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GIGA-564 A THIRD GENERATION ANTI CTLA 4 WITH MINIMAL ABILITY TO BLOCK CTLA 4 BINDING TO B7 LIGANDS HAS ENHANCED EFFICACY BUT REDUCED TOXICITY COMPARED TO IPILIMUMAB IN PRECLINICAL MODELS

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Background Anti-CTLA-4 antibodies such as ipilimumab were among the first immuno-oncology agents to show significantly improved outcomes for patients. However, existing anti-CTLA-4 therapies fail to induce a response in a majority of patients and can induce severe, immune-related adverse events. It has been assumed that checkpoint inhibition, i.e., blocking the interaction between CTLA-4 and its ligands, is the primary mechanism of action for current anti-CTLA-4 therapies.¹ Here we present evidence that anti-CTLA-4 therapies with minimal blocking activity can be efficacious in pre-clinical models.

Methods Mice expressing human CTLA-4 were used to investigate the mechanism of action of anti-CTLA-4 therapies including ipilimumab and GIGA-564. These and other humanized mice were also used to investigate the efficacy and toxicity of GIGA-564.

Results GIGA-564, a third generation anti-CTLA-4 with limited ability to block CTLA-4 binding to its B7 ligands, has increased ability to induce in vitro FcR signaling and in vivo depletion of intratumoral Tregs and induces less proliferation of remaining Tregs. In agreement with this, GIGA-564 has superior anti-tumor activity compared to ipilimumab in a murine model. Further experiments showed that the enhanced FcR activity of GIGA-564 likely contributes to its enhanced anti-tumor activity. Importantly, we also showed that GIGA-564 was associated with lower toxicity in murine models.

Conclusions Our work shows that in pre-clinical models GIGA-564 has enhanced efficacy but reduced toxicity compared to ipilimumab.

REFERENCES

1. Stone EL, Carter KP, Wagner EK, Asensio MA, Benzie E, Chiang YY, Coles GL, Edgar C, Gautam BK, Gras A, Leong J, Leong R, Manickam VA, Mizrahi RA, Niedecken AR, Saini J, Sandhu SK, Simons JF, Stadtmiller K, Tinsley B, Tracy L, Wayham NP, Lim Y, Adler AS, Johnson DS. Lack of blocking activity in anti-CTLA-4 antibodies reduces toxicity, but not anti-tumor efficacy. *bioRxiv*. 2021, <https://doi.org/10.1101/2021.07.12.452090>.

Ethics Approval Murine experiments were done in compliance with all relevant ethical regulations and approved by the Institutional Animal Care and Use Committee of Crown Bioscience.

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