INTRODUCTION

Regulatory T cells (Tregs) play a significant role in the establishment and progression of tumors, and poor prognosis is associated with high tumor infiltration by Tregs and a low ratio of effector T cells (Teffs) to Tregs [1-3].

Selectively blocking or depleting tumor-infiltrating CD25+ Tregs 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 anti-tumor activity of these approaches in syngeneic tumor models [4, 5].

Camalumab tansine (Cam), an anti-CD25 antibody-drug conjugate comprising a human antibody (Ab) directed against CD25 stochastically conjugated through a cleavable linker to a potent pyrrolobenzodiazepine (PBD) warhead, SG3199, has shown promising antitumor activity in multiple cancer models [6].

In this Phase 1 study, we evaluated anti-tumor activity of Cam via the depletion of CD25 Tregs in the tumor microenvironment in being explored in patients with selected advanced solid tumors.

STUDY OBJECTIVES

The primary objective of this study is to characterize the safety and tolerability of Cam and evaluate anti-tumor activity of Cam in patients with selected advanced solid tumors.

Secondary and exploratory objectives are to evaluate pharmacokinetics (PK), immunogenicity, immunomodulatory biomarkers in blood and tissues, and preliminary antitumor activity of Cam.

This presentation reports preliminary PK and biomarker data from the ongoing study.

METHODS

Study design

This is a multicenter, open-label study of Cam in two parts, as reported previously [7]: dose-escalation, using a 3+3 design and a starting dose of Cam 20 µg/kg (n=1) to a maximum of 300 µg/kg, administered by 30-min intravenous infusion every 3 weeks (Cycle 1) 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 60 days, with previously untreated advanced solid tumors are being enrolled.

PK and biomarker analyses

Blood samples for PK and biomarker analyses were collected pre-dose and at doses of 20 (n=1), 30 (n=5), 40 (n=5), 60 (n=1), 80 (n=1), 100 (n=1), 125 (n=6), and 150 µg/kg (n=2) on Cycle 1 (range/patient) days 2-4 (3-4, 2-4, 2-5) years, and median (range) number of prior systemic therapies was 4 (1-6).

The two most common tumor types were colorectal and pancreatic (both n=14, 34.1% each). Other histologies were head and neck cancer and renal cell cancer (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%).

RESULTS

Patient characteristics

As of 31 July 2020, 41 patients were enrolled and treated at doses of 20 (n=3), 30 (n=4), 40 (n=5), 60 (n=1), 80 (n=1), 100 (n=1), 125 (n=6), and 150 µg/kg (n=2) on Cycle 1 (range/patient) days 2-4 (3-4, 2-4, 2-5) years, and median (range) number of prior systemic therapies was 4 (1-6).

No accumulation was evident by the second cycle dose. Unconjugated-warhead SG3199 levels were predominantly below the lower limit of quantification for most patients in cycle (pre).

Figure 1. Mechanism of action of camalumab tansine

Figure 2. PBD-correlated antibody shown for Cycles 1 and 2 by (A) AUC, (B) C(T 1/2), and (C) apparent clearance

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 +45% for both cycles (Figure 4A). An initial rise in absolute values of CD4+ T cells observed in some patients within the first 3 hours (data not shown). CD8+ T cells (as absolute profiles) remained stable in the 20 µg/kg dose group.

Conversely, compared with baseline, Tregs (as absolute cells) after an initial peak around 4 days, decreased in Cycle 1 (Figure 4C), and further decreased in Cycle 2, with a small peak at 4 days (causing a post-treatment effect predominantly in Cycle 2 increase in Tregs), and showing dyskineasial relatedness. This trend was less pronounced in the 20 µg/kg dose group.

Lymphocyte subpopulations in tissue

Twenty-nine patients from low-dose cohorts (20-80 µg/kg) had evaluable baseline biopsies. Paired treatment biopsies after 1 week treatment were available to 6 of these patients; 55% of the on-treatment biopsies showed increased Treg:CD4+ ratio in the local tumor environment relative to the baseline.

Figure 5 shows example baseline and on-treatment biopsy images from a patient with pancreatic carcino tumor treated at the 45 µg/kg dose; CD11c and CD8 marks are shown.

CONCLUSIONS

• Predominant findings from this Phase 1 trial in non-human study, which is continuing to enroll patients, indicate Cam 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 size.

• Increases in lymphocytes and biomarkers 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 bloodstream in a dose-dependent increase in the CD4+ T cells.

• These results support the therapeutic rationale for the treatment of advanced solid tumors with Cam as monotherapy. Future research developments to explore the therapeutic potential of Cam in combination with other immunomodulating therapies are merited.

DISCLOSURES

• All authors contributed to writing the manuscript. All authors gave final approval of the submitted manuscript.

• No proprietary interests to declare.

ACKNOWLEDGMENTS

• This study is sponsored by ADC Therapeutics SA. IN1902927730

1. First author, Prof. Igor Puzanov, declares advisory/consultancy work for Amgen.

2. Data abstracted for the benefit of all authors.

3. Michael of Fishawack Communications Ltd., funded by ADC Therapeutics SA.

4. Staff at ADC Therapeutics SA contributed to writing the manuscript.

5. South Texas Accelerated Research Therapeutics (START), San Antonio, TX, USA; 6. Department of Medical Oncology, Yale Cancer Center, New Haven, CT, USA.

6. The two most common tumor types were colorectal and pancreatic (both n=14; 34.1%).

7. As of 31 July 2020, 41 patients were enrolled and treated at doses of 20 (n=3), 30 (n=4), 40 (n=5), 60 (n=1), 80 (n=1), 100 (n=1), 125 (n=6), and 150 µg/kg (n=2) on Cycle 1 (range/patient) days 2-4 (3-4, 2-4, 2-5) years, and median (range) number of prior systemic therapies was 4 (1-6).

8. No accumulation was evident by the second cycle dose. Unconjugated-warhead SG3199 levels were predominantly below the lower limit of quantification for most patients in cycle (pre).

9. Conversely, compared with baseline, Tregs (as absolute cells) after an initial peak around 4 days, decreased in Cycle 1 (Figure 4C), and further decreased in Cycle 2, with a small peak at 4 days (causing a post-treatment effect predominantly in Cycle 2 increase in Tregs), and showing dyskineasial relatedness. This trend was less pronounced in the 20 µg/kg dose group.

10. Twenty-nine patients from low-dose cohorts (20-80 µg/kg) had evaluable baseline biopsies. Paired treatment biopsies after 1 week treatment were available to 6 of these patients; 55% of the on-treatment biopsies showed increased Treg:CD4+ ratio in the local tumor environment relative to the baseline.

11. Figure 6 shows example baseline and on-treatment biopsy images from a patient with pancreatic carcino tumor treated at the 45 µg/kg dose; CD11c and CD8 marks are shown.

12. These results support the therapeutic rationale for the treatment of advanced solid tumors with Cam as monotherapy. Future research developments to explore the therapeutic potential of Cam in combination with other immunomodulating therapies are merited.