A Tregs-depleting CD25-targeted antibody-drug conjugate synergizes with tumor-targeted radiotherapy and systemic interleukin-2 in pre-clinical models of solid cancers

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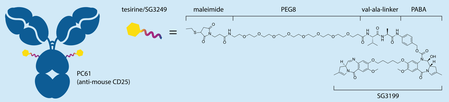
P621
abstract poster number

Introduction

1. Regulatory T cells (Tregs) contribute to an immunosuppressive tumor microenvironment. High tumor infiltration by Tregs and a low ratio of Teffector cells/Tregs is often associated with poor prognosis in solid tumors [1]. Tregs represent a major obstacle to cancer immunotherapies, including checkpoint inhibitors and interleukin-2 (IL-2) and are associated with tumors resistance to radiotherapy [2].
2. CD25-ADC (a.k.a.sur301) is an antibody-drug conjugate (ADC) composed of rat monoclonal antibody PC61, directed against mouse CD25, conjugated to tesirine, a pyrrolobenzodiazepine (PBD) dimer-based protease-cleavable linker [3] (figure 1).

Figure 1.



3. Previously, we showed that single low doses of CD25-ADC resulted in potent and durable antitumor activity in established syngeneic solid tumor models and the combination of a suboptimal dose was synergistic with PD-1 blockade. Tumor eradication by CD25-ADC was CD8+ T cell-dependent and it induced protective immunity. Importantly, while CD25-ADC mediated a significant and sustained intratumoral Tregs depletion, accompanied by a concomitant increase in the number of activated and proliferating tumor-infiltrating CD8+ Teffs cells, systemic Tregs depletion was transient, alleviating concerns of potential autoimmune side effects [4].

Aim of the study

The purpose of this study was to evaluate the anti-tumor activity of CD25-ADC in combination with focal radiotherapy (RT) or systemic IL-2 in syngeneic solid tumor models.

…gle dose on the day indicated
… (i.v.) or intraperitoneally (i.p.)
…C38 tumors or to BALB/c mice
…p mean tumor volumes 84-104

…ministered via the Xstrahl Life
…latform. Treatment was applied
…a total dose of 5 Gy in 2 equally

…s administered i.p. at 0.1 mg/kg

…was assessed for sub-additive,
…perties on the last day at least
…

Results

Figure 2A. Combination of CD25-ADC and focal radiotherapy has synergistic anti-tumor activity

Figure 2B. Combination of CD25-ADC and focal radiotherapy has synergistic anti-tumor activity

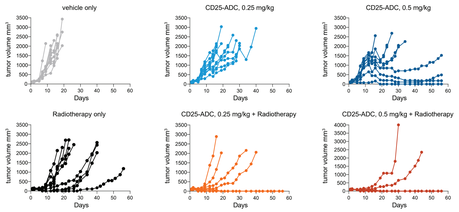


Figure 2C. Response summary and Coefficient of Drug Interaction

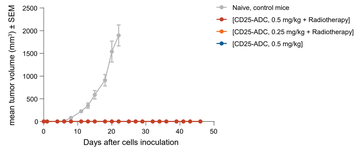
	PR	CR	TFS
Vehicle	0	0	0
CD25-ADC, 0.25 mg/kg	0	0	0
CD25-ADC, 0.5 mg/kg	0	1	1
radiotherapy only, 5Gy	0	3	0
CD25-ADC, 0.25 mg/kg+Radiotherapy, 5 Gy	0	6	6
CD25-ADC, 0.5 mg/kg+Radiotherapy, 5 Gy	0	8	8

Coefficient of drug interaction:

• CD25-ADC, 0.25 mg/kg • Radiotherapy • CD25-ADC, 0.25mg/kg + radiotherapy	day 15 0.88 (synergism)

• CD25-ADC, 0.5 mg/kg • Radiotherapy • CD25-ADC, 0.5 mg/kg + radiotherapy	day 15 0.47 (synergism)

Figure 2D. Re-challenge of Tumor-Free Survivors from CT26 efficacy study



A. Study design for the unilateral CT26 syngeneic model. **B.** Each graph represents tumor volumes (TV) over time for each individual mouse (10 mice/group). CD25-ADC was administered i.v. as single dose on Day 0. Image-guided focal radiation (5 Gy) was administered on Day 1. **C.** (Left) Table with response summary (PR, partial responders; CR, complete responders; TFS, tumor-free survivors) and (right) table with Coefficient of Drug Interaction (CDI). **D.** TFS from the CT26 efficacy study were re-challenged with a subcutaneous (s.c.) implant of CT26 cells and tumor formation was monitored over time. A group of naive mice (10/group) was implanted with CT26 cells and served as control.

Figure 3A. Combination of CD25-ADC with focal radiotherapy has abscopal effect on non-irradiated distal tumor

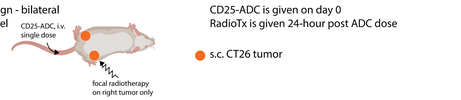


Figure 3B. Combination of CD25-ADC with focal radiotherapy has abscopal effect on non-irradiated distal tumor

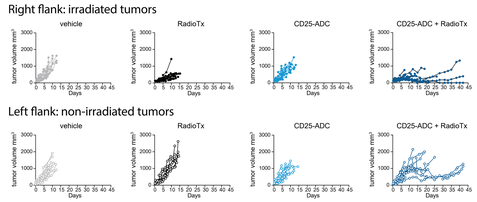


Figure 3C. Coefficient of Drug Interaction

Right flank: irradiated tumors

• CD25-ADC • Radiotherapy • CD25-ADC + radiotherapy	day 20 0.94 (synergism)

Left flank: non-irradiated tumors

• CD25-ADC • Radiotherapy • CD25-ADC + radiotherapy	day 20 0.91 (synergism)

Figure 3D. The order of administration of CD25-ADC and focal radiotherapy has a significant impact on the anti-tumor activity of the combination

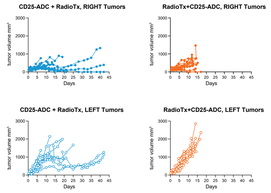
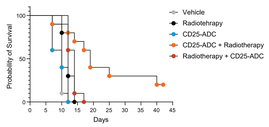


Figure 3E. Survival analysis



A. Study design for the bilateral CT26 syngeneic model. **B.** Each graph represents tumor volumes (TV) over time for each individual mouse (10 mice/group). CD25-ADC was administered i.v. as single dose on Day 0. Image-guided focal radiation (5 Gy) was administered on Day 1. **C.** Coefficient of Drug Interaction (CDI) **D.** Each graph represents tumor volumes (TV) over time for each individual mouse (10 mice/group). CD25-ADC (single dose, i.v.) and image-guided focal radiation therapy (5 Gy) were administered sequentially 1-day apart, the order of administration is indicated in the respective graph's title. **E.** Kaplan-Meier analysis of survival.

Figure 4A. Combination of CD25-ADC with IL-2 results in enhanced anti-tumor activity

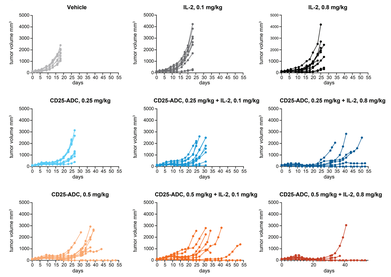


Figure 4B: Response summary and Coefficient of Drug Interaction

	PR	CR	TFS
Vehicle	0	0	0
IL-2, 0.1 mg/kg	0	0	0
IL-2, 0.8 mg/kg	0	0	0
CD25-ADC, 0.25 mg/kg	0	0	0
CD25-ADC, 0.5 mg/kg	0	2	2
CD25-ADC, 0.25 mg/kg + IL-2, 0.1 mg/kg	0	0	0
CD25-ADC, 0.25 mg/kg + IL-2, 0.8 mg/kg	0	5	5
CD25-ADC, 0.5 mg/kg + IL-2, 0.1 mg/kg	0	3	3
CD25-ADC, 0.5 mg/kg + IL-2, 0.8 mg/kg	0	8	8

Coefficient of drug interaction:

• CD25-ADC, 0.25 mg/kg • IL-2, 0.8 mg/kg • CD25-ADC, 0.25 mg/kg + IL-2, 0.8 mg/kg	day 18 0.59 (synergism)

Figure 4C: Mean Body Weights

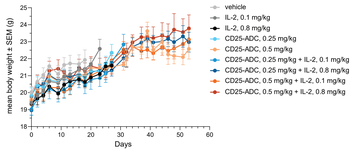
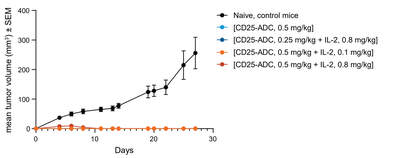


Figure 4D. Re-challenge of Tumor-Free Survivors from MC38 efficacy study



A. Each graph represents tumor volumes (TV) over time for each individual mouse (10 mice/group) from the MC38 syngeneic model. CD25-ADC was administered intraperiteonally (i.p.) as single dose on Day 0. Interleukin-2 (IL-2) was administered i.p. starting from Day 2 (5 days on/2 days off, twice). **B.** (Left) Table with response summary (PR, partial responders; CR, complete responders; TFS, tumor-free survivors) and (right) table with Coefficient of Drug Interaction (CDI). **C.** Mean body weights. **D.** TFS from the MC38 efficacy study were re-challenged with a subcutaneous (s.c.) implant of MC38 cells (contralateral to the original cell implant) and tumor formation was monitored over time. A group of age-matched, naive mice (10/group) was implanted with MC38 cells and served as control.

Conclusions

1. Combination of CD25-ADC with focal radiotherapy resulted in synergistic anti-tumor activity against established CT26 tumors. Re-challenged mice did not develop new tumors indicating tumor-specific protective immunity.
2. In a bilateral CT26 tumor model, combination of CD25-ADC with focal radiotherapy resulted in synergistic anti-tumor activity in both the irradiated and non-irradiated distal tumor (abscopal effect) and the combination significantly increased survival compared to the single treatments.
3. Sequential administration of CD25-ADC followed by radiotherapy resulted in superior anti-tumor activity compared to the reverse order of administration (radiotherapy first, followed by CD25-ADC), suggesting Tregs depletion is required to achieve optimal anti-tumor activity mediated by radiotherapy.
4. Combination of CD25-ADC with IL-2 resulted in improved anti-tumor activity which was synergistic at certain dose schedules and the combination was well tolerated at all doses tested.
5. Together, these new preclinical data show novel promising combination regimens for CD25-ADC and other commonly used anti-cancer treatments and they provide rationale for the investigation of camidanlumab tesirine (ADCT-301), a PBD-based ADC targeting human CD25 [6, 7], in similar clinical combinations settings.

Acknowledgements

In vivo studies: Covance Inc. and Champions Oncology.

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