HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2022 May 04.

Published in final edited form as:

Cancer. 2020 November 15; 126(22): 4826–4837. doi:10.1002/cncr.33159.

The METeoric rise of MET in lung cancer

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Abstract

Over the years there has been a continuous increase in clinically relevant driver mutations in non-small cell lung cancer. Among them dysregulated activation of the MET tyrosine kinase receptor has gained importance due to the recent development of quite effective treatments.

MET dysregulation encompasses a heterogeneous array of alterations leading to the prolonged activation of the cellular MET (c-MET, or MET) receptor and downstream proliferation pathways. It can arise through several mechanisms, including gene amplification, overexpression of the receptor and/or its ligand hepatocyte growth factor and the acquisition of activating mutations

MET mutations are found in 3–5% of NSCLC, mainly adenocarcinoma, and are over-represented in the sarcomatoid subtype. *De novo MET* amplifications are found in 1–5% of NSCLC, also predominantly in adenocarcinoma.

Here, we will bare the biology of MET, how to diagnose clinically relevant alterations, and their rising clinical importance in light of the emergence of multiple targeted therapies, both in the context of MET as a driver of resistance and in its own right.

Precis:

MET exon 14 alterations and amplifications can be primary oncogenic drivers as well as resistance pathways, such as among patients receiving EGFR targeted therapy.MET exon 14 alterations and amplifications have differene degree of responses to targeted therapy

Keywords

MET; NSCLC; Target therapy; molecular oncology; precision medicine

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Introduction

Over the course of the last decade, immunotherapy and targeted therapies have changed the prognosis of non-small cell lung cancer (NSCLC)[1, 2]. Today, there is a continuous increase in clinically relevant driver mutations. Mandatory molecular testing in lung adenocarcinoma according to The National Comprehensive Cancer Network (NCCN)[3] and European Society of Medical Oncology (ESMO) guidelines[4] includes *EGFR*, *ALK*, *ROS1*, *BRAF*, while they advise broader molecular screening for KRAS G12C, *RET*, *ERBB2*, *NTRK* and MET proto-oncogene receptor tyrosine kinase (*MET*, also known as hepatocyte growth factor receptor).

MET dysregulation encompasses a heterogeneous array of alterations leading to the prolonged activation of the cellular MET (c-MET, or MET) receptor and downstream proliferation pathways. MET mutations are found in 3–5% of NSCLC, mainly adenocarcinoma, and are over-represented in the sarcomatoid subtype[5, 6]. *De novo MET* amplifications are found in 1–5% of NSCLC[7], also predominantly in adenocarcinoma.

Here, we will discuss the biology of MET, how to diagnose clinically relevant alterations, and their rising clinical importance in light of the emergence of multiple targeted therapies, both in the context of MET as a driver of resistance and in its own right.

MET biology

The proto-oncogene *MET* is located on chromosome 7q21-q31. It encodes for a precursor that is post-transcriptionally digested and glycosylated, forming extracellular alpha and transmembrane beta chains. The alpha-chain is joined to the beta-chain by disulphide bonds. The alpha-chain contains semaphorin, cysteine-rich and immunoglobulin domains. The beta-chain contains homologous domains which include a transmembrane, juxtamembrane, tyrosine kinase and carboxy-terminal docking domains (Figure 1).

c-MET is a tyrosine kinase receptor. Upon binding with its ligand, hepatocyte growth factor (HGF), MET dimerizes, autophosphorylates and activates intracellular tyrosine kinase catalytic activity. The activation of c-MET regulates distinct downstream signalling including the PI3K/AKT/mTOR, RAS/RAF/ERK/MAPK, RAC/PAK, STAT/JNK, and FAK pathways[8, 9]. This signalling regulates cell survival and proliferation, migration and invasion, angiogenesis, and epithelial to mesenchymal cell transformation (Figure 2).

MET activation can result from various biological mechanisms, including protein overexpression, over-stimulation by HGF, mutations, amplifications and exon 14 skipping alterations. These distinctions may be important as treatment approaches were investigated based on different criteria used as biomarkers. For the purpose of discussing the role of MET in the current NSCLC treatment landscape, the two main subgroups are MET amplification and MET exon 14 mutations.

MET exon 14 partially encodes the c-MET juxtamembrane domain. This domain contains tyrosine 1003 (Y1003), the binding site of Cbl, which functions as an E3-ubiquitin protein ligase that regulates ubiquitin-mediated c-MET receptor degradation. Under normal

circumstances, the introns flanking MET exon 14 are spliced out, yielding an mRNA transcript with exon 14 properly coding for the Cbl-E3 ligase binding site, thus allowing for c-MET degradation[10] (Figure 3).

Somatic missense mutations, insertions, deletions and insertions/deletions (indels) have been identified occurring involving or flanking *MET* exon 14 in lung adenocarcinoma, many of which result in aberrant splicing and skipping of exon 14 in the mRNA transcript. However, not all involve exon 14 skipping. For instance, a hotspot Y1003 mutation has an intact exon 14-encoded juxtamembrane domain save for the Cbl-binding site.

As such, these different alterations lead to a lack of Y1003-Cbl binding. This results in prolonged ligand-dependant activation of the c-MET receptor, downstream proliferation pathways, and oncogenesis. These occur in 3% of adenocarcinoma but also 13–22% of sarcomatoid lung cancers[6, 11, 12] (Figure 3). Exon 14 alterations tend to be mutually exclusive with other primary oncogenic driver except for *MET* amplifications, copy number variants and *MDM2* amplifications[11, 12].

MET amplifications may drive oncogenesis in roughly 4% of TKI-naive NSCLC patients[13]. However, they represent a common acquired resistance mechanism to EGFR and ALK TKIs. *MET* amplification entails increased MET signalling through kinase activity or protein expression. In the treatment-naïve setting, in contrast to MET exon 14 alterations, amplifications are not mutually exclusive with other oncogenic drivers. While overlap is common at low amplification levels, at high levels, there is no oncogenic overlap, suggesting that only high amplification indicates a true MET-driven oncogenic state[7, 14]. Both can develop as secondary drivers upon progression on treatment.

Diagnosis of MET alterations (amplification, copy numbers, exon 14 skipping)

MET has become increasingly relevant as a therapeutic target over the last years, prompting the need to identify the oncogenic role each type of MET alteration and standardize the diagnostic approach. As with *EGFR*, non-smokers are over-represented in *MET*-driven NSCLC. However, a greater proportion of patients with either *MET* amplification (up to 77%) or exon 14 alterations (61–74%) consists of smokers than in most other driver alterations[11, 15, 16].

MET exon 14 alterations have been shown to act as oncogenes and to be potentially actionable, regardless of gene amplification. Both alterations can occur concurrently in NSCLC. Overall, amplification alone appears less strongly correlated with response to MET blockade, while only high amplification, excluding polysomy, seems to drive the malignant phenotype and be predictive of meaningful clinical benefit of targeted treatment.

Amplification

Fluorescence in situ hybridization (FISH) was the first validated technique to assess MET gene copy numbers. By comparing the ratio of *MET* to the centromeric portion of chromosome 7 (CEP7), FISH identifies amplification, when copy numbers increase without a similar increase in CEP7. This allows for the distinction between *MET* copy number

gains via polysomy, and true focal gene amplification. The distinction is important, as amplification but not polysomy likely represents oncogenic *MET* activation[7, 13, 17].

Amplification has been most frequently defined as a MET:CEP7 ratio greater than 2, with ≥5 signals per cell for copy number gain, according to the scoring system established by Cappuzzo *et al.*[14] When assessing de novo *MET* amplification, a MET:CEP7 ratio ≥5 appears to be the strongest predictor of a true MET-driven tumour, yet this only represents 0.34% of lung adenocarcinoma, far less than MET exon 14 skipping in such a population.

Finally, in some cases, the amplicons, which can include the entire centromere or parts thereof, does not include a balanced copy number gain of *MET*, resulting in a falsely low amplification ratio[18].

RT-PCR evaluates copy number without providing information about the underlying cause, therefore it is unable to distinguish between polysomy and gene amplification. It carries an inherent risk of over-estimating amplification and should not be used.

Immunohistochemistry (IHC) on formalin-fixed paraffin-embedded tissue sections can be performed with a semi-quantitative assessment, mainly using the SP44 rabbit monoclonal primary antibody. The SP44 is directed against a membranous and cytoplasmic MET epitope. After staining, intensity scores are multiplied by the percentage of tumour cells to calculate a semi-quantitative histology score, (H-score), considered positive if higher than 200. However, MET protein expression and gene amplification have been shown to be poorly correlated. MET overexpression occurs in 35–72% of NSCLCs. This can be explained by the fact that the most common mechanism leading to protein overexpression is the transcriptional upregulation of the c-MET receptor without *MET* gene amplification[19]. It is also important to note that the association between MET protein overexpression and c-MET activation is not clear, despite its prognostic impact[20]. As such, c-MET IHC is likely unable to select tumours for a MET-directed strategy. In spite of promising phase 2 results, no phase 3 trial using IHC MET assessment has shown positive clinical outcomes by targeting MET[21].

Further reinforcing the limitations of IHC screening, a recent reanalysis of tissue from 181 MET IHC positive NSCLC patients by the Lung Cancer Consortium 2 assessed the sensitivity of IHC in predicting gene amplification and MET exon 14 alterations. Nearly all IHC positive cases were negative for amplification and exon 14 mutations, suggesting that IHC is an inadequate screening tool for relevant MET alterations[22].

MET exon 14

Exon 14 mutations encompass a highly heterogeneous sequence composition, with alterations occurring between exon 13 and 15. RT-PCR has been shown to be a potential tool for analysis, with 100% sensitivity and 97.4% specificity compared to NGS. Messenger RNA is extracted from the tumour sample and analysis generally includes the region between exon 13 and 15, and in case of exon 14 skipping, it is excluded from the transcript.

The molecular diagnosis of MET exon 14 skipping is most often achieved through DNA or RNA NGS. DNA sequencing can only detect a genomic variant that alters or removes a

splicing site. On the other hand, RNA sequencing detects the fusion of exon 13 to 15, as this is the convergent result of any altered splicing mechanism or deletion. It therefore has the advantage of encompassing all causal genomic events that lead to exon 14 skipping[23].

In addition to pre-analytical considerations, such as the vulnerability of RNA to degradation, the sensitivity of amplicon-mediated DNA-based approaches and hybrid-capture RNA-based assays appears to differ. The prevalence of MET exon 14 skipping in NSCLC was 4.2% with RNA-based NGS and 1.3% with the DNA-based approach. In samples tested with both methods, 60% of RNA positive results were false-negatives in DNA assays, the limitation appearing to be primer design unable to capture all known exon 14 skipping events[23]. The probe in amplicon-mediated DNA-based approaches may not cover a sufficient region of interest[16]. Meanwhile, RNA-based analysis is highly reliant on extracted RNA quality[23]. Therefore, a DNA-based hybrid NGS could be the solution to decrease false-negatives of the former and circumvent pre-analytical limitations of the latter.

MET and immuno-oncology

Tumoral c-MET signalling appears to induce the expression of programmed death ligand 1 (PD-L1) immunoregulatory proteins, as well as being associated with the expression of indoleamine-2,3-dioxygenase (IDO). It may therefore participate in immune suppression and evasion[24, 25]. While this could suggest an increased sensitivity to PD-1 blockade, there is little data supporting the efficacy of single-agent ICIs in MET-driven tumours. 36 MET positive patients with advanced NSCLC are included in the IMMUNOTARGET registry, evaluating the efficacy of ICIs in mutation driven NSCLC. Of the 36, 13(36%) had a *MET* amplification and 23 (63.8%) an exon 14 skipping mutation. 16% of these patients presented a partial response to ICIs, with a median PFS of 3.4 months. However, it is worth noting that durable responses, defined as 12 month PFS, were more frequent among MET positive patients (23.4%) than EGFR, ALK, or RET patients (5.9–7.0%). PFS was neither correlated with type of MET alteration nor smoking status[26].

In a retrospective analysis of 63 patients with exon 14 alterations identified by hybrid-based NGS and treated with ICIs, 44% presented PD-L1 greater than 50% and 39% under 1%. The objective response rate (ORR) in the entire cohort was 13%, and it was 33% in the PD-L1 high (≥50%) group, while patients with negative PD-L1 had a 20% ORR. As such, PD-L1 might not be an accurate predictive biomarker for response to ICIs in patients with MET exon 14 alterations, with the limitation of the retrospective nature in a small series[27].

Why certain patients appear to strictly benefit from ICIs while others do not needs further investigation. Current data from the IMMUNOTARGET registry or small case series do not support that smoking-related MET alterations, are more sensitive to ICIs, as is the case with KRAS[26, 28, 29]. As larger datasets emerge, perhaps more light will be shed on this topic. Furthermore, there are currently no data on chemo-immunotherapy or CTLA-4/PD(L)-1 combinations in MET alterations.

Targeting MET

When discussing targeting MET in NSCLC, it is important to specify whether MET positivity is defined as protein expression, gene amplification or exon 14 mutations. Given

the ubiquity of MET protein expression, ranging between 35–72%, and the synergism between *EGFR* and *MET* pathways, attempts were made to add MET TKIs to EGFR TKIs in late lines of treatment[30]. The phase III ATTENTION and MARQUEE trials failed to meet their OS primary endpoint when comparing erlotinib with or without the c-MET targeting tivantinib in EGFR wild-type advanced nonsquamous NSCLC patients[31]. As protein expression was later found not to be a valid predictive biomarker, the lack of benefit in this fairly unselected population comes as no surprise.

Another trial using protein expression to identify MET positivity, the phase 3 METLung trial attempted to explore the benefit of onartuzumab, a MET monoclonal antibody, in combination with erlotinib. It failed to show an OS benefit compared to erlotinib with placebo, with a mOS of 6.8 and 9.1 months (HR 1.27, 95% 0.98–1.65), respectively in favour of the placebo group[21].

While IHC is not a useful predictive biomarker, MET amplification first showed promise in the preliminary analysis of 12 patients from the PROFILE 1001 trial. Crizotinib showed a 33% (95% CI 10–65%) partial response rate in advanced NSCLC patients with *MET* amplification, and this was especially prominent among patient with MET/CEP7 ratios of 5 or higher[15], who had a 50% response rate. Gene amplification thus appears predictive, contrarily to IHC, though it should be noted that the treatment assessed was not the same.

The third biomarker for MET consists of alterations in and around exon 14, the most common being exon 14 skipping. Retrospective data support that MET exon 14 skipping NSCLC confers sensitivity to direct MET-inhibitors, and among patients receiving crizotinib compared to those who did not, the mOS was 24.6 months versus 8.1 months (HR 0.11, 95% CI 0.01–0.92,p=0.04)[15].

Drilon *et al*[32] recently published promising results from a cohort of 65 evaluable NSCLC patients with MET exon 14 alterations and treated with crizotinib. This group comprised 62% of pretreated and 38% first-line patients. The ORR was 32% (95% CI 21–45%), with a median duration of response of 9.1 months and PFS of 7.3 months. Interestingly, the ORR among first-line patients was 25% (95% CI: 9.8–46.7) while it was 36.6% (22.1–53.1) among pretreated patients. There was no correlation between mutation type, splice-site and outcomes. The safety profile was as expected in previous crizotinib trials, with 29% grade 3–4 events, mainly gastro-intestinal and hepatic toxicity, oedema and blurred vision.

The Geometry mono-1 trial has evaluated capmatinib, a new generation oral selective reversible MET-inhibitor, in advanced NSCLC without EGFR or ALK alterations and harbouring MET exon 14 skipping mutations. This study assessed the efficacy as front-line and subsequent line therapy. The updated results for exon 14 mutations found an ORR of 67.9% (CI: 47.6–84.1) in the 28 patient treatment-naïve cohort and 40.6% (CI: 28.9–53.1) among 69 previously treated patients, with a median duration of response of 12.6 months (5.6-not reached) and 9.7 months (5.6–13) in each group, respectively. Furthermore, 7 out of 13 patients with brain metastases reported a partial response. These preliminary results and a favourable toxicity profile comprising mainly peripheral oedema, gastro-intestinal and

creatine increase, with 31.5% grade 3 and 4.5% grade 4 adverse events, led to FDA approval for MET exon 14 skipping NSCLC[33].

Data on the efficacy of capmatinib in patients with NSCLC harbouring *MET* amplification were released at the American Society for Clinical Oncology 2020 meeting[34, 35]. Amplification was defined as gene copy number ≥ 10. Among 15 treatment-naïve patients, the ORR was 40% (CI: 16.3–67.7), while it was 29% (CI: 18.7–41.2) among 69 pre-treated patients. The median DOR was 8.3 (range: 4.2–15.4) and 7.5 (range: 2.6–14.3) months in treatment-naïve and pre-treated patients, respectively. The primary endpoint was not met in these subgroups. Furthermore, among 126 pre-treated patients with gene copy numbers <10, the ORR ranged from 6.7 to 11.9%, with a linear correlation between response and gene copy numbers.

Similarly, the phase 2 VISION trial assessed tepotinib, an oral highly selective, ATP-competitive, reversible MET inhibitor. In the updated analysis, among 41 patients with a tissue-based diagnosis of MET exon 14 alterations, the ORR by independent central review was 41.5% (CI: 26.3–57.9), with a median DOR of 12.4 months (range: 1.1–18.0). Mirroring this, among 35 patients diagnosed on a liquid biopsy, the ORR was 51.4% with a DOR of 9.8 months (range: 1.1–18.0). As with capmatinib, patients responded regardless of previous therapies. The adverse event profile was also similar to that of capmatinib, without grade 4–5 events [36].

The preliminary analysis of 61 patients from a phase 2 trial (NCT02897479) evaluating savolitinib in MET exon 14 altered adenocarcinoma and pulmonary sarcomatoid carcinoma are equally promising. The ORR was 47.5% (CI: 34.6–60.7), with a median DOR that has not yet been reached and a median PFS of 6.8 months (CI: 4.2–13.8). Toxicity was in-line with other MET inhibitors[37]. Today, numerous MET targeting agents are in early phase trials, including TKIs, antibodies, bispecific antibodies and drug-antibody conjugates (Table 1).

Attempts have been made to combine TKIs for NSCLC with ICIs. Toxicity was shown to be the most important limitation – and at the present time, no signal for synergy has clearly emerged. In patients with ALK rearrangements, crizotinib was combined with nivolumab, and the trial was closed prematurely in light of a significant increase in severe hepatic dysfunction, some fatal[38]. It is, however, interesting to note that capmatinib has shown a preclinical immunomodulatory effect when combined with pembrolizumab, a PD-1 inhibitor, irrespective of MET dysregulations. This is under investigation in a phase 2 trial and could provide room for further trials (NCT04139317).

MET as a resistance mechanism

Early generation TKIs in EGFR and ALK often lead to on-target escape mechanisms, such as T790M in EGFR mutations and different kinase domain mutations in ALK fusions. Nonetheless, MET amplification via the ERBB3-dependent activation of PI3K are detected in up to 22% of acquired EGFR resistances to first generation targeted therapy[39]. MET exon 14 alterations have also emerged as resistance mechanisms to EGFR TKI therapy[40]. In parallel to the extension of the potency and scope of targeted therapies, resistance

mechanisms have evolved, with the appearance of more off-target mutations. After third-generation TKIs for EGFR-mutant NSCLC, MET accounts for approximately 10% thereof, with amplification representing 7–15% of resistance to first-line therapy and 5–50% of resistance to second-line and above third-generation TKIs[41, 42].

In patients with NSCLC with ALK rearrangements, *MET* amplifications were detected in 12% of patients who developed resistance to second-generation inhibitors and 22% of those progressing on lorlatinib. Early results of targeting *MET* in this context are promising[43].

Several trials have explored the addition of a MET TKI to an EGFR TKI to overcome acquired resistance mechanisms. The phase 2 INSIGHT trial evaluated the addition of tepotinib (MET TKI) to gefitinib in EGFR mutant MET altered (IHC2–3+ or amplification) adenocarcinoma without T790M mutations at progression, compared to chemotherapy at progression. The experimental arm showed a 45.2% ORR, 4.9 month median PFS and 17.3 month OS overall, with particularly promising results in the MET amplified group, with a 66.7% ORR, 21.2 month PFS and 37.3 month OS[44].

In an expansion arm of the phase Ib TATTON trial, combined osimertinib and savolitinib, a MET TKI, after T790M negative progression on first or second-generation EGFR inhibitors, have shown promising results, with a 64% ORR)[45]. For patients progressing on third generation EGFR therapy, the addition of osimertinib and savolitinib in MET-positive patients yields a 25% ORR and mDOR of 9.7 months. The phase 2 SAVANNAH trial aims to confirm these early results (NCT03778229). Similarly, the INSIGHT 2 trial is evaluating the addition of tepotinib to osimertinib in MET amplified adenocarcinoma, compared to chemotherapy at progression on osimertinib (NCT03940703). A similar ongoing phase I/II trial with capmatinib plus gefitinib after failure of a prior EGFR inhibitor has shown promising data, particularly with a 47% ORR among patients with high MET amplification, defined as a gene copy number ≥6[46].

In addition to acquired resistance while on treatment, co-occurring MET alterations can result in primary resistance to targeted therapy. Among EGFR mutated lung adenocarcinoma patients, MET copy number gains at diagnosis are not associated with primary TKI resistance, while the rarer *MET* amplifications appear to be predictive of poor response, and outcomes[47]

Type of MET inhibitors and resistance mechanisms

MET TKIs, can be divided into three broad classes. Type I TKIs, including crizotinib, tepotinib, savolitinib, bozitinib and capmatinib compete with ATP to bind to the MET receptor in its catalytically active conformation, where aspartic acid phenylalanine-glycine (DFG) motif projects into the ATP-binding site. These are further divided into type Ia inhibitors, like crizotinib, which interact with the solvent front residue G1163, and type Ib, such as capmatinib, savolitinib and tepotinib which bind to the targeted kinase domain independently from this interaction. Type II TKIs, such as multikinase inhibitors cabozantinib, glesatinib and merestinib are ATP competitive and will bind the MET receptor in its inactive DFG conformation[48]. Finally, type III TKIs include tivantinib, an allosteric inhibitor[49].

With response rates ranging from 25 to 68%, a median duration of response between 9 and 16 months, and a favourable toxicity profile, MET TKIs offer a promising treatment option in patients with exon 14 skipping (Table 1). However, it is marred by the invariable emergence acquired resistance pathways. Resistance to type Ia MET TKI appears to be induced by mutations in residues D1228 and Y1230, by weakening the bond between the MET kinase domain and the therapeutic agent [50, 51]. The solvent front G1163R mutation confers resistance to crizotinib but not type Ib nor type II inhibitors. In vitro, acquired resistance mutations to type I TKIs, which were not exposed on the surface of the ATP-binding pocket in the inactive DFG conformation remain sensitive to type II inhibitors[51 49, 52]. Conversely, resistance mutations at L1195 and F1200, which emerge with type II TKIs and are not exposed in the active DFG conformation, are sensitive to type I inhibitors. While changing classes of MET inhibitors appears promising for on-target mutations and focal MET amplifications, resistance pathways also include off-target alterations, mainly KRAS mutations[48, 49].

Limited data are available, however, a recent retrospective analysis of 20 patients who progressed on MET TKIs for advanced NSCLC with exon 14 skipping, sheds some light on the clinical picture. 6 patients changed TKIs at progression, with 5 progressing on this subsequent line. On target resistance pathways were identified in 35% of patients, including focal MET amplification and MET kinase domain mutations. One patient presented on and off-target alterations. Off-target mechanisms of resistance included KRAS mutations or amplification of EGFR, KRAS, HER3 and BRAF and were detected in 45% of cases. In 25%, the mechanism of resistance was not identified. In patients who developed on-target resistance, 33% responded to subsequent TKIs of a different class, irrespective of sequence[48].

Alterations of other pathways can also cause primary resistance to MET TKIs. For instance, PI3K-pathway alterations including PTEN loss appear to cause clinical resistance *in vivo*. In further in *vitro analyses*, sensitivity to MET inhibitors appears restored when a PI3K targeting agent is added[53]. Furthermore, in a study of 74 patients with MET exon 14 altered NSCLC, certain pre-TKI treatment parameters were predictive of non-response. RAS pathway activation, low (< 700 amol/μg) KRAS expression, and absence of MET protein detection in tumour tissue each conferred primary resistance to TKIs, with 0% ORR (0/6, 0/2 and 0/5 patients each), compared to 29%, 50%, and 63% ORR, respectively in patients without these factors. Similarly, acquired resistance was potentially explained by on-target alterations in *MET* and *HGF* in 22% of patients (2/9) and off-target mechanisms involving RAS, EGFR, MDM2 in 44% of patients (5/9)[54].

MET therapies remain in their infancy and while resistance mechanisms are intriguing, they are not yet mature for clinical use and will require validation.

Conclusions

There has been significant progress in the field of MET inhibition. For patients with *MET*-driven NSCLC, the best front-line treatment is yet to be ascertained. As the identification of proper ways to diagnose the presence of MET driver alterations improves, the feasibility

of large prospective, maybe randomized, trials in this rare entity emerges. Today, we would encourage participation in clinical trials, and if unavailable, to use a MET TKI depending on local approval and access.

Given the limited efficacy observed with ICIs to-date in MET altered NSCLC, we would avoid single agent ICIs in early lines. We would favour targeted therapy upfront, whenever possible, as the use of TKIs after immunotherapy could increase the risk of serious immune-related adverse events[38, 55].

As we increasingly understand the mechanism of action of MET TKIs, as well as the type of resistance pathways that emerge with each type, MET treatment sequencing is becoming a fascinating field.

The MET altered NSCLC therapeutic landscape is rapidly evolving and we hope that in the near future, the METeoric rise of MET will provide therapeutic options to all affected patients.

Acknowledgments

Conflict of interests:

Dr. Friedlaender reports personal fees from BMS, from Roche, personal fees from Pfitzer, personal fees from MSD, personal fees from Astellas, outside the submitted work;

Dr. Drilon reports personal fees from Ignyta/Genentech/Roche, personal fees from Loxo/Bayer/Lilly, personal fees from Takeda/Ariad/Millenium, personal fees from TP Therapeutics, personal fees from AstraZeneca, personal fees from Pfizer, personal fees from Blueprint Medicines, personal fees from Helsinn, personal fees from Beigene, personal fees from BergenBio, personal fees from Hengrui Therapeutics, personal fees from Exelixis, personal fees from Tyra Biosciences, personal fees from Verastem, personal fees from MORE Health, personal fees from Abbvie, personal fees from 14ner/Elevation Oncology, personal fees from Axis, personal fees from Peerview Institute, personal fees from OncLive, personal fees from Paradigm Medical Communications, LLC, personal fees from Remedica Ltd., personal fees from ArcherDX, personal fees from Foundation Medicine, personal fees from PeerVoice, personal fees from Research to Practice, personal fees from Medscape, personal fees from WebMD, personal fees from Monopteros, outside the submitted work; and ASSOCIATED RESEARCH PAID TO INSTITUTION: Pfizer, Exelixis, GlaxoSmithKlein, Teva, Taiho,PharmaMar. RESEARCHßoundation Medicine. ROYALTIES:Wolters Kluwer. OTHER: Merck - Food/Beverage Puma - Food/BeverageÐerus Boehringer Ingelheim. CME HONORARIA: Medscape, OncLive, PeerVoice, Physicians Education Resources, Targeted Oncology, Research to Practice.

Dr. Banna reports personal fees from Boehringher, personal fees from Janssen-Cilag, personal fees from Roche, outside the submitted work;

Prof. Peters reports personal fees from Abbvie, personal fees from Amgen, personal fees from AstraZeneca, personal fees from Bayer, personal fees from Biocartis, personal fees from Boehringer-Ingelheim, personal fees from Bistrol-Myers Squibb, personal fees from Clovis, personal fees from Daiichi Sankyo, personal fees from Debiopharm, personal fees from Eli Lilly, personal fees from F. Hoffmann-La Roche, personal fees from Foundation Medicine, personal fees from Illumina, personal fees from Janssen, personal fees from Merck Sharp and Dohme, personal fees from Merck Serono, personal fees from Merrimack, personal fees from Novartis, personal fees from Pharma Mar, personal fees from Pfizer, personal fees from Regeneron, personal fees from Sanofi, personal fees from Seattle Genetics and Takeda, personal fees from AstraZeneca, personal fees from Boehringer-Ingelheim, personal fees from Bristol-Myers Squibb, personal fees from Eli Lilly, personal fees from F. Hoffmann-La Roche, personal fees from Merck Sharp and Dohme, personal fees from Novartis, personal fees from Pfizer, personal fees from Takeda, non-financial support from Sponsored by Amgen, non-financial support from AstraZeneca, non-financial support from Boehringer-Ingelheim, non-financial support from Bristol-Meyers Squibb, non-financial support from Clovis, non-financial support from F. Hoffmann-La Roche, non-financial support from Illumina, non-financial support from Merck Sharp and Dohme, non-financial support from Merck Serono, non-financial support from Novartis, non-financial support from Pfizer, non-financial support from Sanofi, personal fees from Bioinvent, outside the submitted work. All fees to Institution

Dr. Addeo reports personal fees from BMS, personal fees from Astrazeneca, personal fees from Roche, personal fees from Pfizer, personal fees from MSD, personal fees from Boehringer, outside the submitted work;.

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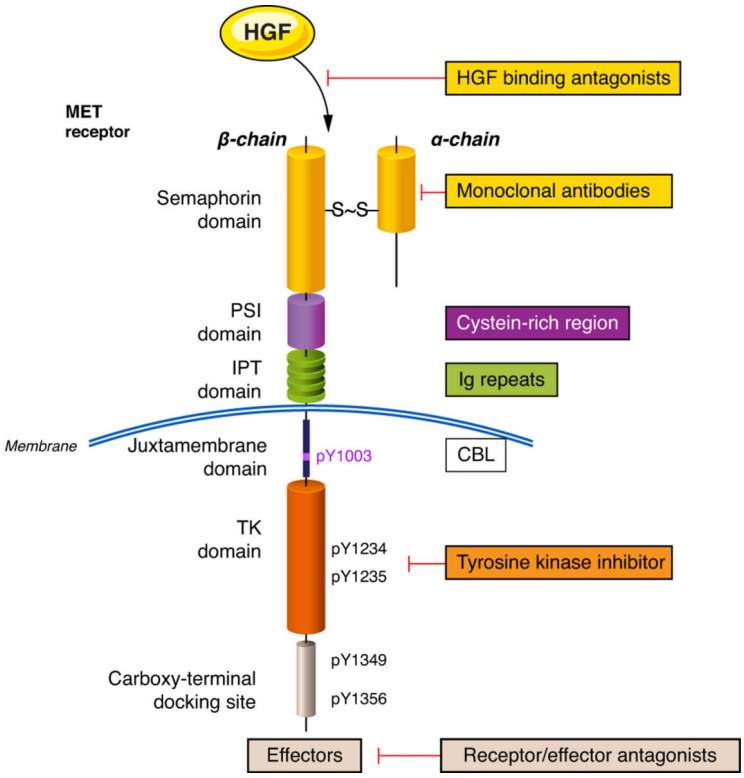

Figure 1:

representation of the MET receptor and possible therapeutic targets

HGF: hepatocyte growth factor, CBL: Casitas B-lineage lymphoma, TK: tyrosine kinase, IPT: immunoglobulin-plexin transcription, PSI: plexin semaphoring integrin domain

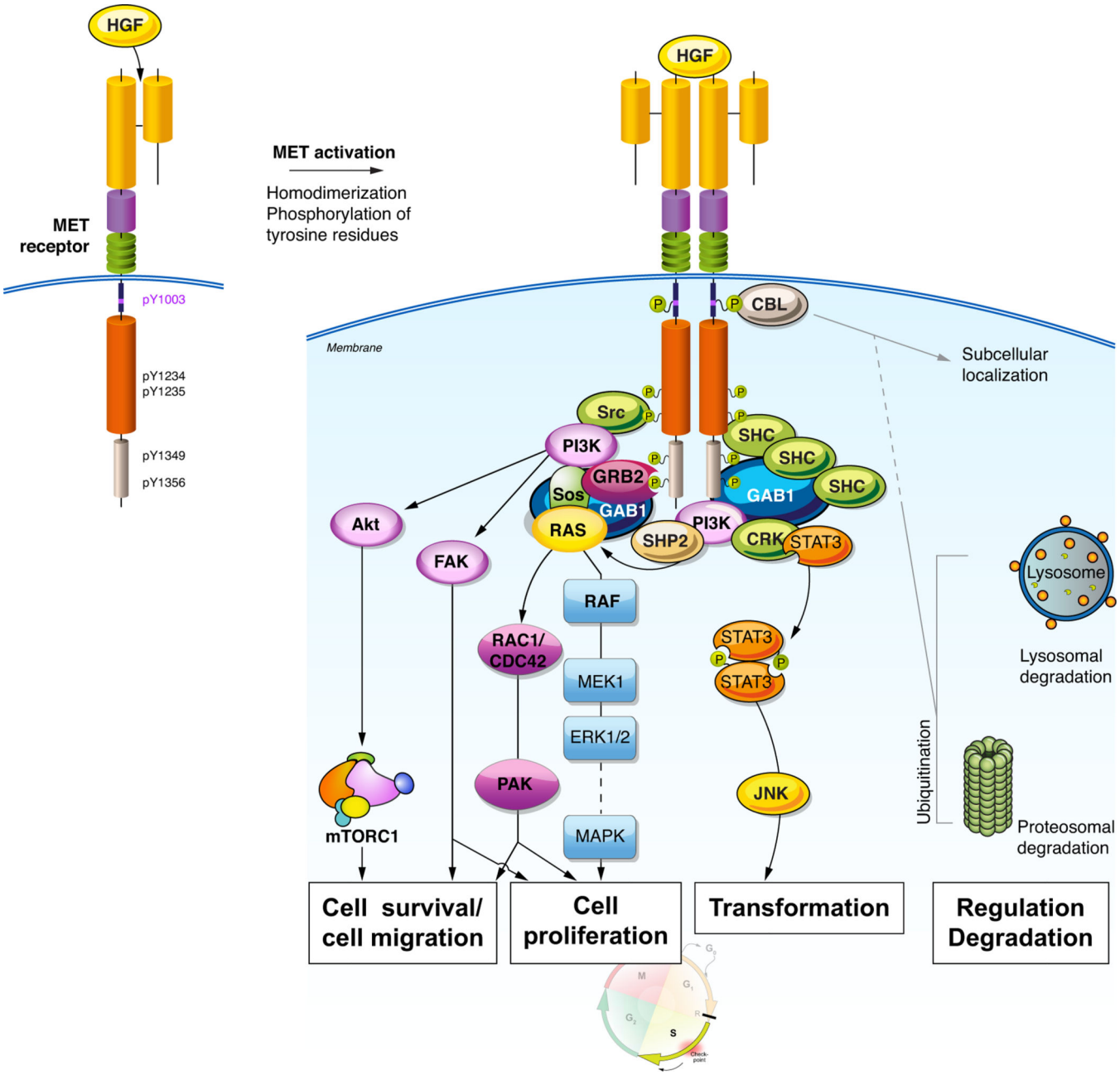

Figure 2:

MET signalling pathways and their effector functions

HGF: hepatocyte growth factor, CBL: Casitas B-lineage lymphoma

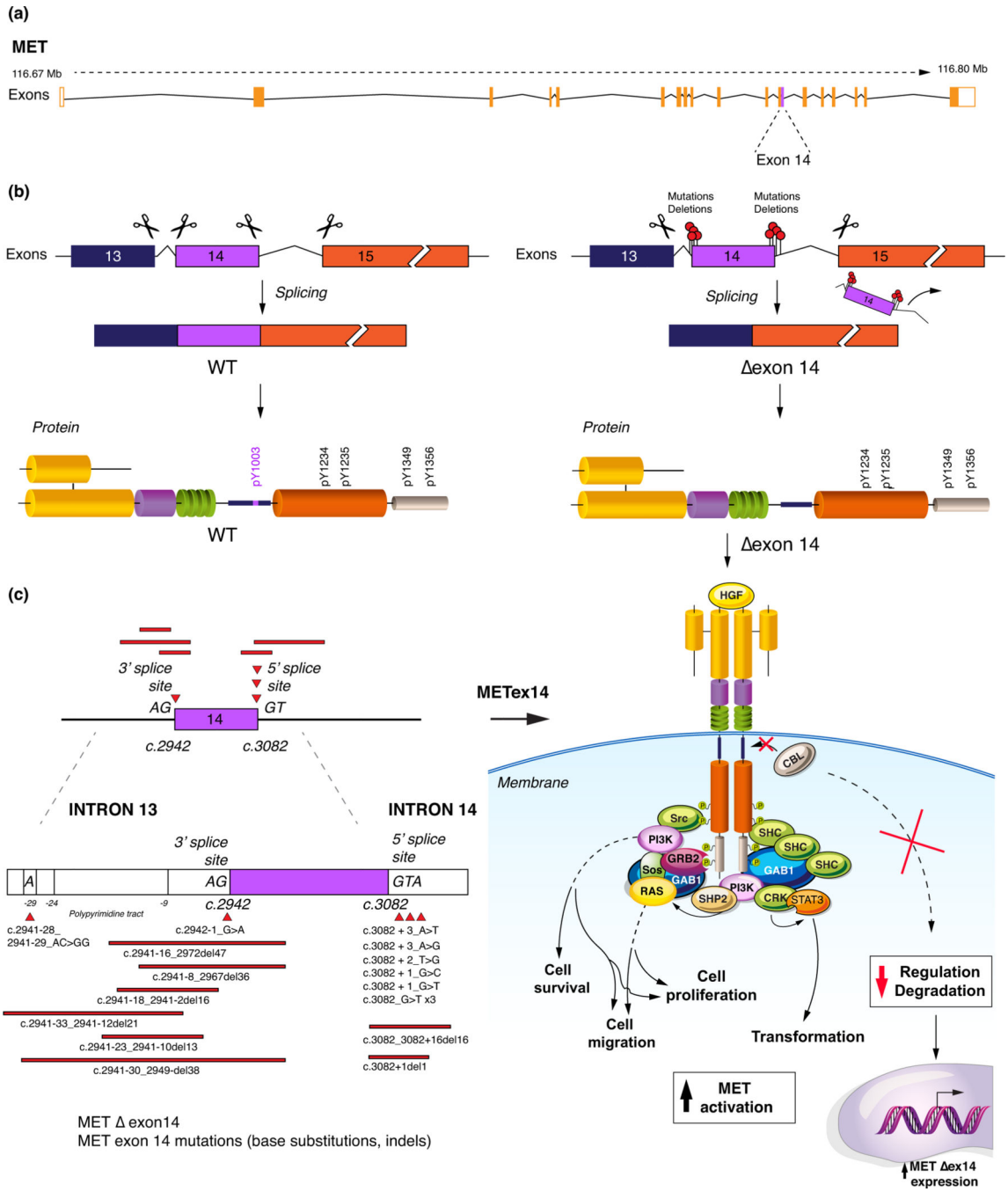

Figure 3:

The pathophysiology of exon 14 alterations. a) the *MET* structure. b) the impact of *MET* exon 14 alterations and development of exon 14 skipping. c) selected *MET* exon 14 alterations and the consequent lack of CBL binding, decreasing the MET polyubiniquitation and degradation

HGF: hepatocyte growth factor, CBL: Casitas B-lineage lymphoma, WT: wild-type, Δexon 14: exon 14 skipping.

Table 1:

Selected trials with different classes of MET targeting agents

TKI	Targets	Type of TKI	MET alteration	Trial(s)	Phase	Results
MET-specific TKI						
Capmatinib [1, 2]	MET	Ib	ex14, amp	**GEOMETRY-mono-1** NCT02544633 NCT03693339	2	Ex14: 1L ORR : 67.9% 2L+ ORR : 40.6% 1L DOR: 11.1m, 2L+ DOR: 9.7m Amp: 1L ORR: 40%, 2L+ ORR : 29%. 1L DOR: 8.3m, 2L+ DOR: 7.5m
Tepotinib [3]	MET	Ib	ex14	NCT02864992 (VISION)	2	ORR 45.1%, DOR 12.4m
Savolitinib	MET	Ib	ex14	NCT02897479	2	NA
SAR125844 [4]	MET	I	amp	NCT02435121	2	*ORR 18.2%
Bozitinib	MET	I	ex14. amp, mut	NCT03175224 NCT02896231 NCT04258033	1–2	NA
Glumetinib	MET	II	ex14, amp, IHC	NCT04270591	1–2	NA
BPI-9016M	MET	II	IHC	NCT02929290	1a	NA
Multikinase inhibitors						
Crizotinib [5]	MET, ALK, ROS1	Ia	ex14 amp	**PROFILE1001** NCT02499614 (METROS)	2	1L ORR 25.0%, 2L+ ORR 36.6%, PFS 7.3m, DOR 9.1m
Cabozantinib (CABinMET)	MET, ROS1, VEGFR, RET, KIT, and FLT3	II	ex14, amp	NCT03911193	2	NA
MGCD265 Glesatinib	MET, AXL	II	amp	NCT02544633	2	NA
Cabozantinib (CABinMET)	MET, ROS1, VEGFR, RET, KIT, and FLT3	II	ex14, amp	NCT03911193	2	NA
Merestinib	ROS1, AXL, RON, MERTK, FLT3, DDR1/2, MST1R, and MKNK-1/2, MET	II	ex14	NCT02920996	2	NA
TPX-0022	MET, CSF1R, SRC	I	ex14, amp, fusion	NCT03993873	1	NA
Antibodies						
Onartuzumab + erlotinib [6]	IgG1 MAb	-		NCT02031744 (NCT00854308)	3	ORR 8.4% vs 9.6% No PFS or OS benefit
Emibetuzumab +/− erlotinib [7]	IgG4 MAb	-	IHC	NCT01900652 (CHIME)	2	DCR 50% vs 26%, PFS 1.6m vs 3.3m
Sym015 [8]	IgG1 MAb mixture	-	amp, ex14	NCT02648724	1–2	ORR 25%, DCR 80%, PFS 5.5m
Other						

TKI	Targets	Type of TKI	MET alteration	Trial(s)	Phase	Results
Telisotuzumab vedotin[9]	Drug Ab conjugate	-	IHC, amp	NCT03539536	2	*ORR 18.8%, PFS 5.7m
REGN5093	MET bispecific Ab	-	ex14, amp, IHC	NCT04077099	1–2	NA

*: earlier phase trial results.

TKI : tyrosine-kinase inhibitor, ex 14 : exon 14 alterations, amp : amplification, ORR : objective response rate, 1L : first-line, 2L+ : second-line and beyond, DOR : mean duration of response, OS: mean overall survival, PFS : mean progression-free survival, DCR: mean disease control rate, m: months, NA: not available, IHC: immunohistochemistry, Ab: antibody, MAb: monoclonal antibody.

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