A Phase I Dose-Escalation Study of Mobocertinib (TAK-788), an Oral Tyrosine Kinase Inhibitor, in Japanese NSCLC Patients

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Background

- Non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancers.[1,2]
- Activating mutations in epidermal growth factor receptor (EGFR) gene have been identified in 15–40% of patients with NSCLC; with 50% of these patients having adenocarcinoma.[3–7]
- Tyrosine kinase inhibitors (TKI) targeting common and treatment emergent EGFR mutations are offering improved patient outcomes.[6,8]
- Most EGFR exon 20 insertion (EGFRex20ins) driver mutations in NSCLC are resistant to approved EGFR-TKIs.[8–11]
- Mobocertinib (TAK-788; AP32788) is an investigational, orally-administrated TKI that is designed to inhibit all activated forms of *EGFR* and *HER2* mutations, including exon 20 insertions.
- Here we present results from the Phase 1 open-label, multicentre, dose-escalation part of a Phase 1/2 study (NCT03807778). The aim of this study was to confirm the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) identified from a global study (160 mg once daily [QD]) in Japanese patients with NSCLC.
- We report pharmacokinetics (PK), safety and tolerability, and preliminary response results of mobocertinib 40 mg QD, 120 mg QD, and 160 mg QD in Japanese patients.

Methods

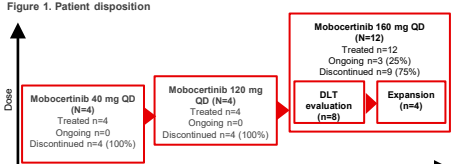
- Patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC refractory to standard available therapies were included.
- Mobocertinib was administered orally with an initial dose-level of 40 mg daily which was increased in increments until the MTD was identified or 160 mg QD was confirmed to be safe and tolerable.
- Doses used in the higher dose cohorts were determined with an adaptive Bayesian logistic regression model.
- The dose-limiting toxicity (DLT) dose was reached when ≥2 of 6 evaluable patients experienced a DLT at a specific dose. The dose immediately below the DLT dose was considered the MTD.

Results

Patient disposition

- Overall, 21 patients were enrolled across 4 sites in Japan; 1 patient was excluded due to screen failure (enrolment completion: 13 November 2019; **Figure 1**).
- Safety population consisted of all patients who received at least one dose of study medication (N=20). All 20 patients were included in the response evaluable population.
- All 4 patients in the 40 mg and 120 mg cohorts and 8 patients firstly enrolled in the 160 mg cohort were evaluated for DLT.
- As of data cut off (DCO; 31 March 2020), 3 patients receiving 160 mg QD remained on study.
- Per protocol, an expansion cohort (160 mg QD) was opened after confirmation of MTD/RP2D; 4/20 patients were enrolled in this cohort.

Figure 1. Patient disposition



Patient demographics and baseline characteristics

- In this study, all patients were Japanese and had adenocarcinoma; the overall median age was 61 years and the majority (70%) of patients were female (**Table 1**).
- At baseline, 95% of patients had tumours harbouring an EGFR mutation; of these, 90% harboured an EGFRex20ins mutation.
- All patients had received at least one prior anti-cancer therapy, and 55% of patients had received ≥3 regimens.
- Overall, 19 of 20 patients (11 of 12 patients who received 160 mg QD) had received prior platinum-based chemotherapy (carboplatin and/or cisplatin); 1 patient had received gefitinib and an unspecified investigational drug.
- The median duration of study drug exposure was 3.45 months (range, 0.4–10.1);median dose intensity was 119.3 mg/day (range, 40–160) and median relative dose intensity was 94.4%.

Table 1. Patient demographic and clinical characteristics

Characteristic	Mobocertinib 40 mg QD (N=4)	Mobocertinib 120 mg QD (N=4)	Mobocertinib 160 mg QD (N=12)	Mobocertinib Total (N=20)
Median age, years (range)	63.5 (41–71)	60.0 (46–71)	61.0 (42–83)	61.0 (41–83)
Aged <65 years / ≥65 years, n (%)	2 (50) / 2 (50)	2 (50) / 2 (50)	6(50) / 6 (50)	10 (50) / 10 (50)
Sex, n (%) male / female	2 (50) / 2 (50)	1 (25) / 3 (75)	3 (25) / 9 (75)	6 (30) / 14 (70)
Stage at diagnosis, n (%) IIIB / IV	0 (0) / 4 (100)	0 (0) / 4 (100)	1 (8) / 11 (92)	1 (5) / 19 (95)
Median time since initial diagnosis, months (range)	26.9 (17.9–157.8)	15.5 (11.8–31.6)	20.2 (2.6–100.4)	19.7 (2.6–157.8)
ECOG PS, n (%) 0 / 1	2 (50) / 2 (50)	0 (0) / 4 (100)	5 (42) / 7 (58)	7 (35) / 13 (65)
CNS involvement at screening, n (%) Y / N	2 (50) / 2 (50)	4 (100) / 0 (0)	4 (33) / 8 (67)	10 (50) / 10 (50)
Smoking history, n (%) Never / Former	2 (50) / 2 (50)	2 (50) / 2 (50)	8 (67) / 4 (33)	12 (60) / 8 (40)
All type of EGFR-mutation positive/negative status, n (%)	3 (75) / 1 (25)	4 (100) / 0	12 (100)	19 (95) / 1 (5)
EGFRex20ins mutation positive/negative status, n (%)	3 (75) / 1 (25)	4 (100) / 0	11 (92) / 1 (8)	18 (90) / 2 (10)
HER2 mutation positive/negative status, n (%)	2 (50)	0	4 (33)	6 (30)
HER2 mutation positive/negative status, n (%) EGFRex20ins mutation positive/negative status, n (%)	1 (50) / 1 (50)	0	0	1 (17) / 5 (83)
	1 (50) / 1 (50)	0	0	1 (17) / 5 (83)

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EGFRex20ins, exon 20 insertion; QD, once daily

Dose-limiting toxicities (DLT) and determination of MTD and RP2D

- No DLT was observed at 40 mg QD, and 1 patient (25%) in 120 mg QD cohort and 2 patients (25%) in 160 mg QD cohort had DLTs. The details of each DLT is summarized in **Table 2**.

Table 2. DLT report[*] across all mobocertinib doses

Patient	DLT	Event outcome
0001-002 (120 mg QD)	Drug-related grade 3 diarrhoea leading to dose interruption/dose reduction	Recovering/resolving at EOT
0003-005 (160 mg QD)	Drug-related grade 3 interstitial lung disease leading to dose discontinuation	Not recovered/resolved at EOT
0003-007 (160 mg QD)	Patient missed ≥25% of planned doses due to TEAEs; AST increased (grade 2), ALT increased (grade 3), and diarrhoea (grade 2)	AST and ALT increased were resolved; diarrhoea not recovered/resolved at EOT

[*]All the patients in the dose escalation cohorts were DLT-evaluable. ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; EOT, end of treatment; QD, once daily; TEAE, treatment-emergent adverse event

Safety and tolerability

- All but 1 patient who received 40 mg QD had at least 1 TEAE of any grade (**Table 3**).
- Treatment-emergent adverse events (TEAEs) of grade ≥3 and treatment-emergent serious adverse events (SAEs) are shown in **Table 4** and **Table 5**, respectively.
- One patient in the 120 mg QD cohort died and the event was related to underlying disease (lung cancer).
- No new safety signals for mobocertinib were observed.

Table 3. TEAEs of any grade reported in ≥3 patients in any treatment group, by preferred term – safety population

Preferred term	Mobocertinib 40 mg QD (N=4)	Mobocertinib 120 mg QD (N=4)	Mobocertinib 160 mg QD (N=12)
Patients with any TEAE, n (%)	3 (75)	4 (100)	12 (100)
Diarrhoea	3 (75)	4 (100)	12 (100)
Lymphocyte count decreased	0	1 (25)	4 (33)
ALT increased	0	0	4 (33)
Decreased appetite	1 (25)	1 (25)	4 (33)
White blood cell decreased	0	0	3 (25)
Stomatitis	0	2 (50)	8 (67)
Dry skin	0	2 (50)	8 (67)
Nausea	2 (50)	2 (50)	6 (50)
Vomiting	0	2 (50)	7 (58)
Dermatitis acneiform	0	2 (50)	7 (58)
Amylase increased	0	1 (25)	5 (42)
Paronychia	0	1 (25)	5 (42)
Blood creatinine increased	0	0	5 (42)
AST increased	0	0	4 (33)
Pyrexia	0	3 (75)	3 (25)
Lipase increased	0	1 (25)	3 (25)
Dysgeusia	1 (25)	1 (25)	3 (25)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; QD, once daily; TEAE, treatment-emergent adverse event

Table 4. TEAEs of grade ≥3 in any treatment group, by preferred term – safety population

Preferred term	Mobocertinib 40 mg QD (N=4)	Mobocertinib 120 mg QD (N=4)	Mobocertinib 160 mg QD (N=12)
Patients with any TEAE of grade ≥3, n (%)	0	3 (75)	4 (33)
Diarrhoea	0	1 (25)	0
Lymphocyte count decreased	0	1 (25)	0
Dehydration	0	1 (25)	0
Depressed level of consciousness	0	1 (25)	0
Embolism	0	1 (25)	0
Pneumonia	0	0	1 (8)
Interstitial lung disease	0	0	1 (8)
ALT increased	0	0	1 (8)
Neutrophil count decreased	0	0	1 (8)
White blood cell count decreased	0	0	1 (8)
Decreased appetite	0	0	1 (8)

ALT, alanine aminotransferase; QD, once daily; TEAE, treatment-emergent adverse event

Table 5. Treatment-emergent SAEs in any treatment group, by preferred term – safety population

Preferred term	Mobocertinib 40 mg QD (N=4)	Mobocertinib 120 mg QD (N=4)	Mobocertinib 160 mg QD (N=12)
Patients with any treatment-emergent SAE, n (%)	0	3 (75)	3 (25)
Dehydration	0	1	0
Depressed level of consciousness	0	1	0
Embolism	0	1	0
Pneumonia	0	0	1
Interstitial lung disease	0	0	1
Pneumonitis	0	0	1

QD, once-daily; SAE, serious adverse event

TEAEs of clinical interest

- Summaries of interstitial lung disease (ILD)/ pneumonitis and diarrhoea are provided in **Table 6** and **Table 7**.
- Incidence of ILD/pneumonitis at 40 mg QD, 120 mg QD, and 160 mg QD were 25% (1 patient), 0%, and 16.7% (2 patients), respectively.
- Almost all patients had at least 1 drug-related diarrhoea event, and the median time to initial onset of event was 3–4 days (post-dose), grade ≤2 and manageable with concomitant loperamide with no need for dose modification.

Table 6. Summary of ILD/pneumonitis – safety population

Preferred term	Dose (QD), mg	Severity (grade)	Onset (study day)	End of event (study day)	Event outcome	Treatment related	Action taken
Radiation pneumonitis	40	1	22	Ongoing	Not recovered/ not resolved	Not related	No dose modification
ILD	160	3	16	Ongoing	Not recovered/ not resolved	Related	Drug withdrawn
Pneumonitis	160	2	121	Ongoing	Not recovered/ not resolved	Related	Drug withdrawn

Data cut-off date: 31 March 2020
ILD, interstitial lung disease; QD, once-daily; TEAE, treatment emergent adverse event

Table 7. Summary of diarrhoea – safety population

Preferred term	Mobocertinib 40 mg QD (N=4)	Mobocertinib 120 mg QD (N=4)	Mobocertinib 160 mg QD (N=12)
Patients who had diarrhoea, n	3	4	12
Drug-related	3	4	12
Grade ≥3	0	1	0
Led to dose modification	0	1	2
Dose interruption	0	1	2
Dose reduction	0	1	1
Median time to initial onset, days (range)	3 (2–9)	4 (3–5)	4 (2–26)

QD, once-daily

Investigator-assessed objective response rate (ORR) and disease control rate (DCR)

- Investigator-assessed ORR was 25.0% (95% CI 0.63, 80.59 [1 patient had partial response, PR]) at 120 mg QD and 16.7% (95% CI 2.09, 48.41 [2 patients had PR]) at 160 mg QD.
- All 3 patients with an objective response (CR or PR) had tumours harbouring EGFRex20ins.
- Investigator-assessed DCR (complete response [CR], PR or stable disease [SD]) was 50%, 75% and 75% in the 40 mg, 120 mg and 160 mg QD cohorts, respectively (**Table 8**).

Table 8. Investigator-assessed ORR – Response evaluable population

	Mobocertinib 40 mg QD (N=4)	Mobocertinib 120 mg QD (N=4)	Mobocertinib 160 mg QD (N=12)
Investigator-assessed ORR, n (%)	0	1 (25)	2 (17)
[95% CI]	[0.00, 60.24]	[0.63, 80.59]	[2.09, 48.41]
Investigator-assessed DCR, n (%)[†]	2 (50)	3 (75)	9 (75)
Investigator-assessed BOR, n			
CR	0	0	0
PR	0	1	2
SD[‡]	2	2	7
PD	2	1	3
NE	0	0	0

[†]Percentage of patients achieving CR, PR or SD. [‡]Defined as ≥42 days
BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease

Pharmacokinetic analysis

- Mobocertinib was readily absorbed with a median time to reach maximum concentration (T_{max}) of approximately 4 h on both Cycle 1, Day 1 (C1D1) and Cycle 2, Day 1 (C2D1). The mean plasma concentration-time profiles on C1D1 and C2D1(Day 29) for mobocertinib are depicted in **Figures 2A and 2B**. The daily dosing schedule was supported by the estimated effective half-life of 9–13 hours (**Table 9**).
- Minimal mobocertinib accumulation of <1.3 was observed following multiple doses (**Table 9**).

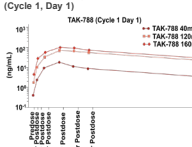
Table 9. Summary of PK parameters of mobocertinib – PK population

		Mobocertinib 40 mg QD	Mobocertinib 120 mg QD	Mobocertinib 160 mg QD
After single oral dose (Cycle 1, Day 1)				
Evaluable patients, n		4	4	12
T_{max}, h	Median (min, max)	3.83 (3.83, 3.88)	3.985 (3.88, 5.92)	3.985 (3.83, 7.87)
C_{max}, ng/mL	Geo mean (Geo %CV)	15.4 (76.1)	70.28 (56.2)	100.2 (36.3)
AUC_{24}, h*ng/mL	Geo mean (Geo %CV)	152.9 (62.2)	858.1 (60.3)	1196 (43.0)
Steady state after multiple oral dose (Cycle 2, Day 1)				
Evaluable patients, n		4	4	5
$t_{max,ss}$, h	Median (min, max)	3.95 (3.83, 4.05)	4.00 (3.97, 4.03)	3.97 (3.92, 5.95)
$C_{max,ss}$, ng/mL	Geo mean (Geo %CV)	17.9 (34.4)	106.2 (39.4)	90.0 (18.4)
$AUC_{24,ss}$, h*g/mL	Geo mean (Geo %CV)	214.8 (29.9)	1195 (50.1)	1141 (25.9)
$R_{ac(AUC24)}$	Geo mean (Geo %CV)	1.096 (43.8)	1.26 (12.9)	0.9227 (39.3)
$t_{1/2el}$[#], h	Geo mean (Geo %CV)	13.19 (4.3)	10.25 (33.4)	9.137 (19.4)

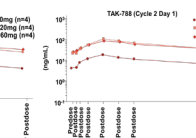
$AUC_{24,ss}$, steady-state area under concentration-time curve over the dosing interval; C_{max}, maximum observed concentration; $C_{max,ss}$, maximum steady-state plasma concentration; CV, coefficient of variation; Geo mean, geometric mean; $R_{ac(AUC24)}$, accumulation ratio calculated from AUC_{24}; PK, pharmacokinetic; $t_{1/2el}$, effective half life; T_{max}, time to reach maximum (peak) plasma concentration; $t_{max,ss}$, time of first occurrence of C_{max} at steady state. [#]40 mg QD: n=2, 120 mg QD: n=2, 160 mg QD: n=3

Figure 2. Mean plasma concentrations of mobocertinib (semi-log scale)

(A) Following single oral dose administration (Cycle 1, Day 1)



(B) Following repeated oral dosing (Cycle 2, Day 1)



Conclusions

- Mobocertinib 160 mg QD (global MTD) was confirmed to be tolerable in Japanese patients with NSCLC.
- In this study, no new safety signals for mobocertinib were observed.
- The PK of mobocertinib and its two active metabolites were characterised in Japanese patients with NSCLC, supporting the QD dosing regimen.

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