Targeting Aberrant Signaling Pathways

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Malignant gliomas are the most common primary brain tumor found in adults [1]. Regretfully, prognosis for these tumors remains dismal despite aggressive treatment with surgical resection, radiation, and chemotherapy. Treatment of glioblastoma patients with the current standard of care consisting of maximal resection, 6 weeks of concurrent chemoradiation with daily temozolomide followed by 6–12 cycles of adjuvant temozolomide, results in a median overall survival of only approximately 16 months [2]. Malignant gliomas have proven to be among the most difficult cancers to treat due to their genetic heterogeneity, elaborate overlapping signaling pathways, and difficulties in delivering drugs across the blood–brain barrier [3]. Recent in-depth description of the distinct molecular and genetic alterations in glioblastomas, using advanced sequencing technologies and large-scale gene expression studies, has inspired interest in the development of targeted therapies. Targeted therapies work by the inhibition of the deregulated cell signaling pathways in cancer cells by small molecules or antibodies, whereas traditional cytotoxic chemotherapies operate by impeding DNA synthesis or cell metabolism. This chapter will explore these aberrant signaling pathways in malignant gliomas and the results of the clinical trials of therapeutics targeting them.

The Cancer Genome Atlas

The Cancer Genome Atlas (TCGA), a collaboration between the National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI), was undertaken to generate comprehensive, multidimensional maps of the major genomic changes in several types of cancer. One of the first cancers studied by the TCGA was glioblastoma, and the analysis characterized a decidedly interrelated network of aberrations. It identified three key pathways: the retinoblastoma (RB) and p53 tumor suppressor pathways, and the receptor tyrosine kinases (RTKs) signaling pathway [4]. For glioblastoma patients with sequencing data, the frequencies of somatic alterations were 78, 87, and 88%, respectively, in each of these pathways (Fig. 9.1). Of further note, 74% of glioblastoma samples contained abnormalities in all three pathways [4].

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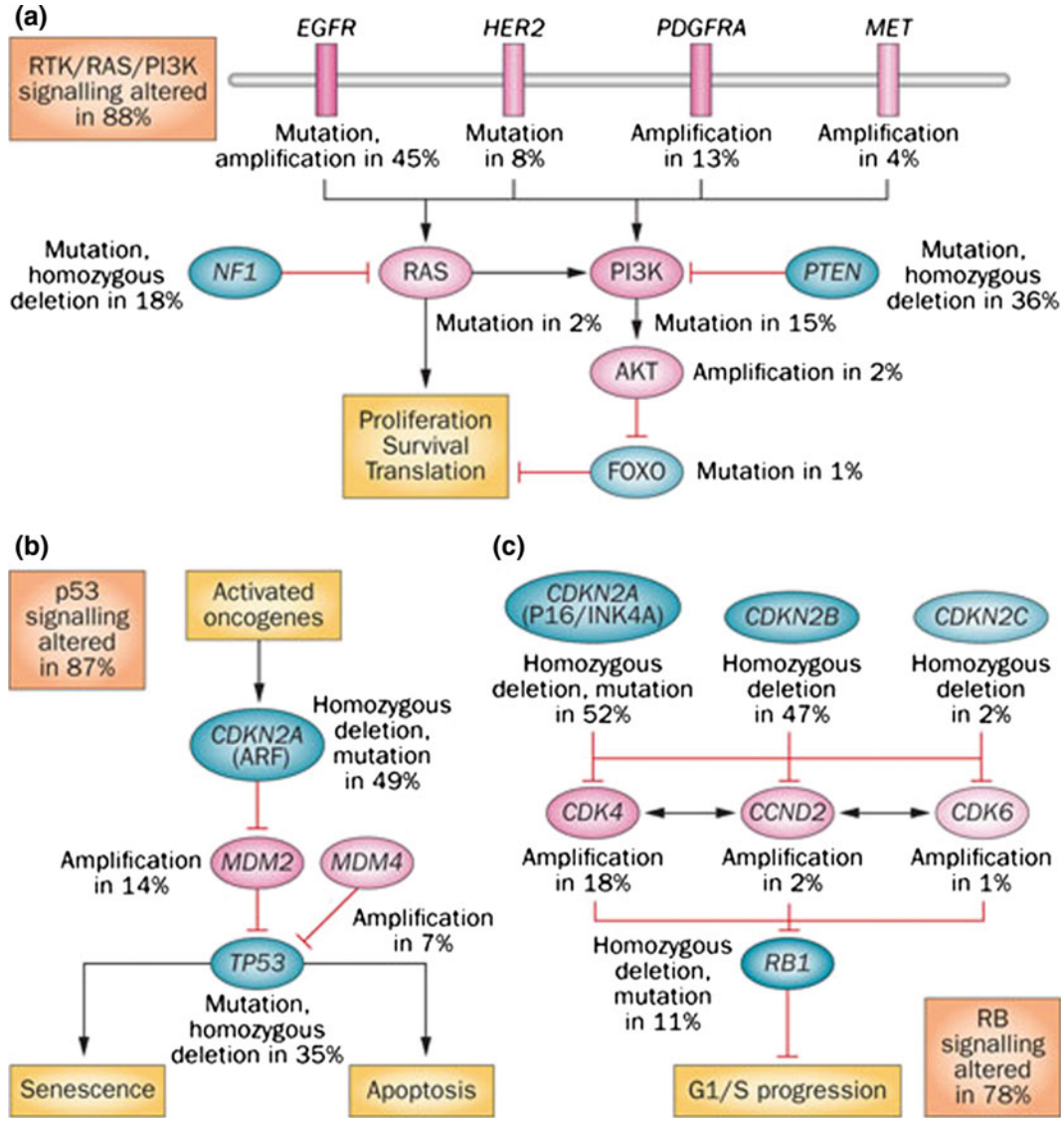

Fig. 9.1 Critical signaling pathways altered in malignant gliomas. Primary sequence alterations and significant copy number changes for the components of the **a** | RTK/RAS/PI3K, **b** | p53, and **c** | Rb signaling pathways are shown. *Red* indicates activating genetic alterations. Conversely, *blue* indicates inactivating alterations. For each altered component of a particular pathway, the nature of the alteration and the percentage of tumors affected are indicated. *Boxes* contain the final percentages of glioblastomas with alterations in at least one known component gene of the designated pathway. Abbreviation: *RTK* receptor tyrosine kinase

Retinoblastoma Tumor Suppressor Pathway

The RB protein is a tumor suppressor protein that is dysfunctional in several cancer types [5]. It is encoded by the RB gene, which is located at chromosome 13q14.1-q14.2. Normally, the RB protein prevents unwarranted cell growth by inhibiting cell cycle progression until a cell is set to undergo mitosis. When ready for cell division, the RB protein is then phosphorylated by cyclin D, cyclin-dependent kinase 4 (CDK4), and cyclin-dependent kinase 6 (CDK6) inactivating

the protein and allowing for cell cycle progression [5]. Most commonly, homozygous deletion of cyclin-dependent kinase inhibitor 2A (CDKN2A) can produce loss of p16INK4a and a suppressor of CDK4, leading to dysregulation of RB signaling [5–7]. Mutations in retinoblastoma protein 1 (RB1) and CDK4 amplification can also trigger dysfunction of the RB signaling pathway. A CDK4 inhibitor, PD-0332991 (palbociclib isethionate), has been examined in two phase I trials leading to a phase II trial in recurrent RB-positive glioblastoma with results not yet reported [8–10].

p53 Tumor Suppressor Pathway

The tumor protein p53 (p53) gene is the most frequently mutated gene in human cancer and performs a critical function in preventing cancer formation [11]. It is located at chromosome 17p13.1 and reacts to DNA injury and toxic pressures by producing cell cycle arrest and apoptosis [12, 13]. Loss of p53 pathway function can be due to p53 mutation/deletion itself or by interferences in other genes that regulate p53 function such as murine double minute (MDM2/4) and the tumor suppressor protein alternate reading frame (ARF) [14–16].

The use of an intratumoral injection of a p53-containing adenovirus vector to increase wild-type p53 expression in tumor cells has been attempted in a phase 1 study in recurrent glioma, but it did not appear to achieve systemic viral dissemination [17]. Phase I trials of wild-type Ad5CMV-p53 gene therapy and recombinant adenovirus p53 (SCH-58500) in combination with surgery in recurrent malignant gliomas have been completed, but the results have yet to be published [18, 19].

SGT-53 is a nanocomplex of cationic liposome encapsulating a normal human wild-type p53 DNA sequence in a plasmid backbone exhibited to supply the p53 cDNA to the tumor cells with the goal of the p53 cDNA sequence to restore wild-type p53 function in the apoptotic pathway [20]. SGT-53 has shown to prolong survival in a mouse model and is currently undergoing investigation in a phase II trial in recurrent glioblastoma [20, 21]. An MDM2 inhibitor, JNJ-26854165, was examined in a phase I study in refractory solid tumors but has yet to be examined in brain tumor patients exclusively [22, 23]. MK-1775, a Wee1 kinase inhibitor, has been shown to radiosensitize p53-defective human tumor cells and is currently under investigation in a multicenter phase I trial in newly diagnosed or recurrent glioblastoma [24, 25].

Receptor Tyrosine Kinase Signaling Pathway

Receptor tyrosine kinases (RTKs) are high-affinity cell surface receptors and primary mediators of signal transduction events shown to have an essential function in the growth and progression of many cancers [26]. Twenty different RTK classes have been identified, and members of this family include the vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and hepatocyte growth factor receptor (MET). The receptor tyrosine kinase signaling pathway has been the most extensively studied pathway in malignant gliomas to date (Table 9.1).

Vascular Endothelial Growth Factor Receptor (VEGFR)

Vascular endothelial growth factor (VEGF) is a significant component implicated in the formation of new blood vessels which is a distinguishing feature of glioblastoma [27]. VEGF binding to its receptors VEGFR-1 and VEGFR-2 leads to phosphorylation of tyrosine kinase and initiation of downstream signaling pathways including phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (Akt/PBK) and Ras/mitogen-activated protein kinases (MAPK) [28].

Bevacizumab, a monoclonal antibody that targets the VEGF-A ligand, was granted

Table 9.1 Targeted therapies for malignant gliomas in published clinical trials

Therapy	Pathway	Target/s
Bevacizumab	RTK	VEGF-A [30–37]
Cediranib	RTK	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/β, FGFR-1, c-Kit [38, 39]
Pazopanib	RTK	VEGFR, c-Kit, FGFR, and PDGFR [40, 41]
Sorafenib	RTK	VEGFR-2, Raf, PDGFR, c-Kit, Flt-3 [42–46]
Nintedanib	RTK	VEGFR 1-3, FGFR 1-3, PDGFR-α/β [47]
Vandetanib	RTK	VEFGR-2, EGFR [48, 49]
Sunitinib	RTK	VEGFR2, PDGFR-α, and c-Kit [50–53]
Aflibercept	RTK	VEGF and PlGF [54]
Vatalanib	RTK	VEGFR, PDGFR, and c-Kit [55–57]
Cabozantinib	RTK	VEGFR-2, MET, and RET [58]
Gefitinib	RTK	EGFR [64–69]
Erlotinib	RTK	EGFR [45, 70–80]
Cetuximab	RTK	EGFR [81, 82]
Lapatinib	RTK	EGFR and HER2 [83–85]
AEE-788	RTK	EGFR, HER2, and VEGFR2 [86]
Nimotuzumab	RTK	EGFR [92]
Imatinib	RTK	PDGFR, Bcr-Abl, and c-Kit [56, 100–105]
Dasatinib	RTK	PDGFR, Src, Bcr-Abl, c-Kit, and EphA2 [106]
PX-866	RTK	PI3K [118]
Enzastaurin	RTK	protein kinase C, PI3K, and Akt [125–128]
Everolimus	RTK	mTOR [135–137]
Temsirolimus	RTK	mTOR [46, 138–140]
Sirolimus	RTK	mTOR [49, 68, 79, 80]
Tipifarnib	RTK	Ras [151, 152]
Lonafarnib	RTK	Ras [155, 156]

Abbreviations: *RTK* receptor tyrosine kinase, *VEGF* vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor, *PDGFR* platelet-derived growth factor receptor, *FGFR* fibroblast growth factor receptor, *FLT3* Fms-like tyrosine kinase-3, *EGFR* epidermal growth factor receptor, *PlGF* placental growth factor receptor, *MET* hepatocyte growth factor receptor, *HER2* human epidermal growth factor receptor 2, *EphA2* ephrin type-A receptor 2, *PI3K* phosphatidylinositide 3-kinases, *mTOR* mammalian target of rapamycin

accelerated approval by the Food and Drug Administration for use as a single agent in recurrent glioblastoma in 2009 [29]. Approval was granted based on the results of two phase II clinical trials that demonstrated durable objective imaging responses based on independent radiologic review with stable or decreasing corticosteroid use [29–31]. Subsequently, two phase III clinical trials (RTOG 0825 and AVAglio) were performed examining the addition of bevacizumab or placebo to the current standard of care regimen of concurrent chemoradiation with temozolomide followed by adjuvant temozolomide in newly diagnosed glioblastoma [32, 33]. Both studies found that the addition of bevacizumab improved progression-free but not overall survival [32, 33]. While the addition of irinotecan to bevacizumab was not beneficial in the early studies of bevacizumab, a subsequent phase II study appeared to suggest that the combination of lomustine and bevacizumab may prolong overall survival compared to either treatment administered alone [30, 31, 34]. Disappointingly, the preliminary report of the results

of an EORTC phase III study comparing lomustine alone versus lomustine and bevacizumab in reccurent glioblastoma failed to demonstrate an improvement in overall survival with the combination treatment [35]. Phase II trials of recurrent glioblastoma examining the addition of fotemustine or carboplatin to bevacizumab also did not demonstrate any increased survival benefit with the addition of these cytotoxic therapies [36, 37]. Despite the improvement in progression-free survival and increased imaging response rate, bevacizumab has yet to improve overall survival in either the upfront or recurrent setting.

Other VEGF inhibitors have failed to even match the limited success of bevacizumab. Cediranib, an oral pan-VEGF receptor tyrosine kinase inhibitor, demonstrated a 6-month progression-free survival of 25.8% and partial radiographic responses in 56.7% of patients in a phase II study of patients with recurrent glioblastoma [38]. However, a phase III randomized trial in recurrent glioblastoma comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone failed to show any improvement with cediranib either as monotherapy or in combination with lomustine versus lomustine alone [39]. Pazopanib, a multikinase inhibitor of c-Kit, FGFR, PDGFR, and VEGFR, also did not show any prolongation of progression-free survival in a phase II study in recurrent glioblastoma [40]. A subsequent phase I/II examining pazopanib in combination with lapatinib (an EGFR inhibitor) in relapsed malignant glioma patients had limited antitumor activity leading to early termination of the study [41]. Sorafenib, an oral VEGFR-2, Raf, PDGFR, c-Kit, and Flt-3 inhibitor, was used in combination with temozolomide for initial adjuvant therapy in a phase II study for patients with glioblastoma but failed to improve the efficacy when compared to historical controls [42]. Additionally, sorafenib has been examined in several other phase II studies in recurrent glioblastoma in combination with temozolomide, bevacizumab, erlotinib, and temsirolimus of which no combination resulted in a prolongation of survival [43–46]. Nintedanib, an inhibitor that targets VEGFR 1-3, FGFR 1-3, and PDGFR-α/β, was studied in a phase II study that was terminated early following a preplanned futility analysis [47]. Vandetanib, an inhibitor of VEFGR-2 and EGFR, failed to display any significant activity in a phase I/II trial of patients with recurrent malignant glioma [48]. In addition, a phase I/II study of vandetanib plus sirolimus (an mTor inhibitor) in adults with recurrent glioblastoma failed to display benefit when compared to historical controls [49]. Sunitinib, an inhibitor of VEGFR-2, PDGFR-α, and KIT, similarly did not show any improvement in survival either as a monotherapy or in combination with irinotecan in phase I or phase II studies in recurrent glioma [50–53]. An inhibitor of VEGF and placental growth factor, aflibercept, also had minimal evidence of single-agent activity in unselected patients with recurrent malignant glioma [54]. Vatalanib, an inhibitor of VEGFR, PDGFR, and c-Kit, was examined alone in newly diagnosed glioblastoma patients and with imatinib and hydroxyurea at time of tumor recurrence in two phase I studies [55, 56]. However, a planned randomized phase II trial was terminated at its initiation (after completion of its phase I component) because of industry decision [57]. Cabozantinib, an inhibitor of VEGFR-2, MET, and RET, was used in a phase II study whose final results are yet to be published [58].

Epidermal Growth Factor Receptor (EGFR)

The epidermal growth factor receptor is located on chromosome 7p12 and is a member of the ErbB family of receptor tyrosine kinases [59]. Overexpression of EGFR is one of the most common signaling mutations in GBM and is thought to occur in around 50% of glioblastomas [60]. Glioblastomas with EGFR overexpression have been demonstrated to potentially be more radioresistant [61]. Additionally, EGFR amplification is often associated with the expression of a constitutively active, ligand-independent mutant form of the receptor called EGFRvIII generated by an in-frame deletion of exons 2–7 [61, 62].

EGFRvIII expression may be an independent prognostic factor for poor survival [63].

Unfortunately, EGFR inhibitors in malignant glioma trials have likewise been disappointing. Gefitinib, an EGFR inhibitor approved to treat non-small-cell lung cancer in 2003, failed to show any benefit when added to the treatment in newly diagnosed glioblastoma patients [64, 65]. Additionally, gefitinib in the treatment of recurrent disease has shown minimal activity alone or in combination with mammalian target of rapamycin (mTOR) inhibitors such as sirolimus or everolimus [66–69]. Another EGFR inhibitor, Erlotinib, also has shown minimal efficacy against newly diagnosed or recurrent glioblastoma [70–76]. Furthermore, several phase II studies in recurrent glioblastoma examining the combination of erlotinib with carboplatin, sorafenib, bevacizumab, or sirolimus have failed to demonstrate significant antitumor activity [45, 77–80]. Cetuximab, another EGFR inhibitor used for the treatment of metastatic colorectal cancer, metastatic non-small-cell lung cancer, and head and neck cancer, regrettably has failed to show benefit in recurrent glioblastoma when used alone or in combination with bevacizumab and irinotecan [81, 82]. Lapatinib, the first dual inhibitor of EGFR and human epidermal growth factor receptor 2 (HER2) tyrosine kinases, also did not show significant activity in recurrent glioblastoma patients [83]. Additionally, lapatinib was studied in a phase I study with temodar and a phase I/II study with pazopanib in recurrent malignant gliomas [84, 85]. The phase II study of lapatinib and pazopanib revealed limited antitumor activity of this combination leading to early study termination [84]. AEE788, another inhibitor of EGFR, HER2, and VEGFR2, was associated with unacceptable toxicity and minimal activity for the treatment of recurrent glioblastoma in a phase I trial [86].

Afatinib, an irreversible covalent inhibitor of the EGFR and HER2, is approved for first-line treatment of patients with EGFR mutation-positive non-small-cell lung carcinoma [87]. Afatinib is currently under investigation in a phase I/II trial in recurrent malignant glioma. Additionally, a phase I trial of afatinib in newly diagnosed glioblastoma patients with radiotherapy alone in patients with an unmethylated MGMT promotor or radiotherapy and temozolomide in patients with a methylated MGMT promotor is ongoing [88, 89]. Dacomitinib is another selective and irreversible inhibitor of EGFR studied in two phase II trials in recurrent glioblastoma with one of the trials limited to only patients with EGFR gene amplification and/or EGFRvIII mutation [90, 91]. Another EGFR inhibitor, nimotuzumab, has received orphan drug status in the USA and EU for glioma. A phase I/II trial in high-grade glioma with nimotuzumab showed an excellent safety profile and significant survival benefit in combination with irradiation, but unfortunately, a subsequent phase III trial of nimotuzumab in newly diagnosed glioblastoma was negative [92, 93].

Platelet-Derived Growth Factor Receptor (PDGFR)

Platelet-derived growth factor receptors (PDGFRs) are cell surface receptors for members of the PDGF family and signal through the alpha and beta PDGF receptor tyrosine kinases [94]. The PDGFR alpha (PDGFRA) gene is located on chromosome *7p22* and amplified in approximately 13% of glioblastomas [4, 95]. PDGFRA can be overexpressed, amplified, mutated, or truncated in gliomas, with *PDGFRA* point mutations being observed exclusively in glioblastomas [96].

Imatinib mesylate is an inhibitor of the PDGFR, Bcr-Abl, and c-Kit tyrosine kinases that have been found to beneficial in the treatment of chronic myelogenous leukemia b and in gastrointestinal stromal tumors [97–99]. However, imatinib alone displayed only minimal activity in recurrent malignant gliomas and in newly diagnosed glioblastoma [100, 101]. Subsequent studies looking at imatinib with the addition of hydroxyurea in recurrent malignant gliomas also failed to show clinically meaningful antitumor activity [102–105]. As discussed previously, imatinib with hydroxyurea was also examined in combination with vatalanib [56].

Dasatinib, an inhibitor of PDGFR, Src, Bcr-Abl, c-Kit, and EphA2 receptors, was studied in a phase 2 trial in target-selected patients (activation or overexpression of ≥2 putative dasatinib targets) with recurrent glioblastoma and was found ineffective with no radiographic responses [106]. Additional, phase II studies with dasatinib in combination with bevacizumab in recurrent glioblastoma and in newly diagnosed glioblastoma with chemoradiation have not yet reported results [107, 108]. A phase I multicenter trial of dasatinib in combination with CCNU was found to have substantial hematological toxicities leading to suboptimal exposure to both agents [109]. Another phase I study of dasatinib in combination with erlotinib was better tolerated [110].

Furthermore, Tandutinib, a small molecule inhibitor of PDGFR, fms-like tyrosine kinase receptor-3 (FLT3), and c-Kit, has been examined alone or with bevacizumab in recurrent glioblastoma with results awaiting publication [111, 112].

PI3K/AKT/mTOR Pathway

Along with targeting cell surface receptors, there has been a significant effort undertaken on inhibiting downstream survival signaling pathways stimulated by these receptors. The PI3K/Akt/mTOR pathway can be crucial in controlling cellular functions regulating cellular proliferation, apoptosis, cell invasion, and mobility. Activation of phosphatidylinositide 3-kinase (PI3K) complex is regulated by several growth factors in conjunction with their receptors, the most frequent of which is the amplification of EGFR [113, 114]. PI3K activation phosphorylates and activates Akt (protein kinase B) a serine/threonine-specific protein kinase [115]. Akt next activates mTOR (mammalian target of rapamycin), another serine/threonine protein kinase that controls cell growth and proliferation via the regulation of protein synthesis and transcription [116]. It is comprised of two parts, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), operating as both a downstream effector and upstream regulator of PI3K [117].

PX-866, an oral PI3K inhibitor, in a recent phase II study had a low overall response rate and failed to improve progression-free survival in patients with recurrent glioblastoma [118]. BKM-120, another oral inhibitor of PI3 kinase, is currently under investigation in combination with standard of care for newly diagnosed glioblastoma and as monotherapy in recurrent glioblastoma [119, 120]. Additionally, a phase II study in recurrent glioblastoma examining the combination of BKM-120 and bevacizumab is underway [121]. XL-147 (a potent inhibitor of PI3K) and XL-765 (a dual PI3K and mTOR inhibitor) are currently being investigated as monotherapy in recurrent glioblastoma [122]. XL-765 has also been studied in combination with temozolomide in malignant glioma patients with no results published yet [123]. Pictilisib (a potent inhibitor of PI3K) and BEZ235 (a dual ATP-competitive PI3K and mTOR inhibitor) are also currently undergoing investigation in a phase II study of recurrent glioblastoma [124].

Enzastaurin is a protein kinase C and phosphoinositide-3 kinase/Akt inhibitor that failed to improve survival in newly diagnosed patients with and without O(6)-methylguanine-DNA-methyltransferase (MGMT) promotor methylation in combination with standard of care and as a monotherapy in recurrent glioblastoma [125–128]. Perifosine, an Akt inhibitor and a PI3K inhibitor, is currently being examined in recurrent malignant gliomas alone or in combination with temsirolimus [129, 130]. Ipatasertib, a highly selective pan-Akt inhibitor targeting Akt1/2/3, is also present in a phase II study of recurrent glioblastoma [131]. Nelfinavir, a protease inhibitor interfering with Akt activity, has been given neo-adjuvantly and concomitant to chemoradiotherapy with temozolomide in a phase I/II study of patients with newly diagnosed glioblastoma [132].

Several mTOR inhibitors have been developed over the past few years. mTOR is inhibited by these agents forming a complex with FK-binding protein-12 (FKBP-12) which joins to mTOR, blocking its stimulation and constraining

tumor cell proliferation [133]. Everolimus, an mTOR inhibitor, has been shown to cause a marked reduction in the volume of subependymal giant cell astrocytomas and seizure frequency in patients with tuberous sclerosis [134]. Unfortunately, everolimus has not displayed durable responses as a monotherapy or when combined with gefitinib in patients with recurrent glioblastoma [69, 135]. Moreover, the addition of everolimus to standard of care in newly diagnosed glioblastoma patients did not translate into an appreciable survival benefit [136]. Furthermore, a phase II study in newly diagnosed glioblastoma patient of concurrent radiation therapy, temozolomide, and bevacizumab followed by bevacizumab/everolimus as first-line treatment failed to improve survival compared to historical controls [137].

Temsirolimus, an mTOR inhibitor approved for the treatment of renal cell carcinoma, likewise has shown limited benefit in recurrent glioblastoma as a monotherapy or in combination with sorafenib [46, 138, 139]. When temsirolimus was used in a phase I study in addition to standard of care in newly diagnosed glioblastoma, an increased risk of infection was noted [140].

Rapamycin (sirolimus), another mTOR inhibitor, has also failed to show benefit in recurrent glioblastoma when used in combination with vandetanib, erlotinib, or gefitinib as discussed earlier [49, 68, 79, 80]. Additionally, a phase II trial of rapamycin in combination with bevacizumab in recurrent glioblastoma patients was stopped early due to lack of response [141].

New mTOR-specific inhibitors are in development which can block activity of both mTOR complexes. AZD8055, one of these dual mTORC1/mTORC2 inhibitors, is currently in a phase I trial in adults with recurrent gliomas [142].

The PTEN (phosphatase and tensin homologue) gene, located on chromosome 10, is a tumor suppressor gene that negatively controls the PI3K/AKT/PKB pathway by preventing Akt signaling via the reduction of intracellular levels of phosphatidylinositol-3,4,5-triphosphate [143]. PTEN mutations have been reported in up to 40% of glioblastoma [4, 144]. In addition to inhibiting the Akt pathway, PTEN has also demonstrated the ability to enable the degradation of activated EGFR leading to the extinction of EGFR signaling [145]. Instigating expression of functional PTEN has been suggested as a potential future therapeutic approach in glioblastoma.

RAS/MAPK Pathway

The RAS/MAPK is another downstream survival signaling pathway stimulated by RTKs such as EGFR and PDGFR. Ras (rat sarcoma) gene mutations are present in a diverse group of tumor types with varying incidence [146]. Mutations in one of the three Ras genes (H-Ras, N-Ras, or K-Ras) in humans transform these genes to operating oncogenes [147]. Ras proteins have critical functions in regulating the activity of vital signaling pathways that control normal cellular proliferation. Activation and deactivation of Ras are regulated by cycling between its binding with the active guanosine triphosphate (GTP) and inactive guanosine diphosphate (GDP) forms [148]. Activated Ras results in activation of a serine/threonine kinase named Raf (rapidly accelerated fibrosarcoma). Raf subsequently phosphorylates and activates a kinase enzyme MEK (mitogen/extracellular signal-regulated Kinase) which in turn then phosphorylates and activates MAPK (mitogen-activated protein kinases).

Ras gene mutations have been found to only rarely occur in glioblastoma [4]. However, activation of Ras can occur by mechanisms that do not involve mutations in Ras. The neurofibromin 1 (NF-1) gene located on chromosomal segment 17q11.2 is a negative regulator of Ras, and loss of NF-1 may activate Ras [149]. NF-1 mutations have been reported in up to 18% of patients with glioblastoma [4].

Ras is posttranscriptionally modified by farnesyltransferase, and in vitro studies of glioblastoma with farnesyltransferase inhibitors have shown reduced cellular proliferation as well as the ability to trigger cell cycle arrest and induce apoptosis [150]. Tipifarnib is a potent and

selective inhibitor of farnesyltransferase that has been examined in a phase I trial in newly diagnosed glioblastoma plus radiation therapy with and without temozolomide [151]. Unfortunately, a phase II trial of tipifarnib as a treatment for recurrent malignant glioma did not show benefit in 6-month progression-free survival compared to historical controls [152]. Lonafarnib, another farnesyltransferase inhibitor, has shown the ability to inhibit cell growth in preclinical studies [153, 154]. Two phase I studies have examined lonafarnib in combination with temozolomide, with one study in patients with malignant glioma after radiation and the other in patients with recurrent glioblastoma [155, 156].

Gene Expression-Based Molecular Classification of GBM into Subtypes

Following The Cancer Genome Atlas Network cataloging recurrent genomic abnormalities in glioblastoma, they subsequently defined four subtypes of glioblastoma (proneural, neural, classical, and mesenchymal) based on gene expression-based molecular classification [157]. Additionally, alterations and gene expression of *EGFR*, *NF1*, and *PDGFRA/IDH1* were found to distinctly delineate the classical, mesenchymal, and proneural subtypes, respectively [157]. These discoveries support the supposition that certain molecular-targeted therapies may potentially be most effective against a segment of glioblastomas. Results from a retrospective analysis of AVAglio (a randomized, placebo-controlled phase III trial examining the addition of bevacizumab to radiotherapy plus temozolomide in newly diagnosed glioblastoma) suggest that patients with IDH1 wild-type proneural glioblastoma may derive an overall survival benefit from first-line bevacizumab treatment [158]. This finding, however, still remains to be independently validated in future studies.

Furthermore, the classification of glioblastoma into unique subtypes based on genomic expression implies that there is a propensity for particular aberrations to group together. This theoretically could enable particular combinations of molecularly targeted agents to be more successful in certain subtypes.

Discussion

Large-scale gene expression studies have recently provided an in-depth description of the distinct molecular and genetic alterations in glioblastomas. This scientific progress has spurred an interest in the development of targeted therapies for these signaling pathways. Unfortunately, despite trying several agents and different pathways, targeted therapies have currently failed to improve the overall survival of glioblastoma patients. New therapies examining novel targets and innovative combinations are presently under investigation (Table 9.2).

Several possible explanations have been proposed on why early clinical results of molecularly targeted agents in malignant glioma have been so disappointing. These include the significant intratumoral heterogeneity, overlapping/redundant signaling pathways, use of molecular data from initial tumor resection as entry criteria in trials of recurrent disease, poor drug delivery to the brain, and unclear pharmacodynamic effects of drugs on tumor tissue.

Tumor heterogeneity poses a significant challenge with glioblastoma being renowned for its intratumoral heterogeneity. Due to the heterogenous nature of these tumors, it is possible that we may be inhibiting a distinct group of cells susceptible to that specific targeted pathway yet still permitting the proliferation of another group of cells whose development is independent of that pathway. A recent study has demonstrated that glioblastoma subtype classifiers can variably be expressed even across individual cells within a tumor [159].

Additionally, these tumors appear to have the intrinsic ability to respond to the inhibition of one pathway by upregulating another different pathway making a single agent unsuccessful in stopping tumor progression. For example, the use of EGFR inhibitors has demonstrated the lack of ability to change downstream targets like Akt and may even upregulate the activity of the

Table 9.2 Targeted therapy for malignant gliomas in ongoing clinical trials or trails with results not yet published

Therapy	Pathway	Target/s
PD-0332991	RB	CDK4 [10]
Ad5CMV-p53	P53	p53 [18]
Adenovirus p53 (SCH-58500)	P53	p53 [19]
SGT-53	P53	p53 [21]
MK-1775	P53	Wee1 [25]
Afatanib	RTK	EGFR and HER2 [88, 89]
Dacomitinib	RTK	EGFR [90, 91]
Dasatinib	RTK	PDGFR, Src, Bcr-Abl, c-Kit, and EphA2 [107, 108]
Tandutinib	RTK	PDGFR, FLT3, and c-Kit [111, 112]
BKM-120	RTK	PI3K [119–121]
XL-147	RTK	PI3K [122]
XL-765	RTK	PI3K and mTOR [122, 124]
Pictilisib	RTK	PI3K [124]
BEZ235	RTK	PI3K and mTOR [122, 124]
Perifosine	RTK	Akt and PI3K [129, 130]
Ipatasertib	RTK	Akt [124]
Nelfinavir	RTK	Akt [132]
AZD8055	RTK	mTORC1/mTORC2 [142]

Abbreviations: *RB* retinoblastoma, *P53* tumor protein p53, *RTK* receptor tyrosine kinase, *CDK4* cyclin-dependent kinase 4, *EGFR* epidermal growth factor receptor, *HER2* human epidermal growth factor receptor 2, *PDGFR* platelet-derived growth factor receptor, *EphA2* ephrin type-A receptor 2, *FLT3* Fms-like tyrosine kinase-3, *PI3K* phosphatidylinositide 3-kinases, *mTOR* mammalian target of rapamycin

PI3K/Akt pathway [160, 161]. Moreover, many of the mutations that we are currently targeting may be essential only for the early development of the tumor and subsequently are superseded by secondary pathways of tumor growth.

Another potential reason for the lack of success with these agents may be that entry into targeted therapy trials for recurrent disease is often based upon molecular characteristics from initial resection due to surgical resections at tumor recurrence not being routinely performed. However, it is possible that these targeted mutations may be altered at time of recurrence compared to initial diagnosis. A recent study in glioblastoma found that of the tumors expressing EGFRvIII at initial diagnosis, approximately one-half loses their EGFRvIII expression at tumor recurrence [162].

Additionally, with surgery at tumor recurrence being difficult, it is often challenging to determine how well the drugs are crossing the blood–brain barrier. Furthermore, even if the agent crosses into the brain, it is often uncertain whether the drug is inhibiting its intended target and having its envisioned effect without pathological confirmation.

Numerous ways to improve the success of targeted therapies in malignant glioma have been propositioned and are currently underway. These include the creation of more advanced preclinical animal models, development of more potent inhibitors that can affect multiple pathways, trials with a combination of drugs designed uniquely for each individual, identification of predictive molecular biomarkers, and novel adaptive trial designs.

Despite the discouraging results to date and the above challenges, the use of targeted therapies remains a promising approach that continues to be explored in malignant glioma and will

hopefully someday prove more beneficial for this patient population in desperate need of more effective treatments.

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