REVIEW ARTICLE

Targeting MET in NSCLC: An Ever-Expanding Territory

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ABSTRACT

MET protooncogene (MET) alterations are known driver oncogenes in NSCLC. Since the identification of MET as a potential therapeutic target, extensive clinical trials have been performed. As a result, MET-targeted therapies, including MET tyrosine kinase inhibitors, monoclonal antibodies, and MET antibody–drug conjugates now play important roles in the standard treatment of MET-altered NSCLC; they have considerably improved the outcomes of patients with tumors that harbor MET oncogenic drivers. Although clinical agents are currently available and numerous other options are in development, particular challenges in the field require attention. For example, the therapeutic efficacy of each drug remains unsatisfactory, and concomitantly, the resistance mechanisms are not fully understood. Thus, there is an urgent need for optimal drug sequencing and combinations, along with a thorough understanding of treatment resistance. In this review, we describe the current landscape of pertinent clinical trials focusing on MET-targeted strategies and discuss future developmental directions in this rapidly expanding field.

Keywords: MET; Tyrosine kinase inhibitor; Monoclonal antibodies; Antibody-drug conjugate; Non–small cell lung cancer

Introduction

MET protooncogene (MET) encodes the c-MET protein,[1] which belongs to the receptor tyrosine kinase family. Among patients with cancer, MET alterations play important roles in promoting tumor invasion, angiogenesis, and metastasis.[2] MET alterations in NSCLC mainly include MET exon 14 skipping mutations (METex14, 2%–4%),[3,4] MET amplification (METamp) (1%–6%),[5,6] MET overexpression (20%–25%),[7,8] and MET fusion (0.2%–0.3%).[9] Of these, secondary METamp is the most common type of EGFR resistance bypass, comprising approximately 7% to 18% of EGFR-acquired resistance mutations.[10,11] Overlap of METex14 skipping mutations and METamp occurs in approximately 7.6% to 13.8% of cases.[12,13]

METex14 and METamp are treatable driver genes for NSCLC. METex14 results in the loss of the cytoplasmic juxtamembrane domain, which contains multiple sites involved in the regulation of MET signaling and cell survival, including the E3 ubiquitin ligase CBLB binding site and associated ubiquitination sites. Loss of this region impairs internalization and degradation of the MET

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protein receptor, leading to a prolonged MET receptor half-life, sustained dysregulated activation of downstream signaling pathways, and resultant cell proliferation and NSCLC tumor growth.[14–16] Elevation of the MET gene copy number (GCN) is caused by gene amplification on chromosome 7 or polysomy or aneuploidy of chromosome 7.[17] METamp refers to the specific gain of gene copies in one arm of chromosome 7, whereas polysomy involves an overall increase in the chromosome copy number. Compared with polysomy, which does not exhibit a favorable response to MET inhibitors, METamp has been identified as another mechanism of oncogenic activation and a therapeutic target of increasing importance.[18,19] METamp can exhibit oncogenic effects by increasing the local receptor concentration, leading to autodimerization of receptors and subsequent hyperactivation of downstream signaling pathways.[20–22]

MET overexpression and fusion also exhibit potential as therapeutic targets.[21,23] Notably, MET overexpression has not been consistently reported to confer sensitivity to MET-targeted therapy, possibly because of the challenges involved in defining normal expression and overexpression; moreover, overexpression may not be equivalent to MET-dependent activation.[8]

The precise detection of MET alterations has gained increasing attention. Assays that combine DNA-based next-generation sequencing (NGS) and RNA-based NGS have exhibited superior performance in detecting METex14 and MET fusion.[20,24] In addition, fluorescence in situ hybridization (FISH), quantitative real-time polymerase chain reaction, and NGS have all been used to detect METamp.[25] Among these methods, FISH is considered the accepted standard because it exhibits a strong correlation with treatment outcomes. It defines METamp on the basis of the MET GCN or MET/enumeration probe (CEP7) ratio, effectively distinguishing focal METamp from polysomy.[26] Nevertheless, there remains a lack of consensus regarding the specific threshold value for the MET/CEP7 ratio or changes in GCN across studies.[27] Various MET/CEP7 ratio cutoffs have been explored across studies to define amplification, including ratios of greater than or equal to 1.8, greater than or equal to 2.0, greater than 2.2, and greater than or equal to 5.0.[5,28] A GCN of greater than or equal to 5.0 was defined as METamp in the TATTON trial and INSIGHT study.[29,30] However, a GCN of greater than or equal to 2.5 was used as the threshold in the VISION study,[31] and a GCN of greater than or equal to 10 were considered indicative of METamp in the GEOMETRY mono-1 trial.[32] Similarly, discrepancies in establishing a definitive threshold for MET overexpression through immunohistochemistry (IHC) have been identified across trials.[3] The interpretation of IHC testing primarily relies on different staining intensities and the proportion of positive tumor cells. The TATTON and SAVANNAH studies defined MET overexpression as IHC 3+ (≥50% of tumor cells with strong staining).[29,33] Another study defined MET overexpression as IHC 2+ (≥50% of tumor cells with moderate to strong staining and less than 50% of tumor cells with strong staining),[34] whereas the INSIGHT study defined MET overexpression as IHC 2+ or IHC 3+.[30] An H-score of greater than or equal to 150 has also been used to define MET overexpression. The H-score (range, 0–300) is calculated through the multiplication of the percentage of stained cells by the intensity of staining (range: 0–3)[35] (Fig. 1).

MET-targeted regimens are divided into three categories: MET tyrosine kinase inhibitors (TKIs), monoclonal antibodies, and antibody-drug conjugates (ADCs). This review describes the clinical development of these three major categories of drugs targeting MET alterations in NSCLC, with a focus on their recent progress and future directions.

Updated Landscapes of MET TKIs

MET TKIs consist of three types: I, II, and III. Type I TKIs are adenosine triphosphate (ATP)–competitive inhibitors that form hydrogen bonds with amino acid residues in the MET backbone. Type I TKIs are further categorized into types Ia and Ib. Type Ib TKIs include capmatinib and tepotinib (approved by the U.S. Food and Drug Administration) and savolitinib, gumarontinib, and bozitinib (approved by the People's Republic of China National Medical Products Administration); these drugs have higher binding selectivity than type Ia TKIs.[36,37] Type Ia MET TKIs include the classic crizotinib and the new-generation drug ensartinib. Ensartinib is a modification of crizotinib that retains the benzyloxy group and replaces aminopyridine with aminopyridazine as the pharmacodynamic group, further increasing its lipid solubility and affinity while enhancing its capacity for blood-brain barrier penetration.[38,39] Ensartinib is a potent TKI against ALK fusions with remarkable intracranial activity both in crizotinib-resistant patients and the first-line setting.[40,41] Type II MET TKIs, such as cabozantinib, merestinib, glesatinib, and foretinib, are also ATP-competitive but bind to the inactive MET conformation. Type III TKIs function at a distinct metastable site, distant from the ATP binding site; thus far, the only reported type III MET TKI is tivantinib.

Type Ib MET TKIs

Type Ib MET TKIs exhibit potent activity against MET signaling in patients with NSCLC exhibiting METex14. GEOMETRY mono-1 was a multicenter, open-label, multicohort, phase 2 study of capmatinib in patients with advanced or metastatic NSCLC. The objective

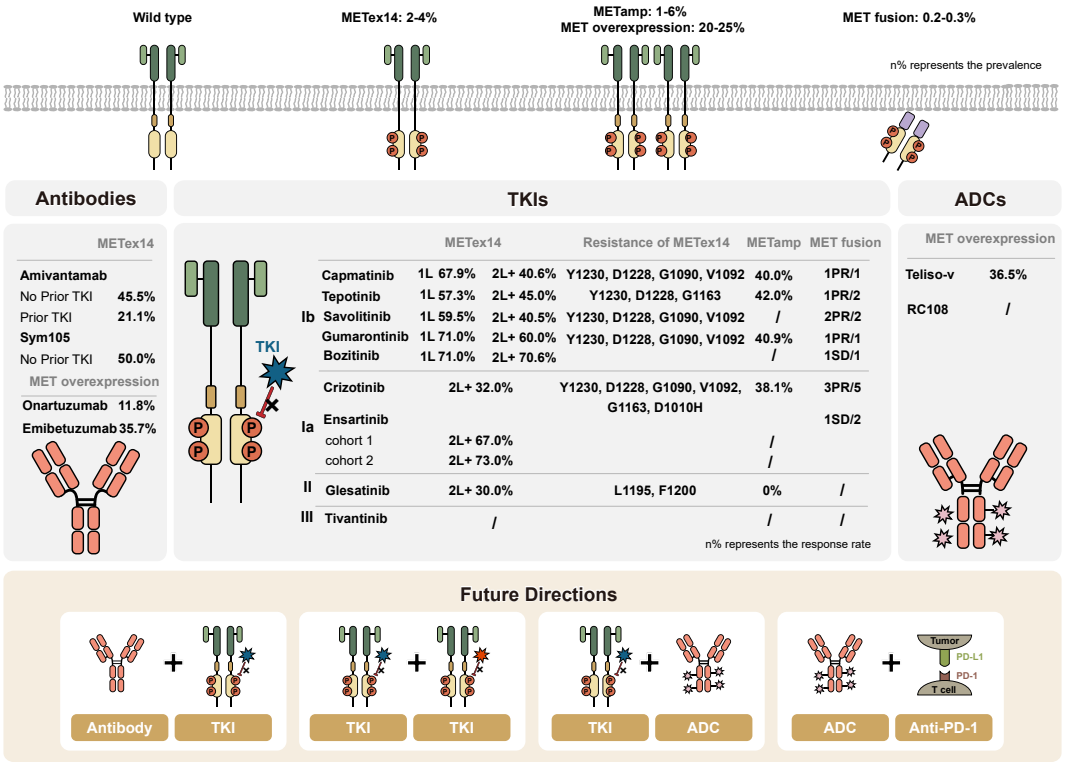

Figure 1. Targeting MET alterations in NSCLC. MET alterations in NSCLC mainly include METex14 skipping mutations (2%–4%), MET amplification (1%–6%), MET fusion (0.2%–0.3%), and MET overexpression (20%–25%). MET-targeted regimens can be divided into three categories: MET TKIs, monoclonal antibodies, and ADCs. In the future, increased therapeutic efficacy remains a focus in the MET field, and combined strategies provide potentially feasible approaches. n% represents the prevalence and n% represents the objective response rate. /, not applicable; 1L, previously untreated patients; 2L+, previously treated patients; ADC, antibody-drug conjugate; METex14, MET exon 14; TKI, tyrosine kinase inhibitor.

response rate (ORR) of capmatinib was 67.9% with a median progression-free survival (mPFS) of 12.4 months and a median overall survival (mOS) of 20.8 months in treatment-naive patients[42] (Table 1). The phase 2 VISION trial evaluated the efficacy and safety of tepotinib in patients with METex14 NSCLC; the results revealed robust clinical activity of tepotinib among 313 patients with METex14. The ORR in the overall population was 51.4%, and greater than 90% of tumors were regressed; the mPFS was 11.2 months, and the mOS was 19.6 months.[31] Among other type Ib MET TKIs, savolitinib was evaluated in a phase 3B study of 87 patients. The first-line treatment data revealed an ORR of 59.5%, a disease control rate (DCR) of 95.2%, and an mPFS of 12.6 months.[43] In other studies, gumarontinib had an ORR of 66%, an mPFS of 8.5 months, and an mOS of 17.6 months,[44] whereas bozitinib had an ORR of 75.0%, an mPFS of 14.1 months, and an mOS of 20.7 months among patients with METex14[45] (Table 2).

Treatment-naive patients and previously treated patients might exhibit differing responsiveness to certain type Ib MET TKIs. Capmatinib exhibited an ORR of 67.9% versus 40.6%, a DCR of 96.0% versus 78.0%, an mPFS of 12.4 versus 5.4 months, and an mOS of 20.8 versus 13.6 months in treatment-naive versus previously treated patients, respectively.[42] Similarly, superior efficacy was observed in treatment-naive patients treated with savolitinib and gumarontinib. Compared with the efficacy derived from backline savolitinib therapy (ORR, 49.2%; mPFS, 6.9 mo),[46] frontline savolitinib therapy resulted in a better ORR (59.5%) and mPFS (12.6 mo).[43] In contrast, tepotinib exhibited a comparable ORR (57.3% versus 45.0%), DCR (78.7% versus 73.8%), mPFS (12.6 versus 11.0 mo), and mOS (21.3 versus 19.3 mo) in treatment-naive and previously treated patients.[31] Gumarontinib yielded an ORR of 71% versus 60%, a DCR of 89% versus 77%, an mPFS of 11.7 versus 7.6 months, and an mOS of not reached versus 16.2 months in treatment-naive versus previously treated patients, respectively.[44] So does bozitinib (77.1% versus 70.6%).[45] The specific mechanism responsible for these differences is unclear; however, it may be associated with the worse performance status of patients who receive backline therapy, and concerns regarding adverse events (AEs) and management practices.

Although the definite copy number remains uncertain, METamp is considered a targetable driver of MET TKIs. In the GEOMETRY mono-1 trial, capmatinib had an

Table 1. Summary of Key Clinical Trials for MET-Altered NSCLC

Category		Agent	Trial	Trial Descriptions		Efficacy ORR (%)	DCR (%)	mPFS (mo)	mDOR (mo)	mOS (mo)
MET TKI	**Ib**	Capmatinib	GEOMETRY Mono1 (NCT02414139)	METex14 advanced NSCLC 1L (n = 28)		67.9	96	12.4	12.6	20.8
				METex14 advanced NSCLC 2L+ (n = 69)		40.6	78	5.4	9.7	13.6
				MET amplified advanced NSCLC 1L (n = 15) (GCN ≥10)		40	67	4.2	7.5	/
				MET amplified advanced NSCLC 2L+ (n = 69) (GCN ≥10)		29	71	4.1	8.3	/
		Tepotinib	VISION (NCT02864992)	METex14 advanced NSCLC 1L (n = 164)		57.3	78.7	12.6	46.4	21.3
				METex14 advanced NSCLC 2L+ (n = 149)		45	73.8	11.0	12.6	19.3
				METex14 advanced NSCLC All (n = 313)		51.4	76	11.2	18	19.6
				MET amplified advanced NSCLC (n = 24) (GCN ≥2.5)		42	/	4.2	/	/
		Savolitinib	NCT02897479	METex14 locally advanced or metastatic NSCLC	1L (n = 28)	46.4	/	5.6	5.6	/
					2L+ (n = 42)	40.5	/	6.9	9.7	/
					All (n = 70)	42.9	82.9	6.8	8.3	/
			NCT04923945	METex14 metastatic NSCLC	1L (n = 87)	59.5	95.2	12.6	/	NR
		Gumarontinib	GLORY (NCT04270591)	METex14 advanced NSCLC	1L (n = 44)	71	89	11.7	15.0	NR
					2L+ (n = 35)	60	77	7.6	8.2	16.2
					All (n = 79)	66	84	8.5	8.3	17.3
		Bozitinib	NCT04258033	METex14 advanced NSCLC	1L (n = 35)	77.1	/	/	/	/
					2L+ (n = 17)	70.6	/	/	/	/
					All (n = 52)	75	96.2	14.1	15.9	20.7
	Ia	Ensartinib	ChiCTR2100048767 (Phase II)	METex14 advanced NSCLC compassionate cohort (n = 18)		67	94	6.1	6.3	/
				METex14 advanced NSCLC phase 2 cohort (Simon stage I) (n = 11)		73	91	6.3	6.0	NR
		Crizotinib	PROFILE-1001 (NCT00585195)	METex14 advanced NSCLC (n = 65)		32	78	7.3	9.1	20.5
				MET amplified advanced NSCLC (MET-to-CEP7 ratio ≥ 4.0) (n=21)		38.1	47.6	6.7	5.2	11.4

(continued)

Table 1. Continued

Category		Agent	Trial	Trial Descriptions		Efficacy				
						ORR (%)	DCR (%)	mPFS (mo)	mDOR (mo)	mOS (mo)
	II	Glesatinib	NCT00697632	Metastatic NSCLC	MET-activating mutations (n = 20)	30	/	5.8	4.8	10
					MET amplification (n = 6)	0	/	1.4	/	7.7
	III	Tivantinib	NCT01244191	c-Met+ advanced nonsquamous NSCLC (subgroup analysis)	Erlotinib + tivantinib (n = 104)	/	/	3.7	/	9.3
					Erlotinib + placebo (n = 107)	/	/	1.9	/	5.9
Antibody		Amivantamab	CHRYSALIS (NCT02609776)	METex14 advanced NSCLC	1L (n = 6)	50	66.7	NR	NR	NR
					No prior MET inhibitor (n = 11)	45.5	54.4	NR	NR	NR
					Prior MET inhibitor (n = 19)	21.1	57.9	NR	NR	NR
					All (n = 36)	33.3	58.3	NR	NR	NR
		Sym015	NCT02648724	METex14 or MET amplified advanced NSCLC (GCN >5)	MET TKI-naive (n = 10)	50	100	6.5	/	/
					Prior MET TKI (n = 10)	/	60	5.4	/	/
					All (n = 20)	25	80	5.5	/	/
		Onartuzumab	METLung (NCT01456325)	MET FISH+ in advanced or metastatic NSCLC (subgroup analysis)	Onartuzumab + erlotinib (n = 71)	11.8	/	2.7	/	6.4
					Placebo + erlotinib (n = 85)	4.2	/	1.5	/	9.4
		Emibetuzumab	NCT01900652	MET IHC+ metastatic NSCLC (MET 3+ expression in ≥90% of tumor cells) (subgroup analysis)	Emibetuzumab+ erlotinib (n = 12)	37.5	/	20.7	/	/
					Emibetuzumab+ placebo (n = 12)	37.5	/	5.4	/	/
ADC		Telisotuzumab Vedotin	LUMINOSITY (NCT03539536)	c-Met+ advanced/metastatic NSCLC (n = 52)		36.5	/	/	6.9	/
			NCT02099058	c-Met+ advanced NSCLC (n = 36)		30.6	86.1	5.9	/	/

/, denotes could not be estimated; 1L, previously untreated patients; 2L+, previously treated patients; ADC, antibody-drug conjugate; All, all patients; DCR, disease control rate; GCN, gene copy number; mDOR, median duration of response; METex14, MET exon 14; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

Table 2. Ongoing Clinical Trials of MET Inhibitors in NSCLC

Category		Agents	Trial ID	Research Time	Sample size	Trial Descriptions	Phase	Primary End Point
MET TKI	**Ib**	Capmatinib	NCT04677595	2021–2025	35	METex14 advanced NSCLC	II	ORR
		Savolitinib	NCT04923945	2021–2024	163	METex14 locally advanced or metastatic NSCLC	III	ORR
		Savolitinib + osimertinib	NCT05015608	2021–2024	250	MET amplified advanced NSCLC	III	PFS
			NCT05261399	2022–2026	324	EGFR-mutated locally advanced or metastatic NSCLC with MET overexpression and/or amplification after Osimertinib resistance	III	PFS
		Gumarontinib	NCT04270591	2019–2023	183	c-MET+ advanced NSCLC	Ib/II	ORR
		Bozitinib	NCT04258033	2020–2024	185	c-MET+ locally advanced/ metastatic NSCLC	II	ORR
		Bozitinib	NCT03175224	2017–2026	497	MET-altered (MET fusion, METex14, and MET amplification) NSCLC	I/II	The MTD and the incidence of DLTs; ORR
	Ia	Ensartinib	ChiCTR2100048767	2021–2024	42	METex14 advanced or metastatic NSCLC	II	ORR
	II	Cabozantinib	NCT01639508	2012–2026	86	MET overexpression, amplification, or mutation in NSCLC	II	ORR
Antibody		Amivantamab	NCT02609776	2016–2024	751	Previously treated METex14 unresectable or metastatic NSCLC	I	Number of participants with DLTs, AEs and SAEs
		Amivantamab+ Capmatinib	NCT05488314	2022–2025	161	METex14 or MET amplified metastatic NSCLC	I/II	Number of participants with Aes, DLTs and ORR
ADC		Telisotuzumab Vedotin	NCT03539536	2018–2025	270	Previously treated c-Met+ locally advanced or metastatic NSCLC	II	ORR; Number of participants with Aes
			NCT05513703	2022–2027	70	Previously untreated MET amplified advanced/metastatic nonsquamous NSCLC	II	ORR
		RC108	NCT04617314	2021–2025	32	c-Met + advanced malignant solid tumors	I	Number of participants with AEs; Maximum tolerated dose

ADC, antibody-drug conjugate; AE, adverse event; DLT, dose limited toxicity; ICI, immune checkpoint inhibitor; ID, identification; METex14, MET exon 14; MTD, maximum tolerated dose; ORR, objective response rate; PFS, progression-free survival; RR, response rate; SAE, serious adverse event; TKI, tyrosine kinase inhibitor.

ORR of 12% and mPFS of 2.7 months at a GCN of less than 10, and an ORR of 40% and mPFS of 4.2 months at a GCN of greater than or equal to 10.[32] Tepotinib had an ORR of 42% and mPFS of 4.2 months at a GCN of greater than or equal to 2.5.[47] Several studies have investigated the effectiveness of combining savolitinib and osimertinib in patients with METamp; these studies used different definitions of METamp.[33,48,49] Notably, a GCN of greater than or equal to 10 (TATTON study) and a GCN of greater than or equal to 5 (SAVANNAH study) yielded similar ORRs (34% and 32%, respectively). In studies using IHC for detection, greater than or equal to 50% of tumor cells with strong staining (TATTON study) and greater than or equal to 90% of tumor cells with strong staining (SAVANNAH study) also exhibited comparable ORRs (46% and 49%, respectively). These results imply that although low-level METamp is associated with worse therapeutic outcomes, an additional increase in METamp or overexpression does not necessarily lead to a higher ORR in populations with high-level METamp. Gumarontinib is also effective in patients with METamp, and an ORR of 40.9% was reported among patients with concurrent MET overexpression and amplification.[50] A recent study found that among 30 patients who received a combination of gumarontinib and osimertinib after the development of EGFR-TKI resistance with a median follow-up time of 11.8 months, the ORR was 60%, the median duration of remission was 5.8 months, mPFS was 6.9 months, and mOS was 16.9 months.[51]

MET fusions have been described only rarely in patients with NSCLC. A recent report described three patients with MET fusion who were treated with type Ib MET TKIs; two of these patients achieved a partial response (PR), whereas one exhibited stable disease.[52] Another recent report described nine patients harboring MET fusion; of the two patients treated with tepotinib, one developed PR, and the other developed progressive disease.[53] These results indicate that, in addition to METex14 and METamp, MET fusion might also be a treatable MET aberration. At the time this review was written, the ongoing phase 1b/2 bozitinib trial was prospectively recruiting patients NSCLC exhibiting MET fusion (NCT03175224) (Table 2).

Notably, type Ib TKIs have non-negligible AEs. AEs associated with type Ib TKIs generally exhibit a relatively comparable pattern. The most common AE is peripheral edema, observed in 32% to 74% of patients, whereas grade greater than or equal to 3 peripheral edema is observed in 9% to 21% of patients.[44,46,54–56] Efficient management of drug-related AEs is markedly associated with treatment outcomes. Nonpharmacologic management of peripheral edema includes bed or foot elevation, compression stockings, massage, reduced salt intake, and exercise. Diuretics are the most typically used medication, and diuretics in combination with nonpharmacologic measures may result in symptomatic improvement. Medication dose reduction or interruption is needed for patients with extremely poor symptomatic improvement. Dose reduction is typically used to control the incidence of AEs other than peripheral edema. Nausea (23%–53%), hypoalbuminemia (23%–41%), and an increased aspartate aminotransferase or alanine aminotransferase level (26%–39%) are prevalent AEs associated with type Ib MET inhibitors.[32,44,46] In the VISION trial, 14.1% of patients underwent dose reduction because of AEs, whereas 16.1% of patients required medication interruption.[57] Similarly, in the GEOMETRY mono-1 trial, 23% of patients underwent AE-related dose reduction, and 54% of patients required medication interruption.[58] The dosing regimen for savolitinib uses the patient's body weight to mitigate the likelihood of AEs. Patients with a body weight greater than or equal to 50 kg are administered oral savolitinib at 600 mg/d, whereas patients weighing less than 50 kg receive 400 mg/d.[46]

Type Ia MET TKIs

Type Ia MET TKIs include the classic drug crizotinib and the emerging drug ensartinib. In the Profile1001 study, crizotinib was assessed in 65 patients with advanced NSCLC harboring METex14. The ORR was 32%, the median duration of remission was 9.1 months, and mPFS was 7.3 months.[59,60] Another type Ia MET TKI is ensartinib. Our recent study was the first to comprehensively present evidence, spanning from the preclinical to clinical stages, regarding ensartinib efficacy in the treatment of METex14 NSCLC. We found that the binding energy of ensartinib to c-Met was similar to the energies of type Ia and Ib TKIs. Furthermore, ensartinib efficiently blunted the proliferation and migration of the METex14 cell line by blocking the phosphorylation of c-MET and downstream signaling activation. Most importantly, ensartinib was effective in patients with METex14 NSCLC. Among 29 patients from two independent cohorts who were treated with ensartinib, the ORR was approximately 70% and the DCR was greater than 90%, with an mPFS of 6.1 months.[61]

For METamp, type Ia MET TKIs also exhibit activity for METamp. In the Profile1001 trial, crizotinib had an ORR of 38.1% among 21 patients with METamp (GCN of $\geq$ 4).[60] Other studies of crizotinib reported response rates of 23% to 38% among patients with METamp.[25,62,63] Our study was the first to report comprehensive preclinical and preliminary clinical data concerning the antitumor effect of ensartinib on METamp. In two patients with secondary METamp after EGFR therapy, we used ensartinib in combination with almonertinib and ensartinib

monotherapy, respectively, and observed substantial tumor regression in both patients.[61]

Among the MET fusion patients, a study found that among six patients with MET fusion who were given crizotinib, half achieved PR, and the treatment duration lasted for 5 to 8 months. In addition, two patients were treated with ensartinib. The effectiveness assessment revealed that one patient had a PFS of 4.0 months after receipt of second-line chemotherapy; another patient developed progressive disease while receiving sixth-line treatment.[52] In another case study, a patient with acquired *SPECC1L* gene–MET fusion was treated with crizotinib plus osimertinib. Unfortunately, the patient died within 1 month of beginning combination therapy.[64] Further studies of MET fusion involving larger sample sizes are needed.

Notably, the AE spectrum of ensartinib exhibits marked dissimilarity compared with type Ib MET TKIs. In a previous study, the prevailing AEs were rash (59%), an increased aspartate aminotransferase level (21%), and nausea (14%). Peripheral edema occurred in only 10% (3 of 29) of patients, and the edema was classified as grade 1 or 2 in all of those patients. Thus, despite the widespread clinical use of selective type Ib MET TKIs and type Ia crizotinib, we believe that ensartinib will remain an important complement to MET pipeline drugs.

Type II MET TKIs

Type II MET TKIs are multitargeted ATP-competitive inhibitors. In contrast to type I TKIs, the binding sites of type II TKIs are mainly located in the regulatory structural domain within the proximal region of the MET membrane.[65,66] No evidence from phase 2 trials has been formally released; all evidence thus far is from case studies and phase 1 trials. A phase 1 study of glesatinib in patients with MET-altered NSCLC reported a 30% ORR and all PRs were observed in patients with METex14.[67] An ongoing phase 2 clinical trial is evaluating the effectiveness of cabozantinib in patients with METamp or METex14, who received previous treatment either with or without MET TKIs (NCT03911193). Intriguingly, several type II MET TKIs can reportedly overcome acquired type I MET TKI resistance; these drugs are reviewed in the following section.

Type III MET TKIs

Thus far, no type III TKI has been approved for clinical use. Although tivantinib is a type III MET TKI, its limited efficacy and serious safety concerns have hindered further development. In the MARQUEE study, although the combination of tivantinib and erlotinib resulted in an improved survival outcome (mOS: 9.3 versus 5.9 mo) in MET with a GCN of greater than 4, the negative OS benefit in the intention-to-treat population (8.5 versus 7.8 mo) led to premature discontinuation of the trial.[34] Recruitment for the phase 3 ATTENTION study was terminated because of a higher incidence of interstitial lung disease and resultant mortality in the tivantinib group.[68]

MET Alterations in Special Populations

Older adults. Because MET alterations mainly occur in older patients, safety and efficacy in such patients are particularly important.[69] The median age of the patients enrolled in the GEOMETRY mono-1 trial was 71 years, and the median age in our study was 73 years.[32,61] Subgroup analysis of older patients in the VISION study reported that the ORRs of tepotinib were 35.1% in patients aged older than 80 years and 48.8% in younger patients.[57] In addition, appropriate management of AEs is crucial for older patients, especially patients receiving regimens with relatively high toxicity. For both capmatinib and tepotinib, the incidence of grade greater than or equal to 3 AEs reached 50% to 60%,[42] and drug-related death was reported. Notably, the AE profile of ensartinib differs from that of type Ib TKIs, which could be advantageous for certain drug selection scenarios.

Brain Metastasis. The incidence of brain metastases in patients with METex14 is 17.0% to 20.6%.[70,71] Among type Ia inhibitors, crizotinib is a classic TKI with poor efficacy toward brain metastases. In contrast, ensartinib exhibited a remarkable improvement in lipid solubility after reconstitution; this led to a 63.6% intracranial remission rate in ALK-positive NSCLC.[41] Our recent report revealed that ensartinib has the potential for activity against brain metastases of NSCLC with MET alterations. Among five patients with baseline brain metastases who received ensartinib without previous or concomitant brain radiotherapy, two developed PR and the other three had stable disease.[61]

With respect to type Ib MET TKIs, an intracranial response was observed in seven of 13 patients treated with capmatinib (4 complete response, 3 PR; 3 patients had previously undergone brain radiotherapy).[32] Among 15 patients with brain metastases, tepotinib was associated with an intracranial ORR of 66.7% (3 complete response, 5 PR; 12 patients had previously undergone brain radiotherapy).[31] Savolitinib and gumarontinib also exhibited intracranial activity.[44,46] Taken together, these results suggest that ensartinib, capmatinib, tepotinib, savolitinib, and gumarontinib can be effective in METex14 NSCLC with brain metastases.

MET TKI Resistance Mechanisms and Strategies for Overcoming Resistance

MET TKIs have altered the treatment paradigm for patients with MET alterations. However, patients

receiving MET TKIs continue to develop primary or acquired resistance. The molecular mechanisms of primary resistance remain unclear.

In the context of on-target resistance, the principal sites of resistance for type Ia and Ib MET TKIs are identical. Resistance sites including Y1230, D1228, G1090, V1092, G1163, and D1010H are typically involved. For type II TKIs, L1195, and F1200 are predominantly involved.[66,72–76] The bypass activation mode encompasses various genetic alterations, such as KRAS amplification, KRAS mutations, NF1/RASA1 mutations, and PI3KCA mutations.[77,78] Here, we mainly discuss the treatment strategies for on-target resistance.

Sequential treatment with structurally distinct MET TKIs is considered to ameliorate MET inhibitor resistance, including cases that involve the same MET TKI subtypes but different MET binding sites and chemical bonds. Capmatinib has exhibited some efficacy in patients with crizotinib resistance (ORR of 10%, DCR of 80%, and mPFS of 5.5 mo).[79] In our study, one patient exhibited responsiveness to savolitinib after exhibiting resistance to ensartinib.[61] In addition, cabozantinib reportedly can overcome crizotinib-induced resistance to the MET D1228N mutation,[80] and a patient with acquired MET Y1230C achieved PR with merestinib therapy after exhibiting resistance to crizotinib.[76] Moreover, preclinical studies have revealed that glesatinib and foretinib can overcome resistance induced by mutations of D1228N and Y1230C/H.[73,81] These observations provide preliminary evidence to support the hypothesis that the use of a sequential approach involving type Ia and Ib MET TKIs or type II MET TKIs is a feasible strategy.

Emerging novel strategies to overcome resistance specifically target the extracellular domain of MET using monoclonal antibodies (e.g., amivantamab) and ADC agents. Next, we will summarize the therapeutic efficacies of these regimens.

Antibody drugs and ADCs

Antibody Drugs

Amivantamab is a fully human bispecific antibody targeting EGFR and MET. The CHRYSALIS trial reported a 33.3% ORR (32/97 patients with PR) for amivantamab in patients with METex14 NSCLC. Notably, the ORRs were 50% (eight of 16 patients with PR) and 45.5% (13 of 28 patients with PR) in treatment-naive patients and patients without previous MET TKI therapy, respectively. In contrast, the ORR was 21.1% (11 of 53 patients with PR) among patients with previous MET TKI therapy.[82] The most common AEs were rash (76%), infusion-related reaction (72%), and paronychia (45%). Grade 3 AEs possibly related to amivantamab occurred in 19 (20%) patients. Amivantamab exhibited a superior response rate in patients with MET TKI–naive METex14 NSCLC versus patients with MET TKI–pretreated NSCLC. The reason for this phenomenon is unclear, and further research is needed. At the time this review was written, a study of amivantamab in patients with METex14 NSCLC was ongoing (NCT05488314) (Table 2).

Recent research findings support the utilization of amivantamab as an initial therapeutic intervention to proactively inhibit the MET pathway; this approach has proven efficacious for patients with EGFR mutations. The MARIPOSA study found that amivantamab plus lazertinib led to a substantial increase in PFS by 23.7 months, compared with 16.6 months in the osimertinib arm.[83]

Sym015, consisting of a balanced mixture of two monoclonal humanized immunoglobulin G1 antibodies (Hu9006 and Hu9338), is directed against nonoverlapping epitopes of the MET ectodomain.[84] Comparable efficacy of Sym015 was observed in a phase 2 trial, comprising an ORR of 50% in MET TKI–naive patients with MET alterations. However, PR was not reached in patients with previous MET TKI therapy; the best outcome in these patients was stable disease.[85]

Other antibodies targeting MET, such as onartuzumab and emibetuzumab, have encountered some obstacles. Onartuzumab is a fully humanized, recombinant, monovalent monoclonal antibody that specifically targets and binds to the extracellular domain of MET. The OAM4971g (MET Lung) phase 3 trial focused on the efficacy and safety of onartuzumab plus erlotinib in patients with MET-positive locally advanced or metastatic NSCLC whose disease had progressed after previous chemotherapy. The addition of onartuzumab to erlotinib in patients previously treated with chemotherapy resulted in no differences in terms of OS, PFS, or ORR between the onartuzumab and placebo groups when stratified according to MET status on FISH.[86]

Emibetuzumab is a humanized immunoglobulin G4 monoclonal bivalent MET antibody that blocks the binding of a MET ligand, hepatocyte growth factor, to c-Met. A phase 2 study compared erlotinib plus emibetuzumab with erlotinib alone in EGFR-mutant metastatic NSCLC. When MET overexpression was defined as c-Met staining of 3+ in greater than or equal to 90% of tumor cells, 24 patients with MET overexpression had a prolonged mPFS (20.7 versus 5.4 mo). However, the study was unsuccessful because it did not exhibit a PFS or OS benefit for the overwhelming most population.[87]

ADCs

Telisotuzumab vedotin (Teliso-V) consists of a humanized monoclonal antibody, telisotuzumab, coupled to

the antimicrotubule drug monomethyl auristatin E through a valine-citrulline junction. Teliso-V has exhibited initial efficacy in patients with MET alterations; its ORR was 30.6% and its mPFS was 5.9 months in 36 heavily treated patients with NSCLC exhibiting c-MET overexpression (membrane staining score of $\geq$ 150).[88] An identical response rate was reported in another study; the ORR was 36.5% in 52 patients exhibiting c-Met overexpression. Both studies were phase 1 trials; therefore, extensive prospective studies are needed to confirm the efficacy of Teliso-V in patients with MET alterations. Teliso-V was moderately well tolerated, and the most common AE was peripheral sensory neuropathy (57%). Ongoing clinical trials (NCT03539536 and NCT05513703) are further exploring the efficacy of Teliso-V.

RC108, another ADC, consists of a targeted MET monoclonal antibody coupled to the antimicrotubule drug monomethyl auristatin E by means of cleavable valine-citrulline (vc-Linker); a phase 1 clinical study of RC108 is ongoing (NCT04617314) (Table 2).

Perspectives Concerning MET Therapeutics

Although MET TKIs, antibody drugs, and ADCs have exhibited antitumor activity, they all have potential for improvement. Thus, the enhancement of therapeutic efficacy for these agents remains an area of focus. Combined strategies would provide potentially feasible approaches (Fig. 1), as discussed below. Although these combinations might lead to greater efficacy, their potential toxicities require attention. Combinations include the following: (1) combined MET TKIs (approximately 30% of cases of acquired MET TKI resistance are located in the MET tyrosine kinase domain,[76,89] and an in vitro study supported the combination of types I and II MET inhibitors); (2) combined MET TKI and ADCs (this combination would overcome therapeutic resistance and clonal heterogeneity, strengthen inhibition of signaling pathways, and modulate the tumor microenvironment, thereby enhancing drug antitumor activity[90,91]); (3) antibody drugs combined with MET TKIs (the first insights into this combination will be gained from an ongoing phase 1/2 study that is evaluating the efficacy of amivantamab plus capmatinib [NCT05488314] [Table2]); and (4) ADC and immune checkpoint inhibitor (mechanistically, ADCs induce immunogenic cell death, enhance antitumor immune responses, increase immunogenicity, and enhance the efficacies of immune checkpoint inhibitors[92,93]). Although these combos might lead to greater efficacy, we need to pay special attention to the superposition of toxicity.

Summary

MET alterations are important targeted therapeutic areas in NSCLC. Nevertheless, although increasing numbers of drugs targeting MET are available in clinical settings, many urgent problems remain. First, there is a need for greater understanding regarding drug resistance mechanisms and the optimal drug sequences that can enhance the efficacy and durability of MET TKI therapy, especially considering the increasing availability of highly selective MET TKIs. Second, although the development of monoclonal antibodies and ADCs has enhanced opportunities in the MET field, the overall efficacy remains unsatisfactory. Thus, it is important to learn from studies of other solid tumors or NSCLC with other driver genes to better characterize the efficacy of combined modes. We eagerly anticipate studies that will provide valuable guidance for the precise management of patients with NSCLC harboring MET alterations.

CRediT Authorship Contribution Statement

Xiuning Le, Wen Li: Conceptualization.

Mo Zhou, Jing Zhao, Zhehua Shao, Rui Jin: Data curation.

Yang Xia: Funding acquisition.

Yinghui Yu, Da Miao, Mo Zhou: Investigation.

Zhehua Shao, Rui Jin: Software.

Xiuning Le, Wen Li: Supervision.

Yang Xia, Ying Han, Yinghui Yu: Roles/Writing - original draft.

Xiuning Le, Wen Li, Yang Xia: Writing - review & editing.

Disclosure

The authors declare no conflict of interest.

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