Poster 562P

Target engagement and clinical safety of CB-103, a first-in-class small molecule inhibitor of the NOTCH transcription complex

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INTRODUCTION

- The relevance of oncogenic activation of NOTCH signalling has been well validated in preclinical and clinical research over the last decades[1]
- CB-103 is an oral selective inhibitor of the NOTCH transcription complex, and has shown potent anti-cancer activity in preclinical models[2]
- The discovery of a novel Mode of Action to control oncogenic activation of NOTCH-related signalling at the level of gene transcription has allowed to overcome dose limiting toxicities (DLT), specifically of the gastrointestinal tract (GI), associated with previous generations of NOTCH inhibitors[2]
- We designed a dose escalation and expansion phase 1/2a study to assess safety, maximum tolerated dose (MTD) / recommended phase 2 dose (RP2D), preliminary activity, pharmacokinetics and pharmacodynamics of CB-103

BACKGROUND

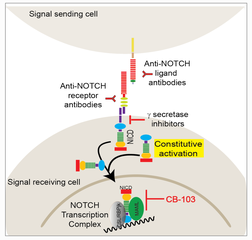


Figure: Schematics of the NOTCH pathway

Interaction between ligand and NOTCH receptors leads to cleavage generating NOTCH intracellular domain (NICD). Once cleaved, NICD translocates to the nucleus to regulate transcription of the target genes

Antibodies against NOTCH receptors and gamma-secretase inhibitors (GSIs) act upstream of the NOTCH transcription complex and lead to GI tract toxicity as major DLT

On the contrary, CB-103 directly targets NOTCH transcription complex and inhibits functional assembly of the complex. Differential gene regulation downstream of CB-103 mediated inhibition of NOTCH circumvents GI tract toxicity[2]

METHOD

Study Design (NCT03422679)

Details of the design have been reported previously[3]. Here data of the dose escalation part of the ongoing study are presented (data cut-off 20 August 2020). Key inclusion criteria:

- Adult patients aged ≥18 years with advanced or recurrent selected solid tumours. In the dose escalation part, patients were unselected for NOTCH aberrations which were evaluated retrospectively
- After the dose escalation, the study will include only patients with NOTCH altered cancers

CB-103 is being administered orally once-daily (QD) in 28-days cycles until disease progression or unacceptable toxicity
An adaptive Bayesian logistic regression model (BLRM) is implemented for the dose escalation to guide determination of MTD/RP2D

Primary endpoint in the dose escalation: number of patients experiencing a DLT during the first 28-days cycle
Secondary endpoints: Incidence of adverse events in each dose group; PK parameters; Tumour response and clinical benefit

RESULTS

Baseline demographics and treatment history

Statistic	Cohort 1 (20 mg) (N=5)	Cohort 2 (40 mg) (N=3)	Cohort 3 (60 mg) (N=7)	Cohort 4 (120 mg) (N=7)	Cohort 5 (170 mg) (N=3)	Cohort 6 (250 mg) (N=4)	Cohort 7 (400 mg) (N=3)	Cohort 8 (600 mg) (N=9)	All Patients (N=41)
Median age (range), y	52 (39,74)	55 (49,63)	56 (25,67)	54 (38,70)	48 (44,62)	55 (41,69)	60 (49,76)	55 (28,76)	55 (25,76)
Female, n (%)	1 (20)	1 (33)	3 (43)	3 (43)	3 (100)	2 (50)	2 (67)	5 (56)	20 (49)
ECOG score, n (%)									
0	3 (60)	2 (67)	5 (71)	4 (57)	2 (67)	2 (50)	1 (33)	5 (56)	24 (59)
1	2 (40)	1 (33)	2 (29)	3 (43)	1 (33)	2 (50)	2 (67)	4 (44)	17 (41)
Tumour type, n (%)									
Adenoid Cystic Carcinoma	2 (40)	1 (33)	5 (71)	5 (71)	2 (67)	1 (25)	0	3 (33)	19 (46)
Breast Cancer*	1 (20)	0	0	0	0	0	1 (33)	2 (22)	4 (10)
Colorectal Cancer	0	2 (67)	2 (29)	2 (29)	1 (33)	3 (75)	2 (67)	4 (44)	16 (39)
Prostate Cancer	2 (40)	0	0	0	0	0	0	0	2 (5)
Stage IV disease, n (%)	5 (100)	3 (100)	7 (100)	7 (100)	3 (100)	4 (100)	2 (67)	8 (89)	39 (95)
Median number of prior lines of therapy (range)	3 (1, 5)	2 (2, 6)	2 (1, 5)	1 (1, 5)	1 (1, 5)	2 (1, 3)	5 (3, 7)	3 (1, 5)	2 (1, 7)

*Breast cancer: 3 triple negative, 1 ER-/HER2+

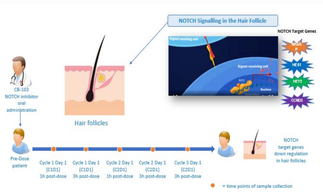
Disposition

Category	Cohort 1 (20 mg) (N=5)	Cohort 2 (40 mg) (N=3)	Cohort 3 (60 mg) (N=7)	Cohort 4 (120 mg) (N=7)	Cohort 5 (170 mg) (N=3)	Cohort 6 (250 mg) (N=4)	Cohort 7 (400 mg) (N=3)	Cohort 8 (600 mg) (N=9)	All Patients (N=41)
Patients ongoing in study, n (%)	0	0	1 (14)	5 (71)	3 (100)	1 (25)	3 (100)	4 (44)	17 (41)
Ongoing on treatment, n (%)	0	0	0	0	0	0	0	1 (11)	1 (2)
Reason for ending treatment, n (%)									
Progressive Disease	4 (80)	1 (33)	5 (71)	6 (86)	3 (100)	3 (75)	3 (100)	5 (56)	30 (73)
Adverse Event	1 (20)	0	0	1 (14)	0	0	0	0	2* (5)
Dose Limiting Toxicity	0	0	0	0	0	0	0	1 (11)	1 (2)
Withdrawal of Consent	0	0	0	0	0	1 (25)	0	0	1 (2)
Other	0	2 (67)	2 (29)	0	0	0	0	2 (22)	6 (15)
Median treatment duration, m (range)	1.4 (.73, 5.9)	1.9 (1.5, 3.6)	3.3 (1.0, 7.5)	3.3 (1.4, 7.2)	3.3 (1.9, 8.6)	1.5 (.80, 8.0)	1.9 (1.5, 2.9)	2.0 (.73, 6.6)	1.9 (.73, 8.6)

*One patient with small intestine hemorrhage; one patient with cardiac failure and respiratory tract infection, all unrelated to study drug

Target engagement

A. Measurement of NOTCH pathway inhibition in surrogate hair follicles (Exploratory study objective)



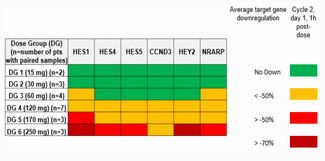
Method:
Hair follicles were obtained to measure changes in NOTCH target genes expression by CB-103 treatment.

Between 5 to 10 hairs were plucked to extract the complete and undamaged hair bulb (full hair follicle), and processed as described elsewhere[4,5].

RNA concentration was measured by Qubit (RNA High Sensitivity), and RNA integrity was evaluated on a RNA 6000 Pico chip. RNA samples were tested for gene expression profiling on a Nanostring platform.

B. NOTCH target gene down-regulation in hair follicles from Phase 1 patients

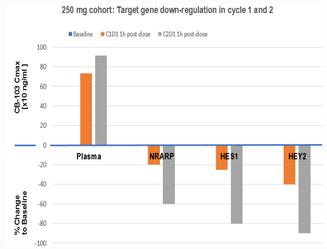
NOTCH target gene down-regulation in hair follicles has been reported to be a robust and indicative biomarker that correlates with both clinical efficacy and the incidence of DLTs[6,7]



Average target gene downregulation on Cycle 2 day 1, 1h post-dose compared to baseline prior to treatment with CB-103.

A strong dose-dependent down-regulation of several NOTCH target genes was observed, reaching values higher than 70% inhibition at the highest CB-103 dose tested in this series (250mg)

C. NOTCH target genes down-regulation in hair follicles from DG 6 (250 mg, n=3)



Average target gene downregulation on Cycle 1 day 1 and Cycle 2 day 1, 1h post-dose, compared to baseline prior to treatment with CB-103.

A sustained time-dependent down-regulation of NOTCH target genes was observed, reaching up to a 90% inhibition after 4 weeks of daily administration of CB-103.

Pharmacokinetics

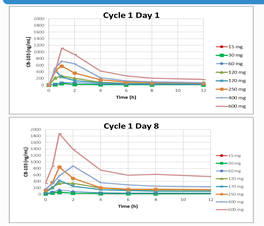


Figure: Mean CB-103 Plasma concentrations versus time by Dose

- CB-103 is rapidly absorbed after oral administration and reaches Cmax within 1 to 2 hours of dosing.
- Plasma exposure increases with increasing doses. No signs of saturated absorption in the dose range tested.
- The elimination half-life is approx. 20 hours and CB-103 accumulates about 2-fold with repeated daily administration.
- Steady state concentrations are reached within one week of dosing.

Summary of preliminary efficacy

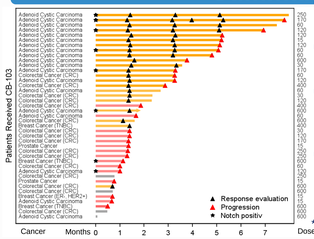


Figure: Swimmer plot by duration of treatment

- Best response was durable stable disease (SD) with no or only mild AE at doses showing target engagement
- 10 patients with ACC had radiologically confirmed SD, of whom 4 patients had a Notch activating mutation. The Notch status of the other patients is under investigation
- Disease control rate (DCR) of 19 ACC patients at 3 months was 68% (DCR defined as number of patient with CR, PR, or SD divided by the number of patients treated)

*Notch positive indicates oncogenic Notch activation by mutation or fusion.

Safety

Most common TEAEs regardless of attribution occurring in >10% of patients

MedDRA Preferred Term Patients, n (%)	Grade 1 or 2 (N=41)	Grade ≥3 (N=41)	Total (N=41)
Nausea	11 (27)	0	11 (27)
Aspartate aminotransferase increased	7 (17)	2 (5)	9 (22)
Fatigue	8 (20)	1 (2)	9 (22)
Constipation	8 (20)	0	8 (20)
Decreased appetite	6 (15)	2 (5)	8 (20)
Diarrhoea	8 (20)	0	8 (20)
Abdominal pain	7 (17)	0	7 (17)
Anaemia	7 (17)	0	7 (17)
Alanine aminotransferase increased	5 (12)	1 (2)	6 (15)
Back pain	6 (15)	0	6 (15)
Cough	6 (15)	0	6 (15)
Dyspepsia	6 (15)	0	6 (15)
Gamma-glutamyltransferase increased	5 (12)	2 (5)	7 (17)
Asthenia	4 (10)	1 (2)	5 (12)
Blood creatinine increased	5 (12)	0	5 (12)
Vision blurred	5 (12)	0	5 (12)

CB-103 related TEAEs (any grade) occurring in >10% of patients overall

MedDRA Preferred Term, Patients, n (%)	Cohort 1 (20 mg) (N=5)	Cohort 2 (40 mg) (N=3)	Cohort 3 (60 mg) (N=7)	Cohort 4 (120 mg) (N=7)	Cohort 5 (170 mg) (N=3)	Cohort 6 (250 mg) (N=4)	Cohort 7 (400 mg) (N=3)	Cohort 8 (600 mg) (N=9)	All Patients (N=41)
Nausea	2 (40)	1 (33)	2 (29)	2 (29)	0	0	1 (33)	2 (22)	10 (24)
Diarrhoea	1 (20)	0	3 (43)	1 (14)	0	1 (25)	0	2 (22)	8 (20)
Dyspepsia	0	0	1 (14)	0	0	1 (25)	0	4 (44)	6 (15)
Fatigue	1 (20)	1 (33)	1 (14)	0	0	0	1 (33)	1 (11)	5 (12)
Vision blurred	0	0	0	1 (14)	1 (33)	1 (25)	0	2 (22)	5 (12)

- CB-103 was well tolerated in patients with advanced solid tumours at doses leading to sustained target engagement
- The majority of TEAEs were of grade 1 or 2. Twelve SAEs were reported in 10 patients. The only SAE considered treatment-related was drug induced liver injury (in cycle 2), fully recovered, at an intermediate exposure level
- One dose limiting toxicity (DLT) occurred in the highest dose group. This was an elevation of the gamma-glutamyl transferase (GGT), grade 3, that was asymptomatic and deemed not clinically significant by the investigator
- Importantly, all reported diarrhoea was grade 1 or grade 2 clinically manageable. No cases of severe diarrhoea observed. There was no relationship of the diarrhoea incidence with dose
- No signal of cardiotoxicity and no QTc or other ECG abnormalities were observed
- Several patients reported visual symptoms of varying phenotype which were fully reversible after ending treatment. Ophthalmologic examination revealed no abnormalities. There seemed to be a trend of higher incidence in dose groups receiving 250mg or higher doses

CONCLUSIONS

- **CB-103 is the first drug in clinical testing that can control oncogenic NOTCH pathway activation effectively and safely, in absence of any severe toxicities**
- **In the dose escalation, 41 patients with advanced metastatic tumors have been treated at doses ranging from 15-600 mg once daily; CB-103 was generally well tolerated**
- **At doses of 120 mg and above, up to 90% down-regulation of NOTCH target genes has been demonstrated, confirming effective and sustained target engagement, in the absence of significant side effects, notably no dose limiting diarrhoea**
- **Target engagement coincided with long-term Stable Disease in NOTCH positive ACC patients**
- **The dose of 600mg QD has been declared as safe dose and further dose escalation is possible; the study is ongoing**

References: Moore G, et al. Cells 2020;9.1503; **2.** Lehal R, et al. PNAS 2020;117:16292-301; **3.** Perez Garcia J, et al. J Clin Oncol 2018;36 (suppl; abstr TPS2619); **4.** Camidge DR, et al. Br J Cancer 2005;92:1837-41; **5.** Bradley BJ, et al. Mol Ecol Notes 2005;5:961-4; **6.** Tanis KQ, et al. Clin Pharmacol Ther 2016;99(4):370-80; **7.** Cook N, et al. BJC 2018;118(6):793-801.

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