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 effectors (Th1 cytokines) and regulatory T-cells (Tregs), as well as T-cell survival. ICOS expression levels vary in different immune cell subtypes. B cells higher on immunosuppressive TRegs (CD4+CD25+FoxP3+) than on effector CD8 T cells (CD8+T effector memory) 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+ TRegs resulting in an increase in Treg: T effector ratio in the TME; and (2) co-stimulation (agonism) of ICOS-positive T effector cells.

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-1.
- 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 TRegs

ICOS expression was determined on tissue microarrays of CD8+ and FoxP3+ intratumoral human TRegs in CRC (n=30), NSCLC (n=26) and MM (n=18). ICOS expression is increased in the tumor microenvironment relative to the periphery in CRC and NSCLC and is higher in FoxP3+ TRegs than in CD8+ T effector memory cells.

(2) ICOS expression strongly co-localizes with PDLP2 expression in HNSCC

ICOS (brown) / PDLP2 (brown)

ICOS (brown) / FoxP3 (brown)

Graph showing the change in KD (as measured by SPR) of different anti-ICOS Fab (including enrichment part): all comers and patients with preferred indications with measurable or non-measurable disease as by RECIST v1.1.

(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 enrichment part): all comers and patients with preferred indications with measurable or non-measurable disease as by RECIST v1.1.

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

Graph showing the change in KD (as measured by SPR) of different anti-ICOS Fab (including enrichment part): all comers and patients with preferred indications with measurable or non-measurable disease as by RECIST v1.1.

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CONCLUSION AND ACKNOWLEDGEMENTS

Following extensive preclinical work, the KY1044-C01 (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 a single agent 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, 1 in Italy and 2 in Taiwan).

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REFERENCES