Phase 1 Study of ADCT-301 (Camidanlumab Tesirine), a Novel Pyrrolobenzodiazepine-Based Antibody Drug Conjugate, in Relapsed/Refractory Classical Hodgkin Lymphoma

M Hamadani¹, GP Collins², F Samaniego³, AI Spira⁴, A Davies⁵, J Radford⁶, P Caimi⁷, T Menne⁸, J Boni⁹, HG Cruz¹⁰, JM Feingold⁹, S He⁹, JU Wuerthner¹⁰, SM Horwitz¹¹

¹Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, USA; ²Department of Clinical Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; ³Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ⁴Virginia Cancer Specialists Research Institute, Fairfax, VA, USA; ⁵Cancer Research UK Centre, University of Southampton, Southampton, UK; ⁶University of Manchester and the Christie NHS Foundation Trust, Manchester, UK; ⁷Case Western Reserve University (CWRU) - University Hospitals Cleveland Medical Center, OH, USA; ⁸The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK; ⁹ADC Therapeutics America, Inc., Murray Hill, NJ, USA; ¹⁰ADC Therapeutics, Epalinges, Switzerland; ¹¹Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

60th American Society of Hematology Annual Meeting & Exposition
December 1–4, 2018, San Diego, CA, USA
Structure and Components of ADCT-301 (camidanlumab tesirine)

Maleimide

dPEG8

Val-Ala dipeptide

Self-immolative group

SG3199 (warhead)

CD25-specific HuMax-TAC

Tesirine/SG3249 (payload)

Drug-antibody ratio = 2.0 (± 0.3)
Camidanlumab Tesirine Mechanism of Action

Molecular mode of action

1. Camidanlumab tesirine binds to the CD25 antigen on the tumor cell surface

2. ADC internalization, linker cleavage and PBD release

3. Cytotoxic DNA cross-link formation
   a) Free PBD dimers bind sequence-selectively in the minor groove of cell DNA
   b) PBD dimers form potent cytotoxic DNA cross-links

4. Stalled DNA replication fork
   Cross-links stall the DNA replication fork, blocking cell division and causing cancer cell death

Immunological rationale

Targeting of CD25+ Tregs may increase the Teff:Treg ratio, thus promoting immunological tumor eradication.

ADC, antibody drug conjugate; PBD, pyrrolobenzodiazepine; Teff, effector T cell; Treg, regulatory T cell

Study Design

Histologically confirmed relapsed/refractory NHL* or HL
*Including Stage ≥Ib Cutaneous T-cell Lymphoma

2-part study:
- **Part 1**: Dose escalation: continual reassessment method;
- **Part 2**: Dose expansion(s)

1-hour intravenous infusion (3–300 µg/kg); Day 1 every 3 weeks

**PRIMARY OBJECTIVE:** Safety and tolerability and determine the MTD / RDE of camidanlumab tesirine

**SECONDARY OBJECTIVES:** Pharmacokinetic profile of camidanlumab tesirine
Clinical activity of camidanlumab tesirine as measured by ORR, DoR, PFS, and OS

For **HL population**: MTD was not reached; 2 RDEs for Part 2 were identified as 30 and 45 µg/kg Q3W
For **NHL population**: Data were presented at this meeting in Poster 1658 on Saturday, December 1

DoR, duration of response; HL, Hodgkin lymphoma; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RDE, recommended dose for expansion

Inclusion and Exclusion Criteria

### Key inclusion criteria

- Age 18 years or older
- Pathologically confirmed relapsed or refractory lymphoma
- Failed, or intolerant to, any established therapy known to provide clinical benefit at current state of disease
- Prior treatment with brentuximab vedotin and checkpoint inhibitor*
- Measurable disease, as defined by the 2014 Lugano Criteria
- Eastern Cooperative Oncology Group performance status 0 to 2

**HIV, human immunodeficiency virus; HSV 1/2, herpes simplex virus type 1/2; VZV; varicella zoster virus; EBV, Epstein Barr virus

* Introduced with Amendment 7 (Jan 2018)**

### Key exclusion criteria

- Active graft-versus-host disease
- History of symptomatic autoimmune disease
- History of neuropathy considered of autoimmune origin; other central nervous system autoimmune disease.
- History of recent infection considered to be caused by: HSV1, HSV2, VZV, EBV, Cytomegalovirus, measles, Influenza A, Zika virus, Chikungunya virus, m. pneumonia, C. jejuni, or enterovirus D68
- Major surgery, chemotherapy, systemic therapy, or radiotherapy within 14 days prior to Day 1 treatment
## HL population: Baseline Characteristics

Data shown as of 16 Oct 2018

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Total (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (59.7)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (40.3)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>55 (82.1)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td><strong>Age, years, median (min, max)</strong></td>
<td>38.0 (19, 80)</td>
</tr>
<tr>
<td><strong>Number of previous systemic therapies, median (min, max)</strong></td>
<td></td>
</tr>
<tr>
<td>Prior brentuximab vedotin (BV), n (%)</td>
<td>65 (97.0)</td>
</tr>
<tr>
<td>Prior checkpoint inhibitor (CHPi), n (%)</td>
<td>47 (70.1)</td>
</tr>
<tr>
<td>Prior BV and CHPi, n (%)</td>
<td>47 (70.1)</td>
</tr>
<tr>
<td>Prior stem cell transplantation, n (%)</td>
<td>40 (59.7)</td>
</tr>
<tr>
<td>• Allogeneic stem cell transplantation, n (%)</td>
<td>7 (10.4)</td>
</tr>
</tbody>
</table>
Pharmacokinetic Analysis Data

- Exposure in serum increases with dose
- Half-life in patients with lymphoma is reasonably long\(^a\)
  - PBD-conjugated antibody – 9.1 days (4.3, 25 days)
  - Total antibody – 12.0 days (4.4, 62 days)
- Modest to moderate drug accumulation expected with multiple (Q3W) doses
  - At 45 µg/kg dose (for n=29 patients),
    - ~1.4x (CV=22%) for PBD-conjugated Ab
    - ~2.1x (CV=63%) for total Ab
- PBD (SG3199) exposure predominantly below quantifiable limits; no accumulation is evident
- No significant anti-drug antibody formation apparent (n=56 patients evaluated)

\(^a\)Presented as median (min, max)

Ab, antibody; AUC, area under the curve; CV, coefficient of variation; Q3W, every 3 weeks; SE, standard error of the mean

Data shown as of 16 Oct 2018
## HL population: Most Common All Grades TEAEs (≥20% Patients) (Safety Analysis Set)

<table>
<thead>
<tr>
<th>TEAEs, n (%)</th>
<th>Dose (µg/kg)</th>
<th>≤20 (n=3)</th>
<th>30 (n=10)</th>
<th>45 (n=37)</th>
<th>60 (n=12)</th>
<th>≥80 (n=5)</th>
<th>Total (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any grade TEAE</td>
<td></td>
<td>3 (100)</td>
<td>10 (100)</td>
<td>37 (100)</td>
<td>12 (100)</td>
<td>5 (100)</td>
<td>67 (100)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>1 (33.3)</td>
<td>5 (50.0)</td>
<td>16 (43.2)</td>
<td>6 (50.0)</td>
<td>2 (40.0)</td>
<td>30 (44.8)</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td></td>
<td>1 (33.3)</td>
<td>5 (50.0)</td>
<td>14 (37.8)</td>
<td>4 (33.3)</td>
<td>2 (40.0)</td>
<td>26 (38.8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td>1 (33.3)</td>
<td>2 (20.0)</td>
<td>12 (32.4)</td>
<td>4 (33.3)</td>
<td>1 (20.0)</td>
<td>20 (29.9)</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td></td>
<td>2 (66.6)</td>
<td>1 (10.0)</td>
<td>7 (18.9)</td>
<td>5 (41.7)</td>
<td>4 (80.0)</td>
<td>19 (28.4)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td></td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>9 (24.3)</td>
<td>5 (41.7)</td>
<td>3 (60.0)</td>
<td>18 (26.9)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7 (18.9)</td>
<td>5 (41.7)</td>
<td>4 (80.0)</td>
<td>16 (23.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>10 (27.0)</td>
<td>0 (0)</td>
<td>4 (80.0)</td>
<td>15 (22.4)</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td>1 (33.3)</td>
<td>1 (10.0)</td>
<td>9 (24.3)</td>
<td>2 (16.7)</td>
<td>1 (20.0)</td>
<td>14 (20.9)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>8 (21.6)</td>
<td>3 (25.0)</td>
<td>2 (40.0)</td>
<td>14 (20.9)</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>0 (0)</td>
<td>4 (40.0)</td>
<td>8 (21.6)</td>
<td>2 (16.7)</td>
<td>0 (0)</td>
<td>14 (20.9)</td>
</tr>
</tbody>
</table>

Grey shading indicates liver test abnormalities; blue indicates other toxicities

HL, Hodgkin lymphoma; TEAE, treatment-emergent adverse event

Data shown as of 16 Oct 2018
## HL population: Most Common TEAEs ≥Grade 3 (≥5% Patients) (Safety Analysis Set)

<table>
<thead>
<tr>
<th>TEAEs ≥Grade 3, n (%)</th>
<th>Dose (µg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤20 (n=3)</td>
</tr>
<tr>
<td><strong>Patients with grade ≥3 TEAE</strong></td>
<td></td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>2 (66.6)</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Guillain–Barré syndrome/Radiculopathy</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Grey shading indicates liver test abnormalities; red shading indicates hematologic abnormalities; blue indicates other toxicities

HL, Hodgkin lymphoma; TEAE, treatment-emergent adverse event

Data shown as of 16 Oct 2018
# HL population: Selected Toxicities Summary

All Grades (Safety Analysis Set),

## Potentially PBD-related toxicities (SMQ)

<table>
<thead>
<tr>
<th>Potential PBD-related toxicities (SMQ)</th>
<th>Dose (µg/kg)</th>
<th>≤20 (n=3)</th>
<th>30 (n=10)</th>
<th>45 (n=37)</th>
<th>60 (n=12)</th>
<th>≥80 (n=5)</th>
<th>Total (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema or effusion</td>
<td></td>
<td>1 (33.3)</td>
<td>3 (30.0)</td>
<td>10 (27.0)</td>
<td>2 (16.7)</td>
<td>1 (20.0)</td>
<td>17 (25.4)</td>
</tr>
<tr>
<td>Skin related</td>
<td></td>
<td>1 (33.3)</td>
<td>9 (90)</td>
<td>25 (67.6)</td>
<td>10 (83.3)</td>
<td>4 (80.0)</td>
<td>49 (73.1)</td>
</tr>
<tr>
<td>Liver function test</td>
<td></td>
<td>3 (100)</td>
<td>1 (10.0)</td>
<td>13 (35.1)</td>
<td>8 (66.7)</td>
<td>4 (80.0)</td>
<td>29 (43.3)</td>
</tr>
</tbody>
</table>

## Selected autoimmune toxicities

<table>
<thead>
<tr>
<th>Selected autoimmune toxicities</th>
<th>Dose (µg/kg)</th>
<th>≤20 (n=3)</th>
<th>30 (n=10)</th>
<th>45 (n=37)</th>
<th>60 (n=12)</th>
<th>≥80 (n=5)</th>
<th>Total (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillain–Barré syndrome/Radiculopathy</td>
<td></td>
<td>0 (0)</td>
<td>1 (10.0)</td>
<td>3 (8.1)</td>
<td>1 (8.3)</td>
<td>0 (0)</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>Colitis</td>
<td></td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>1 (2.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (5.4)</td>
<td>1 (8.3)</td>
<td>1 (20.0)</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (5.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (20.0)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

TEAEs leading to treatment discontinuation occurred in 19/67 (28.4%) patients

PBD, pyrrolobenzodiazepine; SMQ, standardised MedDRA query; TEAEs, treatment-emergent adverse events

Data shown as of 16 Oct 2018
Camidanlumab tesirine exposure

Median (min, max) no. of cycles received
- 30 µg/kg: 4.5 (1, 9)
- 45 µg/kg: 4.0 (1, 10)
- 60 µg/kg: 2.5 (2, 8)
- 80 µg/kg: 4.0 (1, 5)

All dose levels: 3 (1, 15)

At 45 µg/kg:
- ~65% of patients tolerate 3 cycles
- ~60% of patients tolerate 4 cycles without dose modification (dose delay, reduction, or treatment discontinuation)

Time to first AE leading to dose modification

- ≤30 µg/kg
- 45 µg/kg
- 60 µg/kg
- ≥80 µg/kg

Data shown as of 16 Oct 2018
HL population: Response Rates (Efficacy Analysis Set)

<table>
<thead>
<tr>
<th>Response*, n (%)</th>
<th>Dose (µg/kg)</th>
<th>≤20 (n=3)</th>
<th>30 (n=10)</th>
<th>45 (n=37)</th>
<th>60 (n=12)</th>
<th>≥80 (n=5)</th>
<th>Total (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (CR+PR)</td>
<td>1 (33.3)</td>
<td>5 (50.0)</td>
<td>32 (86.5)</td>
<td>7 (58.3)</td>
<td>4 (80.0)</td>
<td>49 (73.1)</td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>0 (0)</td>
<td>4 (40.0)</td>
<td>16 (43.2)</td>
<td>5 (41.7)</td>
<td>2 (40.0)</td>
<td>27 (40.3)</td>
<td></td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>1 (33.3)</td>
<td>1 (10.0)</td>
<td>16 (43.2)</td>
<td>2 (16.7)</td>
<td>2 (40.0)</td>
<td>22 (32.8)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>1 (33.3)</td>
<td>3 (30.0)</td>
<td>0 (0)</td>
<td>1 (8.3)</td>
<td>0 (0)</td>
<td>5 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0 (0)</td>
<td>1 (10.0)</td>
<td>5 (13.5)</td>
<td>4 (33.3)</td>
<td>0 (0)</td>
<td>10 (14.9)</td>
<td></td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1 (33.3)</td>
<td>1 (10.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (20.0)</td>
<td>3 (4.5)</td>
<td></td>
</tr>
</tbody>
</table>

*Best visit response based on 2014 Lugano Criteria

Data shown as of 16 Oct 2018
HL population: Waterfall Plot Showing Responses for Individual Patients (Efficacy Analysis Set)

Data shown as of 16 Oct 2018

Best Percent Change from Baseline (%)

Patients

Total Subjects

5 µg/kg (N=1)  13 µg/kg (N=1)  20 µg/kg (N=1)  30 µg/kg (N=10)  45 µg/kg (N=27)

60 µg/kg (N=11)  80 µg/kg (N=3)  150 µg/kg (N=1)  300 µg/kg (N=1)
HL population: Swimmer Plot Showing Responses for Individual Patients (Efficacy Analysis Set)

40.3% (27/67) CR
32.8% (22/67) PR

*Patients who discontinue study due to reasons other than progression or who go onto a different anticancer treatment

Data shown as of 16 Oct 2018
Overall Response Rate by Prior Treatment (Efficacy Analysis Set), 45 µg/kg and All Doses Groups

<table>
<thead>
<tr>
<th>Prior Treatments</th>
<th>45 µg/kg dose (n=37)</th>
<th>All doses (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab vedotin</td>
<td>ORR 86.5% (32/37 patients)</td>
<td>ORR 73.8% (48/65 patients)</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>ORR 88.5% (23/26 patients)</td>
<td>ORR 72.3% (34/47 patients)</td>
</tr>
<tr>
<td>Checkpoint Inhibitor</td>
<td>ORR 88.9% (16/18 patients)</td>
<td>ORR 67.5% (27/40 patients)</td>
</tr>
<tr>
<td>Stem Cell Transplant</td>
<td>ORR 92.9% (13/14 patients)</td>
<td>ORR 67.9% (19/28 patients)</td>
</tr>
</tbody>
</table>

BV, brentuximab vedotin; CHPi, checkpoint inhibitor; SCT, stem cell transplantation

Data shown as of 16 Oct 2018
HL population, 45 µg/kg dose group: Duration of Response and Progression-free Survival

- Median duration of response: 7.69 months
- Median progression-free survival: 8.25 months

Data shown as of 16 Oct 2018
Duration of Response by PR/Cr – 45 µg/kg

HL patients

Median:
All responders: 7.69 months
CR: 7.69 months
PR: 7.03 months

Data shown as of 16 Oct 2018
Conclusions

➢ In patients with R/R HL, therapy with camidanlumab tesirine provided impressive OR and CR rates in a heavily pre-treated patient population
  ▪ This includes ORR 88.5% in patients in the 45 µg/kg dose group who had received prior BV and CHPi

➢ Camidanlumab tesirine has shown encouraging activity in heavily pretreated patients with HL including the challenging subset of dual BV/CHPi failure

➢ Careful investigation for early identification of patients at high risk of autoimmune events, including Guillain–Barré Syndrome, are ongoing

➢ Enrolment of patients with HL is ongoing in Part 2 at doses 30 µg/kg and 45 µg/kg Q3W

➢ These data support further investigation in a planned Phase 2 study

BV, brentuximab vedotin; CHPi, checkpoint inhibitor; CR, complete response; HL, Hodgkin lymphoma; ORR, overall response rate; R/R, relapsed/refractory

Data shown as of 16 Oct 2018
Acknowledgments

➢ Investigators and affiliations

- M Hamadani, Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, USA
- GP Collins, Department of Clinical Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
- F Samaniego, Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, TX, USA
- AI Spira, Virginia Cancer Specialists Research Institute, Fairfax, VA, USA
- A Davies, Cancer Research UK Centre, University of Southampton, Southampton, UK
- J Radford, University of Manchester and the Christie NHS Foundation Trust, Manchester, UK
- P Caimi, Case Western Reserve University (CWRU) - University Hospitals Cleveland Medical Center, OH, USA
- T Menne, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle
- SM Horwitz, Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

➢ ADC Therapeutics:

- J Boni, ADC Therapeutics America, Inc, Murray Hill, NJ, USA
- HG Cruz, ADC Therapeutics SA, Epalinges, Switzerland
- JM Feingold, ADC Therapeutics America, Inc., Murray Hill, NJ, USA
- S He, ADC Therapeutics America. Inc., Murray Hill, NJ, USA
- JU Wuerthner, ADC Therapeutics SA., Epalinges, Switzerland

The authors would like to thank all the participating patients and their families, all study co-investigators and research coordinators, and editorial support from Fishawack Communications Ltd.

Study sponsored by ADC Therapeutics SA.
http://clinicaltrials.gov/show/NCT02432235