Introduction

PI3Kα is highly mutated in cancer with the most prevalent mutation, H1047R, occurring in approximately 14% of breast cancers. This mutation causes hyperactivation of lipid kinase activity and downstream AKT signaling. Treatment-free-of-concept for targeting PI3Kα mutations was established with alpelisib, an allosteric PI3Kα inhibitor that is expected to antagonize wild-type and mutant forms. However, the therapeutic benefit of alpelisib is limited by the variability in drug responses among xenografts. ST814 is a potent PI3Kα selective allosteric inhibitor, with excellent drug-like properties and exceptional kinase and PI3Kα isoform selectivity. ST-814 has potent activity in cell-based target engagement and tumor cell growth assays and demonstrates robust anti-tumor activity in PIK3CA+ xenografts. ST-814 efficacy was superior to alpelisib at a dose level that excels the clinically relevant exposure. Importantly, ST-814 lacked metabolic dysfunction observed with alpelisib which caused profound insulin resistance.

Selective targeting of mutant PI3Kα improves efficacy

Results

ST-814 is a potent PI3Kα Selective Kinase Inhibitor

PI3K activity in PI3Kα hyperactivation of lipid kinase activity and downstream AKT signaling.

Efficiency and selectivity of ST-814 vs. alpelisib

Efficiency and selectivity of ST-814 vs. alpelisib

Conclusions

ST-814 is a potent and H1047X mutant-selective, allosteric PI3Kα inhibitor. It has exceptional selectivity against PI3Kα isoforms and the kinase. In cell assays, ST-814 selectively inhibits downstream signaling (pAKT) and tumor cell growth of H1047X mutant cell lines. ST-814 is active across a spectrum of PI3Kα-resistant CDX models and tumor types, while sparing metabolic dysfunction and achieving efficacy that is superior to alpelisib at clinically relevant exposures.

References

Fitch 2014, Molecular Cancer Therapeutics 13 1920
NSCLC Multi-disciplinary Review and Evaluation (21.26820) Document (Pipix, Alpelisib)
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Re-curreding PI3Kα mutations were tested for K96R PEase activity using ATP assays (Promega). ST-814-induced phosphorylation was calculated relative to the K96R value in each experiment.