Perspective

MET-inhibitors meet *MET* mutations in lung cancer

Nagio Takigawa

Department of General Internal Medicine 4, Kawasaki Hospital, Kawasaki Medical School, Okayama, Japan

Correspondence to: Nagio Takigawa. Department of General Internal Medicine 4, Kawasaki Hospital, Kawasaki Medical School, Okayama 700-8505, Japan. Email: ntakigaw@gmail.com.

Comment on: Awad MM, Oxnard GR, Jackman DM, *et al.* MET Exon 14 Mutations in Non-Small-Cell Lung Cancer Are Associated With Advanced Age and Stage-Dependent MET Genomic Amplification and c-Met Overexpression. J Clin Oncol 2016;34:721-30.

Abstract: Mesenchymal-to-epithelial transition (*MET*) exon 14 mutation in non-small cell lung cancer (NSCLC) has been recognized. However, clinical, molecular, and pathologic features have not been well understood. Awad *et al.* described NSCLC patients with *MET* exon 14 mutations precisely in the '*Journal of Clinical Oncology* 2016;34:721-30'. Among 933 non-squamous NSCLC patients, they found 28 (3.0%) patients who represented a unique clinical and molecular subtype of NSCLC. Median age of the 28 patients was 72.5 years, 68% were women, 36% were never-smokers, 64% had stage IV, 100% were white, non-Hispanic, and 64% had adenocarcinoma and 14% had pleomorphic carcinoma. Genomic deletions and point mutations occurred in 17 and 11, respectively, occurred of the 28 patients. Although none of the 28 patients with *MET* exon 14 mutations had *KRAS*, epidermal growth factor receptor (*EGFR*), *ERBB2*, anaplastic lymphoma kinase (*ALK*), *ROS1*, or *RET* alterations, mutations of *TP53*, *CDKN2A*/B, *BRAF600E*, *PIK3CA*, *PTEN*, *RB1*, *ATM*, *BRCA2*, *NF1*, or *ARID2* were co-existed. Amplification of *MDM2* was observed in 13 (46%), and 6 (21%) and 8 (29%) had high- and low-level *MET* copy gain, respectively. To date, two MET inhibitors, onartuzumab or tivantinib, combination with erlotinib in previously treated NSCLC were investigated in phase III trials. However, neither showed prolonged overall survival (OS) compared with erlotinib alone in molecularly unselected patients. Several publications including the report of Awad *et al.* revealed that patients with *MET* exon 14 mutation were successfully treated with MET-tyrosine kinase inhibitors (TKIs) such as crizotinib. Prospective trials using MET-TKIs in *MET* exon 14 mutated NSCLC are ongoing. Concerning translational research, significance of co-existed other mutations or amplifications and mechanism of acquired resistance to MET-TKIs remain to be clarified. Finally, the therapeutic strategies against the MET-TKI resistance and intracranial metastasis in NSCLC with *MET* exon 14 mutation should be elucidated.

Keywords: Non-small cell lung cancer (NSCLC); mesenchymal-to-epithelial transition (MET); tyrosine kinase inhibitor (TKI)

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Lung cancer accounts for a leading cause of cancer mortality worldwide. Patients with non-small cell lung cancer (NSCLC) harboring activating mutations in the epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) fusion genes benefit from treatment with EGFR tyrosine kinase inhibitors (TKIs) and ALK-TKIs, respectively. Recently, NSCLC harboring *ROS1* or *RET* fusion genes were also found to be sensitive to respective TKIs. In addition, mesenchymal-to-epithelial transition (MET) protein overexpression and *MET* amplification have been shown in NSCLC irrespective of *EGFR* mutation status (1,2).

MET inhibitors including antibodies and TKIs for NSCLC have been investigated in clinical trials. Although MetMAb (onartuzumab) was most hopeful antibody, a phase III study comparing erlotinib plus onartuzumab

with erlotinib alone in MET positive NSCLC by an immunohistochemistry (IHC) assay did not show its efficacy (*J Clin Oncol* 2014;32:abstr 8000). Furthermore, onartuzumab did not confer any clinical benefit in the MET IHC-positive squamous cell NSCLC when combined paclitaxel plus platinum (3). In case of MET-TKI, the result of a phase III study comparing tivantinib (ARQ 197) plus erlotinib (n=526) with erlotinib alone (n=522) was already published (4). Forty-seven point four percent (211/445) of tumor samples had high MET expression, which was defined if intensity on IHC was >2+ in >50% of tumor cells. Eleven point four percent (54/476) had *MET* copy number >4 and only four patients had *MET* amplification with *MET* to chromosome 7 centromere (*MET*:*CEP7*) ratio >2. Although tivantinib plus erlotinib increased progression-free survival (PFS) (median PFS, 3.6 *vs*. 1.9 months; P<0.001), overall survival (OS) was similar (median OS, 8.5 *vs*. 7.8 months; P=0.81). OS might be improved in patients with MET IHC high expression (hazard ratio: 0.70; 95% CI: 0.49–1.01) (4). Thus, MET-TKI did not seem to be so beneficial for MET IHC-positive NSCLC as was EGFR-TKIs for *EGFR*-mutant NSCLC.

Under the concept that aberrant MET signaling can cause cancer, activating point mutations of *MET* were proved to occur in human renal, hepatocellular, and gastric carcinomas (1,2). *MET* mutations were also clonally selected for during the metastasis of human head and neck cancers, as their frequency increased from 2% in the primary tumors to 50% (5). In NSCLC specimen, there was an alternative splice variant with the 47-amino acid exon 14 (juxtamembrane domain) missing in-frame from the *MET* (6). The skipped transcript produces a constitutively active MET that lacks an E3 ubiquitin protein ligase (Cbl) promoting MET degradation (7,8). Exon 14 skipping in *MET* was found in 4.3%, which was more than a total (3.9%) of *ALK* (1.3%), *ROS1* (1.7%), and *RET* (0.9%) fusions in 230 lung adenocarcinoma (9). Frequencies of driver oncogene aberrations in 319 Japanese lung adenocarcinoma was 53.0% in *EGFR*, 3.8% in *ALK*, 1.9% in *RET*, 0.9% in *ROS1*, and 2.8% in skipping of *MET* exon 14, which was less than *ALK* fusion alone (3.8% *vs*. 2.8%) (10). Thus, we need to know clinical and genomic backgrounds with NSCLC harboring *MET* exon 14 mutation.

Awad *et al*. described unique clinical, molecular, and pathologic features in 28 (3.0%) patients with *MET* exon 14 mutations among 933 non-squamous NSCLC patients (7). Genomic deletions occurred in 17 (61%) of the 28 patients with *MET* exon 14 mutations, ranging in size from a 2-base pair deletion to a 193-base pair deletion, and point mutations occurred in 11 (39%). The median age at diagnosis was 72.5 years, 19 (68%) were women, 10 (36%) were never smokers, their stages I/II/III/IV were 13 (46%)/2 (2%)/4 (14%)/18 (64%), and their histologic subtypes were adenocarcinoma (64%), pleomorphic or sarcomatoid carcinoma with an adenocarcinoma component (14%), poorly differentiated NSCLC not otherwise specified (18%), and adenosquamous carcinoma (4%). Four patients with pleomorphic or sarcomatoid histology and *MET* exon 14 mutations represented 26.7% of 15 total patients with pulmonary sarcomatoid carcinoma. Liu *et al*. also reported that *MET* mutations exon 14 were identified in 8 (22%) of 36 pulmonary sarcomatoid carcinoma (11). The patients with *MET* exon 14 mutations were older than patients with *EGFR*- and *KRAS*-mutant NSCLC, were more likely than those with *KRAS* mutations to be never-smokers and more likely than those with *EGFR* mutations to have a history of tobacco use (7). A higher percentage of patients with *MET* exon 14 mutations had stage I disease compared with those with *EGFR* or *KRAS* mutations.

All 28 NSCLC harboring the *MET* exon 14 in the Awad' cohort were white, non-Hispanic (7). According to a report from China, *MET* exon 14 skipping occurred in only 0.9% of lung adenocarcinomas, which was less than half the frequency previously observed in white patients (3%) (12). *MET* exon 14 mutations occurred at a young median age, 59 years in Chinese patients with stage IV adenocarcinoma, which was similar to the median age of patients with *ALK* and *ROS1* rearrangements. Liu *et al*. suspected that ethnic difference between Western and Chinese patients could explain the variation. Another report showed that *MET* exon 14 skipping was detected in 1.3% (23/1,770) of the NSCLC and in 1.6% (21/1,305) of adenocarcinoma in Chinese patients (13). Because *MET* exon 14 mutation was reported in occurred in 2.8% of Japanese lung adenocarcinomas (10), the difference might be caused by the detection methods. Identifying the intronic mutations responsible for *MET* exon skipping using genomic DNA is difficult because of their highly diverse locations and the occurrence of passenger mutations (8). In 271 Asian NSCLC (stage I mainly) resected at Korean hospital, 1.8% had exon 14 mutation in *MET* (14). Although the ethnicity was not described, 19% (10/54) in never-smoking NSCLC patients without *EGFR*, *KRAS*, *ROS1*, *BRAF*, or *ERBB2* (15), 3% (131/4,402) (16), 3% (8/178) (17), 2.8% (205/7,140) (18), and 2.9% (2/70) (19) in lung adenocarcinoma. Thus, overall 1–4% of lung adenocarcinoma may have *MET* exon 14 mutation, which should be

Table 1 Characteristics of *MET* exon 14 mutated lung cancer patients treated with MET-tyrosine kinase inhibitors

Patient	*MET* amplification	MET IHC	MET inhibitor	Response	PFS (months)	Age (years)	Sex	Smoking, pack-year	Histology	Reference
1	–	NA	Crizotinib	PR	≥6	73	M	F, 45	Sq	(15)
2	NA	+*	Crizotinib	PR	8	76	W	F, 12	Sq	(20)
3	NA	NA	Crizotinib	PR	11	84	W	N, –	Sarcoma†	(16)
4	6 copy gain	3+	Capmatinib	PR	≥5	82	W	F, 25	La	(16)
5	2.3 (MET:CEP7)	3+	Capmatinib	PR	13	66	W	F, 45	Sq	(16)
6	6 copy gain	3+	Cabozantinib	SD	≥5.1	80	W	N, –	Ad	(17)
7	–	3+	Crizotinib	PD**	3.6	80	M	F, 20	Ad	(17)
8	NA	NA	Crizotinib	PR	≥4.6	65	M	C, 20	Ad	(17)
9	–	3+	Crizotinib	PR	≥3.1	90	W	N, –	Ad	(17)
10	8 copy gain	3+	Crizotinib	PR	8	64	W	N, –	Ad	(7)
11	9 copy gain	NA	Crizotinib	PR	≥3	74	W	F, –	Sarcoma#	(11)
12	–	3+	Crizotinib	PD	1	45	M	C, –	Ad	(12)
13	≥5 (MET:CEP7)	2+	Crizotinib	PR	≥9	76	W	N, –	Ad	(12)
14	NA	2+	Crizotinib	NE&	2	86	M	N, –	Ad	(21)
15	–	NA	Crizotinib	PR	≥7	68	W	F, 24	Ad	(22)
16	–	NA	Crizotinib	PR	≥6	71	M	F, 15	Ad	(23)
17	NA	NA	Crizotinib	PR	≥4	76	W	F, –	Sq	(24)
18	≥6 copy gain	NA	Crizotinib	PR	24	NA	NA	NA	NA	(18)
19	–	NA	Crizotinib	PR	≥7	NA	NA	NA	NA	(18)
20	≥6 copy gain	NA	Crizotinib	CR	≥7	NA	NA	NA	NA	(18)
21	–	NA	Crizotinib	SD	≥4	NA	NA	NA	NA	(18)
22	≥6 copy gain	NA	Crizotinib	PR	≥10	NA	NA	NA	NA	(18)
23	–	NA	Crizotinib	PR	NA	NA	NA	NA	NA	(18)
24	–	NA	Crizotinib	CR	≥3	NA	NA	NA	NA	(18)
25	–	NA	Crizotinib	NE‡	NA	NA	NA	NA	NA	(18)
26	–	NA	Crizotinib	PR	13	67	W	N, –	Ad	(25)

*, after treatment with crizotinib; **, PR in primary and PD in liver metastasis; &, tumor shrinkage +; ‡, pathological CR; †, histiocytic sarcoma; #, pulmonary sarcoma. NA, not available; IHC, immunohistochemistry; PR, partial response; SD, stable disease; PD, progressive disease; CR, complete response; NE, not evaluable; M, man; W, woman; F, former smoker; N, never smoker; C, current smoker; Sq, squamous cell carcinoma; Ad, adenocarcinoma; La, large cell carcinoma. MET, mesenchymal-to-epithelial transition.

investigated in all NSCLC subtypes including squamous cell, large cell, and sarcomatoid carcinomas (*Table 1*), especially without other druggable mutations.

Next-generation sequencing (NGS) also clarified genomic alterations such as *KRAS*, *EGFR*, *ERBB2*, *BRAF* and *TP53* mutations; *ALK*, *ROS1*, and *RET* fusions; *MET* and *MDM2* amplifications in the same specimens (7). Although none of the 28 patients with *MET* exon 14 mutations had *KRAS*, *EGFR*, *ERBB2*, *ALK*, *ROS1*, or *RET* alterations, mutations of *CDKN2A/B*, *BRAF600E*, *PIK3CA*, *PTEN*, *RB1*, ATM, *BRCA2*, *NF1*, or *ARID2* were co-existed with *MET* exon 14 mutations. Inactivating mutations in

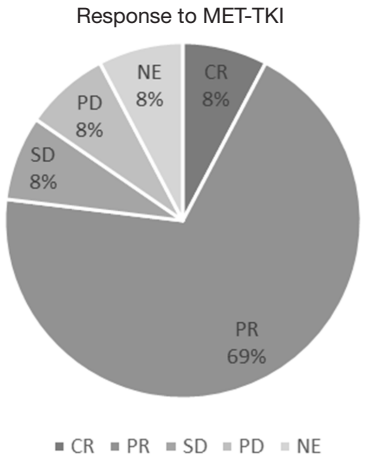

Figure 1 The response to MET-TKIs is shown. Twenty-six patients were treated with MET-TKIs. The responses, complete response (CR)/partial response (PR)/stable disease (SD)/progressive disease (PD)/not evaluable (NE), were observed in 2/18/2/2/2, respectively. Overall response rate was 77% (20/26). MET, mesenchymal-to-epithelial transition; TKI, tyrosine kinase inhibitors.

TP53 were observed in 9 patients (32%), and amplification of *MDM2*, which is a negative regulator of the p53, was observed in 13 patients (46%). When high- and low-level gene copy gains were defined as the *MET*:*CEP7* ratio ≥3 and greater than 1 and less than 3, respectively, 6 (21%) had concurrent high-level *MET* copy gain and 8 (29%) showed low-level *MET* copy gain. MET IHC in *MET* exon 14 mutated NSCLC varied from weak expression to maximum expression. Stage IV NSCLC with *MET* exon 14 mutation had a significantly higher expression than stage I to III NSCLC with *MET* exon 14 mutation and than stage IV NSCLC that lacked the mutation. Park *et al*. showed that *MET* amplification determined by fluorescent in situ hybridization (FISH) was significantly associated with MET overexpression determined by IHC, however, *MET* splice mutation was difficult to identify it by IHC or FISH results (19). The importance of concurrent gene mutations, *MDM2* or *MET* amplifications, and MET overexpression remain to be clarified.

After we have found *MET* exon 14 mutations in NSCLC with accuracy, we should elucidate whether MET-TKI was effective in such patients or not. The characteristics of MET-TKI-treated NSCLC patients with *MET* exon 14 mutation were summarized in *Table 1*, to my knowledge in the literatures. The response to MET-TKIs is shown in *Figure 1*. Twenty-six patients were treated with MET-TKIs (23 crizotinib, 2 capmatinib; 1 cabozantinib). The responses, complete response (CR)/partial response (PR)/stable disease (SD)/progressive disease (PD)/not evaluable (NE), were observed in 2/18/2/2/2, respectively. One patient, who was evaluated as PD, had PR in primary lesion and PD in liver metastasis (17). Two patients, who were judged as NE ('unknown' on Response Evaluation Criteria in Solid Tumors guideline) because tumor response evaluation was not described on the manuscripts, had actually some tumor shrinkage on radiographs. One revealed improvement of the lung mass and a decrease in adrenal metastasis after 5 weeks of crizotinib-treatment, however, drug-induced pneumonitis necessitated crizotinib discontinuation (21). The other was treated with crizotinib as neoadjuvant setting (18). Radiographic response leading to surgical approach was obtained but response was not described. After 2-month treatment with crizotinib, a complete tumor resection and mediastinal lymph node dissection revealed pathological CR. Overall response rate among the 26 patients was 77% (20/26). *MET* amplification in 21 patients was examined by NGS or FISH and 9 were amplified: CR/PR/SD/PD/NE were observed in 1/7/1/0/0, respectively; response rate was 89% (8/9) in *MET* amplified NSCLC. In addition, nine tumors examined by MET IHC in samples before MET-TKI's treatment had all MET overexpression: CR/PR/SD/PD/NE were observed in 0/6/1/1/2, respectively, and response rate was 67% (6/9).

At this time, whether NSCLC patients can benefit from MET-TKIs seems to depend on *MET* exon 14 mutation irrespective MET overexpression or *MET* amplification. Recently two cases of crizotinib-sensitive NSCLC harboring high level *MET* amplification (*MET*:*CEP7* ≥5) without co-incident *MET* exon 14 mutation, *ALK* rearrangement, or *ROS1* rearrangement were reported (26). Such patients might be investigated in prospective clinical trials using MET-TKI for *MET* amplified NSCLC such as NCT02544633 trial. Another question is whether central nervous system metastasis is sensitive to MET-TKI similarly to EGFR-TKI or ALK-TKI (27). A *MET* exon 14 mutated NSCLC patient who had intracranial progression with ongoing response in liver metastases after crizotinib therapy was successfully treated with cabozantinib, which produced rapid intracranial response (28). Prospective trials are needed in order to define the activities of various MET-TKIs for central nervous system metastasis.

Clinical trials of MET-TKIs in NSCLC with *MET* exon 14 mutations have been conducted. Current studies

are available from ClinicalTrials.gov (https://clinicaltrials.gov/ct2/search/index). In the study of 'Targeted therapy directed by genetic testing in treating patients with advanced refractory solid tumors or lymphomas (NCT02465060; NCI-MATCH)' is using crizotinib for *MET* exon 14 mutations. A study of capmatinib (INC280) in NSCLC patients with *MET* exon 14 alterations who have received prior MET inhibitor is for MET inhibitor-resistant NSCLC (NCT02750215). A phase II study of HMPL-504 (AZD6094, savolitinib) in lung sarcomatoid carcinoma is for *MET* exon 14 mutation who has failed prior systemic therapy (NCT02897479). A phase II study in lung adenocarcinoma harboring *MET* exon 14 skipping alterations is using tepotinib (MSC2156119J) (NCT02864992). A phase II study of glesatinib (MGCD265) in patients with NSCLC is for activating genetic alterations in *MET* (mutation or amplification) (NCT02544633). The studies will clarify whether a variety of MET-TKIs may be useful for NSCLC with *MET* exon 14 mutations in various situations.

One of the EGFR or ALK-TKI resistant mechanisms is composed of hepatocyte growth factor (HGF)/MET signal activation (29-31). MET activation is induced by binding to its ligand, HGF and mediates cell scatter, growth, proliferation, transformation, and morphogenesis (32,33). MET interacts with several molecules including PI3K and SRC. Thus, excess ligand or bypass signals can abolish the targeted drugs blocking the original oncogene driver and MET signaling is very important in drug resistance. In addition, alterations of *MET* itself were expected to participate in MET-TKI resistant mechanisms (34,35). Two reports of crizotinib-resistant *MET* exon 14 mutant NSCLC were described (20,25). An acquired mutation, *D1228N* in exon 19 of *MET*, was found at time of progression on crizotinib in a patient with the original exon 14 skipping *D1010H* mutation (20). Analysis of circulating tumor DNA revealed that *Y1230C* resistance mutation in MET activation loop occurred in MET *D1010H* mutant NSCLC post-progression on crizotinib (25). Most MET-TKIs are categorized as three types differing in their mode of binding site in ATP binding pocket in MET kinase. Type I (e.g., crizotinib, capmatinib, tepotinib), type II (e.g., merestinib, cabozantinib, glesatinib) and type III (e.g., MT3) are all ATP competitive inhibitors although tivantinib inhibits ATP binding to the MET kinase in a non-competitive manner (1). Thus, MET-TKI resistant mutations in ATP biding sites (34,35) were expected as T790M in EGFR, and L1196M and G1269A in ALK. MET kinase sites bound to type I MET inhibitors were important interaction sites in *Y1230* and *D1228* (1,20). Because type II MET inhibitors occupy the ATP binding pocket but also extend into a second pocket that is formed when the side chain of *D1222* instead points away from the ATP binding pocket (1), they may be useful for *MET* secondary mutant NSCLC (20,25). In preclinical tests, a newly developed MET antibody (KTN0073-IgG2), was identified as a potential therapeutic for the treatment of NSCLC with *MET* exon 14 mutation (36) although it has not been investigated in MET-TKI resistant circumstances. Drugs to overcome MET-TKI resistant NSCLC with *MET* exon 14 mutation should be developed.

In conclusion, discovery of *MET* exon 14 mutation in NSCLC similarly to *EGFR* mutation and *ALK* fusion was breakthrough because it was targetable oncogenic driver. NSCLC harboring *MET* exon 14 mutation occupy approximately 1–4% containing adenocarcinoma and other histologic subtypes. Although MET-TKIs have been useful in such a situation, we should wait for the results of ongoing clinical trials for the selected patients. Also, we should clarify the mechanisms of acquired resistance to MET-TKIs which are just beginning to be understood. The therapeutic strategies against drug resistance and intracranial metastasis in NSCLC with *MET* exon 14 mutation patients should be investigated.

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Footnote

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