

POSTER PRESENTATION

Open Access

# Agonist anti-GITR monoclonal antibody and stereotactic radiation induce immune-mediated survival advantage in murine intracranial glioma

Mira Patel<sup>1\*</sup>, Jennifer Kim<sup>2</sup>, Debebe Theodros<sup>2</sup>, Christopher Jackson<sup>3</sup>, Ada Tam<sup>4</sup>, Esteban Velarde<sup>5</sup>, Betty Tyler<sup>3</sup>, Xiaobu Ye<sup>3</sup>, Henry Brem<sup>3</sup>, Mark Selby<sup>6</sup>, Charles Drake<sup>7</sup>, Drew Pardoll<sup>1</sup>, Michael Lim<sup>3</sup>

From 30th Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer (SITC 2015)

National Harbor, MD, USA. 4-8 November 2015

## Background

Glioblastoma (GBM) is a poorly immunogenic neoplasm treated with local radiation. Despite the standard of care, median survival remains low. Immunotherapy has synergized with stereotactic radiosurgery (SRS) in murine GBM, as radiation promotes a pro-inflammatory tumor microenvironment amenable to the anti-tumor effects of immune modulation. Glucocorticoid-induced tumor necrosis factor receptor (GITR) is a co-stimulatory receptor expressed constitutively on regulatory T cells and inducibly on effector T cells. We tested the hypothesis that anti-GITR monoclonal antibody (mAb) and SRS combination therapy would confer immune-mediated survival benefit in murine glioma.

## Methods

Mice were implanted with GL261-luc murine glioma cells and began SRS and anti-GITR IgG1 treatment after 10 days. Mice were randomized to four treatment groups: control, SRS only, anti-GITR only, anti-GITR+SRS. SRS was delivered to the tumor in one fraction; mice were given mAb thrice i.p. Mice were euthanized on day 21 to analyze the immunologic profile of tumor, spleen, and tumor draining lymph nodes.

## Results

Anti-GITR mAb plus SRS conferred significantly improved survival over either treatment alone ( $p < .0001$ , cure rate 24%). The increased survival required CD4+T cells but not CD8+T cells or regulatory T cells (Tregs).

There was elevated intratumoral CD4+ effector-cell infiltration (CD4+/Foxp3-/IFN $\gamma$ +) relative to Treg infiltration (CD4+/Foxp3+) at day 21 in mice treated with anti-GITR +SRS, and significantly elevated IFN $\gamma$  and IL-2 production by CD4+T cells and elevated IFN $\gamma$  and TNF $\alpha$  production by CD8+T cells. Intratumoral mononuclear cells demonstrated increased mRNA expression of pro-inflammatory M1 markers and decreased expression of immunosuppressive M2 markers.

## Conclusions

In all, anti-GITR mAb synergizes with SRS to significantly prolong survival in murine orthotopic glioma in a potentially CD4+ Th1-dominant anti-tumor mechanism with M1 polarization. These findings provide preclinical evidence for the use of anti-GITR IgG1 non-depleting antibodies alongside SRS in human GBM.

## Authors' details

<sup>1</sup>Johns Hopkins University School of Medicine, Baltimore, MD, USA. <sup>2</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA. <sup>3</sup>The Johns Hopkins University Department of Neurosurgery, Baltimore, MD, USA. <sup>4</sup>The Johns Hopkins University Department of Immunology, Baltimore, MD, USA. <sup>5</sup>The Johns Hopkins University Department of Radiation Oncology, Baltimore, MD, USA. <sup>6</sup>Bristol-Myers Squibb, Baltimore, MD, USA. <sup>7</sup>The Johns Hopkins University Departments of Oncology and Cancer Immunology, Baltimore, MD, USA.

Published: 4 November 2015

doi:10.1186/2051-1426-3-S2-P194

Cite this article as: Patel et al.: Agonist anti-GITR monoclonal antibody and stereotactic radiation induce immune-mediated survival advantage in murine intracranial glioma. *Journal for ImmunoTherapy of Cancer* 2015 **3**(Suppl 2):P194.

<sup>1</sup>Johns Hopkins University School of Medicine, Baltimore, MD, USA  
Full list of author information is available at the end of the article

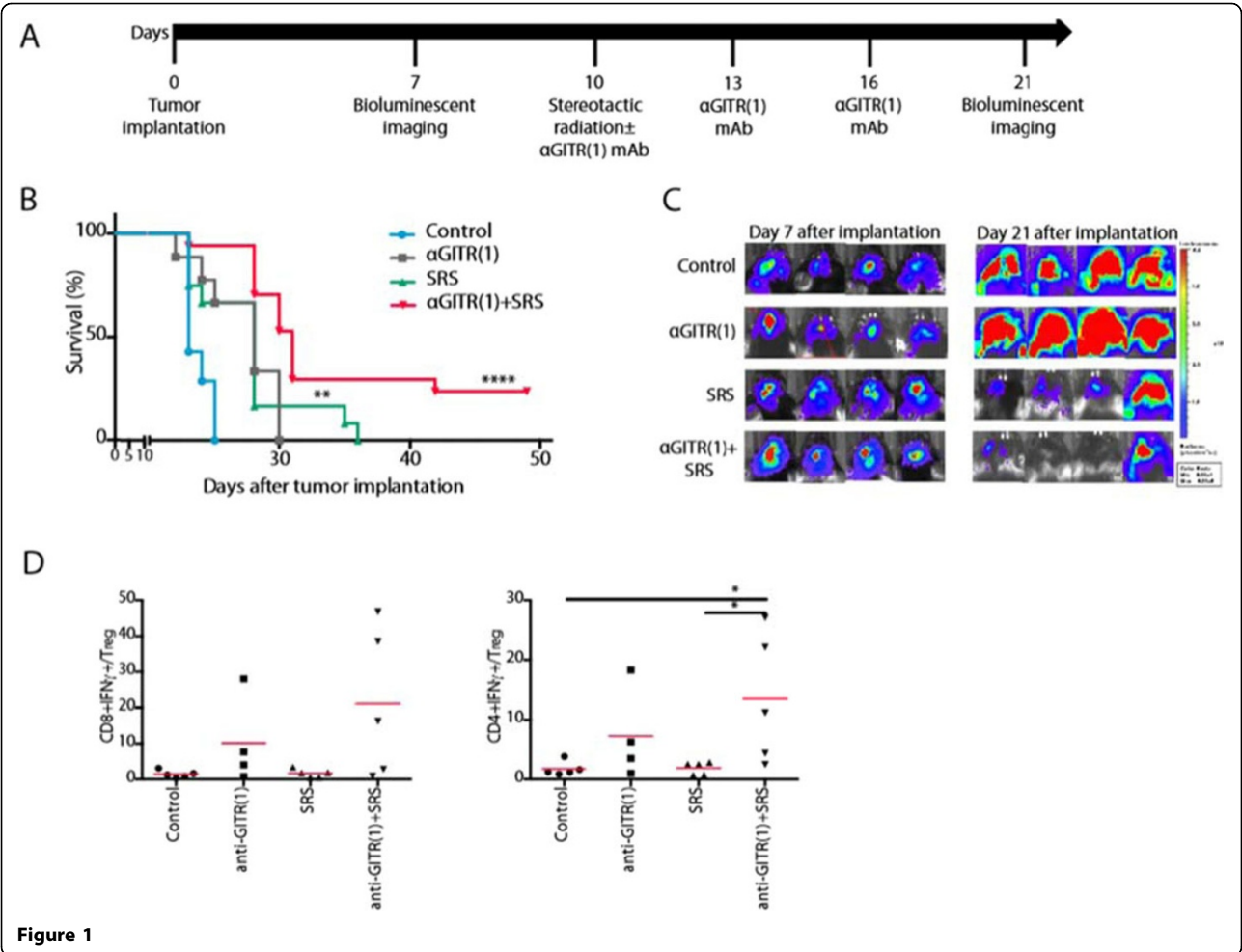


Figure 1