Targeting Tyrosine-protein Kinase Receptor (MET) Gene Alterations in Non-small Cell Lung Cancer – The Efficacy and Safety of Tepotinib + Gefitinib in the INSIGHT Study

An Expert Interview with Y-Long Wu
Guangdong Provincial People’s Hospital, Guangzhou, China

Y-Long Wu
Professor Wu is a tenured professor at the Guangdong Provincial People’s Hospital & Guangdong Academy of Medical Sciences, China, and an honorary director of Guangdong Lung Cancer Institute. He is the past president of the Chinese Society of Clinical Oncology (CSCO), the President of the Chinese Thoracic Oncology Group (C-TONG), and the Conference President of the 2020 World Conference of Lung Cancer (IASLC). Professor Wu graduated from Sun Yat-sen University of Medical Sciences in 1982, and completed his thoracic surgery training in Germany in 1989. Although his main research interest is the multidisciplinary therapy of lung cancer, Professor Wu’s expansive research background covers many areas from basic science to bedside and evidence-based medicine in oncology. He has been a principle investigator (PI) or Co-PI in more than 90 multicentre clinical trials. Professor Wu has published more than 300 articles in peer-reviewed journals and is Editor-in-Chief of the Journal of Evidence-based Medicine, and the Deputy Editor of Lung Cancer.

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Corresponding Author: Guangdong Lung Cancer Institute, Guangdong Provincial People’s Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China. E: syylwu@live.cn

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Non-small cell lung cancer (NSCLC) remains a world-wide health issue, accounting for 85% of all lung cancers, of which there were an estimated 2.1 million new cases and 1.76 million deaths in 2018; equivalent to 11.6% of the global cancer burden. This incidence is expected to rise in the coming years as rates of smoking increase in developing countries. NSCLC remains more difficult to treat than many other cancer types, with a poor prognosis and limited response to many of the treatments developed in recent decades. Many patients present at an advanced disease state, decreasing the chance of treatment success. Effective treatments for this disease therefore remain a substantially urgent and unmet need.

Alterations in signalling resulting from mutations in the gene expressing the c-MET receptor (MET) and its expression are key factors in the pathogenesis of NSCLC and are consequently important targets for treatments. Tepotinib is a highly potent and selective investigational MET inhibitor that has provided promising results in patients with NSCLC.

Q. What is the rationale for targeting MET gene alterations in non-small cell lung cancer and why have previous studies of MET inhibitors yielded negative results?

The c-MET receptor is a membrane-spanning tyrosine kinase protein that is activated when it binds to its ligand, hepatocyte growth factor (HGF), leading to downstream signalling that stimulates cell movement, cell division, angiogenesis and other functions. This process is tightly controlled via binding of c-Cbl protein that promotes breakdown of c-MET which reduces signalling pathways and inhibits these functions. A mutation in the MET gene exon14 that is associated with certain cancer types allows skipping of a 47-amino acid section of the receptor, resulting in a lack of binding of c-Cbl, over-expression of c-MET and HGF binding, leading to loss of tight control of the pathway and its functions, including cell division and metastasis. Given its involvement in cell division control, c-MET has been a target of interest in the development of anticancer therapies.

Some c-MET inhibitors originally showed in vitro efficacy against tumour cell lines but phase III clinical trials investigating the treatment of NSCLC with such agents, including tivantinib or onartuzumab given with or without erlotinib, have all shown disappointing outcomes and failed to improve overall survival (OS). The reasons for these failures are not entirely clear but they may result from patients with inappropriate NSCLC tumour mutation types being selected. These trials used tumour type or protein overexpression as criteria for selecting suitable patients.
but these characteristics are not necessarily indicative of c-MET pathway activation and thus the treatments were ineffective in many of the recruited patients. In addition, the levels of HSF in tumour tissues may be less than those used in in vitro models, leading to an over-estimation of clinical activity.14

Q. Why is tepotinib being investigated in combination with gefitinib?

Tepotinib is an investigational, oral, highly-selective c-MET tyrosine kinase inhibitor (TKI) that targets oncogenic c-MET signalling caused by mutations in the MET gene, including MET exon 14 skipping and MET amplifications. These alterations have been identified as drivers of cancers of the breast, colon, stomach, kidney, liver, lung and thyroid. Tepotinib has shown promising anti-tumour activity in murine xenograft models of human NSCLC tumours. Gefitinib is an epidermal growth factor (EGFR) TKI to which East Asian patients with NSCLC respond very well, with an overall survival of 24–36 months. However, a large proportion of patients in this population have, or develop, resistance to this treatment. In addition, some of these patients (24%) also develop a MET amplification and may be suitable for a c-MET inhibitor treatment.15,16 In the phase II INSIGHT study, due to EGFR TKI resistance, we wanted to determine whether there is efficacy with a combination of an EGFR TKI (gefitinib [Iressa®, AstraZeneca, Cambridge, UK]) plus a c-MET inhibitor (tepotinib) in EGFR-mutant NSCLC and in the MET pathway.17 In this study, when patients with NSCLC developed resistance to first-line EGFR TKI (gefitinib) treatment they were randomised to either continue with gefitinib with tepotinib added, or to chemotherapy. It was hoped that this novel combination would maximise anti-cancer benefits in terms of OS and objective response rate (ORR) by inhibiting two pathways and thus decreasing or delaying the emergence of resistance and extending efficacy.

Q. Could you briefly describe the INSIGHT clinical trial and its findings?

The INSIGHT study is the only randomised study to compare tepotinib + gefitinib with chemotherapy in relapsed EGFR-mutant NSCLC with MET overexpression (IHC3+) or MET amplification. The study was conducted in Asia and recruited a total of 55 patients (age range: 42–82 years, median ages were 61.0 years or 58.3 years for those randomised to tepotinib + gefitinib or chemotherapy, respectively). Patients were required to have tumours with MET IHC3+ or amplification. Patients received either tepotinib 500 mg + gefitinib 250 mg once daily (n=31) or chemotherapy (n=24) consisting of pemetrexed 500 mg/m² + cisplatin 75 mg/m² or carboplatin (area under curve [AUC] 5 or 6 intravenously on day 1).18

Data for ≥18 months of follow-up show notable benefits for the combination therapy for certain patient groups. For tepotinib + gefitinib versus chemotherapy, progression-free survival (PFS) was 4.9 versus 4.4 months in the overall population; 8.3 versus 4.4 months for patients with MET IHC3+, and 16.6 versus 4.2 months for patients with MET amplification, respectively. For ORR there was a substantial benefit in favour of the tepotinib + gefitinib combination: odds ratio (OR) 1.99 (95% confidence interval [CI] 0.56, 6.87) for the overall population, OR 4.33 (95% CI 1.03, 18.33) for patients with MET IHC3+ and OR 2.67 (95% CI 0.37, 19.56) for patients with MET amplifications.19

Median OS showed a similar pattern for the tepotinib + gefitinib combination versus chemotherapy group which was 17.3 versus 18.7 months (hazard ratio [HR] 0.69) for the overall population, 37.3 versus 17.9 months (HR 0.33) for patients with MET IHC3+ and 37.3 versus 13.1 months (HR 0.09) for patients with MET amplification.20

The tepotinib + gefitinib group showed longer median treatment duration than the chemotherapy group (21.4 versus 18 weeks) and similar levels of dose reductions (16.1% versus 17.4%). For tepotinib + gefitinib, incidence of any grades of diarrhoea, peripheral oedema, alanine transaminase (ALT) increase, amylase increase, paronychia and lipase increase were higher compared with chemotherapy. However, rates of any grades of decreased appetite, nausea, anaemia, vomiting, blood creatinine increase, white blood-cell count decrease, neutrophil count decrease, platelet count decrease or neutropenia were lower than with chemotherapy. Overall, tepotinib + gefitinib combination was generally well tolerated and most adverse events were mild to moderate.21

Q. Which patients are most likely to respond to this combination?

The 18-month findings of the INSIGHT study are encouraging for the use of an EGFR TKI/c-MET inhibitor combination in certain patients with NSCLC. They indicate that PFS, ORR and OS were similar or only slightly improved for tepotinib + gefitinib compared with chemotherapy in the overall population.22 However, there were substantial increases in PFS, ORR and OS in patients with MET overexpression or MET amplification when treated with the combination compared with chemotherapy. The greatest increase in PFS and OS were seen in patients with MET amplification and the largest increase in ORR occurred in patients with MET overexpression. This is an important finding which indicates that patients having tumours with these aberrations are most likely to respond to tepotinib + gefitinib treatment. In addition, MET overexpression can be considered a suitable biomarker for screening patients who are suitable candidates for treatment with tepotinib.

Q. What will be the next step in the clinical development of tepotinib for non-small cell lung cancer?

In the near future, the positive results from the INSIGHT study may justify the tepotinib + gefitinib combination becoming the standard treatment for NSCLC in patients with EGFR TKI resistance and MET amplification. The wider use of this combination could improve PFS and OS over current chemotherapy regimens in these patients. However, establishing the optimal sequencing of this combination with other therapies will require more investigation. The tepotinib + gefitinib combination might be effective in treating tumours with less common EGFR mutations. Tepotinib may also provide greater benefits when combined with later generation EGFR TKIs than gefitinib. This approach is currently being investigated in the phase II, open-label, INSIGHT 2 study (ClinicalTrials.gov identifier: NCT03940703, planned n=90), in which patients who become resistant to first- to third-generation EGFR TKIs are treated with osimertinib (TAGRISSO®, AstraZeneca, Cambridge, UK) and tepotinib. Tepotinib in this combination and possibly in others has the exciting potential to further improve outcomes in specific types of NSCLC. □