Figure S1: Initial single cell RNA-sequencing analysis of $CD8^+$ T cell reveals that TCR genes drive the UMAP layout (a) Initial UMAP with cells colored according to graph-based cluster (b) Contribution of each tumor model to the initial cluster reveals clusters 9 and 10 are uniquely comprised of a single tumor model (c) Reanalysis following removal of TCR genes redistributes cells previously in clusters 9 and 10 into multiple clusters.

Figure S2: Development of an exhaustion score. Feature Plot of expression levels of key $CD8^+$ T cell exhaustion genes used to develop an Exhaustion Module Score

Figure S3: Defining exhausted T cell subsets in the tumor-infiltrating $CD8^+$ T cells. Gene lists defining T_{ex} subsets in chronic viral murine models were used to generate module scores and superimposed onto UMAP to define T_{ex}^{prog} and T_{ex}^{term} subsets in the infiltrating $CD8^+$ T cells.[7,12]

Figure S4: Representative gene ontology analyses of the $CD8^+$ T cells. Gene ontology analyses of upregulated biological processes in clusters 3 and 7 is consistent with a proliferating cell subset.

Figure S5: Comparison of absolute number of $CD8^+$ and $CD4^+$ TIL from mouse glioblastoma tumor models. Bar graphs quantifying absolute number of $CD3^+CD8^+$ and $CD3^+CD4^+$ TIL isolated from (a) GL261 and CT2A or (b) GL261 and CD4-depleted GL261 on day 14 post-tumor implantation. Data pooled from at least 2 independent experiments with n=3 mice per group per experiment.

Figure S6: Effect of CD4 T cell Presence on PD-1 blockade monotherapy. CD4-depletion (day 5 post-implantation) of GL261-bearing C57BL/6 mice abrogates PD-1 blockade monotherapy (day 10 post-implantation; p=0.0046, n=5 across 2 independent replicates).

Figure S7: Progressive development of $CD8^+$ T cell dysfunction. A pseudotime trajectory analysis performed using Monocle3 demonstrates a general progression from a T_{ex}^{prog} to T_{ex}^{term} state.

Figure S8: Definition of PD1-blockade therapy-responsive $CD8^+$ T cell clusters. An expression dot plot using genes associated with a response to PD1-blockade therapy demonstrates upregulation within cluster 5, primarily comprised of $CD8^+$ T cells in PD1-blockade treated GL261.

Figure S9: Evaluation of $CD8^+$ T cell clonal diversity. Shannon and Inverse Simpson Indices reveals untreated GL261 is more clonally diverse than CT2A. While PD1-blockade therapy reduces the clonal diversity of GL261, CD4 depletion reduces clonal diversity of GL261 to levels near that of CT2A.

Figure S10: Gene ontology analysis of the $CD4^+$ effector T cell compartment. Gene ontology analysis of the upregulated biological processes of the non-T_{reg} CD4 T cells reveals that cluster 2 is uniquely defined by cellular response to interferon-beta.