A Phase 1b, Open-Label, Dose-Escalation Study to Evaluate Camidanlumab Tesirine (Cami) as Monotherapy in Patients with Advanced Solid Tumors

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BACKGROUND

- A significant association between high FoxP3+ regulatory T cell (T_{reg}) infiltration and shorter overall survival has been observed in some types of solid tumors (odds ratio 1.46; p<0.001)[1]
- Poor prognosis in solid tumors is also associated with a low effector T cell (T_{eff}) to T_{reg} ratio; depletion of tumor-infiltrating lymphocytes, particularly CD25+ T_{regs}, to increase this ratio has been explored to eradicate tumors[2–4]
- Camidanlumab tesirine (Cami; ADCT-301) is an antibody-drug conjugate comprising a human antibody (Ab) directed against CD25, stochastically conjugated via a cleavable linker to a pyrrolobenzodiazepine (PBD) dimer warhead, SG3199[2]
  - Preclinical findings demonstrated potent antitumor activity in solid tumor models using a mouse surrogate[4]
- We report preliminary data from the monotherapy arm of a Phase 1b trial of Cami in selected advanced solid tumors (NCT03621982)

METHODS

Study Design

- This is a multicenter, open-label study with a standard 3+3 dose-escalation design
- After screening, patients receive Cami at a starting dose of 20 µg/kg via 30-min intravenous infusion every 3 weeks (Q3W; 1 cycle)
  - Follow-up visits take place every 12 weeks, for up to 1 year
- Study objectives were:
  - **Primary:** Characterize safety and tolerability of Cami monotherapy, and identify recommended Phase 2 dose for future studies
  - **Key secondary:** Evaluate preliminary Cami antitumor activity; pharmacokinetics (PK); and immunogenicity
  - **Key exploratory:** Assess Cami pharmacodynamics (PD)
- Eligibility criteria: ≥18 years; pathologic diagnosis of solid tumor malignancy locally advanced or metastatic at screening; measurable disease per Response Evaluation Criteria in Solid Tumors v1.1; refractory to or intolerant of existing therapies with known clinical benefit; and no CD25 (interleukin-2R) Ab therapy in last 4 months

Safety and Tolerability Analyses

- Safety and tolerability of study drug were assessed by regular monitoring for adverse events (AEs), serious adverse events, dose interruptions or reductions, and incidence of dose-limiting toxicities (DLTs)

Efficacy Analysis

- Efficacy was evaluated by disease control rate, assessed as stable disease or better (partial or complete response)

Pharmacokinetics and Pharmacodynamics Analyses

- PK profiling of serum drug concentrations used electro-chemiluminescence immunoassay (PBD-conjugated Ab and total Ab) and liquid chromatography–mass spectrometry (unconjugated SG3199)
- Lymphocyte subpopulations were quantified in whole blood using flow cytometry, with T_{eff}: CD8+ and T_{regs}: CD25+/CD127low/FoxP3+ (CD3+/CD4+)
- Linear mixed-effects modeling assessed effects of time and dose on lymphocyte subsets; repeated-measures correlation (r_{rm}) analysis[5] evaluated distinct relationships between endpoint pairs

RESULTS

- Of 44 patients who enrolled (data cut-off Mar 26, 2021), the two most common tumor types were colorectal and pancreatic, experienced by 15 (34.1%) and 14 (31.8%) patients, respectively (**Table 1**)

Table 1. Baseline demographic and clinical characteristics

Characteristic	(N=44)
Age, years	
Median (range)	60.5 (33.0–82.0)
Sex, n (%)	
Male	26 (59.1)
Female	18 (40.9)
Eastern Cooperative Oncology Group score, n (%)	
Grade 0	18 (40.9)
Grade 1	26 (59.1)
Tumor type at stages IV (n=35), IVA (n=6), IVB (n=2), IVC (n=1), n (%)	
Colorectal	15 (34.1)
Pancreatic	14 (31.8)
Ovarian/fallopian	3 (6.8)
Renal cell carcinoma	3 (6.8)
Head and neck	3 (6.8)
Gastric and esophageal/gastroesophageal junction	2 (4.5)
Non-small cell lung cancer	2 (4.5)
Melanoma	1 (2.3)
Triple-negative breast cancer	1 (2.3)
Number of previous systemic therapies	
Median (range)	4 (1–9)

Treatment

- Patients received a median (range) of 2 (1–6) cycles of Cami: 20 µg/kg (n=3), 30/45/60 µg/kg (each n=5), 80 µg/kg (n=8), 100 µg/kg (n=7), 125 µg/kg (n=8), and 150 µg/kg (n=3) Q3W; monotherapy dose escalation is now complete
- Median (range) treatment duration was 22 (1–178) days
- Primary reasons for treatment discontinuation were progressive disease (n=36; 81.8%), patient withdrawal (n=5; 11.4%), death (n=2; 4.5%), and unacceptable toxicity (n=1; 2.3%). Primary reasons for study discontinuation were death (n=33; 75%), patient withdrawal (n=4; 9.1%), completed study (1 year of survival follow-up after last Cami dose, n=2; 4.5%), and lost to follow-up (n=1; 2.3%)

Safety and Tolerability

- No DLTs were reported; maximum tolerated dose (MTD) was not reached
- All-grade treatment-emergent AEs (TEAEs) in ≥20% of patients were nausea (n=18; 40.9%), decreased appetite and fatigue (both n=16; 36.4%), constipation (n=13; 29.5%), abdominal pain (n=12; 27.3%), and rash (n=10; 22.7%)
- The only Grade ≥3 TEAE in ≥10% patients was anemia (n=5; 11.4%)
- Grade 3 autoimmune AEs of colitis, as well as TEAEs of immune-mediated AE and systemic inflammatory response syndrome and pancreatitis, were reported in 1 (2.3%) patient each
- Grade 3 neurologic AEs of asthenia, and TEAEs of dysphagia and muscular weakness, were reported in 1 (2.3%) patient each. No Guillain-Barré syndrome of any grade was reported
- One (2.3%) patient discontinued treatment owing to TEAEs considered probably related to Cami (maculopapular rash [Grade 2], esophagitis [Grade 1], and stomatitis [Grade 1])
- No Cami-related TEAEs were fatal

Efficacy

- Disease control rate was 25.0% (95% CI: 11.1, 34.7), with 11/44 patients attaining stable disease: 20 µg/kg (n=1), 30 µg/kg (n=3), 100 µg/kg (n=3), and 125 µg/kg (n=4) Q3W
- Median (95% CI) duration of stable disease was 2.8 (1.6, 4.4) months

Key Messages

- **Cami monotherapy showed an encouraging safety profile in advanced solid tumors; the MTD was not reached. Cami is now being investigated in combination with pembrolizumab**
- **Treatment with Cami showed:**
  - **Significant time (T_{eff}, T_{reg}) and dose-with-time (T_{eff}:T_{reg}, T_{reg}) related effects**
  - **Significant increase in T_{eff}:T_{reg} ratio, thought to be associated with immune-related antitumor effects[1–4]**
- **PK exposure profile comparable to previous analyses[6]**

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Disclosures

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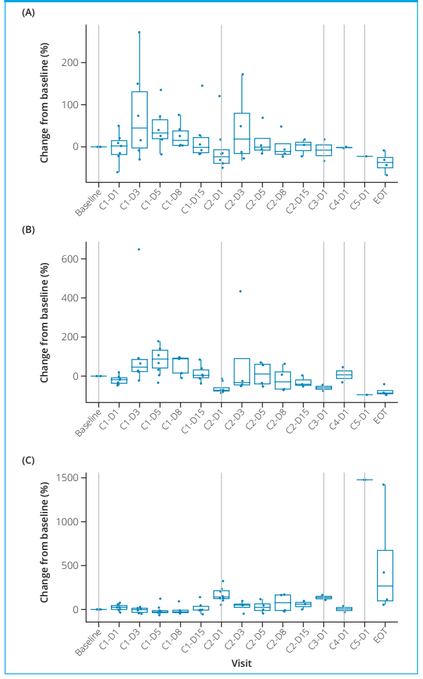
Pharmacokinetics

- PK data were available for 31 (70.5%) patients (20–150 µg/kg Q3W)
- Dose-related increases in PBD-conjugated Ab and total Ab exposure in serum (maximum concentration and area under the curve) were observed across the dose range
- Apparent clearance of PBD-conjugated Ab was ~1.15 L/day (at 125 µg/kg Q3W during Cycle 2), with moderate-to-marked inter-patient variability across doses
- Nominal accumulation was seen with the Q3W dosing regimen
- Concentrations of unconjugated SG3199 were predominantly below the limit of quantification

Pharmacodynamics

- PD data were available for 44 (100%) patients (20–150 µg/kg Q3W)
- Profiles for lymphocyte subsets of CD8+ T_{eff} cells, T_{reg} cells, and T_{eff}:T_{reg} ratio at the 125 µg/kg Q3W dose (n=8) are shown in **Figure 1**
  - In Cycle 1, T_{eff} and T_{reg} cell counts increased transiently, peaking at about Day 5; from Cycle 2, T_{reg} cells decreased over time in comparison with T_{eff} and T_{eff}:T_{reg} ratio values, which both increased
  - Similar trends were observed for all doses (data not shown)

Figure 1. Change from baseline by visit in: (A) CD8+ T_{eff} cells; (B) T_{reg} cells; and (C) T_{eff}:T_{reg} ratio in patients receiving Cami 125 µg/kg Q3W (n=8)



Vertical gray lines denote day (pre-dose) of a planned dosing event.
T_{eff}: CD25+/CD127low/FoxP3+ (CD3+/CD4+) lymphocytes as a fraction of CD4 absolute value.
T_{eff} to T_{reg} ratio: CD8+ to CD25+/CD127low/FoxP3+ (CD3+/CD4+) lymphocytes.
C, cycle; D, day; EOT, end of treatment; Q3W, every 3 weeks; T_{eff}, effector T cell; T_{reg}, regulatory T cell.

- T_{eff} cells were negatively associated with time (p<0.0001) (**Table 2**)
- T_{reg} cells were negatively associated with both dose and time (p=0.0031), and the interaction between dose and time (p=0.0004)
- T_{eff}:T_{reg} ratio was positively associated with time (p<0.0001) and the interaction between dose and time (p<0.0001)

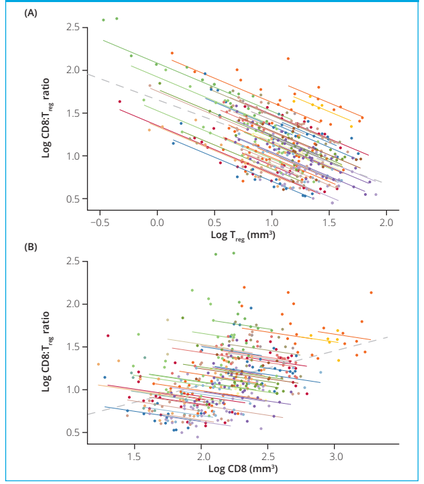
Table 2. Linear mixed-effects models to assess association between lymphocyte subset endpoints, and time and dose

	P values for models tested[a]			
Endpoint	Model 2 (Time)	Model 3 (Time + dose)	Model 4 (Time x dose interaction)	Effect
T_{eff}	**<0.0001**	0.4227	0.3428	Effect of time alone is significant (-)
T_{reg}	<0.0001	0.0031	**0.0004**	Effects of dose and time are significant (-); interaction between dose and time is significant (-)
T_{eff}:T_{reg} ratio	<0.0001	0.3261	**<0.0001**	Effect of time is significant (+); interaction between dose and time is significant (+)

[a]Model 1: Conc ~ 1 + (1 | Subj. ID), Null model; Model 2: Conc ~ Time + (1 | Subj. ID); Model 3: Conc ~ Time + Dose + (1 | Subj. ID); Model 4: Conc ~ Time x Dose + (1 | Subj. ID). Significance values in **bold** indicate model considered best.
T_{eff}: CD25+/CD127low/FoxP3+ (CD3+/CD4+) lymphocytes as a fraction of CD4 absolute value.
T_{eff} to T_{reg} ratio: CD8+ to CD25+/CD127low/FoxP3+ (CD3+/CD4+) lymphocytes.
Conc, concentration; subj, subject; T_{eff}, effector T cell; T_{reg}, regulatory T cell.

- Correlative analysis indicated that Cami has a greater suppressive effect on T_{reg} cells than T_{eff} cells (**Figure 2**)
  - A highly significant and strongly negative correlation was observed between CD8+:T_{reg} ratio and T_{reg} cell count (r_{rm} =-0.812, p=1.29e-98); correlation between CD8+:T_{reg} ratio and CD8 cell count is significant, but modestly negative (r_{rm} =-0.201, p=3.826e-05)

Figure 2. Correlation of: (A) CD8+:T_{reg} ratio with T_{reg} cell count and (B) CD8+:T_{reg} ratio with CD8+ cell count in patients receiving Cami 20–150 µg/kg Q3W (n=44)



T_{reg}: CD25+/CD127low/FoxP3+ (CD3+/CD4+) lymphocytes as a fraction of CD4 absolute value.
Observations (dots) from the same patient are in the same color; corresponding lines show the repeated-measures correlation fit for each patient. Gray dotted line denotes regression line between measures 1 and 2 ignoring the patient variable. Number of patients evaluated: T_{reg} and CD8+:T_{reg} ratio, both n=44; lymphocyte and CD8+, both n=41. Q3W, every 3 weeks; T_{eff}: effector T cell; T_{reg}, regulatory T cell.

Immunogenicity

- There were no instances of confirmed anti-drug Ab response