Stem-like glioma cells, frequently referred to as tumor-propagating cells or cancer stem cells, are culprits for recurrence due to their intrinsic resistance to standard therapy and their ability to regrow the parental tumor in xenografts. Similar to normal neural stem cells, CD133+ tumor-propagating cells undergo asymmetric, self-sustaining cell divisions (Gomez-Lopez S. et al, Cell Mol Life Sci, 2014, 71(4):575-97). Cancer-associated changes in cell division mode contribute to neoplastic transformation of glioma precursors (Sugiarto S. et al, Cancer Cell, 2011 20(3):328-40). While increased symmetric, self-renewing divisions of glioma precursors correlate with therapy sensitivity, asymmetric self-sustaining divisions potentially maintain the pool of tumor-propagating cells and contribute to therapy evasion. How pharmacological MAPK pathway inhibitors clinically evaluated for the treatment of GBM affect the division mode of tumor-propagating cells is unknown. We investigate CD133+ tumor-propagating cell responses to novel targeted therapies, in specifically, small molecule inhibitors of BRAFV600E, a mutant kinase frequently found in pediatric malignant astrocytoma. Our investigations showed that CD133+ tumor-propagating cells have higher asymmetric divisions than progenitor-like glioma cells. CD133+ stem-like GBM subpopulation exhibit decreased sensitivity to the anti-proliferative effects of MAPK pathway inhibition and show extended G2/M phase. We find that the mitotic checkpoint kinase and polarity regulator Plk1 is more active in CD133+ tumor-propagating cells. Plk1 activity links asymmetric division and mitotic entry. In an orthotopic GBM xenograft model, combined MAPK-pathway and PLK1 inhibition showed increased anti-proliferative effects and cell death frequency towards CD133+ cells beyond that achieved by either inhibitor alone. Ongoing work is investigating if Plk1 controls a polarity checkpoint, the integrity of which is especially important in the therapy-evasive compartment in GBM and that provides a rationale for combination therapy.