Editorial

Skipping the line: bringing *MET* exon 14 skipping mutations to the forefront of targeted therapy

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Our understanding of the oncogenic role and targetability of the mesenchymal-to-epithelial transition (*MET*) oncogene in non-small cell lung cancer (NSCLC) has made remarkable strides in the last year through the discovery of recurrent, actionable *MET* exon 14 skipping alterations in NSCLC. The *MET* gene, located at chromosome 7, encodes for the hepatocyte growth factor (HGF) receptor, a tyrosine kinase receptor important for cell proliferation, apoptosis and motility/invasion and has long been believed to be a potentially relevant oncogene in certain settings. In fact, recurrent *MET* gene mutations had been reported in certain types of papillary renal cell cancer, including familial cases, and sporadic *MET* mutations have been previously reported in NSCLC, however until recently, targeting *MET* in NSCLC has been fraught with challenges (1). Several groups have now reported their observations of recurrent, actionable *MET* exon 14 alterations, generating greater interest and improved clarity in the potential incorporation of *MET* testing and *MET* targeting into current treatment algorithms in this age of personalized medicine. We will hereby review the recent important study of Awad and colleagues in the context of other recent discoveries dramatically changing the diagnostic and treatment landscape in this field.

MET targeting for NSCLC has initially been met with setbacks, highlighting the difficulty in identifying a reliable biomarker for MET inhibitor activity. The anti-MET monoclonal antibody onartuzumab was used in combination with erlotinib in a phase II trial showing a trend towards an improved PFS and OS in those patients demonstrating MET IHC positivity (2). This observation led to the METLung trial, a phase III study, focused on those patients with MET IHC 2+ or 3+ in >50% tumor cells, but was unfortunately closed prematurely due to lack of clinical benefit (3). Tivantinib, a non-ATP-competitive small molecular inhibitor of MET, was initially examined in a phase II trial comparing erlotinib and tivantinib with erlotinib and placebo in unselected advanced non-squamous NSCLC patients with initial trends showing a benefit for MET IHC positive patients leading to the MARQUEE trial. This phase III trial, unfortunately, was also closed early due to futility (4). The use of crizotinib, a dual MET/ALK inhibitor, was first reported to show some efficacy in a Phase I study presented by Camidge and colleagues at the American Society of Clinical Oncology (ASCO) 2014 Annual Meeting (5). Patients with advanced NSCLC were categorized by their *MET* amplification status as either low and intermediate or high as determined by FISH, and then treated with crizotinib. They observed that as *MET* amplification increased, an increased percent of objective partial responses was observed.

Activation of *MET* can be mediated by gene amplification, protein overexpression, point mutations and also alternative splicing leading to exon 14 skipping (6). Exon 14 of *MET* encodes the juxtamembrane region which contains key regulatory elements including Y1003, the direct binding site for Cbl, an E3 ubiquitin ligase, that promotes c-Met protein degradation (7). Exon 14 skipping results in loss of Y1003, leading to decreased MET ubiquitination, resulting in increased MET levels (8). Several studies now have identified a special subset of patients with *MET* exon 14 skipping in NSCLC, supporting its role in oncogenesis.

Table 1 *MET* exon 14 skipping mutation frequency

Study	Overall frequency	Frequency by histologic subtype
The Cancer Genome Atlas Research Network (9)	Not reported	4% in lung adenocarcinoma (10 of 230)
Paik *et al*. (10)	Not reported	4% in lung adenocarcinoma (8 of 178)
Frampton *et al*. (11)	2.7% in lung neoplasms (193 of 7,071)	3% in lung adenocarcinoma (131 of 4,402); 2.3% in other lung neoplasms (62 of 2,669)
Liu *et al*. (12)	Not reported	22% in sarcomatoid carcinoma (8 of 36)
Tong *et al*. (13)	2.62% in NSCLC (18 of 687)	2.6% in adenocarcinoma (10 of 392); 4.8% in adenosquamous carcinoma (1 of 21); 31.8% in sarcomatoid carcinoma (7 of 22)
Awad *et al*. (7)	3% in non-squamous NSCLCs (28 of 933)	2% in adenocarcinoma (18 of 873); 26.7% in pleomorphic (including sarcomatoid) carcinoma with an adenocarcinoma component (4 of 15); 6 patients 13.3% in poorly differentiated NSCLC not otherwise specified and adenosquamous carcinoma (6 of 45)

NSCLC, non-small cell lung cancer.

The reported frequencies of *MET* exon 14 skipping mutations in lung adenocarcinomas consistently range in the 3–4% range (*Table 1*) and a uniquely aggressive subtype of lung cancer, so-called sarcomatoid lung cancer has been reported to harbor a much higher, up to 25–35%, frequency of these mutations (9-13).

Several groups have also reported on selected patients with exon 14 skipped tumors treated with MET inhibitors with most cases demonstrating at least a partial response. Collectively, the number of patients with *MET* exon 14 alterations that have been reported and treated with MET inhibitors are limited to small case series, however, the aggregate has shown significant promise and sparked renewed interest in MET inhibition for NSCLC leading to the actual incorporation of testing and MET inhibitor therapy recommendation for exon 14 skipped patients in the NCCN guidelines. *Table 2* lists the reported cases thus far, all of which have demonstrated at least a partial/clinical response to a MET inhibitor (7,10-12,14-17).

In the current manuscript, Awad and colleagues report on the comprehensive analysis of 6,376 cancers, using next generation sequencing (NGS) encompassing the *MET* gene which included 1,141 lung cancers between August 1, 2013 and May 1, 2015 (7). Twenty-eight patients of 933 non-squamous NSCLC (3%) harbored exon 14 mutations, consistent with frequencies previously reported such as in the TCGA database as well other studies (9). Eighteen of the patients had adenocarcinoma, four had pleomorphic (i.e., sarcomatoid) carcinoma with an adenocarcinoma component, five had poorly differentiated NSCLC not otherwise specified, and one had adenosquamous histology. The group made several interesting observations from their cohort. Of note, all 28 patients were white, non-Hispanic. The median age at disease onset was 72.5 years. They found that patients with *MET* exon 14 mutations were significantly older than patients with EGFR mutations (P<0.001) and KRAS mutations (P<0.001) during the same time period. They also found that 64% of patients with *MET* exon 14 mutations had a smoking history.

Of the 28 patients, several different mutation types in *MET* exon 14 and its flanking introns were observed. Genomic deletions were identified in 17 (61%) patients and point mutations in the remaining 11 (39%) patients. A qRT-PCR-based assay on 24 samples with adequate RNA material confirmed exon 14 skipping in 23 samples (96%) showing that the various sequence changes can indeed similarly affect precursor mRNA processing. No concurrent genomic alterations in *KRAS*, *EGFR*, *ERBB2*, *ALK*, *ROS1* or *RET* were identified in the 28 patients suggestive of these being mutually exclusive, driver oncogene events. Analysis of genomic copy number changes showed that 6 tumors (21%) had high-level *MET* copy gain and 8 (29%) had low-level *MET* copy gain. Twenty-five patients had sufficient tissue for immunohistochemical c-MET expression analysis which ranged from weak to maximum expression demonstrating poor concordance questioning the utility of MET IHC in this setting. They also observed that patients with stage IV disease had a significantly higher H score with a mean of 253 than patients with stage I to III disease

Table 2 Patients with *MET* exon 14 mutations treated with MET inhibitors

Study	Patient and disease characteristics	*MET* exon 14 variant characteristics	Treatment	Response to MET inhibition
Awad *et al*. (7)	64-year-old female never smoker: stage IV NSCLC, poorly differentiated carcinoma histology, favoring adenocarcinoma; negative for *KRAS*, *EGFR*, *BRAF*, *ALK* and *ROS1*	c.3028G>A mutation; high-level *MET* amplification	1st line: not specified; 2nd line: crizotinib 250 mg PO BID	Dramatic improvement on CT imaging after 8 weeks; ongoing response at 8 months
Shea *et al*. (14)	74-year-old female with 20 pack year smoking history: initially stage III lung adenocarcinoma, then 6 years later with recurrent/advanced disease and significant cardiopulmonary symptoms	Not specified	1st line: surgical resection and adjuvant platinum-based chemotherapy (not specified); 2nd line: carboplatin/pemetrexed then maintenance pemetrexed; 3rd line: crizotinib 250 mg PO BID then dose reduced to QD after 2 weeks (secondary to GI grade 3 CTCAE)	Improvement in symptoms within 1 week, resolved after 2 months; improvement from ECOG 4 to ECOG 1, then ECOG 0 after 2 months; partial response (RECIST 1.1) on CT imaging after 2 months
Paik *et al*. (10)	80-year-old female never smoker: initially stage IA (pT1aN0M0) lung adenocarcinoma in 2008, recurrence in 2010 to precarinal lymph node, then in 2014 with liver metastasis	c.3028G>C mutation; high level MET amplification	1st line: docetaxel; 2nd line: pemetrexed; 3rd line: cabozantinib 60 mg PO QD (part of phase II clinical trial of cabozantinib)	Complete resolution of the liver lesion on PET (met definition of PERCIST complete response) after 4 weeks
	78-year-old male former smoker: stage IV lung adenocarcinoma; negative for *EGFR*, *ERBB2*, and *ALK*	c.3024 _3028delAGAAGGTATATT mutation; MET IHC: strong MET expression (H-score =300)	1st line: carboplatin/ pemetrexed and bevacizumab then maintenance pemetrexed/ bevacizumab; 2nd line: albumin-bound paclitaxel; 3rd line: crizotinib 250 mg PO BID	Partial response (~30%) in lung tumors (RECIST) on CT imaging after 4 and 8 weeks; however POD in liver metastases; expired due to multilobar pneumonia prior to starting cabozantinib and had stopped crizotinib for washout
	65-year-old male former smoker: stage IV lung adenocarcinoma; negative for *EGFR* or *ALK* alterations	*MET* p.V1001_F1007del mutation	1st line: cisplatin/pemetrexed and bevacizumab then maintenance pemetrexed/ bevacizumab; 2nd line: gemcitabine; 3rd line: crizotinib 250 mg PO BID	Substantial improvement in dyspnea and bone pain after 2 weeks; partial response (~31%) on CT imaging after 6 weeks
	90-year-old female never smoker: recurrent stage IV lung adenocarcinoma	c.3028G>T mutation; 2 copy-number alterations– CDK4 and MDM2 amplification	1st line: pemetrexed; 2nd line: gemcitabine then treatment holiday; 3rd line: crizotinib 250 mg PO BID	Partial response (47%) on CT imaging after 2 months

Table 2 *(continued)*

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Study	Patient and disease characteristics	*MET* exon 14 variant characteristics	Treatment	Response to MET inhibition
Frampton *et al*. (11)	84-year-old female never smoker: unresectable stage III histiocytic sarcoma	c.2888-5_2944del62 mutation and TP53 p.R175H and ZMYM3 c.3008-1G>A	Crizotinib	Partial response (>60%) (RECIST 1.1) on CT imaging after 4 months; POD on reimaging after 11 months
	82-year-old female with 25 pack year smoking history: stage IV large cell carcinoma with right hilar node metastases, then recurrent disease 3.25 years later	c.3028G>C mutation and TP53 p.N30fs*14; *MET* gene copy number: 6 in a triploid cancer genome; MET IHC 3+ (H-score 270)	1st line: complete surgical resection, declined perioperative chemotherapy; 2nd line: capmatinib (investigational MET inhibitor, phase I open-label dose-escalation study) for >5 months	Partial response (53%) on CT imaging
	66-year-old female with 4 pack year smoking history: stage Ib poorly differentiated squamous cell carcinoma of lung, then recurrent disease 9 months later in soft tissue of the axilla and chest wall, later noted to have central nervous system, bone and renal metastases	c.3028+1G>T mutation; *MET* gene copy number: 4; *MET* FISH copy number: 13.8 (*MET*:*CEBP7* ratio 2.3); MET IHC 3+ (H-score 300)	1st line: surgical resection and adjuvant gemcitabine/carboplatin (discontinued after 1 cycle due to toxicity); 2nd line: carboplatin/paclitaxel; 3rd line: CHK1 inhibitor (part of phase I clinical trial); 4th line: capmatinib (part of phase I open-label, dose-escalation study) × 13 months	Partial response (61%) on CT imaging after 13 months
Jenkins *et al*. (15)	86-year-old male never smoker: stage IV lung adenocarcinoma with brain and adrenal gland metastases; negative for *EGFR*, *KRAS*, *ALK*, *ROS1* and *RET*	c.2887-18_2887-7del12 mutation; *CDKN2A/B* loss; *CDK4* and *MDM2* amplification; MET IHC 2+	1st line: RT to obstructing lung mass and brain lesions; 2nd line: pemetrexed × 1 cycle; 3rd line: crizotinib (eventually discontinued due to pneumonitis)	Significant improvement of lung mass and unirradiated adrenal lesion on CT reimaging after 5 weeks; 8 weeks after crizotinib discontinued, patient with POD
Waqar *et al*. (16)	71-year-old male with 15 pack year smoking history; stage IV lung adenocarcinoma	*MET* single nucleotide variant identified, chr7:g.116412043G>C involving the terminal nucleotide of exon 14; *MET* copy number: 2.23; negative for *MET* amplification	1st line: palliative thoracic RT and carboplatin/pemetrexed; 2nd line: crizotinib 250 mg PO BID	Decrease in size of pulmonary lesions on CT imaging after 6 weeks with continued response at 6 months

Table 2 *(continued)*

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Study	Patient and disease characteristics	*MET* exon 14 variant characteristics	Treatment	Response to MET inhibition
Mendenhall *et al*. (17)	76-year-old female former light smoker: stage IV squamous cell carcinoma of the lung with metastases to bone and right gluteal soft tissue	*MET* D1010H mutation and *MDM2* amplification	1st line: combination of a novel MMP9 inhibitor, carboplatin and paclitaxel × 3 cycles; 2nd line: gemcitabine × 1 cycle; 3rd line: crizotinib	Rapid improvement in fatigue and complete resolution of pain; reduction of target lesions (64.4% by RECIST 1.1) and resolution of numerous non-target pulmonary nodules on CT imaging after 7 weeks; near complete response on PET CT in size and decrease in SUV after 19 weeks
Liu *et al*. (12)	74-year-old female former smoker and asbestos exposure; initially stage II pulmonary sarcomatoid carcinoma, then recurrent disease 3 months later with metastases to liver and bulky mesenteric disease	Intron 14 + 3 A>G; *MET* amplification of 9 copies	1st line: neoadjuvant platinum/taxane chemotherapy; 2nd line: crizotinib 250mg PO BID	Rapid dramatic clinical improvement; partial response on CT imaging after 2 months

NSCLC, non-small cell lung cancer; BID, twice daily; QD, daily; GI, gastrointestinal; CTCAE, common terminology criteria for adverse events; IHC, immunohistochemistry; POD, progression of disease; RT, radiation therapy.

(P=0.002) and stage IV NSCLCs without *MET* exon 14 mutations (P<0.001).

Adding to the growing list of patients with *MET* exon 14 mutations reported in the literature treated by MET inhibitors, Awad and colleagues also reported on a patient with stage IV NSCLC with poorly differentiated carcinoma, favoring adenocarcinoma, with *MET* exon 14 skipping and high-level *MET* amplification, who was treated with crizotinib. After 8 weeks, repeat imaging demonstrated a major partial response consistent with a very high likelihood of treatment response highlighted by prior cases as well.

As we continue to see reports of remarkable efficacy with MET inhibitors in patients with *MET* exon 14 mutations, clearly more widespread studies to generate a treatment algorithm need to be designed, however even the current limited information strongly argues for a trial of MET inhibitor therapy on or off study (such as with crizotinib or cabozantinib) in the absence of other options in metastatic disease in patients with *MET* exon 14 skipped, advanced NSCLC. The observed *MET* mutation frequencies have been on par with *ALK* and *ROS* mutations, influencing possible approaches to the way in which patients may be tested for *MET* exon 14 mutations. In patients with lung cancer who have tested negative for *EGFR*, *KRAS*, *ALK* and *ROS1*, adding *MET* to the panel of mutations to be tested should be very strongly considered and this might be best accomplished as part of multi-gene panels. In fact, the NCCN guidelines have already adopted such recommendations given the powerful observations listed without a formal study in this area.

A key component needed to streamline testing for *MET* mutations is the identification of a validated biomarker both for patient selection and as a predictor of response to inhibition. The identification of gene level alterations as opposed to MET expression as measured by IHC perhaps may be the missing piece in identifying such a biomarker. As the technology, feasibility and costs of NGS improve and become more accessible, NGS as the standard for the evaluation of genomic alterations may prove to be the recommended testing modality and recent technological

advances now allow testing for alterations such as *MET* exon 14 skipping as part of ctDNA-based NGS platforms.

The older patient population with *MET* exon 14 mutations, as has been reported by both Awad *et al*. and Tong *et al*., represent a specific group who may benefit from improved patient selection for targeted therapy as these patients frequently present with increased comorbidities and decreased performance status which may limit their tolerability for conventional chemotherapy (13). Demonstrated benefit in this scenario was recently reported in a patient with an ECOG of 4 and significant cardiopulmonary symptoms from stage IV NSCLC with a *MET* exon 14 deletion, treated with crizotinib and a remarkable response within a week including improvement of ECOG to 1 (14).

Once patients have been selected, the question then lies in the optimal approach to treatment. Experience thus far has been in a handful of previously treated patients, faced with limited remaining treatment options. Further investigation of the appropriate timing of MET inhibitor administration, the optimal choice of MET inhibitor from an expanding list of currently approved and actively studied agents and the possibility of combination therapies is sorely needed. Understanding of possible resistance mechanisms similar to other targeted agents will also be of great importance.

Although several unanswered questions regarding *MET* as an actionable target remain, the rapid accumulation of knowledge and the excellent results with patients treated thus far inspire tremendous optimism that a highly effective additional line of care now can be offered to our patients with documented *MET* exon 14 skipped mutations and rapid incorporation of broad-based molecular testing including testing for *MET* exon 14 skipping in diagnostic algorithm is key to allow the largest number of our patients to benefit.

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