A novel antibody targeting ICOS increases intratumoral cytotoxic to regulatory T cell ratio and induces tumour regression

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ICOS (CD152) is an inducible T-cell co-stimulator that is structurally and functionally related to CD28/CTLA-4. ICOS regulates both pro- and anti-inflammatory cytokine production by effector T lymphocytes and regulatory T cells (Tregs) as well as T-cell survival. ICOS expression levels vary in different immune cell subtypes being higher on immunosuppressive Tregs (CD4+FOXP3+) than on effector CD8+ T cells (CD8+ TCM) and higher in the tumor microenvironment (TME) than in the periphery (e.g. blood or semen) [1-5].

**CONCLUSIONS**

**KY1044 IgG1 has a dual mechanism of action (ADCC and co-stimulatory) in vitro**

**KY1044**

KY1044 is a fully human anti-ICOS subclass G1 kappa monoclonal antibody that selectively binds to ICOS. KY1044 has a dual mechanism of action: (1) depletion of intratumoral FOXP3+ Tregs, resulting in an increased TCM: Treg ratio in the TME; and (2) co-stimulation (agonism) of ICOS-positive T effector cells [5].

**Depleting KY1044 preferentially decreases ICOS^+^ cells in mice and Cynomolgus Monkey**

**KY1044 is associated with T cells activation and pro-inflammatory cytokines production in the TME**

**Figure 2.** Spider plots illustrating the intratumoral distribution of ICOS+ cells in various mouse models. (A) KY1044 IgG1 shows a preferential depletion of ICOS+FoxP3+ (dashed line) and ICOS+CD8+ TCM (dotted line) compared to KY1044 IgG1 and KY1044 IgM (solid line). (B) KY1044 IgG1 depletes ICOS+FoxP3+ and ICOS+CD8+ TCM cells in xenograft models, but not in syngeneic models. (C) KY1044 IgG1 depletes ICOS+FoxP3+ and ICOS+CD8+ TCM cells in xenograft models, but not in syngeneic models.

**Figure 3.** A novel fully human anti-ICOS antibody has a dual mechanism of action. KY1044 has the ability of killing ICOS^+^ cells via ADCC. KY1044 also acts as an co-stimulatory against antibody on ICOS^+^ effector cells in vitro (e.g. IFNγ release). As shown in different models, KY1044 (with depletion function) strongly inhibits tumour growth as monotherapy and in combination with anti-PD-L1. KY1044 depletes intratumoral Tregs, improves the effector to Tregs ratio and also induces the up-regulation of inflammatory cytokines in effector T cells in vivo. In summary, our data demonstrated that targeting ICOS with KY1044 is a valid approach for manipulating the immune system and for inducing a strong anti-tumour response.

**Figure 4.** Strong in vivo anti-tumour efficacy as monotherapy or in combination (with anti-PD-L1) for KY1044 mAb with an effector function.