Poster TPS2619

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First-in-human phase 1-2A study of CB-103, an oral Protein-Protein Interaction Inhibitor targeting pan-NOTCH signalling in advanced solid tumors and blood malignancies

Jose Perez-Garcia[1], Javier Cortes[2], Anastasios Stathis[3], Rogier Mous[4], Elena López-Miranda[2], Analía Azaro[5], Sofia Genta[3], Renata Ferrarotto[6], Paolo Nuciforo[5], Ana Vivancos[5], Francesco Bertoni[3], Davide Rossi[3], Nicole Spardy Burr[7], Oliver Schoenborn-Kellenberger[8], Karin Jorga[9], Laura Beni[10], Rajwinder Lehal[10], Michael Bauer[10], Dirk Weber[10], Elena Garralda[5]

1 IOB Institute/ Hospital Quiron, Barcelona, ES, 2 Ramon y Cajal Hospital, Madrid, ES, 3 Oncology Institute of Southern Switzerland, Bellinzona, CH, 4 UMC Utrecht Cancer Center, Utrecht, NL, 5 Vall D¨Hebron Institute of Oncology, Barcelona, ES, 6 Thoracic Head and Neck Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, US, 7 Adenoid Cystic Carcinoma Research Foundation, Needham, US, 8 Cogitars GmbH, Heidelberg, DE, 9 KarinJorga GmbH, Basel, CH, 10 Cellestia Biotech AG, Basel, CH

BACKGROUND

NOTCH signalling is a key development pathway whose aberrant activation is recognised to play an oncogenic role in numerous human solid cancers and haematological malignancies. When NOTCH signalling is inappropriately activated by genetic alterations, e.g. by mutations and/or chromosomal translocations, it becomes an oncogenic driver for NOTCH-dependent cancers, while upregulation of NOTCH receptors is linked to resistance to standard of care treatments (chemotherapy, radiotherapy, targeted therapies).

CB-103 is a new small molecule **protein-protein interaction (PPI) inhibitor** able to target assembly of the NOTCH transcription complex in the cell nucleus leading to down-regulation of NOTCH target genes and inhibition of NOTCH signalling independently of NOTCH mechanisms of activation. CB-103 has demonstrated efficacy and tolerability in different preclinical tumor models derived from various NOTCH-driven cancer indications and in blood from NOTCH-activated paediatric T-ALL leukemia pts.

METHODS

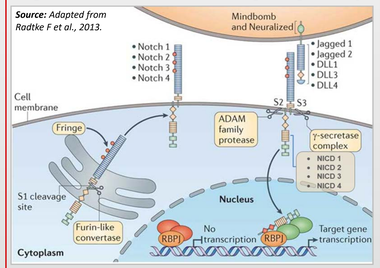
This first-in-human study (CB103-C-101) is a multi-centre, open label, non-randomised, phase 1-2A study in adult patients (pts) with advanced or metastatic solid tumours and haematological malignancies of CB-103 administered per oral daily over 28-day treatment cycles. There are two parts in the study. Aim of phase 1 part with dose escalation is to determine the MTD/RP2D and phase 2A to determine preliminary efficacy. The starting dose is targeting a plasma exposure (daily AUC) that has reasonable safety margin and allows reliable determination of pharmacokinetics (PK). An adaptive Bayesian logistic regression model for dose escalation is implemented in phase 1 to guide determination of MTD/RP2D. Full PK sampling profiles is taken on days 1 & 8 of cycle one (28 days), on day 1 of cycle two and 1 sample on day 1 & 15 of each subsequent cycle. NOTCH-related PD and Biomarker exploratory analyses are planned on tumour biopsies, hair follicles and blood samples. Current administration schedule (once-daily) may be adapted depending on PK and safety. At least 3 eligible pts regardless of NOTCH pathway activation status are enrolled per dose group in phase 1, while pts in phase 2A will be selected for NOTCH pathway genetic alterations. Phase 1 part will be followed by the phase 2A to assess preliminary efficacy of CB-103 in expansion arms across different indications using Bayesian hierarchical design.
Enrolment into 1st dose group started with first pt treated on 20Dec17: 7 pts registered (3 ACC, 2 Prostate, 1 Breast, 1 CCC) with 2 screen failures, 1 discontinued due to early cancer progression and 4 completing the DLT period (cycle 1). One ACC pt is still under treatment with stable disease for > 15 weeks having reached cycle 5. No DLTs occurred in 1st dose group and safety review by the Cohort Review Committee (CRC) revealed no safety concern and CRC recommended to continue with enrolment into 2nd dose group of 30mg CB-103 administered per oral once daily.

CONTACT

- Jose Perez-Garcia, MD/PhD; IOB / Hospital Quiron, Barcelona, Spain. Email: josemanuel.perez@quironsalud.es
- Elena Garralda, MD; Vall D¨Hebron University Hospital, Barcelona, Spain. Email: egarralda@vhio.net
- Dirk Weber, MD; Cellestia Biotech AG, Hochbergerstrasse 60C, Basel, Switzerland. Email: dirk.weber@cellestia.com

CB-103 Phase 1-2A Clinical Study (CB103-C-101)

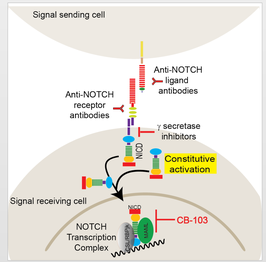
Figure 1: Overview of the NOTCH Signalling Pathway



NOTCH signalling is cell-to-cell communication and consists of:

- 5 Ligands: DLL1, DLL3, DLL4, JAGGED1, JAGGED2
- 4 Receptors: NOTCH1, NOTCH2, NOTCH3, NOTCH4
- Target Genes: HES1/4/5, HEY2/L, NRARP, MYC,…etc.

Figure 2: NOTCH Pathway Inhibition



Therapeutic NOTCH inhibition in clinics:

- **Gamma Secretase Inhibitors (GSI):** inhibition of S3 cleavage of NICD at the receptor level
- **mAB against ligands:** DLL3 (ADC), DLL4
- **mAB against receptors:** Notch 1, 2, 3

Figure 3: Patients with NOTCH-driven cancer have shorter survival

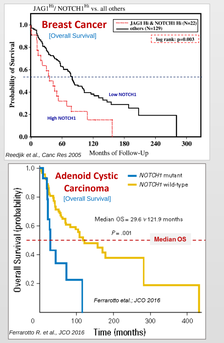


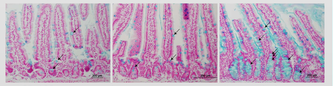
Table 1: Activity of CB-103 in cancer cell lines

INDICATIONS	CELL LINES	NOTCH STATUS (lit. based)	CB-103 IC50 (µM)	GSI LY3039478 IC50 (µM) (in vitro IC50: 0.16 nM)	GSI RO4929097 IC50 (µM) (in vitro IC50: 4 nM)	PD MARKERS (Overexpr.of. NICD1 &/or NOTCH target genes)
Hematological malignancies (examples)						
ALL	RS4 11	Positive	0.23	>10	83	Positive
Lymphoma	NALM-6	NA	1.1	>10	63	Positive
T-ALL	Jurkat	Positive	0.1	>20	>20	Positive
	RPMI8402	Positive	0.5	NA	5	Positive
	KOPTK1	Positive	1	NA	5	Positive
Solid tumors (examples)						
Cervix	C33a	Positive	1.2	>10	>100	Positive
Neuroblastoma	SK-N-MC	Positive	1.5	>10	44	Positive
Osteosarcoma	SK-ES-1	Positive	1.9	>10	>100	Positive

- Screening of > 120 cell lines for CB-103 activity (IC50 values)
- 24 / 120 cell lines showed IC50 < 10 µM

Figure 4: CB-103 shows no Goblet Cell Metaplasia

C57Bl6 mice were administered (p.o) CB-103 and GSI (1x daily, 25mg/kg each) for 7days:



- CB-103 treatment does not cause goblet cell metaplasia at doses tested and sufficient to block NOTCH in vivo

Figure 5: Ex-vivo response to CB-103 in leukemic blasts from T-ALL patients and in TNBC tu model

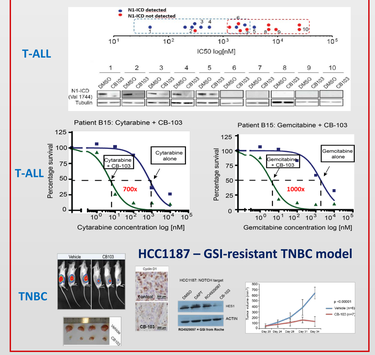
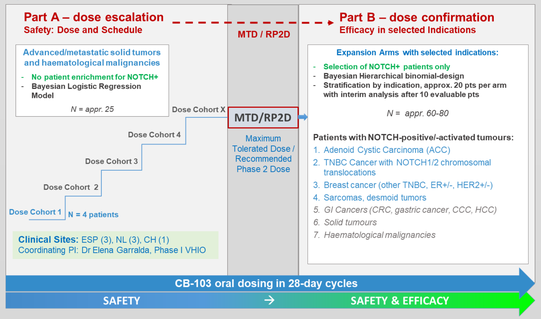
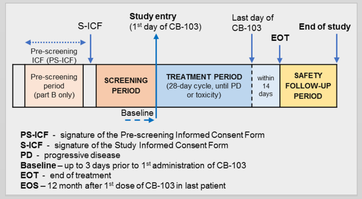


Figure 6: Clinical Development for CB-103 ongoing with first-in-human phase I-IIA study (First patient dosed on Dec 20th, 2017, 1st dose group completed)

Study Design CB103-C-101:



Study Periods CB103-C-101:



PS-ICF - signature of the Pre-screening Informed Consent Form
S-ICF - signature of the Study Informed Consent Form
PD - progressive disease
Baseline – up to 3 days prior to 1st administration of CB-103
EOT - end of treatment
EOS – 12 month after 1st dose of CB-103 in last patient

Study Identifier CB103-C-101:

- **ClinicalTrial.gov: NCT03422679**
- **EUDRACT Number: 2017-001491-35)**
- **Sponsor: Cellestia Biotech AG, Basel**
- **Clinical CRO: Chilton International Ltd, Berkshire**

Figure 7: CB103-C-101 Patient Population & Key Eligibility Criteria

Key Inclusion Criteria:

- Patients with histologically or cytologically confirmed solid tumors that are surgically unresectable, locally advanced, or metastatic and whose disease has progressed on standard therapy and for whom no standard therapy exists.
- **Following solid tumor indications are allowed to be enrolled into phase 1:** Breast cancer (TNBC, ER+/-, HER2+/-), GI cancers (CRC, CCC, gastric cancer), ovarian cancer, cervical cancer, prostate cancer, NSCLC, melanoma, sarcomas, desmoid tumors, adenoid cystic carcinoma and GBM.
- Patients with histologically or cytologically confirmed, **advanced haematological malignancies** (Hodgkin and non-Hodgkin lymphomas, CNS lymphoma and multiple myeloma) whose disease has relapsed or progressed on standard therapy and for whom no standard therapy exists.
- Patients with solid tumors must have at least one measurable lesion (at least 1.0 cm in diameter) according to RECIST v1.1 for solid tumors, according to "The Lugano Classification" for lymphomas (at least 1.0 cm in diameter).
- Patients with MM must have measurable disease (serum M-protein ≥ 10 g/L or urine M-protein ≥ 200 mg/24 hours or abnormal free light chain (FLC) ratio with involved FLC > 100 mg/L) or proven plasmacytoma by biopsy).
- Adequate Organ function, men & women ≥ 18 years old, ECOG 0 or 1.

Key Exclusion Criteria:

- Patients with symptomatic CNS metastases who are neurologically unstable or require increasing doses of steroids to control their CNS disease.
- Prior treatment with any NOTCH signalling pathway inhibitor compound
- Patients with unresolved nausea, vomiting, or diarrhea of CTCAE grade > 1
- Impairment of GI function or presence of GI disease that may significantly alter the absorption of CB-103 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
- Impaired cardiac function or clinically significant cardiac diseases.
- Cytotoxic chemotherapy within 3 wks (6 weeks for nitrosoureas and mitomycin C) of scheduled CB-103 dosing day 1.
- Radiation therapy within 2 weeks of scheduled CB-103 dosing day 1
- Any investigational treatment within 4 weeks of scheduled CB-103 dosing day 1.
- Drugs which prolong QT interval.
- Acid reducing agents (for example, PPI or H2-blocker)

Figure 8: CB103-C-101 Endpoints & Exploratory Analyses

Key Endpoints:

- **Primary:** Number of patients experiencing dose-limiting toxicity (DLT) during the first 28 day cycle of CB-103 treatment (phase 1 dose escalation part)
- Incidence rate, severity and relationship to CB-103 of AEs and SAEs, safety labs, vital signs, cardiac data (central review) in each dose group and expansion arm.
- CB-103 plasma concentrations, PK parameters: Cmax, tmax, AUC during 8 and 24 hours (AUC0 8, AUC0 24), AUC0-∞, Vd/F, Vss/F, CL/F, t1/2 and AR.
- Tumor Response Rates, Clinical Benefit Rates, Duration of response (DOR), time to response, progression-free survival (PFS), OS

Exploratory Analyses:

- NOTCH genes expression (receptors, ligands, NICD1-4 & target gene assessed by Nanostring RNA gene expression analysis in tumour tissue samples, blood / plasma samples and hair follicles and assess relation to activity of CB-103.
- Genotypes (e.g. cytochrome P450 enzymes or NAT) and assess relation to PK data.
- NOTCH genetic aberrations in tumour tissue samples, whole blood and hair follicles and assess relation to clinical activity of CB 103.
- NOTCH1-4 NICD expression assessed by IHC staining in tumour tissue samples and to assess relation to clinical activity of CB-103.
- Genetic aberrations on DNA derived from blood samples (circulating tumour DNA and blood cell-derived DNA).
- To evaluate the relationship between CB-103 plasma concentrations and/or PK parameters (eg, Cmax and AUC0-24) and safety, efficacy and PD parameters.

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2. **Lehal R., Frismantas V., Urech C., Bourquin J-P., Bauer M., Weber D., Murone M., Radtke F. (2017).** Non clinical pharmacology, pharmacokinetics and safety profiling of CB-103. Poster 1163. AACR Annual Meeting 2017, Washington D.C..
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