TARGETING RESISTANCE IN EGFR-MUTANT NON-SMALL CELL LUNG CANCER (NSCLC): PRECLINICAL EVIDENCE SUPPORTING THE COMBINATION OF EGFR TYROSINE KINASE INHIBITORS (TKIS) AZD9291 AND GEFITINIB WITH MOLECULARLY TARGETED AGENTS AND IMMUNOTHERAPEUTICS

D. Cross1, C. D'Cruz2, C. Eberlein1, P. Spitzler3, E. Ichihara3, C. Meador3, S. Ashton1, M. Mellor1, R. Stewart4, P. Smith1, A. Schuller2, M. Frigault5, W. Pao6, P.J. Jewsbury1

1iMED Oncology, AstraZeneca, Macclesfield, UK
2Prin Sci II Biosci, AstraZeneca, Waltham, MA, USA
3Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
4Oncology, MedImmune, Cambridge, UK
5iMED Oncology, AstraZeneca, Waltham, MA, USA
6Hematology/oncology, Vanderbilt University, Nashville, TN, USA

Aim: First-generation EGFR-TKIs, such as gefitinib, are active in first-line, EGFR-TKI-sensitising-mutant (EGFRm+), advanced NSCLC, but the duration of clinical benefit is limited by acquired tumour resistance. A common resistance mechanism is gain of an additional mutation, T790M, and about 5–15% of patients also develop MET amplification, with or without T790M. The recently developed novel third-generation EGFR-TKI, AZD9291 (a selective EGFR-TKI of EGFRm+ and T790M mutations), overcomes T790M-mediated resistance. Combining EGFR-TKIs with selective molecularly targeted agents has the potential to delay the emergence of EGFR-TKI resistance across lines of therapy. Finally, immunotherapeutics, such as checkpoint inhibitors, have the potential to target cancers orthogonally; thus studies to optimise their use with EGFR-TKIs would be of high value to patients.

Methods: In vitro and in vivo preclinical models representing EGFRm+ and T790M NSCLC were used to investigate the potential of combining AZD9291 or gefitinib with immunotherapeutics, and selective small molecule kinase inhibitors, namely selumetinib (AZD6244, ARRY-142886; MEK1/2 inhibitor) and AZD6094 (MET inhibitor).

Results: Preclinical models harbouring MET overexpression demonstrated AZD6094 plus EGFR-TKI was well tolerated and effective in reversing MET-driven resistance. In models of acquired resistance mediated by increased MEK dependency, resistance could be delayed in vitro and in vivo by addition of selumetinib. Finally, a genetically engineered mouse model of mutant EGFR NSCLC was used to assess the impact of AZD9291 treatment on T-cell infiltration; results will be presented.

Conclusions: These preclinical studies provide a strong rationale for the clinical evaluation of AZD9291 and gefitinib in combination with molecularly targeted agents, such as AZD6094 and selumetinib, to delay and/or overcome acquired resistance to single-agent EGFR-TKI therapy. Rational combinations with immunotherapeutics are also worth further investigation.