A first-in-human study of KY1044, a fully human anti-ICOS IgG1 antibody as monotherapy and in combination with *atezolizumab* in patients with selected advanced malignancies

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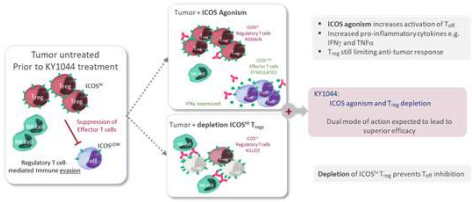
BACKGROUND

ICOS (CD278) 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_{Eff}) and regulatory T-cells (T_{Regs}), as well as T-cell survival. ICOS expression levels vary in different immune cell subtypes being higher on immunosuppressive T_{Regs} ($CD4^+/FOXP3^+$) than on effector $CD8^+$ T_{Eff} cells ($CD8^+$ T_{Eff}), and higher in the tumor microenvironment (TME) than in the periphery (e.g. blood or spleen) [1-5].

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 $ICOS^{high}$ T_{Regs}** resulting in an increase in T_{Eff} : T_{Regs} ratio in the TME; and (2) **co-stimulation (agonism) of ICOS-positive T effector cells** [5].



PRECLINICAL DATA

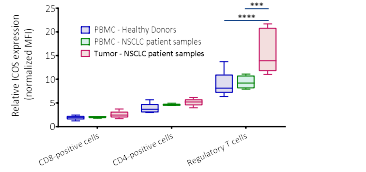
OVERVIEW:

Our preclinical data [5] demonstrated that targeting ICOS with KY1044 is a valid approach for manipulating the immune system and for inducing a strong anti-tumor response. Using different mouse syngeneic tumor models we have shown that KY1044 :

- Strongly inhibits tumor growth as monotherapy and in combination with the checkpoint inhibitor anti-PD-L1.
- Depletes intratumoral TRegs, improves the effector to TRegs ratio in the tumor microenvironment and also induces the up-regulation of inflammatory cytokines *in vivo*.

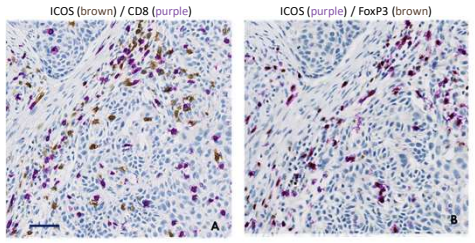
Here, we have shown relevance of ICOS in cancer and some important properties of KY1044, to support the clinical trial.

(1) ICOS is upregulated on intratumoral human T_{Regs}



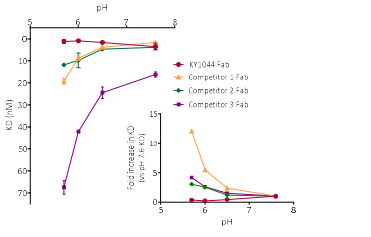
FACS analysis comparing the relative ICOS expression on $CD4^+$, $CD8^+$ and TRegs ($CD4^+/FOXP3^+$) in healthy donor PBMCs (n=5), NSCLC tumour suspension samples (n=5) and matched NSCLC patient PBMCs (n=4). Intratumoral TRegs express higher levels of ICOS than other T cells subtypes in the TME. TRegs in the circulation express lower levels of ICOS than intratumoral TRegs. *** = P value ≤0.001 and **** = P value ≤0.0001 (2-way ANOVA with Tukey's multiple comparison).

(2) ICOS expression strongly colocalizes with FOXP3 expression in HNSCC



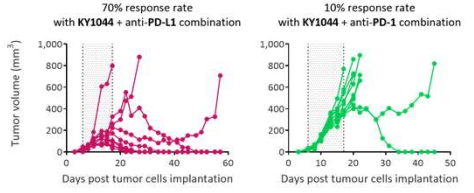
Examples of ICOS staining in the context of CD8 and FOXP3 positive cells in a biopsy from a Head and Neck cancer patient. (A) ICOS/CD8 co-staining by IHC highlights the low expression of ICOS in CD8 positive cells. (B) ICOS/FOXP3 co-staining by IHC highlights the high incidence of ICOS expression in FOXP3 (T_{reg}) cells.

(3) KY1044 affinity is maintained at acidic pH (TME relevance)



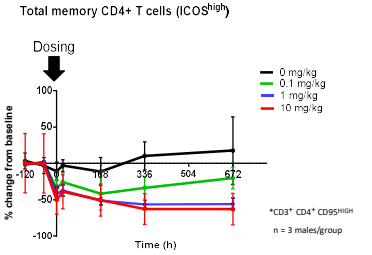
Graph showing the change in KD (as measured by SPR) of different anti-ICOS Fab (including KY1044 Fab) to recombinant ICOS from neutral (7.6) to acidic pH (5.5). Note that KY1044 KD, and therefore its affinity, for ICOS is maintained in acidic pH that are observed in hypoxic tumor microenvironment.

(4) KY1044 shows synergism in combination with anti-PD-L1 (not anti-PD-1)



Comparison of the anti-tumor efficacy of KY1044 mIgG2a in combination with anti-PD-L1 or anti-PD1 (RMP1-14) in the CT26 syngeneic model. (A) Spider plot graphs demonstrating the anti-tumor efficacy of KY1044 mIgG2a in combination with anti-PD-L1 but not with anti-PD-1 in the CT26 model. CT26 cells were implanted sub-cut in the right flank of 8-10 week old Balb/c mice and treated (shaded area) for 2 weeks with KY1044 mIgG2a (3mg/kg, q3w), and either anti-PD-L1 (10mg/kg, q3w) or anti-PD1 (10mg/kg q3w). Mice were dosed IP from day 6 post tumor cells implantation.

(5) KY1044 in-vivo depletes $ICOS^{high}$ cells in Cynomolgus Monkey



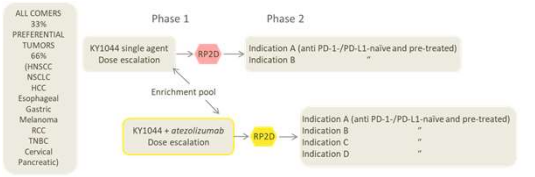
Graph showing the changes (vs mean pre-treatment) in absolute total memory CD4 T cell ($ICOS^{HIGH}$) counts in the blood of monkeys at different timepoints following a single dose of KY1044 hIgG1 at 0, 0.1, 1 and 10 mg/kg (n=3 monkeys per group). The first timepoint post-dose is 0.5h. Monkey CD4 memory T cells were defined as CD4+/CD95high

ADAPTIVE PHASE 1/2 CLINICAL TRIAL

A Phase 1/2, open-label, multi-center study on the safety and efficacy of KY1044 as single agent and in combination with anti-PD-L1 (*atezolizumab*) in adult patients with selected advanced malignancies
PROTOCOL IDENTIFIER: KY1044-CT01

(1) Study design overview

- Phase I dose escalation strategy: Bayesian mTPI2 design (3 patients/cohort)
  Enrichment pool of 40 patients to enrich for selected indications at tolerated dose levels
- Phase 2 expansion cohorts in selected indications in ICI naïve and pre-treated patients



EudraCT Number: *2018-003172-12*; ClinicalTrials.gov Identifier: **NCT03829501**

(2) Key inclusion criteria

- Patients with advanced/metastatic solid tumours (preferably selected tumours), who have progressed despite standard therapy or are ineligible for standard therapy, or for whom no standard or available therapy exists
  - **Phase 1** (including enrichment part): all comers and patients with preferred indications with measurable or non-measurable disease as by RECIST v1.1
  - **Phase 2 - KY1044 single agent:** Indications with signs of anti-tumour activity (CR, PR or durable SD) during Phase 1.
  - **Phase 2 part - KY1044 in combination with atezolizumab:** in preferred indications and indications in which signs of anti-tumour activity (CR, PR or durable SD) during Phase 1 have been observed
- Previous immune therapy (i.e. checkpoint inhibitors) is allowed
- ECOG Performance Status 0-1
- Adequate organ function
- Mandatory biopsies

(3) Key exclusion criteria

- Active autoimmune disease or a documented history of autoimmune disease
- Patients previously exposed to anti-PD-1/PD-L1 treatment who are NOT adequately treated for skin rash or had no replacement therapy for endocrinopathies should be excluded
- Anti-CTLA4, anti-PD-1 or PD-L1 treatment within 4 weeks of the first dose of study treatment
- Patients pre-treated with Anti-CTLA4 antibodies in combination with any other antibody or drugs specifically targeting T-cell co-stimulation or checkpoint pathways
- Patients with a history of drug-induced pneumonitis or current pneumonitis
- Presence of Common Terminology Criteria for Adverse Events (CTCAE) ≥ grade 2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if ≥CTCAE grade 3) due to prior cancer therapy.
- Presence of symptomatic central nervous system (CNS) metastases

(4) Primary Endpoints

- **Phase 1:** Safety and tolerability and DLTs **Phase 2:** Efficacy: ORR according to RECIST 1.1

(5) Secondary Endpoints

- Efficacy: - ORR (in Phase 1), BOR, DOR, PFS by RECIST 1.1 & iRECIST, safety and tolerability (in Phase 2), Survival rate at 12 & 24 months
- PK, ADAs, Biomarkers (TILs IHC ICOS, FoxP3, CD8)

(6) Biomarker strategy: Exploratory Objective and Endpoints (Phase I/II)

Objectives	Endpoints
Tumor tissue (pre and post treatment): • To assess the PD effect of KY1044 as single agent and in combination with atezolizumab	IHC: Expression of immune- and response related markers including ICOS expression in the context of FOXP3
	mRNA gene signature (transcriptomics analysis)
Peripheral blood (pre and post treatment): • To assess the PD effect of KY1044 as single agent and in combination with atezolizumab	Cytokines: Peripheral, soluble ligands and cytokine levels
	Immunoprofiling: longitudinal immune cell phenotyping and markers of immune cell activation in peripheral blood
• To assess target occupancy in response to KY1044 as single agent (Phase 1 only)	PBMC gene signature (transcriptomics)
	Receptor Occupancy (RO) in PBMCs (KY1044 as single agent in Phase 1 only)

CONCLUSION AND ACKNOWLEDGEMENTS

- Following extensive preclinical work, the KY1044-CT01 (NCT03829501) clinical trial was initiated in February 2019 in the US.
- NCT03829501 is a Phase 1/2, open label, multi-center study to evaluate the safety, efficacy and tolerability of KY1044 as single agent and in combination with anti-PD-L1 (*atezolizumab*) in adult patients with selected advanced malignancies.
- Up to 10 sites will be recruiting for the Phase 1 part of the trial (4 in the USA, 2 in the UK, 3 in Italy and 2 in Taiwan).

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