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 pre-clinical models

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Introduction

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 B7 ligands (CD80 and CD86), is the primary mechanism of action for ipilimumab. Here we present evidence that checkpoint inhibition may not be a primary mechanism of action for efficacy of anti-CTLA-4 antibodies. Instead, the primary mechanism for efficacy may be FcR-mediated Treg depletion in the tumor microenvironment.

Our hypothesis is that anti-CTLA-4 therapies should be optimized for Treg depletion rather than checkpoint inhibition.

Note: GIGA-564 is pre-clinical and as such is not an approved therapy at this time

GIGA-564 binds to CTLA-4 with high affinity but weakly blocks CD80/CD86 binding

- GIGA-564 binds to CTLA-4 with high affinity
- Cell-based and ELISA blocking assays show that GIGA-564 has limited ability to block CTLA-4 binding to CD80/CD86 compared to ipilimumab

GIGA-564 induces less Treg proliferation and effectively depletes intratumoral Tregs

- GIGA-564 treatment induces less proliferation of Tregs in the periphery than ipilimumab
- Fewer proliferating Tregs is likely to further enhance efficacy compared to ipilimumab in patients
- hCTLA-4 KI mice bearing MC38 tumors were randomized and treated with 5 mg/kg of ipilimumab or GIGA-564 Q3dx3 and T cells were analyzed one day after last dose

- GIGA-564 has enhanced ability to induce FcR signaling and was more efficient in depleting CTLA-4+ intratumoral Tregs
- hCTLA-4 KI mice bearing MC38 tumors were randomized and treated with a single IP injection of the indicated mAb at 5 mg/kg and then intratumoral T cells were analyzed 24 hours later

Conclusions and Next Steps

GIGA-564, a fully human IgG1 monoclonal antibody with high affinity to CTLA-4 but minimal ability to block CTLA-4 to its B7 ligands, has been shown to target and deplete intratumoral Tregs while inducing less proliferation of the remaining Tregs. Furthermore, in non-clinical models GIGA-564 induced enhanced anti-tumor efficacy but less toxicity than ipilimumab, a monoclonal antibody which was designed to maximize checkpoint inhibition. These findings suggest that new anti-CTLA-4 therapies should be designed to maximize Treg depletion rather than checkpoint inhibition. In future clinical studies, GIGA-564 has the potential to significantly improve patient outcomes by not only inducing responses in more patients but also by lessening the burden of anti-CTLA-4-related toxicities.