Expert Review of Anticancer Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iery20

Characterization and management of adverse events observed with mobocertinib (TAK-788) treatment for *EGFR* exon 20 insertion–positive non–small cell lung cancer

James Chih-Hsin Yang, Caicun Zhou, Pasi A. Jänne, Suresh S. Ramalingam, Tae Min Kim, Gregory J Riely, Alexander I Spira, Zofia Piotrowska, Tarek Mekhail, Maria Rosario Garcia Campelo, Enriqueta Felip, Lyudmila Bazhenova, Shu Jin, Manmit Kaur, Paul M. Diderichsen, Neeraj Gupta, Veronica Bunn, Jianchang Lin, Eric N. Churchill, Minal Mehta & Danny Nguyen

To cite this article: James Chih-Hsin Yang, Caicun Zhou, Pasi A. Jänne, Suresh S. Ramalingam, Tae Min Kim, Gregory J Riely, Alexander I Spira, Zofia Piotrowska, Tarek Mekhail, Maria Rosario Garcia Campelo, Enriqueta Felip, Lyudmila Bazhenova, Shu Jin, Manmit Kaur, Paul M. Diderichsen, Neeraj Gupta, Veronica Bunn, Jianchang Lin, Eric N. Churchill, Minal Mehta & Danny Nguyen (2023) Characterization and management of adverse events observed with mobocertinib (TAK-788) treatment for *EGFR* exon 20 insertion–positive non–small cell lung cancer, Expert Review of Anticancer Therapy, 23:1, 95-106, DOI: 10.1080/14737140.2023.2157815

To link to this article: https://doi.org/10.1080/14737140.2023.2157815

EXPERT REVIEW OF ANTICANCER THERAPY
2023, VOL. 23, NO. 1, 95–106
https://doi.org/10.1080/14737140.2023.2157815

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Characterization and management of adverse events observed with mobocertinib (TAK-788) treatment for *EGFR* exon 20 insertion–positive non–small cell lung cancer

James Chih-Hsin Yang[a], Caicun Zhou[b], Pasi A. Jänne[c], Suresh S. Ramalingam[d], Tae Min Kim[e], Gregory J Riely[f], Alexander I Spira[g], Zofia Piotrowska[h], Tarek Mekhail[i], Maria Rosario Garcia Campelo[j], Enriqueta Felip[k], Lyudmila Bazhenova[l], Shu Jin[m], Manmit Kaur[n], Paul M. Diderichsen[o], Neeraj Gupta[p,s], Veronica Bunn[t], Jianchang Lin[q,t], Eric N. Churchill[r], Minal Mehta[m] and Danny Nguyen[o,s,t]

[a]Graduate Institute of Oncology, National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan; [b]Shanghai Pulmonary Hospital, Shanghai, China; [c]Dana-Farber Cancer Institute, Boston, MA, USA; [d]School of Medicine, Emory University, Atlanta, GA, USA; [e]Seoul National University Hospital, Seoul, South Korea; [f]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [g]Medical Oncology, Virginia Cancer Specialists and US Oncology Research, Fairfax, VA, USA; [h]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [i]Thoracic Cancer Program, AdventHealth Orlando, Orlando, FL, USA; [j]Medical Oncology Department, Thoracic Tumors Unit, University Hospital A Coruña, CHUAC, A Coruña, Spain; [k]Vall d'Hebron University Hospital, Barcelona, Spain; [l]University of California San Diego Moores Cancer Center, La Jolla, CA, USA; [m]Clinical Science, Oncology, Takeda Development Center Americas, Inc., Lexington, MA, USA; [n]Takeda Pharmaceuticals U.S.A., Inc, Lexington, MA, USA; [o]Integrated Drug Development, Certara, Princeton, NJ, USA; [p]Quantitative Clinical Pharmacology, Takeda Development Center Americas, Inc., Lexington, MA, USA; [q]Oncology Statistics, Takeda Development Center Americas, Inc., Lexington, MA, USA; [r]Global Medical Affairs Oncology, Takeda Pharmaceuticals U.S.A., Inc., Lexington, MA, USA; [s]Medical Safety Oncology, Takeda Development Center Americas, Inc., Lexington, MA, USA; [t]City of Hope National Medical Center, USA

ABSTRACT

Background: Mobocertinib has demonstrated durable clinical benefit in platinum-pretreated patients (PPP) with epidermal growth factor receptor exon 20 insertion–positive non–small cell lung cancer (NSCLC).
Research design and methods: Pooled safety analysis of two studies included patients with NSCLC (N = 257) treated with the recommended phase 2 dose (RP2D) of mobocertinib (160 mg once daily). We report overall safety (treatment-emergent adverse events [TEAEs]) in the RP2D population; characterization of GI and skin-related events in 114 PPP from a phase 1/2 study (NCT02716116); and clinical activity in PPP with and without dose reductions due to TEAEs.
Results: In the RP2D population (N = 257), the most common TEAEs were diarrhea (93%), nausea (47%), rash (38%), and vomiting (37%). In PPP (N = 114), median times to diarrhea onset and resolution were 5 and 2 days, respectively. Median times to onset and resolution of skin-related events were 9 and 78 days, respectively. Among PPP with (n = 29) or without (n = 85) dose reductions due to TEAEs, overall response rates were 21% and 31% and median durations of response were 5.7 and 17.5 months, respectively.
Conclusions: GI and skin-related events are common with mobocertinib; minimizing dose reductions with proactive management may improve clinical outcomes.
Trial Registration: NCT02716116; NCT03807778

Plain Language Summary

Mobocertinib is a treatment for patients with a certain type of lung cancer. We analyzed the safety of mobocertinib in 257 patients with lung cancer. The most common side effects with mobocertinib were diarrhea, nausea, vomiting, and skin rash. In 114 patients with lung cancer who were treated in the past with chemotherapy that included platinum-based drugs, diarrhea started after about 5 days of mobocertinib treatment and went away in about 2 days. Skin-related side effects started after about 9 days and went away in about 2.5 months. One-fifth of patients who had to receive a smaller amount of mobocertinib because of side effects responded to treatment compared with one-third of patients who received the recommended mobocertinib amount. Managing side effects quickly can better help patients with lung cancer who are treated with mobocertinib.

ARTICLE HISTORY
Received 29 March 2022
Accepted 28 September 2022

KEYWORDS
Carcinoma; non–small cell lung; epidermal growth factor receptor; patient safety; protein tyrosine kinases; drug-related side effects and adverse reactions

1. Introduction

The development of tyrosine kinase inhibitors (TKIs) has advanced the treatment of patients with non–small cell lung cancer (NSCLC) harboring common epidermal growth factor receptor gene (*EGFR*) mutations. However, the efficacy of these therapies is limited in patients with *EGFR* exon 20 insertion (*EGFR* ex20ins) mutations, which occur in 4% to 12% of NSCLC patients with mutated *EGFR* [1–5]. The EGFR TKIs, afatinib, erlotinib, and gefitinib, are associated with response rates of approximately 0% to

CONTACT James Chih-Hsin Yang chihyang@ntu.edu.tw National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan

This article has been republished with minor changes. These changes do not impact the academic content of the article.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/14737140.2023.2157815

10% and median progression-free survival (PFS) of 1–3 months in patients with *EGFR* ex20ins-positive (*EGFR* ex20ins+) metastatic NSCLC [6,7]. Osimertinib, a third-generation EGFR TKI, resulted in response rates of 0% to 25% (the 25% response rate was observed at 160 mg daily, twice the currently approved dose) and median PFS of 3.6 to 9.7 months in patients with *EGFR* ex20ins+ NSCLC [8–10]. The *EGFR* ex20ins mutations cause steric hindrance resulting in poor binding of these EGFR TKIs, which limits their efficacy and narrows the therapeutic window in this patient population [11]. Platinum-based chemotherapy appears to be more effective in the front-line setting than currently approved EGFR TKIs in patients with *EGFR* ex20ins+ NSCLC [12]. In addition, other standard therapies used for patients with NSCLC have limited activity in *EGFR* ex20ins+ NSCLC. For example, retrospective studies in small cohorts of Asian patients treated with immune checkpoint inhibitors have shown modest response rates ranging from 0% to 14% and PFS of approximately 2 months as second-line monotherapy in this patient population [13–16]. Docetaxel, which is commonly used as a second-line therapy and beyond, has a 14% response rate and a median PFS of 3 months in patients with unspecified mutations who have progressive disease following platinum-based therapy [17–19].

Mobocertinib is a potent, oral, irreversible TKI specifically designed to target in-frame *EGFR* ex20ins mutations in NSCLC [20]. In a phase 1/2 study (NCT02716116), mobocertinib 160 mg orally once daily (QD) demonstrated clinical activity in 114 platinum-pretreated patients (PPP) with *EGFR* ex20ins+ NSCLC by independent assessment, with a confirmed overall objective response rate of 28%, disease control rate of 78%, median DoR of 17.5 months, median PFS of 7.3 months, and median overall survival of 24.0 months [21]. There were no clinically meaningful differences in the area under the concentration–time curve (AUC) when mobocertinib was coadministered with food compared with fasting conditions, suggesting mobocertinib may be taken with or without food [22].

Mobocertinib was granted accelerated approval by the US Food and Drug Administration (FDA) in September 2021 for the treatment of adult patients with locally advanced or mNSCLC with *EGFR* ex20ins mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy [23]. The mobocertinib safety profile was characterized by notable rates of gastrointestinal (GI) and cutaneous adverse events (AEs), most commonly diarrhea and rash [21]. This is consistent with previously reported AEs for the class of EGFR TKIs [24], due to some binding to wild-type EGFR and potentially to human epidermal growth factor receptor 2 (HER2) [25]. Here, we further characterize the safety profile of mobocertinib in a pooled population of patients who received the recommended phase 2 dose (RP2D) of 160 mg QD (N = 257; the RP2D population). We present results of an evaluation of the onset and resolution of the most common AEs observed with mobocertinib and an assessment of the impact of AEs on dose modifications and treatment discontinuation in the PPP population. We also present an analysis of mobocertinib dose intensity, incidence of AEs, and concomitant medications to manage GI and skin-related events among responders to mobocertinib and non-responders in the PPP population. Finally, we discuss the results of an exposure-response analysis conducted to determine the relationship between mobocertinib exposure and the time to first reported Grade ≥2 diarrhea and to assess the impact of various covariates (age, sex, race, performance status, and body weight) on diarrhea.

2. Patients and methods

2.1. Patient population

Overall safety data are reported for a pooled population of patients from two studies who received at least one dose of mobocertinib at the RP2D of 160 mg QD (RP2D population; N = 257). This population included 148 patients from parts 1 and 2 of the 3-part phase 1/2 study (NCT02716116) and 96 patients from part 3 (EXCLAIM). An additional 13 patients from a phase 1 study in Japan (NCT03807778; part 1) were included in the pooled population. Study design, methods, and eligibility criteria for the phase 1/2 study were published previously [21,26]. Briefly, the study included adults (aged ≥18) who had measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [27], Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate renal, hepatic, and bone marrow function, and normal QTc interval [26]. Patients in the EXCLAIM extension cohort were required to have documented in-frame *EGFR* ex20ins mutations and one or two prior regimens of systemic anticancer chemotherapy for locally advanced or metastatic disease [21]. Patients who received prior EGFR TKI treatment were allowed, except for those who had an objective response and subsequent disease progression during TKI treatment. For the Japanese phase 1 study, eligible patients aged ≥20 years had locally advanced or mNSCLC that was refractory to standard therapies, with measurable disease per RECIST version 1.1, ECOG performance status of 0 or 1, adequate renal, hepatic, and bone marrow function, and normal QTc interval. Both studies were conducted in accordance with the Declaration of Helsinki for Good Clinical Practice and applicable local regulations. All patients provided written informed consent.

Additional analyses (described below) were conducted on data from the PPP population of the phase 1/2 study, which included 114 patients (escalation phase [n = 6] + expansion cohort 1 [n = 22] + EXCLAIM [n = 86]) who had *EGFR* ex20ins+ NSCLC, were previously treated with platinum-based chemotherapy, and who received at least 1 dose of mobocertinib at 160 mg QD. Among the PPP population, 32 patients were identified as responders (those achieving either complete or partial response) and 82 patients as nonresponders (those achieving stable disease [n = 57], having progressive disease [n = 13], or not evaluable [n = 12]).

2.2. Study treatment

In the RP2D population (N = 257), patients received mobocertinib 160 mg QD. Dose modification (interruption, reduction, or discontinuation) guidance was prespecified in the protocol. Mobocertinib dose could be reduced to 120 mg QD for the first reduction and further to 80 mg QD per protocol if a second reduction was needed.

2.3. Definition of adverse event categories

Adverse events were coded based on the Medical Dictionary for Regulatory Activities (version 23.0) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 or 5.0, depending on enrollment date. A treatment-emergent AE (TEAE) was defined as any AE that occurred from the first dose of the study drug and through the end of treatment until 30 days after the last dose of the study drug. A treatment-related AE (TRAE) was defined as an AE with a reasonable causal relationship between the study drug or the treatment regimen and the AE per investigator assessment. An AE was considered a serious AE (SAE) if at least one of the following conditions applied: death; life-threatening AE; resulted in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; inpatient hospitalization or prolongation of existing hospitalization; a congenital anomaly/birth defect; occurrence or diagnosis of new cancer that was histopathologically different from the tumor under study; and a significant medical event. Adverse events of clinical interest (AECIs) were chosen based on the following: 1) AEs identified by searches of the clinical database considering the context of the intended patient population; 2) AEs for commercially available EGFR TKIs (e.g. pneumonitis/interstitial lung disease [ILD], GI events, skin events, cardiac events, and stomatitis); 3) AEs reported within the mobocertinib program (e.g. amylase/lipase increases). The AECIs selected for further presentation were pneumonitis/ILD, cardiac disorders, GI toxicities (diarrhea, nausea, vomiting), stomatitis, skin-related events, and amylase/lipase increases.

2.4. Analyses and statistical methods

In the RP2D population (N = 257), the incidence of all-grade TEAEs and TRAEs observed in ≥10% of the patients, Grade ≥3 TEAEs observed in ≥5 patients, and treatment-related SAEs observed in ≥2% of the patients were summarized (data cutoff date: 1 November 2020). In addition, the incidences of other AECIs were summarized, including GI events (diarrhea, nausea, and vomiting), pneumonitis/ILD, cardiac disorders, skin-related events, stomatitis, and amylase/lipase increase. Descriptive statistical methods were used for the characterization of AEs.

Additional analyses were conducted in the PPP population of the phase 1/2 study (N = 114). In the PPP population, GI and skin-related events were further characterized based on grade, onset, and time to resolution. An ad hoc analysis was performed to evaluate any association between QTc interval prolongation and AEs or electrolyte imbalances. GI events leading to dose modifications were also analyzed. Additionally, to examine the potential impact of AEs and dose modifications on clinical activity, an analysis of treatment exposure, incidence of GI and skin-related events, and use of concomitant medications was conducted in confirmed responders versus nonresponders from the PPP population.

An exposure-response analysis was conducted in patients from all three parts of the phase 1/2 study who received mobocertinib doses ranging from 5 mg to 180 mg (N = 295; data cutoff: 29 May 2020) to describe the relationship between daily exposure and time to first reported Grade ≥2 diarrhea and to explore the effect of additional risk covariates (age, sex, race, ECOG status, and body weight) related to diarrhea. The time to first reported Grade ≥2 diarrhea data were merged with the patient covariates and individual daily exposures predicted by a previously developed population pharmacokinetic model [28]. Daily exposure was defined as the AUC of the sum of mobocertinib, metabolite AP32960, and metabolite AP32914 exposures in molar units on a given day. Kaplan–Meier plots of time to first Grade ≥2 diarrhea events were generated and analyzed using a parametric time-to-event model using NONMEM (version 7.3, ICON Development Solutions, Hanover, MD). Equation 1 relates the probability of being event-free (survival) up to time t, ***S(t)***, to the hazard function ***h(t)***:

$$S(t) = e^{-\int_0^t h(\tau)d\tau} \quad (1)$$

The hazard function was modeled according to Equation 2:

$$h(t) = h_0(t) \times \exp(\beta_{AUC} \cdot AUC + \beta_1 \cdot X_1 + \ldots + \beta_n \cdot x_n) \quad (2)$$

$h_0(t)$ was a flexible parametric baseline hazard function based on natural cubic splines. β_{AUC} represented the linear effect of exposure (AUC) on the log-hazard scale, and β_1 to β_n the coefficients (log-hazard ratios [HR]) describing the linear effects of potential or known risk factors (covariates, X_1 to X_n).

Following the construction of a base model (including exposure), the final model was developed by eliminating predictors (other than exposure) from a full model including all relevant risk factors. Risk factors that were not statistically significant at the $\alpha = 0.001$ level were iteratively eliminated until all remaining predictors were statistically significant ($P < 0.001$).

The impact of mobocertinib exposure on HRs was based on a decrease in exposure of 753 nM.hr/day, which reflected the predicted change in dose of 40 mg (dose reduction from 160 mg to 120 mg).

3. Results

3.1. Overall safety analysis

On 1 November 2020, the data cutoff date, a total of 257 patients were included in the RP2D population for the overall safety analysis. Among the 208 patients who discontinued study treatment, reasons included disease progression (clinical or RECIST version 1.1) in 136 (53%), AEs in 29 (11%), withdrawal by patient in 15 (6%), and new anticancer therapy in 3 (1%). The median age was 61.0 years, most patients were female (66%), and most had received prior platinum-based chemotherapy (77%; Table 1). Median (min, max) time on study treatment was 6.1 months (0.0, 40.3). Approximately 50% of the patients had a duration of exposure of ≥6 months. The median (min, max) number of days dosed was 168.0 (1, 1213), and median (min, max) dose intensity was 149.7 mg/day (38.3, 160.0). Patient and disease characteristics in the PPP population were similar to those in the RP2D population, except for a higher proportion of Asian patients in the PPP population (40% in RP2D vs 60% in PPP; Table 1).

Table 1. Patient demographic and baseline characteristics.

Characteristic	RP2D population (N = 257)	PPP population (N = 114)
Age, median (SD), y	61.0 (24–86)	60 (27–84)
Sex, female, n (%)	169 (66)	75 (66)
Race, n (%)		
Asian	102 (40)	68 (60)
White	140 (54)	42 (37)
Black or African American	12 (5)	3 (3)
Not reported	3 (1)	1 (1)
ECOG performance status, n (%)		
0	83 (32)	29 (25)
1	174 (68)	85 (75)
Stage at study entry, n (%)[a]		
IIIA	1 (<1)	0
IIIB	3 (1)	1 (0.9)
IV	244 (95)	113 (99)
Site involvement at study entry, n (%)		
Brain	102 (40)	40 (35)
Bone	117 (46)	47 (41)
Liver	55 (21)	24 (21)
Lung	232 (90)	110 (97)
Other	202 (79)	93 (82)
Median no. of prior lines of systemic anticancer therapy, n (range)[b]	2.0 (1–8)[c]	2.0 (1–7)
Number of prior systemic anticancer lines, n (%)[b]		
1	76 (31)[c]	47 (41)
≥2	140 (57)[c]	67 (59)
Prior systemic anticancer therapy, n (%)[b]		
Platinum-based chemotherapy	189 (77)	114 (100)
Immunotherapy	86 (35)	49 (43)
EGFR TKI	30 (12)	29 (25)
Baseline brain metastases, n (%)	102 (40)	40 (35)
Median time on mobocertinib treatment, mo (range)	6.1 (0.0–40.3)	7.4 (0.0–34.0)

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PPP, platinum-pretreated patients; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.
[a]Information missing for 9 patients in RP2D population.
[b]Patients could have been counted in more than one category.
[c]Data available for 244 patients.

3.1.1. Adverse event overview

In the RP2D population, TEAEs were reported in all treated patients and TRAEs were reported in 253 patients (98%; Table 2). Grade ≥3 TEAEs were observed in 172 patients (67%). SAEs were observed in 118 patients (46%) and treatment-related SAEs in 43 patients (17%). TEAEs resulted in dose modifications in 176 patients (68%), including treatment interruption in 158 patients (61%), dose reduction in 81 patients (32%), and treatment discontinuation in 48 patients (19%). A similar overall safety profile was observed in the PPP population (Table 2).

3.1.2. Treatment-emergent, treatment-related, and serious adverse events

Table 3 summarizes TEAEs observed in ≥10% of the patients, Grade ≥3 TEAEs in ≥5 patients, and TRAEs observed in ≥10% of the patients in the RP2D population. GI events were the most frequently reported TRAEs, including diarrhea (91%), nausea (40%), and vomiting (28%). Skin-related events were the second most frequently reported TRAEs, including rash (37%), dry skin (28%), paronychia (28%), dermatitis acneiform (19%), pruritus (16%), and rash maculopapular (16%). The most frequently reported Grade ≥3 TEAE was diarrhea, which was observed in 51 patients (20%). Other frequently reported Grade ≥3 TEAEs were anemia (7%) and hypertension (7%). Treatment-emergent SAEs observed in ≥2% of the patients included dyspnea (6%), diarrhea (5%), vomiting (5%), pneumonia (4%), acute kidney injury (3%), nausea (2%), dehydration (2%), respiratory failure (2%), NSCLC (2%), and pyrexia (2%); most common treatment-related SAEs (≥2% of the patients) were diarrhea (4%), vomiting (4%), dehydration (2%), and acute kidney injury (2%). Table 5 summarizes TEAEs observed in ≥10% of the patients, Grade ≥3 TEAEs in ≥5 patients, and TRAEs observed in ≥10% of the patients in the PPP population, which were similar to those observed in the RP2D population.

3.1.3. Adverse events of clinical interest

Among the AECIs in the RP2D population, the most common were GI events, with an overall incidence of TRAEs of 94%. Grade ≥3 GI TEAEs were observed in 22% of the patients. GI SAEs were observed in 9% of the patients, and 7% of the patients discontinued treatment due to GI AEs.

Treatment-related skin events were observed in 84% of the patients. Grade ≥3 skin-related TEAEs were observed in 5% of the patients. No skin-related SAEs were observed, and 2% of the patients discontinued treatment due to skin-related AEs.

Treatment-related increase in amylase was observed in 16% of the patients; Grade ≥3 increased amylase was observed in 4% of the patients, with no SAEs and 1 patient (<1%) discontinuing treatment. Treatment-related increase in lipase was observed in 14% of the patients; Grade ≥3 increased lipase was observed in 4% of the patients, with no SAEs and no patients discontinuing treatment.

Table 2. Summary of AEs.

Category of AE, n (%)	RP2D population (N = 257)	PPP population (N = 114)
Any TEAE	257 (100)	114 (100)
Any TRAE	253 (98)	113 (99)
Grade ≥3 TEAEs	172 (67)	79 (69)
Treatment-related Grade ≥3 TEAEs	108 (42)	54 (47)
Treatment-emergent SAEs	118 (46)	56 (49)
Treatment-related treatment-emergent SAEs	43 (17)	22 (19)
TEAEs resulting in study drug dose modification	176 (68)	73 (64)
TEAEs resulting in study drug discontinuation	48 (19)	19 (17)
TEAEs resulting in study drug interruption	158 (61)	61 (54)
TEAEs resulting in study drug dose reduction	81 (32)	29 (25)
On-study deaths	29 (11)	12 (11)

AE, adverse event; PPP platinum-pretreated patients; RP2D, recommended phase 2 dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Table 3. TEAEs in ≥10% of the patients, Grade ≥3 TEAEs (in ≥5 patients), and TRAEs in ≥10% of the patients in the RP2D population (N = 257).

Event, n (%)	TEAEs in ≥10% of patients	Grade ≥3	TRAEs in ≥10% of patients
Patients with any event	257 (100)	172 (67)	253 (98)
Diarrhea	240 (93)	51 (20)	235 (91)
Nausea	121 (47)	8 (3)	102 (40)
Rash	97 (38)	1 (<1)	94 (37)
Vomiting	96 (37)	6 (2)	72 (28)
Decreased appetite	91 (35)	5 (2)	70 (27)
Dry skin	77 (30)	0	71 (28)
Anemia	77 (30)	17 (7)	42 (16)
Stomatitis	74 (29)	9 (4)	69 (27)
Paronychia	73 (28)	1 (<1)	72 (28)
Blood creatinine increased	74 (29)	6 (2)	46 (18)
Fatigue	67 (26)	5 (2)	49 (19)
Amylase increased	52 (20)	9 (4)	40 (16)
Dermatitis acneiform	51 (20)	2 (<1)	49 (19)
Weight decreased	51 (20)	3 (1)	30 (12)
Pruritus	48 (19)	1 (<1)	40 (16)
Dyspnea	46 (18)	13 (5)	4 (2)
Rash maculopapular	40 (16)	4 (2)	40 (16)
Lipase increased	41 (16)	11 (4)	37 (14)
Gastroesophageal reflux disease	38 (15)	1 (<1)	31 (12)
Alopecia	37 (14)	0	27 (11)
Aspartate aminotransferase increased	35 (14)	2 (<1)	24 (9)
Headache	36 (14)	0	8 (3)
Back pain	35 (14)	5 (2)	4 (2)
Hypertension	34 (13)	17 (7)	9 (4)
Hypokalemia	34 (13)	7 (3)	17 (7)
Lymphocyte count decreased	30 (12)	8 (3)	13 (5)
Hypomagnesemia	32 (12)	1 (<1)	13 (5)
Dehydration	31 (12)	8 (3)	21 (8)
Constipation	29 (11)	1 (<1)	5 (2)
Rhinorrhea	29 (11)	0	16 (6)
Alanine aminotransferase increased	28 (11)	4 (2)	20 (8)
Dry mouth	27 (11)	0	23 (9)
Dyspepsia	26 (10)	0	20 (8)
Hyponatremia	25 (10)	7 (3)	3 (1)
Mucosal inflammation	25 (10)	0	24 (9)
Hypophosphatemia	21 (8)	5 (2)	10 (4)
ECG QTc prolonged	20 (8)	5 (2)	18 (7)
Pneumonia	18 (7)	11 (4)	2 (<1)
Mouth ulceration	15 (6)	0	14 (5)
Acute kidney injury	12 (5)	6 (2)	5 (2)
Hypoxia	12 (5)	6 (2)	1 (<1)

ECG, electrocardiogram; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Treatment-related stomatitis was observed in 27% of the patients, with 4% of the patients experiencing Grade ≥3 TEAEs. There were no SAEs of treatment-related stomatitis, and <1% of the patients discontinued treatment.

Treatment-related cardiac disorders, which include cardiac failure and QTc interval prolongation, were observed in 12% of the patients; Grade ≥3 treatment-emergent cardiac disorders were observed in 13% of the patients, 11% with SAEs, and 2% discontinuing. Cardiac failure (including congestive cardiac failure, decreased ejection fraction, and cardiomyopathy) occurred in 2.3% of the patients. Grade 3 cardiac failure occurred in 0.8% of the patients. Grade 4 and fatal cardiac failure occurred in one patient each (0.4%). QTc interval prolongation (including electrocardiogram QT prolongation and ventricular arrhythmia) occurred in 8% of the patients. Grade 3 QTc interval prolongation occurred in 1.6% of the patients and Grade 4 QTc interval prolongation occurred in 1 patient (0.4%).

Treatment-related pneumonitis/ILD was observed in 2% of the patients, with Grade ≥3 TEAEs in <1% of the patients, 2% of the patients with SAEs, and 2% of the patients discontinuing.

To manage AEs, doses of mobocertinib can be reduced to 120 mg daily (first reduction) or 80 mg daily (second reduction). Recommendations for dosage adjustments due to AECIs observed with mobocertinib are shown in **Supplemental Table S1**. Briefly, dose interruption is recommended in cases of Grade 2 or 3 QTc interval prolongation, suspicion of ILD/pneumonitis, Grade 2 decreased ejection fraction, intolerable or recurrent Grade 2 or 3 diarrhea, and first occurrence of Grade 4 diarrhea. Mobocertinib should be permanently discontinued for patients who experience Grade 4 or recurrent Grade 2 or 3 QTc interval prolongation, confirmed ILD/pneumonitis (any grade), Grade >2 heart failure or Grade 3 or 4 decreased injection fraction, or recurrent Grade 4 diarrhea. AECIs were managed per recommendations in the US prescribing information (**Supplemental Table S2**). Early management of skin disorders or diarrhea induced by EGFR TKIs may avoid worsening of symptoms (Table 4) [29,30].

3.2. Characterization of GI events in the PPP population

In the PPP population (N = 114), 106 patients (93%) experienced any-grade diarrhea and 25 patients (22%) experienced Grade 3/4 diarrhea, including 24 with Grade 3 and 1 with Grade 4 (Table 5). The onset of diarrhea was rapid, with a median onset of 5 days; 56% of the patients had the onset of diarrhea within 2–7 days of treatment initiation (Figure 1). In patients who experienced Grade 3 diarrhea, the median time to first onset was 14 days. Among patients with any-grade diarrhea (n = 106), 59 patients (56%) had resolution of all diarrhea events. The median time to resolution of all-grade diarrhea was 2 days, and the median time to resolution of Grade 3 diarrhea was 6.5 days. A total of 105 QTc interval prolongation events occurred in 40 patients. Diarrhea was observed within 7 days before the onset of QTc prolongation in 34% (36/105) of these events; Grade ≥2 electrolyte imbalances were observed within 7 days before the onset in 4% (4/105) of these events.

In the PPP population, diarrhea led to mobocertinib dose modifications in 31 patients (27%), including dose reduction in 12 patients (11%) and dose interruption in 24 patients (21%). Diarrhea resulted in treatment discontinuation in five patients (4%). Diarrhea was managed with antipropulsive medication in 74% of the patients, most commonly loperamide-containing medications (74%) and diphenoxylate/atropine preparations (13%). The use of these medications was similar in responders and nonresponders (75% and 73%, respectively).

Other reported GI events were nausea and vomiting, which were among the most frequently reported TRAEs with rates of 34% and 30%, respectively. The median time to resolution of nausea was 22 days, and the median time to resolution of vomiting was 5 days. A total of 6 patients (5%) had a dose reduction due to nausea and 3 patients (3%) due to vomiting. Anti-emetic medications were used in 40 patients (35%), most commonly prochlorperazine preparations (22%). The use of these medications was similar in responders and nonresponders (31% and 37%, respectively).

3.3. Exposure response analysis for Grade ≥2 diarrhea

An exposure-response analysis was conducted to characterize the relationship between the combined exposures of mobocertinib and its two active metabolites (AP32960 and AP32914) and time to first Grade ≥2 diarrhea with emphasis on understanding the risk factors that may impact diarrhea. Mobocertinib exposure was identified as a statistically significant predictor of Grade ≥2 diarrhea in the base model.

Compared with the base model including only exposure as predictor, only age ≥75 versus <75 years and exposure were found to be statistically significant in the final model at $\alpha = 0.001$ level. There was no effect of race, baseline disease severity, gender, or body weight on the risk of Grade ≥2 diarrhea. In the final model, statistically significant predictors of Grade ≥2 diarrhea were mobocertinib plasma exposure with 40-mg dose change: HR: 1.11 (95% confidence interval [CI]: 1.04–1.19) and age: ≥75 versus <75 years; HR: 2.13 (95% CI, 1.38–3.30). The Kaplan–Meier plot for time to diarrhea in patients by exposure and age is shown in Figure 2 based on observed data from 291 participants (4 participants treated with mobocertinib 180 mg were not included). The observed and model-predicted probability of Grade ≥2 diarrhea based on the final time-to-event model is shown in **Supplemental Figure S1**.

3.4. Characterization of skin toxicity and concomitant medication use in the PPP population

In the PPP population (N = 114), skin-related TEAEs of all grades were observed in 105 patients (92%); however, only 4% of the patients experienced Grade 3 events, and no Grade 4 or 5 events were reported. Rash was the most common skin-related TEAE (46%; no Grade 3), followed by paronychia (39%; <1% Grade 3/4), dry skin (33%; no Grade 3), pruritus (25%; <1% Grade 3), alopecia (20%); dermatitis acneiform (19%; no Grade 3), and rash maculopapular (14%; 2% Grade 3). The median time to onset of all-grade skin-related events was 9 days, and the median time to onset of Grade 3 skin-related

Table 4. Suggested management of diarrhea and skin disorders observed with EGFR TKIs.

Diarrhea [30]	
Nonpharmacologic intervention	
Dietary changes	• Adopt the BRAT diet (i.e. bananas, rice, applesauce, and toast) • Eliminate greasy, spicy, and fried foods • Eliminate cruciferous vegetables • Avoid dairy products
Fluid intake	• Drink 3–4 l of fluid daily
Probiotics	• Supplementation with probiotics
Pharmacologic intervention	
Mild (Grade 1)	• Stop laxatives • Drink 8–10 glasses of clear fluids daily • Immediately start loperamide: 4 mg (2 tablets) followed by 2 mg (1 tablet) after each loose stool (up to 20 mg daily) until bowel movements cease for 12 hours
Moderate (Grade 2)	• See Grade 1 management PLUS • Continue loperamide • Assess for dehydration and electrolyte imbalance • Consider intravenous fluids and electrolyte replacement
Severe (Grade 3)	• See Grade 2 management PLUS • Use stool cultures to rule out an infectious process • Apply aggressive intravenous fluid replacement for 24 hours or more • Use hospitalization to monitor the patient's progress • Consider prophylactic antibiotics if the patient is also neutropenic
Skin disorders [29]	
Acneiform rash	
Mild (Grade 1)	• Apply hydrocortisone valerate topically twice daily as needed
Moderate (Grade 2)	• Oral minocycline 100 mg twice daily for 4 weeks AND hydrocortisone valerate topically twice daily as needed
Severe (Grade 3)	• Oral minocycline 100 mg twice daily for 4 weeks AND hydrocortisone valerate topically twice daily as needed
Stomatitis or mucositis	
Mild (Grade 1)	• Apply triamcinolone in dental paste 2–3 times daily as needed
Moderate (Grade 2)	• Apply triamcinolone in dental paste 2–3 times daily as needed AND oral erythromycin 250–350 mg daily OR minocycline 50 mg daily
Severe (Grade 3)	• Apply clobetasol ointment 2–3 times daily as needed AND oral erythromycin 500 mg daily OR minocycline 100 mg daily
Paronychia	
Local care	• Petroleum jelly emollition • Antimicrobial soaks • Cushioning of affected areas
Mild or moderate (Grade 1 or 2)	• Apply betamethasone valerate 2–3 times daily as needed
Severe (Grade 3)	• Apply clobetasol cream 2–3 times daily as needed

Abbreviations: EGFR TKIs, epidermal growth factor receptor tyrosine kinase inhibitors

events was 56 days. The median time to resolution of all-grade events (n = 195) was 78 days and of events with a maximum Grade 3 (n = 3) was 38 days.

Clinical management of skin-related events included the use of topical corticosteroids in 43% of the patients (including hydrocortisone in 12%), topical antibiotics in 28% of the patients (including clindamycin/clindamycin phosphate in 21% and mupirocin in 18%), oral doxycycline/doxycycline hyclate/doxycycline hydrochloride (16%), and oral minocycline/minocycline hydrochloride (11%). The use of concomitant medications to manage skin-related events was more common among responders to mobocertinib versus nonresponders. Concomitant corticosteroids were used in 18 of 32 (56%) responders versus 31 of 82 (38%) nonresponders, and topical antibiotics were used in 14 (44%) responders versus 18 (22%) nonresponders.

3.5. Drug exposure and adverse events among responders and nonresponders in the PPP population

An analysis of treatment exposure was conducted to examine the potential impact of AEs and dose modifications on clinical activity of mobocertinib. Overall, patients in the PPP population with confirmed responses to mobocertinib had greater treatment exposure. Although the median relative dose intensity was similar (100%) between confirmed responders (n = 32) to mobocertinib and nonresponders (n = 82), responders received a median cumulative mobocertinib dose of 59,200 mg versus 19,340 mg in nonresponders. Time on study treatment was longer, and the median number of treatment days was higher among responders versus nonresponders (Figures 3a,b). Among responders, 22 (69%) had a duration of exposure ≥12 months versus 14 (17%) among nonresponders. Among patients with baseline brain metastases (n = 40), median times on treatment

Table 5. TEAEs in ≥10% of the patients, Grade ≥3 TEAEs in ≥5 patients, and TRAEs in ≥10% of the patients in the PPP population (N = 114).

Event, n (%)	TEAEs in ≥10% of patients	Grade ≥3	TRAEs in ≥10% of patients
Patients with any event	114 (100)	79 (69)	113 (99)
Diarrhea	106 (93)	25 (22)	104 (91)
Rash	52 (46)	0	51 (45)
Decreased appetite	48 (42)	1 (<1)	40 (35)
Vomiting	47 (41)	3 (3)	34 (30)
Nausea	46 (40)	5 (4)	39 (34)
Paronychia	44 (39)	1 (<1)	43 (38)
Anemia	39 (34)	7 (6)	20 (18)
Blood creatinine increased	38 (33)	5 (4)	29 (25)
Dry skin	38 (33)	0	35 (31)
Pruritus	29 (25)	1 (<1)	24 (21)
Stomatitis	29 (25)	5 (4)	27 (24)
Weight decreased	27 (24)	1 (<1)	15 (13)
Amylase increased	26 (23)	5 (4)	21 (18)
Cough	26 (23)	0	2 (2)
Back pain	24 (21)	2 (2)	2 (2)
Alopecia	23 (20)	0	17 (15)
Dermatitis acneiform	22 (19)	0	21 (18)
Fatigue	22 (19)	3 (3)	16 (14)
Lipase increased	22 (19)	5 (4)	22 (19)
Dyspnea	19 (17)	6 (5)	1 (<1)
Gastroesophageal reflux disease	17 (15)	0	14 (12)
Rhinorrhea	17 (15)	0	12 (11)
Rash maculopapular	16 (14)	2 (2)	16 (14)
Hypokalemia	15 (13)	4 (4)	6 (5)
Hypomagnesemia	7 (6)	1 (<1)	7 (6)
Constipation	14 (12)	1 (<1)	2 (2)
ECG QTc prolonged	14 (12)	4 (4)	12 (11)
Hypertension	14 (12)	8 (7)	3 (3)
Mouth ulceration	14 (12)	0	14 (12)
Aspartate aminotransferase increased	13 (11)	0	8 (7)
Asthenia	13 (11)	1 (<1)	6 (5)
Dyspepsia	13 (11)	0	10 (9)
Platelet count decreased	13 (11)	1 (<1)	10 (9)
Pyrexia	13 (11)	1 (<1)	2 (2)
Abdominal pain	12 (11)	2 (2)	4 (4)
Alanine aminotransferase increased	11 (10)	1 (<1)	9 (8)
Dizziness	11 (10)	0	3 (3)
Headache	11 (10)	0	4 (4)
Hypocalcemia	11 (10)	0	2 (2)
Upper respiratory infection	11 (10)	0	0

ECG, electrocardiogram; PPP, platinum-pretreated patients; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

were 14.0 months (range: 10.1–18.8) for responders and 3.7 months (range: 0.7–19.3) for nonresponders. Among patients without baseline brain metastases (n = 74), median times on treatment were 12.8 months (range: 4.4–34.0) in responders and 6.5 months (range: 0.0–26.2) in nonresponders.

The incidence of Grade ≥3 TEAEs was higher in nonresponders than in responders to mobocertinib (73% [60/82] vs 59% [19/32], respectively; Figure 3c). Nonresponders also had a higher incidence of SAEs (57% [47/82] vs 28% [9/32]), TEAEs leading to dose reduction (28% [23/82] vs 19% [6/32]) and TEAEs leading to treatment discontinuation (22% [18/82] vs 3% [1/32]; Figures 3d–f). TEAEs whose incidence was notably higher (>10%) in responders versus nonresponders included paronychia (66% [21/32] vs 28% [23/82]) and rash (56% [18/32] vs 41% [34/82]). Among PPP with (n = 29) and without (n = 85) dose reductions due to TEAEs, overall response rates (ORRs) per IRC were 21% (6/29; 95% CI: 8–40) and 31% (26/85; 95% CI: 21–42), and median duration of response was 5.7 (95% CI: 3.7–not evaluable) and 17.5 months (95% CI: 7.4–not evaluable), respectively.

4. Discussion

The current analyses characterized the safety profile of oral mobocertinib 160 mg QD, an irreversible, oral *EGFR* exon 20–targeted therapy, in a pooled population of 257 patients with NSCLC. The most common TEAEs associated with mobocertinib treatment are GI and skin-related events, which were most frequently low grade and effectively managed with concomitant medications and dose modifications. At a median time on treatment of 6.1 months, all patients experienced TEAEs of any grade (67% were Grade ≥3 TEAEs). However, most (68%) patients' TEAEs were managed with dose modifications, and 19% discontinued treatment because of TEAEs.

The most frequent TRAEs in patients treated with mobocertinib were GI related, with diarrhea being the most common of these events. Most diarrhea events were Grade 1 or 2 in severity, and diarrhea events led to dosage reductions in 11% of the patients in the PPP population (N = 114). Mobocertinib-induced diarrhea had a rapid onset and was generally managed by dose modifications, which included drug interruptions, dose reductions, or discontinuation. Additionally,

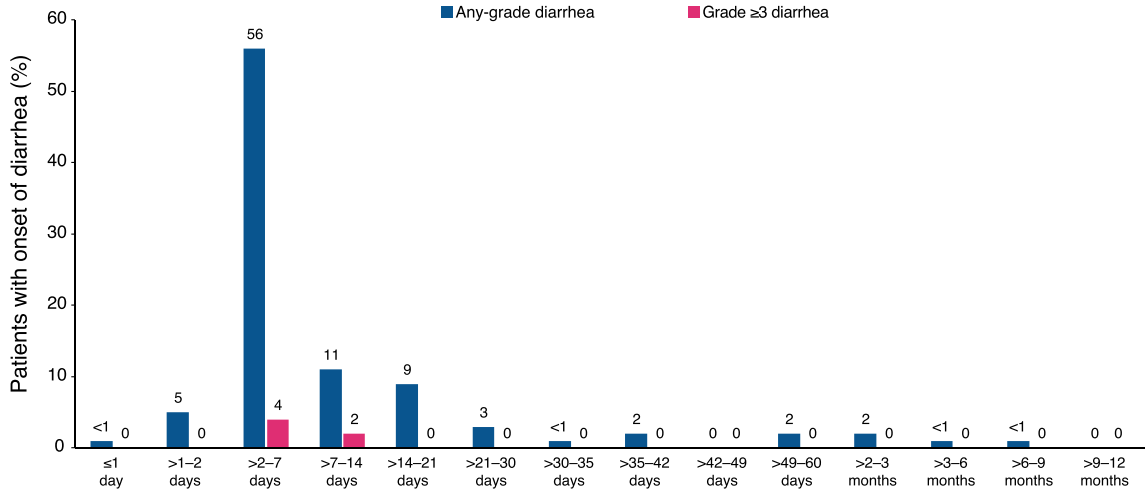

Figure 1. The onset of any-grade and Grade 3/4 treatment-emergent diarrhea in PPP population (n = 106 reporting diarrhea; each patient counted once at first reported onset). PPP, platinum-pretreated patients.

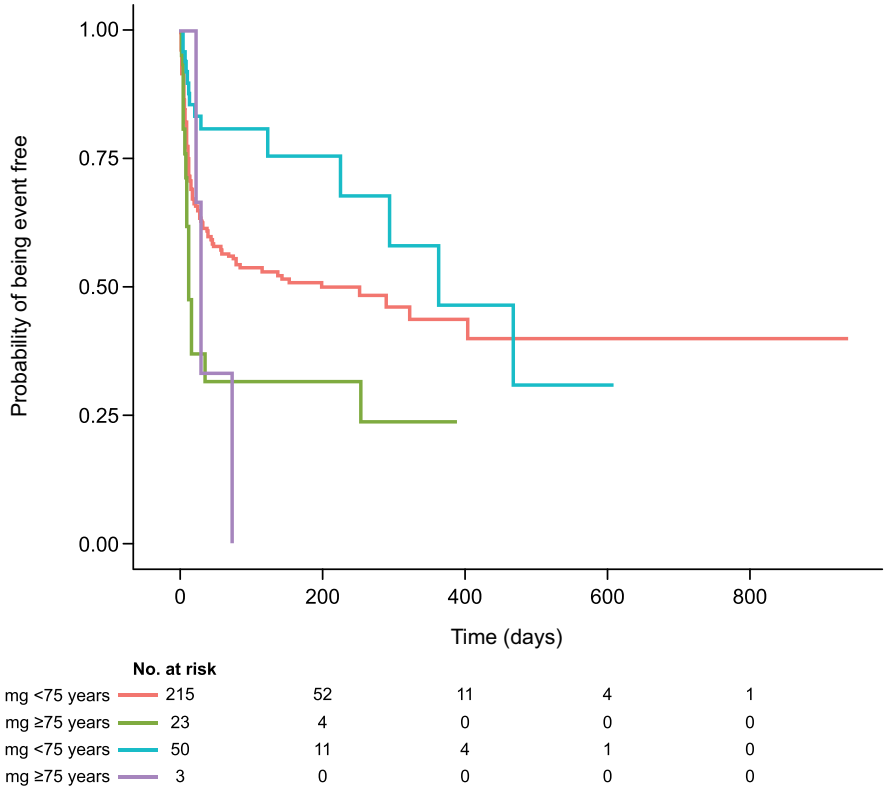

Figure 2. Kaplan–Meier plot of time to first Grade ≥2 diarrhea by mobocertinib dose group and age (N = 291).

antipropulsive medications, such as loperamide and diphenoxylate/atropine, were used in 74% of the patients in the PPP population to manage diarrhea. It is recommended that patients have loperamide on hand to treat the first instance of diarrhea. The exposure-response analysis showed a statistically significant influence of mobocertinib exposure and age ≥75 years on time to first Grade ≥2 diarrhea, predicting a higher risk of diarrhea in older patients (HR: 2.13; 95% CI, 1.38 – 3.30). A systemic exposure-response analysis was performed for AEs, including diarrhea; the results of the analysis showed no statistically significant relationship between systemic exposure and Grade 1 or higher diarrhea (P = 0.156) [31]. In the phase 1/2 clinical trial, improvements in symptoms of nausea and vomiting were observed when mobocertinib was administered with food (data not shown); additional analyses of this trend are ongoing. GI AEs can lead to dehydration and electrolyte imbalances, which can increase the risk of QTc interval prolongation [32]. In our study, among QTc interval prolongation events (105 events in 40 patients), diarrhea and Grade ≥2 electrolyte imbalances within 7 days prior to onset were observed in 34% and 4% of QTc interval prolongation events, respectively; no statistical correlation

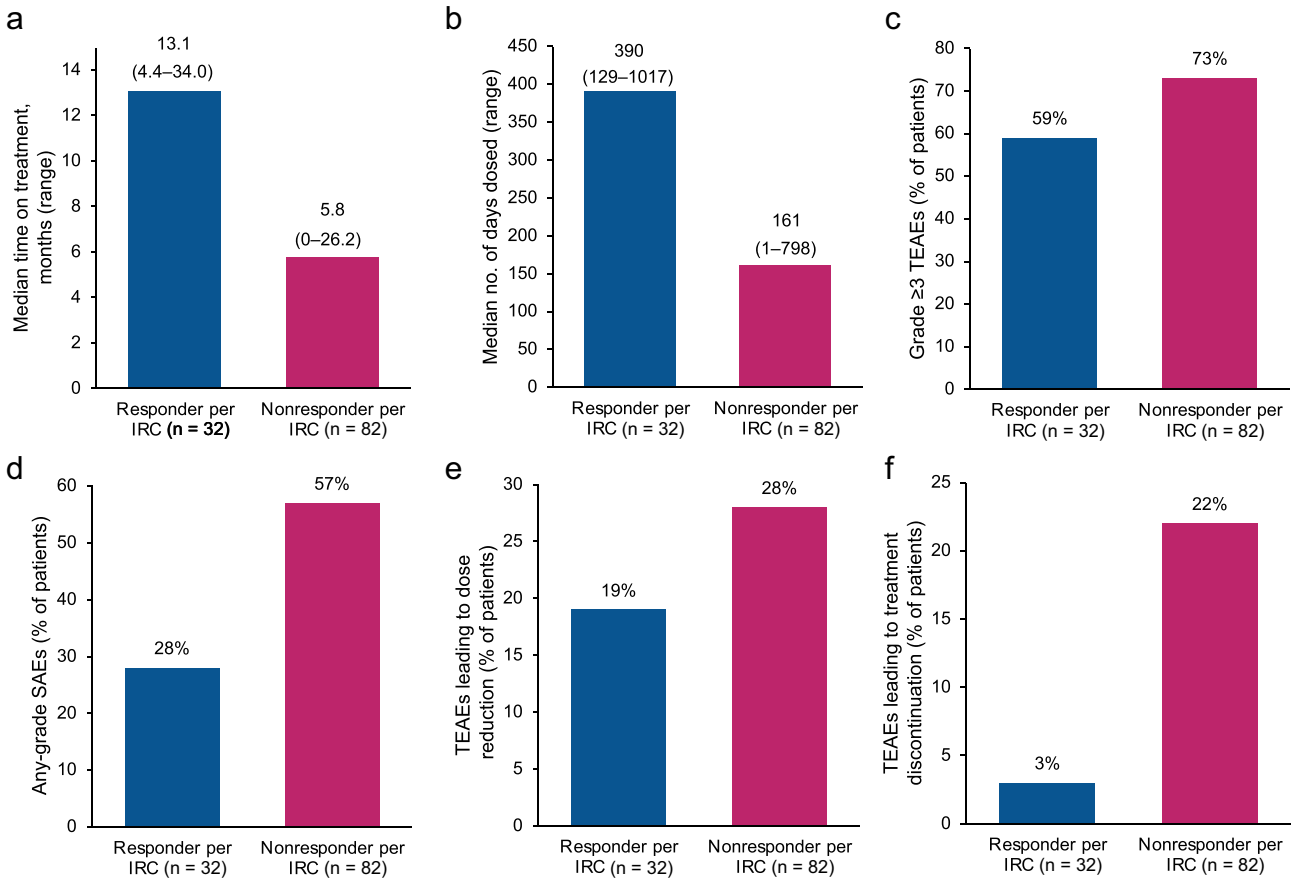

Figure 3. Median (range) time on mobocertinib treatment (a) and median (range) number of days of mobocertinib treatment (b) among confirmed responders and nonresponders. Panels c–f show the percentage of responders and nonresponders who experienced Grade ≥3 TEAEs, any-grade SAEs, TEAEs leading to mobocertinib dose reduction, and TEAEs leading to mobocertinib treatment discontinuation. IRC, independent review committee; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

between diarrhea, electrolyte abnormalities, and QTc interval prolongation was observed. Skin-related events were also among the most common AEs observed with mobocertinib. Most skin-related events were low grade, started within the first 2 weeks of treatment, and were managed with skin care and proactive use of topical corticosteroids and/or antibiotics.

The AEs observed with mobocertinib are consistent with known AEs associated with EGFR TKIs in the class [24], with no new safety signals observed. Diarrhea also is commonly observed with other EGFR TKIs, including afatinib (incidence 83%), dacomitinib (86%), osimertinib (41%), and poziotinib (26%, Grade ≥3 TRAE) [33–37]. The mechanism of TKI-induced diarrhea is unclear, but it is likely due to the expression of EGFR in the normal GI mucosa [25], which may result in secretory diarrhea [24,38]. Although mobocertinib targets *EGFR* ex20ins mutations, significant molecular heterogeneity of *EGFR* ex20ins exist [5], and adverse effects related to *EGFR* wild-type also may occur. The types and severity of skin-related events observed with mobocertinib are also consistent with those reported with the EGFR TKI class [24], with low frequency of severe events. Unlike some other TKIs [39], mobocertinib was not associated with severe skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.

Our analysis showed that patients in the PPP population with confirmed responses to mobocertinib had greater treatment exposure, mostly reflected by longer time on treatment observed with responders versus nonresponders (median of 13.1 months vs 5.8 months, respectively). In addition, nonresponders had higher rates of Grade ≥3 TEAEs, TEAEs leading to treatment discontinuation, and SAEs leading to treatment modifications (including treatment interruptions). Although ORR and DoR were more favorable among patients without dose reductions due to TEAEs versus those with dose reductions due to TEAEs (31% [26/85; 95% CI: 21 –42] and 21% [6/29; 95% CI: 8 –40], respectively, and 17.5 months [95% CI: 7.4 –not evaluable], and 5.7 months [95% CI: 3.7 –not evaluable], respectively), the 95% CIs overlap. However, our analysis did not differentiate between responses occurring before and after the dose reduction, and the sample size was small (only six responders among patients with dose reductions). These results suggest the importance of maintaining mobocertinib dose intensity through supportive measures to manage AEs. Effective and early management of AEs can mitigate the impact of decreased drug exposure due to dose reduction or treatment discontinuation. The onset of mobocertinib-induced diarrhea is within the first 7 days of treatment, and early management may allow for fewer required dose modifications. Additionally, patient education is critical in the early identification and management of AEs [24]. Of

note, the results of a retrospective analysis showed that the presence (vs absence) of brain metastases and the presence (vs absence) of *TP53* mutations were associated with shorter PFS among patients with ex20ins+ NSCLC treated with EGFR TKIs [7]. Results from the mobocertinib phase 1/2 study included in the current analysis showed IRC-confirmed ORRs of 18% (95% CI, 7–33%) and 34% (95% CI, 23–46%) in patients with and in those without baseline brain metastases, respectively [21].

5. Conclusions

The most common mobocertinib-related adverse events (GI and skin toxicities) are manageable. Patient education, early identification, timely and aggressive management, and ongoing assessment may help reduce GI toxicities, thereby minimizing the need for dose reduction and maintaining exposure to mobocertinib for better potential efficacy.

Funding

The paper received funding from Takeda Development Center Americas Inc., Lexington, MA, USA.

Declaration of interest

James Chih-Hsin Yang: Advisory board (Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, GSK, Janssen, Merck Serono, MSD, Novartis, Ono Pharmaceuticals, Pfizer, Puma Pharmaceuticals, Roche/Genentech, Takeda Oncology, Yuhan Pharmaceuticals), invited speaker (AstraZeneca, Boehringer Ingelheim, Novartis), coordinating PI (AstraZeneca, Daiichi Sankyo, Dizal Pharmaceutical, MSD), steering committee (Bayer, Eli Lilly, Ipsen, Janssen, Merck, Novartis, Numab, Takeda Oncology)

Caicun Zhou: Honoraria or advisory role (Eli Lilly China, Sanofi, Boehringer Ingelheim, Roche, MSD, Qilu, Hengrui, Innovent Biologics, C-Stone, LUYE Pharma, TopAlliance Biosciences Inc, Amoy Diagnostics)

Pasi A. Jänne: Consulting (Araxes Pharmaceuticals, ARIAD/Takeda, AstraZeneca, Boehringer Ingelheim, Chugai, Ignyta, Eli Lilly, Loxo Oncology, Merrimack, Mirati Therapeutics, Pfizer, Roche, Novartis, Voronoi, Daiichi Sankyo, SFJ Pharmaceuticals, Biocartis), research support (Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Puma Biotechnology), stock ownership (Gatekeeper and Loxo Oncology), postmarketing royalties from Dana-Farber Cancer Institute–owned patent on *EGFR* mutations licensed to LabCorp

Suresh S. Ramalingam: Honoraria or advisory role (Amgen, AstraZeneca, Bristol Myers Squibb, Merck, Eli Lilly, Genentech/Roche, GSK, Takeda), research support to institution (Amgen, Advaxis, Bristol Myers Squibb, Genmab, AstraZeneca, Takeda)

Tae Min Kim: Honoraria or advisory role (AstraZeneca, Boryung, F. Hoffmann-La Roche Ltd/Genentech, Inc, Janssen, Novartis, Sanofi, Takeda), research funding (AstraZeneca-Korea Health Industry Development Institute)

Gregory J. Riely: Travel (MSD), research funding (all to institution: Novartis, Roche/Genentech, Millennium, GSK, Pfizer, Infinity Pharmaceuticals, ARIAD, Mirati Therapeutics, Merck)

Alexander I. Spira: Consulting/advisory role (ARIAD, AstraZeneca, Clovis Oncology, Roche, Amgen, Mirati, Bristol Myers Squibb, Merck)

Zofia Piotrowska: Consulting/advisory role (Daiichi Sankyo, AstraZeneca, Guardant Health, Eli Lilly, Medtronic, Incyte, Genentech, C4 Therapeutics, Blueprint Medicines, Jazz Pharmaceuticals, Janssen, Takeda), research funding (all to institution: Novartis, ARIAD/Takeda, Spectrum Pharmaceuticals, AstraZeneca, Tesaro/GSK, Janssen, Cullinan Oncology, Daiichi Sankyo Europe GmbH, AbbVie, Blueprint), travel, accommodations, expenses (Genentech, AstraZeneca)

Tarek Mekhail: Speakers bureau (AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck, Takeda), advisory role (AstraZeneca, Eli Lilly)

Maria Rosario Garcia Campelo: Consulting/advisory role (Takeda, AstraZeneca, Roche, Pfizer, Bristol Myers Squibb, Boehringer Ingelheim, Pfizer, Janssen, Eli Lilly, MSD, Sanofi)

Enriqueta Felip: Consulting/advisory role (AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Guardant Health, MSD, Novartis, Pfizer, Roche, Takeda, Merck)

Lyudmila Bazhenova: Stock and other ownership interests (Epic Sciences), consulting or advisory role (Neuvogen, Janssen, Daiichi Sankyo, Boehringer Ingelheim, Merck, Regeneron, Bristol Myers Squibb, Novartis), research funding (BeyondSpring)

Shu Jin: Employment (Takeda)

Manmit Kaur: Employment (Takeda)

Paul M. Diderichsen: Employment (Certara); consulting (Takeda)

Neeraj Gupta: Employment (Takeda)

Veronica Bunn: Employment (Takeda)

Jianchang Lin: Employment (Takeda)

Eric N. Churchill: Employment (Takeda)

Minal Mehta: Employment (Takeda)

Danny Nguyen: Fees associated with publications (Takeda)

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Tae Min Kim http://orcid.org/0000-0001-6145-4426
Lyudmila Bazhenova http://orcid.org/0000-0001-8764-4359
Jianchang Lin http://orcid.org/0000-0002-9123-0690

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. 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. 2018;13(10):1560–1568.
2. Arcila ME, Nafa K, Chaft JE, et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. Mol Cancer Ther. 2013;12(2):220–229.
3. Oxnard GR, Lo PC, Nishino M, et al. Natural history and molecular characteristics of lung cancers harboring *EGFR* exon 20 insertions. J Thorac Oncol. 2013;8(2):179–184.
4. Fang W, Huang Y, Hong S, et al. EGFR exon 20 insertion mutations and response to osimertinib in non-small-cell lung cancer. BMC Cancer. 2019;19(1):595.
5. Yasuda H, Kobayashi S, Costa DB. *EGFR* exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. Lancet Oncol. 2012;13(1):e23–e31.
6. O'Kane GM, Bradbury PA, Feld R, et al. Uncommon *EGFR* mutations in advanced non-small cell lung cancer. Lung Cancer. 2017;109:137–144.
7. Christopoulos P, Kluck K, Kirchner M, et al. The impact of TP53 co-mutations and immunologic microenvironment on outcome of lung cancer with EGFR exon 20 insertions. Eur J Cancer. 2022;170:106–118.
8. van Veggel B, Santos JFV MR, Hashemi SMS, et al. Osimertinib treatment for patients with *EGFR* exon 20 mutation positive non-small cell lung cancer. Lung Cancer. 2020;141:9–13.

9. Piotrowska Z, Wang Y, Sequist LV, et al. ECOG-ACRIN 5162: a phase II study of osimertinib 160 mg in NSCLC with EGFR exon 20 insertions [abstract]. J Clin Oncol. 2020;38(15 Suppl):9513.
10. Yasuda H, Ichihara E, Sakakibara-Konishi J, et al. A phase I/II study of osimertinib in EGFR exon 20 insertion mutation-positive non-small cell lung cancer. Lung Cancer. 2021;162:140–146.
11. Vyse S, Huang PH. Targeting *EGFR* exon 20 insertion mutations in non-small cell lung cancer. Signal Transduct Target Ther. 2019;4(5). 10.1038/s41392-019-0038-9
12. Burnett H, Emich H, Carroll C, et al. Epidemiological and clinical burden of *EGFR* exon 20 insertion in advanced non-small cell lung cancer: a systematic literature review. PLoS One. 2021;16(3):e0247620.
13. Udagawa H, Matsumoto S, Ohe Y, et al. Clinical outcome of non-small cell lung cancer with EGFR/HER2 exon 20 insertions identified in the LC-SCRUM-Japan [abstract OA07.03]. J Thorac Oncol. 2019;14 (10 suppl):S224.
14. 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. 2020;145:186–194.
15. Negrao MV, Reuben A, Ponville Robichaux J, et al. Association of EGFR and HER-2 exon 20 mutations with distinct patterns of response to immune checkpoint blockade in non-small cell lung cancer [abstract]. J Clin Oncol. 2018;36(15 suppl):9052.
16. Takeda M, Sakai K, Hayashi H, et al. Clinical characteristics of non-small cell lung cancer harboring mutations in exon 20 of EGFR or HER2. Oncotarget. 2018;9(30):21132–21140.
17. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014;384(9944):665–673.
18. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627–1639.
19. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255–265.
20. 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. 2021;11(7):1672–1687.
    • **Key preclinical data for mobocertinib.**
21. 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. 2021;7(12):e214761.
    •• **Phase 1/2 efficacy and safety results with mobocertinib in platinum-pretreated patients with EGFR ex20ins+ NSCLC; led to regulatory approval in this population.**
22. Zhang S, Jin S, Griffin C, et al. Single-dose pharmacokinetics and tolerability of the oral epidermal growth factor receptor inhibitor mobocertinib (TAK-788) in healthy volunteers: low-fat meal effect and relative bioavailability of 2 capsule products. Clin Pharmacol Drug Dev. 2021;10(9):1028–1043.
23. Takeda Pharmaceuticals America, Inc. Exkivity [package insert]. Lexington, MA; 2021.
    •• **Prescribing information for mobocertinib**
24. Hirsh V. Managing treatment-related adverse events associated with EGFR tyrosine kinase inhibitors in advanced non-small-cell lung cancer. Curr. Oncol. Rep. 2011;18(3):126–138
25. Chen J, Zeng F, Forrester SJ, et al. Expression and function of the epidermal growth factor receptor in physiology and disease. Physiol Rev. 2016;96(3):1025–1069.
26. 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. 2021;11(7):1688–1699.
    •• **First phase 1/2 results with mobocertinib in EGFR ex20ins+ NSCLC.**
27. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–247.
28. Gupta N, Pierillas PB, Hanley MJ, et al. Population pharmacokinetics of mobocertinib in healthy volunteers and patients with non–small cell lung cancer. CPT Pharmacometrics Syst Pharmacol. 2022;11 (6):731–744.
29. Melosky B, Leighl NB, Rothenstein J, et al. Management of EGFR TKI-induced dermatologic adverse events. Curr Oncol. 2015;22 (2):123–132.
30. Hirsh V, Blais N, Burkes R, et al. Management of diarrhea induced by epidermal growth factor receptor tyrosine kinase inhibitors. Curr Oncol. 2014;21(6):329–336.
31. Gupta N, Largajolli A, Witjes H, et al. Mobocertinib dose rationale in patients with metastatic NSCLC with EGFR exon 20 insertions: exposure–response analyses of a pivotal phase I/II study. Clin Pharmacol Ther. 2022 April Online Ahead of Print 25; 112(2):327–334.
32. Coppola C, Rienzo A, Piscopo G, et al. Management of QT prolongation induced by anti-cancer drugs: target therapy and old agents. Different algorithms for different drugs. Cancer Treat Rev. 2018;63:135–143.
33. Yang JC, Reguart N, Barinoff J, et al. Diarrhea associated with Afatinib: an oral ErbB family blocker. Expert Rev. Anticancer Ther. 2013;13(6):729–736.
34. Rugo HS, Di Palma JA, Tripathy D, et al. The characterization, management, and future considerations for ErbB-family TKI-associated diarrhea. Breast Cancer Res Treat. 2019;175(1):5–15.
35. Ramalingam SS, O'Byrne K, Boyer M, et al. Dacomitinib versus erlotinib in patients with EGFR-mutated advanced nonsmall-cell lung cancer (NSCLC): pooled subset analyses from two randomized trials. Ann Oncol. 2016;27(3):423–429.
36. Odogwu L, Mathieu L, Goldberg KB, et al. FDA benefit-risk assessment of osimertinib for the treatment of metastatic non-small cell lung cancer harboring epidermal growth factor receptor T790M mutation. Oncologist. 2018;23(3):353–359.
37. Socinski MA, Cornelissen R, Garassino MC, et al. ZENITH20, a multinational, multi-cohort phase II study of poziotinib in NSCLC patients with EGFR or HER2 exon 20 insertion mutations [LBA60]. Ann Oncol. 2020;31:S1188.
38. McCole DF, Barrett KE. Decoding epithelial signals: critical role for the epidermal growth factor receptor in controlling intestinal transport function. Acta Physiol (Oxf). 2009;195(1):149–159.
39. Coleman EL, Olamiju B, Leventhal JS. Potentially life-threatening severe cutaneous adverse reactions associated with tyrosine kinase inhibitors (Review). Oncol Rep. 2021;45(3):891–898.