

New Drugs

Capmatinib for patients with non-small cell lung cancer with *MET* exon 14 skipping mutations: A review of preclinical and clinical studies

Yi-Long Wu^{a,*}, Egbert F. Smit^b, Todd M. Bauer^c

^a Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, 106 Zhongshan Er Rd, Guangzhou 510080, Guangdong, People's Republic of China

^b Department of Thoracic Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, Netherlands

^c Sarah Cannon Research Institute / Tennessee Oncology, PLLC., 250 25th Avenue, Nashville, TN 37203, USA

ARTICLE INFO

Keywords:

Non-small cell lung cancer
Tyrosine kinase inhibitor
MET inhibitor
Capmatinib
MET exon 14 skipping mutation

ABSTRACT

The mesenchymal-epithelial transition (MET) receptor tyrosine kinase binds the hepatocyte growth factor to activate downstream cell signaling pathways involved in cell proliferation, survival, and migration. Several genetic mechanisms can result in an aberrant activation of this receptor in cancer cells. One such activating mechanism involves the acquisition of gene mutations that cause *MET* exon 14 skipping (*MET*ex14) during mRNA splicing. Mutations leading to *MET*ex14 are found in approximately 3–4% of patients with non-small cell lung cancer (NSCLC). Accumulating evidence suggests that *MET*ex14 is a true, independent oncogenic driver in NSCLC, as well as being an independent prognostic factor for poorer survival in patients with NSCLC. The successes of target therapies have relied on improved understanding of the genetic alterations that lead to the dysregulation of the molecular pathways and more advanced molecular diagnostics. Multiple efforts have been made to target the MET pathway in cancer; however, real clinical progress has only occurred since the emergence of *MET*ex14 as a valid biomarker for MET inhibition. Capmatinib is a highly potent and selective type Ib inhibitor of MET. Following preclinical demonstration of activity against MET-dependent cancer cell line growth and MET-driven tumor growth in xenograft models, data from a phase 1 clinical trial showed an acceptable safety profile of capmatinib and preliminary evidence of efficacy in patients with MET-dysregulated NSCLC. The multicohort GEOMETRY mono-1 phase 2 trial reported objective response rates of 68% and 41% in treatment-naïve and in pre-treated patients with *MET*ex14 advanced NSCLC, respectively. These results have supported the approval of capmatinib by the US Food and Drug Administration for patients with metastatic NSCLC harboring *MET*ex14.

Introduction

Lung cancer was the most commonly diagnosed type of cancer in 2018 and the leading cause of cancer death in both men and women [1]. Worldwide, the estimated incidence of lung cancer was over 2 million cases and more than 1.7 million deaths in 2018 [1]. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases

[2]. Curative treatment of NSCLC remains a challenge because more than 60% of cases are diagnosed at a locally advanced or metastatic stage (III or IV), when surgical resection may no longer be a viable option [3].

Due to an increased understanding of the molecular pathways involved in cancer development, the availability of targeted therapies that are more effective for specific genetic alterations (e.g., epidermal

Abbreviations: 1L, treatment-naïve; 2L, 1 prior line of treatment; 2/3L, 1 or 2 prior lines of treatment; AE, adverse event; ALK, anaplastic lymphoma kinase; BID, twice daily; BIRC, Blinded Independent Review Committee; CI, confidence interval; CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; ESMO, European Society for Molecular Oncology; GCN, gene copy number; HGF, hepatocyte growth factor; IC₅₀, half maximal inhibitory concentration; L, line of treatment; MET, mesenchymal-epithelial transition; *MET*ex14, MET exon 14 skipping mutation; NCCN, National Comprehensive Cancer Network; NE, not estimable; NGS, next-generation sequencing; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PFS, progression-free survival; PR, partial responses; qRT-PCR, quantitative reverse transcription PCR; RT-PCR, reverse transcriptase polymerase chain reaction; SD, stable disease; TKI, tyrosine kinase inhibitor.

* Corresponding author at: Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, 106 Zhongshan Er Rd, Guangzhou 510080, People's Republic of China.

E-mail address: syylwu@live.cn (Y.-L. Wu).

<https://doi.org/10.1016/j.ctrv.2021.102173>

Received 18 December 2020; Received in revised form 18 February 2021; Accepted 21 February 2021

Available online 1 March 2021

0305-7372/© 2021 The Authors.

Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

growth factor receptor [*EGFR*] mutation, anaplastic lymphoma kinase [*ALK*] rearrangement, *ROS1* rearrangement, *BRAF* mutation) and the evolving techniques for molecular diagnostics, routine testing for a number of driver mutations in patients with NSCLC has become part of clinical practice [4–6]. The National Comprehensive Cancer Network (NCCN), the European Society for Molecular Oncology (ESMO), and the Pan-Asian treatment guidelines recommend early, broad molecular testing to identify driver mutations and ensure that patients receive the most appropriate treatment [5–7]. Targeted therapy is recommended for the treatment of advanced/metastatic NSCLC with driver mutations, for which effective, approved therapies have been identified. Additionally, the goal of broad molecular profiling is to also identify rare driver mutations for which effective drugs may already be available within the context of trials or recent approvals [5–7].

Mesenchymal-epithelial transition (*MET*) exon 14 skipping mutation (*MET*ex14) is an oncogenic driver found in approximately 3–4% of patients with NSCLC and is emerging as a biomarker that is associated with poor prognosis [6,8–14]. The *MET* inhibitors, tepotinib and capmatinib (INC280), have recently been approved in Japan and capmatinib only in the United States of America as the first agents for the treatment of patients with advanced/metastatic NSCLC harboring *MET*ex14. Savolitinib is another *MET* inhibitor under clinical investigation [15]. Capmatinib is a highly potent and selective inhibitor of the *MET* receptor tyrosine kinase that has been shown to be effective as a single-agent treatment in patients with advanced or metastatic NSCLC harboring *MET*ex14. The NCCN guidelines recommend molecular testing for *MET*ex14 in patients with NSCLC and recommend capmatinib as the preferred treatment option for patients with metastatic NSCLC with *MET*ex14 [6]. This review aims to provide an overview of the preclinical evidence that underpinned the development of capmatinib for the treatment of patients with *MET*ex14 NSCLC, as well as outline the results from the clinical trials in this indication.

MET signaling

The *MET* proto-oncogene encodes a receptor tyrosine kinase that activates downstream signaling pathways, including MAPK, PI3K/AKT, STAT, and NF- κ B [16]. In physiological conditions, *MET* is activated via binding of its ligand, hepatocyte growth factor. The *MET* pathway has an essential role during embryogenesis, affecting the development of a diverse set of organs and systems. Beyond embryonic development, *MET* signaling is important for wound healing and tissue regeneration, most notably liver regeneration [17]. Enhanced *MET* signaling supports tumor cell growth, survival, migration, and invasion. Genomic *MET* alterations, including mutations and amplification, can cause activation of the *MET* signaling pathway. Both mutations and amplification of the *MET* gene have been identified in NSCLC and are associated with poor prognosis [10,16,18]. *MET* amplification occurs in up to 20% of patients as a mechanism of acquired resistance to *EGFR* tyrosine kinase inhibitors (TKIs), but can also occur *de novo* in approximately 1–6% of patients with NSCLC [9,19–22]. While high-level *MET* amplification is recognized by the NCCN guidelines as an emerging biomarker to guide treatment decisions for NSCLC [6], more clinical trials are needed to confirm its predictive value and to define suitable detection methods and thresholds. Conversely, the predictive value of *MET*ex14 is now established; it is the clearest proven target for capmatinib activity and is a validated biomarker for selecting patients for *MET* TKI therapies, such as capmatinib [6,23].

METex14 in non-small cell lung cancer

The molecular alterations in the *MET* gene that can cause exon 14 skipping are diverse, including base substitutions, insertions, and deletions, which are primarily located in splice donor and acceptor sites of exon 14 [12]. These *MET* mutations are gain-of-function, leading to a decrease in internalization and degradation of the *MET* receptor, and

thus increasing *MET* signaling (Fig. 1). Patients with NSCLC harboring *MET*ex14 usually do not have other known molecular drivers of NSCLC (e.g., *EGFR*, *ALK*, *ROS1*, *BRAF*), which supports the role of *MET*ex14 as an independent oncogenic driver [8–12,18]. Additionally, *MET*ex14 is associated with a low tumor mutational burden [12]. *MET*ex14 occurs in 3–4% of NSCLC adenocarcinoma and 8–32% of NSCLC with sarcomatoid histologies [8–13,18,24]. A study in Chinese patients ($n = 1296$; 85% adenocarcinoma) identified *MET*ex14 in only 0.9% of those patients [25]. Notably, *MET*ex14 was found to be an independent prognostic factor for poorer survival in patients with NSCLC [10,18].

The presence of *MET*ex14 in NSCLC is not associated with any specific patient characteristics but studies have shown that it occurs more frequently in females than males and it is found in a relatively elderly population of patients with NSCLC [8,12,14,26]. Patients with *MET*ex14 NSCLC are more likely to have a history of non-smoking [14]. However, it is important to note that this mutation is also found in the smoking population, and the proportion of smokers in patients with NSCLC harboring *MET*ex14 is significantly higher than in those harboring *EGFR* mutations, which are classically associated with never/light smokers [14,27,28]. This lack of clear clinical association between *MET*ex14 and patient-specific clinical characteristics supports broad molecular testing to determine which patients would benefit most from *MET* inhibitor therapy. *MET* testing has yet to become common practice; however, this will potentially be facilitated with the increasing use of broad molecular testing techniques, as well as with guideline recommendations following recent regulatory approvals of *MET* inhibitors. *MET*ex14 has become part of the molecular testing recommendations in the NCCN guidelines for patients with metastatic NSCLC [6].

Numerous and diverse alterations that lead to exon 14 not being transcribed have been identified and constitute *MET*ex14 skipping mutations [11]. There are several approaches available to test for these known alterations, including Sanger sequencing, quantitative reverse transcription PCR (qRT-PCR) and DNA/RNA-based next generation sequencing (NGS) [29]. Sanger can sequence a low number of genes (1–20 targets) [30] and qRT-PCR can only test one at a time, while NGS allows for detection of multiple gene alterations from a single sample, providing a higher throughput than traditional methods [31,32]. Given the complexity and diversity of the mutations driving *MET*ex14, NGS represents the most suitable method of testing. In line with this, NCCN guidelines recommend NGS testing as the primary method for the detection of *MET*ex14 [6]. However, targeted NGS panels need to be optimized to detect mutations leading to *MET*ex14 considering the diversity in position and size of the *MET*ex14 alterations [11,33].

Preliminary clinical evidence has demonstrated that *MET*-specific therapies, including capmatinib, significantly prolonged survival in patients with advanced, *MET*ex14 NSCLC compared with those treated with other therapies [34,35]. These results reinforce the importance of an identification of patients with this driver mutation to ensure that these patients receive an appropriate targeted therapy in order to improve treatment outcomes.

Capmatinib preclinical development

Capmatinib is an oral, ATP-competitive, highly potent, and selective type Ib inhibitor of the *MET* receptor tyrosine kinase [15,36,37]. In *in vitro* assays, capmatinib was shown to be more potent than other *MET* inhibitors (half maximal inhibitory concentration [IC_{50}] of 0.6 nmol/L): approximately 30 times more potent than crizotinib (IC_{50} 22 nmol/L), and five times more potent than tepotinib (IC_{50} of 3.0 nmol/L) [38]. Moreover, capmatinib is highly selective for *MET* compared with other kinases, as demonstrated by testing over large panels of kinases in biochemical and binding assays [36,37]. Using a selectivity screening platform of 442 kinases and disease-associated variants, capmatinib bound to only nine kinases (including wild-type *MET* and two *MET* variants: *MET* M1250T and Y1235D). Additionally, binding affinities of capmatinib for both wild-type and the two variants of *MET* were several

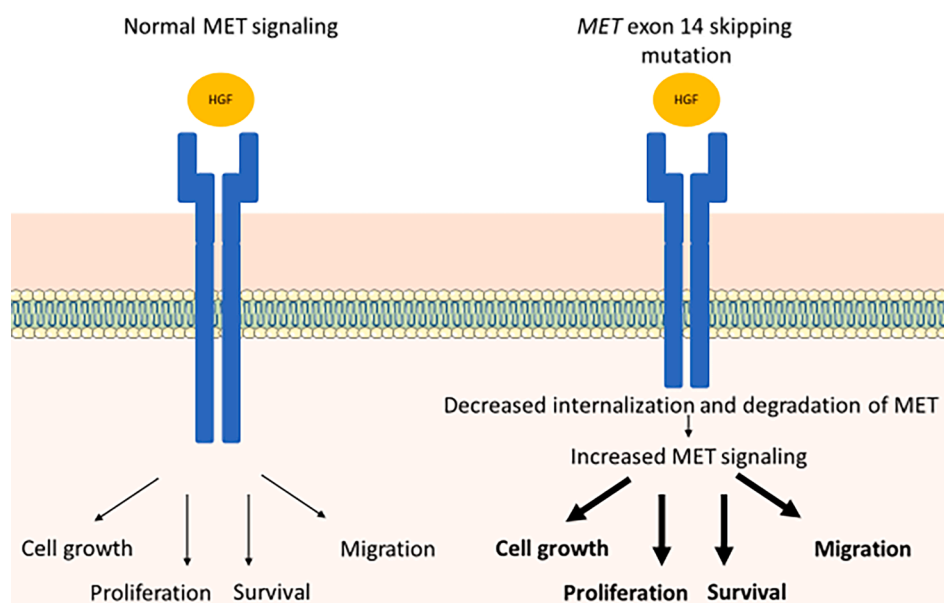


Fig. 1. Schematic representation of the effect of *MET*ex14 on MET stability and signaling. Abbreviations: HGF, hepatocyte growth factor; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping mutation.

magnitudes higher than those for other kinases, which corroborates the selectivity for MET binding [37].

Capmatinib effectively inhibits MET downstream signaling and consequently hinders tumor growth and progression [36]. Cancer cell growth in MET-dependent cancer cell lines was blocked by capmatinib treatment, and hepatocyte growth factor-stimulated cell migration was decreased by capmatinib in a concentration-dependent manner [36]. MET signaling is known to mediate cell resistance to apoptosis [39–41]. Treatment with capmatinib induced apoptosis in MET-dependent cell lines, as shown by increased levels of fragmented DNA and by poly (ADP-ribose) polymerase activation [36]. In MET-dependent tumor cell lines, capmatinib inhibited the phosphorylation of downstream effectors of the MET pathway, such as ERK1/2, AKT, FAK, GAB1, and STAT3/5, and inhibited tumor cell proliferation and migration [36].

Capmatinib has also demonstrated *in vivo* activity against MET-driven tumors in preclinical models [36,37]. MET inhibition by capmatinib was dose dependent and this was sustained over time [36]. Furthermore, capmatinib treatment demonstrated anti-tumor activity in xenograft models, with tumor regression shown in some of these models [36,37], including in tumors. This included the regression of tumors in a patient-derived xenograft model with *MET*ex14 [37].

Clinical studies

Early clinical trial

A multicenter phase 1 clinical trial (NCT01324479) in patients with solid tumors (including NSCLC) harboring *MET* alterations (but not *MET*ex14) aimed to identify the recommended phase 2 dose regimen and evaluate preliminary safety and efficacy of capmatinib as a single agent [42].

During the dose-escalation phase, a capsule formulation of capmatinib was used; however, this was replaced by a tablet formulation. The recommended phase 2 dose regimen was identified as capmatinib 400 mg twice daily (BID) tablets, which was found to be equivalent to capmatinib 600 mg BID capsules. This study showed that capmatinib was rapidly absorbed after oral administration, with a median time to peak plasma concentration of 1–4 h for the capsule formulation, and capmatinib exposure increased with dose up to the 600 mg BID level [42].

Patients with NSCLC ($n = 55$) in the expansion phase included two

groups: the original cohort, with patients who completed the dose escalation phase, and an additional cohort, which differed based on slightly different molecular diagnostic criteria for inclusion. The original cohort had MET alterations defined as an H-score ≥ 150 or a ratio of MET/centromere ≥ 2 or MET gene copy number (GCN) ≥ 5 , or $\geq 50\%$ of tumor cells with an immunohistochemistry score of 2+ or 3+, with either local or central testing. However, in the additional expansion cohort, patients had to be *EGFR* wild-type and to have centrally tested MET with $\geq 50\%$ of tumor cells with an immunohistochemistry score of 3+ [43]. Enrollment in this study was completed in February 2016, and the results for the primary analysis with a cut-off date of July 17, 2017 have been published; all patients had discontinued treatment [43]. The median age of the patients was 60 years (range: 29 to 84 years), and all patients had an Eastern Cooperative Oncology Group performance status ≤ 2 (≤ 1 in 96% of patients). Approximately 90% of patients had non-squamous histology and 95% of patients had received prior therapy [43]. Treatment with capmatinib resulted in an overall response rate (ORR) of 22%, as determined by a Blinded Independent Review Committee (BIRC), including 11 partial responses (PR) and one complete response (CR). In addition, 16 patients (29%) had BIRC-assessed stable disease (SD) as their best response, resulting in an overall disease control rate of 51%. Notably, it was clear that the response rates were higher in the subgroup of patients with higher *MET* amplification: the proportion of patients with a PR in the subgroup with *MET* GCN ≥ 6 ($n = 15$) was 47% (compared with 22% overall). Notably, the single CR was reported in the *MET* GCN ≥ 6 subgroup. The median progression-free survival (PFS) was 3.7 months (95% CI 1.9–7.4, 67% PFS events), but this was doubled in the subgroup with GCN ≥ 6 , with a PFS of 7.9 months (95% CI 3.6–12.8, 67% PFS events) [43]. Retrospectively, four patients have been identified as having *MET*ex14 (central next-generation sequencing [NGS] testing), all of whom had demonstrated tumor shrinkage (one CR, two PR, and one SD confirmed by the BIRC) [43]. Despite the low number of patients, these results provided the first evidence of capmatinib efficacy in patients with advanced NSCLC with *MET*ex14.

Phase 2 trial

GEOMETRY mono-1 (NCT02441439) is an ongoing multicenter, open-label, multicohort, phase 2 study of capmatinib with the recommended 400 mg BID tablet dose, in patients with advanced or metastatic

NSCLC (stage IIIB and IV). Eligible patients were *EGFR* wild-type, *ALK* fusion-negative, and had *MET*ex14 or *MET* amplification [44]. *MET*ex14 testing was performed by a central laboratory with reverse transcriptase polymerase chain reaction (RT-PCR) and *MET* amplification was detected by fluorescence in situ hybridization (FISH) using tissue-based samples. Patients were assigned to one of several cohorts to assess which patients may benefit most from capmatinib treatment (e.g., *MET*ex14, different levels of *MET* GCN gain, and line of therapy), with each cohort analyzed separately (Table 1). Patients were treated with capmatinib in fasting condition in Cohorts 1 to 5, whereas the food restriction was removed in the expansion Cohorts 6 and 7 based on pharmacokinetic and safety data collected in a separate study [44,45]. The primary endpoint was ORR (defined as the proportion of patients with a best overall response of PR or CR), assessed by the BIRC, and the key secondary endpoint was duration of response (DOR) by BIRC. Other secondary endpoints included ORR and DOR by investigator assessment, disease control rate, time to response, PFS by investigator and BIRC assessment, overall survival, pharmacokinetics, and safety.

As of January 6, 2020, 364 patients had been enrolled in the study. Efficacy results have been reported for the 128 patients with *MET*ex14 advanced NSCLC from Cohort 4 (1 or 2 prior lines of treatment [2/3L], $n = 69$), Cohort 5b (treatment-naïve [1L], $n = 28$), and Cohort 6 (1 prior line of treatment [2L], $n = 31$) [44]. The responses were consistent whether assessed by the BIRC or by the investigator, and here we mention responses assessed by the BIRC. The ORR (95% CI) was 68% (48–84) in treatment-naïve patients in Cohort 5b. In pretreated patients, the ORR was 41% (29–53) in 2/3L (Cohort 4), and 48% (30–67) in 2L (expansion Cohort 6). In treatment-naïve patients, the median DOR (95% CI) was 12.6 (5.6–not estimable [NE]) and the median PFS (95% CI) was 12.4 months (8.2–NE). The median DOR in 2/3L was 9.7 months (5.6–13.0) and the median PFS was 5.4 months (4.2–7.0). In the expansion cohort in a 2L setting, the median DOR was 6.9 months (4.2–NE) and the median PFS was 8.1 months (4.2–9.9) in patients with *MET*ex14; however, these results were not mature (Table 2) [44]. This differential benefit observed between treatment-naïve and pre-treated patients highlights the need for an early diagnosis in patients with *MET*ex14, advanced NSCLC, given that this trial clearly shows very high response rates in the first-line setting, as well as a small increase in ORR in the 2L setting compared with the 2/3L setting.

Brain metastases are frequent in metastatic NSCLC, occurring in up to 40% of patients, and represent a challenge to effective treatment [46,47]. The frequency of brain metastases in *MET*ex14 NSCLC is similar to this proportion [34]. As such, the availability of targeted systemic therapies that can cross the blood–brain barrier and reach the brain is an

Table 2

Key efficacy outcomes from patients with *MET*ex14 in Cohorts 4, 5b, and 6 of the GEOMETRY mono-1 trial [34].

Efficacy outcomes (BIRC assessment)	Cohort 5b (treatment-naïve) $N = 28$	Cohort 4 (pre-treated 2/3L) ^a $N = 69$	Cohort 6 (pre-treated 2L) $N = 31$
ORR, % (95% CI)	68 (48–84)	41 (29–53)	48 (30–67)
DOR, median (95% CI)	12.6 (5.6–NE)	9.7 (5.6–13.0)	6.9 (4.2–NE)
PFS, months, median (95% CI)	12.4 (8.2–NE)	5.4 (4.2–7.0)	8.1 (4.2–9.9)

Data cut-off: January 6, 2020.

BIRC, blinded independent review committee; CI, confidence interval; DOR, duration of response; L, line of treatment; *MET*ex14, *MET* exon 14 skipping mutation; NE, not estimable; ORR, objective response rate; PFS, progression-free survival.

^a Two patients in Cohort 4 had received three prior lines of therapy.

important unmet need. Patients with asymptomatic brain metastasis were allowed in this trial. Capmatinib can cross the blood–brain barrier and has shown preliminary activity in brain metastasis. A neuro-radiologic review was retrospectively conducted by the BIRC on 13 evaluable patients with brain metastasis at baseline (10 pretreated and three treatment-naïve). Seven patients (54%) attained an intracranial response, of which four patients had a complete resolution of their brain lesions. Intracranial responses occurred by the first assessment at week 6. Remarkably, 12 of the 13 patients with intracranial disease experienced disease control [44]. Despite being a very small sample size, these results are encouraging, and further evidence is being pursued to confirm the efficacy of capmatinib in the brain (NCT04427072).

As described above, the GEOMETRY mono-1 trial also included cohorts of patients with *MET* amplification without *MET*ex14. Previously treated patients (2/3L) with *MET* amplification were assigned to cohorts based on their GCN: Cohort 1a (GCN ≥ 10 , $n = 69$), Cohort 1b (GCN 6–9, $n = 42$), Cohort 2 (GCN 4 or 5, $n = 54$), and Cohort 3 (GCN ≤ 4 , $n = 30$). The expansion Cohort 6 ($n = 34$) enrolled patients with one previous line of treatment (2L) and either *MET* GCN ≥ 10 or *MET*ex14, but only enrolled three *MET*ex14 patients. The study also included one cohort of patients with no previous treatment (1L) and *MET* amplification: Cohort 5a (GCN ≥ 10 , $n = 15$). Capmatinib showed anti-tumor activity in patients with and without prior treatment with *MET* amplification of GCN ≥ 10 . The ORR (95% CI) as assessed by BIRC was 40% (16–68) in the 15 treatment-naïve patients in Cohort 5a and 29% (19–41) in the 69 pretreated patients who had 2/3L in Cohort 1a. However, neither responses in treatment-naïve or pretreated patients met the prespecified threshold for clinically relevant activity. In treatment-naïve patients, the median DOR (95% CI) was 7.5 (2.6–14.3) and the median PFS (95% CI) was 4.2 months (1.4–6.9). The median DOR in pretreated patients was 8.3 months (4.2–15.4) and the median PFS was 4.1 months (2.9–4.8). The same cutoff date of January 6, 2020 was used for the efficacy analyses in patients with *MET* amplification and GCN ≥ 10 . The three cohorts in which patients had a GCN < 10 were closed earlier for futility. These results suggest that patients with high *MET* amplification may benefit from treatment with capmatinib, but further investigation to determine the threshold level of *MET* amplification is required. Therefore, to date, *MET*ex14 remains the most relevant biomarker [44].

Safety profile of capmatinib

The safety of capmatinib as a single agent in advanced NSCLC was assessed in the phase 1 trial and in the phase 2 GEOMETRY mono-1 study, with similar findings in both studies. Most treatment-related adverse events (AEs) were grade 1 or 2 in these trials [43,44].

During the dose-escalation part of the phase 1 study, doses ranging from capmatinib 100 mg BID to 600 mg BID in capsule formulation were evaluated. Dose-limiting toxicities were observed at 200 and 450 mg BID

Table 1

GEOMETRY mono-1 study cohorts [34].

Treatment-naïve (1L)		Pre-treated (2/3L)	
<i>MET</i> ex14 regardless of <i>MET</i> amplification	<i>MET</i> amplification	<i>MET</i> ex14 regardless of <i>MET</i> amplification	<i>MET</i> amplification
Cohort 5b Cohort 7 (expansion)	Cohort 5a (GCN ≥ 10)	Cohort 4 Cohort 6 ^a (expansion)	Cohort 1a (GCN ≥ 10) Cohort 1b ^b (GCN 6–9) Cohort 2 ^b (GCN 4 or 5) Cohort 3 ^b (GCN < 4) Cohort 6 ^a (expansion; GCN ≥ 10)

GCN, gene copy number; L, line of treatment; *MET*, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping mutation.

^a Cohort 6 enrolled patients with either *MET*ex14 (regardless of *MET* amplification) or *MET* amplification with a GCN ≥ 10 .

^b Cohorts 1b, 2, and 3 were closed for futility.

(both grade 3 fatigue, one patient each), and at 250 mg BID (grade 3 bilirubin increased, one patient), with no dose-limiting toxicity at the maximum dose tested of 600 mg BID capsules, and the maximum tolerated dose was not reached.

The most frequent AEs ($\geq 20\%$) in the phase 1 study were nausea, peripheral edema, vomiting, decreased appetite, fatigue, and increased blood creatinine levels. Study-drug related AEs in $\geq 10\%$ of patients were nausea, vomiting, peripheral edema, fatigue, decreased appetite, and diarrhea [43].

The reported safety results for GEOMETRY mono-1 included 364 patients across Cohorts 1 to 7 (cut-off data for analysis January 6, 2020), with a median exposure to capmatinib of 15.3 weeks. Peripheral edema (42.9%), nausea (34.3%), vomiting (18.7%), and increased blood creatinine levels (18.4%) were the most frequent treatment-related AEs reported in the GEOMETRY mono-1 study [44]. Grade 3/4 treatment-related AEs were reported in 137 patients (37.6%), including 30 cases of peripheral edema (8.2%). Treatment-related AEs leading to discontinuation occurred in 39 patients (10.7%) [44]. When looking at the safety results from the expansion Cohort 6 and Cohort 7 ($n = 57$), in which capmatinib was given without food restrictions, compared with the cohorts with fasting conditions ($n = 307$), there may be a decrease in all-cause gastrointestinal AEs when taking capmatinib without food restrictions: nausea (36.8% versus 46.3%), vomiting (21.1% versus 29.3%), decreased appetite (12.3% versus 22.5%), and diarrhea (5.3% versus 19.9%) [44].

Both peripheral edema and gastrointestinal toxicity seem to occur as AEs associated with the MET inhibitor class [48]. Indeed, gastrointestinal AEs are among the most common side effects observed with tyrosine kinase inhibitors, and several management strategies have been developed and applied across different types of cancer with diverse drugs [49,50]. Nevertheless, awareness of all possible AEs and close monitoring and management, according to the clinical practice protocols in place at the different institutions, can make a difference in improving patient tolerability.

Discussion

MET pathway activation through *MET*14 is an important oncogenic mechanism in NSCLC. *MET*14 is not currently part of routine molecular testing in NSCLC. However, the recent approvals of two MET inhibitors and the accumulation of data showing that *MET*14 is strongly predictive of responses to MET inhibition may influence testing levels, as an assessment of temporal trends of tumor biomarker testing identified dramatic uptakes in testing for specific biomarkers following publication of seminal clinical trials and regulatory approvals [51]. Additionally, *MET*14 testing is now recommended by the NCCN guidelines, which state capmatinib as the preferred treatment option for patients with advanced or metastatic NSCLC whose tumors harbor *MET*14 [6].

Although there are several testing methodologies able to detect *MET* gene alterations, the complexity and diversity of the *MET*14 mutations leading to constitutive activation of MET requires testing methods that can detect these alterations with high sensitivity and specificity, such as NGS [11,29]. Early, broad molecular testing is recommended to select the optimal treatment for each patient [6]. Upfront, multiplex molecular profiling (including NGS) could avoid testing delays and tissue shortages associated with sequential testing and facilitate early, appropriate upfront targeted treatment [31,52]. Most patients with NSCLC are diagnosed with advanced metastatic disease [53]. Many of these patients may have tumors that are difficult to biopsy, are very small, and biopsies with minimal tumor content [54,55]. NGS allows detection of multiple gene alterations from a single sample, avoiding tissue exhaustion. Furthermore, modeling analysis of newly diagnosed patients with metastatic NSCLC demonstrated that NGS was associated with the same (versus hotspot panel) or shorter (versus exclusionary and sequential testing) time-to-test results, with lower testing costs than sequential,

exclusionary, and hotspot panel testing [31,56].

Prior to the approval of additional MET inhibitors, crizotinib was recommended for patients with *MET*14; crizotinib is indicated for the treatment of patients with advanced NSCLC harboring *ALK* translocations or *ROS1* rearrangements [5–7]. Data from the PROFILE 1001 clinical trial showed that the ORR with crizotinib treatment in patients with *MET*14 was 32.3% [57]. However, one important aspect to consider is the poor blood–brain barrier penetration of crizotinib, which may limit its effectiveness in patients with brain metastases [58].

Capmatinib is a highly potent and selective MET inhibitor with *in vitro* and *in vivo* anti-tumor activity against NSCLC. Results from the GEOMETRY mono-1 study in patients with advanced/metastatic NSCLC harboring *MET*14 showed that capmatinib was highly effective for treating these patients, with particularly good results in the first-line treatment setting, where an ORR of 68% was observed [44]. Nonetheless, in patients who have received one to two prior lines of therapy, the ORR was 41%, and 48% with only one prior line of treatment, demonstrating that pre-treated patients can also derive a benefit from capmatinib treatment [44]. These results reinforce the importance of an early molecular diagnosis in patients with *MET*14. Furthermore, scope for improvement in overall efficacy across all treatment settings also underpins the need for ongoing research into intrinsic and acquired mechanisms for resistance to MET inhibition. Regarding intrinsic resistance, a recent preliminary analysis of patients with *MET*14 NSCLC who were treated with MET inhibitors demonstrated that the absence of either MET protein expression or the activation of the RAS pathway at baseline had negative predictive value for treatment response, with no responses reported in patients with either undetectable MET protein expression (by mass spectroscopy; $n = 6$) or a concordant RAS pathway mutation ($n = 5$) [59]. A preliminary biomarker analysis of the GEOMETRY mono-1 study identified concurrent *KRAS* alterations in 7% of *MET*14 patients before capmatinib treatment; there was no association of *KRAS* alterations with differences in ORR or PFS [60]. Knowledge of acquired resistance is steadily accumulating, with both on-target and off-target mechanisms known to be involved. *MET* kinase domain, *KRAS* and *RASA1* mutations, as well as *EGFR*, *HER2*, *HER3*, *KRAS*, and *BRAF* gene amplifications have been identified [59,61].

Guidelines recommend broad molecular testing of patients with advanced NSCLC to guide treatment decisions since several targeted therapies are available for established or emerging biomarkers that are efficacious in the specific sub-group of patients that they are intended for [5–7]. A more ubiquitous use of diagnostic platforms such as NGS may facilitate the identification of patients with driver mutations (including the ones with rare incidence) and allow a prompter treatment with appropriate targeted therapies, if available. These diagnostic platforms also enable comprehensive genomic profiling of tumors to identify the landscape of concurrent alterations; therefore, they can facilitate even more personalized future treatment options. In the GEOMETRY mono-1 study, tumor samples from 73 patients with *MET*14 (as detected by RT-PCR) enrolled into Cohorts 4 and 5b were retrospectively analyzed using a Foundation Medicine NGS panel, FoundationOne® CDx (<https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx>). NGS testing detected *MET*14 in 72 of those samples, indicating a 99% concordance between the two tests [44]. The additional patient had a non-canonical *MET*14 rearrangement [44]. Overall, these results are reassuring and indicate that both RNA-based and DNA-based techniques can be used to detect *MET*14 in tumor samples from patients with NSCLC.

Data from the GEOMETRY mono-1 study suggest a potential beneficial effect of treatment with capmatinib in high *MET*-amplified patients, including both treatment-naïve and pretreated (2/3L) patients, with ORRs of 40% and 29%, respectively. However, the endpoint of ORR was not reached in these cohorts [45]. These results were inconclusive with regards to the use of *MET* amplification as a biomarker for selecting patients for *MET*-targeted therapy.

In a recent study of 373 unselected patients with NSCLC who were

consecutively tested for GCN by FISH, the molecular subgroup with GCN ≥ 10 , which represented 2.1% of all patients, had a significantly shorter overall survival (HR = 3.61; median 8.2 months versus 23.6 months) compared with those with GCN < 10 and *MET* FISH-negative, nearly independent of chemotherapy and immune-checkpoint inhibitor treatment [21]. In a phase 1 clinical trial investigating capmatinib treatment in 55 *MET*-amplified patients (*MET*/CEP7 ≥ 2 or GCN ≥ 5 by FISH) with NSCLC refractory to currently available therapies or for which no effective treatment is available, the highest ORR to capmatinib of 47% was observed in patients with GCN ≥ 6 ($n = 15$) [43]. The definition of *MET* amplification as either GCN gain or *MET*/CEP7 ratio and appropriate cut-offs to predict response to treatment are still under debate and there are limited data on the frequency of different amplification levels in patients with NSCLC [62,63]. Therefore, a key challenge in interpreting efficacy data for patients with *MET* amplification is to further refine an appropriate, standardized, methodology for detection and defined cut-off value. For the reasons stated above, NGS may be the preferable approach for selecting patients who may benefit from treatment with *MET* inhibitors.

While *MET* TKIs hold promise for use in clinical practice, development of resistance has the potential to diminish their clinical efficacy. To improve clinical efficacy through the early identification of resistance, it is of utmost importance to understand the molecular mechanisms that regulate it. However, molecular mechanisms of acquired resistance to *MET* TKIs are poorly understood. On-target single and polyclonal genomic mutations in the *MET* kinase domain have been shown to mediate resistance to type I kinase inhibitors (such as crizotinib) in patients with NSCLC and *MET*ex14 [64,65]. Some off-target mechanisms of resistance, including mutations and amplifications in *KRAS*, *EGFR*, *HER 3*, and *BRAF* have also been reported [65]. Activation of the *EGFR* pathway due to overexpression of transforming growth factor α , bypassing the need for *MET* signaling to activate downstream signaling, and inactivation of NF2 concurrent with *NRG1* overexpression have also been demonstrated in *in vitro* studies [66,67]. Further understanding of these molecular mechanisms is required to devise sequential or combinatorial therapeutic strategies to overcome resistance.

Conclusions

Although no specific clinical characteristics have been identified in patients with *MET*ex14, patients are generally older than the general NSCLC population and have a poorer prognosis. Available evidence has demonstrated that patients with *MET*ex14 benefited from *MET*-targeted therapy with capmatinib, with preliminary evidence of activity against brain metastases in patients with NSCLC. These results, therefore, support the inclusion of *MET*ex14 testing in clinical panels to ensure that the benefit of this medicine that has been recently approved by the US FDA is extended to the appropriate patients. Currently, *MET*ex14 has the best predictive value for response to *MET* inhibitors, including capmatinib.

Declaration of Competing Interest

Y-LW received grants to his institute and personal speaker fees from AstraZeneca, Boehringer Ingelheim, Pfizer, BMS, and Roche, personal speaker fees from Eli Lilly, and was a principal investigator in a Novartis-sponsored clinical trial.

EFS received financial compensation for advisory boards and was an investigator in the GEOMETRY mono-1 clinical trial, with financial compensation to his institution from Novartis.

TMB was a principal investigator on clinical trials and received payments to his institution from AbbVie, Aileron Therapeutics, Amgen, ARMO BioSciences, Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Clovis Oncology, Calithera Biosciences, Daiichi Sankyo, Deciphera, Eli Lilly, Five Prime Therapeutics, Foundation Medicine, Genentech, GlaxoSmithKline, Ignyta, Immunocore, Immunogen, Incyte, Jacobio, Janssen, Karyopharm Therapeutics, Kolltan Pharmaceuticals,

Leap Therapeutics, Loxo, MabVax, MedPacto, Merck, MedImmune, Merrimack, Millennium, Moderna Therapeutics, Mirati Therapeutics, Novartis, Onyx, Peleton, Pfizer, Phosphatin Therapeutics, Principia Biopharma, Roche, Sanofi, Stemline Therapeutics, Takeda, and Top Alliance BioScience, and received personal or institutional consultancy fees or speaker bureau fees from Blueprint Medicines, BMS, Eli Lilly, Exelexis, Foundation Medicine, Guardant Health, Ignyta, Leap Therapeutics, Loxo, Moderna Therapeutics, and Pfizer and non-financial support (payment or reimbursement of exact amount of expenses) from Bayer, BMS, Eli Lilly, Foundation Medicine, Guardant Health, and Loxo.

Acknowledgements

Editorial support was provided by Ana Costa, PhD, and Oana Coban, PhD, from Chameleon Communications International with funding from Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, in accordance with Good Publication Practice (GPP3) guidelines (<http://www.ismpp.org/gpp3>).

Funding

This work was sponsored by Novartis Pharmaceuticals Corporation.

References

- [1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
- [2] Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. *Transl Lung Cancer Res* 2016;5:288–300.
- [3] Osmani L, Askin F, Gabrielson E, et al. Current WHO guidelines and the critical role of immunohistochemical markers in the subclassification of non-small cell lung carcinoma (NSCLC): moving from targeted therapy to immunotherapy. *Semin Cancer Biol* 2018;52:103–9.
- [4] Chan BA, Hughes BG. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. *Transl Lung Cancer Res* 2015;4:36–54.
- [5] Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018;29:iv192–237.
- [6] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). 2021.
- [7] Wu YL, Planchard D, Lu S, et al. Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. *Ann Oncol* 2019;30:171–210.
- [8] Awad MM, Oxnard GR, Jackman DM, et al. *MET* exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent *MET* genomic amplification and c-Met overexpression. *J Clin Oncol* 2016;34:721–30.
- [9] Onozato R, Kosaka T, Kuwano H, et al. Activation of *MET* by gene amplification or by splice mutations deleting the juxtamembrane domain in primary resected lung cancers. *J Thorac Oncol* 2009;4:5–11.
- [10] Tong JH, Yeung SF, Chan AW, et al. *MET* amplification and exon 14 splice site mutation define unique molecular subgroups of non-small cell lung carcinoma with poor prognosis. *Clin Cancer Res* 2016;22:3048–56.
- [11] Frampton GM, Ali SM, Rosenzweig M, et al. Activation of *MET* via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to *MET* inhibitors. *Cancer Discov* 2015;5:850–9.
- [12] Schrock AB, Frampton GM, Suh J, et al. Characterization of 298 patients with lung cancer harboring *MET* exon 14 skipping alterations. *J Thorac Oncol* 2016;11:1493–502.
- [13] Seo JS, Ju YS, Lee WC, et al. The transcriptional landscape and mutational profile of lung adenocarcinoma. *Genome Res* 2012;22:2109–19.
- [14] Vuong HG, Ho ATN, Altibi AMA, et al. Clinicopathological implications of *MET* exon 14 mutations in non-small cell lung cancer - A systematic review and meta-analysis. *Lung Cancer* 2018;123:76–82.
- [15] Reungwetwattana T, Liang Y, Zhu V, et al. 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. *Lung Cancer* 2017;103:27–37.
- [16] Smyth EC, Sclafani F, Cunningham D. Emerging molecular targets in oncology: clinical potential of *MET*/hepatocyte growth-factor inhibitors. *Oncotargets Ther* 2014;7:1001–14.
- [17] Nakamura T, Sakai K, Nakamura T, et al. Hepatocyte growth factor twenty years on: much more than a growth factor. *J Gastroenterol Hepatol* 2011;26(Suppl 1):188–202.
- [18] Yeung SF, Tong JHM, Law PPW, et al. Profiling of oncogenic driver events in lung adenocarcinoma revealed *MET* mutation as independent prognostic factor. *J Thorac Oncol* 2015;10:1292–300.

- [19] Cappuzzo F, Janne PA, Skokan M, et al. MET increased gene copy number and primary resistance to gefitinib therapy in non-small-cell lung cancer patients. *Ann Oncol* 2009;20:298–304.
- [20] Schildhaus HU, Schultheis AM, Ruschoff J, et al. MET amplification status in therapy-naïve adeno- and squamous cell carcinomas of the lung. *Clin Cancer Res* 2015;21:907–15.
- [21] Overbeck TR, Cron DA, Schmitz K, et al. Top-level MET gene copy number gain defines a subtype of poorly differentiated pulmonary adenocarcinomas with poor prognosis. *Transl Lung Cancer Res* 2020;9:603–16.
- [22] Go H, Jeon YK, Park HJ, et al. High MET gene copy number leads to shorter survival in patients with non-small cell lung cancer. *J Thorac Oncol* 2010;5: 305–13.
- [23] Novartis Pharmaceuticals Corporation. TABRECTA (Capmatinib) US Prescribing information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213591s000lbl.pdf. Accessed October 6, 2020.
- [24] Liu X, Jia Y, Stoopler MB, et al. Next-generation sequencing of pulmonary sarcomatoid carcinoma reveals high frequency of actionable MET gene mutations. *J Clin Oncol* 2016;34:794–802.
- [25] Liu SY, Gou LY, Li AN, et al. The unique characteristics of MET exon 14 mutation in chinese patients with NSCLC. *J Thorac Oncol* 2016;11:1503–10.
- [26] Heist RS, Shim HS, Gingipally S, et al. MET exon 14 skipping in non-small cell lung cancer. *Oncologist* 2016;21:481–6.
- [27] Imielinski M, Berger AH, Hammerman PS, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. *Cell* 2012;150:1107–20.
- [28] Govindan R, Ding L, Griffith M, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. *Cell* 2012;150:1121–34.
- [29] Kim EK, Kim KA, Lee CY, et al. Molecular diagnostic assays and clinicopathologic implications of MET exon 14 skipping mutation in non-small-cell lung cancer. *Clin Lung Cancer* 2019;20:e123–32.
- [30] Key differences between next-generation sequencing and Sanger sequencing. Available at <https://emea.illumina.com/science/technology/next-generation-se-quencing/ngs-vs-sanger-sequencing.html>. Accessed January 20, 2021.
- [31] Pennell NA, Mutebi A, Zhou Z-Y, et al. Economic impact of next-generation sequencing versus single-gene testing to detect genomic alterations in metastatic non-small-cell lung cancer using a decision analytic model. *JCO Precis Oncol* 2019;1–9.
- [32] Colomer R, Mondejar R, Romero-Laorden N, et al. When should we order a next generation sequencing test in a patient with cancer? *EclinicalMedicine* 2020;25: 100487.
- [33] Descarpentries C, Leprêtre F, Escande F, et al. Optimization of routine testing for MET exon 14 splice site mutations in NSCLC patients. *J Thorac Oncol* 2018;13: 1873–83.
- [34] Awad MM, Leonardi GC, Kravets S, et al. Impact of MET inhibitors on survival among patients with non-small cell lung cancer harboring MET exon 14 mutations: a retrospective analysis. *Lung Cancer* 2019;133:96–102.
- [35] Wolf J, Seto T, Han JY, et al. Results of the GEOMETRY mono-1 phase II study for evaluation of the MET inhibitor capmatinib (INC280) in patients (pts) with METΔex14 mutated advanced non-small cell lung cancer (NSCLC). *European Society for Medical Oncology*. Munich, Germany, 19–23 October 2018. Oral presentation LBA52.
- [36] Liu X, Wang Q, Yang G, et al. A novel kinase inhibitor, INCB28060, blocks c-MET-dependent signaling, neoplastic activities, and cross-talk with EGFR and HER-3. *Clin Cancer Res* 2011;17:7127–38.
- [37] Baltschukat S, Engstler BS, Huang A, et al. Capmatinib (INC280) is active against models of non-small cell lung cancer and other cancer types with defined mechanisms of MET activation. *Clin Cancer Res* 2019;25:3164–75.
- [38] Fujino T, Kobayashi Y, Suda K, et al. Sensitivity and resistance of MET exon 14 mutations in lung cancer to eight MET tyrosine kinase inhibitors in vitro. *J Thorac Oncol* 2019;14:1753–65.
- [39] Chakraborty S, Balan M, Flynn E, et al. Activation of c-Met in cancer cells mediates growth-promoting signals against oxidative stress through Nrf2-HO-1. *Oncogenesis* 2019;8:7.
- [40] Tang MK, Zhou HY, Yam JW, et al. c-Met overexpression contributes to the acquired apoptotic resistance of nonadherent ovarian cancer cells through a cross talk mediated by phosphatidylinositol 3-kinase and extracellular signal-regulated kinase 1/2. *Neoplasia* 2010;12:128–38.
- [41] Xiao GH, Jeffers M, Bellacosa A, et al. Anti-apoptotic signaling by hepatocyte growth factor/Met via the phosphatidylinositol 3-kinase/Akt and mitogen-activated protein kinase pathways. *Proc Natl Acad Sci USA* 2001;98:247–52.
- [42] Bang YJ, Su WC, Schuler M, et al. Phase 1 study of capmatinib in MET-positive solid tumor patients: dose escalation and expansion of selected cohorts. *Cancer Sci* 2020;111:536–47.
- [43] Schuler M, Berardi R, Lim WT, et al. Molecular correlates of response to capmatinib in advanced non-small-cell lung cancer: clinical and biomarker results from a phase I trial. *Ann Oncol* 2020;31:789–97.
- [44] Wolf J, Seto T, Han JY, et al. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. *N Engl J Med* 2020;383:944–57.
- [45] Groen HJM, Akerley W, Souquet P, et al. Capmatinib in patients with METex14-mutated or high-level MET-amplified advanced non-small-cell lung cancer (NSCLC): results from cohort 6 of the phase 2 GEOMETRY mono-1 study. *American Society of Clinical Oncology*. 29–31 May 2020. Poster 9520. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.9520. Accessed June 2, 2020.
- [46] Ali A, Goffin JR, Arnold A, et al. Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. *Curr Oncol* 2013;20:e300–6.
- [47] Barlesi F, Gervais R, Lena H, et al. Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multicenter phase II trial (GFPC 07–01). *Ann Oncol* 2011;22:2466–70.
- [48] Heist RS, Seto T, Han J-Y et al. Capmatinib (INC280) in METΔex14-mutated advanced non-small cell lung cancer (NSCLC): efficacy data from the phase 2 GEOMETRY mono-1 study. *Neuro Oncol* 2019; 21: vi56. Abstract CMET-22.
- [49] Rimassa L, Danesi R, Pressiani T, et al. Management of adverse events associated with tyrosine kinase inhibitors: improving outcomes for patients with hepatocellular carcinoma. *Cancer Treat Rev* 2019;77:20–8.
- [50] Califano R, Tariq N, Compton S, et al. Expert consensus on the management of adverse events from EGFR tyrosine kinase inhibitors in the UK. *Drugs* 2015;75: 1335–48.
- [51] VanderLaan PA, Rangachari D, Majid A, et al. Tumor biomarker testing in non-small-cell lung cancer: a decade of change. *Lung Cancer* 2018;116:90–5.
- [52] Drilon A, Wang L, Arcila ME, et al. Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches. *Clin Cancer Res* 2015;21:3631–9.
- [53] Howlader N, Noone AM, Krapcho M et al. SEER cancer statistics review (CSR) 1975–2017. National Cancer Institute. 2020. Available at: https://seer.cancer.gov/csr/1975_2017/. Accessed June 23, 2020.
- [54] Kim L, Tsao MS. Tumour tissue sampling for lung cancer management in the era of personalised therapy: what is good enough for molecular testing? *Eur Respir J* 2014;44:1011–22.
- [55] Schwartzberg LS, Horinouchi H, Chan D, et al. Liquid biopsy mutation panel for non-small cell lung cancer: analytical validation and clinical concordance. *NPJ Precis Oncol* 2020;4:15.
- [56] Gregg JP, Li T, Yoneda KY. Molecular testing strategies in non-small cell lung cancer: optimizing the diagnostic journey. *Transl Lung Cancer Res* 2019;8: 286–301.
- [57] Drilon A, Clark JW, Weiss J, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. *Nat Med* 2020;26:47–51.
- [58] Lockney NA, Wu AJ. Alectinib for the management of ALK-positive non-small cell lung cancer brain metastases. *J Thorac Dis* 2017;9:E152–4.
- [59] Lu S, Fang J, Cao L, et al. Preliminary efficacy and safety results of savolitinib treating patients with pulmonary sarcomatoid carcinoma (PSC) and other types of non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations. *American Association for Cancer Research Annual Meeting*. Atlanta, USA, March 29–April 3 2019. Abstract CT031. Available at: https://cancerres.aacrjournals.org/content/79/13_Supplement/CT031. Accessed June 2, 2020.
- [60] Heist R, Garon E, Tan D, et al. Biomarker analysis of patients with METΔex14 mutated non-small-cell lung cancer (NSCLC) treated with capmatinib in the GEOMETRY mono-1 study. *Mol Cancer Ther* 2019;18. Abstract A029.
- [61] Recondo G, Jr., Bahcall M, Sholl L, et al. Mechanisms of resistance to MET tyrosine kinase inhibitors in patients with MET exon 14 mutant non-small cell lung cancer. *World Conference on Lung Cancer*. 2019. Poster MA09.11. Available at: <https://doi.org/10.1016/j.jtho.2019.08.573>. Accessed June 2, 2020.
- [62] Fang L, Chen H, Tang Z, et al. MET amplification assessed using optimized FISH reporting criteria predicts early distant metastasis in patients with non-small cell lung cancer. *Oncotarget* 2018;9:12959–70.
- [63] Drilon A, Cappuzzo F, Ou S-HI, et al. Targeting MET in lung cancer: will expectations finally be MET? *J Thorac Oncol* 2017;12:15–26.
- [64] Ou SI, Young L, Schrock AB, et al. Emergence of preexisting MET Y1230C mutation as a resistance mechanism to crizotinib in NSCLC with MET exon 14 skipping. *J Thorac Oncol* 2017;12:137–40.
- [65] Recondo G, Bahcall M, Spurr LF, et al. Molecular mechanisms of acquired resistance to MET tyrosine kinase inhibitors in patients with MET exon 14-mutant NSCLC. *Clin Cancer Res* 2020;26:2615–25.
- [66] Qi J, McTigue MA, Rogers A, et al. Multiple mutations and bypass mechanisms can contribute to development of acquired resistance to MET inhibitors. *Cancer Res* 2011;71:1081–91.
- [67] Gimenez-Xavier P, Pros E, Bonastre E, et al. Genomic and molecular screenings identify different mechanisms for acquired resistance to MET inhibitors in lung cancer cells. *Mol Cancer Ther* 2017;16:1366–76.