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Review

The expanding role of the receptor tyrosine kinase MET as a therapeutic target in non-small cell lung cancer

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SUMMARY

Aberrant regulation of MET receptor tyrosine kinase activity is a frequent event in non-small cell lung cancer (NSCLC), even though the frequency of oncogenic driver mutations of MET is low. Our discovery of oncogenic MET exon 14 skipping mutations, the characterization of the first prototype MET kinase inhibitor, and characterization of MET expression levels have led the way to novel therapeutic approaches with improved outcomes in NSCLC. MET exon 14 mutations are the most consequential but not the only alterations that can be targeted through small molecule tyrosine kinase inhibitors. The abundant expression of cellular MET (c-MET) in cancer cells has provided new opportunities for immuno-oncology approaches in a broader patient population, and the integration of MET-targeted personalized medicine with immunotherapy has not been fully exploited yet. Here, we highlight essential facets of MET as a therapeutic target in NSCLC and provide an outlook for future approaches.

INTRODUCTION

The MET proto-oncogene and other tyrosine kinases have been found to be frequent targets of aberrant expression and oncogenic activation in non-small cell lung cancer (NSCLC) and to various degrees across a wide spectrum of malignancies. Whereas these changes can lead to gain-of-function events, they also share specific signaling mechanisms with their normal counterparts, but, instead, the chronic oncogenic dysregulation of MET signaling and of cellular events significantly contributes to multiple aspects of transformation. Unsurprisingly, oncogenic addiction is often associated with this class of oncogenes, which has made them opportune targets for drug development. The MET gene itself was originally discovered as part of a chromosomal rearrangement in 1984 by George F. Vande Woude's group in human osteogenic sarcoma cell line after exposure to the N-methyl-N′-nitro-N-nitrosoguanidine carcinogen, but its name does not represent any apparent acronym.[1] The chromosomal alteration led to the fusion of the translocated promoter region (TPR) gene with MET, forming the TPR-MET oncogene, encoding for a fusion protein with constitutively active MET kinase activity. The TPR portion, encoding for a nuclear pore complex subunit, provides the structural basis for MET kinase activation through dimerization of TPR through a helix structure.[2] In human disease, the TPR-MET fusion is not known to play a relevant role, but its discovery highlights the significance of chronic MET tyrosine activation for transformation or even the role of aberrant receptor tyrosine kinase (RTK) activation and stimulation of growth factor signaling per se. Oncogenic activation of RTKs is a frequent event in NSCLC and can also include other RTKs, such as EGFR (epidermal growth factor receptor), ROS1 (v-Rros avian UR2 sarcoma viruoOncogene homolog 1), RON (recepteur d'origine Nantais), ERBB2 (HER2 or v-erb-B2 avian erythroblastic leukemia viral oncogene homolog 2), RET (rearranged during transfection), ALK (anaplastic lymphoma kinase), NTRK (neurotrophic tyrosine receptor kinase), and others.[3] The mechanism of oncogenic activation can vary among these kinases, and the occurrence is usually mutually exclusive as a disease-initiating event. This is further underlined by the fact that patients carrying any of these mutations are usually sensitive to specific tyrosine kinase inhibitors (TKIs) that block their activity, initially at least in some of the tumor cells or until drug resistance ensues. For MET dysregulation, there are essentially three major alterations that have been observed, including (1) acquired activating mutations in MET; (2) overexpression of MET, sometimes in conjunction with its ligand; and (3) oncogenic fusions of MET. As it is true for most RTKs, mutations of MET can occur as initial disease-driving events or as part of resistance mechanisms. To detect MET mutations, the European Society of Medical Oncology (ESMO) recommends cell-free DNA (liquid biopsy) testing, preferably with next-generation sequencing using peripheral blood, but a tissue biopsy must follow a negative result. MET amplifications and polysomy can also be detected and distinguished by *in situ* hybridization.[4] In this review, we highlight essential facets of MET as a therapeutic target in NSCLC and provide an outlook for future approaches.

THE MET RTK

After the initial discovery of TPR-MET as a chemically induced oncogene, the hunt for its true twin in cancer specimens was disappointing, and, although this oncoprotein has no meaningful

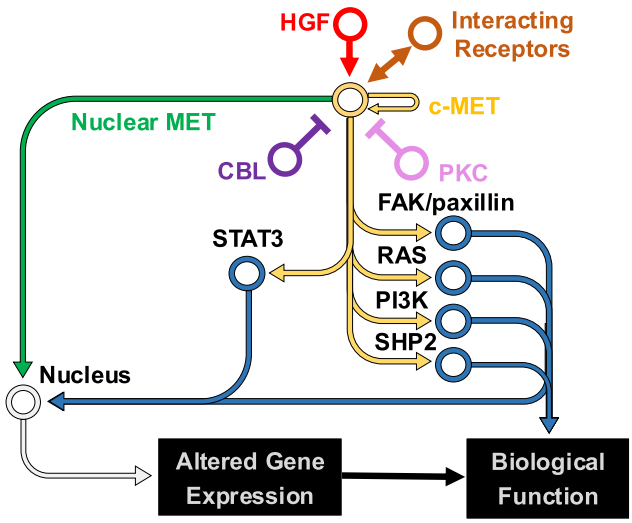

Figure 1. Common c-MET signaling pathways

The c-MET receptor tyrosine kinase is normally activated by its ligand HGF. It can activate signaling pathways, including FAK/paxillin, RAS, PI3K, SHP2, STAT3, and others. c-MET can serve as its own substrate and interact with other receptors. After its activation, negative signals through CBL and PKC can downregulate the c-MET signal. The receptor can also translocate to the nucleus, where it is likely to contribute with other factors to altered gene expression. Activation of c-MET has been associated with many biological effects, such as regulation of cytoskeletal functions, growth, survival, differentiation, stemness, or epithelial-mesenchymal transition.

relevance in human cancer, it served as an important tool to understand MET signaling and biology. The normal human *MET* gene encodes for a 190 kDa transmembrane protein, and its gene (21 exons and 20 introns) was found to be located on chromosome 7q31.[5,6] MET expression was thought to be restricted to epithelial cells, but it can also be found on hematopoietic cells, endothelial cells, hepatocytes, neurons, and others (query for MET at proteinatlas.org). It is therefore not surprising that it has been also linked to transformation or drug resistance in a wide variety of solid tumors and hematologic malignancies. In normal cells, MET is activated after engaging with its ligand HGF (hepatocyte growth factor), leading to receptor dimerization and activation of its intrinsic intracellular tyrosine kinase. These changes create additional transient phosphorylation sites in the cytoplasmic tail of MET and recruitment of signaling proteins that activate signaling cascades (Figure 1), including MAPK (mitogen-activated protein kinase), STAT (signal transducer and activator of transcription), PI3K (phosphoinositide 3-kinase), and others, thereby acting as effectors of MET.[7] There are several aspects of MET that are of particular interest for cancer biology. (1) MET signaling pathways mediate signals that are frequently dysregulated by other oncogenes, including reduced apoptosis, cellular proliferation, cell mobilization, and invasion. (2) MET has an essential role in tissue remodeling, more so in embryogenesis than in adults where it plays some role in tissue repair.[8] At least some of this function may be linked to its interaction with the cytoskeleton and focal adhesions, which enables altered cell morphology and changes of cell-cell and cell-matrix interactions. (3) Traditionally, growth factor receptors were thought to only function through membrane proximal signaling events, eventually leading to activation of transcription factors in the nucleus or STAT proteins. However, particularly, receptors that do not contain intrinsic tyrosine kinase activity can for example signal through Janus kinases. These kinases can translocate to the nucleus and phosphorylate histones and potentially other proteins, thereby participating in the modification of proteins involved in chromatin remodeling and gene expression. MET itself is known to also partially function within the nucleus.[9,10] Some of the signals transmitted to the nucleus may ultimately lead to epithelial-mesenchymal transition.[7] (4) Tyrosine residues phosphorylated by MET itself can also be transphosphorylated by related RTKs, and, similarly, MET can transphosphorylate homologous residues in related RTKs and thereby control a network of interactions. This mechanism has particular relevance to EGFR in cancer, and, in case of the RON RTK, it may even facilitate MET dependency.[11,12] (5) In normal signaling, the activity of MET is tightly regulated by Tyr1003, which is encoded by exon 14 of *MET*. Phosphorylated Tyr1003 in the cytoplasmic juxtamembrane (JM) domain creates a binding site for CBL (Casitas B-lineage lymphoma), a ubiquitin E3 ligase that facilitates MET ubiquitinylation, ultimately leading to removal of the receptor from the cell surface and degradation.[13] At some level, this mechanism can be disrupted by many oncogenic RTKs, creating an imbalance between cell surface expression, intracellular signaling, and control mechanisms. (6) MET can interact and cooperate with other non-RTK receptors such as integrins or CD44 and either enhance or facilitate additional biological functions.[14,15]

THE MANY ONCOGENIC FACETS OF MET ALTERATIONS

Typically, oncogenic mutations cause or contribute to a transforming phenotype, turning normal cells into cancer cells. This can certainly be true for some MET mutations, such as deletions within MET or MET fusion proteins (Figure 2). However, MET is unique in this aspect as changes in its expression levels, such as MET amplifications and, to a lesser extent, MET overexpression, can drive transformation as well. Thus, it is not surprising that increasing clinical evidence suggests a tendency for higher expression levels of MET to be a stronger indicator for its oncogenic potency. How the promiscuity of MET to interact with other receptors and vice versa plays into this phenotype has not been well defined, but it seems apparent that, if MET is the primary oncogenic driver, inhibition of its activity is sufficient to initiate a clinical response. Therefore, all aberrations in MET expression or MET mutations need to be carefully considered during the clinical decision process.

MET exon 14 skipping alterations are oncogenic drivers in NSCLC

Multiple somatic MET mutations have been found in lung cancer cells, but probably the most consequential are exon 14 skipping mutations. In 2003, we described the first somatic MET exon 14 skipping (MET^{exon14}) mutation (5′ splice site) in small cell lung cancer (SCLC), followed by our discovery in NSCLC in 2005.[16,17] A larger study by Frampton et al. involving more than thirty-eight thousand distinct tumor specimens discovered 126 variants in 221 specimens,[18] suggesting that mutations in

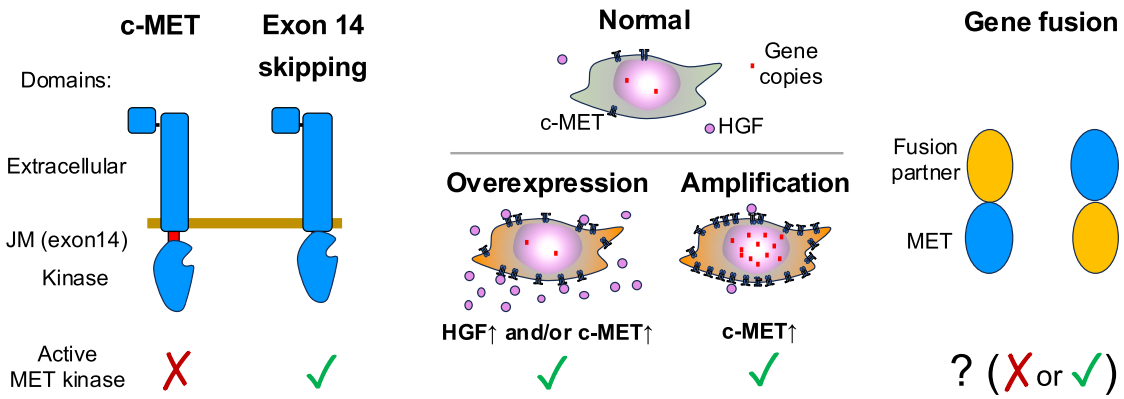

Figure 2. Alterations of MET in NSCLC

The major forms of MET that can drive transformation include the exon 14 skipping mutation, overexpression of c-MET and/or its ligand HGF, *MET* gene amplification, or MET gene fusions with other genes, containing various portions of MET. These mechanisms are not mutually exclusive and may require a protein expression threshold to unleash its transforming activity.

MET are not limited to exon 14 skipping mutations.[16,17] The significance of the in-frame MET^{exon14} mutations lies in the production of a shortened MET protein, including deletion of Tyr1003 contained within the JM region. As a biological consequence of MET^{exon14}, the receptor remains aberrantly active in cancer cells. This oncogenic MET^{exon14} receptor retains its ability to bind HGF and activate its intrinsic kinase activity, but the protein has impaired degradation due to loss of the CBL binding site.[19,20] Changes in CBL binding might not explain the entire oncogenic characteristic of MET^{exon14} as the JM region also contains a phosphorylation site for PKC (protein kinase C) at serine 985 (Ser985), which can negatively regulate the MET kinase activity.[21] Conformational changes as a consequence of exon 14 skipping may also allow a more open and active conformation of the MET kinase domain. Interestingly, oncogenic mutations and deletion have also been found in CBL in NSCLC. Both oncogenic CBL mutations and MET^{exon14} can lead to activation of RTKs, including MET, and define their responsiveness to MET inhibitors.[22,23] Whereas MET mutations are targetable by specific inhibitors, CBL mutations may not necessarily depend on MET and can utilize other RTKs and function in other malignancies.[24] Therefore, MET inhibitors by themselves may not necessarily be efficacious at targeting cancers with CBL mutations.

The frequency of MET alterations (amplification and overexpression) in NSCLC and other malignancies, in particular hepatocellular carcinoma, is rather high, but oncogenic MET^{exon14} mutations are fairly low compared to more frequent EGFR or KRAS mutations.[3] In a review of 139 research studies including more than 350 thousand patients, the median frequency of MET^{exon14} mutations was found to be 2% in NSCLC with no apparent ethnic, geographical, sex, or smoking history bias.[25] However, we and others have observed at least some ethnic differences in the frequency of MET mutations.[26,27] Patients with sarcomatoid histology had the highest frequency (12%), followed by adenocarcinoma/non-squamous (2.4%) and squamous histology (1.3%). In 39 studies where patient outcome was reported, first-line treatment with MET TKI had the highest median response rate (50.7%–68.8%) followed by immunotherapy (33.3%) and chemotherapy, which had the worst rate (23.1%–27.0%).

More MET mutations

Beyond MET^{exon14} mutations, there are no clinically relevant alterations within the MET sequence that have been defined as primary drivers of transformation in NSCLC. However, changes in MET do not have to be driver mutations to contribute to transformation. A series of MET mutations have been identified and associated with functional changes in experimental models that contain at least some oncogenic features. We have previously identified a series of additional mutations with functional consequences identified in SCLC and NSCLC. Two gain-of-function c-MET missense mutations (Arg988Cys and Thr1010Ile) in the intracellular JM domain of SCLC cells were further characterized. Both were sufficient to induce modest factor-independent growth as well as clonogenic growth and alter cytoskeletal function with increased receptor activation and phosphorylation of the focal adhesion protein paxillin.[17] The same mutations in the JM domain were also found in NSCLC, as well as an additional Ser1058Pro point mutation.[16] A structure function analysis has shown that Tyr 13–16 in the C-terminal kinase domain (Tyr1311, Tyr1347, Tyr1354, and Tyr1363) were required for cytoskeletal function, whereas mutation of Tyr1001 had opposing effects.[28] Even though MET mutations are most common in NSCLC, they can also occur in other malignancies, and some of these alterations may have oncogenic potential and are susceptible to existing MET inhibitors. For example, infrequent MET kinase domain mutation of His1094 and Phe1200 can lead to factor-independent growth in a murine cell line model, but partial responses have also been observed in NSCLC patients carrying these mutations treated with the MET inhibitor elzovantinib.[29] The cbioportal.org database (TCGA dataset, queried November 21, 2024) suggests a total of at least 25 missense mutations as potential oncogenic drivers. To what extent most of these mutations contribute to transformation is not known, but it is conceivable that some changes

in the JM domain or tyrosine kinase domain may affect the function of the MET receptor and could contribute at some level to a transforming phenotype.

MET overexpression and amplification

There are multiple mechanisms that can lead to abnormal MET activity, but they may not equally cause addiction to this pathway and may display different oncogenic potential. MET overexpression and amplification are also thought to support MET^{exon14} as both events can frequently be associated.[30] Whereas co-expression of MET and its ligand HGF is often found in lung cancer cells, such as in EGFR inhibitor resistance settings, *MET* amplifications are infrequent events.[31] Both high-level *MET* amplification and MET^{exon14} mutations are independent prognostic factors of poor survival,[32] and the prognosis of this patient population with MET is superior with MET TKI.[25,33,34] At least for patients with MET^{exon14} mutations, the overall survival appears to be similar compared to patients harboring other oncogenic drivers, including EGFR mutations, ROS1 fusions, ALK fusions, RET fusions, or others in NSCLC.[35] Also, in contrast to MET overexpression and mere pathway activation, MET amplification appears to have a more defined association with oncogenic potential, but a threshold for copy numbers to drive transformation may depend on other alterations and has not yet been well defined.[36,37] Dysregulation may not be a good predictive or prognostic factor, and it requires further evaluation and consideration in the context of concomitant mutations. As MET^{exon14} mutations have shown, MET expression can be altered by interfering with intrinsic degradation pathways but could also be altered by increasing transcription levels through increased promotor activity. A series of transcription factors have been described that may regulate c-MET expression (e.g., ETS [E-twenty six],[38] PAX3 [paired box 3],[39] and TCF-4 [transcription factor 4][40]), and a query of the genecards.org database (queried November 21, 2024) suggests additional sites in the c-MET promotor for factors involved in gene regulation (e.g., AP1, N-MYC, and p300). It is unclear whether any of these contributes to the overexpression in NSCLC, but it is interesting to note that, for example, the HIF1 (Hypoxia-inducible factor 1) transcription factors may be associated with EGFR oncogene-dependent upregulation of c-MET in NSCLC.[41]

MET fusions

Fusion genes of RTKs have been long known to act as oncogenic drivers in NSCLC, such as fusions of RET, ROS1, and ALK.[42] MET fusions have also been identified, and some have been characterized, such as kinesin family member 5B (KIF5B)-MET, fusing KIFB5B exon 24 to MET exon 15. This mutation was found in NSCLC patients with a frequency of 0.5% (1/206). Expression of KIF5B-MET in cell lines led to the activation of growth pathways and crizotinib-dependent tumor growth in mice.[43] Similarly, in a set of 4,429 NSCLC patients, 13 (0.29%) unique *de novo* MET fusions with TNPO3, THAP5, CAV1, CD74, HLA-DRB1, and DST were identified. Within this study an EPHB4(exon9)-MET(exon15) fusion was further characterized and found to promote cell growth *in vitro*, and it showed sensitivity toward MET TKIs.[44] In a more comprehensive database survey of ~39,000 lung cancer patients, MET fusions were found to be rare (~0.2%–0.3%) and occurred as primary or acquired fusions. About half of them were intragenetic fusions, and the MET portion was fused to either the C terminus or the N terminus of MET. This study also underlined that there is a large diversity of these fusions and a lack of preference for a specific fusion partner.[45] It should be noted that the vast majority of MET fusions have not been characterized *in vitro* for their transforming potential, but there is evidence that at least some patients with MET fusions can be sensitive to MET TKIs.[46–48] The MET gene can also fuse with a partner gene without including the kinase domain, such as an MET(exon7)-ATXN7L1(exon1) fusion. A patient with this fusion showed a partial response to crizotinib, but it is unclear whether this was truly a response to MET kinase inhibition or how this fusion contributes to transformation.[49] Some experimental evaluation would be required to at least confirm whether any MET fusion is constitutively active or can contribute to MET activation in order to deem it a likely clinically actionable target. It is expected that MET fusions would be constrained by the same limitations as other oncogenic forms of MET, and one would predict that higher protein expression could lead to higher oncogenic potential.

TARGETING MET WITH SMALL MOLECULE INHIBITORS

After our initial characterization of the first prototype MET TKI,[50] the efficacy of MET TKI in lung cancer patients with MET^{exon14} mutations has now been well established in clinical trials, indicating superior objective response rate (ORR) compared to immunotherapy and chemotherapy, and additional formal comparisons between these treatments are pending. Even though small molecule MET inhibitors have shown significant clinical relieve in MET^{exon14} patients (see also Salgia et al.[51] for review), results were initially disappointing in NSCLC patients presenting with aberrant MET expression.[52] We now understand that the dependency is more context specific, and MET inhibitors (Figure 3; Table S1) can be particularly effective when the mutated protein is expressed at higher levels or present in high copy numbers as primary driver, but not necessarily with MET overexpression. Current Food and Drug Administration (FDA)-approved MET TKIs or those with orphan designation fall into two categories according to the nature of their kinase-bound interaction, relative to the DFG (Asp-Phe-Gly) motif that plays an essential role in the regulation of its tyrosine kinase activity. For example, type I ATP-competitive inhibitors bind to active conformation, either deep within the pocket (Ia—depend on interaction with Gly1163, e.g., crizotinib) or closer to the front of the pocket (Ib—do not depend on the Gly1163 residue, e.g., tepotinib, capmatinib, and savolitinib), and type II inhibitors (e.g., cabozantinib) bind to the inactive kinase with the DFG motif outwards rotated (DFG-out), allowing for binding outside of the ATP-binding region and interaction with the hinge region through hydrogen bonds. The different binding modes of MET TKIs allow for activity against additional mutations in MET.[53]

Crizotinib was the first multi-kinase inhibitor with activity in patients with MET^{exon14} mutations, with additional activity against RON, ROS1, and ALK.[22,54–57] This was confirmed in the phase 1 PROFILE 1001 (NCT00585195) trial of the dose-expansion cohort involving 69 NSCLC patients with MET^{exon14} mutations,

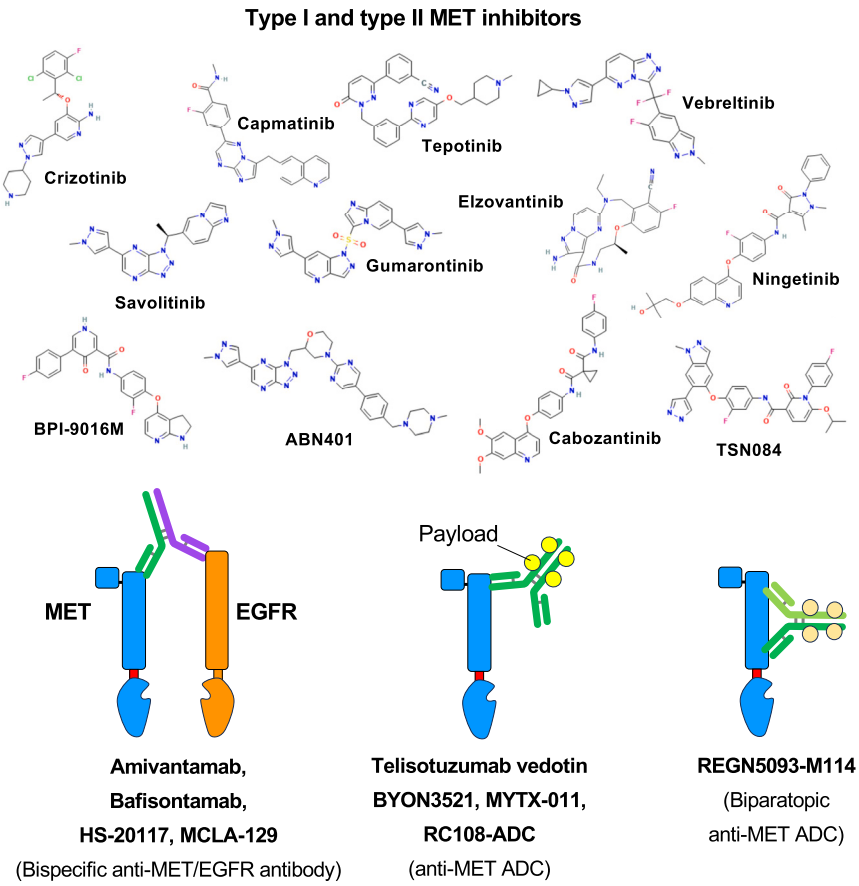

Figure 3. MET-targeting therapies

There are currently three types (Ia, Ib, and II) of MET TKIs that are distinguished by their binding mode. Structures of TKIs were retrieved from https://pubchem.ncbi.nlm.nih.gov/, but the structure of HS-10241 has not been released (top). Whereas MET- or HGF- targeting antibodies have not yet shown clinical efficacy, current efforts focus on bispecific anti-MET/EGFR antibodies, anti-MET ADCs, and a biparatopic MET ADC (bottom).

and in 2018 crizotinib received breakthrough therapy designation from the US FDA for advanced NSCLC with MET^{exon14} mutations as second-line therapy after platinum-based chemotherapy.[54] Even though the French AcSé crizotinib program (NCT02034981) reported an ORR of 32% in patients with MET $\geq$ 6 copies and 36% in the MET^{exon14} cohort,[58] the METROS phase 2 trial of crizotinib (NCT02499614) in patients with pretreated NSCLC (*MET* amplification [*n* = 16], MET^{exon14} [*n* = 10, one patient with both changes]) found limited benefit with all patients rapidly progressing and deceasing.[59] Capmatinib is a selective MET inhibitor approved for advanced NSCLC with MET^{exon14} mutations, which was tested in the phase 2 GEOMETRY mono-1 trial (NCT02414139) in patients with *MET*-dysregulated advanced NSCLC. The ORR in patients with MET^{exon14} mutation who were pretreated was 44% (95% confidence interval [CI]: 34.1%–54.3%; *n* = 100; median overall survival was 5.5 months [95% CI: 4.2–8.1 months]) and 68% (95% CI: 55.0%–79.7%; *n* = 60; median overall survival was 21.4 months [95% CI: 15.2–30.5 months]) in patients who were treatment naive. In patients with gene amplification (MET copy number > 10), the ORR was 29% (95% CI: 18.7%–41.2%; *n* = 69), but arms with lower copy numbers were closed for futility.[60] In a smaller study of 20 NSCLC patients pretreated with crizotinib and with MET^{exon14} or MET amplification, the activity of capmatinib was lower in some patients, likely due to overlapping resistance mechanisms.[61] Cabozantinib, as a multi-RTK inhibitor (MET, VEGFR1/2/3, RET, KIT, FLT3, and AXL), may not only suppress MET-dependent tumor growth but also have some anti-angiogenic effects through the inhibition of VEGFR.[62] It is approved for renal cell carcinoma and advanced metastatic medullary thyroid carcinoma, based on the phase 3 METEOR trial (NCT01865747) comparing cabozantinib to everolimus,[63] but a formal analysis of cabozantinib in NSCLC with MET^{exon14} is pending. However, case reports show efficacy in drug resistance settings, such as with MET D1228N, Y1230H, or secondary RET fusion proteins.[64–66] Savolitinib is an MET inhibitor that is conditionally approved in China for patients with MET^{exon14} mutations but failed to meet FDA requirements. Results from a phase 2 trial of NSCLC patients with locally advanced/metastatic MET^{exon14} mutations that were MET inhibitor treatment naive (NCT02897479) were encouraging and showed an ORR of 42.9% (95% CI: 31.1%–55.3%; 30/70 patients) with median duration of response of 8.3 months. The median progression-free survival was 6.8 months, and the median overall survival was 12.5 months (95% CI: 10.5–23.6 months).[67] Improved results were obtained in the phase 3b trial (NCT04923945) with an ORR of 62% (95% CI: 51%–72%; *n* = 87) and medium progression-free survival at 11.0 months in treatment-naive patients. Side effects caused by this drug were manageable, but also two treatment-related deaths were observed.[68] Similarly, vebreltinib (bozitinib) has been approved in China for NSCLC with MET^{exon14}, and the FDA has granted orphan drug designation for these patients, but little information is available. The safety and preliminary efficacy were tested in patients with secondary glioma containing various MET alterations, including MET^{exon14}, MET amplifications, and MET fusions.[69] Data from the KUNPENG phase 2 trial (NCT04258033) of 52 NSCLC patients with MET^{exon14} showed an ORR of 75% (95% CI: 61.1%–86.0%), which was similar in treatment-naive (77.1%; 95% CI: 59.9%–89.6%; 35 patients) or previously treated patients (70.6%; 95% CI: 44.0%–89.7%; 17 patients). Median progression-free survival was 14.1 months, median duration of response was 15.9 months, and median overall survival was 20.7 months, wherein all five patients with brain metastases

responded to vebreltinib. While vebreltinib showed some advantages to other MET kinase inhibitors in progression-free survival and overall survival, no significant statistical differences were reported.[70] Also, the MET inhibitor gumarontinib (glumetinib) was granted orphan drug designation by the FDA for NSCLC patients with MET genomic aberrations. Results from the multi-center phase 2 GLORY trial (NCT04270591) conducted in China and Japan showed an ORR of 66% (95% CI: 54%–76%, *n* = 79) in NSCLC with MET^{exon14} (71% in treatment-naive [*n* = 44] and 60% in pretreated [*n* = 35]). 8% (7/84) of patients showed treatment-related adverse effects that led to discontinuation of treatment.[71] Tepotinib is the most recent MET inhibitor that received FDA approval in 2024 for the treatment of NSCLC patients harboring the exon 14 mutations. Tepotinib was evaluated in the phase 2 VISION trial (NCT02864992) with 99/152 patients that were followed for at least 9 months with a response rate of 46% and median duration of response of 11.1 months.[72] This was confirmed in a follow-up analysis of 313 patients with an ORR of 51.4% (95% CI: 45.8%–57.1%). In treatment-naive patients (*n* = 164) versus previously treated patients, the ORR was 57.3% (95% CI: 49.4%–65.0%) versus 45.0% (95% CI: 36.8%–53.3%) and the medium duration of response was 46.4 months (95% CI: 13.8 months, not estimable) versus 12.6 months (95% CI: 9.5–18.5 months).[73] The MET/AXL inhibitor ningetinib was evaluated in a phase 1b trial (NCT03758287) of advanced EGFR-mutant NSCLC (*n* = 108). The ORR was 30.8% (4/19; 95% CI: 17.0%–59.8%) for patients with MET focal amplification (18.1% of patients), 0% (0/6; 95% CI: 54.1%–100%) for MET polysomy (5.6%), 24.1% (7/29; 95% CI: 7.6%–40.7%) for MET overexpression (55.8%), 20% (1/5; 95% CI: 0.5%–71.6%) for AXL amplification (8.1%), and 27.6% (8/29; 95% CI: 10.3%–44.9%) AXL overexpression (45.3%).[74] BPI-9016M is currently tested in a phase 1b trial including NSCLC patients with locally advanced or metastatic MET^{exon14} or MET (NCT02929290). Preliminary data from 38 patients suggest limited efficacy with an ORR of 2.6% (95% CI: 0.1%–13.8%) and disease control rate of 42.1% (95% CI: 26.3%–59.2%).[75] HS-10241 is tested in clinical trials (NCT05430386 and NCT06110663) in MET-positive NSCLC patients with EGFR mutations in combination with the EGFR inhibitor almonertinib. Published data from a phase 1 clinical trial of HS-10241 (NCT04477057) in NSCLC patients (*n* = 26) suggest that the drug is well tolerated and shows some efficacy in 4/5 patients with MET abnormalities.[76] Elzovantinib (TPX-0022) is an MET, SRC, and CSF1R inhibitor, tested in the phase 1/2 SHIELD-1 clinical trial (NCT03993873).[77] The MET inhibitor ABN401 has been tested preclinically alone or in combination with erlotinib in NSCLC models and is currently in clinical trials (NCT04052971 and NCT05541822).[78] TSN084 is a multi-kinase MET inhibitor that also targets TRK kinases, FLT3, AXL, DDR (discoid domain receptor) kinases, and CDK8/19 and has shown efficacy in preclinical studies. A phase 1 clinical trial (NCT05300438) is currently ongoing.[79]

At first glance, highly MET-selective TKIs appear to be more desirable potential treatments for MET^{exon14} NSCLC because off-target activity can be avoided and dosing can be maximized. However, under some circumstances when additional drivers are present with overlapping activity, early-generation multi-kinase inhibitors may be advantageous. The ESMO guidelines recommend capmatinib or tepotinib for patients with MET^{exon14} or capmatinib for patients with high MET amplification following prior treatment with immunotherapy and/or platinum-based chemotherapy,[4] but treatment choices may depend on individual patient characteristics.

THE ROLE OF MET ALTERATIONS IN DRUG RESISTANCE

There is a significant overlap between growth signaling pathways activated by oncogenic MET and other oncogenic RTKs, such as EGFR. In addition, KRAS forms a signaling nexus that is utilized by theses RTKs, but it can act as an oncogene itself. In patients, MET^{exon14} mutations are mostly mutually exclusive with other oncogenic drivers including EGFR, KRAS, or HER2 as redundancy in oncogenic signaling would not be required for transformation.[18,25] Nevertheless, likely as a result of low allele frequency, MET^{exon14} mutations can occasionally co-occur with mutations in *KRAS*, *ROS1*, and *EGFR* driver mutations,[18,34] essentially signifying pre-existing resistance to MET TKI monotherapy. However, it would be reasonable to assume that common mechanisms initiating carcinogenesis and playing a key role in tumor development may also have common off-target mechanisms leading to drug resistance. This is notwithstanding the fact that resistance mechanisms are notoriously diverse, and there are unique aspects for each oncogene that may affect genomic stability, metastasis, immune evasion, or other tumor-associated phenotypes. Nevertheless, some lessons learned from these more prevalent oncogenes and drug resistance mechanisms related to their inhibitors may also apply to MET TKI resistance (Figure 4). Probably one of the more direct mechanisms of MET TKI resistance involves on-target mutations, including additional mutations in MET^{exon14} and increased HGF expression. Common sites of this acquired resistance include mutations at amino acids that prevent binding of inhibitors to Asp 1228 (D1228) and Tyr 1230 (Y1230) or binding to Leu1195 (L1195) and Phe1200 (F1200).[61,80–86] Additional mutations may not necessarily alter the binding affinity of the inhibitor but rather increase the MET signaling strength. Another resistance mechanism commonly employed by cancer cells in response to inhibition of oncogene addiction involves the upregulation or activation of bypass signaling pathways.[87,88] An early study looking at resistance to crizotinib and glesatinib found both MET mutations (exon 14 amplification and tyrosine kinase domain mutation) as well as alterations in EGFR and KRAS/BRAF.[86] Cases of crizotinib resistance in MET^{exon14} patients was also associated with wild-type *KRAS* amplification or *KRAS* G12 mutations, further supporting a role for KRAS signaling in MET TKI resistance.[85,89,90] Additional EGFR and RAS alterations were also found in other studies, including amplifications.[82] However, in about half the patients, alterations could not be identified, which is similar to the rate of nongenetic changes in KRAS.G12C and oncogenic EGFR inhibitor resistance.[87,88] Mechanisms associated with RAS/MAPK kinase pathway alterations may be sensitive to the MEK inhibitor trametinib.[90] Different MET TKI inhibitors may lead to somewhat different on-target resistance mechanisms, but the overlap of

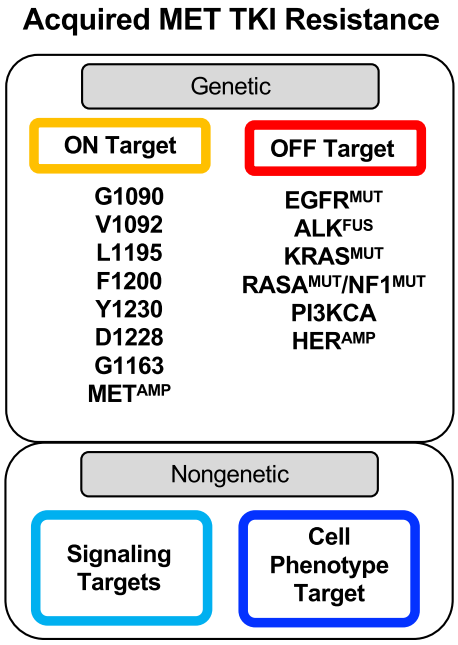

Figure 4. Acquired MET TKI resistance

Resistance to MET TKIs can be caused on-target by interference with its binding through point mutations or elevated levels of MET itself. Off-target alterations usually substitute for the loss of MET signaling through alternate mechanisms. Nongenetic mechanisms of MET inhibitor resistance have been poorly defined and aim to sustain oncogenic signaling and/or prevent terminal differentiation.

MET, EGFR, or KRAS alterations between oncogenic forms of these three proteins in the resistance settings suggests a certain interdependency or at least susceptibility for this mechanism in NSCLC. Combination treatments should be further explored to evaluate whether the co-occurrence can be exploited as vulnerability for a subset of patients.

EXPLOITING MET EXPRESSION

In addition to immune checkpoint inhibitors, there are two major antibody-based approaches considered for the treatment of MET-expressing NSCLC, including antibody drug conjugates (ADCs) and mono/bi-specific antibodies (Figure 3; Table S1). Additional approaches that have been considered to target mutant MET include the development of cancer vaccines, a class of therapeutics that until recently did not contain sufficient immunogenicity to be broadly applicable. In particular, MET neoantigens, such as MET fusion regions, may be of interest here, but the diversity of these MET mutations and low frequency may make clinical evaluation difficult. MET-targeting chimeric antigen receptor-T cell therapy is in its infancy for NSCLC, and clinical trial data are not available. None of these therapies have been FDA approved for MET alteration in NSCLC. Mono-specific antibodies targeting MET or its ligand HGF do not appear to show clinical benefit, and the hope is that next-generation anti-MET-antibody approaches may be more efficacious.[91–94]

Bispecific MET/EGFR antibody: The mechanism of action of this class of drug is diverse. In general, they can block ligand binding and ligand-dependent receptor stimulation but, it can also induce Fc-mediated antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cytokine release, whereas complement-dependent cytotoxicity may not necessarily play a role. Amivantamab (amivantamab-vmjw) is a first-in-class bispecific antibody that can bind to both EGFR and MET with multiple mechanisms of action.[95] It is an FDA-approved therapeutic approved for NSCLC patients with mutation in EGFR exon 20 that have progressed on platinum-based therapy or as first-line treatment with carboplatin and pemetrexed, and it is directed against both EGFR and c-MET. The results of the CHRYSALIS trial (NCT02609776) allowed for the first FDA approval of amivantamab in 2021 in patients that advanced on platinum-based chemotherapy ($n = 81$), with an ORR of 40% (95% CI: 29%–51%), a median response duration of 11.1 months (95% CI: 6.9 months, not reported), and a median progression-free survival of 8.3 months (95% CI: 6.5–10.9 months).[96]

The efficacy of amivantamab as first-line therapy was evaluated in the PAPILLON trial (NCT04538664), which led to the FDA approval of combining amivantamab with carboplatin and pemetrexed in 2024. The combination improved median progression-free survival to 11.4 months (95% CI: 9.8–13.7 months) from 6.7 months (95% CI: 5.6–7.3 months) with a hazard ratio (HR) of 0.40 (95% CI: 0.30–0.53; $p < 0.001$).[97] Similarly, the phase 3 MARIPOSA NSCLC trial (NCT04487080) did not have MET expression as a participation criterion but compared the efficacy of amivantamab/lazertinib combinations with osimertinib in patients with EGFR exon 19 deletions or L858R point mutations in advanced or metastatic disease. The median progression-free survival for amivantamab/lazertinib was 23.7 months (95% CI: 19.1–27.7 months; $n = 429$) versus 16.6 months (95% CI: 14.8–18.5 months; $n = 429$) for osimertinib and 18.5 months (95% CI: 14.8–20.1 months; $n = 216$) for lazertinib alone. While the ORR for the amivantamab/lazertinib arm (86%; 95% CI: 83%–89%) and the osimertinib arm (85%; 95% CI: 81%–88%) were similar, differences in the median response duration were observed with 25.8 months (95% CI: 20.1 months, not determined) versus 16.8 months (95% CI: 14.8–18.5 months), respectively. Adverse events led to 10% discontinuation in the combination arm versus 3% with osimertinib, and HR for death was 0.80 (95% CI: 0.61–1.05) between the trial groups.[98] Similarly, data from the MARIPOSA-2 study (NCT04988295) of 657 patients that had progressed on or after osimertinib monotherapy with locally advanced or metastatic *EGFR*-mutated (exon 19 deletions or L858R) NSCLC showed improved progression-free survival when amivantamab was combined with the EGFR inhibitor lazertinib and/or chemotherapy versus chemotherapy alone with an HR for disease progression or death of 0.48 and 0.44, respectively. In the amivantamab group versus the chemotherapy group, the progression-free survival (6.3 and 8.3 versus 4.2 months), the ORRs (64% and 63% versus 36%), and the median intracranial progression-free survival (12.5 and 12.8 versus 8.3 months) were higher.[99] Interestingly, results from the phase 3 PALOMA-3 study (NCT05388669) suggest that subcutaneous amivantamab/lazertinib injection may result in fewer

infusion-related side effects and yield increased median progression-free survival (6.1 months versus 4.3 months) with an HR for death of 0.62 (95% CI: 0.42–0.92; nominal $p = 0.02$). Even though this therapeutic is primarily intended for patients with EGFR mutations, an open phase 1/2 clinical trial (METalmark; NCT05488314) evaluates the efficacy of capmatinib in patients with MET^{exon14} or amplified MET, either alone or in combination with amivantamab in unresectable metastatic NSCLC. The bispecific antibody bafisontamab (EMB-01) is currently tested in advanced solid tumors (NCT03797391), and preliminary data suggest a disease control rate of 42.1%.[100] Its efficacy will also be evaluated in lung cancer patients with EGFR mutations in combination with osimertinib (NCT05498389). MCLA-129 has been tested preclinically and has comparable activity to amivantamab but recognizes different epitopes.[101] It is currently under evaluation in clinical trials (NCT04868877, NCT04930432, and NCT06015568). There is little disclosure about the MET/EGFR bispecific HS-20117 antibody, which is evaluated in patients with advanced solid tumors (NCT05940116).

Anti-MET ADC: The mechanisms of action for ADCs rely on the internalization of the antibody and release of the payload toxin that is bound by a linker. Cleavage of the linker releases the toxin that can then kill the cancer cell and sometimes bystander cells in proximity. Telisotuzumab vedotin was developed as a first-in-class anti-MET ADC to be active against cells with MET overexpression, linked to the toxic tubulin inhibitor monomethyl auristatin E (MMAE) payload.[102] The efficacy of telisotuzumab vedotin in MET-expressing squamous cell lung cancer was evaluated in the Lung-MAP S1400K trial (NCT03574753) but was closed due to lack in efficacy.[103] Results from a phase 1b trial (NCT02099058) with dual targeting of NSCLC containing EGFR mutations and overexpression of MET with the EGFR inhibitor erlotinib and the anti-MET ADC telisotuzumab vedotin were encouraging. 36 patients were evaluated, and the median progression-free survival was 5.9 months (95% CI: 2.8 months, not reached). The ORR was 32.1% (95% CI: 15.9%–52.4%) for patients with EGFR mutation and MET expression ($n = 28$) and 52.6% in those that also had high MET expression ($n = 15$). The median progression-free survival in patients with the EGFR T790M mutations was lower (3.7 months), versus those with a mutation (6.8 months).[104] The more recent phase 2 LUMINOSITY trial (NCT03539536) of telisotuzumab vedotin monotherapy identified responders in treated (at least 2 lines of therapy) non-squamous NSCLC (EGFR wild-type) patients ($n = 172$) based on their level of c-MET overexpression ($\geq$25% tumor cells with 3+ staining). The ORR was 28.6% (95% CI: 21.7%–36.2%), but some differences were observed between c-MET high (34.6% [95% CI: 24.2%–46.2%]; $\geq$50% c-MET expression 3+) and c-MET intermediate (22.9% [95% CI: 14.4–33.4%]; $\geq$25%<50% c-MET expression). The median progression-free survival (5.7 months; 95% CI: 4.6–6.9 months) was similar between the c-MET-high group (5.5 months; 95% CI: 4.1–8.3 months) and c-MET-intermediate group (6.0 months; 95% CI: 4.5–8.1 months). A control arm is included in the phase 3 TeliMET NSCLC-01 trial (NCT04928846) in a comparable patient population with direct comparison between this ADC and docetaxel.[105] Currently, there are five clinical trials evaluating the efficacy of telisotuzumab vedotin (NCT02099058, NCT04928846, and NCT05513703), including two trials testing combinations with the EGFR inhibitor osimertinib (NCT03539536 and NCT06093503).

BYON3521 is a novel c-MET-targeting ADC linked with the DNA alkylating reagent duocarmycin.[106] Early clinical trial (NCT05323045) results from eight MET-expressing patients, including one NSCLC, suggest good tolerability and stable disease in two patients.[107] The anti-MET ADC MYTX-011 delivers vcMMAE (valine-citrulline MMAE) as a payload to the target cells.[108] MYTX-011 will be evaluated in a phase 1 clinical trial (NCT05652868) in NSCLC patients that overexpress c-MET as well as in patients with MET^{exon14} or MET amplifications. RC108-ADC is another anti-MET ADC with an MMAE payload, which is tested in an ongoing phase 1 clinical trial (NCT04617314). REGN5093-M114 is a biparatopic anti-MET ADC with a maytansinoid M114 payload, a microtubulin inhibitor. The ADC showed therapeutic efficacy in preclinical studies in tumors with MET-driven NSCLC that had acquired resistance to EGFR TKIs.[109] REGN5093-M114 is currently tested in clinical trials in cancers with MET-overexpressing advanced tumors (NCT04982224). Interestingly, results from the first-in-human trial of the parent biparatopic MET antibody davutamig (REGN5093) (NCT04077099) indicate some preliminary efficacy, but not in MET^{exon14} patients with prior TKI treatment. Median duration of response was 7.4 months (95% CI: 2.2–24.9 months; $n = 74$) for patients at the same dose, wherein 12% had a partial response and 58% showed disease control. While the ORR for patients with MET^{exon14} and MET overexpression was 25% (4/16) and 13% (4/32), respectively, the antibody did not show a response in MET^{exon14} patients that received previous TKI treatment.[110]

MET IN THE AGE OF IMMUNOTHERAPY

With the discovery of immune checkpoint inhibitors, new antibody therapeutics became available that target either the PD-1 (programmed cell death)/PD-L1 (programmed cell death-ligand 1) or the CTLA4/CD80 (CD86) interaction to reactivate the T cell response against cancer cells. Even though MET^{exon14} mutations can be frequently associated with high levels of PD-L1, the association with a good response to immunotherapy or even high PD-L1 expression is controversial.[34,111–115] Indeed, MET TKIs may even be more efficacious than immunotherapy in NSCLC.[25,34] An analysis of German clinical data suggests that the combination of chemotherapy with immunotherapy provides a more effective outcome than either treatment alone in MET^{exon14} patients, and this may be independent of PD-L1 expression. Combined chemotherapy/immunotherapy was given to 35/110 (32%) patients, immunotherapy alone to 43/110 (39%), and chemotherapy to 32/110 (29%) upfront. Compared to chemotherapy, combination therapy had longer median progression-free survival than chemotherapy (32/110 patients) (6 months [95% CI: 4 months, not reached] vs. 2.5 months [95% CI: 1–5 months], higher ORR (49% [17/35] vs. 28% [9/32]) and a shift toward longer overall survival (16 vs. 10 months [$p = 0.24$]). The parameters between combination therapy and immunotherapy alone were not significantly different.[116] There is also concern for the use of immunotherapy in MET^{exon14} NSCLC patients as increased capmatinib-induced

liver toxicity was found in NSCLC patients that were pretreated with immunotherapy.[117] The efficacy of immunotherapy suggests that at least MET^{exon14} mutations to some degree contribute to immuno-evasiveness and can lead to an immunological "cold tumor." In the resistance setting, alterations in MET may simply act as disease-driving factors, but it is not entirely clear whether MET is also required to maintain or if other co-mutations can initiate an immune-suppressive phenotype. Additional studies are required to further evaluate the combination of immunotherapy or targeted therapy with immune checkpoint inhibitors. Toxicity observed with capmatinib suggests that timing and the choice of TKI should be carefully considered. Nevertheless, immunotherapy clearly can bring benefits to some patients with oncogenic MET.

The limited activity of immune checkpoint inhibitors in lung cancers is generally thought to be caused by an immune-suppressive microenvironment. Mechanistic insights about the role of MET have been sparse, but clinical studies with anti-PD-1 immune checkpoint inhibitors suggest that patients with MET amplification are more likely to be resistant to treatment. High MET copy-number variations (<5 versus >5) were associated with shorter progression-free survival ($p < 0.00017$; HR, 3.4; 95% CI: 1.7–6.6), and this was also linked to low STING (stimulator of interferon genes) expression, a protein that can negatively regulate immune function. The mechanisms of STING regulation by MET occur, at least in part, through phosphorylation of UPF1 (Up-frameshift 1), which can modulate STING expression by modifying the 3′ untranslated region.[118] Targeting of MET is one possible approach of restoring this pathway, but STING also presents a targetable opportunity. Despite on-target activity, STING agonists have not been successfully applied in clinical trials within this context, and either that may require further development of these therapeutics or it could be hindered by epigenetic factors and alternative pathways.[119] Additional studies on EGFR inhibitor-resistant lung adenocarcinoma with MET overexpression suggest a mechanism whereby MET activity restricts STING activation through upregulation of the ectonucleosidase CD73, likely through increased activity of the FOSL1 (fos-like1) transcription factor. Whereas CD73 increases immunosuppressive adenosine, the STING pathway contributes to the production of immunostimulatory cytokines. It was suggested that combination of the chemotherapeutic pemetrexed, which has a positive effect on the STING pathway, with inactivation of CD73 would promote immunogenicity.[120] These mechanisms point at pathways that are MET dependent, and the limited available aforementioned data indicate that they do not universally apply to all patients with MET amplification. It would be interesting to evaluate whether some of these effects are also associate in a subset of patients with other forms of oncogenic MET and whether nongenetic mechanisms described with MET inhibitor resistance play a role in the immune-suppressive phenotype.

CONCLUSIONS

The role of MET as a therapeutic target has been underappreciated due in part to the low frequency of MET^{exon14} mutations, but it has now become clear that its activity can play a unique role in all stages of treatment. Whereas high levels of MET^{exon14} mutations or amplifications of the MET gene can act as targetable primary oncogenic drivers, low levels may coexist with other driver mutations, and inhibition may not be sufficient to inhibit tumor growth. The therapeutic target list may be expanded by other activating MET mutations or activating MET fusions. When MET is a primary driver, specific TKIs are expected to be efficacious; the role of MET in the resistance setting may be more complicated. Either MET can act as a substitute primary driver for another oncogene or the unfortunate ability of MET and related RTKs to be transactivated may contribute to receptor signaling. Even though these effects are known, they have not been well studied in resistant cells. Lessons learned from TKIs in malignant growth would suggest that even low levels of constitutive MET activation, insufficient to act as primary drivers, may still contribute to some degree to a transforming phenotype. It may therefore be interesting to determine whether they provide some level of protection at the cancer stem cell level. The propensity of MET to be overexpressed or to undergo amplification also makes it an ideal target for ADCs, independent of any oncogenic function. The expanding role of MET as a therapeutic target in NSCLC beyond inhibition of its kinase activity has provided a boost in the quest for a curative treatment of this disease. Overlap and redundancy in signaling mechanisms may also require the use of combination treatments. Whether MET TKIs can be combined with immuno-oncology approaches requires a better understanding of their efficacy in NSCLC. Initial data are promising, and the field is expected to move toward therapeutic approaches that try to integrate personalized pharmacological approaches with approaches that direct immune cells to attack tumor cells. Targeting MET may not be a singular solution to eradicate NSCLC, but understanding the biology of oncogenic MET is an essential clue that cannot be underestimated.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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