Tepotinib plus osimertinib in patients with *EGFR*-mutated non-small-cell lung cancer with *MET* amplification following progression on first-line osimertinib (INSIGHT 2): a multicentre, open-label, phase 2 trial

*Yi-Long Wu, Valentina Guarneri, Pei Jye Voon, Boon Khaw Lim, Jin-Ji Yang, Marie Wislez, Cheng Huang, Chong Kin Liam, Julien Mazieres, Lye Mun Tho, Hidetoshi Hayashi, Nguyen Viet Nhung, Puey Ling Chia, Filippo de Marinis, Jo Raskin, Qinghua Zhou, Giovanna Finocchiaro, Anh Tuan Le, Jialei Wang, Christophe Dooms, Terufumi Kato, Ernest Nadal, How Soon Hin, Egbert F Smit, Martin Wermke, Daniel Tan, Masahiro Morise, Aurora O'Brate, Svenja Adrian, Boris M Pfeiffer, Christopher Stroh, Dilafruz Juraeva, Rainer Strotmann, Kosalaram Goteti, Karin Berghoff, Barbara Ellers-Lenz, Niki Karachaliou, Xiuning Le, Tae Min Kim, for the INSIGHT 2 investigators**

Summary

Background Patients with *EGFR*-mutated non-small-cell lung cancer (NSCLC) and *MET* amplification as a mechanism of resistance to first-line osimertinib have few treatment options. Here, we report the primary analysis of the phase 2 INSIGHT 2 study evaluating tepotinib, a highly selective MET inhibitor, combined with osimertinib in this population.

Methods This open-label, phase 2 study was conducted at 179 academic centres and community clinics in 17 countries. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0 or 1 and advanced or metastatic *EGFR*-mutated NSCLC of any histology, with *MET* amplification by tissue biopsy fluorescence in-situ hybridisation (FISH; *MET* gene copy number of ≥5 or *MET*-to-*CEP7* ratio of ≥2) or liquid biopsy next-generation sequencing (*MET* plasma gene copy number of ≥2·3), following progression on first-line osimertinib. Patients received oral tepotinib 500 mg plus oral osimertinib 80 mg once daily. The primary endpoint was independently assessed objective response in patients with *MET* amplification by central FISH treated with tepotinib plus osimertinib with at least 9 months of follow-up. Safety was analysed in patients who received at least one study drug dose. This study is registered with ClinicalTrials.gov, NCT03940703 (enrolment complete).

Findings Between Feb 13, 2020, and Nov 4, 2022, 128 patients (74 [58%] female, 54 [42%] male) were enrolled and initiated tepotinib plus osimertinib. The primary activity analysis population included 98 patients with *MET* amplification confirmed by central FISH, previous first-line osimertinib and at least 9 months of follow-up (median 12·7 months [IQR 9·9–20·3]). The confirmed objective response rate was 50·0% (95% CI 39·7–60·3; 49 of 98 patients). The most common treatment-related grade 3 or worse adverse events were peripheral oedema (six [5%] of 128 patients), decreased appetite (five [4%]), prolonged electrocardiogram QT interval (five [4%]), and pneumonitis (four [3%]). Serious treatment-related adverse events were reported in 16 (13%) patients. Deaths of four (3%) patients were assessed as potentially related to either trial drug by the investigator due to pneumonitis (two [2%] patients), decreased platelet count (one [1%]), respiratory failure (one [1%]), and dyspnoea (one [1%]); one death was attributed to both pneumonitis and dyspnoea.

Interpretation Tepotinib plus osimertinib showed promising activity and acceptable safety in patients with *EGFR*-mutated NSCLC and *MET* amplification as a mechanism of resistance to first-line osimertinib, suggesting a potential chemotherapy-sparing oral targeted therapy option that should be further investigated.

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Introduction

In patients with *EGFR*-mutated non-small-cell lung cancer (NSCLC), *MET* amplification is the most common secondary driver of resistance to EGFR tyrosine kinase inhibitors (TKIs).[1,2] The reported incidence of *MET* amplification in *EGFR*-mutated NSCLC with resistance to EGFR TKIs varies, with estimates from 10% to 66%, depending on the detection methods and definition.[3] *MET* amplification occurs more commonly with osimertinib, a third-generation EGFR TKI and the preferred standard of care for previously untreated *EGFR*-mutated NSCLC,[4] than with earlier generations of EGFR TKIs.[1] Following EGFR TKI treatment, clinical practice guidelines recommend thorough testing for resistance mechanisms, including *MET* amplification, to guide subsequent treatment.[4] Currently, the mainstay of

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*INSIGHT 2 investigators are listed in the appendix (pp 2–3)

Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China (Prof Y-L Wu MD, Prof J-J Yang MD); **Department of Surgery, Oncology and Gastroenterology, University of Padova, Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy** (Prof V Guarneri PhD); **Hospital Umum Sarawak, Kuching, Sarawak, Malaysia** (P J Voon MD); **Department of Internal and Respiratory Medicine, Sunway Medical Centre, Selangor, Malaysia** (B K Lim MRCP); **Service de Pneumologie, Hôpital Cochin, Assistance Publique—Hôpitaux de Paris, Paris, France** (Prof M Wislez PhD); **Université Paris Cité, Paris, France** (Prof M Wislez); **Department of Thoracic Oncology, Fujian Cancer Hospital, Fuzhou, China** (Prof C Huang PhD); **Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia** (Prof C K Liam MBBS [UM]); **CHU de Toulouse, Université Paul Sabatier, Toulouse, France** (Prof J Mazieres PhD); **Department of Oncology, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia** (L M Tho PhD); **Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan** (Prof H Hayashi PhD); **National Lung Hospital, University of**

Medicine and Pharmacy, Vietnam National University Hanoi, Viet Nam (N V Nhung PhD); **Department of Medical Oncology, Tan Tock Seng Hospital, Singapore** (P L Chia PhD); **Division of Thoracic Oncology, European Institute of Oncology, IRCCS, Milan, Italy** (Prof F de Marinis PhD); **Department of Pulmonology and Thoracic Oncology, Antwerp University Hospital (UZA), Edegem, Belgium** (J Raskin MD); **Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China** (Prof Q Zhou MD); **IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy** (G Finocchiaro MD); **Cho Ray Hospital, Ho Chi Minh City, Viet Nam** (A T Le PhD); **Department of Oncology, Fudan University Shanghai Cancer Center, Shanghai, China** (Prof J Wang MD); **Department of Respiratory Diseases and Respiratory Oncology Unit, University Hospitals Leuven, Leuven, Belgium** (C Dooms PhD); **Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan** (T Kato MD); **Department of Medical Oncology, Catalan Institute of Oncology IDIBELL, L'Hospitalet, Barcelona, Spain** (E Nadal PhD); **Hospital Tengku Ampuan Afzan, Pahang, Malaysia** (Prof H S Hin MD); **Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands** (Prof E F Smit PhD); **Department of Pulmonary Diseases, Leiden University Medical Center, Leiden, Netherlands** (Prof E F Smit); **TU Dresden, Faculty of Medicine Carl Gustav Carus, Department of Medicine I/NCT/UCC Early Clinical Unit, Dresden, Germany** (Prof M Wermke MD); **Division of Medical Oncology, National Cancer Centre Singapore, Singapore** (D Tan PhD); **Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan** (M Morise PhD); **Global Medical Affairs** (A O'Brate PhD), **Global Clinical Development** (S Adrian MD, N Karachaliou MD), **Global Patient Safety** (K Berghoff MD), **Department of Biostatistics** (B Ellers-Lenz MSc), **Merck, Darmstadt, Germany; Global**

Research in context

Evidence before this study

MET amplification is the most common secondary driver of resistance to EGFR tyrosine kinase inhibitors (TKIs), but there are few treatment options in this setting. We searched PubMed for articles published in any language from database inception to Dec 12, 2023, using the search string ("MET inhibitor" OR "MET TKI" OR "MET-TKI" OR "MET tyrosine kinase inhibitor") AND ("EGFR inhibitor" OR "EGFR TKI" OR "EGFR-TKI" OR "EGFR tyrosine kinase inhibitor") AND "MET amplification" AND "lung cancer". Of 34 articles retrieved, phase 2 clinical data were reported in two articles, both of which were related to the randomised phase 1b/2 INSIGHT trial. INSIGHT evaluated tepotinib plus gefitinib versus chemotherapy in patients with *EGFR*-mutant NSCLC with *MET* amplification or MET overexpression and acquired resistance to a previous EGFR TKI. Although no significant differences in outcomes were observed in the overall population, the subgroup of patients with *MET* amplification (n=19) showed notable improvements in progression-free survival and overall survival with tepotinib plus gefitinib compared with chemotherapy. Searches of recent congress abstracts also identified phase 2 data for savolitinib plus osimertinib after progression on osimertinib: an objective response rate of 32% (95% CI 26–39) in patients with *EGFR*-mutant NSCLC with *MET* amplification or MET overexpression was seen in the SAVANNAH trial, and of 41% (80% CI 25–59) in patients with *EGFR*-mutant NSCLC with *MET* amplification was seen in the ORCHARD trial.

Added value of this study

To our knowledge, INSIGHT 2 is the first phase 2 trial of a MET TKI in combination with a third-generation EGFR TKI in patients with *MET*-mediated osimertinib resistance to be reported in full. The primary analysis showed the promising activity of tepotinib plus osimertinib in patients with *MET* amplification detected by central tissue biopsy fluorescence in-situ hybridisation after first-line osimertinib. The combination showed a manageable safety profile, with a low rate of discontinuations due to treatment-related adverse events. Overall health-related quality of life was maintained, with improvements in cough and pain and, in exploratory analyses, intracranial activity was observed. Co-occurring *EGFR* mutations at Cys797, *RAS* or *BRAF* mutations, and *ALK* fusions were potential negative predictors for combination therapy, and secondary *MET* mutations seemed to be a mechanism of acquired resistance.

Implications of all the available evidence

The promising activity and favourable safety of tepotinib plus osimertinib showed in the INSIGHT 2 trial suggest that this combination is a potential chemotherapy-sparing oral targeted therapy option in patients with *EGFR*-mutant NSCLC and osimertinib resistance due to *MET* amplification. Tepotinib plus osimertinib might help to address the high unmet medical need in this setting by providing an effective regimen with manageable safety, enabling patients to defer any intravenous treatment burden.

treatment after EGFR TKI failure remains platinum-based chemotherapy. Concurrent MET and EGFR inhibition might offer a therapeutic advantage in patients with *EGFR*-mutated NSCLC who have *MET* amplification following progression on EGFR TKIs.

Tepotinib is a highly selective oral MET TKI approved for treatment of advanced or metastatic *MET* exon 14 skipping NSCLC[5] and is recommended as a treatment option for NSCLC with high-level de-novo *MET* amplification.[4] As a result of its high selectivity, tepotinib shows a low risk of off-target toxicities, enabling combination with EGFR TKIs.[5] Preclinical and clinical studies have supported combining tepotinib with EGFR TKIs in *EGFR*-mutated, *MET*-amplified NSCLC.[6,7] The phase 2 INSIGHT trial indicated improved clinical benefit with tepotinib plus gefitinib versus chemotherapy in patients with *EGFR*-mutated, Thr790Met-negative NSCLC and *MET* amplification, whose disease had progressed on a previous EGFR TKI.[6,7]

We report the primary analysis of the INSIGHT 2 trial, which was conducted to evaluate the antitumour activity and tolerability of tepotinib plus osimertinib in patients with *EGFR*-mutated NSCLC and *MET* amplification after disease progression on first-line osimertinib.

Methods

Study design and participants

INSIGHT 2 is an open-label, phase 2 trial being conducted at 179 academic medical centres and community clinics in Belgium, China, France, Germany, Hong Kong, Italy, Japan, Malaysia, the Netherlands, Russia, Singapore, South Korea, Spain, Taiwan, Thailand, the USA, and Viet Nam. The trial design has been published previously,[8] and further information is provided in the protocol and statistical analysis plan (appendix). A plain language summary of this report is also provided in the appendix (pp 4–12).

Eligible patients were aged 18 years or older with advanced or metastatic *EGFR*-mutated NSCLC whose disease had progressed on first-line osimertinib, after objective clinical benefit from this therapy.[9] Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; a minimum life expectancy of 12 weeks; measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1); and *MET* amplification, as determined by local or central tissue biopsy fluorescence in-situ hybridisation (FISH; gene copy number [GCN] ≥5 or *MET*-to-*CEP7* ratio ≥2), central liquid biopsy next-generation sequencing (NGS; plasma GCN ≥2·3; Archer

Reveal ctDNA; ArcherDX, Boulder, CO, USA), or both. Tissue and blood samples were collected after progression on first-line osimertinib. Patients with asymptomatic brain metastases not requiring steroids or radiotherapy or surgery within 2 weeks before study treatment were eligible. Complete enrolment criteria are provided in the protocol (appendix). Participant sex and ethnicity were reported based on information in electronic medical records.

The original protocol allowed enrolment of patients with any previous first-generation to third-generation EGFR TKI, included a single treatment group (tepotinib plus osimertinib), and used only liquid biopsy NGS for central *MET* amplification detection. In April, 2020, a protocol amendment, which was approved by institutional review boards or independent ethics committees, introduced several key changes to the study design.[8] First, eligibility was restricted to require progression on first-line osimertinib, to reflect evolution in the first-line standard of care. Second, a tepotinib monotherapy group was introduced to enable examination of the contribution of osimertinib in this setting. Third, to enhance detection and mitigate potential underestimation of *MET* amplification from non-shedding tumours detected by liquid biopsy NGS, tissue biopsy FISH, which is known for its higher sensitivity, was also incorporated into central *MET* testing. Following the amendment, the primary objective was to assess tepotinib plus osimertinib in patients with *MET* amplification detected by central tissue biopsy FISH after first-line osimertinib. The primary analysis of the study was conducted in accordance with the protocol, when all globally enrolled patients in the primary activity analysis (those with *MET* amplification detected by FISH) had at least 9 months of follow-up. To meet regulatory requirements in China, the study was continued to include an additional enrolment phase exclusively for patients in China, referred to as the Chinese extension period. All available safety data up to the cutoff date of the primary analysis have been included in this report, including data from patients enrolled during the Chinese extension period, some of whom had less than 9 months of follow-up at the time of analysis.

The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice, local laws, and applicable regulatory requirements. Institutional review boards or independent ethics committees at each centre approved the protocol. All patients provided written informed consent. This study is registered with ClinicalTrials.gov, NCT03940703.

Randomisation and masking

The trial design included an initial safety run-in period to determine the recommended phase 2 dose of tepotinib plus osimertinib, followed by the main treatment period (appendix p 14). All patients enrolled in the safety run-in received tepotinib plus osimertinib.[8] Thereafter, patients with *MET* amplification detected by tissue biopsy FISH were randomly assigned (2:1) to receive tepotinib plus osimertinib or tepotinib monotherapy. After 12 patients were enrolled in the monotherapy group, all patients were assigned to the tepotinib plus osimertinib group. Patients with *MET* amplification detected only by liquid biopsy NGS were assigned to the tepotinib plus osimertinib group.

Patients were randomly assigned via an interactive voice-response system using a blocked randomisation schedule (block size of three). The randomisation sequence was generated by computer by a third-party vendor (Cenduit, Durham, NC, USA). Investigators enrolled participants, and neither investigators nor participants were masked to treatment assignment.

Procedures

Both drugs were administered orally once daily at their approved doses: tepotinib 500 mg (450 mg active moiety) and osimertinib 80 mg.[8] Dose reductions of tepotinib to 250 mg and osimertinib to 40 mg once daily were allowed, if required, due to intolerable adverse events. Dose interruptions of either or both study drugs were allowed for up to 3 weeks if patients had a grade 3 or worse adverse event related to either or both study drugs. Patients received treatment until disease progression, death, an adverse event leading to discontinuation, or study or consent withdrawal. Following study treatment discontinuation, patients had an end-of-treatment visit within 14 days and safety follow-up 30 days (±3 days) after the last dose of study treatment; patients who withdrew for reasons other than disease progression or death had tumour assessments every 6 weeks for 9 months, and every 12 weeks thereafter, and survival follow-up occurred every 3 months. INSIGHT 2 is planned to end when all patients have discontinued treatment, are followed up for 3 years or more, or two-thirds of patients have died, whichever occurs first.

Tumour assessments were performed by CT, MRI, or both CT and MRI at baseline, every 6 weeks for 9 months, and every 12 weeks thereafter. Brain imaging is described in the appendix (p 13). Plasma samples for biomarker analyses were collected at baseline and within 14 days of treatment discontinuation. Blood samples were collected for clinical laboratory tests at baseline and every 3 weeks (±3 days) thereafter, at the end of treatment, and during the safety follow-up. Urine samples were collected at baseline and every 6 weeks. NGS analysis was done using Guardant360 (Guardant Health, Palo Alto, CA, USA) to analyse cell-free DNA in pretreatment and post-progression plasma specimens (appendix p 13). Health-related quality of life (HRQOL) was assessed using the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ), which was administered electronically for patient self-report at visits at baseline, every 6 weeks for 9 months, and every 12 weeks thereafter

Value Demonstration, Market Access and Pricing, Merck, Darmstadt, Germany (B M Pfeiffer MD)**; Companion Diagnostics & Biomarker Strategy** (C Stroh PhD)**, Data Sciences** (D Juraeva PhD)**, and Quantitative Pharmacology** (R Strotmann MD)**, Clinical Measurement Sciences, Merck, Darmstadt, Germany; Quantitative Pharmacology, Clinical Measurement Sciences, EMD Serono Research & Development Institute, Billerica, MA, USA, an affiliate of Merck** (K Goteti MD)**; Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA** (X Le MD)**; Seoul National University Cancer Research Institute, Seoul, South Korea** (Prof T M Kim MD)**; Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea** (Prof T M Kim)

Correspondence to:
Prof Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou 510515, China
wuyilong@gdph.org.cn

or

Prof Tae Min Kim, Department of Internal Medicine, Seoul National University Hospital, Seoul 03080, South Korea
gabriel9@snu.ac.kr

See **Online** for appendix

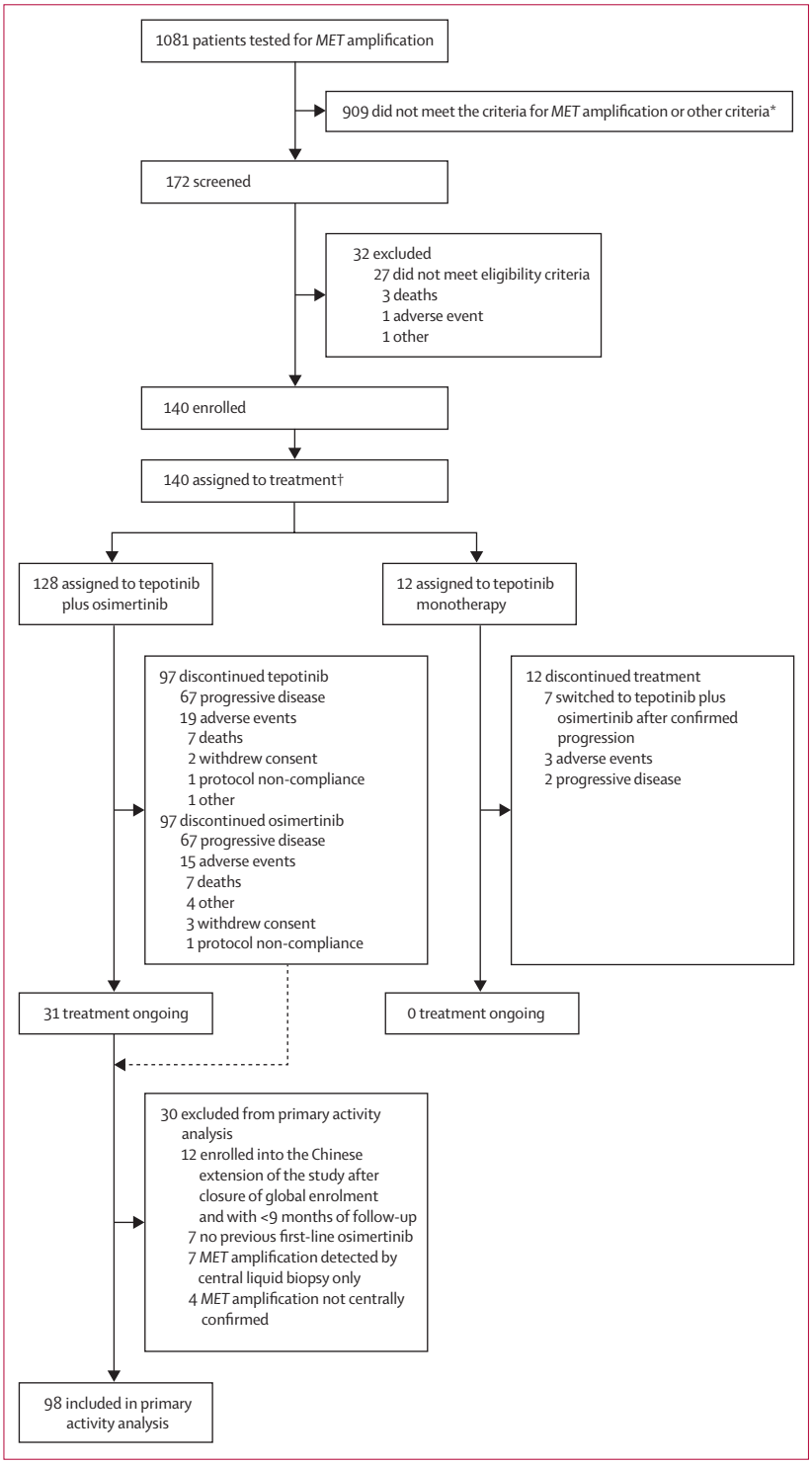


Figure 1: **Trial profile**
FISH=fluorescence in-situ hybridisation. *Reasons for pre-screening failures not analysed; patients might not have met criteria for *MET* amplification or other criteria necessary to proceed with screening. Before the procotol amendment, *MET* amplification was defined based on liquid biopsy next-generation sequencing, which might have resulted in a false negative result. †Following the safety run-in, patients with *MET* amplification detected by tissue biopsy FISH were randomly assigned (2:1) to receive tepotinib plus osimertinib or tepotinib monotherapy. After 12 patients were enrolled in the tepotinib monotherapy group, all patients were assigned to the tepotinib plus osimertinib group.

until progression, death, or study or consent withdrawal. The NSCLC-SAQ comprises seven items covering five domains (including cough, pain, and dyspnoea), with higher scores indicating more severe symptoms.

Adverse events were assessed continuously and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Outcomes

The primary endpoint was confirmed objective response, assessed by a central independent review committee based on RECIST (version 1.1), in patients enrolled in the tepotinib plus osimertinib group who had *MET* amplification detected by central tissue biopsy FISH following progression on first-line osimertinib. Patients had an objective response if they had an observed partial or complete response (confirmed by a second tumour assessment ≥4 weeks later) from the first administration of study drug to the first observation of progressive disease. Secondary endpoints included duration of response (defined as time from when objective response criteria were first met until progressive disease or death from any cause), progression-free survival (defined as time from first study drug administration until progressive disease or death from any cause), overall survival (defined as time from first study drug administration until death), and HRQOL, as reported using the NSCLC-SAQ. All antitumour activity endpoints were also assessed in patients in the tepotinib plus osimertinib group with *MET* amplification detected by liquid biopsy NGS and in patients in the monotherapy group as secondary endpoints (except for overall survival in the monotherapy group). Safety was another secondary endpoint, for which adverse events were evaluated in the combination and monotherapy groups. Additionally, a secondary endpoint assessed resistance mechanisms through NGS analysis of cell-free DNA in pretreatment and post-progression plasma specimens.

Prespecified exploratory endpoints included intracranial response, including confirmed objective response, disease control, duration of response, and progression-free survival, which were evaluated centrally by a board-certified neuroradiologist using Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria (appendix p 13),[10] and tepotinib pharmacokinetic sampling for exposure–response analyses.

Statistical analysis

Statistical analyses are detailed in the statistical analysis plan (appendix). Assuming a true objective response rate of 50%, a sample size of at least 80 patients in the primary activity population was planned to provide a 78% probability that the lower limit of the 95% CI would exceed 35%.[11] No formal sample size calculations were performed for the tepotinib monotherapy group or safety run-in.

Analyses were conducted according to assigned treatment (intention to treat). The primary activity population consisted of patients in the tepotinib plus osimertinib group with *MET* amplification detected by central tissue biopsy FISH after progression on first-line osimertinib, who had at least 9 months of follow-up.

Regular interim analyses for the Independent Data Monitoring Committee were planned to ensure continued participant safety, as well as the validity and scientific merit of the study.

Analyses were descriptive, and no formal statistical hypotheses were tested. Objective response was summarised as rates with two-sided exact Clopper–Pearson 95% CIs. Preplanned analyses used Kaplan–Meier methods to analyse duration of response, progression-free survival, and overall survival, and to estimate the median and 6-month and 9-month event-free rates with associated 95% CIs. For patients who did not have an event (disease progression or death), or for patients with an event 126 days or more after the last tumour assessment, duration of response and progression-free survival data were censored on the date of the last evaluable tumour assessment; overall survival was censored at the last date the patient was known to be alive. Safety was analysed descriptively in patients who received any study treatment. Prespecified NSCLC-SAQ score analyses evaluated change in the key symptoms of pain, cough, and dyspnoea from baseline to week 12, with a Cohen's *d* effect size of at least ±0·2 considered clinically meaningful. Preplanned exploratory analyses evaluated antitumour activity in subgroups of the primary activity population defined by age, sex, smoking history, ECOG performance status, brain metastasis at baseline, time on first-line osimertinib, *MET* GCN, *MET*-to-*CEP7* ratio, and ethnicity. Subgroup analysis by *EGFR* mutation was post hoc.

Analyses were done using SAS (version 9.4). A Safety Monitoring Committee (SMC) continuously assessed safety and made recommendations to the sponsor regarding trial continuation.

Role of the funding source

The study was designed and funded by Merck (CrossRef Funder ID: 10.13039/100009945), and sponsor representatives were responsible for data collection, data analysis, data interpretation, and writing of the report.

Results

Between Sept 19, 2019, and Oct 9, 2022, 1081 patients were tested for *MET* amplification (600 before and 481 after the protocol amendment). A total of 140 patients were enrolled, of whom 128 were assigned to tepotinib plus osimertinib and 12 were assigned to tepotinib monotherapy, with the first tepotinib dose received between Feb 13, 2020, and Nov 4, 2022 (figure 1; appendix p 7). The primary activity population comprised 98 patients in the tepotinib plus osimertinib group with centrally confirmed *MET* amplification by tissue biopsy FISH after first-line osimertinib and at least 9 months of follow-up. The data cutoff date was March 28, 2023.

During the safety run-in, six patients who had no dose-limiting toxicities post-cycle 1 treatment were evaluated by the SMC in two meetings, confirming the recommended phase 2 dose of tepotinib 500 mg plus osimertinib 80 mg once daily. Enrolment continued uninterrupted during the preparation for the SMC meetings, resulting in a total of nine patients in the safety run-in.[8]

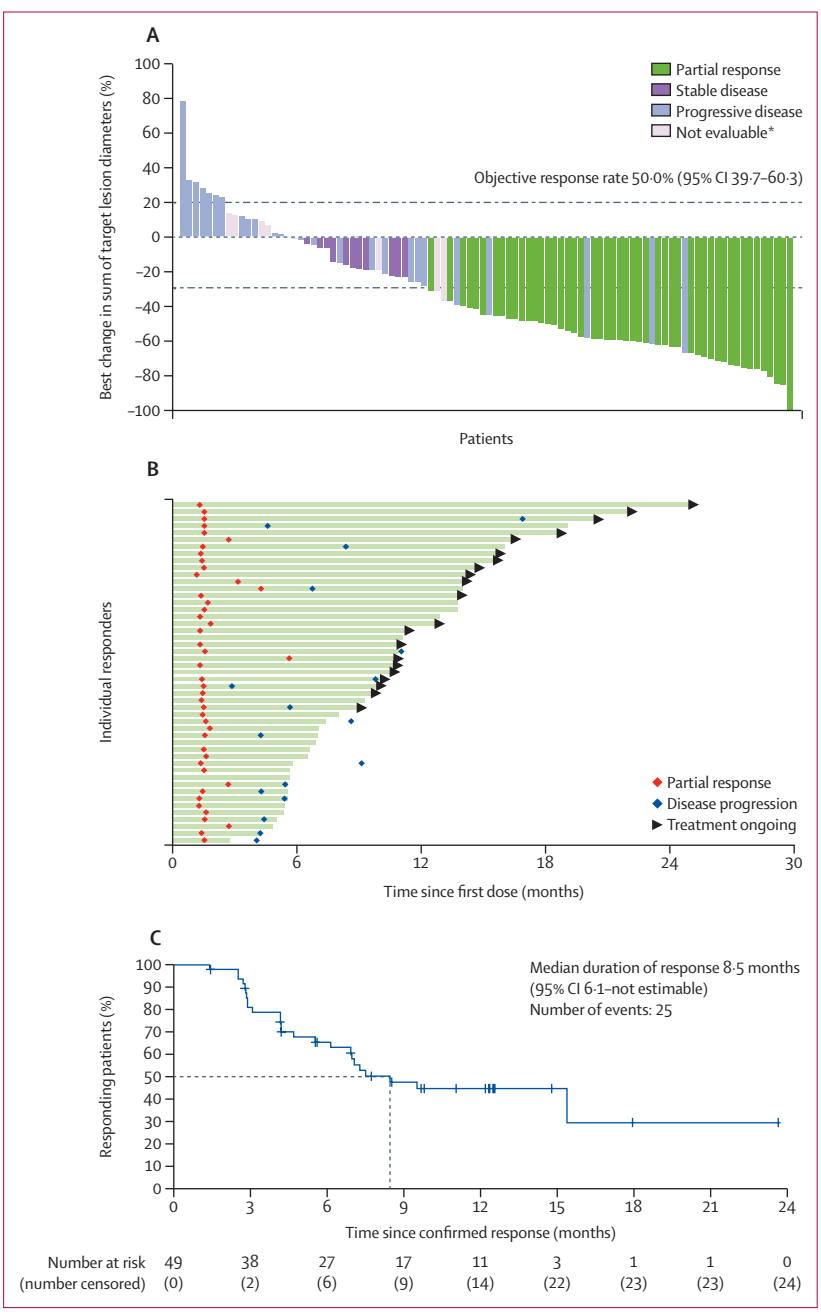
In the tepotinib plus osimertinib group, the median age was 61 years (IQR 52–67), 74 (58%) patients were female, 79 (62%) were Asian, 86 (67%) had never smoked, 93 (73%) had an ECOG performance status of 1, 45 (35%) had brain metastases, 76 (59%) had *EGFR* exon 19

	Tepotinib plus osimertinib group (n=128)
Age, years	61 (52–67)
Sex	
Female	74 (58%)
Male	54 (42%)
Ethnicity	
Asian	79 (62%)
White	43 (34%)
Other or not collected	6 (5%)
Smoking status*	
Never	86 (67%)
Former	39 (30%)
Current	2 (2%)
Eastern Cooperative Oncology Group performance status	
0	35 (27%)
1	93 (73%)
Adenocarcinoma	128 (100%)
Sum of target lesion diameters by IRC, mm	62·6 (44·8–86·6)
Brain metastases	
By RECIST (version 1.1)†	45 (35%)
By RANO-BM	29 (23%)
Time on first-line osimertinib‡, months	15·4 (10·3–22·5)
MET amplification by tissue biopsy FISH§	
Gene copy number	11·2 (7·2–16·6)
MET-to-*CEP7* ratio	2·3 (1·0–4·3)
EGFR mutation¶‖	
Exon 19 deletion	76 (59%)
Leu858Arg	44 (34%)
Other (eg, Leu861Gln)	8 (6%)

Data are n (%) or median (IQR). FISH=fluorescence in-situ hybridisation. IRC=independent review committee. RANO-BM=Response Assessment in Neuro-Oncology Brain Metastases. RECIST=Response Evaluation Criteria in Solid Tumours. *Smoking history missing (n=1). †As determined by IRC and/or investigator. ‡Did not receive first-line osimertinib (n=7). §Tissue biopsy FISH data available from 114 patients. ¶Two patients reported to have both exon 19 deletion and Leu858Arg mutations were counted as exon 19 deletion mutation cases. ‖NM_005228.5.

Table 1: **Baseline characteristics**

deletions, and 44 had (34%) *EGFR* 2573T>G (Leu858Arg) mutations (table 1). The median time on previous first-line osimertinib was 15·4 months (IQR 10·3–22·5). Patient characteristics of the primary activity population (n=98), patients in the tepotinib plus osimertinib group with *MET* amplification detected by liquid biopsy NGS (n=31), and the tepotinib monotherapy group (n=12) are provided in the appendix (p 27). The median sum of target lesion diameters by the independent review committee were 64·3 mm (IQR 45·0–89·6) in the primary activity population, 76·2 mm (62·7–142·0) in patients in the tepotinib plus osimertinib group with *MET* amplification detected by liquid biopsy NGS, and 75·3 (46·2–111·7) in the tepotinib monotherapy group.



(Figure 2 continues on next page)

The confirmed objective response rate was 50·0% (95% CI 39·7–60·3; 49 of 98 patients) in the primary activity population (figure 2A, B). Tumour shrinkage of any magnitude was observed in 77 (79%) patients. 49 (50%) patients had a partial response, and 13 (13%) had stable disease for a minimum of 6 weeks; progressive disease was the best overall response in 23 (23%) patients. No patient had a complete response. The objective response rate remained mostly consistent across prespecified subgroups (appendix p 15). Patients with a *MET* GCN of 10 or higher had an objective response rate of 56·6% (95% CI 42·3–70·2; 30 of 53 patients) and those with a *MET* GCN of less than 10 had an objective response rate of 42·2% (27·7–57·8; 19 of 45 patients). Patients with a *MET*-to-*CEP7* ratio of 2 or higher had an objective response rate of 56·3% (95% CI 41·2–70·5; 27 of 48 patients) and those with a *MET*-to-*CEP7* ratio of less than 2 had an objective response rate of 44·0% (30·0–58·7; 22 of 50 patients).

Among 49 patients with a response in the primary activity population, the median duration of response was 8·5 months (95% CI 6·1–not estimable [NE]), with 66% (95% CI 50–77) of patients being event free at 6 months and 48% (33–62) at 9 months (figure 2C). Responses were typically observed at the first tumour assessment (figure 2B).

At data cutoff, 65 progression-free survival events (disease progression or death) had occurred, and median duration of follow-up for progression-free survival was 11·5 months (IQR 9·0–13·8). Median progression-free survival was 5·6 months (95% CI 4·2–8·1), with event-free rates of 48% (95% CI 37–58) at 6 months and 30% (20–40) at 9 months (figure 2D). Median duration of follow-up for overall survival was 12·7 months (IQR 9·9–20·3). After 42 (43%) patients had died, median overall survival was 17·8 months (95% CI 11·1–NE) , with event-free rates of 81% (95% CI 72–88) at 6 months and 71% (60–79) at 9 months (figure 2E; appendix p 30).

Of 76 patients who discontinued treatment, 41 (54%) received further anticancer drug therapy, primarily carboplatin and pemetrexed (appendix pp 28–29).

Exposure–response analyses in the primary activity population (n=98) showed consistent antitumour activity across the observed tepotinib exposure for key activity endpoints (appendix pp 16–18).

Improvements in cough (mean change −0·38 [95% CI −0·64 to −0·12]; d=−0·37) and pain (−0·32 [−0·66 to 0·02]; d=−0·24), and stability in dyspnoea (0·05 [−0·26 to 0·36]; d=0·04) were seen, based on NSCLC-SAQ responses from 63 (64%) of 98 patients at week 12 (appendix p 19).

In 31 patients with *MET* amplification detected by liquid biopsy NGS, of whom 24 had *MET* amplification also detected by central tissue biopsy FISH, the objective response rate was 54·8% (95% CI 36·0–72·7; 17 of

31 patients; appendix pp 20, 30). Outcomes for the other antitumour activity endpoints in this group are presented in the appendix (pp 21–22, 30).

In the tepotinib monotherapy group (n=12), the objective response rate was 8·3% (95% CI 0·2–38·5; appendix p 30), with one patient with partial response. Outcomes for the other antitumour activity endpoints in this group are presented in the appendix (p 30). Seven patients switched to the tepotinib plus osimertinib combination following disease progression, of whom three had a partial response and two remained on combination therapy at the data cutoff date.

24 patients had baseline brain metastases evaluable by RANO-BM criteria in the primary activity population, of whom seven had brain metastases as target lesions. The intracranial confirmed objective response rate by independent review committee was 29·2% (95% CI 12·6–51·1); with six (25%) patients in complete response and one (4%) patient in partial response. 12 (50%) patients had stable disease, and the intracranial disease control rate was 79·2% (95% CI 57·8–92·9; appendix p 31). Median duration of intracranial response was NE (95% CI 3·6–NE). Median intracranial progression-free survival was 7·8 months (95% CI 3·9–NE). Seven (29%) patients received brain radiotherapy before enrolment.

Genomic alterations in cell-free DNA were assessed in 69 pretreatment plasma specimens (figure 3A). Sensitising *EGFR* mutations (exon 19 deletions, 2573T>G [Leu858Arg], or 2582T>A [Leu861Gln]) were found in 56 (81%) patients, of whom 31 (55%) had a response, and *MET* amplification (plasma GCN ≥2·3) in 26 (38%) patients, of whom 17 (65%) had a response. Of seven (10%) patients with co-occurring *EGFR* mutations at Cys797 (2389T>A or 2390G>C [Cys797Ser], n=6; 2389_2391delTGCinsGCT [Cys797Ala], n=1), one had a partial response to tepotinib plus osimertinib. Among other patients with co-occurring alterations, no responses were observed in those with *ALK* fusions (n=2), activating *RAS* mutations (n=4), *BRAF* mutation (n=1), *PIK3CA* mutation (n=1), *FGFR1* amplification (n=1), or *RB1* loss-of-function mutation (n=1), whereas response was noted in those with an *FGFR3* fusion (n=1), a *PTEN* loss-of-function mutation (n=1), one (33%) of three patients with *MYC* amplification, and 21 (49%) of 43 patients with *TP53* mutations.

In 29 patients with post-progression plasma specimens following tepotinib plus osimertinib treatment, on-target resistance mutations in *EGFR* or *MET* were detected in ten (34%) patients (figure 3B). Nine patients (31%) had putative resistance mutations in *EGFR*, including five (17%) with Cys797Ser (in three of these five patients, the mutation was already detected at baseline) and four (14%) had emerging *MET* kinase domain mutations at Asp1228 (3682G>A [Asp1228Asn] and 3682G>C [Asp1228His], n=1; 3682G>A [Asp1228Asn], n=1; 3682G>T [Asp1228Tyr], n=1) or Tyr1230 (3688T>C [Tyr1230His], n=1), with concurrent *EGFR* and *MET* resistance mutations in three (10%) patients. Loss of *MET* amplification was observed in nine of 12 patients with detectable baseline *MET* amplification by liquid biopsy NGS. In three patients with non-detectable baseline *MET* amplification by NGS, *MET* amplification was detected at progression. In one of these three patients, the *MET* gene copy gain was pronounced (>10 gene copies in ctDNA) and associated with a *MET* kinase domain mutation. 11 (38%) patients had alterations in other signalling pathways, including in *KRAS*, *MYC*, *BRAF*, and *PIK3CA*.

Among 128 patients who received tepotinib plus osimertinib, median duration of study therapy was 5·5 months (IQR 2·8–9·9) with study therapy ongoing in 31 (24%) patients as of data cutoff (figure 1). Treatment-related adverse events of any grade were reported in 113 (88%) patients and those of grade 3 or worse were reported in 44 (34%) patients (table 2). The most common treatment-related adverse events of any grade were

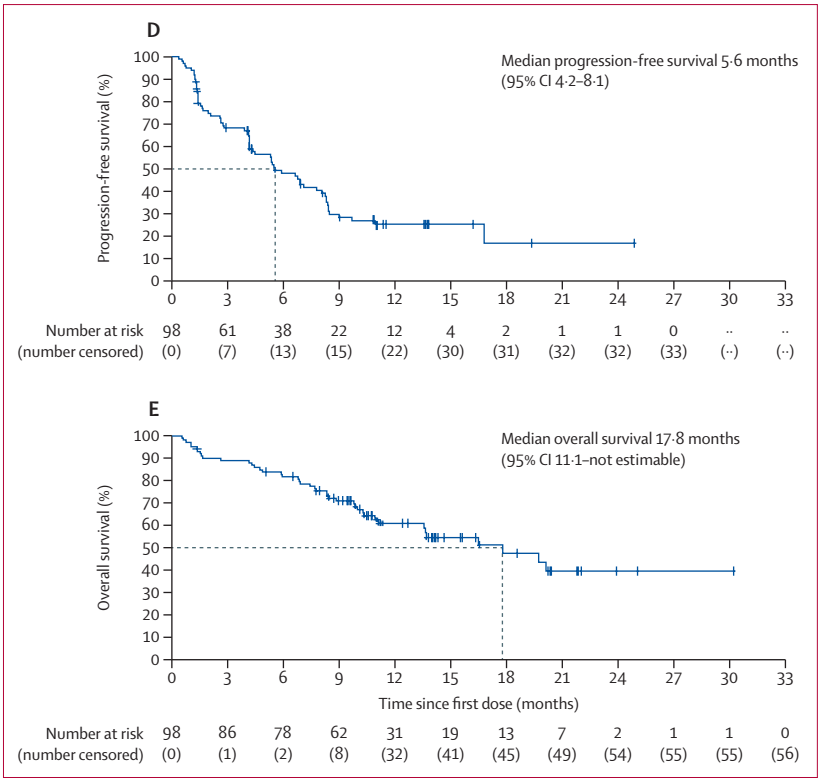


Figure 2: **Antitumour activity analysis in the primary activity population (n=98)**
(A) Tumour shrinkage by IRC. The dashed lines indicate the Response Evaluation Criteria in Solid Tumors (version 1.1) cutoff points for partial response (–30%) and progressive disease (+20%). (B) Time on treatment, and time to and duration of response by IRC. (C) Duration of response by IRC. Only patients with a response were included in Kaplan–Meier analyses of duration of response (25 progression events or deaths occurred after an initial response). (D) Progression-free survival by IRC (65 progression events or deaths occurred after an initial response). (E) Overall survival (42 deaths occurred after an initial response). IRC=independent review committee. *13 patients were non-evaluable for best overall tumour response assessment in accordance with Response Evaluation Criteria in Solid Tumours (version 1.1), due to missing post-baseline assessments at the cutoff date (n=4; not included in the waterfall plot), discontinuation from the study before assessment of best overall response (n=8), or less than two post-baseline assessments available at the cutoff date (n=1).

diarrhoea (63 [49%] patients), peripheral oedema (52 [41%]), paronychia (29 [23%]), nausea (27 [21%]), and decreased appetite (26 [20%]). The most common grade 3 or worse treatment-related adverse events were peripheral oedema (six [5%] patients), prolonged electrocardiogram QT interval (five [4%]), decreased appetite (five [4%]), and pneumonitis (four [3%]). Four (3%) deaths due to adverse events were assessed as potentially related to either trial drug by the investigator: pneumonitis (two [2%] patients), decreased platelet count (one [1%]), respiratory failure (one [1%]), and dyspnoea (one [1%]), one death was attributed to both pneumonitis and dyspnoea (table 2). 16 (13%) patients had serious treatment-related adverse events, of which the most common were pneumonitis (five [4%]), decreased appetite (two [2%]), and platelet count decreased (two [2%]). Adverse events of any grade and causality are presented in the appendix (pp 32–33). Death due to any cause were disease progression (four [3%] patients), pneumonia (three [2%]), pulmonary embolism (three [2%]), dyspnoea (two [2%]), pneumonitis (two [2%]), COVID-19 (one [1%]), decreased platelet count (one [1%]), interstitial lung disease (one [1%]), pneumothorax (one [1%]), respiratory failure (one [1%]), and upper gastrointestinal haemorrhage (one [1%]).

Treatment-related adverse events led to dose reduction of at least one trial drug in 26 (20%) of 128 patients, and temporary and permanent discontinuation of at least one trial drug in 38 (30%) and 13 (10%) patients, respectively. The most frequent treatment-related adverse events leading to permanent discontinuation of at least one trial drug were pneumonitis (six [5%] patients) and peripheral oedema (three [2%]; appendix p 34).

Treatment-related adverse events were reported in nine (75%) of 12 patients who received tepotinib monotherapy; the most common were diarrhoea (three [25%] patients) and peripheral oedema (three [25%]), all of which were grade 1 or 2 (appendix p 35). A serious treatment-related adverse event (general physical health deterioration) was reported in one (8%) patient. There were no deaths due to adverse events in the monotherapy group. No patients had treatment-related adverse events that led to dose reduction or temporary discontinuation of tepotinib monotherapy, whereas two (17%) patients had treatment-related adverse events that led to permanent discontinuation (general physical health deterioration in one [8%] patient and gastric haemorrhage in one [8%] patient).

Exposure–safety analysis showed consistent safety across the observed tepotinib exposures for key safety endpoints (appendix pp 23–26).

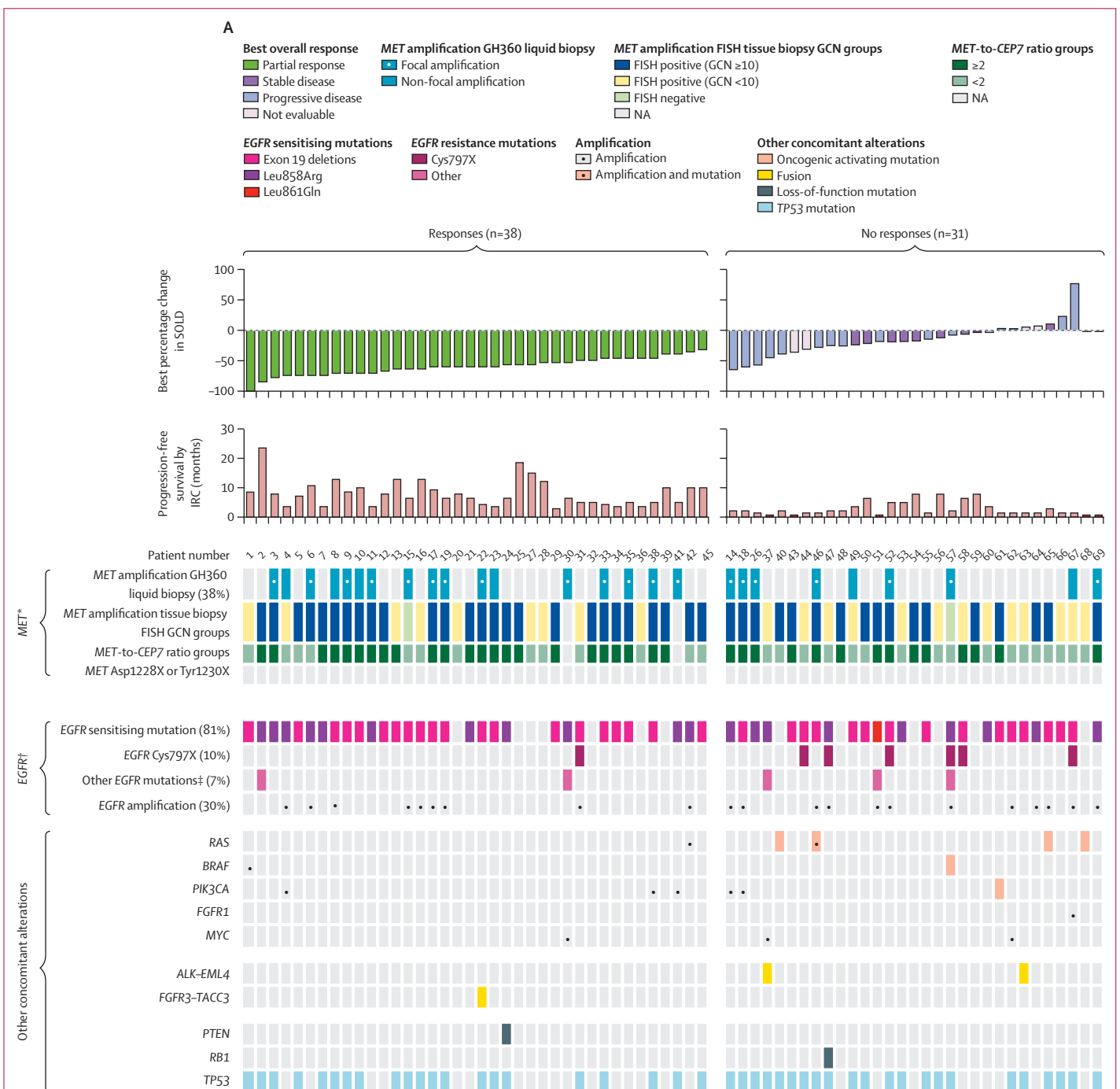
Discussion

In the INSIGHT 2 study, the combination of tepotinib plus osimertinib showed an objective response rate of 50·0% in patients with *EGFR*-mutated NSCLC and *MET* amplification as a resistance mechanism to first-line osimertinib. Median duration of response was 8·5 months, median progression-free survival was 5·6 months, and median overall survival was 17·8 months. The study therefore suggests a potential therapeutic advantage of combining tepotinib with osimertinib in this clinical context, where no approved targeted therapies exist. Tepotinib monotherapy showed limited antitumour activity, with an objective response rate of 8·3%, confirming the benefit of the combined inhibition of EGFR and MET. This finding suggests that controlling both oncogenic drivers is crucial once NSCLC cells acquire resistance to osimertinib via *MET* amplification, rather than targeting MET alone. In patients with *EGFR*-mutated NSCLC who develop high-level *MET* amplification, administration of tepotinib with continuation of osimertinib is an acceptable treatment option.[4]

MET amplification is the most frequent resistance mechanism to first-line osimertinib.[1] Currently, FISH is the gold-standard DNA-based method for detection of *MET* amplification, ensuring timely diagnosis unless tissue samples are unavailable.[12] Although liquid biopsy NGS is highly specific, its limited sensitivity necessitates confirmation of negative results by tissue biopsy FISH as an essential step.[13] Conversely, a positive biomarker detection via liquid biopsy often indicates a higher disease burden, as it requires adequate circulating tumour DNA levels from tumour shedding for detection, suggesting a more aggressive and active disease state.[5] In the INSIGHT 2 study, the median sum of target lesions for patients with *MET* amplification identified by liquid biopsy NGS was 76·2 mm, compared with 64·3 mm in those identified by tissue biopsy FISH. Additionally, liquid biopsy NGS identified mostly *MET* amplification that had focal amplification (*MET*-to-*CEP7* ratio ≥2) and high GCN (≥10), as determined by FISH.[3] For these reasons, integration of both liquid biopsy NGS and tissue biopsy FISH broadened detection of *MET* amplification and enabled demonstration of the meaningful activity of tepotinib plus osimertinib when either detection method was used.

Treatment options for *EGFR*-mutated NSCLC following progression on osimertinib are limited to cytotoxic chemotherapy, while the role of immunotherapy is uncertain. Platinum–pemetrexed yields an objective response rate of 27–42·9% and median progression-free survival of 4·4–5·6 months,[7,11,14,15] with poorer outcomes in the *MET*-amplified population.[16,17] Exploratory analysis of the IMpower150 study suggested improved progression-free survival (hazard ratio [HR] 0·61 [95% CI 0·36–1·03]) with atezolizumab plus carboplatin plus paclitaxel and bevacizumab compared with carboplatin plus paclitaxel and bevacizumab in patients with *EGFR*-mutated NSCLC.[18] In phase 3 trials, the addition of pembrolizumab or nivolumab to platinum-based chemotherapy in *EGFR*-mutated NSCLC post-EGFR TKI failed to improve progression-survival or overall survival.[14,15] In the ORIENT-31 study, sintilimab plus chemotherapy with or without a bevacizumab biosimilar

significantly improved progression-free survival versus chemotherapy alone (HR 0·51 [95% CI 0·39–0·67], p<0·0001, and 0·72 [0·55–0·94], p=0·016, respectively).[19] In the phase 3 MARIPOSA-2 study, amivantamab, a bispecific anti-EGFR and anti-MET antibody, plus chemotherapy with or without lazertinib improved the objective response rate and progression-free survival versus chemotherapy alone (HR 0·48 [95% CI 0·36–0·64], p<0·001, and 0·44 [0·35–0·56], p<0·001, respectively). The objective response rate for amivantamab–chemotherapy was 64% (95% CI 55–72), for amivantamab–lazertinib–chemotherapy 63% (57–69), and for chemotherapy alone 36% (30–42), with significant improvements for the amivantamab combinations (odds



(Figure 3 continues on next page)

ratio [OR] 3·10, p<0·001, and 2·97, p<0·001, respectively). This study did not select for patients with *MET* amplification or other resistance mechanisms.[20] Nevertheless, physician and patient survey data suggest that non-chemotherapy regimens might be preferred owing to greater convenience (ie, avoidance of regular clinic visits for intravenous treatment), lower toxicity, and patient fear of chemotherapy.[21]

Antibody–drug conjugates (ADCs) are being assessed in patients with *EGFR*-mutated NSCLC after progression on EGFR TKIs, with reported objective response rates of 29·8% (95% CI 23·9–36·2) with patritumab deruxtecan (anti-HER3 ADC)[22] and 35% (19·7–53·5) with datopotamab deruxtecan (anti-TROP2 ADC).[23]

Investigations specifically in patients with MET-mediated osimertinib resistance include telisotuzumab vedotin, an anti-MET ADC, plus osimertinib with an objective response rate of 50% (95% CI 29–71) in patients with MET-overexpressing non-squamous NSCLC after failure on previous osimertinib.[24] As for MET TKIs, an objective response rate of 36·4% was reported with glumetinib plus osimertinib in patients with NSCLC with *MET* amplification, following progression on third-generation EGFR TKIs.[25] Savolitinib combined with osimertinib showed promising results in patients with MET upregulation (MET overexpression or *MET* amplification) after progression with an EGFR TKI or osimertinib in TATTON or post-osimertinib in the ORCHARD and SAVANNAH studies, with objective response rates of 32–67% across different studies and patient cohorts.[26–28] In the SAVANNAH study, there were improved outcomes in patients with high-level *MET* amplification (*MET* GCN ≥10), high MET overexpression (immunohistochemistry 3+ in ≥90% of tumour cells), or both, with an objective response rate of 49% (95% CI 39–59), compared with 9% (4–18) in patients without these features.[27] In INSIGHT 2, tepotinib plus osimertinib showed clinical antitumour activity across both higher and lower *MET* amplification levels. However, although exploratory, low activity was observed in patients with co-occurring *EGFR* alterations at Cys797, *RAS*, or *BRAF* mutations, and *ALK* fusions. Resistance mechanisms to combination therapies of EGFR and MET TKIs remain poorly characterised. A retrospective analysis of 17 patients who developed MET resistance after treatment with a combination of a MET TKI and another TKI (not limited to osimertinib), and who underwent post-progression biopsies, revealed that 15 (88·2%) of 17 patients exhibited loss of *MET* amplification.[29] Additionally, seven (41·2%) of 17 patients showed MET on-target resistance mechanisms. Bypass signalling pathways, including *EGFR* amplification (observed in four patients) and RAS–RAF–MAPK alterations, were also identified as potential resistance mechanisms.[29] In our analysis of 29 patients with plasma specimens collected after progression on tepotinib plus osimertinib, we observed on-target

Figure 3: **Biomarker profiles in patients treated with tepotinib plus osimertinib, with *MET* amplification confirmed by central FISH in tissue biopsy, NGS in liquid biopsy, or both, and further analysed using the GH360 assay**

(A) Baseline molecular profiles and response to treatment. Baseline plasma samples were available from 69 patients. Mutations, fusions, and copy number variations were evaluated using the GH360 assay (version 2.11). (B) Post-progression molecular profiles and response to treatment (n=29). Post-progression plasma samples were available from 29 patients. Seven patients did not have baseline profiles. For patients with baseline data, a black border indicates variants that emerged after the baseline assessment. For the remaining patients, it was not possible to confirm whether alterations were present at baseline or emerged at end of treatment. Proportions of patients with particular alterations are given in parentheses. FISH=fluorescence in-situ hybridisation. GCN=gene copy number. GH360=Guardant360. IRC=independent review committee. NA=not available. NGS=next-generation sequencing. SOLD=sum of lesion diameter. *NM_000245.4. †NM_005228.5. ‡Other *EGFR* mutations are those affecting amino acid positions Leu718, Gly719, Gly724, Glu762, Met766, Ser768, Leu792, Pro794, Gly796, and Leu798.

	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	69 (54%)	37 (29%)	3 (2%)	4 (3%)
Diarrhoea	62 (48%)	1 (1%)	0	0
Peripheral oedema	46 (36%)	6 (5%)	0	0
Paronychia	28 (22%)	1 (1%)	0	0
Nausea	24 (19%)	3 (2%)	0	0
Hypoalbuminaemia	22 (17%)	1 (1%)	0	0
Decreased appetite	21 (16%)	5 (4%)	0	0
Aspartate aminotransferase increased	16 (13%)	0	0	0
Blood creatinine increased	15 (12%)	0	0	0
Vomiting	14 (11%)	1 (1%)	0	0
Rash	14 (11%)	0	0	0
Anaemia	13 (10%)	2 (2%)	0	0
Alanine aminotransferase increased	12 (9%)	2 (2%)	0	0
Lipase increased	11 (9%)	2 (2%)	1 (1%)	0
Electrocardiogram QT prolonged	6 (5%)	5 (4%)	0	0
Asthenia	6 (5%)	3 (2%)	0	0
Platelet count decreased	6 (5%)	1 (1%)	1 (1%)	1 (1%)*
Neutrophil count decreased	5 (4%)	1 (1%)	1 (1%)	0
Blood alkaline phosphatase increased	5 (4%)	1 (1%)	0	0
Generalised oedema	4 (3%)	2 (2%)	0	0
White blood cell count decreased	3 (2%)	1 (1%)	2 (2%)	0
Pleural effusion	3 (2%)	0	1 (1%)	0
Dyspnoea	3 (2%)	0	0	1 (1%)
Pneumonitis	2 (2%)	2 (2%)	0	2 (2%)†
Leukopenia	2 (2%)	1 (1%)	0	0
Neutropenia	2 (2%)	1 (1%)	0	0
Dehydration	1 (1%)	1 (1%)	0	0
Lymphocyte count decreased	1 (1%)	1 (1%)	0	0
Pneumonia	0	2 (2%)	0	0
Acute kidney injury	0	1 (1%)	0	0
Carbuncle	0	1 (1%)	0	0
Dermatitis	0	1 (1%)	0	0
Febrile neutropenia	0	1 (1%)	0	0
Hepatic cytolysis	0	1 (1%)	0	0
Malaise	0	1 (1%)	0	0
Myelosuppression	0	1 (1%)	0	0
Respiratory failure	0	0	0	1 (1%)‡

Data are n (%). Listed adverse events were reported in at least 10% of patients at any grade, or in at least one patient at grade 3 or worse. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 25.1). *Grade 5 non-haemorrhage-associated decreased platelet count (a known adverse event associated with osimertinib) occurred in a patient, whose disease progressed after treatment discontinuation and so might have been related to the underlying cancer. †Grade 5 pneumonitis occurred 32 patients and 27 days after initiation of the combination treatment. ‡Grade 5 respiratory failure occurred following COVID-19.

Table 2: **Treatment-related adverse events in the tepotinib plus osimertinib group (n=128)**

resistance mutations in *EGFR* or *MET* in about a third of cases (34%). Putative resistance mutations in *EGFR* (often already detected at baseline after previous osimertinib treatment) were identified in 31% of these patients, with the well characterised Cys797Ser mutation (2389T>A or 2390G>C) being the most prevalent (17%). Additionally, emerging *MET* kinase domain mutations at Asp1228 or Tyr1230 were detected in 14% of patients. Notably, concurrent resistance mutations in both *EGFR* and *MET* were found in 10% of patients, highlighting the complexity of resistance mechanisms that emerge following treatment. Loss of *MET* amplification was observed in nine (75%) of 12 patients with detectable *MET* amplification by NGS at baseline. Emerging *MET* amplification was seen in three patients, with one case of high-level *MET* amplification (>10 *MET* gene copies in circulating tumour DNA) being associated with an emerging *MET* kinase domain mutation. *EGFR* amplification was detected in 55% of cases and emerged in post-baseline samples for five patients. Furthermore, alterations in other signalling pathways, including *KRAS*, *MYC*, *BRAF*, and *PIK3CA*, were identified in 38% of patients, suggesting that resistance to tepotinib plus osimertinib might not solely be driven by changes in *EGFR* or *MET*. The diversity in resistance mechanisms underscores the need for comprehensive molecular testing and subsequent treatment strategies involving various targeted agents, including EGFR–MET bispecific antibodies.[30]

Brain metastases occur frequently in patients with *EGFR*-mutated NSCLC[31] and can be targeted by osimertinib as a CNS-penetrant TKI. At the time of osimertinib progression, brain metastases occur in 34–37% of patients with *MET* amplification and the choice of subsequent treatment should consider the importance for intracranial control.[25,27] Consistent with the CNS penetration of tepotinib,[32] the combination with osimertinib showed clinical activity per RANO-BM in patients with stable CNS metastases, with an intracranial objective response rate of 29·2%, intracranial disease control rate of 79·2%, and median intracranial progression-free survival of 7·8 months.

The safety profile of tepotinib plus osimertinib was consistent with previous reports for the respective monotherapies.[5,33] The frequency of treatment-related adverse events leading to treatment discontinuation was low, and dose reductions or treatment interruptions were used to manage most common treatment-related adverse events such as diarrhoea or peripheral oedema, the latter of which is a MET inhibitor class effect.[5] Importantly, HRQOL was maintained during treatment with improvements in key symptoms, notably cough and pain. Overall, tepotinib plus osimertinib showed a manageable safety profile and allowed patients to defer chemotherapy. This is important because chemotherapy typically necessitates intravenous treatments at the clinic every 3 weeks and is perceived by many patients as psychologically burdensome, especially following an oral treatment such as osimertinib.[21]

Study limitations include the protocol amendment to mandate tissue biopsy FISH alongside liquid biopsy NGS, which reflects the complementary roles of these approaches in capturing *MET* amplification, and the non-comparative, open-label, phase 2 design lacking a control group, which necessitates contextualisation of the results using historical or real-world evidence. Given the evolving treatment landscape, including the addition of chemotherapy to targeted therapies in the first-line treatment of patients with *EGFR*-mutated NSCLC, conducting further studies is challenging.[20,34] The ongoing phase 3 SAFFRON trial (NCT05261399) is comparing savolitinib plus osimertinib against platinum-based doublet chemotherapy. Meanwhile, the phase 3 GEOMETRY-E trial (NCT04816214), which was assessing capmatinib plus osimertinib versus platinum-based doublet chemotherapy, has been terminated.

In conclusion, the INSIGHT 2 study showed that tepotinib plus osimertinib provided promising clinical benefit with a manageable safety profile in patients with *EGFR*-mutated NSCLC, whose disease had progressed on first-line osimertinib and had *MET* amplification. Our findings suggest tepotinib plus osimertinib as a potential chemotherapy-sparing oral targeted therapy option for patients in this setting, who have a high unmet need.

Contributors

Y-LW, AO'B, NK, and CS were responsible for conceptualisation of the study. BE-L, AO'B, NK, KB, CS, KG, and RS contributed to the methodology of the study. EN, Y-LW, TMK, VG, PJV, LBK, J-JY, MW, CH, CKL, JM, TLM, HH, NVN, PLC, FdM, JR, QZ, GF, ATL, JW, CD, TK, HSH, EFS, MW, DT, MM, and XL participated in study investigations. TMK provided resources for the study. BE-L, BMP, AO'B, NK, KB, CS, DJ, KG, and RS were responsible for data curation. Y-LW, BMP, BE-L, SA, AO'B, NK, SB, CS, DJ, KG, and RS contributed to formal analysis of the data. NK, BE-L, AO'B, CS, and RS were responsible for validation of the data. Y-LW, AO'B, SA, BMP, CS, DJ, RS, KG, KB, BE-L, and NK directly accessed and verified the data. YW, TMK, NK, and AO'B were responsible for drafting the original report. All authors had access to the data included in the report, and were responsible for reviewing, editing, and approving the final paper. All authors were involved in data analysis and manuscript preparation; vouch for the completeness and accuracy of the data, and adherence to the study protocol; and had final responsibility for the decision to submit for publication. Funding for a professional medical writer, with access to the data, was provided by the sponsor for support in drafting the manuscript.

Declaration of interests

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Data sharing

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck's Data Sharing Policy. All requests should be submitted in writing to Merck's data sharing portal. When Merck has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck will endeavour to gain agreement to share data in response to requests.

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