CNS 2018 ANNUAL MEETING
HOUSTON, TEXAS
OCTOBER 6-10, 2018

# Longitudinal genomic study of response to anti-PD-1 immunotherapy in Glioblastoma

Junfei Zhao PhD; Andrew Chen BS; Andrew Silverman; Robyn D Gartrell; Luis Aparicio de Santiago; Timothy Chu; Jorge Samanamud; Jonathan Tad Yamaguchi BS; Craig Horbinski BS, MD, PhD; Rimas Vincas Lukas MD; Jeffrey Raizer MD; Ali I Rae; Jinzhou Yuan; Peter D. Canoll MD PhD; Jeffrey N. Bruce MD; Yvonne Saenger; Peter Sims; Fabio Iwamoto; Raul Rabadan; Adam M. Sonabend MD

## Introduction

Immunotherapies are successful across several tumor types; however, their efficacy has been uncommon and unpredictable in glioblastomas (GBM), where only 10-12% of patients show

long-term responses. To understand the molecular determinants of immunotherapeutic response in GBM, we studied the longitudinal genomic, transcriptomic, and histological profiles of patients that were treated with PD1 immune check-point inhibitors.

## Methods

We analyzed 42 patients, including 15 long-term responders, collected after standard therapy, prior to PD1-blockade with nivolumab or pembrolizumab and after this treatment. We defined response as stable disease per MR imaging for >6 months after initiation of PD1-targeting therapy, or relative absence of tumor and robust lymphocyte infiltrate in specimens collected following this immunotherapy. Patients were profiled using exome sequencing, clinical gene analysis platforms, multiplex immunofluorescence, and analysis of clinical and MRI data.

## Results

Patients that responded to PD1 inhibitors had significant longer survival compared to non-responders, which is accounted by the time from initiation of PD1-targeted therapy to death, whereas there were no differences in time between diagnosis and initiation of this immunotherapy among responders vs non-responders. We found PTEN mutations associated with expression of immunosuppressive genes in the non-responders, whereas mutations in the MAPK pathway were enriched in the responder group. We also noticed that tumors responsive to immunotherapy were associated with a branched pattern of evolution following the elimination of neo-epitopes upon recurrence after immunotherapy in responder patients, suggesting that tumor immunoediting was prompted by this therapy. Genomic and quantitative multiplex immunofluorescence profiles showed differences in microenvironmental immunosuppressive features between these groups. Moreover, non-responders tend to have homozygous HLA loci, reduced lymphocyte infiltration, and greater increases in T-cell clonal diversity.

## Conclusions

Our study shows that clinical responses to anti PD1 immunotherapy in GBM are associated with specific molecular alterations, immune expression signatures, and immune infiltration that reflect the tumor’s clonal evolution during treatment.

## Learning Objectives

Understand the molecular factors that influence response to immune-checkpoint blockade in glioblastomas.

Understand the effect of immunotherapy in the immunoediting of glioblastoma genome.

**[Default Poster]**