, Agena Bioscience) iPLEX assay to interrogate DNA methylation following bisulfite treatment. After in vitro validation, the assay was applied to 101 DNA extracts from FFPE and nuclear (<30,000 nuclei) tumour material. Subgroup assignments from an optimised classifier were compared against gold-standard 450k calls. Following validation, subgrouping was attempted for standard-risk PNET4 samples where possible.

A total of 95 of the 101 validation samples had high-confidence assignments which recapitulated 450k subgroup calls. Subsequently, high-confidence calls could be made for 107 of 153 PNET4 samples. Notably, a worse survival was observed for standard-risk PNET4 group 4 patients (80% event free survival rate; p = 0.01). SIOP-PNET4: NCT01351870. Schwalbe *et al.* Abstract 325O

Practice point and future research opportunities

This study used data from the PNET4 trial to demonstrate that routine subtyping of medulloblastoma can be performed using minimal DNA methylation signatures. The assay is suitable for reliable, robust testing of poor-quality, degraded samples using <100ng DNA. The assay's low-cost, rapidity and application to single samples demonstrate its potential for routine use. It can be retrospectively applied to archival cohorts where material is scant to contemporise historical studies. This first demonstration of multiplexed, methylation subtyping holds promise for future molecular subclassification and prognostication across diverse tumour types using methylomics.

Meta-analysis of pooled data reveals improved PFS only with bevacizumab but no OS benefit with antiangiogenic drugs in glioblastoma

Giuseppe Lombardi, and colleagues at the U.O.C. Oncologia Medica 1, Veneto Institute of Oncology- IRCCS in Padua, Italy evaluated the efficacy of antiangiogenic drugs in patients with glioblastoma, which are highly vascularised tumours, in this meta-analysis. MEDLINE, WEB of SCIENCE, ASCO, ESMO and SNO databases were search for relevant published and unpublished randomised controlled trials (RCTs) of antiangiogenic drugs versus chemotherapy in patients with glioblastoma from 2000 to January 2016. The investigators reviewed progression-free survival (PFS) and overall survival (OS) in 4566 patients with glioblastoma receiving antiangiogenic agents as first or second-line therapy and with chemotherapy. In all, 16 RCTs were included, 9 testing bevacizumab, 2 cilengitide, and 1 trial each of enzastaurin, dasatinib, vandetanib, temsirolimus, and cediranib.

Taken together, the analysis of data from all trials revealed no improvement in OS, with a pooled hazard ratio [HR] of 1.02 (95% confidence interval [CI] 0.93, 1.1; p = 0.7). The 7 RCTs wherein

a different antiangiogenic was tested showed no improvement in OS over standard treatment, pooled HR 1.05 (95% CI 0.89,1.23; p = 0.5).

In particular, bevacizumab did not improve OS; in 2752 patients participating in 9 trials the pooled HR for OS was 0.98 (95% CI 0.89, 1.08; p = 0.7). An assessment of OS the 2084 patients receiving bevacizumab as first-line in 6 RCTs demonstrated a pooled HR 1.02 (95% CI 0.88, 1.19; p = 0.8), whereas the pooled HR was 0.95 (95% CI 0.77, 1.17; p = 0.6) for OS in the 3 RCTs of second-line bevacizumab. Similarly, no improvement in OS was demonstrated in 2588 patients receiving bevacizumab associated with chemotherapy, pooled HR 0.99 (95% CI 0.88, 1.11; p = 0.8).

An analysis of PFS in 4349 patients treated in 14 RCTs did demonstrate that PFS was statistically prolonged with antiangiogenic drugs; pooled HR 0.73 (95% CI 0.62, 0.86; p < 0.01). However, bevacizumab emerged as the only antiangiogenic drug that demonstrated improved PFS. Data from 2752 patients treated with bevacizumab showed significantly improved PFS, pooled HR 0.6 (95% CI 0.5, 0.7; p < 0.01). This benefit remained consistent across all treatment regimens reviewed, whether bevacizumab was administered as monotherapy, HR = 0.6; CI 95% 0.44, 0.82; p < 0.01) or combined with chemotherapy, HR 0.6; (95% CI 0.4, 0.7; p < 0.01). PFS was significantly improved with first-line bevacizumab, HR 0.65 (95% CI 0.52, 0.83; p < 0.01) or with second-line bevacizumab in recurrent disease, HR 0.51 (95% CI 0.43, 0.61; p < 0.01). Lombardi *et al.* Abstract 328PD

Practice point and future research opportunities

In an effort to resolve the unclear findings from various trials of antiangiogenic drugs in patients with glioblastoma, the authors conducted this large, pooled data meta-analysis. Although glioblastomas are highly vascularised tumours, treatment with antiangiogenic drugs, including bevacizumab, did not improve OS, when administered either as first or second-line treatment.

The PFS was not improved by antiangiogenic drug treatments, except for bevacizumab, which demonstrated a PFS benefit when administered as a single agent, combined with chemotherapy, and also as first or second-line treatment in patients with glioblastoma.

Synchronous breast cancer and meningioma is an indicator of poorer survival

Aiming to determine the possible prognostic relationship between breast cancer and meningioma Catarina Ribeiro, Department of Oncology, Centro Hospitalar Lisboa Central-CHLC-Hospital São Jose, Lisbon, Portugal, and colleagues evaluated the impact on survival of the tumour exposure sequence in patients registered in a large retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) database. Patients were stratified according to whether the tumours were synchronous or metachronous into a variable arm, defined as patients diagnosed with meningioma prior to developing breast cancer, or a synchronous arm wherein patients developed both conditions simultaneously, or into an arm of patients diagnosed with breast cancer before meningioma.

The analysis comprised data from 1715 patients with a median follow-up of 84 months. The poorest prognosis and shortest median survival of 32 months was observed in patients diagnosed with breast cancer and meningioma at the same time, whereas women developing breast cancer prior to the onset of meningioma had the longest median survival of 110 months. The unadjusted analysis showed a statistical association between the simultaneous group and the shortest survival, hazard ratio [HR] 3.13 (95% confidence interval [CI] 1.62, 6.04) that was confirmed in the adjusted analysis, HR 3.11 (95%CI 1.58, 6.19). The adjusted analysis also determined that there was no statistical difference between the metachronous tumours, regardless of the sequence.

Poorer survival was also associated with increasing age, HR 1.13; 95%CI 1.11, 1.15 ($p < 0.005$), and the presence of grade III meningioma, HR 4.51; 95%CI 1.90,10.69 ($p < 0.005$). The authors reported that meningioma treatment did not impact survival or breast cancer ($p > 0.05$), whereas the presence of grade III meningioma and hormone receptor status influenced survival in synchronous tumours ($p > 0.05$) but had no influence on survival in women with metachronous tumours ($p < 0.05$) on stratified analysis. Ribiero *et al.* Abstract 329PD

Practice point and future research opportunities

This large analysis revealed that women having a synchronous development and/or diagnosis of breast cancer and meningioma faced the poorest prognosis of shorter survival than women developing both breast cancer and meningioma in a metachronous manner. The sequence of which cancer developed first had no effect on survival, but increasing age also showed an association with poorer survival.

Single agent ibrutinib demonstrates clinical benefit in recurrent/refractory primary and secondary CNS lymphoma

Christian Grommes, Neurology, Memorial Sloan Kettering Cancer Center, New York, USA underscored the need for new treatment options in primary central nervous system lymphoma (PCNSL). Even fewer treatment options are available for recurrent/refractory disease, which carries a poor prognosis with objective response rates (ORR) ranging between 30 to 60% and median progression-free survival (PFS) of just 2 to 5 months.

Dr. Grommes and colleagues assessed the efficacy of ibrutinib in patients with recurrent/refractory PCNSL and secondary CNSL (SCNSL); ibrutinib is a first-in-class oral once-daily targeted treatment that blocks Bruton's tyrosine kinase, which promotes tumour viability and growth. Ibrutinib is approved by the US Food and Drug Administration for the treatment of patients with chronic lymphocytic leukaemia and mantle cell lymphoma.

The trial enrolled 20 adult patients with ECOG performance status ≤2 PCNSL and SCNSL and normal end-organ function. Patients could have had an unrestricted number of CNS-directed prior therapies, but patients with SCNSL plus systemic disease were ineligible. The median age was 69 (range: 21 to 85) years and 12 patients were female. PCNSL was diagnosed in 65% and 35% of patients had SCNSL; 70% of patients had recurrent disease. Parenchymal disease was

reported in 11 patients, 3 had isolated cerebrospinal fluid (CSF) involvement, and 6 patients had both. The prior CNS directed therapy was methotrexate regimens and the median number received was 2. Ibrutinib was administered daily to 3 patients at 560 mg and 17 patients received 840 mg; the mean ibrutinib concentration in the CSF at days 1 and 29 was 1.75 ng/mL (3.97 nM) and 2.51 ng/mL (5.6 nM), which are both above the IC50 of 1nM required in vitro to reduce growth of lymphoma cells.

After a median follow-up of 147 days, 16 of the 20 patients were evaluated for response. The ORR was 65% and included 4 complete response (CR), including 3 patients with CSF involvement and one parenchymal, and 9 partial response (PR). Progressive disease was reported in 3 patients. Response in 3 patients has not been confirmed in a second assessment. The median PFS to date was 5.5 months and the longest is continuing past 13.2 months. Despite clinical and radiographic response, 2 patients withdrew from the study, and one stopped due to a fungal infection.

The most commonly reported toxicities were hyperglycaemia, anaemia, and thrombocytopenia. Four grade 4 toxicities were observed in 4 patients that consisted of lymphopenia in 2 patients, and one patient each had sepsis and neutropenia. Grade 3 toxicities occurred in 10 patients, including lymphopenia in 3 patients, 2 patients each had thrombocytopenia, hyperglycaemia, or lung infection and one patients each had grade 3 neutropenia, urinary tract infection, colitis, and fungal encephalitis. Molecular testing is in process to associate genomic alterations with patient outcome. NCT02315326. Grommes *et al.* Abstract 331PD

Practice point and future research opportunities

This trial demonstrated clinical benefit with ibrutinib in patients with this aggressive cancer, including prolonged PFS beyond that noted in literature. Patients with primary and secondary recurrent/refractory CNS lymphoma tolerated ibrutinib and showed manageable toxicities. Ibrutinib may be a putative therapeutic alternative in this setting that should be further investigated. The ongoing molecular analysis could aid in patient selection.

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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