CBT-502 (TQB2450), a novel anti-PD-L1 antibody, demonstrates favorable activity in MC-38/H-11 murine colon and A375 human melanoma animal models

Abstract No. A200

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Background

CBT-502 (TQB2450) is a novel humanized IgG1 antibody against programmed cell death-ligand 1 (PD-L1) developed by CBT Pharmaceuticals, Inc. and CTTQ. CBT-502 shows significant sequence divergence in CDRs from other anti-PD-L1 antibodies in the market today including atezolizumab[1], durvalumab[2] and avelumab[3]. Several human cancer cells express high levels of PD-L1. PD-L1 binds to its receptor, PD-1 on activated T cells, CD80 on dendritic cells and monocytes and inhibits cytotoxic T cells. Therapeutic blockade of PD-L1 reduces the growth of tumors in the presence of immune cells.

In-Vitro Characteristics

- Binding affinity to human PD-L1 (SPR) Kd ~ 250 pM
- Binds to Cyno PD-1 Kd ~ 240 pM; not to mouse or rat PD-L1
- Significant sequence divergence in complementarity-determining regions(CDRs) from Genentech, AZ and BMS anti-PD-L1 Abs
- Binds to cell surface PD-L1 EC50 370 pM
- Blocks PD-L1 binding to PD-1 and CD80
  IC50 (PD-1) ~47.97 pM
  IC50 (CD80) ~1000 pM
- No binding with human PD-L2, CD28, ICOS, CTLA4
- No Fc receptor activity

Figure 1. CBT-502 binds to PD-L1-293T cells

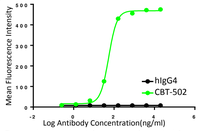
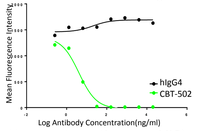


Figure 2. CBT-502 inhibits PD-1 binding to PD-L1-293T cells



- Dose dependent increase in cytokine production in mixed lymphocyte reaction assay (MLR) with allogeneic dendritic cells (DC)

Figure 3. Effect of CBT-502 on IL-2 (3A.) and IFNγ (3B.) production in MLR assay with allogeneic DC

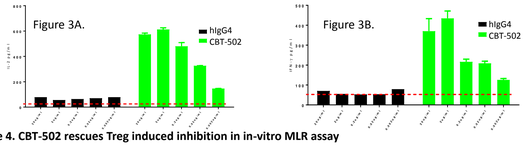
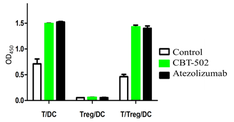


Figure 4. CBT-502 rescues Treg induced inhibition in in-vitro MLR assay



- CBT-502 and atezolizumab rescue Treg induced inhibition in in-vitro MLR assay

In-Vivo Efficacy Studies

Efficacy of CBT-502 in Mice Subcutaneously Transplanted with MC-38/H-11 Cells

Method: MC-38/H-11 is a mouse colon cancer cell line with mouse PD-L1 deleted by CRISPR/Cas9 technique and transformed to highly express human PD-L1. Fifty C57BL/6 mice were subcutaneously (SC) inoculated with 1×10^5 MC-38/H-11 cells and randomly divided into five groups. The test article was injected intraperitoneally (IP) with 1.5, 5 and 15 mg/kg once every other day (Q2D), positive control (atezolizumab) was administered IP at 15 mg/kg, and negative control (human IgG) was injected IP at 15 mg/kg.

Figure 5. Effect of CBT-502 in MC-38/H-11 syngeneic mouse model

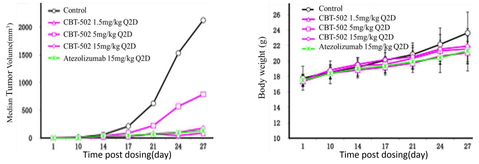


Table 1. Effect of CBT-502 in MC-38/H-11 syngeneic mouse model

Group	Drug administration	Dose(mg/kg)	Tumor volume(mm³)	Tumor growth inhibition(%)
Human IgG	Q2D×11	15	2126.7	-
CBT-502		1.5	88.6	95.8
		5	787.4	63.0
		15	176.7	91.7
Atezolizumab		15	132.0	93.8

Efficacy of CBT-502 in Transgenic Mice (Human PD-1) Subcutaneously Transplanted with MC-38/H-11 cells

Method: 10 Pdcd1-KI mice were SC inoculated with 1×10^6 MC-38/H-11. After the tumor grew to about 100 mm^3, the mice were randomly divided into two groups. The test article was injected IP with 1.5 mg/kg CBT-502 and the negative control (human IgG) was injected at 1.5 mg/kg Q2D.

Figure 6. Effect of CBT-502 in MC-38/H-11 transgenic mouse model

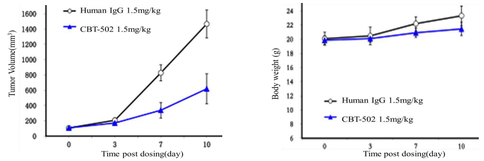


Table 2. Effect of CBT-502 in MC-38/H-11 transgenic mouse model

Group	Drug administration	Dose(mg/kg)	Mean tumor volume(mm³)	Tumor growth inhibition(%)
Human IgG	Q2D×4	1.5	1466.4	-
CBT-502		1.5	618.4	62

Efficacy of CBT-502 in Mice Subcutaneously Transplanted with A375 Human Melanoma Cells

Method: A375 human melanoma cells (5 x 10^6) were implanted SC in the flank region of highly immune-deficient mouse (NCG mouse, n=36). The mouse immune system was replaced with human PBMC. Only mice with high CD45 ratio are included in the study. CBT-502 was dosed IP at 5 and 10 mg/kg once weekly (qw) and three times weekly (tiw), and atezolizumab was dosed 10 mg/kg (tiw).

Figure 7. Effect of CBT-502 in A375 NCG mouse model

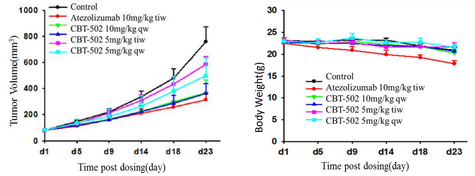


Table 3. Effect of CBT-502 in A375 NCG mouse model

Group	Dose (mg/kg)	Frequency	Tumor volume (mm^3) D1	Tumor volume (mm^3) D23	Tumor Inhibition (%)
Control	-	-	80 ± 8	759 ± 113	-
Atezolizumab	10	tiw	80 ± 11	314 ± 52**	59.44
CBT-502	10	tiw	81 ± 6	367 ± 100*	56.50
	10	qw	81 ± 10	363 ± 73*	53.47
	5	tiw	81 ± 11	585 ± 59	22.69
	5	qw	81 ± 9	497 ± 134	45.83

Pharmacokinetics

Table 4. Pharmacokinetics parameters for CBT-502 in Cynomolgus monkeys

Dose (mg/kg)	C_{max} (μg/mL)	AUC_{0-t} (μg·h/mL)	AUC_{0-inf} (μg·h/mL)	$T_{1/2}$ (h)	CL (mL/h/kg)	V_d (mL/kg)
1	18.4 ± 1.7	1346.7 ± 387.6	1353.4 ± 388.5	51.6 ± 18.5	0.79 ± 0.2	54.8 ± 9.5
10	210.3 ± 29.9	22574.3 ± 4303.9	22639.8 ± 4355.7	67.2 ± 18.2	0.46 ± 0.1	43.5 ± 11.3
60	1305.8 ± 120.7	158877.8 ± 45668.5	173409.7 ± 68044.5	150.5 ± 96.3	0.39 ± 0.1	72.4 ± 25.7
10 (qw×4)	223.3 ± 35.6	68752.0 ± 31178.7	70300.5 ± 34058.7	130.9 ± 82.1	0.73 ± 0.1	535.4 ± 269.5

C_{max} = maximum concentration; AUC = area under the curve; $T_{1/2}$ =half-life; CL = clearance, V_d = volume of distribution

Conclusions

In vitro, CBT-502 demonstrated binding affinity to human PD-L1 by SPR of 250 pM and cyno-PD-L1 of 240 pM. In cell based assay, CBT-502 effectively blocked the interaction of hPD-1 and hPD-L1 (IC_{50} 47.97 pM); and blocked binding of PD-L1 with CD80 (IC_{50} 1.09 nM). CBT-502 strongly activates T cells as measured by IFN-gamma production in a mixed lymphocyte reaction assay. CBT-502 demonstrated no binding with human PD-L2, CD28, ICOS and CTLA4. There was no Fc receptor activity.

In-vivo efficacy and safety data in the A375 model compared favorably to atezolizumab, with the MC-38 model confirming activity of CBT-502. Tumor growth inhibition (TGI) % at 10 mg/kg tiw was 53.5% and 59.4% for CBT-502 and atezolizumab, respectively. There was no obvious loss of body weight (BW) with administration, although a slight reduction in body weight was observed with atezolizumab 10 mg/kg tiw. In the MC-38/H-11 model, relative to atezolizumab, CBT-502 demonstrated comparable TGI rates, 91.7% versus 93.8% in the 15 mg/kg dose group and further demonstrated potent activity (TGI 62%) in MC-38/H-11 transgenic mouse model. In Cynomolgus monkeys, serum drug exposure level is significantly dose-dependent, and CBT-502 exhibits linear pharmacokinetic characteristics.

Pre-clinical pharmacodynamics and toxicology (data not shown) studies of CBT-502 demonstrated pharmacological activity and is well tolerated at effective doses with a wide margin of safety.

With these promising preclinical data, CBT Pharmaceuticals and its China partner CTTQ, plan to develop and evaluate CBT-502 in multiple solid tumors, anticipated in 2018.

References

1. Tencentriq® (atezolizumab) injection, prescribing information, April, 2017
2. Imfinzi™ (durvalumab) injection, prescribing information, April 2017
3. Bavencio (avelumab) injection, prescribing information, March 2017

Acknowledgements

Sarath Kanekal, PhD, DABT, RAC; Mike Li, MS, CBT Pharmaceuticals, Inc.

Further Information

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

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AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, October 26–30, 2017, Philadelphia, Pennsylvania