However, the majority ultimately progress, highlighting the need for combinatorial therapies for sustained immune-surveillance. METHODS: We performed transcriptomic analyses of human RRD-GBM specimens for immune checkpoint expression, and accordingly, tested combined ICI in immunocompetent murine models. Based on these preclinical data, we treated refractory patients using a combination of anti-PD1 and anti-LAG3 through single-patient trials/compassionate access. Complimentary immuno-genomic biomarker analyses including circulating tumor DNA (ctDNA) were performed to study mechanisms and track responses. RESULTS: Human RRD-GBM (n=80) demonstrated high LAG3 expression, providing a strong rationale for targeting. We tested combined anti-PD1 and anti-LAG3 inhibition in three immunocompetent RRD-GBM murine models. In the anti-PD1-responsive (Nestin-Cre-MSH2<sup>lox/lox</sup>-Pole<sup>E3<sup>TM1flv</sup></sup>) model, combined inhibition resulted in universal tumor response and survival. In the anti-PD1 resistant models (Mlr<sup>+</sup>/Nestin-Cre-Trip53<sup>1lox/lox</sup>) and therapy-induced hypermutant ENU/Trip53<sup>−</sup> gliomas), the combination improved survival despite a lack of response to anti-PD1 monotherapy. Biologically, high LAG3 expression and exhaustion was observed in CD8 T-cells after treatment with anti-PD1, which was subsequently ablated by the addition of anti-LAG3. Serially transplanted mice showed response and improved survival to the combination, suggesting that resistance to anti-PD1 could be abrogated by the combination. Four patients with RRD-GBM who had failed anti-PD1 treatment were treated using the combination, resulting in objective radiological responses and prolonged ongoing survival in patients with RRD-GBM and high LAG3 expression. Tolerability was better than a previous study of combined CTLA4 and PD1 inhibition for similar patients. Correlation with paired immuno-genomic tumor analyses, flow-cytometry, T-cell receptor clonotype and CSF ctDNA are ongoing prospectively. CONCLUSION: LAG3 is an effective target in refractory RRD-GBM. Combined inhibition with anti-PD1 inhibition demonstrated radiological response, prolonged survival and manageable toxicities in patients, and will be tested in future clinical trials.