305 COMBINATION IMMUNOTHERAPY USING A NOVEL CHIMERIC ONCOLYTIC VIRUS TO REDIRECT CD19 BISPECIFIC T CELL ENGAGERS TO TARGET SOLID TUMORS

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Background Bispecific T cell engager (BiTE) monoclonal antibodies have emerged as a promising immunotherapy strategy for the treatment of hematological malignancies. Blinatumomab, an FDA approved BiTE carrying CD19 and CD3 epitopes has shown durable clinical responses for the treatment of B-cell acute lymphoblastic leukemia (B-ALL) and non-Hodgkins lymphomas. Despite a wide array of research in hematological malignancies, BiTE therapies for the treatment of solid tumors have remained a significant challenge in demonstrating comparable efficacy. Solid tumors often lack amenable and targetable tumor antigens, and in many solid tumors the tumor microenvironment (TME) is largely known to be immunologically "cold" and a barrier to immunotherapy responses. Oncolytic viruses have recently gained traction in the field for the treatment of solid tumors because of their ability to target tumor-intrinsic properties and reshape the immunosuppressive TME. We have previously described the use of a chimeric oncolytic vaccinia virus (CF33) for the treatment of a variety of tumor cell types, including triple-negative breast cancer, lung cancer, and liver cancer. Building on this, we generated an OV that expresses a non-signaling, truncated CD19 antigen (CF33-CD19t or onCARlytics, in collaboration with Imugene Limited), onto the surface of infected tumor cells prior to virus mediated tumor lysis, which redirected CD19-targeting chimeric antigen receptor (CAR) T cell activity against solid tumors (Park *et al*. STM 2020). Using this combination, we have created a universal system that is agnostic to solid tumor type and can be provided with a targetable and well-characterized antigen. We now show that blinatumomab can be redirected to solid tumors with CF33-CD19t, enabling an off-the-shelf combinatorial immunotherapy strategy.

Methods For preclinical testing, we utilized *in vitro* co-culture assays using human healthy donor-derived T cells and human triple-negative breast cancer cells treated with CF33-CD19t and blinatumomab. We evaluated tumor cell killing and T cell activation using flow cytometry and cytokine assays. Humanized NSG mice were used to evaluate anti-tumor activity of the combination *in vivo*.

Results Tumors infected with CF33-CD19t along with blinatumomab show specific tumor cell killing *in vitro* and robust anti-tumor efficacy using *in vivo* human triple-negative breast cancer xenograft models.

Conclusions Using this approach, we show that a clinically-approved CD19-directed BiTE can be combined with oncolytic viruses to activate and redirect endogenous anti-tumor immunity against solid tumors.

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