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Curing glioblastoma with oncolytic virus and immune checkpoint blockade

Cancer immunotherapy utilizes the patient's immune system to recognize and/or destroy tumors. The immune system has both positive activator/effector and negative inhibitory functions. Immune checkpoints are one such inhibitory function that can be overcome by immune checkpoint inhibitors (ICIs), such as anti-PD-1. ICIs have had a groundbreaking impact on cancer therapy in some cancers, but did not work in a majority of cancer patients. In glioblastoma (GBM), an invariably lethal primary brain tumor, ICIs have not been effective so far (i.e. CheckMate-143 clinical trial). The possible reasons for ICI immunotherapy failure in GBM are: (i) highly aggressive and invasive tumor; (ii) treatment-resistant GBM stem cells (GSCs); (iii) abundant presence of immune inhibitory regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), including pro-tumorigenic macrophages in the tumor; (iv) tumor cells and immune inhibitory cells release a variety of immunosuppressive molecules (e.g. TGFb, IL-10) that impair immune cells (e.g. T cells) from recognizing and/or attacking tumor cells; and (v) GBM cells are not highly mutated, so few nonself-antigens are expressed. Thus, GBM is considered an immunologically 'cold' tumor. To create and test new immunotherapy drugs for GBM we developed a 'cold' mouse GSC-derived GBM model (005). In this model, single ICIs (anti-PD-1, anti-PD-L1, or anti-CTLA-4) or dual ICIs (anti-PD-1+anti-CTLA-4) only modestly improved survival (Fig. 1), reflective of the lack of success in GBM clinical trials.

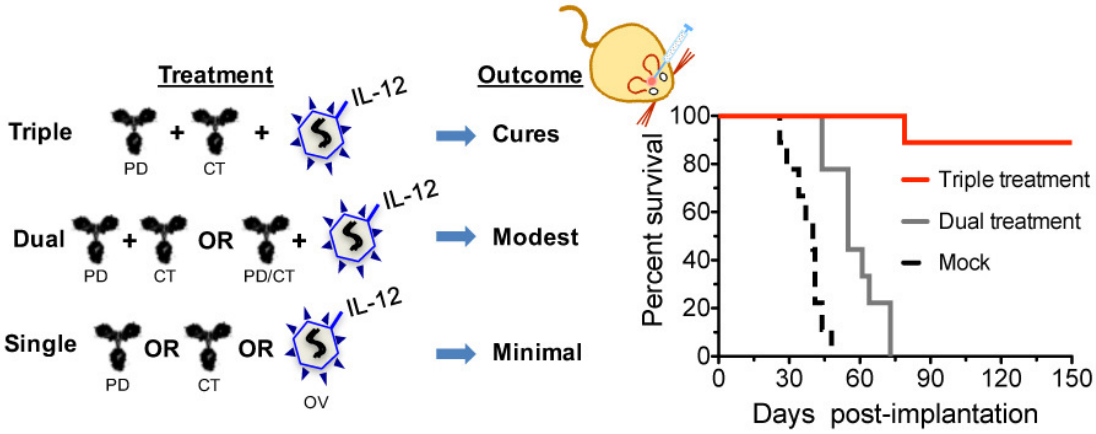

Fig. 1. Outcomes of different combination therapies. Effect of single (systemic ICI or intratumoral oHSV), dual, or triple (2 ICIs + oHSV) combination therapy in syngeneic 005 GBM tumors. Right. Representative mouse treatment experiment (Kaplan-Meier survival analysis) illustrating differences in survival between dual and triple treatment groups.
ICI, immune checkpoint inhibitor; PD, anti-PD-1; CT, anti-CTLA-4; OV, G47Δ-IL12.

Oncolytic herpes simplex virus (oHSV) is genetically engineered so that it both selectively kills cancer cells (oncolysis) but not normal cells, and educates the patients' immune system to attack tumor cells, i.e. *in situ* vaccination or immunovirotherapy. In addition to these direct anti-tumor effects, oHSV can also be armed with immune stimulators to further weaponize the immune system against the tumor. Imlygic®, an oHSV

armed with immune activator GM-CSF, produced significant clinical benefit in advanced melanoma and was recently approved by the FDA. Similar to Imlygic, G47Δ, an oHSV currently in a registration [not phase III] clinical trial for GBM in Japan, has been 'armed' with an immune stimulator IL-12 (G47Δ-IL12) and tested in 005 tumors. Intratumoral injection of G47Δ-IL12 increased efficacy in 005 tumors compared to non-armed G47Δ, but efficacy was still limited. Despite this, G47Δ-IL12 induced important anti-tumor immune responses over mock treatment: increased infiltration of anti-tumor effector T cells, effector/inhibitory T cell ratio (a hallmark of clinical success), and anti-tumor macrophages (M1-like), and reduced inhibitory T and tumor cells.

Since G47Δ-IL12 induced strong anti-tumor immune responses and a 'hot'-like tumor, and ICIs unleash anti-tumor immunity, we hypothesized that G47Δ-IL12 might synergize with ICIs and improve the therapeutic outcome of G47Δ-IL12 immunovirotherapy. Dual combination of G47Δ-IL12+single ICI (anti-PD-1, anti-PD-L1, or anti-CTLA-4) improved survival, but only modestly compared to single treatments alone (Fig. 1). Since PD-1/PD-L1 and CTLA-4 produce their immunosuppressive actions via independent immune inhibitory pathways, we hypothesized that blocking both PD-1 and CTLA-4 pathways (i.e. anti-PD-1+anti-CTLA-4) would be more beneficial in combination with G47Δ-IL12, than blocking a single pathway. This was indeed true and triple combination therapy (G47Δ-IL12+anti-PD-1+anti-CTLA-4) cured most mice with 005 tumors, which is unprecedented. This was associated with an increase in anti-tumor macrophages (M1-like) and the effector/inhibitory T cell ratios within the tumor. Further immune mechanistic studies revealed that three types of immune cells (mainly $CD4^+$ T, and $CD8^+$ T cells and macrophages) were major contributors. This illustrates the complex interplay between different anti-tumor immune cells ($CD4^+$, $CD8^+$, macrophages) required for complete therapeutic activity, and portends a difficult, but attainable road to successful patient treatment. The multimodal combination strategy we describe should be translatable to the clinic for GBM and other immunosuppressive cancers.

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Publication

Macrophage Polarization Contributes to Glioblastoma Eradication by Combination Immunovirotherapy and Immune Checkpoint Blockade.
Saha D, Martuza RL, Rabkin SD
Cancer Cell. 2017 Aug 14