Osimertinib plus Selumetinib in *EGFR*-Mutated Non–Small Cell Lung Cancer After Progression on EGFR-TKIs: A Phase Ib, Open-Label, Multicenter Trial (TATTON Part B)

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ABSTRACT

Purpose: MEK/ERK inhibition can overcome acquired resistance to osimertinib in preclinical models. Osimertinib [EGFR–tyrosine kinase inhibitor (TKI)] plus selumetinib (MEK1/2 inhibitor) was assessed in the global TATTON study.

Patients and Methods: This multicenter, open-label, phase Ib study expansion cohort enrolled patients (aged ≥18 years) with *MET*-negative, *EGFR*m advanced NSCLC who had progressed on EGFR-TKIs. Patients were assigned to one of two cohorts by prior first- or second-generation or T790M-directed EGFR-TKI and received osimertinib 80 mg every day and intermittent selumetinib 75 mg twice a day orally. Safety and tolerability (primary objective) and antitumor activity determined by objective response rate (ORR), and progression-free survival (PFS) using RECIST v1.1 were assessed. Data cutoff: March 4, 2020.

Results: Forty-seven patients received treatment (prior first- or second-generation EGFR-TKI, $n = 12$; prior T790M-directed EGFR-TKI, $n = 35$). Forty-four (94%) patients were Asian; 30 (64%) had baseline exon 19 deletion. Most common AEs were diarrhea (89%), decreased appetite (40%), and stomatitis (32%); 11/47 patients (23%) had an AE Grade ≥3 possibly causally selumetinib-related. ORR was 66.7% [95% confidence interval (CI), 34.9–90.1] in the prior first- or second-generation EGFR-TKI group, 22.9% (95% CI, 10.4–40.1) in the prior T790M-directed EGFR-TKI group, and 34.0% (95% CI, 20.9–49.3) overall; median PFS was 15.0 (95% CI, 2.7–33.0), 2.8 (95% CI, 1.6–5.5), and 4.2 months (95% CI, 2.7–7.2), respectively.

Conclusions: In this small study, AEs and tolerability of osimertinib plus selumetinib were as expected, on the basis of previous studies. The combination demonstrated antitumor activity supportive of further investigation in patients with *MET*-negative, *EGFR*m advanced NSCLC who had progressed on a previous EGFR-TKI.

Introduction

EGFR–tyrosine kinase inhibitors (TKI) are recommended for the first-line treatment of patients with *EGFR*-mutated (*EGFR*m) non–small cell lung cancer (NSCLC; refs. 1, 2). Despite the well-established initial efficacy of EGFR-TKIs, patients ultimately develop resistance.

The *EGFR* T790M mutation occurs in approximately 50% of patients who develop resistance to a first- or second-generation EGFR-TKI (3), but has not been reported among patients who develop resistance to osimertinib (4, 5). Other resistance mechanisms that appear with all EGFR-TKIs include *MET* amplification and activation of the RAS/RAF/MEK/ERK (MAPK/ERK) pathway (5–10). The MAPK/ERK signaling pathway is central to cellular proliferation and survival; its upregulation is associated with several resistance mechanisms, including epithelial–mesenchymal transition, a transcription-mediated cellular phenotypic shift that makes cells more invasive and migratory; and it is implicated in both tumor progression and acquired resistance to chemotherapy, targeted therapy, and radiation therapy (11, 12).

Osimertinib is a third-generation, central nervous system active, irreversible, oral EGFR-TKI that potently and selectively inhibits both *EGFR*m and *EGFR* T790M resistance mutations (13–17). Osimertinib is the preferred first-line treatment option for patients with *EGFR*m advanced NSCLC, and the treatment of choice for patients with T790M-positive NSCLC following disease progression on first-line, first- or second-generation EGFR-TKIs (1, 2). Although osimertinib has been shown to elicit tumor responses in patients with advanced NSCLC and T790M-mediated resistance following progression on prior first- or second-generation EGFR-TKIs (14), effective therapies to overcome other resistance mechanisms, such as *MET* or *ERBB2 (HER2)* amplification and MAPK/ERK pathway upregulation, remain elusive, representing a major therapeutic challenge in NSCLC. Furthermore, resistance mechanisms developed by *EGFR*m tumors in response to third-generation EGFR-TKIs are characterized by considerable inter- and intrapatient heterogeneity, and the co-occurrence of multiple resistance mechanisms, further complicating the development of therapeutic strategies to overcome secondary resistance (4, 18, 19).

Preclinical studies have demonstrated that targeting MAPK/ERK signaling through either MEK or ERK inhibition can achieve promising results in delaying or overcoming acquired resistance to osimertinib in several preclinical models (20–24). As previously described in

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Clin Cancer Res 2022;28:4222–31

doi: 10.1158/1078-0432.CCR-21-4329

Translational Relevance

Osimertinib is the preferred first-line treatment for patients with *EGFR*-mutated (*EGFR*m) advanced non–small cell lung cancer (NSCLC), and the treatment of choice for patients with T790M-positive NSCLC following disease progression on first-line first- or second-generation EGFR–tyrosine kinase inhibitors (TKI). Although osimertinib has shown efficacy in patients with T790M-mediated resistance, effective therapies to overcome other resistance mechanisms, such as MAPK/ERK pathway upregulation, remain elusive, representing a major therapeutic challenge in NSCLC. Preclinical studies have shown that MEK/ERK inhibition can delay or overcome acquired resistance to osimertinib. The phase Ib TATTON study expansion cohort investigated the combination of osimertinib and selumetinib, a MEK1/2 inhibitor, in patients with *EGFR*m, *MET*-negative, advanced NSCLC who had progressed on prior EGFR-TKI treatment. The combination showed some promising preliminary antitumor activity and safety profile in this patient population. However, further research is required to determine the overall effectiveness of this therapy in NSCLC.

TATTON Part A, combining osimertinib with an agent that inhibits MAPK/ERK signaling, such as selumetinib, has the potential to enhance activity in patients with acquired resistance to EGFR-TKIs, or delay the development of subsequent resistance (25). Furthermore, the tolerable toxicity profile of osimertinib may support synergistic therapy combinations without excessive overlapping toxicity, which can occur with combination therapy (25).

Selumetinib (ARRY-142886) is an oral, selective inhibitor of MEK1/2 (MAPKK1/2) that has been investigated for the treatment of several cancers and is approved in the United States and other countries for the treatment of children ages 2 or 3 years and above who have symptomatic inoperable neurofibromatosis type 1–related plexiform neurofibromas (26–31). Here we report data from the phase Ib TATTON Part B study expansion cohort, investigating the combination of osimertinib and selumetinib in patients with *EGFR*m, *MET*-negative, advanced NSCLC who had progressed on prior EGFR-TKI treatment.

Patients and Methods

Study design and participants

TATTON (NCT02143466) is a multi-arm, open-label, phase Ib, multicenter study conducted in eight countries (Canada, Japan, Poland, Russia, South Korea, Taiwan, Ukraine, and the United States) to assess the safety, tolerability, and preliminary antitumor activity of osimertinib 80 mg orally every day, in combination with ascending doses of investigational therapeutics in patients with *EGFR*m advanced NSCLC who have progressed following therapy with an EGFR-TKI (25). The TATTON study was a four-part study (Parts A–D). Herein we report the findings of the Part B selumetinib dose-expansion cohort (Supplementary Fig. S1). Results for the Part A dose-escalating cohort and Part B and Part D savolitinib dose-expansion cohorts have been reported previously (5, 32). Results for Part C will be reported separately.

Eligible participants in TATTON Part B were aged ≥18 years (depending on regional age of consent for treatment), with *MET*-negative (no genomic alterations in *MET*), *EGFR*m advanced NSCLC, a World Health Organization performance score (WHO PS) of 0–1, and a minimum life expectancy of 12 weeks. Patients were enrolled following histological or cytological confirmation of *EGFR*m NSCLC (including exon 19 deletion and L858R) and local and central confirmation of *MET* (negative) from a biopsy taken after disease progression. *MET*-negative status was confirmed before study entry using a test undertaken after the most recent disease progression, as previously described (32). Patients required radiological documentation of disease progression on previous EGFR-TKI treatment (which could include osimertinib) and were assigned to one of two cohorts: prior first- or second-generation EGFR-TKI therapy (excluding third-generation; second-line setting and beyond), or immediate prior T790M-directed EGFR-TKI therapy (T790M positive; third-line setting and beyond). At least one lesion was required (not previously irradiated or biopsied during the screening period) that could be accurately measured at baseline as ≥10 mm in the longest diameter with a CT or MRI and was suitable for accurate repeated measurements (according to RECIST v1.1). Adequate bone marrow, organ, liver, and renal function was required, and asymptomatic, stable brain metastases (not requiring steroids for at least 2 weeks prior to receiving study treatment) were permitted. Patients were excluded if they had received treatment with an EGFR-TKI within approximately 5 × half-life (e.g., within 8 days for erlotinib, gefitinib, or afatinib, or within 10 days for dacomitinib) of the first dose of study treatment or any cytotoxic chemotherapy, investigational agents, or other anticancer drugs for the treatment of *EGFR*m advanced NSCLC from a previous treatment regimen or clinical study within 14 days of the first dose of study treatment. Patients who were taking osimertinib as their immediate prior therapy could continue with their current osimertinib treatment without interruption.

The study was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Conference on Harmonization), applicable regulatory requirements, and the policy on bioethics and human biologic samples of the trial sponsor, AstraZeneca. All patients provided informed written consent prior to participation. Provision of standard data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Procedures

Patients received osimertinib 80 mg every day and intermittent (4 consecutive days on/3 days off) selumetinib 75 mg twice a day. The study comprised 28-day cycles with physical examinations performed on Day 1 of each cycle and clinical chemistry, liver function tests, and electrocardiogram assessments conducted at screening, Cycle 1 (Days 1, 8, 15, and 22), Day 1 of Cycles 2–7, and every 8 weeks until treatment discontinuation. Brain imaging was performed at baseline in patients with known or suspected metastases.

Adverse events (AE) were collected throughout the study, from informed consent until the end of follow up (28 ± 7 days after study treatment discontinuation) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Tumors were assessed using CT scans or MRI at baseline (within 28 days of first dose) and every 6 weeks (±7 days) after the first dose until disease progression as defined by RECIST v1.1. After disease progression, patients were followed up every 12 weeks until withdrawal from the study or death.

Criteria for dose reductions and interruptions differed for osimertinib and selumetinib. For osimertinib, if a patient experienced a

Grade 3 or unacceptable toxicity including a dose-limiting toxicity not attributable to the disease or disease-related processes under investigation, dosing could be interrupted, and appropriate supportive therapy administered. If a toxicity resolved or reverted to Grade 2 or lower within 3 weeks of onset, treatment with osimertinib could be restarted at the same dose of 80 mg or a lower dose of 40 mg. If the toxicity did not resolve to Grade 2 or lower after 3 weeks, the patient was withdrawn from the study.

Treatment with selumetinib could be temporarily interrupted if any of the following AEs occurred: a new AE of dyspnea or worsening of pre-existing dyspnea Grade >1 that does not resolve; persistent (>24 hours) Grade 1 or 2 diarrhea despite 24 hours of treatment with high-dose loperamide or any Grade 3 or 4 diarrhea; left ventricular ejection fraction less than lowest limit of normal and >39% (selumetinib dose interruption for up to 6 weeks; if ≤39%, patient was to discontinue selumetinib); creatine kinase >10 × upper limit of normal (ULN; Grade 4) or >5 to ≤10 × ULN with neuromuscular symptoms without obvious cause (Grade 3); diagnosis of retinal pigment epithelial detachment/central serous retinopathy with best corrected visual acuity worse than 20/40; or Grade ≥3 rash or Grade 2 rash considered by the patient to be intolerable. If the toxicity resolved or improved and the patient was showing clinical benefit, treatment with selumetinib could be restarted at the same dose or at a reduced dose at the discretion of the investigator.

Patients could continue to receive osimertinib plus selumetinib beyond disease progression if they were deemed to be receiving clinical benefit in the absence of discontinuation criteria, per investigator assessment. If osimertinib was discontinued due to toxicity, selumetinib could be continued until disease progression, and if selumetinib was discontinued, then osimertinib could be continued beyond disease progression until the investigator judged there to be no further clinical benefit. Toxicity causality was investigator-assessed.

Patients could be discontinued from treatment due to the following: patient decision; severe noncompliance to the study protocol as judged by the investigator or study sponsor; AEs; disease progression as per RECIST v1.1; patients incorrectly initiated on investigational product; pregnancy; and specific stopping criteria: interstitial lung disease, confirmed corneal ulceration, and QTc prolongation with signs or symptoms of serious arrhythmia.

Outcomes

The primary objective of the study was to investigate the safety and tolerability of osimertinib in combination with selumetinib. The secondary objective was a preliminary assessment of antitumor activity of osimertinib plus selumetinib by evaluating objective response rate (ORR), duration of response (DoR), change in tumor size, and progression-free survival (PFS) using RECIST v1.1.

Objective tumor response was assessed using RECIST v1.1 every 6 weeks until disease progression and categorized using: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). For ORR, a response of CR or PR was confirmed by a later scan conducted at least 4 weeks after the initial response was observed. The DoR was defined as the time from the date of first documented response (subsequently confirmed) until the date of documented progression or death in the absence of disease progression. PFS was defined as the time from date of first dosing until the date of objective disease progression as defined by RECIST v1.1 or death (by any cause in the absence of progression) regardless of whether the subject withdrew from osimertinib therapy or received another anticancer therapy prior to progression. The best percentage change in target lesion size was defined as the maximum reduction from baseline or the minimum increase from baseline (in the absence of a reduction) and included all assessments prior to progression or start of subsequent anticancer therapy.

An exploratory objective was a preliminary efficacy assessment of osimertinib plus selumetinib in patients with *RAS/RAF* alterations. Tissue and/or ctDNA analyses were performed to determine *RAS/RAF* mutational status in all 47 patients included in this study, with valid results from at least one assay obtained for 45 patients. ctDNA next-generation sequencing (NGS) was performed on the Guardant Health G360 assay and tissue NGS was performed on the Foundation Medicine FoundationOne Assay. Our analysis focused on the following genes within the G360 panel related to the RAS/RAF signaling pathway: *BRAF*, *HRAS*, *NRAS*, *KRAS*, and *NF1*.

Statistical methods

The sample size was on the basis of providing a preliminary assessment of antitumor activity assuming no activity if ORR was ≤25%. With this assumption, 20 evaluable patients in total would provide reasonable confidence of estimating the chance of observing response rate [0 and ≤2 responses (10%) would be <1% and <10%, respectively]. Data from at least 40 patients would therefore provide a more precise estimation of antitumor activity on the basis of ORR.

Safety data were summarized in the safety analysis set, defined as all patients who received at least one dose of study drug. The analysis population for best objective response, ORR, DoR, change in tumor size, and PFS included those with at least one target lesion measurable at baseline per RECIST v1.1. The proportion of patients with an objective response was presented along with 95% (Clopper–Pearson) confidence intervals (CI). The Kaplan–Meier method was used to summarize time-to-event data. When calculating PFS, patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST assessment. Data are presented from a data cutoff of March 4, 2020. As is usually the case for phase I studies, the results of this study are described with descriptive statistics, and no formal statistical testing was undertaken.

Data availability

De-identified participant data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Requests for data collected for this study, including individual participant data and a data dictionary defining each field in the set, will be considered in line with the above policy. Additional to the clinical study protocol, related documents (e.g., the statistical analysis plan, informed consent form) can be made available.

Results

Patients and treatment

From May 2015 to February 2016, 48 patients with *MET*-negative (*MET* not amplified), *EGFR*m advanced NSCLC were enrolled, 4 of whom had important protocol deviations. Two patients did not meet all inclusion criteria; 1 patient had a baseline left ventricular ejection fraction <55% and 1 had a diastolic blood pressure reading of >95 mmHg at screening. In addition, 2 patients had dose deviations and were prescribed osimertinib 80 mg every day + intermittent selumetinib 50 mg twice a day in error.

Of the 48 patients enrolled, 12 patients had received prior first- or second-generation EGFR-TKI therapy and 36 patients had received a

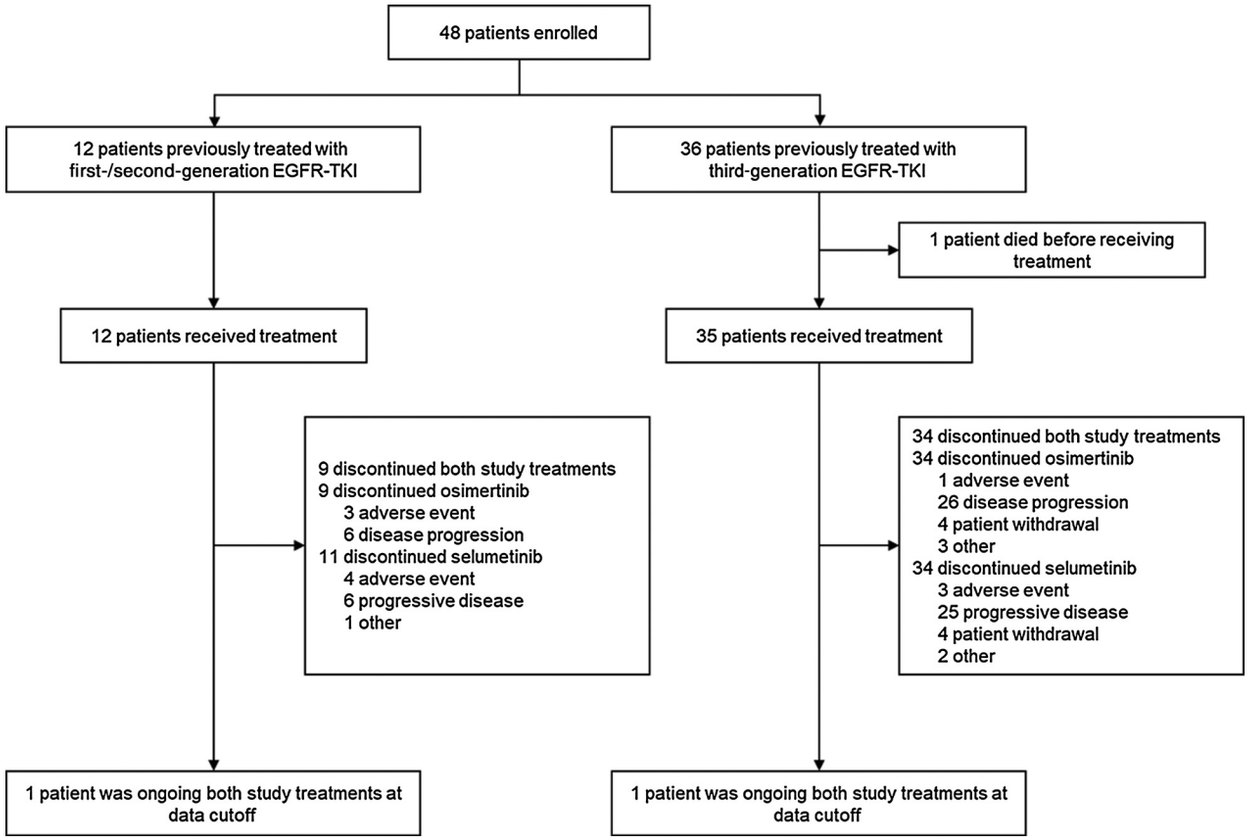

Figure 1.
Patient disposition. Data cutoff: March 4, 2020.

prior T790M-directed EGFR-TKI. Overall, 47 patients received study treatment; 1 patient in the prior T790M-directed EGFR-TKI cohort died prior to receiving any study treatment. Of those patients who had received prior first- or second-generation EGFR-TKI therapy, 9 patients (75%) were known T790M-positive and 3 patients (25%) were known T790M-negative prior to study initiation. Note that T790M status for all patients in this cohort was not mandatory at study entry. All 12 patients received study treatment, with 1 patient still receiving both treatments at data cutoff. Of the patients who had received prior T790M-directed EGFR-TKI therapy, 18 patients (51.4%) had known T790M-positive tumor status at study entry and 35 patients (97.2%) received study treatment, with 1 patient (2.9%) still receiving both treatments at data cutoff (March 4, 2020; **Fig. 1**). No patients were lost to follow-up in either cohort. The median (range) actual treatment duration for osimertinib treatment was 4.37 (0.5–50.4) months; 17.08 (1.6–49.3) months in the prior first- or second-generation EGFR-TKI group and 2.76 (0.5–50.4) months in the prior T790M-directed EGFR-TKI group. The median actual treatment duration for selumetinib treatment was 1.58 months; 4.02 months in the prior first- or second-generation EGFR-TKI group and 1.54 months in the prior T790M-directed EGFR-TKI group. Progressive disease was the most common reason for discontinuation of osimertinib treatment [prior first- or second-generation EGFR-TKI: 6 (50.0%); prior T790M-directed EGFR-TKI: 26 (74.3%)] and selumetinib treatment [prior first- or second-generation EGFR-TKI: 6 (50.0%); prior T790M-directed EGFR-TKI: 25 (71.4%); **Fig. 1**].

Enrolled patients were predominantly female [prior first- or second-generation EGFR-TKI: 10 (83.3%); prior T790M-directed EGFR-TKI: 19 (54.3%)], and Asian [11 (91.7%) and 33 (94.3%), respectively], with a median (range) age of 61 (56–81) and 62 (34–78) years, respectively. Most patients (64%) had a baseline exon 19 deletion (**Table 1**); prior first- or second-generation EGFR-TKI: 5 (41.7%), prior T790M-directed EGFR-TKI: 25 (71.4%). Erlotinib was the most frequently prescribed EGFR-TKI in the prior first- or second-generation EGFR-TKI group [8 (66.7%)] followed by gefitinib [7 (58.3%)]; among patients in the prior T790M-directed EGFR-TKI group, osimertinib was most commonly prescribed [20 (57.1%)] followed by olmutinib [8 (22.9%); **Table 1**].

Safety

All patients who received study treatment ($N = 47$) were included in the safety analysis set, with 100% experiencing any treatment-emergent AE (TEAE; **Table 2**). Overall, the most common TEAEs in patients treated with osimertinib plus selumetinib, regardless of grade, were diarrhea [42 (89.4%)], decreased appetite [19 (40.4%)], and stomatitis [15 (31.9%); **Table 3**]. In the prior first- or second-generation EGFR-TKI group, the most common TEAEs were diarrhea [11 (91.7%)], stomatitis [4 (33.3%)], and anemia [4 (33.3%)]; in the prior T790M-directed EGFR-TKI group, the most common TEAEs were diarrhea [31 (88.6%)], decreased appetite [16 (45.7%)], and fatigue [12 (34.3%); **Table 3**]. Overall, 21 patients (44.7%) had TEAEs Grade ≥3 [7 (58.3%) in the prior

Table 1. Patient demographics and disease characteristics (safety analysis set).

	Osimertinib 80 mg every day + intermittent (4 days on/3 days off) selumetinib 75 mg twice a day ≥2nd line, *MET*-negative status		
Characteristic	**Prior first- or second-generation EGFR-TKI (*n* = 12)**	**Prior T790M-directed EGFR-TKI (*n* = 35)**	**Total (*N* = 47)**
Female sex, *n* (%)	10 (83.3)	19 (54.3)	29 (61.7)
Age, median (range), years	61.0 (56–81)	62.0 (34–78)	61 (34–81)
Race, *n* (%)			
Asian	11 (91.7)	33 (94.3)	44 (93.6)
White	1 (8.3)	2 (5.7)	3 (6.4)
Black/African American	0	0	0
ECOG PS, *n* (%)			
0	3 (25.0)	13 (37.1)	16 (34.0)
1	9 (75.0)	22 (62.9)	31 (66.0)
Histology, *n* (%)			
Adenocarcinoma	11 (91.7)	33 (94.3)	44 (93.6)
LCC	0	1 (2.9)	1 (2.1)
SCC	0	1 (2.9)	1 (2.1)
Missing	1 (8.3)	0	1 (2.1)
Overall disease classification, *n* (%)			
Metastatic[a]	11 (91.7)	35 (100)	46 (97.9)
Locally advanced[b]	1 (8.3)	0	1 (2.1)
Missing	0	0	0
Number of prior lines of anticancer therapy[c], *n* (%)			
0	0	0	0
1	7 (58.3)	0	7 (14.9)
2	1 (8.3)	10 (28.6)	11 (23.4)
3	2 (16.7)	11 (31.4)	13 (27.7)
>3	2 (16.7)	14 (40)	16 (34)
Prior first- or second-generation EGFR-TKI, *n* (%)			
Afatinib	1 (8.3)	5 (14.3)	6 (12.8)
Erlotinib	8 (66.7)	18 (51.4)	26 (55.3)
Gefitinib	7 (58.3)	26 (74.3)	33 (70.2)
Prior third-generation EGFR-TKI, *n* (%)			
Osimertinib	0	20 (57.1)	20 (42.6)
Olmutinib	0	8 (22.9)	8 (17.0)
Naquotinib	0	2 (5.7)	2 (4.3)
Nazartinib	0	2 (5.7)	2 (4.3)
Rociletinib	0	2 (5.7)	2 (4.3)
TAS121	0	1 (2.9)	1 (2.1)
AZD3759	0	1 (2.9)	1 (2.1)
Poziotinib	0	1 (2.9)	1 (2.1)
Central *EGFR* mutations at baseline[d], *n* (%)			
Exon 19 deletion	5 (41.7)	25 (71.4)	30 (63.8)
L858R	7 (58.3)	9 (25.7)	16 (34.0)
Exon 20 insertion	0	1 (2.9)	1 (2.1)
T790M	9 (75.0)	18 (51.4)	27 (57.4)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LCC, large cell carcinoma; SCC, squamous cell carcinoma.
[a]Patient could have any metastatic site of disease.
[b]Patient could only have locally advanced sites of disease.
[c]Only anticancer therapy, excluding adjuvant and neoadjuvant except if they include EGFR-TKI.
[d]Central laboratory data; patients could have more than one mutation.

first- or second-generation EGFR-TKI group and 14 (40.0%) in the prior T790M-directed EGFR-TKI group; **Table 2**].

A total of 42 patients (89.4%) had AEs (of any grade) possibly causally related to selumetinib as assessed by the investigator, including 11 patients (23.4%) with AEs that were Grade ≥3. The most commonly reported AE of Grade ≥3 possibly causally related to selumetinib was diarrhea, reported in 7 patients (14.9%); all other AEs were each reported in 1 patient (Supplementary Table S1).

A total of 31 patients (66.6%) had AEs (of any grade) possibly causally related to osimertinib, of whom 5 patients (10.6%) had AEs that were Grade ≥3: one case each of pulmonary embolism, upper abdominal pain, diarrhea, maculo-papular rash, ejection fraction decreased, and neutrophil count decreased (Supplementary Table S2).

AEs led to the discontinuation of osimertinib in 4 patients [8.5%; 3 patients (25.0%) in the prior first- or second-generation EGFR-TKI group and 1 patient (2.9%) in the prior T790M-directed EGFR-TKI group; **Table 2**]. Influenza, pneumonia, and hepatitis were reported by 1 patient each; another patient reported dyspnea and diarrhea. AEs led to the discontinuation of selumetinib in 8 patients [17.0%; 5 patients (41.7%) in the prior first- or second-generation EGFR-TKI group and 3 patients (8.6%) in the prior T790M-directed EGFR-TKI group]: 4 patients (8.5%) with ejection fraction decreased, 3 patients (6.4%) with diarrhea (including 1 patient who also had dyspnea), and 1 patient (2.1%) with pneumonia.

Serious AEs (SAE) were experienced by 15 (31.9%) patients [4 patients (33.3%) in the prior first- or second-generation EGFR-TKI group; 11 patients (31.4%) in the prior T790M-directed EGFR-TKI group], including 5 (10.6%) patients who had SAEs causally

Table 2. Summary of TEAEs.

	Osimertinib 80 mg every day + intermittent (4 days on/3 days off) selumetinib 75 mg twice a day ≥2nd line, *MET*-negative status		
Patients with an event, *n* (%)	**Prior first- or second-generation EGFR-TKI (*n* = 12)**	**Prior T790M-directed EGFR-TKI (*n* = 35)**	**Total (*N* = 47)**
Any TEAE	12 (100)	35 (100)	47 (100)
Any TEAE Grade ≥3	7 (58.3)	14 (40.0)	21 (44.7)
Any TEAE leading to death	1 (8.3)	1 (2.9)	2 (4.3)
Any TEAE leading to discontinuation			
Osimertinib	3 (25.0)	1 (2.9)	4 (8.5)
Selumetinib	5 (41.7)	3 (8.6)	8 (17.0)
Any TEAE leading to interruption or reduction			
Osimertinib	5 (41.7)	6 (17.1)	11 (23.4)
Selumetinib	7 (58.3)	9 (25.7)	16 (34.0)
Any treatment-emergent SAE[a]	4 (33.3)	11 (31.4)	15 (31.9)
Any treatment-emergent SAE leading to discontinuation			
Osimertinib	3 (25.0)	1 (2.9)	4 (8.5)
Selumetinib	1 (8.3)	1 (2.9)	2 (4.3)
Any treatment-emergent SAE leading to interruption or reduction			
Osimertinib	1 (8.3)	4 (11.4)	5 (10.6)
Selumetinib	2 (16.7)	3 (8.6)	5 (10.6)

Note: Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
Patients with an action taken of "drug permanently discontinued" recorded on the AE CRF are included in the "AE leading to discontinuation" line.
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
Common Terminology Criteria for Adverse Events (version 4.0).
Medical Dictionary for Regulatory Activities (MedDRA) version 22.1.
Abbreviation: CRF, case report form.
[a]Including events leading to death.

Table 3. Most common TEAEs reported in ≥10% of patients in the total population ($N = 47$).

	Osimertinib 80 mg every day + intermittent (4 days on/3 days off) selumetinib 75 mg twice a day ≥2nd line, *MET*-negative status, patients *n* (%)		
Preferred term	**Prior first- or second-generation EGFR-TKI ($n = 12$)**	**Prior T790M-directed EGFR-TKI ($n = 35$)**	**Total ($N = 47$)**
Patients with any TEAE	12 (100)	35 (100)	47 (100)
Diarrhea	11 (91.7)	31 (88.6)	42 (89.4)
Decreased appetite	3 (25.0)	16 (45.7)	19 (40.4)
Stomatitis	4 (33.3)	11 (31.4)	15 (31.9)
Paronychia	3 (25.0)	11 (31.4)	14 (29.8)
Fatigue	1 (8.3)	12 (34.3)	13 (27.7)
Nausea	3 (25.0)	10 (28.6)	13 (27.7)
Rash[a]	3 (25.0)	10 (28.6)	13 (27.7)
Cough	3 (25.0)	8 (22.9)	11 (23.4)
Pyrexia	3 (25.0)	7 (20.0)	10 (21.3)
Anemia	4 (33.3)	5 (14.3)	9 (19.1)
Constipation	1 (8.3)	8 (22.9)	9 (19.1)
Vomiting	1 (8.3)	7 (20.0)	8 (17.0)
Pruritus	2 (16.7)	5 (14.3)	7 (14.9)
White blood cell count decreased	3 (25.0)	4 (11.4)	7 (14.9)
Dry skin	3 (25.0)	3 (8.6)	6 (12.8)
Hypokalemia	0	6 (17.1)	6 (12.8)
Neutrophil count decreased	2 (16.7)	4 (11.4)	6 (12.8)
Arthralgia	3 (25.0)	2 (5.7)	5 (10.6)
Aspartate aminotransferase increased	1 (8.3)	4 (11.4)	5 (10.6)
Hypocalcemia	0	5 (14.3)	5 (10.6)
Peripheral edema	3 (25.0)	2 (5.7)	5 (10.6)

Note: Number (%) of patients with AEs, sorted in decreasing frequency of preferred term (total). Patients with multiple events in the same preferred term are counted only once in the preferred term. Patients with events in more than one preferred term are counted once in each of those preferred terms. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
[a]Represents grouped term reporting.

related to selumetinib. There were no SAEs causally related to osimertinib only (**Table 2**). The most common SAEs were pneumonia, dyspnea, and pyrexia (each 6.4%).

Two (4.3%) patients experienced an AE leading to death (one case of pneumonia and one case in which the AE was not specified); neither were considered causally related to either study treatment.

For osimertinib, no patients required a dose reduction during the treatment period (dose reduction data were not available for 2 patients). For selumetinib, in the first 28 days of treatment, 2 patients (4.3%) required one dose reduction, both due to an AE. After Day 28, 5 patients (10.6%) required one dose reduction, 1 patient (2.1%) required two dose reductions, and 3 patients (6.4%) required three dose reductions. Of these patients, 9 patients (100%) had AEs and 1 patient had additional reasons.

Antitumor activity

All patients who received study treatment ($N = 47$) were included in response analyses. Overall, 16 (34.0%; 95% CI, 20.9–49.3) patients had an objective response: 8 patients (66.7%; 95% CI, 34.9–90.1) in the prior first- or second-generation EGFR-TKI group and 8 patients (22.9%; 95% CI, 10.4–40.1) in the prior T790M-directed EGFR-TKI group (**Table 4**).

Across all 16 patients who had an objective response, the median DoR was 9.1 months (95% CI, 4.2–15.0): 16.3 months [95% CI, 2.9–not calculated (NC)] in the prior first- or second-generation EGFR-TKI group and 7.9 months (95% CI, 2.6–9.7) in the prior T790M-directed EGFR-TKI group (**Fig. 2**; **Table 4**; Supplementary Fig. S2).

In the prior first- or second-generation EGFR-TKI group, the median PFS was 15.0 months (95% CI, 2.7–33.0) and 10 of 12 patients (83.3%) subsequently progressed or died. At 6 and 12 months, 66.7% (95% CI, 33.7–86.0) and 58.3% (95% CI, 27.0–80.1) of patients, respectively, remained progression free. In the prior T790M-directed EGFR-TKI group, median PFS was 2.8 months (95% CI, 1.6–5.5) and 32 of 35 patients (91.4%) subsequently progressed or died (**Table 4**; Supplementary Fig. S3). At 6 and 12 months, 25.3% (95% CI, 12.0–41.1) and 6.3% (95% CI, 1.1–18.3) of patients, respectively, remained progression free.

Median best percentage change from baseline to Week 12 in target lesion size was −45.3% (range: −100% to −8%) in the prior first- or second-generation EGFR-TKI group and −15.3% (range: −65% to 85%) in the prior T790M-directed EGFR-TKI group (Supplementary Fig. S4).

Biomarker analyses

Of the 47 patients who received study treatment, valid genomic results were obtained for 45. Of those, 6 patients had known *RAS*/*RAF* alterations; 2 patients had *BRAF* V600E (tissue and ctDNA $n = 1$, ctDNA only and tissue NGS unavailable $n = 1$); 2 patients had *KRAS* G12X (tissue and ctDNA) and *KRAS* G13X (ctDNA only), respectively; 1 patient had *NRAS* Q61K (ctDNA only and tissue NGS unavailable) alterations; and 1 patient had *NF1* loss of function alteration [ctDNA only and tissue NGS unavailable (*NF1* W1952*)]. Overall, an ORR of 17% was achieved in patients with a *RAS*/*RAF* mutation and the median PFS was 3.4 months (95% CI, 1.6–NC).

In patients with any known *RAS*/*RAF* mutation, ORR was 0% in the prior first- or second-generation EGFR-TKI group ($n = 1$) and 25% in the prior T790M-directed EGFR-TKI group ($n = 5$). Median PFS in patients with any known *RAS*/*RAF* mutation ranged from 1.4 to 5.5 months. Two patients had a PFS of 5.5 months, with a best overall response of SD; 1 patient had *NRAS* Q61K mutation (ctDNA only and tissue NGS unavailable) and 1 patient had *BRAF* V600E mutation (ctDNA only and tissue NGS unavailable).

Discussion

Combination therapy, as a potential strategy to overcome or delay acquired resistance to third-generation EGFR-TKIs in *EGFR*m NSCLC, is supported by a wealth of preclinical data (20–24). However, several clinical trials combining various agents targeting EGFR and MET (hepatocyte growth factor receptor) have failed to make a clinical impact, and patients with acquired resistance to EGFR-TKIs have limited therapeutic options (33, 34).

In preclinical models, targeting MAPK/ERK signaling through either MEK or ERK inhibition has been shown to achieve promising results in helping to delay or overcome acquired resistance to osimertinib (20–24). In light of these findings, the phase Ib TATTON Part B study expansion cohort investigated the combination of osimertinib and selumetinib, a MEK1/2 inhibitor, in patients with *MET*-negative, *EGFR*m advanced NSCLC who had progressed on prior first-, second-, or third-generation EGFR-TKI treatment.

Table 4. Secondary activity endpoints in the evaluable for response set.

	Osimertinib 80 mg every day + intermittent (4 days on/3 days off) selumetinib 75 mg twice a day, ≥2nd line, *MET*-negative status		
	Prior first- or second-generation EGFR-TKI	**Prior T790M-directed EGFR-TKI**	**Total**
Best response, *n* (%)			
Number assessed	12	35	47
Complete response[a]	1 (8.3)	0	1 (2.1)
Partial response[a]	7 (58.3)	8 (22.9)	15 (31.9)
Stable disease[b]	3 (25.0)	13 (37.1)	16 (34.0)
Progressive disease	1 (8.3)	10 (28.6)	11 (23.4)
Death	0	2 (5.7)	2 (4.3)
Not evaluable	0	2 (5.7)	2 (4.3)
Onset and duration of response			
Number assessed	8	8	16
Median (IQR) time to response, months	1.3 (1.2–1.5)	1.3 (1.3–1.5)	1.3 (1.2–1.5)
Median (95% CI) duration of response, months	16.3 (2.9–NC)	7.9 (2.6–9.7)	9.1 (4.2–15.0)
Responders who subsequently progressed or died, *n* (%)	6 (75.0)	8 (100)	14 (87.5)
PFS			
Number assessed	12	35	47
Median (95% CI) PFS, months	15.0 (2.7–33.0)	2.8 (1.6–5.5)	4.2 (2.7–7.2)
Progression-free survival at 6 months, % (95% CI)	66.7 (33.7–86.0)	25.3 (12.0–41.1)	36.6 (22.8–50.5)
PFS at 12 months, % (95% CI)	58.3 (27.0–80.1)	6.3 (1.1–18.3)	20.6 (10.2–33.5)
Progression events, *n* (%)	9 (75.0)	29 (82.9)	38 (80.9)
Median (range) duration of follow-up in censored patients, months	47.62 (46.9–48.3)	0.03 (0.0–1.4)	1.45 (0.0–48.3)

Note: Best response data are for patients who had two follow-up scans. Time to onset of response after first dose was analyzed *post hoc*.
[a]Complete response or partial response confirmed at ≥4 weeks.
[b]Stable disease for ≥6 weeks.

The dosing schedule of osimertinib 80 mg every day and intermittent selumetinib 75 mg twice a day was chosen as the regimen with the most favorable therapeutic index, on the basis of findings of the previous phase Ib dose-finding trial. In TATTON Part A, osimertinib 80 mg every day plus (intermittent or continuous) selumetinib 25 to 75 mg twice a day was assessed in patients with *EGFR*m advanced NSCLC. The most common AEs in the osimertinib plus selumetinib arm were diarrhea (75%), rash (58%), and nausea (47%) across all dose groups; 58% of patients had an AE Grade ≥3 (25). In TATTON Part B, we found the safety profile of this combination to be broadly in line with that reported in TATTON Part A. The most common AEs in the Part B osimertinib plus selumetinib arm were diarrhea (89.4%), decreased appetite (40.4%), and stomatitis (31.9%); 44.7% of patients had an AE Grade ≥3. However, selumetinib appeared to be discontinued more frequently than osimertinib in the prior first- or second-generation EGFR-TKI cohort (17.0% vs. 8.5%) and AEs leading to dose interruption or reduction of osimertinib and selumetinib were reported for 58.3% and 41.7% of patients, respectively. Therefore, the tolerable toxicity profile of osimertinib may support synergistic therapy combinations without excessive overlapping toxicity (25).

It should be noted that it was not possible to prespecify tolerability criteria in the absence of efficacy evaluation (if a combination provides superior outcomes, then higher levels of toxicity may be considered acceptable). At the time of this study, the efficacy of osimertinib was already well documented; however, selumetinib had no significant efficacy data published. Therefore, in the context of tolerability, it is possible that investigators may have selected to discontinue selumetinib earlier than osimertinib if there were concerns over the emerging profile. The combination is currently being tested in a phase II platform study (the biomarker-matched study ORCHARD) for *BRAF* V600E or *BRAF* fusion tumors following progression on first-line osimertinib (35).

Antitumor activity was of interest; however, our findings must be interpreted with caution due to several important limitations, including the small sample size, high discontinuation rate (due to challenges of dosing the combination of osimertinib and selumetinib), and a heterogeneous patient population. Among patients who received a prior first- or second-generation EGFR-TKI, the ORR was 66.7% (8 of 12 patients), median DoR was 16.3 months, and median PFS was 15.0 months. Notably, patients in the prior T790M-directed EGFR-TKI cohort experienced a DoR of 7.9 months despite a low ORR (22.9%, 8 of 35 patients), indicating that for those patients whose tumors did respond, this response was relatively durable. However, the low ORR and PFS (2.8 months) found in the prior T790M-directed EGFR-TKI cohort may indicate some limitations in patient selection for this cohort and the population of patients with long DoR were not molecularly defined.

Furthermore, all patients in the prior T790M-directed EGFR-TKI cohort received osimertinib plus selumetinib in the third-line setting and beyond, while the majority of patients in the prior first- or second-generation EGFR-TKI cohort were treated in the second-line setting. Also, the prior T790M-directed EGFR-TKI cohort in this study included patients who had received prior osimertinib in clinical trials, but not all patients in the prior T790M-directed EGFR-TKI cohort had received agents that were subsequently approved for this indication.

Another potential limitation of the present investigation is the fact that no efficacy analysis by T790M status was performed, and hence we cannot comment on any possible differences in antitumor activity according to whether patients were T790M-positive or -negative, only by immediate prior therapy as a surrogate. However, although there was no efficacy analysis by T790M status, the substantial efficacy observed in the prior first- or second-generation EGFR-TKI cohort was likely attributable to T790M-positive disease and a response to the osimertinib component of the combination. In addition, the ORR,

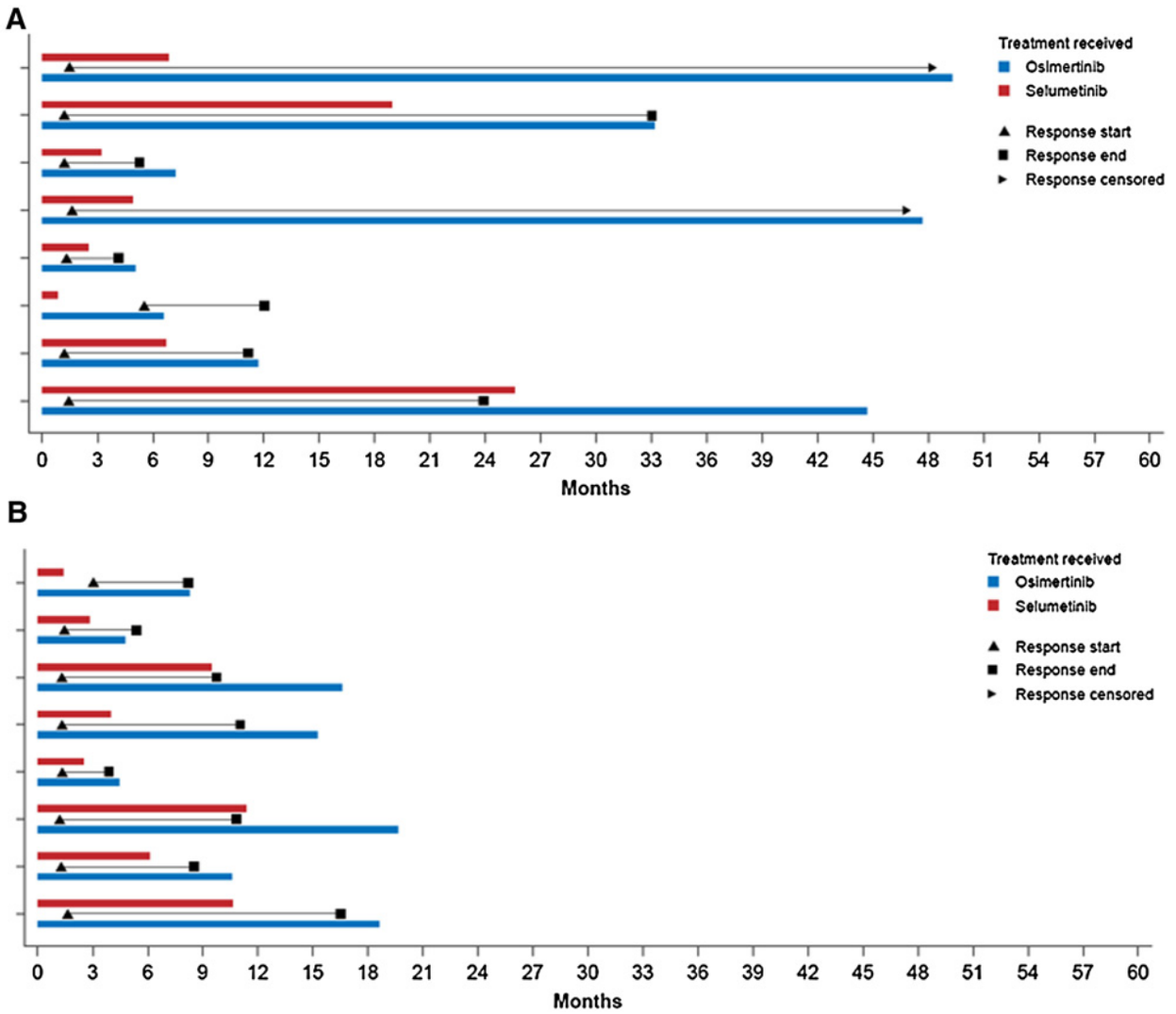

Figure 2.
Swimmer plot of duration and onset of objective response in patients (**A**) previously treated with first- or second-generation EGFR-TKI and (**B**) previously treated with a T790M-directed EGFR-TKI.

median DoR, and median PFS outcomes of the prior first- or second-generation EGFR-TKI cohort on the osimertinib and selumetinib combination were not dissimilar from those seen with osimertinib monotherapy in prior trials (e.g., AURA3; BLOOM); hence, it is unclear how much the combination with a MEK inhibitor is adding in terms of therapeutic benefit (14, 36).

This study did not collect data on the time interval between discontinuation of prior third-generation EGFR-TKI and start of study combination regimen, but in cases of short duration of one of the combination agents, it is unlikely that efficacy was substantially impacted. Therefore, in these limited cases [e.g., patients who received minimal duration (≤1 month) of selumetinib therapy], the rechallenge with osimertinib may have been responsible for the antitumor activity observed. Finally, the generalizability of our findings may be limited by the fact that 93.6% of the patients included in the study were Asian, although monotherapy with osimertinib in the AURA3 trial showed similar efficacy in Asian and non-Asian patients (14, 37).

In exploratory genomic biomarker analyses, ORR was similar between patients with detectable mutations in *RAS*/*RAF* genes and the overall population (ORR = 17% vs. 34%, respectively). Because selumetinib inhibits MEK, which is immediately downstream of RAS/RAF signaling, it was hypothesized that tumors with activating mutations in *RAS/RAF* would be sensitive to osimertinib plus selumetinib; of note, the 6 patients with these alterations did not have a dramatic or potentially outlying response outcome. The data may suggest that these patients do not have increased sensitivity to osimertinib in combination with selumetinib. Our negative biomarker results are disappointing for a biomarker-directed strategy involving osimertinib plus a MEK inhibitor, but the present data are not conclusive and it is hoped that the ongoing ORCHARD trial, which is testing the *BRAF* V600E or *BRAF* fusions, will be a more definitive clinical test of the osimertinib plus MEK inhibitor hypothesis for a relevant biomarker population. In conclusion, the safety profile of osimertinib plus selumetinib demonstrated in this study was found to

be broadly in line with that reported in TATTON Part A (25). The combination showed some promising preliminary antitumor activity in patients with *MET*-negative, *EGFR*m advanced NSCLC who had experienced disease progression on prior first-, second-, or third-generation EGFR-TKIs. However, further research is required to determine the overall effectiveness of this therapy in NSCLC. An ongoing phase II study will explore the combination of osimertinib and intermittent selumetinib (4 consecutive days on/3 days off) as a first-line treatment for patients with *EGFR*m advanced NSCLC (NCT03392246).

Authors' Disclosures

J.C.-H. Yang reports personal fees and other support from Amgen, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Merck KGaA, Novartis, Roche/Genentech, Takeda Oncology, and Yuhan Pharmaceuticals; grants, personal fees, and other support from AstraZeneca; other support from Eli Lilly, JNJ, Puma Technology, Gilead, and GlaxoSmithKline; and personal fees from Ono Pharmaceuticals and Pfizer outside the submitted work. Y. Ohe reports grants and personal fees from AstraZeneca during the conduct of the study; Y. Ohe also reports grants and personal fees from Bristol Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Janssen, Kyorin, Kissei, Merck Sharp & Dohme, Ono Pharmaceutical, Novartis, Nippon Kayaku, and Taiho Pharmaceutical, as well as personal fees from Celtrion and Boehringer Ingelheim outside the submitted work. C.-H. Chiu reports personal fees from Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Janssen, Merck KGaA, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Roche, Takeda, and AstraZeneca outside the submitted work. M. Cantarini reports personal fees and other support from AstraZeneca outside the submitted work. P.A. Jänne reports grants and personal fees from AstraZeneca during the conduct of the study. P.A. Jänne also reports grants and personal fees from Boehringer Ingelheim, Eli Lilly, Daiichi Sankyo, and Takeda Oncology; personal fees from Pfizer, Roche/Genentech, Chugai Pharmaceutical, ACEA Biosciences, SFJ Pharmaceuticals, Voronoi, Biocartis, Novartis, Sanofi Oncology, Mirati Therapeutics, Transcenta, Silicon Therapeutics, Syndax, Nuvalent, Bayer, Eisai, Allorion Therapeutics, Accutar Biotech, and AbbVie; and grants from Puma Technology and Revolution Medicine outside the submitted work. In addition, P.A. Jänne has a patent for EGFR mutations issued and licensed to LabCorp. R.J. Hartmaier reports a patent for US11066709B2 issued. M.J. Ahn reports personal fees from AstraZeneca, Alpha Pharmaceuticals, Merck, Takeda, Eli Lilly, Yuhan Pharmaceuticals, Merck Sharp & Dohme, and Ono Pharmaceuticals outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

J.C.-H. Yang: Conceptualization, resources, data curation, formal analysis, supervision, methodology, project administration, writing–review and editing. **Y. Ohe:** Investigation, writing–review and editing. **C.-H. Chiu:** Investigation, writing–review and editing. **X. Ou:** Formal analysis, validation, writing–review and editing. **M. Cantarini:** Conceptualization, resources, data curation, formal analysis, methodology, writing–review and editing. **P.A. Jänne:** Resources, investigation, writing–review and editing. **R.J. Hartmaier:** Data curation, formal analysis, writing–review and editing. **M.J. Ahn:** Writing–review and editing.

Acknowledgments

The authors thank all of the patients and their families, as well as the staff and investigators at all of the study sites. The study (NCT02143466) was funded by AstraZeneca, Cambridge, UK, the manufacturers of osimertinib and selumetinib. The authors would like to acknowledge Rachel Gater of iMed Comms, an Ashfield Company, part of UDG Healthcare plc and Victoria Jones of OPEN Health Communications, London, UK, for medical writing support that was funded by AstraZeneca, and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, in accordance with Good Publications Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

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Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Received January 26, 2022; revised April 20, 2022; accepted May 24, 2022; published first May 26, 2022.

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