Promising results shown with targeted approaches in subsets of non-small cell lung cancer

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The BRAF inhibitor dabrafenib has significant anti-tumour activity in patients with advanced BRAF V600E mutant non-small cell lung cancer whose disease has progressed after chemotherapy, according to phase II data presented at the ESMO 2014 Congress in Madrid, Spain.

"Reports of lung cancers bearing mutations in BRAF have generated considerable interest because these mutations may be associated with increased sensitivity to BRAF tyrosine-kinase inhibiting agents," says lead author Dr David Planchard, pulmonary oncologist at the Gustav-Roussy Cancer Campus, Paris, France.

Planchard says studies suggest that activating BRAF mutations are present in around 2% of lung carcinomas—approximately 80% of which are V600E mutations. The BRAF V600E mutations are frequently associated with shorter disease-free, overall survival, and lower response rates to platinum-based chemotherapy.

This open-label phase II study involves patients with BRAF V600E mutant non-small cell lung cancer, treated with dabrafenib alone (150 mg, twice daily). The primary endpoint is investigator-assessed overall response rate, with secondary endpoints of progression-free survival, duration of response, overall survival, safety and tolerability, and population pharmacokinetics.

Data from the 78 patients enrolled in the study showed an overall response rate of 32% in patients who had already received one or more prior treatments, and a disease control rate of 56% after 12 weeks of treatment.

The median duration of response was 11.8 months, and among the six first-line patients, three of them had partial response to the treatment.

The safety profile with dabrafenib was similar to that observed with previous studies in melanoma, the most common adverse events being fever (36% of patients), asthenia (30%), hyperkeratosis (30%), loss of appetite (29%), nausea (27%), cough (26%), fatigue (26%), and skin papilloma (26%). Cutaneous squamous-cell carcinomas, including keratoacanthoma, were also reported in 18% of patients.

Based on earlier interim efficacy and safety data from this study, dabrafenib received a Breakthrough Therapy designation in lung cancer from the FDA in January this year, Planchard says.

In summary, Planchard says, "These findings establish dabrafenib as an effective treatment option for patients with previously treated advanced BRAF V600E non-small cell lung cancer."

HER2 inhibition shows promise in HER2-positive non-small cell lung cancer

Human epidermal growth factor receptor 2 (HER2) mutations may offer an important treatment target in a subset of patients with non-small cell lung cancer, according to data from a phase II randomised trial of neratinib and temsirolimus, also presented at ESMO 2014 in Madrid.

"HER2 mutated non-small cell lung cancer patients are a small subset of

non-small cell lung cancer patients—around 1-2%—but it seems important to inhibit HER2 for these patients," says lead author Dr Benjamin Besse, head of the thoracic cancer unit at Gustave Roussy, Paris, France.

Neratinib inhibits the HER2 receptor while temsirolimus inhibits mTOR, a protein that belongs to the signaling cascade of HER2, Besse says.

In a randomised, two-stage study, 27 patients with advanced, metastatic non-small cell lung cancer whose tumours tested positive for HER2 somatic mutations were randomised either to treatment with oral neratinib (240 mg od continuously) alone, or in combination with intravenous temsirolimus (8 mg/week, dose escalation to 15 mg/week after one three-week cycle if tolerated, at the investigator's discretion).

Preliminary results from stage one of the ongoing study show the combination of neratinib and temsirolimus has a 21% overall response rate in 14 patients, with a median progression-free survival of 4 months.

Researchers did observe more gastrointestinal effects such as diarrhea from combination therapy compared to neratinib alone, but it was not a limiting toxicity and the side effect was managed up front with prophylactic loperamide.

In summary, Besse says, "HER2 mutated non-small cell lung cancer represents a very small number of patients, but it reflects the new face of NSCLC —it is not a single homogeneous disease, but a lot of different molecularly defined subsets of patients with potential 'drugable targets', for which specific strategies should be addressed."

Commenting on the two studies, Dr Fiona Blackhall, medical oncologist and senior lecturer at The Christie NHS Foundation Trust, and

Manchester University, Manchester, United Kingdom, says the results reinforce that diagnosis of the molecular subtype of lung cancer is central to identification of more effective treatments.

"Studies of targeted approaches in molecularly defined subsets of non-small cell lung cancer are consistently yielding better response rates and survivals than historical studies conducted in non molecularly selected populations," Blackhall says.

"The principles of precision medicine are proven for non-small cell lung cancer, and now efforts must intensify to ensure equitable access to molecular diagnostics for patients with this disease."

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