Mobocertinib efficacy in patients with NSCLC and *EGFR* exon 20 insertion (ex20ins) mutations identified by next-generation sequencing (NGS) of circulating tumor DNA (ctDNA)

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Background

- Epidermal growth factor receptor (*EGFR*) ex20ins mutations are present in ~2% of all non–small cell lung cancer (NSCLC) cases[1]
  - *EGFR* ex20ins mutations are heterogeneous, and more than 100 unique variants have been identified[2]
- Standard assays to detect *EGFR* ex20ins mutations include polymerase chain reaction (PCR) testing from tissue samples
  - However, many PCR testing platforms can only detect a limited number of these mutations, which can lead to undetected disease in ~40%–50% of cases,[2,3] whereas NGS can identify all such mutations
- Testing plasma ctDNA using NGS is a noninvasive approach for detection of genomic variants, including *EGFR* ex20ins[4]
- Mobocertinib, a first-in-class oral tyrosine kinase inhibitor (TKI) designed to selectively target *EGFR* ex20ins mutations in NSCLC, has demonstrated clinical activity and a manageable safety profile in the platinum-pretreated patient (PPP) cohort of a phase 1/2 study of patients with *EGFR* ex20ins+ metastatic NSCLC[5,6]
- We evaluated the efficacy of mobocertinib in the PPP cohort of the phase 1/2 study who were tested for *EGFR* ex20ins variants using FoundationOne Liquid CDx (F1LCDx), a comprehensive NGS-based plasma ctDNA assay that was recently approved by the US Food and Drug Administration (FDA) as a companion diagnostic for mobocertinib to identify patients with *EGFR* exon20ins mutations in metastatic NSCLC[7]

Methods

- In the mobocertinib phase 1/2 study (NCT02716116), patients were enrolled based on *EGFR* ex20ins mutation status detected by various local tissue or liquid clinical trial assays (CTAs)
- Baseline plasma samples were collected and processed to extract circulating tumor DNA and were evaluated for *EGFR* ex20ins status using F1LCDx
- Concordance between the CTAs and F1LCDx was evaluated by testing patient samples from the phase 1/2 trial and paired tissue and plasma samples from commercially acquired patients with NSCLC (N=342; **Table 1)**
- Efficacy analyses by assay method were performed in *EGFR* ex20ins+ PPP (n=114 [FDA-approved new drug application target population]; data cutoff: November 1, 2021) in the phase 1/2 trial

Table 1: F1LCDx sample accountability for *EGFR* ex20ins assessment in CTAs

CTA status	Sample source	Phase 1/2 study population	No. of patients	No. of failed or unavailable samples	F1LCDx evaluable		
					No. of F1LCDx-evaluable samples	No. of F1LCDx samples ≥30 ng[a]	No. of F1LCDx samples ≥20 ng and <30 ng[b]
Positive	Phase 1/2 study	NDA target population	114	34	80	71	9
	Phase 1/2 study	Non-NDA target population[c]	116	37	79	61	18
		Positive subtotal	**230**	**71**	**159**	**132**	**27**
Negative	Phase 1/2 study	Non-NDA target population[c]	43	3	40	34	6
	Procured	N/A	46	0	46	43	3
	Retrospective	N/A	23	0	23	23	0
		Negative subtotal	**112**	**3**	**109**	**100**	**9**
		Total	**342 (100.0%)**	**74 (21.6%)**	**268 (78.4%)**	**232 (67.8%)**	**36 (10.5%)**

[a]30 ng is standard DNA input for F1LCDx; [b]20 ng is minimal acceptable standard DNA input for F1LCDx; [c]Non-NDA target population includes patients from phase 1/2 study other than the PPP cohort
N/A, not applicable; NDA, new drug application

Results

- Demographic and baseline characteristics in PPP by F1LCDx testing status are shown in **Table 2**

Concordance between CTAs and F1LCDx

- Concordance between CTAs and F1LCDx was demonstrated with samples from the CTA-positive (n=159) and CTA-negative populations (n=109) tested by F1LCDx where tissue and plasma were assessable
  - The point estimate of positive percentage agreement (95% CI) was 68.6% (61.0–75.3), and the point estimate of negative percentage agreement was 100% **(**96.8–100.0; **Table 3)**

Key Question

How does the efficacy of mobocertinib in platinum-pretreated patients with *EGFR* ex20ins+ NSCLC who were tested for *EGFR* ex20ins variants using F1LCDx compare with the efficacy observed in those tested using CTAs?

Investigation

Key Results

Mobocertinib efficacy by F1LCDx status

- Patients who tested *EGFR* ex20ins positive by F1LCDx (n=55) demonstrated a confirmed objective response rate (ORR) of 34.5% and disease control rate of 74.5%, assessed by an independent review committee (IRC), which were comparable to those observed among all PPP in the phase 1/2 trial (IRC-confirmed ORR: 28%; confirmed disease control rate: 78%)[8]
- Duration of response (DOR), progression-free survival (PFS), and overall survival (OS) were numerically longer in patients who were F1LCDx–/CTA+ compared with those who were F1LCDx+, suggesting that negative ctDNA at baseline is associated with a better prognosis

Efficacy of mobocertinib in PPP by F1LCDx status

Efficacy results	PPP cohort (N=114)[a]	PPP with F1LCDx+/CTA+ (n=55)	PPP with F1LCDx–/CTA+ (n=25)	PPP with F1LCDx NE/CTA+ (n=34)
ORR, % (95% CI)	28 (20–37)	34.5 (22.2–48.6)	20.0 (6.8–40.7)	23.5 (10.8–41.2)
DCR, % (95% CI)	78 (69–85)	74.5 (61.0–85.3)	76.0 (54.9–90.6)	85.3 (68.9–95.1)
Median DOR, months (95% CI)	15.8 (7.4–19.4)	7.4 (3.8–17.5)	22.1 (19.4–NE)	16.6 (3.7–NE)
Median PFS, months (95% CI)	7.3 (5.5–9.2)	5.5 (3.7–7.3)	14.7 (5.5–23.9)	7.6 (3.8–15.7)
Median OS, months (95% CI)	20.2 (14.9–25.3)	14.6 (11.5–21.1)	32.0 (19.9–37.9)	21.7 (10.5–NE)

Data cutoff date: November 1, 2021
DCR, disease control rate; NE, not estimable

Key Takeaway

F1LCDx, a comprehensive NGS-based plasma ctDNA assay, effectively identified patients with *EGFR* ex20ins+ NSCLC who may derive clinical benefit from mobocertinib

Table 2: Demographic and baseline characteristics in PPP cohort by F1LCDx testing status

Characteristic	F1LCDx+/CTA+ (n=55)	F1LCDx–/CTA+ (n=25)	F1LCDx NE/CTA+ (n=34)
Age, median (range), years	59.0 (27–84)	66.0 (35–80)	58.5 (34–72)
Female, n (%)	38 (69)	17 (68)	20 (59)
Race, n (%)			
Asian	26 (47)	13 (52)	29 (85)
White	27 (49)	11 (44)	4 (12)
Black or African American	2 (4)	1 (4)	0
Not reported	0	0	1 (3)
ECOG performance status, n (%)			
0	13 (24)	10 (40)	6 (18)
1	42 (76)	15 (60)	28 (82)
Histology, n (%)			
Adenocarcinoma	53 (96)	25 (100)	34 (100)
Squamous cell carcinoma	1 (2)	0	0
Large cell carcinoma	1 (2)	0	0
Smoking history, n (%)			
Never	39 (71)	19 (76)	23 (68)
Current	1 (2)	0	1 (3)
Former	15 (27)	6 (24)	10 (29)
No. of prior systemic anticancer regimens, n (%)			
1	26 (47)	11 (44)	10 (29)
2	15 (27)	4 (16)	17 (50)
≥3	14 (26)	10 (40)	7 (21)
Prior systemic anticancer therapy, n (%)			
Immunotherapy	22 (40)	14 (56)	13 (38)
EGFR TKI	8 (15)	9 (36)	12 (35)

Data cutoff date: November 1, 2021
ECOG, Eastern Cooperative Oncology Group; NE, nonevaluable

Table 3: Concordance between enrollment CTAs and F1LCDx

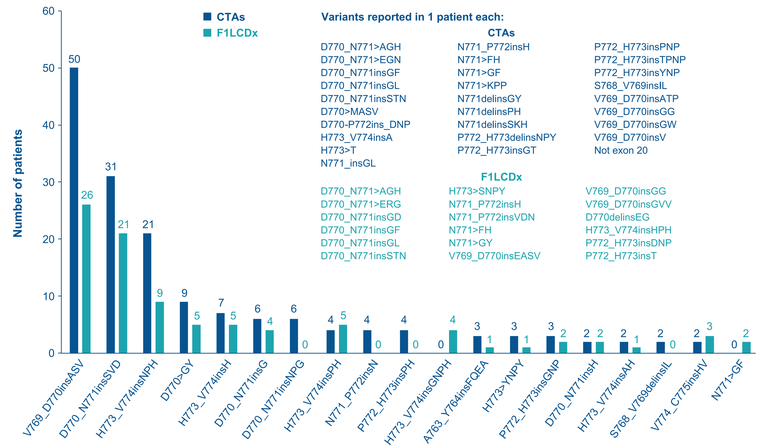
EGFR ex20ins status	CTA result		
	CTA+	CTA–	Total
F1LCDx+, n	109	0	109
F1LCDx–, n	50	109	159
Total, n	159	109	268
Positive agreement point estimate (n/N) [95% CI]	68.6% (109/159) [61.0–75.3]		
Negative agreement point estimate (n/N) [95% CI]	100.0% (109/109) [96.8–100.0]		

Data cutoff date: November 1, 2021. 71 CTA+ and 3 CTA– patients either had no plasma sample available or failed the F1LCDx quality control metrics and therefore were not evaluable. Of the 159 CTA+ samples, 149 were from tissue, 5 were from plasma, and 5 were designated as "other."
CI, confidence interval

EGFR ex20ins variants detected by CTAs and F1LCDx

- The CTAs detected a total of 44 unique *EGFR* ex20ins variant types in 233 patient samples, and F1LCDx detected 33 unique variant types from 109 patient samples **(Figure 1)**

Figure 1: *EGFR* ex20ins variants reported by CTAs[a] (n=233) and by F1LCDx (n=109)



Variants reported in 1 patient each:

CTAs

D770_N771>AGH
D770_N771>EGN
D770_N771insGF
D770_N771insGL
D770_N771insSTN
D770>MASV
D770-P772ins_DNP
H773_V774insA
H773>T
N771_insGL
N771_P772insH
N771>FH
N771>GF
N771>KPP
N771delinsGY
N771delinsPH
N771delinsSKH
P772_H773delinsNPY
P772_H773insGT
P772_H773insPNP
P772_H773insTPNP
P772_H773insYNP
S768_V769insIL
V769_D770insATP
V769_D770insGG
V769_D770insGW
V769_D770insV
Not exon 20

F1LCDx

D770_N771>AGH
D770_N771>ERG
D770_N771insGD
D770_N771insGF
D770_N771insGL
D770_N771insSTN
H773>SNPY
N771_P772insH
N771_P772insVDN
N771>FH
N771>GY
V769_D770insEASV
V769_D770insGG
V769_D770insGVV
D770delinsEG
H773_V774insHPH
P772_H773insDNP
P772_H773insT

[a]A total of 47 patients had mutations that were undefined

Conclusions

- Mobocertinib has shown efficacy in PPP with *EGFR* ex20ins+ NSCLC and is also effective in PPP with *EGFR* ex20ins+ NSCLC identified by liquid biopsy
- Concordance between CTAs and F1LCDx was demonstrated, with 68.6% positive percentage agreement and 100% negative percentage agreement
- These results suggest that negative ctDNA at baseline is associated with a numerically longer PFS and OS and better prognosis
- F1LCDx effectively identified patients with *EGFR* ex20ins who may benefit from mobocertinib, providing an additional noninvasive diagnostic option to guide treatment

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Acknowledgments

The authors would like to thank the patients, their families, and their caregivers; the study investigators and their team members at each study site; and colleagues from Takeda and its subsidiaries. Medical writing support for the development of this poster, under the direction of the authors, was provided by Corey Burgin, PhD, of Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, USA; was funded by Takeda Development Center Americas, Inc., Lexington, MA, USA; and was complied with the Good Publication Practice (GPP) guidelines (DeTora LM, et al. Ann Intern Med 2022;175:1298–1304).
The study was sponsored by Takeda Development Center Americas, Inc.

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