Abstract 2096

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

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Updated Abstract

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 active and cause abnormal signaling, which leads to tumor growth, angiogenesis, and metastasis. In vitro studies have demonstrated that bozitinib (CBT-101, PLB-1001, CBI-3103) is a highly selective and specific inhibitor (8 nM) of tumor cell proliferation. **Methods**: In-vivo PD studies of gastric (MKN45), lung (LUM858, LU1901, LU2503), hepatic (LIM0612, LIM0801), and pancreatic (KP4) were evaluated. These models covered both the HGF-dependent and HGF-independent mechanisms. Among these models, LUM858, LU1901, LU2503, LIM0612 and LIM0801 are PDX models. In particular, in the LU1901 model, bozitinib (BT) was compared to capmatinib (INC280). Groups included: BT at 1, 3 and 10 mg/kg QD×21 and INC280 at 1, 3, and 10 mg/kg QD×21 and 10 mg/kg BID×21 via IG, CDDP 5 mg/kg, Q7D×3 as a positive control via IP and the vehicle control (QD×21 via IG). Each group (n=8 mice) and the tumor volume was evaluated on D21. **Results**: In MKN45, LU2503, LIM0612 and LIM0801, the effect of BT seemed superior than that of crizotinib; in LUM858, its effect was higher than that of erlotinib; in LU1901, its effect was higher than that of crizotinib and INC280. In the LU1901 model, the strongest activity was observed at BT 10 mg/kg with a T/C ratio of 2%, compared to an equi-dose of INC280 (T/C of 22%). All doses of BT and INC280 were well tolerated; no mouse experienced weight loss. In MKN45 model, BT showed a PK/PD correlation and dose-dependence. BT inhibited the phosphorylation of c-Met protein; the rate of target inhibition exceeded 90% at >7 mg/kg. The plasma concentration for BT decreased over time with a significant decrease 16h after its administration, conferring at least 16h of phosphorylation inhibition of the c-MET protein. **Conclusions:** In conclusion, BT was well-tolerated, with no animal death nor major weight loss. The in vivo experiments demonstrated that BT is a viable candidate with effective anti-tumor activities. BT is currently under evaluation in c-MET dysregulated NSCLC (NCT02896231) and in PTPRZ1-MET fusion gene positive high grade gliomas (NCT02978261) with additional trials planned.

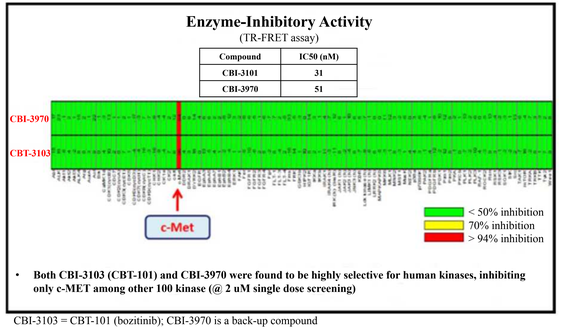
MET Targeted Therapies[1]

Agent	Target	Company	Status (MET + target indications)
Crizotinib (PF-02341066)	ALK/ROS/MET	Pfizer	Phase 2 (NSCLC, GC, UC, pRCC)
Capmatinib (INC280)	MET	Novartis	Phase 2 (NSCLC, HCC, pRCC, CRC, HNSCC)
SAR125844	MET	Sanofi	Phase 2 (NSCLC)
Cabozantinib (XL184)	MET/RET/others	Exelixis	Phase 2 (NSCLC)
Glesatinib (MGCD265)	MET/AXL/others	Mirati	Phase 2 (NSCLC)
Tepotinib (MSC2156119J)	MET	Merck KGaA	Phase 2 (NSCLC, HCC)
Merestinib (LY2801653)	MET/ROS1/AXL/FLT 3/others	Eli Lilly	Phase 2 (NSCLC)
AMG337	MET	Amgen	Phase 1 (GC, ST)
Savolitinib (AZD6094, volitinib)	MET	Astra Zeneca	Phase 1 (pRCC, GC, NSCLC)
Sitravatinib (MGCD516)	MET/VEGFR/others	Mirati	Phase 1 (NSCLC, ST)
Emibetuzumab (LY2875358)	MET	Eli Lilly	Phase 2 (NSCLC, GC)
Ficlatuzumab (AV-299)	HGF	AVEO	Phase 2 (NSCLC), Phase 1 (HNSCC)

CRC=colorectal; GC=gastric; HCC=hepatic, HNSCC=head/neck squamous cell, pRCC=papillary renal cell, ST=sold tumors; UC=urothelial cancer

Results

Figure 1: Selectivity of CBT-101 to Kinases



- **Both CBI-3103 (CBT-101) and CBI-3970 were found to be highly selective for human kinases, inhibiting only c-MET among other 100 kinase (@ 2 uM single dose screening)**

CBI-3103 = CBT-101 (bozitinib); CBI-3970 is a back-up compound

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

Compound	CBT-101	Crizotinib	Capmatinib (INC280)
IC_{50} (nM)	0.52	174	0.039

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

Cell Line	LU1901	EBC-1	MKN45
IC_{50} (nM)	5.8	12.2	14.3
Cell Line	**LI0612**	**H1993**	**KP4**
IC_{50} (nM)	17	18.6	176

LI0612, LU1901: lung cancer cells of the HuPrime® origin; LI0612: liver cancer cell of the HuPrime® origin; H1993 and EBC-1: human lung cancer cell lines; MKN45 and KP4 are gastric and pancreatic cancer cell lines, respectively

Figure 2: Dose Dependent Phosphorylation of c-MET in MKN45 Gastric HuPrime®

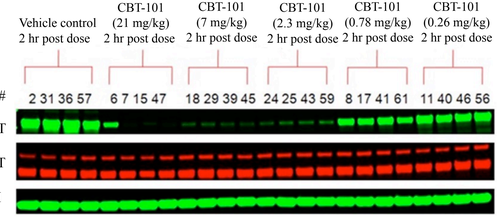


Figure 3: MKN45 Gastric HuPrime® c-MET amplified, HGF-Independent

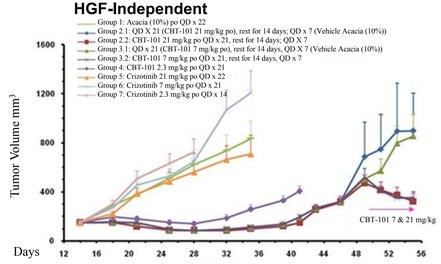


Figure 4: LIM0612 Hepatic HuPrime® c-MET amplified, HGF-Independent

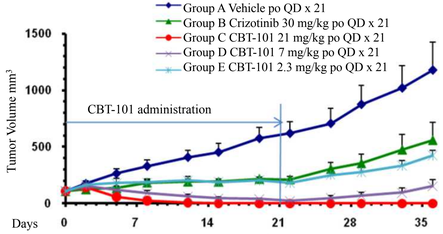


Figure 5: KP4 Pancreatic HuPrime® c-MET amplified, HGF-Dependent

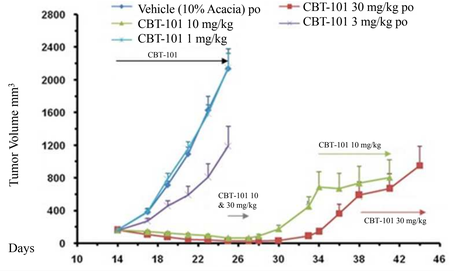
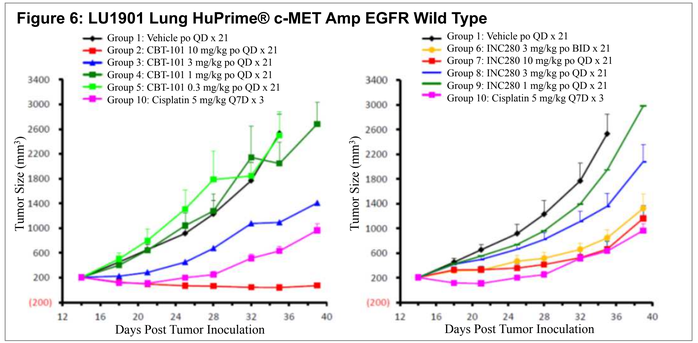


Figure 6: LU1901 Lung HuPrime® c-MET Amp EGFR Wild Type



Conclusions

Bozitinib is a highly selective c-MET inhibitor with strong inhibition of tumor growth in cell lines and patient derived models at doses that were well tolerated with no animal death nor major weight loss. GLP safety studies have been completed in rat and dog. Bozitinib is currently under evaluation in c-MET dysregulated NSCLC (NCT02896231)[2] and in PTPRZ1-MET fusion gene positive high grade gliomas (NCT02978261)[2] in People's Republic of China. An Investigational New Drug submission in the United States is planned with a Phase1a/1b multi-center trial initiation in 2017.

References

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2. www.clinicalcaltrials.gov (accessed: 22 March 2017).

Further Information

Please email gavin.choy@cbtpharma.com or visit website at www.cbtpharma.com for a PDF version of the poster presentation.

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