We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

8

Evolvement of Molecular Biomarkers in Targeted Therapy of Malignant Gliomas

Erica Hlavin Bell*, Mersiha Hadziahmetovic* and Arnab Chakravarti
Department of Radiation Oncology
The Ohio State University
U.S.A.

1. Introduction

Gliomas account for almost half of all diagnosed adult brain tumors (Siker et al., 2006). Glioblastoma multiforme (GBM), the most aggressive type of glioma, is also the most common primary malignant brain tumor. Even though tremendous effort has been made to treat high grade gliomas, the prognosis for patients with malignant gliomas remains poor. The dismal prognosis of patients with glioblastoma is in part caused by the resistance of these tumors to both chemotherapy and radiation. Furthermore, high grade gliomas often diffusely infiltrate into neighboring brain tissue, thus complicating treatment and commonly preventing a cure for the disease. Treatment modalities containing chemotherapy often have high levels of toxicity and depending on the drug have to be locally injected as crossing the blood-brain barrier is an impediment for certain drug therapies. The addition of temozolomide (TMZ) to the standard of care treatment for GBM in 2005 circumvented the aforementioned problems as it is taken orally, crosses the blood-brain barrier, and has a relatively low toxicity profile. However, the average life expectancy of patients treated with the addition of temozolomide increased by only a couple of months. Therefore, more effective treatment strategies are critically needed for the treatment of gliomas. In recent years, the research efforts in identifying molecular biomarkers for tumor subtypes have exponentially increased. These biomarkers can help serve a diagnostic role by helping classify grade or subtype, as well as a predictive role in determining the expected response to a specific treatment, and/or a prognostic role in estimating the natural course of the disease. Furthermore, gaining a better understanding of the molecular mechanisms involved in gliomagenesis, migration, and tumor resistance is essential for identifying novel tumor targets to overcome the poor prognosis of patients harboring gliomas. Additionally, characterizing the best treatment(s) for each grade and molecular subtype of gliomas will enable clinicians to increase efficacy of therapies for patients. The ability to categorize tumors based on molecular biomarkers for each glioma grade will further enhance the effectiveness of treatments by broadening the therapeutic window between normal and malignant tissues. In this chapter, molecular mechanisms (see Figure 1) and genetic alterations underlying the etiology of gliomas, corresponding molecular biomarkers (see

* These authors contributed equally to this manuscript.

Table 1) within the discussed pathways, and novel targeted therapies currently being investigated (see Table 2) are reviewed in detail.

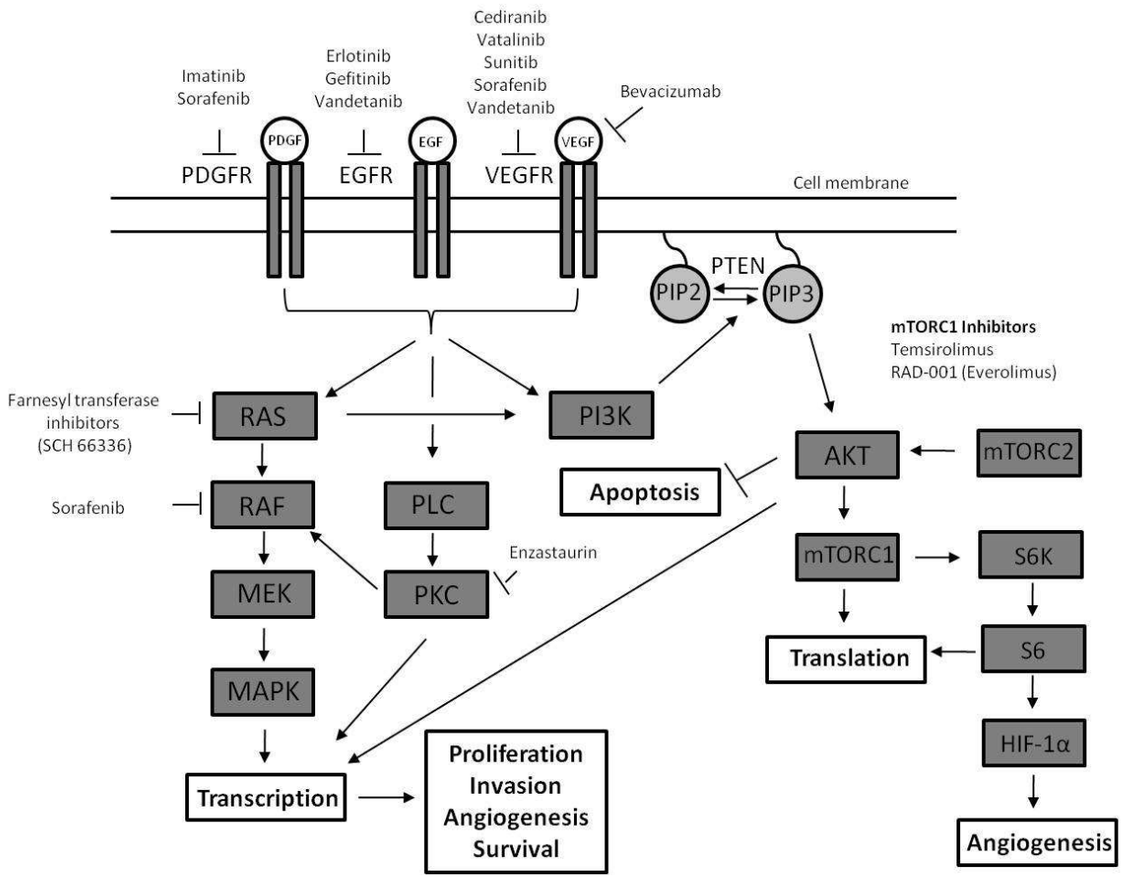


Fig. 1. Growth Factor Signaling Pathways in Malignant Gliomas and Corresponding Targeted Therapies

2. Molecular mechanisms contributing to gliomas, corresponding molecular biomarkers, and relevant targeted therapies

2.1 LOH of 1p/19q

Loss of heterozygosity (LOH) of chromosomes 1p and 19q is the most common genetic alteration in oligodendroglioma tumors (Gladson et al., 2010). This hallmark alteration is detected in 40-90% of oligodendrogliomas (Cairncross & Jenkins, 2008; Gladson et al., 2010; Jansen et al., 2010; Riemenschneider et al., 2010) and can be readily detected by fluorescent *in situ* hybridization (FISH) or southern blotting in the pathology lab. Therefore, loss of 1p/19q is used as a diagnostic marker of oligodendrogliomas. Co-deletion of 1p/19q is also found in 20-30% of mixed glial tumors (Aldape et al., 2007) and <10% of diffuse astrocytic gliomas (including GBMs) (Riemenschneider et al., 2010) . Although the regions of chromosomes 1p and 19q have been mapped, the actual tumor suppressor genes whose loss is involved in the promotion of growth in oligodendroglioma tumors are yet to be identified.

Interestingly, LOH at these loci confers a favorable response to chemotherapy, radiation, and survival (Nutt, 2005; Gladson et al., 2010). Exactly how the unidentified genes on chromosomes 1p and 19q contribute to a more favorable therapeutic response remains to be determined. Initially, the favorable response was first observed in a large percentage (approximately two-thirds) of patients with anaplastic oligodendrogliomas (grade III) that had a sustained response to chemotherapy. In 1998, Cairncross and colleagues first identified that coincident loss of chromosomal arms 1p and 19q confers chemotherapeutic sensitivity, prolonged recurrence-free and overall survival in patients with anaplastic oligodendroglioma (AO) treated with combination of procarbazine, lomustine and vincristine (PCV) chemotherapy (Cairncross et al., 1998). Following this discovery, interest in the use of chemotherapy for patients with oligodendroglial or mixed gliomas (oligoastrocytoma) was the impetus behind several clinical trials that corroborated these findings. In a series of 162 patients with either pure or mixed glioma, Smith et al. showed that the combined loss of 1p and 19q is a statistically significant predictor of prolonged survival in patients with pure oligodendroglioma, independent of tumor grade (Smith et al., 2000). No such association was demonstrated in patients with astrocytic neoplasms. All patients with the co-deletion were alive after a median follow-up of 67.5 months, as opposed to 73% of those without the combined deletion. In this study, loss of 1p or 19q in isolation was not a significant predictor of overall survival in any of the subtypes examined, but patients with pure oligodendroglioma did demonstrate a trend ($p = 0.15$) toward better survival if their tumors exhibited loss of 1p or loss of 19q. In another series, 50 patients with anaplastic oligodendroglioma were treated with a chemotherapeutic regimen (PCV in 48 patients) as the main initial adjuvant therapy, and patients with combined deletion of 1p and 19q had marked and durable responses to chemotherapy, resulting in longer overall survival, with or without postoperative radiation therapy (Ino et al., 2001). Patients with chromosome 1p alterations also responded superiorly to chemotherapy, but had shorter duration of response and patient survival. Tumors lacking 1p loss, but having a *TP53* gene mutation, responded to chemotherapy but recurred quickly. The group that fared the worst included tumors with intact 1p and wild-type *TP53*; these were poorly responsive, aggressive tumors that were clinically similar to glioblastomas. Loss of 1p has also been shown to increase radiation sensitivity (Bauman et al., 2000). Within the subset of patients with anaplastic oligodendroglioma who have the 1p/19q co-deletion, those with polysomy of chromosomes 1 and 19 were found to have an earlier recurrence than those without polysomy (Snuderl et al., 2009). Hirose and colleagues classified microdissected tissue from 140 patients with WHO grade II-III supratentorial gliomas based on whole genome profile, and reaffirmed that patients with 1p/19q deletion show long progression-free survival, while loss of 10q in association with gain of 7p appeared to predict poor outcome (Hirose et al., 2011).

Loss of both 1p and 19q has also been shown to increase sensitivity to temozolomide (TMZ), a monofunctional alkylating agent (Kouwenhoven et al., 2006). Due to a more favorable toxicity profile of TMZ compared with PCV, Radiation Therapy Oncology Group (RTOG) conducted a phase II trial of pre-irradiation and concurrent TMZ in patients with newly diagnosed anaplastic or mixed oligoastrocytoma. The objective response rate was 58% (32% complete response), and rate of progression during the pre-RT TMZ was only 10%, as compared to 20% in historical control with PCV (Vogelbaum et al., 2009). All patients with

codeletion of 1p/19q and/or O6-methyl guanine DNA methyltransferase gene (MGMT) promoter methylation were free from progression at 6 months. Whether a chemotherapy-only regimen is sufficient to provide long-term control in patients with 1p/19q co-deleted anaplastic oligodendroglioma or mixed oligoastrocytoma without the use of concurrent or serial radiotherapy remains to be determined. European Organisation for Research and Treatment of Cancer (EORTC) is currently conducting CATNON, a Phase III intergroup trial on concurrent and adjuvant TMZ chemotherapy in patients with non-1p/19q deleted anaplastic glioma. The objectives of this trial are to assess whether RT concurrent with daily TMZ improves OS as compared to no daily TMZ in this patient population, and whether adjuvant TMZ improves overall survival as compared to no adjuvant TMZ.

Due to the overall increased survival of patients with co-deletions it is thought that LOH of 1p and 19q might be a prognostic marker of increased survival rather than a predictive marker of specific therapies. Nevertheless, this classification remains to be determined although there are retrospective data that demonstrated absence of increased survival without treatment, a result that suggests that 1p/19q co-deletion is a predictive marker of favorable response to many treatment regimens since it is not treatment specific (Riemenschneider et al., 2010).

Furthermore, there are common alterations that are found with 1p/19q co-deletion, such as isocitrate dehydrogenase 1 (IDH1) and IDH2 mutations (Yan et al., 2009). LOH of 1p/19q also has been shown to be mutually exclusive of *TP53* mutations, 10q deletion, and amplification of epidermal growth factor receptor (EGFR) (Nutt, 2005). Surprisingly, the location of the tumor site also appears to be associated with 1p/19q co-deletions (Jansen et al., 2010). In glioblastoma, deletions involving 1p and 19q are uncommon, but have been identified in a small percentage and appear to predict shortened survival (Smith et al., 2000).

At the present time in the clinic, determining 1p/19q status is part of the standard of care for patients with oligodendroglial tumors, to help guide choice and sequencing of therapy. This information often serves as useful information when clinicians are determining the course of therapy based on the knowledge that patients with oligodendrogliomas that harbor co-deletions of chromosomes 1p and 19q will likely survive longer and be more responsive to a broad range of treatments.

2.2 Cell cycle regulation

2.2.1 p53

TP53 is the gene that encodes the important tumor suppressor protein, p53. In 1989, further karyotypic and LOH analysis defined the location of a tumor suppressor on chromosome 17, and the *TP53* tumor suppressor gene was later identified to be responsible for alterations in GBM at this locus (Van Meir et al., 2010). p53 is often referred to as the "guardian of the genome" as it is involved in a multitude of critical processes that regulate normal cell function, such as cell cycle control, DNA damage response, cell death, differentiation, and inhibition of angiogenesis (Fischer & Aldape, 2010). It is a critical factor in the G1/S checkpoint whereby activated p53 can signal increased levels of p21, a CDK2 inhibitor, resulting in cell cycle arrest (Van Meir et al., 2010). In the absence of p53, the cell cycle can become unregulated and lead to uncontrolled proliferation resulting in tumorigenesis. p53 prevents excess proliferation from triggering apoptosis because p53 also regulates the apoptosis response by controlling pro-apoptotic proteins, such as Bax and Fas (Fischer & Aldape, 2010; Van Meir et al., 2010).

Low grade astrocytomas often possess inactivating mutations of the tumor suppressor gene, *TP53*. Therefore it is thought that p53 mutations are a hallmark of low-grade gliomas and consequently also occur in secondary GBM that arise from lower grade gliomas (Noda et al., 2009). Loss of p53 is observed in grade II astrocytomas (35-60%), grade III astrocytomas (~50%), primary GBM (~30%), and secondary GBM (~60-65%) (Sulman et al., 2009; Bourne & Schiff, 2010; Gladson et al., 2010). Additionally, p53 mutations are found in ~44% of grade II oligoastrocytoma and ~13% of oligodendroglioma cases (Bourne & Schiff, 2010). Overexpression of p53 has also been observed in ~50% of GBM cases (Kim et al., 2010). Interestingly, tumors that harbor 1p/19q co-deletions do not contain p53 mutations (Noda et al., 2009; Fischer & Aldape, 2010). MDM2, a negative regulator of p53, has also been reported to be amplified or mutated in anaplastic astrocytoma (AA) (13-43%) and in glioblastoma (~10-27%) (Gladson et al., 2010; Kim et al., 2010). Currently, p53 is not thought to be predictive or prognostic (Tabatabai et al., 2010). However, it does have a role in the diagnostic setting as it can help distinguish tumor grade.

2.2.2 Rb/P16INK4A/CDK4

Rb, also known as the retinoblastoma protein, is a tumor suppressor that is the central protein responsible for antiproliferative signaling. Rb blocks proliferation by binding and inhibiting the E2F transcription factors, which are necessary for the G1 to S phase transition and DNA replication (Fischer & Aldape, 2010; Van Meir et al., 2010). Furthermore, Rb is normally inactivated by cyclin D1 and CDK4/CDK6 complexes in order for DNA synthesis to proceed. p16, which is located on chromosome 19, is an additional regulator of this pathway as it negatively regulates CDK4 and CDK6 and therefore also functions as a tumor suppressor (Fischer & Aldape, 2010; Van Meir et al., 2010).

Inhibition of the Rb pathway is common in high grade gliomas, and tumors usually only harbor a single altered component of the pathway (Fischer & Aldape, 2010). Tumor progression to anaplastic astrocytomas is typically characterized by common mutations in this pathway, such as p16 or Rb mutations and amplification or overexpression of CDK4 (Noda et al., 2009; Fischer & Aldape, 2010). Loss of the Rb gene and mutation occur in approximately 30% and 13-25% of grade II and III astrocytomas, respectively (Gladson et al., 2010). Additionally, deletions or mutations of the Rb gene occur in 40% of secondary GBM cases (Gladson et al., 2010). The frequency of Rb mutations in all high grade-gliomas is common and is estimated to occur in approximately 25% of all cases (Fischer & Aldape, 2010). Deletion or mutation of p16INK4A as a consequence of loss of chromosome 9p or hypermethylation occurs in approximately 12-62.5% of anaplastic astrocytoma cases (Gladson et al., 2010). p16 loss has also been reported in 20-57% of GBM cases (Sulman et al., 2009; Kim et al., 2010).

Interestingly, since cyclins and cyclin-dependent kinase (CDK) inhibitors are subject to proteosomal degradation, cell cycle regulation can be modified through proteasome inhibitors. Bortezomib, a proteasome inhibitor, has been shown to induce cell death in cultured glioma cell lines by decreasing levels of CDK2, CDK4, and E2F4 subsequently leading to apoptosis in cultured glioma cell lines (Fischer & Aldape, 2010). Although alterations of the Rb pathway are very common in gliomas, it remains to be determined how these hallmark mutations will translate into a clinically meaningful target. However, a recent study did demonstrate that p16 mutations were strong prognostic indicators of OS in GBM patients treated with TMZ (Ang et al., 2010). Recently, two Phase I trials using bortezomib with and without concurrent temozolomide and radiotherapy for glioblastoma

have been reported, and found the combination to be well-tolerated and safe (Kubicek et al., 2009; Phuphanich et al., 2010).

2.3 Proliferation, invasion, and angiogenesis pathways

2.3.1 IDH

Isocitrate dehydrogenase (IDH), is an enzyme that catalyzes the conversion of isocitrate into α-ketoglutarate within the citric acid cycle. IDH1 and IDH2 are involved in a variety of metabolic processes such as signal transduction, lipid synthesis, oxidative stress, and oxidative respiration (Riemenschneider et al., 2010). IDH mutations were initially identified to be associated with gliomas in 2008 when a genome-wide mutational analysis was conducted in GBM (Riemenschneider et al., 2010; Yen et al., 2010). IDH1 and IDH2 mutations were also found in lower grade gliomas in addition to glioblastomas, making IDH the first discovery of somatic genetic alterations in metabolic enzymes in gliomas (Yen et al., 2010). In low grade brain tumors, IDH mutations are common genetic alterations of gliomas arising from the astrocytic and oligodendroglial lineage. These mutations are also identified in secondary GBMs from a lower grade origin (Fischer & Aldape, 2010; Jansen et al., 2010). IDH1 and IDH2 mutations are currently used as diagnostic markers for diffuse WHO grade II and III gliomas as well as secondary GBMs (Jansen et al., 2010; Riemenschneider et al., 2010). IDH1 and IDH2 mutations are often identified concomitantly with 1p/19q co-deletions or p53 mutations (Jansen et al., 2010; Riemenschneider et al., 2010). Mutations in the IDH1 gene were identified in approximately 80% of diffuse astrocytomas and 85% of secondary glioblastomas. In contrast, only 5% of primary glioblastomas carry an IDH mutation (Yan et al., 2009; Fischer & Aldape, 2010).

It remains to be determined how these alterations cause tumorigenesis, although the metabolic role of IDH has been recently examined in the context of oncogenesis. IDH1 mutations are thought to lead to increased formation of 2-hydroxyglutarate (2HG) through a gain of function mutation (Jansen et al., 2010; Riemenschneider et al., 2010; Yen et al., 2010). There is evidence that D-2HG can exert a direct inhibitory effect on adenosine 5′ triphosphate synthase, which interrupts mitochrondrial processes and gives rise to selective pressure to promote metabolic adaptation and a shift towards aerobic glycoysis. This metabolic shift could confer a growth advantage in an increased proliferative state, such as in tumor progression (Yen et al., 2010). Additionally, another possible tumorigenic role of 2HG is its involvement in hypoxia-inducible factor 1 alpha (HIF1α) degradation, thus IDH mutations are thought to lead to increased levels of HIF1α which can facilitate tumor growth (Jansen et al., 2010; Riemenschneider et al., 2010; Yen et al., 2010). Other hypotheses on the role of IDH mutations in gliomagenesis that are being explored are its possible involvement in angiogenesis, glucose transport, glycolysis, and inhibition of apoptosis (Riemenschneider et al., 2010; Yen et al., 2010). Therefore, 2HG has been implicated in tumorigenesis, and is thought to be a potential therapeutic target, a serum biomarker for cancers harboring IDH1 and IDH2 mutations, and a potential response biomarker. Interestingly, there is evidence that D-2HG may be visualized via magnetic resonance spectroscopy, which in theory could make it possible to perform non-invasive detection of tumors with IDH mutations to help diagnose and guide therapy before surgery (Yen et al., 2010).

Patients that harbor IDH mutations appear to have a prognostic advantage compared with patients without IDH mutations for all gliomas (Jansen et al., 2010; Riemenschneider et al.,

2010). Specifically, somatic mutations were present in 18 of 149 (12%) GBMs and seemed to correlate with increased survival, as the overall survival was 31 months in patients with IDH mutations compared to 15 months in those without IDH mutations (Jansen et al., 2010). Although IDH is a useful diagnostic and prognostic tool, it currently does not appear to be able to predict responsiveness to a particular type of therapy (Riemenschneider et al., 2010). More clinical trials examining IDH mutations need to be performed to determine its role as a predictive molecular biomarker.

2.3.2 PDGFR

Platelet-derived growth factor (PDGF) plays an important role in cell proliferation, cell migration, and angiogenesis. Thus, PDGF receptor (PDGFR) is classified as producing a pro-proliferative signal and both the level of PDGF and PDGFRs is important in angiogenesis and tumor growth in gliomas (Noda et al., 2009; Gladson et al., 2010). Amplification of PDGFRα occurs in approximately 7% of oligodendroglial tumors (Gladson et al., 2010). Astrocytic tumors commonly (3-33%) exhibit amplification of the PDGFRα and/or PDGFRβ genes and of the genes encoding their ligands (Gladson et al., 2010). Also, PDGFRα and PDGFRβ amplification occurs in approximately 20-29% of primary GBM and 60% of secondary GBM. Due to its frequency, amplification of PDGF appears to be a key regulator of gliomagenesis, specifically overexpression of PDGFRβ was shown to initiate gliomagenesis when expressed in the neural stem progenitor cell (Gladson et al., 2010). Amplification of PDGFR has also been associated with patient outcome, thus suggesting it could serve as a prognostic biomarker (Toedt et al., 2011). Imatinib is an orally administered tyrosine kinase inhibitor (TKI) of PDGFR, c-abl and c-kit, and is currently being tested in clinical trials to assess its efficacy in malignant gliomas. A multicenter phase II study evaluating imatinib plus hydroxyurea in 231 patients with recurrent glioblastoma did not demonstrate a clinically meaningful anti-tumor activity (Reardon et al., 2009). Precisely, progression-free survival at 6 months and median overall survival were 10.6% and 26.0 weeks, respectively. A Phase II trial has been initiated by Supko et al. that will test the efficacy of tandutinib, a PDGFRβ inhibitor, in patients with recurrent GBM (Supko, 2009).

2.3.3 EGFR/NFKBIA

PDGFR is not the only common growth factor receptor involved in gliomagenesis. Epidermal growth factor receptor (EGFR) also promotes a pro-proliferative signal, and is another common molecular hallmark of glioblastoma (Fischer & Aldape, 2010). In 1984, extra copies of chromosome 7 were identified in malignant gliomas, which resulted in EGFR amplification/overexpression (Van Meir et al., 2010). EGFR promotes cell proliferation, invasion and angiogenesis, induces resistance to apoptosis, and may mediate radiation resistance (Sulman et al., 2009; Gladson et al., 2010). EGFR amplification at 7p12 is the most commonly amplified and overexpressed gene in primary GBM (30-70%) (Fischer & Aldape, 2010; Gladson et al., 2010; Kim et al., 2010; Riemenschneider et al., 2010). Additionally, EGFRvIII is the most prominent mutated receptor tyrosine kinase receptor in GBM (Noda et al., 2009; Riemenschneider et al., 2010). This mutation occurs in ~50% of GBM cases that overexpress EGFR (Riemenschneider et al., 2010). EGFRvIII arises from loss of exons 2 and 7 which leads to loss of the ligand binding domain, thereby promoting constitutive activation of EGFR and the PI3K/AKT pathway (Noda et al., 2009; Jansen et al., 2010). Both EGFR and PDGFR coordinate with integrins and other cell adhesion receptors. In glioma tissue, an

increase in growth factors as well as receptors is typically observed (Gladson et al., 2010). EGFR also contributes to invasion as evidenced by the observation that GBMs harboring constitutively active EGFRvIII receptors display a more invasive phenotype than those with wild-type EGFR (Fischer & Aldape, 2010). One of the main molecular distinctions between primary and secondary GBMs is that primary GBMs tend to have EGFR amplifications (~30-70%), whereas secondary GBMs that arise from lower grade gliomas tend to not have EGFR alterations (~5-8%) (Noda et al., 2009; Sulman et al., 2009; Fischer & Aldape, 2010; Kim et al., 2010). In addition, EGFR amplifications occur in approximately 15% of grade III anaplastic astrocytomas (Sulman et al., 2009; Gladson et al., 2010).

One example of targeted therapy is the inhibition of EGFR tyrosine kinase (TKI). Several studies using EGFR TKIs have shown some anti-tumor activity in patients with glioblastoma. EGFR overexpression has been demonstrated in malignant gliomas, and is associated with anti-apoptotic tendency conferred by activated signaling pathways, tumor survival, and proliferation (Nicholas et al., 2006). Surprisingly, the activity did not correlate with the level of EGFR overexpression. Gefinitib and erlotinib are examples of EGFR TKIs that inactivate the downstream signaling pathways, and have been tested in the recurrent GBM setting (Perez-Soler, 2004). However, clinical studies utilizing EGFR inhibitor monotherapy have shown only marginal results for patients with recurrent glioblastoma (Rich et al., 2004; Prados et al., 2009; van den Bent et al., 2009). When used in combination with ionizing radiation, however, the EGFR inhibitors have been shown to augment the anti-proliferative and pro-apoptotic activity induced by ionizing radiation in several human cancer cell lines, as well as in mice bearing human colon cancer xenografts, as demonstrated by Bianco and colleagues (Bianco et al., 2002).

RTOG conducted a phase I/II study (0211) utilizing gefitinib with radiotherapy in patients with newly diagnosed GBM, and compared with historical studies, the combined therapy did not improve survival (Chakravarti, 2006). Prados and colleagues performed a phase II study of combining erlotinib with RT and TMZ in patients with newly-diagnosed GBM, and demonstrated a 5-month improvement in the median survival with this approach (19.3 months *versus* 14.1 months in the combined historical control studies) (Prados et al., 2009). In this study, a strong positive correlation between MGMT promoter methylation and survival was re-demonstrated. However, other studies utilizing a similar approach of combined targeted and conventional therapy showed inferior outcomes and high treatment-related toxicity and death rate (Brown et al., 2008; Peereboom et al., 2010).

The efficacy of EGFR inhibitors remains controversial for newly diagnosed glioblastoma, although some patients have been reported to respond dramatically to EGFR inhibitors. To reconcile the disparity between EGFR overexpression in glioblastomas (up to 50% tumors) with only 10-20% of GBM patients that have a response to EGFR TKIs, biological markers to predict treatment response have been reported, and these can potentially be used to identify the patients that will derive survival benefit from the addition of an EGFR inhibitor (Mellinghoff et al., 2005). Specifically, co-expression of EGFR deletion mutant variant III (EGFRvIII) and the tumor-suppressor protein PTEN was significantly associated with a clinical response to EGFR TKI. In a recent phase II multicenter trial of EGFRvIII-targeted vaccination in 18 patients with glioblastoma who received the standard therapy of gross total resection followed by RT and concurrent TMZ, the 6-month PFS after vaccination was 67%, and median overall survival was 26 months (Sampson et al., 2010). The development of specific antibody or delayed-type hypersensitivity to EGFRvIII had a significant effect on OS. When these patients recurred, 82% had lost EGFRvIII expression.

Resistance to these EGFR inhibitors is thought to be due to other mutations downstream of EGFR, such as PTEN inactivation (Noda et al., 2009). Another potential problem with this type of targeted therapy is that EGFR activates several downstream pathways that might act in parallel to drive oncogenesis. In addition, patients with GBM treated with TMZ that had EGFR amplification, maintenance of PTEN, and wild-type p53 and p16 were strong prognostic indicators of overall survival (Ang et al., 2010). Furthermore, coexpression of normal PTEN and mutant EGFRvIII, combined with lower levels of AKT and overexpressed EGFR have been identified as predictive markers of radiation response (Fischer & Aldape, 2010). Although the predictive and prognostic use of EGFR remains to be completely defined, it does appear that there is some correlation with survival and treatment response (Tabatabai et al., 2010). In addition, the high percentage of GBM cases with EGFR overexpression and EGFR mutations strengthens the possibility that targeted therapy of EGFR may be a useful treatment for gliomas.

Due to high frequency of amplification and activating mutations of EGFR in gliomas, the deletion of NFKBIA, an inhibitor of the EGFR-signaling pathway, was hypothesized to be an additional putative molecular biomarker of gliomas as well. A recent study examined 790 human GBM cases for deletions, mutations, or expression of NFKBIA and EGFR (Bredel et al., 2010). The molecular data was then correlated to outcome data in 570 patients. The results showed that NFKBIA is often deleted, but not mutated in glioblastomas. Most deletions occurred in nonclassical subtypes of GBM and were inversely correlated with EGFR alterations. Importantly, deletion and decreased expression levels of NFKBIA were associated with decreased survival and displayed similar outcomes to patients with EGFR amplifications (Bredel et al., 2010).

2.3.4 VEGF

The formation of new blood vessels (angiogenesis) is one of the major steps in progression of malignant gliomas. Angiogenesis is controlled through many factors, such as vascular endothelial growth factor (VEGF) which is controlled by the transcription factor HIF1α, EGF and PDGF (Deighton et al., 2010; Fischer & Aldape, 2010). VEGF is considered to be the driving factor of angiogenesis in astrocytic gliomas. It has been identified in grade II astrocytoma (36.8%), grade III astrocytoma (66.7%) and in glioblastomas (64.1%) (Oehring et al., 1999). Additionally, a strong correlation between VEGF expression and survival was identified indicating VEGF as a possible prognostic factor in patients with gliomas (Oehring et al., 1999).

One class of targeted therapy includes antiangiogenic agents that target VEGF. Glioblastoma has long been recognized as a highly angiogenic tumor (Ahluwalia & Gladson, 2010). Bevacizumab, a humanized monoclonal antibody that recognizes and blocks VEGF, was approved by the Food and Drug Administration (FDA) as a second-line or salvage treatment of glioblastoma. Recent studies of recurrent glioblastoma have shown that bevacizumab improved response rate and progression-free survival, but specific adverse effects have also been reported, such as intracranial hemorrhage, gastrointestinal perforation, and thromboembolic complications (Vredenburgh, 2010; Friedman, 2009). In one study of 73 patients with recurrent high-grade gliomas who already received a VEGFR TKI (cediranib, sorafenib, pazopanib, or sunitinib), bevacizumab salvage therapy conferred 21% radiologic partial response rate; 12.5% patients were alive and progression-free at six months, and median overall survivial was 5.2 months (range 1.3-28.9+ months) after bevacizumab (Scott et al., 2010).

To evaluate its effect in the up-front setting, Lai et al. conducted a phase II study of bevacizumab plus TMZ during and after RT for patients with newly diagnosed glioblastoma (Lai et al., 2011). They reported a median overall survival and progression-free survival of 19.6 and 13.6 months, respectively. The authors concluded that the addition of bevacizumab improved progression-free survival, but not overall survival, compared with their historical studies. Currently, RTOG is conducting a Phase III double-blind placebo-controlled trial of conventional concurrent chemoradiation and adjuvant TMZ plus bevacizumab versus conventional concurrent chemoradiation and adjuvant TMZ in patients with newly diagnosed GBM. Results are awaited, as this study will determine the efficacy of adding bevacizumab to the current standard treatment of GBM.

Sathornsumetee and colleagues recently reported results of a Phase II trial with bevacizumab and erlotinib, an EGFR inhibitor, in patients with recurrent high grade gliomas (both GBM and anaplastic astrocytoma (AA)). In this trial, the progression-free survival at six months (PFS-6) was 28% for patients with GBM and 44% for patients with AA. Median overall survival was 42 and 71 weeks for patients with GBM and AA, respectively (Sathornsumetee et al., 2010).

In another study evaluating the efficacy of adding sorafenib, an oral VEGFR TKI, to maintenance TMZ following the standard radiotherapy and TMZ in the first-line treatment of 47 patients with GBM, the addition of sorafenib did not appear to improve the efficacy of the standard therapy (Hainsworth et al., 2010). However, 40% patients in this study did not receive any maintenance sorafenib due to early disease progression, lending credence to the hypothesis that the administration of angiogenesis inhibitors concurrently with RT and TMZ may optimize the opportunity to improve therapy. The aforementioned RTOG Phase III trial will help answer this question.

Cilengitide, one of the other anti-angiogenic drugs, inhibits αvβ3 and αvβ5 integrin receptors, resulting in apoptosis of glioblastoma cells (Taga et al., 2002). Cilengitide monotherapy for recurrent glioblastoma has a modest effect and confers an approximate 6-month progression-free survival of 15% (Reardon et al., 2008). Currently, Stupp and colleagues are conducting randomized studies of RT plus TMZ with or without cilengitide for newly diagnosed glioblastoma. The Phase I/IIa study of cilengitide and temozolomide with concomitant radiotherapy followed by cilengitide and temozolomide maintenance therapy in 52 patients with newly diagnosed glioblastoma demonstrated promising activity in patients with MGMT promoter methylation. Specifically, 6- and 12-month progression-free survival rates were 69% and 33%, while the 12- and 24-month overall survival rates were 68% and 35% for all patients. The PFS and OS benefit was most pronounced in patients with MGMT promoter methylation (13.4 and 23.2 months versus 2.4 and 13.1 months) (Stupp et al., 2010).

2.4 Signal transduction pathways

Alterations of signaling molecules in gliomas are often involved in gliomagenesis. These signaling molecules act downstream of the cell surface growth factors and cell adhesion receptors to amplify and propagate growth and proinvasion signals. Examples of these signaling molecules include: tyrosine kinase FAK, src family tyrosine kinases, RAS, PI3K, and PTEN. PI3K and PTEN are molecules that regulate glioma cell survival and proliferation. Normally, PI3K promotes proliferation and survival, where as PTEN negatively regulates this process. Many glioblastomas have dysregulation of signaling cascades downstream of the growth factor, such as PTEN mutations and mutations within the PI3K/AKT pathway (Jansen et al., 2010).

2.4.1 PI3K/AKT/PTEN pathway

PTEN (phosphatase and tensin homolog) is a tumor suppressor gene, a negative regulator of the P13K/AKT pathway, and a known inhibitor of angiogenesis. It was first identified as a tumor suppressor located on chromosome 10 in 1997 (Van Meir et al., 2010). PTEN codes for a protein that preferentially dephosphorylates the phosphoinositide substrate, PIP3, and once PTEN is lost PIP3 levels accumulate and lead to constitutive P13K signaling and AKT activation (Maehama & Dixon, 1998). Thus, it is not surprising that loss of PTEN is associated with poor prognosis (Ermoian et al., 2002; Ang et al., 2010; Gladson et al., 2010).

PTEN mutations are common in ~8% of oligodendrogliomas and there is evidence that the presence of this mutation in patients is associated with poor prognosis (Sasaki et al., 2001). Downregulation of this gene has also been found in 50% of grade II and grade III oligodendrogliomas, which appears to be a consequence of promoter methylation (Wiencke et al., 2007; Bourne & Schiff, 2010). In grade II and III astrocytomas, PTEN promoter methylation occurs in ~43-67% of cases (Wiencke et al., 2007; Bourne & Schiff, 2010). In glioblastoma, PTEN is deleted due to LOH of chromosome 10q in ~50-70% of primary cases and ~54-63% secondary cases as well as mutated in ~14-47% of primary cases (Fujisawa et al., 2000; Ohgaki et al., 2004). Methylation of the PTEN promoter in glioblastoma (9%) has also been observed (Wiencke et al., 2007). In many cases loss of PTEN (50% of high grade gliomas) results in unregulated PI3K signaling, AKT activation, and upregulation of mTOR (mammalian target of rapamycin) signaling, which increases protein translation through activation of S6 kinase 1 (S6K1) and eIF4E-binding protein 1 (4E-BP1) (Fischer & Aldape, 2010; Zoncu et al., 2011). mTOR signaling is also known to play a role in hypoxic adaptation of tumors (Van Meir et al., 2010).

Currently, PTEN is thought to be a prognostic molecular marker as patients with loss of PTEN have decreased survival. Based on preclinical evidence that loss of PTEN activates the mTOR pathway, and thereby sensitizes tumors to the inhibition of mTOR, a proof-of-concept Phase I trial utilizing neoadjuvant rapamycin in patients with recurrent GBM showed dramatic anticancer activity in half of the patients (7/14) (Cloughesy et al., 2008). However, rapamycin treatment led to AKT activation in 7/14 patients, implying inadequate inhibition of the mTOR complex 2 (mTORC2). In a Phase II trial utilizing CCI-779, a dihydroxylmethyl propionic acid ester of sirolimus that targets the mTORC pathway, there was no evidence of efficacy in patients with recurrent GBM, as only 1/43 patients was progression-free at 6 months (Chang et al., 2005). North Central Cancer Treatment Group Study (NCCTG) conducted a Phase II trial of once-weekly intravenous temsirolimus, an mTORC1 inhibitor, in 63 patients with recurrent GBM, improving radiographic response in 36% of patients, as well as conferring a significantly longer time to progression in responders (5.4 months versus 1.9 months) (Galanis et al., 2005). In a more recent Phase I trial by NCCTG, the combination of everolimus, an mTORC1 inhibitor, with chemoradiotherapy in 18 patients with newly diagnosed GBM showed that the combination was reasonably well-tolerated, and Phase II dose established (Sarkaria et al., 2010). To date, no clinical trials combining inhibition of both the mTORC1 and mTORC2 have been reported.

In recent years, PTEN status has also been examined as a predictive factor for efficiency of certain targeted therapies, such as poly (ADP-ribose) polymerase (PARP) inhibitors (Dedes et al., 2010; McEllin et al., 2010). It is now known that PTEN is important for maintaining the levels of key proteins involved in homologous recombination, such as Rad51B, Rad51C and Rad51D (Shen et al., 2007). McEllin and colleagues demonstrated that PTEN-null astrocytes had decreased transcript levels of these proteins, consistent with deficiency in homologous

recombination in PTEN-null cells. In their experiments, PTEN-null astrocytes were significantly more sensitive to PARP inhibitor compared with PTEN-proficient cells (McEllin et al., 2010). Data from clinical trials utilizing PARP inhibitors in patients with recurrent or newly diagnosed GBM are awaited.

Mutations of PTEN are not the only molecular markers of gliomas in the PI3K pathway. PI3K signaling is an important mediator of cell growth and proliferation, thus its activation is frequent and associated with poor prognosis in glioma patients (Fischer & Aldape, 2010). Multiple growth factors, such as EGFR, exert their oncogenic effects through activation of PI3K/AKT pathway, which is constitutively activated in up to 70% of GBM due to PTEN loss (Kreisl et al., 2009). An additional study looking at 84 cases in GBM identified pAKT overexpression and PI3K overexpression in 16% and 6% of the cases, respectively (Kim et al., 2010). Downstream of AKT is the serine/threonine kinase, mammalian target of rapamycin (mTOR), which regulates protein biosynthesis, ribosome biogenesis, and the transcription of essential genes (Fischer & Aldape, 2010; McBride et al., 2010). As noted above, inhibitors of mammalian target of rapamycin (mTOR) have been shown to decrease PI3K/AKT activation, and combined mTOR and EGFR inhibition has demonstrated synergy in GBM xenografts (Goudar et al., 2005). In a pilot study of everolimus, an mTOR inhibitor, and gefitinib, an EGFR inhibitor, in the treatment of 22 patients with recurrent GBM, 36% of patients had stable disease and 14% a partial response (PR) (Kreisl et al., 2009). Although disease control was short lived (median progression-free survival (PFS) 2.6 months), the patients with PR all had intact PTEN, and AKT activation was observed in 80% of tumors in which PTEN was lost. In another Phase II study with erlotinib, an EGFR TKI, and sirolimus, an mTOR inhibitor, in 32 patients with recurrent GBM, were also well-tolerated, but had negligible activity among unselected patients. Precisely, no patients achieved either a complete or partial response, and the estimated 6-month progression-free survival for all patients was 3.1%, but somewhat better for patients not on enzyme-inducing antiepileptic drugs (Reardon et al., 2010). Of all tumor markers tested (EGFR, EGFRvIII, PTEN, pAKT and pS6), only pAKT expression achieved borderline significance in association with PFS. Coexpression of EGFR vIII with intact PTEN has been shown to predict sensitivity to EGFR inhibitor monotherapy (Mellinghoff et al., 2005). Activation of the PI3K/mTOR pathway occurs in most adult low grade gliomas, too (McBride et al., 2010). In a recent study, methylation of PTEN, expression of phospho-PRAS40 and phospho-S6 all correlated with decreased survival which suggests that these molecular alterations can be used as prognostic markers for both high and low grade gliomas. Phospho-S6 is a downstream mediator of mTOR, whereas PRAS40 is phosphorylated by AKT and inhibits negative regulation of mTOR thereby further increasing PI3K/AKT signaling (McBride et al., 2010).

In summary, PTEN may be a possible predictive biomarker of glioma response to specific therapies, in addition to its role as a prognostic marker due to its association with aggressive tumor phenotypes and survival. Since upregulation of the P13K/mTOR pathway through a variety of mechanisms predicts overall decreased survival, the use of selective PI3K, AKT, or mTOR inhibitors in the treatment of gliomas appears to be a valid therapeutic target to combat gliomagenesis.

2.4.2 RAS/MAPK pathway

The MAPK pathway, an additional important signal transduction pathway involved in gliomagenesis, is initiated through integrins or receptor tyrosine kinase (RTK) receptors. Growth factors can bind to these RTKs, such as TGF-β, and stimulate the downstream

activation of RAS and phosphorylation of MAPK (mitogen-activated protein kinase) by MEK. Phosphorylated MAPK then signals the activation of nuclear transcription factors, such as genes involved in cell cycle progression (Fischer & Aldape, 2010). MAPK signaling is also involved in apoptosis, cell differentiation, and cell migration (Sulman et al., 2009). RAS is often activated in gliomas, however it does not usually contain mutations, but rather an unregulated RTK or integrin activation (Fischer & Aldape, 2010). Specifically, the rate limiting step of RAS activation is farnesylation, which explains the use of farnesyltransferase inhibitors in gliomas. Two separate farnesyl transferase inhibitors, tipifarnib and lonafarnib, have led to mixed results in clinical trials. A Phase II trial with pre-radiation tipifarnib (R115777) in patients with newly diagnosed GBM with residual enhancing disease on postoperative MR imaging showed that there were no tumor responses, and the study was stopped early due to progression of disease in 12 (48%) patients (Lustig et al., 2008). In a Phase II study by North American Brain Tumor Consortium, tipifarnib in patients with recurrent malignant glioma showed modest evidence of activity. Precisely, 12% of GBM patients had progression-free survival more than 6 months (Cloughesy et al., 2006).
In terms of biomarkers, MAPK proteins appear to be both predictive and prognostic molecular biomarkers. Phosphorylated MAPK was found to be inversely correlated with survival, as well as associated with increased radiation resistance (Pelloski et al., 2006). Additionally, upregulation of the MAPK pathway can occur through the proto-oncogene BRAF. Abnormal activation of BRAF, most commonly by gene duplication and fusion, has recently been identified as the characteristic genetic aberration in pilocytic astrocytomas. It occurs in ~60-80% of pilocytic astrocytoma cases (Riemenschneider et al., 2010).

2.5 DNA repair

2.5.1 MGMT

DNA repair response is a critical factor that greatly influences the effectiveness of the majority of chemotherapy agents and radiation. O6-methyl guanine DNA methyltransferase gene (MGMT) is located at chromosome 10q26 and encodes a DNA repair protein that removes the alkyl groups from the O6 position of guanine, which are commonly produced by chemotherapeutic alkylating agents. MGMT is one of the principal enzymes involved in DNA repair, and it is irreversibly inactivated upon removing alkyl groups from the O6 position of guanine. *De novo* synthesis of MGMT is required to replenish the enzyme, and the MGMT promoter needs to be functional if DNA repair is to take place. The MGMT promoter is downregulated by hypermethylation of a CpG island in a 5′ region of the gene (Gerson, 2004). Once hypermethylated, the promoter downregulates MGMT and thereby hampers this enzyme's ability to repair DNA damage induced by alkylating agents such as temozolomide. Methylation status of the MGMT promoter, as well as its association with other genetic parameters, has become a major focus of biological marker research. Gliomas often possess decreased MGMT expression levels, which are thought to be primarily due to increased MGMT promoter methylation as previously mentioned. A correlation between MGMT promoter methylation and response of malignant gliomas to alkylating chemotherapy has been observed (Riemenschneider et al., 2010). MGMT hypermethylation has been identified in 11% of grade II astrocytoma, 27% of oligoastrocytoma, and 62% of oligodendroglioma cases (Bourne & Schiff, 2010). In addition, DNA hypermethylation was found in 36% of primary GBM and 75% of secondary GBM cases (Gladson et al., 2010). The heretofore reported frequencies of MGMT promoter methylation vary widely. In the EORTC-NCIC cohort, 45% of assessable cases had MGMT promoter methylation. In a series

of 102 patients with various grades and gliomas subtypes, Jha and colleagues found the presence of MGMT promoter methylation in 67.6% cases (79% in Grade II gliomas, 71% in Grade III gliomas, and 57% in GBM), suggesting an inverse relationship between methylation status and tumor grade (Jha et al., 2010). Purely oligodendroglial tumors showed the highest percentage of cases with MGMT promoter methylation (84%), compared with 63.5% in astrocytic tumors. The methylation status of MGMT promoter was not shown to be significantly associated with 1p/19q loss of heterozygosity, nor was there significant association of promoter methylation with EGFR amplification or *TP53* mutation.

Genetic /Protein Alteration	Normal Gene Function	Putative Biomarker Status
1p/19q co-deletion	unknown, involved in gliomagenesis	diagnostic, prognostic, predictive
p53/MDM2/p14ARF	cell cycle arrest, apoptosis, genomic stability	p53-diagnostic
Rb/p16/CDK4	regulates cell cycle progression	p16-prognostic
IDH	citric acid cycle (cell metabolism)	diagnostic, prognostic
PDGFR	cell proliferation signaling	prognostic
EGFR	cell proliferation signaling	diagnostic, prognostic, predictive
VEGF	angiogenesis	prognostic
PTEN	negative regulator of PI3K/AKT activation	prognostic, predictive
PI3K/AKT	cell proliferation, survival	prognostic
MAPK	signaling pathway involved in gene expression, cell cycle, apoptosis, cell differentiation and migration	prognostic, predictive
MGMT	DNA repair enzyme	prognostic, predictive

Table 1. Common Alterations in Malignant Gliomas and their Putative Biomarker Status

In the landmark EORTC/NCIC study by Stupp and colleagues, 573 patients with newly-diagnosed GBM, 84% of which were surgically debulked, were randomized to receive RT alone (60 Gy in 30 fractions) or RT plus continuous daily TMZ (75 mg/m^2 BSA from the first to the last day of RT), followed by six cycles of adjuvant TMZ (150-200 mg/m^2 BSA for 5 days during each 28-day cycle). At a median follow-up of 28 months, the median survival was 14.6 months with RT plus TMZ versus 12.1 months with RT alone, rendering the hazard

TARGETS	AGENTS	PATIENT	PHASE	RESULTS	REFERENCE
Growth factor ligands					
VEGF	BEV + RT + TMZ → TMZ + BEV	New Dx	II	OS 19.6 months, PFS 13.6 months versus 21.1 and 7.6 months in control cohort, and versus 14.6 and 6.9 months in EORTC cohort.	Lai
VEGF	BEV + RT + TMZ → TMZ + BEV	New Dx	III	mPFS 17mo (vs 7 mo without BEV). mOS not reached (17 mo without BEV).	Gruber
VEGF	BEV + Irinotecan	Recurrent	II	PFS-6 37%	Gilbert
VEGF	BEV + Fotemustine	Recurrent	II	Overall response 35%. mTTP 2.6 mo. 15/31 FFP (2-8 mo)	Soffietti
VEGF	BEV q 3 weeks	Recurrent	II	PFS-6 32%, mPFS 3.9 mo, mOS 6.6 mo. 0% CR, 25% PR, 50% SD.	Raizer
VEGF, Vascularity	BEV + Fosbretabulin	Recurrent	I	Pilot study outline only reported.	Altaha
TGF-β 2	Trabedersen	Recurrent	IIb	AA: OS-24mo 83% with lower dose. GBM: mOS 17.4 mo. Phase III started.	Bogdahn
Growth factor receptors					
pan-VEGFR	Cediranib + RT+ TMZ	New Dx	Ib	MTD reached. 6/6 pts alive at 156 days median follow up. Phase II underway.	Chi
pan-VEGFR	Vatalanib + RT + TMZ	New Dx	I/II	MTD reached. Phase II discontinued due to industry decision not to further develop agent.	Brandes
pan-VEGFR	Cediranib	Recurrent	II	56.7% radiologic response, PFS-6 25.8%, manageable toxicity. Biomarkers associated with response and survival.	Batchelor
VEGFR-2	CT-322	Recurrent	II	MTD reached. Clinically active. PFS-6 with CT-322 alone 21.4%, with CT-322 plus irinotecan 57.1%	Schiff
VEGFR	RT + TMZ → TMZ + Sorafenib	New Dx		Median PFS 6 months; PFS-1 year 16%. Median OS 12 months. 40% patients did not receive maintenance sorafenib.	Hainsworth
VEGFR	Sunitinib + Irinotecan	Recurrent	I	MTD reached. 73% SD.	Friedman
VEGFR	Sunitinib	Recurrent	II	mTTP 1.6 mo, mOS 3.8 mo.	Neyns
PDGFR-β	Tandutinib	Recurrent	I	MTD achieved. Phase II initiated.	Supko
Intracellular effectors					
PKC-β and PI3K/Akt pathway	Enzastaurin vs Lomustine	Recurrent	III	n=266; OS 6.6 vs 7.1 months, median PFS 1.5 vs 1.6 months. No superior efficacy compared with lomustine, but better hematologic toxicity.	Wick
PKC-β and PI3K/Akt pathway	Enzastaurin + RT + TMZ	New Dx	II	24/60 PD. OS, PFS will be reported.	Butowski
mTOR	Temsirolimus + RT + TMZ	New Dx	I	MTD established. Increased risk of opportunistic infections.	Sarkaria
mTOR	RAD001 + TMZ (maintenance)	New Dx	I	MTD reached.	Mason
bcl-2	R-(-)-gossypol	Recurrent	II	OS pending. 1/43 PR. 7/43 SD.	Fiveash
VEGFR, PDGFR, *RAF*	TMZ + Sorafenib (maintenance)	New Dx	II	CR 1%, PR 11%, SD 49%, PD 31%. mPFS 6 mo. mOS 16 mo.	Lamar
RAS (Farnesyl transferase)	SCH 66336 + TMZ	Recurrent	I	MTD reached. 2 PR, 14 SD, 11 PD	Desjardins
VEGF, Histone De-acetylase	Vorinostat + BEV + Irinitecan	Recurrent	I	Currently enrolling at the Dose Level 3 vorinostat, with planned follow-up Phase II trial.	Chinnaiyan
PARP-1	BSI-201	New Dx	I	MTD not reached with TMZ, encouraging safety profile.	Blakeley
Multitargeted kinase inhibitors					
VEGF, EGFR	BEV + Erlotinib	Recurrent	II	PFS-6 28% (GBM) and 44% (AA); median OS 42 weeks (GBM) and 71 weeks (AA).	Sathornsumetee
VEGFR, EGFR	Vandetanib + RT+ TMZ	New Dx	I	MTD reached. DLTs included GI hemorrhage, GI perforation and cytopenias. Phase II under way.	Drappatz
VEGFR, EGFR	Vandetanib + Etoposide	Recurrent	I	MTD not reached. "Patients remaining stable on study."	Herndon
VEGFR, EGFR, PDGFR	Vandetanib + Imatinib + Hydroxyurea	Recurrent	I	MTD reached. 1/16 PR, 15/16 SD for at least 4 weeks.	Kirkpatrick
VEGFR-2, EGFR	Vandetanib	Recurrent	I/II	MTD reached; median PFS6 1.8 mo, median OS 7.4 mo	Mcnicol
VEGFR, EGFR	BEV + Cetuximab + Irinotecan	Recurrent	II	Radiographic response 34%, PFS-6 30%. 3/32 patients with DVT. Efficacy not superior compared with Bev + Irinotecan alone.	Hasselbalch
EGFR, mTOR	Erlotinib + Temsirolimus	Recurrent	I/II	MTD reached. No PR, 30% SD. PFS-6 12.5%	Chang
EGFR, mTOR	Erlotinib + Sirolimus	Recurrent	II	47% with SD, no patients with PR or CR. PFS-6 3.1%. PFS better for patinets not on EIAEDs (p=0.03).	Reardon
EGFR, VEGFR	Erlotinib + Sorafenib	Recurrent	I/II	MTD reached. Outcome data pending.	Prados
VEGFR, mTOR	Sorafenib + Temsirolimus	Recurrent	I/II	MTD reached. PFS-6 0%.	Wen
MET, RET, VEGFR2	XL184	Recurrent	II	38% had > 50% tumor reduction (PR), 35% between +24% and -49% enhancement, 27% > 25% PD.	De Groot
MET, RET, VEGFR2	XL184	Progressive	II	PFS6 21%; ORR 21% (AAT naïve) vs 8% (prior AAT); mean duration of response 5.9 months.	Wen
VEGFR, PDGFR, *KIT*, EGFR, HER-2	Pazopanib + Lapatinib	Recurrent	I/II	MTD reached. Ph I: 3% PR, 18% SD. Ph II: 1/2 PR, 1/2 CR.	Frentzas
Miscellaneous					
Integrins	Cilentide + RT + TMZ → RT + TMZ	New Dx	I/IIa	PFS-6 69%, PFS-12 33%, OS-12 68%, OS-12 35%. PFS and OS longer if MGMT promoter methylated.	Stupp
Selective Inegrin	Cilengitide	Recurrent	IIa	OS at all time points significantly higher with 2 gr dose vs 0.5 gr dose	Fink
LDL receptor-related protein	ANG1005	Recurrent	I	MTD Reached; SD in 56% pts. Median time to progression in responders 23.9 weeks	Drappatz
CDK/TRKA	PHA-848125	Recurrent	I	MTD reached; transaminase elevation dose-limiting.	Benouaich-Amiel

Table 1. Recent clinical trials with targeted therapy. OS - overall survivial. PFS - progression free survival. MTD - maximum tolerated dose. SD - stable disease. PR - partial response. CR - complete response. GBM - glioblastoma. AA - anaplastic astrocytoma. RT - radiation therapy. TMZ - temozolomide. BEV – bevacizumab. (Bogdahn, 2009; Chang, 2009; Soffietti, 2009; Batchelor et al., 2010; Brandes et al., 2010; Drappatz et al., 2010; Hainsworth et al., 2010; Hasselbalch et al., 2010; Reardon et al., 2010; Sarkaria et al., 2010; Sathornsumetee et al., 2010; Stupp et al., 2010; Wick et al., 2010; Lai et al., 2011; Altaha, June 2010; Benouaich-Amiel, June 2010; Blakeley, June 2010; Chinnaiyan, June 2010; Drappatz, June 2010; Fink, June 2010; Mcnicol, June 2010; Schiff, June 2010; Wen,

June 2010; Butowski, May 2009; Chi, May 2009; De Groot, May 2009; Desjardins, May 2009; Fiveash, May 2009; Frentzas, May 2009; Friedman, May 2009; Gilbert, May 2009; Gruber, May 2009; Herndon, May 2009; Kirkpatrick, May 2009; Lamar, May 2009; Mason, May 2009; Neyns, May 2009; Prados, May 2009; Raizer, May 2009; Supko, May 2009; Wen, May 2009)

ratio (HR) for death 0.63 in the combined modality group. Moreover, the two-year overall survival (OS-2) was 26.5% with RT+TMZ and 10.4% with RT alone (Stupp et al., 2005). The 5-year analysis showed that OS-5 was 9.8% with RT and TMZ, versus 1.9% with RT alone (Stupp et al., 2009). In this trial, patients whose tumor had a methylated MGMT gene promoter had improved survival (median 21.7 *versus* 12.7 months, OS-2 46% *versus* 13.8%) relative to those with an unmethylated *MGMT* promoter, and the methylation status was the strongest predictor for outcome and benefit from TMZ chemotherapy (Hegi et al., 2005). Another study analyzing 125 patients with GBM showed that MGMT promoter methylation was associated with improved median overall survival (61 weeks vs. 42 weeks) (Ang et al., 2010). These studies suggest that MGMT promoter methylation status could possibly be used as a strong predictive marker of response to chemotherapeutic alkylating agents. Furthermore, it is thought that the benefit of MGMT promoter hypermethylation only applies to chemotherapy. However, one study suggested that decreased MGMT confers sensitivity to radiation alone, as well (Rivera et al., 2010). However, this remains controversial as it is thought that this observation is due to the overall prognostic value of MGMT and is independent of the treatment type (Riemenschneider et al., 2010).

Given the increased prevalence of MGMT promoter methylation in lower grade tumors, the effectiveness of adjuvant monotherapy with TMZ has been tested in a trial setting, with reported response rates of up to 52%. Kesari and colleagues conducted a phase II study of protracted daily TMZ (75 mg/m^2/d for 49 consecutive days of each cycle, followed by 28 days off between cycles, until evidence of progression or unacceptable toxicity for a maximum of six cycles) in 44 patients with newly diagnosed low-grade glioma. After a median follow-up of 39.4 months, 21 patients progressed with an overall median progression-free survival of 38 months (Kesari et al., 2009). Patients with methylated MGMT promoter had a significantly longer overall survival (100% alive at analysis, *versus* 29 months with unmethylated promoter), as did patients with single or co-deleted 1p or 19q. The efficacy of protracted TMZ for the treatment of low grade gliomas was also shown in another series with 25 patients, with a response rate of 52%, and a relatively well-tolerated toxicity profile (Pouratian et al., 2007).

An even more pressing clinical challenge is improving the chemotherapy response in GBM patients without the MGMT promoter methylation. Optimizing the adjuvant chemotherapy regimen is one potential strategy to improve patient outcomes, given the inverse relationship between the level of tumoral MGMT and chemosensitivity. A randomized Phase II trial of adjuvant dose-dense (150 mg/m^2 days 1 to 7 and 15 to 21) or metronomic (50 mg/m^2 continuous daily) TMZ showed that the former approach conferred a 1 year survival of 80%, median survival 17.1 months and PFS-6 months of 56% (Clarke et al., 2009). Specifically, in the unmethylated MGMT subset, the median survival was 15.4 months, which was superior to the 12.7 months reported for the patients with unmethylated MGMT in the EORTC/NCIC trial. The dose-dense TMZ schedule suggests that the more effective inhibition of MGMT may be most beneficial to GBM patients with unmethylated MGMT promoter.

In patients that do not have suppressed levels of MGMT, O6-benzylguanine can be used as a MGMT-inactivating agent. This treatment has shown synergistic effects in combination with TMZ and RT in several pre-clinical models (Wedge et al., 1997; Noda et al., 2009). However, GBMs often have decreased concentrations of MGMT, which could make these tumors more susceptible to TMZ (Jansen et al., 2010). Decreased MGMT appears to serve a prognostic role in GBM, as a recent study showed that 46% of patients with MGMT-methylated tumors were alive at 2 years *versus* 23% of unmethylated patients when treated with RT plus TMZ (Jansen et al., 2010). MGMT promoter methylation as a biomarker in grade II gliomas remains controversial. However, for grade III gliomas MGMT promoter hypermethylation appears to be a positive prognostic marker and for grade IV it is believed to be a prognostic as well as a predictive marker for alkylating agent chemotherapy (Riemenschneider et al., 2010; Tabatabai et al., 2010). Furthermore, it is believed that the predictive power of MGMT is only for chemotherapy, although this remains a controversial topic as discussed before (Riemenschneider et al., 2010). Moreover, MGMT promoter methylation has been shown to be closely linked to pseudoprogression (Nutt, 2005; Riemenschneider et al., 2010). Although MGMT can be useful as a marker of survival, the current standard of care for GBM does not require knowing MGMT status; however, it may help distinguish between pseudoprogression and true progression (Nutt, 2005; Riemenschneider et al., 2010) as well as possibly determining if a MGMT-specific inhibitor should be combined with the current standard treatment modality.

2.6 Other pathways

2.6.1 Glutamatergic system

The glutamatergic system has been found to play a key role in the proliferation, survival and migration of gliomas (Ishiuchi et al., 2007; De Groot et al., 2008). Glioma cells release glutamate in concentrations that are toxic to surrounding neurons and glia (Takano et al., 2001). However, the glutamate reuptake is reduced due to downregulation of glutamate transporters (EAAT2/GLT-1) (Ye et al., 1999). In a phase II trial with talampanel, an oral noncompetitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor and standard RT + TMZ in patients with newly diagnosed glioblastoma, a median survival of 18.3 months was reached in all patients. In patients 70 years or younger, the median survival was 20.3 months. The two year survival was also superior compared with EORTC RT + TMZ data (41.7% vs 26.5%, respectively) (Grossman et al., 2009).

2.6.2 Epigenetic regulation

Histone deacetylases (HDAC) are enzymes that affect acetylation status of histones, as well as that of cell cycle regulatory proteins (Arts et al., 2003). Histone deacetylation leads to tight coiling of chromatin and silencing of expression of various genes, including those implicated in the regulation of cell survival, tumor cell differentiation, cell cycle arrest and apoptosis (Jones & Baylin, 2002). North Central Cancer Treatment Group (NCCTG) conducted a Phase II trial of vorinostat, a small-molecule inhibitor of human HDAC1, 2, 3, 6 and 8 that crosses the blood-brain barrier, in 66 patients with recurrent glioblastoma (Galanis et al., 2009). The agent was administered at a dose of 200 mg twice a day for 14 days every 3 weeks, and was well tolerated. The 6-month PFS was 15.2%, with median time to progression of 1.9 months and median survival of 5.7 months. However, in patients who

were progression-free at 6 months, the duration of disease stability ranged from 6.8 to 28+ months, suggesting that there is a patient sub-population that can derive definite clinical benefit from this therapy. Incorporation of vorinostat in the current standard of care with RT + TMZ will be tested by the NCCTG/North American Brain Tumor Coalition in a phase I/II trial.

3. Conclusion

As we learn more about cellular pathways and effectors involved in gliomagenesis, there will likely be a paradigm shift from the uniform standard-of-care treatment for all patients to a more individualized treatment based on molecular biomarkers. The aforementioned novel targeting therapies add to our armamentarium both as single agents and in combination with radiation, chemotherapy, and other targeted molecular agents. Ultimately, this will enable us to devise a more effective treatment strategy by tackling the underpinnings of resistance of malignant gliomas. As our knowledge increases, the challenge before the scientific and clinical community will be to identify the key targets and formulate therapy accordingly. Foregoing the "kitchen sink" approach will lessen the harm done to patients, as the aforementioned clinical trials show that targeted therapies may cause serious toxicities.

Although most studies mentioned are phase I or II, with a relatively short follow-up time, several of these agents warrant testing in a larger and randomized setting to truly discern their efficacy and safety, with the overarching hope of improving our patients' prognosis. The most recent update from Stupp and colleagues regarding integrin inhibition with addition of cilengitide to standard chemoradiotherapy shows promise to potentially become the new standard-of-care for patients with GBM, suggesting that the most effective strategy is to target both the extracellular (*e.g.,* integrin) and intracellular effectors. Moreover, just as the methylation status of the MGMT promoter did, greater characterization of gene expression by epigenetic regulation may help us elucidate additional mechanisms of resistance or sensitivity to therapy.

In summary, gaining a better understanding of the molecular brain tumor population(s) that benefit from each targeted therapy will lead to more effective personalized therapy. It is hoped that a more targeted therapeutic approach will overcome the current limitations in the treatment of patients with malignant gliomas and result in a better prognosis for patients with brain tumors.

4. Acknowledgements

E. Hlavin Bell and M. Hadziahmetovic contributed equally to this chapter. We thank the Department of Radiation Oncology at the James Cancer Hospital and Richard Solove Research Institute at The Ohio State University. E. Hlavin Bell was funded by the Barbara Hughes Fellowship.

5. References

Ahluwalia, M. S. & C. L. Gladson (2010). Progress on antiangiogenic therapy for patients with malignant glioma. *J Oncol,* Vol. 2010, No., 689018, ISBN 1687-8469

Aldape, K., P. C. Burger, et al. (2007). Clinicopathologic aspects of 1p/19q loss and the diagnosis of oligodendroglioma. *Arch Pathol Lab Med,* Vol. 131, No. 2, (Feb), 242-251, ISBN 1543-2165

Altaha (June 2010). A pilot study of fosbretabulin with bevacizumab in recurrent high-grade gliomas. ASCO Annual Meeting,28:15s, San Diego, California

Ang, C., M. C. Guiot, et al. (2010). Clinical significance of molecular biomarkers in glioblastoma. *Can J Neurol Sci,* Vol. 37, No. 5, (Sep), 625-630, ISBN 0317-1671

Arts, J., S. de Schepper, et al. (2003). Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem,* Vol. 10, No. 22, (Nov), 2343-2350

Batchelor, T. T., D. G. Duda, et al. (2010). Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. *J Clin Oncol,* Vol. 28, No. 17, (Jun 10), 2817-2823, ISBN 1527-7755

Bauman, G. S., Y. Ino, et al. (2000). Allelic loss of chromosome 1p and radiotherapy plus chemotherapy in patients with oligodendrogliomas. *Int J Radiat Oncol Biol Phys,* Vol. 48, No. 3, (Oct 1), 825-830, ISBN 0360-3016

Benouaich-Amiel, A. (June 2010). Phase I study of the oral CDK-TRKA inhibitor PHA-848125 in recurrent malignant glioma (MG). ASCO Annual Meeting,28:15s, San Diego, California

Bianco, C., G. Tortora, et al. (2002). Enhancement of antitumor activity of ionizing radiation by combined treatment with the selective epidermal growth factor receptor-tyrosine kinase inhibitor ZD1839 (Iressa). *Clin Cancer Res,* Vol. 8, No. 10, (Oct), 3250-3258, ISBN 1078-0432

Blakeley, J. O. (June 2010). Poly (ADP-ribose) polymerase-1 (PARP1) inhibitor BSI-201 in combination with temozolomide (TMZ) in malignant glioma. J Clin Oncol,28:15s, San Diego, California

Bogdahn, U. (2009). Randomized, active-controlled phase IIb study with trabedersen (AP 12009) in recurrent or refractory high-grade glioma patients: basis for phase III endpoints. ASCO Annual Meeting,27:15s, Orlando, Florida

Bourne, T. D. & D. Schiff (2010). Update on molecular findings, management and outcome in low-grade gliomas. *Nat Rev Neurol,* Vol. 6, No. 12, (Dec), 695-701, ISBN 1759-4766

Brandes, A. A., R. Stupp, et al. (2010). EORTC study 26041-22041: phase I/II study on concomitant and adjuvant temozolomide (TMZ) and radiotherapy (RT) with PTK787/ZK222584 (PTK/ZK) in newly diagnosed glioblastoma. *Eur J Cancer,* Vol. 46, No. 2, (Jan), 348-354, ISBN 1879-0852

Bredel, M., D. M. Scholtens, et al. (2010). NFKBIA Deletion in Glioblastomas. *N Engl J Med,* Vol., No., (Dec 22), ISBN 1533-4406

Brown, P. D., S. Krishnan, et al. (2008). Phase I/II trial of erlotinib and temozolomide with radiation therapy in the treatment of newly diagnosed glioblastoma multiforme: North Central Cancer Treatment Group Study N0177. *J Clin Oncol,* Vol. 26, No. 34, (Dec 1), 5603-5609, ISBN 1527-7755

Butowski, N. (May 2009). Phase II and pharmacogenomics study of enzastaurin plus temozolomide and radiation therapy in patients with glioblastoma multiforme or gliosarcoma. ASCO Annual Meeting,27:15s, Orlando, Florida

Cairncross, G. & R. Jenkins (2008). Gliomas with 1p/19q codeletion: a.k.a. oligodendroglioma. *Cancer J,* Vol. 14, No. 6, (Nov-Dec), 352-357, ISBN 1528-9117

Cairncross, J. G., K. Ueki, et al. (1998). Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst,* Vol. 90, No. 19, (Oct 7), 1473-1479, ISBN 0027-8874

Chakravarti, A. (2006). An update of phase II results from RTOG 0211: a phase I/II study of gefitinib with radiotherapy in newly diagnosed glioblastoma. ASCO Annual Meeting,24:18s, Atlanta, Georgia

Chang, S. M. (2009). Phase I/II study of erlotinib and temsirolimus for patients with recurrent malignant gliomas (MG) (NABTC 04-02). ASCO Annual Meeting,27:15s, Orlando, Florida

Chang, S. M., P. Wen, et al. (2005). Phase II study of CCI-779 in patients with recurrent glioblastoma multiforme. *Invest New Drugs,* Vol. 23, No. 4, (Aug), 357-361, ISBN 0167-6997

Chi, A. S. (May 2009). Phase Ib study of cediranib in combination with daily temozolomide and radiation in patients with newly diagnosed glioblastoma. ASCO Annual Meeting,27:15s, Orlando, Florida

Chinnaiyan, P. (June 2010). A phase I trial of vorinostat in combination with bevacizumab and irinotecan in recurrent glioblastoma. ASCO Annual Meeting,28:15s, San Diego, California

Clarke, J. L., F. M. Iwamoto, et al. (2009). Randomized phase II trial of chemoradiotherapy followed by either dose-dense or metronomic temozolomide for newly diagnosed glioblastoma. *J Clin Oncol,* Vol. 27, No. 23, (Aug 10), 3861-3867, ISBN 1527-7755

Cloughesy, T. F., P. Y. Wen, et al. (2006). Phase II trial of tipifarnib in patients with recurrent malignant glioma either receiving or not receiving enzyme-inducing antiepileptic drugs: a North American Brain Tumor Consortium Study. *J Clin Oncol,* Vol. 24, No. 22, (Aug 1), 3651-3656, ISBN 1527-7755

Cloughesy, T. F., K. Yoshimoto, et al. (2008). Antitumor activity of rapamycin in a Phase I trial for patients with recurrent PTEN-deficient glioblastoma. *PLoS Med,* Vol. 5, No. 1, (Jan 22), e8, ISBN 1549-1676

De Groot, J. F. (May 2009). A phase II study of XL184 in patients (pts) with progressive glioblastoma multiforme (GBM) in first or second relapse. ASCO Annual Meeting,27:15s, Orlando, Florida

De Groot, J. F., Y. Piao, et al. (2008). Knockdown of GluR1 expression by RNA interference inhibits glioma proliferation. *J Neurooncol,* Vol. 88, No. 2, (Jun), 121-133, ISBN 0167-594X

Dedes, K. J., D. Wetterskog, et al. (2010). PTEN deficiency in endometrioid endometrial adenocarcinomas predicts sensitivity to PARP inhibitors. *Sci Transl Med,* Vol. 2, No. 53, (Oct 13), 53ra75, ISBN 1946-6242

Deighton, R. F., R. McGregor, et al. (2010). Glioma pathophysiology: insights emerging from proteomics. *Brain Pathol,* Vol. 20, No. 4, (Jul), 691-703, ISBN 1750-3639

Desjardins, A. (May 2009). Phase I trial combining SCH 66336 to temozolomide (TMZ) for patients with grade 3 or 4 malignant gliomas (MG). ASCO Annual Meeting,27:15s, Orlando, Florida

Drappatz, J. (June 2010). ANG1005: Results of a phase I study in patients with recurrent malignant glioma. ASCO Annual Meeting,28:15s, San Diego, California

Drappatz, J., A. D. Norden, et al. (2010). Phase I study of vandetanib with radiotherapy and temozolomide for newly diagnosed glioblastoma. *Int J Radiat Oncol Biol Phys,* Vol. 78, No. 1, (Sep 1), 85-90, ISBN 1879-355X

Ermoian, R. P., C. S. Furniss, et al. (2002). Dysregulation of PTEN and protein kinase B is associated with glioma histology and patient survival. *Clin Cancer Res,* Vol. 8, No. 5, (May), 1100-1106, ISBN 1078-0432

Fink, K. (June 2010). Long-term effects of cilengitide, a novel integrin inhibitor, in recurrent glioblastoma: A randomized phase IIa study. ASCO Annual Meeting,28:15s, San Diego, California

Fischer, I. & K. Aldape (2010). Molecular tools: biology, prognosis, and therapeutic triage. *Neuroimaging Clin N Am,* Vol. 20, No. 3, (Aug), 273-282, ISBN 1557-9867

Fiveash, J. B. (May 2009). NABTT-0702: A phase II study of R-(-)gossypol (AT-101) in recurrent glioblastoma multiforme (GBM). ASCO Annual Meeting,27:15s, Orlando, Florida

Frentzas (May 2009). Pazopanib and lapatinib in patients with relapsed malignant glioma: results of a phase I/II study. ASCO Annual Meeting,27:15s, Orlando, Florida

Friedman, H. S. (May 2009). A phase I study of sunitinib plus irinotecan in the treatment of patients with recurrent malignant glioma. ASCO Annual Meeting,27:15s, Orlando, Florida

Fujisawa, H., R. M. Reis, et al. (2000). Loss of heterozygosity on chromosome 10 is more extensive in primary (de novo) than in secondary glioblastomas. *Lab Invest,* Vol. 80, No. 1, (Jan), 65-72, ISBN 0023-6837

Galanis, E., J. C. Buckner, et al. (2005). Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: a North Central Cancer Treatment Group Study. *J Clin Oncol,* Vol. 23, No. 23, (Aug 10), 5294-5304, ISBN 0732-183X

Galanis, E., K. A. Jaeckle, et al. (2009). Phase II trial of vorinostat in recurrent glioblastoma multiforme: a north central cancer treatment group study. *J Clin Oncol,* Vol. 27, No. 12, (Apr 20), 2052-2058, ISBN 1527-7755

Gerson, S. L. (2004). MGMT: its role in cancer aetiology and cancer therapeutics. *Nat Rev Cancer,* Vol. 4, No. 4, (Apr), 296-307, ISBN 1474-175X

Gilbert, M. R. (May 2009). RTOG 0625: A phase II study of bevacizumab with irinotecan in recurrent glioblastoma (GBM). ASCO Annual Meeting,27:15s, Orlando, Florida

Gladson, C. L., R. A. Prayson, et al. (2010). The pathobiology of glioma tumors. *Annu Rev Pathol,* Vol. 5, No., 33-50, ISBN 1553-4014

Goudar, R. K., Q. Shi, et al. (2005). Combination therapy of inhibitors of epidermal growth factor receptor/vascular endothelial growth factor receptor 2 (AEE788) and the mammalian target of rapamycin (RAD001) offers improved glioblastoma tumor growth inhibition. *Mol Cancer Ther,* Vol. 4, No. 1, (Jan), 101-112, ISBN 1535-7163

Grossman, S. A., X. Ye, et al. (2009). Talampanel with standard radiation and temozolomide in patients with newly diagnosed glioblastoma: a multicenter phase II trial. *J Clin Oncol,* Vol. 27, No. 25, (Sep 1), 4155-4161, ISBN 1527-7755

Gruber, M. L. (May 2009). Bevacizumab in combination with radiotherapy plus concomitant and ajuvant temozolomide for newly diagnosed glioblastoma: update progression-free survival, overall survival, and toxicity. ASCO Annual Meeting,27:15s, Orlando, Florida

Hainsworth, J. D., T. Ervin, et al. (2010). Concurrent radiotherapy and temozolomide followed by temozolomide and sorafenib in the first-line treatment of patients with glioblastoma multiforme. *Cancer,* Vol. 116, No. 15, (Aug 1), 3663-3669, ISBN 0008-543X

Hasselbalch, B., U. Lassen, et al. (2010). Cetuximab, bevacizumab, and irinotecan for patients with primary glioblastoma and progression after radiation therapy and temozolomide: a phase II trial. *Neuro Oncol,* Vol. 12, No. 5, (May), 508-516, ISBN 1523-5866

Hegi, M. E., A. C. Diserens, et al. (2005). MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med,* Vol. 352, No. 10, (Mar 10), 997-1003, ISBN 1533-4406

Herndon, J. (May 2009). Phase I trial of vendetanib and oral etoposide for recurrent malignant gliomas. ASCO Annual Meeting,27:15s, Orlando, Florida

Hirose, Y., H. Sasaki, et al. (2011). Whole genome analysis from microdissected tissue revealed adult supratentorial grade II-III gliomas are divided into clinically relevant subgroups by genetic profile. *Neurosurgery,* Vol., No., (Feb 23), ISBN 1524-4040

Ino, Y., R. A. Betensky, et al. (2001). Molecular subtypes of anaplastic oligodendroglioma: implications for patient management at diagnosis. *Clin Cancer Res,* Vol. 7, No. 4, (Apr), 839-845, ISBN 1078-0432

Ishiuchi, S., Y. Yoshida, et al. (2007). Ca2+-permeable AMPA receptors regulate growth of human glioblastoma via Akt activation. *J Neurosci,* Vol. 27, No. 30, (Jul 25), 7987-8001, ISBN 1529-2401

Jansen, M., S. Yip, et al. (2010). Molecular pathology in adult gliomas: diagnostic, prognostic, and predictive markers. *Lancet Neurol,* Vol. 9, No. 7, (Jul), 717-726, ISBN 1474-4465

Jha, P., V. Suri, et al. (2010). O6-methylguanine DNA methyltransferase gene promoter methylation status in gliomas and its correlation with other molecular alterations: first Indian report with review of challenges for use in customized treatment. *Neurosurgery,* Vol. 67, No. 6, (Dec), 1681-1691, ISBN 1524-4040

Jones, P. A. & S. B. Baylin (2002). The fundamental role of epigenetic events in cancer. *Nat Rev Genet,* Vol. 3, No. 6, (Jun), 415-428, ISBN 1471-0056

Kesari, S., D. Schiff, et al. (2009). Phase II study of protracted daily temozolomide for low-grade gliomas in adults. *Clin Cancer Res,* Vol. 15, No. 1, (Jan 1), 330-337, ISBN 1078-0432

Kim, B., J. K. Myung, et al. (2010). The clinicopathologic values of the molecules associated with the main pathogenesis of the glioblastoma. *J Neurol Sci,* Vol. 294, No. 1-2, (Jul 15), 112-118, ISBN 1878-5883

Kirkpatrick (May 2009). Phase I study of vandetanib, imatinib mesylate, and hydroxyurea for recurrent malignant glioma. ASCO Annual Meeting,27:15s, Orlando, Florida

Kouwenhoven, M. C., J. M. Kros, et al. (2006). 1p/19q loss within oligodendroglioma is predictive for response to first line temozolomide but not to salvage treatment. *Eur J Cancer,* Vol. 42, No. 15, (Oct), 2499-2503, ISBN 0959-8049

Kreisl, T. N., A. B. Lassman, et al. (2009). A pilot study of everolimus and gefitinib in the treatment of recurrent glioblastoma (GBM). *J Neurooncol,* Vol. 92, No. 1, (Mar), 99-105, ISBN 0167-594X

Kubicek, G. J., M. Werner-Wasik, et al. (2009). Phase I trial using proteasome inhibitor bortezomib and concurrent temozolomide and radiotherapy for central nervous system malignancies. *Int J Radiat Oncol Biol Phys,* Vol. 74, No. 2, (Jun 1), 433-439, ISBN 1879-355X

Lai, A., A. Tran, et al. (2011). Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. *J Clin Oncol,* Vol. 29, No. 2, (Jan 10), 142-148, ISBN 1527-7755

Lamar, R. E. (May 2009). Phase II trial of radiation therapy/temozolomide followed by temozolomide/sorafenib in the first-line treatment of glioblastoma multiforme. ASCO Annual Meeting,27:15s, Orlando, Florida

Lustig, R., T. Mikkelsen, et al. (2008). Phase II preradiation R115777 (tipifarnib) in newly diagnosed GBM with residual enhancing disease. *Neuro Oncol,* Vol. 10, No. 6, (Dec), 1004-1009, ISBN 1522-8517

Maehama, T. & J. E. Dixon (1998). The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. *J Biol Chem,* Vol. 273, No. 22, (May 29), 13375-13378, ISBN 0021-9258

Mason, W. P. (May 2009). A phase I study of temozolomide (TMZ) and RAD001 in patients (pts) with glioblastoma multiforme (GBM). ASCO Annual Meeting,27:15s, Orlando, Florida

McBride, S. M., D. A. Perez, et al. (2010). Activation of PI3K/mTOR pathway occurs in most adult low-grade gliomas and predicts patient survival. *J Neurooncol,* Vol. 97, No. 1, (Mar), 33-40, ISBN 1573-7373

McEllin, B., C. V. Camacho, et al. (2010). PTEN loss compromises homologous recombination repair in astrocytes: implications for glioblastoma therapy with temozolomide or poly(ADP-ribose) polymerase inhibitors. *Cancer Res,* Vol. 70, No. 13, (Jul 1), 5457-5464, ISBN 1538-7445

Mcnicol, K. A. (June 2010). Phase I/II study of vandetanib for patients with recurrent malignant gliomas. ASCO Annual Meeting,28:15s, San Diego, California

Mellinghoff, I. K., M. Y. Wang, et al. (2005). Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. *N Engl J Med,* Vol. 353, No. 19, (Nov 10), 2012-2024, ISBN 1533-4406

Neyns, B. (May 2009). Phase II trial of sunitinib malate in patients with temozolomide refractory recurrent high-grade glioma. ASCO Annual Meeting,27:15s, Orlando, Florida

Nicholas, M. K., R. V. Lukas, et al. (2006). Epidermal growth factor receptor - mediated signal transduction in the development and therapy of gliomas. *Clin Cancer Res,* Vol. 12, No. 24, (Dec 15), 7261-7270, ISBN 1078-0432

Noda, S. E., A. El-Jawahri, et al. (2009). Molecular advances of brain tumors in radiation oncology. *Semin Radiat Oncol,* Vol. 19, No. 3, (Jul), 171-178, ISBN 1532-9461

Nutt, C. L. (2005). Molecular genetics of oligodendrogliomas: a model for improved clinical management in the field of neurooncology. *Neurosurg Focus,* Vol. 19, No. 5, (Nov), E2, ISBN 1092-0684

Oehring, R. D., M. Miletic, et al. (1999). Vascular endothelial growth factor (VEGF) in astrocytic gliomas--a prognostic factor? *J Neurooncol,* Vol. 45, No. 2, 117-125, ISBN 0167-594X

Ohgaki, H., P. Dessen, et al. (2004). Genetic pathways to glioblastoma: a population-based study. *Cancer Res,* Vol. 64, No. 19, (Oct 1), 6892-6899, ISBN 0008-5472

Peereboom, D. M., D. R. Shepard, et al. (2010). Phase II trial of erlotinib with temozolomide and radiation in patients with newly diagnosed glioblastoma multiforme. *J Neurooncol,* Vol. 98, No. 1, (May), 93-99, ISBN 1573-7373

Pelloski, C. E., E. Lin, et al. (2006). Prognostic associations of activated mitogen-activated protein kinase and Akt pathways in glioblastoma. *Clin Cancer Res,* Vol. 12, No. 13, (Jul 1), 3935-3941, ISBN 1078-0432

Perez-Soler, R. (2004). HER1/EGFR targeting: refining the strategy. *Oncologist,* Vol. 9, No. 1, 58-67, ISBN 1083-7159

Phuphanich, S., J. G. Supko, et al. (2010). Phase 1 clinical trial of bortezomib in adults with recurrent malignant glioma. *J Neurooncol,* Vol. 100, No. 1, (Oct), 95-103, ISBN 1573-7373

Pouratian, N., J. Gasco, et al. (2007). Toxicity and efficacy of protracted low dose temozolomide for the treatment of low grade gliomas. *J Neurooncol,* Vol. 82, No. 3, (May), 281-288, ISBN 0167-594X

Prados, M. (May 2009). Phase I/II study of sorefenib and erlotinib for patients with recurrent glioblastoma (GBM) (NABTC 05-02). ASCO Annual Meeting,27:15s, Orlando, Florida

Prados, M. D., S. M. Chang, et al. (2009). Phase II study of erlotinib plus temozolomide during and after radiation therapy in patients with newly diagnosed glioblastoma multiforme or gliosarcoma. *J Clin Oncol,* Vol. 27, No. 4, (Feb 1), 579-584, ISBN 1527-7755

Raizer, J. J. (May 2009). A phase II trial of single-agent bevacizumab given every 3 weeks for recurrent malignant gliomas. ASCO Annual Meeting,27:15s, Orlando, Florida

Reardon, D. A., A. Desjardins, et al. (2010). Phase 2 trial of erlotinib plus sirolimus in adults with recurrent glioblastoma. *J Neurooncol,* Vol. 96, No. 2, (Jan), 219-230, ISBN 1573-7373

Reardon, D. A., G. Dresemann, et al. (2009). Multicentre phase II studies evaluating imatinib plus hydroxyurea in patients with progressive glioblastoma. *Br J Cancer,* Vol. 101, No. 12, (Dec 15), 1995-2004, ISBN 1532-1827

Reardon, D. A., K. L. Fink, et al. (2008). Randomized phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme. *J Clin Oncol,* Vol. 26, No. 34, (Dec 1), 5610-5617, ISBN 1527-7755

Rich, J. N., D. A. Reardon, et al. (2004). Phase II trial of gefitinib in recurrent glioblastoma. *J Clin Oncol,* Vol. 22, No. 1, (Jan 1), 133-142, ISBN 0732-183X

Riemenschneider, M. J., J. W. Jeuken, et al. (2010). Molecular diagnostics of gliomas: state of the art. *Acta Neuropathol,* Vol. 120, No. 5, (Nov), 567-584, ISBN 1432-0533

Rivera, A. L., C. E. Pelloski, et al. (2010). MGMT promoter methylation is predictive of response to radiotherapy and prognostic in the absence of adjuvant alkylating chemotherapy for glioblastoma. *Neuro Oncol,* Vol. 12, No. 2, (Feb), 116-121, ISBN 1523-5866

Sampson, J. H., A. B. Heimberger, et al. (2010). Immunologic escape after prolonged progression-free survival with epidermal growth factor receptor variant III peptide vaccination in patients with newly diagnosed glioblastoma. *J Clin Oncol,* Vol. 28, No. 31, (Nov 1), 4722-4729, ISBN 1527-7755

Sarkaria, J. N., E. Galanis, et al. (2010). North Central Cancer Treatment Group Phase I Trial N057K of Everolimus (RAD001) and Temozolomide in Combination with Radiation Therapy in Patients with Newly Diagnosed Glioblastoma Multiforme. *Int J Radiat Oncol Biol Phys,* Vol., No., (Sep 22), ISBN 1879-355X

Sasaki, H., M. C. Zlatescu, et al. (2001). PTEN is a target of chromosome 10q loss in anaplastic oligodendrogliomas and PTEN alterations are associated with poor prognosis. *Am J Pathol,* Vol. 159, No. 1, (Jul), 359-367, ISBN 0002-9440

Sathornsumetee, S., A. Desjardins, et al. (2010). Phase II trial of bevacizumab and erlotinib in patients with recurrent malignant glioma. *Neuro Oncol,* Vol. 12, No. 12, (Dec), 1300-1310, ISBN 1523-5866

Schiff, D. (June 2010). Phase II study of CT-322, a targeted biologic inhibitor of VEGFR-2 based on a domain of human fibronectin, in recurrent glioblastoma (rGBM). ASCO Annual Meeting,28:15s, San Diego, California

Scott, B. J., E. C. Quant, et al. (2010). Bevacizumab salvage therapy following progression in high-grade glioma patients treated with VEGF receptor tyrosine kinase inhibitors. *Neuro Oncol,* Vol. 12, No. 6, (Jun), 603-607, ISBN 1523-5866

Shen, W. H., A. S. Balajee, et al. (2007). Essential role for nuclear PTEN in maintaining chromosomal integrity. *Cell,* Vol. 128, No. 1, (Jan 12), 157-170, ISBN 0092-8674

Siker, M. L., A. Chakravarti, et al. (2006). Should concomitant and adjuvant treatment with temozolomide be used as standard therapy in patients with anaplastic glioma? *Crit Rev Oncol Hematol,* Vol. 60, No. 2, (Nov), 99-111, ISBN 1040-8428

Smith, J. S., A. Perry, et al. (2000). Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. *J Clin Oncol,* Vol. 18, No. 3, (Feb), 636-645, ISBN 0732-183X

Snuderl, M., A. F. Eichler, et al. (2009). Polysomy for chromosomes 1 and 19 predicts earlier recurrence in anaplastic oligodendrogliomas with concurrent 1p/19q loss. *Clin Cancer Res,* Vol. 15, No. 20, (Oct 15), 6430-6437, ISBN 1078-0432

Soffietti, R. (2009). Phase II study of bevacizumab and nitrosourea in patients with recurrent malignant glioma: a multicenter Italian study. ASCO Annual Meeting,27:15s, Orlando, Florida

Stupp, R., M. E. Hegi, et al. (2009). Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol,* Vol. 10, No. 5, (May), 459-466, ISBN 1474-5488

Stupp, R., M. E. Hegi, et al. (2010). Phase I/IIa study of cilengitide and temozolomide with concomitant radiotherapy followed by cilengitide and temozolomide maintenance therapy in patients with newly diagnosed glioblastoma. *J Clin Oncol,* Vol. 28, No. 16, (Jun 1), 2712-2718, ISBN 1527-7755

Stupp, R., W. P. Mason, et al. (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med,* Vol. 352, No. 10, (Mar 10), 987-996, ISBN 1533-4406

Sulman, E. P., M. Guerrero, et al. (2009). Beyond grade: molecular pathology of malignant gliomas. *Semin Radiat Oncol,* Vol. 19, No. 3, (Jul), 142-149, ISBN 1532-9461

Supko, J. G. (May 2009). Feasibility and phase I trial of tandatunib in patients with recurrent glioblastoma. ASCO Annual Meeting,27:15s, Orlando, Florida

Tabatabai, G., R. Stupp, et al. (2010). Molecular diagnostics of gliomas: the clinical perspective. *Acta Neuropathol,* Vol. 120, No. 5, (Nov), 585-592, ISBN 1432-0533

Taga, T., A. Suzuki, et al. (2002). alpha v-Integrin antagonist EMD 121974 induces apoptosis in brain tumor cells growing on vitronectin and tenascin. *Int J Cancer,* Vol. 98, No. 5, (Apr 10), 690-697, ISBN 0020-7136

Takano, T., J. H. Lin, et al. (2001). Glutamate release promotes growth of malignant gliomas. *Nat Med,* Vol. 7, No. 9, (Sep), 1010-1015, ISBN 1078-8956

Toedt, G., S. Barbus, et al. (2011). Molecular signatures classify astrocytic gliomas by IDH1 mutation status. *Int J Cancer,* Vol. 128, No. 5, (Mar 1), 1095-1103, ISBN 1097-0215

van den Bent, M. J., A. A. Brandes, et al. (2009). Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034. *J Clin Oncol,* Vol. 27, No. 8, (Mar 10), 1268-1274, ISBN 1527-7755

Van Meir, E. G., C. G. Hadjipanayis, et al. (2010). Exciting new advances in neuro-oncology: the avenue to a cure for malignant glioma. *CA Cancer J Clin,* Vol. 60, No. 3, (May-Jun), 166-193, ISBN 1542-4863

Vogelbaum, M. A., B. Berkey, et al. (2009). Phase II trial of preirradiation and concurrent temozolomide in patients with newly diagnosed anaplastic oligodendrogliomas and mixed anaplastic oligoastrocytomas: RTOG BR0131. *Neuro Oncol,* Vol. 11, No. 2, (Apr), 167-175, ISBN 1522-8517

Vredenburgh, J. (2010). Bevacizumab (BEV) in combination with temozolomide (TMZ) and radiation therapy (XRT) followed by BEV, TMZ, and irinotecan for newly diagnosed glioblastoma multiforme (GBM). ASCO Annual Meeting,28:15s, San Diego, California

Wedge, S. R., J. K. Porteous, et al. (1997). In vitro evaluation of temozolomide combined with X-irradiation. *Anticancer Drugs,* Vol. 8, No. 1, (Jan), 92-97, ISBN 0959-4973

Wen, P. Y. (June 2010). Phase II study of XL184 (BMS 907351), an inhibitor of MET, VEGFR2, and RET, in patients with progressive glioblastoma (GB). ASCO Annual Meeting,28:15s, San Diego, California

Wen, P. Y. (May 2009). Phase I/II study of sorafenib and temsirolimus for patients with recurrent glioblastoma (GBM) (NABTC 05-02). ASCO Annual Meeting,27:15s, Orlando, Florida

Wick, W., V. K. Puduvalli, et al. (2010). Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. *J Clin Oncol,* Vol. 28, No. 7, (Mar 1), 1168-1174, ISBN 1527-7755

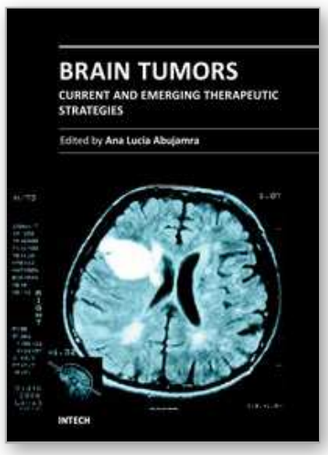
Wiencke, J. K., S. Zheng, et al. (2007). Methylation of the PTEN promoter defines low-grade gliomas and secondary glioblastoma. *Neuro Oncol,* Vol. 9, No. 3, (Jul), 271-279, ISBN 1522-8517

Yan, H., D. W. Parsons, et al. (2009). IDH1 and IDH2 mutations in gliomas. *N Engl J Med,* Vol. 360, No. 8, (Feb 19), 765-773, ISBN 1533-4406

Ye, Z. C., J. D. Rothstein, et al. (1999). Compromised glutamate transport in human glioma cells: reduction-mislocalization of sodium-dependent glutamate transporters and enhanced activity of cystine-glutamate exchange. *J Neurosci,* Vol. 19, No. 24, (Dec 15), 10767-10777, ISBN 1529-2401

Yen, K. E., M. A. Bittinger, et al. (2010). Cancer-associated IDH mutations: biomarker and therapeutic opportunities. *Oncogene,* Vol. 29, No. 49, (Dec 9), 6409-6417, ISBN 1476-5594

Zoncu, R., A. Efeyan, et al. (2011). mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat Rev Mol Cell Biol,* Vol. 12, No. 1, (Jan), 21-35, ISBN 1471-0080



Brain Tumors - Current and Emerging Therapeutic Strategies
Edited by Dr. Ana Lucia Abujamra

ISBN 978-953-307-588-4
Hard cover, 422 pages
Publisher InTech
Published online 23, August, 2011
Published in print edition August, 2011

Brain Tumors: Current and Emerging Therapeutic Strategies focuses on tumor models, the molecular mechanisms involved in the pathogenesis of this disease, and on the new diagnostic and treatment strategies utilized to stage and treat this malignancy. A special section on immunotherapy and gene therapy provides the most up-to-date information on the pre-clinical and clinical advances of this therapeutic venue. Each chapter in Brain Tumors: Current and Emerging Therapeutic Strategies is authored by international experts with extensive experience in the areas covered.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen