Pharmacokinetic and Pharmacodynamic Correlates From the Phase 1 Study of Camidanlumab Tesirine (Cami) in Patients With Relapsed or Refractory Hodgkin Lymphoma and Non-Hodgkin Lymphoma

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Poster Session III, Monday, December 7, 2020:
7:00 am – 3:30 pm (Pacific Time)
Background

Camidanlumab tesirine (Cami)
• An ADC comprising a human mAb, HuMax®-TAC, directed against human CD25, stochastically conjugated to a PBD dimer warhead

Mechanism of action\textsuperscript{1–3}
• Death of CD25-positive tumor cells
• Depletion of CD25-positive T cells
• Possible bystander killing of CD25-negative cells


ADC, antibody-drug conjugate; mAb, monoclonal antibody; PBD, pyrrolobenzodiazepine.
Study Methods and Objectives

Phase 1, first-in-human, open-label, single-arm, dose-escalation\textsuperscript{a}, dose-expansion trial (NCT02432235) of patients ≥18 years of age with R/R cHL or NHL receiving Cami in doses of 3–150 µg/kg IV Q3W\textsuperscript{b}

- The two recommended doses for expansion in the cHL population were 30 and 45 µg/kg

Primary objectives:
- Characterize Cami safety and tolerability, and determine MTD

Secondary and exploratory objectives:
- Evaluate antitumor activity of Cami, including ORR and DoR
- PK profile of Cami, PBD-cAb\textsuperscript{c}, tAb\textsuperscript{d}, and unconjugated warhead, SG3199
- ADA response in serum
- PK/PD correlates to:
  - sCD25 concentrations
  - time course of peripheral B cells, NK cells, T-cell subsets (T\textsubscript{eff}, T\textsubscript{reg}), and T\textsubscript{eff}:T\textsubscript{reg} ratio
  - IHC on archival or pre-treatment tumor biopsies for CD25 expression

Here, we report PK/PD correlates using data from 133 patients (77 with R/R cHL, 56 with R/R NHL)

\textsuperscript{a}Conducted per continual reassessment method; \textsuperscript{b}One patient received an unplanned dose of 300 µg/kg for the first dose but continued in the study with subsequent dosing as planned at 30 µg/kg; \textsuperscript{c}DAR ≥1; \textsuperscript{d}DAR ≥0. ADA, anti-drug antibody; cAb, conjugated antibody; cHL, classical Hodgkin lymphoma; DAR, drug-to-antibody ratio; DoR, duration of response; IHC, immunohistochemistry; IV, intravenous; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; NK, natural killer; ORR, overall response rate; PBD, pyrrolobenzodiazepine; PD, pharmacodynamic; PK, pharmacokinetic; Q3W, every 3 weeks; R/R, relapsed or refractory; sCD25, soluble CD25; tAb, total antibody; T\textsubscript{eff}, effector T cell (CD8\textsuperscript{+}); T\textsubscript{reg}, regulatory T cell (CD25\textsuperscript{+}/CD127\textsuperscript{low}/FoxP3\textsuperscript{+}[CD3\textsuperscript{+}/CD4\textsuperscript{+}]).
Results: Pharmacokinetics and Immunogenicity

PK for 3–300 μg/kg doses
- Mean exposures increased with dose
- CL for doses 30–80 μg/kg relatively constant

PK for 45 μg/kg dose (Table)
- Good linker stability of immunoconjugate – close similarity in cAb and tAb profiles
- By Cycle 2, similar respective exposures with lower inter-patient variability relative to Cycle 1
- Apparent half-life of cAb 2.69 days (CV=40.2%)
- No accumulation by end of 3-week cycle
- SG3199 levels below LLOQ

Immunogenicity
- No instances of positive ADA response

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Analyte</th>
<th>C_{max} (μg/L)</th>
<th>AUC_{inf}a (day*μg/L)</th>
<th>T_{half} (day)</th>
<th>CL (L/day)</th>
<th>V_{ss} (L)</th>
<th>Al</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBD-cAb</td>
<td>648 (51.0)</td>
<td>1846 (59.9)</td>
<td>2.31 (45.5)</td>
<td>1.68 (50.3)</td>
<td>5.08 (23.3)</td>
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<tr>
<td></td>
<td>tAb</td>
<td>803 (54.4)</td>
<td>3001 (75.0)</td>
<td>2.62 (44.1)</td>
<td>1.29 (64.0)</td>
<td>4.57 (26.9)</td>
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<tr>
<td></td>
<td>SG3199</td>
<td>0.0120 (8.04)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>PBD-cAb</td>
<td>808 (55.8)</td>
<td>2183 (61.6)</td>
<td>2.69 (40.2)</td>
<td>1.37 (55.3)</td>
<td>4.91 (29.9)</td>
<td>1.01 (1.48)</td>
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<tr>
<td></td>
<td>tAb</td>
<td>1040 (60.0)</td>
<td>3604 (68.9)</td>
<td>3.26 (38.0)</td>
<td>1.03 (61.2)</td>
<td>4.54 (36.0)</td>
<td>1.02 (2.59)</td>
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<tr>
<td></td>
<td>SG3199</td>
<td>0.0170 (46.9)</td>
<td>-</td>
<td>-</td>
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</tr>
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</table>

Summary of PK Parameters in Serum Following Cami 45 μg/kg Q3W

Data shown as geometric mean (geometric CV%)[n]. *AUC_{inf} for Cycle 2 observations.

ADA, anti-drug antibody; AI, accumulation index; AUC_{inf}, area under concentration–time curve from time zero to infinity (Cycle 1 in Table); AUC_{ss}, area under concentration–time curve over Q3W duration of dosing interval (Cycle 2 in Table); cAb, conjugated antibody; CL, apparent clearance; C_{max}, observed maximum concentration; CV, coefficient of variation; LLOQ, lower limit of quantification; PBD, pyrrolobenzodiazepine; PK, pharmacokinetic; Q3W, every 3 weeks; tAb, total antibody; T_{half}, apparent terminal half-life; V_{ss}, apparent steady-state volume of distribution; "-", value not available.
Results: Modulation of Lymphocyte Populations Post-Dosing

- Lymphocyte populations including total lymphocytes, CD8+ and CD4+ T cells showed transient increases following dosing (Figure)
- Similar pattern seen for CD3+ T cells and CD16+/CD56+ NK cell subsets
- Modulations by time were similar for 30 and 45 μg/kg doses
- No difference by response group at 30 μg/kg; the low rate of non-responders precluded comparison for the 45 μg/kg dose

Dashed vertical lines in figure denote planned dosing event. Available paired lymphocyte and response data for 45 μg/kg predominantly limited to patients achieving CR or PR.

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease.
Results: $T_{\text{reg}}$ Counts and $T_{\text{eff}}:T_{\text{reg}}$ Ratios Post-Dosing

- Small absolute decreases in $T_{\text{reg}}$ cell counts over time seen following the 30 and 45 $\mu$g/kg doses (Figure)
- No distinction by best overall clinical response (CR + PR vs. non-responders)
- Most patients had clear increases in $T_{\text{eff}}:T_{\text{reg}}$ ratios over time; greater effects seen in Cycle 2 relative to Cycle 1

Dashed vertical lines in figure denote planned dosing event. Available paired $T_{\text{reg}}$ and response data for 45 $\mu$g/kg predominantly limited to patients achieving CR or PR.

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; $T_{\text{eff}}$, effector T cell (CD8$^+$); $T_{\text{reg}}$, regulatory T cell (CD25$^+$/CD127low/FoxP3$^+$/CD3$^+$/CD4$^+$).
Results: CD25 Expression and Response

- With the 45 µg/kg dose, mean sCD25 concentrations displayed apparent decreases from baseline over time.
- In cHL, higher baseline sCD25 levels associated with lower Cami exposure in responders and non-responders.
- Clustering suggested with sCD25 concentrations <~10,000 ng/L at baseline, particularly for patients with CR (Figure).
- Data from IHC on tumor biopsies\(^a\) for CD25 expression showed no relationship between CD25 histoscore and clinical response.

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Data derived from non-compartmental analysis. \(^a\)Archival or pre-treatment biopsies.

AUC, area under the curve; cAb, conjugated Ab; cHL, classical Hodgkin lymphoma; CR, complete response; IHC, immunohistochemistry; NE, not evaluable; PBD, pyrrolobenzodiazepine; PD, progressive disease; PR, partial response; sCD25, soluble CD25; SD, stable disease.
Conclusions

- These data suggest patients with cHL achieving complete response have higher exposure to Cami.
- Higher exposure appears to result from lower baseline sCD25 and possibly lower tumor burden.

- Exposure at the 45 µg/kg dose was associated with:
  - cycle-related modulation in circulating T_{regs}
  - increased T_{eff}:T_{reg} ratios, thought to favor disease response

- T_{reg} modulation was seen with all populations and these data support further study of T-cell subpopulations in patients treated with Cami.

\( \text{cHL} \), classical Hodgkin lymphoma; \( s\text{CD25} \), soluble CD25; \( T_{eff} \), effector T cell; \( T_{reg} \), regulatory T cell.
Disclosures and Acknowledgments

**J. Boni:** employee of ADC Therapeutics America, Inc., with ownership interests

**K. Havenith, K. Anderson** and **T. Kopotsha:** employees of ADC Therapeutics (UK) Ltd with ownership interests

**H. G. Cruz** and **J. Wuerthner:** employees of ADC Therapeutics SA, with ownership interests

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