

# 2015 EUROPEAN CANCER CONGRESS

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Vienna, Austria

## SUMMARY

The European Cancer Congress (ECC 2015) combined the 40th European Society for Medical Oncology (ESMO) congress with the 18th congress of the European Cancer Organisation (ECCO) and was held 25 to 29 September, 2015. The meeting was organised in partnership with the European Society of Radiation and Oncology (ESTRO), the European Society of Surgical Oncology (ESSO), the European Academy for Cancer Research (EACR), the European Oncology Nursing Society (EONS), and International Society of Paediatric Oncology (SIOPE). The efforts of all partner organisations were united to continue advancing multidisciplinary as the way forward to optimise the prevention, diagnosis, treatment, and care of cancer patients by encouraging participants to leverage knowledge, promote education and build awareness for patient-centred oncology.

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## BASIC SCIENCE

### Combined inhibition of IGF1R and EGFR signalling overcomes the resistance to third-generation EGFR kinase inhibitors due to IGF1R activation in cell lines

Sun Cheol Park, Asan Medical Center, Pulmonology and Critical Care Medicine, Seoul, Korea and colleagues investigated the mechanism behind the loss of clinical efficacy due to the development of resistance to the highly effective third generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). Since third generation of EGFR-TKIs are known to control growth in lung cancer cells with T790M-mediated resistance, the investigators used PC-9/GR cells, which contain both EGFR exon 19 deletions and T790M mutations, to develop cell sublines (the PC-9/GR/WR cell line), that are also resistant to WZ4002 (a third generation EGFR TKI). They also blocked IGF1R signaling with AG1024 (a small molecule IGF1R inhibitor) and then used a multi-kinase assay to determine the activation of a bypass signal.

In their assay, the subline PC-9/GR/WR demonstrated cross-resistance to other third generation EGFR-TKIs, including AZD9291 and CO1686 but WZ4002 was unable to inhibit the growth of cancer cells despite the effective suppression of EGFR activation. EGFR down-regulation by small hairpin RNA (shRNA) also could not control cancer cell proliferation, suggesting the activation of a bypass growth signal. The PC-9/GR/WR cells showed activation of IGF1R plus IGFBP3 loss, which suggested that the down-regulation of IGF1R by shRNA and the inhibition of IGF1R signal by AG1024 could restore WZ4002. Park et al. Abstract 101.

#### Practice point and future research opportunities

Strategies to overcome resistance to third generation of EGFR-TKIs is an important therapeutic goal; this team has made a significant step forward by identifying a possible mechanism of IGF1R activation accompanied by IGFBP3 loss and postulating the combined inhibition of IGF1R plus EGFR signalling could restore sensitivity to WZ4002.

### Combination treatment with a tyrosine kinase inhibitor plus an IL-6 receptor antibody assessed in renal cell carcinoma cell lines and mice

According to findings presented by Kei Ishibashi, Fukushima Medical University, Fukushima, Japan, treatment with TKIs against the vascular endothelial growth factor (VEGF) pathways, which represents the current standard of care in advanced renal cell carcinoma (RCC), activates the

interleukin-6 (IL-6) signalling pathway, and induces IL-6, suggesting that activity with these TKIs may be improved by adding an IL-6 agonist such as the humanised monoclonal antibody to the IL-6 receptor, tocilizumab.

Human RCC cell lines 786-O, Caki-2, CCF-RC1 and A498 were treated in this study with the TKIs sorafenib and sunitinib at concentrations of 0.5, 1.0, 5.0, 10.0µM. Following this treatment, the 786-O RCC cell line secreted IL-6 and VEGF, as measured by the VersaMAP Development System. Western blot analyses revealed that Akt and mTOR were activated by TKI treatment even at the lowest concentration of 0.5 mM. HIF2a expression and the phosphorylation of NFκB were also demonstrated by Western blot; these changes are linked to VEGF and IL-6 expression. Analysis of the IL-6 signaling pathway using an IL-6R antibody, the MTT assay and Western blot, showed that tocilizumab treatment plus TKIs could reduce the activation of the IL-6 signaling pathway and also suppressed cell proliferation.

The mean SUVmax indicating tumour viability was compared in athymic mice receiving tocilizumab plus sorafenib with similar mice receiving sorafenib and was found to be decreased in athymic mice receiving combination therapy; the mean SUVmax was 9.8±1.6 compared with 11.5±0.8, respectively (p = 0.04). The investigators also noted that the areas of necrosis in the tumours were significantly increased (206±56mm<sup>3</sup>) in mice receiving the combination compared with similar areas in tumours of mice receiving sole sorafenib (117±31mm<sup>3</sup>; p = 0.02). CD31 expression was also reduced with tocilizumab plus sorafenib compared with sorafenib alone. The investigators concluded that TKIs induce IL-6 secretion in RCC cells, leading to VEGF secretion, angiogenesis, and increased cell proliferation. Ishibashi et al. Abstract 102.

### Practice point and future research opportunities

These results suggest that co-administration of an IL-6 antibody with TKIs decreases angiogenesis and cell proliferation in renal cell carcinoma cells in vitro and in mice, warranting further investigation.

### Subtype of CDH2 negative oesophageal squamous cell carcinoma with cytotoxic T-lymphocyte signatures shows a good response to definitive chemoradiotherapy

A team led by Yashuhito Tanaka, Nagoya City University Hospital, Nagoya, Japan previously reported that tumour-specific cytotoxic T-lymphocyte (CTL) activation signatures were preferentially found in long-term survivors after definitive chemoradiotherapy (dCRT). In the study presented at

the ECC, the investigators sought to determine whether CRT actually drives the CTL activation by evaluating the effect of CRT on tumour tissues. Expression profiles of needle biopsy specimens obtained from 30 patients with oesophageal squamous cell carcinoma before and after treatment were created by gene expression profiling, using oligonucleotide microarrays. The specimens included 19 complete response (CR) and 11 non-CR cases. Gene expression profiles were also obtained from another 125 samples, with survival analysis performed in 121 of the 125 cases where clinical data was available.

The investigators found the post-treatment samples from the 19 CR cases contained 1014 up-regulated genes, including at least 240 tumour-specific CTL-activation associated genes including IFNG, PRF1, and GZMB. The expression profiles of these 240 tumour specific genes could distinguish immune-activated cases, from other cases. Although the CR rate was better in the immune-activated gene cases, no association with overall survival (OS) was found in the 30 patient samples or in the additional 125 samples.

A comparison of expression profiles between cases with and without early relapse identified a series of epithelial to mesenchymal transition-related genes that were over-expressed in early relapse cases. Since it had been shown that the intestinal-type with epithelial characteristics and the diffuse-type with mesenchymal characteristics of oesophageal squamous cell carcinoma could be distinguished by the ratio of CDH1 and CDH2 in gastric cancer, the investigators applied this ratio to the oesophageal cancer analysis, which showed that OS in CDH2 negative cases was significantly better than in CDH2 positive cases ( $p = 0.012$ ). Furthermore, the 5-year survival was 56% versus 20% in CDH2 negative versus CDH2 positive cases, respectively. The clinical outcome, represented by the OS and recurrence rates, associated with the immune-activated gene cases; the outcome of CDH2-negative cases was significantly better than that of CDH2-positive cases ( $p = 0.012$ ). The 5-year survival rate was 73% versus 7%, respectively in the immune-activated gene cases. Tanaka et al. Abstract 104.

### Practice point and future research opportunities

This analysis identifies genes, crucially many immune-related genes, that are upregulated after dCRT treatment of oesophageal squamous cell carcinoma and also shows an association between a phenotype that is CDH2 negative with cytotoxic T-lymphocyte signatures and improved clinical benefit from dCRT.

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## AFFILIATION AND DISCLOSURE

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### Disclosure

No conflicts of interest to disclose.

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