BRIEF REPORT

High MET Overexpression Does Not Predict the presence of *MET* exon 14 Splice Mutations in NSCLC: Results From the IFCT PREDICT.amm study

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Received 9 May 2019; revised 23 September 2019; accepted 30 September 2019
Available online - 9 October 2019

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Disclosure: Dr. Cortot has received grants from Roche; personal fees from AstraZeneca, Bristol-Myers Squibb, MSD, Pfizer, Novartis; and nonfinancial support from Takeda. Dr. Baldacci has received grants from Intergroupe Francophone de Cancerologie thoracique; and personal fees from Lilly, GlaxoSmithKline, MSD, Roche, and Pfizer. Dr. Figeac has received grants from Canceropole Nord-Ouest, French ANR, and Merck. Dr. Antoine has received personal fees from Roche, Bristol-Myers Squibb, and MSD. Dr. Descarpentries has received personal fees from AstraZeneca, Novartis Pharma SAS; and nonfinancial support from Roche SAS and Boehringer Ingelheim France. Dr. Kherrouche has received personal fees from Institut Pasteur de Lille; and grants from Intergroupe Francophone de Cancerologie Thoracique, Canceropole Nord Ouest, French ANR, and Merck. Dr. Jamme has received personal fees from Boehringer Ingelheim; and nonfinancial support from Chugai Pharma and AstraZeneca. Dr. Quoix has received support from Roche, Bristol-Myers Squibb, Boehringer Ingelheim, Chugai, Takeda, AstraZeneca, and Novartis. Dr. Moro-Sibilot has received personal fees from Roche, AstraZeneca, Novartis, Pfizer, Bristol-Myers Squibb, MSD, Boehringer Ingelheim, and Takeda. Dr. Friard has received nonfinancial support from Pfizer, Roche, Bristol-Myers Squibb, Lilly, Novartis, Boehringer Ingelheim, and AstraZeneca. Dr. Barlesi has received grants and personal fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Eli Lilly Oncology, F. Hoffmann-La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer, Takeda, Boehringer Ingelheim; and grants from AbbVie, ACEA, Amgen, Esai, Genentech, Ipsen, Ignyta, Innate Pharma, Loxo, MedImmune, Sanofi-Aventis, and Null. Dr. Cadranel has received grants for his institution from AstraZeneca; and has received personal fees from AstraZeneca, Roche, and Boehringer Ingelheim. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2019.09.196

ABSTRACT

Introduction: *MET proto-oncogene (MET)* exon 14 splice site (*MET*ex14) mutations were recently described in NSCLC and has been reported to correlate with efficacy of MET tyrosine kinase inhibitors. High diversity of these alterations makes them hard to detect by DNA sequencing in clinical practice. Because *MET*ex14 mutations induce increased stabilization of the MET receptor, it is anticipated that these mutations are associated with MET overexpression. We aim to determine whether NSCLC with high MET overexpression could define a subset of patients with a high rate of *MET*ex14 mutations.

Methods: From The French Cooperative Thoracic Intergroup PREDICT.amm cohort of 843 consecutive patients with a treatment-naive advanced NSCLC who were eligible for a first-line therapy, 108 NSCLC samples with high MET overexpression defined by an immunochemistry score 3+ were tested for *MET*ex14 mutations using fragment length analysis combined with optimized targeted next-generation sequencing. *MET* copy number analysis was also derived from the sequencing data.

Results: *MET*ex14 mutations were detected in two patients (2.2%) who also displayed a *TP53* mutation and a *PIK3CA* mutation, respectively. An *MET* gene copy number increase was observed in seven additional patients (7.7%). Next-generation sequencing analysis revealed inactivating mutations in *TP53* (52.7%) and *PTEN* (1.1%), and oncogenic mutations in *KRAS* (28.6%), *EGFR* (7.7%), *PIK3CA* (4.4%), *BRAF* (4.4%), *NRAS* (2.2%), *GNAS* (1.1%), and *IDH1* (1.1%).

Conclusions: The rate of *MET*ex14 mutations in NSCLC with high MET overexpression was similar to that found in unselected NSCLC. Moreover, we observed a high frequency of driver alterations in other oncogenes. Consequently these findings do not support the use of MET immunohistochemistry as a surrogate marker for *MET*ex14 mutations.

Keywords: NSCLC; MET; Receptor tyrosine kinase; Next-generation sequencing; Immunohistochemistry

Introduction

The dysregulation of the MET tyrosine kinase receptor is involved in the development and spreading of various cancers. Several mechanisms of MET aberrant activation have been described in cancers including paracrine or autocrine secretion of the MET ligand, the hepatocyte growth factor, overexpression of the receptor, amplification or rearrangements of the *MET proto-oncogene (MET)*, and mutations of key residues in the MET kinase domain.[1] Recently a new class of mutations disrupting the splice sites of the *MET* exon 14 has been reported in approximately 3% of lung adenocarcinoma and lung sarcomatoid carcinomas.[2,3] These alterations, also named *METΔ14*, lead to MET exon 14 skipping during the splicing process. MET exon 14 encodes the juxtamembrane domain of the receptor that contains negative regulatory sites such as the tyrosine 1003 whose phosphorylation is involved in the receptor degradation through the recruitment of the ubiquitin ligase CBL.[1] Several cases of NSCLC harboring a *MET* exon 14 splice (*MET*ex14) mutation and displaying an objective tumor response to MET inhibitors have been reported suggesting oncogenic addiction induced by these alterations.[2] However, the *MET*ex14 mutations are very heterogeneous, with more than 120 different reported mutations, which makes their detection challenging with high throughput DNA sequencing techniques used in routine practice.[2] Thus, a prescreening test would be useful to select patients with NSCLC who are at high probability of harboring a *MET*ex4 mutation. Given the functional consequences of *MET*ex14 mutations, MET overexpression could appear as a potential surrogate marker for *MET*ex14 mutations. However, conflicting results have been reported regarding the relationship between *MET*ex14 mutations and MET expression (immunohistochemistry [IHC]).[3,4] In a recent report, Mignard et al.[5] found no relationship between MET expression and *MET*ex14 or *MET* amplification. However, the authors focused only on lung sarcomatoid carcinomas and the number of patients with high MET overexpression was low, preventing definitive conclusion on the relevance of screening MET overexpression as a surrogate marker for *MET*ex14 mutation in unselected NSCLC. In this report we investigate the prevalence of *MET*ex14 mutations in advanced NSCLC displaying a high MET overexpression.

Methods

Patients and Tumor Samples

Between January 2013 and February 2014, 843 consecutive patients with a treatment-naive advanced NSCLC who were eligible for a first-line therapy were included in the French multicentric prospective cohort IFCT-PREDICT.amm.[6] For all patients, MET expression was assessed by IHC using the Ventana SP44 antibody on the initial formalin-fixed paraffin-embedded (FFPE) samples. Patients from the IFCT-PREDICT.amm cohort were included in the present study if all the following criteria were met : (1) MET 3+ immunoscore (≥50% of tumor cells showing high-intensity staining); and (2) initial tumor material (DNA or FFPE sample) still available.[7] DNA and FFPE samples of included patients were then centralized in the pathology department of Lille University Hospital. When only FFPE samples were available, DNA was extracted using QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. This study was approved by a national ethics committee and the National Commission of Informatics and Freedom. All subjects provided written informed consent before entering the study.

Table 1. Clinical Characteristics of Patients

	Overall Population
	n = 108
Median age, years	63 (31.3-85.6)
Sex	
Male	74 (68.5)
Female	34 (31.5)
Smoking status	
Never smoker	11 (10.2)
Former smoker	30 (27.8)
Current smoker	67 (62)
Performance status	
0	17 (15.7)
1	67 (62.0)
2	18 (16.7)
3	6 (5.6)
Stage at initial diagnosis	
Stage IA - IIIA	2 (1.9)
Stage IIIB	4 (3.7)
Stage IV	102 (94.5)
Histology	
Squamous	11 (10.2)
Adenocarcinoma	85 (78.7)
Large cell	6 (5.6)
Sarcomatoid	1 (0.9)
NSCLC NOS	5 (4.6)

Values shown are n (%) unless otherwise stated.
NOS, not otherwise specified.

Molecular Analyses

Fragment-length analysis followed by targeted next-generation sequencing (NGS) with panel CLAPv1 was performed as previously described.[8] This panel was specifically designed to detect most *MET*ex14 mutations. Analysis settings and quality metrics were adapted to avoid false-negative results: mean read length greater than or equal to100 bp, coverage at 100X greater than or equal to 95% and number of variants less than 80. If these quality metrics were not achieved, the sample was considered not interpretable. *MET* copy number analysis of the NGS data was also performed as previously described with a stricter threshold for copy number aberration detection: log2Ratio $>$ 2 $\times$ derivative log ratio spread.[8]

Results

Among the 843 patients included in the IFCT-PREDICT.amm cohort, 146 of 576 with centrally evaluable MET IHC displayed a high MET overexpression on local or centralized MET IHC assessment. Tumor material was available for molecular analyses in 108 patients of 146 patients. These 108 patients were then included in the present study and their clinical characteristics are summarized in Table 1. Median age was 62.7 years (range: 31.3–85.6 years). The majority of patients was male (68.5%), smoked (88.8%), and had stage IV NSCLC at diagnosis. Histology was adenocarcinoma and squamous cell carcinoma in 78.7% and 10.2% of the patients, respectively.

The samples were tested for both fragment-length analysis and targeted NGS with the optimized panel CLAPv1 covering the *MET* exon 14 and flanking regions.[8] This method allows, in routine practice, the identification of 95% of the *MET*ex14 mutations reported by Frampton et al.[2] Fragment-length analysis was performed on all 108 included patients. For 22 patients, data were inconclusive due to DNA of poor quality or insufficient quantity. Among the 86 patients with interpretable results, no *MET*ex14 mutation was detected. CLAPv1 NGS was performed on 105 samples containing suitable quality and quantity of DNA. Among them, 91 patients had interpretable results and two *MET*ex14 mutations (2.2%) were detected (Fig. 1). These two mutations (c.3082+2T>A and c.3082+1G>A) occurred in two nonsmoker women with metastatic lung adenocarcinoma (Table 2). These two patients also harbored a *PIK3CA* activating mutation (E545K) and a deleterious *TP53* mutation (C135Y), respectively. To provide supplementary data on the association of MET expression and METex14 mutations, we performed an additional analysis of an independent cohort of prospectively collected advanced NSCLC samples from one of the centers that participated in the IFCT PREDICT.amm study. Among 286 NSCLC samples for which MET IHC was performed in this center, we identified 131 samples with low or no MET expression (0 or 1+ MET immunoscore). All 131 samples were tested for *MET*ex14 mutations using targeted NGS CLAPv1 panel combined with fragment-length analysis. We identified an *MET*ex14 mutation in two samples (1.5%). Thus, these results suggest that the rate of *MET*ex14 mutations is similar in NSCLC samples with high and low MET expression.

A gene copy number analysis based on read counts was then performed on the sequencing data of 91 patients. We observed an *MET* gene copy number increase in 7 patients (7.7%) (Fig. 1). The majority of these patients was male, and all of them were current or former smokers (Table 2). Four were classified as lung adenocarcinoma, 1 as a squamous NSCLC, and 2 as NSCLC not otherwise specified. *MET*ex14 mutations were not observed among the patients with *MET* gene copy number increase. Altogether, in this study, we found a 2.2% rate of *MET*ex14 mutations and a 7.7% rate of *MET* gene copy number increase in NSCLC patients with high MET overexpression.

Additionally, known oncogenic mutations in *KRAS* (26 of 91 patients; 28.6%), *EGFR* (7 of 91patients; 7.7%), *PIK3CA* (4 of 91 patients; 4.4%), *NRAS* (2 of 91 patients; 2.2%), *GNAS* (1 of 91 patients; 1.1%), and *IDH1* (1 of 91 patients; 1.1%) were observed (Fig. 1). Four (4.4%) patients also displayed oncogenic non-V600 *BRAF* mutations, including one patient with *MET* gene copy number increase, and 2 of 87 patients (2.3%) who were found to be ALK-positive by IHC. NGS analysis revealed

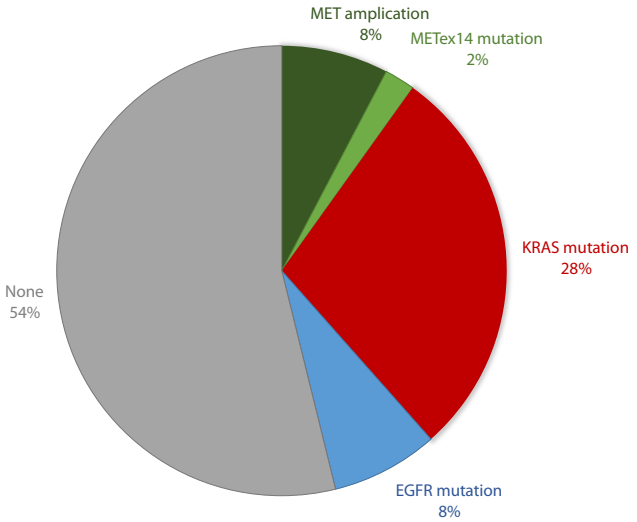

Figure 1. *MET*, *KRAS*, and *EGFR* alterations in MET IHC3+ NSCLC. IHC, immunohistochemistry.

deleterious *TP53* mutations in 48 of 91 patients (52.7%) and *PTEN* mutation in 1 of 91 patients (1.1%).

Discussion

To the best of our knowledge, this is the first study assessing the prevalence of *MET*ex14 mutations in a prospective cohort of treatment-naive advanced NSCLC with high MET overexpression. Importantly, the prevalence of these mutations was similar in our cohort to that found in unselected NSCLC, suggesting that MET IHC cannot serve as a surrogate marker for prescreening of *MET*ex14 mutations.[2,3] Although preclinical data have shown that *MET*ex14 mutations encode a more stable form of the MET receptor, which is no longer amenable to ubiquitination and degradation, the association between MET overexpression and *MET*ex14 mutations remains controversial.[9] Some studies have reported a significant association between *MET*ex14 mutations and MET overexpression whereas others have not found any association.[3,4,10,11] These discrepancies could be explained by technical issues in MET IHC assessment and interpretation, which may be partly explained by heterogeneity of MET expression, and the limited number of patients included in previous studies. Here, we chose to focus on NSCLC patients with high MET overexpression (IHC3+) to minimize the risk of heterogeneity. Still, no enrichment in *MET*ex14 mutations was observed.

Although lack of MET ubiquitination and subsequent MET overexpression is usually presented as the main functional consequence of *MET*ex14 mutations, other mechanisms may account for the transforming phenotype induced by these mutations.[12] MET juxtamembrane domain is known to harbor a serine residue (S985) involved in activation of protein kinase C, which downregulates MET kinase activity. MET juxtamembrane domain is also a site for MET cleavage by calpains, which enhances apoptosis. Thus, loss of the juxtamembrane domain due to exon 14 skipping may induce transforming properties even in absence of MET overexpression. However, whether MET inhibitors are active in this setting has still to be determined.

Our study also provides new insights about the molecular landscape of NSCLC with high MET overexpression. First, we observed by NGS analysis an *MET* gene copy number increase rate of 7.7%, suggesting an enrichment of MET amplification in NSCLC with high MET overexpression, which is in line with previous reports.[13,14] Second, we found a rate of oncogenic driver alterations similar to what is observed in large cohorts of unselected NSCLC, including *KRAS* mutations, *EGFR* mutations, and *PIK3CA* mutations.[15] This result might partly explain the failure of phase III trials investigating the efficacy of MET inhibitors in NSCLC displaying an MET IHC score greater

Table 2. Clinical and Molecular Characteristics of Patients With *MET* Exon 14 Splice Mutations or *MET* Gene Copy Number Increase

Patient No.	1	2	3	4	5	6	7	8	9
Age, years	53.9	63.6	52.3	31.3	71.8	47.0	58.2	82.9	56.6
Sex	Male	Male	Male	Female	Female	Male	Male	Female	Female
Smoking status	Former	Former	Current	Current	Current	Current	Current	Never	Never
Performance status	1	2	1	1	3	1	1	1	1
Stage at initial diagnosis	IV	IV	IV	IV	IV	IIIB	IV	IV	IV
Histology	NSCLC NOS	NSCLC NOS	ADK	ADK	ADK	Squamous	ADK	ADK	ADK
MET alteration	*MET* gene copy number increase	*MET* gene copy number increase	*MET* gene copy number increase	*MET* gene copy number increase	*MET* gene copy number increase	*MET* gene copy number increase	*MET* gene copy number increase	*MET* exon 14 splice site mutation c.3082+2T>A	*MET* exon 14 splice site mutation c.3082+1G>A
Associated mutations	—	*TP53* A159P	*TP53* V157F	*TP53* L265R	*TP53* R248L	*TP53* Q100stop	BRAF D594N	PIK3CA E545K	*TP53* C135Y

ADK, adenocarcinoma; NOS, not otherwise specified.

than or equal to 2+.[7] These findings also have implications regarding the interpretation of the future results of ongoing trials evaluating MET inhibitors in NSCLC and using MET IHC as inclusion criteria for MET dysregulation (NCT01982955, NCT01911507, and NCT01610336). Recent data suggest that MET expression may impact the clinical course of patients with known oncogenic drivers.[16] Overall, the low prevalence of *MET*ex14 mutations in our study and the high rate of driver alterations in other oncogenes do not support the use of MET IHC as a surrogate marker for MET alterations in therapeutic clinical trials.

This study was limited by the low number of *MET*ex14 mutations. Moreover, *MET*ex14 mutations were tested on DNA rather than RNA, raising the possibility of false-negative results.[17,18] However, we used an optimized DNA-based approach that is expected to minimize such false-negative results, combining a dedicated NGS panel with fragment-length analysis to cover 95% of described abnormalities.[2] Finally, we assessed *MET* amplification by NGS rather than fluorescence in situ hybridization. However, DNA-based NGS is more and more commonly used for identifying patients with *MET* amplification because it is widely available, time-sparing, and it allows detection of other key oncogenic alterations. A growing number of clinical studies are now reporting results regarding *MET* amplification based on NGS data.[19,20]

Acknowledgments

Supported by the Intergroupe Francocophone de Cancérologie Thoracique. The authors thank Patrick Gelé and Bertrand Accard for their kind support regarding the archiving of tumor samples; Shéhérazade Sebda, Frédéric Leprêtre, and Audrey Vinchent for their support in processing biological samples; and Roche for providing the anti-MET sp44 antibody.

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