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Exploring the landscape of targetable alterations in patients with glioblastoma

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Abstract

Glioblastomas remain the most lethal primary brain tumour in adults, with targeted therapies delivering only limited benefit despite deep molecular characterization. Several targeted drugs have received regulatory approval for low-grade gliomas, although progress in glioblastomas remains constrained by, among other aspects, extensive intratumoural heterogeneity, pathway redundancy, cellular plasticity and limited drug delivery to the central nervous system. Some of these challenges might be mitigated through strategies that enhance blood–brain penetration, including focused ultrasonography, convection-enhanced delivery, efflux avoidance and chemical modifications. Improved tumour profiling through multiregional sampling, prioritization of truncal dependencies and the development of novel therapeutic modalities, such as antibody–drug conjugates and theranostics, might also further improve outcomes. In this Review, we summarize the therapeutic landscape of targeted therapies in glioblastomas, spanning major target classes including receptor tyrosine kinases, intracellular signalling proteins, cell-cycle dysregulation and synthetic-lethal vulnerabilities. We also examine emerging strategies targeting genome integrity and telomeres, epigenetic modulators, and tumour–neural circuitry. Furthermore, we highlight tumour heterogeneity and extrachromosomal DNA dynamics as key drivers of oncogene amplification and therapeutic resistance as well as the roles of novel clinical trial designs and liquid biopsy-based monitoring strategies. Lastly, we discuss pathway-based glioblastoma classification and master kinase mapping as methods for aligning drugs with functional tumour states.

Key points

- Despite extensive research, progress in developing targeted therapies for patients with glioblastomas has been limited to the rare subsets of tumours harbouring either *BRAF*^{V600E} mutations or *NTRK* fusions.
- Factors contributing to this limited progress include the complexity of driver alterations, the paucity of responsive targets, redundancy among signalling pathways, tumour heterogeneity and plasticity, and the blood–brain barrier.
- Strategies to improve the effectiveness of molecular therapies include enhancing brain penetration, improved tumour profiling through multiregional sampling, prioritization of clonal over subclonal dependencies and the adoption of pathway-based classification systems.
- Novel therapeutic modalities, such as antibody–drug conjugates and theranostics, as well as improved clinical trial designs will likely all be required to develop more effective targeted therapies for patients with glioblastomas.