Potent in vitro Activity of Tarloxotinib for EGFR and HER2 Mutations Refractory to Current EGFR Tyrosine Kinase Inhibitors

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Introduction

Mutant epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have become an important treatment option for non-small cell lung cancer (NSCLC) patients who harbor activating EGFR mutations. Following first-generation TKIs, erlotinib and gefitinib, approval of second-generation TKIs such as afatinib, ceritinib, osimertinib, and dacomitinib, which are more potent drug-protein adducts of the EGFR kinase domain, provided major progress in the treatment of EGFR-mutated NSCLCs. However, resistance acquired to TKIs, such as T790M resistant disease, is a major clinical challenge.

Tarloxotinib is a novel prodrug of tarloxotinib, a potent irreversible EGFR TKI. The objective of this study was to evaluate the in vitro efficacy of Tarloxotinib against EGFR and HER2 mutations resistant to current EGFR TKIs, including T790M and HER2 mutations, which are currently unmet needs.

Methods

Establishment of cell lines expressing mutant forms of EGFR or HER2

The human panel of cell lines (HPC) was generated as previously described.2,7,8,9,10,11-13 Cell lines were established using hormones in the presence of serum-free medium or serum supplemented medium, in the presence or absence of EGFR TKI for each drug, respectively.

Table 1. Characteristics of the HPC panel

Conclusion

This study demonstrates potent in vitro activity of Tarloxotinib against a broad variety of EGFR and HER2 mutations, including acquired resistance mutations. The potent in vitro activity of Tarloxotinib against these resistant mutations has the potential to generate a wide therapeutic window for clinical trials.

References