Abstract 3020

Phase 1 study of CB-103, a novel first-in-class inhibitor of the CSL-NICD gene transcription factor complex in human cancer

Elena López-Miranda[1], Anastasios Stathis[2], Dagmar Hess[3], Fabricio Racca[4], Doris Quon[5], Jordi Rodon[6], Omar Saavedra[7], Jose Manuel Perez Garcia[8], Paolo Nuciforo[9], Ana Vivancos[10], Javier Cortes[8], Renata Ferrarotto[11], Oliver Schönborn-Kellenberger[12], Michele Vigolo[13], Maria Bobadilla[14], Laura Beni[14], Rajwinder Lehal[14], Michael P. Bauer[14], Florian D. Vogl[14], Elena Garralda[15]

[1]Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain, [2]Oncology Institute of Southern Switzerland, Bellinzona, Switzerland, [3]Department of Medical Oncology, Kantonsspital St Gallen, St Gallen, Switzerland, [4]IOB – Institute of Oncology Barcelona and Madrid, Hospital Quironsalud Barcelona, Barcelona, Spain, [5]Sarcoma Oncology Research Center, Santa Monica, CA, [6]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, [7]Department of Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO),Barcelona, Spain, [8]International Breast Cancer Center (IBCC), Quiron Hospital, Barcelona, Spain, [9]Molecular Oncology Group, Vall d'Hebron Institute of Oncology(VHIO), Barcelona, Spain, [10]Cancer Genomics, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [11]Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, [12]Cogitars GmbH, Heidelberg, Germany, [13]R&D, Cellestia Biotech AG, Epalinges, Switzerland, [14]Cellestia Biotech AG, Basel, Switzerland, [15]Early Drug Development Unit (UITM), Vall d'Hebron University Hospital and Institute of Oncology (VHIO) and Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain

INTRODUCTION

- CB-103 selectively inhibits the CSL-NICD interaction leading to down-regulation of CSL-NICD mediated oncogenic pathway activation downstream of NOTCH receptor/ligand signaling
- The discovery of a novel Mode of Action to control oncogenic activation of NOTCH-related signaling at the level of gene transcription has allowed to overcome dose limiting toxicities (DLT), specifically of the gastrointestinal tract, associated with previous generations of NOTCH inhibitors
- CB-103 has shown potent anti-cancer activity as single agent and in combination with targeted/chemotherapies in preclinical models of leukemias and solid tumors
- The aim of this dose escalation/expansion phase 1/2a study is to assess safety, determine maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D), preliminary activity, pharmacokinetics and pharmacodynamics of CB-103

BACKGROUND

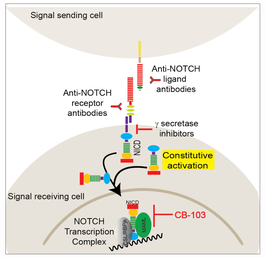


Figure: Schematics of the NOTCH pathway

CB-103 is a highly specific inhibitor of oncogenic CSL-NICD gene transcription factor (GTF) complex:

Sequential binding of CSL and NICD is a prerequisite step in the formation of the NOTCH GTF complex. This complex modulates transcription of oncogenic signature downstream of NOTCH signaling. However, therapeutic targeting of CSL-NICD GTF complex remained elusive due to the nature of protein-protein interaction between CSL and NICD. Previous attempts to target NOTCH signaling upstream of CSL-NICD complex with blocking Abs and gamma-secretase inhibitors (GSIs) were marred by severe GI tract toxicity, thereby limiting their therapeutic potential. Here we report development of CB-103, a specific inhibitor of CSL-NICD GTF. We have demonstrated that targeting of this complex with CB-103 circumvents GI tract toxicity associated with upstream targeting of the pathway. This safety feature is facilitated by a differential regulation of NOTCH target genes in small intestine. Specifically, while CB-103 inhibits direct NOTCH target genes (Hes1, Olfm4) in small intestine, it spares Atoh1 which is responsible for the GI tract toxicity[1].
The safety profile of CB-103 allows application of this novel inhibitor in human cancers as a single agent as well as in combination with other anticancer agents.

METHOD

Study Design (NCT03422679)

- Details of the design have been reported previously[2,3]. Here data of the dose escalation part of the ongoing study are presented (data cut-off 02 December 2020)
- Key inclusion criteria:
  - Adult patients aged ≥18 years with advanced or recurrent selected solid tumors. In the dose escalation part, patients were unselected for NOTCH aberrations. Tumor tissue, where available, and liquid biopsies were retrospectively tested for NOTCH pathway alterations; surrogate tissues were evaluated for gene expression of related target genes.
  - In a dose confirmatory cohort, NOTCH activation will be prospectively assessed to determine eligibility.
- 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) was 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
  - Tumor response and clinical benefit

RESULTS

Baseline demographics and treatment history

Statistic	Cohort 1 (15 mg) (N=5)	Cohort 2 (30 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)
Tumor 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+

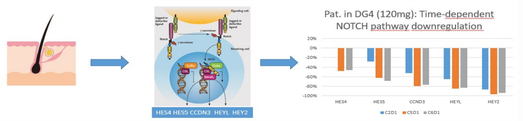
Disposition

Category	Cohort 1 (15 mg) (N=5)	Cohort 2 (30 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)	3 (43)	2 (67)	1 (25)	1 (33)	3 (33)	11 (27)
Reason for ending treatment, n (%)									
Progressive Disease	4 (80)	1 (33)	5 (71)	6 (86)	3 (100)	3 (75)	3 (100)	6 (67)	31 (76)
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	1 (14)	0	0	1 (25)	0	0	2 (5)
Other	0	2 (67)	1 (14)	0	0	0	0	2 (22)	5 (12)
Median treatment duration, m (range)	1.4 (.5, 5.9)	1.9 (1.5, 3.6)	3.3 (1.0, 7.5)	3.3 (1.0, 7.2)	3.3 (1.9, 8.6)	1.5 (0.80, 8.0)	1.9 (1.5, 2.9)	0.8 (0.2, 4.0)	1.7 (0.2, 8.6)

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

Target engagement

Analysis of NOTCH pathway target genes: hair follicles as surrogate tissue (Exploratory study objective)



5 to 10 hairs with intact hair follicles were plucked and processed for RNA extraction [4,5]

Gene expression profiling was performed with Nanostring technology using a NOTCH pathway customised panel

NOTCH target gene expression is quantified at different timepoints to monitor target engagement

A strong CSL-NICD-mediated, time-dependent target gene downregulation was observed that achieved almost a 100% pathway inhibition after 6 cycles of treatment

Safety

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

MedDRA Preferred Term, Patients, n (%)	Cohort 1 (15 mg) (N=5)	Cohort 2 (30 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)

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

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

Summary of preliminary efficacy

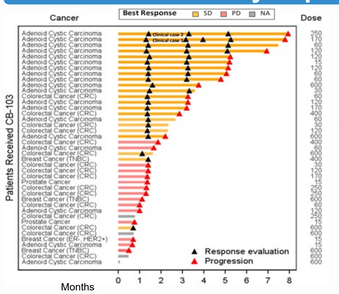


Figure: Swimmer plot by duration of treatment

- 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 8 patients had a Notch alteration

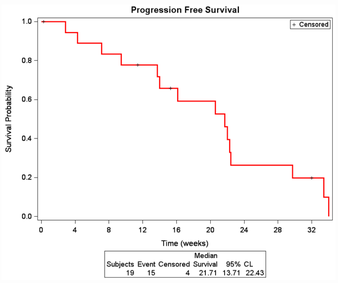


Figure: Progression-free survival and disease control rate in patients with ACC (N=19)

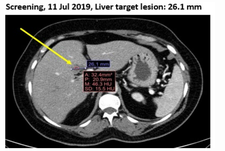
- Median PFS for patients with mACC was 21.7 weeks (95% CI: 13.7-22.4 weeks)
- Disease control rate (DCR)* at 8 weeks and 20 weeks was 79% and 58%, respectively.

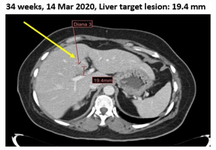
*DCR: number of patient with CR, PR, or SD divided by the number of patients treated.

Summary of dose escalation

- In the dose escalation, 41 patients with advanced / metastatic solid tumors were treated with CB-103 at doses ranging from 15mg - 600mg once daily; CB-103 was generally well tolerated
- 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
- Importantly, all reported diarrhea was grade 1 or grade 2, and clinically manageable. No cases of severe diarrhea were observed. There was no relationship of the diarrhea incidence with dose
- 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
- 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
- Plasma exposure increases with increasing doses. Elimination half-life of CB-103 is approx. 20 hours[3]
- Mechanistically, during treatment strong downregulation of Notch target genes was observed confirming the on-target activity of CB-103
- The dose of 600mg was declared the RP2D for a once-daily regimen
- Preliminary efficacy shows promising response signals: 8 patients with ACC harboring NOTCH alterations had radiologically confirmed stable disease (SD) and showed temporary stop of tumor growth

Clinical cases

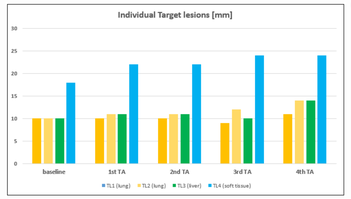




Case 1: ACC patient with Notch1 mutation

Woman (48y) with metastatic ACC, multiple metastases in lung, pleura and large lesion in the liver.
Prior to study participation, patient had received 1 prior line of combination chemotherapy because of disease progression; that treatment was discontinued after 3 cycles because of toxicity and further disease progression.

- CB-103 (170mg OD) achieved sustained long-term disease control with radiologically confirmed stable disease for nearly 8 months
- Different responses of metastases suggests heterogenous disease:
  - Largest metastasis in the liver decreased by 26%
  - Pleura metastasis, after initial growth, stopped growing after cycle 4
  - Two lung metastases showed only slow and modest growth
  - Progression at 8 months was due to new lesions and growth of existing lesions



Case 2: ACC patient with Notch1 mutation

41 year-old woman with metastatic ACC, multiple metastases in the liver, lung, and bone.

Prior therapy consisted of radiation to the bone; systemic treatment with a TKI was interrupted after the first month due to toxicity.

- During treatment with CB-103, tumor growth significantly slowed down and patient had radiologically confirmed stable disease for 7 months.
- After 7 months on treatment, some of the metastases grew again.

CONCLUSIONS

- **CB-103 is a breakthrough in targeting Notch: CB-103 is the first drug controlling oncogenic CSL-NICD mediated pathway activation safely and potently through a novel mechanism of action targeting gene transcription**
- **CB-103 is the first drug in clinical testing to effectively control the CSL-NICD complex**
- **CB-103 is well tolerated in patients with advanced tumors and without the typical toxicities associated with Notch targeting GSIs or mAbs**
- **Preliminary efficacy show strong and long-term disease control in ACC patients with Notch-activated tumors who have a poor prognosis and rapid disease progression**
- **The RP2D has been established for advancing clinical development into Phase 2**

References: 1. Lehal R, et al. PNAS 2020;117:16292-301; **2.** Perez Garcia J, et al. J Clin Oncol 2018;36 (suppl; abstr TPS2619); **3.** Azaro Pedrazolli AB, et al, Ann Oncol 2020 ;31(S4, abstract 562P); **4.** Camidge DR, et al. Br J Cancer 2005;92:1837-41; **5.** Bradley BJ, et al. Mol Ecol Notes 2005;5:961-4

Acknowledgements: We would like to express our gratitude to all study participants and the teams at the study sites. We thank Karin Jorga, PhD, for conducting the pharmacokinetic analyses and critical review of the presentation.

Study sponsored by Cellestia Biotech AG, Hochbergerstrasse 60C, 4057 Basel, Switzerland. Additional info: www.cellestia.com

Presented at ASCO Virtual Congress 2021, 4-8 June

For inquiries: info@cellestia.com