Non-clinical tumor models reveal broad combination potential of ICOS agonist antibodies

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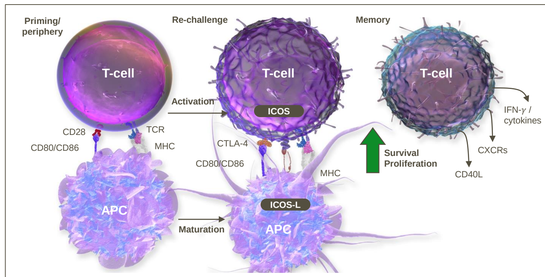
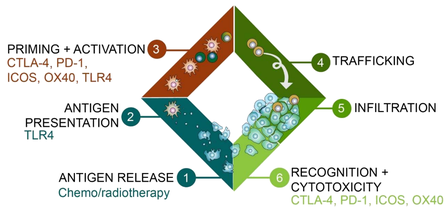
Background

- Inducible T-cell costimulator (ICOS) is a CD28 superfamily receptor, predominantly expressed on subsets of T cells shortly after TCR activation.[1,2]
- In addition to promoting T/B-cell collaboration, ICOS signaling has been shown to enhance T-cell antitumor activity and result in durable tumor rejection.[3,4]



APC, antigen presenting cell; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CXCR, C-X-C motif chemokine receptor; ICOS-L, ICOS-ligand; IFN-γ, interferon gamma; MHC, major histocompatibility complex.

- The cancer immunity cycle posits that multiple points of intervention exist for anticancer therapy, and should be considered to identify complementary strategies.[5]
- Here, we sought to evaluate the **broad combination potential of ICOS co-stimulation** with different intervention strategies targeting distinct nodes of the cancer immunity cycle (shown below).[5]



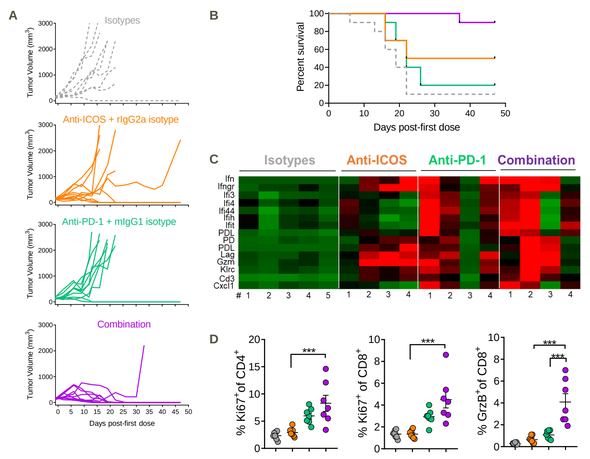
Methods

- **ICOS monoclonal antibody (mAb)**: Murinized 7E.17G9 (mIgG1) with fragment crystallizable (Fc) characteristics analogous to **GSK3359609** (Fc-engineered hIgG4 ICOS agonist).
- **Tumor models evaluated:** EMT6 (breast), CT26 (colon), H22 (liver).
- **Combinations evaluated:** anti-programmed cell death protein-1 (PD-1), CTLA-4, toll-like receptor 4 (TLR4) and OX40 agonists, chemo, and focal irradiation (RT).
- **Statistical analysis:** *P*-values of ≤0.05 were considered statistically significant (*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.005$).
- Studies were conducted in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals and were reviewed by IACUC at GSK or by the ethical review process at the institution where work was performed.

Results

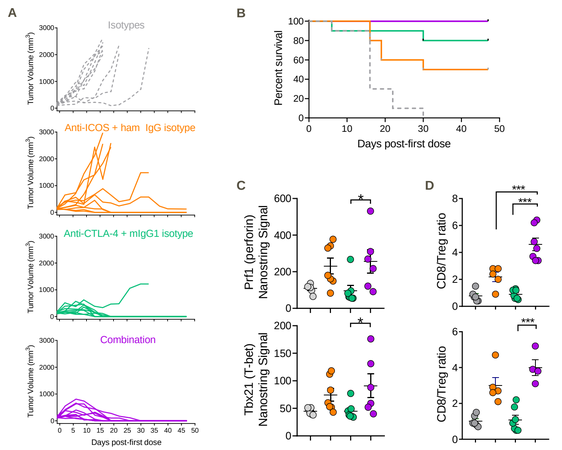
- Anti-ICOS mAb demonstrated complementarity with various therapeutic strategies, across different non-clinical tumor models.
- Combination effects with PD-1, CTLA-4, and RT were pronounced.
- Focal RT enabled ICOS efficacy in an ICOS-insensitive tumor model (CT26).

Figure 1. ICOS co-stimulation + anti-PD-1 in EMT6 mammary carcinoma



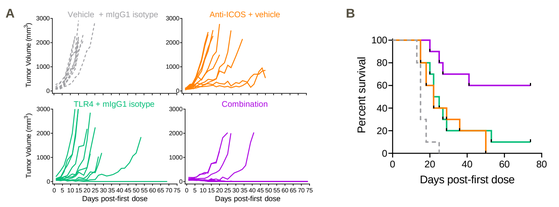
EMT6 subcutaneous (SC) tumor-bearing BALB/c mice were administered intraperitoneal (IP) twice weekly (biw) (x3) with ICOS mAb (7E.17G9 mIgG1, 10 µg), PD-1 mAb (RMP1-14, 200 µg), or isotype controls (mIgG1 and rat IgG2a, respectively) alone and in combination. Mice were evaluated for (**A**) tumor growth and (**B**) survival. (**C**) Transcriptional analysis (Nanostring) from EMT6 tumors harvested on study day 5. (**D**) % Ki67⁺ CD4⁺ or CD8⁺ T cells and granzyme B (GrzB)⁺ CD8⁺ T cells in the tumor-draining lymph nodes of EMT6 tumor-bearing mice on study day 7, as determined by flow cytometry.

Figure 2. ICOS co-stimulation + anti-CTLA-4 in EMT6 mammary carcinoma



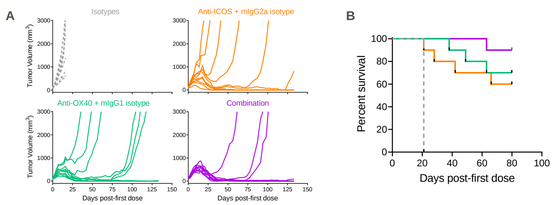
EMT6 (SC) tumor-bearing BALB/c mice were administered IP biw (x3) with ICOS mAb (7E.17G9 mIgG1, 10 µg), CTLA-4 mAb (9H10 hamster IgG, 1 µg), or isotype controls (mIgG1 and hamster IgG, respectively) alone and in combination. Mice were evaluated for (**A**) tumor growth and (**B**) survival. (**C**) Transcriptional analysis (Nanostring for T-Bet [Tbx21] and perforin [Prf1]) from EMT6 tumors harvested on study day 7. (**D**) CD8⁺/regulatory T (Treg) (CD4⁺ FoxP3⁺ CD25⁺) cell ratio in EMT6 tumors harvested on study days 5 (top) and 7 (bottom), as determined by flow cytometry.

Figure 3. ICOS co-stimulation + TLR4 agonist in CT26 colon carcinoma



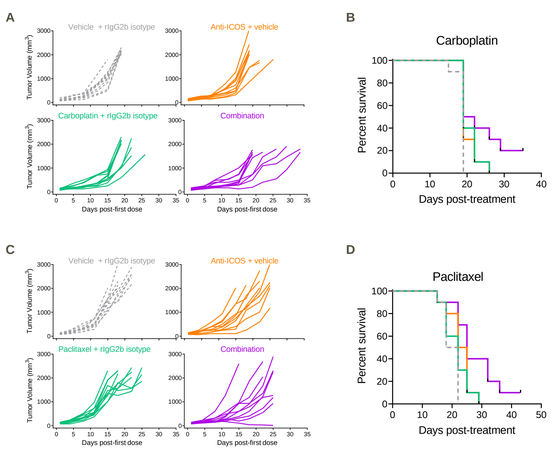
CT26 (SC) tumor-bearing BALB/c mice were administered IP with ICOS mAb (7E.17G9 mIgG1, 100 µg, biw), TLR4 agonist (GSK1795091, 5 µg, once weekly), or controls (mIgG1 and TLR4 vehicle, respectively) alone and in combination. Mice were evaluated for (**A**) tumor growth and (**B**) survival.

Figure 4. Dual co-stimulation (ICOS + OX40) in H22 hepatocellular carcinoma



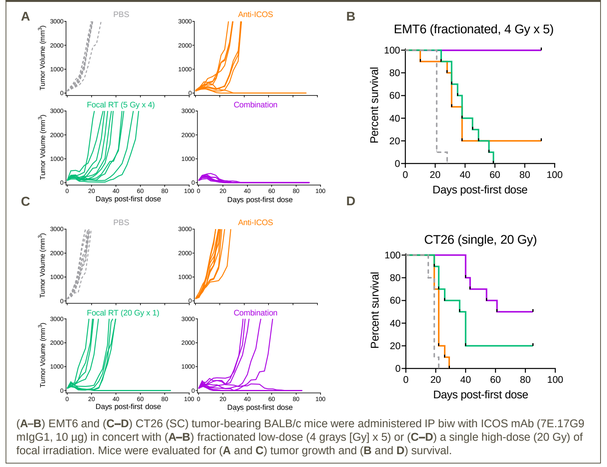
H22 (SC) tumor-bearing BALB/c mice were administered IP biw with ICOS mAb (7E.17G9 mIgG1, 200 µg), OX40 mAb (OX86, rIgG1, 5 µg) alone and in combination. Mice were evaluated for (**A**) tumor growth and (**B**) survival.

Figure 5. ICOS co-stimulation + chemotherapy in CT26 colon carcinoma



CT26 (SC) tumor-bearing BALB/c mice were administered IP biw with ICOS mAb (7E.17G9, [**A–B**] 5 µg or [**C–D**] 200 µg), carboplatin (**A–B**, 75 mg/kg), or paclitaxel (**C–D**, 24 mg/kg) alone and in combination. Mice were evaluated for (**A** and **C**) tumor growth and (**B** and **D**) survival.
Note: In this study parental 7E.17G9 rat IgG2b was used.

Figure 6. ICOS co-stimulation + focal irradiation in EMT6 and CT26 tumor models



(**A–B**) EMT6 and (**C–D**) CT26 (SC) tumor-bearing BALB/c mice were administered IP biw with ICOS mAb (7E.17G9 mIgG1, 10 µg) in concert with (**A–B**) fractionated low-dose (4 grays [Gy] x 5) or (**C–D**) a single high-dose (20 Gy) of focal irradiation. Mice were evaluated for (**A** and **C**) tumor growth and (**B** and **D**) survival.

Table 1. Tabulated mono and combo overall survival (OS) across models

Target	Figure	Model	Mono (OS)	ICOS Mono (OS)	Combo (OS)
PD-1	**1**	EMT6	20%	50%	90%
CTLA-4	**2**	EMT6	80%	50%	100%
TLR4	**3**	CT26	10%	0%	60%
OX40	**4**	H22	70%	60%	90%
Carboplatin	**5A-B**	CT26	0%	0%	TGD only
Paclitaxel	**5C-D**	CT26	0%	0%	10%
RT (20 Gy x 1)	**6A-B**	CT26	20%	0%	50%
RT (4 Gy x 5)	**6C-D**	EMT6	0%	20%	100%

% of tumor-free mice following monotherapy (mono) and combination therapy (combo) across associated models/figures.

Conclusions

- ICOS agonist mAb demonstrated broad mono and combo activity across divergent therapeutic modalities and tumor models.
- These data highlight the combination potential of anti-ICOS agonist mAbs.
- Combinations, such as those presented, are or will be incorporated into the ICOS clinical program, including in the INDUCE-1 (204691; NCT02723955) study, a first-in-human clinical trial evaluating ICOS agonist GSK3359609 as monotherapy and in combination with other regimens in selected solid tumors.

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