

The Current Landscape for *MET*ex14 Skipping Mutations in Non–Small Cell Lung Cancer

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Authors' disclosures of conflicts of interest are found at the end of this article.

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<https://doi.org/10.6004/jadpro.2022.13.5.8>

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Abstract

Capmatinib and tepotinib received US Food and Drug Administration (FDA) approval for mesenchymal-epithelial transition (*MET*) exon 14 (*MET*ex14) skipping alteration in 2020 and 2021, respectively. Capmatinib was FDA approved in May 2020 under accelerated approval for the treatment of patients with metastatic non–small cell lung cancer (NSCLC) whose tumors have a mutation that leads to *MET*ex14 skipping. Accelerated approval was based on overall response rate and response duration to capmatinib, and it was granted orphan drug and breakthrough therapy designation. Capmatinib is a potent selective kinase inhibitor of the *MET* receptor, crosses the blood-brain barrier, and has shown low-grade adverse events. Based on phase II data, capmatinib demonstrated an overall response rate (ORR) of 41% and a median duration of response (DOR) of 9.7 months in those who previously received one or two lines of therapy. In treatment-naïve patients, capmatinib demonstrated a 68% ORR with a median DOR of 12.6 months. The FDA also granted accelerated approval to tepotinib for adult patients with metastatic NSCLC harboring *MET*ex14 skipping alteration. Accelerated approval for tepotinib was based on an ORR of 43% with a median DOR of 10.8 months in treatment-naïve patients. Among previously treated patients, the ORR was 43% with a median DOR of 11.1 months. Continued approval for capmatinib and tepotinib is contingent upon confirmatory trials. Both agents are now considered first-line therapy or a subsequent therapy option in patients with metastatic NSCLC who are positive for *MET*ex14 skipping alterations.

There are an estimated 609,360 cancer deaths projected to occur in the United States in 2022 (Siegel et al., 2022). Almost one quarter of those cancer deaths are due to lung cancer. These low survival rates reflect 57% of patients diagnosed with metastatic disease for which the 5-year survival rate is 6%, in contrast with patients who have localized stage disease, for which the 5-year survival rate is 59%. Despite the high incidence of lung cancer deaths, reductions in smoking and improvements in early detection and treatment have led to a continuous decline in cancer deaths. The incidence of non-small cell lung cancer (NSCLC) declined slower than the mortality, attributing the fast decline in mortality to the timing of approval of targeted therapy (Howlander et al., 2020). The introduction of targeted therapy and identification of oncogenic drivers has become a vital component of diagnosis and treatment. Identifying driver mutations in patients avoids first-line therapy options such as chemotherapy, thus making a substantial difference in patient care.

The mesenchymal-epithelial transition (*MET*) oncogene encodes for the hepatocyte growth receptor, which is a tyrosine kinase (Frampton et al., 2015). *MET* plays a key role in regulating development and cell growth and once stimulated, leads to mitogenesis, motility, invasion, and morphogenesis. In cancer, activation of *MET* leads to tumor proliferation, invasive growth, and angiogenesis. *MET* alterations include amplification, which occurs in 1% to 6% of patients with NSCLC, exon 14 skipping, which occurs in an estimated 3% to 4% of patients with NSCLC, and *MET* fusions, which are present in 0.13% of AACR GENIE cases, with lung adenocarcinoma being the most prevalent (Wolf et al., 2020). *MET*ex14 skipping in cancer leads to oncogenic *MET* activation; therefore, patients with tumors that have *MET* alterations can benefit from targeted therapy.

Current treatments that target *MET*ex14 skipping include capmatinib (Tabrecta), tepotinib (Tepmetko), and crizotinib (Xalkori). Crizotinib is FDA indicated for the treatment of patients with metastatic NSCLC whose tumors are *ALK* or *ROS1* positive. Crizotinib is a multikinase inhibitor with potent activity against *MET* and was assessed in 69 patients with advanced NSCLC and

*MET*ex14 alterations for antitumor activity and safety. This study published an objective response rate of 32% among 65 evaluable patients with a median duration of response (DOR) of 7.3 months. The most common treatment-related adverse events (TRAEs) that were grades 1 or 2 were edema, vision disorder, nausea, diarrhea, and vomiting. There were three reported grade 4 TRAEs, which included hypophosphatemia, lymphopenia, and pulmonary embolism. There was one patient who had treatment-related grade 5 interstitial lung disease (Drilon et al., 2020). Capmatinib and tepotinib were granted accelerated approval for the treatment of metastatic NSCLC whose tumors have a mutation that leads to *MET*ex14 skipping. The purpose of this article is to describe the therapy options for NSCLC with *MET*ex14 skipping mutations, safety, and the implications for oncology advanced practitioners.

PHARMACOLOGY AND MECHANISM OF ACTION

MET is a transmembrane receptor tyrosine kinase that is encoded by the *MET* gene and activated by hepatocyte growth factor. *MET* alterations include amplification, mutation, and fusion. Specifically, the exon 14 of the *MET* encodes the intracellular juxtamembrane (JX) domain. This domain contains the PKS phosphor-site, caspase cleavage site, and E3 ubiquitin ligase CBL (Casitas-B-lineage lymphoma) docking site, which are all responsible for controlling downregulation of the tyrosine kinase activity. Alterations that lead to *MET*ex14 include point mutations, deletions, or insertions. When this occurs, it results in the activation of the *MET*-hepatocyte growth factor pathway and thus leads to tumor cell proliferation, migration, and the prevention of apoptosis. Small-molecule *MET* TKIs are subdivided into three types (type I, type II, and type III), with type I being further divided into type Ia and type Ib (Hong et al., 2021).

Crizotinib was the first targeted therapy that showed efficacy against *MET*ex14 in NSCLC and is a type Ia multi-tyrosine kinase inhibitor (TKI) with a variety of receptor targets (Pfizer Inc., 2021). A type Ia TKI interacts with the Y1230 residue, the hinge region, and the solvent front G1163. Type Ib TKIs include capmatinib and tepotinib. These have a strong connection with the Y1230 residue

and the hinge region but lack an interaction with G1163. Capmatinib inhibits MET phosphorylation as well as the MET-mediated phosphorylation of downstream signaling proteins. Tepotinib targets MET and inhibits hepatocyte growth factor-dependent and -independent MET phosphorylation, as well as MET-dependent downstream signaling pathways (EMD Serono Inc., 2021). Unlike crizotinib, capmatinib and tepotinib have central nervous system activity.

CLINICAL TRIALS

Capmatinib was studied in the prospective, international, open-label, multi-cohort, phase II GEOMETRY mono-1 study that evaluated the safety and efficacy of capmatinib 400 mg orally twice daily in 364 patients (Wolf et al., 2019). Patients were assigned to different cohorts based on previous lines of therapy and *MET* status (*MET*ex14 skipping mutation or *MET* amplification). Patients in this study had stage IIIb or stage IV NSCLC without an activating *EGFR* mutation or *ALK* fusion and included patients with stable brain metastases. There were five cohorts in which capmatinib was given under fasting conditions and two expansion cohorts (6 and 7) in which capmatinib was given without fasting restrictions.

Patients with *MET*ex14 skipping mutation demonstrated an overall response rate (ORR) of 41% (95% confidence interval [CI] = 29–53) and a median DOR of 9.7 months (95% CI = 5.6–13.0) in those who previously received one or two lines of therapy. In treatment-naïve patients, capmatinib demonstrated a 68% (95% CI = 48–84) ORR with a median DOR of 12.6 months (95% CI = 5.6–could not be estimated). Median progression-free survival was 5.4 months (95% CI = 4.2–7.0) among previously treated patients and 12.4 months (95% CI = 8.2–could not be estimated) in those who were treatment naïve. Of the 14 patients with brain metastases at baseline and *MET*ex14 skipping mutation, 13 could be evaluated and 12 of them had intracranial disease. Seven patients had an intracranial response, including four who had a complete response and three who had received brain radiotherapy previously.

Tepotinib 500 mg orally daily was studied in the open-label phase II VISION study. This study included three biopsy groups (liquid biopsy, tis-

sue biopsy, and combined biopsy). Results are presented for the combined-biopsy group. 152 patients were treated with tepotinib and included in the safety population; 99 of these patients had at least 9 months of follow-up. Of the 99 patients, 56 of them had undergone previous treatment. Among the 99 patients, the objective response rate was 46% (95% CI = 36–57), with all responses being partial. However, the response rate according to investigator assessment was 56% (95% CI = 45–66), and two patients were found to have a complete response and 53 to have a partial response. In previously treated patients, the median DOR by independent review was 11.1 months (95% CI = 9.5–18.5), and median progression-free survival was 10.8 months (95% CI = 8.2–12.7). In treatment-naïve patients, the median DOR was 10.8 months (95% CI = 6–could not be estimated), and median progression-free survival was 8.5 months (95% CI = 6.8–11.3). Among those with brain metastases, there was a 47.8% response rate (95% CI = 26.8–69.4), with a median DOR of 9.5 months (95% CI = 6.6–could not be estimated) and a median duration of progression-free survival of 9.5 months (95% CI = 5.7–11.2; Le et al., 2022).

DOSING AND ADVERSE EVENTS

The recommended starting dose of capmatinib is 400 mg twice daily and for tepotinib is 450 mg once daily. Dose modifications and monitoring parameters are displayed in Table 1. It is recommended to avoid concomitant use of tepotinib with dual strong CYP3A inhibitors and P-glycoprotein (P-gp) inhibitors as well as strong CYP3A4 inducers. If using with a P-gp substrate, a reduction of the substrate dosage is recommended (EMD Serono Inc., 2021). Concomitant use of strong and moderate CYP3A inducers should be avoided with capmatinib. Common strong CYP3A inhibitors are azole antifungals, clarithromycin, cobicistat, and ritonavir. Common strong CYP3A inducers include carbamazepine, phenytoin, rifampin, and St. John's wort. Common P-gp inhibitors are amiodarone, carvedilol, clarithromycin, cobicistat, conivaptan, cyclosporine, diltiazem, dronedarone, itraconazole, quinidine, ritonavir, and verapamil. Like crizotinib, the most common (> 10%) reported adverse events with capmatinib were peripheral edema (52%), nausea (44%), fatigue (32%),

Table 1. Dose Modifications and Monitoring Parameters of Capmatinib and Tepotinib

	Capmatinib	Tepotinib
Starting dose	400 mg orally twice daily with or without food until disease progression or unacceptable toxicity	450 mg orally once daily with food until disease progression or unacceptable toxicity
1st reduction	300 mg orally twice daily	225 mg orally once daily
2nd reduction	200 mg orally twice daily	-
<i>Interstitial lung disease (ILD)/Pneumonitis</i>		
Any grade	Permanently discontinue.	Hold if ILD is suspected. Permanently discontinue if ILD is confirmed.
<i>Increased ALT and/or AST <u>without</u> increased total bilirubin</i>		
Grade 3	Hold until recovery to baseline. If recovered within 7 days, resume at same dose. If not, resume at reduced dose.	
Grade 4	Permanently discontinue.	Permanently discontinue.
<i>Increased ALT and/or AST <u>with</u> increased total bilirubin in absence of cholestasis or hemolysis</i>		
ALT and/or AST > 3x ULN with total bilirubin > 2x ULN	Permanently discontinue.	Permanently discontinue.
<i>Increased total bilirubin <u>without</u> concurrent increased ALT and/or AST</i>		
Grade 2	Hold until recovery to baseline bilirubin. If recovered within 7 days, resume at same dose. If not, resume at reduced dose.	-
Grade 3	Hold until recovery to baseline bilirubin. If recovery within 7 days, resume at reduced dose. If not, permanently discontinue.	
Grade 4	Permanently discontinue.	Permanently discontinue.
<i>Other adverse reactions</i>		
Grade 2	Maintain dose level. If intolerable, consider withholding until resolved, then resume at a reduced dose.	
Grade 3	Hold until resolved, then resume at a reduced dose.	
Grade 4	Permanently discontinue.	Permanently discontinue.

Note. AST = aspartate aminotransferase; ALT = alanine transaminase; ULN = upper limit of normal.

and vomiting (28%), with most events being grade 1 or 2. Grade 3 or 4 adverse events were reported in 67% patients, with the most common being peripheral edema (9%), nausea (2.7%), vomiting (2.4%), and increased blood creatinine level (0.3%; Novartis Pharmaceuticals Corporation, 2020). Death from any cause other than NSCLC occurred in 4% of patients with a variety of causes.

Adverse events were reported in 86% of patients on tepotinib, with the most common events being edema (54%), nausea (20%), and diarrhea (20%). The most common grade 3 events were peripheral edema (7%; EMD Serono Inc., 2021). Two deaths occurred during the study and were due to acute respiratory failure secondary to interstitial lung disease and severe worsening of dyspnea. A

third death occurred due to acute hepatic failure after withdrawing consent to continue participating in the study (Le et al., 2022). Among all three medications, the most common adverse effect to be seen is edema.

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

In contrast with tepotinib, the FDA also approved the FoundationOne CDx assay as a companion diagnostic for capmatinib. According to the American Society of Clinical Oncology (ASCO), for first-line treatment for patients with a *MET*ex14 skipping mutation, either standard treatment or *MET*-targeted therapy with capmatinib or tepotinib may be offered. In the second-line setting,

for patients with an *MET*ex14 mutation who previously received or were ineligible for first-line chemotherapy with or without immunotherapy (i.e., if *MET*-targeted therapy was not given in the first-line setting), capmatinib or tepotinib may be offered. Similarly, according to the National Comprehensive Cancer Network (NCCN), capmatinib or tepotinib are preferred first-line therapy agents in patients with *MET*ex14 skipping mutations discovered prior to first-line systemic therapy, and crizotinib is considered useful in certain circumstances. Additionally, if *MET*ex14 mutation is discovered during first-line systemic therapy, NCCN recommends completing systemic and maintenance therapy or interrupting and preferably following with capmatinib or tepotinib vs. crizotinib.

When treating patients with *MET*ex14 NSCLC, patients should be monitored for new or worsening pulmonary symptoms that may indicate interstitial lung disease or pneumonitis. Liver function tests should be routinely monitored for hepatotoxicity, and therapy should be withheld, dose reduced, or permanently discontinued based on severity. All three agents have an additional warning for embryo-fetal toxicity; therefore, women of child-bearing potential should be evaluated throughout treatment. Capmatinib has an additional photosensitivity warning; it is important to counsel patients to limit direct ultraviolet exposure. NCCN lists capmatinib as a moderate emetic risk, so premedications should be considered for patients. If a patient begins to experience edema, management should include support stockings, limb elevation, increased movement, and diuretics (Alexander et al., 2021). Additionally, a case report documented a previously treated patient who was subsequently started on tepotinib and within 2 weeks experienced grade 3 edema in the extremities. After a 2-week recovery and dose reduction to 250 mg, grade 3 edema developed again. The patient was then on a 250-mg every-other-day dosing schedule, but the edema continued to worsen and was consequently switched to capmatinib. The starting dose was reduced to 400 mg with no exacerbation of edema and a well-controlled tumor (Kunimasa et al., 2021). This report provides an additional option if patients begin to experience edema on one TKI agent.

CONCLUSION

With published phase II data, the FDA granted accelerated approval for capmatinib and tepotinib in patients with metastatic NSCLC whose tumors have a mutation that leads to *MET*ex14 skipping. This approval made both agents preferred first-line options for this population according to NCCN and ASCO guidelines, rendering crizotinib useful in certain circumstances. Monitoring and management of edema, pulmonary symptoms, hepatotoxicity, and fetal toxicity are important parameters to be aware of when treating patients with either agent. ●

Disclosure

The authors have no conflicts of interest to disclose.

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