LUNG CANCER

Combating resistance through IGF-1R and ALK co-targeting

Patients with ALK-positive lung cancer who initially respond to the ALK-targeting agent crizotinib eventually develop resistance. Now, analysis of an exceptional responder from a phase I trial has not only provided new insight into the mechanisms of resistance, but has also unveiled a therapeutic synergism between ALK and IGF-1R inhibitors.

A female patient with stage IV lung adenocarcinoma was enrolled on a clinical trial of erlotinib followed

by erlotinib plus the addition of an IGF-1R monoclonal antibody at the time of disease progression. Importantly, the mutational status of her tumour was not known before study enrolment. She did not respond to erlotinib alone; however, upon the addition of the IGF-1R antibody, the patient had a remarkable response lasting 17 months. “We were interested in why this particular patient’s tumour responded to the experimental therapy so dramatically when others did not,” explains Christine Lovly, lead investigator of the study.

At the time of disease progression on the IGF-1R antibody, molecular profiling revealed that the tumour was negative for an *EGFR* activating mutation (as expected based on the lack of response to erlotinib alone), but harboured an ALK rearrangement. This trial was conceived before ALK fusions were identified in lung cancer. “The patient’s surprising response to an IGF-1R inhibitor and the later finding that her tumour was ALK-positive sparked a new line of research to identify

and explain the biological mechanisms at work,” explains Lovly. Using multiple different model systems and patient tumour biopsy samples, the researchers showed that ALK inhibitors are synergistic with IGF-1R inhibitors in ALK-positive lung cancer cell lines. Furthermore, they showed that the IGF-1R pathway was upregulated in ALK-inhibitor resistant cells, and that IGF-1R inhibition sensitized resistant cells to the effects of ALK blockade. IGF-1R phosphorylation was increased in tumour samples taken from patients with ALK-positive lung cancer at the time of acquired resistance to ALK inhibitor therapy.

This study identifies the IGF-1R–IRS-1 signalling axis as a potential therapeutic target in ALK-positive lung cancer, and may help design rational clinical trials.

Lisa Hutchinson

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