BRIEF REPORT

Brief Report: Tepotinib as a Treatment Option in *MET* Exon 14 Skipping-Positive Lung Cancers—Investigating Discordance Between ArcherMET and the Oncomine Dx Target Test

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ABSTRACT

Introduction: NSCLC is a leading cause of cancer-related mortality worldwide. Specific genetic alterations, such as *MET* exon 14 (*MET*ex14) skipping, have been identified in NSCLC, allowing targeted therapy. Tepotinib, a highly selective MET inhibitor, has displayed promise in patients with advanced NSCLC. Nevertheless, challenges arise when identifying treatment strategies for patients with discordant results regarding *MET*ex14 skipping detection between diagnostic tests.

Methods: We investigated patients with NSCLC and discordant results for *MET*ex14 skipping between the Oncomine Dx Target Test (ODxTT) and ArcherMET. Clinical response, adverse events, and the duration of tepotinib treatment were assessed, and statistical analysis was performed.

Results: Among the 19 patients deemed *MET*ex14 skipping positive by ODxTT, only 10 had concordant results with ArcherMET. The number of *MET*ex14 skipping reads detected by ODxTT was significantly lower in discordant cases. Of the 19 patients, 14 received tepotinib, and comparable response and disease control rates were observed in both concordant and discordant cases. The duration of treatment did not significantly differ between the two groups.

Conclusions: Our findings suggest that tepotinib has comparable therapeutic effects in patients with *MET*ex14 skipping-positive NSCLC irrespective of the concordance of results between ODxTT and ArcherMET. Tepotinib is a possible treatment option for patients with *MET*ex14 skipping, even in patients with discordant test results.

Keywords: Lung cancer; *MET*; Tepotinib; Oncomine; Archer

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Introduction

Lung cancer is a major cause of cancer-related death worldwide, and NSCLC is the most common subtype.[1] Molecular profiling has revealed specific genetic alterations in NSCLC, enabling the development of targeted therapies for individual molecular subtypes.[2–4]

There is growing interest in the clinical setting in identifying genetic alterations in the *MET* gene, which encodes the hepatocyte growth factor receptor (HGNC ID: 7029).[5] MET plays a crucial role in regulating cell growth, survival, and invasive properties.[6] Various mechanisms can lead to *MET* alterations in NSCLC, including exon 14 (*MET*ex14) skipping, protein overexpression, and gene amplification. Notably, *MET*ex14 skipping has been observed in approximately 3% to 4% of NSCLC cases, particularly in adenocarcinoma, squamous cell carcinoma (SCC), and sarcomatoid subtypes in older patients.[7] *MET*ex14 skipping disrupts protein degradation by the ubiquitin–proteasome pathway, leading to increased MET stability and oncogenic potential. *MET*ex14 skipping represents a promising therapeutic biomarker for patients with NSCLC, as those harboring this alteration could benefit from MET inhibitors.[8,9] Identifying *MET*ex14 skipping permits personalized treatment selection for patients with NSCLC.

Tepotinib is an oral, highly selective, and potent drug that inhibits MET kinase activity and downstream signaling.[10] The phase 2 VISION study reported an investigator-assessed response rate of 56% and a median duration of response of 11.1 months in patients with advanced lung cancer who received tepotinib.[9]

In Japan, the Oncomine Dx Target Test (ODxTT) has been used as a companion diagnostic test for patients with lung cancer.[11] ODxTT comprises DNA-based and RNA-based assays that detect genetic abnormalities such as single-nucleotide variants, insertions and deletions, and fusion genes. Currently, ODxTT is used as a companion diagnostic test for mutations including *EGFR* mutations, *BRAF* V600E, *ALK* fusion, *ROS1* fusion, and *RET* fusion. Although *MET*ex14 skipping can be assessed using ODxTT, it is not approved as a companion diagnostic test for this alteration. Instead, ArcherMET and The AmoyDx Pan Lung Cancer PCR Panel are used as companion diagnostic tests for *MET*ex14 skipping.[9,12] Therefore, when *MET*ex14 skipping is detected using ODxTT, another test is necessary to validate the findings. A previous study revealed discordant results between ODxTT and ArcherMET in some samples,[13] whereas a case report revealed the potential efficacy of tepotinib in a patient with discordant results.[14] These data pose a challenge for physicians in determining treatment strategies for patients with *MET*ex14 skipping-positive lung cancer with discordant results. To this end, we investigated whether tepotinib is effective in patients with discordant results for *MET*ex14 skipping between ODxTT and ArcherMET.

Methods

The study, which used the opt-out consent method for patient enrollment, was approved by the Institutional Review Board of the hospital's Clinical Research and Genome Research Committee, and the requirement for written informed consent was waived (approval number G2018-4). ODxTT (Thermo Fisher Scientific, Waltham, MA) was performed in the Division of Genetics and Clinical Laboratory, whereas ArcherMET (Invitae Corp., San Francisco, CA) was outsourced to a testing company. To detect DNA variants for *MET*ex14 skipping, we performed next-generation sequencing on the Ion Torrent Genexus System (Thermo Fisher Scientific) using an in-house lung cancer panel.[15] The assessment of tepotinib efficacy was based on computed tomography performed by respiratory physicians according to the Response Evaluation Criteria in Solid Tumours. The detailed methodology is described in the Supplementary Information.

Results

Patient Characteristics

In total, 296 samples from 286 patients with lung cancer were tested by ODxTT. On the basis of the results, 264 patients (92.3%) were *MET*ex14 skipping negative and 22 patients (7.7%) were *MET*ex14 skipping positive. Among the 22 *MET*ex14 skipping-positive patients, 19 patients whose samples were also submitted to ArcherMET testing were included in the study. The median patient age was 75 years (interquartile range [IQR]: 65–80 y), and the cohort included five women (26%) and 14 men (74%). The histologic subtypes were adenocarcinoma (n = 13, 68%), NSCLC (n = 3, 16%), SCC (n = 2, 11%), and sarcomatoid carcinoma (n = 1, 5%). Programmed death-ligand 1 immunohistochemistry revealed that the tumor proportion score was less than 1%, 1% to 49%, and more than or equal to 50% in four, six, and nine patients, respectively (Supplementary Table 1). Sequencing analysis yielded an average of 58,417 total mappable reads in the ODxTT RNA analysis (range: 24,513–122,704) and an average coverage uniformity of 99.2% (range: 97.4%–100%, Supplementary Table 2). The concurrent occurrence of *EGFR* exon 19 deletion (n = 1) and *PIK3CA* mutations (n = 2, including one case each of *PIK3CA* E542K and E545K) was observed (Fig. 1*A*). *BRAF* V600E, *KRAS* G12C, *HER2* mutation, *ALK* fusion, *ROS1* fusion, and *RET* fusion were not detected (Fig. 1*A*).

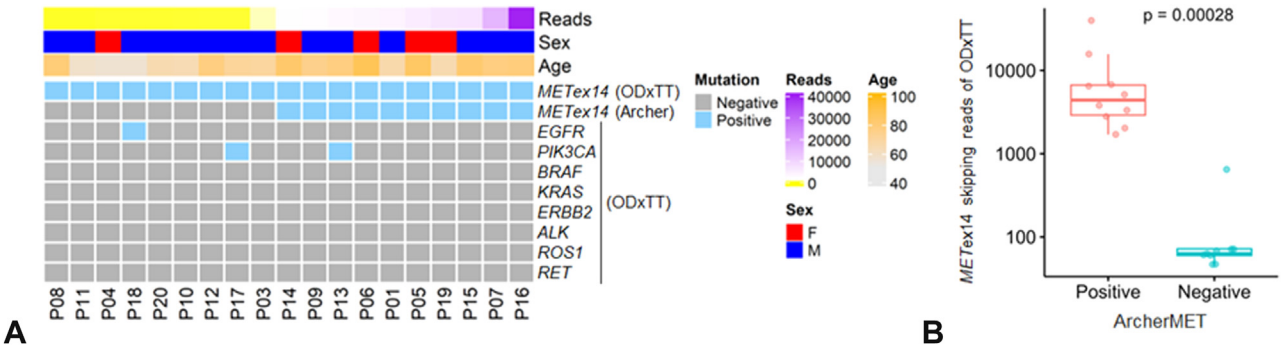

Figure 1. Genetic analysis results of the subjects. (*A*) The heatmap presents the genetic analysis results obtained using the ODxTT and ArcherMET (n = 19). The upper annotations denote the number of *MET*ex14 skipping reads determined by ODxTT, including gender and age for the corresponding patients. (*B*) Among the 19 patients considered positive by ODxTT, 10 and nine patients tested positive and negative by ArcherMET, respectively. The box plot presents the distribution of *MET*ex14 skipping reads of ODxTT sequencing analysis. Each box indicates the interquartile range (top: the third quartile; bottom: the first quartile) with a horizontal line indicating the median. Statistical analysis was performed using Wilcoxon's ranked sum test. *MET*ex14, *MET* exon 14; ODxTT, Oncomine Dx Target Test.

Discordant Results for METex14 Skipping

Of the 19 *MET*ex14 skipping-positive patients identified by ODxTT, only 10 patients (53%) had concordant results with ArcherMET (concordant group), whereas nine patients (47%) were deemed *MET*ex14 skipping negative (discordant group). DNA variants for *MET*ex14 skipping were identified in some concordant samples but not in discordant samples (Supplementary Table 1). The median tumor content in the specimens was 30% (range: 10%–80%). Consistent with a previous report,[13] the number of *MET*ex14 skipping reads detected by ODxTT was significantly lower in the discordant cases (median: 63 reads, IQR: 60–72) than in the concordant cases (median: 4448 reads, IQR: 2912–6668 reads, $p = 0.00028$, Wilcoxon's ranked sum test; Fig. 1*B*).

To confirm the results using an orthogonal method, we used the *MET*ex14-negative samples (negative control [NC], n = 13) identified by ODxTT as the reference and performed validation in both concordant (n = 10) and discordant (n = 9) samples using digital polymerase chain reaction (PCR). Compared with NC samples, both concordant and discordant cases had a significantly higher number of *MET*ex14 transcripts (concordant versus NC, $p = 1.7 \times 10^{-6}$; discordant versus NC, $p = 0.0089$, Wilcoxon's ranked sum test; Supplementary Fig. 1*A*). These results suggest the possibility of low-level *MET*ex14 skipping in some discordant cases (Supplementary Fig. 1*B*).

Therapeutic Effects of Tepotinib

Among the 19 enrolled patients, five who did not receive tepotinib treatment were excluded from the analysis of therapeutic efficacy (Supplementary Table 3) and the remaining 14 patients were analyzed (initial therapy: 500 mg; maintenance therapy: 250 or 500 mg). Among them, 10 patients received tepotinib as first-line treatment, three patients received second-line treatment, and one patient received third-line treatment. The treated patients included eight patients with concordant results for *MET*ex14 skipping and six patients with discordant results. Five patients (36%) experienced grade 3 or higher adverse events, including three and two patients with concordant and discordant results, respectively. The response rate according to physician assessment was 50% (four of eight) in the concordant group versus 33% (two of six) in the discordant group ($p > 0.6$, Fisher's exact test, Table 1). The disease control rate was 88% (seven of eight) in the concordant group, compared with 50% (three of six) in the discordant group ($p = 0.5$, Fisher's exact test, Table 1). Two cases were evaluated using non-target lesions; therefore, they were determined to have non-complete responses/non-progressive disease. Nevertheless, clinically significant improvement corresponding to stable disease was observed in these patients. Collectively, no significant difference was observed in the response to tepotinib between the concordant and discordant groups.

Duration of Treatment

The median follow-up period from the start of treatment was 10.9 months (range: 1.3–26.1 mo). Treatment continued for more than 10 months in 25% of the concordant patients (two of eight) and 50% of the discordant patients (three of six, Fig. 2). The median duration of treatment was 2.3 months (IQR: 1.2–6.6) in the concordant group versus 7.1 months (IQR: 1.5–11.3) in the discordant group ($p = 0.7$, Wilcoxon's ranked sum exact test, Table 1). Despite a low number of reads (60 reads) in ODxTT, one patient with discordant results (P04) had the longest treatment duration of 20.8 months

Table 1. Patient Characteristics

Characteristic	Concordant Cases (n = 8)	Discordant Cases (n = 6)	*p* Value
Age, median (IQR)	80 (77-84)	64 (60-69)	0.003[a]
Sex, n (%)			0.6[b]
Female	3 (38)	1 (17)	
Male	5 (62)	5 (83)	
Adverse event, n (%)	8 (100)	3 (50)	0.055[b]
Response, n (%)			0.6[b]
PR	4 (50)	2 (33)	
SD	2 (25)	0 (0)	
PD	1 (12)	3 (50)	
Non-CR/non-PD	1 (12)	1 (17)	
Response rate, n (%)			0.6[b]
CR + PR	4 (50)	2 (33)	
Disease control rate, n (%)			0.2[b]
CR + PR + SD + non-CR/non-PD	7 (88)	3 (50)	
Grade of adverse event, n (%)			0.4[b]
G1	4 (50)	0 (0)	
G2	1 (12)	1 (33)	
G3	2 (25)	2 (67)	
G5	1 (12)	0 (0)	
Duration of treatment, median (IQR)	2.3 (1.2-6.6)	7.1 (1.5-11.3)	0.7[a]

[a]Statistical analysis was performed using Wilcoxon's ranked sum test.
[b]Statistical analysis was performed using Fisher's exact test.
IQR, interquartile range; PR, partial response; SD, stable disease; PD, progressive disease; CR, complete response; G, grade.

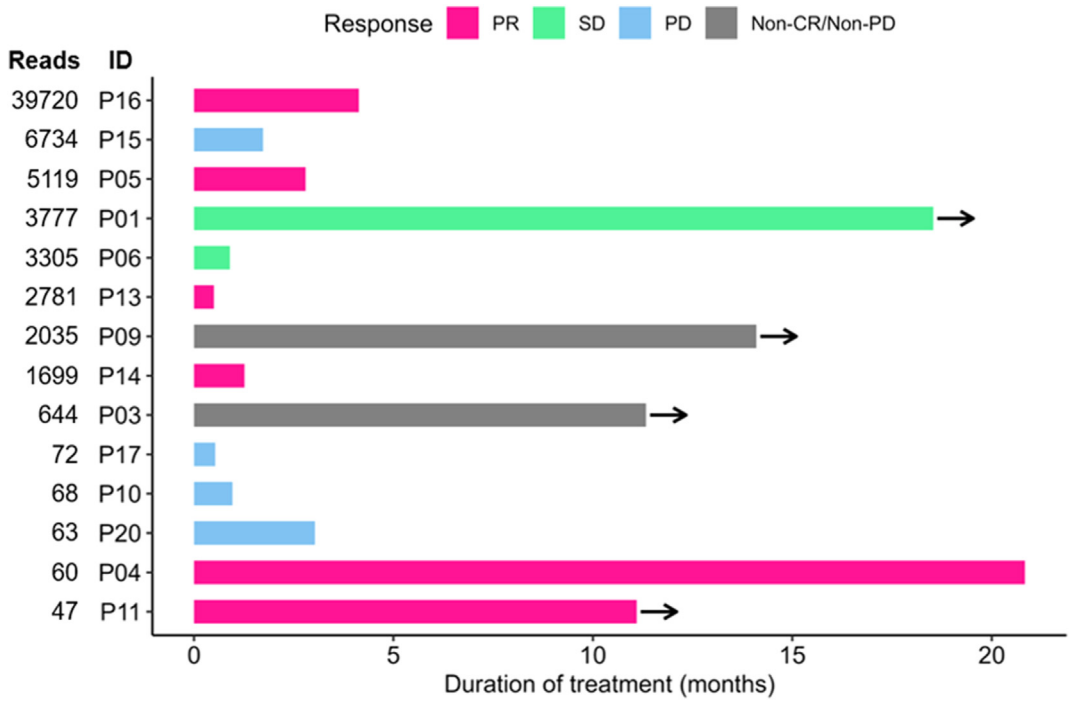

Figure 2. Clinical response of tepotinib according to *MET*ex14 skipping reads. The swimmer plot presents the duration of response and clinical outcomes among patients treated with tepotinib. The duration of treatment was measured from the start date of tepotinib treatment to the end of treatment. The arrows in the swimmer plot indicate the continuation of treatment. The numbers on the left side of the case IDs denote the number METex14 skipping read counts identified by the Oncomine Dx Target Test and listed in descending order. *MET*ex14, *MET* exon 14.

(Fig. 2). Among patients treated with tepotinib, two (P13, P17) carried concurrent *PIK3CA* mutations (Fig. 1*A*). These two patients had shorter treatment durations (Fig. 2), suggesting that the presence of activating *PIK3CA* mutations contributed to reduced treatment efficacy.[9]

Discussion

This study provides in-depth knowledge of the companion diagnostic test results and response to tepotinib therapy in patients with *MET*ex14 skipping-positive lung cancer. In current clinical practice in Japan, ODxTT is used to detect *MET*ex14 skipping, followed by confirmatory testing using the ArcherMET companion diagnostic assay. In this cohort, the prevalence of *MET*ex14 skipping determined by ODxTT was 7.7%. On the basis of genetic test results, we administered tepotinib to patients categorized into concordant and discordant groups. Our results revealed that tepotinib therapy is potentially effective regardless of the concordance of *MET*ex14 skipping test results. A previous report interpreted the results of discordant cases as false-positives in ODxTT[13]; however, the key point is that some patients with lung cancer did not receive optimal MET inhibitor treatment as a consequence.

Both ODxTT and ArcherMET analyze *MET*ex14 skipping using RNA extracted from tissue samples. In ODxTT, RNA is reverse-transcribed into cDNA, followed by targeted amplification of *MET*ex14 skipping using specific primers. This is accompanied by tagging barcodes for sample discrimination and subsequent detection through sequencing analysis after emulsion PCR. By contrast, ArcherMET uses anchored multiplex PCR chemistry with two rounds of PCR amplification using gene-specific primers, followed by detection using molecular barcodes for error correction.[16] The detection criteria for ODxTT require the presence of more than 40 *MET*ex14 skipping reads, whereas ArcherMET has a minimum detection sensitivity of at least 2% *MET*ex14 skipping reads compared with wild-type reads. It is possible that the discordance is attributable to the differences in the use of molecular barcodes and the detection criteria. Another possibility is issues regarding calibration or the detection criteria because DNA variants for *MET*ex14 skipping were not detected in discordant samples. Therefore, samples with low numbers of *MET*ex14 skipping reads require further validation.

The response rate reported in the VISION trial was 56%.[9] In our analysis of 14 patients, we observed response rates of 50% and 33% in concordant and discordant patients, respectively. The disease control rates were relatively favorable at 88% and 50% in the concordant and discordant groups, respectively. Nevertheless, the incidence of all-grade adverse events was high (100% in the concordant group and 50% in the discordant group). The rate of grade 3 or higher adverse events of 36% (37% in the concordant group and 67% in the discordant group) was higher than that (28%) reported in the VISION trial, and this difference might be associated with treatment discontinuation in our cohort.

This study had several limitations. First, this was a single-center study, and its statistical power might be inadequate because of the small number of patients from a heterogeneous population. Further accumulation of cases from other institutions is needed to obtain robust data. Second, a *MET*ex14 skipping-negative cohort treated with tepotinib was not included. Thus, the impact of tepotinib in patients with low numbers of *MET*ex14 skipping reads remains unclear.

In conclusion, our findings highlighted that approximately 50% of patients with low numbers of *MET*ex14 skipping reads detected by ODxTT responded to tepotinib. These results provide important insights into treatment optimization for patients with *MET*ex14 skipping-positive lung cancer.

CRediT Authorship Contribution Statement

Yoshihiro Miyashita: Validation, Investigation, Resources, Data Curation, Writing—Review and Editing, Project Administration.

Yosuke Hirotsu: Formal analysis, Data Curation, Writing—Original Draft, Visualization, Funding Acquisition.

Yuki Nagakubo: Validation, Investigation, Data Curation.

Hiroaki Kobayashi: Investigation, Resources.

Makoto Kawaguchi: Investigation, Resources.

Koki Hata: Investigation, Resources.

Ryota Saito: Investigation, Resources.

Yumiko Kakizaki: Investigation, Resources.

Toshiharu Tsutsui: Investigation, Resources.

Toshio Oyama: Investigation, Resources.

Masao Omata: Conceptualization, Supervision, Writing—Review & Editing.

Data Availability

The source data underlying figures and tables are available on request.

Disclosure

The authors declare no competing interests.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100679.

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