1218P

Characterization of GI Toxicities and Their Impact on Efficacy in Patients With *EGFR* Exon 20 Insertion+ (ex20ins+) Non–Small Cell Lung Cancer (NSCLC) Treated With Mobocertinib (TAK-788) Who Previously Received Platinum Chemotherapy

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Introduction

- Epidermal growth factor receptor gene (*EGFR*) exon 20 insertion (*EGFR* ex20ins) mutations are observed in up to 12% of *EGFR*-mutated non–small cell lung cancer (NSCLC) tumors[1,2]
- The prognosis in patients with *EGFR* ex20ins+ NSCLC is poor, with median overall survival ranging from 7.1 months to 13.6 months in the second-line treatment setting per real-world data[3]
- Mobocertinib (TAK-788) is a potent oral tyrosine kinase inhibitor (TKI) designed to selectively target *EGFR* ex20ins[4]
- The phase 1/2 study (NCT02716116) of mobocertinib 160 mg once daily (QD) in platinum-pretreated patients (PPP) with *EGFR* ex20ins+ NSCLC demonstrated a confirmed objective response rate (ORR) of 28% per independent review committee (IRC) and median duration of response of 17.5 months (data cutoff: 1 November 2020)[5]
- In the PPP cohort of the phase 1/2 study, 17% of patients discontinued mobocertinib therapy due to adverse events (AEs)
- Gastrointestinal (GI) toxicities, in particular diarrhea, were the most common AEs
- GI toxicities are commonly observed in the EGFR TKI class, and are thought to be associated with the off-target binding of wild-type EGFR in the GI mucosa[6]
- The potential impact of AEs leading to dose reductions on the efficacy of mobocertinib in PPP with *EGFR* ex20ins+ NSCLC is unknown

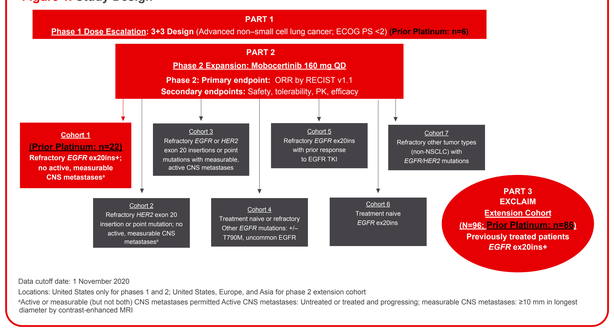
Objectives

- To characterize GI toxicities associated with mobocertinib treatment in the PPP cohort of the phase 1/2 study and examine the effects of dose reductions due to AEs on mobocertinib clinical activity

Methods

- Data were analyzed from the phase 1/2 study in the PPP cohort, which included patients with *EGFR* ex20ins+ NSCLC from parts 1, 2, and 3 (EXCLAIM) who received mobocertinib 160 mg orally QD (N=114; **Figure 1**)
- Rates of all-Grade and Grade ≥3 GI treatment-emergent AEs, including diarrhea, vomiting, and nausea, were analyzed in the PPP cohort
- The onset and duration of treatment-emergent diarrhea was characterized in the PPP cohort
- A subgroup analysis of the PPP cohort was performed to determine ORR, duration of response (DoR), and progression-free survival (PFS) per IRC among patients with and without AEs leading to dose reductions
- An exposure-response analysis was conducted in patients from all 3 parts of the phase 1/2 study (N=295; data cutoff: 29 May 2020) to describe the relationship between the molar sum of mobocertinib and metabolites exposures (area under the concentration-time curve) and time to first reported Grade ≥2 diarrhea and explore the effect of additional risk covariates (age, sex, race, Eastern Cooperative Oncology Group [ECOG] status, and body weight) related to diarrhea
  - Kaplan-Meier plots of time to first Grade ≥2 diarrhea events were generated and analyzed using a parametric time-to-event model
  - The impact of mobocertinib exposure on hazard ratios (HRs) was estimated on a decrease of exposure of 753 nM.hr/day, corresponding to the typical change in exposure following a change in dose of 40 mg (eg, reduction from 160 mg to 120 mg) predicted by a population PK model

Figure 1. Study Design



Data cutoff date: 1 November 2020

Locations: United States only for phases 1 and 2; United States, Europe, and Asia for phase 2 extension cohort

[a]Active or measurable (but not both) CNS metastases permitted Active CNS metastases: Untreated or treated and progressing; measurable CNS metastases: ≥10 mm in longest diameter by contrast-enhanced MRI

Results

Treatment-Emergent Gastrointestinal Adverse Events in the PPP Cohort

- 96% of patients in the PPP cohort had at least 1 GI toxicity
  - Most GI toxicity was low grade in severity
- Diarrhea was the most common toxicity observed in 93% of patients (**Table 1**)
  - Grade 3 diarrhea was reported in 21% and Grade 4 diarrhea in 1% of patients
  - Diarrhea was reported as a serious AE in 8% of patients
  - Diarrhea led to dose reductions in 11% of patients and treatment discontinuation in 4% of patients
- Nausea and vomiting were reported in 40% and 41% of patients, respectively
  - Grade 3 nausea and vomiting were observed in 4% and 3% of patients, respectively, with 3% and 5% reporting nausea and vomiting as a serious AE
  - Nausea and vomiting led to dose reduction in 5% and 3% of patients, and to discontinuation in 4% and 2% of patients, respectively

Table 1. Summary of GI Treatment-Emergent Adverse Events (N=114)[a]

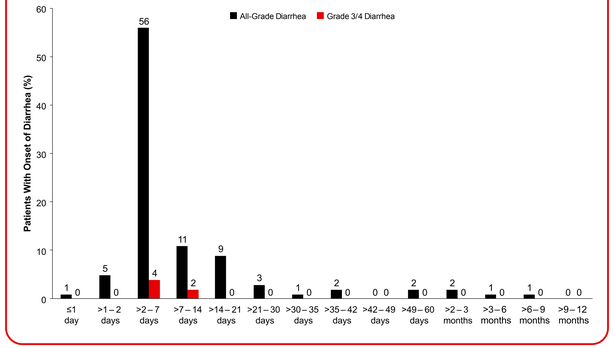
GI AEs, n (%)	All-Grade	Grade 3	Grade 4	Serious	Led to Dose Reduction	Led to Discontinuation
Diarrhea	106 (93)	24 (21)	1 (1)	9 (8)	12 (11)	5 (4)
Nausea	46 (40)	5 (4)	0	3 (3)	6 (5)	4 (4)
Vomiting	47 (41)	3 (3)	0	6 (5)	3 (3)	2 (2)

[a] Treatment-related GI AEs included diarrhea (all-Grade: 91%; Grade 3/4: 21%), nausea (all-Grade: 34%; Grade 3/4: 4%), and vomiting (all-Grade: 30%; Grade 3/4: 3%)

Diarrhea Onset, Resolution, and Predictors

- In the PPP cohort, 62% of all patients had onset of all-Grade diarrhea within the first 7 days of treatment
  - The incidence of diarrhea onset over time is shown in **Figure 2**

Figure 2. Onset of Diarrhea Over Time in PPP Cohort



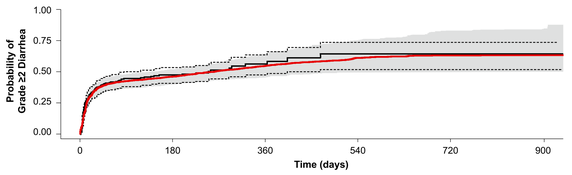
- In the PPP cohort, median time to onset of all-Grade diarrhea was 5 days; median time to resolution of all-Grade diarrhea was 2 days (**Table 2**)

Table 2. Median Time to Onset and Duration of Diarrhea in PPP Cohort

	All-Grade Diarrhea	Grade 3 Diarrhea
Median time to onset, d	5.0	–
Median time to resolution, d	2.0	6.5

- The observed and model-predicted probability of Grade ≥2 diarrhea based on the final time-to-event model is shown in **Figure 3**
  - The model is able to capture observed probability of Grade 2 or higher diarrhea reasonably well
- Among patients from all 3 parts of the phase 1/2 study, statistically significant predictors of Grade ≥2 diarrhea were:
  - Mobocertinib plasma exposure with 40-mg dose change: HR 1.11 [95% CI: 1.04, 1.19; P<0.005]
  - Age: ≥75 vs <75 years; HR: 2.13 [95% CI, 1.38, 3.30; P≤0.001]

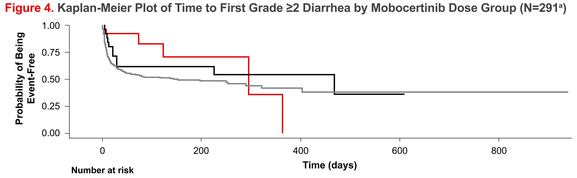
Figure 3. Observed and Model-Predicted Probability of Grade ≥2 Diarrhea Based on Final Time-to-Event Model



Note: Black line indicates observed probability; red line, model-predicted probability; black dotted lines, 95% CI for observed probability; and gray shading, 90% CI for model-predicted probability

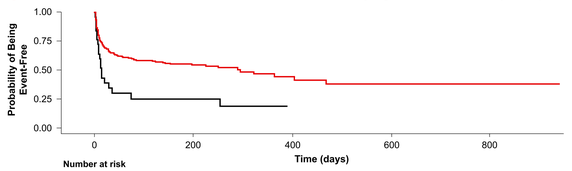
- Kaplan-Meier plots for time to diarrhea in patients by exposure and age are shown in **Figures 4 and 5**

Figure 4. Kaplan-Meier Plot of Time to First Grade ≥2 Diarrhea by Mobocertinib Dose Group (N=291[a])



[a] Four patients treated with mobocertinib 180 mg were not included

Figure 5. Kaplan-Meier Plot of Time to First Grade ≥2 Diarrhea by Age ≥75 vs <75 Years (N=295)



Diarrhea Management

- Diarrhea was managed with antidiarrheal medication in 74% of patients, most commonly loperamide-containing medications (**Table 3**)

Table 3. Concomitant Antipropulsive Medications Used in PPP Cohort (N=114)

Medication	n (%)
Any antipropulsive medication	84 (74)
Loperamide-containing medications	84 (74)
Atropine/diphenoxylate	15 (13)

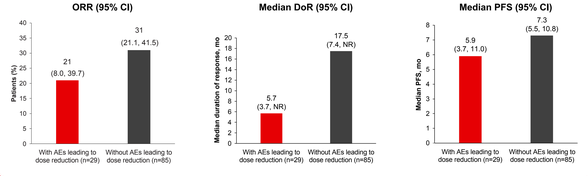
Dose Reductions Due to Adverse Events

- AEs led to dose reductions in 25% of PPP (29/114)
  - GI toxicities were the most common AEs leading to dose reductions, including diarrhea in 11% of patients, nausea in 5%, and vomiting in 3%

Impact of Adverse Events Leading to Dose Reduction on Mobocertinib Clinical Activity

- Clinical outcomes were impacted in patients with any AEs leading to dose reductions (n=29) compared with patients without AEs leading to dose reductions (n=85) (**Figure 6**)

Figure 6. Clinical Outcomes in Patients With and Without AEs Leading to Mobocertinib Dose Reductions in PPP Cohort (N=114)



Conclusions

- In patients with *EGFR* ex20ins+ NSCLC previously treated with platinum-based chemotherapy (N=114), GI toxicity observed with mobocertinib was common; however, most events were low grade in severity
- In the PPP population, diarrhea, the most frequent GI toxicity, occurred most often during the first week of treatment, with a median time to resolution of 2 days for all-Grade diarrhea and 6.5 days for Grade 3 diarrhea
- There was a statistically significant influence of mobocertinib exposure and age ≥75 years on time to first Grade ≥2 diarrhea
- Concomitant antidiarrheal medications were used in 74% of patients
- Efficacy outcomes were affected by dose reductions due to AEs, which were primarily due to GI toxicity
- These results highlight the importance of early recognition and proactive management of GI toxicities, especially diarrhea, in patients receiving mobocertinib to minimize dose reductions and potentially improve patient outcomes

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Abbreviations

AE, adverse event; CI, confidence interval; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor gene; ex20ins, exon 20 insertions; GI, gastrointestinal; *HER2*, human epidermal growth factor receptor 2 gene; HR, hazard ratio; IRC, independent review committee; MRI, magnetic resonance imaging; NSCLC, non–small cell lung cancer; NR, not reported; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; PPP, platinum-pretreated patients; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TKI, tyrosine kinase inhibitor

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