ESMO 2016 Congress

7-11 October, 2016

Copenhagen, Denmark

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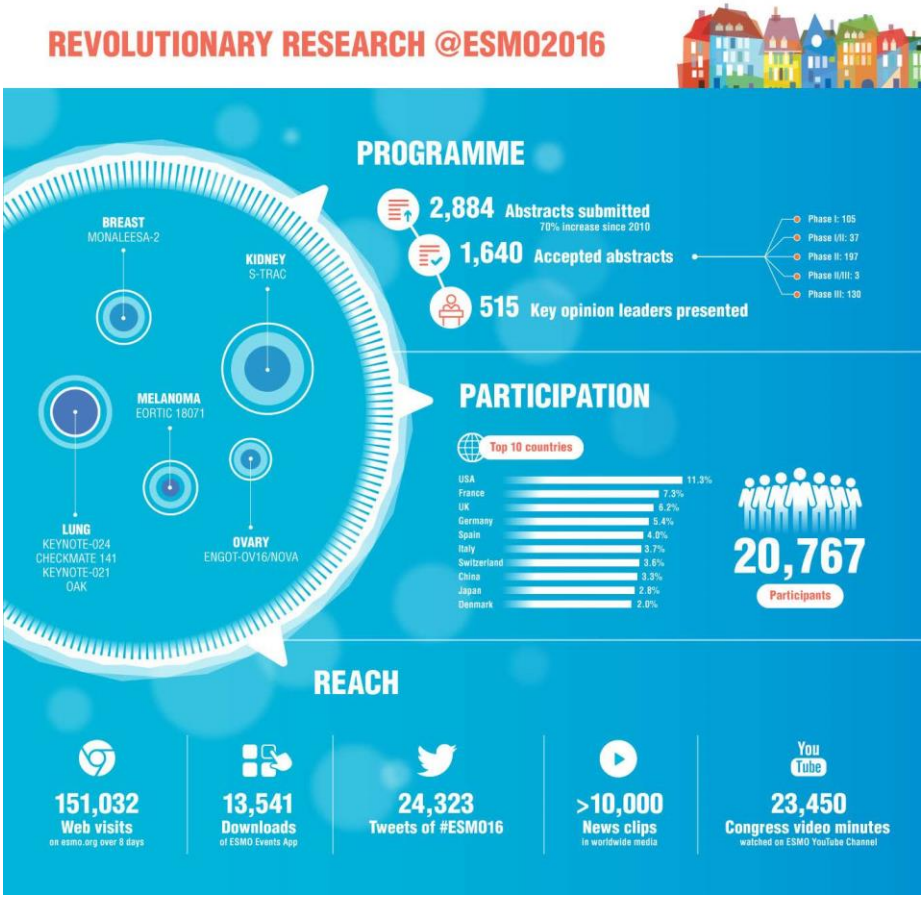
Summary

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

TRANSLATIONAL RESEARCH

Tumour gene expression used to direct clinical decision-making for patients with advanced cancers

Janessa Laskin, Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, headed a team of Canadian investigators in evaluating the integration of whole genome sequencing, including DNA and RNA expression information, into oncology practice in the Personalized OncoGenomics (POG) study. Between July 2012 and April 2016, patients were enrolled with advanced tumours and minimum survival of 6 months. All patients provided a tumour biopsy and blood sample for comprehensive DNA (80X) and RNA sequencing followed by bioinformatic analysis including assembly, annotation, and mining of the data to identify potentially targetable somatic aberrations, gene expression changes, or other putative cancer "drivers". RNA expression information from tumour RNA sequencing was also compared to the TCGA and Illumina body map. The results obtained from sequencing patient tumours were assessed in a multidisciplinary Clinical Genomics Tumour board and categorised the results for clinical actionability as informative, actionable or neither.

Complete sequencing data were available for 217 patients. The vast majority, 165 patients, had clinically actionable results and no actionable pathway could be identified in just 52 patients. No samples were found to be informative only. The information from the 165 actionable patients was used to provide personalised therapy directed by POG data for 71 patients and POG directed therapy could be offered upon progression to 34 patients. POG directed therapy was not administered to 60 patients; 24 due to poor performance status or death, and 16 did not receive POG directed therapy because no clinical trial or off-label treatment was available. In 20 patients, the POG data was not utilised. Of the 71 patients having POG directed treatment, 13 received this treatment within a clinical trial, 29 patients received off label treatment, and 29 patients received treatment within guidelines of disease site. RNA information was used in 40% of treatment decisions, 45% of treatment decisions were based on a combination of DNA and RNA information, and 15% of treatment decisions were based on solely on DNA information. NCT02155621. Laskin *et al.* Abstract 1519O

Practice point and future research opportunities

This study demonstrated that sequencing information from patients' tumours can provide information on targetable DNA or RNA aberrations to be directly translated into clinical treatment decisions. The whole genome analyses used here have the potential to identify the full landscape of genomic abnormalities within cancers, and can therefore be used to provide rationales for cancer treatments. This analysis evaluated how physicians used the data for clinical decisions and the role of RNA data in identifying actionable targets. Data from DNA abnormalities alone corresponds to the rate noted in historical panel-associated drug matching trials; however, the availability of RNA expression information or both DNA/RNA information greatly increased the ability to identify clinically actionable targets. With the support of the multidisciplinary tumour

board and a tiered data system, oncologists had sufficient confidence in the results to seek clinical trials and off-label therapies based on genomic data in the majority of patients.

Lurbinectedin is active in PARP-inhibitor resistant germline BRCA patient derived xenographs and cisplatin efficacy is unaffected by lurbinectedin resistance

Cristina Cruz, Medical Oncology, Hospital Vall d'Hebron and Vall d'Hebron Institute of Oncology, Barcelona, Spain and colleagues used 10 patient-derived xenographs (PDXs) obtained from lurbinectedin-naive patients who had germline BRCA mutations (gBRCA) to characterise resistance to PARP inhibitors and the mechanism of this resistance, including its effect on lurbinectedin. The investigators evaluated the antitumor activity of lurbinectedin at 0.18mg/kg i.v. plus cisplatin at 6 mg/kg i.v. every 7 days for 5 cycles in the previously lurbinectedin-naïve patients. Of the 10 patient samples, 8 showed resistance to PARP inhibitors and 2 were PARP inhibitor-sensitive; additionally, the combination was tested on one additional PDX implanted at time of progression on lurbinectedin. Exome sequencing analysis was done in 5 paired tumour biopsies taken pre- and post-lurbinectedin treatment.

The results suggest that the mechanisms of resistance to PARP inhibitors does not confer resistance to lurbinectedin. Lurbinectedin was active and showed antitumour activity, consisting of partial response, complete response or stabilisation in 6 (75%) of the 8 PDXs that were resistant to PARP inhibitors. Exome sequencing of gBRCA tumours that were resistant to lurbinectedin resistant tumours revealed the acquisition of genetic alterations in 5 samples that could disrupt the nucleotide excision repair (NER) pathway, which may impair sensitivity to PM01183. These same alterations confer sensitivity to cisplatin in vitro and in vivo. The PDX model implanted at progression on lurbinectedin demonstrated lurbinectedin resistance but remained sensitive to cisplatin, suggesting that the NER alterations putatively driving resistance to lurbinectedin do not compromise cisplatin efficacy. Cruz *et al.* Abstract 1520O

Practice point and future research opportunities

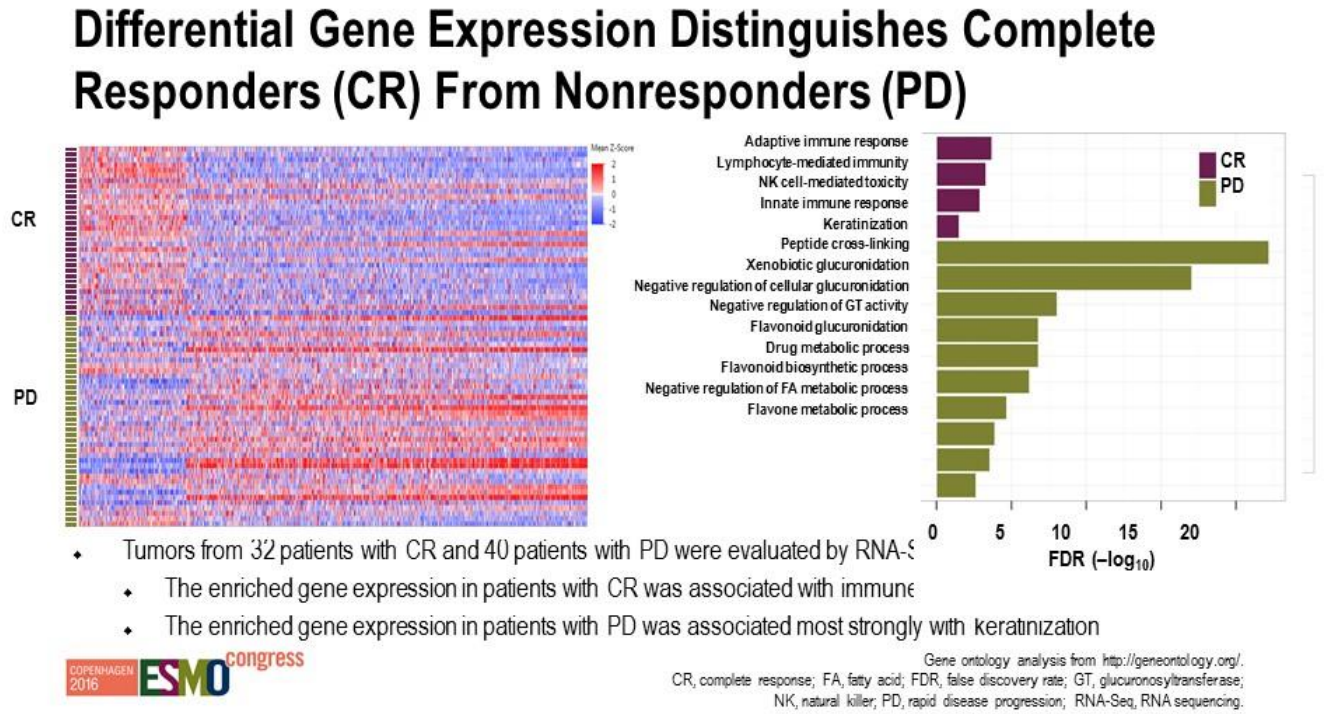
Lurbinectedin is a trabectedin analogue that inhibits transactivated transcription and induces DNA double-strand breaks that has demonstrated remarkable clinical activity in patients with germline BRCA-related metastatic breast cancer. Previous studies also demonstrated lurbinectedin activity in patients resistant to platinum-based chemotherapy. This study assessed the activity of lurbinectedin and the mechanisms of primary and acquired resistance to lurbinectedin and the potential impact on the efficacy of PARP inhibitors or platinum salts.

These findings suggest that lurbinectedin is active in the presence of resistance of PARP inhibitors and that primary or developed resistance to lurbinectedin does not compromise platinum efficacy. This knowledge may aid in determining the optimal therapeutic sequence to maximise the clinical benefit in the metastatic breast cancer setting.

Baseline immune factors differ between responding and non-responding patients with BRAFV600-mutated melanoma

Lead investigator Antoni Ribas, Jonsson Comprehensive Cancer Center, University of California, Los Angeles, Los Angeles, CA, USA, explained that patient responses to the BRAF inhibitor, vemurafenib, and the MEK inhibitor cobimetinib vary, although both sole vemurafenib and vemurafenib plus cobimetinib have demonstrated improved objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) in patients with BRAFV600-mutated metastatic melanoma.

Together with colleagues, Dr. Yibing Yan, Oncology Biomarker Development, Genentech, Inc., South San Francisco, USA, and Dr. Ribas conducted this study to identify the baseline genetic features in responding and non-responding patients to determine the role they play in response to these agents. This study compared genomic features of tumours at baseline with respect to patients achieving complete response (CR) versus those showing progressive disease (PD) in response to treatment. Tumour samples taken prior to treatment in the BRIM2, BRIM3, BRIM7, and coBRIM trials from patients showing CR or PD at the first evaluation were analysed by whole exome sequencing (WES) and RNA sequencing. The differences in gene signatures between patients having CR and PD were tested by ANOVA and represent the mean Z-score of all components. Associations of gene expression with PFS or OS were assessed by Cox proportional hazards modelling.



Differential gene expression distinguishes complete responders from non-responders.

WES was performed on baseline melanoma samples from 52 patients having CR, and 78 patients showing PD following treatment with cobimetinib combined with vemurafenib or sole vemurafenib.

Analysis of the genomic features of biopsies of patients with metastatic BRAFV600-mutated melanoma revealed that tumour samples taken at baseline from patients who went on to achieve CR showed higher expression of pre-existing tumour immunity features than patients who experienced PD at the first evaluation.

Although the overall mutational load was not significantly different in samples from both groups, samples from patients with PD showed higher rates of MITF amplification and TP53 mutation than patients with CR; the respective rates were of MITF amplification were 18% versus 4% and TP53 mutation rates were 19% versus 5% in patients with PD and CR, respectively. The profile of patients with CR more commonly included NF1 deletion and deleterious mutations at 12% versus 3% in PD.

Gene expression was analysed with RNA sequencing on tumours from 32 CR and 40 PD revealed differential expression of 415 genes between patient cohorts that were also associated with PFS or OS. The investigators found that gene expression profiles in tumours of patients with CR were over-represented with adaptive and innate immune responses, such as gene signatures of CD8 T effector cells, cytolytic T-cells, antigen presentation and NK cells.

Previously, Dr. Ribas and colleagues identified common features of melanoma that showed innate resistance to anti-PD1 immune therapy, defined as innate anti-PD1 resistance signatures (IPRES; Hugo et al. Cell. 2016;165:35-44). In this analysis of resistance to BRAF/MEK inhibition, the authors found it interesting that there were higher levels of gene expression of 19 keratin and 7 kallikrein genes in tumours from patients having PD tumours and remarked that this was reminiscent of the “keratin” subtype of tumour proposed by The Cancer Genome Atlas (TCGA) project. Ribas *et al.* 1111O

Practice point and future research opportunities

These exploratory analyses revealed baseline genomic differences between melanoma from patients showing CR compared to those having PD after treatment with cobimetinib combined with vemurafenib or vemurafenib alone. Overall, melanomas from patients achieving CR with either regimen had higher levels of pre-existing tumour immunity features, whereas melanoma samples from patients showing PD predominately display the “keratin” molecular subtype. This finding calls for further investigation of interaction of all significantly enriched molecules.

RELATED INFORMATION

Click here to access the Congress abstracts.

Click here to access the meeting webcast page.

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.

Acknowledgment

ESMO would like to thank you Virginia Powers, PhD for editorial assistance in preparation of this report.

ESMO would like to thank you Drs Judith Balmaña, Mark Andrew Glaire, Pierre Laurent-Puig, Sara Pusceddu, Antoni Ribas, Phillipe Rochigneux, Alexa Schrock and Yibing Yan for giving their permission to publish the images from the studies presented during the ESMO 2016 Congress in the ESMO Scientific report.

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