Activity and Safety of Mobocertinib (TAK-788) in Previously Treated Non–Small Cell Lung Cancer with EGFR Exon 20 Insertion Mutations from a Phase I/II Trial

Gregory J. Riely¹, Joel W. Neal², D. Ross Camidge³, Alexander I. Spira⁴, Zofia Piotrowska⁵, Daniel B. Costa⁶, Anne S. Tsao⁷, Jyoti D. Patel⁸, Shirish M. Gadgeel⁹, Lyudmila Bazhenova¹⁰, Viola W. Zhu¹¹, Howard L. West¹², Tarek Mekhail¹³, Ryan D. Gentzler¹⁴, Danny Nguyen¹⁵, Sylvie Vincent¹⁶, Steven Zhang¹⁶, Jianchang Lin¹⁷, Veronica Bunn¹⁶, Shu Jin¹⁶, Shuanglian Li¹⁶, and Pasi A. Jänne¹⁸
Mobocertinib, an oral epidermal growth factor receptor (EGFR) inhibitor targeting EGFR gene mutations, including exon 20 insertions (EGFRex20ins), in non–small cell lung cancer, was evaluated in a phase I/II dose-escalation/expansion trial (ClinicalTrials.gov NCT02716116). Dose escalation identified 160 mg/d as the recommended phase 2 dose and maximum tolerated dose. Among 136 patients treated with 160 mg/d, the most common any-grade treatment-related adverse events (TRAE; ≥25%) were diarrhea (63%), nausea (43%), rash (33%), and vomiting (26%), with diarrhea (21%) the only grade ≥3 TRAE ≥5%. Among 28 EGFRex20ins patients treated at 160 mg/d, the investigator-assessed confirmed response rate was 43% (12/28; 95% confidence interval, 24%-63%) with median duration of response of 14 months (5.0–not reached) and median progression-free survival of 7.3 months (4.4–15.6). Mobocertinib demonstrated antitumor activity in patients with diverse EGFRex20ins variants with a safety profile consistent with other EGFR inhibitors.

SIGNIFICANCE: No oral EGFR-targeted therapies are currently approved for patients with EGFRex20ins NSCLC. Mobocertinib demonstrated antitumor activity with manageable toxicity in patients with advanced EGFRex20ins NSCLC in this study, supporting additional development of mobocertinib in this patient population.

See related commentary by Pacheco, p. 1617.

INTRODUCTION

Epidermal growth factor receptor gene (EGFR) exon 20 insertion (EGFRex20ins) mutations represent approximately 4% to 12% of EGFR mutations in patients with non–small cell lung cancer (NSCLC; ref. 1–4). No oral EGFR-targeted therapies are currently approved for the treatment of patients with NSCLC with this uncommon subset of EGFR mutations. Although EGFR mutations are the prototypical targetable driver oncogenes in patients with NSCLC, only the most common EGFR mutants, including those with the amino acid substitution L858R and in-frame exon 19 deletions, can be effectively treated with the approved EGFR tyrosine kinase inhibitors (TKI) erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib (5–10). The structural, preclinical, and clinical characterization of the most common EGFRex20ins mutations suggest that they are unique in their ability to activate the kinase domain of EGFR without the typical structural changes associated with the EGFR L858R and exon 19 deletions (11), reducing the efficacy of first-, second-, and third-generation EGFR TKIs currently approved for NSCLC. The identification of active EGFR TKIs and other treatment strategies for patients with these recalcitrant mutations has been an ongoing priority.

Patients with NSCLC with EGFRex20ins mutations are currently treated with chemotherapy, immunotherapy, or TKIs approved for other EGFR mutations (4, 12–16). First- and second-generation EGFR TKIs are associated with response rates of <30% and progression-free survival (PFS) of <3 months in patients with EGFRex20ins-mutated NSCLC (2, 13, 14, 17–22). Platinum-based systemic chemotherapy in the first-line setting has been associated with response rates of 50% to 63% in patients with EGFRex20ins mutations, but most patients progress within 6 months (median PFS: 4.1–6.4 months; refs. 14, 23, 24). Docetaxel monotherapy, as second-line systemic cytotoxic chemotherapy after failure of first-line platinum-based
chemotherapies in patients with unselected stage IV NSCLC, is associated with an objective response rate (ORR) of 14% with a median PFS of 3 months (25) and a median duration of response of approximately 6 months (26, 27). Patients with unselected NSCLC receiving the ramucirumab plus docetaxel combination had an ORR of 23% with a median PFS of 4.5 months (25). Patients with previously treated NSCLC whose tumors harbor an EGFRex20ins mutation do not appear to benefit from immune checkpoint inhibitors, with an ORR of 0% and median PFS of 2 months (28). Pemetinib, a third-generation EGFR TKI that demonstrated potent inhibition of EGFRex20ins mutants in vitro (29), has recently demonstrated limited efficacy in patients with NSCLC with EGFRex20ins mutations, with an independent review committee–assessed ORR of 15% to 19%, median PFS of 4 to 6 months, and median duration of response of 7.4 months (30, 31). Osimertinib, another third-generation EGFR TKI, has some clinical efficacy (confirmed ORR, 25%; median PFS, 9.7 months; median duration of response of 5.7 months) at higher than approved doses (i.e., 160 mg/d) as second-line or greater therapy in patients with NSCLC with some EGFRex20ins mutations (32–35). In a recent preclinical study, the selective EGFRex20ins inhibitor DS-2087b inhibited proliferation of Ba/F3 cells expressing EGFRex20ins and demonstrated selectivity over wild-type EGFR (36). Tarloxoertinib, a hypoxia-activated prodrug of a pan-ERBB kinase inhibitor, demonstrated preclinical efficacy in EGFRex20ins-mutant NSCLC; however, in a small phase II study, the response rate in the cohort of patients with EGFRex20ins was 0% (best response, stable disease in 6/11 patients; ref. 37). Preclinical and early clinical data have been reported supporting the efficacy of amivantamab (investigator-assessed response rate, 36%; median PFS, 8.3), an intravenous bispecific antibody that targets EGFR and MET for patients with NSCLC with EGFRex20ins and other EGFR mutations (38, 39).

Mobocertinib is an irreversible small-molecule EGFR TKI designed to selectively target EGFR and HER2 (ERBB2) exon 20 insertion mutants. Mobocertinib and its two active metabolites, AP32960 and AP32914, are approximately equally potent in inhibiting EGFR. Results of preclinical studies characterizing mobocertinib’s binding properties and its activity against EGFRex20ins mutant cell lines and in vivo tumor models of EGFRex20ins-mutated NSCLC are reported in a companion article in this issue by Gonzalez and colleagues (40). Here, we present the results of a dose-escalation phase I/II trial with expansion cohorts that assessed the safety, tolerability, and antitumor activity of mobocertinib in patients with metastatic EGFRex20ins-mutated NSCLC.

RESULTS

Dose Escalation and Pharmacokinetics

The dose-escalation study followed a conventional 3 + 3 design. The dose-escalation phase followed a conventional 3 + 3 design. The dose level for each new cohort was up to 100% higher than the dose level in the previous cohort until a grade 2 drug-related toxicity of diarrhea or skin rash occurred, based on expected class effects for EGFR TKIs or until other DLTs were identified. Further dose escalation involved increments of ≤50% of the previous dose, depending on safety findings. Seven patients were enrolled in the dose escalation to evaluate DLT; additional patients were included to further confirm safety observations.

Figure 1. Schema for the dose-escalation phase of the phase I/II trial of mobocertinib. The dose-escalation phase followed a conventional 3 + 3 design. The dose level for each new cohort was up to 100% higher than the dose level in the previous cohort until a grade 2 drug-related toxicity of diarrhea or skin rash occurred, based on expected class effects for EGFR TKIs or until other DLTs were identified. Further dose escalation involved increments of ≤50% of the previous dose, depending on safety findings. Seven patients were enrolled in the dose escalation to evaluate DLT; additional patients were included to further confirm safety observations.
Mobocertinib in NSCLC with EGFR Exon 20 Insertions

120 mg/d (grade 5 pneumonia), one of six evaluable patients at 160 mg/d (grade 3 mucositis), and two of four evaluable patients at 180 mg/d (grade 3 diarrhea and missing >25% of planned doses due to a treatment-related adverse event). The maximum tolerated dose (MTD) and recommended phase II dose (RP2D) was determined to be 160 mg/d.

Plasma concentrations of mobocertinib after single and multiple doses are shown in Fig. 2A and B, respectively. Mobocertinib was orally absorbed with a median time to maximum plasma concentration \(T_{\text{max}}\) of 4 hours. Mobocertinib exposure [area under the concentration-time curve from time 0 to 24 hours (AUC0–24)] increased in an approximately dose-proportional manner following oral administration over the dose range of 5 to 180 mg/d. The geometric mean effective half-life based on accumulation was in the range of 11 to 17 hours across the 20- to 160-mg/d dose range.

Expansion Phase

Patients

The expansion phase enrolled seven histologically and molecularly defined cohorts (Supplementary Table S1) at the RP2D (160 mg/d). Here, we present safety data in all patients (regardless of cancer type) treated with mobocertinib 160 mg/d as of the data cutoff for this analysis (January 27, 2020; \(n = 136\)). A total of 23 patients had previously treated non-small cell lung cancer (NSCLC) and 23 patients with EGFRex20ins mutations treated with mobocertinib \([5-40 \text{ mg/d (}\ n = 12\text{), 80 mg/d (}\ n = 9\text{), 120 mg/d (}\ n = 21\text{), and 160 mg/d (}\ n = 28\text{)}]\), with a focus on the 28 patients with previously treated NSCLC and EGFRex20ins mutations who had either not received \((n = 22)\) or not shown \((n = 6)\) an objective response to a prior EGFR TKI administered at 160 mg/d (cohort 1). As of the data cutoff, 46 (34%) of the 136 patients treated with mobocertinib 160 mg/d remained on study. Median time on treatment in the 136 patients was 4.2 months (range, 0.03–24.74). Seven (25%) of the 28 patients with EGFRex20ins mutations treated at 160 mg/d remained on study. Median time on treatment in the 28 patients was 12.4 months (range, 0.7–24.7). Patient disposition is shown in Supplementary Fig. S1.

Demographic and baseline characteristics of patients treated with mobocertinib 160 mg/d are presented in Table 1.

Safety and Tolerability

Among the 136 patients treated at 160 mg/d, 134 (99%) experienced a treatment-emergent adverse event (TEAE) and 131 (96%) had TEAEs that were considered related to mobocertinib treatment (Table 2). The most common treatment-related TEAEs of any grade (>25% of all patients treated at 160 mg/d) were diarrhea (83%), nausea (43%), rash (33%), and vomiting (26%). Grade 3 or higher treatment-related TEAEs occurred in 54 patients (40%). The only grade ≥3 treatment-related TEAE reported in greater than 5% of patients was diarrhea (21%; Table 2). Serious treatment-related TEAEs were reported in 18 patients (13%), most frequently diarrhea (4%) and vomiting (4%). In all, 74 patients (54%) had TEAEs requiring dose interruption, 23 (17%) had TEAEs requiring dose reduction, and 22 (16%) had TEAEs requiring discontinuation of mobocertinib. The most common TEAE leading to discontinuation was diarrhea (7/136; 5%).

Treatment-related TEAEs in patients with NSCLC with EGFRex20ins mutations were similar to those observed in all...
Table 1. Characteristics of patients treated with mobocertinib 160 mg/d

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with EGFRex20ins* (n = 28)</th>
<th>All patients (n = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>62 (28–84)</td>
<td>62 (24–86)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21 (75)</td>
<td>90 (66)</td>
</tr>
<tr>
<td>Male</td>
<td>7 (25)</td>
<td>46 (34)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20 (71)</td>
<td>103 (76)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (18)</td>
<td>20 (15)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (4)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>2 (7)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>27 (96)</td>
<td>128 (94)</td>
</tr>
<tr>
<td>Squamous</td>
<td>0</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Large cell</td>
<td>1 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>3 (2)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (21)</td>
<td>48 (35)</td>
</tr>
<tr>
<td>1</td>
<td>22 (79)</td>
<td>88 (65)</td>
</tr>
<tr>
<td>Number of prior systemic anticancer regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>26 (19)</td>
</tr>
<tr>
<td>1</td>
<td>4 (14)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>2</td>
<td>9 (32)</td>
<td>16 (12)</td>
</tr>
<tr>
<td>≥3</td>
<td>15 (54)</td>
<td>29 (21)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>53 (39)</td>
</tr>
<tr>
<td>Type of prior systemic anticancer therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>28 (100)</td>
<td>54 (40)</td>
</tr>
<tr>
<td>Prior checkpoint inhibitor therapy</td>
<td>17 (61)</td>
<td>32 (24)</td>
</tr>
<tr>
<td>EGFR/HER2 TKI</td>
<td>6 (21)</td>
<td>26 (19)</td>
</tr>
<tr>
<td>History of smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>17 (61)</td>
<td>83 (61)</td>
</tr>
<tr>
<td>Former</td>
<td>11 (39)</td>
<td>51 (38)</td>
</tr>
<tr>
<td>Current</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Baseline CNS metastases</td>
<td>12 (43)</td>
<td>52 (38)</td>
</tr>
</tbody>
</table>

NOTE: Values are number (%) of patients, unless specified otherwise. Data cutoff: January 27, 2020. Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Among the 28 patients treated at 160 mg/d (Table 2). Among the 28 patients with EGFRex20ins mutations treated at 160 mg/d, 16 (57%) had adverse events (AE) requiring dose interruption, 5 (18%) had AEs requiring dose reduction, and 7 (25%) had AEs leading to discontinuation of mobocertinib.

Antitumor Activity

Investigators assessed radiographic responses (RECIST version 1.1; ref. 41) in patients with previously treated NSCLC with EGFRex20ins mutations treated with mobocertinib daily doses ranging from 5 to 160 mg (Table 3). The confirmed ORR tended to increase with mobocertinib dose, such that the ORR was 0% (n/N = 0/12) at 5 to 40 mg/d, 22% (2/9) at an 80-mg total daily dose (combining those who received 80 mg once daily or 40 mg twice daily), 19% (4/21) at 120 mg/d, and 43% (12/28) at 160 mg/d (Table 3).

Best percent change in target lesions and objective responses by time on treatment in patients with EGFRex20ins mutations treated with the 160-mg/d dose are shown in Fig. 3A and B, respectively; treatment history and mutation status are also shown. Among the 28 patients with EGFRex20ins mutations treated with mobocertinib 160 mg/d, the confirmed ORR was 43% [12/28; 95% confidence interval (CI), 24–63%] and the median duration of response in confirmed responders was 13.9 months (95% CI, 5.0–not reached). The disease control rate was 86% (24/28; 95% CI, 67%–96%). Median PFS was 7.3 months (95% CI, 4.4–15.6; 12-month event-free rate: 34%; 95% CI, 16%–53%). Responses to mobocertinib...
160 mg/d were observed in patients with a diverse array of EGFRex20ins variants (Fig. 3A). No molecular subgroup of EGFRex20ins mutants appeared to have a higher response rate than others.

The investigator-assessed confirmed ORR was 56% (9/16; 95% CI, 30%–80%) in patients without baseline brain metastases and 25% (3/12; 95% CI, 5%–57%) in patients with baseline brain metastases. The median duration of response in confirmed responders was 13.8 months (95% CI, 5.0–16.6) in patients without baseline brain metastases and 5.5 months (95% CI, 3.9–14.2) in patients with baseline brain metastases. Median investigator-assessed PFS was 10.2 months (95% CI, 5.6–not reached; 12-month event-free rate: 43%; 95% CI, 18%–66%) in patients without baseline brain metastases and 3.7 months (95% CI, 1.8–15.9; 12-month event-free rate: 23%; 95% CI, 3%–52%) in patients with baseline brain metastases.

### DISCUSSION

Mobocertinib, an irreversible EGFR TKI designed via an iterative structure-guided platform to target EGFRex20ins mutations (40), demonstrated antitumor activity in patients with metastatic, previously treated NSCLC harboring EGFRex20ins mutations. Although this analysis included a small number of patients, mobocertinib 160 mg/d demonstrated a high response rate (43%) and favorable median PFS (7.3 months). Studies of first- and second-generation EGFR TKIs have reported an ORR of 8% to 27% and a median PFS of ≈3 months (13, 14, 18–22); other EGFR TKIs that have been tested in patients with EGFRex20ins mutations such as poziotinib and osimertinib have reported similar results (30, 33, 35). Studies of the current standard of care, docetaxel, reported an ORR of 14% and median PFS of 3 months in patients with previously treated stage IV NSCLC of unspecified mutation (25). Amivantamab, a human anti-EGFR–MET bispecific antibody, demonstrated an investigator-assessed ORR of 36% and a median PFS of 8.3 months in 39 response-evaluable patients with advanced NSCLC and EGFRex20ins mutations, including patients with and without prior anticancer therapy, in a phase I study (39). Thus, mobocertinib and amivantamab appear to have similar efficacy profiles at this early stage in development despite inhibiting EGFR by completely different mechanisms.

The AEs seen with mobocertinib were similar to those seen with other EGFR inhibitors, which are typically characterized by gastrointestinal and cutaneous adverse events (42, 43). Mobocertinib treatment led to treatment-related grade ≥3 TEAEs in 40% of treated patients, with diarrhea as the most common TEAE (21%). No primary prophylaxis plan for

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Patients with EGFRex20ins treated at 160 mg/d (n = 28)</th>
<th>All patients treated at 160 mg/d (n = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (82)</td>
<td>9 (32)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (39)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Rash</td>
<td>13 (46)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (36)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>5 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11 (39)</td>
<td>0</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>6 (21)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (14)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>7 (25)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>8 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>5 (18)</td>
<td>0</td>
</tr>
<tr>
<td>GERD</td>
<td>3 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>7 (25)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5 (18)</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: Values are presented as number (%). Data cutoff: January 27, 2020.
Abbreviation: GERD, gastroesophageal reflux disease.

a Patients with EGFRex20ins mutations with prior therapy who received 160 mg/d (initial dose) during dose escalation (n = 6) and in expansion cohort 1 (n = 22).

b Patients who received at least one dose of mobocertinib at 160 mg/d (initial dose) during dose-escalation or expansion phases.
Table 3. Investigator-assessed antitumor activity of mobocertinib in patients with NSCLC with EGFRex20ins

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>5-40 mg/d (n = 12)</th>
<th>80 mg total daily dosea (n = 9)</th>
<th>120 mg/d (n = 21)</th>
<th>160 mg/d (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best confirmed response, n (%)+</td>
<td>2 (17)</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>0</td>
<td>1 (11)</td>
<td>3 (14)</td>
<td>12 (43)</td>
</tr>
<tr>
<td>Stable disease+</td>
<td>3 (25)</td>
<td>6 (67)</td>
<td>11 (52)</td>
<td>12 (43)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7 (58)</td>
<td>1 (11)</td>
<td>3 (14)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>2 (17)</td>
<td>0</td>
<td>3 (14)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Confirmed ORR, n (%) [95% CI]</td>
<td>0 [0–26]</td>
<td>2 (22) [3–60]</td>
<td>4 (19) [5–42]</td>
<td>12 (43) [24–63]</td>
</tr>
<tr>
<td>Confirmed disease control rate, n (%) [95% CI]</td>
<td>3 (25) [5–57]</td>
<td>8 (89) [52–100]</td>
<td>15 (71) [48–89]</td>
<td>24 (86) [67–96]</td>
</tr>
</tbody>
</table>

+Includes 80 mg/d and 40 mg twice daily.
+Patients treated with at least one dose of mobocertinib.
+By RECIST version 1.1.
+Stable disease observed ≥6 weeks after first study drug administration.

diarrhea was in place during the dose-escalation and early expansion phases of this study. Food instructions in this ongoing study have been updated to allow dosing with or without a low-fat meal, which may improve gastrointestinal tolerability; this guidance was based on data in healthy participants, suggesting a lack of an effect of a low-fat meal (≤350 calories and ≤15% of calories from fat) on the pharmacokinetics (PK) of mobocertinib (NCT03482453). The AE management guidelines for diarrhea have been updated to allow symptomatic treatment at first evidence of increased frequency of bowel movement or at grade 1 diarrhea.

Because mobocertinib was rationally designed to specifically target difficult-to-treat EGFRex20ins mutant NSCLC, mobocertinib may have a narrower therapeutic window than that observed for another EGFR inhibitor, osimertinib, which was rationally designed to target the more common T790M EGFR exon 19 deletions, and L858R mutation (44). Although in this study we could not identify a clear relationship between the specific subtype of EGFRex20ins and mobocertinib efficacy, it is possible that such trends will emerge in future clinical studies. This study included six patients who had received but, per study inclusion criteria, had not responded to prior EGFR TKI therapy. Given the lack of objective response to prior EGFR TKIs and the observation that three of these six patients had a confirmed response to mobocertinib, it is thought that EGFRex20ins was still the driver mutation when these patients entered the study. Mechanisms of acquired resistance to mobocertinib are not yet well understood. Mobocertinib was designed to form a covalent interaction with cysteine 797 in EGFR. Therefore, a common mechanism of resistance may be the development of mutations affecting the C797 binding site (45). As part of this study, two additional cohorts of patients have been enrolled that will be of interest: patients with metastatic EGFRex20ins-mutated NSCLC who were treatment-naïve and an extension cohort of patients with previously treated NSCLC with EGFRex20ins mutations in which we hope to confirm and extend the findings presented here. Mobocertinib demonstrated a low ORR in patients with baseline brain metastases, suggesting limited intracranial activity. Based on this observation, the enrollment criteria for the pivotal extension cohort excluded patients with active brain metastases (i.e., previously untreated brain metastases or previously treated brain metastases with radiologically documented new or progressing brain lesions). Mobocertinib was granted Breakthrough Therapy Designation from the FDA in April 2020 based on the ORR and the long-term benefit seen in the data presented here. A global phase III randomized trial (EXCLAIM-2, NCT04129502) evaluating the efficacy of mobocertinib as first-line treatment compared with platinum-based chemotherapy is ongoing in patients with treatment-naïve advanced NSCLC whose tumors harbor EGFRex20ins mutations.

**Conclusions**

Mobocertinib, an EGFR TKI designed to target EGFRex20ins mutations, showed antitumor activity at an RP2D of 160 mg/d in patients with EGFRex20ins-positive NSCLC, with a 43% confirmed ORR, a 14-month median duration of response, and a 7-month median PFS. The AE profile of mobocertinib was manageable and consistent with that of other EGFR TKIs. Mobocertinib demonstrated responses in patients with diverse EGFRex20ins variants and is being further explored in a single-arm extension cohort of patients with previously treated NSCLC with EGFRex20ins mutations.

**METHODS**

**Study Design and Participants**

This was a first-in-human, phase I/II study (ClinicalTrials.gov NCT02716116; ClinicalTrials.jp 195000; EudraCT 2016-001271-68). The first part was a dose-escalation study (3 + 3 design) in patients with advanced NSCLC refractory to standard therapies. The second part, initiated after the RP2D was established, was an expansion study in seven histologically and molecularly defined expansion
**Figure 3.** Response to mobocertinib in patients with EGFRex20ins mutations treated at 160 mg/d (n = 28). A, Best percentage change from baseline in target lesions by molecular subtype. Mutations by patient are shown under the figure. B, Plot showing objective responses by time on treatment and baseline CNS metastasis status. Three patients were excluded from these plots: one patient had nonmeasurable baseline target lesions, and two patients had no follow-up scans. IO, immune-oncology therapy; PD, progressive disease; PR, partial response; SD, stable disease. *Active brain metastases were either never treated or progressed after radiation.

**Table:**

<table>
<thead>
<tr>
<th>EGFR exon 20 insertion variant</th>
<th>No. of patients</th>
<th>No. of confirmed responders</th>
<th>Confirmed ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>769_ASV</td>
<td>5</td>
<td>2</td>
<td>40%</td>
</tr>
<tr>
<td>773_NPH</td>
<td>4</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td>Other exon 20 insertion</td>
<td>12</td>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td>Exact variant unknown</td>
<td>4</td>
<td>2</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Legend:**

- Baseline brain metastases:
  - No
  - Active
  - Treated
- Remains on treatment
- Discontinued treatment
- PR Partial response
- SD Stable disease
- PD Progressive disease
cohort (Supplementary Table S1). The first two parts of the study were conducted at 28 sites in the United States between June 16, 2016, and March 13, 2020. Eligible patients were required to have histologically or cytologically confirmed locally advanced (and not a candidate for definitive therapy) or metastatic disease (stage IIIB or IV). Cohort-specific inclusion criteria for each of the expansion cohorts are provided in Supplementary Table S1. Efficacy data reported here were from the dose-escalation cohort and expansion cohort 1 only, which included patients with NSCLC previously treated with systemic therapy who had EGFR-20ns mutations; safety data are reported for all patients who received mobocertinib 160 mg/d in dose escalation and expansion.

Patients were excluded from the dose-escalation phase if they had symptomatic central nervous system (CNS) metastases at screening or asymptomatic CNS disease requiring corticosteroids to control symptoms within 7 days prior to the first dose of mobocertinib; however, patients with active brain metastases (defined as either previously untreated intracranial CNS metastases or previously treated intracranial CNS metastases with radiologically documented new or progressing CNS lesions) were allowed in the dose-escalation cohort. Expansion cohort 1 excluded patients with active and measurable brain metastases but allowed patients with active nonmeasurable brain metastases. Patients with active measurable brain metastases were enrolled in a separate cohort (Supplementary Table S1).

General eligibility criteria required that patients were 18 years of age or older with measurable disease according to RECIST version 1.1 (41), Eastern Cooperative Oncology Group performance status of 0 or 1, adequate renal and hepatic function, adequate bone marrow function, and normal QT interval according to screening electrocardiogram assessment. Patients must not have received small-molecule anticancer therapy (including cytotoxic chemotherapy and investigational agents) ≤14 days prior to the first dose of mobocertinib; antineoplastic monoclonal antibodies, including immunotherapy, within 28 days of the first mobocertinib dose; moderate or strong CYP3A inhibitors or inducers within 10 days prior to the first dose of mobocertinib; or radiotherapy ≤14 days prior to the first dose of mobocertinib or had not recovered from radiotherapy-related toxicities. We excluded patients with leptomeningeal disease (symptomatic or asymptomatic); interstitial lung disease, radiation pneumonitis that required steroid treatment, or drug-related pneumonitis; or significant uncontrolled or active cardiovascular disease or uncontrolled hypertension. There was no limit on the number of previous systemic therapies.

The study protocol was approved by appropriate local review boards or ethics committees. The study was conducted in accordance with the ethical standards established by the Declaration of Helsinki, the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice, and applicable local regulations. Patients provided written informed consent before enrollment.

Procedures

Dose escalation followed a conventional 3 + 3 design (Fig. 1); expansion at any dose was permitted to confirm safety, efficacy, and PK observations. Mobocertinib (manufactured by ARIAD Pharmaceuticals) was provided as 5-mg, 20-mg, and 40-mg capsules for oral dosing in continuous 28-day cycles, with an initial dose-level cohort of 5 mg/d and increasing in increments until the MTD was identified. The dose level for each new cohort was up to 100% higher than the dose level in the previous cohort until a grade 2 drug-related toxicity of diarrhea or skin rash occurred, based on expected class effects for EGFR TKIs, or until other DLTs were identified. Further dose escalation involved increments of no more than 50% of the previous dose, depending on safety findings. The MTD was defined as the highest dose at which one of six evaluable patients experienced a DLT within the first 28 days of treatment (end of cycle 1). Evaluable patients must have completed at least 75% of their planned doses, unless missed doses were due to TEAEs.

In the expansion phase, all patients received initial dosing with mobocertinib 160 mg/d. Patients could continue mobocertinib until they experienced progressive disease requiring alternate therapy or intolerable toxicity. Treatment could be continued after disease progression if, in the opinion of the investigator, the patient continued to experience clinical benefit. Dose interruptions and reductions could be implemented to manage adverse events. For grade 3 to 4 toxicity, therapy was withheld until toxicity lessened to grade 2 or lower for hematologic toxicities, grade 1 or lower for nonhematologic toxicities, or returned to baseline severity. Treatment could then be resumed at the same dose or next-lowest dose level based on the investigator’s judgment. For any grade 2 nonhematologic toxicity that was intolerable, recurrent, or not adequately controlled by supportive care, therapy was withheld until symptoms remitted, and then the dose was reduced to the next-lowest dose level. Up to two rounds of dose reduction were permitted to manage toxicity. If therapy was held for longer than 2 weeks, resumption of therapy was decided on a case-by-case basis. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 (before Amendment 3) and NCI CTCAE version 5.0 (after Amendment 3) and coded according to the Medical Dictionary for Regulatory Activities version 22.0 preferred terms.

Blood samples were collected at prespecified time points (Supplementary Table S2) to assess the plasma concentrations of mobocertinib and active metabolites (AP32960 and AP32914) following a single dose and multiple doses (steady state) of mobocertinib in the dose-escalation and dose-expansion cohorts. Mobocertinib concentrations over the dose range of 5 to 180 mg/d were determined using validated liquid chromatography mass spectrometry methods. PK parameters [i.e., Tmax, maximum concentration (Cmax), and AUC0-t] were estimated using noncompartmental methods (Phoenix WinNonlin, version 8.1; Certara).

Disease assessment included imaging of the chest, abdomen, pelvis, and brain using appropriate radiologic procedures (computed tomography scans or magnetic resonance imaging with contrast, unless contrast media were contraindicated) at screening and at 8-week intervals thereafter [on day 28 (±3 days) of every even-numbered cycle] through cycle 14 after the initial dose of mobocertinib and every 3 cycles thereafter. Scans were assessed by investigators according to RECIST version 1.1 (41). Confirmed responses were defined as those responses that persisted at least 4 weeks after the initial response was observed.

Mutation status at baseline (e.g., activating mutations in EGFR or HER2, as well as other previously identified abnormalities in other genes) was recorded at screening. Enrollment was based on local testing results (either next-generation sequencing or polymerase chain reaction testing) obtained in a Clinical Laboratory Improvement Amendments–certified laboratory. Formalin-fixed, paraffin-embedded tumor tissue samples (archived or fresh if archived was not available) were collected for all patients at screening for molecular profiling and exploratory biomarker studies.

Outcomes

The primary endpoint of the phase I dose-escalation study was to establish the RP2D of orally administered mobocertinib. Secondary endpoints of the dose-escalation study included DLTs, the MTD, the safety profile of orally administered mobocertinib, and plasma PK parameters of mobocertinib and its active metabolites (AP32960 and AP32914) after a single oral dose and at steady state after multiple oral doses. The primary endpoint of the expansion cohorts was the
Mobocertinib in NSCLC with EGFR Exon 20 Insertions

investigator-assessed confirmed ORR (using RECIST v1.1). Results for other expansion cohorts will be reported separately. Secondary endpoints of the expansion phase included safety and efficacy assessments, including best overall response, best target lesion response, duration of response, disease control rate, and PFS, as assessed by the investigator.

**Statistical Analysis**

Sample size was determined based on clinical rather than statistical considerations. The number of patients was consistent with phase I dose-finding studies; the historically and molecularly defined expansion cohorts facilitated obtaining estimates of clinical activity. With this design, the estimate of the rate of DLT at the MTD was in the range of 0.17 to 0.26. The estimate of the rate of DLT at the highest dose, which is 1 step above the MTD, was 0.33 (46).

For the safety analysis, we pooled phase I and phase II data in patients who had received at least one dose of mobocertinib 160 mg/d. The proportions of patients with EGFReX20ins-positive NSCLC with confirmed objective response as assessed by the investigator and exact 95% binomial CIs are reported. Duration of response and PFS as assessed by the investigator were analyzed using Kaplan-Meier methods. Statistical analyses were conducted using SAS version 9.4 (SAS Institute).

**Data Sharing Statement**

The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participant data supporting the results of the completed study, will be made available after the publication of the final study results 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.

**Authors’ Disclosures**

G.J. Riely reports institutional research funding from Takeda/Millennium/ARIAD, Pfizer, Novartis, Roche/Genentech, GSK, Infinity Pharmaceuticals, Merck, and Mirati; and travel reimbursement from Merck. J.W. Neal reports having a consultant/advisory role with AstraZeneca, Genentech/Roche, Exelixis, Jounce Therapeutics, Takeda, Eli Lilly, Calithera Biosciences, Regeneron Pharmaceuticals, Amgen [DSMB], Iovance Biotherapeutics [DSMB], Blueprint Pharmaceuticals; receiving honoraria from Research to Practice, MLI Peerview, Medscape, Biomedical Learning Institute, Prime Oncology, Rockpointe, CME Matters, MJH CME; and institutional research funding from Genentech/Roche, Merck, Novartis, Boehringer Ingelheim, Exelixis, Nektar, Takeda, Adaptimmune, GSK. D.R. Camidge reports receiving honoraria from AstraZeneca, Takeda, Amgen/Kyn, Genoptix, G1 Therapeutics [DSMB]; Mersana Therapeutics, Roche/Genentech, Ignyta, Daiichi Sankyo [ILD adjudication committee], Hansoh SNC, Bio-Thera DSMB, Lycera, Revolution Med, Orion, Clovis, Celgene, Novartis; and research funding from ARIAD/Takeda, D.B. Costa.

A.I. Spira reports having a consultant/advisory role with ARIAD, Astellas, AstraZeneca, BMS, Clovis Oncology, Janisens, Merck, Roche; receiving research support from AstraZeneca, Millennium, Merck, Janssen, Roche, Novartis, Cullinan Pearl, Daiichi Sankyo; and serving as a speaker for Roche. Z. Piotrowska reports having a consultant/advisory role with AstraZeneca, ARIAD/Takeda, AbbVie, Novartis, Guardant Health, Spectrum, Genentech, ImmunoGen, C4 Therapeutics, Blueprint Medicines, Jazz Pharmaceuticals, Janssen; receiving research support from Novartis, ARIAD/Takeda, GuardantHealth, Spectrum, AstraZeneca, Tesaro, and Cullinan; and travel reimbursement from AstraZeneca, ARIAD/Takeda. D.B. Costa reports personal fees (consulting fees and honoraria) and nonfinancial support (institutional research support) from Takeda/Millennium Pharmaceuticals, AstraZeneca, and Pfizer, as well as nonfinancial support (institutional research support) from Merck Sharp and Dohme Corporation, Merrimack Pharmaceuticals, Bristol-Myers Squibb, Clovis Oncology, Spectrum Pharmaceuticals, Blueprint Medicines, Genentech, and Tesaro, all outside the submitted work. A.S. Tsao reports having a consultant/advisory role with Novartis, Boehringer Ingelheim, Genentech/Roche, MedImmune, Imexed, Lilly, BMS, Epizyme, AstraZeneca/MedImmune, ARIAD, EMD Serono, Takeda, HERON; receiving royalties from Uptodate; research funding from Seattle Genetics, Millennium, Polaris, BMS, following to institution MedImmune, Merck, Genentech/Roche, BMS, Boehringer Ingelheim. J.D. Patel reports having an advisory role with AbbVie, AstraZeneca, Takeda. S.M. Gedgeland reports having a consultant/advisory role with Pfizer, Genentech/Roche, ARIAD, AstraZeneca, BMS, AbbVie; being a member of a speakers bureau for AstraZeneca; receiving travel/accommodations/expenses from ARIAD/Takeda, Genentech/Roche; and research funding from Merck, (following to institution) Pfizer, Genentech/Roche, Merck, Blueprint Medicines, ARIAD/Takeda. L. Bazhenova reports having an advisory role with Genentech, Novartis, Regeneron, BI, BMS, Johnson and Johnson, Merck; receiving research funding from BeyondSpring Pharmaceuticals, and being a shareholder in Epic Sciences. V.W. Zhu reports receiving honoraria from AstraZeneca, Roche-Foundation Medicine, Roche/Genentech, Takeda; having a consultant/advisory role with TP Therapeutics; owning stock or other ownership options with TP Therapeutics; and being a member of a speakers bureau for AstraZeneca, Roche-Foundation Medicine, Roche/Genentech, Takeda. H.L. West reports receiving personal fees as an advisory board member, consultant, and speaker from Genentech/Roche, Takeda/ARIAD, and as a consultant and speaker from Novartis, Pfizer. T. Mekhail has no disclosures to report. R.D. Gentzler reports receiving honoraria from Rockpointe CME; consulting fees from AstraZeneca, Pfizer, Blueprint Medicines, ARIAD; and research funding to institution from Merck, Bristol-Myers Squibb, Takeda, Jounce Therapeutics, Helsinn, and Pfizer. D. Nguyen has no disclosures to report. S. Vincent reports employment with Takeda. S. Zhang reports employment with Takeda. J. Lin reports employment with Takeda. V. Bunn reports employment with Takeda. S. Jin reports employment with Takeda. S. Li reports former employment with Takeda. P.A. Jänne reports grants and personal fees from Takeda Oncology during the conduct of the study; grants from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, PUMA, Astellas Pharmaceuticals, and Daiichi Sankyo; and personal fees from Araxes Pharmaceuticals, ARIAD/Takeda; AstraZeneca, AbbVie, Mirati Therapeutics, Boehringer Ingelheim, Pfizer, Roche/Genentech, Chugai Pharmaceuticals, Eli Lilly and Company, Ignyta, Merrimack, Novartis, Voronoi, SFJ Pharmaceuticals, Biocartis, LOXO Oncology, PUMA, Sanofi, Transcenta, Daiichi Sankyo, and Silicon Therapeutics, outside the submitted work; and is a shareholder of Gatekeeper and LOXO Oncology. In addition, Dr. Jinne receives postmarketing royalties from a DFCI-owned patent on EGFR mutations licensed to LabCorp.

**Authors’ Contributions**

G.J. Riely: Conceptualization, data curation, formal analysis, supervision, investigation, methodology, writing–original draft, project administration, writing–review and editing. J.W. Neal: Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, project administration, writing–review and editing. D. Camidge: Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, project administration, writing–review and editing. A.I. Spira: Data curation, formal analysis, investigation, writing–original draft, writing–review and editing. Z. Piotrowska: Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, project administration, writing–review and editing. D.B. Costa: Conceptualization, data curation, formal analysis, funding acquisition.
research-article

investigation, methodology, writing–original draft, project administration, writing–review and editing. A.S. Tsao: Investigation, writing–original draft, writing–review and editing. J.D. Patel: Investigation, writing–original draft, writing–review and editing. L. Bazhenova: Investigation, writing–original draft, writing–review and editing. V.W. Zhu: Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, project administration, writing–review and editing. H.L. West: Investigation, writing–original draft, writing–review and editorial. T. Mekhail: Investigation, writing–original draft, writing–review and editing. R.D. Gentzler: Data curation, investigation, writing–original draft, writing–review and editing. D. Nguyen: Investigation, writing–original draft, writing–review and editing. S. Vincent: Data curation, formal analysis, methodology, writing–original draft, writing–review and editing. S. Zhang: Conceptualization, formal analysis, methodology, writing–original draft, project administration, writing–review and editing. J. Lin: Data curation, formal analysis, writing–original draft, writing–review and editing. V. Bunn: Data curation, formal analysis, writing–original draft, writing–review and editing. S. Jin: Data curation, formal analysis, supervision, writing–original draft, writing–review and editing. S. Li: Conceptualization, supervision, methodology, writing–original draft, writing–review and editing. P.A. Janne: Conceptualization, data curation, formal analysis, supervision, investigation, writing–original draft, project administration, writing–review and editing.

Acknowledgments

We thank the patients, their families, and their caregivers; the investigators and their team members at each study site; and colleagues from Millennium Pharmaceuticals, Inc., Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Professional medical writing assistance was provided by Lauren Gallagher, RPh, PhD, and Lela Creutz, PhD, of Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and funded by Millennium Pharmaceuticals, Inc. Teodor G. Paunescu, PhD (Millennium Pharmaceuticals, Inc., Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited) is acknowledged for editorial assistance. This work was funded in part through a National Institutes of Health/National Cancer Institute (NCI) grant (R37CA218707) to D.B. Costa for case preselection and genomic analyses at Beth Israel Deaconess Medical Center, a member of the NCI-designated Dana-Farber/Harvard Cancer Center.

Received November 25, 2020; revised January 27, 2021; accepted February 22, 2021; published first February 25, 2021.

REFERENCES


Mobocertinib in NSCLC with EGFR Exon 20 Insertions


Activity and Safety of Mobocertinib (TAK-788) in Previously Treated Non–Small Cell Lung Cancer with EGFR Exon 20 Insertion Mutations from a Phase I/II Trial

Gregory J. Riely, Joel W. Neal, D. Ross Camidge, et al.

Cancer Discov 2021;11:1688-1699. Published OnlineFirst February 25, 2021.

Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-20-1598

Supplementary Material
Access the most recent supplemental material at:
http://cancerdiscovery.aacrjournals.org/content/suppl/2021/02/25/2159-8290.CD-20-1598.DC1

Cited articles
This article cites 45 articles, 8 of which you can access for free at:
http://cancerdiscovery.aacrjournals.org/content/11/7/1688.full#ref-list-1

Citing articles
This article has been cited by 2 HighWire-hosted articles. Access the articles at:
http://cancerdiscovery.aacrjournals.org/content/11/7/1688.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link
http://cancerdiscovery.aacrjournals.org/content/11/7/1688.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.