Dual Agonist Bispecific Antibody Targeting OX40 and CD137 Mediates Anti-Tumour Immunity and Synergises with PD-1/PD-L1 Blockade to Improve Survival in a Syngeneic Mouse Model


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Background

CD137 and OX40, members of the TNF receptor superfamily, are key mediators of costimulatory signals and they play important roles in driving anti-tumour immunity. However, to date, limited clinical activity has been observed with first generation OX40 or CD137 agonists. We hypothesise that the activity of monospecific FcR-receptor-dependent agonists may be limited by 1) suboptimal co-stimulation of CD8+ T cells by OX40 agonists, or 2) insufficient ‘help’ from CD4+ T cells for optimal CD137 agonist activity and 3) inadequate level of clustering via Fcγ receptors (FcγR) at the relevant sites.

FS120 mAb² is a novel dual agonist bispecific antibody that is capable of driving potent immune cell activation in vitro through dual engagement of OX40 and CD137, decoupled from the requirement for Fcγ-mediated clustering of receptors. Here we present the relationship between dose, pharmacodynamic and pharmacokinetic activity of an anti-OX40/CD137 surrogate mAb² in vivo (FS120 surrogate mAb²).

Mechanistically, anti-tumour activity was not dependent on FcγR-binding proficiency, and CD4+ T cells play a role in OX40/CD137 mAb² mediated increases in peripheral CD8+ T cell response. Furthermore, combining OX40/CD137 mAb² and PD-1/PD-L1 inhibitors results in significantly enhanced in vitro and in vivo activity.

1. FS120 mAb² and its surrogate are superior to combinations of OX40 and CD137 antibodies in primary cell assays and have differentiated mechanism of action

2. FS120 surrogate mAb² has superior anti-tumour activity to combinations of OX40 and CD137 antibodies and FcγR-binding proficiency is dispensable

3. FS120 surrogate mAb² induces dose-dependent anti-tumour activity and significant survival benefit

4. FS120 surrogate mAb² induces activation and proliferation of peripheral T cell and promotes optimal CD8+ T cell response when CD4+ T cells are present

5. FS120 mAb² in combination with PD-1/PD-L1 blockade is more active than single agents in vitro

6. Combination of FS120 surrogate mAb² and PD-1 mAb significantly improves survival benefit in a PD-1 mAb refractory tumour model

Conclusions

The dual costimulatory receptor agonist FS120 and a murine surrogate mAb² showed superior in vitro activities in primary immune cell assays over monospecific OX40 or CD137 monoclonal antibodies as single agents or in combination. The activities of both mAb² are conditional and dependent on dual engagement of both OX40 and CD137 as demonstrated in vitro and in vivo by comparison, and importantly unlike the monoclonal antibodies, are not reliant on FcγR-mediated clustering of receptors.

In a CT26 syngeneic colon carcinoma model, anti-tumour activity of FS120 surrogate mAb² was increased in a dose-dependent manner between 0.1 to 3 mg/kg. This resulted in a significant decrease in tumour growth rate and improved survival. FS120 surrogate mAb² induced substantial increases in proliferating CD8+ and CD4+ T cells in the blood, and our findings support an inverse correlation between the extent size and dose treated between 1 to 3 mg/kg. In a depletion study, FS120 surrogate mAb² drove increases in peripheral proliferating CD8+ T cells, which were partially inhibited by CD8 T cell depletion suggesting a variable role for CD4+ T cell help in potentiating FS120 surrogate mAb² effects on CD8+ T cell response. Combination with PD-1 antibody led to the significant improvements in survival compared to either FS120 surrogate mAb² or PD-1 antibody alone and complete tumour regression was observed in 47% of animals compared to 7% and 0%, respectively. Taken together, these preclinical results demonstrate the potential for FS120 mAb², as a single agent or in combination with PD-1/PD-L1 blockade, to drive an effective anti-tumour immune response, therefore warranting further investigation in the clinic.