Background: c-MET is a receptor tyrosine kinase that is located on the cell surface and is activated by the binding of its ligand, hepatocyte growth factor (HGF). In cancer cells, MET can be aberrantly activated and cause numerous signaling pathways to become upregulated, angiogenesis, and metastasis. In vitro studies have demonstrated that Bozitinib (CBT-101, Pl-101, CBT-3101) is a highly selective and specific inhibitor of c-MET and PTPRZ. Methods: In vitro studies of proliferation in cancer cell lines (MKN45, lung LI568, H1993, LUM, and LI569), hepatocellular carcinoma (HCC, HCCLM3), and glioblastoma (C6) with Bozitinib (0.01 to 100 μM) compared to the positive control (c-MET inhibitor) or vehicle control (Acacia (10%)). In vivo, the antitumor activity of Bozitinib was observed in BT-474 (PTPRZ high and c-MET positive). Results: In vitro studies showed that Bozitinib significantly inhibited the growth of cancer cell lines (MKN45, LG1201, H1993, LI568, and LI569) in a dose-dependent manner. In the BT-474 model, Bozitinib demonstrated robust activity in vivo, with a significant decrease in tumor volume and inhibition of tumor growth compared to the control group. Conclusions: Bozitinib is a highly selective c-MET inhibitor with strong inhibitory action on tumor growth in cell lines and patient derived models at doses that were well tolerated with no animal death or major weight loss. The in vivo experiments demonstrated that Bozitinib is a viable candidate with effective anti-tumor activities. Bozitinib is currently under evaluation in Phase I/II trials in lymphoma (NCT03386321) and in PTPRZ-MET fusion gene positive high grade glioma (NCT02729216) with additional trials planned.

Figure 1: Selectivity of CBT-101 to Kinases

Figure 2: Inhibitory Effect of CBT-101 and Other c-MET Inhibitors on Intracellular c-MET

Figure 3: MKN45 Gastric HuPrime® c-MET amplified, HGF Independent

Figure 4: LU1901 Lung HuPrime® c-MET Amplified, EGFR Wild Type

Figure 5: Results

Figure 6: LU1901 Lung HuPrime® c-MET Amplified, EGFR Wild Type

Table 1: Inhibitory Effect of CBT-101 and Other c-MET Inhibitors on Intracellular c-MET

Table 2: Inhibitory Activity of CBT-101 in Cancer Cell Lines

Table 3: PK/PD of CBT-101 in Cancer Cell Lines

Table 4: In Vivo Tumor Growth Inhibition of CBT-101 in Cancer Models

Table 5: PK Parameters of CBT-101 in Cancer Models

Conclusions

Bozitinib is a highly selective c-MET inhibitor with strong inhibitory action on tumor growth in cell lines and patient derived models at doses that were well tolerated with no animal death or major weight loss. GLP safety studies have been completed in rat and dog. Bozitinib is currently under evaluation in c-MET dysregulated NCLC (NCT02862212) and in PTPRZ-MET fusion gene positive high grade glioma (NCT02792610) in People’s Republic of China. An Investigational New Drug submission in the United States is planned with a Phase 1b/2b clinical trial initiation in 2017.

Further Information

References


Bozitinib, a highly selective inhibitor of c-MET, demonstrates robust activity in gastric, lung, hepatic and pancreatic in vivo models

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