2268: Agonistic T-cell non-depleting ICOS antibody strongly enhances anti-tumor activity with CTLA4 blocking monoclonal antibody without exacerbating colitis

Clélia Coutzac[1], Jean Jouniaux[1], Aurore Vozy[1], Marc Ballas[2], Sara Brett[2] and Sapna Yadavilli[2], Eric Angevin[1], Axel Hoos[2], Nathalie Chaput[1]

[1]Gustave Roussy Institute, Villejuif Cedex, France; [2]Oncology R&D, GlaxoSmithKline, 1250 S Collegeville Rd, Collegeville, USA

Introduction

Blocking immune checkpoints such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) has proven its efficacy in metastatic melanoma with increased efficacy observed in combination with other immune modulating antibodies, for example, nivolumab in melanoma, non-small cell lung cancer and renal cell carcinoma.[1,2] Although efficacious, their utility is limited due to grade 3–4 immune-related adverse events necessitating the need for other immune combinations, showing improved clinical responses with fewer toxicities. ICOS is a member of the CD28 superfamily mainly expressed on activated T cells. We and others have demonstrated an up-regulation of ICOS+ T cells in patients that have long-term benefit with ipilimumab[3] treatment supporting the role of ICOS as a biomarker of response to CTLA-4 blockade. Additionally, it has also been demonstrated that ICOS deficiency leads to diminished anti-tumor activity with CTLA4 blockade in syngeneic mouse tumor models. These findings prompt further studies examining the synergy between CTLA-4 blockade and ICOS stimulation in generating optimal anti-tumor T-cell immunity. Since both CD4 and CD8 T cells upregulate ICOS with anti-CTLA4 treatment, a non-depleting ICOS agonist antibody (GSK335609) was chosen to evaluate the combination.

Objectives

1. Test the impact of stimulating ICOS in combination with anti-CTLA4 on the development of colitis in mice.
2. To test the impact of stimulating ICOS in combination with anti-CTLA4 in tumor-bearing mice using 2 different mouse models.
3. Test the impact of engagement of ICOS expressed on T cells from patients treated with CTLA-4 blocking antibody.

Results

No induction of colitis as determined by weight loss and clinical observations (no diarrhea and no rectal bleeding) was observed in mice with anti-CTLA-4 in combination with agonistic anti-ICOS monoclonal antibodies in mice (**Figure 1**). In mice tumor models benefit of anti-CTLA4 + aICOS agonist combination at 10 µg per injection, was observed in two independent mouse tumor models (**Figure 2**).

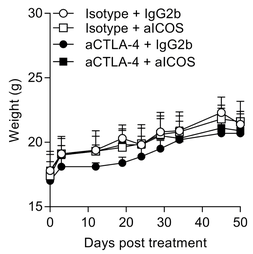

Figure 1. Mouse body weight changes during treatments compared with that of control animals. Body weights are shown as means± SEMs. No statistical differences were observed. SEM: standard error of the mean

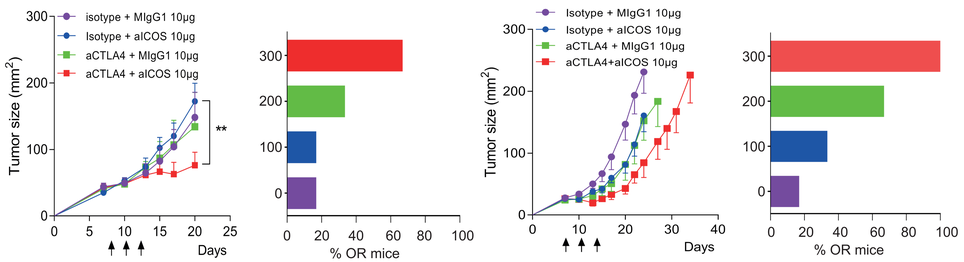

Figure 2. Anti-tumor activity of anti-mouse ICOS at 10 µg in combination with anti-mouse CTLA-4 in the CT26 (A) and MC38 (B) models. Statistics are shown on the graphs; *p<0.05; **p<0.01. OR: objective response

PBMC from human patients were stimulated ex vivo. Stimulation with αCD3+αICOS seemed to rescue activation of T cells in poor benefit (PB) patients compared with long-term benefit (LTB) patients after one injection of anti-CTLA-4 (V2) (**Figure 3**). Moreover, αCD3 + αICOS favored T-helper type 1 polarization without inducing strong interleukin-10 secretion in patients with PB compared with patients with LTB (**Figure 4**).

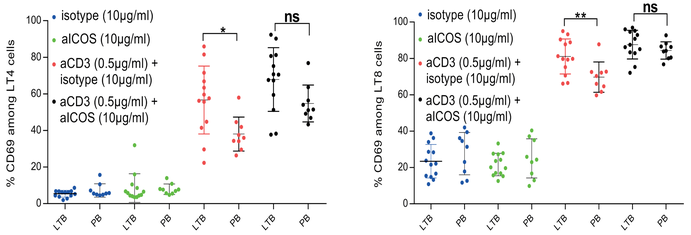

Figure 3. CD69 expression among CD4+ T cells (left panel) and CD8+ T cells (right panel) in patients with LTB of PB after the first ipilimumab injection (V2). Statistics are shown on the graphs; *p<0.05; **p<0.01.

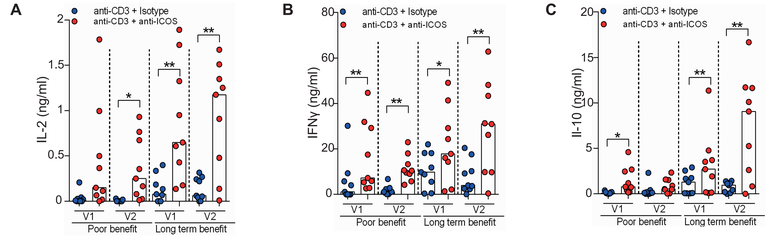

Figure 4. IL-2 (A), IFNγ (B) and IL-10 (C) production in patients with LTB of PB. Cytokine concentrations were determined at baseline (V1) and after 1 ipilimumab injection (V2). Statistics are shown on the graphs; *p<0.05; **p<0.01. IFNγ: interferon gamma.

Methods

For in vivo induction of colitis experiments, C57Bl/6 mice were treated with αCTLA4 or isotype +/- αICOS or isotype (clone 17G9 or rat IgG2b). Intra-peritoneal injections of each antibody or isotype were given at Day 0, Day 3, Day 6, Day 16, and then once a week until Day 50. Mice were weighted from Day 0 and every 3 days consecutively until Day 50. For anti-tumor experiments, C57Bl/6 and BALB/c mice were inoculated subcutaneously with MC38 and CT26 tumor cell lines, respectively. Mice received intra-peritoneal injections of anti-CTLA4 or its isotype control along with anti-mouse ICOS (clone 7E-17G9) or its corresponding isotype (MIgG1) at Day 7, Day 10, and Day 13 with tumor growth assessments three times a week. For data generated from human patients, peripheral blood mononuclear cells (PBMC) were collected from patients with metastatic melanoma treated with ipilimumab at baseline that is prior to ipilimumab treatment (V1) and after ipilimumab infusion (V2). The PBMC were re-stimulated in vitro with aCD3 +/- anti-human non-depleting agonist ICOS IgG4 isotype antibodies. T-cell activation was determined after 24 hours and supernatants were collected after 48 hours of incubation.

Conclusions

This study provides evidence in mice and in human tissues that non-depleting agonistic ICOS monoclonal antibodies may increase the anti-tumor activity of anti-CTLA-4, particularly in patients that do not benefit from anti-CTLA-4 alone without exacerbation of colitis. A clinical study to test this combination in patients with cancer for the first time with GSK3359609 and tremelimumab has been initiated by GSK in collaboration with AstraZeneca (*Hansen A, et al. AACR 2019 Poster CT166*).

References

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3. Chaput N, et al. *Ann Oncol* 2017;28:1368-79.

Acknowledgments

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Human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol. Immune monitoring in the blood of patients was approved by the Kremlin Bicêtre Hospital Ethics Committee (SC12-018; ID-RCB-2012-A01496-37) and the Declaration of Helsinki protocols were followed. Patients provided their written informed consent to participate in these studies prior to inclusion in the study. All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals. Animal experiments were carried out in accordance with French and European laws and regulations and approved by the French Animal Experimentation. Ethics Committee n°26 (02004.02)

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