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Citation for published version (APA):

Remon, J., Hendriks, L. E. L., Mountzios, G., García-Campelo, R., Saw, S. P. L., Uprety, D., Recondo, G., Villacampa, G., & Reck, M. (2023). MET alterations in NSCLC-Current Perspectives and Future Challenges. *Journal of Thoracic Oncology*, *18*(4), 419-435. https://doi.org/10.1016/j.jtho.2022.10.015

Document status and date:
Published: 01/04/2023

DOI:
10.1016/j.jtho.2022.10.015

Document Version:
Publisher's PDF, also known as Version of record

Document license:
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REVIEW ARTICLES

MET alterations in NSCLC—Current Perspectives and Future Challenges

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Received 22 August 2022; revised 17 September 2022; accepted 19 October 2022
Available online - XXX

ABSTRACT

Targeted therapies have revolutionized the treatment and improved the outcome for oncogene-driven NSCLC and an increasing number of oncogenic driver therapies have become available. For MET-dysregulated NSCLC (especially *MET* exon 14 skipping mutations and *MET*-amplifications, which is one of the most common bypass mechanisms of resistance in oncogene-addicted NSCLC), several anti–MET-targeted therapies have been approved recently (*MET* exon 14 skipping mutation) and multiple others are in development. In this narrative review, we summarize the role of *MET* as an oncogenic driver in NSCLC, discuss the different testing methods for exon 14 skipping mutations, gene amplification, and protein overexpression, and review the

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Drs. Remon and Hendriks contributed equally to this work.

Disclosure: Dr. Remon reports serving on advisory boards of Merck Sharp & Dohme, Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca, Roche, Bayer, and Sanofi; as speaker for Pfizer and Janssen; and receiving travel reimbursement from Ose immunotherapeutics, Bristol-Myers Squibb, AstraZeneca, and Roche, all outside the submitted work. Dr. Hendriks reports receiving research funding on behalf of institution from Roche Genentech, Boehringer Ingelheim, AstraZeneca, Takeda, and BeiGene (the latter two under negotiation); serving on advisory boards for Bristol-Myers Squibb, Eli Lilly, Roche Genentech, Pfizer, Takeda, Merck Sharp & Dohme, Boehringer Ingelheim, Amgen, and Janssen (all institution, Roche one time self); as speaker for Merck Sharp & Dohme, Eli Lilly (institution); receiving travel/conference reimbursement from Roche Genentech; participating in a mentorship program with key opinion leaders funded by AstraZeneca; receiving fees for educational webinars from Benecke, Medtalks, and VJOncology (self), high5oncology (institution); participating in interview sessions funded by Roche Genentech, Bayer, and Lilly (institution); and serving as local principal investigator (PI) of clinical trials sponsored by AstraZeneca, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme /Merck, GlaxoSmithKline, Takeda, Blueprint Medicines, Roche Genentech, Janssen Pharmaceuticals, and Mirati, all outside the submitted work. Dr. Mountzios reports receiving honoraria from Roche, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, AstraZeneca, Takeda, Pierre-Fabre, Janssen, GlaxoSmithKline, Amgen, Sanofi, and Boehringer Ingelheim outside the submitted work. Dr. García-Campelo reports receiving honoraria from AstraZeneca, Roche, Eli Lilly, Novartis Merck Sharp & Dohme, and Takeda outside the submitted work. Dr. Saw reports receiving honoraria from Pfizer and Bayer; and grants from Merck Sharp & Dohme and AstraZeneca outside the submitted work. Dr. Uprety reports receiving honoraria from Daiichi Sankyo, Sanofi, and AstraZeneca outside the submitted work. Dr. Reck reports receiving honoraria from Amgen, AstraZeneca, Beigene, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Janssen, Eli Lilly, Merck, Mirati, Novartis, Roche, Samsung, Bioepis, and Sanofi outside the submitted work. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2022.10.015

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existing data and ongoing clinical trials regarding targeted therapies in MET-altered NSCLC. As immunotherapy with or without chemotherapy has become the standard of care for advanced NSCLC, immunotherapy data for MET-dysregulated NSCLC are put into perspective. Finally, we discuss future challenges in this rapidly evolving landscape.

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Keywords: MET exon 14; MET amplified; Non–small cell lung cancer; Capmatinib; Amivantamab; Tepotinib

Introduction

MET aberrations have been well documented in multiple oncogenic processes, promoting tumor invasion, angiogenesis, and metastasis.[1] In NSCLC, the three main mechanisms of MET dysregulation include protein overexpression, exon 14–skipping (*MET*ex14) mutations, or gene amplification (*MET*-amp).[2] A deeper understanding of MET dysregulations as the primary driver and in the acquired resistance (AR) setting, coupled with the advent of novel MET inhibitors, have revealed new therapeutic opportunities. In this review, we summarize existing data and discuss future challenges in the rapidly evolving landscape of MET alterations in NSCLC.

MET-Deregulated NSCLCs

MET Exon 14-Skipping Mutations

MET exon 14 encodes the 47-amino acid juxtamembrane domain of the MET receptor, a key regulatory region that prevents MET oversignaling. In *MET*ex14-mutant cancers, alterations are located in the intronic regions surrounding exon 14, within exon 14 itself, or there is a complete genomic deletion of exon 14—all of which disrupt splicing in the transcription process of the *MET* gene. The loss of this region impairs the MET protein receptor degradation as the ubiquitination and receptor internalization required for this process are blocked, leading to overactive *MET*-mediated signaling and, thus, cell proliferation and tumor growth (Fig. 1A and B).[2]

Around 2% to 4% of advanced NSCLC harbor *MET*ex14 point mutations or deletions.[3–5] Patients with

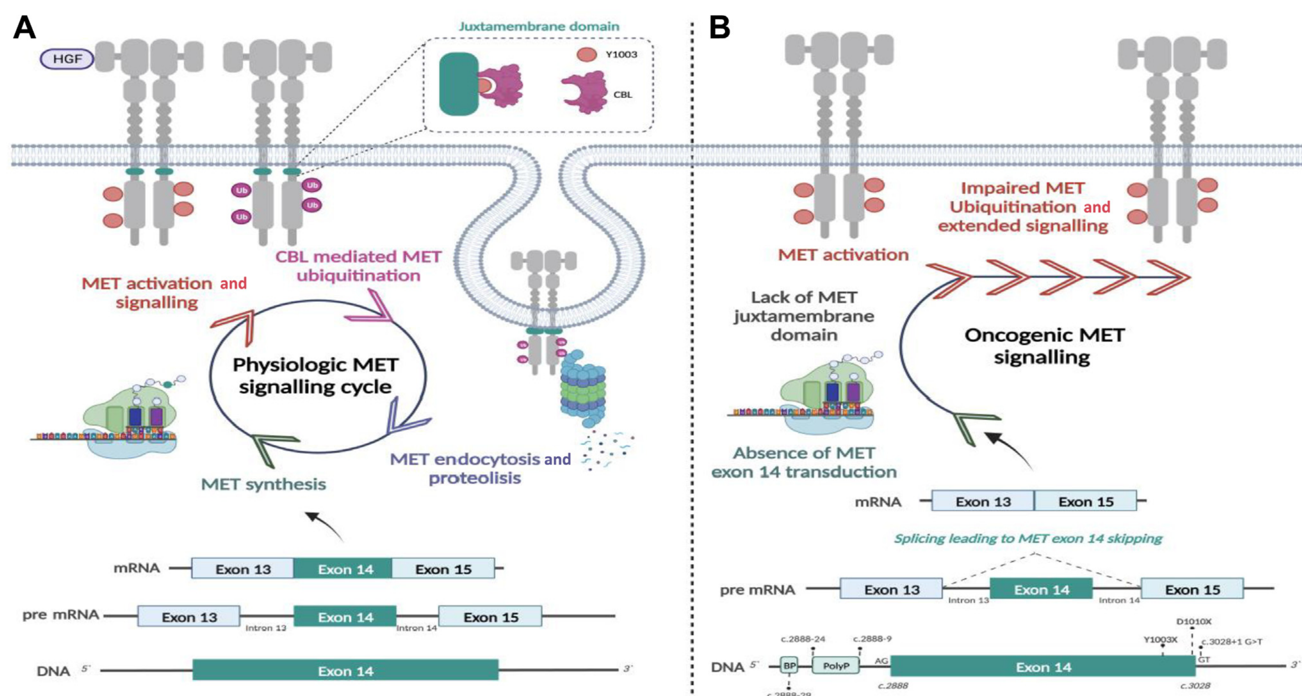

Figure 1. Mechanism of tumorigenesis of MET exon 14 skipping mutation. In physiological MET signaling (*A*), the wild-type *MET* gene is transcribed including exon 14, which encodes the juxtamembrane domain of the MET receptor. The HGF binds to the receptor extracellular domain, inducing MET phosphorylation in the juxtamembrane and kinase domain and MET signaling. Phosphorylation of the Y1003 residue recruits the CBL, which induces receptor ubiquitination, leading to receptor endocytosis and degradation as a mechanism of MET signaling down-regulation. (*B*) In oncogenic *MET* signaling such as MET exon skipping lung cancer, the genomic mutations or deletions in *MET* exon 14 splicing sites including the PPT, splicing acceptor site, D1010 codon, or splicing donor site results in abnormal splicing of the exon 14 or exon 14 skipping, which results in a MET receptor that lacks the juxtamembrane domain containing the Y1003 residue, impairing CBL binding and ubiquitination and leading to prolonged activated MET receptor signaling, which then leads to oncogenic cell transformation, growth, and survival. MET Y1003 mutations at the DNA level also disable CBL binding leading to the same oncogenic activation in the absence of *MET* exon 14 skipping. Figure created by BioRender. HGF, hepatocyte growth factor; PPT, polypyrimidine tract.

METex14-mutant NSCLC tend to be older (median age 70 y old), with a more frequent history of tobacco exposure compared with other oncogenic drivers (up to half of the patients are smokers) compared with other oncogene-addicted NSCLC. *MET*ex14 mutations occur predominantly in adenocarcinoma and pulmonary sarcomatoid carcinoma NSCLC subtypes—the latter reaching an incidence of approximately 20%.[3,6–8] Furthermore, *MET*ex14 can also be found in squamous NSCLCs,[9] with a prevalence of up to 9% in most recent trials.[7] Although *MET*ex14 mutations are generally mutually exclusive with other oncogenic drivers, recent studies support the co-existence of *MDM2, CDK4,* and *MET* co-amplifications and *TP53* mutations in 34%, 19%, 11%, and 42% of tissue samples, respectively.[4,5]

Current methods used to identify *MET*ex14 mutant tumors include DNA next-generation sequencing (NGS) platforms, Sanger sequencing, and RNA-based assays, like reverse transcription polymerase chain reaction and RNA-based NGS.[10] Among DNA-based NGS panel tests, the sensitivity of hybrid capture-based NGS seems to be higher than amplicon-based NGS.[11] RNA-based methodology could offer a higher sensitivity than DNA-based methodology because DNA-based approaches can be limited in their ability to capture the breadth of *MET*ex14 alterations.[12,13] However, the FoundationOne CDx DNA assay (Foundation Medicine, Cambridge, MA) was found to be highly concordant with RNA sequencing approaches.[5] Molecular counting using the nCounter system (NanoString) has also been used to identify *MET*ex14 at the RNA level.[14] Finally, with the increasing use of blood-based NGS, recent studies have reported high concordance comparing tissue and liquid biopsies, with a similar percentage of co-alterations profile. More importantly, *MET*ex14 alterations were less often detected in circulating tumor DNA (ctDNA), probably related to the dependency on tumor shedding.[4,5] Similar to other oncogenic drivers, the positivity of *MET*ex14 in a liquid biopsy is a predictive biomarker for personalized treatment approaches in daily clinical practice.[15]

MET Amplification

MET copy number gains consist of polysomy or amplification. Polysomy happens when multiple copies of chromosome 7 that carry MET are present. With amplification, *MET* undergoes regional or focal gain in copy number in one specific arm of chromosome 7 (located at 7q31) without alteration in other regions. Therefore, the MET to CEP7 (centromere 7 enumeration probe) ratio is well preserved in polysomy, whereas it is increased in *MET*-amp (Fig. 2).[16] Compared with polysomy, amplification is more likely to lead to oncogene addiction. The latter is recognized as an actionable driver alteration in NSCLC, either as a de novo driver alteration (in around 1%–5% of untreated NSCLC tumors and with a strong smoking association),[17–19] or as a mechanism of AR after treatment with tyrosine kinase inhibitors (TKIs).[20,21]

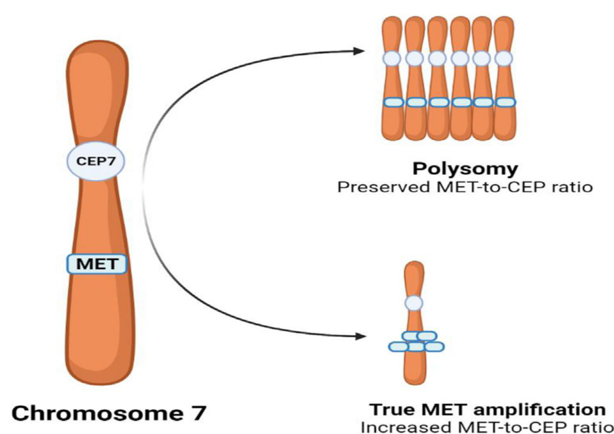

Figure 2. Simplified diagram depicting the difference between polysomy and true MET amplification. Figure created by BioRender.

Different assays can detect MET copy number changes, including fluorescence in situ hybridization (FISH), quantitative reverse transcription polymerase chain reaction, and NGS[22] with notable caveats for all technologies, including the difficulty to establish cutoff points that define *MET*-amp and interobserver variability. Unfortunately, inconsistent definitions are used across various clinical trials, hampering the translation of trial data to daily clinical practice.[7,23] Indeed, the higher the *MET*-amp cutoff, the better the response to MET inhibitors. Clinicians should be aware of the potential limitations of interpreting gene copy numbers (GCN) from single biopsies.[24,25] Possible solutions include using orthogonal assays to confirm the presence of *MET*-amp (e.g., corroborating FISH and NGS results), and reducing interobserver variability in FISH interpretation through digital pathology. Finally, compared with *MET*ex14-mutant tumors, a higher rate of co-occurring mutations—mostly *TP53, KRAS*, and *KEAP1*—have been described in *MET*-amp tumors.[24]

MET Overexpression

The incidence of dysregulation of c-MET signaling by means of receptor overexpression by immunohistochemistry (IHC) ranges from 35% to 72%[26,27] in NSCLC and correlates with poorer outcomes. Although MET overexpression may co-occur either with *MET*ex14 mutation or *MET*-amp, MET IHC is a poor screen for any of the other two potential biomarkers.[28] Various MET IHC antibodies and different scoring systems have been used to define MET overexpression. Most often, staining has

been based on a 0 to 3+ scale, and a common cutoff for MET overexpression is 2+ in at least 50% of the cells (MetMab criterion)[29] or an H-score ranging from 0 to 300, with greater than 200 usually denoting overexpression.[30] Although MET expression by IHC is an accessible biomarker, spatial heterogeneity may be observed in up to 40%.[31]

Targeting *MET* Exon 14-Skipping Mutant NSCLC

The *MET*ex14 mutations confer sensitivity to MET TKIs and different types of MET TKI exist. These include type I, which binds to the active conformation of the kinase in the adenosine triphosphate (ATP) pocket, including unselective type IA MET TKI (crizotinib) and selective type IB MET TKIs (capmatinib, tepotinib, savolitinib, and glumetinib); type II inhibitors, which bind to the inactive conformation of the kinase in the ATP pocket; and type III inhibitors, which are non–ATP-competitive allosteric inhibitors, binding outside the ATP pocket.

In the PROFILE 1001 trial, crizotinib was the first drug reporting activity in this setting, with a response rate (RR) of 32% and a median duration of response (DoR) of 9.1 months. The median progression-free survival (PFS) and overall survival (OS) were 7.3 months and 20.5 months, respectively.[32] In contrast, two additional phase 2 crizotinib trials, (AcSé[33] and METROS[34]) reported only modest activity. Selective MET TKI has been tested in several single-arm phase 2 trials (Table 1[32-41] and Fig. 3), such as capmatinib (GEOMETRY mono-1), tepotinib (VISION); savolitinib, and finally glumetinib (GLORY). These studies have reported a RR ranging from 40.5% to 68.3%, a median DoR from 5.1 to 46.4 months, a median PFS from 5.5 to 12.6 months, and a median OS ranging from 10.9 months to 25.5 months, depending on the drug and line of treatment (Table 1[32-41] and Fig. 3).[35–40] Of note, capmatinib and glumetinib reported better outcomes in treatment-naive patients than in patients who received the MET TKI as second- or third-line treatment.[35,36,40] In contrast, tepotinib reported similar efficacy regardless of treatment line, method of *MET*ex14 testing (liquid or tissue biopsy), patient age, and type of previous therapy.[37,42] Savolitinib reported similar RR and PFS regardless of the line of treatment and histologic subtypes (pulmonary sarcomatoid carcinoma versus other NSCLC subtypes).[38] Grade greater than or equal to 3 treatment-related adverse events (TRAEs) reported with selective MET TKI ranged from 34% to 58%, with peripheral edema being the most common. Grade 3 liver test abnormalities were reported in up to 15% of patients treated with savolitinib,[38] whereas it was 6% and 2% with capmatinib and tepotinib, respectively.[35,37] Approximately 29% to 47% of patients required dose reductions and up to 20% discontinued the treatment owing to TRAEs.[35–40] (Table 1[32-41]).

Taken together, these data support incorporating selective MET TKIs in the first-line setting, as the efficacy with the standard (chemo)immunotherapy in the first-line setting in nonsquamous NSCLC[43] remains unknown in *MET*-deregulated tumors, with no efficacy when immunotherapy is applied as monotherapy in this subset of tumors. As patients with *MET*ex14 NSCLC are older[35–39] than patients with other oncogene-driven NSCLC, the prioritization of effective and tolerable therapies is warranted in this population. A multicenter retrospective analysis in advanced *MET*ex14 NSCLC suggested that personalized therapy was associated with significantly improved survival (hazard ratio [HR] = 0.11, 95% confidence interval [CI]: 0.01–0.92, $p = 0.04$) compared with patients who did not receive any MET TKI.[44] However, close monitoring and proper management of TRAE is strongly recommended[45,46] as in the VISION trial—older participants (≥75 y) had a higher incidence of grade greater than or equal to 3 TRAEs (33.9% versus 18.5%), required more dose reductions (33.9% versus 23.3%), and more patients permanently discontinued tepotinib (14.7% versus 7.5%) compared with younger patients.[42]

In the absence of head-to-head comparisons, none of the selective MET inhibitors can claim a clear superiority over the others.[35–39] On the basis of the initial results from the GEOMETRY mono-1 study, capmatinib was the first MET TKI with accelerated approval by the U.S. Food and Drug Administration (FDA) in 2020 and was granted regular approval on August 2022, whereas the European Medicines Agency (EMA) approved the drug as second-line treatment in June 2022. Similarly, in 2021, tepotinib was approved by both the U.S. Food and Drug Administration and the EMA, but the EMA restricted the approval to the previously treated population; whereas savolitinib was approved only in the People's Republic of China (2021). Other MET TKIs are being tested in ongoing clinical trials such as ALP-101 (SPARTA, NCT03175224) and elzovantinib or TPX-0022 (SHIELD-1, NCT03993873 initial RR 36%).[47]

Future studies should assess the role of combination therapies with MET inhibitors (Supplementary Table 1). Interestingly, concurrent *MET* amplification with *MET*ex14 did result in a high RR (over 60%) to tepotinib,[15] and higher RR, and PFS with savolitinib,[38] but not for capmatinib.[7] Unfortunately, levels of co-amplification were not reported, and whether high-level co-amplification can serve as a predictive biomarker warrants further investigation. Similarly, responses to MET TKI were not observed in tumors with undetectable MET expression by IHC (0% versus 60%, $p = 0.04$).[48] This suggests that low MET expression can serve as a marker for primary resistance as these tumors may be reliant on

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Table 1. Efficacy of MET Tyrosine Kinase Inhibitors in *MET* Exon 14-Mutant NSCLC

	Nonselective TKI			Selective TKI								Bispecific mAb
Drug	CRIZOTINIB[32-34]			CAPMATINIB[35,36]		TEPOTINIB[37]		SAVOLITINIB[38,39]		GLUMETINIB[40]		AMIVANTAMAB[41]
Dose	250 mg BID			400 mg BID		500 mg QD		400-600 mg QD		300 mg QD		1050 / 1400 mg iv
Trial	PROFILE 1001	AcSé	METROS[a]	GEOMETRY Mono-1		VISION (Cohort A+C)				GLORY		CHRYSALIS
Line	≥1	≥2	≥2	1 (cohort 5b+7)	≥2 L (cohort 4+6)	1	≥2	1	≥2	1	≥2	1 and ≥2
N	69	25	26	60	100	164	149	28	42	42	27	55
RR (%)	32[b]	40	27	68.3	44	56.1	45.0	46.4	40.5	66.7	51.9	33.0 (57% in naive)
DoR (mo)	9.1	NR	NR	16.6	9.7	46.4	12.4	5.6	9.7	NE	5.1	Not estimable
PFS (mo)	7.3	3.6	4.4	12.5	5.5	12.6	11.0	6.9	6.9	NE	5.7	6.7 (NE in naive)
OS (mo)	20.5	9.5	5.4	25.5	Cohort 4: 13.6	19.1	19.6	10.9	19.4	NR	NR	NR
G3 TRAE's (%)	25	NR	NR	56.7	58.1	34		46		44		NR
Dose R (%)	38	NR	15	46.7	NR	34		44		29		NR
Disc (%)	7	24	6	16.7	NR	15		20		7		NR

[a]Cohort B of METROS trial included MET-deregulated tumors (*MET* exon14-mutant and *MET*-amplified).
[b]RR in treatment-naive: 25% and RR in previously treated population: 36.6%.
≥1, first-line and beyond; ≥2, second-line and beyond; 1, first-line; BID, twice per day; Disc, discontinuations owing to toxicity; DoR, duration of response; Dose R, dose reductions; G3 AE's, grade 3 adverse events; mAb, monoclonal antibody; NE, not estimated; NR, not reported; OS, overall survival; PFS, progression-free survival; QD, daily; RR, response rate; TKI, tyrosine kinase inhibitor.

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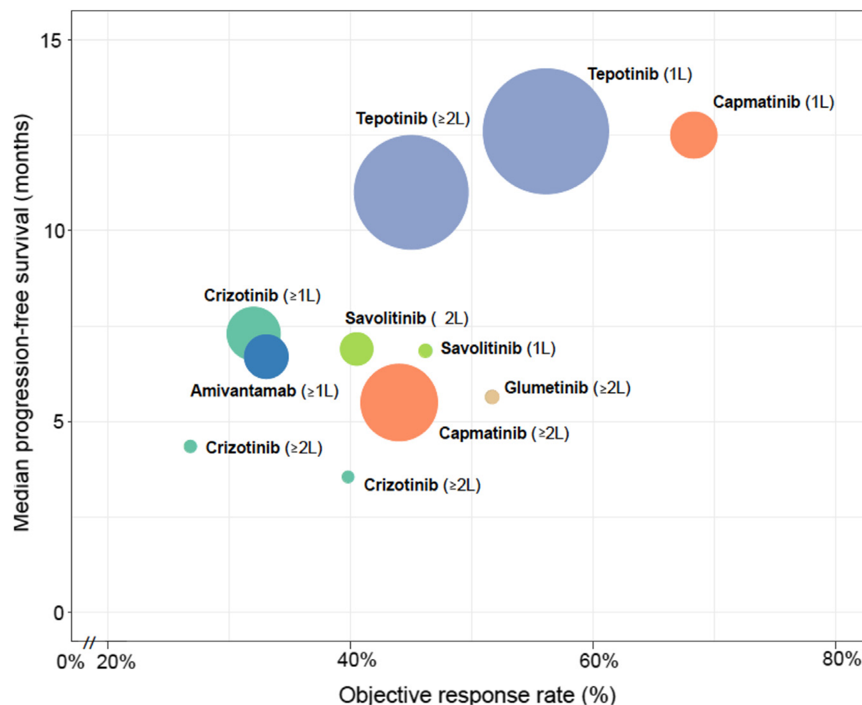

Figure 3. Efficacy of MET tyrosine kinase inhibitors in MET exon 14 mutant NSCLC. ≥2L: second-line and beyond; 1L: first-line.

more than one oncogenic pathway, bypassing MET inhibition.[48] Regarding *TP53* co-mutation, some authors reported shorter PFS on tepotinib or savolitinib,[15,32,38] but others did not report influence in the outcome on the basis of TP53-status.[48] Similarly, *MDM2* amplification was detected in nonresponders on crizotinib, but did not influence savolitinib efficacy.[32,38]

Finally, adaptive changes in ctDNA could be used to tailor therapy. The ctDNA molecular response to MET TKI (defined as the depletion of *MET*ex14 in ctDNA) correlates with longer PFS,[32,49] suggesting that ctDNA clearance could be an early marker of efficacy in daily clinical practice. Similarly, treatment escalation strategies can be designed for patients who do not exhibit clearance of ctDNA.

Novel agents have exhibited promising preliminary activity in *MET*ex14 NSCLC. Amivantamab is a bispecific monoclonal antibody comprising anti-EGFR and anti-MET and has immune-cell-directed activity.[50] Amivantamab has a higher affinity for *MET* (40 pM) than *EGFR* (1.4 nM). In the cohort MET-2 (N = 55, 9 treatment-naive) from the phase 1 CHRYSALIS trial, amivantamab reported a RR of 33% (57% in treatment-naive patients, 47% versus 17% in patients without versus with previous MET inhibitor). The median PFS was 6.7 (not reached in treatment-naive, 8.3 versus 4.2 months for those without versus with previous MET inhibitor, respectively). Dose reductions and discontinuation occurred in 12% and 5% of patients with TRAEs, respectively. The most common TRAEs were infusion-related reactions (69%, grade ≥3 in 5%), rash (grade ≥3 in 7%), and paronychia and peripheral edema, none with a grade greater than or equal to 3.[41] Enrollment in this cohort is ongoing. Despite these promising results and manageable toxicity profile, the optimal treatment sequence with amivantamab remains unknown. Finally, whether the combination of MET TKI plus amivantamab is safe and feasible is also being explored in the ongoing phase 2 METalmark trial (NCT05488314).

The SYM015 study (a synergistic mixture of two recombinant humanized monoclonal antibodies against nonoverlapping epitopes of MET) reported high efficacy in three treatment-naive patients with *MET*ex14 NSCLC (RR = 90% and PFS = 9.2 mo).[51] Also, the dual MET antibody REGN5093 is currently being clinically developed for patients with *MET*-altered NSCLC (NCT04077099).

MET overexpression

Though MET overexpression is not traditionally viewed as an actionable biomarker, developments in the therapeutic landscape of MET inhibitors could change this in the foreseeable future.[52] Telisotuzumab Vedotin (Teliso-V [AbbVie, North Chicago, IL]) is an antibody-drug conjugate that links the anti–c-MET humanized monoclonal antibody ABT-700 with the potent anti-microtubule pharmacophore monomethyl auristatin E. In a phase 1 study, the most common AEs with Teliso-V were fatigue (54%), peripheral neuropathy (42%), and nausea (38%). The recommended phase 2 dose was established at 1.9 mg/kg every 2 weeks. Among 40

Table 2. Efficacy of MET Inhibitors in *MET*-Amplified NSCLC

Study	Drug	MET Amplification Definition	Amplification Stratification	Sample Size	ORR (%)	PFS (mo)	Median OS (mo)
PROFILE 1001[18]	Crizotinib	MET-to-CEP7 ratio ≥1.8	Total	38	28.9	5.1	11.0
			≥1.8 and ≤2.2	3	33.3	1.8	5.6
			>2.2 and <4.0	14	14.3	1.9	9.2
			≥4.0	21	38.1	6.7	11.4
METROS Trial[34]	Crizotinib	MET-to-CEP7 ratio >2.2	Total	16	31.3	5.0	5.4
			> 2.2 and < 5	14	35.7	4.4	5.4
			≥ 5	2	0	NE	NE
AcSé Trial[33]	Crizotinib	MET-to-CEP ratio ≥6	NR	25	32	3.2	7.7
Phase 1 trial[57]	Capmatinib	MET-deregulated tumors[a]	MET GCN				NR
			<4	17	6	NR	
			≥4 and <6	12	25	NR	
			≥6	15	47	7.9	
			MET-to-CEP7 ratio				
			<2	32	22	5.6[b]	
			≥2	9	44	NR	
GEOMETRY mono-1 trial[7,58]	capmatinib	EGFR wild-type and c-MET-amplified by FISH	GCN <4 pretreated[c]	30	7	3.6	NR
			GCN ≥4 to <6 pretreated	54	9	2.7	NR
			GCN ≥6 to <10 pretreated	42	12	2.7	NR
			GCN ≥10 pretreated	69	29	4.1	10.6
			GCN ≥10 naive	15	40	2.8	9.6
VISION[59]	Tepotinib	MET amplification by liquid biopsy (MET gene copy ≥2.5)	NR	24	42	NR	NR
Phase 1/2[51]	Sym015	> 5 MET copies by NGS or MET-to-CEP ratio >2.2 updated to ≥3.0 by FISH	NR	7	28.6	5.5	NR

[a]IHC 2+ or 3+ or H-score ≥150, or MET-to-centromere ratio ≥2.0 or gene copy number ≥5 or *EGFR* wild-type and MET IHC 3+. We only report data in MET-amplified NSCLC.
[b]Per investigator assessment.
[c]Arm closed owing to futility.
FISH, fluorescent in situ hybridization; GCN, gene copy number; IHC, immunohistochemistry; NE, not estimable; NR, Not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

pretreated patients with MET-positive NSCLC, the RR was 23% and the median DoR and PFS were 8.7 months and 5.2 months, respectively. Neither NSCLC histology nor c-MET H-scores were found to be relevant covariates in exposure-efficacy analyses.[53] In the phase 2 LUMINOSITY trial,[52] Teliso-V reported a promising RR (from 24.1% in intermediate MET expression to 52.2% in high MET expression ≥50% with 3+) and DoR (6.9 mo) in patients with previously treated MET-overexpressing nonsquamous *EGFR* wild-type NSCLC, whereas the efficacy in squamous NSCLC was limited (RR = 11.1%, DoR = 4.4 mo). Similarly, in the phase 2 LUNGMAP substudy S1400K, Teliso-V failed to meet the prespecified RR in patients with MET-positive squamous cell carcinoma, and there were three grade 5 events. However, the dose of Teliso-V in this trial was 2.7 mg/kg every 3 weeks.[54] Therefore, on the basis of these data, Teliso-V versus docetaxel is being explored in the ongoing phase 3 TeliMET trial (NCT04928846) only in nonsquamous pretreated NSCLC with MET overexpression. In contrast, although Teliso-V plus nivolumab was well tolerated in patients with c-MET–positive NSCLC, the efficacy was limited (RR = 7.4%).[55] Finally, in 25 patients with osimertinib-relapsed NSCLC and MET overexpression (≥25% tumor cells at 3+ intensity), the combination of osimertinib and Teliso-V reported an RR of 58% with 32% grade greater than or equal to 3 AEs.[56] REGN5093-M114 is a MET-MET bispecific antibody with a linked payload conjugate of a cytotoxic inhibitor of microtubule assembly. This compound is being explored in a phase 1/2 trial in MET-positive NSCLC (NCT04982224).

MET Amplification

De Novo MET-Amplified NSCLC

Different trials have assessed the role of MET TKI in the setting of *MET*-amp NSCLC. An expansion cohort of PROFILE-1001 included 38 patients (31 pretreated)

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with *MET*-amp (MET-to-CEP7 ratio ≥1.8) advanced NSCLC.[18] Patients were allocated to three groups on the basis of *MET*-amp levels: low (MET-to-CEP7 ratio ≥1.8 and ≤2.2), medium (>2.2 and <4.0), and high (≥4.0). The overall RR was 28.9% and was 38.1%, 14.3%, and 33.3% for high, medium, and low MET-amp groups, respectively. The median DoR was 5.2, 3.8, and 12.2 months, and the median PFS was 6.7, 1.9, and 1.8, respectively, suggesting that, in this trial, the efficacy of the TKI was dependent on the level of amplification. In both the METROS trial in *MET*-amp (MET-to-CEP7 ratio of >2.2 by FISH, "medium amplification") and the ACSé trial in *MET*-amp (GCN ≥6 by FISH),[33] crizotinib reported an RR of approximately 30% but limited PFS and OS (Table 2[7,18,33,34,51,57,58,59]). These data suggest that more potent TKI is required in *MET*-amp NSCLC. In a phase 1 study of 55 patients with MET-dysregulated (MET-to-CEP7 ratio ≥2.0 or GCN ≥5) NSCLC, capmatinib reported an RR of 20%.[57] More importantly, the RR reached 47% and the median PFS was 7.9 months by independent review assessment for patients with MET GCN greater than or equal to 6. In addition, in the GEOMETRY mono-1 study, capmatinib exhibited an RR of 29% and 40% for *MET*-amplified (GCN ≥10) NSCLC in previously treated and treatment-naive patients, respectively, with similar OS regardless of the line of treatment. The RR was lower in lower cutoff points of GCN (Table 2[7,18,33,34,51,57,58,59]).[7,58] In another study, tepotinib induced an RR of 42% in patients with *MET*-amp detected by liquid biopsy (GCN ≥2.5).[59] In addition to oral TKI, REGN5093 is also been investigated in patients with *MET*-amp advanced NSCLC (NCT04077099). In addition, Sym015 has also been studied in this population. In a phase 1/2 trial, Sym015 exhibited, in 7 TKI-naive patients, an RR of 28.6% and a median PFS of 5.5 months.[51] In summary, *MET*-amp NSCLC represents an aggressive subgroup of NSCLC. Various trials have reported an objective response rate (ORR) from 30% to 40%, and high levels of amplification correlate with a higher likelihood of responses to MET inhibition therapy. However, the inconsistent definitions of *MET*-amp across different clinical trials have confounded the interpretation of the efficacy of available MET TKI.

Acquired MET Amplification

Genomic profiling on resistance to TKI has led to the identification of *MET*-amp as a driver of AR in several oncogene-addicted NSCLCs (Fig. 4). The incidence of AR ranges from 4% to 30%, depending on the method and criteria used and the oncogenic driver and TKI type.[60–67] This reveals a new therapeutic opportunity for the design of new clinical trials with combination strategies upfront to avoid the occurrence of this mechanism of AR, or sequential treatment approaches at progression on TKI (Supplementary Table 1).

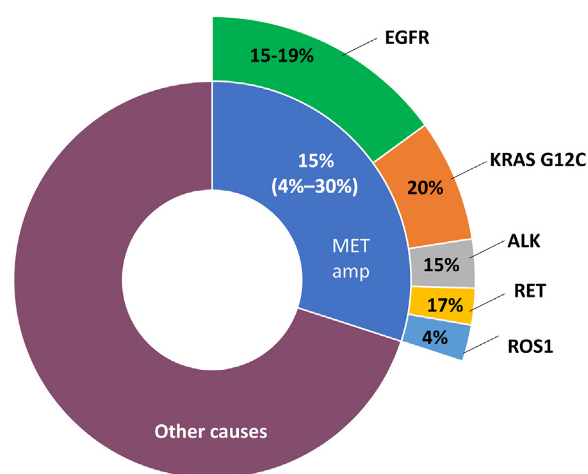

Figure 4. MET amplification as a mechanism of acquired resistance in oncogenic-addicted NSCLC. Figure created by BioRender. MET amp, MET amplification.

The most well-characterized *MET*-amp-driven resistance is among *EGFR*-mutant NSCLC. The distinction between passenger and driver mutations is crucial in interpreting the significance of *MET*-amp among *EGFR*-mutated NSCLC and, hence, selecting patients for combination therapy. It was found that de novo MET GCN greater than or equal to 5 in the absence of MET/CEP7 ratio greater than or equal to 2 did not significantly affect response to first-line EGFR TKI, whereas those with MET/CEP7 ratio greater than or equal to 2 had a significantly shorter time to treatment failure.[68] Initial data in *EGFR*-mutant tumors reported that *MET*-amp was detected in 5% to 22% of NSCLC with AR to first-generation EGFR TKI,[60,69] being the second most common mechanism of AR after the acquired *EGFR* T790M mutation in exon 20.[69] The *MET*-amp resistance triggers EGFR-independent phosphorylation of ERBB3 and downstream activation of PI3K/AKT pathway, providing a bypass track even in the presence of an EGFR inhibitor.[60] After second-line osimertinib, *MET*-amp occurs in up to 19%,[61,70] whereas plasma genotyping of patients receiving first-line osimertinib exhibited acquired *MET*-amp in 15% of cases, making *MET*-amp the main off-target mechanism of AR.[62] Tissue analysis could reveal much higher rates of *MET*-amp because of a potential underestimation or a lower sensitivity of gene amplification assessment in liquid biopsy.[71] Clinical characteristics associated with a high probability of *MET*-amp include a history of smoking, a lower probability for intracranial progression, and a short PFS on the most recent TKI.[72]

Several phase 1 and 2 trials in *EGFR*-mutant tumors and acquired *MET*-amp reported the efficacy of dual EGFR TKI plus MET inhibitor therapy. The combination

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of capmatinib plus gefitinib or savolitinib plus gefitinib yielded an RR of 47% and 52%, respectively.[73,74] Similarly, in the TATTON trial, the combination of osimertinib plus savolitinib reported an RR ranging from 33% to 67% (overall RR 48%) and median PFS ranging from 5.5 to 11.0 months in different cohorts according to previous treatment or not with osimertinib and T790M status.[75] The efficacy of this combination was endorsed in the preliminary results from the ORCHARD trial (NCT03944772), a biomarker-directed phase 2 platform study, which reported an RR of 41% (*MET*-amp cohort) after first-line osimertinib.[76] Further exploration of this combination is underway in the SAVANNAH study (NCT03778229). Similarly, the phase 1b/2 INSIGHT study (N = 19) reported that tepotinib plus gefitinib improved efficacy versus chemotherapy in terms of median PFS (16.6 versus 4.2 mo, HR = 0.13, 90% CI: 0.04–0.43), median OS (37.3 versus 13.1 mo, HR = 0.08, 90% CI: 0.01–0.51), RR (67% versus 43%), and median DoR (19.9 versus 2.8 mo).[23] Despite the limited sample size, this trial suggests that a personalized approach improves outcomes compared with conventional chemotherapy. Subsequently, the phase 2 INSIGHT2 trial (NCT03940703) explores the combination of tepotinib plus osimertinib in patients with advanced NSCLC with *MET*-amp AR to first-line osimertinib. Among 22 patients with a follow-up of more than 9 months, the combination reported an RR of 54.5%, whereas the RR was only 8.3% in 12 patients treated with tepotinib monotherapy. These data support that, in acquired *MET* amplification, a dual TKI strategy is the optimal approach. Indeed, the trial supported that the optimal definition of *MET*-amp in tissue is FISH MET GCN of 5 or MET/CEP7 greater than or equal to 2. Finally, in this setting of acquired *MET*-amp tumors, two phase 3 trials are ongoing: the GEOMETRY-E (NCT04816214) with capmatinib plus osimertinib and the SAFFRON (NCT05261399) with savolitinib plus osimertinib. In both trials, the comparator arm is the standard platinum-doublet chemotherapy.

In the CHRYSALIS study, amivantamab in combination with lazertinib (a third-generation EGFR TKI) for the treatment of osimertinib-relapsed, chemotherapy-naive *EGFR*-mutant NSCLC (N = 45, 11% with *MET*-amp) reported clinically meaningful outcomes, including a 36% RR, 9.6 months DoR, and 4.9 months median PFS with a manageable toxicity profile. The RR occurred in patients with and without identified EGFR/MET resistance (47% and 29%, respectively). However, among 10 patients with a positive IHC score (EGFR+MET score ≥400), the RR reached 90% with a median DoR and PFS of 9.7 months and 12.5 months, respectively.[77] Amivantamab monotherapy has also been tested in 121 patients with osimertinib-refractory tumors (RR = 19%, DoR = 5.9 mo, and PFS = 4.2 mo). However, the combination with lazertinib reported longer durability and potentially improved central nervous system (CNS) protection (intracranial progression 7% versus 17% with amivantamab monotherapy), supporting the combination approach.[78] The results of the combination in the post-osimertinib and postchemotherapy population have been confirmed in cohort A of the CHRYSALIS-2 study (NCT04077463).[79] The trial did not select patients according to *MET*-status (N = 162) and reported an RR by blinded independent central review of 33%, median DoR of 9.6 months; the PFS and OS were 5.1 months and 14.8 months, respectively. The intracranial RR was 26%. The most common grade greater than or equal to 3 TRAEs were infusion-related reactions (8%), acneiform dermatitis (5%), and hypoalbuminemia (7%). TRAEs leading to reductions and discontinuation of either or both amivantamab and lazertinib occurred in 9% and 7%, respectively.[79] These data suggest that, compared with the CHRYSALIS trial,[77] intervening chemotherapy does not decrease the activity of the combination. Cohort D of the CHRYSALIS-2 study will assess the results according to biomarker validation in a new tissue biopsy after osimertinib.[80] Finally, to overcome *MET*-amp as a mechanism of AR, the MARIPOSA trial (NCT04487080) evaluates in a treatment-naive population the combination of amivantamab plus lazertinib compared with lazertinib and osimertinib. Similarly, the MARIPOSA-2 (NCT04988295) evaluates amivantamab plus lazertinib plus platinum-pemetrexed chemotherapy compared with chemotherapy with or without amivantamab in the postosimertinib setting.

In progressive disease, dual combination treatment approaches may increase toxicity and risk of treatment discontinuation. However, recent preclinical data revealed that a subset of *EGFR*-mutant, *MET*-amp lung cancers develop a dependence on MET activation alone, suggesting a subgroup of tumors with primary resistance to EGFR TKI that could be treated with a MET TKI monotherapy rather than with an EGFR/MET combination.[81,82] The identification of these tumors will require additional investigation.

In *ALK*-positive NSCLC, *MET*-amp has also been implicated as an AR mechanism.[83–85] Recently, using FISH or NGS on 207 posttreatment tissue (n = 101) or plasma (n = 106) specimens from patients with *ALK*-positive NSCLC, acquired *MET*-amp occurred in 15% of cases, including 12% and 22% of biopsies from patients progressing on second-generation inhibitors and lorlatinib, respectively.[63] More importantly, tumors from patients previously treated with crizotinib followed by next-generation TKIs were significantly less likely to harbor *MET*-amp than those from patients treated only with next-generation TKIs (9% versus 33%, $p = 0.019$).[63] Although monotherapy with crizotinib could be of

interest, its activity may ultimately be limited by secondary *ALK* mutations, suggesting that combination strategies with ALK and MET inhibitors with high intracranial activity would be more appropriate. As one-third of patients who received upfront next-generation ALK TKIs developed *MET*-amp, it justifies exploring upfront ALK/MET combinations for advanced *ALK*-positive NSCLC.

For other oncogenic-driven NSCLC such as *KRAS* G12-mutant,[64] *RET*-fusion,[65] *ROS1*-positive NSCLC postlorlatinib,[66] and *NTRK*-fusion,[86] the *MET*-amp is also a potential druggable mechanism of AR (Fig. 4). The incidence in *NTRK*-positive tumors is unknown. In RET-fusion tumors, without RET resistance mutations, MET-amp is the most probable driver of disease progression,[65] and a dual strategy of RET TKI plus crizotinib was able to overcome *MET*-dependency, with one out of four patients experiencing a response lasting for 10 months.[87] A similar approach has been found to reestablish disease control in the face of off-target resistance in *NTRK*-positive tumors.[67]

Taken together, *MET*-amp is a driver of resistance in approximately 15% of the TKI-pretreated tumors across several oncogenic-driven NSCLCs. This may suggest potential upfront combinations to overcome the onset of this mechanism of resistance and prolong the benefit of a first-line treatment strategy.

Mechanisms of AR to MET TKIs

Similar to other targeted therapies, resistance to MET-targeted therapies can be classified as primary resistance, reflected as the lack of efficacy and primary disease progression, and secondary resistance, when disease progression is followed after an initial partial response or lasting stable disease.[88] In addition, molecular mechanisms of resistance can be classified into three groups: (1) on-target resistance, when a genomic alteration occurs within the targeted protein hampering target inhibition by the drug; (2) off-target resistance or bypass mechanism of resistance, when the target is correctly inhibited but tumor growth is driven by oncogenic activation of alternative pathways; and finally (3) mechanisms that include histologic transformation and apoptotic defects.[89]

In the setting of driver *MET* genomic alterations like *MET*ex14 skipping and *MET*-amp, several mechanisms that convey AR to MET TKIs have been discovered and characterized in vitro and clinically.[90–92] On-target or *MET*-dependent resistance occurs mainly by the acquisition of secondary mutations in the tyrosine kinase domain in up to 35% of patients, including mutations in codons G1090, H1094, G1163, L1195, F1200, D1228, Y1230, METD1246N, and Y1248H, and high levels of *MET*-amp.[90–93] Among the listed on-target resistant mutations, only D1228 and Y1230 have been validated using functional assays. The others have been inferred but not biologically validated. Indeed, the *MET* kinase domain mutations profile correlates with different MET inhibitors. For MET type Ib inhibitors like capmatinib, tepotinib, and savolitinib, the most frequently detected mutations involve codons D1228 and Y1230.[92] On-target resistance mutations to type Ib inhibitors also confer resistance to the type Ia MET TKI, crizotinib. In contrast, *MET* mutation in G1163R (analog to the *ALK* G1202R mutation) confers resistance to crizotinib but not to type Ib TKIs.[4] For type II MET inhibitors such as merestinib, glesatinib, and cabozantinib, the resistance involves mutations in codons L1195 and F1200.[92,94] Type II inhibitors can bind to the MET kinase domain in the presence of G1163R and mutations in codons D1228 and Y1230, and inhibit MET phosphorylation.[90,92,95] Conversely, type I inhibitors can overcome resistance to most mutations that confer resistance to type II TKIs (Fig. 5).

Interestingly, some of these resistance mutations have also been reported in papillary renal cell carcinomas as primary *MET* tyrosine kinase mutations and have recently been reported as primary *MET* mutations in lung cancer samples without concurrent *MET* exon 14 skipping in 0.5% to 0.9%.[96,97]

Overcoming *MET*-dependent resistance is challenging, as there is a lack of clinical access to effective targeted therapies to develop a sequential treatment strategy, such as with *EGFR* or *ALK*-driven cancers.[98] Sequential treatment with a structurally different MET TKI was effective in overcoming single on-target resistance mechanisms in up to one-third of patients, although data are limited.[90,95] Similarly, in a phase 2 trial, sequential capmatinib reported modest activity in crizotinib-pretreated MET-altered NSCLC (15 *MET*ex14–mutant, 5 *MET*-amp), potentially owing to overlapping resistance mechanisms.[99] This may suggest that blinded sequential approaches do not have any impact on the outcome. Therefore, systematic acquired genomic profiling in tissue or plasma can be informative in the treatment decision process and can identify patients who might benefit from sequential MET inhibitors and contribute to the design of future clinical trials.[90]

One of the novel strategies aiming to overcome resistance is targeting the extracellular domain of MET with monoclonal antibodies. In this setting, amivantamab recently reported in the phase 1 CHRYSALIS trial an RR of 21.1% and a clinical benefit rate of 57.9% among 19 patients previously treated with MET TKIs.[41] With Sym-015, a mixture of two humanized MET antibodies, early efficacy in 10 patients previously treated with MET TKIs exhibits a disease control rate of 60% and a median PFS of 5.4 months; however, further evidence is required.[51]

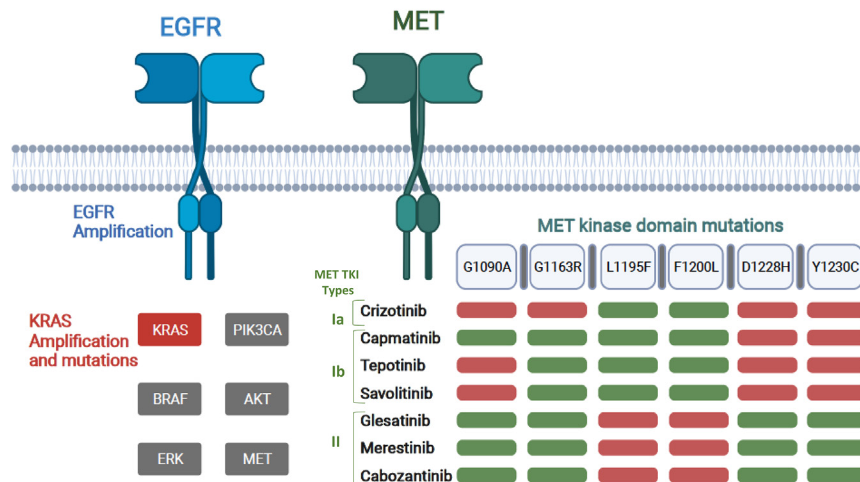

Figure 5. Mechanism of acquired resistance to MET TKIs in *MET* exon 14-mutant NSCLC, including secondary MET kinase domain mutations. Red color corresponds to potential mutation with resistance to specific MET TKI, whereas green color corresponds to mutation with specific sensitivity to MET TKI. Figure created by BioRender. TKI, tyrosine kinase inhibitor.

The off-target resistance mechanism occurs mainly through the oncogenic activation of other driver genes independent from MET, mainly *EGFR* and *KRAS* amplification, and mutations in key downstream signaling pathways like *KRAS.*[90,91,100] Preclinical research suggests that the dual inhibition of MET or EGFR/ERBB2 together with MEK inhibitors can effectively overcome the resistance mediated by *KRAS* mutations, but this strategy has not yet been translated into clinical drug development. Finally, to the best of our knowledge, there is no histologic transformation reported as a mechanism of AR on MET TKI.

Aside from the lack of MET expression as a mechanism of primary resistance,[48] recently, it has been reported that PI3K pathway alterations are common in *MET*ex14 NSCLC and may confer primary resistance to MET TKIs. Indeed, in preclinical models, PI3K inhibition restores sensitivity to MET TKIs.[101] Finding novel strategies to prevent primary and AR are needed to improve patient outcomes. In this sense, the combination of type I and II MET inhibitors has been found to prevent the emergence of *MET*-dependent resistance in vitro.[102]

From a future perspective, the understanding of *MET*-dependent cancer biology and the development of novel therapies directed against MET will evolve and shape the design of treatment strategies in this subgroup of patients.

Early-Stage *MET*-Dysregulated NSCLC

The prevalence of *MET*ex14 mutations among resected stage I to III NSCLC has been reported to be 2.8%, similar to the metastatic setting, and concurrent *MET*-amp detected in 5.3% was found to be independently associated with worse disease-free survival (DFS).[103] Preclinical functional studies have revealed that *MET*ex14 skipping mutations facilitate cell invasion and metastasis, whereas MET inhibitors were conversely able to repress metastasis in vivo.[104] Indeed, it has been reported that de novo high MET GCN correlates with shorter OS in patients with surgically resected NSCLC.[105–107] These observations support evaluating the role of MET inhibitors in the early-stage setting.

Although the impact of individual driver mutations on the prognosis of early-stage NSCLC remains relatively undefined, a cohort study comprising 159 patients with stage II to III NSCLC found that targetable gene alterations were significantly associated with a shorter DFS compared with wild-type tumors. However, these data could be biased by the enriched *KRAS*-mutant tumors included in this cohort,[108] which are known to be poor prognostic markers,[109] as other series have not reported differences in DFS between *EGFR*-mutant tumors and wild-type tumors.[110] After the ADAURA trial,[111] an expanded role of targeted therapies in the early-stage setting is anticipated, and there is a renewed interest in neoadjuvant settings including TKI. Geometry-N (NCT04926831) is investigating the role of perioperative capmatinib in early-stage *MET*ex14 skipping or *MET*-amp NSCLC, with major pathologic response as the primary end point (Supplementary Table 1). Given the impracticalities of conducting a phase 3 randomized controlled trial in the era of rapid drug development, the success of targeted therapies in rare NSCLC subtypes including *MET* alterations will ultimately hinge on the robustness of pathologic response as a surrogate for OS, the traditionally accepted standard in early-stage treatment. To that end, adaptive responses using clearance of

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ctDNA are relevant end points that should be explored in tandem with advancements in minimal residual disease technology.[112]

Brain Metastases in *MET*-Dysregulated NSCLC

The incidence of brain metastases (BM) in patients with *MET*ex14 skipping positive metastatic NSCLC has not been thoroughly evaluated prospectively, with only one retrospective series (N = 83, all baseline brain magnetic resonance imaging or computed tomography) reporting an incidence of 17%, increasing to a 36% lifetime incidence.[113] Other small retrospective series without standardized baseline brain imaging reported similar percentages of BM (21%–23%) in *MET*-dysregulated NSCLC.[114,115]

Crizotinib has a poor CNS penetration rate. Among 54 *MET*ex14 patients, the rate of CNS progression on crizotinib was 22% and the median time to radiological CNS progression was 5.8 months.[113] The selective MET TKIs have reported improved CNS penetration and promising initial data on intracranial disease control. Tepotinib can penetrate the blood-brain barrier, with CSF concentrations reaching 25% of the plasma concentration and CNS efficacy in preclinical models.[116] In the VISION trial, across cohort A plus C, 43 patients with baseline asymptomatic BM were assessable by response assessment in neuro-oncology brain metastases criteria (23 in first-line and 20 in second-line), 30 (68.9%) were previously treated with brain radiotherapy or surgery. Out of 15 patients with target lesions, intracranial RR was 66.7% with intracranial DoR not estimated, whereas, in patients with target and nontarget lesions (N = 43), the intracranial disease control rate was 88.4% with an intracranial median PFS of 20.9 months.[37] Capmatinib can also cross the blood-brain-barrier with a brain-to-blood capmatinib concentration of 9%, as has been exhibited in animal models. In the GEOMETRY-1 study, 14 patients had baseline asymptomatic BM, including 13 patients (3 without previous cranial radiotherapy) with assessable CNS disease. The intracranial RR was 54% (7 of 13), including four complete responses. Intracranial disease control was achieved in 12 of 13 patients.[117] BM outcomes in the MET-amplified group were not reported.[7] Sequential capmatinib at crizotinib failure did not result in intracranial responses although all patients (N = 4) had intracranial disease control.[99] Finally, for savolitinib, even fewer data are available. Among 15 of 70 patients enrolled in the phase 2 study with baseline BM, savolitinib resulted in disease control in all patients, and the three patients with measurable BM had a partial response, but information regarding the previous radiotherapy was not provided.[38]

Although the first data regarding selective MET TKI and intracranial efficacy are promising, more data are needed to reliably estimate the true CNS efficacy, as patient numbers are small, and most patients received previous cranial radiotherapy, prohibiting to evaluate the efficacy of only the TKI. Unfortunately, a capmatinib trial specifically enrolling patients with BM and *MET*ex14-mutated NSCLC was terminated (company decision, NCT04460729). The phase $^{1}/_{2}$ NCT02132598 trial assesses the dose and schedule of tepotinib alone or in combination with other TKI in MET-driven NSCLC, and the combination with capmatinib in MET-amplified tumors was prematurely closed owing to poor accrual. To the best of our knowledge, except for this trial (tepotinib), no other trials are specifically enrolling patients with BM and MET-altered NSCLC.

Immuno-Oncology in *MET*-Dysregulated NSCLC

*MET*ex14-altered NSCLCs have a higher percentage of high programmed death-ligand 1 (PD-L1) expression compared with wild-type NSCLC. In a large series (N = 69219, of which 1592 were *MET*ex14-positive), PD-L1–positive tumors (PD-L1 >1%, PD-L1 status available for 25% of the patients) were more frequent in the *MET*ex14-altered (84%) compared with the wild-type subgroup (59%),[4] and especially high PD-L1 expression (≥50%) was enriched in *MET*ex14 versus wild-type (60% versus 30%).[4] Concordant with previous cohorts,[118] median tumor mutational burden was significantly lower for METex14 versus wild-type tumors (3.8 mutations per megabase versus 7.0 mutations per megabase), and neither median tumor mutational burden nor PD-L1 expression significantly differed across alteration functional sites.[4] Similarly, another cohort reported neither differences in PD-L1 expression level between *MET*-amp versus *MET*ex14 tumors nor between the different levels of *MET*-amp.[24]

Limited and conflicting data are available regarding immune checkpoint inhibitor (ICI) efficacy in *MET*-altered NSCLC. In some small retrospective series (N = 24–36), ICI efficacy in previously treated patients was modest with an RR of 16% to 17% and a median PFS of only 1.7 to 3.4 months regardless of PD-L1 expression.[118,119] In contrast, other retrospective series (N = 13–30) revealed an ORR of 36% to 46%, median PFS of 4.9 months, and durable responses of 10 to 49 months.[120,121] Another retrospective series (N = 59 METex14-mutated and N=278 *MET*-amp NSCLC) suggested that patients with MET-amplified NSCLC obtain benefit with ICI compared with chemotherapy, whereas those with *MET*ex14-mutated NSCLC do not, which is of particular relevance for the prognostically poor

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MET-amp GCN greater than or equal to 10 subgroup.[24] Of note, all data have been obtained with monotherapy ICI, and to the best of our knowledge, the efficacy of chemotherapy-ICI combinations has not been evaluated in *MET*-altered NSCLC. Furthermore, limited data exist about the potential risk of immune-related adverse events with sequential TKI after previous ICI.[42]

MET expression modulates the tumor microenvironment (TME) and makes it more immunosuppressive, for example, through hepatocyte growth factor/c-MET signaling resulting in the accumulation of, for example, neutrophils with immunosuppressive properties. Furthermore, the hepatocyte growth factor can inhibit dendritic cells. MET inhibition can overcome this immunosuppression (reviewed, including MET expression and the TME modulation, by Dempke et al.[122]) Therefore, a combination of a MET inhibitor with an ICI seems of interest. This strategy is being evaluated in both *MET*-altered NSCLC, in which the MET inhibition targets the *MET* alteration and the MET pathway in the TME (NCT04323436, NCT02323126) and a MET wild-type/unselected population, in which the MET pathway in the TME is targeted to overcome this immunosuppression (NCT04797702; NCT03170960 and NCT04471428; NCT03647488; NCT04139317; NCT03468985).

Conclusion

Recently, MET TKI, bispecific antibodies, and antibody-drug conjugates have enlarged the therapeutic arsenal for *MET*-deregulated NSCLC. However, to date, MET TKI is approved only for *MET*ex14 NSCLC. With the increasing use of *MET* inhibitors, a deeper understanding of the mechanisms of AR will help to design rational combination therapies and guide the sequencing of treatment options. Finally, more data are needed to reliably estimate the true CNS efficacy of these MET TKI and the role of immunotherapy in this subset of NSCLC.

CrediT Authorship Contribution Statement

Jordi Remon: Conceptualization, Acquisition and interpretation of data, Validation, Investigation, Writing (original draft, review and editing), Supervision.

Lizza Hendriks: Conceptualization, Acquistion and interpretation of data, Validation, Investigation, Writing (original draft, review and editing).

Giannis Mountzios: Acquisition and interpretation of data, Validation.

Rosario García-Campelo: Acquisition and interpretation of data, Validation.

Stephanie P. L. Saw: Acquisition and interpretation of data, Validation.

Dipesh Uprety: Acquisition and interpretation of data. Figures, Validation.

Gonzalo Recondo: Acquisition and interpretation of data. Figures, Validation.

Guillermo Villacampa: Acquisition and interpretation of data, Validation.

Martin Reck: Acquisition and interpretation of data, Validation.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2022.10.015.

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