Glioblastoma (GBM) is a universally fatal brain tumor. Numerous chemotherapy, targeted therapies and immunotherapies are in development but few have led to overall survival benefit for GBM patients. For example, mono- or combinatorial treatment with anti-vascular endothelial growth factor (aVEGF) (bevacizumab) and immunotherapy using immune checkpoint blockers (ICBs) such as anti-programmed cell death protein 1 (aPD1) have failed in multiple clinical trials and in some cases has led to aggravated adverse events. A major source of the lack of efficacy to traditional or targeted therapies is the formidable GBM tumor microenvironment (TME), which enables evasion of immune surveillance and resistance to natural antitumor activities and therapies. I focused on overcoming these barriers and rendering GBM more sensitive to therapies. Because resistance to cancer immunotherapy is multifactorial, I will discuss these approaches to overcome resistance to cancer immunotherapy. Specifically, I will describe normalizing the tumor vasculature and reprogramming regulatory T cells for GBM therapy. These strategies have the potential to be translated to the benefit of GBM patients.