CBT-102, an oral multi-kinase small molecule, demonstrates favorable activity in LIMsh050 and PLCPRF5 human hepatocellular carcinoma animal models and cardiac safety in rabbit Purkinje and Beagle dogs compared to sorafenib

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Background

Cancer is a complex disease involving disruption of more than one receptor or signaling pathway. Inhibiting multiple oncogenic targets have been shown to be an important strategy in managing relapse and resistance. CBT-102 is an oral multi-targeted kinase inhibitor (mTKI) inhibiting several key oncogenic drivers including angiogenesis via VEGFR and PDGFR, MAPK pathway via bRAF and cRAF, in addition to inhibiting RET, CSF1R and c-KIT.

Tumor regressions were observed in fifty-two patient derived xenograft (PDX) models including gastric, colorectal, esophageal and lung cancers. Antitumor activity of CBT-102 was compared to sorafenib in two human primary HCC carcinoma xenografts in nude mice (LIMsh050 and PLCPRF5) and cardiac safety was evaluated in rabbit heart Purkinje fibers and in awake telemetered Beagle dogs. CBT-102 demonstrated superior efficacy in HCC xenografts models compared to sorafenib and does not appear to have the cardiac liability observed with sorafenib.

In Vitro Characteristics

Table 1: CBT-102 in vitro activity

	IC50				
	Enzymatic Assays			Cellular Assays	
	bRaf	cRaf	VEGFR	ERK phosphorylation	PLC-PRF-5 anti-proliferation
Sorafenib	60 nM	41 nM	13 nM	37 nM	3.9 µM
CBT-102	41 nM	24 nM	14 nM	23 nM	6.7 µM

Figure 1a: bRaf kinase assay

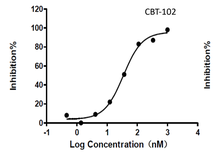


Figure 1b: cRaf kinase assay

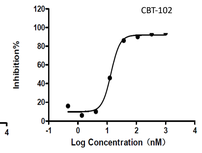
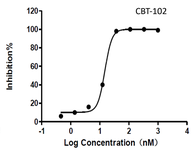
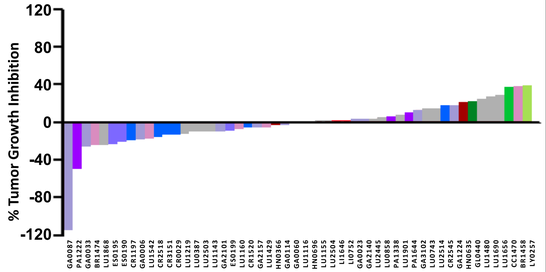


Figure 1c: VEGFR kinase assay



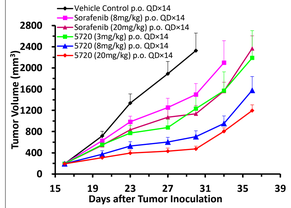
Pre-Clinical Rationale

Figure 2: Waterfall plot of tumor regressions in fifty-two PDX models including gastric, colorectal, esophageal and lung cancers



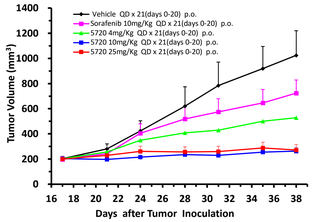
Female Balb/C nude mice were injected subcutaneously in the flank region with human primary cell lines, LIMsh050 and PLCPRF5 cells to establish the tumor models. Mice were randomized at ~200 mm^3. Vehicle, sorafenib and CBT-102 were dosed orally daily to tumor bearing mice. Tumor volumes were measured twice weekly using calipers. Percent tumor growth inhibition was calculated using the formula %TGI = [(meanTVcontrol – meanTVtreated) / meanTVcontrol] x 100. In the LIMsh050 model, CBT-102 was administered orally QD x 21 days at 4, 10, and 25 mg/kg and sorafenib at 10 mg/kg (n=8/group). In the PLCPRF5 model, CBT-102 was administered orally QD x 14 days at 3, 8, and 20 mg/kg vs. 8 and 20 mg/kg sorafenib group (n=7/group). In both experiments, in addition to tumor volume, body weight and mortality were monitored.

Figure 3: Antitumor activity in human primary HCC PDX model PLC-PRF-5



Experimental group	Tumor volume (Mean ± SD)	%TGI	p-value (compared to control group)
Control	2,328 ± 330	--	--
Sorafenib 8 mg/kg	1,500 ± 207	37	0.008
Sorafenib 20 mg/kg	1,137 ± 154	53	<0.001
CBT-102 3 mg/kg	1,232 ± 233	52	<0.001
CBT-102 8 mg/kg	706 ± 110	72	<0.001
CBT-102 20 mg/kg	473 ± 53	81	<0.001

Figure 4: Antitumor activity in human primary HCC PDX model LIMsh050



Experimental Group	Tumor volume (Mean ± SD)	%TGI	p-value (compared to control group)
Control	1024 ± 195	--	--
Sorafenib 10 mg/kg	724 ± 104	29	0.665
CBT-102 4 mg/kg	528 ± 111	48	0.246
CBT-102 10 mg/kg	263 ± 29	74	0.033
CBT-102 25 mg/kg	272 ± 43	73	0.035

Cardiac Safety Studies

CBT-102 safety assessment on action potential duration (APD90) in rabbit heart Purkinje fibers

Three doses of CBT-102 (1, 3, 10 µM), sorafenib (10 µM), vehicle (Tyrode's solution + 0.1% DMSO) and positive control (dofetilide (0.3 µM) (data not shown) were tested for effects on various action potential (AP) parameters in acutely isolated rabbit heart Purkinje fibers.

Vehicle did not influence AP parameters of rabbit heart Purkinje fibers. CBT-102, up to 10 µM, did not significantly influence the AP parameters of rabbit heart Purkinje fibers. The positive control and sorafenib, significantly prolonged APD40, APD60 and APD90 duration at 0.5 Hz and 1 Hz (data not shown) stimulation ($p < 0.05$).

Figure 5a: Vehicle controls and sorafenib effects on action potential

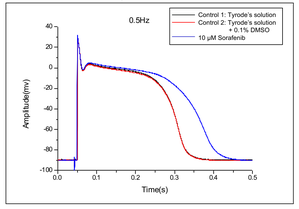


Figure 5b: Vehicle controls and CBT-102 effects on action potential

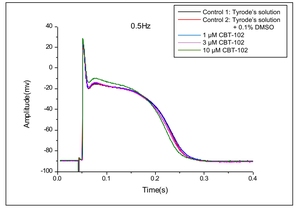


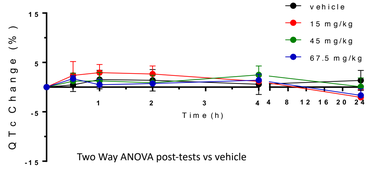
Table 2: CBT-102 IC50 on whole cell hERG current

Compound	IC50(uM)	HillSlope	Number of Cells
Amitriptyline	3.66	1.19	3
CBT-102	> 10.00	-	2

CBT-102 cardiac safety assessment on telemetry ECG in awake Beagle dogs

Adult male Beagle dogs N=6, age 6-12 M, BW 9-13 kg were implanted with electrodes and treated with vehicle or CBT-102 at 15, 45 and 67.5 mg/kg and recorded for ECG. CBT-102 did not show significant influence on HR, RR interval, PR interval, QRS interval, (data not shown) QT and QTc at 15, 45, 67.5 mg/kg in Beagle dogs.

Figure 6: Percent QTc change in awake Beagle dogs to CBT-102



Two Way ANOVA post-tests vs vehicle

Summary

CBT-102 inhibits angiogenesis via VEGFR, PDGFR and MAPK pathway via bRAF and cRAF. It has a unique kinase selection profile with inhibition of several other key immuno-oncogenic drivers (c-KIT, RET and CSF1R).

Tumor regressions were observed in fifty-two PDX models including gastric, colorectal, esophageal and lung cancers. CBT-102 demonstrated improved efficacy in HCC xenograft models compared to sorafenib.

CBT-102 does not have cardiac liability observed with sorafenib. CBT-102 (1 to 10 µM) does not have significant influence on AP of heart Purkinje fibers. CBT-102 also did not demonstrate significant influence on QT and QTc at 15, 45, 67.5 mg/kg in Beagle dogs.

CBT-102 is currently being evaluated in toxicology studies with a potential IND filing planned in 2H 2018. A Phase 1/2 study is planned for 2019.

Contact / Further Information

Please visit CBT Pharmaceutical's website at www.cbtpharma.com for a PDF version of the poster presentation.

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American Association for Cancer Research (AACR) Annual Meeting 2018, April 14–18, 2018, McCormick Place, Chicago, IL