The antibody-drug conjugate (ADC) loncastuximab tesirine (ADCT-402) targeting CD19 shows strong \textit{in vitro} anti-lymphoma activity both as single agents and in combination.

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Conflict of Interest Disclosure – Chiara Tarantelli, Presentation Nr. 84

- Employment or leadership position: 

- Consultant or advisory role: N/A

- Stock ownership: N/A

- Honoraria: N/A

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- Other remuneration: N/A
Antibody Drug Conjugate (ADC)

Chalouni and Doll, J Exp & Clin Cancer Res, 2018
CD19: expressed across all B cell development stages

Adapted from Blanc V et al, CCR, 2011
Loncastuximab tesirine (ADCT-402) is a new anti-CD19 ADC active against hematological malignancies.

Zammarchi F et al, Blood 2018
# Clinical trials

<table>
<thead>
<tr>
<th>NCT number</th>
<th>Study title</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02669017</td>
<td>Dose-escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-402 in Patients With Relapsed or Refractory B-NHL</td>
<td>Phase 1</td>
<td>Completed *</td>
</tr>
<tr>
<td>NCT03589469</td>
<td>Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients With Relapsed or Refractory DLBCL</td>
<td>Phase 2</td>
<td>Recruiting</td>
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<tr>
<td>NCT03684694</td>
<td>Safety and Antitumor Activity Study of Loncastuximab Tesirine + Ibrutinib in DLBCL or MCL</td>
<td>Phase 1</td>
<td>Recruiting</td>
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<tr>
<td>NCT03685344</td>
<td>Safety and Antitumor Activity Study of Loncastuximab Tesirine and Durvalumab in DLBCL, MCL, or FL</td>
<td>Phase 1</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

* Oral (abstract 054) by J. Radford approximately one hour ago also here at the ICML

*Data from www.clinicaltrial.gov*
MTT proliferation assay and IC50 calculation on cell lines exposed (96h) to increasing ADCT-402 concentrations

*, P<0.05; **, P<0.01
Sensitivity to ADCT-402 is higher in B than T-cell lymphomas

B-cell lymphoma (n=48)
median IC50=4 pM (95%C.I, 2-10 pM)

T-cell lymphoma (n=9)
median IC50=3.5 nM (95%C.I, 0.8-11 nM)

MTT proliferation assay and IC50 calculation on cell lines exposed (96h) to increasing ADCT-402 concentrations
ADCT-402 *in vitro* activity correlates with CD19 surface protein expression in B cell lines

Pearson correlation ($r$)

- **MFI absolute expression**
  - $r = -0.37$
  - $P = 0.02$
  - $n = 40$

- **MFI relative expression**
  - $r = -0.48$
  - $P = 0.01$
  - $n = 42$

**Graphs:**
- **Left:** CD19 protein expression (Log2 MFI, absolute expression) vs. IC$_{50}$ ADCT402 (Log2, pM)
- **Right:** CD19 protein expression (Log2 MFI, relative expression) vs. IC$_{50}$ ADCT402 (Log2, pM)
ADCT-402 *in vitro* activity correlates with CD19 RNA levels in B cell lines

Illumina HT-12 array

- $r = -0.69$
- $P < 0.001$
- $n = 39$

HTG EdgeSeq Oncology Biomarker Panel

- $r = -0.73$
- $P = 0.001$
- $n = 33$

Pearson correlation ($r$)
### Drugs tested in combination with ADCT-402

<table>
<thead>
<tr>
<th>Second drug</th>
<th>Target / MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>venetoclax</td>
<td>BCL2 inhibitor</td>
</tr>
<tr>
<td>Ibrutinib *</td>
<td>BTK inhibitor</td>
</tr>
<tr>
<td>bendamustine</td>
<td>Chemotherapy agent</td>
</tr>
<tr>
<td>lenalidomide</td>
<td>Immunomodulator</td>
</tr>
<tr>
<td>copanlisib</td>
<td>PI3K inhibitor</td>
</tr>
<tr>
<td>idelalisib</td>
<td>PI3K δ inhibitor</td>
</tr>
<tr>
<td>olaparib</td>
<td>PARP inhibitor</td>
</tr>
<tr>
<td>bortezomib *</td>
<td>Proteasome inhibitor</td>
</tr>
</tbody>
</table>

* ABC only

MTT proliferation assay, 96h, 2 ABC – 2 GCB DLBCL cell lines
Synergy assessed by Chou-Talalay combination index (CI)
synergism CI<0.9, additive CI=0.9-1.1, antagonism/no benefit CI> 1.1
ADCT-402: best synergism with venetoclax, idelalisib and bendamustine

MTT proliferation assay, 96h, 2 ABC – 2 GCB DLBCL cell lines
Synergy assessed by Chou-Talalay combination index (CI)
synergism CI<0.9, additive CI=0.9-1.1, antagonism/no benefit CI>1.1
Conclusions

• ADCT-402 is strongly active in vitro in a wide panel of lymphoma cell lines

• ADCT-402 in vitro activity correlates with CD19 expression at protein and RNA level

• The results support the currently on-going clinical studies in relapsed/refractory DLBCL

• The novel combination data provide rational for further clinical development, such as combination with venetoclax, idelalisib and bendamustine.
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