Editorial Commentary

MET targeted therapy in non-small cell lung cancer patients with *MET* exon 14-skipping mutations

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Non-small-cell lung cancer (NSCLC) is a heterogeneous disease with several histological subtypes and a range of known driver molecular alterations. Over the past few decades, the treatment landscape for NSCLC has undergone significant transformation owing to the emergence of targeted therapies related to specific oncogenic drivers such as *ALK*, *BRAF*, *EGFR*, *HER2*, *KRAS*, *NTRK*, *RET*, *ROS1*, and recently *MET* exon 14-skipping mutations (*MET*ex14) (1). The occurrence of *MET*ex14 is relatively rare in NSCLC, with a frequency of 2–4% depending on the histological subtype (2,3). The frequency in patients with pulmonary pleomorphic carcinomas was reported to be 17.4%, in sarcomatoid histology 12%, followed by those with adenocarcinoma and squamous cell carcinoma, with frequencies of 2.4% and 1.3%, respectively. Additionally, patients with NSCLC and *MET*ex14 tend to be older, with only minor differences with respect to sex or smoking history (2). Mutations leading to *MET*ex14 typically result in the loss of CBL ubiquitin ligase binding sites on the MET receptor and reduced ubiquitination, allowing for sustained activation of the receptor (4). Different other MET dysregulations, such as gene amplification or fusion, mutations localized in the kinase domain, and protein overexpression, may lead to the oncogenic activation of MET-mediated signaling (1). *MET*ex14 is prone to emerge in the absence of other oncogenic alterations. However, co-existing mutations in *TP53* and *MET* amplification were identified in 56% and 13.3% of patients, respectively (5). *MET* amplification has also been recognized as a mechanism for acquired resistance to EGFR tyrosine kinase inhibitors (TKI) in patients with *EGFR*-mutated NSCLC (6,7). The main objective of this Editorial Commentary was to present and discuss long-term follow-up data for tepotinib, a selective MET inhibitor, in NSCLC patients with *MET*ex14 mutations from the VISION Phase II clinical trial.

The treatment of patients with NSCLC harboring *MET*ex14 has undergone significant changes in recent years, with the regulatory approval of several selective MET-TKIs. These compounds specifically bind to the intracellular part of the MET receptor and inhibit its kinase activity and downstream signaling pathways (8,9). Initial data were available for crizotinib, where in the PROFILE 1001 study, 18 NSCLC patients with *MET*ex14 had an objective response rate (ORR) of 44%. Based on this data, the US Food and Drug Administration (FDA) granted a breakthrough designation in 2018. More mature data published in 2020 showed though a lower ORR of 32%, median progression-free survival (PFS) of 7.3 months and a median overall survival (OS) of 20.5 months (10). The first

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Table 1 The FDA and EMA approved indication for tepotinib and capmatinib (8,9,11,12)

Drug	FDA indication/year of approval	EMA indication/year of approval
Tepotinib (Tepmetko)	Treatment of adult patients with metastatic NSCLC harboring *MET* exon 14 skipping alterations (2021)	Treatment of adult patients with advanced NSCLC harboring alterations leading to *MET* exon 14 skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based. Chemotherapy (2022)
Capmatinib (Tabrecta)	Treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to *MET* exon 14 skipping as detected by an FDA-approved test (2020)	Treatment of adult patients with advanced NSCLC harboring alterations leading to *MET* exon 14 skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based. Chemotherapy (2022)

FDA, Food and Drug Administration; EMA, European Medicines Agency; NSCLC, non-small cell lung cancer.

approval of a more promising MET-TKI came from Japan in 2020, when tepotinib was approved for the treatment of patients with unresectable, advanced, or recurrent NSCLC with *MET*ex14 (2). In 2021, a similar approval came from the FDA and the European Medicines Agency (EMA) in 2022 (8,11). Tepotinib is not the only selective MET-TKI that has regulatory approval. Capmatinib obtained approval by FDA in 2020, and subsequently by EMA in 2022 (9,12). Savolitinib is another selective MET-TKI that has been approved in China for the treatment of patients with advanced NSCLC with *MET*ex14 (13). This approval was based on the results of a phase II trial (NCT02897479) in NSCLC patients with *MET*ex14, who had progressed on or were unable to tolerate platinum-based chemotherapy. The ORR was 49.2% after a median follow-up of 17.6 months, and all responses were partial. Savolitinib showed similar ORR in first line as in later lines, 46.4% versus 40.5%, and a PFS of 6.9 months in both groups, regardless of the treatment line and histologic subtypes such as pulmonary sarcomatoid carcinoma or other histological subtypes (13). The indications approved by the FDA and EMA for tepotinib and capmatinib are listed in *Table 1*. It is noteworthy that only capmatinib has been approved with a companion diagnostic, and this is the next-generation sequencing (NGS) FoundationOne CDx assay (14).

When the FDA granted approval for tepotinib, it was based on clinical outcome data obtained from cohort A of the VISION phase 2 clinical trial (NCT02864992), a single-arm, open-label, multicenter, multi-cohort study (8,15). Adult patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC with *MET*ex14 (cohort A) or *MET* amplification (cohort B) were enrolled. The third cohort (cohort C) also included NSCLC patients with *MET*ex14, which continued enrollment after the completion of cohort A. All enrolled patients had measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1), a performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale and were negative for *EGFR* mutations or *ALK* rearrangements. Patients were also allowed up to two courses of previous treatment for advanced or metastatic disease. Prospective testing for *MET*ex14 was performed centrally from liquid biopsies using the Guardant360 NGS assay, or from tumor tissue biopsies using the Oncomine Focus NGS assay. Enrollment did not require testing using both methods. The primary endpoint of the study was ORR according to RECIST v.1.1, as assessed by an independent review, with secondary objectives including median duration of response (DOR), PFS, and OS. The safety of tepotinib was assessed according to the Common Terminology Criteria for Adverse Events (8,15).

The results from cohort A, of the VISION phase 2 clinical trial, were initially reported by Paik *et al.* in the *New England Journal of Medicine* in 2020 (15). In this cohort, 152 patients were administered tepotinib, 66 were enrolled based on liquid biopsy, 60 were enrolled based on tissue biopsy, and 26 were positive according to both types of biopsies. Of the 152 patients, 99 had at least 9 months of follow-up (efficacy population), with a median follow-up of 17.4 months. The median age of the study population was 74 years, with an equal distribution according to sex and smoking history. Approximately 90% of the patients had adenocarcinoma. In the efficacy population, the overall ORR was 46%, more specifically 48% and 50% in the liquid and tissue biopsy groups, respectively. The

Table 2 Outcome following treatment with tepotinib in the long-term follow-up VISION clinical trial for cohorts A and C in treatment-naïve and previously treated patients, respectively

Outcome (IRC)	Cohort A			Cohort C		
	Overall (N=152)	Treatment-naïve (N=69)	Pretreated (N=83)	Overall (N=161)	Treatment-naïve (N=95)	Pretreated (N=66)
ORR, % (95% CI)	46.7 (38.6–55.0)	50.7 (38.4–63.0)	43.4 (32.5–54.7)	55.9 (47.9–63.7)	62.1 (51.6–71.9)	47.0 (34.8–59.7)
DOR, months [median (95% CI)]	15.4 (9.7–33.6)	46.4 (7.2–NE)	12.4 (8.4–18.5)	20.8 (12.6–NE)	NE (13.4–NE)	12.6 (5.1–NE)
PFS, months [median (95% CI)]	10.3 (8.2–12.7)	10.3 (8.0–15.3)	10.9 (8.2–12.7)	13.8 (10.4–22.0)	16.5 (10.4–NE)	12.1 (6.9–24.9)
OS, months [median (95% CI)]	19.8 (15.2–22.9)	19.1 (9.9–25.9)	19.8 (15.0–22.3)	19.3 (14.6–26.5)	21.3 (13.7–32.7)	18.0 (14.1–25.5)

The data in *Table 2* are extracted from Mazieres *et al*. Supplemental Online Content (eTable 3 - Efficacy in Cohort C and Cohort A) (19). IRC, independent review committee; ORR, objective response rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival; CI, confidence interval; NE, not estimable.

secondary endpoint of DOR was 11.1 months in the efficacy population and 9.9 and 15.7 months in the liquid and tissue biopsy groups, respectively. The PFS was 8.5 months in the efficacy population and 8.5 and 11.0 months in the liquid and tissue biopsy groups, respectively. The OS was 17.1 months, which was estimated using immature data. In 11 patients with brain metastases, an ORR of 55% was achieved. No analyses were performed regarding the efficacy of tepotinib in treatment-naïve versus previously treated patients. Regarding safety, treatment-related adverse events of grade 3 or higher were reported in 28% of the patients, with peripheral edema being the most common event (15). Finally, co-occurrence of *MET* amplification was not found to increase the response to tepotinib in this study. This is contrary to the results of the GEOMETRY study, in which an increased response to capmatinib was observed in patients with coexisting *MET* amplification (16).

In 2021, the FDA granted accelerated approval for tepotinib, specifying in the approval letter that additional clinical data were necessary to verify its efficacy in treating NSCLC patients with *MET*ex14 (17). The FDA specifically emphasized the need for additional clinical data that could document the benefits of tepotinib in treatment-naïve and previously treated patients. Furthermore, the FDA requested clinical data to support the labeling of an *in vitro* diagnostic device to guide the use of tepotinib. According to the FDA, a companion diagnostic assay is defined as an *in vitro* diagnostic device that provides essential information for the safe and effective use of a corresponding therapeutic product (14,18). The labeling text for tepotinib indicates that no FDA-approved test is currently available for detecting *MET*ex14 in patients who might benefit from treatment with tepotinib (8). This contrasts with capmatinib, in which the labeling text clearly states that *MET*ex14 should be detected using an FDA-approved test (9). However, over the past few years, the FDA has approved several new targeted oncological drugs without a companion diagnostic, despite the use of a predictive biomarker assay for patient selection during clinical development, and tepotinib belongs to this group of drugs (18).

In a recent publication by Mazieres *et al.* in *JAMA Oncology*, long-term follow-up of the VISION phase 2 clinical trial was reported (19). When the recruitment of patients for cohort A was completed, enrollment for cohort C continued to assess the long-term efficacy and safety of tepotinib and confirm finding from Cohort A. Between August 2019 and May 2021, 161 patients were recruited for this cohort. The same descriptive efficacy analyses were conducted for cohort C as for the data from Cohort A, described in the publication by Paik *et al.* (15). Additional analyses on the treatment outcomes in treatment-naïve and previously treated patients were performed. These analyses were conducted separately for cohort A and C, as well as for the pooled data across cohorts A and C. At the time of data cutoff, the patients in cohort A (N=152) had been followed for more than 35 months, and for the patients in cohort C (N=161), the follow-up time was more than 18 months. The median follow-up period across cohorts A and C was 32.6 months. For the pooled cohort A and C efficacy population (N=313), the ORR was 51.4%, with a DOR of 18 months, PFS of 11.2 months, and OS of 19.6 months (19). Across cohorts A and C, 164 patients were treatment-naïve and 149 were previously treated. *Table 2* provides an overview of the treatment outcomes for cohorts A and C for treatment-naïve and previously treated patients, respectively.

According to the data in *Table 2*, treatment-naïve patients, and in particular those in cohort C appear to have better outcomes in terms of ORR and several of the time-dependent endpoints than pretreated patients. Among both treatment-naïve and previously treated patients, the majority had *MET*ex14 detected through tissue biopsy (N=111 and N=97, respectively), which may have influenced the results. Liquid biopsy methods are increasingly used because of their noninvasive and convenient nature. However, analysis of circulating tumor DNA from plasma samples is limited by lower sensitivity and a higher risk of false-negative test results due to the amplicon-based method (1,20). A negative test result does not necessarily rule out the presence of *MET*ex14, as patients with a lower tumor burden may not shed sufficient DNA into the blood to be detected through a liquid biopsy. Patients who have been found to test positive through a liquid biopsy may have a more unfavorable outcome, due to a suspected higher tumor burden and DNA shedding. The tendency to a less favorable prognosis in patients tested positive with liquid biopsy can be seen as lower ORR and disease control rate (DCR), as well as lower DOR, PFS and OS for the liquid biopsy group in the data presented by Mazieres *et al.* (19). Owing to the lower sensitivity of liquid biopsy assays, the FDA has included a statement in the labeling for this type of companion diagnostic assay. In the labeling text for the FoundationOne Liquid CDx assay, which is linked to the use of capmatinib, it is stated that a negative result does not rule out the presence of genomic alteration, and a reflex test should be performed to confirm the mutation status using an FDA-approved tumor tissue test (21).

In addition to the efficacy analyses for the pooled cohort A and C efficacy population, separate analyses were conducted for patients with liquid or tissue biopsies. These results demonstrated a slightly better outcome in patients with tissue biopsies, as discussed above (19). For patients with brain metastases, long-term follow-up data revealed an ORR of 56.1%, which was comparable to the original data from cohort A (11). Similar outcomes have been obtained using capmatinib and savolitinib, as these drugs are also capable of crossing the blood-brain barrier (9,13,16,22). The efficacy of tepotinib observed in the VISION study is comparable to that of other oncogene-defined NSCLC patients treated with targeted therapies (23-28). Both the ORR and DOR reported in the VISION trial are clinically meaningful and constitute a good basis for the use of targeted therapy with tepotinib in NSCLC patients with *MET*ex14, both as first and further lines. Long-term follow-up safety data showed that treatment-related adverse events of grade 3 or higher occurred in 34.8% of patients, and peripheral edema was the most frequently reported event, affecting 67.1% of patients (19).

In the VISION trial, the investigators opted to use two different NGS assays to identify patients with *MET*ex14: one employing liquid biopsies and the other utilizing tissue biopsies. Although the liquid biopsy assay exhibited reduced sensitivity, the rationale behind this choice likely stemmed from its ability to enroll more patients, as some may have been excluded due to the difficulty in obtaining a tissue biopsy. However, this decision presents challenges to the study design and complicates data interpretation as the two assays select different patient populations. Patients enrolled in the VISION trial, based on tissue biopsy results, demonstrated extended time-dependent endpoints compared to patients enrolled via liquid biopsies (19). This observation suggests variation in sensitivity between the methods used for enrollment. To enable safe and effective treatment decisions, sampling methods and assays should represent the highest possible sensitivity and specificity. Therefore, it is imperative to develop companion diagnostic that guarantee high precision, repeatability, overall robustness, and sensitivity to ensure correct clinical and therapeutic decisions for every patient. Taking the comments made by the FDA in the approval letter into account, it is regrettable that none of the assays used for patient selection have been adequately validated to be approved as a companion diagnostic for tepotinib. To address this issue, it would be prudent to employ only one assay in the VISION trial, preferably a validated NGS tissue assay (17). Following the completion of the trial, a liquid biopsy assay could be developed as part of the post-approval activities and utilize blood samples obtained from the patients in the VISION trial for the clinical validation. This approach would also allow for the documentation of the concordance between liquid and tissue biopsy assays.

Over the past decades, a significant number of targeted therapies have been developed for molecular subgroups of cancer and hematological patients. If the biological rationale for these therapies is strong, clinical trials will often be open-label and non-comparative, similar to the VISION trial. The number of patients in these molecularly defined subgroups is often low, making it challenging to conduct large-scale randomized comparative trials (29). For the selective MET inhibitors, the prevalence of *MET*ex14 in patients with NSCLC is 2–4%, which is comparable to that of other molecular aberrations such as *ROS1*, *RET*,

and *BRAF* (1). Without a randomized comparative study, it is difficult to determine the relative efficacy of targeted therapies compared to other types of therapies, and an indirect comparison is the only option left. However, data on NSCLC patients with *MET*ex14 treated with chemotherapy are limited. In one retrospective study, data were available from 20 NSCLC patients who had received different types of chemotherapy and achieved a PFS of 4.0 months and an OS of 9.5 months. Twelve of the 20 patients who received pemetrexed-based chemotherapy had an ORR of 33.3% (30). In another retrospective study, 3 of 11 patients with NSCLC treated with chemotherapy achieved a partial response (31). As these data are not head-to-head comparative, they should be interpreted with caution and can only provide a weak idea of what can be achieved with chemotherapy in NSCLC patients with *MET*ex14. Furthermore, NSCLC patients with *MET*ex14 appear to be less responsive to immunotherapy, and the reported response rates are inconsistent (32,33). According to the National Comprehensive Cancer Network (NCCN) guidelines 2024, immunotherapy is not recommended even in patients with high PD-L1 levels (34).

The efficacy and safety data from the VISION trial support the use of tepotinib as first or subsequent line of treatment, as it has recently been recommended by the NCCN (34). In regions where tepotinib or capmatinib are available, these MET-TKIs should be used because of their efficacy in terms of high ORR and median PFS (35). No head-to-head comparison has been performed with different MET inhibitors, but using the matching-adjusted indirect comparison methodology, a potential difference was identified in the efficacy endpoints with prolonged PFS and OS with tepotinib compared to capmatinib and crizotinib (36). If the MET-TKIs are not approved or available, patients may be offered standard of care or be screened to clinical studies with tepotinib or capmatinib or other MET-TKIs. No direct comparison of MET-TKIs with the current first line standard treatment is available in NSCLC-patients with *MET*ex14. However, the recently published retrospective review collected data of 1,401 NSCLC patients with *MET*ex14 showed higher ORR and longer median PFS in patients treated with MET-TKIs comparing to patients treated with chemotherapy +/– immunotherapy or immunotherapy alone (2).

With regard to the secondary endpoints of PFS and OS, the follow-up time is still relatively short, and more mature data may help specify these endpoints in the future. Furthermore, the use of different NGS assays to identify patients with *MET*ex14 in the VISION trial identified different patient populations with different disease dynamics, which may also have affected PFS and OS. Based on data from the VISION trial in previously treated patients in cohorts A and C, the efficacy of second-line treatment in terms of an ORR of 45% and a DOR of 12.6 months represents a good therapeutic option as there is no other second-line treatment with such efficacy for these patients (19).

In summary, the long-term results of the VISION trial showed that tepotinib provided clinically meaningful benefits in both treatment-naïve and pretreated NSCLC patients treated with *MET*ex14. As tepotinib is still not approved in the majority of countries as a first-line treatment, the efficacy of the second-line observed in cohorts A + C in terms of DCR of 67–80% also represents a very gainful treatment option for these patients (19). Furthermore, tepotinib crosses the blood-brain barrier, resulting in an ORR of over 50% in patients with brain metastases, and these patients have comparable clinical benefits to patients without brain metastases (19,37). Additionally, the effectiveness of tepotinib is comparable to that of other selective MET inhibitors (13,16). Lastly, it is important to mention that nearly three years after the FDA approval of tepotinib, a clinically and analytically validated *in vitro* companion diagnostic assay that supports its safe and effective use, has yet to be approved.

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