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. Abrupt 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 have limited clinical benefits. Here we report, discovery and development of a novel orally active small molecule 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 CB-103 was further confirmed by downregulation of NOTCH signalling with a unique mechanism.

RESULTS

We demonstrate that in vitro CB-103 potently inhibits NOTCH efficient signalling in various lymphoma, leukemia 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 toxicity 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/II clinical study in advanced or metastatic solid tumours, lymphoma subtypes and multiple myeloma is under Health Authority review.

REFERENCES