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REVIEW

Novel Therapies for Metastatic Non-Small Cell Lung Cancer with MET Exon 14 Alterations: A Spotlight on Capmatinib

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Abstract: MET exon 14 (METex14) alterations are now an established therapeutically tractable target in non-small cell lung cancer (NSCLC). Recently reported trials of several MET tyrosine kinase inhibitors (TKI) in this patient population have demonstrated promising efficacy data in both the treatment naïve and pre-treated settings and have led to regulatory approvals. This review will focus on practical diagnostic considerations for METex14 alterations, the trial evidence for capmatinib in this molecular subset including dosing and toxicity management, and the future therapeutic landscape of METex14 altered NSCLC.

Keywords: capmatinib, MET exon 14 skipping, non-small cell lung cancer, targeted therapy

Introduction

Non-small cell lung cancer (NSCLC) remains a leading cause of cancer death globally.[1] With greater understanding of the molecular alterations that underpin lung cancer pathogenesis, there are now multiple tyrosine kinase inhibitors (TKI) approved for a myriad of targets including activating mutations in *BRAF* and *EGFR* as well as fusions involving *ALK, NTRK, RET* and *ROS1*.[2] Additionally, there is emerging data for therapies targeting oncogenic drivers such as *HER2* mutations, *KRAS* G12C mutations, *MET* exon 14 (METex14) alterations and *NRG1* fusions.[3–6] Targeting the MET signaling pathway to date has yielded disappointing results in several randomized trials of MET TKIs.[7–9] However, these studies were conducted in either *MET* unselected populations or patients with *MET* overexpression, and there has since been a growing body of literature characterizing METex14 alterations as therapeutically tractable. This review will focus on METex14 alterations, including practical diagnostic considerations, the promising efficacy data for capmatinib in early trials and future directions for the therapeutic landscape of METex14 altered NSCLC.

Biology of METex14 Alterations in NSCLC

In cancer, activation of the MET pathway is involved in cellular transformation, vasculogenesis, tumor motility and invasion.[10] The *MET* gene is located on chromosome 7 and is translated as a precursor protein, which is then split into an α-chain (extracellular) and a β-chain (transmembrane) after cleavage to form the mature protein.[11] The intracellular component contains a juxtamembrane domain consisting of the binding site for an E3 ubiquitin-protein ligase, c-CBL, including Y1003 which is encoded by exon 14. In the 1980s, a *TPR-MET* oncogenic fusion was first

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discovered in a chemically transformed osteosarcoma cell line.[12] Subsequent findings illustrated that activation of the MET receptor results in activation of downstream signaling pathways such as RAS/ERK/MAPK, PI3K/Akt and STAT (Figure 1). The importance of *MET* exon 14 in the regulation of MET activation was also an important finding.[13] A *MET* splice variant resulting in an in-frame deletion of the 47 amino acids composing the juxtamembrane domain was first detected in mice.[14] It was also then found that mutations in Y1003 prevented binding of c-CBL to MET, disrupted c-CBL mediated degradation and resulted in MET oncogenic activity.[15] In NSCLC, splice site mutations in *MET* were first detected in 2005, and further characterization revealed the resulting skipping of *MET* exon 14.[16,17] The incidence of METex14 alterations in NSCLC has been estimated at 2–4%, and lung adenocarcinoma is the predominant tumor type harboring METex14 skipping alterations.[18,19] Numerous case series demonstrating response to MET TKI in patients with METex14 altered NSCLC then emerged[20–23] and has reinvigorated interest in the development of MET targeted therapies in lung cancer.

Molecular Diagnostic Approaches for METex14 Skipping Alterations

METex14 alterations are diverse and can be challenging to detect.[18] Immunohistochemical (IHC) studies, while relatively inexpensive, have not been proven useful thus far in detection of METex14 alterations. IHC is only able to detect MET overexpression, which may occur due to not only METex14 alterations but also increased gene copy number and gene amplification.[24] Several studies have shown MET IHC overexpression poorly predicts for the presence of METex14 alterations.[25–27] Furthermore, there may be a high degree of inter-observer variability in the interpretation of IHC.[28] As such, most of the assays for METex14 involve molecular techniques (Figure 2). These assays can be divided into two main groups based on their starting nucleic acid substrate, i.e. DNA or RNA and their respective advantages and disadvantages will be discussed subsequently.

DNA-based assays range from Sanger sequencing of single genes to next-generation sequencing (NGS) panels which can simultaneously analyze multiple regions of multiple genes. In either scenario, primer design is vital, as genomic deletion of sequences within the primer binding site impairs primer binding and can prevent amplification of the mutant allele, leading to a false-negative result.[29,30] Sanger sequencing has a high specificity but has a relatively lower sensitivity compared to NGS panels.[31] This, in combination with the scarcity of diagnostic tissue and the increasing approval of targeted therapies has led to the increasing implementation of NGS in clinical practice.
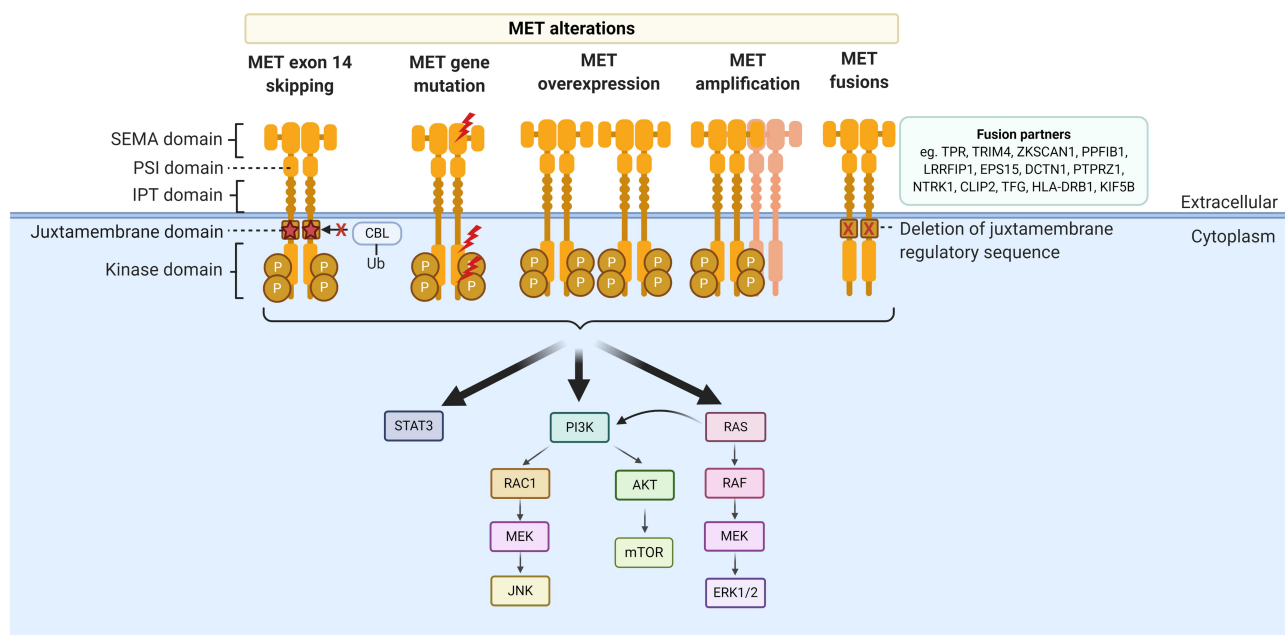

Figure 1 Structure of the MET receptor and MET alterations. MET alterations include MET exon 14 skipping mutations, other MET gene mutations, MET overexpression, MET amplification and MET fusions.
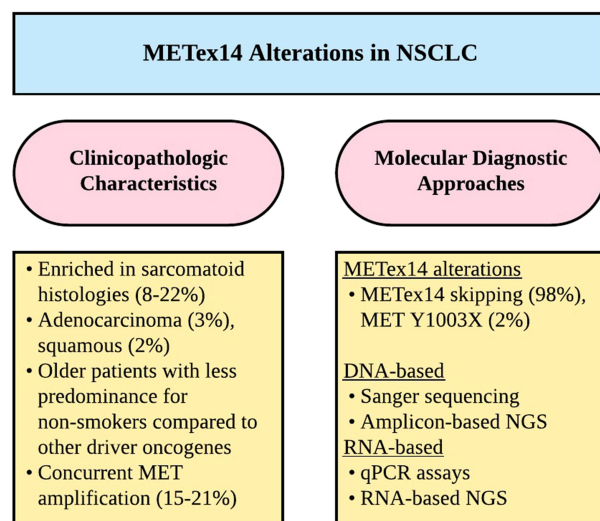
Figure 2 Diagnostic considerations for METex14 alterations in NSCLC.
Abbreviations: METex14, MET exon 14; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; qPCR, quantitative PCR.

NGS panels can be further subdivided into hybrid capture-based panels including whole-exome panels and amplicon-based panels which tend to target clinically significant genes.[32] With appropriate probe/bait design to cover the region of interest and algorithms to detect large deletions, hybrid capture mediated target enrichment tends to produce fewer false-negative results.[18,33,34] However, hybrid capture-based panels have historically required more tumor DNA compared to amplicon-based panels and were often not implemented clinically.[33] The diversity of METex14 alterations, however, could be important, and the ability to detect large insertions or deletions may provide advantages to hybrid capture-based panels.[29]

Amplicon-based NGS panels are not standardized and detection of specific alterations depends heavily on the primers within the panel.[35] To highlight the importance of primer design, an earlier in silico analysis study of 8 amplicon-based NGS panels by Poirot et al[30] highlighted limitations in accuracy, with only 63% of the literature reported cases of METex14 alterations being detected. However, as more is known about METex14 alterations, NGS panels can be optimized for greater accuracy and in a more recent study conducted by Pruis et al,[36] in silico analysis of their customized NGS panel was able to detect 96% of reported METex14 alterations.

RNA-based methods of detecting METex14 skipping mutations such as quantitative PCR assays[24,37] are based on the detection of a fusion transcript, which in this case, is between MET exon 13 and 15. As such, the

interpretation of this assay is more straightforward than that of DNA-based assays for screening purposes.[37] The main weakness of PCR-based assays is that for the purposes of primer design, knowledge of the fusion partner is required which makes the detection of novel fusions difficult. In contrast, RNA-based NGS panels for example the ArcherDX FusionPlex Solid Tumor Assay allow for fusion gene detection without a priori knowledge of the fusion partner.[29,38]

Another possible advantage of RNA-based methods is that the over-expression of MET can theoretically yield higher proportional concentrations of altered MET RNA transcripts available for analysis - especially if further enriched through micro dissection. This is as compared to extracted genomic DNA which is often derived not only from tumor cells but also from the admixed non-neoplastic inflammatory and stromal cells. As such, in some cases with a low proportion of tumor cells, the wild-type DNA can reduce the proportion of mutant DNA and lead to false-negative results.[31] A study by Davies et al[29] compared a DNA-based approach (Illumina TruSight Tumor 26 assay) and RNA-based detection (ArcherDX FusionPlex Solid Tumor Assay) of METex14 skipping events in lung cancer, and albeit not unexpectedly, found that RNA-based detection detected a higher proportion of METex14 skipping alteration cases as compared to DNA-based detection. Other studies have also demonstrated the detection of METex14 alterations using RNA-based NGS that were not detected using DNA-based assays.[39] The main disadvantage of RNA-based testing is that RNA is less stable than DNA and in clinical samples, which are predominantly formalin fixed and paraffin-embedded (FFPE) tissues, poor quality RNA can lead to uninformative results on testing.[29]

Liquid biopsy, with the detection of alterations in plasma cell-free DNA (cfDNA) or circulating tumor cells (CTCs), is also emerging as a feasible diagnostic approach.[40] METex14 alterations and MET amplification are detectable on numerous commercially available assays with high sensitivity, although are currently restricted to DNA-based assays.[41,42] These diagnostic assays have already been incorporated in many of the clinical trials evaluating MET inhibitors in METex14 altered NSCLC.[43–45]

Pharmacology of Capmatinib and Early Phase Data

MET TKI can be broadly categorized based on the binding site and mechanism.[46] Type I inhibitors are ATP-competitive

and bind to Y1230 in the MET activation loop. Type Ia inhibitors such as crizotinib also interact with the solvent front glycine residue G1163, resulting in greater off-target effects, whereas type Ib inhibitors such as capmatinib, tepotinib and savolitinib have stronger interactions with Y1230 without interaction with G1163.[10,47] Type II inhibitors, such as cabozantinib bind to the ATP adenine binding site extending to the hydrophobic back pocket, meaning potency depends on the activation state of the MET protein.[10,47]

Capmatinib (INC280), a type Ib inhibitor, is a potent highly selective oral MET inhibitor. In pre-clinical studies, it has been demonstrated to block MET phosphorylation and activation of key downstream effectors in MET-dependent cell lines.[48] Furthermore, pleiotropic effects on other signaling pathways such as EGFR and HER3 were also seen. In the dose-escalation part of the Phase 1 trial (NCT01324479), 38 patients were treated with capmatinib, starting at 100mg bid in capsule formulation.[49] There were no NSCLC patients in this cohort. Dose-limiting toxicities (DLT) occurred at dose levels 200mg bid (grade 3 fatigue), 250mg bid (grade 3 bilirubin increase) and 450mg bid capsules (grade 3 fatigue); however, the maximum tolerated dose (MTD) was not reached. There were no DLTs at the 600mg bid capsule formulation dose level, and additionally, 400mg bid tablets were found to have comparable tolerability and exposure. As this dose level was expected to achieve and maintain inhibition of MET, this became the recommended Phase 2 dose (RP2D). Overall, capmatinib was well tolerated, with nausea (32%), decreased appetite (29%), vomiting (29%) and fatigue (26%), the most frequent all grade capmatinib-related adverse events (AE). Fatigue (8%), ALT increase (5%) and hypophagia (5%) were the most frequent grade 3 or 4 capmatinib-related AEs.

There were several dose-expansion cohorts included in the trial, including two cohorts for advanced NSCLC patients.[50] The first consisted of MET dysregulated NSCLC, defined as MET overexpression and amplification. The second cohort consisted of *EGFR* wild-type NSCLC with MET overexpression by IHC. A post hoc analysis further evaluated MET status using gene copy number (GCN) and amplification by fluorescence in-situ hybridization (FISH) and *MET* mutation by NGS. A total of 55 patients were enrolled (26 in the first cohort and 29 in the second cohort). The overall response rate was 20% (95% CI 10.4–33.0), with a response rate of 47% in patients with MET GCN ≥6 (n=15). Importantly however, all four patients with METex14 alterations achieved tumor

response, including one complete response (CR). Most frequent all grade capmatinib-related AEs included nausea (42%), peripheral edema (33%) and vomiting (31%), with no grade 3 or 4 capmatinib-related AEs occurring in >10% of patients.

The Pivotal GEOMETRY Mono-1 Trial

GEOMETRY mono-1 (NCT02414139) is an ongoing phase II single-arm, multi-centre, multi-cohort trial of capmatinib tablets at 400mg bid in advanced *EGFR* and *ALK* wild-type NSCLC. There are seven cohorts, each analysed separately, based on centrally prescreened MET status and prior therapy. Enrollment in cohorts 1b, 2 and 3 (pre-treated patients with MET amplification <10 GCN) has been stopped early due to futility at a pre-planned interim analysis. Preliminary results have been reported for METex14 altered (regardless of GCN status) NSCLC patients in cohort 4 (1–2 prior lines of therapy, n=69) and cohort 5b (treatment naïve, n=28).[6] The primary endpoint was objective response rate (ORR) by Blinded Independent Review Committee (BIRC), with key secondary endpoint of duration of response (DOR) by BIRC (Table 1). In pre-treated patients (cohort 4), the ORR was 41% (95% CI 27.6–51.6), with a median DOR of 9.7 months (95% CI 5.5–13.0). In treatment naïve patients (cohort 5b), the ORR was 68% (95% CI 47.6–84.1), with a median DOR of 12.6 months (95% CI 5.5–25.3). There were a small number of patients with brain metastases included in cohorts 4 and 5b, with intracranial response in 54% (7/13) of patients, including several cases of complete intracranial response.

In the overall study population (n=334), the safety profile was consistent with the earlier trials of capmatinib.[6,51] The most common all grade capmatinib-related AEs were peripheral edema (42%), nausea (33%), creatinine increase (20%), vomiting (19%), fatigue (14%), decreased appetite (13%) and diarrhea (11%) – the majority of which were grade 1 or 2. Pneumonitis was seen in 4.5% of patients, with grade 3 pneumonitis in 1.8%, and one death (0.3%). Treatment was discontinued in 8 (2.4%) patients due to pneumonitis. Hepatotoxicity with AST/ALT elevation was seen in 13% of patients, with grade 3 or 4 elevation in 6% and treatment discontinued in 3 (0.9%) patients.

Based on this data, the United States (US) Food and Drug Administration (FDA) granted accelerated approval for capmatinib (Tabrecta[TM]) in NSCLC patients with

Table 1 Clinical Trials of MET Inhibitors in METex14 Altered NSCLC

Drug	Trial	Line of Therapy	Phase	n	ORR% (95% CI)	Median DOR (Months, 95% CI)	Ref
Capmatinib 400mg bid	GEOMETRY mono-1, cohort 4	Second or third-line	II	69	68 (48–84)	9.7 (5.5–13.0)	[6]
Capmatinib 400mg bid	GEOMETRY mono-1, Cohort 5b	First-line	II	28	41 (29–53)	12.6 (5.5–25.3)	[75]
Crizotinib 250mg bid	PROFILE 1001	Any line	I (expansion cohort)	69	32 (21–45)	9.1 (6.4–12.7)	[45]
Tepotinib 500mg daily	VISION	Any line	II	99	46 (36–57)	11.1 (7.2-NE)	[43]
Savolitinib 600mg daily	NCT02897479*	Any line	II	34	39 (NR)	NR	[44]

Note: *Trial ongoing, interim data only.
Abbreviations: CI, confidence interval; DOR, duration of response; NE, not estimable; NR, not reported; ORR, overall response rate.

a METex14 alteration detected by a companion diagnostic (FoundationOne CDx assay).[52]

Practical Clinical Considerations Including Dosing and Toxicity Management

Capmatinib is approved in tablet formulation at a starting dose of 400mg bid with or without food, coming in tablets with strengths of 150mg or 200mg. In patients that experience adverse reactions, dose reductions to 300mg bid and subsequently 200mg bid may be considered. Permanent discontinuation is recommended in patients that do not tolerate the 200mg bid dose level.

Clinically significant adverse reactions include pneumonitis and hepatotoxicity.[51] In GEOMETRY mono-1, the median time to onset was 1.4 months (range 0.2–14.4) for grade 3 or higher pneumonitis, and 1.4 months (range 0.5–4.1) for grade 3 or higher AST/ALT elevation. Permanent treatment discontinuation is recommended for any grade pneumonitis and grade 4 AST/ALT elevation, or grade 2 or higher AST/ALT elevation in the presence of bilirubin increase >2 times upper limit of normal (ULN). For Grade 3 AST/ALT elevation without increase in bilirubin, dose interruption with subsequent dose reduction if recovery to baseline AST/ALT takes longer than 7 days is suggested.

Common toxicities, as described previously, include peripheral edema, nausea, fatigue, vomiting, dyspnea and decreased appetite. Dose interruptions were required in 54% of patients in GEOMETRY mono-1, with dose reductions in 23% of patients.[6,51] Dose reductions were most commonly due to peripheral edema, increased ALT, increased blood creatinine and nausea. Peripheral edema, in particular, has also been seen in other agents targeting the MET pathway and may require additional management

with limb elevation, compression stockings and occasionally diuretics.[53,54]

Therapeutic Resistance to Capmatinib

Despite promising efficacy data, drug resistance inevitably ensues, and the mechanisms of resistance to capmatinib in METex14 NSCLC is yet to be well characterized. In *EGFR* mutant and *ALK* rearranged NSCLC, for which resistance to TKI therapy is better understood, a diverse range of mechanisms may occur.[55–57] This includes acquisition of secondary resistance mutations or alterations, activation of bypass signaling pathways or phenotypic change such as small cell transformation.

Secondary resistance *MET* mutations in D1228 and Y1230 to type I MET inhibitors have been demonstrated in in vitro drug screens and mutagenesis assays.[58,59] Numerous case studies have described these resistance mutations to crizotinib therapy in METex14 altered NSCLC.[60–63] In vitro studies of MET-amplified cell lines treated with capmatinib, also suggest activation of EGFR signaling and downstream effectors such as PIK3CA may mediate resistance.[64] The EGFR pathway has further been implicated in resistance to MET kinase inhibition in other studies.[58,65] MET-directed therapy in EGFR TKI resistant *EGFR* mutant NSCLC is an area of ongoing investigation, including clinical trials with capmatinib.[66] The cross-talk between the MET and EGFR signaling pathways in NSCLC therefore has potential significance in resistance.[67] Similarly, there is pre-clinical data suggesting KRAS signaling may be upregulated in METex14 tumors, and expression of mutant *KRAS* may induce resistance to MET-directed therapy.[68] The PI3K pathway is also implicated in resistance, and potentially primary resistance.[69] In a series of 20 MET TKI treated patients with post-treatment NGS testing,

acquired *MET* resistance mutations, *MET* exon 14 mutant allele amplification, *KRAS* mutations and *KRAS, EGFR, HER3* and *BRAF* amplifications were seen.[70] There were two patients treated with capmatinib, with post-resistance NGS demonstrating acquisition of *MET* D1228N mutation, *EGFR* and *HER3* amplification in the first patient, and *EGFR* amplification and *HER3* gain in the second patient.

A large series of 298 patients with METex14 altered NSCLC indicated rates of concurrent *MDM2* amplification in 35%, *CDK4* amplification in 21%, *EGFR* amplification in 6% and *KRAS* mutation in 3%.[34] Additionally, concurrent *MET* amplification was seen in 15%, and this was also associated with higher tumor mutation burden (TMB). Another series of 289 patients suggested co-occurring RAS-MAPK pathway gene alterations such as *KRAS* and *NF1*, may be associated with decreased response to MET TKI.[71] Ultimately though, any potential implication of these concurrent alterations on response and resistance to capmatinib is yet to be validated.

Patterns of clinical progression to capmatinib are also important to evaluate. In particular, brain metastases occur with greater frequency in oncogenic driven NSCLC.[72] However, the prevalence of brain metastases in METex14 altered NSCLC and indeed the overall natural history of disease remains to be completely elucidated. In one series of 34 patients with METex14 altered NSCLC, brain metastases were seen in 21% of patients and were the second most common site of metastases after bone.[73] In another series of 71 patients, the incidence of brain metastases was 37%.[74] As described previously, only a small number of patients with brain metastases were included on GEOMETRY mono-1,

although intracranial responses were seen in over half,[75] suggesting reasonable intracranial activity for capmatinib.

Therapeutic Landscape of METex14 Altered NSCLC

Capmatinib is the first FDA-approved therapy for patients with METex14 altered NSCLC (Figure 3). However, there are other MET TKIs which have also been studied in this patient population (Table 1). Crizotinib was evaluated in an expansion cohort of the PROFILE 1001 trial (NCT00585195), in patients with METex14 altered NSCLC.[45] A total of 69 patients were enrolled, with 62% having received at least one prior line of therapy, and 96% had METex14 alterations detected by NGS. Among 65 evaluable patients, ORR was 32% (95% CI 21–45) with median progression-free survival (PFS) of 7.3 months (95% CI 5.4–9.1) and median DOR of 9.1 months (95% CI 6.4–12.7). Subsequently, crizotinib was granted FDA breakthrough therapy designation in 2018, and has also been incorporated into the National Comprehensive Cancer Network (NCCN) guidelines for NSCLC.[76]

Tepotinib was evaluated in the phase II VISION trial (NCT02864992), in patients with METex14 altered NSCLC.[43] A total of 152 patients were treated (safety population), with 99 having follow-up of at least 9 months (efficacy population). In the efficacy population, METex14 alterations were detected using NGS on liquid biopsy (66%) and/or tissue biopsy (60%), and 43% of patients were treatment naïve. The ORR was 46% (95% CI 36–57) with median PFS of 8.5 months (95% CI 6.7–11.0) and
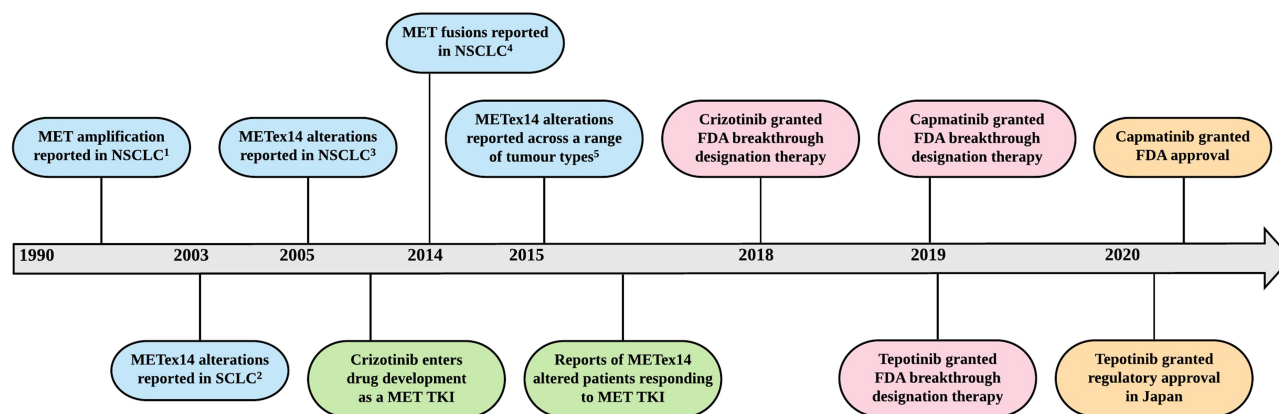
¹ Ichimura et al, Jpn J Cancer Res, 1996; ² Ma et al, Cancer Res, 2003; ³ Ma et al, Cancer Res, 2005; ⁴ Stransky et al, Nat Comm, 2014; ⁵ Frampton et al, Cancer Discov, 2015.

Figure 3 Timeline of key events in the development of METex14 altered NSCLC targeted therapies.
Abbreviations: FDA, Food and Drug Administration; METex14, MET exon 14; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

median DOR of 11.1 months (95% CI 7.2-NE). Outcomes were similar comparing METex14 alterations detected on liquid versus tissue biopsy. Tepotinib was also granted FDA breakthrough therapy designation in 2019 and has been fully approved in Japan with a companion diagnostic (ArcherMET CDx) assay.[77] For tepotinib, in contrast to capmatinib, response rates and PFS was no different comparing patients treated as first-line versus subsequent lines of therapy.[6,43]

Finally, savolitinib is being evaluated in an ongoing phase II trial (NCT02897479) in China.[44] Patients may be treatment naïve or pre-treated. Preliminary data demonstrated an ORR of 39% in 34 patients treated on the trial to date.

The therapeutic landscape in METex14 altered NSCLC is evolving, with numerous aforementioned TKIs showing promising early efficacy data leading to regulatory approvals. A confirmatory phase III trial for capmatinib (NCT04427072) in pre-treated METex14 altered NSCLC patients versus docetaxel chemotherapy is due to commence recruitment. Crizotinib continues to be evaluated in basket trials for METex14 altered NSCLC such as the National Lung Matrix trial (NCT02664935). Other MET TKI in development for METex14 altered NSCLC include cabozantinib, glesatinib and merestinib.[47,78] With confirmation of METex14 alterations as a bona fide target in NSCLC, careful consideration on sequencing and combining therapies becomes crucial. Accordingly, there are also ongoing trials to address these questions. Phase II trials of capmatinib after resistance to prior MET TKI (NCT02750215) and capmatinib in combination with immunotherapy with spartalizumab (NCT04323436) are examples of currently recruiting or planned trials.

Conclusion

METex14 alterations in advanced NSCLC are now established as a therapeutic target in both the treatment naïve and pre-treated settings. It joins a growing list of biomarkers in NSCLC, further emphasizing the importance of molecular profiling and diagnosis in this patient population. Consequently, this also brings greater complexity in the appropriate selection and sequencing of therapies. Ongoing clinical trials and translational studies will aid in determining the role for capmatinib and other MET-directed therapies in METex14 altered NSCLC.

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