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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
BIOMARKERS

Large-scale evaluation of tumour mutational burden and microsatellite instability status

Garrett M. Frampton, Research and Development, Foundation Medicine, Cambridge, USA, and collaborators used comprehensive genomic profiling (CGP) targeting greater than 500x sequencing coverage (non-PCR duplicate reads) to capture the full coding regions of 315 genes. The investigators performed CGP on more than 40,000 cancer specimens from individual patients, representing over 400 unique sub-types of cancer to determine the contribution made by microsatellite instability (MSI) to the overall tumour mutational burden (TMB). MSI and TMB were each then assessed as biomarkers of response to immunotherapy in a large cohort of patients with advanced cancer representing a broad array of tumour types. MSI status was determined by assessing the indel alterations occurring at 114 microsatellites covered by the CGP test. TMB was determined by evaluating the number of somatic, coding, base substitution, and indel mutations occurring per megabase of coding genome targeted on the test. Tumours with ≥ 20 mutations per megabase were considered to have high TMB.

The investigators found that 1.4% of cases were MSI-High, while 7.1% of cases had high TMB. High TMB was observed in 85% of MSI-High cases; interestingly, the converse was not observed, with numerous cases with high TMB being observed that did not show evidence of MSI.

The results were highly disease specific with some tumour types, notably lung, skin, and urinary cancers, that were MSI-High but with very few (<5%) high TMB cases. In gastrointestinal, ovarian, and endometrial cancers more than 75% of high TMB cases were also MSI-High. A meaningful fraction of cases with high TMB and no evidence of MSI was observed in all tumour types. The full landscape of TMB and MSI across 40,000 cases and hundreds of cancer subtypes was presented at the conference. Frampton et al. Abstract 52O

Practice point and future research opportunities

These results support the understanding that TMB and MSI status in cancer genomes are correlated. Although the majority of MSI-High cases also had high overall TMB, these data also demonstrate that both are highly specific to tumour subtypes and a large portion of cancers with high TMB are microsatellite stable. This indicates that assessment of both TMB and MSI will be most useful for identifying patients that are likely to benefit from immunotherapy.

Multidisciplinary molecular tumour board enables selection accrual for clinical trials and targeted therapy in cancer patients

Christian D. Rolfo, Early Clinical Trials Unit & Center for Oncological Research of Antwerp (CORE), Antwerp University Hospital in Edegem, Belgium, noted that using Next-Generation Sequencing (NGS) and other molecular profiling techniques to identify druggable targets has
changed clinical practice in oncology. To facilitate these gains, the Molecular Tumour Board (MTB) has become a crucial multidisciplinary tool for results interpretation and implementation of treatment, including the inclusion of patients in clinical trials. Professor Rolfo and colleagues conducted a retrospective analysis of a cohort of patients with several advanced solid tumours that were not candidates for standard treatment that had been included in the MTB, which is a consultation for the phase I – Early Clinical Trials Unit of the Antwerp University Hospital. The patients all had a molecular profile (MP) that was discussed in the MTB and this analysis included patients with MTBs done in house and also by commercial NGS platforms. A subgroup of these patients also had samples for immunochemistry (IHC) and/or in situ hybridization (ISH) analysis.

This study included 133 national and international patients who provided 141 tissue samples. The median patient age was 59 years old (range: 18 to 85), and 56% of patients were female. Genomic alterations were detected in 107 (75.9%) samples at an average of 3.44 alterations; 86 (80.4%) of these alterations corresponded to gene mutations in the NGS panel. Approximately 50 (58.1%) samples harboured more than one mutated gene.

The most frequently mutated genes in this cohort were TP53 at 32%, KRAS at 13%, PIK3CA at 8%, and 7% of the alterations were in the APC gene. In the subgroup analysis of patients with additional MP information (IHC=X: CISH=4: FISH=6) the more common alterations were 9% each in TOPO1 and TOP2A, and 8% in both MGMT and PTEN. The primary tumour sites most frequently implicated were lung in 14.9% of samples, colon in 12.1%, pancreas in 9.2%, and breast in 7.8% cases. The MTB recommended treatment in 78 (55%) of the cases, including matched therapy in 55 (70.5%) of cases, and non-matched therapy in 23 (29.5%) cases. Based on MP information 29 (37%) patients were included in clinical trials, and 5 (6.4%) patients received compassionate use. Rolfo et al. Abstract 54PD

Practice point and future research opportunities

The multidisciplinary molecular tumour board review enabled a majority of patients with advanced cancer to be offered targeted therapy or entry into clinical trials based on molecular profiling. Access to suitable target drugs and clinical trials are crucial to guarantee that cancer treatment moves forward at the same rate as scientific discovery. National programmes for reimbursement would facilitate these efforts.

Dabrafenib shows anti-tumour activity in paediatric patients with BRAF V600–mutant relapsed or refractory low-grade gliomas

Principle investigator Mark Kieran of the Paediatric Medical Neuro-Oncology Department of Dana-Farber Cancer Institute and Boston Children’s Hospital pointed out that BRAF V600 mutations are present in approximately 15%-20% of patients with paediatric low-grade gliomas who are known to have poorer survival and lower objective response rates than paediatric patients with gliomas and wild-type BRAF. Dr. Kieran and colleagues conducted the first study

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to evaluate dabrafenib, which inhibits the V600-mutant form of the BRAF kinase, in 32 paediatric patients aged 2 to 17 years with BRAF V600-mutant relapsed or refractory disease. The phase I dose-finding part of the study comprised 15 patients and tested 4 dose levels up to, and including, the recommended phase II (RP2) dose of 4.5 mg/kg/day in patients aged 12 or older; patients younger than 12 received 5.25 mg/kg/day of dabrafenib divided into two equal daily doses. Overall 24 patients, including 17 patients in the phase II part of the study, received the RP2 dose of dabrafenib.

At data cut-off, 22 patients remained on study. The independently confirmed overall response rate (ORR), by Response Assessment in Neuro-Oncology (RANO) criteria, was 41% (95% confidence interval [CI] 24%, 59%), and consisted of 2 complete responses (CRs) and 11 partial responses (PRs). The median duration of response was 11 months and 8 responders had an ongoing response. An additional 13 (41%) patients had stable disease lasting 6 months or more, of whom 11 showed an ongoing response. The confirmed ORR per investigator assessment was 72% (95% CI 53, 86), which included one complete response (CR) and 2 partial responses (PRs).

The paediatric patients showed adverse events (AEs) with dabrafenib that were similar to adults, and included frequent low-grade pyrexia, vomiting, fatigue, headache, and rash. The most frequent grade 3/4 AE was pneumonia. No cases of cutaneous squamous cell carcinoma occurred. One patient discontinued the study due to a significant allergic reaction following the initial dosing and again upon re-challenge. The investigators are planning to give dabrafenib together with the MEK inhibitor trametinib in a future trial, since the combination has shown a longer duration of progression-free survival than either drug used alone in adults. EudraCT Number: 2012-001499-12. Kieran et al. Abstract LBA19_PR

Practice point and future research opportunities

Although paediatric low-grade glioma generally carries a good prognosis, the 15% to 20% of children with BRAF V600 mutation fare less well. There is a need for improved treatment options for these patients who often have lifelong cognitive damage and secondary malignancies due to radiation therapy. There is a paucity of randomised data for treatment of brain tumours in children since the tumours are rare and the trials are difficult for ethical reasons. The promising results seen with targeted therapy in this study are limited by the small population and short follow-up. These findings will have implications for clinical practice, however, longer follow-up is needed to find out how long the responses last and whether there is any long-term toxicity.

Vemurafenib is active in diverse BRAF V600-mutated tumour types but not in tumours without V600 mutation

Patients with BRAF non-V600 mutated tumours showed no benefit from vemurafenib, according to Jean-Yves Blay, Medical Oncology, Centre Léon Bérard, in Lyon, France. Professor Blay presented results from the second ACSE vemurafenib study, which is part of a programme undertaken by the French National Cancer Institute to allow patients to have safe and controlled access to targeted therapies outside of the labelled indication. More than 1500 patients were
screened for mutations at 96 centres throughout France, which yielded 78 patients with tumours harbouring BRAF V600 and BRAF non-V600 mutations. These patients were enrolled in this phase II study, which comprised 2 cohorts: The dedicated treatment cohort contained patients with diverse BRAF V600 mutation positive cancers including lung, ovarian, bladder, thyroid, prostate cancers, cholangiocarcinoma, sarcoma/gastrointestinal stromal tumour (GIST), multiple myeloma, chronic lymphocytic leukaemia (CLL), and HCL, and the specific miscellaneous cohort containing 6 patients with BRAF V600 mutation, and 14 patients with non-V600 BRAF (exon 11, 15) mutated tumours, or other BRAF alterations.

All patients were treated with vemurafenib at 960 mg twice daily. The median age of the patients was 67 (range: 18 to 84) years and 51% of patients were female. The efficacy endpoint was objective response rate (ORR), which was evaluated every 8 weeks by RECIST v1.1 criteria for solid tumours and by specific criteria for myeloma, CLL and HCL. Data from 56 patients were analysed for response, which was reported by mutation status and cancer subtype.

The median duration of treatment was 1.9 months (range: 0.2 to 11.0 months). In the dedicated cohort of patients with BRAF V600 positive cancers, 31 patients with NSCLC demonstrated an ORR of 43%; 13 patients achieved partial response (PR), 6 showed stable disease (SD), 7 patients experienced progressive disease (PD), 4 patients died, and the data were missing for one patient. In patients with HCL, 4 of 4 patients having evaluable data showed an ORR of 100%; 2 patients demonstrated PR and 2 patients had SD. The one patient with sarcoma died. Of the 2 patients with cholangiocarcinoma, one patient also died and one patient demonstrated SD. Of the 3 patients with thyroid cancer, one patient demonstrated SD and 2 patients had PD.

In the miscellaneous cohort, 5 of 6 patients with BRAF V-600 mutations had evaluable data: PR was achieved by 3 of these patients and 2 patients showed SD, resulting in an ORR of 60%. All 6 patients with BRAF non-V-600 mutated tumours experienced PD. The most frequently reported treatment-related adverse events of grade 3 or greater were skin and gastrointestinal toxicities. Blay et al. Abstract 55PD

Practice point and future research opportunities

Nationwide screening for patients with BRAF mutation enabled rapid access to vemurafenib treatment in this trial. Vemurafenib is approved for BRAF mutated melanoma and has shown activity in other non-melanoma tumours that harbour BRAF-V600E-mutations. Findings from a phase II trial of vemurafenib in previously treated patients with advanced disease and BRAF mutated tumours indicate the drug is effective in patients with diverse BRAF V600-mutated tumours, which have been reported to be present at low (<5%) frequency. These reports were confirmed by results from this trial where important antitumour activity was seen with vemurafenib in NSCLC, HCL, and miscellaneous V600 mutated tumours, but not in patients with BRAF non-V600 mutations.
RELATED INFORMATION

Click here to access the Congress abstracts.

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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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