

[PubMed](#)**Format:** Abstract

*Semin Neurol.* 2018 Feb;38(1):50-61. doi: 10.1055/s-0038-1623534. Epub 2018 Mar 16.

## New Directions in the Treatment of Glioblastoma.

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Glioblastoma (GBM) is the most common primary malignant tumor of the central nervous system. The current standard of care for GBM is maximal resection followed by postoperative radiation with concomitant and adjuvant temozolomide. Despite this multimodality treatment, the median survival for GBM remains marginally better than 1 year. In the past decade, genome-wide analyses have uncovered new molecular features of GBM that have refined its classification and provided new insights into the molecular basis for GBM pathogenesis. Here, we review these molecular features and discuss major clinical trials that have recently defined the field. We describe genetic alterations in isocitrate dehydrogenase, ATRX, the telomerase promoter, and histone H3 variants that promote GBM tumorigenesis and have altered GBM categorization. We also discuss intratumoral genetic heterogeneity as one explanation for therapeutic failures and explain how ultra-long extensions of glioma cells, called tumor microtubes, mediate therapeutic resistance. These findings provide new insights into GBM biology and offer hope for the development of next-generation therapies.

PMID: 29548052 DOI: [10.1055/s-0038-1623534](https://doi.org/10.1055/s-0038-1623534)