Effect of Camidanlumab Tesirine (Cami) as Monotherapy and in Combination With Pembrolizumab (PEM) on the Immune Cell Profile in Patients With Selected Advanced Solid Tumors

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INTRODUCTION

- Regulatory T cells (T_{regs}) promote the establishment and progression of tumors in pre-clinical models, and high tumor infiltration by T_{reg} cells with a low ratio of effector T cells (T_{effs}) to T_{regs} may contribute to poor prognosis in patients with solid tumors.[1]
- Pre-clinical studies have evaluated blocking or depleting CD25+ T_{regs} and demonstrated tumor growth inhibition and improved survival.[1]
- Camidanlumab tesirine (Cami) is an antibody-drug conjugate (ADC) comprising an anti-CD25 antibody conjugated through a cleavable linker to a pyrrolobenzodiazepine (PBD) dimer. After internalization of Cami by CD25+ tumor cells, the PBD dimer binds in the minor groove of DNA and creates interstrand crosslinks, ultimately causing the tumor cells to undergo apoptosis (**Figure 1A**).[2,3]
- Cami might also impart immunomodulatory effects to deplete CD25+ T_{regs}, thereby modifying the effector T cells (T_{eff}):T_{reg} intra-tumoral balance (**Figure 1B**).[2,3]
- There is potential for synergy between Cami and anti-PD-1 antibodies, such as pembrolizumab, which are know to inhibit PD-1 and subsequently activate a CD8+ T cell–mediated response to kill cancer cells.[4,5]
- In this phase 1b study (NCT03621982), the immune-mediated antitumor activity of Cami via the depletion of CD25+ T_{regs} in the tumor microenvironment is being explored in patients with selected advanced solid tumors.

Figure 1A. Mechanism of action of camidanlumab tesirine

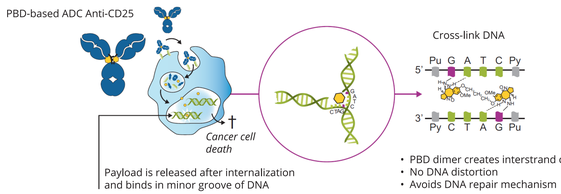
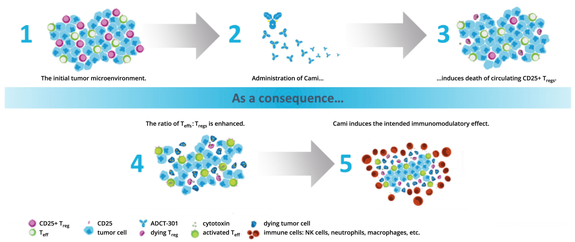


Figure 1B. Effect of camidanlumab tesirine on immune cells in the tumor microenvironment



OBJECTIVE

- To describe the pharmacokinetics (PK) and circulating immune cell profiles for Cami monotherapy and Cami in combination with pembrolizumab in a phase 1b trial in patients with selected advanced solid tumors.

METHODS

Study Design

- This is a phase 1b, multicenter, open-label, dose-escalation, and dose-expansion study currently enrolling patients (age ≥18 years) with advanced solid tumors who have experienced treatment failure of recommended therapies.
  - Cami monotherapy was administered in a dose-escalation using a 3+3 design at a starting dose of Cami 20 µg/kg and up to a maximum of 150 µg/kg, given as a 30-minute intravenous infusion once every 3 weeks (Q3W).
  - Cami was administered at escalating doses—ranging from 30 to 60 µg/kg—in combination with pembrolizumab (PEM) at 200 mg Q3W for 2 cycles and then PEM was administered alone for 2 cycles (Cycles 3 and 4), repeated for up to 1 year.
- The primary study objective is to characterize the safety and tolerability of Cami and identify a recommended dose(s) and schedule(s). Laboratory values were monitored at least weekly for the first 2 cycles and every 3 weeks thereafter.
  - Secondary/exploratory study objectives include characterization of preliminary antitumor activity, PK, immunogenicity, soluble CD25 (sCD25) in serum, and immune cells in blood and tissues.

PK and Biomarker Analyses

- Blood samples for PK and biomarker analyses were collected pre-dose and at 4, 48, 96, 168, and 336 hours post-dose from the start of infusion in cycles 1–4 and then at pre-dose for subsequent cycles (**Table 1**).
  - Additionally, during cycles 1 and 2, blood samples for PK analyses were collected at the end of infusion.
- Cami conjugated antibody (cAb) and total antibody (tAb) moieties in serum were quantified using validated electrochemiluminescence assays; SG3199 was quantified via tandem liquid chromatography (LC)/mass spectrometry (MS)-MS.
- Soluble CD25 in serum was quantified using a qualified enzyme-linked immunoassay.
- PK parameters assessed by noncompartmental analysis included maximum serum concentration (C_{max}), area under the curve (AUC), clearance, volume of distribution, and apparent half-life.
- Circulating immune cell counts in blood were assessed using flow cytometry for T_{regs} (FoxP3+CD25+CD127$_{low}$) as a fraction of absolute CD4+ cells; T_{eff} (CD8+ absolute); and a T_{eff}:T_{reg} ratio.

Table 1. Schedule of PK assessments

Cycle	C1 & C2				C3 onwards		EOT
Day	1	3 & 5	8	15	1	8[a]	
PK sample	✓Pre, EOI, post[b]	✓	✓	✓	✓C3, C4 (pre and post), then every cycle (pre)		✓
ADA sample	✓Pre[c]			✓(C1 only)	✓C3, C4, C5 (pre), then every other cycle (pre)		✓
Soluble biomarkers	✓Pre, post[b]	✓	✓	✓	✓C3, C4, C5 (pre), then every other cycle (pre)		✓
CD markers	✓Pre, post[b]	✓	✓	✓	✓C3, C4 (pre)	✓C3, C4	✓

[a]After completion of C4, Day 8 visit not required unless clinically indicated; [b]Pre-dose is preferably 2 hours prior to start of Cami infusion, EOI assessment to be done 5-10 minutes prior to EOI, and post-dose is 4 hours from start of Cami infusion; [c]Pre-dose is within 2 hours prior to start of Cami infusion, and post-dose is 4 hours from start of Cami infusion; [d]Patients who test positive for ADAs will be requested to supply additional ADA samples.
ADA, anti-drug antibody; C, cycle; Cami, camidanlumab tesirine; CD, cluster of differentiation; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetic; post, post-dose; pre, pre-dose.

Statistical Analysis

- Statistical assessments of the cell count and sCD25 data were performed using a linear mixed-effects model (maximum likelihood method) for biomarker effect models with cAb cycle 1 AUC, treatment (monotherapy vs. PEM combination), and treatment cycle as fixed effects; random effects included intercepts for visits, patients, and the slope for cAb AUC during cycle 1.
  - The dose effect was not evaluated due to the confounding with the cAb cycle 1 AUC parameter.
- The following equations were used to describe the null and full models:
  - Null model: log cell count ~ log AUC + cycle + (1+ log AUC|Subject) + (1+ log AUC|Visit Day).
  - Full model: log cell count ~ log AUC + PEM*cycle + (1+ log AUC|Subject) + (1+ log AUC|Visit Day).

RESULTS

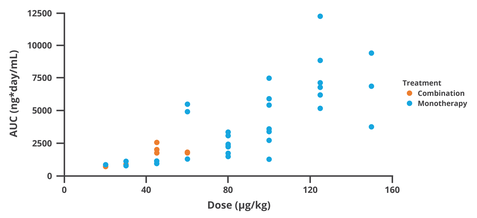
Patient Characteristics

- As of January 28, 2022, 44 patients were enrolled and treated at doses of 20 (n=3), 30 (n=5), 45 (n=5), 60 (n=5), 80 (n=8), 100 (n=7), 125 (n=8), and 150 µg/kg (n=3) Q3W with Cami monotherapy; there were 11 patients treated with 200 mg PEM and 30 (n=4), 45 (n=6), and 60 µg/kg (n=1) Cami as a combination therapy.
- Pancreatic (30.9%), colorectal (30.9%), and ovarian/fallopian (9.1%) cancers were the most common tumor types.

PK Profile

- Cami exposure increased with dose during cycles 1 and 2 (**Figure 2**).
- The variability of mean exposures (AUC_{inf} for conjugated Ab in cycle 1) over discrete dose groups appears modest to marked (CV=14.8% to 97.9%).
- Clearance for conjugated Ab ranged from 1.34 to 3.33 L/day with no apparent differences between the monotherapy and combination treatments.
- Free unbound SG3199 levels were at or below the lower limit of quantification preventing definitive characterization.

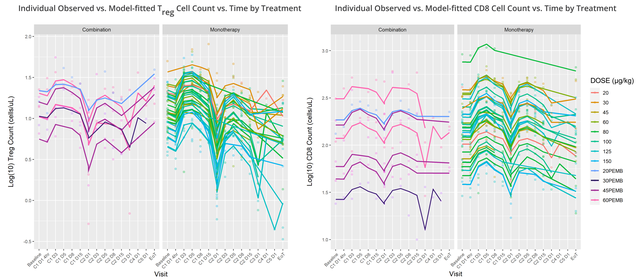
Figure 2. Cami cAb AUC in cycle 1 vs. dose



Circulating Immune Cell Profile

- Cami treatment-related modulations of immune cells were observed within each treatment cycle for all dose levels for monotherapy and combination treatment.
- Cami therapy significantly decreased T_{reg} FoxP3+ cells across treatment cycles, especially during cycle 2 (**Figure 3A**).
  - Circulating T_{reg} cells exhibited temporal changes, initially increasing across cycle 2, which may be attributable to an overall immune stimulation affecting all lymphocytes, followed by a decrease in T_{reg} cells that ultimately led to a significant decrease in T_{reg} cells across the treatment cycle.
- Across all dose levels for monotherapy and combination treatment, a limited effect of Cami treatment on CD8+ cells was observed across treatment cycles (**Figure 3B**).
- The CD8-to-T_{reg} FoxP3+ ratio was significantly increased across treatment cycles (**Figure 3C**) and appeared to be driven by the decrease in T_{reg} cells.
- Modulation of sCD25 was apparent in both Cami monotherapy and Cami + PEM combination arms (**Figure 3D**). Relative to monotherapy, levels of free sCD25 were significantly decreased by Cami + PEM combination treatment in cycle 1, whereas levels of free sCD25 were significantly increased by cycle 2.
  - The uniform initial decline in sCD25 at the 4-hour time point are thought to be due to the direct drug effect of Cami in circulation.

Figure 3A. T_{reg} cell count over time by treatment with Cami monotherapy and Cami + PEM combination



PEM combination AUC and cycle negative effects significant	Cami monotherapy AUC negative effect significant
AUC, p=0.002083 Cycle 2, p=0.023236 Cycle 3, p=0.054509	AUC, p=0.0039

Figure 3B. CD8+ cell count versus time by treatment with Cami monotherapy and Cami + PEM combination

PEM combination cycle negative effect significant	Cami monotherapy cycle negative effect significant
Cycle 3, p=0.0013	Cycle 3, p=0.008071

Figure 3C. CD8-to-T_{reg} FoxP3+ cell count over time by treatment with Cami monotherapy and Cami + PEM combination

PEM combination AUC and cycle positive effects significant	Cami monotherapy AUC and cycle positive effects significant
AUC, p=0.010654 Cycle 2, p=3.01e-05	AUC, p=0.00119 Cycle 2, p=1.35e-05 Cycle 3, p=0.05710

Figure 3D. sCD25 concentration over time by treatment with Cami monotherapy and Cami + PEM combination

PEM combination PEM treatment negative effect and cycle positive effects significant	Cami monotherapy modulations apparent but not statistically significant
PEM combo, p=0.00111 Cycle 2, p=0.00224	AUC, p=0.0772

T_{reg} denoted as product of FoxP3+CD25+CD127$_{low}$ (%) and absolute CD4+ cells x 0.01; symbols denote individual patient observations; lines denote individual patient model-predicted values 'C'=cycle; 'D'=day.

CONCLUSIONS

- PK exposure following treatment with Cami was dose-related, with varying degrees of interpatient variability.
  - There were no apparent differences in Cami clearance between monotherapy and combination treatments.
- sCD25 appeared to be modulated during treatment, particularly with Cami in combination with PEM, marked by an initial decline in sCD25 levels followed by a subsequent rebound, suggesting potential compensatory immune involvement.
- Cami treatment modulation of immune cell populations was observed within cycle for all doses and conditions.
- The fixed effect of Cami treatment by cycle 3 on CD8+ T cells appears limited.
- Circulating T_{regs} were significantly decreased across cycles, and the T_{eff}:T_{reg} ratio was significantly increased by Cami exposure, demonstrating the intended immunomodulatory effect of Cami in circulation and suggesting that a combination approach with Cami could address an immune-resistance mechanism.

Acknowledgments

- ADC Therapeutics; medical writing support: CiTRUS Health Group.

Disclosures

I Puzanov: medical writing, article processing charges for Bristol Myers Squibb; consulting charges for Amgen, Merck, Nouscom, Nektar, Iovance. **C T Chen**: research funding for Nuvelution Pharma, Foundation Medicine, Takeda, Seattle Genetics, Oric Pharmaceuticals, ADC Therapeutics. **P LoRusso**: advisory/consultancy for AbbVie, Agios (DSMB), Five Prime (DSMB), GenMab, Haolzyme (DSMB), Roche-Genentech, Genentech, CytomX, Takeda, Sotio, Cybrexa, Agenus (2018-20), Tyme (DSMB), IQVIA, TRIGR, Pfizer, I-MAB, ImmunoMet, GSK, Black Diamond, QED Therapeutics, AstraZeneca, EMD Serono, Shattuck, Astellas, Salarius, Silverback, MacroGenics, Kyowa Kirin Pharmaceutical Development, Kineta, Inc., Zentalis Pharmaceuticals, and Molecular Templates; research funding (institution) for AbbVie, ADC Therapeutics, ALX Oncology, Inc., Astellas Pharma US, Inc., Astex Pharmaceuticals, Inc., AstraZeneca, Bayer Healthcare Pharmaceuticals, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Research & Development, Corvus Pharmaceuticals, Inc., CytomX Therapeutics, Daiichi Sankyo, Eisai Pharmaceuticals, Eli Lilly & Company, EMD Serono, Five Prime Therapeutics, Inc., Rapt Therapeutics, F-Star Delta Limited, Genentech, Inc., Genmab, Inc., Incyte Corporation, Linnaeus Therapeutics, Inc., MedImmune, Inc., Merck Sharp & Dohme, Moderna Therapeutics, Inc., NextCure, Inc., Novartis Pharmaceuticals, Radius Pharmaceuticals, Sotio, Stemline Therapeutics, Inc., Tesaro, Inc. **K P Papadopoulos**: advisory/consultancy, research funding (self and institution) for Argule, Basilia, Bayer, AbbVie, Daiichi Sankyo, Anheart, MedImmune, Peleton Therapeutics, Regeneron, Sanofi, ArQule, Amgen, Calithera Biosciences, Curegenix, Incyte, F-Star Delta Limited, Merck, Jounce Therapeutics, ADC Therapeutics, Tempest Therapeutics, Linnaeus Therapeutics, Formation Biologics, EMD Serono, Syros Pharmaceuticals, Mersana, and MabSpace Biosciences. **S Kummar**: advisory/consultant for Boehringer Ingelheim, Springworks Therapeutics, Gilead, EcoR1, Seagen, Mundibiopharma, Bayer, Genome & Company, Mirati, OxfordBiotherapeutics, and Harbour Biomed; co-founder and equity holder for PathomIQ, and spouse is a scientific advisor for Cadila Pharmaceuticals Ltd. and founder of Arxeon Inc. **E Hamilton**: research funding (institution) for AbbVie, Acerta Pharma, ADC Therapeutics, Mabspace Biosciences, Macrogenics, MedImmune, Merck, Mersana, Merus, Millennium, Molecular Templates, Myraid Genetic Laboratories, Novartis, Nucana, Olema, OncoMed, Onconova Therapeutics, ORIC Pharmaceuticals, Orinove, Pfizer, PharmaMar, Pieris Pharmaceuticals, Pionyr Immunotherapeutics, Plexxikon, Radius Health, Regeneron, Repertoire Immune Medicine, Rgenix, Roche/Genentech, Seattle Genetics, Sermonix Pharmaceuticals, Shattuck Labs, Silverback, StemCentRx, Sutro, Syndax, Syros, Taiho, TapImmune, Tesaro, Treadwell Therapeutics, Verastem, Vincerx Pharma, Zenith Epigenetics, Zymeworks; consultancy/advisory for Arcus, Arvinas, AstraZeneca, Black Diamond, Boehringer Ingelheim, CytomX, Daiichi Sankyo, Dantari, Deciphera Pharmaceuticals, Eisai, H3 Biomedicine, iTeos, Janssen, Lilly, Loxo, Merck, Mersana, Novartis, Pfizer, Puma Biotechnology, Relay Therapeutics, Roche/Genentech, Seattle Genetics, Silverback Therapeutics. **Y LeBruchec**, **S Pantano**, and **J Wuerthner**: employed and current equity holders at ADC Therapeutics SA, a publicly traded company. **K Havenith**: employed and a current equity holder at ADC Therapeutics (UK) Ltd, a publicly traded company. **M Toukam** and **J Boni**: employed and current equity holders at ADC Therapeutics America, Inc., a publicly traded company.

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Poster presented at the AACR Annual Meeting 2022. April 8–13, 2022, New Orleans, LA.