

Targeting MET and EGFR in NSCLC—what can we learn from the recently reported phase III trial of onartuzumab in combination with erlotinib in advanced non-small cell lung cancer?

Michail Charakidis, Michael Boyer

Chris O'Brien Lifehouse, Department of Medical Oncology, Camperdown, NSW 2050, Australia

Correspondence to: Michael Boyer, AM, MBBS, PhD, FRACP. Chris O'Brien Lifehouse, Department of Medical Oncology, Camperdown, NSW 2050, Australia. Email: Michael.Boyer@lh.org.au.

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The epidermal growth factor (EGFR) is overexpressed in non-small cell lung cancer (NSCLC), and treatment with erlotinib as monotherapy in patients previously treated with chemotherapy is associated with improved overall survival (OS) (1). However, resistance to tyrosine kinase inhibitors targeting the EGFR is observed in the majority of patients and may be associated with the overexpression and/or amplification of the tyrosine kinase receptor MET (2). Increased MET expression in NSCLC has also been associated with worse prognosis and is co-expressed in 70% of EGFR mutant tumours (2). This data generated a valid rationale for combining MET and EGFR targeted agents in the management of advanced NSCLC.

Onartuzumab is a humanised one-armed monoclonal antibody against the extracellular domain of the MET tyrosine kinase receptor. In a phase II trial of onartuzumab plus erlotinib *vs.* erlotinib alone in patients with previously treated advanced NSCLC, patients with MET positive immunohistochemistry (IHC) treated with onartuzumab had a prolonged PFS (median, 1.5 *vs.* 2.9 months; HR, 0.53; $P=0.04$) and better OS (median, 3.8 *vs.* 12.6 months; HR, 0.37; $P=0.002$) (2).

The encouraging results from the phase II trial led the investigators to conduct a double-blind phase III trial of onartuzumab plus erlotinib *vs.* erlotinib plus placebo in previously treated stage IIIb or IV NSCLC (MET-lung) (3). Based on the subset of patients that benefited from onartuzumab in the phase II trial, the patients in this phase III trial were selected for MET 2+ or 3+ positivity, centrally tested by IHC. Other key eligibility criteria were an ECOG performance status ≤ 1 and one or two prior systemic

regimens (including platinum-based chemotherapy).

The patients were stratified according to tumor EGFR mutation status (mutant *vs.* wild type), MET expression (2+ *vs.* 3+), the number of previous treatments and histology. Between January 2012 and August 2013, there were 499 patients recruited. The enrolment to the trial was ceased early due to an interim analysis, which crossed the futility boundary. There were 249 patients in the erlotinib plus placebo arm and 250 patients in the onartuzumab plus erlotinib arm. Patient demographics were well balanced, but it is worth noting that 80% of patients had 2+ MET expression, and 20% of patients had 3+ MET expression. A total of 11% of patients had tumors with EGFR mutations in each arm.

The median OS for the onartuzumab plus erlotinib arm was 6.8 months (95% CI: 6.1-7.5), and 9.1 months for the erlotinib plus placebo arm (95% CI: 7.7-10.2), with HR 1.27 (95% CI: 0.98-1.65) and $P=0.07$. A subgroup analysis showed consistency across the groups and failed to identify a particular subset of patients that may have benefited from onartuzumab. In contrast to the phase II trial, there was no difference in survival amongst the patients with MET IHC 2+ or 3+, nor was there a difference in patients with MET FISH positive or negative tumours. It should also be noted that in EGFR mutant patients there appeared to be an advantage in favour of not receiving onartuzumab, but the numbers are too small to draw definitive conclusions.

The progression free survival was 2.6 months for the erlotinib plus placebo arm and 2.7 months for the onartuzumab plus erlotinib (HR, 0.99; 95% CI: 0.81-1.2; $P=0.92$). The MET fish/IHC and EGFR mutation status

did not have an impact in the subgroup analysis for PFS. This again contradicts the findings from the phase II trial.

The adverse events recorded are similar to those observed with EGFR tyrosine kinase inhibition. It was overall a very tolerable combination, with the most common events being diarrhoea (39%) and rash (39%). Peripheral oedema (22% *vs.* 8%) and hypoalbuminaemia (17% *vs.* 4%) were more frequent in the onartuzumab arm. Data on discontinuation of treatment due to adverse events is not available.

The reason for the differential results between the phase II and the phase III trial is not yet fully understood. There are preclinical data to suggest that gene amplification confers oncogenic driver potential to MET (4), and therefore IHC may not have been the ideal biomarker in selecting an appropriate population for the study. In another study of a MET TKI, increasing MET amplification was associated with better response to treatment (5).

Despite the negative results of this study, inhibition of the MET pathway continues to be of clinical interest, and further research should be aimed at detecting the right biomarker and singling out the correct group of patients, that may benefit from treatment directed at this target. The role of MET overexpression, amplification and gene mutations in the appropriate selection of patients is yet to be determined. Finally, there is evidence that crizotinib may be an effective agent in targeting MET (5) and perhaps small molecule tyrosine kinase inhibitors may be superior

compared to monoclonal antibodies in targeting the hepatocyte growth factor receptor.

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References

1. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123-32.
2. Spigel DR, Ervin TJ, Ramlau RA, et al. Randomized phase II trial of Onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2013;31:4105-14.
3. Spigel DR, Edelman MJ, O'Byrne K, et al. Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: Results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial. *J Clin Oncol* 2014;32:abstr 8000.
4. Kawakami H, Okamoto I, Okamoto W, et al. Targeting MET Amplification as a New Oncogenic Driver. *Cancers (Basel)* 2014;6:1540-52.
5. Camidge DR, Ou SI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC). *J Clin Oncol* 2014;32:abstr 8001.

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