Phase I study to evaluate the safety and to assess the food effect of HM781-36B, a novel pan-HER inhibitor continuously given in patients with advanced solid tumors

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Abstract #: 2565
2013 ASCO

Introduction

The function of EGFR family (EGFR/HER1/ErbB1, HER2/ErbB2/Erbb2, HER3/ErbB3, and HER4/ErbB4) is related with cell proliferation, migration, and survival. After receptor-specific ligand binding, the receptors form homodimers or heterodimers with each other, which leads to the activation of downstream signaling. The mutation or overexpression of EGFR and HER2 are observed in many human solid tumors. A strong correlation has been found between solid tumors with high levels of EGFR and HER2 and poor prognosis\(^1\).

EGFR specific tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib are widely used for EGFR mutant non-small-cell lung cancer (NSCLC). However, efficacy of the EGFR specific TKIs has been limited by drug resistance mechanism including T790M mutation of EGFR gene. Met amplification, and other secondary EGFR gene mutations (7p11.1, L747S, T845A)\(^2\).

In preclinical study, HM781-36B, an irreversible pan-HER inhibitor, showed potent growth inhibitory activity against mutated EGFRs, including EGFR\(^{L858R}\) and EGFR\(^{L858R/T790M}\) in both EGFR mutant NSCLC cell lines and xenograft models\(^3\). HM781-36B also showed potent in vitro and in vivo activities for HER2 amplified gastric/breast cancer models\(^4\).

In the previous 2-weeks on, 1-week off phase I study, the maximum tolerated dose (MTD) was determined as 24 mg/day. This phase I study with a continuous daily dosing schedule was conducted to determine the maximum tolerated dose (MTD), recommended dose (RD), and to evaluate the effect of food on pharmacokinetics (PK) and the antitumor activity in patients with advanced solid tumors.

Methods

This is an open label, multicenter, phase I study composed of dose escalation study and food effect study.

Eligible patients were 2 18 years of age with advanced malignancies refractory to standard therapies. HM781-36B was administered once daily on a 4-weeks-on schedule.

Dose escalation study: We used a standard 3+3 dose escalation design with MTD being as the maximum highest dose with DLTs in 1/6 or fewer pts in the first cycle using NCI-CTCAE(version 3.0). Dose levels were 12mg, 18mg, 24mg.

Dose effect study(2+2 cross over design): When RD was determined, pharmacokinetic characteristics of HM781-36B by food intake was evaluated after registering an additional eight subjects.

Results

Demographic

A total of 20 pts (median age: 55 years [range32-77], ECOG PS 0/1/2/8/12) were enrolled (5 NSCLC, 3 stomach cancer, 2 breast cancer, 6 colorectal cancer, 4 other cancers(2 common bile duct cancer, 1 pancreatic cancer and 1 esophageal cancer)); 12 in the dose escalation and 8 in the food effect study cohort. All pts were included in safety analysis. One pt with breast cancer is on treatment. Twelve pts were pretreated with 4 or more regimens (Table 1).

Safety

DLTs were evaluated in dose escalation pts. DLTs were G3 anorexia in 1 pt at 18 mg/day, G3 diarrhea in 1 pt, and drugs-related AE. The most common drug-related AEs were diarrhea, stomatitis, paronychia, rash, pruritus, and anorexia.

• Table 1. Patient demographics and characteristics (N=20)

Pharmacokinetics

For the food effect study, PK samples were collected up to 24 hrs on fasting or fed condition in 8 pts. There were slight decreases in peak plasma levels but did not result in a significant change in exposure to HM781-36 (Figure 2).

Table 5. PK parameters of HM781-36

Anticancer Activity

Among 20 evaluable pts, 4 achieved partial responses (PR)[1NSCLC, 2 breast cancer, 1 common bile duct cancer], and the response rate was 20%. Five pts had stable disease (SD). The median duration of treatment in pts with PR or SD was 15.42 weeks (range, 15-42). The median PFS was 8 wks (95% CI, 5.3-34.6;Table 4). Waterfall plot is shown in Figure 1.

Table 4. Tumor response

Conclusion

Continuous daily dosing schedule of HM781-36B is safe and well tolerated in advanced solid tumors.

It exerts anticancer activity without being influenced by food.

References