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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

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 Li^{16,*}, Pasi A. Jänne¹⁸

¹Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA

²Division of Oncology, Department of Medicine, Stanford University, Stanford, CA, USA

³Division of Medical Oncology, Department of Medicine, University of Colorado Cancer Center, Aurora, CO, USA

⁴Department of Thoracic Oncology, Virginia Cancer Specialists, Fairfax, VA, USA

⁵Department of Medicine, Division of Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA

⁶Department of Medicine, Division of Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Address for correspondence: Gregory J. Riely, MD, PhD, Vice Chair, Clinical Research, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Phone: 646-608-3913, Fax: 929-608-3913, rielyg@MSKCC.ORG.

*Current affiliation: Ansun Biopharma, San Diego, CA, USA

Authors' Contributions:

Conception and design: G.J. Riely, J.W. Neal, D.R. Camidge, Z. Piotrowska, D.B. Costa, V.W. Zhu, S. Zhang, S. Li, P.A. Jänne
Data curation (provided animals, acquired and managed patients, provided facilities, etc.): G.J. Riely, J.W. Neal, D.R. Camidge, A.I. Spira, Z. Piotrowska, D.B. Costa, V.W. Zhu, R.D. Gentzler, S. Vincent, J. Lin, V. Bunn, S. Jin, P.A. Jänne

Formal analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G.J. Riely, J.W. Neal, D.R. Camidge, A.I. Spira, Z. Piotrowska, D.B. Costa, V.W. Zhu, S. Vincent, S. Zhang, J. Lin, V. Bunn, S. Jin, P.A. Jänne

Funding acquisition: D.B. Costa

Investigation: G.J. Riely, J.W. Neal, D.R. Camidge, A.I. Spira, Z. Piotrowska, D.B. Costa, A.S. Tsao, J.D. Patel, S.M. Gadgeel, L. Bazhenova, V.W. Zhu, H.L. West, T. Mekhail, R.D. Gentzler, D. Nguyen, P.A. Jänne

Development of methodology: G.J. Riely, J.W. Neal, D.R. Camidge, Z. Piotrowska, D.B. Costa, V.W. Zhu, S. Vincent, S. Zhang, S. Li

Project administration (administrative, technical, or material support [i.e., reporting or organizing data, constructing databases]): G.J. Riely, J.W. Neal, D.R. Camidge, Z. Piotrowska, D.B. Costa, V.W. Zhu, S. Zhang, P.A. Jänne

Supervision: G.J. Riely, S. Jin, S. Li, P.A. Jänne

Writing—original draft: All authors

Writing—review & editing: All authors

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 three months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

⁷Department of Thoracic/Head & Neck Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA

⁸Department of Medicine, Northwestern University, Feinberg School of Medicine Chicago, IL, USA

⁹Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI, USA

¹⁰Department of Medicine, UC San Diego Moores Cancer Center, La Jolla, CA, USA

¹¹Department of Medicine, Division of Hematology/Oncology, University of California Irvine, Orange, CA, USA

¹²Department of Medical Oncology & Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

¹³Thoracic Cancer Program, AdventHealth Orlando, Orlando, FL, USA

¹⁴Hematology/Oncology, University of Virginia Cancer Center, Charlottesville, VA, USA

¹⁵Department of Hematology and Oncology, Pacific Shores Medical Group, Long Beach, CA, USA

¹⁶Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA

¹⁷Statistical and Quantitative Sciences, Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA

¹⁸Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Abstract

Mobocertinib, an oral epidermal growth factor receptor (EGFR) inhibitor targeting *EGFR* gene mutations including exon 20 insertions (*EGFR*ex20ins) in non-small cell lung cancer, was evaluated in a phase 1/2 dose-escalation/expansion trial ([ClinicalTrials.gov NCT02716116](https://clinicaltrials.gov/ct2/show/study/NCT02716116)). Dose escalation identified 160 mg daily as the recommended phase 2 dose and maximum tolerated dose. Among 136 patients treated with 160 mg daily, the most common any grade treatment-related adverse events (TRAEs; >25%) were diarrhea (83%), nausea (43%), rash (33%), and vomiting (26%), with diarrhea (21%) the only grade 3 TRAE >5%. Among 28 *EGFR*ex20ins patients treated at 160 mg daily, the investigator-assessed confirmed response rate was 43% (12/28; 95% confidence interval (CI): 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 *EGFR*ex20ins variants with a safety profile consistent with other EGFR inhibitors.

Keywords

Carcinoma; Non-Small-Cell Lung; ErbB Receptors; Epidermal Growth Factor Receptor

INTRODUCTION

Epidermal growth factor receptor gene (*EGFR*) exon 20 insertion (*EGFR*ex20ins) mutations represent approximately 4–12% of *EGFR* mutations in patients with non–small cell lung cancer (NSCLC) (1–4). No 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 epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib (5–10). The structural, preclinical, and clinical characterization of the most common *EGFR*ex20ins 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.

In the absence of approved targeted therapies, patients with NSCLC with *EGFR*ex20ins 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 <30% and progression-free survival (PFS) \approx 3 months in patients with *EGFR*ex20ins mutated NSCLC (2, 13, 14, 17–22). Platinum-based systemic chemotherapy in the first-line setting has been associated with response rates of 50–63% in patients with *EGFR*ex20ins mutations, but most patients progress within 6 months (median PFS: 4.1–6.4 months) (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 3.0 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 *EGFR*ex20ins mutation do not appear to benefit from immune checkpoint inhibitors, with an ORR of 0% and median PFS of 2 months (28). Poziotinib, a third-generation EGFR TKI that demonstrated potent inhibition of *EGFR*ex20ins mutants in vitro (29), has recently demonstrated limited efficacy in patients with NSCLC with *EGFR*ex20ins 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 daily) as second-line or greater therapy in patients with NSCLC with some *EGFR*ex20ins mutations (32–35). In a recent preclinical study, the selective *EGFR*ex20ins inhibitor DS-2087b inhibited proliferation of Ba/F3 cells expressing *EGFR*ex20ins and demonstrated selectivity over WT EGFR (36). Tarloxotinib, a hypoxia-activated prodrug of a pan-ErbB kinase inhibitor, demonstrated preclinical efficacy in *EGFR*ex20ins mutant NSCLC; however, in a

small phase 2 study, the response rate in the cohort of patients with *EGFR*ex20ins was 0% (best response, stable disease in 6/11 patients) (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 *EGFR*ex20ins 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 *EGFR*ex20ins mutant cell lines and in *in vivo* tumor models of *EGFR*ex20ins-mutated NSCLC are reported in a companion article in this issue by Gonzalez and colleagues titled "*Mobocertinib (TAK-788): A Targeted Inhibitor of EGFR Exon 20 Insertion Mutants in Non-Small Cell Lung Cancer*"(40). Here, we present the results of a dose-escalation phase 1/2 trial with expansion cohorts that assessed the safety, tolerability, and antitumor activity of mobocertinib in patients with metastatic *EGFR*ex20ins-mutated NSCLC.

RESULTS

Dose Escalation and Pharmacokinetics

The dose-escalation study followed a conventional 3+3 design, starting with a dose of 5 mg daily (Fig. 1). A total of 73 patients with NSCLC refractory to standard therapies were enrolled in the dose-escalation study; 44 patients were evaluable for dose-limiting toxicities (DLTs). No DLTs were observed in 20 evaluable patients at daily doses ranging from 5 mg to 40 mg. DLTs occurred in 1 of 7 evaluable patients at 80 mg daily (grade 3 pneumonitis), 1 of 7 evaluable patients at 120 mg daily (grade 5 pneumonitis), 1 of 6 evaluable patients at 160 mg daily (grade 3 mucositis), and 2 of 4 evaluable patients at 180 mg daily (grade 3 diarrhea and missing >25% of planned doses due to a treatment-related adverse event). The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) was determined to be 160 mg daily.

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

Expansion Phase

Patients—The expansion phase enrolled 7 histologically and molecularly defined cohorts (Supplementary Table S1) at the RP2D (160 mg daily). Here, we present safety data in all patients (regardless of cancer type) treated with mobocertinib 160 mg daily as of the data cutoff for this analysis (January 27, 2020; n=136) and efficacy results in 70 patients with

previously treated NSCLC and *EGFR*20ins mutations treated with mobocertinib (5–40 mg daily [n=12], 80 mg daily [n=9], 120 mg daily [n=21], and 160 mg daily [n=28]), with a focus on the 28 patients with previously treated NSCLC and *EGFR*20ins mutations who had either not received (n=22) or not shown (n=6) an objective response to a prior EGFR TKI treated at 160 mg daily (cohort 1). As of the data cutoff, 46 (34%) of the 136 patients treated with mobocertinib 160 mg daily 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 *EGFR*20ins mutations treated at 160 mg daily 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 daily are presented in Table 1.

Safety and Tolerability—Among the 136 patients treated at 160 mg daily, 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 daily) 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 *EGFR*20ins mutations were similar to those observed in all patients treated at 160 mg daily (Table 2). Among the 28 patients with *EGFR*20ins mutations treated at 160 mg daily, 16 (57%) had AEs 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 (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) (41) in patients with previously treated NSCLC with *EGFR*20ins mutations treated with mobocertinib daily doses ranging from 5 mg up 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 5–40 mg daily, 22% (2/9) at 80-mg total daily dose (combining those who received 80 mg daily or 40 mg twice daily), 19% (4/21) at 120 mg daily, and 43% (12/28) at 160 mg daily (Table 3).

Best percent change in target lesions and objective responses by time on treatment in patients with *EGFR*20ins mutations treated with the 160-mg daily dose are shown in Fig. 3A and 3B, respectively; prior treatment history and mutation status are also shown. Among the 28 patients with *EGFR*20ins mutations treated with mobocertinib 160 mg daily, the

confirmed ORR was 43% (12/28; 95% 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 daily were observed in patients with a diverse array of *EGFR*Ex20ins variants (Fig. 3A). No molecular subgroup of *EGFR*Ex20ins 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 *EGFR*Ex20ins mutations (40), demonstrated antitumor activity in patients with metastatic, previously treated NSCLC harboring *EGFR*Ex20ins mutations. Although this analysis included a small number of patients, mobocertinib 160 mg daily demonstrated a high response rate (43%) and favorable median PFS (7.3 months). Studies of first- and second-generation EGFR TKIs have reported ORR of 8–27% and median PFS: \approx 3 months (13, 14, 18–22); other EGFR TKIs that have been tested in patients with *EGFR*Ex20ins 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 median PFS of 8.3 months in 39 response-evaluable patients with advanced NSCLC and *EGFR*Ex20ins mutations, including patients with and without prior anticancer therapy, in a phase 1 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 adverse events 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 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 subjects 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 adverse event 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 *EGFR*ex20ins 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 mutation, *EGFR* exon 19 deletions, and L858R mutation (44). Although in this study we could not identify a clear relationship between the specific subtype of *EGFR*ex20ins 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 *EGFR*ex20ins 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 *EGFR*ex20ins-mutated NSCLC who were treatment-naive and an extension cohort of patients with previously treated NSCLC with *EGFR*ex20ins 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 US Food and Drug Administration in April 2020 based on the ORR and the long-term benefit seen in the data presented here. A global phase 3 randomized trial (EXCLAIM-2, [NCT04129502](https://clinicaltrials.gov/ct2/show/study/NCT04129502)) evaluating the efficacy of mobocertinib as first-line treatment compared with platinum-based chemotherapy is now enrolling patients with treatment-naive advanced NSCLC whose tumors harbor *EGFR*ex20ins mutations.

Conclusions

Mobocertinib, an EGFR TKI designed to target *EGFR*ex20ins mutations, showed antitumor activity at a RP2D of 160 mg daily in patients with *EGFR*ex20ins-positive NSCLC, with a 43% confirmed ORR, a 14-month median duration of response, and a 7-month median PFS. The adverse event profile of mobocertinib was manageable and consistent with that of other EGFR TKIs. Mobocertinib demonstrated responses in patients with diverse *EGFR*ex20ins variants and is being further explored in a single-arm extension cohort of patients with previously treated NSCLC with *EGFR*ex20ins mutations.

METHODS

Study Design and Participants

This was a first-in-human, phase 1/2 study ([ClinicalTrials.gov NCT02716116](https://ClinicalTrials.gov/ct2/show/study/NCT02716116); [ClinicalTrials.jp 195000](https://ClinicalTrials.gov/ct2/show/study/NCT01950000); [EudraCT 2016–001271-68](https://ClinicalTrials.gov/ct2/show/study/NCT020127168)). 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 cohorts (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, that included patients with NSCLC previously treated with systemic therapy who had *EGFR*ex20ins mutations; safety data are reported for all patients who received mobocertinib 160 mg daily in dose escalation and expansion.

Patients were excluded from the dose-escalation phase if they had symptomatic 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 first dose of mobocertinib (except for reversible EGFR TKIs [i.e., erlotinib or gefitinib], which were allowed up to 7 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, Cambridge, MA, USA) 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 daily, 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 daily. 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 3–4 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 5–180 mg daily were determined using validated liquid chromatography mass spectrometry methods. PK parameters (i.e., T_{max} , maximum concentration [C_{max}], and

AUC_{0–24}) were estimated using noncompartmental methods (Phoenix WinNonlin, version 8.1; Certara, Princeton, NJ, USA).

Disease assessment included imaging of the chest, abdomen, pelvis, and brain using appropriate radiological procedures (computed tomography scans or magnetic resonance imaging with contrast, unless contrast media was contraindicated) at screening and at 8-week intervals thereafter (on Day 28 [\pm 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) were 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 1 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 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 1 dose-finding studies; the histologically 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 1 and phase 2 data in patients who had received at least one dose of mobocertinib 160 mg daily. The proportions of *EGFR*^{ex20ins}-positive NSCLC patients 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 (Cary, NC, USA).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Statement:

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Statement of Significance

No targeted therapies are currently approved for patients with *EGFR*ex20ins NSCLC. Mobocertinib demonstrated antitumor activity with manageable toxicity in patients with advanced *EGFR*ex20ins NSCLC in this study, supporting additional development in previously treated *EGFR*ex20ins NSCLC and a phase 3 trial comparing first-line mobocertinib with platinum-based chemotherapy in advanced *EGFR*ex20ins NSCLC.

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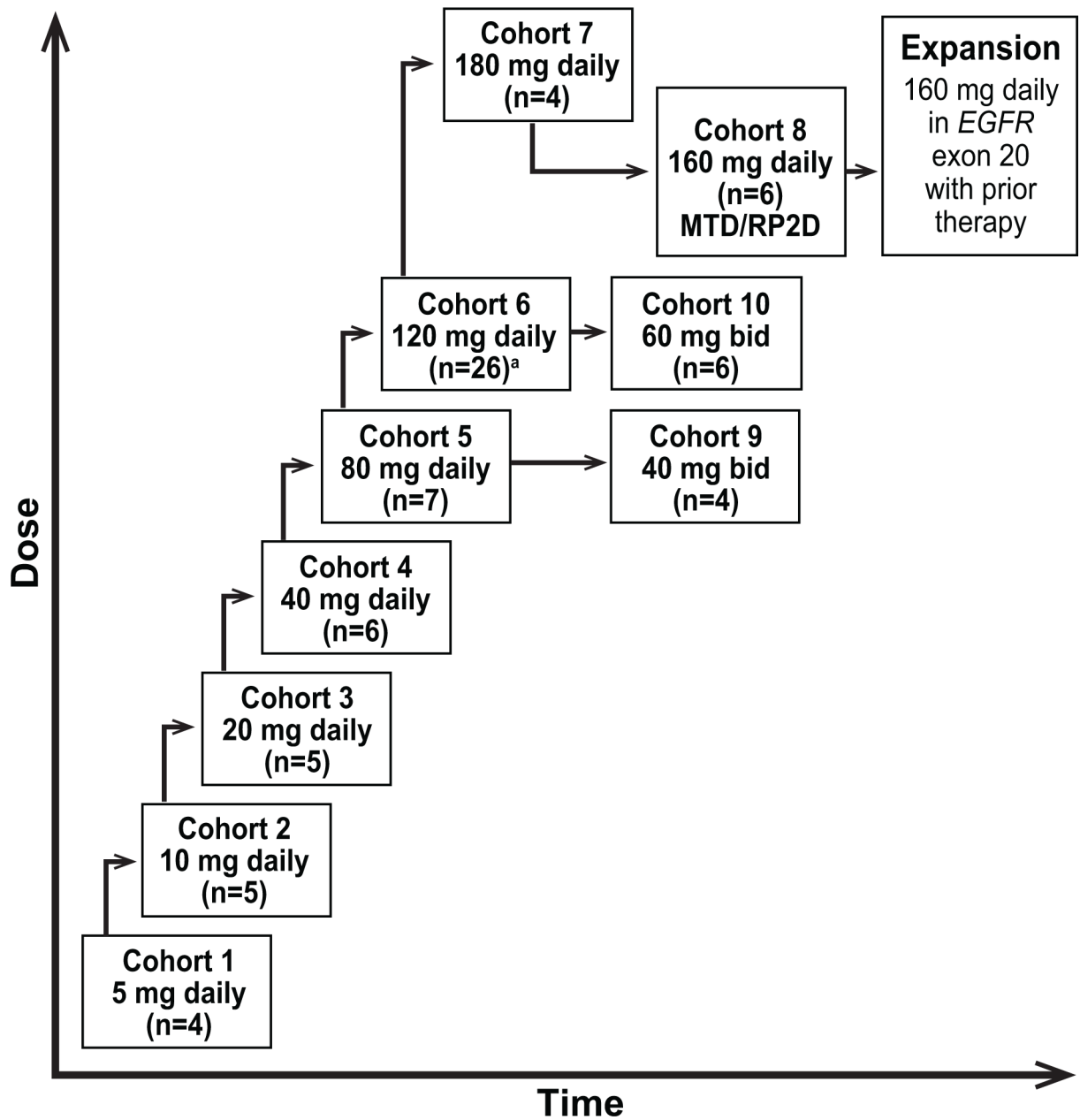


Figure 1. Schema for the dose-escalation phase of the phase 1/2 trial of mobocertinib. The dose-escalation phase followed a conventional 3+3 design. The dose level for each new cohort was up to 100% higher than the dose level in the previous cohort until a grade 2 drug-related toxicity of diarrhea or 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
Abbreviations: bid, twice daily; DLTs, dose-limiting toxicities; EGFR, epidermal growth factor receptor; *EGFR*, epidermal growth factor receptor gene; MTD, maximum tolerated dose; daily, once daily; RP2D, recommended phase 2 dose

^a Seven patients were enrolled in the dose escalation to evaluate DLT; additional patients were included to further confirm safety observations.

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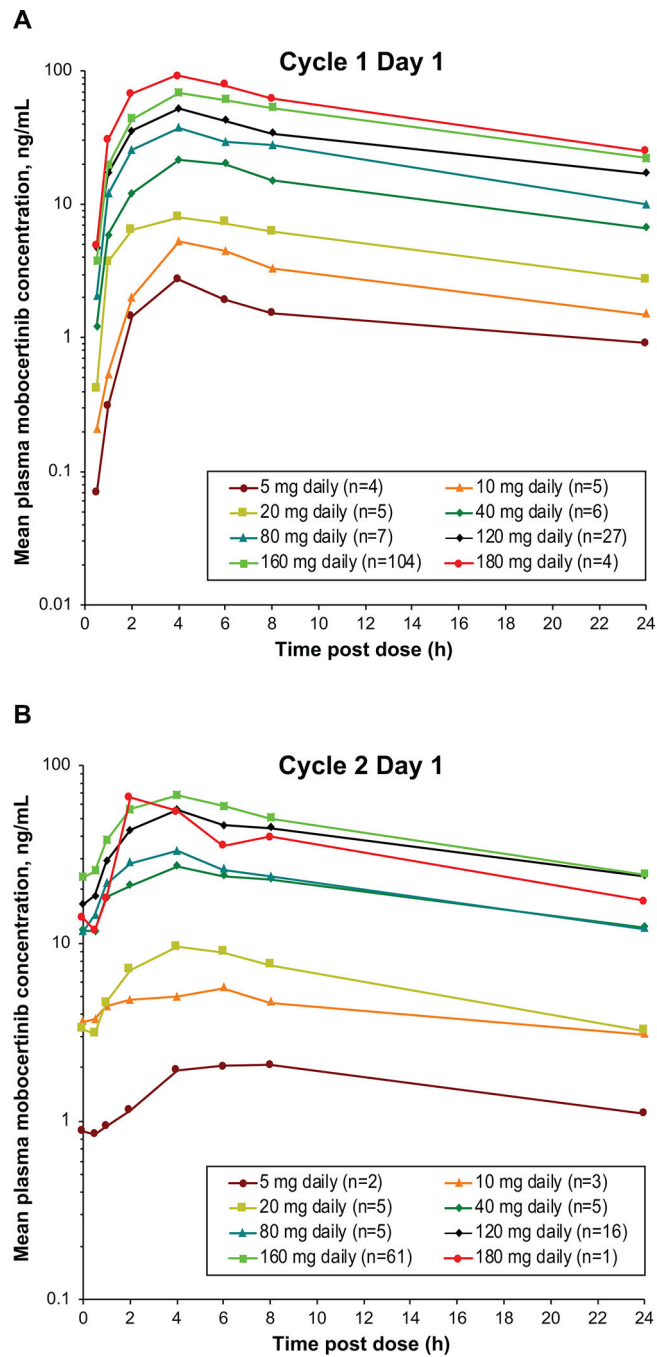


Figure 2. Mean plasma concentrations of mobocertinib **A.** following the first oral administration of mobocertinib on Cycle 1, Day 1 and **B.** following repeated oral dosing on Cycle 2, Day 1 in patients with NSCLC in the dose-escalation study (semi-log scale). Abbreviations: NSCLC, non-small cell lung cancer. Preliminary pharmacokinetic data as January 27, 2020.

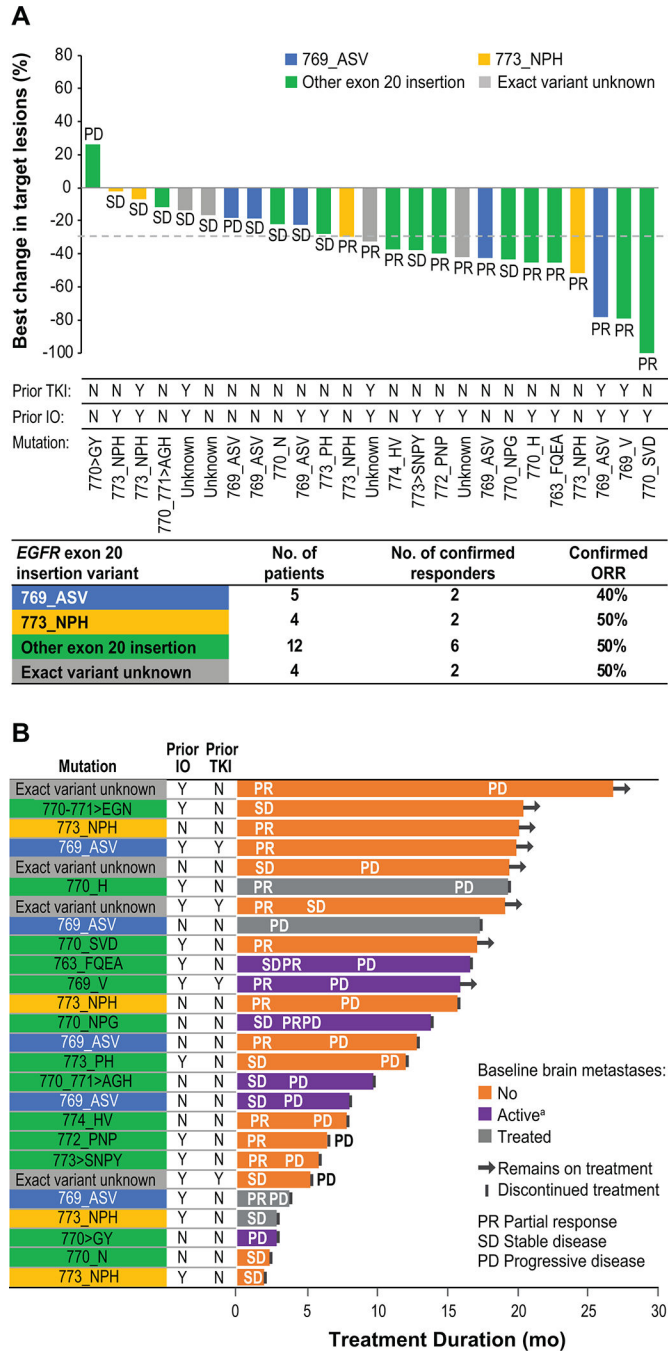


Figure 3. Response to mobocertinib in patients with *EGFR*ex20ins mutations treated at 160 mg daily (n=28). **A.** Best percentage change from baseline in target lesions by molecular subtype. Mutations by patient are shown under the figure. **B.** Plot showing objective responses by time on treatment and baseline CNS metastases status. Three patients were excluded from these plots: 1 patient had nonmeasurable baseline target lesions, and 2 patients had no follow-up scans.

Abbreviations: CNS, central nervous system, *EGFR*ex20ins, epidermal growth factor receptor gene exon 20 insertion; IO, immune-oncology therapy; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

^a Active brain metastases were either never treated or progressed after radiation.

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Table 1.

Characteristics of patients treated with mobocertinib 160 mg daily

Characteristic	Patients with <i>EGFR</i> ex20ins ^a (n=28)	All patients (n=136)
Median age, years (range)	62 (28–84)	62 (24–86)
Sex		
Female	21 (75)	90 (66)
Male	7 (25)	46 (34)
Race		
White	20 (71)	103 (76)
Asian	5 (18)	20 (15)
Black	1 (4)	9 (7)
Other or unknown	2 (7)	4 (3)
Histology		
Adenocarcinoma	27 (96)	128 (94)
Squamous	0	3 (2)
Large cell	1 (4)	2 (1)
Missing	0	3 (2)
ECOG performance status		
0	6 (21)	48 (35)
1	22 (79)	88 (65)
No. of prior systemic anticancer regimens		
0	0	26 (19)
1	4 (14)	12 (9)
2	9 (32)	16 (12)
3	15 (54)	29 (21)
Unknown	0	53 (39)
Type of prior systemic anticancer therapy		
Chemotherapy	28 (100)	54 (40)
Prior checkpoint inhibitor therapy	17 (61)	32 (24)
EGFR/HER2 TKI	6 (21)	26 (19)
History of smoking		
Never	17 (61)	83 (61)
Former	11 (39)	51 (38)
Current	0	1 (1)
Unknown	0	1 (1)
Baseline CNS metastases	12 (43)	52 (38)

NOTE: Values are number (%) of patients, unless specified otherwise.

Data cutoff: January 27, 2020.

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; *EGFR*ex20ins, epidermal growth factor receptor gene exon 20 insertion; HER2, human epidermal growth factor receptor 2; TKI, tyrosine kinase inhibitor.

^aPatients who received 160 mg daily (initial dose) during dose escalation (n=6) and in expansion cohort 1 (n=22).

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Table 2.

Treatment-related TEAEs of any grade reported in at least 10% and grade 3 or higher TEAEs reported in at least 3% of all patients treated with the mobocertinib RP2D (160 mg daily)

TEAE	Patients with <i>EGFR</i> ex20ins treated at 160 mg daily ^a (n=28)		All patients treated at 160 mg daily ^b (n=136)	
	Any Grade	Grade 3	Any Grade	Grade 3
Diarrhea	23 (82)	9 (32)	113 (83)	28 (21)
Nausea	11 (39)	3 (11)	58 (43)	5 (4)
Rash	13 (46)	0	45 (33)	1 (1)
Vomiting	10 (36)	2 (7)	36 (26)	5 (4)
Dry skin	5 (18)	0	30 (22)	0
Decreased appetite	11 (39)	0	29 (21)	1 (1)
Stomatitis	6 (21)	2 (7)	28 (21)	5 (4)
Fatigue	4 (14)	1 (4)	28 (21)	2 (1)
Rash maculo-papular	7 (25)	1 (4)	22 (16)	1 (1)
Paronychia	8 (29)	0	22 (16)	0
Anemia	5 (18)	0	19 (14)	3 (2)
Dermatitis acneiform	5 (18)	0	19 (14)	1 (1)
GERD	3 (11)	0	17 (13)	0
Dyspepsia	6 (21)	0	16 (12)	0
Increased lipase	7 (25)	2 (7)	15 (11)	7 (5)
Pruritus	5 (18)	0	14 (10)	0

Data cutoff: January 27, 2020

Abbreviations: *EGFR*ex20ins, epidermal growth factor receptor gene exon 20 insertion; GERD, gastroesophageal reflux disease; RP2D, recommended phase 2 dose; TEAEs, treatment-emergent adverse events.

^aPatients with *EGFR*ex20ins mutations with prior therapy who received 160 mg daily (initial dose) during dose escalation (n=6) and in expansion cohort 1 (n=22).

^bPatients who received at least one dose of mobocertinib at 160 mg daily (initial dose) during dose-escalation or expansion phases.

Table 3.

Investigator-assessed antitumor activity of mobocertinib in NSCLC patients with *EGFR*ex20ins

	5–40 mg daily (n=12)	80 mg total daily dose ^a (n=9)	120 mg daily (n=21)	160 mg daily ^b (n=28)
Best confirmed response, n (%) ^c				
Complete response	0	1 (11)	1 (5)	0
Partial response	0	1 (11)	3 (14)	12 (43)
Stable disease ^d	3 (25)	6 (67)	11 (52)	12 (43)
Progressive disease	7 (58)	1 (11)	3 (14)	2 (7)
Not evaluated	2 (17)	0	3 (14)	2 (7)
Confirmed ORR, n (%) [95% CI]	0 [0–26]	2 (22) [3–60]	4 (19) [5–42]	12 (43) [24–63]
Confirmed disease control rate, n (%) [95% CI]	3 (25) [5–57]	8 (89) [52–100]	15 (71) [48–89]	24 (86) [67–96]

Data cutoff: January 27, 2020

Abbreviations: CI, confidence interval; *EGFR*ex20ins, epidermal growth factor receptor gene exon 20 insertion; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

^aIncludes 80 mg daily and 40 mg twice daily.

^bPatients treated with at least one dose of mobocertinib.

^cBy RECIST version 1.1.

^dStable disease observed 6 weeks after first study drug administration.

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