# First-Line Mobocertinib Versus Platinum-Based Chemotherapy in Patients With *EGFR* Exon 20 Insertion–Positive Metastatic Non–Small Cell Lung Cancer in the Phase III EXCLAIM-2 Trial

Pasi A. Jänne, MD, PhD[1]; Bin-Chao Wang, MD[2]; Byoung Chul Cho, MD, PhD[3]; Jun Zhao, MD[4]; Juan Li, MD[5]; Maximilian Hochmair, MD[6]; Solange Peters, MD, PhD[7]; Benjamin Besse, MD, PhD[8]; Nick Pavlakis, PhD, MBBS[9]; Joel W. Neal, MD, PhD[10]; Terufumi Kato, MD[11]; Yi-Long Wu, MD[12]; Danny Nguyen, MD[13]; Junjing Lin, PhD[14]; Jianchang Lin, PhD[14]; Florin Vranceanu, MD, PhD[15]; Annette Szumski, MA, BS[14,16]; Huamao M. Lin, PhD[17]; Robert J. Fram, MD[15]; and Tony S.K. Mok, MD[18]

DOI https://doi.org/10.1200/JCO-24-01269

## ABSTRACT

**PURPOSE** Mobocertinib is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that targets *EGFR* exon 20 insertion (ex20ins) mutations in non–small cell lung cancer (NSCLC). This open-label, phase III trial (EXCLAIM-2, ClinicalTrials.gov identifier: NCT04129502) compared mobocertinib versus platinum-based chemotherapy as first-line treatment of *EGFR* ex20ins+ advanced/metastatic NSCLC.

**METHODS** Patients with treatment-naive *EGFR* ex20ins+ locally advanced/metastatic NSCLC were randomly assigned 1:1 to mobocertinib 160 mg once daily or pemetrexed plus cisplatin or carboplatin every 3 weeks for four cycles followed by maintenance pemetrexed. The primary end point was progression-free survival (PFS) by blinded independent central review (BICR), with planned interim analysis (IA) after approximately 70% of 227 expected PFS events.

**RESULTS** A total of 354 patients were randomly assigned (mobocertinib: n = 179; chemotherapy: n = 175). Baseline characteristics were balanced between arms. At IA (cutoff: April 4, 2023), the median PFS per BICR was 9.6 months in each treatment arm (hazard ratio [HR], 1.04 [95% CI, 0.77 to 1.39]; $P$ = .803). The primary end point crossed the prespecified futility boundary (HR > 1). The confirmed objective response rate (95% CI) per BICR was 32% (26 to 40) with mobocertinib versus 30% (24 to 38) with chemotherapy; the median duration of response was 12.0 versus 8.4 months. Quality-of-life assessments indicated clinically meaningful delays in time to deterioration of lung cancer symptoms, cognitive function, and constipation with mobocertinib versus chemotherapy. Grade ≥3 adverse events in >5% of patients (mobocertinib, chemotherapy) were diarrhea (20%, 1%), anemia (6%, 10%), increased lipase (6%, 0%), and decreased neutrophil count (1%, 7%).

**CONCLUSION** The EXCLAIM-2 trial did not meet its primary end point. The efficacy of mobocertinib was not superior to platinum-based chemotherapy for first-line treatment of patients with *EGFR* ex20ins+ advanced/metastatic NSCLC.

ACCOMPANYING CONTENT

Editorial, p. 1523, and Oncology Grand Rounds, p. 1527

Data Sharing Statement

Data Supplement

Protocol

Accepted December 16, 2024
Published January 29, 2025

J Clin Oncol 43:1553-1563


View Online Article



## INTRODUCTION

Epidermal growth factor receptor (*EGFR*) exon 20 insertion (ex20ins) mutations represent approximately 6%-12% of all *EGFR*+ non–small cell lung cancer (NSCLC) cases.[1,2] First- and second-generation EGFR tyrosine kinase inhibitors (TKIs) are associated with an objective response rate (ORR) of approximately 10% and a progression-free survival (PFS) of approximately 1-3 months in patients with *EGFR* ex20ins+ NSCLC.[2-5] Platinum-based chemotherapy, commonly the first line of therapy for patients with *EGFR* ex20ins mutations,[6] has resulted in ORRs of 24.6%-47.0%, a median PFS of 5.6-7.1 months, and a median overall survival (OS) of 19.6-24.4 months.[6-8] On the basis of real-world evidence, the median PFS ranges from 4.2 to 6.4 months with platinum-based chemotherapy,[9-12] underscoring an unmet need for effective therapies for patients with *EGFR* ex20ins+ NSCLC.

## CONTEXT

**Key Objective**

To assess whether mobocertinib is superior to platinum-based chemotherapy for first-line treatment of patients with advanced epidermal growth factor receptor (*EGFR*) exon 20 insertion (ex20ins) mutation–positive non–small cell lung cancer in a phase III trial (EXCLAIM-2).

**Knowledge Generated**

The primary end point of EXCLAIM-2 was not met, indicating that the efficacy of mobocertinib was not superior to platinum-based chemotherapy.

**Relevance *(T.E. Stinchcombe)***

The next generation of EGFR tyrosine kinase inhibitor (TKI)'s targeting *EGFR* ex20ins mutations will need to have greater efficacy and better tolerability. The preferred phase III trial design, EGFR TKI compared with platinum-based chemotherapy or EGFR TKI in combination with platinum-based chemotherapy compared with chemotherapy alone is undetermined.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

Mobocertinib is a first-in-class, oral EGFR TKI that targets in-frame *EGFR* ex20ins mutations.[13,14] In a phase I/II study of mobocertinib in platinum-pretreated *EGFR* ex20ins+ locally advanced or metastatic NSCLC,[15,16] the confirmed ORR by independent review committee (IRC) was 28%, the median duration of response (DoR) was 15.8 months, and the median PFS by IRC was 7.3 months (November 1, 2021 data cutoff).[17] Mobocertinib received accelerated approval from the US Food and Drug Administration (FDA) in September 2021 for patients with locally advanced or metastatic *EGFR* ex20ins+ NSCLC whose disease has progressed on or after platinum-based chemotherapy[18-20] and was subsequently approved in multiple additional countries worldwide.[19,21]

Here, we report results of the phase III trial (EXCLAIM-2), a confirmatory trial to fulfill the data requirements of the accelerated approval granted by the FDA and conditional marketing approvals granted in other countries. In this trial, we compared the efficacy and safety of first-line mobocertinib with platinum-based chemotherapy in patients with advanced *EGFR* ex20ins+ NSCLC.

## METHODS

### Study Design and Patients

EXCLAIM-2 was a phase III, open-label, multicenter, randomized, active-comparator study (ClinicalTrials.gov identifier: NCT04129502) that was conducted globally (site locations are listed in Data Supplement, Table S1, online only). Patients with previously untreated *EGFR* ex20ins+ NSCLC were randomly assigned (1:1 ratio using block-stratified random assignment with an interactive response system) to receive either mobocertinib 160 mg orally once daily, with or without food, or investigator's choice of intravenous chemotherapy (pemetrexed plus cisplatin or pemetrexed plus carboplatin; Data Supplement). Random assignment was stratified according to the presence of CNS metastases at baseline (yes *v* no) and race (Asian *v* non-Asian). Patients continued treatment until they experienced progressive disease (PD) as assessed by blinded independent central review (BICR), had intolerable toxicity, or met another discontinuation criterion. Patients in the chemotherapy arm could cross over to treatment with mobocertinib after BICR-assessed PD was documented and crossover eligibility criteria were met. Patients in the crossover population started loperamide for diarrhea prophylaxis on the day of their first mobocertinib dose. For patients not in the crossover arm, extensive guidelines were provided for loperamide use on diarrhea onset (Protocol, online only).

Eligible patients were adults with locally advanced or metastatic NSCLC and a documented *EGFR* in-frame ex20ins mutation (central confirmation not required before random assignment; Data Supplement). Additional inclusion criteria were at least one measurable lesion per RECIST v1.1,[22] life expectancy ≥3 months, an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ and hematologic function, and normal QT interval on screening ECG. Patients were excluded if they had untreated symptomatic brain metastases (patients with brain metastases treated with surgery and/or radiation who were stable without requiring corticosteroids to control symptoms within 7 days before random assignment and no evidence of new or enlarging brain metastases were allowed); had symptomatic or asymptomatic spinal cord compression or leptomeningeal disease; received previous systemic treatment for locally advanced or metastatic disease, including local administration, with the exception of neoadjuvant or adjuvant chemotherapy or immunotherapy for stage I-III disease or combined modality chemotherapy/radiation for locally advanced disease if

completed >6 months before development of metastatic disease; or received radiotherapy ≤14 days before random assignment or had not recovered from radiotherapy-related toxicities. Palliative radiation administered outside the chest and brain, stereotactic radiosurgery, and stereotactic body radiotherapy were allowed up to 7 days before random assignment. Complete eligibility criteria are described in the Protocol.

All patients provided written informed consent. The study was conducted in accordance with Good Clinical Practice and ethics in the Declaration of Helsinki. The protocol and informed consent documents were approved by local institutional review boards or ethics committees.

### Assessments

Disease was assessed by computed tomography (CT) and magnetic resonance imaging (MRI) at screening, at 6-week intervals through cycle 18, and every 12 weeks thereafter. Screening disease assessment included imaging of the chest, abdomen, brain, and other metastatic sites (eg, neck, pelvis) only if clinically indicated using CT or MRI with contrast (unless contraindicated). Brain imaging, preferably by contrast-enhanced MRI, was required at screening for all patients and was repeated postbaseline for patients with baseline CNS metastases. Target lesion response (ie, partial response or complete response) was confirmed at least 4 weeks after the response was first documented. All radiographic images were submitted to the imaging core laboratory for central review. Severity of treatment-emergent adverse events (TEAEs) was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. The European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) and the lung cancer module (EORTC quality-of-life questionnaire-lung cancer 13 [QLQ-LC13]) were administered at screening, day 1 of every cycle up to cycle 19, and every four cycles thereafter until the end of treatment.

### Outcomes

The primary end point was PFS assessed by the BICR, per RECIST v1.1. Key secondary end points were confirmed ORR by BICR per RECIST v1.1 and OS. Other secondary end points were PFS and confirmed ORR, as assessed by the investigator; DoR, time to response, and disease control rate (DCR) as assessed by BICR and the investigator; time to deterioration[23] (TTD; Data Supplement) in patient-reported symptoms (particularly core lung cancer and gastrointestinal-related symptoms); and health-related quality-of-life (HRQoL) functioning assessed with the EORTC QLQ-C30[24] and the EORTC QLQ-LC13.[25] Safety end points were TEAEs. Exploratory end points included efficacy in patients who crossed over to mobocertinib after platinum-based chemotherapy.

### Statistical Analysis

Efficacy was analyzed in the intention-to-treat (ITT) population, which included all patients randomly assigned to treatment. Safety was analyzed in all patients who received at least one dose of the study drug. HRQoL end points were analyzed in the patient-reported outcomes (PROs)-ITT population, which included all randomly assigned patients who had baseline and at least one postbaseline HRQoL measurements.

Per the statistical analysis plan, approximately 318 patients were to be enrolled to provide a 90% power to detect a 3.5-month improvement in median PFS (hazard ratio [HR] for disease progression or death, 0.65), after approximately 227 PFS events (PD or death) had occurred, assuming a median PFS of 6.5 months for platinum-doublet chemotherapy and 10 months for mobocertinib in treatment-naïve patients in the target population. This power calculation was based on a two-sided log-rank test controlled at the two-sided 0.05 level, adjusting for the proposed interim analysis (IA) plan and assuming an exponential distribution for PFS. We used an adaptive event-size reassessment approach for the primary end point and a sequential testing procedure for type I error control. One IA was planned after observation of approximately 70% of the minimum total expected PFS events (159 of 227 expected events). An O'Brien-Fleming Lan-DeMets alpha spending function was used for PFS to control the overall two-sided alpha level at .05. The study was to be stopped early for futility if the observed HR was >1 at the IA.

Primary analysis of the primary end point was performed using a two-sided stratified log-rank test stratified by the presence of intracranial CNS metastases at baseline (yes *v* no) and race (Asian *v* non-Asian). The HR was estimated using a stratified Cox regression model. Formal statistical tests of the key secondary efficacy end points were only to be performed if the analysis of the primary end point demonstrated a statistically significantly longer PFS on mobocertinib versus platinum-based chemotherapy with strong control for type I error rate. Kaplan-Meier methods were used to estimate the medians of time-to-event end points and associated two-sided 95% CIs. Statistical analyses were performed using SAS version 9.4 or higher (SAS Institute, Cary, NC).

## RESULTS

### Study Population

Between January 2020 and December 2022, 354 patients were randomly assigned to mobocertinib (n = 179) or platinum-based chemotherapy (n = 175), with 144 patients receiving carboplatin and 19 patients receiving cisplatin (Fig 1). Baseline demographic and disease characteristics were balanced between arms (Table 1). Approximately one

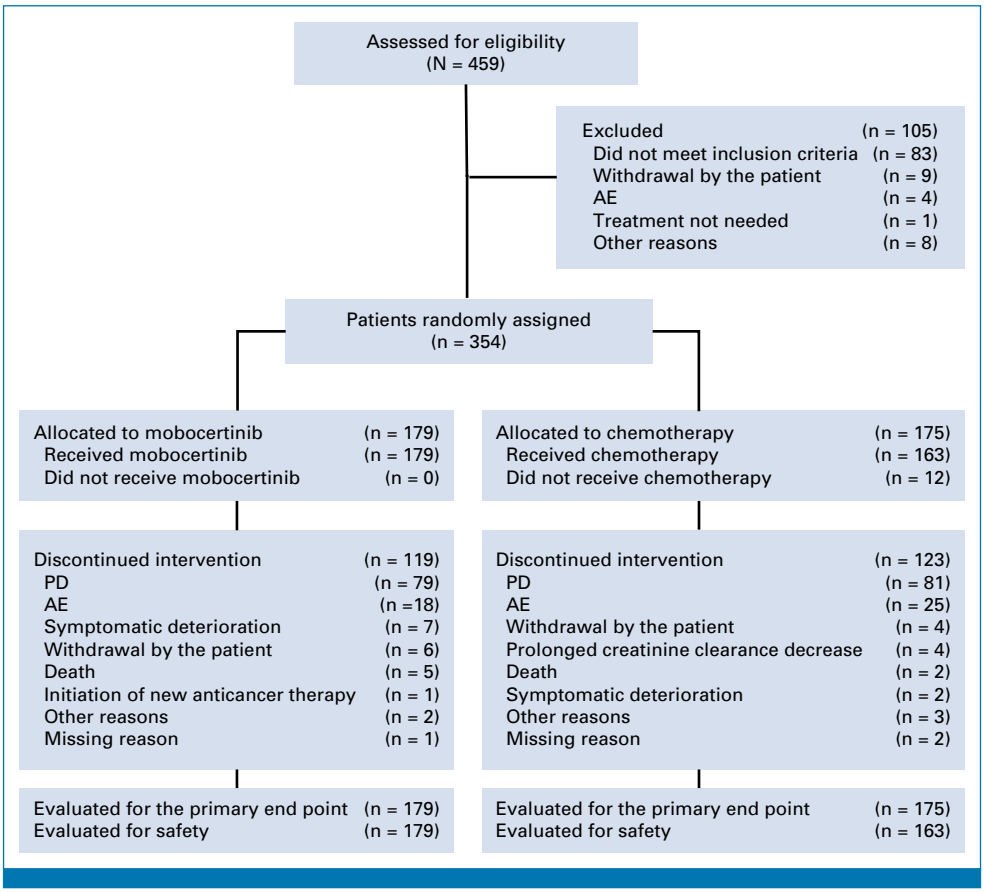


**FIG 1.** CONSORT diagram for the EXCLAIM-2 trial. Data are reported as of the cutoff date for the interim analysis (April 4, 2023). AE, adverse event; PD, progressive disease.

third of patients had intracranial metastases at baseline in the mobocertinib (33%) and chemotherapy arms (31%).

As of April 4, 2023, 60 patients (34%) in the mobocertinib arm and 40 patients (23%) in the chemotherapy arm remained on assigned treatment. The median (range) follow-up was 13.1 months (0.5-36.4) for mobocertinib and 13.8 months (0.03-37.8) for chemotherapy. The median (range) relative dose intensity was 91.5% (3.1-100) in the mobocertinib arm and 100% for cisplatin (93.7-100), carboplatin (62.5-100), and pemetrexed (62.5-100) in the chemotherapy arm. The median dose in the 60 patients remaining on mobocertinib was 120 mg once daily.

Subsequent anticancer therapies are summarized in the Data Supplement (Table S2).

## Efficacy

### *Progression-Free Survival*

The median BICR-assessed PFS was 9.6 months (95% CI, 7.1 to 11.1) in the mobocertinib arm and 9.6 months (95% CI, 7.2 to 11.4) in the chemotherapy arm (HR, 1.04 [95% CI, 0.77 to 1.39]; log-rank $P = .803$; Fig 2A). Thus, the primary end point crossed the prespecified futility boundary (HR >1), as concluded by an independent data monitoring committee, and the study was discontinued. The median PFS by investigator assessment was 8.6 months (95% CI, 6.9 to 9.9) in the mobocertinib arm and 8.4 months (95% CI, 7.1 to 11.1) in the chemotherapy arm. Subgroup analyses of BICR-assessed PFS revealed no apparent differences between prespecified groups (Fig 2B). In post hoc subgroup analyses, there were no apparent differences between patients with near-loop versus far-loop *EGFR* ex20ins mutations (Data Supplement, Tables S3 and S4). Exploratory analyses of CNS progression are reported in the Data Supplement.

Sixty-three patients crossed over from chemotherapy to mobocertinib. These patients had a median BICR-assessed PFS of 6.8 months (95% CI, 3.9 to 10.6) on second-line mobocertinib. Additional results for these patients are reported in the Data Supplement (Table S5).

### *Antitumor Response*

The confirmed ORR with mobocertinib versus chemotherapy was 32% (95% CI, 26 to 40) versus 30% (95% CI, 24 to 38) by

**TABLE 1.** Patient Demographics and Baseline Characteristics

| Characteristic | Mobocertinib (n = 179) | Chemotherapy (n = 175) |
|---|---|---|
| Age, years, median (range) | 64 (25-87) | 62 (31-88) |
| Sex, female, No. (%) | 108 (60) | 116 (66) |
| Race, No. (%) | | |
| Asian | 98 (55) | 98 (56) |
| White | 72 (40) | 65 (37) |
| Black or African American | 3 (2) | 0 |
| Native Hawaiian or other Pacific Islander | 1 (1) | 0 |
| Not reported | 5 (3) | 12 (7) |
| Histology, No. (%) | | |
| Adenocarcinoma | 178 (99) | 172 (98) |
| Adenocarcinoma with mixed subtypes | 0 | 1 (1) |
| Adenosquamous carcinoma | 0 | 1 (1) |
| Other | 1 (1) | 1 (1) |
| ECOG performance status, No. (%) | | |
| 0 | 84 (47) | 74 (42) |
| 1 | 95 (53) | 101 (58) |
| History of cigarette smoking, No. (%) | | |
| Never | 97 (54) | 106 (61) |
| Former | 78 (44) | 62 (35) |
| Current | 4 (2) | 7 (4) |
| Disease stage at study entry, No. (%) | | |
| IIA/B | 2 (1) | 1 (1) |
| IIIA/B/C | 9 (5) | 7 (4) |
| IVA | 70 (39) | 61 (35) |
| IVB | 98 (55) | 105 (60) |
| Time since initial diagnosis, months, median (range) | 1.7 (0.1-82.8) | 1.8 (0.3-151.9) |
| Baseline brain metastases, No. (%) | 59 (33) | 55 (31) |

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

BICR assessment and 37% (95% CI, 30 to 45) versus 30% (95% CI, 24 to 38) by investigator assessment (Table 2). The DCR was 87% with mobocertinib and 80% with chemotherapy by BICR and 93% and 83%, respectively, by investigator assessment. The median time to response by BICR was 1.5 months with mobocertinib and 2.8 months with chemotherapy. The median DoR by BICR was 12.0 months (95% CI, 8.5 to 23.6) with mobocertinib and 8.4 months (95% CI, 5.7 to 11.0) with chemotherapy (Fig 2C).

### *Overall Survival*

The median OS was not estimable (NE) in the mobocertinib arm (95% CI, 22.6 to NE) and 30.0 months (95% CI, 29.0 to NE) in the chemotherapy arm (HR, 0.98 [95% CI, 0.62 to 1.54]; Fig 2D), with 39 (22%) deaths in the mobocertinib arm and 38 (22%) in the chemotherapy arm. The 2- and 3-year OS rates were 61% (95% CI, 49 to 71) and 51% (95% CI, 36 to 64) in the mobocertinib arm and 62% (95% CI, 50 to 73) and 47% (95% CI, 30 to 63) in the chemotherapy arm, respectively.

### *Patient-Reported Outcomes*

The median TTD in EORTC QLQ-LC13 composite lung cancer symptom score (cough, dyspnea, chest pain) was 9.4 months and 5.0 months for the mobocertinib and chemotherapy arms, respectively; event rates were 46% and 56% in the mobocertinib and chemotherapy arms, respectively (HR, 0.68 [95% CI, 0.50 to 0.93]; Fig 3). TTD was shorter for diarrhea and appetite loss but longer for constipation in the mobocertinib arm versus the chemotherapy arm (Data Supplement, Fig S1). For diarrhea, events occurred in 84% of patients in the mobocertinib arm versus 12% in the chemotherapy arm (HR, 16.73 [95% CI, 10.21 to 27.41]). Appetite loss events occurred in 52% versus 34% in the mobocertinib and chemotherapy arms, respectively (HR, 1.90 [95% CI, 1.35 to 2.68]). Constipation events occurred in 9% of patients in the mobocertinib arm versus 38% in the chemotherapy arm (HR, 0.185 [95% CI, 0.105 to 0.328]). TTD for global health status/quality-of-life and other functional domains is shown in the Data Supplement (Fig S2).

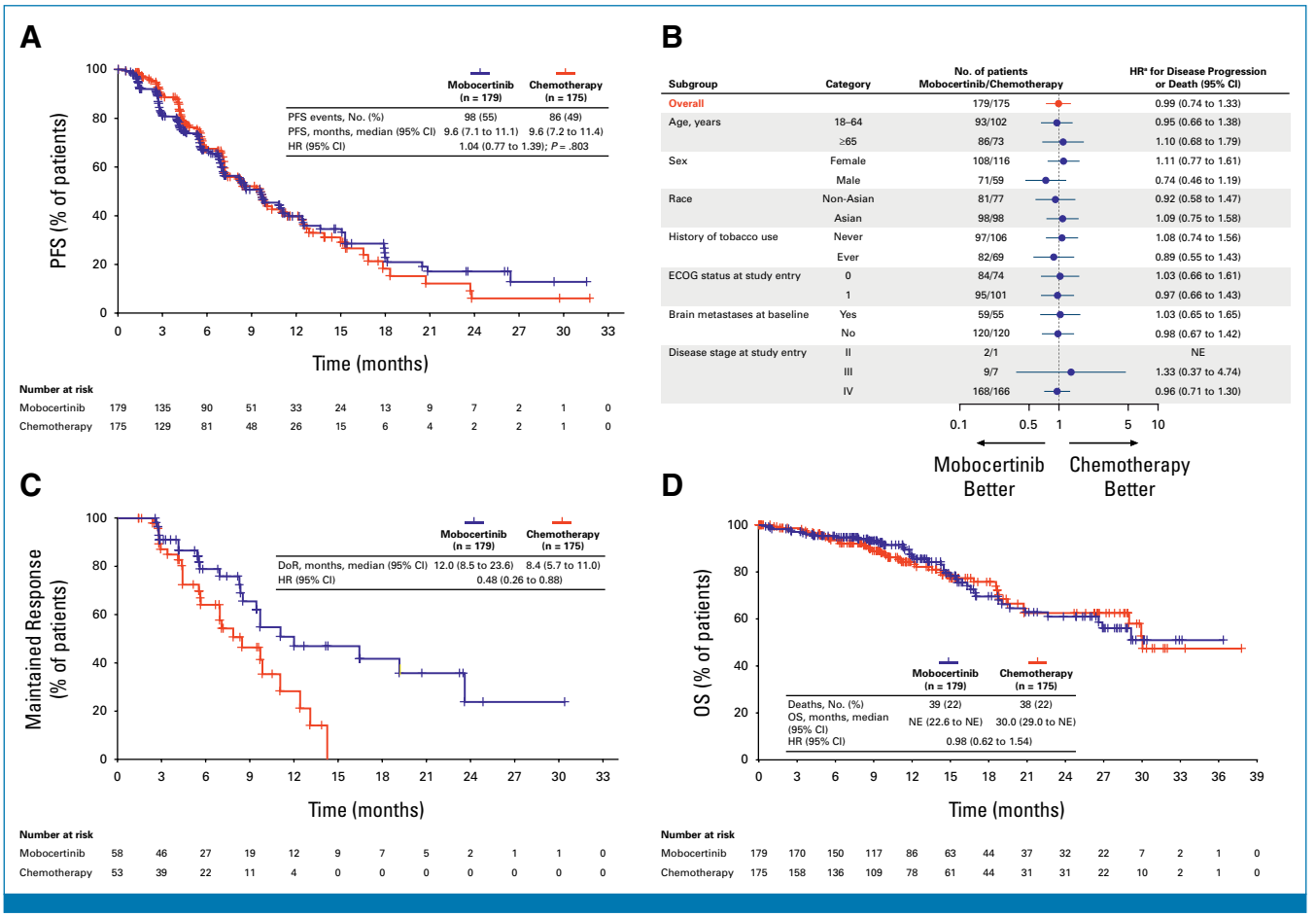


**FIG 2.** Efficacy of first-line mobocertinib versus platinum-based chemotherapy in patients with *EGFR* ex20ins+ NSCLC. (A) Kaplan-Meier–estimated PFS by BICR assessment in the ITT population. (B) Forest plot of HRs for BICR-assessed PFS across patient subgroups. HRs are based on an unstratified Cox proportional hazards regression model. (C) DoR in confirmed responders. (D) OS in the ITT population. [a]<1 HR for treatment indicates better prevention of progression or death in the mobocertinib arm compared with the chemotherapy arm. BICR, blinded independent central review; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; *EGFR* ex20ins, epidermal growth factor receptor exon 20 insertion; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; NSCLC, non–small cell lung cancer; OS, overalll survival; PFS, progression-free survival.

### Safety

In the mobocertinib arm, the most common any-grade TEAEs were diarrhea (96%), paronychia (47%), decreased appetite (43%), and stomatitis (40%; Table 3). In the chemotherapy arm, the most common any-grade TEAEs were constipation (48%), nausea (47%), and anemia (42%). The most common grade ≥3 TEAEs were diarrhea (20%), lipase increased (6%), and anemia (6%) in the mobocertinib arm and anemia (10%), neutropenia (9%), and neutrophil count decreased (7%) in the chemotherapy arm. Treatment-related adverse events and TEAEs of clinical interest are summarized in the Data Supplement (Tables S6 and S7).

Dose modifications because of TEAEs (including dose reduction, dose rate reduction, dose interruption, drug withdrawal, dose delay, or drug infusion interruption) occurred more frequently with mobocertinib (77%) versus chemotherapy (63%; Table 3). The incidences of TEAEs leading to dose interruption and to reduction were 70% and 45% in the mobocertinib arm versus 6% and 20% in the chemotherapy arm, respectively. In the chemotherapy arm, 49% of patients had dose delays because of TEAEs. TEAEs led to treatment discontinuation in 18% in the mobocertinib arm and 20% in the chemotherapy arm. Deaths occurred in 10 patients in the mobocertinib arm and three patients in the chemotherapy arm (Data Supplement, Table S8). No deaths in the mobocertinib arm were deemed treatment-related; one death in the chemotherapy arm resulted from sepsis that was considered related to pemetrexed/carboplatin. The HR for PFS between the two treatment arms did not appear to be affected by dose reduction for TEAEs (Data Supplement, Table S3). In the mobocertinib arm, 24% of patients had one dose reduction (regardless of cause) and 26% had ≥two dose reductions.

## DISCUSSION

At the IA of EXCLAIM-2, the primary end point was not met. The efficacy of mobocertinib was not superior to platinum-

**TABLE 2.** Efficacy of First-Line Mobocertinib Versus Platinum-Based Chemotherapy

| Assessment | Mobocertinib (n = 179) | Chemotherapy (n = 175) |
|---|---|---|
| BICR-assessed confirmed objective response[a] | | |
| No. of patients | 58 | 53 |
| % (95% CI) | 32 (26 to 40) | 30 (24 to 38) |
| CR, No. (%) | 0 | 1 (1) |
| PR, No. (%) | 58 (32) | 52 (30) |
| Stable disease, No. (%)[b] | 97 (54) | 87 (50) |
| PD, No. (%) | 14 (8) | 6 (3) |
| Not evaluable, No. (%) | 10 (6) | 29 (17) |
| Confirmed DCR, No. (%) [95% CI] | 155 (87) [81 to 91] | 140 (80) [73 to 86] |
| Investigator-assessed confirmed objective response[a] | | |
| No. of patients | 67 | 53 |
| % (95% CI) | 37 (30 to 45) | 30 (24 to 38) |
| CR, No. (%) | 1 (1) | 3 (2) |
| PR, No. (%) | 66 (37) | 50 (29) |
| Stable disease, No. (%)[b] | 98 (55) | 91 (52) |
| PD, No. (%) | 8 (5) | 10 (6) |
| Not evaluable, No. (%) | 6 (3) | 21 (12) |
| Confirmed DCR, No. (%) [95% CI] | 165 (92) [87 to 96] | 144 (82) [76 to 88] |
| DoR in confirmed responders, months, median (95% CI) | | |
| BICR-assessed | n = 58 | n = 53 |
| | 12.0 (8.5 to 23.6) | 8.4 (5.7 to 11.0) |
| Investigator-assessed | n = 67 | n = 53 |
| | 8.3 (6.9 to 11.5) | 9.7 (4.5 to 11.3) |
| Time to response, months, median (range) | | |
| BICR-assessed | n = 58 | n = 53 |
| | 1.5 (1.2-9.7) | 2.8 (1.3-8.5) |
| Investigator-assessed | n = 67 | n = 53 |
| | 1.4 (1.2-8.4) | 1.9 (1.3-20.7) |

Abbreviations: BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DoR, duration of response; PD, progressive disease; PR, partial response.
[a]Objective response by RECIST version 1.1.
[b]Stable disease observed ≥6 weeks after first study drug administration.

based chemotherapy as first-line treatment of *EGFR* ex20ins+ NSCLC. The median PFS by BICR was 9.6 months in both arms (HR, 1.04 [95% CI, 0.77 to 1.39]; $P = .803$). The primary end point crossed the prespecified futility boundary, and the trial was discontinued prematurely. For mobocertinib, the median PFS by BICR of 9.6 months was close to the assumed PFS of 10 months as defined in the EXCLAIM-2 study protocol, exceeding previous reports of median PFS achieved with platinum-based chemotherapy in this setting, ranging from 4.2 to 7.1 months.[6,8,9,11,12,26] It is unclear why the chemotherapy arm showed a longer median PFS compared with historical data. Comparisons of patient populations among different studies are challenging. Effective management of adverse events resulting in a high median relative dose intensity among patients in the chemotherapy arm (100% among patients treated with pemetrexed or cisplatin/carboplatin) might have contributed to the outcomes in our study. For mobocertinib, there was a higher rate of dose reductions because of TEAEs in this study (45%) versus the previous phase I/II trial (27%), which could have potentially affected response to treatment, although median PFS was longer in the present study (9.6 months *v* 7.3 months)[17] and median relative dose intensity was high (91.5%). Other clinical features of patients may be relevant, such as differences in subtypes of *EGFR* exon20ins+ mutations between trials. Despite the lack of superiority of the primary end point of median PFS by BICR, mobocertinib performed better on some secondary efficacy end points. Patients in the mobocertinib arm had a shorter median time to response by BICR (1.5 months *v* 2.8 months) and longer DoR by BICR (12.0 months *v* 8.4 months) compared with the chemotherapy arm. Furthermore, median OS was NE in the mobocertinib arm (*v* 30 months in the chemotherapy arm).

The median PFS among patients who crossed over from chemotherapy to mobocertinib during the study was

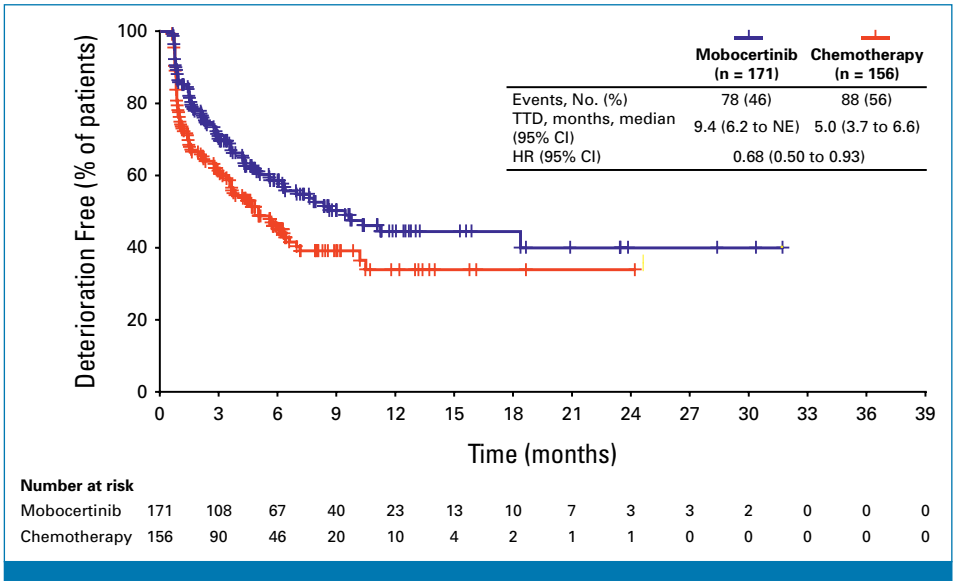


**FIG 3.** TTD in patient-reported lung cancer symptoms. TTD in the EORTC QLQ-LC13 composite lung cancer symptom score (cough, dyspnea, and chest pain). A clinically meaningful change was defined as an 11.1-point (for dyspnea) or 33.3-point (for cough or chest pain) deterioration for the EORTC QLQ-LC13 composite score scale. EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; NE, not estimable; QLQ-LC13, quality-of-life questionnaire-lung cancer 13; TTD, time to deterioration.

comparable with previous results with mobocertinib in the phase I/II study in platinum-pretreated patients with *EGFR* ex20ins+ NSCLC.[17] In that study, the median PFS was 7.3 months,[17] compared with 6.8 months in patients who crossed over to mobocertinib in the current study.

The safety and tolerability of mobocertinib were consistent with previous reports.[16,17] No new safety signals were identified. The overall incidence of TEAEs and rates of discontinuation because of TEAEs were similar between treatment arms. Dose reductions and interruptions because of TEAEs were more frequent in the mobocertinib arm than in the chemotherapy arm, whereas dose delays were considerably more frequent with chemotherapy. The incidences of any-grade and grade ≥3 treatment-related diarrhea in EXCLAIM-2 were consistent with those observed in the phase I/II study.[16] The high rate of diarrhea was reflected in a decreased TTD in diarrhea with mobocertinib compared with chemotherapy in the patient-reported EORTC QLQ-C30 symptom scale. As expected, any-grade nausea was more prevalent with chemotherapy, consistent with previous reports.[27,28] Myelosuppression, a substantial medical burden associated with chemotherapy,[29] was less common with mobocertinib than chemotherapy.

Compared with chemotherapy, mobocertinib demonstrated clinically meaningful delays in TTD of the LC13 lung cancer composite end point and cognitive function but was associated with earlier worsening of diarrhea and appetite loss. These results align with a previous evaluation of PROs after mobocertinib treatment in patients with *EGFR* ex20ins+ NSCLC who had previously received platinum-based chemotherapy.[30]

On the basis of these interim results from EXCLAIM-2, the trial did not fulfill the legal and regulatory data requirements of the accelerated approval granted by the FDA and the conditional marketing approvals granted in other countries.[31] Takeda has voluntarily withdrawn all marketing authorizations for mobocertinib globally. The accelerated approval pathway is intended for treatments that potentially fulfill a high unmet medical need for patients with serious or life-threatening diseases. Although EXCLAIM-2 did not meet its primary end point, the results provide additional supportive evidence of clinical activity with mobocertinib in patients with *EGFR* ex20ins+ NSCLC, shown in the phase I/II study that led to mobocertinib's accelerated approval.[16] The clinical activity of mobocertinib compares favorably with that observed historically in other studies of single-agent first-generation EGFR TKIs as first-line therapy in patients with NSCLC with *EGFR*-sensitizing mutations, for which the median PFS ranged from 4.7 to 16.6 months in a systematic review.[32] The confirmatory EXCLAIM-2 study was designed as a head-to-head comparison of mobocertinib against standard-of-care chemotherapy, rather than as an add-on combination study comparing mobocertinib plus chemotherapy versus chemotherapy alone, which was used in PAPILLON, the confirmatory phase III trial for amivantamab,[8] the only other agent currently approved for *EGFR* ex20ins+ NSCLC. In PAPILLON, median PFS with amivantamab plus chemotherapy (11.4 months [95% CI, 9.8 to 13.7]) was significantly longer than with chemotherapy alone (6.7 months [95% CI, 5.6 to 7.3]).[8] It is unclear why PFS in patients treated with chemotherapy alone differed between the PAPILLON and EXCLAIM-2 studies, despite similar

**TABLE 3.** Safety Overview and TEAEs of Any Grade Reported in ≥15% of Patients and Grade ≥3 TEAEs Reported in ≥3% of Patients

| | Mobocertinib (n = 179) | | Chemotherapy (n = 163)[a] | |
|---|---|---|---|---|
| TEAE | Any Grade, No. (%) | Grade ≥3, No. (%) | Any Grade, No. (%) | Grade ≥3, No. (%) |
| Overview of TEAEs | | | | |
| ≥One TEAE | 178 (99) | 111 (62) | 160 (98) | 86 (53) |
| ≥One TRAE | 177 (99) | 82 (46) | 154 (95) | 60 (37) |
| ≥One serious TEAE | 64 (36) | — | 41 (25) | — |
| TEAE leading to | | | | |
| Dose modification[b] | 137 (77) | — | 103 (63) | — |
| Dose interruption | 125 (70) | — | 9 (6) | — |
| Dose reduction | 81 (45) | — | 32 (20) | — |
| Treatment discontinuation | 33 (18) | — | 33 (20) | — |
| TEAEs of any grade reported in ≥15% or of grade ≥3 reported in ≥3% of patients | | | | |
| Diarrhea | 172 (96) | 36 (20) | 30 (18) | 2 (1) |
| Paronychia | 84 (47) | 1 (1) | 1 (1) | 0 |
| Decreased appetite | 77 (43) | 4 (2) | 47 (29) | 2 (1) |
| Stomatitis | 72 (40) | 7 (4) | 23 (14) | 0 |
| Nausea | 66 (37) | 2 (1) | 77 (47) | 3 (2) |
| Dermatitis acneiform | 63 (35) | 2 (1) | 3 (2) | 0 |
| Dry skin | 61 (34) | 1 (1) | 8 (5) | 0 |
| Fatigue | 56 (31) | 4 (2) | 56 (34) | 3 (2) |
| Increased blood creatinine | 53 (30) | 2 (1) | 11 (7) | 1 (1) |
| Increased lipase | 53 (30) | 11 (6) | 8 (5) | 0 |
| Anemia | 52 (29) | 10 (6) | 68 (42) | 16 (10) |
| Vomiting | 46 (26) | 4 (2) | 42 (26) | 2 (1) |
| Increased amylase | 45 (25) | 3 (2) | 8 (5) | 0 |
| Weight decreased | 43 (24) | 2 (1) | 12 (7) | 0 |
| Pruritus | 35 (20) | 0 | 8 (5) | 0 |
| Alopecia | 34 (19) | 0 | 17 (10) | 0 |
| Cough | 34 (19) | 0 | 26 (16) | 0 |
| Increased ALT | 33 (18) | 3 (2) | 46 (28) | 4 (3) |
| COVID-19 | 33 (18) | 1 (1) | 27 (17) | 1 (1) |
| Mouth ulceration | 32 (18) | 1 (1) | 6 (4) | 0 |
| Back pain | 30 (17) | 2 (1) | 26 (16) | 1 (1) |
| Increased AST | 28 (16) | 0 | 44 (27) | 0 |
| QT-interval prolonged on ECG | 28 (16) | 5 (3) | 2 (1) | 1 (1) |
| Constipation | 22 (12) | 1 (1) | 78 (48) | 0 |
| Asthenia | 20 (11) | 4 (2) | 24 (15) | 0 |
| Dyspnea | 18 (10) | 0 | 27 (17) | 4 (3) |
| Headache | 18 (10) | 1 (1) | 27 (17) | 0 |
| Decreased platelet count | 10 (6) | 1 (1) | 26 (16) | 5 (3) |
| Decreased WBC count | 9 (5) | 1 (1) | 28 (17) | 5 (3) |
| Decreased neutrophil count | 8 (4) | 2 (1) | 34 (21) | 12 (7) |
| Decreased lymphocyte count | 18 (10) | 6 (3) | 7 (4) | 1 (1) |
| Neutropenia | 2 (1) | 1 (1) | 27 (17) | 14 (9) |

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a]Twelve patients randomly assigned to chemotherapy did not receive treatment.
[b]A dose modification was defined as any of the following: dose reduction, dose rate reduction, dose interruption, drug withdrawal, dose delay, or drug infusion interruption.

inclusion criteria.[8] The mobocertinib accelerated approval experience highlights the need to thoroughly assess the pros and cons of potential study designs of phase III confirmatory trials for full regulatory approval. Several EGFR TKIs in clinical development for patients with *EGFR* ex20ins+ NSCLC, including sunvozertinib/DZD9008 (phase III, ClinicalTrials.gov identifier: NCT05668988), zipalertinib/CLN-081 (phase III, ClinicalTrials.gov identifier: NCT05973773), and ORIC-114 (phase I/II, ClinicalTrials.gov identifier: NCT05315700), may provide additional treatment options for this patient population.

In conclusion, the EXCLAIM-2 trial did not meet its primary end point. The efficacy of mobocertinib was not superior to platinum-based chemotherapy for first-line treatment of *EGFR* ex20ins+ NSCLC.

## AFFILIATIONS

[1]Lowe Center for Thoracic Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA
[2]Guangdong Lung Cancer Institute, Guangzhou, China
[3]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea
[4]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department I of Thoracic Oncology, Peking University Cancer Hospital and Institute, Beijing, China
[5]Sichuan Cancer Hospital, Chengdu, China
[6]Klinik Floridsdorf, Vienna Healthcare Group and Karl Landsteiner Institute for Lung Research and Pulmonary Oncology, Vienna, Austria
[7]Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
[8]Gustave Roussy, Paris-Saclay University, Villejuif, France
[9]Genesis Care, North Shore Health Hub and Northern Clinical School, University of Sydney, Sydney, Australia
[10]Division of Oncology, Department of Medicine, Stanford Cancer Institute, Stanford, CA
[11]Kanagawa Cancer Center, Yokohama, Japan
[12]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China
[13]City of Hope National Medical Center, Duarte, CA
[14]Department of Statistics and Quantitative Sciences, Takeda Development Center Americas, Inc, Lexington, MA
[15]Department of Clinical Science, Takeda Development Center Americas, Inc, Lexington, MA
[16]Department of Statistics, Cytel Inc, Cambridge, MA
[17]Department of Global Evidence and Outcomes Research, Takeda Development Center Americas, Inc, Lexington, MA
[18]Department of Clinical Oncology, State Key Laboratory of Translational Oncology, Chinese University of China, Shatin, Hong Kong Special Administrative Region, China

## CORRESPONDING AUTHOR

Tony S.K. Mok, MD; e-mail: tony@clo.cuhk.edu.hk.

## PRIOR PRESENTATION

Presented at the European Society for Medical Oncology (ESMO) Asia Congress, Singapore, Singapore, December 1-3, 2023.

## SUPPORT

Supported by Takeda Development Center Americas, Inc and complied with the Good Publication Practice (GPP) guidelines.

## CLINICAL TRIAL INFORMATION

NCT04129502

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-24-01269.

## DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-24-01269. The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participant data supporting the results reported in this article, will be made available from the completed study within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Pasi A. Jänne, Bin-Chao Wang, Byoung Chul Cho, Maximilian Hochmair, Solange Peters, Yi-Long Wu, Junjing Lin, Florin Vranceanu, Tony S.K. Mok
**Financial support:** Bin-Chao Wang
**Administrative support:** Bin-Chao Wang, Robert J. Fram
**Provision of study materials or patients:** Pasi A. Jänne, Bin-Chao Wang, Jun Zhao, Juan Li, Solange Peters, Joel W. Neal, Terufumi Kato, Junjing Lin
**Collection and assembly of data:** Bin-Chao Wang, Byoung Chul Cho, Jun Zhao, Juan Li, Benjamin Besse, Nick Pavlakis, Terufumi Kato, Yi-Long Wu, Danny Nguyen, Junjing Lin
**Data analysis and interpretation:** Pasi A. Jänne, Bin-Chao Wang, Byoung Chul Cho, Maximilian Hochmair, Solange Peters, Benjamin Besse, Joel W. Neal, Terufumi Kato, Yi-Long Wu, Junjing Lin, Jianchang Lin, Florin Vranceanu, Annette Szumski, Huamao M. Lin, Robert J. Fram, Tony S.K. Mok
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors

## ACKNOWLEDGMENT

We thank the patients, their families, and their caregivers; the EXCLAIM-2 investigators and their team members at each study site; and colleagues from Takeda Development Center Americas, Inc, Lexington, MA. Professional medical writing assistance was provided by Corey Burgin, PhD, and Lela Creutz, PhD, of Peloton Advantage, LLC, an OPEN Health company, and funded by Takeda Development Center Americas, Inc, Lexington, MA.

## REFERENCES


1. Kobayashi Y, Mitsudomi T: Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy. Cancer Sci 107:1179-1186, 2016
2. Riess JW, Gandara DR, Frampton GM, et al: Diverse *EGFR* exon 20 insertions and co-occurring molecular alterations identified by comprehensive genomic profiling of NSCLC. J Thorac Oncol 13: 1560-1568, 2018
3. O'Kane GM, Bradbury PA, Feld R, et al: Uncommon *EGFR* mutations in advanced non-small cell lung cancer. Lung Cancer 109:137-144, 2017
4. Lin HM, Yin Y, Crossland V, et al: EGFR testing patterns and detection of EGFR exon 20 insertions in the United States. JTO Clin Res Rep 3:100285, 2022
5. Lau SC, Chooback N, Ho C, et al: Outcome differences between first- and second-generation EGFR inhibitors in advanced EGFR mutated NSCLC in a large population-based cohort. Clin Lung Cancer 20:e576-e583, 2019
6. Shah MP, Aredo JV, Padda SK, et al: EGFR exon 20 insertion NSCLC and response to platinum-based chemotherapy. Clin Lung Cancer 23:e148-e153, 2022
7. Kwon CS, Lin HM, Crossland V, et al: Non-small cell lung cancer with EGFR exon 20 insertion mutation: A systematic literature review and meta-analysis of patient outcomes. Curr Med Res Opin 38: 1341-1350, 2022
8. Zhou C, Tang KJ, Cho BC, et al: Amivantamab plus chemotherapy in NSCLC with EGFR exon 20 insertions. N Engl J Med 389:2039-2051, 2023
9. Yang G, Li J, Xu H, et al: *EGFR* exon 20 insertion mutations in Chinese advanced non-small cell lung cancer patients: Molecular heterogeneity and treatment outcome from nationwide real-world study. Lung Cancer 145:186-194, 2020
10. Ou SHI, Lin HM, Hong JL, et al: Real-world response and outcomes in NSCLC patients with EGFR exon 20 insertion mutations. J Clin Oncol 39, 2021 (suppl 15; abstr 9098)
11. Byeon S, Kim Y, Lim SW, et al: Clinical outcomes of *EGFR* exon 20 insertion mutations in advanced non-small cell lung cancer in Korea. Cancer Res Treat 51:623-631, 2019
12. Wang Y, Yang G, Li J, et al: Real-world treatment outcome of advanced Chinese NSCLC EGFR exon 20 insertion patients. J Clin Oncol 37, 2019 (suppl 15; abstr 9043)
13. Gonzalvez F, Vincent S, Baker TE, et al: Mobocertinib (TAK-788): A targeted inhibitor of *EGFR* exon 20 insertion mutants in non–small cell lung cancer. Cancer Discov 11:1672-1687, 2021
14. Wang J, Lam D, Yang J, et al: Discovery of mobocertinib, a new irreversible tyrosine kinase inhibitor indicated for the treatment of non-small-cell lung cancer harboring EGFR exon 20 insertion mutations. Med Chem Res 31:1647-1662, 2022
15. Riely GJ, Neal JW, Camidge DR, et al: Activity and safety of mobocertinib (TAK-788) in previously treated non–small cell lung cancer with *EGFR* exon 20 insertion mutations from a phase 1/2 trial. Cancer Discov 11:1688-1699, 2021
16. Zhou C, Ramalingam SS, Kim TM, et al: Treatment outcomes and safety of mobocertinib in platinum-pretreated patients with *EGFR* exon 20 insertion–positive metastatic non–small cell lung cancer: A phase 1/2 open-label nonrandomized clinical trial. JAMA Oncol 7:e214761, 2021
17. Ramalingam SS, Zhou C, Kim TM, et al: Phase 1/2 study of mobocertinib in EGFR exon 20 insertion (ex20ins)+ metastatic NSCLC (mNSCLC): Updated results from platinum-pretreated patients (PPP) [poster 988P]. Presented at Annual Congress of the European Society for Medical Oncology, Paris, France, September 9-13, 2022
18. Duke ES, Stapleford L, Drezner N, et al: FDA approval summary: Mobocertinib for metastatic non-small cell lung cancer with EGFR exon 20 insertion mutations. Clin Cancer Res 29:508-512, 2023
19. Exkivity [package insert]. Takeda Pharmaceuticals America, Inc, Lexington, MA, 2023
20. FDA grants accelerated approval to mobocertinib for metastatic non-small cell lung cancer with EGFR exon 20 insertion mutations [press release]. U.S. Food & Drug Administration, 2021. https://ecancer.org/en/news/20939-fda-grants-accelerated-approval-to-mobocertinib-for-metastatic-non-small-cell-lung-cancer-with-egfr-exon-20-insertion-mutations
21. Takeda's EXKIVITY (mobocertinib) receives approval from the NMPA of China, becoming the first and only therapy available for patients with EGFR exon20 insertion+ NSCLC [press release]. Takeda Pharmaceutical Company Limited, Cambridge, MA, 2023
22. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009
23. Coon CD, Schlichting M, Zhang X: Interpreting within-patient changes on the EORTC QLQ-C30 and EORTC QLQ-LC13. Patient 15:691-702, 2022
24. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-376, 1993
25. Bergman B, Aaronson NK, Ahmedzai S, et al: The EORTC QLQ-LC13: A modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer 30a:635-642, 1994
26. Xu CW, Wang WX, Wang D, et al: Pemetrexed-based chemotherapy for non-small-cell lung cancer patients with EGFR exon 20 insertion mutation: A multicenter study. Transl Lung Cancer Res 9: 1853-1861, 2020
27. Borghaei H, Langer CJ, Paz-Ares L, et al: Pembrolizumab plus chemotherapy versus chemotherapy alone in patients with advanced non-small cell lung cancer without tumor PD-L1 expression: A pooled analysis of 3 randomized controlled trials. Cancer 126:4867-4877, 2020
28. Borghaei H, Paz-Ares L, Horn L, et al: Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373:1627-1639, 2015
29. Epstein RS, Aapro MS, Basu Roy UK, et al: Patient burden and real-world management of chemotherapy-induced myelosuppression: Results from an online survey of patients with solid tumors. Adv Ther 37:3606-3618, 2020
30. Garcia Campelo MR, Zhou C, Ramalingam SS, et al: Mobocertinib (TAK-788) in EGFR exon 20 insertion+ metastatic NSCLC: Patient-reported outcomes from EXCLAIM extension cohort. J Clin Med 12:112, 2022
31. Takeda provides update on EXKIVITY (mobocertinib) [press release]. Takeda Pharmaceuticals, 2023. https://www.takeda.com/newsroom/newsreleases/2023/takeda-provides-update-on-exkivity-mobocertinib/
32. Wu Q, Luo W, Li W, et al: First-generation EGFR-TKI plus chemotherapy versus EGFR-TKI alone as first-line treatment in advanced NSCLC with EGFR activating mutation: A systematic review and meta-analysis of randomized controlled trials. Front Oncol 11:598265, 2021

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**First-Line Mobocertinib Versus Platinum-Based Chemotherapy in Patients With *EGFR* Exon 20 Insertion–Positive Metastatic Non–Small Cell Lung Cancer in the Phase III EXCLAIM-2 Trial**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

**Pasi A. Jänne**
**Stock and Other Ownership Interests:** Gatekeeper Pharmaceuticals, Loxo
**Consulting or Advisory Role:** Pfizer, Boehringer Ingelheim, AstraZeneca, Merrimack, Chugai Pharma, Roche/Genentech, Loxo, Mirati Therapeutics, Araxes Pharma, Ignyta, Lilly, Takeda, Novartis, Biocartis, Voronoi Health Analytics, SFJ Pharmaceuticals Group, Sanofi, Daiichi Sankyo, Silicon Therapeutics, Nuvalent, Inc, Eisai, Bayer, Syndax, AbbVie, Allorion Therapeutics, Accutar Biotech, Transcenta, Monte Rosa Therapeutics, Scorpion Therapeutics, Merus, Frontier Medicines, Hongyun Biotech, Duality Biologics, Blueprint Medicines
**Research Funding:** AstraZeneca (Inst), Astellas Pharma (Inst), Daiichi Sankyo (Inst), Lilly (Inst), Boehringer Ingelheim (Inst), Puma Biotechnology (Inst), Takeda (Inst), Revolution Medicines (Inst)
**Patents, Royalties, Other Intellectual Property:** I am a co-inventor on a DFCI owned patent on EGFR mutations licensed to Lab Corp. I receive post-marketing royalties from this invention
**Expert Testimony:** AstraZeneca

**Byoung Chul Cho**
**Employment:** Yonsei University Health System
**Leadership:** J INTS BIO
**Stock and Other Ownership Interests:** Theravance, Gencurix, Bridgebio, Kanaph Therapeutics, Cyrus Therapeutics, Interpark Bio, J INTS BIO
**Consulting or Advisory Role:** AstraZeneca, Boehringer Ingelheim, Roche, Yuhan, Pfizer, Janssen, Takeda, MSD, Lilly, Medpacto, Blueprint Medicines, Cyrus Therapeutics, Guardant Health, Novartis, CJ Bioscience, Abion, BeiGene, CureLogen, GI Cell, inno.N, Imnewrun, Hanmi, RandBio, Kanaph Therapeutics, Bridgebio, Oscotec, BMS, Ono Pharmaceutical, Onegene Biotechnology, J INTS BIO, Therapex Co, Ltd, Gilead Sciences, Amgen
**Research Funding:** Novartis, Bayer, AstraZeneca, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, MSD, AbbVie, GI Innovation, Blueprint Medicines, Interpark Bio, LG Chem, Oscotec, GI Cell, Abion, Boehringer Ingelheim, CJ Bioscience, CJ Blossom Park, Cyrus Therapeutics, Genexine, Nuvalent, Inc, Oncternal Therapeutics, Regeneron, Bridgebio, ImmuneOncia, Illumina, Kanaph Therapeutics, Therapex, J INTS BIO, Hanmi, CHA Bundang Medical Center, Mogam Biotechnology Research Institute, Lilly, Vertical Bio AG
**Patents, Royalties, Other Intellectual Property:** Champions Oncology, Crown Bioscience, Imagen, PearlRiver Bio GmbH
**Other Relationship:** DAAN Biotherapeutics

**Maximilian Hochmair**
**Consulting or Advisory Role:** Takeda, Roche, Lilly, AstraZeneca/Daiichi Sankyo
**Speakers' Bureau:** Lilly, MSD Oncology, Novartis, Roche

**Solange Peters**
**Honoraria:** Roche (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Pfizer (Inst), MSD (Inst), AstraZeneca (Inst), Takeda (Inst), Illumina (Inst), Medscape (Inst), Prime Oncology (Inst), RMEI Medical Education (Inst), Research to Practice (Inst), PER (Inst), Imedex (Inst), Ecancer (Inst), OncologyEducation (Inst), Fishawack Facilitate (Inst), Peerview (Inst), Medtoday (Inst), Mirati Therapeutics (Inst), Sanofi (Inst), Incyte (Inst)
**Consulting or Advisory Role:** Roche/Genentech (Inst), Novartis (Inst), Bristol Myers Squibb (Inst), Pfizer (Inst), MSD (Inst), Amgen (Inst), AstraZeneca (Inst), Janssen (Inst), Regeneron (Inst), Merck Serono (Inst), Boehringer Ingelheim (Inst), Takeda (Inst), Lilly (Inst), AbbVie (Inst), Bayer (Inst), Biocartis (Inst), Debiopharm Group (Inst), Illumina (Inst), PharmaMar (Inst), Sanofi (Inst), Seagen (Inst), Blueprint Medicines (Inst), Daiichi Sankyo (Inst), Incyte (Inst), Bioinvent (Inst), Clovis Oncology (Inst), Vaccibody (Inst), Phosplatin Therapeutics (Inst), Foundation Medicine (Inst), Arcus Biosciences (Inst), F-Star Biotechnology (Inst), Genzyme (Inst), Gilead Sciences (Inst), GlaxoSmithKline (Inst), ITeos Therapeutics (Inst)
**Research Funding:** Roche (Inst), BMS (Inst), MSD (Inst), Amgen (Inst), Lilly (Inst), AstraZeneca (Inst), Pfizer (Inst), Illumina (Inst), Merck Serono (Inst), Novartis (Inst), Biodesix (Inst), Boehringer Ingelheim (Inst), Iovance Biotherapeutics (Inst), Phosplatin Therapeutics (Inst)
**Travel, Accommodations, Expenses:** Roche, Bristol Myers Squibb, MSD, Sanofi, Incyte
**Uncompensated Relationships:** Annals of Oncology (I), ESMO, ETOP Scientific Chair, JTO Past Deputy Editor, SAMO President

**Benjamin Besse**
**Honoraria:** AbbVie (Inst), MSD (Inst), AstraZeneca (Inst), Daiichi Sankyo (Inst), Sanofi/Aventis (Inst), Bristol Myers Squibb (Inst), Lilly (Inst), OSE Immunotherapeutics (Inst), Servier (Inst)
**Consulting or Advisory Role:** F. Hoffmann LaRoche (Inst), PharmaMar (Inst), Sanofi/Aventis (Inst), AbbVie (Inst), Lilly (Inst), Ellipses Pharma (Inst), BioNTech SE (Inst), Bristol Myers Squibb (Inst), CureVac (Inst), Regeneron (Inst), Immunocore (Inst), Owkin (Inst), Beijin Avistone (Inst), Foghorn Therapeutics (Inst)
**Research Funding:** Genmab (Inst), PharmaMar (Inst), Enliven Therapeutics (Inst), Prelude Therapeutics (Inst), Takeda (Inst), BeiGene (Inst), OSE Immunotherapeutics (Inst), Anheart Therapeutics (Inst), AstraZeneca (Inst), Amgen (Inst), CureVac (Inst), Janssen (Inst), MSD (Inst), Sanofi (Inst), Lilly (Inst), Daiichi Sankyo Europe GmbH (Inst)

**Nick Pavlakis**
**Honoraria:** BeiGene, Bayer, Takeda, Pierre Fabre
**Consulting or Advisory Role:** Roche, Boehringer Ingelheim, AstraZeneca, Merck KGaA, Merck Serono, Amgen, Merck Sharp &

Dohme, Novartis, Pfizer, Takeda, Bristol Myers Squibb, Beigene, Gilead Sciences, Janssen Oncology, Duo Oncology
**Speakers' Bureau:** Merck KGaA
**Research Funding:** Bayer (Inst), Pfizer (Inst), Roche (Inst)

**Joel W. Neal**
**Honoraria:** CME Matters, Clinical Care Options, Research to Practice, Medscape, Biomedical Learning Institute, Peerview, Prime Oncology, Projects in Knowledge, Rockpointe CME, MJH Life Sciences, Medical Educator Consortium, HMP Education
**Consulting or Advisory Role:** AstraZeneca, Genentech/Roche, Exelixis, Takeda, Lilly, Amgen, Iovance Biotherapeutics, Blueprint Medicines, Regeneron, Natera, Sanofi/Regeneron, D2G Oncology, Surface Oncology, Turning Point Therapeutics, Mirati Therapeutics, Gilead Sciences, AbbVie, Summit Therapeutics, Novartis, Novocure, Janssen Oncology, Anheart Therapeutics, Bristol Myers Squibb, Daiichi Sankyo/AstraZeneca, Nuvation Bio
**Research Funding:** Genentech/Roche (Inst), Merck (Inst), Novartis (Inst), Boehringer Ingelheim (Inst), Exelixis (Inst), Nektar (Inst), Takeda (Inst), Adaptimmune (Inst), GlaxoSmithKline (Inst), Janssen (Inst), AbbVie (Inst), Novocure (Inst)
**Patents, Royalties, Other Intellectual Property:** Up To Date—Royalties

**Terufumi Kato**
**Employment:** Lilly (I)
**Honoraria:** Chugai Pharma, Ono Pharmaceutical, Lilly, AstraZeneca, Pfizer, Merck Sharp & Dohme, Novartis, Daiichi Sankyo, Amgen, Merck KGaA, Takeda, Boehringer Ingelheim, Janssen, Bristol Myers Squibb Japan
**Consulting or Advisory Role:** AstraZeneca, MSD, Pfizer, Novartis, Daiichi Sankyo, Janssen, Merck KGaA
**Research Funding:** Chugai Pharma (Inst), Merck Sharp & Dohme (Inst), Pfizer (Inst), AstraZeneca (Inst), Lilly (Inst), AbbVie (Inst), Regeneron (Inst), Novartis (Inst), Amgen (Inst), Merck KGaA (Inst), Takeda (Inst), Haihe Biopharma (Inst), Blueprint Medicines (Inst), Daiichi Sankyo (Inst), BeiGene (Inst), Gilead Sciences (Inst), Bayer, GlaxoSmithKline (Inst), Janssen (Inst), ArriVent Biopharma (Inst), Bristol Myers Squibb Japan (Inst)

**Yi-Long Wu**
**Honoraria:** AstraZeneca, Roche, Pfizer, Boehringer Ingelheim, MSD Oncology, Bristol Myers Squibb/China, Hengrui Pharmaceutical, BeiGene Beijing
**Consulting or Advisory Role:** AstraZeneca, Roche, Boehringer Ingelheim, Takeda
**Research Funding:** Boehringer Ingelheim (Inst), Roche (Inst), Pfizer (Inst), BMS (Inst)

**Danny Nguyen**
**Stock and Other Ownership Interests:** Intuitive Surgical (I), Teladoc (I)
**Honoraria:** Janssen Oncology, Taiho Pharmaceutical
**Consulting or Advisory Role:** Janssen Oncology, Black Diamond Therapeutics
**Travel, Accommodations, Expenses:** Taiho Oncology
**Other Relationship:** Takeda, Novartis, Seagen, Pfizer
**Uncompensated Relationships:** Takeda, Novartis

**Junjing Lin**
**Employment:** Takeda
**Stock and Other Ownership Interests:** Takeda
**Travel, Accommodations, Expenses:** Takeda

**Jianchang Lin**
**Stock and Other Ownership Interests:** Takeda

**Florin Vranceanu**
**Employment:** Takeda

**Annette Szumski**
**Employment:** Cytel Inc

**Huamao M. Lin**
**Employment:** Takeda
**Travel, Accommodations, Expenses:** Takeda

**Robert J. Fram**
**Employment:** Takeda
**Stock and Other Ownership Interests:** Takeda, Bristol Myers Squibb, Gilead Sciences, Johnson & Johnson/Janssen, Kenvue, Pfizer, Teva, Viatris, Zimmer BioMet, Zimvie, Zoetis, Baxter
**Research Funding:** Takeda
**Travel, Accommodations, Expenses:** Takeda

**Tony S.K. Mok**
**Employment:** The Chinese University of Hong Kong
**Leadership:** AstraZeneca, HUTCHMED, Aurora Tele-Oncology Platform, Insighta Holdings Limited
**Stock and Other Ownership Interests:** Aurora Tele-Oncology Platform, HUTCHMED, AstraZeneca, Biolidics, Prenetics, Alentis Therapeutics, D3 Bio, Lunit
**Honoraria:** AstraZeneca, Alpha Biopharma, ACEA Pharmaceutical Research, Amgen, Amoy Diagnostics, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo/UCB Japan, Fishawack Facilitate, InMed, Lilly, Merck Sharp & Dohme, Novartis, Origimed, Pfizer, Prime Oncology, Roche, Sanofi Aventis GmbH, Taiho Pharmaceutical, Takeda, Lucence, Medscape, Permanyer Publications, PeerVoice, Physicans' Education Resource, Research to Practice, Shanghai BeBirds Translation & Consulting, Suzhou Liangyihui Network Technology, AbbVie, Berry Oncology, Blueprint Medicines, C4 Therapeutics, CStone Pharmaceuticals, Curio Science, D3, Eisai, Gilead Sciences, Gritstone Bio, Guardant Health, touchIME, Adagene, Daz Group, Janssen, Jiahui Holdings Co, MD Health Brazil, Merck, MiRXES, Shanghai Promedican Pharmaceuticals Co, Ltd, Aveo, GLG's Healthcare, Illumina, Hengrui Therapeutics, Novocure, Omega Therapeutics, Prenetics, Regeneron, Xencor, Qiming Development (HK) Ltd, Summit Therapeutics Sub, Inc, Da Volterra, Lakeshore Biotechnology, AnHeart Therapeutics, Simcere of America Inc, SFJ Pharmaceutical Ltd, Synergy Research, Tigermed, Vertex, Virtus Medical Group, Yuhan, Ignyta, Incyte, Inivata, Iqvia
**Consulting or Advisory Role:** AbbVie, ACEA Pharmaceutical Research, Alpha Biopharma, Amgen, Amoy Diagnostics, AstraZeneca, BeiGene, Berry Oncology, Boehringer Ingelheim, Blueprint Medicines, Bristol Myers Squibb, CStone Pharmaceuticals, Curio Science, Daiichi Sankyo/UCB Japan, Eisai, Fishawack Facilitate, Gritstone Bio, Guardant Health, Hengrui Therapeutics, Ignyta, Incyte, Inivata, IQvia, Lilly, Loxo, Lunit, Merck Serono, Merck Sharp & Dohme, Mirati Therapeutics, Novartis, Pfizer, Puma Biotechnology, Roche, SFJ Pharmaceuticals Group, Takeda, Vertex, Yuhan, Qiming Development (HK) Ltd, D3, C4 Therapeutics, G1 Therapeutics, Gilead Sciences, Janssen, geneDecode, Adagene, Bayer HealthCare Pharmaceuticals, BerGenBio, Bowtie Life Insurance Company, Bridgebio, Covidien/Medtronic, Cirina, Da Volterra, Elevation Oncology, Genentech, HUTCHMED, Lakeshore Biotechnology, Lucence, Medtronic, MiRXES, Omega Therapeutics, OrigiMed, OSE Immunotherapeutics, PrIME Oncology, Prenetics, Regeneron, Simcere,

Summit Therapeutics, Synergy Research, Tigermed, Virtus Medical Group, Imagene AI Ltd
**Research Funding:** AstraZeneca (Inst), Boehringer Ingelheim (Inst), Pfizer (Inst), Novartis (Inst), SFJ Pharmaceuticals Group (Inst), Roche (Inst), Merck Sharp & Dohme (Inst), Bristol Myers Squibb (Inst), Xcovery (Inst), G1 Therapeutics (Inst), Merck Serono (Inst), Takeda (Inst)
**Travel, Accommodations, Expenses:** AstraZeneca, Daiichi Sankyo, MiRXES, Pfizer, Novartis, AbbVie, Roche, Zai Lab, Pfizer, Liangyihui

No other potential conflicts of interest were reported.