KDDF
Korea Drug Development Fund

Asset #34
Cancer Research Horizons

CDC7 Inhibitors

Therapeutic Area	Oncology	**Indications**	Cancer
Modality	Small Molecule	**Development Stage**	Pre-clinical

Overview

Background

- Cell division cycle 7-related kinase (CDC7) is a nuclear serine/threonine kinase that is of critical importance to the regulation of normal cell cycle progression during the G1 to S transition. CDC7 is a highly explored cancer target owing to its potential to selectively induce apoptosis in cancer cells. CDC7 overexpression is correlated with poor clinical outcomes in several cancers, and it has been identified in 50% of human cancer cell lines tested, correlated strongly with TP53 overexpression (Bonte et al., 2008, Neoplasia). However, a clear disease position for inhibiting CDC7 is yet to be robustly identified.

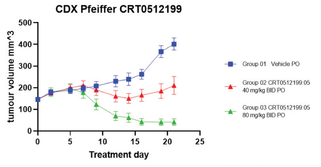
Technology Advantages

- Potent, selective and orally bioavailable CDC7 inhibitor
- Demonstrated target engagement in vivo in tumour models
- Potent tumor inhibition in DLBCL and renal xenograft models
- Favourable PD, PK and toxicology, with low predicted human efficacious dose

Key Data

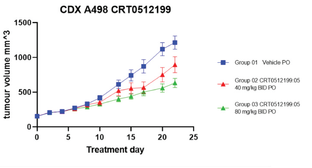
Lead compounds demonstrated potent tumour inhibition (TGI) in in nod/scid mice

A



Pfeiffer 21 days	40 mg/kg BID		p value	80 mg/kg BID		p value
	TGI[1]	TGI[2]		TGI[1]	TGI[2] PR	
D9	8	29	ns	41	138 16	<0.05
D12	30	83	ns	70	191 52	<0.05
D14	37	96	ns	74	191 58	<0.05
D16	37	83	ns	84	189 71	<0.05
D19	50	83	<0.05	89	147 71	<0.05
D21	48	75	<0.05	90	141 71	<0.05

B



A498 23 days	40 mg/kg BID		p value	80 mg/kg BID		p value
	TGI[1]	TGI[2]		TGI[1]	TGI[2]	
D15	25	32	ns	41	52	<0.05
D17	35	43	<0.05	42	52	<0.05
D20	33	38	<0.05	50	58	<0.05
D22	26	30	ns	48	55	<0.05

[1]- %TGI =(1-T/T1)*100
[2]- %TGI = (1-(Tf1/T0) / Cs/C0)) / 1-(C0/C0)) X 100
Percent Regression PR = (T0-Tf1/T0)x 100

(A) A498 SC xenograft (renal cancer) showed 55 TGI after 22 treatment days. (B) Pfeiffer SC xenograft (DLBCL) showed 141% TGI after 21 treatment days. (C) Well tolerated at 40mg/kg and 80mg/kg p.o with no treatment related deaths.

Pre-candidate molecule profiles: Pharmacodynamics

C

Molecule ID	CRT'2199	CRT'2000
Potency		
Enzyme IC_{50}	4 nM	4 nM
CTG Phenotypic (SW48) EC_{50}	371 nM	1.3 µM
CTG Phenotypic (COLO205) EC_{50}	399 nM	1.1 µM
Biomarker (SW48, pMCM2 ELISA, SAP93) EC_{50}	76 nM	202 nM
ADME		
PPB (% Bound)	86.3 (m), 93.8 (h)	20 (m) 50 (h)
Permeability (Caco-2)	P_{A-B}: 7.3x10^{-6} cm/s P_{B-A}: 46.7x10^{-6} cm/s ER: 6.4	PA-B: 1.2x10-6 cm/s PB-A: 21.4x10-6 cm/s ER: 18.4
CYP450s	IC_{50} ≥ 25 µM for all isozymes	IC_{50} ≥ 25 µM for all isozymes

(D) Lead compound CRT'2199 and backup CRT'2000 deliver potent, orally bioavailable CDC7 inhibition.

(E) Lead compound CRT'2199 and backup CRT'2000 deliver potent CDC7 inhibition with favourable PK and low toxicity and a low predicted human dose.

Pre-candidate molecule profiles: Pharmacokinetics

D

Molecule Identity	CRT'7461	CRT'2199	CRT'2000	LY3177833
Pharmacokinetics: SD male rats, 1 mg/kg IV, 3 mg/kg PO				
Cl b mL/min/kg	6	3	20	10
T1/2 h	5.6	5.6	5.7	3.7
Vss L/kg	0.9	0.5	1.7	2.7
%F po	53	38	39	174
PD Biomarker				
In vitro potency SW48, pMCM2 ELISA (SAP93) EC_{50}	135 nM	76 nM	202 nM	1.4 µM
PK/PD in mouse xenografts				
In vivo free EC_{50} nM / 24 h % Inh Colo205 model SW48 model	115 / nd 39 / nd	2 / 83% 67 / 65%	12 / 74% 70 / 84%	nd / 88% 610 / nd
Estimated Human Pharmacokinetics: single species allometry from rat and free concentration ≥ free EC90				
Cl b mL/min/kg	Not testsd	0.7	4.9	2.4
T1/2 h	Not testsd	7.9	4	12.8
Vss L/kg	Not testsd	0.5	1.7	2.7
%F po	Not testsd	38	39	100
Predicted human efficacious dose				
Based on free MEC *ca. in vivo* Colo205 free EC_{90}	Not testsd	**64 mg QD 17 mg BID**	**120 mg BID**	nd
Based on free MEC *ca. in vivo* SW48 free EC_{90}	Not tested	557 mg BID	690 mg BID	1470 mg BID

IP Status & Publication(s)

Intellectual Property

Patent Number
US 10919896 B2 (2021.02.16)
US 11020396 B2 (2021.06.01)

Patent Family
PCT, US, EP, JP, CN, CA, AU
PCT, US, EP, JP, CN, CA, AU

Publication(s)

-