Enhancement of radiation therapy through VISTA blockade in flank tumor murine models

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INTRODUCTION & METHODS

- Radiation therapy (RT) is a primary treatment for various cancers, often in combination with surgery or chemotherapy.
- Unfortunately, RT also triggers various immune suppressive signals that limit the anti-tumor response.
- Therefore, immune modulating therapies have the potential to enhance the effect of RT without increasing the radiation dose.
- Several promising immune checkpoint inhibitors have been identified and studied both alone and in combination with RT, such as anti-PD1 and anti-CTLA4.
- VISTA is a checkpoint expressed on hematopoietic and myeloid derived cells, tumor cells, as well as various T cell populations. The presence of VISTA on both antigen presenting cells and regulatory T cells appears to be most important for limiting cytotoxic T cell activity and function
- The goal of our study was to determine if combining VISTA inhibition with RT would result in improved tumor control in B16 and MC38 murine flank tumor models.
- Thus, in separate studies, we utilized VISTA knock-out (KO) mice and anti-VISTA antibodies to achieve VISTA blockade and combined this with a single dose of 15 Gy radiation.
- Treatment was delivered when flank tumors reached a volume of 100 m^3 and time to tumor volume tripling was used as the primary study endpoint.

Acknowledgements

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Radiation therapy combined with VISTA blockade significantly improves survival in B17 and MC38 murine flank tumor models

Figure 1

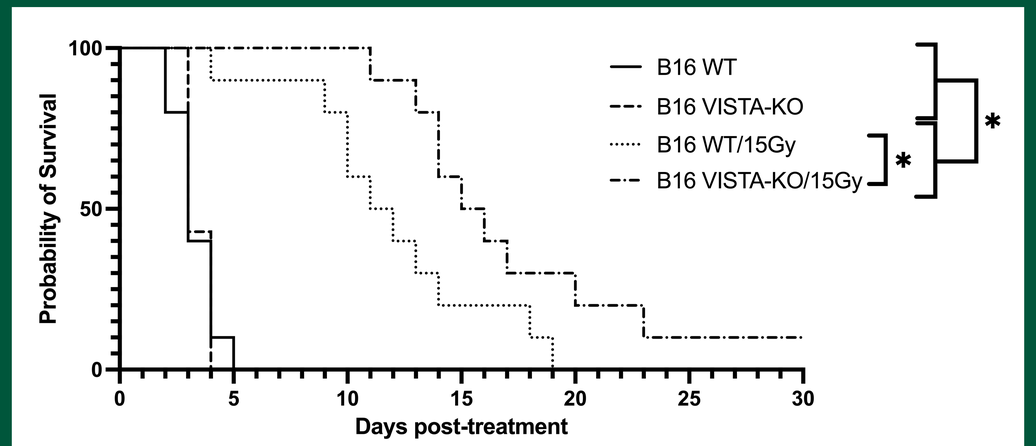
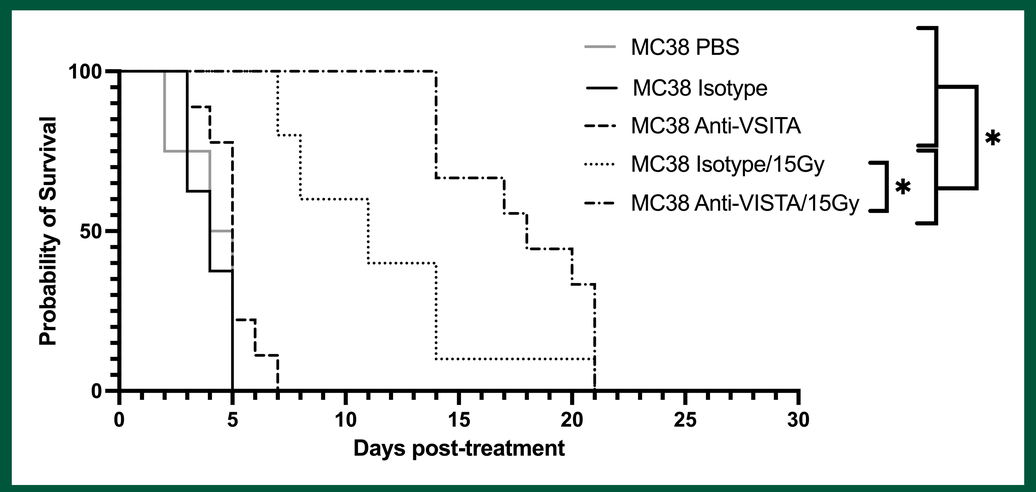


Figure 2



Figures 1 and 2. Kaplan-Meier survival curves demonstrating tumor control of flank tumors in B16 and MC38 models. When combined with a single 15 Gy dose of radiation, VISTA blockade via genetic knockout in the B16 model (Figure 1) and via anti-VISTA antibodies in the MC38 model (Figure 2) significantly improved survival by an average of 5.5 days and 6.3 days compared to RT alone, respectively (P<0.05).

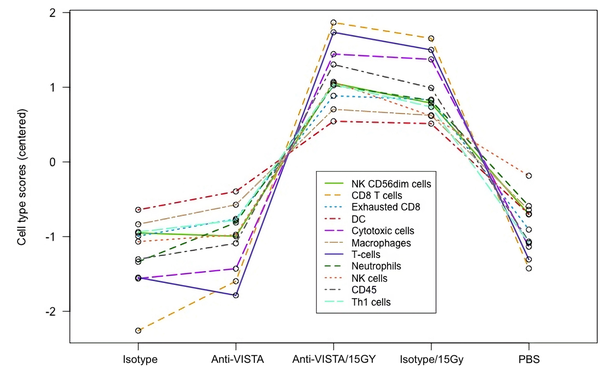


Figure 3. Immune Cell Abundance (mRNA) in B16 melanoma tumor. The RNA data(mRNA) demonstrates that VISTA blockade with radiation leads to increased cytotoxic immune cell presence in B16 melanoma tumor. Raw cell scores for an array of immune cell types for the different treatment cohorts. Activated T cells and NK cells (CD8 and CD56dim) were slightly higher in the anti-VISTA/15Gy than the isotype/15Gy cohort.

DISCUSSION

- The VISTA-KO and anti-VISTA blockade resulted in significantly longer survival in the B16 and MC38 models by an average of 5.5 and 6.3 days compared to RT alone, respectively (p<0.05).
- The gene expression data suggests that the mechanism behind the enhanced tumor control is primarily a result of increased apoptosis and immune mediated cytotoxicity.
- An interesting feature of the VISTA/radiation treatment is the heterogeneity of the individual response. In our study, we saw evidence that some animals who received VISTA blockade and RT showed a marked tumor control response, whereas others showed a lesser or minimal response. This distinction between “responders” and “non-responders” is characteristic of existing immune therapies and is observed with VISTA blockade as well.

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