Optimal clinical dose-finding strategies: Translational pre-clinical pharmacokinetics, pharmacodynamics and efficacy analysis of HM61713, an orally selective EGFR mutant inhibitor

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Abstract:

**Introduction**

- HM61713 is a third-generation EGFR tyrosine kinase inhibitor that has been evaluated as a novel therapeutic agent for the treatment of non-small cell lung cancer with EGFR mutations.
- HM61713 showed excellent in vitro and in vivo activities in HCC827 harboring exon 19 deletion mutation as well as H1975 harboring L858R/T790M mutation with good selectivity over wild-type EGFR.
- PK/PD modeling approach was a well-recognized powerful tool that enables researchers to integrate the data from diverse assays and investigate the relationship between PK and PD of the drug. Translational research from pre-clinic to the clinic by application of this technique could provide a set of tools for the prediction of human dose.
- Integrated pharmacokinetic-pharmacodynamic-xenograft tumor model (PK-PD-XTG) was used to characterize the relationship between HM61713 plasma and tumor growth inhibition (TGI) in H1975 (T790M) resistant xenograft model.
- The clinical human exposures of HM61713 were used to drive the PK-PD-XTG model to simulate inhibition of phospho-EGFR and inhibition of tumor growth. Assuming that human tumors and PD markers behave in a similar way to those in mouse xenografts, these simulations suggest that a dose of 300-800 mg of HM61713 once a day would be efficacious in patients with advanced NSCLC harboring the EGFR activating and T790M resistant mutations.
- Currently, HM61713 is in phase 2 clinical studies for NSCLC patients with EGFR T790M after failure of the 1st generation EGFR TKIs as well as phase 2 clinical studies for EGFR TKI naive NSCLC patients with EGFR activating mutants.

**Method**

- Pre-clinical assessment: H1975 xenograft mice were received single or multiple oral dose of HM61713 (QD) for 3 months.
- HM61713 plasma concentration was measured using liquid chromatography tandem mass spectrometry (LC-MS/MS) assay.
- ELISA was used for the analysis of p-EGFR tyrosine modulation.
- Clinical assessment: Nine healthy volunteers received multiple oral dose of HM6173 300 mg or 800 mg for 24 days.
- Modeling and simulation assessment: PK/PD modeling and simulation were performed using PhoenixTM WinNonlin 6.1 (Pharsight, USA).
- Model Principle: One-compartmental model incorporating re-absorption compartment with first-order absorption/elimination was used. Efficacy modeling was processed by HM6173 free concentration using plasma protein binding (PPB) in H1975 xenograft model.
- Bio distribution model with baseline inhibition E<sub>0</sub> equation was applied to characterize the PD marker (p-EGFR) and tumor volume shrinkage was explained by michaelis-menten kinetics of p-EGFR<sup>-1</sup>.
- PD equation were represented.

**Results**

- Pharmacokinetics, pharmacodynamics, and efficacy analysis in H1975 xenograft model.
- Pharmacokinetic study in xenograft model.

**Translational Strategy**

- Developed xenograft mice PK-PD-XTG model and estimated PD parameters were used to simulate tumor volume shrinkage aspects in cancer patients.
- PK data of healthy volunteers was obtained from phase 1 clinical studies.
- The human PD response curve and the tumor growth inhibition plot were obtained by replicating the mice PK to human PK in our developed model.

**Conclusion**

- Pharmacokinetic-pharmacodynamic-xenograft tumor model (PK-PD-XTG) was developed to characterize the relationship between HM61713 plasma concentration - p-EGFR inhibition, and tumor growth inhibition (TGI) in H1975 xenograft model.
- The IC<sub>50</sub> value of p-EGFR based on xenograft model was 1.14 ng/ml for free p-EGFR conjugate.
- PK-PD study in H1975 xenograft model is good correlated with the observed efficacy in phase 1 clinical study.

- According to our simulated curve, we predicted appropriate human oral dose as (300-800 mg) and it would be an efficacious dose in patients with NSCLC harboring the EGFR activating and also with T790M resistant mutation.

**References**