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

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- Honoraria: N/A

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Antibody Drug Conjugate (ADC)

[Diagram of ADC mechanism]

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

- Stem cell
- Pro-B cell
- Pre-B cell
- Naïve B cell
- Activated B cell
- Memory GC B cell
- Late plasmablast
- Plasma cells

Associated B cell malignancies:
- ALL
- MCL
- MZL
- DLBCL
- CLL
- FL
- WM
- MM

CD19

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

r value -0.7, p-value 0.024
## 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,</td>
<td>Phase 1</td>
<td>Completed *</td>
</tr>
<tr>
<td></td>
<td>and Antitumor Activity of ADCT-402 in Patients With Relapsed or Refractory B-NHL</td>
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<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
Activity on lymphoma cell lines

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**
  - $r = -0.48$
  - $P = 0.01$
  - $n = 42$
ADCT-402 *in vitro* activity correlates with CD19 RNA levels in B cell lines

Pearson correlation ($r$)

- **Illumina HT-12 array**
  - $r = -0.69$
  - $P < 0.001$
  - $n = 39$

- **HTG EdgeSeq Oncology Biomarker Panel**
  - $r = -0.73$
  - $P = 0.001$
  - $n = 33$
**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>
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<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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