First-in-Human Study of Camidanlumab Tesirine (ADCT-301, Cami), an anti-CD25 Targeted Therapy in Patients with Advanced Solid Tumors: Pharmacokinetics (PK) and Biomarker Evaluation

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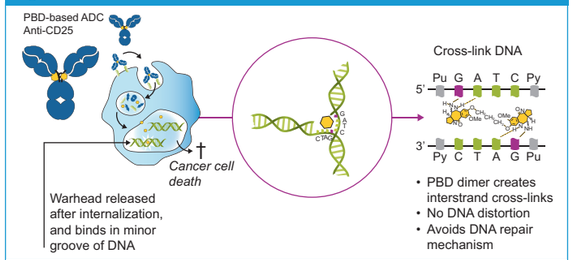
INTRODUCTION

- Regulatory T cells (T_{regs}) play a significant role in the establishment and progression of tumors, and poor prognosis in solid tumors is often associated with high tumor infiltration by T_{regs} and a low ratio of effector T cells (T_{effs}) to T_{regs}.[1–4]
- Selectively blocking or depleting tumor-infiltrating CD25+ T_{regs} has been explored as a strategy for tumor eradication, alone or in combination with other immunotherapeutic strategies such as checkpoint blockade, and preclinical research has demonstrated potent and durable antitumor activity of these approaches in syngeneic tumor models.[1]
- Camidanlumab tesirine (Cami) is an antibody-drug conjugate comprising a human antibody (Ab) directed against CD25 stochastically conjugated through a cleavable linker to a potent pyrrolobenzodiazepine (PBD) dimer warhead, SG3199.
- PBD dimers form non-distortive interstrand cross-links in the minor groove of DNA, which are refractory to DNA repair allowing them to persist in the DNA (**Figure 1**).
- In this Phase 1b study (NCT03621982), 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 1. Mechanism of action of camidanlumab tesirine



ADC, antibody-drug conjugate; PBD, pyrrolobenzodiazepine.

STUDY OBJECTIVES

- The primary objective of this study is to characterize the safety and tolerability of Cami and identify recommended dose(s) and schedule(s) for future studies.
- Secondary and exploratory objectives are to evaluate pharmacokinetics (PK), immunogenicity, immunologically-relevant biomarkers in blood and tissues, and preliminary antitumor activity of Cami.
- This presentation reports preliminary PK and biomarker data from this ongoing study.

METHODS

Study design

- This is a multicenter, open-label study of Cami in two parts, as reported previously:[5]
  - dose-escalation, using a 3+3 design and a starting dose of Cami 20 µg/kg, up to a maximum of 300 µg/kg, administered by 30-min intravenous infusion once every 3 weeks (Q3W; 1 cycle) on Day 1.
  - dose-expansion, using the recommended dose derived from the dose-escalation phase.
- Patients aged ≥18 years, with no prior therapy with a CD25 (IL-2R) Ab in the last 4 months and a pathologic diagnosis of a selected locally advanced or metastatic solid tumor are being enrolled.

PK and biomarker analyses

- Blood samples for PK and biomarker analyses were collected pre-dose and 48, 96, 168 and 336 h post-dose from start of infusion in Cycles 1–4, then pre-dose only for subsequent cycles (**Table 1**).

Table 1. Schedule of PK assessments

Cycle	C1 and C2				C3 onwards		EOT
Day	1	3 and 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)		✓[d]
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 h prior to start of Cami infusion, EOI assessment to be done 5–10 min prior to EOI, post-dose is 4 h from start of Cami infusion; [c]Pre-dose is within 2 h prior to start of Cami infusion, post-dose is 4 h 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.

- PK profiling (total Ab, PBD-conjugated Ab, and unconjugated warhead, SG3199) was conducted using electrochemiluminescence immunoassay and liquid chromatography–mass spectrometry.
- Soluble CD25 (sCD25) and pro-inflammatory cytokines were quantified in serum using qualified bioanalytical methods.
- Lymphocyte subpopulations were quantified in whole blood using flow cytometry, with T_{eff}: CD3+CD8+ and T_{reg}: CD3+CD4+CD25+CD127lowFoxP3+.
- Tumor tissue from patients (some with paired pre- and on-treatment biopsies) was stained by fluorescence multiplex using Ultivue Ab-DNA reagent technology for CD8 to identify CD8+ T_{effs}, CD25 and FoxP3 to identify T_{regs}, and PanCK/SOX10 to identify tumor cells (SOX10 for melanoma samples).

RESULTS

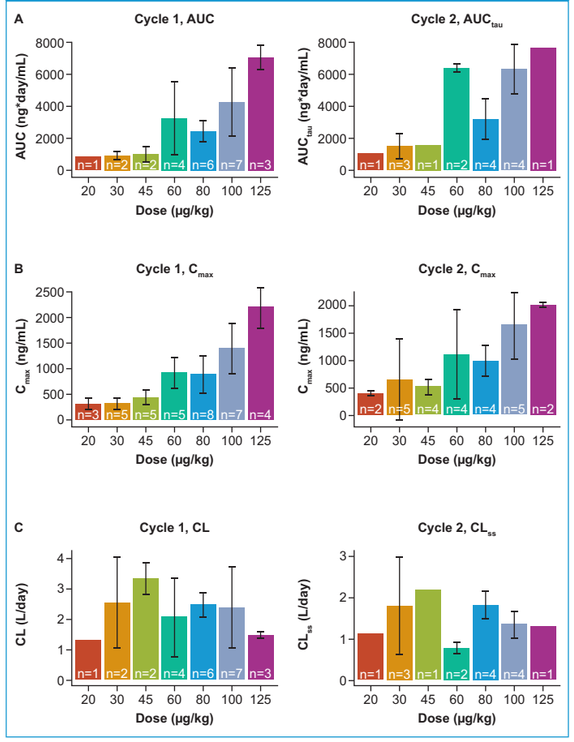
Patient characteristics

- As of 31 July 2020, 41 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=6), and 150 µg/kg (n=2) Q3W. Median (range) patient age was 62.4 (34.3–82.9) years, and median (range) number of prior systemic therapies was 4 (1–9).
- The two most common tumor types were colorectal and pancreatic (both n=14; 34.1%). Other histologies were head and neck cancer and renal cell carcinoma (both n=3; 7.3%), ovarian cancer (n=2; 4.9%), and esophageal cancer, gastric cancer, melanoma, non-small cell lung cancer, and triple-negative breast cancer (each n=1; 2.4%).

Pharmacokinetics in serum

- Exposures increased with dose (**Figure 2**) and were associated with modest to moderate inter-patient variability.
- PK profiles for conjugated Ab were similar to those for total Ab.
- Unconjugated-warhead SG3199 levels were predominantly below the lower limit of quantification for most patients and time points.
- No accumulation was evident by the second cycle dose.

Figure 2. PBD-conjugated antibody shown for Cycles 1 and 2 by (**A**) AUC, (**B**) C_{max} and (**C**) apparent clearance

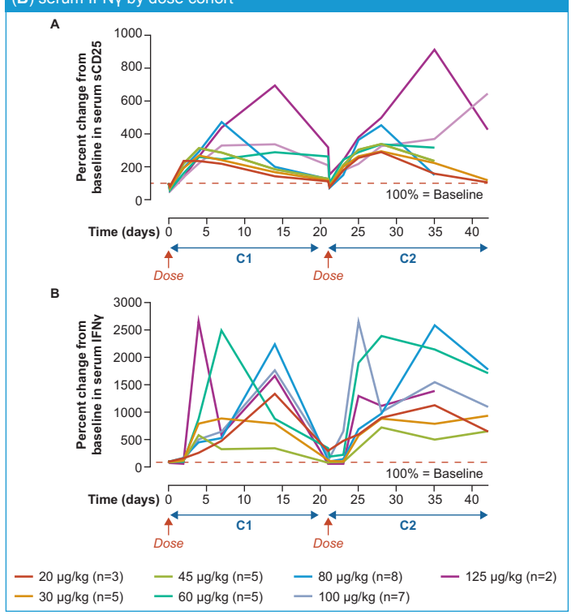


Data shown as arithmetic mean +/- standard deviation. AUC, area under the concentration-time curve; CL, apparent clearance; CL_{ss}, apparent clearance steady-state; C_{max}, observed maximum concentration; PBD, pyrrolobenzodiazepine.

Soluble CD25 and cytokines in serum

- In general, levels of sCD25 were low pre-dose and peaked at Days 4–7, with increases appearing to be dose-related (**Figure 3A**).
- Although data were limited, pro-inflammatory cytokines, including IFNγ, in human serum generally showed increases after dosing, peaking at Days 4–7 before decreasing (**Figure 3B**).

Figure 3. Percent change from baseline in (**A**) serum sCD25 and (**B**) serum IFNγ by dose cohort



For the purpose of graphical representation, patients received the first dose on Day 0.
C, cycle; IFNγ, interferon gamma; sCD25, soluble CD25.

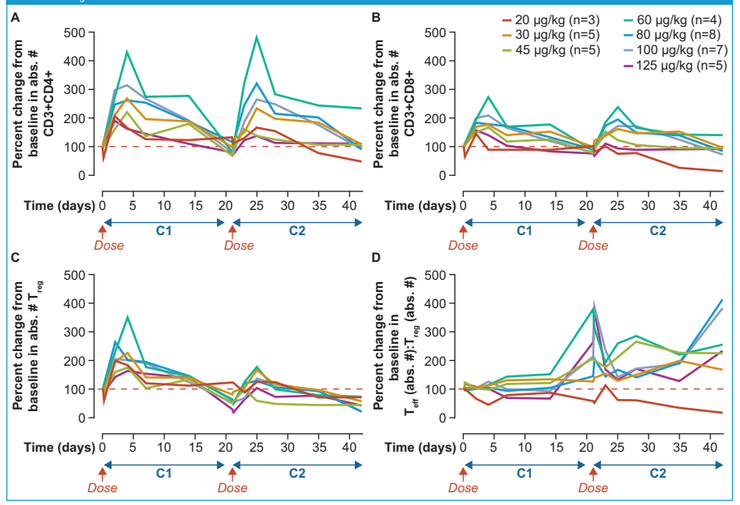
Lymphocyte subpopulations in blood

- In Cycles 1 and 2, CD4+ T cells (as absolute cells/µL blood) increased post-treatment, peaking at about Day 4 with a maximal increase from baseline to ~450% for both cycles (**Figure 4A**). An initial dip in absolute values of CD4+ T cells was observed in some patients within the first 3 hours (data not shown). CD8+ T cells (as absolute cells/µL) showed a similar pattern, with increases to ~250% (**Figure 4B**).
- Compared with baseline, T_{regs} (as absolute cells/µL) after an initial peak around 4 days, decreased in Cycle 1 (**Figure 4C**), and further decreased in Cycle 2, with a smaller peak at 4 days, causing a post-treatment effect predominantly in Cycle 2 with increase in T_{eff}:T_{reg} ratio (**Figure 4D**) and showing dose/cycle relatedness. This trend was less pronounced in the 20 µg/kg cohort.

Lymphocyte subpopulations in tissue

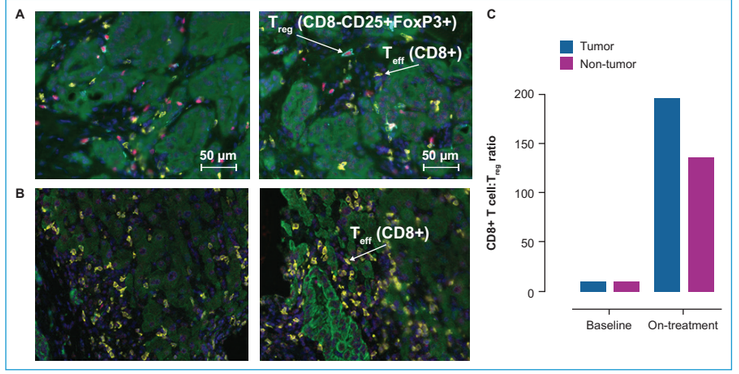
- Twenty-one patients from low-dose cohorts (20–80 µg/kg) had evaluable baseline biopsies. Paired on-treatment biopsies after 3 weeks' treatment were available for 6 of these patients; 50% of the on-treatment biopsies showed increased T_{eff}:T_{reg} ratio in the local tumor environment relative to baseline.
- **Figure 5** shows example baseline and on-treatment biopsy images from a patient with pancreatic cancer treated at the 45 µg/kg dose.
  - CD8+ cells (yellow) and T_{regs} (CD25: turquoise and FoxP3: pink) can be observed in the baseline sample, with a greater proportion of CD8+ cells observed in the on-treatment sample.
  - Quantitative whole section analyses showed an increase in CD8+ T_{eff}:T_{reg} ratio in both tumor and non-tumor areas of biopsies.

Figure 4. Percent change from baseline values of absolute cell numbers/µL blood in (**A**) CD4+ T cells and (**B**) CD8+ T cells (CD45+ lymphocyte population); (**C**) T_{regs} (CD4+ population) and (**D**) T_{eff}:T_{reg} ratio, by dose cohort



For the purpose of graphical representation, patients received the first dose on Day 0.
Abs., absolute; C, cycle; T_{eff}: CD3+CD8+; T_{reg}: CD3+CD4+CD25+CD127lowFoxP3+.

Figure 5. Images from two representative areas of biopsy sections at (**A**) baseline and (**B**) after 3 weeks' treatment (45 µg/kg Q3W); (C) CD8+ T cell:T_{reg} ratio in a patient with pancreatic cancer



Q3W, every 3 weeks; T_{eff}, T effector cell; T_{reg}, T regulatory cell.

CONCLUSIONS

- Preliminary findings from this Phase 1b first-in-human study, which is continuing to enroll patients, indicate Cami treatment is associated with clinically relevant modulation of immune cells, both in the circulation and in tumor tissue, albeit with substantial inter-patient variability in tumor tissue.
- Increases in sCD25 and cytokines in serum post-dosing followed a similar pattern to increases in CD4+ and CD8+ T cells, suggesting an increase in activated lymphocytes.
- Changes in lymphocyte subpopulations in the blood resulted in a dose-related increase in the T_{eff}:T_{reg} ratio.
- These results support the therapeutic rationale for the treatment of advanced solid tumors with Cami as monotherapy. Future research developments to explore the therapeutic prospects of Cami in combination with other immunomodulating therapies are merited.

Acknowledgments

- This study is sponsored by ADC Therapeutics SA (NCT03621982). The authors would like to thank and acknowledge the participating patients and their families, and all study co-investigators and research coordinators. The authors received editorial/writing support in the preparation of this poster provided by Heather St Michael of Fishawack Communications Ltd., funded by ADC Therapeutics SA.

Disclosures

- First author, Prof. Igor Puzanov, discloses advisory/consultancy work for Amgen.
- See abstract book for the full list of all authors' disclosures.

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