YH25448, an irreversible 3rd-generation EGFR TKI, exhibits superior anticancer effects with potent brain BBB penetration in NSCLC

Jiyeon Yun1, Min Hee Hong2, Seok-Young Kim1, Chae Won Park1, So-Young Kim4, Mi Ran Yun1, Han Na Kang1, Kyoung Ho Pyo1, Jong Sung Koh1, Ho-Juhn Song1, Young-Sung Lee2, Se-Woong Oh1, Soongyu Choi3, and Byoung-Chul Cho4

1Nursery University College of Medicine, Cancer Research Inst, Seoul, Republic of Korea; 2Nursery University College of Medicine, Cancer Research Inst, Seoul, Republic of Korea; 3Nursery University College of Medicine, Cancer Research Inst, Seoul, Republic of Korea; 4Nursery University College of Medicine, Cancer Research Inst, Seoul, Republic of Korea; 5Yuhan Co., Ltd, Cambridge, MA, Yukan R&D Institute, Yukan Corporation, Seoul, Republic of Korea

Abstract No. 4790 | AACC Annual Meeting 2018 | April 14-18, Chicago

ABSTRACT

YH25448 is a novel, highly potent, and mutant-selective EGFR TKI with a wide therapeutic index and exceptional intracranial activity. To evaluate the efficacy of YH25448 in an early clinical trial of YH25448. We have embarked on a phase II study (NCT03046992) of YH25448 in NSCLC patients with EGFR mutations who have failed to respond to prior EGFR TKI treatment.

RESULTS

1. YH25448 is a novel, irreversible inhibitor of EGFR kinase activity, selectively targeting mutant EGFRs.

2. YH25448 significantly regresses lung cancer with EGFR mutations in vitro and in vivo.

3. YH25448 shows superior efficacy for tumor regression in an EGFR mutant brain metastasis model, with a high BBB penetration profile.

CONCLUSIONS

YH25448 has demonstrated important competitive advantages in clinical study.

5. YH25448 shows greater selectivity against wild-type EGFR results in lower suppression of wild-type pEGFR in skin and lower skin toxicity than osimertinib in animals.

Epidemiological study of OS (overall survival) was performed for 20 patients with EGFR mutant NSCLC. The OS rate was 15% when metastatic EGFR-mutated NSCLC is treated with EGFR TKIs (2-3). However, the majority of patients eventually relapse with disease progression 1 to 2 years after receiving EGFR TKI treatment (3). For this reason, there have been many efforts to target the EGFR T790M mutation and third-generation EGFR TKIs including rociletinib, osimertinib, and entinostat have been developed. Brain metastasis is present in 1-third of patients at diagnosis, and about half of patients with EGFR-mutant lung cancer develop brain metastases within 3 years (4).

Despite the introduction of third-generation EGFR TKIs, significant unmet needs remain. Many of these agents exhibit unintended side effects as they show target wide-type EGFR to some degree. Only osimertinib (AZD9291) has been approved for this indication by the U.S. FDA and the European Medicines Agency. However, even in a phase II trial of osimertinib, adverse events at all grades occurred in almost every patient (30%), and 22% of the patients experienced grade 3 or higher adverse events (5). The incidence of diarrhea and rash with osimertinib therapy at any grade were 47% and 34%, respectively. These adverse events were considered to be caused by the low selectivity of osimertinib against WT EGFR. Another pitfall of the EGFR TKIs developed to date is their relative inability to penetrate the blood-brain barrier (BBB). The central nervous system (CNS) is one of the most common sites of progression during EGFR TKI treatment, and NSCLC patients with CNS metastases have a very poor prognosis (6-8).

YH25448 is in a novel, highly potent, and mutant-selective EGFR TKI with a wide therapeutic index and exceptional intracranial activity. To evaluate the efficacy of YH25448 in an early clinical trial of YH25448. We have embarked on a phase II study (NCT03046992) of YH25448 in NSCLC patients with EGFR mutations who have failed to respond to prior EGFR TKI treatment.

RESULTS

1. YH25448 is a novel, irreversible inhibitor of EGFR kinase activity, selectively targeting mutant EGFRs.

2. YH25448 significantly regresses lung cancer with EGFR mutations in vitro and in vivo.

3. YH25448 shows superior efficacy for tumor regression in an EGFR mutant brain metastasis model, with a high BBB penetration profile.

CONCLUSIONS

YH25448 has demonstrated important competitive advantages in clinical study.

- Superior in vitro potency and selectivity over osimertinib.
- Superior in vivo efficacy over osimertinib in both single (del19, L858R) and double (L858R/T790M) mutant xenograft models.
- Excellent BBB penetration and superior in vivo efficacy over osimertinib in a brain metastasis model.
- Lower skin toxicity over osimertinib.

Phase III clinical study in EGFR mutant-positive NSCLC patients are underway (NCT03046992).

- Representative cases presented here demonstrate promising anti-tumor efficacy for both intracranial and extracranial lesions.

YH25448 is a promising novel 3rd generation EGFR TKI for patients with EGFR sensitizing or T790M resistant mutations.