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

Mira Patel1*, Jennifer Kim2, Debebe Theodros2, Christopher Jackson3, Ada Tam4, Esteban Velarde5, Betty Tyler3, Xiaobu Ye3, Henry Brem3, Mark Selby6, Charles Drake7, Drew Pardoll1, Michael Lim3

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+ effector-cell infiltration (CD4+/Foxp3−/IFNγ+) relative to Treg infiltration (CD4+/Foxp3+) at day 21 in mice treated with anti-GITR +SRS, and significantly elevated IFNγ and IL-2 production by CD4+T cells and elevated IFNγ and TNFα 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.

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.
Figure 1

A) Timeline of events following tumor implantation:
- Days 0: Tumor implantation
- Days 7: Bioluminescent imaging
- Days 10: Stereotactic radiation + αGITR(1) mAb
- Days 13: αGITR(1) mAb
- Days 16: αGITR(1) mAb
- Days 21: Bioluminescent imaging

B) Survival analysis over time:
- Control
- αGITR(1)
- SRS
- αGITR(1) + SRS

C) Bioluminescent imaging results:
- Day 7 after implantation
- Day 21 after implantation

D) Quantitative analysis of CD4+FoxP3+ Tregs:
- Control
- αGITR(1)
- SRS
- αGITR(1) + SRS