Pharmacological Activity of CB-103 in Haematological Malignancies – An Oral pan-NOTCH Inhibitor with a Novel Mode of Action

D. Weber¹, R. Lehal¹, V. Frismantas², J. Bourquin², M. Bauer¹, M. Murone¹, F. Radtke¹

¹ Clinical Development, Cellestia Biotech AG, Basel, Switzerland, ² Division of Pediatric Oncology, University Children’s Hospital Zurich, Zürich, Switzerland.

(Abstract #029)

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Cellestia Biotech AG & CB-103

- Spin-off from EPFL, Lausanne, Switzerland
- NOTCH pathway is a validated target
  ✔ Oncogenic role confirmed in many haematological malignancies and solid tumours
  ✔ Negative prognostic value in many cancers

Pan-NOTCH inhibitor CB-103 with novel MoA:
- Small molecule, oral administration
- Targets NOTCH signalling pathway at the transcription complex in the nucleus
- FIH clinical study start expected in Sep/Oct 2017

Cellestia Biotech Locations:
- HQ & Development
  Hochbergerstrasse 60C
  CH-4057 Basel
  Switzerland

- Research Lab
  UPRAD Life Science Faculty Innovation Square
  EPFL Building C
  CH-1015 Lausanne
  Switzerland

https://www.cellestia.com/
Overview of the NOTCH signalling pathway and unique features of CB-103:

Adapted from Radtke (Radtke et al., 2013).

CB-103 is a First-in-Class pan-NOTCH protein-protein interaction inhibitor
Controlling A Complex Pathway by Inhibition of NOTCH Target Genes

- CB-103 is specific for NOTCH pathway and inhibits NOTCH target genes
- CB-103 inhibits NOTCH target genes by blocking the NOTCH transcription factor complex
- CB-103 overcomes crosstalk and escape mechanisms of NOTCH and other pathways
CB-103 inhibits NOTCH Target Genes in GSI-Resistant Cell Lines

Pharmacodynamics in T-ALL and TNBC cell lines with constitutive NOTCH activation

- Human T-ALL cell lines **RPMI8402/DND41** engineered to express constitutive active NOTCH1 Intracellular Domain (NICD1)
- Triple Negative Breast Cancer **HCC1187** constitutively NOTCH2 active by chromosomal translocation and GSI resistant
- Downregulation of NOTCH Target Genes HES1 and cMYC gene in NOTCH activated RPMI8402/DND41 by CB-103, but not GSIs
- CB-103 is specific for NOTCH pathway and inhibits NOTCH target genes
Ex-Vivo Response to CB-103 in Leukemic Blasts from T-ALL Patients

- Proof-of-Principle with CB-103 ex vivo in T-ALL patient blood samples
- Responsiveness of CB-103 correlate to level of NOTCH activation (NICD1 expression)
- Normal blood cells and NOTCH-negative leukaemia samples not affected by CB-103
T-ALL: Acute Lymphocytic T-Cell Leukaemia, patient derived blood sample, resistant to chemo & experimental therapies

Selective killing of leukemic cells in NOTCH positive disease

- **Combinations:** 100-1000x enhancement of chemo
- **Selectivity:** Only effective in patients with NOTCH pathway activation

Clear cytotoxic efficacy, selective on NOTCH-positive leukemic cells
Activity of CB-103 in Panel of Cancer Cell Lines –  Lymphomas (1/2)

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

<table>
<thead>
<tr>
<th>INDICATIONS</th>
<th>CELL LINES</th>
<th>NOTCH STATUS (lit. based)</th>
<th>CB-103 IC50 (μM)</th>
<th>GSI RO4929097 IC50 (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immortalized T cell</td>
<td>Jurkat</td>
<td>Positive</td>
<td>0.1</td>
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<tr>
<td>Lymphoma</td>
<td>NALM-6</td>
<td>NA</td>
<td>1.1</td>
<td>63</td>
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<tr>
<td></td>
<td>U-937</td>
<td>Positive</td>
<td>9.4</td>
<td>59</td>
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<tr>
<td>Mantle cell lymphoma</td>
<td>REC-1</td>
<td>Positive</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>B lymphoma</td>
<td>RAJI</td>
<td>Negative</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td></td>
<td>HBL1</td>
<td>Negative</td>
<td>&gt;10</td>
<td>&gt;10</td>
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## Activity of CB-103 in Panel of Cancer Cell Lines – Haematological & Breast (2/2)

<table>
<thead>
<tr>
<th>INDICATIONS</th>
<th>CELL LINES</th>
<th>NOTCH STATUS (lit. based)</th>
<th>CB-103 IC50 (μM)</th>
<th>GSI RO4929097 IC50 (μM)</th>
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<tbody>
<tr>
<td>ALL</td>
<td>RS4 11</td>
<td>Positive</td>
<td>0.23</td>
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<tr>
<td>T-ALL</td>
<td>RPMI8402</td>
<td>Positive</td>
<td>0.7</td>
<td>5</td>
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<tr>
<td></td>
<td>RPMI8402-NICD</td>
<td>Positive</td>
<td>1-2</td>
<td>&gt;10</td>
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<tr>
<td></td>
<td>DND41</td>
<td>Positive</td>
<td>3</td>
<td>&gt;10</td>
</tr>
<tr>
<td></td>
<td>DND41-NICD</td>
<td>Positive</td>
<td>5</td>
<td>&gt;10</td>
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<tr>
<td></td>
<td>KOPTK1</td>
<td>Positive</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>CUTL1</td>
<td>Positive</td>
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<td>CLL</td>
<td>JVM-3</td>
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<td>7.2</td>
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<tr>
<td>MM</td>
<td>KMS-12-BM</td>
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<td>Breast</td>
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<td>5.3</td>
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<td>Breast</td>
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<td>&gt;100</td>
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THE NOVEL NOTCH-INHIBITOR CB103: ANTI-PROLIFERATIVE ACTIVITY ON LYMPHOMA CELL LINES

Lymphoma & Genomics Group
Institute of Oncology Research (IOR), Bellinzona, CH

PI: Francesco Bertoni, MD
Head, Lymphoma & Genomics Research Program
Vice-Director, IOR Institute of Oncology Research
**CB-103: Anti-Proliferative Activity on Lymphoma Cell Lines**

- **CB-103 median IC50s among lymphoma subtypes**

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**CB-103 - GCB-DLBCL**

- **CB-103 - MCL**

- **CB-103 - ABC-DLBCL**

- **CB-103 is active in GCB-DLBCL, ABC-DLBCL & MCL cell lines**

- **Further research on selected cell lines with combinations**

**Source:** Results from F. Bertoni Lab, Bellinzona
Patients´ life expectancy depends on NOTCH status

**CLL – Chronic Lymphocytic Leukaemia**

*Overall Survival*

* p = 0.03

**MCL – Mantle Cell Lymphoma**

*Overall Survival*

* logrank, P=0.002

Puente et al., Nature 2011; Rossi et al., Blood 2012

Kridel, Blood 2012

Significantly shorter survival for patients with upregulated NOTCH activation

NOTCH is a clinically validated target – anti NOTCH drugs show clinical efficacy
CB-103 Clinical Development Strategy
Phase I–IIa Study Design

**Part A – dose escalation**

- Advanced/metastatic solid tumors and haematological malignancies
  - no patient enrichment for NOTCH
  - Bayesian Logistic Regression Model
  
  \[ N = \text{appr. 25} \]

- Dose Cohort 1
- Dose Cohort 2
- Dose Cohort 3
- Dose Cohort X
- MTD / RP2D

**Part B – dose confirmation**

- Expansion Arms with selected indications:
  - Selection of NOTCH+ patients
  - Bayesian Hierarchical binomial design
  - Approx. 20 pts per arm with interim analysis after 10 evaluable pts

\[ N = \text{appr. 140} \]

- Patients with NOTCH-positive/-activated tumours:
  1. Solid tumours 1 (NSCLC, lung adenocarcinoma, ovarian ca, cervical ca, prostate ca, melanoma, GBM)
  2. Solid tumours 2 (sarcomas, desmoid tumors, adenoid cystic carcinoma)
  3. TNBC Cancer with NOTCH-specific chromosomal translocations
  4. Breast cancer (other TNBC, ER+/-, HER2+/–)
  5. GI Cancers (CRC, gastric cancer, CCC)
  6. Hodgkin, non-Hodgkin and CNS lymphomas
  7. Multiple Myeloma

**Clinical Sites:** CH, ESP, NL

**CB-103 continuous oral dosing I 28-day cycles**

- 1st CTA submission in Spain done on 19 May 2017, study start in Q3-2017
- T-ALL, Leukaemia and Ib combination studies planned
For more information contact:

Dirk Weber, CMO
Cellestia Biotech AG
Hochbergerstrasse 60C, 4057 Basel, Switzerland
Mobile: +41 79 9441580
Email: dirk.weber@cellestiabiotech.com
www.cellestia.com

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