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Lung Cancer

MET Exon 14 Skipping in Non-Small Cell Lung Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Lung cancer • *MET* exon 14 skipping • Targeted therapy

Abstract

Background. Non-small cell lung cancers (NSCLCs) harboring specific genetic alterations can be highly sensitive to targeted therapies.

Materials and Methods. We performed a targeted rearrangement assay on 54 NSCLCs across all stages that were from patients who were never smokers and did not have driver mutations. Because *MET* exon 14 skipping was the most frequent alteration found, we surveyed the results for *MET* exon 14 skipping at Massachusetts General Hospital (MGH) since the inclusion of this alteration into our current molecular profiling panel.

Results. In a cohort of 54 never-smokers with lung cancers that were wild-type for known driver mutations, *MET* exon 14 skipping was the most frequently recurring alteration, occurring in 10 cancers (19%). Clinical testing at MGH via our next-generation sequencing (NGS) and NGS-rearrangement panels showed an additional 16 cases of *MET* exon 14 skipping, for an overall estimated frequency of 5.6%. A clinical case of a patient with *MET* exon 14 skipping treated with the MET inhibitor crizotinib is also described.

Conclusion. *MET* exon 14 skipping is a targetable gene alteration found in NSCLC. Patients with these alterations may respond well to MET inhibition. ***The Oncologist*** 2016;21:481–486

Implications for Practice: MET exon 14 skipping occurs with an approximately 5% frequency in NSCLC and is seen in both squamous and adenocarcinoma histology. Patients whose cancers have MET exon 14 skipping can respond well to MET inhibitors. Molecular testing for MET exon 14 skipping should be performed on all lung cancers because this is a targetable alteration.

Introduction

The discovery of oncogenic driver mutations and translocations has transformed the treatment of lung cancer, and patients with sensitizing *EGFR* mutations or *ALK* or *ROS1* translocations can have remarkable responses to targeted inhibition, leading to significant clinical benefit [1–8]. The advent of new technologies has spurred more comprehensive molecular profiling of lung cancers, and the mutational spectrum of lung cancers, both adenocarcinoma and squamous cell carcinoma, is becoming better defined [9–12].

Molecular testing of tumors for genomic changes has been integrated into the oncology clinic as a part of standard care at Massachusetts General Hospital since 2009 with the SNaPshot platform (LifeTechnologies/Applied Biosystem, ThermoFisher Scientific, Foster, CA, https://www.thermofisher.com), a validated, Clinical Laboratory Improvement Amendments-approved, multiplexed tumor genotyping assay that is used for real-time testing of tumors. More than 50 commonly mutated loci in 14 key oncogenes were tested in the original SNaPshot panel, and fluorescent in situ hybridization (FISH) assays for other genetic changes of interest, such as *ALK* and *ROS1* translocation, were performed separately [13, 14]. However, a substantial number of cancers (~40%–50%) have no mutations identified by this platform.

Gene rearrangements and fusions can lead to constitutive activation of a kinase and are a key mechanism by which some cancers become "oncogene addicted." The ability to target these oncogenic fusions is exemplified by the examples of *ALK* and *ROS1* rearranged lung cancer. We performed targeted rearrangement sequencing using the recently described anchored multiplex polymerase chain reaction PCR (AMP) method [15] on a cohort of 54 never-smokers with lung cancer whose tumors were known to be wild-type on SNaPshot testing. We hypothesized that such a cohort would be enriched for driver genetic alterations. The overall goal was to identify fusion

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Table 1. Clinical characteristics of patients with *MET* splice site alterations among never-smokers without driver alterations

Case	Genomic DNA alteration	SNaPShot	Age (yr)	Sex	Stage	Smoking status	Histology
1	Deletion in 3′ splice site of intron 13 (32-bp deletion)	wt	79	Female	IB	Never	ADC
2	Point mutation in 5′ splice site of intron 14 (G>A) adjacent to position D1010	wt	65	Female	IV	Never	ADC
3	Tumor DNA not available	wt	73	Female	IIB	Never	SQC
4	Point mutation in 5′ splice site of intron 14 (G>A) adjacent to position D1010	wt	84	Female	IA	Never	ADC
5	Deletion in 3′ splice site of intron 13 (12-bp deletion)	PI3K CTNNB	47	Female	IIA	Never	ADC
6	Deletion in 3′ splice site of intron 13 (14-bp deletion)	wt	43	Male	IV	Never	SQC
7	Deletion in 3′ splice site of intron 13 (27-bp deletion)	wt	78	Female	IB	Never	ADC/PLEO
8	Deletion in 3′ splice site of intron 13 (24-bp deletion)	wt	74	Female	IA	Never	ADC
9	Point mutation in 5′ splice site of intron 14 (G>A) adjacent to position D1010	wt	70	Male	IIA	Never	ADC
10	Deletion in 3′ splice site of intron 13 (32-bp deletion)	wt	79	Female	IV	Never	ADC

Abbreviations: ADC, adenocarcinoma; bp, base pair; PLEO, pleomorphic carcinoma; SQC, squamous cell carcinoma; wt, wild type.

Table 2. Clinical characteristics of patients identified with MET exon 14 skipping

Case	Other SNaPShot alterations	Age (yr)	Sex	Stage	Smoking status	Pack-years of smoking	Histology
1	wt	68	Female	IV	Former	20	ADC
2	wt	80	Male	IV	Former	36	ADC
3	wt	62	Male	IA	Former	25	ADC
4	PTEN, p53, ADC	71	Female	IB	Former	16	ADC
5	Borderline MET amp	73	Male	IV	Former	45	SQC
6	EGFR amp	77	Female	IV	Former	15	ADC
7	CDKN2A, SMAD4	56	Female	IIIA	Former	7	ADCSQC
8	P53	77	Female	IA	Former	20	ADC
9	P53, ROS Leu2035Phe	76	Female	IIIA	Former	12	SQC
10	wt	60	Male	IB	Former	<5	ADC
11	PI3K H1047R	72	Female	IIIB	Former	5	ADC
12	EGFR Arg255Gln	79	Male	IA	Never	0	ADC
13	EGFR amp	83	Female	IB	Former	40	ADC
14	wt	76	Female	IA	Former	60	ADC
15	wt	78	Male	IA	Never	0	ADC
16	wt	76	Male	IA	Former	20	ADC

Abbreviations: ADC, adenocarcinoma; ADCSQC, adenosquamous carcinoma; SQC, squamous cell carcinoma; wt, wild type.

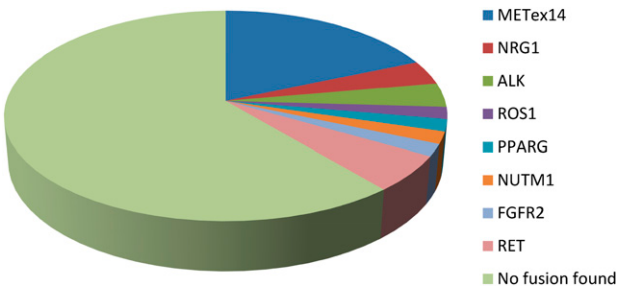

Figure 1. Rearrangements identified among never-smokers with cancers that were wild-type on SNaPshot for known drivers.

drivers in lung cancer that might lead to new targets for therapy. A unique feature of our investigation was the enrichment for patients whose cancers were known to be wild-type on a large panel of driver mutations.

Materials and Methods

We performed a targeted rearrangement assay on 54 NSCLC patients across all stages who were never-smokers and were not known to have driver mutations on SNaPshot testing. Specifically, we excluded patients known to have *EGFR, KRAS, BRAF,* or *ERBB2* mutations or *ALK* or *ROS1* rearrangements. Supplemental online Table 1 shows the patient characteristics. We used a gene enrichment method, anchored multiplex PCR, to perform next-generation sequencing (NGS) using HiSeq (Illumina, San Diego, CA, https://www.illumina.com/) as previously described in detail [15]. Total nucleic acid (TNA) containing total RNA and genomic DNA were extracted from formalin-fixed, paraffin-embedded tissue by using the Agencourt FormaPure Kit (Beckman Coulter, Indianapolis, IN, https://www.beckmancoulter.com). We used at least 50 ng of TNA for RNA rearrangement analysis using the AMP method with exonic anchored primers. The genes covered in each primer panel are shown in supplemental online Table 2.

Table 3. Summary of clinical characteristics of all patients identified with MET exon 14

Patient characteristic	Value
Age (minimum, maximum), yr	43, 84
Male	9
Female	17
Adenocarcinoma	20
Squamous cell carcinoma	4
Adenosquamous carcinoma	1
Adeno/pleomorphic carcinoma	1
Stage I	13
Stage II	3
Stage III	3
Stage IV	7
Never-smoker	12
Former smoker	14
Current smoker	0
0 pack-years	12
1–20 pack-years	9
>20 pack-years	5
Coexisting alterations	
Classic EGFR sensitizing mutations	0[a]
ALK rearrangement	0
ROS1 rearrangement	0[b]
PI3K	2
P53	3
CTNNB	1
PTEN	1
CDKN2A	1
SMAD4	1

Unless otherwise noted, values are the numbers of patients.
[a]Although no sensitizing *EGFR* mutations were detected, one patient had an Arg277Gln mutation in *EGFR* of unknown significance, and two patients had *EGFR* amplification.
[b]Although no *ROS1* rearrangements were detected, one patient had a Leu2035Phe mutation of unknown significance

Targeted DNA sequencing using intronic primers was then performed to confirm genomic DNA alterations when RNA *MET* exon 14 skipping events were found. In our validation studies, we found that AMP requires 15% tumor content for a successful analysis and that 10 unique sequencing reads spanning the exon 13–15 boundary are the minimum needed for confident calls. All patients provided written informed consent under an institutional review board-approved protocol at Dana-Farber/Harvard Cancer Center.

Results

MET Exon 14 Skipping Is Frequent Among Never-Smokers With Tumors Wild-Type for Other Drivers

Figure 1 shows the rearrangement events that were found in this cohort of 54 never-smokers with lung cancers that were wild-type on SNaPshot testing for known drivers. Specifically, we excluded patients known to have *EGFR, KRAS, BRAF,* or *ERBB2* mutations or *ALK* or *ROS1* rearrangements. *MET* exon 14 skipping was the most frequently recurring alteration, occurring in 10 patients (19%). *MET* exon 14 skipping occurred with both adenocarcinoma and squamous histology. One patient had coexisting *PI3KCA E545K* and *CTNNB1* mutations. We confirmed genomic DNA alterations in *MET* in 9 cases; 1 case had no further available tumor nucleic acid. Six of these had deletions in the 3′ splice site of intron 13; the length of the intronic deletions ranged from 10 to 32 base pairs. Three had point mutations in the 5′ splice site of intron 14 (Table 1).

Rearrangements in *RET* and *NRG1* were also recurring events in this cohort of patients (Fig. 1). Interestingly, two patients who were thought to be *ALK*-negative tested positive for an *ALK* translocation on the AMP panel; one of these patients had tested ALK FISH-negative at our institution, and the other had ALK testing outside, results of which were negative. One patient who had tested *ROS1* negative by FISH at our institution tested positive for *ROS1* rearrangement on the AMP panel.

Clinical Testing of MET

Clinical testing for *MET* exon 14 skipping has since been incorporated into the current standard tumor molecular profiling at Massachusetts General Hospital (MGH). The current tumor molecular profiling at MGH uses anchored multiplex PCR technology [15] to provide targeted NGS for single-nucleotide variant (SNV) and insertions/deletions of interest (SNapShot-NGS), as well as rearrangements (NGS-rearrangement panel). Both tests are ordered on all lung cancer patients seen at MGH to provide comprehensive profiling of tumor tissue.

Detection of *MET* exon 14 skipping has been incorporated in a phased manner: Since May 2014, the SNaPshot-NGS panel has provided targeted next-generation DNA sequencing of specific exons in *MET*; this allowed us to identify *MET* exon 14 skipping events that result from specific SNVs (e.g., a common point mutation affecting position 1010 that leads to exon 14 skipping). However, this method does not identify all the genomic events that can lead to exon 14 skipping, many of which may occur in intronic segments. Therefore, since March 2015, the NGS-rearrangement panel has been tailored to identify *MET* exon 14 skipping events, thus allowing broad capture of this event regardless of the specific genomic change that produced it. Specifically, the NGS-rearrangement panel uses targeted RNA sequencing to detect gene rearrangements from clinical formalin-fixed, paraffin-embedded material, by using exonic anchor primers in MET exon 15. This allows detection of *MET* exon 14 skipping (which always appears as the same sequence at the RNA level) regardless of the specific DNA change (which varies from case to case) that produced it.

Because we perform tumor genomic profiling using both SNaPshot-NGS and NGS-rearrangement panel on all cases of non-small cell lung cancer seen in our thoracic oncology clinic, regardless of smoking status or histology, we are able to determine the frequency of the *MET* exon 14 skipping mutations in a cohort that is not selected for any specific histology or smoking status. Among 89 NGS-rearrangement panel cases run since March 2015, 5 have been identified to have *MET* exon 14 skipping (~5.6%). In addition, another 11 cases of *MET* exon 14

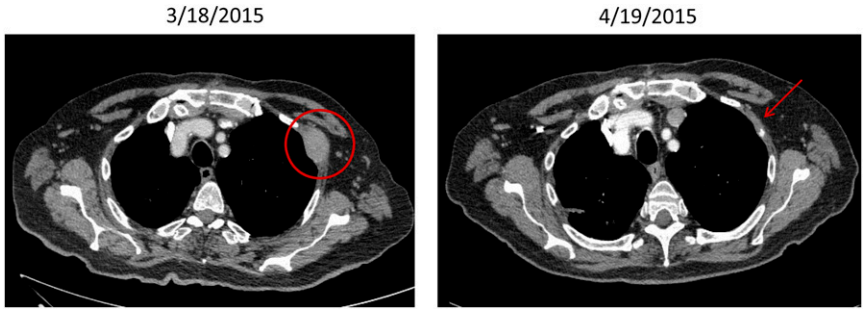

Figure 2. Computed tomographic scans obtained after 4 weeks of crizotinib treatment in a 73-year-old man with metastatic squamous cell lung cancer and MET exon 14 skipping.

skipping using all methods have been identified at MGH. Table 2 details the additional cases of *MET* exon 14 skipping that have been identified at our institution, and Table 3 summarizes clinical characteristics of all cases. Notably, none of the cancers with *MET* exon 14 skipping mutations harbored bona fide activating mutations in *EGFR*, *KRAS*, or *BRAF*, and they did not harbor concurrent *ALK*, *ROS1,* or *RET* translocations.

Of note, although *MET* exon 14 skipping appears enriched among wild-type never-smokers, we have found this alteration across all smoking histories and histologic types. Indeed, among the additional cases of MET exon 14 skipping found with the newer clinical SNaPshot-NGS testing, most former smokers had a range in pack-year history ranging from 0 to 60, with 9 of the 16 patients having smoking histories of greater than 15 pack years.

Case Vignette

A 73-year-old man presented with dyspnea was found to have extensive bilateral pulmonary emboli with right ventricular strain. He underwent bilateral pulmonary thromboendarterectomy; pathology of the right and left pulmonary artery clots revealed metastatic squamous cell carcinoma. SNaPshot testing revealed the *D1010N* mutation in *MET,* which leads to *MET* exon 14 skipping. FISH testing was borderline for *MET* amplification, with a *MET*-to-centromere 7 ratio of 2.2. No other alterations were detected on SNaPshot. Chest, abdomen, and pelvic computed tomography (CT) showed a lytic lesion on the left third rib with associated soft tissue mass, a right adrenal nodule, and small liver lesions consistent with metastatic disease. The patient was treated with crizotinib off-label at 250 mg twice daily. CT scans obtained after 4 weeks of crizotinib treatment revealed near-complete resolution of the soft tissue mass around the lytic rib lesion and resolution of the right adrenal and liver lesions, as well as decreased thrombus in the right main pulmonary artery (Fig. 2). The patient has continued to receive crizotinib and at the time of this writing was starting his seventh month of therapy, with scans showing that the initial response has been maintained.

Discussion

We report here our experience with *MET* exon 14 skipping in NSCLC. We found 10 cases of *MET* exon 14 skipping among a group of 54 never-smokers whose cancers were wild-type for other drivers. Since incorporating *MET* exon 14 skipping into our standard clinical testing, we have found multiple additional cases and estimate a frequency of approximately 5%. Most of these occurred in the absence of other key driver alterations, supporting the notion that this is a driver event. *MET* exon 14 skipping events occurred in both adenocarcinoma and squamous cell carcinoma histology. Although enriched among wild-type never-smokers, *MET* exon 14 skipping is found across all smoking histories and histologic types. As noted in other published reports further described in this section, we saw a dramatic clinical response in a patient with widespread metastatic lung squamous cell cancer with *MET* exon 14 skipping who was treated with crizotinib.

MET exon 14 skipping results from somatic mutations in the introns of *MET*; these mutations lead to an alternatively spliced transcript of MET in which deletion of the juxtamembrane domain results in the loss of Cbl E3-ligase binding [16, 17]. The alternatively spliced MET receptor exhibits decreased ubiquitination and delayed downregulation, leading to prolonged activation of MET and MAP kinase, which is thought to be transforming [16]. Overall, reports of MET exon 14 skipping have ranged from 1.5% to 6% of NSCLC [10, 11, 16, 18–20], and a recent report noted 22% of pulmonary sarcomatoid carcinomas had *MET* exon 14 skipping [21]. Among 38,028 patients with advanced cancers who underwent comprehensive genomic profiling using the Foundation platform (Foundation Medicine, Cambridge, MA, http://www.foundationmedicine.com), the highest rates of *MET* exon 14 skipping occurred in lung cancers, with rates of 3% (131 of 4,402) in lung adenocarcinoma and 2.3% (62 of 2,669) in other lung neoplasms [18]. Eight patients with lung adenocarcinoma and *MET* exon 14 skipping were identified with comprehensive profiling at Memorial Sloan Kettering Cancer Center; although a denominator is not reported, the authors estimate a frequency of 4% [22]. Three cases of *MET* exon skipping were identified among 87 lung adenocarcinomas from Korea [10]. In The Cancer Genome Atlas, 10 of 230 lung adenocarcinomas had *MET* exon 14 skipping. In 9 of these, a 5′ or 3′ splice site mutation or deletion was found; 1 case of *MET* exon 14 skipping occurred in the setting of *MET* Y1003* stop codon [11]. Across all the studies, *MET* exon 14 skipping occurred in the absence of other known drivers.

Preclinical data have shown that cell lines with *MET* exon 14 skipping may respond well to MET inhibition [16, 18], although data are mixed [23, 24]. Kong-Beltran showed prolonged phosphorylation of MET and MAPK with stimulation by HGF in a cell line with *MET* exon 14 skipping, and increased cell proliferation, which was inhibited by treatment with a MET inhibitor [16]. Frampton et al. showed that human *MET* exon 14 skipping and the homologous mouse MET exon 15 skipping alteration are transforming in cell lines, at least partly through activation of the MEK/ERK pathway. A mouse model of the

Table 4. Summary of case reports of patients with *MET* exon 14 and responses to MET treatment

MET exon 14	MET amplification	Selected other alterations	Drug	Age (yr)	Sex	Smoking	Histology	Reported estimated PFS (mo)	Reference
c.3028G>C	*MET* amp	*MDM2* amp and multiple others	Cabozantinib	80	Female	Never	Adenocarcinoma	5.1+	22
c.3024_3028delAGAA GGTATATT	No amp IHC H Score 300	Multiple	Crizotinib	78	Male	Former	Adenocarcinoma	3.6	22
c.3028+1G>T	*MET* amp IHC NA	Multiple	Crizotinib	65	Male	Former	Adenocarcinoma	4.6+	22
c.3028G>C	No amp IHC H score 300	*CDK4* amp, *MDM2* amp	Crizotinib	90	Female	Never	Adenocarcinoma	3.1+	22
c.2888-5_2944del62	NA	*TP53 ZMYM3*	Crizotinib	84	Female	Never	Histiocytic sarcoma	11	18
c.3028G>C	FISH not done 3+IHC	*TP53*	INC280	82	Female	Former	Large cell	5+	18
c.3028+1G>T	Copy number 4; *MET:CEP7* 2.3	None reported	INC280	66	Female	Former	Squamous	13	18
c.3028 G>A	Borderline *MET:CEP7* 2.2	SNaPshot wt	Crizotinib	73	Male	Former	Squamous	6+	This study
c.3028G>C	BA (presume negative, Foundation)	*MDM2* amp	Crizotinib	76	Female	Former	Squamous	NA	25
Chr7:g.116412043G>C	No amp *MET/CEP7* 0.96	NA	Crizotinib	71	Male	Former	Adenocarcinoma	6+	26
c.2887-18>2887-7del12	NA	*CDKN2A/B* loss, *CDK4* amp, *MDM2* amp	Crizotinib	86	Male	Never	Adenocarcinoma	Crizotinib discontinued because of pneumonitis	27
Intron 14 +3 A>G	9 copies	None reported	Crizotinib	74	Female	Former	Sarcomatoid	NA	21

Abbreviations: amp, amplification; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; NA, not available; PFS, progression-free survival.

homologous exon 15 deletion in MET showed sensitivity to MET inhibition with the oral MET inhibitor INC280 [18]. Interestingly, Liu et al. reported that combined MET and PI3K inhibition was required for maximal inhibition of a cell line harboring *MET* exon 14 skipping and concurrent *PI3K E545K* mutation [21].

Clinically, several reports have shown promising signals of clinical activity among patients with *MET* exon 14 skipping treated with MET inhibitors, including crizotinib, cabozantinib, and INC280 [18, 21, 22, 25–27]. Paik et al. identified eight patients with *MET* exon 14 skipping, among whom four were treated with MET inhibitors (three with crizotinib and one with cabozantinib). These four patients all experienced significant regression of their tumor burden on the MET inhibitor therapy [22]. Frampton et al. described one patient who responded to crizotinib and two patients who were treated in a phase I study of INC280 who also demonstrated a partial response to therapy [18]. Liu et al. reported an increased frequency of *MET* exon 14 skipping among patients with pulmonary sarcomatoid carcinoma and noted one case that showed a response to crizotinib [21]. Other case reports have shown similar marked responses [25–27]. *MET* amplification is seen in some, but not all, of these cases, and the interplay among *MET* exon 14 skipping, *MET* amplification, and response to MET inhibitor therapy remains to be further clarified.

Similar to these other reports, this article describes a patient newly diagnosed with metastatic squamous cell carcinoma and *MET* exon 14 skipping with extensive disease, including bilateral pulmonary tumor thrombi and bony, adrenal, and liver metastases, with the MET inhibitor crizotinib. A dramatic treatment response was seen at 4 weeks and has been maintained for at least 6 months. Table 4 shows a summary of the reported cases in the literature that have shown response to MET therapy. Reported durations on therapy are preliminary but range from approximately 3 months to 13 months. Multiple MET inhibitors are in clinical testing, and studies will be needed to determine clinical activity in patients with *MET* exon 14 skipping.

Conclusion

We estimate that *MET* exon 14 skipping occurs at a frequency of approximately 5.6% in NSCLC. This is a single-institution experience, and it is possible that referral biases in terms of who is seen at our institution may skew this percentage; however, we perform tumor molecular profiling on all NSCLC cases regardless of any predefined selection criteria, such as smoking status or histology. Preliminary reports suggest significant activity of MET inhibitors against these cancers. Further studies are needed to determine the true response rate and best targeted therapies for this subset of lung cancer.

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Disclosures

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References

1. Lynch TJ, Bell DW, Sordella R et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129–2139.

2. Paez JG, Jänne PA, Lee JC et al. EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 2004;304:1497–1500.

3. Pao W, Miller V, Zakowski M et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci USA 2004;101:13306–13311.

4. Mok TS, Wu YL, Thongprasert S et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–957.

5. Soda M, Choi YL, Enomoto M et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561–566.

6. Kwak EL, Bang YJ, Camidge DR et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693–1703.

7. Shaw AT, Kim DW, Mehra R et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370:1189–1197.

8. Shaw AT, Ou SH, Bang YJ et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 2014;371:1963–1971.

9. Ding L, Getz G, Wheeler DA et al. Somatic mutations affect key pathways in lung adenocarcinoma. Nature 2008;455:1069–1075.

10. Seo JS, Ju YS, Lee WC et al. The transcriptional landscape and mutational profile of lung adenocarcinoma. Genome Res 2012;22:2109–2119.

11. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014;511:543–550.

12. Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. Nature 2012;489:519–525.

13. Dias-Santagata D, Akhavanfard S, David SS et al. Rapid targeted mutational analysis of human tumours: A clinical platform to guide personalized cancer medicine. EMBO Mol Med 2010;2:146–158.

14. Sequist LV, Heist RS, Shaw AT et al. Implementing multiplexed genotyping of non-small-cell lung cancers into routine clinical practice. Ann Oncol 2011;22:2616–2624.

15. Zheng Z, Liebers M, Zhelyazkova B et al. Anchored multiplex PCR for targeted next-generation sequencing. Nat Med 2014;20:1479–1484.

16. Kong-Beltran M, Seshagiri S, Zha J et al. Somatic mutations lead to an oncogenic deletion of met in lung cancer. Cancer Res 2006;66:283–289.

17. Ma PC, Jagadeeswaran R, Jagadeesh S et al. Functional expression and mutations of c-Met and its therapeutic inhibition with SU11274 and small interfering RNA in non-small cell lung cancer. Cancer Res 2005;65:1479–1488.

18. Frampton GM, Ali SM, Rosenzweig M et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov 2015;5:850–859.

19. Onozato R, Kosaka T, Kuwano H et al. Activation of MET by gene amplification or by splice mutations deleting the juxtamembrane domain in primary resected lung cancers. J Thorac Oncol 2009;4:5–11.

20. Awad MM, Oxnard GR, Jackman DM et al. MET exon 14 mutations in nonsmall cell lung cancer are associated with advanced age and stage dependent MET genomic amplification and c-met overexpression. J Clin Oncol 2016 [Epub ahead of print].

21. Liu X, Jia Y, Stooper MB et al. Next generation sequencing of pulmonary sarcomatoid carcinoma reveals high frequency actionable MET gene mutations. J Clin Oncol 2015 [Epub ahead of print]

22. Paik PK, Drilon A, Fan PD et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. Cancer Discov 2015;5:842–849.

23. Tanizaki J, Okamoto I, Okamoto K et al. MET tyrosine kinase inhibitor crizotinib (PF-02341066) shows differential antitumor effects in non-small cell lung cancer according to MET alterations. J Thorac Oncol 2011;6:1624–1631.

24. Matsubara D, Ishikawa S, Oguni S et al. Molecular predictors of sensitivity to the MET inhibitor PHA665752 in lung carcinoma cells. J Thorac Oncol 2010;5:1317–1324.

25. Mendenhall MA, Goldman JW. MET-mutated NSCLC with major response to crizotinib. J Thorac Oncol 2015;10:e33–e34.

26. Waqar SN, Morgensztern D, Sehn J. MET mutation associated with responsiveness to crizotinib. J Thorac Oncol 2015;10:e29–e31.

27. Jenkins RW, Oxnard GR, Elkin S et al. Response to crizotinib in a patient with lung adenocarcinoma harboring a MET splice site mutation. Clin Lun Cancer 2015;6:e101–104.

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