KY1043, a novel PD-L1 IL-2 immunocytokine directed towards CD25, delivers potent anti-tumour activity in vitro and in vivo

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Introduction

- IL-2 therapy has been approved for use in certain cancers since 1989.
- The major limitation with this therapy is tolerability, with many patients experiencing grade 3 or higher adverse events.
- Approaches to improve this have focused on engineering molecules with selectivity towards the dimers: IL-2 receptor (CD122 and CD132), IL-2β chain and common γ chain, respectively.
- This form of the receptor complex is expressed on peripheral naïve T cells as well as memory T cells and NK cells, potentially leading to unproductive stimulation of irrelevant cell populations and an increased possibility of systemic toxicity.
- KY1043 is a highly differentiated immunocytokine consisting of a neutralising anti-PD-L1 antibody, fused via its light chains to an attenuated IL-2, in which the balance of signalling has been adjusted to favour the trimERIC form of the IL-2R, which contains CD25 (IL-2Rα).

Ky1043 neutralises PD-L1/PD-1 and PD-L1/CD28 interactions similarly to the parental antibody

In a proliferation assay, the EC50 of KY1043 was similar to that of mHL-2 on IL-2-stimulated TF1 cells (a), but approximately 300-fold lower on βγ expressing cells (b). Blockade of CD28 reduces KY1043 activity to that seen on the TF1-βγ cells, demonstrating the importance of CD28 binding for KY1043 function.

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Reference


KY1043 in vitro

Targeting of immunocytokine to PD-L1 increases efficacy

KY1043 non-targeted immunocytokine

KY1043 induces potent, dose dependent anti-tumour response in vivo

- Human PD-L1 KO mice were implanted with human PD-L1-KO MCF7 cells.
- Mice were treated with KY1043 from day 8, receiving two further doses on day 10 and 13
- At 1 mg/kg of KY1043, 3 of 8 animals rejected the tumour challenge
- At 3 mg/kg, 6 of 8 animals survived
- All mice survived at 10 mg/kg
- No significant weight loss was observed

KY1043 generates a tumour specific memory response

- Mice that survived a tumour challenge with MCF7 cells following KY1043 treatment were re-challenged at day 56 with the same tumour or B16 F10 melanoma cells
- MCF7 tumours were rejected without further treatment, while the melanoma tumours were not, suggesting that KY1043 generates a tumour specific memory response

KY1043 induces strong CD8+ T cell proliferation in the tumour microenvironment

KH-1 L1 M138 tumour samples were analysed by flow cytometry following a single dose of KY1043 at 10 mg/kg. KY1043 induces CD8+ T cell proliferation (as shown by Ki67) that peaks at 72 hours, resulting in an expansion of CD8+ T cells in the TME, and an increase of the CD8:T cell ratio.

KY1043 leads to a large expansion of Treg in the peripheral lymphoid tissue

Tumour draining lymph nodes were analysed by flow cytometry following a single dose of KY1043 at 10 mg/kg. KY1043 induces a spike in CD8+ T cell proliferation at 72 hours, but an even greater expansion of CD8+ Treg: FoxP3+ Treg. This results in the decrease of the CD8:T cell:Treg ratio. A similar effect was noted in the spleen.

Conclusion

- KY1043 induces potent T cell activation and can direct highly effective tumour killing in vitro and in vivo.
- Maximal tumour cell killing is achieved by targeting PD-L1 in vitro compared to untagged immunocytokine.
- Peripheral expansion of Treg is not detrimental to tumour control in vivo.
- These results challenge the dogma that effective binding to dimeric (CD122/CD132) IL-2R is required for tumour control.
- KY1043 α-CD25 (IL-2Rα) directed immunocytokine may provide an advantage therapeutically higher index for the treatment of cancer.
- KY1043 is currently in development at Kymab