Poster 411P

PHARMACOLOGICAL ACTIVITY OF CB-103 – AN ORAL PAN-NOTCH INHIBITOR WITH A NOVEL MODE OF ACTION

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BACKGROUND

NOTCH signalling is a developmental pathway known to play critical roles during embryonic development as well as for the regulation of self-renewing tissues. Aberrant activation of NOTCH signalling leads to deregulation of the self-renewal process resulting in sustained proliferation, evasion of cell death, loss of differentiation capacity, invasion and metastasis, all of which are hallmarks of cancer. When the NOTCH pathway is activated by genetic lesions (overexpression of NOTCH ligands/ receptors, GOF mutations in NOTCH receptors as well as chromosomal translocations), it becomes a major driver for NOTCH-dependent cancers and resistance to standard of care.

OBJECTIVES

Several therapeutic NOTCH inhibitors are currently in clinical testing with a) mAbs against NOTCH ligands and receptors and b) gamma-secretase inhibitors (GSIs). However clinical activity and exposure of these in clinical studies were limited due to GI-tract toxicities. In solid tumour and haematological malignancies with constitutive NOTCH activation (gene fusion due to chromosomal translocations or NOTCH mutations), mAbs and GSIs will have limited clinical benefits. Here we report, discovery and development of a novel orally active small molecule protein-protein interaction inhibitor (CB-103) of the NOTCH pathway. CB-103 is a pan-NOTCH inhibitor with a novel mode of action, directly targeting the NOTCH transcriptional activation complex. We will further present the in vitro and in vivo pharmacological characterization of CB-103.

MATERIALS & METHODS

Pharmacodynamic (PD) studies were conducted to investigate CB-103 in relation to its desired therapeutic effect in blood and solid cancers as a pan-NOTCH pathway inhibitor. Regarding the PD effect, in vitro studies showed for CB-103 a dose-dependent decrease in NOTCH signalling with a unique mechanism compared to GSIs and mAbs. The NOTCH inhibitory potential of CB-103 was further confirmed by downregulation of NOTCH target genes in human T-cell acute lymphoblastic leukaemia (T-ALL), suggesting therapeutic efficacy in T-ALL. In a panel of 123 cancer cell lines, CB-103 was active in 24 cell lines matching to tumour types with known activated NOTCH lesions. Moreover, CB-103 showed activity in the Triple-Negative Breast Ca (TNBC) HCC1187 cell line (resistant to GSI due to NOTCH 2 chromosomal translocation).

RESULTS

Figure 1: Patients with NOTCH-driven cancer have shorter survival

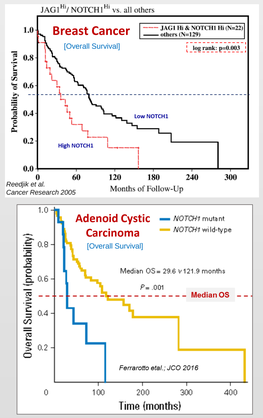
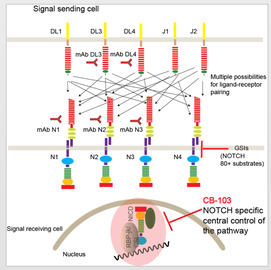
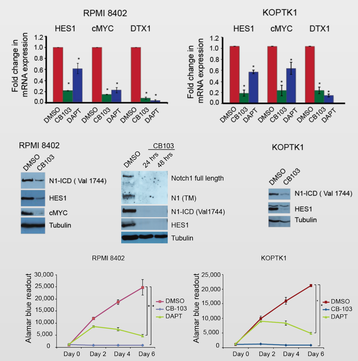


Figure 2: CB-103 blocks NOTCH pathway at the transcription complex level



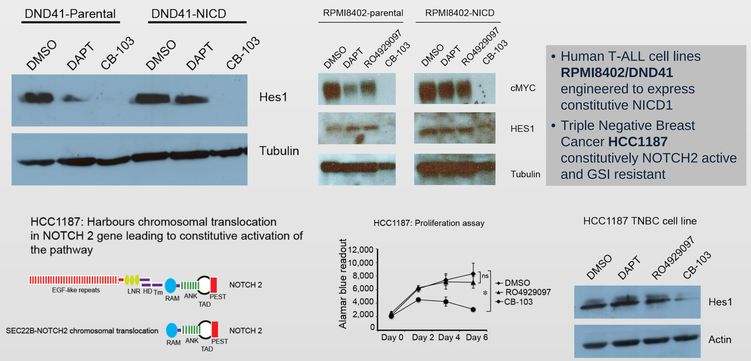
- CB-103 is a first-in-class pan-NOTCH inhibitor
- CB-103 is specific for NOTCH pathway and inhibits NOTCH target genes
- CB-103 overcomes crosstalk and escape mechanisms of NOTCH and other pathways

Figure 3: CB-103 blocks NOTCH signalling in human T-ALL leukaemia cell lines



- CB-103 blocks NOTCH signalling in human T-ALL cell lines harboring GOF mutations in NOTCH1 receptor (Inhibition of target gene expression at mRNA and protein levels)

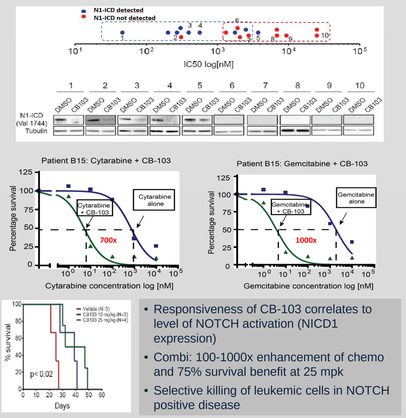
Figure 4: CB-103 inhibits NOTCH in GSI/ mAbs resistant human cancer cell lines



- Human T-ALL cell lines **RPMI8402/DND41** engineered to express constitutive NICD1
- Triple Negative Breast Cancer **HCC1187** constitutively NOTCH2 active and GSI resistant

- Downregulation of NOTCH Target Genes HES1 and cMYC in NOTCH activated RPMI8402, DND41 and HCC1187 by CB-103, but not GSIs

Figure 5: Ex-vivo response to CB-103 in leukaemic blasts from T-ALL patients



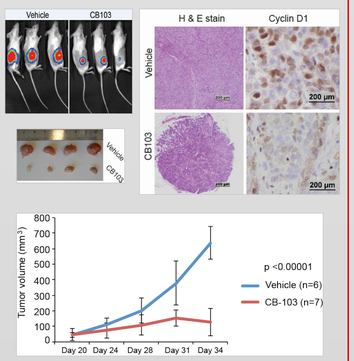
- Responsiveness of CB-103 correlates to level of NOTCH activation (NICD1 expression)
- Combi: 100-1000x enhancement of chemo and 75% survival benefit at 25 mpk
- Selective killing of leukemic cells in NOTCH positive disease

Table 1: Activity of CB-103 in panel of cancer cell lines (IC50 < 10 µM)

INDICATIONS	CELL LINES	NOTCH STATUS (lit. based)	CB-103 IC50 (µM)	GSI RO4929097 IC50 (µM)
Breast	HCC 1569	Positive	5.3	100
	HCC1187	Positive	5	>10
Lung	NCI-H1581	NA	5.5	60
Cervix	C33a	Positive	1.2	>100
Neuroblastoma	SK-N-MC	Positive	1.5	44
Osteosarcoma	SK-ES-1	Positive	1.9	>100
Endometrium	Ishikawa	Positive	3	81
CLL	JVM-3	NA	7.2	65
MM	KMS-12-BM	NA	8.2	>100
Lymphoma	NALM-6	NA	1.1	63
	U-937	Positive	9.4	59
Mantle cell lymphoma	REC-1	Positive	1	---
T-ALL	RPMI8402	Positive	0.7	5
	KOPTK1	Positive	1	5
	CUTL1	Positive	3	>10
Cervical	HeLa	Negative	>100	>100

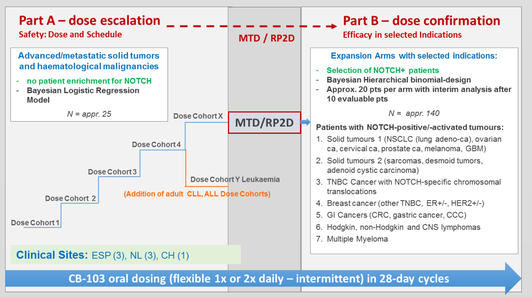
- Screening of > 120 cell lines for CB-103 activity (IC50 values)
- 24 / 120 cell lines showed IC50 < 10 µM
- Several solid tumours, lymphomas, ALL, CLL and MM among responding cell lines

Figure 6: CB-103 reduces tumour growth in a GSI-resistant Triple Negative Human Breast Cancer (HCC1187)



- Anti-tumor efficacy (TGI: 80-90%) of CB-103 in NOTCH2-driven and GSI resistant model of TNBC

Figure 7: Clinical Development for CB-103 will be initiated with first-in-human phase I/IIA study (under preparation, planned start Q3-2017)



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SUMMARY

We demonstrate that in vitro CB-103 potently inhibits NOTCH signalling in various lymphoma, leukaemia and solid tumour cell lines (e.g. breast cancer, lung, osteosarcoma, cervical), and ex vivo in T-ALL blasts derived from relapsed/refractory patients. In addition, CB-103 exhibited anti-tumor efficacy in in vivo models of NOTCH-driven T-ALL using T-ALL cell lines and PDX models derived from T-ALL and TNBC.

CONCLUSIONS

PD and toxicology studies have revealed an excellent efficacy and safety profile in the expected human therapeutic dose range. Clinical development of CB-103 with a first-in-human Phase I/IIA clinical study in advanced or metastatic solid tumours, lymphoma subtypes and multiple myeloma is under Health Authority review.

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3. Ferrarotto R, Mitani Y, Diao L, et al. Activating NOTCH1 Mutations Define a Distinct Subgroup of Patients With Adenoid Cystic Carcinoma Who Have Poor Prognosis, Propensity to Bone and Liver Metastasis, and Potential Responsiveness to Notch1 Inhibitors. J Clin Oncol. 2017;35(3):352-360.