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Phase 1/2 study of mobocertinib in *EGFR* exon 20 insertion (ex20ins)+ metastatic NSCLC (mNSCLC): Updated results from platinum-pretreated patients (PPP)

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Introduction

- Epidermal growth factor receptor exon 20 insertion (*EGFR* ex20ins) mutations are present in approximately 5% to 12% of *EGFR*-mutated non–small cell lung cancer (NSCLC) tumors[1,2]
- First- and second-generation EGFR tyrosine kinase inhibitors (TKIs) afatinib, erlotinib, and gefitinib have demonstrated limited efficacy against *EGFR* ex20ins mutations[3]
- Two FDA-approved treatments, amivantamab and mobocertinib, are currently available to patients with *EGFR* ex20ins+ metastatic NSCLC (mNSCLC) refractory to platinum-based chemotherapy.[4,5]
- Mobocertinib, a potent, irreversible, oral EGFR TKI that selectively targets *EGFR* ex20ins mutations,[6,7] previously demonstrated clinical activity and a manageable safety profile in the platinum-pretreated patients (PPP) cohort of a phase 1/2 study of patients with *EGFR* ex20ins+ mNSCLC[8]

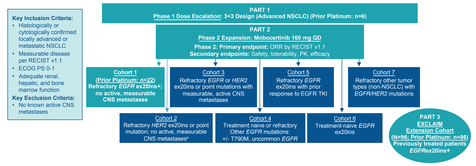
Objective

- Here we report updated primary efficacy results in the PPP cohort of the phase 1/2 study of mobocertinib

Methods

- **Study Design:** 3-part, open-label, multicenter study (NCT02716116), which included dose-escalation, expansion cohorts, and the EXCLAIM extension cohort **(Figure 1)**
  - The PPP cohort (N=114) included patients from the dose-escalation and expansion cohorts (n=28) and from EXCLAIM (n=86)[9]
- **Patients:** ECOG performance status 0–1; had received ≥1 prior therapy line for locally advanced/metastatic *EGFR* ex20ins+ NSCLC; no response to prior EGFR TKI, and no active brain metastasis at baseline[8]
- **Treatment:** Mobocertinib 160 mg orally QD until progressive disease requiring alternate treatment, intolerable AEs, or other reasons for discontinuation[8]
  - Mobocertinib could be continued beyond radiologic disease progression (per RECIST v1.1), if evidence of clinical benefit existed (per investigator)[9]

Figure 1. Study design



Data cutoff date: November 1, 2021
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

- At the November 1, 2021 data cutoff date, median duration of follow-up was 25.8 months (range, 24.6–26.7)
  - 10 patients (9%) remained on mobocertinib therapy
  - Median time on treatment was 7.4 months (range, 0.0–48.0)
- Baseline characteristics are shown in **Table 1**

Table 1. Demographic and baseline characteristics

Characteristic	PPP Cohort (N=114)
Median age, years (range)	**60 (27–84)**
Female, %	**66**
Race: Asian/White/Black/Not Reported, %	**60/37/3/1**
Histology: Adenocarcinoma/Squamous/Large cell, %	**98/1/1**
ECOG PS: 0/1, %	**25/75**
History of smoking: Never/Current/Former, %	**71/2/27**
Prior systemic anticancer regimens, 1/2/≥3, %	**41/32/27**
Median number of prior regimens	**2**
Prior platinum-based chemotherapy, %	**100**
Prior immunotherapy, %	**43**
Prior EGFR TKI, %	**25**
Baseline brain metastases, %	**35**

Results

Efficacy

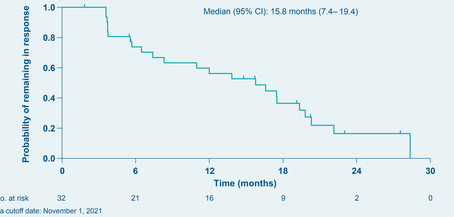
- At the November 1, 2021 data cutoff date, confirmed ORR was 28% (95% CI: 20%–37%) per IRC, with median duration of response of 15.8 months (95% CI: 7.4–19.4 months) **(Table 2; Figure 2)**
  - Confirmed ORR was 35% (95% CI: 26%–45%) per investigator assessment, with a median duration of response of 13.9 months (95% CI: 5.6–19.4 months)
- 96 patients (84%) had a reduction from baseline in sum of target lesion diameters per IRC **(Figure 3)**
- Time on treatment among confirmed responders to mobocertinib is shown in **Figure 4**
- Median PFS per IRC was 7.3 months (95% CI: 5.5–9.2 months) and median OS was 20.2 months (95% CI: 14.9–25.3 months; **Figure 5**)

Table 2. Mobocertinib clinical activity in PPP with *EGFR* ex20ins+ mNSCLC

	November 1, 2020 Data Cutoff	November 1, 2021 Data Cutoff
IRC assessments		
Confirmed ORR (95% CI)	**28% (21%–37%)**	**28% (20%–37%)**
Median DoR, months (95% CI)[a]	**17.5 (7.4–20.3)**	**15.8 (7.4–19.4)**
Confirmed DCR (95% CI)[b]	**78% (69%–85%)**	**78% (69%–85%)**
Investigator assessments		
Confirmed ORR, % (95% CI)	**35% (26%–45%)**	**35% (26%–45%)**
Median DoR, months (95% CI)[a]	**11.2 (5.6–NE)**	**13.9 (5.6–19.4)**
Confirmed DCR (95% CI)[b]	**78% (69%–85%)**	**78% (69%–85%)**

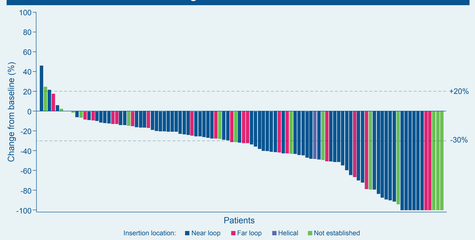
[a]DoR per Kaplan-Meier estimates; [b]DCR defined as confirmed CR or PR, or best response of stable disease for at least 6 weeks after initiation of study drug.

Figure 2. Duration of response (IRC-assessed)



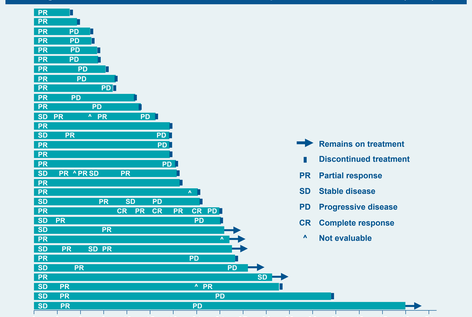
Data cutoff date: November 1, 2021

Figure 3. Waterfall plot of IRC-assessed best percentage change in sum of target lesion diameters[a]



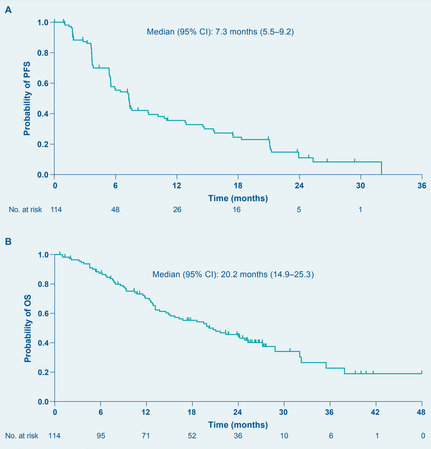
Data cutoff date: November 1, 2021
[a]Includes patients with measurable disease who have at least 1 post-baseline assessment.

Figure 4. Time on treatment in confirmed responders to mobocertinib (n=32)



Data cutoff date: November 1, 2021

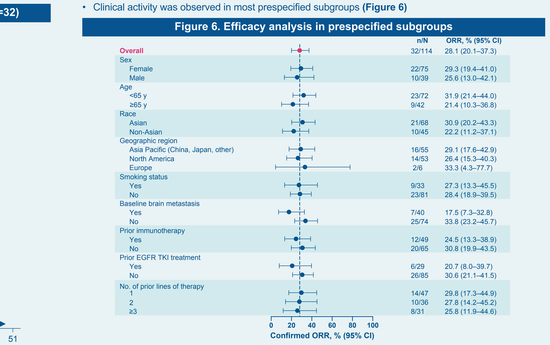
Figure 5. PFS by IRC assessment (A) and overall survival (B)



Data cutoff date: November 1, 2021

- Clinical activity was observed in most prespecified subgroups **(Figure 6)**

Figure 6. Efficacy analysis in prespecified subgroups

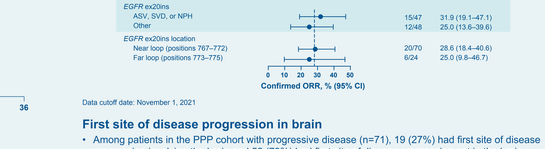


Data cutoff date: November 1, 2021

EGFR ex20ins variant characterization

- The most frequent *EGFR* ex20ins variants were ASV (25 patients), SVD (13 patients), and NPH (9 patients); 48 patients had uncommon *EGFR* ex20ins variants
- 70 patients had near-loop insertions (positions 767–772), 24 had far-loop insertions (positions 773–775)
- Response rates by *EGFR* ex20ins category are shown in **Figure 7**

Figure 7. Efficacy by *EGFR* ex20ins category



Data cutoff date: November 1, 2021

First site of disease progression in brain

- Among patients in the PPP cohort with progressive disease (n=71), 19 (27%) had first site of disease progression involving the brain and 52 (73%) had first site of disease progression not in the brain **(Table 3)**
- Median time on treatment after disease progression among patients who remained on mobocertinib was 4.4 months (range: 1.4–15.4) in those who received radiotherapy to the brain and 2.0 months (range: 0.1–8.4) in those who did not receive radiotherapy to the brain

Table 3. First site of IRC disease progression

Characteristic	PPP Cohort (N=114)
PD per IRC, n/N (%)	**71 (62%)**
First site of PD in brain	**19 (27%)**
Continued mobocertinib ≥3 mo after initial PD, n (%)[a]	**7 (37%)**
Median time on treatment beyond initial PD (95% CI)	**2.5 months (0.13–13.6)**
First site of PD not in brain	**52 (73%)**
Continued mobocertinib ≥3 mo after initial PD, n (%)[a]	**20 (39%)**
Median time on treatment beyond initial PD (95% CI)	**3.4 months (0.07–26.9)**

Data cutoff date: November 1, 2021
[a]Mobocertinib could be continued after PD if the patient was experiencing clinical benefit in the opinion of the investigator

Results

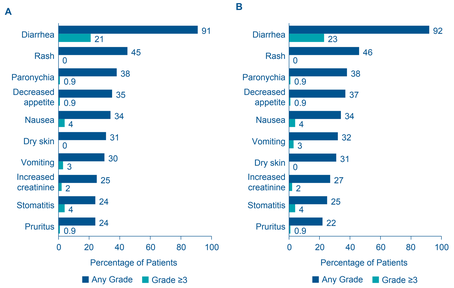
Safety

- The AE profile is summarized in **Table 4**.
- At the November 2021 data cutoff date,18% of patients had AEs leading to treatment discontinuation, most commonly diarrhea (4%), nausea (2%), vomiting (2%), decreased appetite (2%), stomatitis (2%), and cardiac failure (2%)
- The most common treatment-related AEs (TRAEs) were diarrhea (92%), rash (46%), paronychia (38%), and decreased appetite (37%) **(Figure 8)**
  - The only Grade ≥3 TRAE observed in ≥10% of patients was diarrhea (23%)
- One treatment-related death occurred due to cardiac failure in a platinum-pretreated patient in the EXCLAIM cohort as of the November 2020 data cutoff date; no additional treatment-related deaths occurred as of the November 2021 data cutoff date

Table 4. Overview of AEs (N=114)

AE, n (%)	November 1, 2020 Data Cutoff	November 1, 2021 Data Cutoff
Any AE	**114 (100)**	**114 (100)**
Grade ≥3	**79 (69)**	**86 (75)**
Any TRAE	**113 (99)**	**113 (99)**
Grade ≥3	**54 (47)**	**59 (52)**
Serious AE	**56 (49)**	**60 (53)**
Grade ≥3	**52 (46)**	**55 (48)**
Serious TRAE	**22 (19)**	**22 (19)**
Grade ≥3	**20 (18)**	**20 (18)**
AE leading to dose reduction	**29 (25)**	**31 (27)**
AE leading to treatment discontinuation	**19 (17)**	**21 (18)**

Figure 8. Treatment-related AEs observed in >20% of PPP at the November 1, 2020 data cutoff (A; N=114) and at the November 1, 2021 data cutoff (B; N=114)



Conclusions

- Mobocertinib, a first-in-class oral EGFR TKI, demonstrated rapid, deep, and durable responses in patients with platinum-pretreated *EGFR* ex20ins+ mNSCLC
  - Confirmed ORR was 28% per IRC and 35% per investigator assessments
  - Median DoR was 15.8 months and median PFS was 7.3 months (per IRC)
  - Median OS was 20.2 months
- Responses were observed in all evaluated subgroups, including patients with prior EGFR TKI treatment, and who had received prior immunotherapy and across *EGFR* ex20ins mutation subtypes
- Similar to the earlier data cutoff date of November 1, 2020, the safety profile was well characterized, with manageable gastrointestinal and cutaneous AEs, consistent with the known profile for EGFR TKIs
- At more than 2 years of follow-up in the phase 1/2 trial, efficacy and safety outcomes are consistent with those reported at the previous data cutoff date; mobocertinib continues to demonstrate clinically meaningful benefit for PPP with *EGFR* ex20ins+ mNSCLC, with a manageable safety profile

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Abbreviations

AE, adverse event; CI, confidence interval; CNS, central nervous system; CR, complete response; d, day; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor gene; EGFR, epidermal growth factor receptor; *EGFR* ex20ins, *EGFR* exon 20 insertion; EOT, end of treatment; GI, gastrointestinal; *HER2*, human epidermal growth factor receptor 2 gene; IRC, independent review committee; mNSCLC, metastatic NSCLC; mo, month; MRI, magnetic resonance imaging; NE, not estimable; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PPP, platinum-pretreated patients; PR, partial response; QD, once daily; QoL, quality of life; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease; TKI, tyrosine kinase inhibitor

Disclosures

SSR: Honoraria or advisory role (Amgen, AstraZeneca, Bristol Myers Squibb, Merck, Lilly, Genentech/Roche, GlaxoSmithKline, Takeda); research support to institution (Amgen, Advaxis, Bristol Myers Squibb, Genmab, AstraZeneca, Takeda); **CZ:** Honoraria or advisory role (Lilly China, Sanofi, Boehringer Ingelheim BI, Roche, MSD, Qilu, Hengrui, Innovent Biologics, C-Stone, LUYE Pharma, TopAlliance Biosciences Inc, Amoy Diagnostics); **TMK:** Honoraria or advisory role (AstraZeneca, BeiGene, Boryung, F. Hoffmann-La Roche Ltd/Genentech, Inc; Novartis, Sanofi, Takeda, Yuhan); research funding outside this work (AstraZeneca-Korea Health Industry Development Institute); **JCHY:** Honoraria or advisory role (Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech/Chugai, Astellas, MSD, Merck Serono, Pfizer, Novartis, Celgene, Merrimack, Yuhan Pharmaceuticals, Bristol Myers Squibb, Ono Pharmaceutical, Daiichi Sankyo, Takeda, AstraZeneca, Hansoh Pharmaceuticals); **GJR:** Travel (MSD); research funding (all to institution: Novartis, Roche/Genentech, Millennium, GSK, Pfizer, Infinity Pharmaceuticals, ARIAD, Mirati Therapeutics, Merck); **TM:** Speakers bureau (AstraZeneca, Bristol Myers Squibb, Lilly, Merck, Takeda); advisory role (AstraZeneca, Lilly); **DN:** Stock and other ownership interests (all to an immediate family member: Intuitive Surgical, Teledoc); publication fees (Takeda); **MRGC:** Honoraria (Takeda, AstraZeneca, Roche, Pfizer, Bristol Myers Squibb, Boehringer Ingelheim); speakers bureau and/or advisory role (Takeda, AstraZeneca, Roche, Pfizer, Bristol Myers Squibb, Boehringer Ingelheim, Janssen, Novartis, MSD); **EF:** Consulting/advisory role (AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Guardant Health, MSD, Novartis, Pfizer, Roche, Takeda, Merck); **DM:** Consulting/advisory role (AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Lilly, MSD, Novartis, Roche, Sanofi and Takeda; institution, no personal honoraria); **MK:** Employment (Takeda); **VB:** Employment (Takeda); **HML:** Employment (Takeda); **PZ:** Employment (Takeda); **PAJ:** Consulting (Araxes Pharmaceuticals, ARIAD/Takeda, AstraZeneca, Boehringer Ingelheim, Chugai, Ignyta, Lilly, Loxo-Oncology, Merrimack, Mirati Therapeutics, Pfizer, Roche, Novartis, Voronoi, Daiichi Sankyo, SFJ Pharmaceuticals, Biocartis); research support (Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Lilly, Puma Biotechnology); stock ownership (Gatekeeper and Loxo Oncology); postmarketing royalties from Dana-Farber Cancer Institute–owned patent on *EGFR* mutations licensed to LabCorp

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