Clinical Trial Protocol

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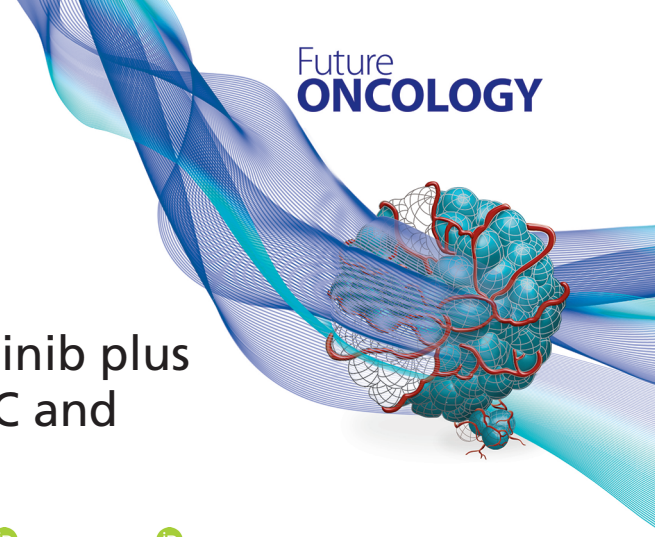

INSIGHT 2: a Phase II study of tepotinib plus osimertinib in *MET*-amplified NSCLC and first-line osimertinib resistance

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MET amplification *(MET*amp), a mechanism of acquired resistance to EGFR tyrosine kinase inhibitors, occurs in up to 30% of patients with non-small-cell lung cancer (NSCLC) progressing on first-line osimertinib. Combining osimertinib with a MET inhibitor, such as tepotinib, an oral, highly selective, potent MET tyrosine kinase inhibitor, may overcome *MET*amp-driven resistance. INSIGHT 2 (NCT03940703), an international, open-label, multicenter Phase II trial, assesses tepotinib plus osimertinib in patients with advanced/metastatic *EGFR*-mutant NSCLC and acquired resistance to first-line osimertinib and *MET*amp, determined centrally by fluorescence *in situ* hybridization (gene copy number ≥5 and/or *MET*/*CEP7* ≥2) at time of progression. Patients will receive tepotinib 500 mg (450 mg active moiety) plus osimertinib 80 mg once-a-day. The primary end point is objective response, and secondary end points include duration of response, progression-free survival, overall survival and safety.

Trial registration number: NCT03940703 (clinicaltrials.gov)

Lay abstract: Osimertinib is used to treat a type of lung cancer that has specific changes (mutations) in a gene called *EGFR*. Although tumors will usually shrink (respond) during treatment with osimertinib, they can stop responding, or become resistant, to osimertinib. A common cause of resistance is '*MET* amplification,' which describes when extra copies of a gene called *MET* are present. Lung cancer that is resistant to osimertinib due to *MET* amplification could be treated by combining osimertinib with a treatment that blocks MET, such as tepotinib. INSIGHT 2 is an ongoing study that is designed to learn about the effects and safety of tepotinib combined with osimertinib, in patients with lung cancer that has stopped responding to osimertinib because of *MET* amplification.

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Keywords: EGFR tyrosine kinase inhibitors • *MET* amplification • non-small-cell lung cancer • osimertinib • tepotinib

Introduction to the INSIGHT 2 trial

Here, we describe the rationale and design of the INSIGHT 2 trial (NCT03940703; EudraCT 2019-001538-33), a global, two-arm, open-label, Phase II trial assessing the efficacy, safety and tolerability of tepotinib plus osimertinib in patients with advanced/metastatic non-small-cell lung cancer (NSCLC) harboring activating *EGFR* mutations, who have progressed on first-line osimertinib and have *MET* amplification (*MET*amp).

Background & rationale

EGFR mutations are a common oncogenic driver in patients with metastatic NSCLC and are a predictive marker for response to EGFR tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib and icotinib (first generation), afatinib and dacomitinib (second generation) and osimertinib (third generation) [1–4]. Initially, first- and second-generation EGFR TKIs became standard of care first-line therapy for *EGFR*-mutant NSCLC, following Phase III trials demonstrating superior efficacy over chemotherapy (Supplementary Table 1) [5]. The most common TKI-sensitizing EGFR mutations are exon 19 deletions and L858R point mutations in exon 21; however, uncommon EGFR mutations occur in 10–20% of patients with *EGFR*-mutant NSCLC and confer varying sensitivity to different EGFR TKIs [6]. Importantly, *EGFR* T790M confers resistance to first- and second-generation EGFR TKIs [5,7].

Osimertinib differs from early-generation EGFR TKIs as it potently and selectively inhibits both EGFR-TKI-sensitizing and *EGFR* T790M resistance mutations [7]. The efficacy and safety of osimertinib for metastatic *EGFR*-mutant NSCLC has been demonstrated in two Phase III trials (AURA 3 and FLAURA) [8,9]. The AURA 3 trial evaluated 419 patients with *EGFR* T790M-positive NSCLC who had disease progression after a first-line EGFR TKI. In AURA 3, osimertinib demonstrated greater efficacy than platinum-pemetrexed chemotherapy (n = 279 vs n = 140; median progression-free survival [PFS] was 10.1 vs 4.4 months; hazard ratio [HR] = 0.30 [95% CI: 0.23, 0.41]) and fewer Grade ≥3 adverse events (23 vs 47%) [8]. Osimertinib was initially approved to treat patients with metastatic *EGFR* T790M-positive NSCLC who had progressed on or after an EGFR TKI [10].

In the FLAURA trial, which assessed 556 patients with *EGFR*-mutant metastatic NSCLC, first-line osimertinib (n = 279) demonstrated superior efficacy to gefitinib or erlotinib (n = 277), with longer median PFS (18.9 vs 10.2 months; HR = 0.46 [95% CI: 0.37, 0.57]), and a comparable safety profile to gefitinib or erlotinib and lower rates of Grade ≥3 adverse events [9]. Patients were stratified by race, and the median PFS with osimertinib was 16.6 months (95% CI: 13.8, 20.7) in the Asian population (n = 174) and 24.3 months (95% CI: 16.4, not calculable) in the non-Asian population (n = 105) [9,11]. Clinical practice data for first-line osimertinib are comparable to data reported in FLAURA. In Caucasian patients, the MYKONOS study in the USA (n = 548) reported a median time to next treatment or death of 17.9 months (95% CI: 16.2, 23.6) and the FLOWER study in Italy (n = 126) reported a median PFS of 18.9 months (95% CI: 11.2, 26.7) [12,13]. In Asian patients, a study in Japan (n = 326) reported a median time to discontinuation of 20.5 months (95% CI: 13.8, not reached) [14], and a study in Singapore (n = 66) reported a median PFS of 16.7 months (95% CI: 13.2, 20.9) [15].

Osimertinib has now become the standard of care for the first-line management of metastatic *EGFR*-mutant NSCLC based on the results reported in the pivotal FLAURA trial [9]. In another Phase III trial, ADAURA, patients with *EGFR*-mutant early-stage (II–IIIA) NSCLC after complete surgical resection (n = 682) had significantly longer 24-month disease-free survival with adjuvant osimertinib (n = 339) than placebo (n = 343) (90 vs 44%; HR = 0.17 [99.06% CI: 0.11, 0.26]), with no new safety concerns reported [16]. In December 2020, the US FDA approved osimertinib as adjuvant treatment following tumor resection in patients with *EGFR*-mutant NSCLC, and osimertinib is included in the guidelines for this patient population [17].

Although first-line osimertinib can provide effective disease control in patients with NSCLC, most patients develop resistance after approximately 16–20 months of treatment [9,12–15]. Apart from chemotherapy, there are no further clear-cut therapeutic options for *EGFR*-mutant NSCLC after progression on osimertinib, representing a clear unmet medical need [10,18,19]. Outcomes with chemotherapy in a post-EGFR TKI setting are not very encouraging; in the chemotherapy arm (n = 132) of the IMPRESS study, the median PFS was low (5.4 months) in patients with *EGFR*-mutant NSCLC with progression on first-line gefitinib [20]. In the INSIGHT study, patients

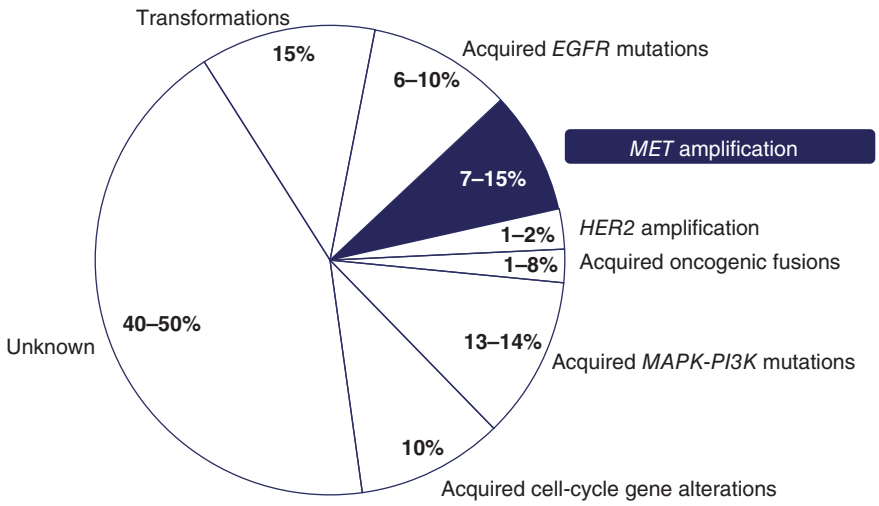

Figure 1. Resistance mechanisms to first-line osimertinib. Resistance mechanisms to first-line osimertinib were identified in tissue/and or liquid biopsies [10].
MAPK: Mitogen-activated protein kinase; MET: Mesenchymal–epithelial transition factor; PI3K: Phosphoinositide 3-kinase.
Adapted with permission from [10].

with *EGFR*-mutant NSCLC with MET-driven resistance mechanisms to EGFR TKIs who received chemotherapy (n = 24) had a median PFS of 4.4 months [21]. The IMpower150 trial, which evaluated the combination of a checkpoint inhibitor, atezolizumab (anti-PD-L1) with bevacizumab and platinum-doublet chemotherapy in a subgroup patients with sensitizing *EGFR* mutation who had previously received EGFR TKI therapy (n = 50, of whom five received prior osimertinib), showed an improvement in overall survival (OS) versus bevacizumab and platinum-doublet chemotherapy only (HR = 0.39 [95% CI: 0.14, 1.07]), as well as an improved median PFS of 9.7 versus 6.1 months (HR = 0.42 [95% CI: 0.22, 0.80]), respectively [22]. The ORIENT-31 study, which evaluated 444 patients with progression after EGFR TKI therapy (8.1% of whom received first-line third-generation EGFR TKIs), reported a median PFS of 6.9 months in patients receiving the checkpoint inhibitor sintilimab (anti-PD-1) plus a bevacizumab biosimilar plus chemotherapy (Arm A), 5.6 months in patients receiving sintilimab plus chemotherapy (Arm B; A vs B, HR = 0.726 [95% CI: 0.528, 0.998]) and 4.3 months in patients receiving chemotherapy (Arm C; A vs C, HR = 0.464 [95% CI: 0.337, 0.639]) [23]. The use of checkpoint inhibitors with/without an antiangiogenic in combination with chemotherapy requires further investigation as a treatment option following progression on first-line osimertinib.

The type and pattern of disease progression with osimertinib can vary, as demonstrated in FLOWER, an observational multicenter study in patients with *EGFR*-mutant advanced NSCLC receiving first-line osimertinib. In this study, progressive disease (PD) was reported in 34.9% of patients (44/126), of whom 18.2% (8/44) had isolated PD (appearance or growth of one lesion), 20.5% (9/44) had oligoprogression (in $\leq$3 lesions in two organs), 54.5% (24/44) had systemic progression (appearance or progression in >3 lesions) and 6.8% (3/44) had an unknown type of progression; the most frequent PD sites were lung, bone and brain [13]. Osimertinib-acquired resistance mechanisms can be broadly divided into EGFR-dependent (e.g., acquired *EGFR* mutations) and EGFR-independent mechanisms of resistance by activation of alternative bypass pathways (e.g., *HER2* amplification, RAS-MAPK pathway aberrations, *MET*amp, and histologic transformation) (Figure 1). A fast time to PD occurs when resistance is mediated by transformation to small-cell lung cancer; an intermediate time to PD occurs when resistance is driven by *MET*amp; and a longer time to PD occurs through the development of *EGFR* C797S resistance mutations [10,24].

In terms of EGFR-independent mechanisms, *MET*amp is the most commonly acquired resistance mechanism to osimertinib, with an estimated occurrence of 7–15% of patients who progress on first-line osimertinib therapy. However, this has been reported in up to 30% of patients, and incidence may vary depending on both the method used and criteria applied for detecting *MET*amp [10,25,26]. In 186 patients with *EGFR*-mutant lung cancer, for the most recent EGFR TKI treatment, the median PFS was shorter in patients with *MET*amp (n = 30) than in

Table 1. Assay methods and the prevalence of *MET*amp in studies of patients with *EGFR*-mutant non-small-cell lung cancer with acquired osimertinib resistance.

Author (year), study or center	Line of therapy	Patients (n)	*MET*amp	Assay method and criteria	Ref.
Tissue biopsy					
Bauml *et al.* (2021), ATOMIC registry†	1L/2L+	94	16 (17%)	NR	[31]
Piotrowska *et al.* (2018), MGH†	1L/2L+	32	7 (22%)	*MET*/*CEP7* ratio ≥2.2 by FISH	[32]
Roper *et al.* (2020)	1L	9	6 (66%)	*MET*/*CEP7* ratio ≥2.0 or mean *MET* ≥6 copies per cell by FISH	[33]
Schoenfeld *et al.* (2020), MSK	1L 2L+	27 35	2 (7%) 2 (6%)	NGS (*MET*amp criteria NR; fold-change ranged from 1.5 to 4.0 and copy number from 5 to 23)	[34]
Oxnard *et al.* (2018)	2L‡	41	4 (10%)	NGS or FISH (*MET*amp criteria NR)	[24]
Lin *et al.* (2018), AURA Asian Cohort	2L	10	5 (50%)	*MET*/*CEP7* ratio ≥5:1 by FISH	[39]
Liquid biopsy					
Bauml *et al.* (2021), ATOMIC†	1L/2L+	87	9 (10.3%)	NR	[31]
Piotrowska *et al.* (2018), MGH†	1L/2L+	22	5 (23%)	ctDNA: mean plasma copy number ≥2.1	[32]
Guibert *et al.* (2018)	NR	25	1 (4%)	Amplicon-based NGS using InVision™ (*MET*amp criteria NR)	[36]
Le *et al.* (2018), MDACC, MCC	2L§	42	6 (14%)	Guardant Health; Guardant360 (*MET*amp criteria NR)	[37]
Papadimitrakopoulou *et al.* (2018), AURA 3	2L	73	14 (19%)	ctDNA using NGS, Guardant Health (*MET*amp criteria NR)	[38]
Wang *et al.* (2018), Chinese Cohort	2L	13	4 (31%)	ctDNA using NGS (*MET* CNG threshold 2.3 normalized to control)	[25]
Yang *et al.* (2018), Chinese Cohort	2L¶	93	5 (5%)	cfDNA using NGS (CNG ≥1.5)	[40]
Cho *et al.* (2018), FLAURA	1L	91	14 (15%)	ctDNA, Guardant Health (*MET*amp criteria NR)	[41]

†Studies reported both tissue and liquid biopsy results from the same patient population and, as such, a subset of patients in these studies are included in both datasets [31,32].
‡Includes one patient with plasma sample and *MET*amp by NGS [24].
§Tissue samples were also evaluated using MD Anderson Molecular Diagnostic Laboratory test [37].
¶Includes one patient with 1L treatment [40].
1L: First line; 2L+: Second line and above; *CEP7*: Centromere of chromosome 7; cfDNA: Cell-free DNA; CNG: Copy number gain; ctDNA: Circulating tumor DNA; FISH: Fluorescence *in situ* hybridization; MCC: Moffit Cancer Center; MDACC: MD Anderson Cancer Center; MET: Mesenchymal–epithelial transition factor; *MET*amp: *MET* amplification; MGH: Massachusetts General Hospital; MSK: Memorial Sloan Kettering; NGS: Next-generation sequencing; NR: Not reported; NSCLC: Non-small-cell lung cancer.

patients without *MET*amp (median PFS, 7.0 vs 10.4 months; HR = 0.898 [95% CI: 0.84, 0.97]) [27]. A shorter time to treatment failure with first-line osimertinib was reported in patients with *MET*amp (n = 8), as detected by fluorescence *in situ* hybridization (FISH), compared with patients for whom *MET*amp was not detected (n = 58) (HR = 3.33; p = 0.01) [15]. Clinical characteristics associated with a high probability of *MET*amp include a history of smoking, less intracranial progression, and a short PFS on the most recent TKI [27].

FISH is the gold standard for detecting *MET*amp [28,29], which can largely be missed by current next-generation sequencing (NGS) assays [26,30]. However, *MET*amp is part of many NGS tissue biopsy (TBx) and liquid biopsy (LBx) panels, and the technology is still evolving to more accurately determine *MET*amp [9,29,30]. With the current assays available, *MET*amp detected by FISH is a more predictive marker of clinical response with MET inhibitors than *MET*amp detected by NGS (in either TBx or LBx) or MET overexpression by immunohistochemistry (IHC) [30]. Table 1 shows the prevalence of *MET*amp in different studies in patients with *EGFR*-mutant NSCLC and acquired osimertinib resistance, in the range of 6–66% with TBx and 4–31% with LBx [31–41].

In patients with *EGFR*-mutant NSCLC and *MET*amp, the concurrent inhibition of both MET and EGFR may potentially overcome resistance to single EGFR TKI therapy [18,35,42–44]. Patients with *EGFR*-mutant NSCLC and *MET*amp with disease progression on EGFR TKI treatment, who were subsequently treated with a MET inhibitor and EGFR TKI combination, experienced clinical benefit in Phase I/II studies (Table 2) [45,46].

Tepotinib is a once-daily (QD), orally available, potent and highly selective MET TKI that blocks MET-mediated signaling pathways involved in tumorigenesis [43,45,46,50–53]. Tepotinib is approved for the treatment of adult patients with metastatic NSCLC harboring *MET* exon 14 skipping alterations at a dose of 500 mg QD (450 mg active moiety) with food, until disease progression or unacceptable toxicity [37,53]. In preclinical models, tepotinib was able to overcome acquired resistance to EGFR TKIs due to *MET*amp [21,51]. In a Phase I trial in patients with advanced solid tumors, tepotinib was well tolerated with clinical activity in MET-dysregulated tumors [53]. Based on the activity of tepotinib combined with an EGFR TKI in preclinical models, and the potential

Table 2. Selected studies of MET inhibitors combined with EGFR tyrosine kinase inhibitors in patients with *EGFR*-mutant non-small-cell lung cancer and *MET*amp after progression on an EGFR tyrosine kinase inhibitor.

Author (year), study	Prior EGFR TKIs (n)	EGFR TKI + METi combination	Patients assessed for efficacy (n)	*MET*amp assay method	Efficacy	Safety	Ref.
Sequist *et al.* (2020), TATTON	≥1 prior EGFR TKI	Osimertinib 80 mg QD + savolitinib 600 mg QD	69 in Phase Ib part B1[†]	*MET*/*CEP7* ratio ≥2 by FISH	• ORR: 30% (21/69, all PR) • DCR: 75% (52/69) • mDOR: 7.9 months (95% CI: 4.0, 10.5) • mPFS: 5.4 months (95% CI: 4.1, 8.0)	• Assessed in all part B (n = 138) • AEs Grade ≥3: 57% • Most common AEs (any grade): nausea (49%), fatigue (35%), decreased appetite (34%)	[45]
Yu *et al.* (2021), ORCHARD	A prior EGFR TKI[‡]	Osimertinib 80 mg QD + savolitinib 300 or 600 mg QD	17 with *MET*amp or *MET* exon 14 skipping	Tumor biopsy with NGS (criteria NR; GCN ranged from 7 to 68)	• ORR: 41% (7/17, all PR) • DCR: 82% (14/17)	• Assessed in all patients (n = 20) • AEs Grade ≥3: 30% • Most common AEs (any grade): NR	[47]
Wu *et al.* (2018)	≥1 prior EGFR TKI	Gefitinib 250 mg QD + capmatinib 400 mg BID	36 with *MET*amp (GCN) in Phase II	*MET* GCN ≥6 by FISH	• ORR: 47% (17/36, all PR) • DCR: 75% (27/36) • mPFS: 5.5 months (95% CI: 4.2, 7.3)	• Assessed in all Phase Ib and II patients (n = 161) • AEs Grade 3/4: 57% • Most common AEs (any grade): nausea (36%), deceased appetite (32%), peripheral edema (30%)	[46]
Wu *et al.* (2020), INSIGHT	A prior EGFR TKI	Gefitinib 250 mg QD + tepotinib 500 mg QD (450 mg active moiety) vs CT	19 (12 on combination and 7 on CT) *EGFR* T790M-negative in Phase II	*MET* GCN ≥5 and/or *MET*/*CEP7* ratio ≥2 by FISH	In *EGFR* T790M-negative: • Tepotinib + gefitinib vs CT • ORR: 67 vs 43% • mDOR: 19.9 vs 2.8 months • mPFS: 16.6 vs 4.2 months • mOS: 37.3 vs 13.1 months	• Assessed in Phase II patients treated with gefitinib + tepotinib (n = 31) • AEs Grade ≥3: 65% • Most common AEs (any grade): diarrhea (58%), peripheral edema (39%), increased amylase (36%)	[21]
Yang *et al.* (2021)	A prior EGFR TKI	Gefitinib 250 mg QD + savolitinib 600 mg QD	23 *EGFR* T790M-negative in Phase Ib	*MET* GCN ≥5 or *MET*/*CEP7* ratio ≥2 by FISH	In *EGFR* T790M-negative: • ORR: 52% (12/23) • mDOR: 7.2 months • mPFS: 4.2 months (95% CI: 3.5, 8.5)	• Assessed in safety run-in + expansion (n = 57) • AEs Grade ≥3: 37% • Most common AEs (any grade): vomiting (46%), nausea (40%), AST increased (39%)	[48]
McCoach *et al.* (2021)	≥1 prior EGFR TKI	Erlotinib 150 mg QD + capmatinib 400 mg BID	Two patients had *MET*amp in Cohort A (*EGFR*-mutant NSCLC and acquired TKI resistance)	Patient 22: NGS (>10 copies) and *MET*/*CEN7* ratio 1.1 by FISH; Patient 21: NGS and *MET*/*CEN7* ratio 3.4 by FISH	In *EGFR* T790M-negative: • Patient 22 had a complete response • Patient 21 was not evaluable for response	• Assessed in all patients (n = 35) • AEs Grade ≥3: NR (TRAEs Grade ≥3: 34.2%) • Most common AEs: NR (TRAEs [any grade]: acneiform rash [62.9%], fatigue [51%], nausea [45.7%])	[49]

[†] Cohort B1 in the TATTON study includes *MET*amp *EGFR*-mutant NSCLC patients who had previously received a third-generation EGFR TKI [45].
[‡] Received only one line of prior therapy, single agent osimertinib (i.e., osimertinib-resistant) [47].
AE: Adverse event; AST: Aspartate aminotransferase; BID: Twice daily; *CEP7* (also known as *CEN7*): Centromere of chromosome 7; CT: Chemotherapy; DCR: Disease control rate (complete response + partial response + stable disease); FISH: Fluorescence *in situ* hybridization; GCN: Gene copy number; mDOR: Median duration of response; MET: Mesenchymal–epithelial transition factor; *MET*amp: *MET* amplification; METi: MET inhibitor; mOS: Median overall survival; mPFS: Median progression-free survival; NGS: Next-generation sequencing; NR: Not reported; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; PR: Partial response; QD: Once daily; TKI: Tyrosine kinase inhibitor; TRAE: Treatment-related adverse event.

for the combination to overcome EGFR TKI resistance in NSCLC due to *MET*amp, a study of tepotinib plus the EGFR TKI gefitinib was conducted [21]. The efficacy and safety of tepotinib plus gefitinib was compared with chemotherapy in INSIGHT, a Phase Ib/II, open-label, randomized trial in patients with relapsed *EGFR*-mutant NSCLC with MET overexpression IHC2+ and IHC3+ and/or *MET*amp (gene copy number [GCN] ≥5 and/or *MET*/*CEP7* ratio ≥2) with acquired resistance to EGFR TKIs [21]. In 19 patients with *MET*amp (12 patients in the tepotinib plus gefitinib arm and seven patients in the chemotherapy arm), treatment with tepotinib plus gefitinib showed improvement over chemotherapy in investigator-reported median PFS (16.6 vs 4.2 months [HR = 0.13; 90% CI: 0.04, 0.43]), median OS (37.3 vs 13.1 months [HR = 0.08; 90% CI: 0.01, 0.51]), objective response rate

Table 3. Overview of INSIGHT 2 protocol changes.

Key changes to protocol in April 2020	Rationale
Enrollment eligibility of patients was changed: From version 1 of the protocol: Eligible patients must have advanced/metastatic NSCLC harboring activating *EGFR* mutations with acquired resistance to prior first- to third-generation EGFR TKIs, with *MET*amp To version 2 of the protocol: Eligible patients must have advanced/metastatic NSCLC harboring activating EGFR mutations, who have progressed on first-line osimertinib due to *MET*amp	Ensures that the study is relevant to real-world clinical practice, following the emergence of osimertinib as preferred first-line therapy
Introduction of a tepotinib 500 mg (450 mg active moiety) monotherapy arm	Enables the assessment of the clinical benefit of tepotinib monotherapy
The inclusion of TBx by FISH for prescreening *MET* resistance mutations, and the primary objective now includes the assessment of tepotinib and osimertinib in patients with *MET*amp by FISH by TBx	NGS (LBx) underestimate *MET* resistance mutations in patients with NSCLC. The protocol was changed to include TBx to detect *MET*amp; this was done due to the low detection rate using LBx NGS. FISH is currently considered to be the gold standard for detection of *MET*amp to predict benefit of MET-targeted therapy

FISH: Fluorescence *in situ* hybridization; LBx: Liquid biopsy; MET: Mesenchymal–epithelial transition factor; *MET*amp: *MET* amplification; NGS: Next-generation sequencing; NSCLC: Non-small-cell lung cancer; TBx: Tissue biopsy; TKI: Tyrosine kinase inhibitor.

(ORR; 67 vs 43% [odds ratio, 2.67; 90% CI: 0.37, 19.56]) and median duration of response (DOR; 19.9 [90% CI: 7.0, not estimable] vs 2.8 months [90% CI: 2.8, 9.7]) (Figure 2) [21]. These findings suggest improved clinical activity for tepotinib plus gefitinib compared with standard chemotherapy in patients with *EGFR*-mutant NSCLC and *MET*amp [21]. In the long-term follow-up of 18 patients with *MET*amp who received tepotinib plus gefitinib in INSIGHT (six patients in Phase Ib and 12 patients in Phase II), the treatment duration was more than 1 year in eight patients (44.4%) and more than 4 years in three patients (16.7%). The time on treatment ranged from 13.1 to 56.5+ months for these eight patients, seven of whom had a partial response and one had stable disease as best response [54].

An unmet need exists for targeted treatments for patients with *EGFR*-mutant NSCLC who develop resistance to EGFR TKIs through *MET*amp [21,55]. Osimertinib is a standard of care for first-line therapy in *EGFR*-mutant NSCLC, and *MET*amp is a common mechanism of resistance to osimertinib; therefore, the observations that tepotinib was able to overcome acquired resistance to EGFR TKIs due to *MET*amp in preclinical and clinical studies provide a strong rationale to evaluate the combination of tepotinib and osimertinib in this patient population [9,21,53–55]. Here, we discuss the trial design of INSIGHT 2, a clinical trial assessing the efficacy and safety of the tepotinib and osimertinib combination in *EGFR*-mutant NSCLC with acquired resistance to first-line osimertinib due to *MET*amp.

INSIGHT 2 trial

Study design

INSIGHT 2 (NCT03940703) is a global, two-arm, open-label, Phase II trial assessing the efficacy, safety and tolerability of tepotinib plus osimertinib in patients with advanced/metastatic NSCLC harboring activating *EGFR* mutations, who have progressed on first-line osimertinib and have *MET*amp (Figures 3 & 4).

The study began in September 2019 (17 countries are expected to participate; Figure 5) and a key protocol amendment was performed in April 2020 (Table 3). The key protocol amendment was a change from LBx to TBx to detect *MET*amp in order to improve the robustness of the detection and to avoid the potential underestimation of *MET*amp with LBx NGS due to nonshedding tumors [26,28–31,56]. Furthermore, the protocol amendment restricted enrollment to patients with *EGFR*-mutant NSCLC who have progressed on first-line osimertinib, and introduced a tepotinib monotherapy arm to assess the contribution of tepotinib to the activity of the combination.

The trial consists of a safety run-in period, followed by a main treatment period. The safety run-in was performed to determine the recommended Phase II dose (RP2D) of tepotinib plus osimertinib by assessing dose-limiting toxicities during the first treatment cycle. The safety run-in period was completed in August 2020. Patients received tepotinib 500 mg QD (450 mg active moiety) plus osimertinib 80 mg QD, and no dose-limiting toxicities were identified among six patients who had completed Cycle 1 of treatment. The RP2D for the combination is, therefore, tepotinib 500 mg QD (450 mg active moiety) plus osimertinib 80 mg QD, both of which are also the previously determined recommended monotherapy doses [51,53,57].

Initially, eligible patients detected as positive for *MET*amp by central or local FISH testing were randomly assigned in a ratio of 2:1 to either the combination of tepotinib plus osimertinib or tepotinib alone. Following the enrollment of 12 patients in the monotherapy arm with *MET*amp centrally tested by FISH, all subsequent patients

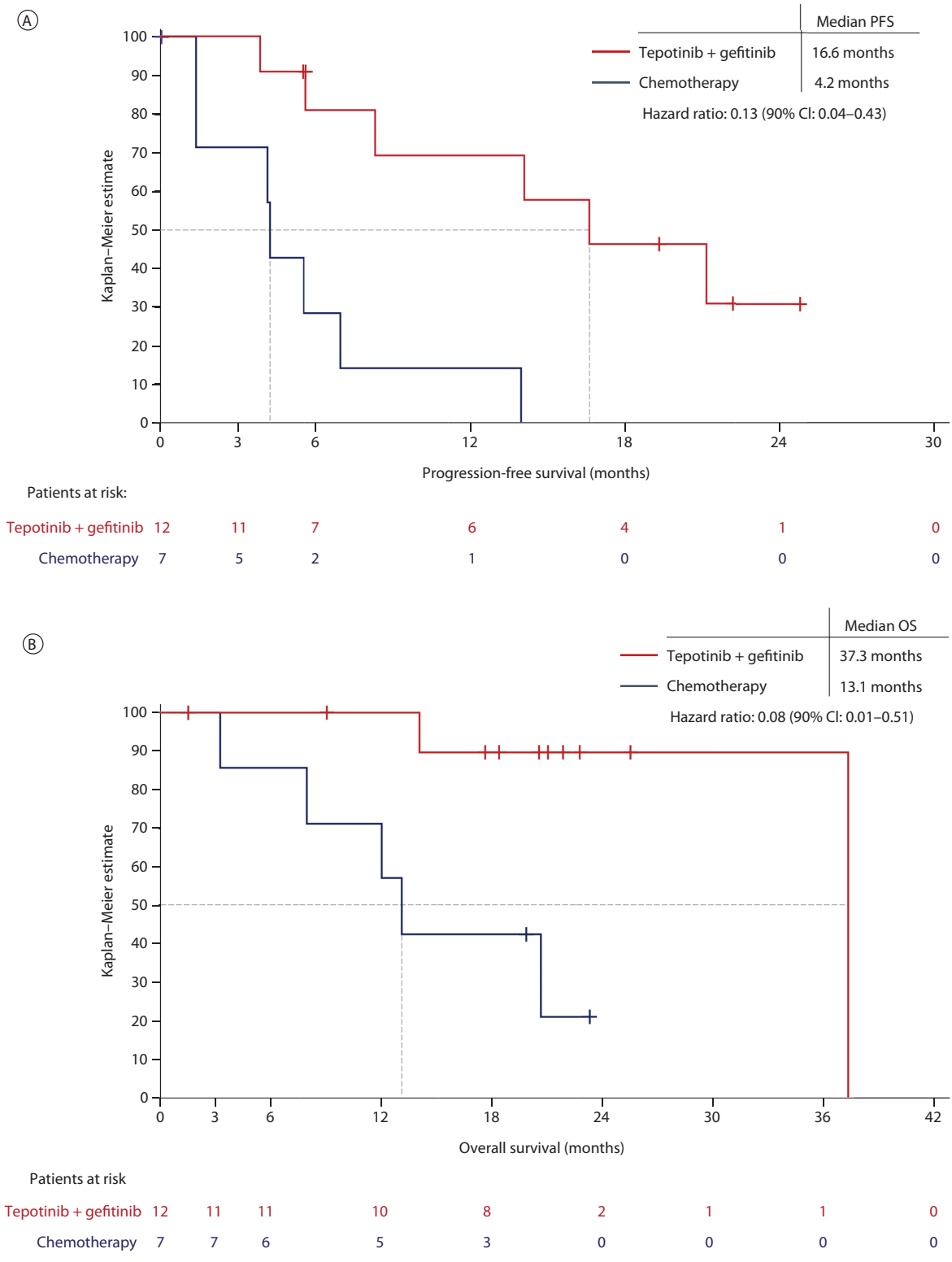

Figure 2. Kaplan-Meier estimates in patients treated with tepotinib plus gefitinib or chemotherapy for untreated *MET*-amplified *EGFR*-mutant non-small cell lung cancer in the INSIGHT study; (A) PFS or (B) OS.
Censored data are indicated by tick marks.
MET: Mesenchymal–epithelial transition factor; OS: Overall survival; PFS: Progression-free survival.
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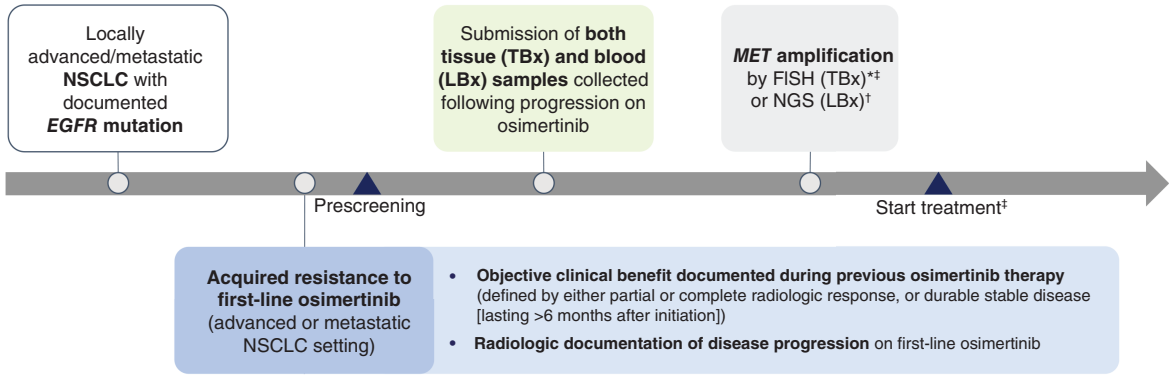

Figure 3. Molecular testing prior to enrollment in INSIGHT 2.
*GCN ≥5 and/or *MET*/*CEP7* ratio ≥2 by TBx.
†GCN ≥2.3 by LBx.
‡If local FISH-positive results are available, treatment can start without waiting for central confirmation.
CEP7: Centromere of chromosome 7; FISH: Fluorescence *in situ* hybridization; GCN: Gene copy number; LBx: Liquid biopsy; MET: Mesenchymal–epithelial transition factor; NSCLC: Non-small-cell lung cancer; TBx: Tissue biopsy.

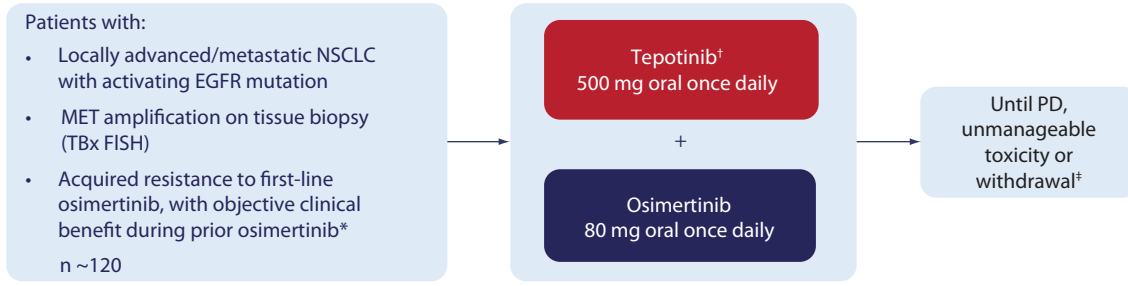

Figure 4. INSIGHT 2 study design.
*Objective clinical benefit documented during previous osimertinib therapy defined by either partial or complete radiologic response, or durable stable disease lasting more than 6 months after initiation.
†Initially, eligible patients who were detected to be positive for *MET*amp were randomly assigned in a ratio of 2:1 to either the combination of tepotinib and osimertinib or tepotinib alone until 12 patients with *MET*amp centrally tested by FISH (TBx) were enrolled in the monotherapy arm. After this, all patients are assigned to the combination. Patients who were randomized to the tepotinib monotherapy will have the opportunity to switch over to the combination at the time of disease progression.
‡Treatment continues until disease progression, death, an adverse event leading to discontinuation, study withdrawal or consent withdrawal.
FISH: Fluorescence *in situ* hybridization; MET: Mesenchymal–epithelial transition factor; *MET*amp: *MET* amplification; NSCLC: Non-small-cell lung cancer; PD: Progressive disease; TBx: Tissue biopsy.

are assigned to the combination (Figure 4). Patients who were randomized to tepotinib monotherapy will have the opportunity to switch over to the combination at the time of disease progression, which is determined by an independent review committee (IRC). For both the monotherapy and combination arms of the study, treatment continues until disease progression, death, an adverse event leading to discontinuation, study withdrawal or consent withdrawal.

Eligibility criteria

Study entry is limited to adults ≥18 years of age, with locally advanced or metastatic NSCLC, activating *EGFR* mutations and the presence of ≥1 independently verified measurable lesion (Table 4). Patients must have *MET*amp determined by central or local FISH testing (GCN ≥5 and/or *MET*/*CEP7* ratio ≥2) or *MET*amp determined by central LBx using NGS (GCN ≥2.3), received first-line therapy with osimertinib and acquired resistance with radiologic documentation of disease progression on first-line osimertinib, and have had an objective clinical benefit documented during previous osimertinib therapy (defined by either partial or complete radiologic response, or durable stable disease [lasting >6 months after initiation]). Criteria for *MET*amp in each assay were defined

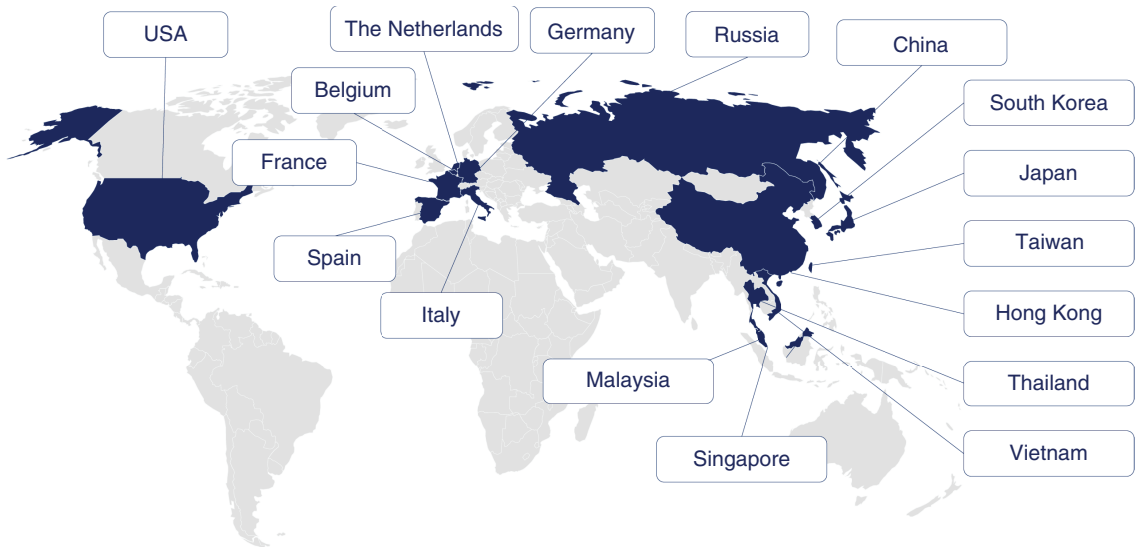

Figure 5. Countries involved in the INSIGHT 2 study.

Table 4. INSIGHT 2 key inclusion and exclusion criteria.

Key inclusion criteria	Key exclusion criteria
≥18 years of age	Any unresolved NCI-CTCAE Grade ≥2 toxicity from previous therapies
Locally advanced or metastatic NSCLC with activating *EGFR* mutation	Inadequate hematologic, liver, renal or cardiac function
Presence of ≥1 independently verified measurable lesion	History of interstitial lung disease
MET amplification determined by FISH (GCN ≥5 and/or *MET*/*CEP7* ratio ≥2) by TBx, or NGS (GCN ≥2.3) by LBx	Contraindication to osimertinib
Received only first-line therapy with osimertinib for advanced or metastatic NSCLC and acquired resistance on previous first-line osimertinib	Prior HGF/MET pathway-targeted therapy
ECOG PS 0–1	Participation in another interventional clinical study within 30 days prior to first dose (except in studies where the investigational product was osimertinib as the first-line of therapy)
Life expectancy ≥12 weeks	

CEP7: Centromere of chromosome 7; ECOG PS: Eastern Cooperative Oncology Group performance status; FISH: Fluorescence *in situ* hybridization; GCN: Gene copy number; HGF: Hepatocyte growth factor; LBx: Liquid biopsy; MET: Mesenchymal–epithelial transition factor; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NGS: Next-generation sequencing; NSCLC: Non-small cell lung cancer; TBx: Tumor biopsy.

according to the manufacturer's instruction manual, and were aligned with available literature at the time of study design [58,59]. Enrollment is allowed based on local FISH testing while awaiting central confirmation of *MET*amp.

Key exclusion criteria were spinal cord compression or brain metastasis unless asymptomatic, stable or not requiring steroids for at least 2 weeks prior to start of study intervention, any unresolved National Cancer Institute-Common Terminology Criteria for Adverse Events Grade ≥2 toxicity from previous therapies, inadequate hematologic, liver, renal or cardiac function, and a history of interstitial lung disease. Patients must not have a contraindication to osimertinib and must not have had prior hepatocyte growth factor/MET pathway-targeted therapy or be participating in another interventional clinical study within 30 days prior to the first dose.

Planned sample size

The study is estimated to enroll 120 patients, with 80 patients planned for the primary analysis set (i.e., 80 patients with advanced or metastatic *EGFR*-mutant NSCLC and *MET*amp determined centrally by FISH [TBx] treated with the combination of tepotinib plus osimertinib) and 12 patients planned for the monotherapy arm. Assuming an ORR of 50% for the combination of tepotinib and osimertinib, a sample size of 80 in the primary analysis set gives a 78% probability of the 95% CI lower bound being observed above the assumed 35% ORR for standard of care. Assumptions for ORRs of tepotinib and osimertinib or standard of care were based on the available literature at the time of the study design [20,45,60,61].

Planned study period

Enrollment began in September 2019. The primary analysis will be conducted once all patients with *MET*amp centrally tested by FISH have either been treated with tepotinib 500 mg QD (450 mg active moiety) plus osimertinib 80 mg QD for ≥9 months, died or have permanently discontinued from the study intervention for any reason, whichever comes first. During the study, regular interim analyses are provided to the Independent Data Monitoring Committee to assess the efficacy and safety of the patients in the study, as well as evaluating the ongoing validity and scientific merit of the study. The final analysis will be performed 3 years after the last patient's first dose, or when all patients have discontinued study treatment and two-thirds of the patients have died, whichever comes first.

Study procedures

After obtaining written informed patient consent for prescreening procedures, tumor tissue and a blood sample, both obtained after progression on first-line osimertinib, are submitted for central assessment of *MET*amp by FISH and NGS (LBx) testing (Figure 3). Patients with *MET*amp detected by local FISH have to submit tumor tissue and a blood sample for central assessment of *MET*amp and can proceed to screening and study treatment initiation without waiting for central confirmation. Although NGS has become routine in molecular diagnostics, patients with a pre-existing negative local NGS (LBx) *MET*amp result should still be considered for prescreening in INSIGHT 2, as NGS testing can fail to identify a significant percentage of patients who would test positive for *MET*amp by FISH. If *MET*amp is not detected and a patient fails prescreening, further prescreening is not permitted.

Following *MET*amp detection, patients who have given written informed consent for screening procedures will be assessed for study eligibility 28 days to 1 day prior to Day 1 of tepotinib plus osimertinib coadministration. The screening period will include a baseline tumor assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and the confirmation of measurable tumor disease by two independent radiologists. Objective response by RECIST v1.1, DOR and PFS is determined by investigator assessment and by an IRC.

Outcome measures/end points

One of the important protocol changes in the amendments implemented in April 2020 was the inclusion of *MET*amp detection by central FISH testing in the primary objective. This was changed because LBx NGS may underestimate *MET*amp in patients with NSCLC, which may be due to inherent technical limitations associated with low levels of circulating tumor DNA as a result of nonshedding tumors [26,28–30,35,56,62].

The primary objective of INSIGHT 2 is to assess the efficacy of tepotinib combined with osimertinib in patients with advanced or metastatic *EGFR*-mutant NSCLC and *MET*amp, determined centrally by FISH (the primary efficacy analysis set). Two secondary analysis sets for efficacy include patients with *MET*amp determined centrally by LBx, and patients with *MET*amp determined centrally by FISH or NGS in LBx. Patients lacking central confirmation of *MET*amp by FISH or NGS in LBx, and patients enrolled prior to the protocol amendment who do not meet the updated eligibility criteria, are included in the safety analyses population.

The primary end point is objective response, including confirmed complete response (CR) or partial response (PR), by an IRC using RECIST v1.1. Tumor assessments are carried out every 6 weeks following the Cycle 1 Day 1 visit until 9 months, and every 12 weeks thereafter until disease progression, death or study discontinuation. Key secondary end points are shown in Table 5.

Statistical analyses

Standard descriptive statistics and graphical representations are used to summarize the data, along with two-sided exact Clopper–Pearson 95% CIs for objective response (CR or PR) and disease control. Unless otherwise stated, the calculation of proportions is based on the sample size of the analysis set of interest. Kaplan–Meier methods are used for time-to-event variables, such as DOR, PFS and OS. Statistical analyses are performed using SAS® Version 9.2 or higher.

Subgroup analyses based on patients' baseline demographics and disease characteristics are planned. Other preplanned analyses include the efficacy results for patients in the primary analysis set split by C797X status; intracranial response by an IRC based on Response Assessment in Neuro-Oncology Brain Metastases criteria will also be analyzed for patients with brain metastases [63].

Table 5. INSIGHT 2 study end points.

End points	
Primary	Objective response by an IRC (in patients with advanced or metastatic *EGFR*-mutant NSCLC and *MET* amplification based on central FISH treated with tepotinib and osimertinib in combination)
Secondary	Objective response by investigator assessment
	DOR by an IRC and investigator assessment
	PFS by an IRC and investigator assessment
	OS
	HRQoL
	Safety[†]

[†]Patients enrolled prior to the protocol amendment, who do not meet eligibility criteria under the updated protocol, and patients lacking central confirmation of *MET* amplification by FISH or LBx will be included in safety analyses only.
DOR: Duration of response; FISH: Fluorescence *in situ* hybridization; HRQoL: Health-related quality of life; IRC: Independent review committee; MET: Mesenchymal–epithelial transition factor; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival.

Conclusion

*MET*amp represents a mechanism of acquired resistance to EGFR TKIs and is associated with resistance to first-line osimertinib, for which only chemotherapy is available as a treatment option. Combining an EGFR TKI with a MET inhibitor may overcome MET-related resistance and may be a better option than chemotherapy. INSIGHT 2 (NCT03940703) is a global, two-arm, open-label, Phase II trial designed to assess the efficacy and safety of tepotinib plus osimertinib in patients with *MET*-amplified, advanced or metastatic NSCLC harboring activating *EGFR* mutations and acquired resistance to first-line osimertinib. Data from this study will enable a robust characterization of the benefit-to-risk ratio of combination therapy and assess the potential to fulfill an unmet need by providing a targeted therapy option for patients with *EGFR*-mutant NSCLC who progress on first-line osimertinib.

Executive summary

Background & rationale

- Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) osimertinib is a standard of care for first-line management of metastatic *EGFR*-mutant non-small-cell lung cancer (NSCLC).
- *MET* amplification (*MET*amp) is a common cause of acquired resistance to first-line osimertinib, occurring in up to 30% of patients.
- Apart from chemotherapy, there are no further clear-cut therapeutic options for *EGFR*-mutant NSCLC after progression on osimertinib, suggesting a high unmet need as outcomes with chemotherapy are not very encouraging.

Osimertinib plus tepotinib

- Osimertinib in combination with a MET TKI may overcome osimertinib resistance due to *MET*amp.
- Tepotinib is a once-daily, orally available, potent and highly selective MET TKI, and approved for the treatment of adult patients with metastatic NSCLC harboring *MET* exon 14 skipping alterations.
- In preclinical models, tepotinib was able to overcome acquired resistance to EGFR TKIs due to *MET*amp.
- In a Phase Ib/II study, tepotinib plus gefitinib (n = 12) improved outcomes versus chemotherapy (n = 7) in patients with *EGFR*-mutant *MET*amp NSCLC with acquired EGFR TKI resistance (median progression-free survival: 16.6 vs 4.2 months; median overall survival: 37.3 vs 13.1 months; objective response rate: 67 vs 43%; median duration of response: 19.9 vs 2.8 months).
- Thus, a strong rationale exists to evaluate osimertinib plus tepotinib in *EGFR*-mutant *MET*amp NSCLC with acquired resistance to first-line osimertinib.

INSIGHT 2

- INSIGHT 2 (NCT03940703) is a global, two-arm, open-label, Phase II trial assessing the efficacy, safety and tolerability of tepotinib plus osimertinib in patients with advanced/metastatic *EGFR*-mutant NSCLC with acquired resistance to first-line osimertinib due to *MET*amp.
- Eligible patients: ≥18 years, Eastern Cooperative Oncology Group performance status 0/1, normal organ function and patients with locally advanced/metastatic NSCLC with acquired resistance to first-line osimertinib (radiologic documentation of disease progression following previous objective clinical benefit) due to *MET*amp by central or local fluorescence *in situ* hybridization (gene copy number ≥5 or *MET*/*CEP7* ratio ≥2) or central liquid biopsy.
- The study is expected to enroll 120 patients.
- The primary end point is objective response by an independent review committee (RECIST v1.1). The primary efficacy analysis for the primary end point will be conducted in all patients with *MET*amp centrally tested by

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fluorescence *in situ* hybridization, treated with tepotinib plus osimertinib. Key secondary end points include progression-free survival, duration of response, overall survival, safety and tolerability.

Conclusion

- Combining an EGFR TKI with a MET inhibitor may overcome *MET*amp resistance.
- INSIGHT 2 is assessing the potential of osimertinib plus tepotinib to fulfill an unmet need for patients with *EGFR*-mutant NSCLC who progress on first-line osimertinib due to *MET*amp.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-1406

Author contributions

All the authors meet the criteria for authorship described by the International Committee of Medical Journal Editors. Each author contributed to the conception, preparation, revision process and approval of the manuscript.

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Ethical conduct of research

This study is conducted in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable Good Clinical Practice (GCP) guideline of the International Conference on Harmonization, the Japanese ministerial ordinance on GCP, and applicable laws and regulations. Appropriate institutional review board/independent ethics committee approval is obtained prior to study center initiation. Written informed consent is required and obtained from all study participants.

Data sharing statement

Merck Healthcare KGaA support the sharing of clinical trial information, to further develop the medical and scientific knowledge base. Merck Healthcare KGaA share trial protocols, anonymized or pseudonymized patient level data and redacted clinical trial reports with qualified scientific and medical researchers. Such requests must be submitted in writing. For further details, please see: https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. In accordance with current laws and regulations, Merck Healthcare KGaA take great precautions to ensure the privacy of their clinical trial participants. The INSIGHT 2 study currently appears in the following clinical studies registries: ClinicalTrials.gov (NCT03940703) and EudraCT 2019-001538-33.

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