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 (METamp) is thought to increase MET signaling as a result of the associated protein overexpression and constitutive kinase activation. De novo METamp 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). METamp 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
MET ex14 alterations were initially mutated and MET-dysregulated NSCLC, 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 ≥2+ 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 ≥5) 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 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...
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<tr>
<th>Trials</th>
<th>Phase</th>
<th>EGFR status</th>
<th>Setting</th>
<th>MET criteria</th>
<th>Treatments</th>
<th>Efficacy</th>
<th>Trial number</th>
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<tr>
<td>Current study</td>
<td>II</td>
<td>Mutated</td>
<td>First line</td>
<td>No restriction&lt;br&gt;MET expression was evaluated at baseline (MET positive: ≥60% of tumor cells with IHC 2+ or 3+)</td>
<td>Eributuzumab + erlotinib vs. Placebo + erlotinib</td>
<td>mOS 34.3 vs. 25.4 M&lt;br&gt;mPFS 9.3 vs. 9.5 M&lt;br&gt;ORR 84.5% vs. 65.7%&lt;br&gt;MET-high positive (≥90% of tumor cells with IHC 3+): mPFS 20.7 vs. 5.4 M</td>
<td>NCT01897480</td>
</tr>
<tr>
<td>(13)</td>
<td>Ib/I</td>
<td>Mutated</td>
<td>Acquired resistance to EGFR TKIs</td>
<td>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</td>
<td>Capmatinib + gefitinib</td>
<td>ORR across phase Ib/I 27%. The best observed ORR was 47% in patients (n=36) with MET GCN ≥6 tumors&lt;br&gt;PFS: MET GCN &lt;4: 3.9 M; 4≤ MET GCN &lt;6: 5.4 M; MET GCN ≥6: 5.5 M</td>
<td>NCT01610336</td>
</tr>
<tr>
<td>INSIGHT</td>
<td>Ib/I</td>
<td>Mutated</td>
<td>Acquired resistance to EGFR TKIs</td>
<td>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</td>
<td>Tepotinib + gefitinib vs. Platinum + pemetrexed</td>
<td>MET amplification or MET over-expression:&lt;br&gt;mPFS 4.9 vs. 4.4 M; ORR 45.2% vs. 33.3%&lt;br&gt;MET amplification: mOS 37.3 vs. 13.1 M; mPFS 21.2 vs. 4.2 M; ORR 66.7% vs. 42.9%&lt;br&gt;MET IHC 3+: mPFS 8.3 vs. 4.4 M; ORR 68.4% vs. 33.3%</td>
<td>NCT01982955</td>
</tr>
<tr>
<td>INSIGHT2</td>
<td>II</td>
<td>Mutated</td>
<td>Acquired resistance to EGFR TKIs</td>
<td>MET amplification by liquid biopsy after the most recent disease progression</td>
<td>Tepotinib + osimertinib</td>
<td>Recruiting</td>
<td>NCT03940703</td>
</tr>
<tr>
<td>TATTON (16)</td>
<td>Ib</td>
<td>Mutated</td>
<td>Acquired resistance to EGFR TKIs</td>
<td>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</td>
<td>Savolitinib + osimertinib</td>
<td>Cohort B [previously received 3rd gen EGFR-TKI, no previous 3rd gen EGFR-TKI (T790M+ or −)]: ORR 48%, mPFS 7.6 M&lt;br&gt;Cohort D (no previous 3rd gen EGFR-TKI T790M−): ORR 64%, mPFS 9.1 M</td>
<td>NCT02143466</td>
</tr>
<tr>
<td>SAVERNAH</td>
<td>II</td>
<td>Mutated</td>
<td>Acquired resistance to osimertinib</td>
<td>MET amplification/high expression as determined by FISH, IHC or NGS testing on tumor tissue collected following progression on prior osimertinib treatment</td>
<td>Savolitinib + osimertinib</td>
<td>Recruiting</td>
<td>NCT03778229</td>
</tr>
<tr>
<td>ORCHARD</td>
<td>II</td>
<td>Mutated</td>
<td>Acquired resistance to osimertinib</td>
<td>MET amplification on tumor tissue collected following progression on prior osimertinib treatment</td>
<td>Savolitinib + osimertinib</td>
<td>Recruiting</td>
<td>NCT03944772</td>
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mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; M, months.
MET turnover. Ubiquitination of MET thus results in its internalization and degradation and thereby attenuates its promotion of cell survival and proliferation. METex14 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). METex14 alterations have been detected in 4.3% of lung adenocarcinomas and in 3.0% of squamous cell lung cancers (2). Lung adenocarcinomas harboring METex14 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 METex14 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).

<table>
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</tr>
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<tbody>
<tr>
<td>PROFILE1001</td>
<td>I</td>
<td>No restriction</td>
<td>Any line</td>
<td>MET exon 14 skipping alteration or MET amplification (MET/CEP7 ratio ≥1.8)</td>
<td>Crizotinib</td>
<td>MET exon 14 skipping mutation: mPFS 7.3 M; ORR 32%</td>
<td>NCT00585195</td>
</tr>
<tr>
<td>GEOMETRY mono-1</td>
<td>II</td>
<td>Wild type</td>
<td>Any line</td>
<td>MET exon 14 skipping alteration</td>
<td>Capmatinib</td>
<td>2/3 line setting: ORR 39.1%, mDOR 9.72 M; mPFS 5.42 M</td>
<td>NCT02414139</td>
</tr>
<tr>
<td>VISION</td>
<td>II</td>
<td>No restriction</td>
<td>Any line</td>
<td>MET exon 14 skipping alteration</td>
<td>Tepotinib</td>
<td>Liquid biopsy (+): ORR 51.4%, mDOR 9.8 M</td>
<td>NCT02864992</td>
</tr>
</tbody>
</table>

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

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

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

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-20-707). MT reports honoraria from Boehringer Ingelheim, Chugai Pharmaceutical, AstraZenec,a Ono Pharmaceutical, and Novartis during the conduct of the study. MT serves as an unpaid editorial board member of Translational Lung Cancer Research from August 2019 to August 2021. KN reports grants and personal fees from AstraZeneca K.K., grants and personal fees from Astellas Pharma Inc., grants and personal fees from MSD K.K., grants, personal fees and other from Ono Pharmaceutical Co., Ltd., grants and personal fees from Nippon Boehringer Ingelheim Co., Ltd., grants and personal fees from Novartis Pharma K.K., grants, personal fees and other from Pfizer Japan Inc., grants and personal fees from Bristol Myers Squibb Company, grants, personal fees and other from Eli Lilly Japan K.K., grants and personal fees from Chugai Pharmaceutical Co., Ltd., grants and personal fees from Daiichi Sankyo Co., Ltd., grants and personal fees from Merck Serono Co., Ltd./Merck Biopharma Co., Ltd., during the conduct of the study; personal fees from Clinical Trial Co., Ltd., personal fees from MEDICUS SHUPPAN, Publishers Co., Ltd., personal fees from Care Net, Inc., personal fees from Reno. Medical K.K., personal fees and other from KYORIN Pharmaceutical Co., Ltd., personal fees from Medical Review Co., Ltd., personal fees from Roche Diagnostics K.K., personal fees from Bayer Yakuhin, Ltd., personal fees from Medical Mobile Communications co., Ltd., personal fees from 3H Clinical Trial Inc., personal fees from Nichi-Iko Pharmaceutical Co., Ltd., grants, personal fees and other from Takeda Pharmaceutical Co., Ltd., grants and personal fees from Taiho Pharmaceutical Co., Ltd., grants and personal fees from SymBio Pharmaceuticals Limited., personal fees from NANZANDO Co., Ltd., personal fees from YODOSHA CO., LTD., personal fees from Nikkei Business Publications, Inc., personal fees from Thermo Fisher Scientific K.K., personal fees from YOMIURI TELECASTING CORPORATION., personal fees from Nippon Kayaku Co., Ltd., grants and personal fees from AbbVie Inc, grants from inVentiv Health Japan, grants from ICON Japan K.K., grants from GRITSONE ONCOLOGY, INC, grants from PAREXEL International Corp., grants from Kissei Pharmaceutical Co., Ltd., grants from EPS Corporation., grants from Syneos Health., grants from Pfizer R&D Japan K.K., grants from A2 Healthcare Corp., grants from Quintiles Inc./IQVIA Services JAPAN K.K., grants from EP-CRSU CO., LTD., grants from Linical Co., Ltd., grants from Eisai Co., Ltd., grants from CMIC Shift Zero K.K., grants from Kyowa Hakko Kirin Co., Ltd., grants from Bayer Yakuhin, Ltd, grants from EPS International Co., Ltd., grants from Otsuka Pharmaceutical Co., Ltd., outside the submitted work. HK has no conflicts of interest to declare.

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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