Published in final edited form as:
*Annu Rev Pathol*. 2010 ; 5: 33–50. doi:10.1146/annurev-pathol-121808-102109.

# The Pathobiology of Glioma Tumors

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## Abstract

The ongoing characterization of the genetic and epigenetic alterations in the gliomas has already improved the classification of these heterogeneous tumors and enabled the development of rodent models for analysis of the molecular pathways underlying their proliferative and invasive behavior. Effective application of the targeted therapies that are now in development will depend on pathologists' ability to provide accurate information regarding the genetic alterations and the expression of key receptors and ligands in the tumors. Here we review the mechanisms that have been implicated in the pathogenesis of the gliomas and provide examples of the cooperative nature of the pathways involved, which may influence the initial therapeutic response and the potential for development of resistance.

### Keywords

glioblastoma; astrocytoma; genetic alterations; signaling pathway alterations

## GLIOMAS

### Introduction and Histological Classification

The most common primary brain tumor is the glioma. Histologically, gliomas can resemble astrocytes, oligodendrocytes, or ependymal cells; thus, on the basis of their morphologic appearance they are classified as astrocytomas, oligodendrogliomas, or ependymomas, respectively (1–5). Astrocytomas express glial fibrillary acidic protein, an intermediate filament found in astrocytes that is routinely used as an aid in classifying a glioma as an astrocytoma. Because astrocytomas and oligodendrogliomas account for the vast majority of gliomas, we focus on these two types in this review.

Primary brain tumors account for 1.4% of all cancers and 2.4% of all cancer deaths in the United States, and approximately 20,500 newly diagnosed cases and 12,500 deaths are attributed to primary malignant brain tumors each year (see http://www.cbtrus.org). The risk factors for the development of a glioma are not clear, but occupational exposure to organic solvents or pesticides appears to be a predisposing factor (6; http://www.cancer.gov/cancertopics/wyntk/brain). It has also been suggested that cytomegalovirus (CMV) infection may play a role in the etiology or progression of some gliomas, based on detection of CMV RNA in glioblastoma (GBM) tumors (7). There are two

**DISCLOSURE STATEMENT**
The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

peak incidences of gliomas, one in the age group of 0 to 8 years (8) and the second in the age group of 50 to 70 years (5), and there is a slight male predominance (9).

The symptoms of patients presenting with a glioma depend on the anatomical site of the glioma in the brain and can include headaches; nausea or vomiting; changes in speech, vision, hearing, or balance; mood and personality alterations; seizures or convulsions; and memory deficits (see http://www.cancer.gov/cancertopics/wyntk/brain). The time frame of the onset of symptoms depends in part on the grade of the glioma; with GBM tumors the onset of symptoms is typically rapid. Surgical biopsy is necessary to determine whether the tumor is a primary brain tumor and to diagnose the tumor type and grade.

Glioma tumors are histologically separated into Grades I through IV according to the World Health Organization (WHO) criteria. Grade I tumors typically have a good prognosis and more frequently occur in children (5,8), and Grade II tumors are characterized on histologic examination by hypercellularity: These Grade II tumors have a 5–8-year median survival. Grade III astrocytoma tumors (anaplastic astrocytoma tumors) are characterized on histologic examination according to hypercellularity, as well as nuclear atypia and mitotic figures (see Figure 1). Anaplastic astrocytoma has a 3-year median survival (10–14). Grade IV gliomas, also known as GBMs, are characterized on histologic examination according to hypercellularity, nuclear atypia, mitotic figures, and evidence of angiogenesis and/or necrosis (see Figure 2). The median survival for patients with GBM tumors is 12–18 months (5,15), and older patients (>60 years of age) typically have a survival that is somewhat shorter than the median.

Oligodendroglioma tumors are histologically separated into Grades II and III according to the WHO criteria. The Grade II tumors exhibit hypercellularity and bland nuclei on histologic examination (see Figure 3), and the Grade III tumors (anaplastic oligodendrogliomas) exhibit the additional histologic features of prominent mitotic figures and evidence of angiogenesis (see Figure 4) (5).

## Major Genetic Alterations

The ongoing characterization of the genetic alterations in glioma tumor cells is revealing considerable variability among tumors of the same type and grade. This heterogeneity may contribute to the current limitations in predicting patient survival on the basis of histologic analysis of glioma type and grade alone (1–5) and suggests that classification of certain types and grades of gliomas according to their genetic phenotype will lead to a more accurate prediction of survival and response to therapy (1–4).

Grade I tumors, which are benign, typically do not progress to Grade II, III, or IV tumors, and their genetic alterations are different from those found in the Grade II–IV tumors; thus, they are not discussed herein. Oligodendroglioma (WHO Grade II) and anaplastic oligodendroglioma tumors (WHO Grade III) frequently exhibit loss of heterozygosity (LOH) on chromosomes 1p and 19q (observed in 40%–90% of biopsies, depending on the study) (see Table 1; 1–4). This is the most common genetic alteration found in oligodendroglioma tumors and predicts a favorable response to certain chemotherapeutic agents, a favorable response to radiation therapy, and longer survival even after recurrence (16). Glioma biopsy tissue can be routinely tested for LOH of 1p and 19q by fluorescence in situ hybridization (FISH) or by Southern blotting in the pathology laboratory. It is not yet known which genes at the 1p and 19q loci are involved in the promotion of growth of the oligodendroglioma tumors nor how the loss of these genes contributes to a more favorable therapeutic response and a more favorable prognosis (17); however, at least one of these genes may be involved in the initiation of oligodendroglial tumorigenesis (1–4). Another common genetic alteration in oligodendroglial tumors is downregulation of the tumor suppressor and lipid phosphatase

*PTEN* gene. Downregulation of this gene has been found in 50% of these tumors, and this downregulation appears to be a consequence of methylation of the promoter region (18). Amplification of platelet-derived growth factor receptor alpha (PDGFRα) occurs in approximately 7% of oligodendroglial tumors (19,20).

Astrocytoma tumors (WHO Grade II) frequently (3%–33%) exhibit amplification of the *PDGFRα* and/or *PDGFRβ* genes and of the genes encoding their ligands, PDGF-A and -B or -C and -D (1–4,14,25,52). The amplification of the *PDGFRα* gene may result from amplification of chromosome 4q12 (14,25,52). These genetic alterations probably play an important role in gliomagenesis, given that retroviral expression of PDGF-B in neural progenitor cells can initiate gliomagenesis in newborn mice and in adult rats (see Table 1) (1, 10,63). In astrocytomas that do not express high levels of PDGF-A and -B, expression of PDGF-C and -D may be increased and is thought to substitute for the protumorigenic role of PDGF-B (25). Loss of *p53* is also a common genetic event in astrocytoma tumors (WHO Grade II) (2–4).

In the more malignant form of astrocytoma, anaplastic astrocytoma (WHO Grade III), loss of the gene that encodes the cell-cycle progression regulator Rb, which occurs as a consequence of the deletion of chromosome 13q13, is detected in approximately 30% of tumors (Table 1) (1–4,31). Downregulation or mutation of the tumor-suppressor gene $p16^{INK4A}$/*CDKN2A* occurs in approximately 50% of these tumors. The downregulation can occur as a result of either hypermethylation of the promoter region or loss of the chromosome 9p region (1). The $p16^{INK4A}$ and *ARF* genes are encoded by a single genetic locus known as *INK4a*/*ARF*, which is located at chromosome 9p21 (1) and encodes the precursor of $p16^{INK4A}$ and ARF (1). Approximately 50% of anaplastic astrocytoma tumors have a mutation of the *p53* gene (1–4). In addition, the gene encoding the endogenous p53 inhibitor, MDM2 (on chromosome 12q), is amplified in 13% to 43% of these tumors (37–40). As a consequence of the alterations in the *Rb1*/*CDK4*/$p16^{INK4A}$ and *p53*/$p14^{ARF}$ genes, signals that negatively regulate the cell cycle are interrupted, resulting in deregulated cell proliferation (3,31). Loss of chromosome 22q and gain of chromosome 7q are also found in approximately 20% of anaplastic astrocytoma tumor samples, but the identity of the gene(s) or loci that contribute to anaplastic astrocytoma tumorigenesis or progression is not yet known (42,43).

GBM tumors (WHO Grade IV) can be subdivided into primary and secondary tumors on the basis of the patient's age at presentation and the genetic alterations in the tumor. Primary GBM tumors present de novo in older patients (typically >60 years of age) without a preexisting lower-grade glioma, and they account for approximately 90% of all GBM tumors. Secondary GBM tumors arise from a pre-existing Grade II or III astrocytoma or from a mixed glioma (oligoastrocytoma) (1–4). In primary GBM tumors, amplification and/or mutation of the gene encoding epidermal growth factor receptor (EGFR), found on chromosome 7, occurs in up to 60% of tumors (3,31). The most common mutation is a gain-of-function mutation due to an in-frame deletion of exons 2–7; this mutation results in the constitutive activation of EGFR, which can promote glioma cell proliferation and invasion (3,31,32,46,47). Deletion of the lipid phosphatase gene, *PTEN*, due to LOH of chromosome 10q or mutation, is also a common genetic occurrence in the primary GBM tumors; this deletion results in increased AKT/mTOR activity, which promotes cell survival, proliferation, and invasion (1–4). Both amplification of the *EGFR* gene and LOH of the *PTEN* gene can be readily detected by FISH or Southern blotting in the pathology laboratory. Several other potential tumor-suppressor gene candidates on chromosome 10q, such as *DMBT1* (deleted in malignant brain tumors 1) (54) and the Myc antagonist *Mxi1* (17,55), have been proposed. Also, the *MDM2* gene (an inhibitor of p53 on chromosome 12q) is amplified in approximately 10% to 15% of GBM tumor samples (38). Hypermethylation of the promoter of the gene encoding the DNA-repair enzyme, MGMT,

occurs in both primary GBM (36%) and secondary GBM (75%) tumors and indicates a better response to temozolomide therapy (32,60,61).

Heterogeneity in glioma tumors is also found within individual tumors. For example, certain areas of a glioma tumor may experience hypoxic conditions. Hypoxia results in the activation of proangiogenic genes and a focally increased angiogenic response (64). Also, breakdown of the blood-brain barrier can occur focally within a glioma tumor, resulting in leakage of serum-derived extracellular matrix proteins into certain areas of the tumor. Focal expression of serum-derived extracellular matrix proteins can alter integrin signaling and the motility of the glioma cells.

## Molecular Mechanisms Contributing to the Proliferative and Invasive Phenotype

Like other malignant tumors, glioma tumors proliferate rapidly. This highly proliferative phenotype is due to the loss of multiple cell-cycle inhibitors as well as to increased signaling from multiple growth factor receptors that act through downstream effectors to exert positive effects on the regulation of the cell cycle. The growth factors receptors that initiate a proproliferative signal in these tumors include EGFR and PDGFR (1–4). Frequently, expression of both the ligand and the receptor is increased in glioma tumors, suggesting that there exists an autocrine or paracrine loop that amplifies signaling (65,66).

Importantly, the EGFR and the PDGFR growth factor receptors cooperate or coordinate with cell-adhesion receptors, such as integrins and ephrins, resulting in an amplification of the growth factor receptor signal (67–71). Growth factor receptors and cell-adhesion receptors typically rapidly activate focal adhesion kinase (FAK), a cytoplasmic nonreceptor tyrosine kinase. FAK is a major positive regulator of cell-cycle progression (72,73) and acts by increasing extracellular signal–regulated kinase (ERK) activity and cyclin D1 transcription, as well as by inhibiting expression of $p27^{Kip1}$ (74–77).

Gliomas are invasive tumors (78). For the malignant gliomas, the invasive phenotype is a highly characteristic feature; others have referred to this phenotype as a signature feature (78–80). As with the proliferative phenotype, growth factor receptor signaling plays a major role in promoting the invasive phenotype in cooperation with, or in coordination with, cell-adhesion receptors and proteases (67–71,81). Multiple growth factor receptors have been shown to promote glioma cell migration and invasion, including c-Met (82), EGFR (83,84), and PDGFR (67,85). Typically, there is increased expression of both the growth factor receptor and ligand in the tumor, again suggesting that an autocrine or paracrine loop that promotes signaling is in place (1–4).

Members of several different families of cell-adhesion receptors, including members of the integrin family (86,87), the Eph/Ephrin family (88–90), and the CD44 family (91–93), have been shown to promote glioma cell migration and invasion. In some instances, expression of cell-adhesion receptors, such as integrins alpha v beta 3 and alpha v beta 5 (87,94–96), is increased in malignant glioma tumors. The integrin receptors provide the interaction with the cytoskeleton of the cell that generates the traction that enables the cell to pull itself forward. Regarding the Eph/Ephrin family, current data indicate that the Ephrin-B3 ligand and the Eph-B3 receptor promote glioma cell invasion (88–90). Cell-surface receptors from different classes or families probably cooperate or coordinate signaling events in a context-dependent manner that is also regulated temporally.

Signaling molecules in the glioma cells act downstream of the cell-surface growth factor receptor and cell-adhesion receptor to amplify and propagate the proinvasion signal. These signaling molecules include cytoplasmic tyrosine kinases, adaptor molecules, and cytoskeletal proteins (97). For example, both the tyrosine kinase FAK (72,86,98,99) and another member

of this family, Pyk2 (100,101), can promote glioma cell migration and invasion in a context-dependent manner. The Src family tyrosine kinases also are necessary for glioma cell invasion (67,73,102). Adaptor molecules from the Crk-associated substrate (CAS) family, such as HEF1 and p130CAS, promote glioma invasion (86), and members of the Crk family of adaptor molecules act downstream of HEF1 or CAS proteins in this process (103,104). Two signaling molecules that regulate glioma cell survival and proliferation, phosphatidylinositol-3-kinase (PI3K) and PTEN, also regulate glioma cell migration and invasion (103,105). PI3K positively regulates glioma cell migration and invasion (105). PTEN appears to negatively regulate these processes; thus, the loss of PTEN function in malignant gliomas can promote glioma cell invasion (103).

Glioma cell invasion most likely requires protease degradation of the extracellular matrix. Several families of proteases, including the serine proteases, cathepsins, matrix metalloproteinases (MMPs), and the ADAMTS family of metalloproteases (81,88,106), have been shown to play a role in glioma cell migration and invasion. Protease activity can be regulated by multiple factors in a tumor. One important aspect of this regulation is the localization of protease function in specific regions of the tumor cell membrane. An example of this process is the localization of the serine protease, urokinase. Urokinase expression is increased in GBM tumors in vivo (96,107–109), and downregulation either of urokinase or of its receptor (the urokinase receptor) inhibits glioma cell invasion (110,111). The binding of urokinase to its receptor localizes this protease to specific areas of the cell membrane and promotes its activity in these areas because the binding of urokinase to its receptor is necessary for optimal protease activity. Also, the receptor colocalizes with specific integrin receptors on the cell membrane, further specifying the membrane region that exhibits protease activity (81,112). A second example is the binding of MMP-2 to integrin alpha v beta 3 on the cell surface, which both localizes and enhances the activity of this protease (113). Thus, proteases act in concert with cell-surface receptors and downstream signaling molecules to promote glioma cell invasion (114).

## Animal Models of Malignant Astrocytoma and Oligodendroglioma

Animal models of astrocytoma tumors have been created. Central nervous system–specific inactivation of the genes encoding the tumor suppressors p53 and Nf1 leads to the spontaneous onset of Grade II and III astrocytoma tumors, as well as to GBM tumors in mice (115). This gliomagenesis can be accelerated by haploinsufficiency of the *PTEN* gene (116), and in neural progenitor cells conditional inactivation of *p53* coordinates with a haploinsufficiency of *PTEN* and *Nf1* to induce astrocytoma tumor formation (117). These models support the concept that the genetic alterations in human tumors, such as p53 loss and loss of PTEN function, are probably important in the development of astrocytomas (Grades II and III).

Rodent models of GBM tumors are also available. In a somatic gene-transfer model, simultaneous retroviral expression of constitutively active *Ras* and *Akt* gives rise to the formation of high-grade gliomas that are morphologically similar to human GBM tumors (118). Although *Ras* mutations are uncommon in GBM tumors, one study (119) suggests that Ras activity is increased in human GBM biopsies due to a point mutation. In mice, the combination of *EGFR* amplification and either loss of *p53* plus *CDK4* overexpression or loss of *INK4a-ARF* is sufficient to induce glioma tumor formation that resembles that of human GBM tumors (120,121). In an *EGFR* transgenic mouse model, LOH of *p16INK4a*, *p19ARF*, and *PTEN* cooperates with the amplification of *EGFR* to induce a highly infiltrative GBM tumor (121). Also, simultaneous deletion of *p53* and *PTEN* in the mouse central nervous system generates an acute-onset, high-grade malignant glioma tumor that is histologically similar to human GBM tumors (122). A new model of GBM tumor has been created by retroviral expression of *PDGF-B* in adult rat neural progenitor cells (85). In this model, intracranial

injection of retrovirus containing *PDGF-B* alone or in combination with *PDGFRα* results in the development of GBM-like tumors (63,85). To date, individual disruption or LOH of a single gene regulating the cell cycle, such as *p53*, *INK4a*, or *ARF*, has been insufficient to initiate gliomagenesis in vivo (123). Taken together, these studies suggest that alterations in neural progenitor cells probably give rise to at least some high-grade gliomas.

There are limitations in the use of the above-discussed models. These include the facts that the tumor cells are not of humor origin and that the rodents can in some instances require several months to reliably develop glioma tumors.

Xenograft models of malignant astrocytoma have been extensively used to assess the function of various signaling molecules or matrix proteins in glioma growth and invasion (74,124). Xenograft models that transplant human malignant astrocytoma/glioma cells into the brains of immunocompromised mice (athymic nude or SCID) have the advantage of being relatively rapid models with which to assess the role of a particular molecule in positively or negatively regulating proliferation and/or regulating invasion in vivo. One disadvantage of human xenograft models is that most human glioma cell lines are not invasive when propagated in vivo (125–128). Another disadvantage is that the propagation of human malignant astrocytoma/glioma cell lines in culture can result in their loss of key genetic alterations, such as expression of the mutant EGFR (129,130), that are the most likely to be important in gliomagenesis. This limitation has been overcome by propagating primary human GBM tumors in the nude mouse (either subcutaneously or intracerebrally) instead of in culture; when these tumors are propagated in vivo, the genetic alterations found in the patients biopsy are retained (131). For xenograft models it is also important to propagate the tumors for experimental analysis in an orthotopic environment (the brain) because the microenvironment in the brain (i.e., the extracellular matrix, growth factors, and stromal cells) is different from that found in the subcutaneous tissue.

Several animal models of oligodendroglioma tumors have been established. One model uses the somatic gene-transfer technology in which retrovirally expressed *PDGF-B* is injected intracranially into newborn mice, resulting in PDGF-B expression in neural progenitor cells and the induction of oligodendroglioma tumors (63). Xenografts of neural progenitor cells or of astrocytes expressing ectopic *PDGF-B* can also induce oligodendroglioma tumors in mice after 12 weeks (10). These models support the concept that upregulation of PDGFR signaling through upregulation of the PDGF-B ligand is sufficient to induce gliomagenesis (10,14).

### Contribution of Cancer Stem Cells

Tumor cells expressing markers of neural progenitor cells, which are able to self-renew and to differentiate, have been termed cancer stem cells (79). Typically, these cells account for less than 5% of the tumor cells within one tumor, although the number varies significantly among different studies (79,132–135). A key feature of these cells is their ability, when injected, to more rapidly form a tumor in immunocompromised mice, as compared to injection of the non–cancer stem cell tumor population (79,132,135). Another key feature of these cells is their ability to form a highly invasive xenograft tumor in immunocompromised mice (79,132, 135). These cells are thought to reside in the perivascular area of the tumor, referred to as the vascular niche (133). The molecules typically used to identify these cancer stem cells include CD133 (79,132,135). Cancer stem cells in gliomas probably contribute to tumorigenesis, development into the highly invasive phenotype, and radiation resistance (134).

## CONCLUSIONS

Characterization of the genetic and epigenetic alterations in gliomas has led to protein structure-function studies that have elucidated both how the signaling pathways are altered and their

effect on cell proliferation, survival, and invasion. These studies clearly indicate the complexity of the regulation of these processes and suggest a dynamic process in which the cells of the tumor respond in a context-dependent manner to their microenvironment by cooperation and cross talk among receptors and intersecting signaling pathways. They also indicate how the tumor cells can promote invasion through remodeling of their microenvironment. Importantly, knowledge of these genetic alterations has allowed scientists to create rodent models to test the importance of such alterations in vivo, to determine whether they are necessary for gliomagenesis or tumor progression (see Table 1), and to test novel therapeutic approaches that target the pathways associated with the alterations.

Increasing knowledge of the genetic and epigenetic alterations in the different types and stages of gliomas has already had an impact on diagnosis. As profiles generated for glioma tumors create subcategories of each tumor type and grade, therapy will likely become more individualized and lead toward a personalized medicine approach for treating glioma tumors. Currently, for Grade IV tumors (GBMs) the standard therapeutic approach is surgical tumor debulking, followed by radiation and chemotherapy (15). Several different approaches that target various aspects of the tumorigenesis cascade are in various stages of development, and some have been entered into clinical trials (see Table 2). Animal models have shown, however, that malignant glioma tumors develop resistance to new therapies; thus, the field must continue to advance so that new therapeutic approaches and strategies that match the pace of development of tumor resistance can be developed.

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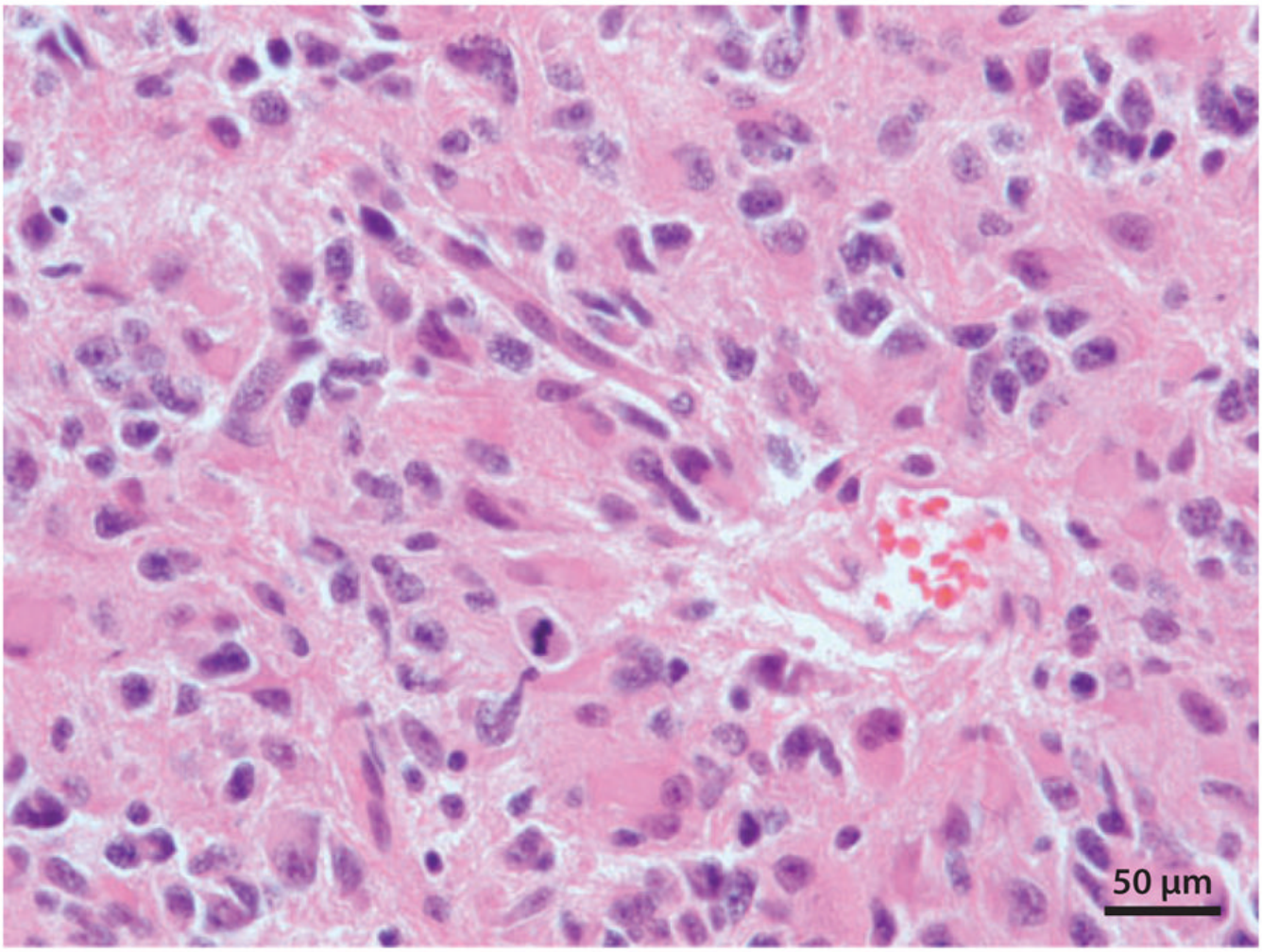


**Figure 1.**
Anaplastic astrocytoma (World Health Organization Grade III). A mitotic figure is shown in the bottom center of the photomicrograph, and tumor nuclei are pleomorphic. Both are typical of an anaplastic astrocytoma.

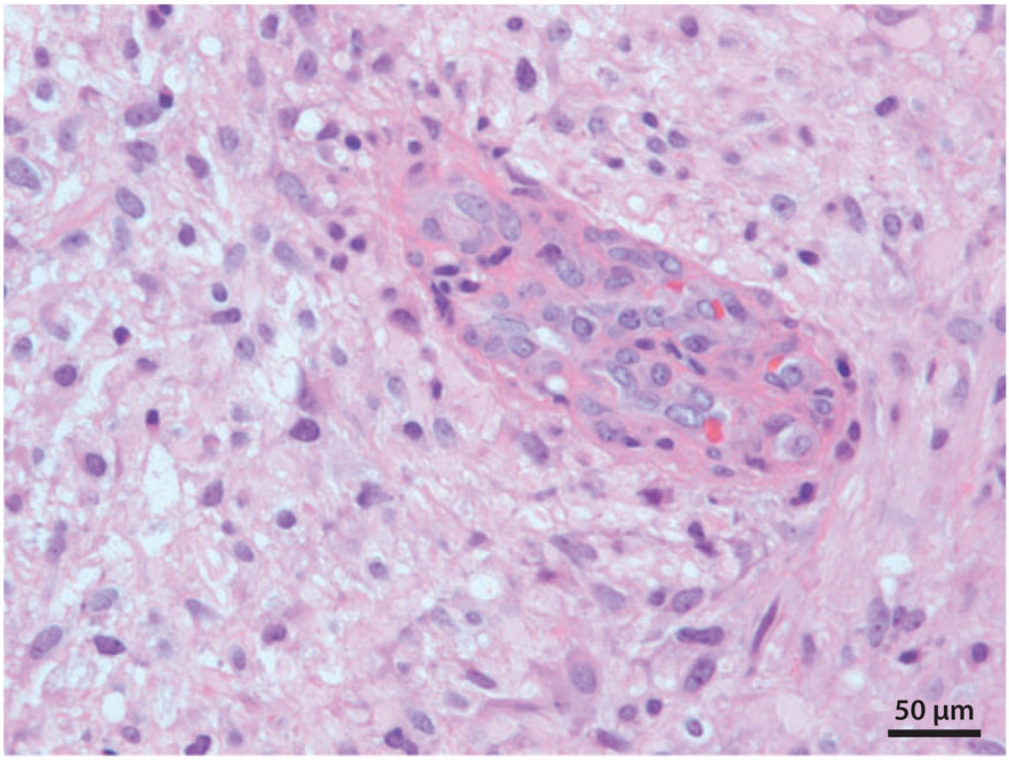


**Figure 2.**
Glioblastoma tumor (World Health Organization Grade IV). Endothelial cell proliferation (angiogenesis) is shown in the center of this photomicrograph.

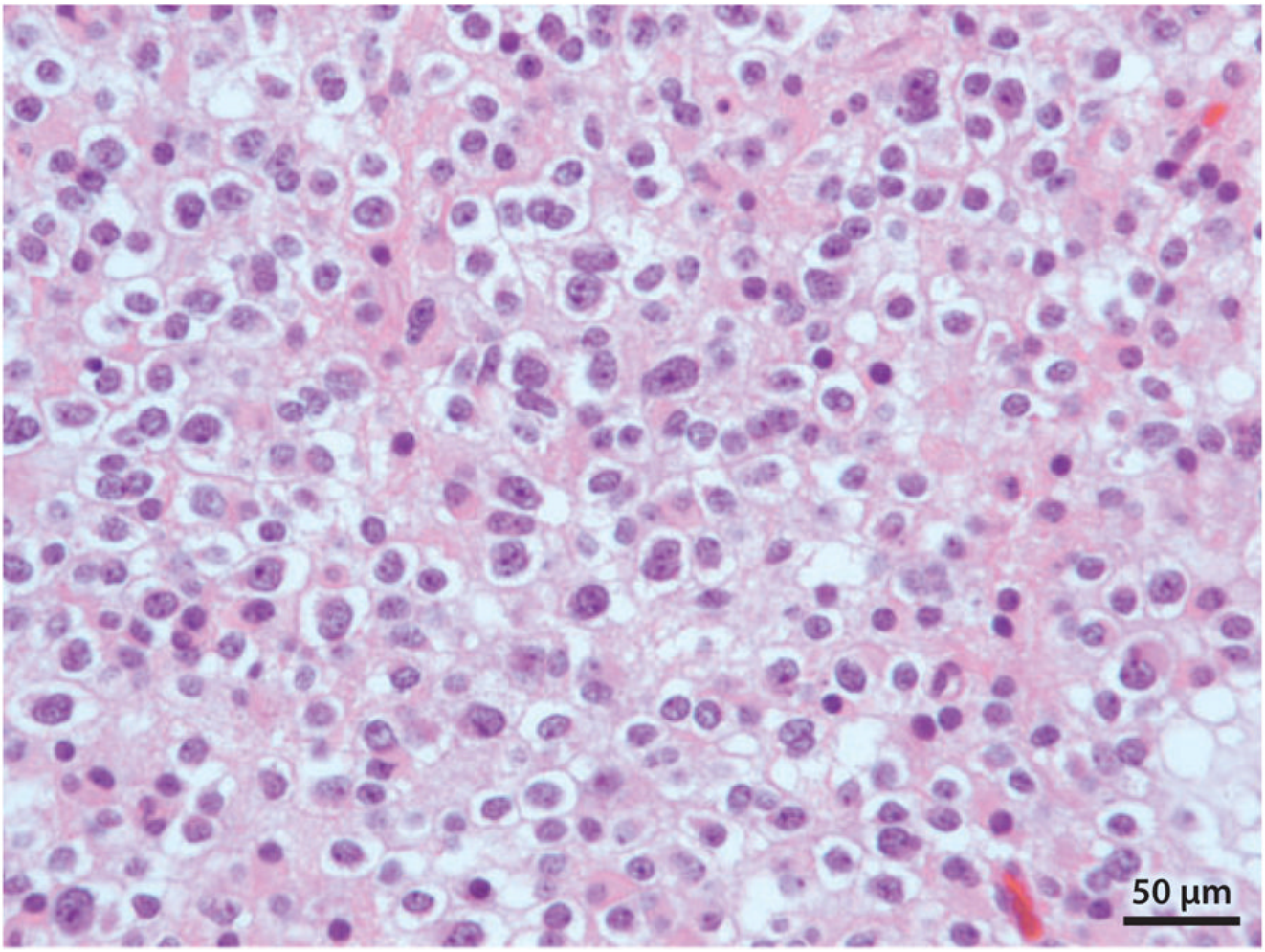


**Figure 3.**
Oligodendroglioma (World Health Organization Grade II). The cleared cytoplasm and bland monomorphic nuclei typical of an oligodendroglioma are shown in this photomicrograph.

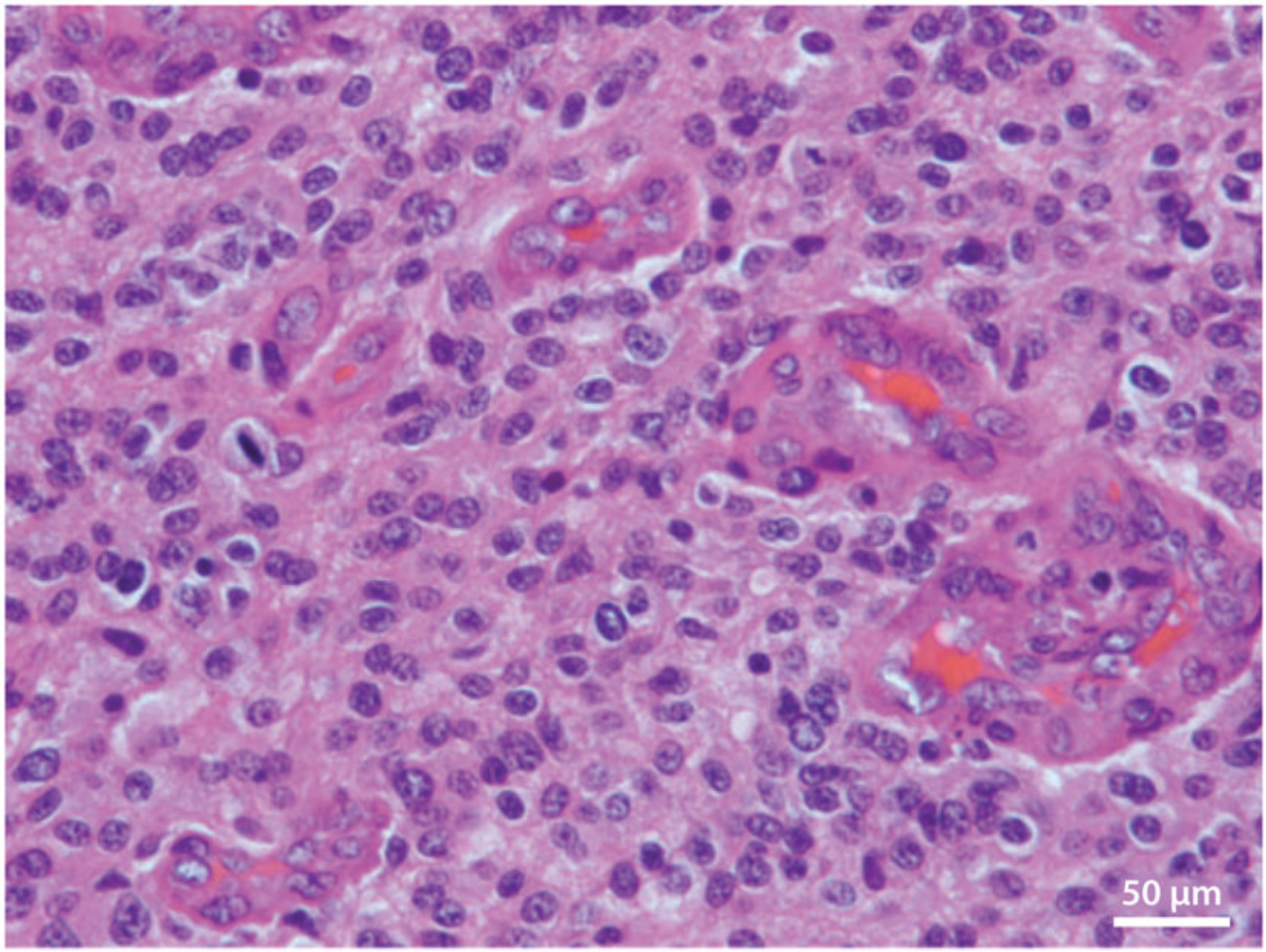


**Figure 4.**
Anaplastic oligodendroglioma (World Health Organization Grade III). Nuclear atypia and endothelial cell proliferation (angiogenesis) typical of an anaplastic oligodendroglioma are shown in this photomicrograph.

**Table 1**

Common genetic alterations in gliomas[a]

| Genetic alteration | Normal gene function | Incidence | Laboratory tests | Reference(s) |
|---|---|---|---|---|
| **Oligodendrogliomas (WHO Grades II and III)** | | | | |
| LOH of 1p/19q | Unknown; multiple tumor-suppressor genes at these loci, e.g., *DMBT1*, *Mxi* | 40%–90%, depending on the study | aCGH (21,22) | 1_4,21,22 |
| | | | FISH | 21,22 |
| | | | LOH | 21,22 |
| *PDGFRα* amplification | Stimulates cell proliferation and migration due to an autocrine loop | 7% | aCGH (23) | 19,20,23 |
| | | | FISH | 20 |
| | | | Southern blot | 20 |
| *PTEN* (10q23) deletion due to LOH of chromosome 10q | Tumor suppressor; negatively regulates AKT signaling | 21% | aCGH (23) | 23,24 |
| *PTEN* mutation | Inhibits angiogenesis | 8% | LOH | 24 |
| | Poor prognosis if mutation present | | SSCP | 23,24 |
| *PTEN* promoter methylation | Tumor suppressor; negatively regulates AKT signaling | 50% | Methylation-specific PCR (18) | 18 |
| | Inhibits angiogenesis | | | |
| | Poor prognosis if mutation present | | | |
| **Astrocytomas (WHO Grade II) and anaplastic astrocytomas (WHO Grade III)** | | | | |
| *PDGFRα* and *-β* amplification/mutation | Stimulates cell proliferation and migration due to an autocrine loop | PDGFRα (3%–33%) | aCGH (23) | 1_4,23,25_27 |
| *PDGF-A/-B/-C/-D* amplification | Overexpression of PDGF-B can initiate gliomagenesis when expressed in the neural stem/progenitor cell | | FISH | 26 |
| | | | Southern blot | 27 |
| *p53* mutation (chromosome 17p) | Cell-cycle arrest | Grade II astrocytoma (35%–50%) | PCR-DGGE (28) | 1_4,28,29 |
| | | | PCR-SSCP | 29 |
| *Rb* deletion or mutation (chromosome 13q14) | Regulates cell-cycle progression | LOH (30%) | LOH (30) | 1_4,30_33 |
| | | Mutation (13%–25%) | PCR-SSCP | 30,33 |
| Deletion or mutation of *p16*$^{INK4A}$/*CDKN2A* due to either loss of chromosome 9p or hypermethylation | Encodes *p16* and *ARF* genes | Anaplastic astrocytoma (12%–62.5%) | LOH (34–36) | 1,34_36 |
| | Cyclin-dependent kinase inhibitor | | | |

| Genetic alteration | Normal gene function | Incidence | Laboratory tests | Reference(s) |
|---|---|---|---|---|
| *MDM2* amplification or mutation (chromosome 12q) | P53 regulator | Anaplastic astrocytoma (13%–43%) | Southern blot (37) | 37_40 |
| | | | aCGH (41) | |
| Loss of chromosome 22q and gain of 7q | Unknown | Grade II astrocytoma (20%–30% of all gliomas) | LOH (42,43) | 42,43 |
| *PTEN* promoter methylation | Tumor suppressor; negatively regulates AKT signaling | 43% | Methylation-specific PCR (18) | 18 |
| | Inhibits angiogenesis | | | |
| | Poor prognosis if mutation present section | | | |
| *c-Kit* (4q12) | Class III receptor tyrosine kinase (RTK) | 6%–28% | FISH (26,44) | 26,44 |
| | Oncogene to promote tumorgenesis | | | |
| **Glioblastomas (WHO Grade IV)** | | | | |
| *EGFR* amplification (aneuploidy of chromosome 7)/gain-of-function mutation (in frame deletion of exons 2–7 on chromosome 7) | Promotes cell proliferation, invasion, and angiogenesis | Primary GBM (36%–60%), secondary GBM (8%) | Southern (45) | 3,31,32,45_48 |
| | Induces resistance to apoptosis | Anaplastic Astrocytomas (15%) | aCGH | 48 |
| | May mediate radiation resistance | – | – | – |
| *PTEN* (10q23) deletion due to LOH of chromosome 10q or mutation, or methylaton of *PTEN* promoter | Tumor suppressor; negatively regulates AKT signaling | LOH: primary GBM (47%–70%), secondary GBM (54%–63%) | aCGH (23) | 46,47 |
| | Inhibits angiogenesis | Mutation: primary GBM (14%–47%) | LOH (24) | 46,47,49_51 |
| | Poor prognosis if mutation present | Secondary GBM (4%) | SSCP (23,24) | 18 |
| | | PTEN promoter methylation: primary GBM (9%) | Methylation-specific PCR | 18 |
| *PDGFR-α* and *-β* (4q12) amplification | Stimulates cell proliferation and migration due to an autocrine loop | Primary GBM (20%–29%) | FISH (44) | 1_4,14,25,27,44,52 |
| | Overexpression of PDGF-B can initiate gliomagenesis when expressed in the neural stem and progenitor cell | Secondary GBM (60%) | Southern blot | 27 |
| *p53* mutation (chromosome 17p) | Cell-cycle arrest | Primary GBM (28%) | PCR-DGGE (28) | 28,29,32,53 |
| | | Secondary GBM (65%) | PCR-SSCP | 29,53 |
| *Rb* deletion or mutation (chromosome 13q14) | Regulates cell-cycle progression | Secondary GBM (40%) | LOH (30) | 1_4,30_33 |
| | | | PCR-SSCP | 30,33 |
| *DMBT1* deletion due to LOH of chromosome 10q | Homolog of the scavenger receptor cysteine-rich (SRCR) superfamily | LOH (59% of all GBM) | Differential duplex PCR (54) | 54 |

| Genetic alteration | Normal gene function | Incidence | Laboratory tests | Reference(s) |
|---|---|---|---|---|
| | Potential tumor suppressor | Homozygous deletion (22% of all GBM) | – | – |
| *Mxi1* (10q25 deletion) due to LOH of chromosome 10q | Putative tumor suppressor, potent antagonist of Myc oncogene | LOH (65% of all GBM) | Genomic PCR (55) | 17,55 |
| *MDM2* amplification or mutation | P53 regulator | 10%–15% | Southern (32,37,56,57) | 32,37,38,56,57 |
| *KIT* (4q12) | Class III receptor tyrosine kinase (RTK) | 15% | MLPA (58) | 58 |
| | Oncogene; promotes tumorgenesis | | | |
| *MGMT* promoter methylation (chromosome 10q) | DNA-repair enzyme | Primary GBM (36%) | Chromatin accessibility assay (59) | 32,59_62 |
| | | Secondary GBM (75%) | Methylation-specific PCR | 59,62 |

[a]Abbreviations: aCGH, array comparative genomic hybridization; CDKN, cyclin-dependent kinase inhibitor; DMBT, deleted in malignant brain tumors; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; GBM, glioblastoma; c-Kit, Hardy-Zuckerman 4 feline sarcoma viral homolog; LOH, loss of heterozygosity analysis; MDM2, ouse double minute 2 homolog; MGMT, O6-methylguanine–DNA methyltransferase; MLPA, multiplex ligation-dependent probe amplification; Mxi1, max interactor 1; PCR-DGGE, polymerase chain reaction–based denaturing gradient gel electrophoresis analysis; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PTEN, lipid phosphatase and tensin homolog; Rb, retinoblastoma gene; SSCP, single-strand conformation polymorphism analysis.

**Table 2**

Clinical trials with different inhibitors targeting molecules that facilitate glioma invasion

| Mechanism(s) | Targeted molecule or pathway | Drug (company)/compound | Phase/condition | Reference(s) |
|---|---|---|---|---|
| Cell adhesion, proliferation, and migration | Integrin α5β1 | ATN-161 (Attenuon)/antagonist | Phase II: malignant glioma | 136 |
| | Integrins αvβ3 and αvβ5 | Cilengitide (EMD Pharmaceuticals)/antagonist | Phase I: pediatric brain tumors<br>Phase II: gliomas | 136 |
| ECM | Tenascin | 131I-81C6 (NCI)/mAb | Phase I: brain and CNS tumors | NIH[a] |
| Cytoplasmic kinase | Src | Dasatinib (Bristol-Myers Squibb)/inhibitor | Phase II: recurrent GBM | NIH |
| | PI3K/mTOR | XL765 (Exelixis)/inhibitor | Phase I: GBM malignant gliomas, mixed gliomas | NIH |
| Growth factors | EGFR | ZD6474 (AstraZeneca) | Phases I and II: gliomas | 136 |
| | | MAb-425 (Drexel University)/anti-EGFR-425 mAb | Phase II: high-grade gliomas | NIH |
| | | Erlotinib/(TARCEVA/NCI)/antagonist | Phases I and II: recurrent malignant gliomas | NIH |
| | | Gefitinib (NIH)/peptide | Phases I and II: GBM | – |
| | PDGFR | AZD2171 (AstraZeneca)/kinase inhibitor | Phase I: CNS tumors<br>Phase II: GBM | 136 |
| | | Imatinib (Novartis)/inhibitor | Phase II: GBM | NIH |
| | | Suramin (Bayer/NCI)/inhibitor | Phase II: GBM | 136 |
| | | Vatalanib (Novartis)/kinase inhibitor | Phase II: GBM | 136 |
| | | Sorafenib (Bayer)/kinase inhibitor | Phase II: GBM | NIH |
| | c-Met | MGCD265 (MethylGene)/kinase inhibitor | Phase I: GBM | 137 |
| | | XL184 (Exelixis)/kinase inhibitor | Phase II: GBM | NIH |
| Cytoskeletal machinery | Microtubule | Panzem (EntreMed)/colchicine site-binding microtubule depolymerizing agent | Phase II: recurrent GBM | NIH; 136,138 |
| Matrix proteinase | MMP | Prinomastat (Agouron)/inhibitor | Phase II: GBM | 136 |

[a]The information in this table was extracted from the National Institutes of Health (NIH) website (http://www.clinicaltrials.gov) through a search for "glioma, brain cancer, glioblastoma and angiogenesis." Clinical trials that are open, closed, enrolling, or completed are included in this table. Irrelevant drug listings were excluded. Many drugs have been utilized in multiple concurrent clinical trials. The primary investigator and clinical trial information can be found on this website.

Abbreviations: ECM, extracellular matrix; GBM, glioblastoma; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; MLCK, myosin light chain kinase; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase; PDGFR, platelet-derived growth factor receptor.