BLU-945, a highly potent and selective 4th generation EGFR TKI for the treatment of EGFR T790M/C797S resistant NSCLC

S.S. Schalm¹, T. Dineen¹, S.M. Lim², C-W. Park², J. Hsieh¹, R. Woessner¹, Z. Zhang¹, K. Wilson¹, M. Eno¹, D. Wilson¹, B. Williams¹, J. Campbell¹, C. De Savi¹, F. Stevison¹, C. Utt¹, T. Guzi¹, M. Dorsch¹, K. Hoeflich¹, B.C. Chul Cho³

¹ Biology, Blueprint Medicines - Global Headquarters, Cambridge, MA, USA, ² Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea, ³ Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

Background

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have changed the treatment landscape for EGFR-mutant (L858R and ex19del) driven non-small-cell lung cancer (NSCLC). T790M is the most prevalent acquired EGFR resistance mutation to treatment with 1st and 2nd generation TKIs. 3rd generation TKIs, such as osimertinib, were developed to treat patients with tumors driven by this mutation. The C797S mutation is the most significant on-target resistance mechanism to osimertinib, leading to EGFR T790M/C797S double-resistant mutants. There are currently no approved targeted therapies for NSCLC patients with T790M/C797S mutations. BLU-945 is designed to target and selectively inhibit the EGFR T790M/C797S and T790M resistant mutations.

Methods

BLU-945 activity on EGFR mutants and EGFR wild-type (WT) was tested in biochemical assays and cellular phosphorylation specific EGFR AlphaLisa assays. The in vivo anti-tumor activity of BLU-945 was evaluated in an NCI-H1975 cell line-derived tumor xenograft (CDX) model, as well as in osimertinib-resistant CDX- and patient-derived xenograft (PDX) models of NSCLC.

Results

BLU-945 inhibits EGFRex19del/T790M/C797S, EGFRL858R/T790M/C797S, EGFRex19del/T790M, and EGFRL858R/T790M mutants with sub-nanomolar IC₅₀ values in an enzyme assay with a >1000-fold window over EGFRWT enzyme activity. BLU-945 achieves potent EGFR pathway inhibition in NCI-H1975 EGFRL858R/T790M, Ba/F3 EGFRL858R/T790M/C797S, and Ba/F3 EGFRex19del/T790M/C797S cell lines and a large window relative to EGFRWT inhibition. Oral administration of BLU-945 to tumor-bearing mice demonstrated potent EGFR pathway inhibition and anti-tumor activity at well-tolerated doses in the subcutaneous NCI-H1975 CDX model, and osimertinib-resistant CDX and PDX models, as well as in the intracranial luc-H1975 model of NSCLC.

Conclusions

BLU-945 is a potent, selective, and orally available EGFR inhibitor that shows robust anti-tumor activity in osimertinib-resistant EGFR xenograft models. Because of its pharmacological activity and selectivity for mutant EGFR, BLU-945 has the potential to demonstrate activity in osimertinib-resistant EGFR-mutant NSCLC.

Legal entity responsible for the study

Blueprint Medicines.

Funding

Blueprint Medicines.

Disclosure
