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

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Introduction

Blocking immune checkpoints such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) has proven its efficacy in malignant 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 known checkpoint in the CD28 family 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 ipilimumab3 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 (GSK353609) was chosen to be evaluated the combination.

Objectives

1. To 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. To test the impact of engagement of ICOS expressed on T cells from patients treated with CTLA4 blocking antibody.

Methods

For in vivo induction of colitis experiments, C57Bl/6 mice were treated with aCTLA4 or isotype +/- aICOS 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 10 and Day 13 consecutively until Day 50. Mice were weighed on Day 0 and every 3 days during treatments for 10 weeks. For in vivo induction of colitis, mice received intra-peritoneal injections of anti-CTLA4 or its isotype control along with anti-mouse ICOS (clone 17E-10G) or its corresponding isotype (IgG1) at Day 7, Day 10, Day 13 and Day 16 of tumor-bearing, brood mononuclear cells (PBMC) from patients with metastatic melanoma treated with interfering antibodies before and after ipilimumab treatment. The PBMC were re-stimulated in vitro with aCTLA4 +/- 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.

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-CTLA4 in combination with agonistic anti-ICOS monoclonal antibodies in mice (Figure 3). In mice tumor models benefit of anti-CTLA4 + aICOS against combination at 10 µg per injection, was observed in two independent mouse tumor models (Figure 2).

PBMC from human patients were stimulated ex vivo. Stimulation with aICOS/aICOS seemed to rescue activation of T cells in poor benefit (PB) patients compared with long-term benefit (LTB) patients after one injection of anti-CTLA4 (V2) (Figure 1). aICOS favored T-helper type 1 polarization without inducing strong interleukin-10 secretion-10 to 100% specific activity with PB compared with patients with LTB (Figure 4).

Conclusions

This study provides evidence in mice and in human tissues that non-depleting agonistic ICOS antibodies may increase the anti-tumor activity of anti-CTLA4, particularly in patients that do not benefit from anti-CTLA4 alone without exacerbatating colitis. A clinical study to test this combination in patients with cancer for the first time with GSK33609 and tremelimunumab has been initiated by GSK in collaboration with AstaZeneca (Hanssen A et al. AACR 2019 Poster CT166).

Acknowledgments

This study was part of research collaboration between Gustave-Roussy Institute and GSK. GSK provided funding and materials. Editorial support was provided by Fiona Woodward, PhD, at Fishawack Indicia Ltd, UK. GSK was fully blinded.

References


Figure 1. CD69 expression among CD4+ T cells (left panel) and CD8+ T cells (right panel) in patients with LTB. 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.

Figure 2. Anti-tumor activity of anti-CTLA4 and aICOS monoclonal antibodies in combination with anti-CTLA4 (A) and MCB6-B (B) models. Statistics are shown on the graphs; *p<0.05; **p<0.01. OR: objective response.

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.