Poster #356

YH25448, a 3rd Generation EGFR-TKI, in Patients with EGFR-TKI-resistant NSCLC: Phase I/II Study Results

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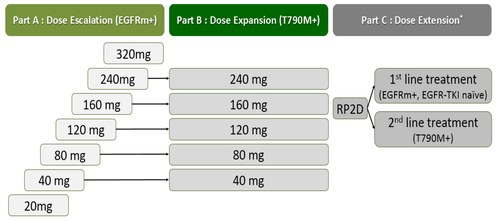
INTRODUCTION

- **The majority of patients who had treated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) eventually relapse with disease progression within 1 to 2 years[1]). The T790M mutation in exon 20 of EGFR was present up to 60 % of resistant cases[2]).**
- **Brain metastasis (BM) is present in one-quarter of patients at diagnosis, and about half of patients with EGFR-mutated lung cancer develop brain metastases within 3 years[3]).**
- **YH25448 (lazertinib) is a potent, highly mutant-selective and irreversible 3rd generation EGFR-TKI that is able to penetrate the blood-brain barrier, and targets both the T790M mutation and activating EGFR mutations (EGFRm) while sparing wild type.**

METHODS

- The aim of this study was to evaluate the safety, tolerability, pharmacokinetics and efficacy of YH25448 when given orally to Korean patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with acquired resistance to prior EGFR-TKI treatments (ClinicalTrials.gov identifier NCT03046992).
- An open-label, multicenter, phase I/II study was performed with YH25448 20 to 320 mg once daily in the dose escalation cohort across 7 dose levels and 40 to 240 mg once daily in the expansion cohort across 5 dose levels (Figure 1).
- In the dose escalation cohort, 6 patients were enrolled in each dose level using the rolling six manner. The safety review committee determined the escalation of next dose level using the safety assessment during the 28-day evaluation period.
- In the dose expansion cohort, up to 20 patients were enrolled. The T790M-positive of tissue biopsy was confirmed using Roche cobas® EGFR mutation test v2 at central laboratory.

Figure 1. Study Design



* The dose extension cohort was initiated at April 2018.
RP2D; recommended phase 2 dose

RESULTS

Baseline Demographics and Characteristics

- A total of 118 patients were enrolled as of 20 April 2018.
- Thirty-eight patients were in the dose escalation cohort and 80 patients were in the dose expansion cohort (Table 1).
- Median age was 62.5 years and 60% of patients were female.
- 83% of patients were T790M+ NSCLC.

Table 1. Baseline Demographics and Characteristics

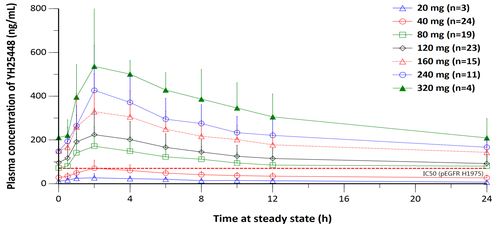
	Dose escalation (n=38)	Dose expansion (n=80)	Overall (N=118)
Age in years, median (range)	60 (28, 82)	63 (37, 84)	62.5 (28, 84)
Male, n (%)	13 (34)	34 (43)	47 (40)
Adenocarcinoma, n (%)	37 (97)	80 (100)	117 (99)
T790M status*, n (%)			
Positive	18 (47)	80 (100)	98 (83)
Negative	20 (53)	0	20 (17)
AJCC stage, n (%)			
IIIB	2 (5)	1 (1)	3 (3)
IV	36 (95)	79 (99)	115 (97)
Prior lines of systemic therapy, median (range)	2 (1, 6)	1 (1, 6)	1.5 (1, 6)
Number of prior EGFR-TKIs, median (range)	1 (1, 2)	1 (1, 3)	1 (1, 3)
Regimen#, n (%)			
Gefitinib	27 (71)	54 (68)	81 (69)
Erlotinib	9 (24)	21 (26)	30 (25)
Afatinib	5 (13)	15 (19)	20 (17)

* Tested in a central laboratory. # Patients may have more than one prior regimen. Percentages are calculated based on number of patients in the safety analysis population who received at least one dose of IP.

Pharmacokinetics

- Median $T_{max,ss}$ of YH25448 was 2 hours.
- Mean terminal elimination half-life of YH25448 was 64.7 hours following single dose of 240 mg.
- Steady state was achieved by 7-15 days after first-dosing, and mean AUC accumulation ratio was 1 to 2 following multiple doses.
- AUC_{ss} of YH26334 (major metabolite) was 2 to 4% of that of YH25448.
- Exposures of YH25448 increased dose-dependently at steady state (Figure 2)

Figure 2. Plasma Concentrations of YH25448 at Steady State



Data represents the arithmetic mean+standard deviation
Red dashed line represents the IC_{50} value (70 ng/mL) of EGFR phosphorylation in H1975 cell line

Anti-tumor Efficacy

- Of the evaluable patients (n=110) with the confirmed response at the date of data cut-off (DCO), the objective response rate (ORR) was 61% (95% confidence interval [CI], 51.8 to 70.0) across all dose levels by investigator assessment (Table 2, Figure 3).
  - The ORR for 92 of the T790M+ patients was 66% (95% CI, 56.6 to 76.0), and for 18 of the T790M- patients was 33% (95% CI, 11.6 to 55.1).
- The disease control rate (DCR) was 89% across all dose levels (95% CI, 83.3 to 94.9).
- In patients with BM (n=11), the intracranial ORR was 55% (95% CI, 25.1 to 84.0) (Figure 3C).
- The longest duration of response was 9.7 months and the median duration of response has not reached yet.
- The median progression-free survival has not calculated yet at the date of DCO.

Table 2. Summary of Anti-tumor Efficacy (Confirmed Response)

T790M +/-	20mg	40mg	80mg	120mg	160mg	240mg	320mg	Overall
Evaluable patients[a]	3	27	20	25	23	9	3	110
Best overall response[b], n (%)								
Complete response	0	0	0	0	0	0	0	0
Partial response	2 (67)	17 (63)	11 (55)	18 (72)	12 (52)	7 (78)	0	67 (61)
Stable disease	1 (33)	7 (26)	6 (30)	7 (28)	8 (35)	2 (22)	0	31 (28)
Progressive disease	0	2 (7)	3 (15)	0	1 (4)	0	3 (100)	9 (8)
Not evaluable	0	1 (4)	0	0	2 (9)	0	0	3 (3)
ORR, n (%)	2 (67)	17 (63)	11 (55)	18 (72)	12 (52)	7 (78)	0	67 (61)
DCR, n (%)	3 (100)	24 (89)	17 (85)	25 (100)	20 (87)	9 (100)	0	98 (89)
T790M +	**20mg**	**40mg**	**80mg**	**120mg**	**160mg**	**240mg**		**Overall**
Evaluable patients[a]	2	25	18	22	18	7		92
Best overall response[b], n (%)								
Complete response	0	0	0	0	0	0		0
Partial response	2 (100)	16 (64)	11 (61)	16 (73)	10 (56)	6 (86)		61 (66)
Stable disease	0	7 (28)	4 (22)	6 (27)	7 (39)	1 (14)		25 (27)
Progressive disease	0	2 (8)	3 (17)	0	1 (6)	0		6 (7)
Not evaluable	0	0	0	0	0	0		0
ORR, n (%)	2 (100)	16 (64)	11 (61)	16 (73)	10 (56)	6 (86)		61 (66)
DCR, n (%)	2 (100)	23 (92)	15 (83)	22 (100)	17 (94)	7 (100)		86 (93)

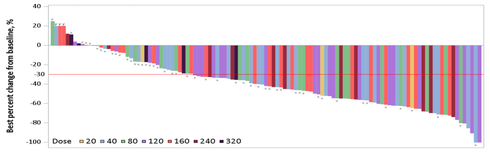
[a] Patients who have baseline and two post-baseline RECIST assessments, or patients who have discontinued prior to the second post-baseline RECIST assessment; [b] Best overall response is based on investigator's assessment of disease status or lesion measurements using RECIST v1.1.

Safety and Tolerability

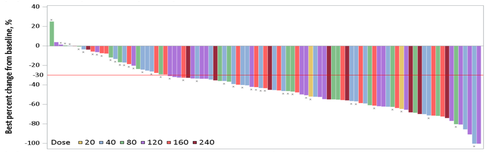
- No dose-limiting toxicities (DLT) were observed up to YH25448 320 mg in the dose escalation cohort.
- A total of 89% of treatment-emergent adverse events (TEAEs) were mild (CTCAE grade ≤ 2) at all dose levels (Table 3).
- The most common TEAEs were pruritus (24%), rash (19%), decreased appetite (17%), constipation (16%) and diarrhea (12%) (Table 4). There was no interstitial lung disease.
- The TEAEs leading to dose-reduction, interruption and discontinuation were observed in 4%, 9% and 3% of patients, respectively.
- Any TEAEs of CTCAE grade ≥ 3 was observed in 11% of patients. The most frequently TEAEs of CTCAE grade ≥ 3 were pulmonary embolism (3%), hyponatremia (2%), nausea (2%) and pneumonia (2%).
- There were no dose-dependently increased TEAEs.

Figure 3. Best Percentage Change in Target-Lesion Size

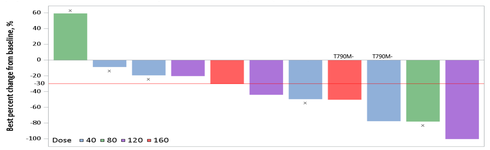
(A) Overall patients (n=110)



(B) T790M+ patients (n=92)



(C) Intracranial lesion in patients with BM (n=11)



These waterfall plots include the unconfirmed response data; x: discontinuation or disease progression; y: Imputed values for patients who discontinued and had no evaluable target lesion assessments

Table 3. Safety Overview of Overall TEAEs

Patients with TEAEs, n (%)	20mg (n=3)	40mg (n=27)	80mg (n=20)	120mg (n=25)	160mg (n=23)	240mg (n=15)	320mg (n=5)	Overall (N=118)
TEAEs	3 (100)	24 (89)	17 (85)	23 (92)	20 (87)	15 (100)	5 (100)	107 (91)
Drug related TEAEs	2 (67)	16 (59)	11 (55)	18 (72)	14 (61)	13 (87)	4 (80)	78 (66)
Serious TEAEs	1 (33)	4 (15)	3 (15)	4 (16)	3 (13)	0	2 (40)	17 (14)
Drug related serious TEAEs	0	2 (7)	1 (5)	1 (4)	0	0	0	4 (3)
TEAEs with grade ≥ 3	0	3 (11)	1 (5)	2 (8)	4 (17)	1 (7)	2 (40)	13 (11)
Drug related TEAEs with grade ≥ 3	0	1 (4)	0	1 (4)	0	0	0	2 (2)
TEAEs leading to								
Death	0	0	0	0	0	0	0	0
Dose reduction	0	0	0	2 (8)	0	2 (13)	1 (20)	5 (4)
Dose interruption	1 (33)	3 (11)	2 (10)	3 (12)	1 (4)	0	1 (20)	11 (9)
Discontinuation	0	2 (7)	1 (5)	0	0	0	0	3 (3)

Percentages are based on the total number of patients in the safety analysis population. Drug related TEAEs are events with relationship certain, probable/likely, possible, unlikely, unassessable/unclassifiable, or missing.

Table 4. TEAEs Occurring ≥ 10 % of All Patients

Patients with TEAEs, n (%)	20mg (n=3)	40mg (n=27)	80mg (n=20)	120mg (n=25)	160mg (n=23)	240mg (n=15)	320mg (n=5)	Overall (N=118)
Pruritus	0	4 (15)	4 (20)	4 (16)	8 (35)	7 (47)	1 (20)	28 (24)
Rash	0	5 (19)	1 (5)	6 (24)	6 (26)	3 (20)	2 (40)	23 (19)
Decreased appetite	1 (33)	4 (15)	3 (15)	3 (12)	5 (22)	2 (13)	2 (40)	20 (17)
Constipation	1 (33)	3 (11)	6 (30)	4 (16)	3 (13)	1 (7)	1 (20)	19 (16)
Diarrhea	0	3 (11)	0	2 (8)	4 (17)	4 (27)	1 (20)	14 (12)

Percentages are based on the total number of patients in the safety analysis population within relevant dose level. Patients with two or more adverse events with the same AE term is counted only once for that AE term.

CONCLUSIONS

- **YH25448 (lazertinib) demonstrated the promising antitumor efficacy.**
  - **The confirmed ORR was 61% across all dose levels in patients with locally advanced or metastatic NSCLC with acquired resistance to prior EGFR-TKI treatments.**
  - **In particular, the confirmed ORR in patients with T790M+ was 86% at lazertinib 240 mg dose level.**
  - **In patients with BM, the intracranial ORR was 55% across all dose levels.**
- **Lazertinib demonstrated a good safety profile and tolerability.**
  - **No DLT was observed up to lazertinib 320 mg.**
  - **A total of 89% of TEAEs were mild.**
  - **There were no dose-dependently increased TEAEs.**
- **In conclusion, lazertinib was safe, well-tolerated and exhibits promising systemic and intracranial antitumor activities at multiple dose levels in EGFRm+ NSCLC patients.**
- **The dose extension cohort as the first-line setting has been initiated from April 2018.**

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