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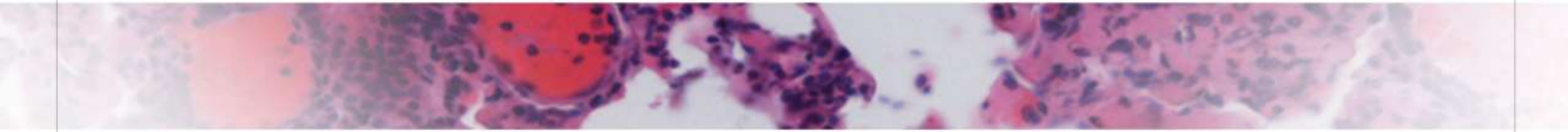

Pharmacokinetic and Pharmacodynamic Correlates From the Phase 1 Study of Camidanlumab Tesirine (Cami) in Patients With Relapsed or Refractory Hodgkin Lymphoma and Non-Hodgkin Lymphoma

Joseph Boni,[1] Karin Havenith,[2] Mehdi Hamadani,[3] Paolo Caimi,[4] Katie Anderson,[2] Tim Kopotsha,[2] Hans G. Cruz,[5] Jens Wuerthner[5]

[1]Clinical Development, ADC Therapeutics America, Inc., Murray Hill, NJ, USA; [2]Clinical Research, ADC Therapeutics (UK) Ltd, London, UK; [3]Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, USA; [4]University Hospitals Cleveland Medical Center/Case Western Reserve University, Cleveland, OH, USA; [5]Clinical Development, ADC Therapeutics SA, Epalinges, Switzerland

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

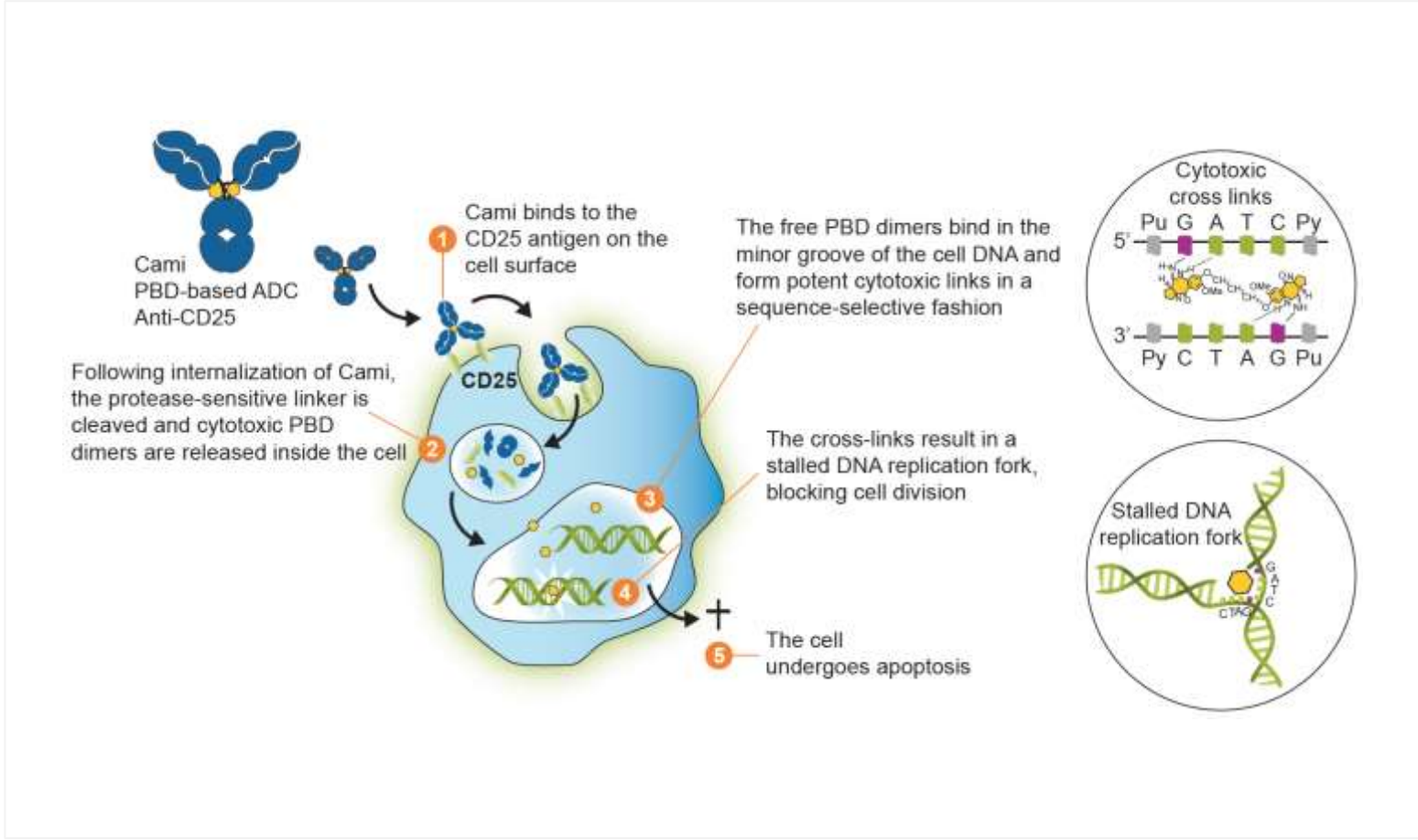
Background

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[1–3]

- Death of CD25-positive tumor cells
- Depletion of CD25-positive T cells
- Possible bystander killing of CD25-negative cells



1. Hartley JA. *Expert Opin Investig Drugs* 2011;20:733–44; 2. Flynn MJ, et al. *Mol Cancer Ther* 2016;15:2709–21; 3. Zammarchi F, et al. *J ImmunoTher Cancer* 2020;8:e000860.

ADC, antibody-drug conjugate; **mAb**, monoclonal antibody; **PBD**, pyrrolobenzodiazepine.

Study Methods and Objectives

Phase 1, first-in-human, open-label, single-arm, dose-escalation[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[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[c], tAb[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_{eff}, T_{reg}), and T_{eff}:T_{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)

[a]Conducted per continual reassessment method; [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; [c]DAR ≥1; [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_{eff}**, effector T cell (CD8+); **T_{reg}**, regulatory T cell (CD25+/$CD127_{low}$/FoxP3+[CD3+/CD4+]).

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

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

Cycle	Analyte	C_{max} (µg/L)	AUC_{inf}[a] (day*ug/L)	T_{half} (day)	CL (L/day)	V_{ss} (L)	AI
1	PBD-cAb	648 (51.0) [41]	1846 (59.9) [29]	2.31 (45.5) [29]	1.68 (50.3) [29]	5.08 (23.3) [29]	-
	tAb	803 (54.4) [41]	3001 (75.0) [23]	2.62 (44.1) [23]	1.29 (64.0) [23]	4.57 (26.9) [23]	-
	SG3199	0.0120 (8.04) [5]	-	-	-	-	-
2	PBD-cAb	808 (55.8) [35]	2183 (61.6) [33]	2.69 (40.2) [30]	1.37 (55.3) [33]	4.91 (29.9) [30]	1.01 (1.48) [30]
	tAb	1040 (60.0) [35]	3604 (68.9) [33]	3.26 (38.0) [33]	1.03 (61.2) [33]	4.54 (36.0) [33]	1.02 (2.59) [33]
	SG3199	0.0170 (46.9) [3]	-	-	-	-	-

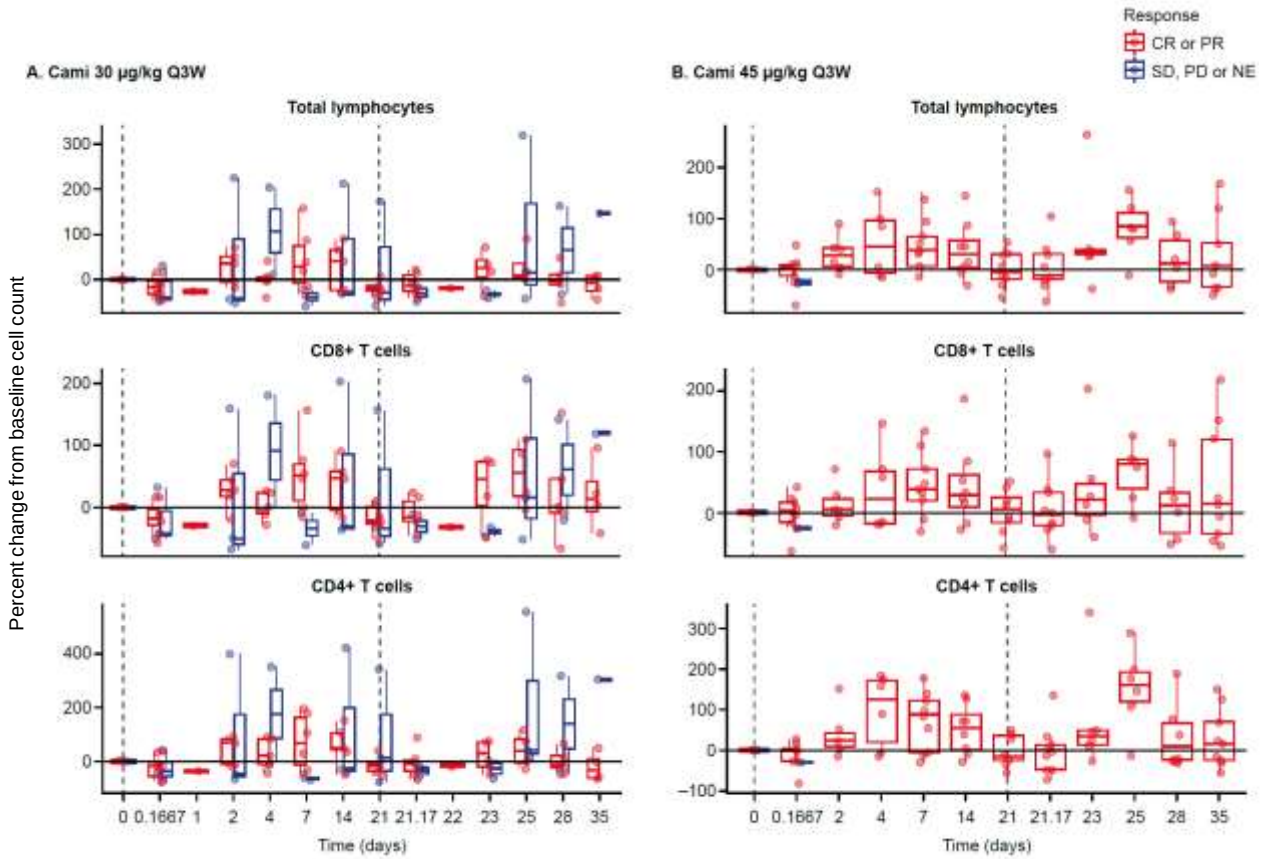
Data shown as geometric mean (geometric CV%)[n]. [a]AUC_{tau} for Cycle 2 observations.

ADA, anti-drug antibody; **AI,** accumulation index; **AUC_{inf}**, area under concentration–time curve from time zero to infinity (Cycle 1 in Table); **AUC_{tau}**, 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

Lymphocyte Populations by Percent Change From Baseline vs. Time by Best Overall Response



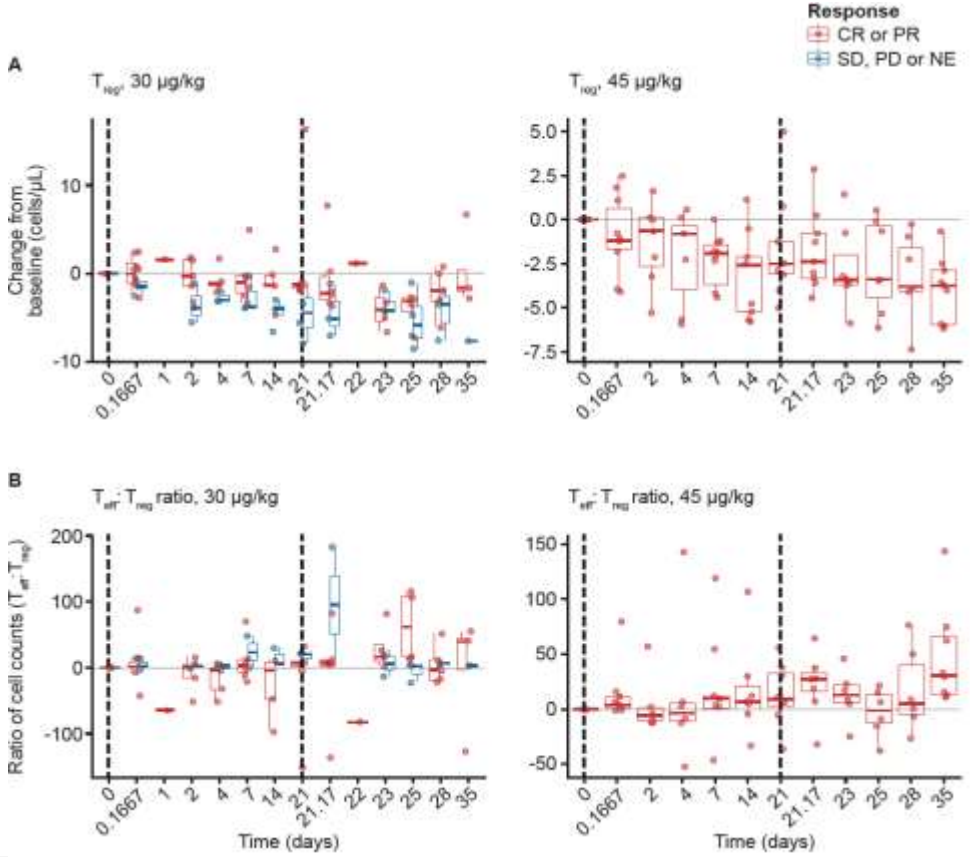
Dashed vertical lines in figure denote planned dosing event. Available paired lymphocyte and response data for 45 µg/kg predominantly limited to patients achieving CR or PR.

CR, complete response; **NE**, not evaluable; **PD**, progressive disease; **PR**, partial response; **Q3W**, every 3 weeks; **SD**, stable disease.

Results: T_{reg} Counts and T_{eff}:T_{reg} Ratios Post-Dosing

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

T_{reg} (A) and T_{eff}:T_{reg} (B) Ratio Profiles for Cami 30 and 45 µg/kg by Best Overall Response



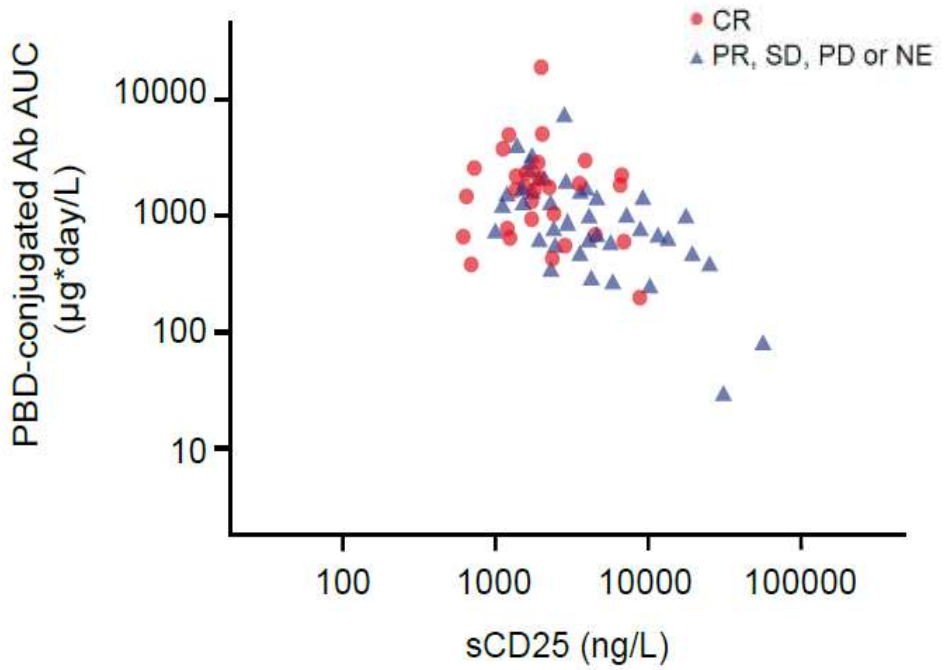
Dashed vertical lines in figure denote planned dosing event. Available paired T_{reg} and response data for 45 µg/kg predominantly limited to patients achieving CR or PR.

CR, complete response; **NE**, not evaluable; **PD,** progressive disease; **PR**, partial response; **SD**, stable disease; **T_{eff}**, effector T cell (CD8+); **T_{reg}**, regulatory T cell ($CD25+/CD127_{low}/FoxP3+[CD3+/CD4+]$).

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

PBD-cAb AUC (Cycle 1) vs. Baseline sCD25 by Best Overall Response in Patients with cHL



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

cHL, classical Hodgkin lymphoma; **sCD25**, soluble CD25; **T_{eff}**, effector T cell; **T_{reg}**, regulatory T cell.

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