Editorial Commentary

Telisotuzumab vedotin with erlotinib in the treatment of non-small cell lung cancer: a well MET combination?

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The hepatocyte growth factor and c-Met receptor tyrosine kinase axis plays a key role in normal biological functions including embryogenesis, cell proliferation, and tissue regeneration (1). Several malignancies, including lung cancer, exploit abnormal activation of c-Met for carcinogenesis. Early efforts to target c-Met in lung cancer were unsuccessful but that has changed recently with the development of MET tyrosine kinase inhibitors (TKI) targeting *MET* exon 14 skipping (METex14) mutation (2-4). The MET TKIs capmatinib and tepotinib are FDA-approved in the United States for patients with METex14 mutation-positive non-small cell lung cancer (NSCLC), and approved by the EMA in Europe as a second-line treatment option. Savolitinib is approved in the second-line setting in China. Apart from MET TKIs, amivantamab [a bispecific antibody targeting epidermal growth factor receptor (EGFR) and MET] and Sym015 (a mixture of two humanized monoclonal antibodies that degrade MET receptor by binding to its extracellular domain), have shown activity against METex14 positive NSCLC (5,6) (*Figure 1*). These MET TKIs and antibodies have shown activity against both de-novo and acquired *MET*-amplification in NSCLC but further studies are needed to delineate the role of these agents in treating patients with *MET*-amplified NSCLC (reviewed in Remon *et al.*, 2023) (7).

Treatment with MET TKIs currently benefits only a small proportion (4%) of patients with NSCLC that harbor METex14 mutation. However, c-Met overexpression is far more common than METex14 and *MET* amplification in patients with NSCLC at 30–70% (1). Previous efforts to target the hepatocyte growth factor (HGF) and c-Met axis using monoclonal antibodies proved to be unsuccessful (8-10). Similarly small molecule kinase inhibitors have not been effective against MET overexpressing tumors. The presence of c-Met overexpression does not indicate activation of the MET pathway and that may explain the lack of benefit. Advances in antibody design now allow targeted delivery of cytotoxic agents to the tumor cells and these antibody-drug conjugates (ADC) present a novel mechanism to target cancer cells. They target specific surface proteins expressed on cancer cells regardless of their role in cell signaling and survival.

Telisotuzumab vedotin (Teliso-V) is an ADC with a c-Met targeting humanized monoclonal antibody combined with the microtubule inhibitor monomethyl auristatin by a cleavable valine-citrulline peptide linker. The combination has approximately three molecules of monomethyl auristatin per antibody. In preclinical studies, Teliso-V is active against cancer cells overexpressing c-Met or with *MET* amplification and its activity is independent

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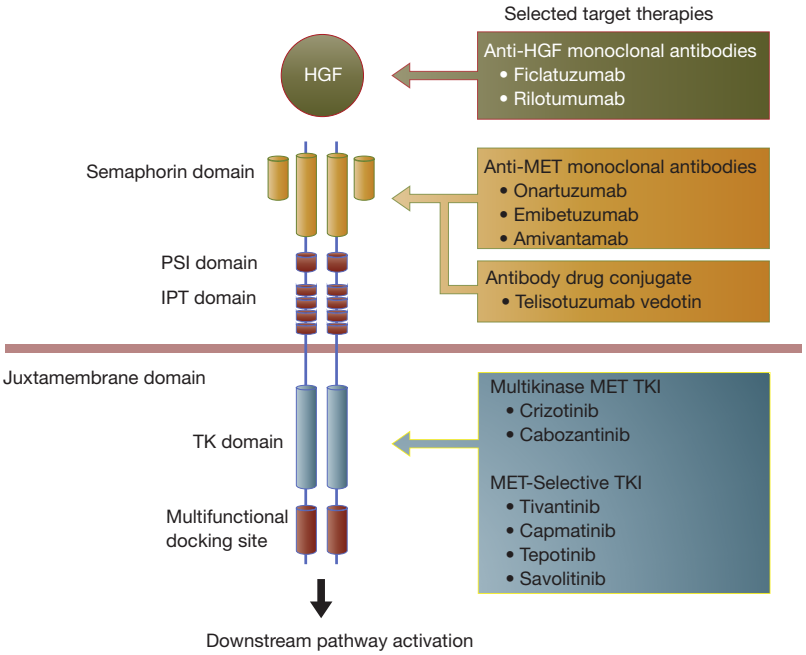

Figure 1 Selected target therapies of the c-Met receptor. HGF, hepatocyte growth factor; PSI, plexin-semaphorin-integrin; IPT, immunoglobulin-like, plexin, transcription factors; TK, tyrosine kinase; MET, MMNG HOS transforming gene; TKI, tyrosine kinase inhibitor.

of the cell's MET pathway activity (11). The cytotoxic activity of Teliso-V appears to be dependent on the cell surface expression of c-Met, and tumor cells with higher levels of c-Met expression are more sensitive to Teliso-V. A subsequent first in human trial reported favorable safety and promising activity for single agent Teliso-V in c-Met expressing NSCLC (12). However, studies in squamous NSCLC have shown limited response and severe toxicity with grade 5 pneumonitis (13,14).

In this phase Ib study by Camidge and colleagues evaluated the safety and efficacy of the combination of Teliso-V with the EGFR TKI erlotinib in patients with c-Met expressing advanced NSCLC in whom no other approved therapies were available (15). Archival tissue was required to confirm c-Met overexpression, *MET* exon 14 mutation, or *MET* amplification. c-Met-overexpression in this study was defined as histology (H)-score of 150 or greater. The study primarily focused on patients (n=31) with activating *EGFR* TK mutations (EGFRm) who had progressed on EGFR TKIs. Patients with activating EGFRm can develop resistance to EGFR TKIs due to on-target *EGFR* mutations, off-target bypass pathway signaling including *MET* amplification in 15–30% or lineage transformation (16,17). Combining Teliso-V with erlotinib can target MET pathway-activated tumors as well as tumors that express MET but do not depend on its signaling. The study enrolled 42 patients and 36 were evaluable for efficacy since six patients were not included in the efficacy analysis due to low H-score or no available tissue for H-score evaluation. Five *EGFR* wild-type patients were enrolled prior to study amendments that mandated the presence of *EGFR* mutation. The reported median progression-free survival (PFS) was 5.9 months, and the overall response rate (ORR) was 30.6%. In patients with EGFRm, the median PFS was 5.9 months and ORR of 32.1%, including one patient with complete response (CR). Sub-analysis identified that patients with *EGFR* T790M mutation (n=13) had a median PFS of 3.7 months versus 6.8 months in patients without *EGFR* T790M (n=15) mutation. Patients with high c-Met scores (H-score >225) had an ORR of 52.6% including one CR whereas there were no CRs and partial response (PR) of 12.5% in patients with low c-Met scores. Neuropathy was the most common adverse event, reported in 43% of patients and other unique adverse events included dermatitis acneiform (38%), keratitis (14%), and pulmonary embolism (14%). Adverse events were similar to prior studies of Teliso-V (18).

In this study, Teliso-V is a reasonably well-tolerated agent, which could be useful in EGFRm patients in whom there is an unmet need for effective treatments after

progression on first-line therapy. In a prior study, single-agent Teliso-V in c-Met high EGFRm population had an ORR of 11.6%, whereas in this study the combination of erlotinib with Teliso-V in the c-Met high EGFRm population demonstrated an ORR of 32.1%; suggesting that the addition of erlotinib improved treatment efficacy (14). Presence of *EGFR* T790M mutations, which are resistant to 1st and 2nd generation EGFR TKIs, had a negative impact on the therapeutic efficacy of Teliso-V combined with erlotinib (15). A phase I/Ib study combining Teliso-V with the 3rd generation EGFR TKI osimertinib in patients with c-Met-overexpression who previously failed osimertinib, reported an ORR of 58%, while in this study the ORR of patients with c-Met-overexpression previously on osimertinib was 27% (15,19). The value of Teliso-V plus erlotinib may be mainly in regions of the world where osimertinib is unavailable—otherwise, the combination of Teliso-V plus osimertinib may be the more relevant combination.

The trial thoroughly examined the molecular biology of the tumors, providing data regarding *EGFR* wild-type versus *EGFR* mutant (del 19 versus L858R) versus *EGFR* rare or unknown mutations, *EGFR* T790M mutations, c-Met positive, c-Met high, and *MET* amplification status (15). While some of these data were based on archival tissue and may have changed over the course of treatment, perhaps resulting in misrepresentation of the actual biology of the tumor at the time of clinical trial enrollment, its level of detail highlights the critical need to understand the underlying biology in order to provide precision treatment. Additionally, ctDNA and ctRNA testing could provide valuable information when repeat solid tissue biopsy is not feasible.

Targeting of c-Met exemplifies the complex biology of cancer, and agents with a variety of targeting mechanisms—from TKIs to bispecific antibodies—are part of the collection of treatment options. ADCs are a welcome addition in the effort to target c-Met overexpression. Teliso-V for c-Met-overexpressing non-squamous NSCLC preliminarily demonstrates promising activity. This is particularly relevant for patients with *EGFR* activating mutations who have developed resistance to EGFR TKIs via c-Met overexpression. Teliso-V plus osimertinib is likely to represent a more effective combination than with first-generation EGFR TKIs, although this may still be relevant in regions where third-generation EGFR TKIs are unavailable. Biomarker identification is critical to the success of these therapies. The role of this new treatment combination in clinical practice needs additional study.

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