Editorial Commentary

Simultaneous targeting of MET overexpression in *EGFR* mutation-positive non-small cell lung cancer can increase the benefit of EGFR-TKI therapy?

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The hepatocyte growth factor receptor (MET) is a receptor tyrosine kinase that is activated by binding of its ligand, hepatocyte growth factor (HGF), and which triggers signaling via the RAS-MEK-ERK, PI3K-AKT, Wnt-β-catenin, and STAT pathways (1). The extracellular region of MET contains semaphorin, cysteine-rich, and immunoglobulin domains, and the intracellular region comprises a juxtamembrane domain, the tyrosine kinase catalytic domain, and a carboxyl-terminal docking site (1). *MET* is a proto-oncogene, and dysregulation of MET signaling in lung cancer occurs through a variety of mechanisms, including gene mutation, amplification, and rearrangement as well as protein overexpression (1). *MET* amplification (*MET*amp) is thought to increase MET signaling as a result of the associated protein overexpression and constitutive kinase activation. De novo *MET*amp has been detected in ~1% to 5% of lung adenocarcinomas and ~1% of squamous cell lung cancers (1-3). Individuals with non–small cell lung cancer (NSCLC) positive for activating mutations of the epidermal growth factor receptor gene (*EGFR*) receive clinical benefit from treatment with EGFR tyrosine kinase inhibitors (TKIs) (4). However, such patients eventually develop resistance to these drugs, with the mechanism of acquired resistance being the development of a secondary T790M mutation of *EGFR* in ~60% of cases (4). *MET*amp has also been identified as a mechanism of acquired resistance to first-, second-, and third-generation EGFR-TKIs in patients with *EGFR*-mutated NSCLC (4). Conversely, preclinical studies have shown that *MET*-amplified lung cancer cells exposed to MET inhibitors for a prolonged period develop resistance to these agents through up-regulation of the EGFR signaling pathway (5). Given this background, Scagliotti and colleagues hypothesized that the addition of a MET inhibitor to an EGFR-TKI might prolong progression-free survival (PFS) in *EGFR*-mutated NSCLC by delaying treatment-emergent EGFR-TKI resistance due to MET signaling (6).

These researchers thus designed a randomized, controlled phase 2 study to evaluate the potential benefit of combination treatment with the MET inhibitor emibetuzumab and the first-generation EGFR-TKI erlotinib in chemotherapy-naïve patients with *EGFR* mutation–positive NSCLC. No significant difference in median PFS was detected between patients receiving both drugs and those receiving erlotinib alone in the intention-to-treat population, and the study did not meet its primary end point. However, exploratory analysis based on MET expression in tumor cells revealed that patients with a high level of MET expression (MET immunohistochemistry score of 3+ in at least 90% of tumor cells) might receive a clinically meaningful PFS benefit from the addition of emibetuzumab to erlotinib (median PFS of 20.7 versus 5.4 months). Given that an analysis of baseline characteristics in this

patient subpopulation did not show any imbalance between treatment arms with regard to covariates known to be of prognostic relevance in *EGFR*-mutant NSCLC patients, and that the MET-high patients showed a substantially shorter median PFS during erlotinib treatment compared with the corresponding MET-low patients, the findings of this study indeed suggest that there is potential benefit of adding emibetuzumab to erlotinib for *EGFR* mutation–positive NSCLC with a high level of MET expression. However, the results must be carefully interpreted according to the level of MET expression. Exploratory post-hoc analysis showed that the PFS improvement was relevant in only 12 of 71 patients (17%) with the highest MET expression level (MET score of 3+ in ≥90% of tumor cells). It will be necessary to confirm that staining intensity and the cutoff value are reproducible and can be standardized.

MET status in clinical trials has been defined mainly by three tests: immunohistochemistry (IHC) for detection of MET protein overexpression, fluorescence in situ hybridization (FISH) for detection of *MET* copy number alterations (CNAs) including *MET*amp, and next-generation sequencing (NGS) analysis of *MET* mutations including exon-14 (*MET*ex14) alterations. The frequency of MET protein overexpression in NSCLC is variable, ranging from 5% to 75% (7), and the finding by Tsuta *et al.* that ~60% of their patients had a MET IHC score of ≥2+ in ≥60% of tumor cells is compatible with previous reports. MET IHC has led to conflicting results regarding the role of MET as a predictive biomarker in several previous trials, given that MET protein overexpression does not always reflect increased MET receptor activation (8). In addition, the frequency of dual positivity for MET overexpression and *MET* CNA in NSCLC specimens was found to be only ~30% (8). Indeed, MET IHC appears to be an inefficient screen for *MET*amp or for *MET*ex14 alterations (9).

Although FISH analysis has been performed to investigate *MET* CNA in NSCLC, there is no consensus on the definition of *MET* CNA (3,10). The definition has thus been based on the number of *MET* signals per cell [*MET* gene copy number (GCN), Cappuzzo scoring system] or on the ratio of the copy number for *MET* to that of chromosome 7 (*MET*/CEP7 ratio) (3). *MET*amp is defined by *MET* GCN or the *MET*/CEP7 ratio. About 20% of NSCLC patients with *MET*ex14 alterations were found to be positive for concurrent high-level *MET*amp (*MET*/CEP7 ratio of ≥3) in surgically resected tumor specimens, and these genomic alterations were associated with a poorer prognosis (10,11). Patients with lung adenocarcinoma positive for high-level *MET*amp (*MET*/CEP7 ratio of ≥5) were found not to harbor concurrent driver mutations in known oncogenes (*EGFR*, *KRAS*, *ALK*, *ERBB2*, *BRAF*, *NRAS*, *ROS1*, or *RET*) (12). A high *MET* CNA represents the best case for a true *MET* copy number gain-dependent MET-driven state.

MET IHC depends on the pathologist performing the analysis and is not readily standardized. The MET expression cutoffs based on increments of 10% of positive tumor cells adopted in the study by Scagliotti and colleagues are thus likely not to be highly reproducible. In a phase Ib/II study of combined treatment with the MET inhibitor capmatinib and the first-generation EGFR-TKI gefitinib after failure of EGFR-TKI monotherapy in patients with *EGFR*-mutated and MET-dysregulated NSCLC, *MET* GCN was selected as a biomarker because the response correlated better with *MET* GCN (with a cutoff of ≥6) than with the MET IHC score (13).

The promising data of the INSIGHT (14,15) and TATTON (16) studies is expected to spur the further pursuit of treatment with a MET inhibitor in combination with an EGFR-TKI in patients with *EGFR*-mutated advanced NSCLC positive for *MET*amp after the development of EGFR-TKI resistance. The third-generation EGFR-TKI osimertinib has recently become established as a new standard of care in the first-line setting for patients with NSCLC harboring *EGFR* mutations, on the basis of a pivotal phase III trial (FLAURA trial) showing that osimertinib monotherapy conferred a significantly longer PFS compared with the first-generation EGFR-TKIs gefitinib or erlotinib (17). *MET*amp was the most common mechanism underlying acquired resistance to first-line osimertinib, being detected in ~15% of patients by NGS of circulating DNA (4,18). Given this background, several clinical trials (including SAVANNAH and ORCHARD) designed to assess the combination of a MET inhibitor and osimertinib after the development of *MET*amp-mediated resistance to osimertinib are underway. There are currently no approved targeted therapies for NSCLC positive for *MET*amp (*Table 1*).

In contrast to treatment for *MET*amp, molecularly targeted therapy for lung adenocarcinoma harboring a *MET*ex14 skipping mutation has been introduced into clinical practice. *MET*ex14 alterations were initially identified in SCLC and NSCLC in 2003 and 2005, respectively (19). *MET*ex14 encodes the juxtamembrane domain and tyrosine-1003 residue that serves as the binding site for CBL, an E3 ubiquitin ligase that controls

Table 1 Recent and ongoing clinical trials of MET-targeting agents in combination with EGFR-TKIs in advanced NSCLC

Trials	Phase	EGFR status	Setting	MET criteria	Treatments	Efficacy	Trial number
Current study	II	Mutated	First line	No restriction MET expression was evaluated at baseline (MET positive: ≥60% of tumor cells with IHC 2+ or 3+)	Emibetuzumab + erlotinib *vs.* Placebo + erlotinib	mOS 34.3 *vs.* 25.4 M mPFS 9.3 *vs.* 9.5 M ORR 84.5% *vs.* 65.7% MET-high positive (≥90% of tumor cells with IHC 3+): mPFS 20.7 *vs.* 5.4 M	NCT01897480
(13)	Ib/II	Mutated T790M negative	Acquired resistance to EGFR TKIs	MET amplification (FISH: MET GCN ≥5 and/or MET/CEP7 ratio ≥2.0) or MET over-expression (≥50% of tumor cells with IHC 2+ or 3+) on tumor tissue collected after the most recent disease progression	Capmatinib + gefitinib	ORR across phase Ib/II 27%. The best observed ORR was 47% in patients (n=36) with MET GCN ≥6 tumors PFS: MET GCN <4: 3.9 M; 4≤ MET GCN <6: 5.4 M; MET GCN ≥6: 5.5 M	NCT01610336
INSIGHT (14,15)	Ib/II	Mutated T790M negative	Acquired resistance to EGFR TKIs	MET amplification (FISH: MET GCN ≥5 and/or MET/CEP7 ratio ≥2.0) or MET over-expression (≥50% of tumor cells with IHC 2+ or 3+) on tumor tissue collected after the most recent disease progression	Tepotinib + gefitinib *vs.* Platinum + pemetrexed	MET amplification or MET over-expression: mPFS 4.9 *vs.* 4.4 M; ORR 45.2% *vs.* 33.3% MET amplification: mOS 37.3 *vs.* 13.1 M; mPFS 21.2 *vs.* 4.2 M; ORR 66.7% *vs.* 42.9% MET IHC 3+: mPFS 8.3 *vs.* 4.4 M; ORR 68.4% *vs.* 33.3%	NCT01982955
INSIGHT2	II	Mutated Regardless of T790M status	Acquired resistance to EGFR TKIs	MET amplification by liquid biopsy after the most recent disease progression	Tepotinib + osimertinib	Recruiting	NCT03940703
TATTON (16)	Ib	Mutated	Acquired resistance to EGFR TKIs	MET positive [NGS, FISH (GCN ≥5 or MET/CEP7 ratio ≥2), or IHC (+3 in ≥50% of tumor cells)] on tumor tissue collected after the most recent disease progression	Savolitinib + osimertinib	Cohort B [previously received 3rd gen EGFR-TKI, no previous 3rd gen EGFR-TKI (T790M + or –)]: ORR 48%, mPFS 7.6 M Cohort D (no previous 3rd gen EGFR-TKI T790M–): ORR 64%, mPFS 9.1 M	NCT02143466
SAVANNAH	II	Mutated	Acquired resistance to osimertinib	MET amplification/high expression as determined by FISH, IHC or NGS testing on tumor tissue collected following progression on prior osimertinib treatment	Savolitinib + osimertinib	Recruiting	NCT03778229
ORCHARD	II	Mutated	Acquired resistance to osimertinib	MET amplification on tumor tissue collected following progression on prior osimertinib treatment	Savolitinib + osimertinib	Recruiting	NCT03944772

mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; M, months.

Table 2 Recent and ongoing clinical trials of MET-targeting agents in advanced NSCLC

Trials	Phase	EGFR status	Setting	MET criteria	Treatments	Efficacy	Trial number
PROFILE1001 (22,23)	I	No restriction	Any line	MET exon 14 skipping alteration or MET amplification (MET/CEP7 ratio ≥1.8)	Crizotinib	MET exon 14 skipping mutation: mPFS 7.3 M; ORR 32% MET amplification: 1.8≤ MET/CEP7 ratio ≤2.2, ORR 33.3%; 2.2< MET/CEP7 ratio <5, ORR 14.3%; 5≤ MET/CEP7 ratio, ORR 40.0%	NCT00585195
GEOMETRY mono-1 (21)	II	Wild type	Any line	MET exon 14 skipping alteration	Capmatinib	2/3 line setting: ORR 39.1%, mDOR 9.72 M; mPFS 5.42 M 1 line setting: ORR 71.4%, mDOR 8.41 M; mPFS 9.13 M	NCT02414139
VISION (24)	II	No restriction	Any line	MET exon 14 skipping alteration	Tepotinib	MET exon 14 skipping mutation Liquid biopsy (+): ORR 51.4%, mDOR 9.8 M Tissue biopsy (+): ORR 41.5%, mDOR 12.4 M	NCT02864992

mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; M, months; mDOR, median duration of response.

MET turnover. Ubiquitination of MET thus results in its internalization and degradation and thereby attenuates its promotion of cell survival and proliferation. *MET*ex14 mutations that disrupt splice sites flanking the exon result in aberrant splicing and exon skipping. The resulting mutant protein is less susceptible to ubiquitination and consequent degradation, resulting in sustained MET activation and oncogenesis (1,2). *MET*ex14 alterations have been detected in 4.3% of lung adenocarcinomas and in 3.0% of squamous cell lung cancers (2). Lung adenocarcinomas harboring *MET*ex14 alterations manifest a substantial clinical response to MET inhibition (2,20). These mutations thus join those in *EGFR* and *ALK* as targetable driver alterations that occur in a not insignificant proportion of lung cancer patients (8). Capmatinib was approved by the U.S. Food and Drug Administration in May 2020 for the treatment of advanced NSCLC positive for *MET*ex14 skipping mutations on the basis of the GEOMETRY mono-1 phase II trial (21) (*Table 2*). The MET inhibitor tepotinib was similarly approved in Japan in March 2020 on the basis of the results of the VISION phase II trial (24).

There are several limitations to the study of Scagliotti *et al.* First, osimertinib has supplanted gefitinib and erlotinib for first-line treatment of patients with NSCLC harboring *EGFR* mutations (14). However, the same strategy may be applicable to patients treated with osimertinib. Although there are no data with regard to how the MET pathway might be affected by osimertinib treatment, the concept of adding emibetuzumab to osimertinib in the same setting thus warrants further investigation. A second limitation of the study relates to MET biomarker selection. Accurate biomarker selection is necessary to identify patients who are expected to benefit from emibetuzumab. Although MET IHC was selected as the biomarker in this trial, this method is more difficult to standardize with clear criteria than is FISH analysis of *MET* CNA including *MET*amp. It might actually be necessary to combine several test methods for determination of MET status so as not to overlook patients with MET dysregulation. In the TATTON trial, three test methods—IHC, FISH, and NGS—were adopted to detect MET dysregulation, and the results of the three tests did not overlap completely (16). MET IHC alone thus cannot be considered a reliable biomarker for prediction of emibetuzumab efficacy.

In conclusion, the study by Scagliotti and colleagues showed that the combination of emibetuzumab and erlotinib provided a clinically meaningful benefit in first-line treatment of the subgroup of *EGFR*-mutated NSCLC patients whose tumors express MET at a high level. The translation of this finding to actual clinical practice will require establishment of an optimal predictive biomarker for MET-targeted therapy.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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