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Review

The race to target *MET* exon 14 skipping alterations in non-small cell lung cancer: The Why, the How, the Who, the Unknown, and the Inevitable

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ABSTRACT

A number of small molecule tyrosine kinase inhibitors (TKIs) have now been approved for the treatment of non-small cell lung cancers (NSCLC), including those targeted against epidermal growth factor receptor, anaplastic lymphoma kinase, and ROS1. Despite a wealth of agents developed to target the receptor tyrosine kinase, MET, clinical outcomes have as yet been disappointing, leading to pessimism about the role of MET in the pathogenesis of NSCLC. However, in recent years, there has been a renewed interest in *MET* exon 14 alterations as potential drivers of lung cancer.

MET exon 14 alterations, which result in increased MET protein levels due to disrupted ubiquitin-mediated degradation, occur at a prevalence of around 3% in adenocarcinomas and around 2% in other lung neoplasms, making them attractive targets for the treatment of lung cancer. At least five MET-targeted TKIs, including crizotinib, cabozantinib, capmatinib, tepotinib, and glesatinib, are being investigated clinically for patients with *MET* exon 14 altered-NSCLC. A further two compounds have shown activity in preclinical models. In this article, we review the current clinical and preclinical data available for these TKIs, along with a number of other potential therapeutic options, including antibodies and immunotherapy. A number of questions remain unanswered regarding the future of MET TKIs, but unfortunately, the development of resistance to targeted therapies is inevitable. Resistance is expected to arise as a result of receptor tyrosine kinase mutation or from upregulation of MET ligand expression; potential strategies to overcome resistance are proposed.

Contents

Abbreviation: ALK, anaplastic lymphoma kinase; CNS, central nervous system; EGFR, epidermal growth factor receptor; FDA, food and drug administration; GCN, gene copy number; HGF, hepatocyte growth factor; IC_{50}, half inhibitory concentration; IHC, immunohistochemistry; mAb, monoclonal antibody; *MET*ex14, *MET* exon 14; *MET*ex14+ NSCLC, *MET*ex14 altered NSCLC; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD-1, programmed cell death protein 1; RTK, receptor tyrosine kinase; SqCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor; TMB, tumor mutational burden; VEGFR, vascular endothelial growth factor receptor.

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1. Introduction (the Why)

Orally available small molecule tyrosine kinase inhibitors (TKIs) have now been approved for epidermal growth factor receptor (*EGFR*)-mutated, anaplastic lymphoma kinase (*ALK*)-rearranged, and *ROS1*-rearranged non-small cell lung cancers (NSCLC), altering the treatment landscape of NSCLC [1]. Alterations (point mutations, amplifications, protein overexpression, and fusions) in another receptor tyrosine kinase (RTK), the hepatocyte growth factor (HGF) receptor (MET), have been identified in NSCLC, and a plethora of MET-targeted agents (small molecular TKIs and antibodies against HGF or MET) have been investigated in this disease type [2]. Disappointingly, despite the wide spectrum of MET alterations in NSCLC, randomized trials with MET inhibitors have not resulted in clinical benefit [3–5]. These disappointing results have led to pessimism about the role of MET in the pathogenesis of NSCLC and the validity of MET as a targetable driver in NSCLC. This review will concentrate on the recent re-emergence of *MET* exon 14 (*MET*ex14) splicing alterations in NSCLC that has led to renewed optimism of *MET*ex14 alteration as a targetable mutation that may lead to the approval of MET-specific inhibitors in NSCLC.

1.1. *METex14 splicing mutations in NSCLC*

The MET signaling pathway has recently been reviewed in detail [6]. The timeline of events leading to the recognition of *MET*ex14 alteration as an important driver in lung cancer is summarized in Fig. 1. In 1994, an alternatively spliced MET RTK with deletion of the 47-amino acid juxtamembrane region of the MET receptor was reported [7], followed by the demonstration that mutation of a tyrosine residue at position 1001 in this juxtamembrane region led to a partial gain of function [8]. In 2001, Peschard and colleagues reported that mutation of tyrosine residue 1003 in the binding domain of the E3 ubiquitin-protein ligase, c-CBL, abolished c-CBL binding to MET, disrupting c-CBL-mediated degradation and leading to MET oncogenic activity [9]. Y1003 is located in the juxtamembrane region of MET and is encoded by exon 14 [6]. Subsequently, mutations in the *MET*ex14 splice sites were reported by Ma and colleagues in small cell lung cancer in 2003 and NSCLC in 2005 [10,11]. The significance of these splice site mutations was further characterized by Kong-Beltran and colleagues in 2006, when they identified both single nucleotide substitutions and small deletions in the 5′ and 3′ splice sites around *MET*ex14 in lung tumor samples, and demonstrated that these mutations resulted in *MET*ex14 skipping. The exon 14-spliced protein had abolished c-CBL E3 ligase binding, resulting in decreased ubiquitination, and leading to a relative increase in MET protein levels. Additionally, MET Y1003 mutation was shown to result in decreased ubiquitination and increased stability of the MET protein. Both *MET*ex14-spliced and MET Y1003-mutated proteins were transforming *in vitro* and in a xenograft model that was inhibited by an anti-MET antibody [12]. Since then, sporadic case series have reported the incidence of *MET*ex14 alterations in NSCLC to be around 2–4% [13–15]. It was not until 2015 that large scale molecular profiling of *MET*ex14 alterations in 38,028 tumor samples by Frampton and colleagues led to renewed focus on *MET*ex14 alterations in lung carcinomas [16]. Among the 221 tumor samples harboring *MET*ex14 alterations, 193 were in lung carcinomas, including 131 lung adenocarcinoma samples. No other common solid tumor malignancies harbored *MET*ex14 alterations to the same degree as lung neoplasms [16]. Furthermore, in 2015, an *in vitro* model using the CRISPR/Cas9 system in HEK293 cell lines demonstrated that *MET*ex14 deletion resulted in higher MET protein expression levels, enhanced MET phosphorylation, prolonged MET activation, and enhanced cellular growth, colony formation, and MET inhibitor sensitivity [17]. Contemporaneously, case reports and case series have reported that patients with *MET*ex14 altered NSCLC (*MET*ex14+ NSCLC) respond to MET TKIs [18–22].

Since late 2015, reports characterizing patients with *MET*ex14+ NSCLC have been published in rapid succession in the literature (Table 1) [16,23–31]. To date, it can be summarized that *MET*ex14 alterations are found in a relatively elderly population of patients with NSCLC, and are enriched in sarcomatoid histologies, with a prevalence ranging from 8 to 22% [25,31]. On average, *MET*ex14 alterations occurred at a prevalence of about 3% in lung adenocarcinoma, and notably, at a prevalence of slightly higher than 2% in squamous cell carcinoma (SqCC) [31]. Available data on the overlap between *MET*ex14 alterations, *MET* amplification, and *MET* point mutations are sparse, but concurrent *MET* amplification has been reported in 15–21% of *MET*ex14+ NSCLC [24,26,31], and MET Y1003X mutations account for around 2% of the *MET*ex14 alterations in NSCLC [31]. Based on 28 patients, Awad and colleagues showed that Stage IV *MET*ex14–mutated NSCLCs were significantly more likely to have concurrent *MET* genomic amplification and