Lung Cancer: Targets and Therapy

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REVIEW

Lung Cancer with *MET* exon 14 Skipping Mutation: Genetic Feature, Current Treatments, and Future Challenges

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Abstract: *MET* exon 14 skipping mutation (*MET*Δex14) is present about 3% of non-small cell lung cancers (NSCLCs). NSCLC patients with *MET*Δex14 are characterized by an average age of over 70 years at diagnosis, a smoking history and a higher frequency in pleomorphic carcinoma and adenosquamous cell carcinoma than in adenocarcinoma. It has also been reported that NSCLCs with *MET*Δex14 often have codriver alterations such as *EGFR* amplification (6–28%), *FGFR1* alterations (5–17%), *KRAS* alterations (~8%), *BRAF* alterations (~21%), or *PIK3CA* mutation/amplification (~14%). In 2020, the approval of two MET-tyrosine kinase inhibitors (TKIs), capmatinib and tepotinib, for NSCLCs carrying *MET*Δex14 dawned a new era for MET-targeted therapy. These drugs yielded progression-free survival of 5.4−12.4 months in clinical trials; however, it has also been reported that one-third to half of patients show inherent resistance to MET-TKIs. In addition, the emergence of acquired resistance to MET-TKIs is inevitable. In this review, we summarize the clinical and molecular characteristics of NSCLCs with *MET*Δex14, the efficacy and safety of capmatinib and tepotinib, the inherent and acquired resistance mechanisms to MET-TKIs, and new treatment strategies for NSCLCs with *MET*Δex14 in the near future.

Keywords: non-small cell lung cancer, *MET* exon 14 skipping, capmatinib, tepotinib, resistance mechanisms, immune checkpoint inhibitors

Introduction

The *MET* proto-oncogene, located in the 7q31 locus of chromosome 7, encodes a receptor tyrosine kinase (RTK) for hepatocyte growth factor (HGF), also known as scatter factor. MET is essential for embryonic development, organogenesis and wound healing.[1] The *MET* gene was originally discovered as a part of an oncogenic fusion with the *TPR* (translocated promoter region) gene in a chemically induced human osteosarcoma cell line in 1984.[2] MET was named after the first three letters of the chemical mutagen "N-methyl-N'-nitro-N-nitrosoguanidine." Subsequently, increased *MET* expression and/or *MET* gene copy number gain was reported to be correlated with a poor prognosis in several types of carcinoma,[3–6] and thus, molecular targeted therapies against MET have been developed and tested in many clinical trials. However, the results of all these trials, which enrolled unselected populations or patients with MET protein overexpression, were disappointing.[7–9] These failures are attributable mainly to the insufficient selection of patients with tumors that are truly driven by MET.

Several types of *MET* aberrations, such as *MET* gene amplification, point mutations, gene fusions, exon 14 skipping mutations, or protein overexpression, have been reported

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in many types of carcinoma.[10–13] Among these *MET* aberrations, *MET* exon 14 skipping mutation (*MET*Δex14) in non-small cell lung cancer (NSCLC) became the first target for which MET-targeted therapy was approved in 2020. In this review, we summarize the normal structure and function of MET, the activation mechanism of MET by exon 14 skipping, the clinicopathological characteristics of NSCLCs with *MET*Δex14, the efficacies of currently available MET-TKIs (capmatinib and tepotinib) in this cohort, the inherent and acquired resistance mechanisms to MET-TKIs, and future directions to improve treatment outcomes of NSCLC patients with *MET*Δex14.

Normal MET Structure and Function

In human cells, the MET protein is first synthesized as a 190 kDa single-chain precursor that is cleaved within the SEMA domain by the intracellular endoprotease furin during transport to form the mature MET protein. The mature MET protein consists of a 50 kDa α chain and a 145 kDa β chain connected through disulfide bonds (Figure 1).[14] The extracellular domain contains the semaphorin (SEMA), plexin-semaphorin-integrin (PSI) and immunoglobulin-plexin-transcription (IPT) domains followed by a single-pass transmembrane segment. The intracellular domain contains juxtamembrane, tyrosine kinase, and multifunctional docking site domains.

HGF and its two shorter splicing isoforms (the N domain and kringle 1 and 2 (NK1 and NK2)) are the only known ligands for MET. NK1 acts as a partial agonist, while NK2 acts as an antagonist. The binding of HGF to the SEMA domain induces MET homodimerization, which causes the autophosphorylation of tyrosine residues at codons 1234 and 1235 (Y1234 and Y1235) in the activation loop of the tyrosine kinase domain. Subsequently, Y1349 and Y1356 in the carboxy-terminal

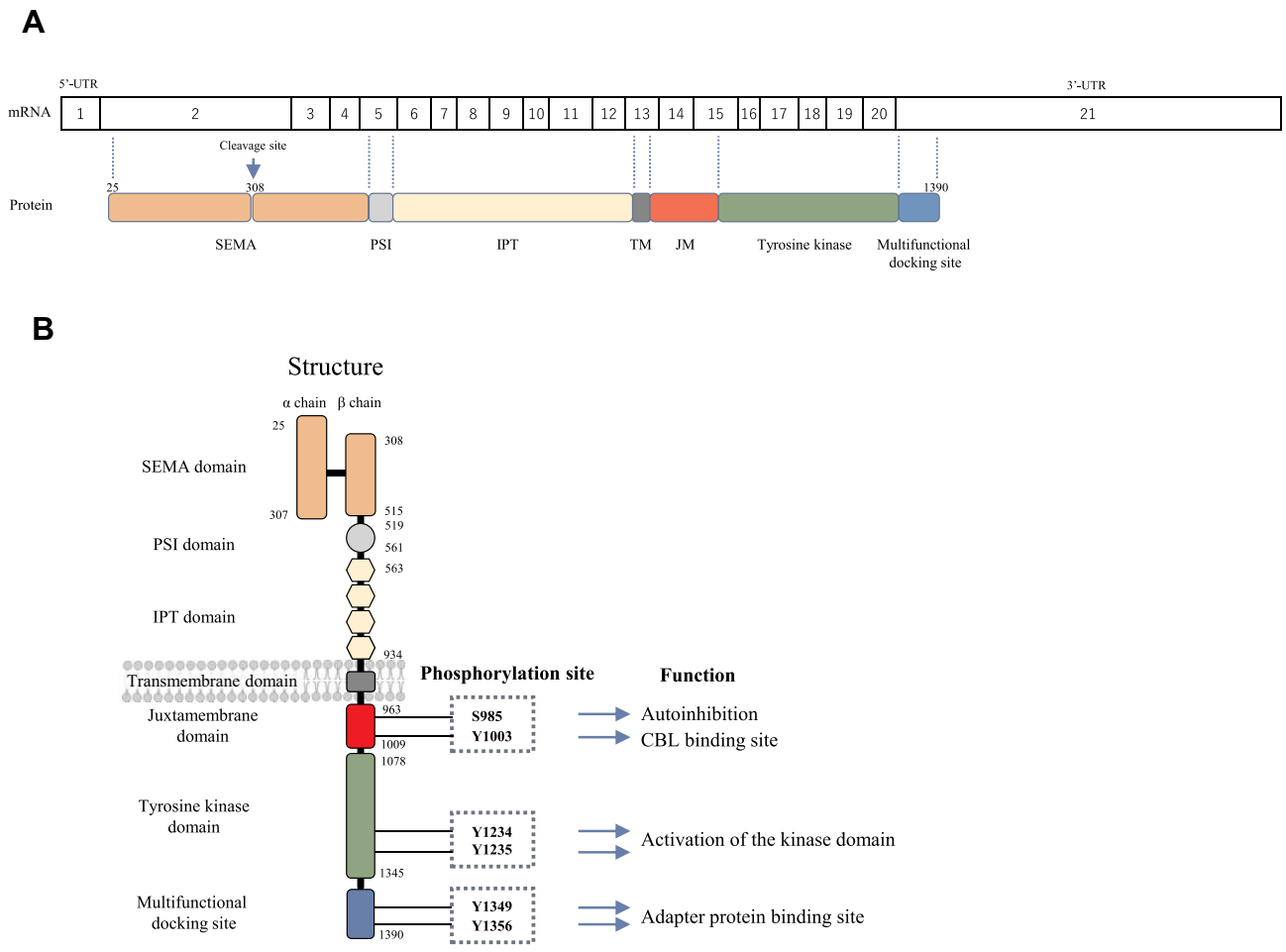

Figure 1 (**A**) Relationship between the MET protein and mRNA coding region and (**B**) the structure of normal MET. Mature MET consists of a 50 kDa alpha chain and a 145 kDa beta chain heterodimer through disulfide bonds. The extracellular domain of MET consists of the semaphorin (SEMA), plexin-semaphorin-integrin (PSI), and immunoglobulin-plexin-transcription (IPT) domains; the intracellular domain consists of juxtamembrane, tyrosine kinase and multifunctional docking site domains.

tail are phosphorylated and serve as docking sites for several SRC (SRC proto-oncogene, non-receptor tyrosine kinase) homology (SH)2 domain-containing intracellular molecules, such as PI3K, GRB2 (growth factor receptor-bound protein 2), GAB1 (GrB2-associated binder 1), PLCγ (phospholipase C), SRC, STAT3 (signal transducer and activator of transcription 3), CRK (CT10 regulator of kinase), and SHP2 (Figure 1B). Recruitment of these molecules results in the activation of several downstream pathways, including the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways.[15,16] The MET protein is often expressed on epithelial cells, while HGF is secreted by mesenchymal cells such as fibroblasts. HGF/MET signaling has important roles in cell motility, proliferation, embryogenesis, organogenesis, liver regeneration, and wound healing.[15,17–19]

Discovery of *MET* exon 14 Skipping and Its Activation Mechanisms

MET exon 14 skipping was originally discovered as an alternative splicing variant in cDNA isolated from normal mouse kidney, liver and brain tissues without any changes that disrupted the so-called splicing consensus sequence in 1994.[20] More than 10 years later in 2005, *MET*Δex14 was first reported in human NSCLC tissues as a result of a somatic mutation.[21] In NSCLCs, *MET*Δex14, deletion of the entire juxtamembrane amino acid (Δaa963-1009), is caused by several molecular aberrations, such as point mutations, insertions, deletions, or indels, that disrupt consensus sequences such as branch sites, polypyrimidine tracts, splice acceptors and splice donor sites for RNA splicing (Figure 2A).[22] It has been reported that there are more than 500 different mutations at the genomic DNA level that cause *MET* exon 14 skipping from the analysis of 1387 patients carrying this *MET* mutation.[23] Among these numerous aberrations, point mutations at the splice donor site are the most common. As expected, no phenotypic or therapeutic differences were recorded according to the difference in the molecular mechanisms.

The molecular mechanism by which *MET*Δex14 elicits oncogenic activity in NSCLCs was clarified by Kong-Beltran et al in 2006.[24] MET exon 14 contains Y1003, which forms a binding site for CBL, an E3 ubiquitin ligase, which was reported by Peschard et al.[25] Therefore, when exon 14 is skipped, CBL-mediated MET protein degradation is impaired, leading to the accumulation of MET receptors and the aberrant activation of MET oncogenic signaling (Figure 2B).

However, later studies have suggested additional molecular mechanisms by which *MET*Δex14 confers oncogenic activity. First, Lu et al showed that the half-life of the MET protein lacking the MET exon 14 region generated using the CRISPR/Cas9 system is extended only by 15% compared with the wild-type MET protein in airway epithelial cells.[26] This result may suggest that accumulation of the MET protein is not the sole molecular mechanism of MET activation. The authors also observed that *MET*Δex14 induced by editing the endogenous *MET* gene using the CRISPR/Cas9 system in $Trp53^{flox}$ mice was not oncogenic, whereas *MET*Δex14 in $Trp53^{flox}$ mice induced by a lentivirus system that could express MET lacking the exon 14 region stably from cDNA successfully induced a cancer phenotype.[26] This phenomenon suggests that the additive effect of increased *MET* expression, in addition to the skipping of exon 14, plays important roles in tumorigenesis driven by MET. In addition, other groups reported the role of the S985 residue, which is also located in exon 14 of *MET*. The phosphorylation of this amino acid residue by protein kinase C negatively regulates the kinase activity of MET (Figures 1B and 2B).[27,28]

Clinical Characteristics of NSCLC Patients with *MET* exon 14 Skipping

*MET*Δex14 is present in up to 3% of NSCLCs, and this incidence is comparable to that of ALK fusions in NSCLCs.[29–31] NSCLC patients with *MET*Δex14 tend to be older and have a smoking history than patients with other driver mutations. In addition, they have a higher frequency in pleomorphic carcinoma and adenosquamous cell carcinoma than in adenocarcinoma.[29,30,32] Among the histologic subtypes of lung adenocarcinoma, some studies have reported that *MET*Δex14 is associated with the acinar or solid predominant subtype.[30,33,34] The correlation between the frequency of *MET*Δex14 and race, sex, stage, and histological grade has not yet been reported or is still controversial. Some studies reported the detection of *MET*Δex14 in squamous cell carcinoma (~2%) and large cell carcinoma (0.8%).[30,33,35,36]

There are several methods to detect *MET*Δex14 in NSCLCs. These include next-generation sequencing (NGS)-based panel tests with RNA-based or DNA-based technique. In Japan, an anchored multiplex PCR-based

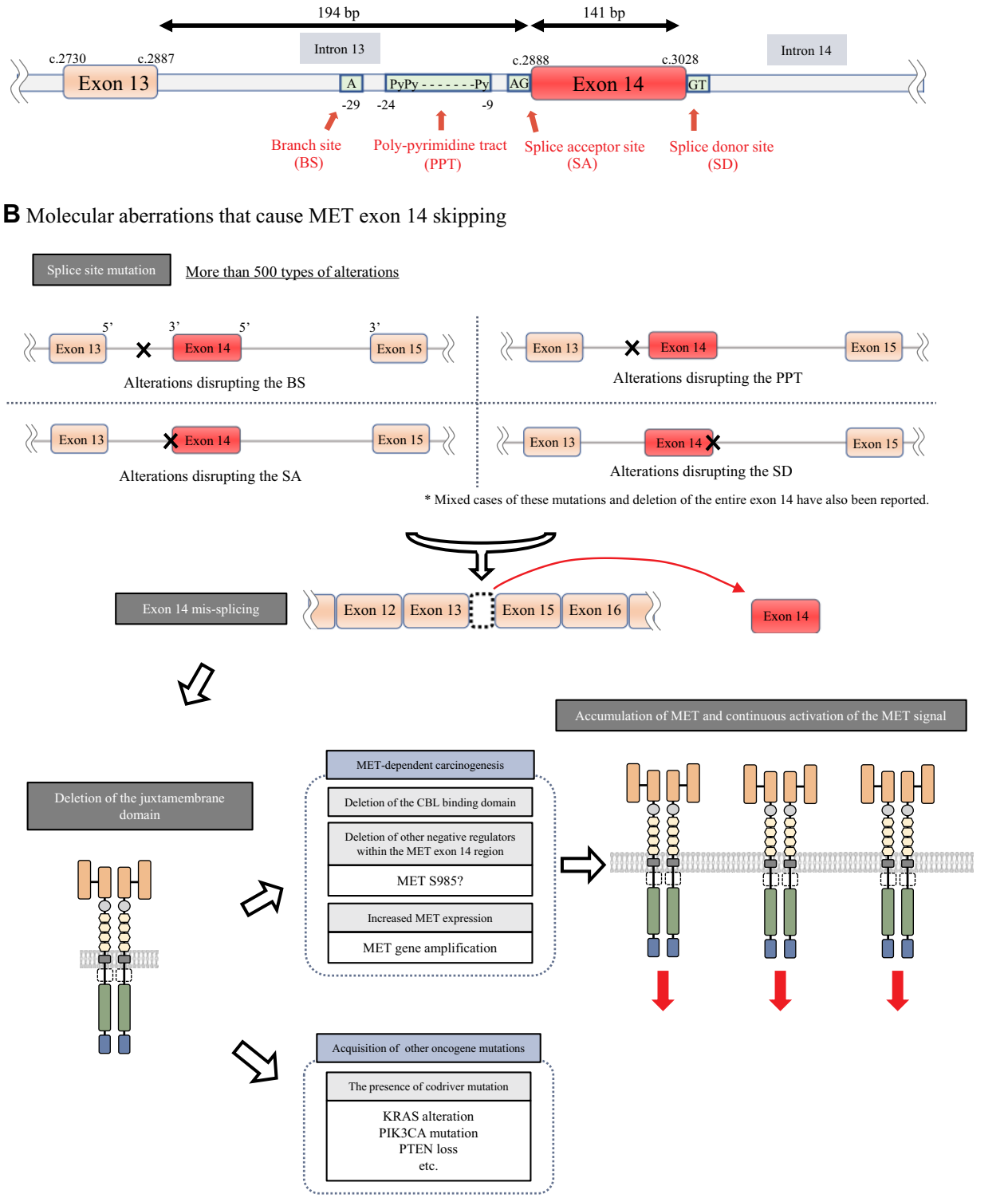

Figure 2 (**A**) Splicing consensus sequence consisting of a branch site, polypyrimidine tract, splice acceptor site and splice donor site. (**B**) Activation mechanism by *MET* exon 14 skipping. A large number of alterations, such as point mutations or insertions or deletions in the 3′ or 5′ splice site in *MET* exon 14, cause the mis-splicing of *MET* exon 14 by disrupting the splicing consensus, which results in an abnormal MET protein lacking a CBL-binding site. This causes the accumulation of shrinked MET receptors followed by increased MET signaling.

method (ArcherMET®) is approved to detect MET exon 14 skipping using RNA from tissue or ctDNA from liquid samples. Because there are more than 500 patterns of genomic DNA aberrations which cause MET exon 14 skipping as described above, as long as the quality of RNA is ensured, it has been reported that the sensitivity of RNA-based tests are better than DNA-based tests.[37,38] Among DNA-based NGS panel tests, it is suggested that the sensitivity of hybrid capture based NGS (represented by Foundation One® that are approved in US and in Japan) is better than that of amplicon-based NGS.[37]

Clinical Efficacies of MET-TKIs in NSCLCs with *MET* exon 14 Skipping

In 2015, Paik et al first reported the clinical efficacy of crizotinib and cabozantinib as 3rd-line therapies in NSCLC patients with *MET*Δex14.[39] In this report, crizotinib showed antitumor activity in three of four patients, and cabozantinib showed stable disease in one patient, suggesting that tumors with *MET*Δex14 depend on the *MET* pathway. Currently, there are many MET-TKIs under clinical development.[40] In 2020 and 2021, two MET-TKIs, capmatinib and tepotinib, were approved in the USA and Japan for use as monotherapies in NSCLC patients carrying *MET* exon 14 skipping. Both MET-TKIs are potent and highly selective ATP competitors for MET in in vitro or in vivo models carrying *MET*Δex14. Both drugs are classified as type Ib MET-TKIs and bind to an activated form of MET through interaction with the Y1230 residue in the activation loop of MET. It has also been reported that these type Ib MET-TKIs do not interact with the solvent front residue G1163 (homologous to G1202 and G2032 in the ALK and ROS1 genes, respectively).[41–44]

Capmatinib (Tabrecta®, INC280; Novartis)

The efficacy and safety of capmatinib were evaluated in the GEOMETRY mono-1 Phase II clinical trial (NCT02414139). A total of 97 NSCLC patients with *MET*Δex14 were recruited, consisting of the untreated (n=69) and previously treated (n=28) cohorts (Table 1). In this study, *MET*Δex14 was confirmed by qRT-PCR in a central laboratory using tumor tissues. Patients received a 400 mg dose of capmatinib twice daily. The objective response rates (ORRs) for the pretreated and treatment-naïve cohorts were 40.6% (95% CI, 28.9–53.1) and 67.9% (95% CI, 47.6–84.1), respectively. The median progression-free survival (PFS) times were 9.7 months (95% CI, 5.6–13.0) and 12.6 months (95% CI, 5.6-NE), respectively.[45] Based on this result, health authorities in the USA and Japan approved the use of capmatinib for NSCLC patients with *MET*Δex14 in May 2020 and June 2020, respectively.

Tepotinib (TEPMETKO®, EMD1214063, MSC2156119J; Merck [Darmstadt, Germany])

The efficacy and safety of tepotinib were evaluated in a phase II trial (VISION trial, NCT02864992). A total of 152 NSCLC patients with *MET*Δex14 were recruited regardless of previous treatment (Table 1). The patients were divided into two cohorts: those diagnosed by liquid biopsy (DNA-based assay) and those diagnosed by tissue biopsy (RNA-based assay). These patients received a 500 mg dose of tepotinib once daily.

In the total cohort, the ORR and median PFS were 46% (95% CI, 36–57) and 11.1 months (95% CI, 7.2-NE), respectively. The ORRs of patients diagnosed by liquid biopsy and tissue biopsy were 48% (95% CI, 36–61) and 50% (95% CI, 37–63), respectively.[46] In addition, the median PFS times were 8.5 months (95% CI, 6.7–11.0) and 11.0 months (95% CI, 5.7–17.1), respectively. The patients who received tepotinib in the first-line setting (n=43) showed an ORR of 44.2% (95% CI, 29.1–60.1), and those who received tepotinib in the second-line or later setting (n=56) showed an ORR of 48.2% (95% CI, 34.7–62.0).[46]

Based on this favorable result, in March 2020, tepotinib became the first approved MET-TKI for NSCLCs with *MET*Δex14 in Japan. In February 2021, the USA FDA also approved its use. In addition, the European Medicines Agency is now validating the approval of tepotinib for the treatment of advanced NSCLCs carrying *MET*Δex14.

Toxicities of Type Ib MET-TKIs

Common toxicities that will lead to the dose reduction or discontinuation of capmatinib and tepotinib are peripheral edema and increased serum creatinine.[45,46] Because peripheral edema has also been observed in clinical trials of antibody drugs targeting HGF or MET,[47,48] it is considered an on-target side effect of MET-HGF axis inhibition. Growth factors, including HGF, increase vascular endothelial barrier function, and inhibition of this barrier function is speculated to be a potential molecular mechanism.[49]

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Table 1 Clinical Efficacy of Capmatinib and Tepotinib

Compound/Clinical Trial/ Dose	Histology	Diagnostic Method	Prior Treatment		Number of Evaluated Patients	ORR (%) [95% CI]	DCR (%) [95% CI]	Median Duration of Response (Months) [95% CI]	Median PFS (Months) [95% CI]	Ref
Capmatinib/GEOMETRY mono-1 (NCT02414139)/ 400 mg BID	NSCLC (Ad 89%)	RT-PCR	Treatment-naïve	(cohort 5b)	28	68% [48–84]	96% [82–100]	12.6 [5.6 - NE]	12.4[8.2 - NE]	[45]
	NSCLC (Ad 77%)		Pre-treated	Previous 1 or 2 lines of therapy (cohort 4)	69	41% [29–53]	78% [67–87]	9.7[5.6–13.0]	5.42[4.2–7.0]	
				Previous 1 line of therapy (cohort 6)	31	N/A	N/A	N/A	N/A	
			Post-hoc analysis	Patietns with prior IO	32	62.5% [43.7–78.9]	87.5% [71.0–96.5]	9.95[5.55–19.52]	N/A	[87]
				Patietns without prior IO	68	33.8% [22.8–46.3]	79.4% [67.9–88.3]	6.93[4.17–11.14]	N/A	
Tepotinib/VISION study (NCT02864992)/500 mg QD	NSCLC (Ad 90%)	Combined biopsy (Liquid + Tissue)	All patients	1st-, 2nd-, 3rd-line	99	46.5% [36.4–56.8]	65.7% [55.4–74.9]		8.5 [6.7–11.0]	[46]
		Liquid biopsy (DNA)	All patients	1st-, 2nd-, 3rd-line	66	48.5% [36.0–61.1]	65.2 [52.4–76.5]		8.5 [5.1–11.0]	
			Treatment-naïve		15	58.8% [32.9–81.6]	N/A			
			Pre-treated		31	45.2% [27.3–64.0]	N/A			
		Tissue biopsy (RNA)	All patients	1st-, 2nd-, 3rd-line	60	50.0% [36.8–63.2]	68.3% [55.0–79.7]		11.0[5.7–17.1]	
			Treatment-naïve		18	44.4% [21.5–69.2]	N/A			
			Pre-treated		33	45.5% [28.1–63.6]	N/A			

Notes: *Assessed by investigator. ** Calculated by author.

Abbreviations: ORR, objective response rate; DCR, disease control rate; NSCLC, non-small cell lung cancer; Ad, adenocarcinoma; PSC, pulmonary sarcomatoid carcinoma; GCN, gene copy number; qPCR, quantitative polymerase chain reaction; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; N/A, not available; NE, not evaluable.

The increase in serum creatinine is suspected to be due to the inhibitory effects of organic cation transporters (OCTs) and multidrug and toxin extrusion protein transporters (MATEs) in the human kidney by capmatinib and tepotinib. OCTs and MATEs are known as the major transporters for cation drugs (such as capmatinib and tepotinib) from the blood and into the urine.[50] Because 10–20% of eliminated creatinine is due to creatinine secretion via these transporters in the renal tubules,[51] it is hypothesized that capmatinib or tepotinib will antagonize serum creatinine. Therefore, it is believed that the increases in serum creatinine levels are due to the inhibition of creatinine transport by capmatinib or tepotinib and are not due to true renal function failure.

Inherent and Acquired Resistance Mechanisms to MET-TKIs

With the approval of capmatinib and tepotinib, these drugs will be used for the treatment of NSCLC patients carrying *MET*Δex14 in clinical practice. However, the results of clinical trials have shown that approximately one-third to one-half of patients show initial resistance to capmatinib or tepotinib.[45,46] In addition, even in patients who show an initial clinical response to capmatinib or tepotinib, the emergence of acquired resistance is almost inevitable.[52] In this section, we summarize inherent and acquired resistance mechanisms to MET-TKIs and potential therapeutic strategies to overcome resistance.

Potential Factors Related to Inherent Resistance to MET-TKIs

As described above, the ORRs of two approved MET-TKIs in NSCLC patients carrying *MET*Δex14 in each clinical trial were 44–68%, even in treatment-naïve patients.[45,46] These numbers are much lower than those in epidermal growth factor receptor (*EGFR*)-mutated NSCLC patients treated with EGFR-TKIs or NSCLC patients with ALK fusions treated with ALK-TKIs.[53–56] Therefore, some clinical trials of MET-TKIs for NSCLCs with *MET*Δex14 have explored factors that are associated with the efficacy of MET-TKIs by performing molecularly defined subgroup analyses based on (1) the location of the splicing site mutation at the genomic DNA level, (2) the coexistence of *MET* amplification, and (3) the presence of codriver gene alterations. Among them, it has been reported that the mutation site at the genomic DNA is not associated with the efficacy of MET-TKIs.[46,57]

The frequency of coexisting *MET* amplification is reportedly approximately 4–40% among NSCLCs with *MET*Δex14 (Table 2).[29,30,35,45,46,57–59] Although *EGFR* amplification or *ALK* amplification has been reported as an acquired resistance mechanism to EGFR-TKIs or ALK-TKIs, respectively, some studies have reported that the ORRs of MET-TKIs are better in *MET*Δex14-positive NSCLC patients with coexisting *MET* amplification than in patients without *MET* amplification. This result may indicate that the coexistence of *MET* amplification suggests that tumors depend solely on MET signaling.[60,61] On the other hand, Guo et al reported that some patients with *MET*Δex14 had no detectable MET protein expression on MET immunohistochemistry (IHC)/mass spectrometry.[61] The authors found that these tumors, without a detectable MET protein, had a high frequency of codriver alterations in the RAS/RAF/MAPK or PI3K/AKT pathway, suggesting that these tumors are refractory to MET-targeted therapies.

Another possible reason for the low sensitivity of NSCLCs with *MET*Δex14 to MET-TKIs is (3) the presence of codriver gene alterations. As summarized in Table 2, tumors with *MET*Δex14 often harbor codriver mutations/amplifications. Potential codrivers include alterations of other RTKs, such as *EGFR* amplification (6.4–28.5%) or *FGFR1* alteration (4.8–16.6%); aberrant activation of the RAS-RAF-MAPK pathway, such as *KRAS* alteration (~8%) or *BRAF* alteration (~21.4%); and activation of the PI3K-AKT pathway, such as *PIK3CA* mutation/amplification (~14.2%).[58,59] As a preclinical model, the NCI-H596 lung cancer cell line harbors *MET*Δex14; however, this cell line is resistant to MET inhibition. The coexistence of *PIK3CA* mutation is the mechanism of resistance to MET inhibition, and it was reported that NCI-H596 cells were effectively killed by the combination of a PI3K inhibitor and a MET-TKI.[62,63] Indeed, a retrospective analysis reported that the coexistence of these mutations resulted in primary resistance to MET-TKIs or a short response duration in NSCLC patients with *MET*Δex14.[58,59,61,64]

Mutations of the *TP53* gene (27–50%) and the amplification of *MDM2* (2–46%), which is an E3 ubiquitin ligase for TP53, are frequently identified in NSCLCs with *MET*Δex14. In addition, they are reportedly mutually exclusive.[13] Although the coexistence of *TP53* mutation is associated with reduced efficacy in *EGFR*-mutated NSCLCs treated with EGFR-TKIs,[65] we could not find evidence that showed the impact of *TP53* or *MDM2*

Table 2 Exploration of Biomarker for Efficacy of MET-TKI

No	Author/Country/ Ref	Detection Method/ Biposy Method/ Targeted Genes	Number of Patients	MET Amp (Cut Off)	Other RTK	RAS/RAF/MAPK	PI3K/AKT/ MTOR	TP53	Cell Cycle	Others.
1	Awad, et al./US[29]	Hybrid capture based NGS/Tumor/282	28	21% by FISH (MET: CEP7≧3)	EGFR:28.5% (Amp) HER2:7.14% (Amp) HER3:3.5% (Amp) FGFR1:16.6% (Alt) FGFR3: 10.7%(Alt)	KRAS:7.14% (Amp) BRAF:21.4% (Alt) NF1:14.2% (Mt)	PIK3CA:3.5% (Mt)/10.7% (Amp) PTEN:3.5% (Mt)	TP53:32% (Mt) MDM2:46% (Amp)	CDK1:7.1% (Amp) CDK4:17.8% (Amp) CDK6:21.4% (Amp) CDKN2A/B::25% (Alt) RB1:14% (Alt)	ARID2:21.4% (Alt) ATM: 10.7% (Alt) MYC:14.2% (Amp) TERT:21.4% (Amp)
2	Shrock, et al./US[30]	Hybrid capture based NGS/Tumor/236	298	14.80%	EGFR:6.4% (Amp)/0.3% (Mt) HER2:0.7% (Amp) ALK:0.3% (Fusion)	KRAS:3% (Mt) BRAF:0.3% (Mt)	NA	MDM2:34.6% (Amp)	CDK4:21.1%	NA
3	Rotow, et al./US[58]	NGS/cfDNA/73	289	6.60%	EGFR:23% (Alt) HER2:4.2% (Alt) ALK:4.5% (Alt) KIT:4.2% (Alt) FGFR1:4.8% (Alt) PDGFRA:4.5% (Alt)	KRAS:8.0% (Alt) NRAS:2.4% (Alt) BRAF:10.7% (Alt) NF1:15.6% (Alt) RAF1:2.1% (Alt)	PIK3CA:9.0% (Alt)	TP53:49.5% (Mt)	CDK4:10.4% (Alt) CDK6:6.2% (Alt) CDK2NA:4.8% (Alt) RB1:4.5% (Alt)	APC:7.3% (Alt) AR:2.1% (Alt) ARID1A:4.2% (Alt) ATM:4.5% (Alt) BRCA1:4.5% (Alt) BRCA2:4.5% (Alt) MYC:2.8% (Alt) STK11:4.2% (Alt) SMAD4:3.5% (Alt) TSC1:2.1% (Alt)
4	Jamme, et al./ France[59]	Amplicon based NGS/ Tumor/32	65	13% by FISH (MET: CEP7≧1.8)	EGFR:1.5% (Mt)	KRAS:3% (Mt) NRAS:1.5% (Mt)	PIK3CA:3% (Mt) PTEN loss 23% by IHC (n=6/25)	TP53:27% (Mt)	NT	SMAD4:1.5%(Mt)

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5	Cheng, et al./China[35]	Hybrid capture based NGS/Tumor/139 or 425	175	4%	EGFR:8% (Amp)/10% (Mt) HER2:1% (Mt) ALK:2% (Mt) NTRK1:2% (Alt) RET:1% (Alt) ROS11% (Alt)	KRAS:0% (Amp)/4% (Mt) NRAS:2% (Alt) BRAF:1% (Mt) NF1:5% (Alt) MAP2K1:1%(Mt)	PIK3CA 4% (Mt)	TP53:43% (Alt) MDM2:2% (Amp)	CDK4:5% (Alt) CDK6:2% (Amp) CDK2NA:3% (Alt) RB1:3% (Alt)	APC:2% (Mt) ATM:5% (Alt) GNAS:2%(Alt) MYC:6% (Alt) SMAD4:3% (Alt) SMARCA4:2% (Alt) LRP1B:7%(Alt) HGF:5% (Alt)
6	Drilon, et al./Phase I Global(crizotinib)[57]	Hybrid capture based NGS/Tumor or cfDNA/ 324 or 64	35	4%	EGFR: 3%(Amp) HER2: 3% (Mt) HER3:3% (Mt) KIT: 3% (Mt) NTRK3:6% (Alt)	KRAS:3% (Mt) BRAF:3% (Mt) NF1:3% (Mt)	PIK3CA: 6% (Mt) PTEN:3% (Mt)	TP53:40% (Alt) MDM2:20% (Amp)	CDDK4:14% (Amp) CDK6:3% (Amp) CDK2NA:23% (Alt) CDK2NB:17% (Loss) MTAP:9% (Loss) RB1: 6% (SNV)	AXIN1:9% (Mt) ATM:6% (Mt) BRCA1:6% (Mt) BRCA2:9% (Mt) CHEK2: 6% (Mt) RADD21:11% (Amp) RBM2:9% (Mt) SMAD4: 6% (Mt)
7	Wolf, et al./Phase II Global (capmatinib)[45]	Hybrid capture based NGS/Tumor/324	69 Pre-treated	40.5% (GCN≧6)	EGFR:11% (Amp)	KRAS:8% (Alt)	NA	TP53:45% (Mt) MDM2:36% (Amp)	CDKN2A:20–25% (Del) CDKN2B:20–25% (Del) MTAP:20–25% (Del)	NA
			28 Treatment naïve	25% (GCN≧6)		KRAS:5% (Alt)	NA	TP53:40% (Mt) MDM2:40% (Amp)		
8	Paik, et al./Phase II Global (tepotinib)[46]	NGS/cfDNA/73	62 (Any line)	8%	EGFR:10% (Amp) HER2:2% (Mt)	KRAS:2% (Amp)/2% (Mt) NRAS:2% (Mt) NF1:10% (Mt)	PIK3CA:3% (Mt) PTEN:3% (Mt)	TP53:48% (Mt)	CDK6:2% (Amp)	GNAS: 8% (Mt)

Abbreviations: NGS, next-generation sequencing; Alt, alterations; Mt, mutations, Amp, amplification; NA, not available; NT, not tested; No. 1-5; retrospective analysis, No. 6-8; Clinical trial cohort. Alteration includes single nucleotide variant (SNV), insertion, deletion, rearrangement, copy number variation (CNV). Mutation includes single nucleotide variant(SNV), insertion and deletion.

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alterations on the efficacy of MET-TKIs in NSCLC patients with *MET*Δex14. Taken together, these results indicate that the coexistence of gene aberrations in the p53 pathway may be involved in the process of oncogenic transformation in NSCLC with *MET*Δex14.

Acquired Resistance Mechanisms to MET-TKIs

As with other TKI therapies, such as EGFR-TKIs or ALK-TKIs, for NSCLCs with a driver mutation, acquired resistance to MET-TKIs is also inevitable Some studies have reported acquired resistance mechanisms to MET-TKIs in patient specimens obtained after MET-TKI treatment failure. In addition, we reported potential acquired resistance mechanisms that were identified by in vitro experiments. Acquired resistance mechanisms to MET-TKIs can be classified into secondary mutations of *MET* (on-target resistance mechanisms) and activation of bypass signaling (off-target resistance mechanisms). Recondo et al analyzed resistance mechanisms to MET-TKIs (mainly crizotinib) in 20 patients with *MET*Δex14 and reported that the on-target and off-target mechanisms accounted for 35% and 45%, respectively.[52] However, it is not clear whether more specific MET-TKIs, capmatinib and tepotinib show similar frequencies of on-target and off-target resistance mechanisms because crizotinib is a multitarget TKI.

As acquired resistance mechanisms to capmatinib or tepotinib, we found through an in vitro analysis using Ba/F3 models that *MET* secondary mutations involving D1228 or Y1230 in the activation loop are common as on-target resistance mechanisms.[43] In a clinical case report, it was reported that a variety of amino acid substitutions at codons D1228 and Y1230 occurred in a single patient.[66] As an acquired resistance mechanism to crizotinib, the MET solvent front mutation G1163R has been reported.[67] However, it has been shown that capmatinib and tepotinib do not interact with the *MET* G1163 residue; therefore, secondary mutations involving G1163 will not occur as a resistance mechanism to capmatinib or tepotinib.[43] Our in vitro study also showed that the potential on-target resistance mechanisms to capmatinib or tepotinib, D1228 or Y1230 secondary mutations, can be overcome by so-called type II MET-TKIs[43] such as merestinib, cabozantinib and glesatinib, which bind to the inactive state of MET.[68] However, in clinical cases, type II MET-TKIs, cabozantinib and glesatinib showed antitumor activity against Y1230X-mediated resistance but not against D1228X-mediated resistance.[52,69–71]

As off-target resistance mechanisms to MET-TKIs, genetic alterations that cause activation of the RAS/RAF/MAPK pathway (such as *KRAS* amplification or *KRAS* mutations) and/or the PI3K/AKT pathway (such as *PIK3CA* mutation) have been reported.[52,58,64,72] Preclinical studies have shown that combination therapy with trametinib, a MEK inhibitor, or GDC0941, a PI3K inhibitor, can overcome these acquired resistance mechanisms to MET-TKIs.[46,59,64,72] A few studies reported that *EGFR, HER3*, and *MDM2* amplification was detected after acquired resistance to MET-TKIs; however, it is not clear whether amplification of these genes is truly associated with acquired resistance to MET-TKIs.[58,66]

Future Treatment Strategies for NSCLCs with *MET* exon 14 Skipping

At present, after capmatinib or tepotinib treatment failure, NSCLCs with *MET*Δex14 are treated following the recommendations for NSCLCs with no detectable driver mutation or an unknown mutational status. As a future treatment strategy, MET antibody drugs are now being evaluated in clinical trials. In addition, some recent studies have reported the superior efficacy of immune checkpoint inhibitors (ICIs) in NSCLC patients with *MET*Δex14. In this section, we summarize the efficacies of these treatments in NSCLC patients with *MET*Δex14.

MET Antibodies

Antibodies targeting MET are designed to bind to the SEMA domain of MET, which is important in HGF binding to MET. These MET antibodies are also expected to promote receptor internalization and degradation, resulting in inhibition of the MET signaling pathway, and to enhance complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). MET antibodies have been clinically developed for some time.[7,73] In a Phase III trial (NCT01456325) that compared the efficacy of onartuzumab (a MET monoclonal antibody) plus erlotinib with placebo plus erlotinib in advanced NSCLC patients exhibiting MET expression (>50% by IHC), improved clinical outcomes were not observed. This disappointing result could be attributed to insufficient patient selection. At present, it is believed that MET overexpression itself does not necessarily indicate a truly MET-driven state from the two findings that MET overexpression coexists with various oncogenic mutations[74] and that MET overexpression is independent of *MET*Δex14.[74,75] On the other hand, these

findings may show antitumor activity for NSCLC patients with *MET*Δex14, which results in accumulation of the MET protein. Selecting patients with both METΔex14 and Met overexpression may be a useful strategy to test anti-MET antibodies.

One MET antibody being developed for use in NSCLC patients with *MET*Δex14 is Sym015 (Symphogen, Copenhagen, Denmark) (Table 3). This drug consists of two recombinant humanized IgG1 monoclonal antibodies targeting different epitopes of MET. MET internalization/degradation and the stimulation of CDC/ADCC have been observed in in vitro and in vivo experiments after treatment with Sym015.[76] A phase I/II trial (NCT02648724) of Sym015 in NSCLC patients with *MET*Δex14 who progressed on a MET-TKI is currently ongoing.

Immunotherapies

Immunotherapy with/without chemotherapy has become a standard front-line therapy for NSCLCs without detectable driver mutations. On the other hand, it has been reported that the efficacy of immunotherapies is low in NSCLC patients with *EGFR* mutations or *ALK* fusions.[77,78] However, as described above, the clinicopathological characteristics of NSCLC patients with *MET*Δex14, such as smoking status or histology, are different from those of NSCLC patients with *EGFR* mutations or *ALK* fusions. Therefore, it is not surprising that some retrospective studies showed that the expression of PD-L1, a potential biomarker used to predict the efficacy of ICIs, is high in NSCLCs with *MET*Δex14 (43–-91% if 1% ≧ PD-L1 is used as a cutoff) (Table 4).[23,79–85] This high PD-L1 expression may be due not only to so-called adaptive immune resistance but also to activated MET signaling; a preclinical study showed that MET activation induced the expression of several immune checkpoints, including PD-L1, through a *JAK2*-independent pathway.[86] Therefore, the efficacy of ICIs in NSCLC patients with *MET*Δex14 has received a great deal of attention. Some retrospective studies have reported the efficacy of ICI monotherapy in NSCLC patients with *MET*Δex14. However, the efficacy of ICI monotherapy is controversial because any reported results were obtained from retrospective, small cohort analyses, and the efficacy varied depending on the report.[79–81] On the other hand, the efficacy of ICI + chemotherapy in NSCLCs with *MET*Δex14 is currently unknown, and further analysis is warranted.

Combination or sequential treatments involving ICIs and MET-TKIs could be promising strategies in the treatment of NSCLC patients with *MET*Δex14. In the post hoc analysis that compared the type of prior therapy before capmatinib in the GEOMETRY phase II trial, there was a large difference in the response rate to capmatinib: 32% in the chemotherapy-pretreated group and 64% in the ICI-pretreated group (Table 1).[87] One possible reason for this difference is that the residual effect of ICIs used in the previous treatment was boosted by the use of MET-TKIs because MET signaling reportedly affects the immune system.[88] For example, Glodde e2t al showed the synergistic efficacy of MET inhibition and ICIs regardless of the tumor's MET status in vivo.[89] The authors reported that MET-expressing neutrophils are mobilized from the bone marrow to tumors in response to ICIs, these neutrophils confer immunosuppressive properties in tumors, and MET inhibition impairs reactive neutrophil

Table 3 MET Antibody Under Clinical Development for NSCLC Patients Carrying MET Exon 14 Skipping Mutation

Compound/ Clinical Trial	Dose	Class	Prior Treatment	Number of Evaluated Patients	ORR (%) [95% CI]	DCR (%) [95% CI]	Median Duration of Response (Months) [95% CI]	Median PFS (Months) [95% CI]	Ref
Sym 015/Phase 1/2a (NCT002648724)	Loading: 18mg/kg C1D1 Maintenance: 12mg/kg	IgG1 mAb	MET-TKI naïve	3	100%	100%	6.5 [3.8–9.2]	9.2 [7.4–11.0]	[76]
			MET-TKI pre-treated	9	0.00%	55.60%	(-)	5.4 [1.2–9.7]	
REGN5093/ Phase I/II (NCT04077099)	NA	Human bispecific antibody	MET-TKI naïve	Recruting	NA				

Note: *Assessed by investigator.

Abbreviations: ORR, objective response rate; DCR, disease control rate; NSCLC, non-small cell lung cancer; Ad, adenocarcinoma; PSC, pulmonary sarcomatoid carcinoma; GCN, gene copy number; qPCR, quantitative polymerase chain reaction; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; N/A, not available; NE, not evaluable.

Table 4 Summary of Studies Which Analyzed PL-L1 Status in NSCLC with MET Aberrations

Year	Country	Number of Patients	Histolgy	MET Mutation Status	Smoking Status	PD-L1 Expression rate (%)			TMB (mts/ Megabase)	Efficacy of ICI as Monotherapy			Ref
						< 1%	1%≦	50%≦		ORR (%) [95% CI]	mPFS (Month) [95% CI]	OS (Month) [95% CI]	
2018	US	147	NSCLC (74% Ad)	MET exon 14 skip	Never 35% Former or Current 65%	37	63	41	3.8 in cohort A 7.3 in cohort B	17 [6–36]	1.9 [1.7–2.7]	N/A	[79]
2018	Global	36	All lung neoplasms (94.4% Ad)	MET exon 14 skip or MET amp	Never 25% Former or Current 76.5%	25	75	46.7	NA	16	3.4 [1.7–6.2]	18.4 [7.0-NE]	[80]
				MET exon 14 skip (23; 64%)	N/A		N/A			N/A	4.7 [1.8–7.8]	25.0 [18.4-NE]	
				MET amp (13; 36%)	N/A		N/A			N/A	1.3 [0.-6.2]	8.0 [1.0–11.4]	
2019	France	30	NSCLC (93% Ad)	MET mutation	Never 37% Former or Current 64%	17%	43	37	N/A	36	4.9	13.4	[81]
2020	Germany	59	NSCLC (93.2% Non-sq)	MET exon 14 skip	Never 35.6% Former or Current 59.3%	27.8	72.2	36.1	N/A	N/A	N/A	16.0 [10.0–22.0]	[82]
2020	Netherands	17	All lung neoplasms (Unknown histlogy status)	MET exon 14 skip	N/A	5.9	94.1	64.7	N/A	N/A	N/A	N/A	[83]
2020	US	82	Ad	MET mutation	N/A	35*	65*	38	N/A	N/A	N/A	N/A	[84]
2020	US	352	NSCLC	MET exon 14 skip	N/A	25*	75*	48	N/A	N/A	N/A	N/A	[23]
2020	France	13	NSCLC	MET exon 14 skip	N/A	N/A			N/A	46%	N/A	N/A	[85]

Notes: *Estimated number from figure N/A, not available; N/E, not evaluable.

Abbreviations: NSCLC, non-small cell carcinoma; Ad, adenocarcinoma; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.

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recruitment to tumors. It has also been reported that the combination of ICIs plus MET-TKIs is tolerable in NSCLC patients.[90] In addition, in January 2021, the FDA approved the combination of nivolumab and cabozantinib, a type II MET-TKI, as a first-line treatment for patients with advanced renal cell carcinoma based on the results of a phase III trial.[91]

Conclusion

The approval of two MET-TKIs, capmatinib and tepotinib, for NSCLCs with *MET*Δex14 marked a new revolution of MET-targeted therapy. However, as summarized in this review, NSCLCs with this mutation often have codriver mutations and are highly heterogeneous; therefore, it is understandable that some patients show inherent resistance to MET-TKIs. In addition, some studies reported on-target and off-target mechanisms of acquired resistance to MET-TKIs. In addition to immunotherapy, novel treatments, including novel MET-TKIs, MET antibodies, and novel combination therapies, are now being evaluated in clinical trials.

Disclosure

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