CCS1477: A novel small molecule inhibitor of p300/CBP for the treatment of acute myeloid leukaemia and multiple myeloma

CellCentric

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Introduction

- E1A binding protein (p300) and CREB binding protein (CBP) are two closely related histone acetyl transferase proteins with oncogenic roles in acute myeloid leukemia (AML) and multiple myeloma (MM)
- CCS1477 is a potent, selective and orally bioavailable p300/CBP bromodomain inhibitor, currently in Phase I/II clinical trials
- Here we report the pre-clinical characterization of CCS1477 and its therapeutic application in AML and MM

3. CCS1477 causes tumour regression in a xenograft model of multiple myeloma (OPM-2); continued inhibition following drug withdrawal



1. CCS1477 is a potent and selective inhibitor of p300/CBP bromodomains



	CCS1477	
p300/CBP Kd (nM)	1.3 / 1.7	
BRD4 Kd (nM)	222	
Selectivity	170	
Bromoscan @ 1µM; 32 bromodomains (% control)	BRD4 (18%); BRD1/2/3/T (15-43%) WDR (33%)	

2. CCS1477 is a potent inhibitor of proliferation in a panel of multiple myeloma and AML cell lines in vitro



4. CCS1477 inhibits proliferation in lenalidomide resistant cell lines

A) Intrinsic resistance

	Cell Line	Lenalidomide GI50 (µM)	CCS1477 GI50 (μM)
Lenalidomide resistant	RPMI-826	>10	0.006
	LP1	>10	0.006
	KMS-11	>10	0.041
Lenalidomide sensitive	OPM-2	0.102	0.005

Lenalidomide resistant and sensitive cells lines were treated with CCCS1477 for 5days. Proliferation was measured by CellTiter Glo

5. Superior efficacy and combination benefit of CCS1477 with standard of care therapies for multiple myeloma



Time (days)

B) Acquired resistance



cMYC

🗖 IRF4

Tumour cMYC and IRF4 gene expression by qPCR at day 6 of treatment

Lenalidomide resistant OPM-2 cells were generated following continuous and increasing exposure to Lenalidomide for >6 months. Proliferation was measured by CellTiter glo

CCS1477 CCS1477+0.3uM Len CCS1477+1.0uM Le . _ _ _ _ _ _ _ _ _ _ 10⁻⁶ 10⁻⁵ 10⁻⁴ гм1 Proliferation measured by CellTier Glo in OPM-2 cells treated with CCS1477 +/- lenalidomide for 72h Vorinostat Vehicle_ (50mg/kg CCS1477 (5mg/kg CCS1477+

20

25



OPM-2 bearing athymic nude mice treated by oral gavage with CCS1477 once daily and standard of care therapies, alone or in combination





Fucci flow analysis of THP-1 cell cycle following incubation with DMSO vehicle or CCS1477 (100nM) for 48 hrs

7. Tumour regression after CCS1477 treatment in a xenograft model of AML (MOLM-16): continued inhibition following drug withdrawal



Summary

Conflict of interests: Nigel Brooks and Neil Pegg are employees and Copies of this poster obtained through Quick Response (QR) stockholders in CellCentric Ltd. There are no relationships to disclose Code are for personal use only and may not be reproduced without permission from the author of this poster. for Meera Raja, Barbara Young, Gary Spencer or Tim Somervaille.



Flow cytometry analysis of differentiation markers (CD86 and CD11b) in patient derived cells following treatment with DMSO vehicle or CCS1477 (100nM) for 7 days

B)

A) CCS1477 given by oral gavage once daily to MOLM-16 bearing athymic nude mice



B) Impact on cMYC gene expression at d21 of treatment (5 & 10mg/kg) and at d38 following drug withdrawal at 20mg/kg

• CCS1477 is a potent and selective small molecule inhibitor of the bromodomain of p300/CBP

• Pre-clinical data presented here, support the clinical development of CCS1477 in MM and AML, either as monotherapy or in combination with standard of care therapies, incl. lenalidomide

• CCS1477 is the first p300/CBP inhibitor to be tested clinically in a Phase I/II trial of haematological malignancies, including MM, AML and NHL (NCT04068597)