Malignant gliomas (MGs), including glioblastomas (GBMs) and anaplastic astrocytomas (AAs), are the most common primary brain tumors (1). The prognosis for patients diagnosed with MG remains poor, with a median survival time of up to 3 years (2,3). Current conventional treatment protocols include maximally safe surgical resection followed by fractioned radiation therapy of the tumor and surrounding brain parenchyma and systemic chemotherapy with alkylating compounds. The efficacy of alkylating compounds, however, such as nitrosoureas or temozolamide, is fairly limited by the epigenetic inactivation of the DNA repair enzyme methylguanine methyltransferase (MGMT). Other DNA repair pathways, such as the DNA mismatch repair and the base excision repair pathways, have also been proposed as significant mechanisms of resistance to alkylating agents (4).

In this review, developments in molecularly targeted therapies for MGs are critically evaluated, and advances in the molecular and genetic pathogenesis of these lethal brain malignancies are also discussed.

MOLECULAR PATHOGENESIS OF GLIOMAS

The biological features of MGs consist of high resistance to apoptosis and florid necrosis (5). Briefly, common molecular, genetic, and epigenetic alterations in primary GBMs include amplification of the epidermal growth factor receptor (EGFR), deletion or mutation of homozygous cyclin-dependent kinase (CDK) inhibitor p16INK4A (CDKN2A), and alterations in tumor suppressor phosphatase and tensin homolog (PTEN) on chromosome 10 (6). Primary and secondary GBMs share similar characteristics, and few molecular and genetic alterations make them distinguishable from one another. For instance, human double-minute 2 (HDM2) and p53 mutations are often observed to be amplified in secondary GBMs (7).

In regard to AAs, inactivating mutations of tumor-suppressor gene TP53 and elevated expression of platelet-derived growth factor (PDGF) ligands and receptors are commonly observed in grade III AAs (8). Loss of heterozygosity in chromosome 10q has also been detected in primary high-grade AAs, and the inactivation of PTEN is observed in approximately 40% of AAs that have lost chromosome 10q (9).

Mutations in p16 are also involved, because hypermethylation in the promoter region of p16 has been detected in several cases of MGs, thus silencing p16 expression and possibly contributing to tumor genesis (10). Additionally, Bcl2-like 12 (Bcl2L12) interacts with and neutralizes caspase-7; and increased Bcl2L12 expression inhibits apoptosis (11). The astrocyte elevated gene-1 (AEG-1) has also been implicated in the pathogenetic hallmark of MGs (12). AEG-1 is overexpressed in the majority of human MG samples, and cooperates with the Ha-ras.
family of retrovirus-associated DNA sequences (RAS) to promote cellular transformation and subsequently to augment invasion and growth of transformed cells (8,9). Furthermore, oncogenic Ha-ras induces AEG-1 expression by modulating the phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathway, thus contributing to the growth of MGs (13).

MOLECULARLY TARGETED THERAPY

Elevated expression or mutation of receptors and intracellular downstream effectors has been observed in MGs (14). These pathways are regulated by several growth factors linked to tyrosine kinase, such as the EGFR, insulin-like growth factor receptor (IGFR), PDGF receptor (PDGFR), and vascular EGF receptor (VEGFR). Specific targeting of these signaling pathways that lead to uncontrolled cellular proliferation and cell migration and invasion could provide new molecularly targeted treatment options for MGs. The growth factor signaling pathways and their inhibition in MGs are shown in Figure 1 (14), and Table 1 summarizes the major clinical trials of molecularly targeted therapies in MGs.

EGFRs

The EGFR belongs to the ErbB family of tyrosine kinase receptors. The presence of EGFRvIII, a specific variant of the EGFR lacking exons 2 to 7, is an independent predictor of poor survival in patients with primary MGs (15). Treatment options that target EGFRs include gefitinib (ZD-1839) and erlotinib (OSI-774). However, efficacy of these agents is modest.

Gefitinib was evaluated in an open-label, single-center phase II clinical trial in patients (n = 57) with the first recurrence of a GBM (16). Each patient initially received 500 mg of gefitinib (orally, once a day), and the dose was escalated up to 1000 mg in patients receiving enzyme-inducing antiepileptic drugs or dexamethasone. Quantification of gefitinib antigenemia efficacy was assessed by 6-month progression-free survival (PFS-6) and brain magnetic resonance imaging (MRI) quantification of tumor response (radiographic response). The study population had a PFS-6 of 13% (7 of 53 patients) and a median overall survival (OS) time from treatment initiation of 39.4 weeks, but no radiographic response was observed (16). In a multi-center, open-label, single-arm phase II clinical trial of gefitinib in patients (n = 28) with recurrent MG after surgery plus radiotherapy and first-line chemotherapy, overall median time to progression (TTP) was 8.4 weeks, PFS-6 was 14.3%, and median OS was 24.6 weeks (17).

None of the patients presented objective radiographic response (17), and it was concluded that gefitinib demonstrated limited efficacy against GBM compared with the standard Stupp regimen (radiotherapy plus temozolomide; median PFS 6.9 months; PFS-6 53.9%, and median OS 58 weeks) (18).

In several phase I/II clinical trials, OS rates for erlotinib and gefitinib treatment were similar, but erlotinib was more effective than gefitinib treatment in terms of objective radiographic responses (19,20). A multicenter, open-label phase I clinical trial evaluated the efficacy of erlotinib plus radiation therapy in patients (n = 19) with GBM. With a median follow-up of 52 weeks, progression was assessed in 16 patients and 13 deaths occurred. Median TTP was 26 weeks and median OS was 55 weeks (19). Additionally, in an open-label phase I dose-escalation clinical trial, patients (n = 83) with stable or progressive malignant pri-
mary gliomas received erlotinib alone or combined with temozolomide (20). Of the patients assessed (n = 57), eight patients demonstrated a PR and six patients demonstrated a median PFS of greater than 6 months, which included four patients with a PR (20). Erlotinib treatment was equally as effective as the standard Stupp regimen (median OS 58 weeks; median PFS 6.9 months; 7 [11.3%] CRs and 17 [27.4%] PRs) (18). The favorable tolerability profile and evidence of antitumor activity suggest that additional evaluation of erlotinib treatment is warranted. However, it should also be noted that responders to drugs targeting EGFR usually have intact PTEN and EGFR-amplified GBM cells (23). Cetuximab, a human-murine chimeric anti-EGFR mAb, increased apoptosis in EGFR-amplified GBM cells (23). Cetuximab treatment alone or in combination with radiation therapy or chemotherapy was also assessed in vivo in female athymic nude mice 4 to 6 weeks old (23). Treated mice received cetuximab (0.5 mg, intraperitoneal injection twice weekly) for 5 wk, and the control group received an IgG-1 isotype-matched antibody (0.5 mg, intraperitoneal injection twice weekly) for the same period. Treatment with cetuximab significantly increased median OS compared with the control treatment, with median survival for cetuximab-treated mice (65 days) increased by more than 200% compared with IgG-treated mice (24 days) (23).

**PDGFR**

PDGFRs regulate angiogenesis and are overexpressed in approximately 75% of MGs (24). Administration of imatinib (STI-571), a PDGFR inhibitor, either as monotherapy or in combination with hydroxyurea or radiotherapy, has been associated with modest activity in open-label, phase II clinical trials in patients with MG (25,26).

An open-label phase II trial of imatinib monotherapy (400 mg, once a day) in patients (n = 55) with anaplastic glioma or GBM demonstrated minimal efficacy (25). Radiographic response was <6% for both types of brain tumors; in patients with GBM (n = 34) two patients (6%) demonstrated partial responses (PRs) and six patients (18%) demonstrated stable disease, but there were no complete responses (CRs) (25). One patient with GBM was removed from the study because of toxicity. Among the patients (n = 21) with anaplastic glioma, there were no CRs or PRs, and five patients had stable disease (25). The PFS-6 was 10% (2 of 21) in patients with anaplastic glioma, and PFS-6 was just 3% (1 of 33) in patients with GBM (25). In an open-label, single-arm phase II clinical trial, patients with recurrent GBM (n = 33) received imatinib mesylate (500 mg, twice a day) plus hydroxyurea (orally) on a continuous daily schedule (26). At a median follow-up of 58 weeks, 27% of patients (9 of 33) were progression free at 6 months, with a median OS of 14.4 weeks (26). Radiographic responses were observed in 3 patients (9%), 14 (42%) achieved stable disease, and the median OS rates were 48.9 weeks (26). In all cases, the responses observed in these clinical trials in patients with recurrent GBM were inferior to those observed with the standard Stupp regimen (PFS-6, 53.9%; me-

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**Table 1. Major clinical trials (completed and/or are ongoing) and their main efficacy results with each drug category.**

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent (phase of trial)</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Gefitinib (I)</td>
<td>Rec GBM; PFS-6: 13-14.3%, mOS: 24.6-39.4 weeks</td>
<td>16,17</td>
</tr>
<tr>
<td></td>
<td>Erlotinib + TMZ (I)</td>
<td>Rec GBM; mOS: 55 weeks</td>
<td>19,20</td>
</tr>
<tr>
<td></td>
<td>Cetuximab (II)</td>
<td>Ongoing</td>
<td>—</td>
</tr>
<tr>
<td>PDGFR</td>
<td>Imatinib + hydr/rea (II)</td>
<td>Rec GBM; PFS-6: 3%, mPFS: 14.4 weeks, mOS: 48.9 weeks, Rec AAs; PFS-6: 10%</td>
<td>25,26</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Bevacizumab + IRI (I)</td>
<td>Rec GBM; PFS-6: 38%-46%, PR: 57%</td>
<td>29,30</td>
</tr>
<tr>
<td></td>
<td>Vatalanib (I/II)</td>
<td>Rec GBM; PR: 4%, stable disease: 56%</td>
<td>32</td>
</tr>
<tr>
<td>mTOR</td>
<td>Temsirolimus (II)</td>
<td>Rec GBM; PFS-6: 7.8%, mOS: 44 months</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Tems. + erlotinib (I/II)</td>
<td>Ongoing</td>
<td>—</td>
</tr>
<tr>
<td>RAS</td>
<td>Tipifarnib (I)</td>
<td>Rec GBM; PFS-6: 33%</td>
<td>40</td>
</tr>
<tr>
<td>PKC-b</td>
<td>Tipifarnib + TMZ (I)</td>
<td>Rec GBM; PFS-6: 12%</td>
<td>41</td>
</tr>
<tr>
<td>EGFR/HER-2</td>
<td>Lapatinib (I)</td>
<td>Ongoing</td>
<td>—</td>
</tr>
<tr>
<td>HER-1/EGFR</td>
<td>125I-MAb 425 (I/II)</td>
<td>Rec GBM/AAAs; OS range: 4–150/4–270 months</td>
<td>47</td>
</tr>
<tr>
<td>Tenascin-C</td>
<td>131I-81C6 (II)</td>
<td>Rec GBM; mOS: 78 weeks</td>
<td>49</td>
</tr>
<tr>
<td>Integins</td>
<td>Cilengitide (I/II)</td>
<td>Rec MGs; CR: 4%; PR: 6%; stable disease: 8%</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Cilengitide + RT (II)</td>
<td>Ongoing</td>
<td>—</td>
</tr>
</tbody>
</table>

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aEGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor; mTOR, mammalian target of rapamycin; HER, human epidermal growth factor receptor; TMZ, temozolomide; hydr/rea, hydroxyurea; IRI, irinotecan; Tems, temsirolimus; RT, radiation; Rec, recurrent; GBM, glioblastoma multiforme; AAs, anaplastic astrocytomas; MGs, malignant gliomas; PFS-6, 6-month progression-free survival; mPFS, median progression-free survival; mOS, median overall survival; RR, response rate; PR, partial response; C, complete response.
dian, PFS 6.9 months; overall response rate 38.7%, including 7 [11.3%] CRs and 17 [27.4%] PRs (18,27).

**VEGFR**

VEGFRs are overexpressed in MGs (14); therefore, inhibiting their function may block angiogenesis and limit peritumoral edema. A phase II clinical trial in patients (n = 16) with recurrent GBM (10 mg/kg) plus irinotecan demonstrated a PFS-6 of 46% and a 6-month OS of 77%, and PRs were observed in 57% of patients (30). Overall, regimens consisting of bevacizumab plus irinotecan demonstrated similar survival and progression rates compared with the standard Stupp regimen (18). Of note, however, is that trials assessing the efficacy of bevacizumab plus irinotecan (29,30) enrolled a relatively small number of patients and therefore were not powered adequately to provide more significant results.

Vatalanib (PTK-787; ZK-222584; Novartis AG, Basel, Switzerland), an oral controlled-release PDGF/VEGF-receptor tyrosine kinase angiogenesis inhibitor, was assessed in preclinical models for efficacy against VEGF-dependent glioma vascularization and growth. Vatalanib significantly limited VEGF-mediated glioma growth, thereby providing a promising new treatment option for MGs. Vatalanib was evaluated in patients with recurrent MGs in an open-label, nonrandomized phase II clinical trial in patients (n = 65) with GBM, temsirolimus (CCI-779; 250 mg intravenously once a week) demonstrated modest efficacy, with 20 patients (36%) demonstrating radiographic improvement (36). Observed radiographic indications of improvement consisted of significant decreases in T2 signal abnormality (tumor volume) and/or improvement in gadolinium (contrast medium) enhancement in patients receiving stable or decreased steroid doses. The PFS-6 was 7.8% and the median OS was 4.4 months (37). Similarly, in another open-label, single-arm, phase II clinical trial in patients (n = 43) with recurrent GBM, 1 patient remained progression free at 6 months, and of the patients (n = 41) assessable for response, 2 PRs were observed and 20 patients had stable disease (38). In addition, the median time to progression was 9 weeks (38); therefore, compared with the standard Stupp regimen (PFS-6 53.9, median OS 58 weeks, median PFS 6.9 months; OR rate of 38.7%) (18,26), there was no evidence of an improved response to temsirolimus treatment in patients with recurrent GBM (38). Overall, temsirolimus treatment appears to be less effective than the standard Stupp regimen.
RAS
MGs often show increased RAS activity (cell growth and differentiation) because of mutation or amplification of upstream growth factor receptors (39). Farnesyltransferases are part of the RAS signal transduction pathway, and farnesyltransferase inhibitors, including tipifarnib (R-115777; Johnson and Johnson Pharmaceutical Research and Development, Brunswick, NJ, USA), and lonafarnib (Sch-66336), have been assessed and shown to have modest survival benefits in phase I and II clinical trials in patients with recurrent MGs (40,41). For example, in an open-label, nonrandomized, phase II clinical trial to determine the efficacy and safety of tipifarnib in patients (n = 67) with recurrent GBM, eight patients (11.9%) had a PFS of >6 months (40). In addition, a PFS of 33% was observed in a nonrandomized phase I clinical trial of temozolomide and lonafarnib in patients (n = 15) with recurrent GBM (41). However, PFS rates following administration of tipifarnib or temozolomide plus lonafarnib were inferior to those observed after administration of the standard Stupp regimen (18).

Protein Kinase C
Enzastaurin (LY-317615; Eli Lilly, Indianapolis, IN, USA), a selective inhibitor of activated protein kinase C (PKC)β suppressed tumor cell proliferation (42). In addition, enzastaurin treatment suppressed the phosphorylation of glycogen synthase kinase 3β (GSK3β), a serine/threonine PK, in GBM xenograft tumor tissues. Enzastaurin also limited the growth of human GBM xenografts (43). These effects are supported by data from a preclinical study that investigated the effects of enzastaurin and radiotherapy in vitro, and in vivo compared with either treatment alone (44). This study demonstrated that combining cerebral irradiation with enzastaurin decreased the following parameters: tumor volume, irradiation-induced tumor satellite formation, upregulation of VEGF expression in vitro and in vivo, and enhanced microvessel density in vivo (44). However, in an open-label, multicenter phase III clinical trial that compared enzastaurin with lomustine treatment in patients (n = 266) with recurrent GBM, treatment effects were modest (45). Median PFS, OS, and PFS-6 rates were not significantly different between treatment arms, and therefore enzastaurin was not superior to lomustine in patients with recurrent GBM (45).

Ligand–Toxin Conjugates
The Her1/EGFR-expressing tumors are specifically targeted by radioisotopes or toxic compounds conjugated to Her1/EGFR-specific antibodies or ligands, including 125I-iodine (I)-MAb 425, TP-38, and DAB389-EGF (46). Regional administration of radiolabeled mAbs targeting tumor-specific antigens expressed by MGs has demonstrated encouraging antitumor activity and acceptable toxicity in clinical trials (34). The 125I-MAb 425, an IgG2a antibody that binds to a protein determinant on the external domain of human EGFRs, is internalized upon binding to EGFRs and downregulates EGFR expression without stimulating receptor tyrosine kinase activity (47). In an open-label, nonrandomized phase I/II clinical trial, adjuvant administration of 125I-MAb 425 (50 μCi, intravenous, once a week) in patients (n = 180) with MGs significantly increased median survival compared with controls receiving radiotherapy alone (47). The actuarial OS range for GBM and AA patients was 4 to 150 and 4 to 270 months, respectively (47). A similar study investigated the putative benefits of teleradiotherapy and 125I-MAb 425 radioimmunotherapy administered after neurosurgery in high-grade gliomas compared with teleradiotherapy alone (48). A median OS of 14 months for both treatment groups was observed, with no improvement in disease-free survival or OS in either treatment group after neurosurgery (48). Therefore, radiotherapy and radioimmunotherapy with anti-EGFR 125I-MAb 425 was not beneficial compared with radiotherapy alone for the adjuvant treatment of high-grade gliomas following neurosurgery (48). Therefore, compared with the standard Stupp regimen (OS range for GBM was 13.2 to 16.8 months) (18), 125I-MAb 425 greatly increased the OS range. In addition, mAb-806 (Life Science Pharmaceuticals) and 3C10 mAb are mAbs directed against EGFR-vIII with conjugated toxins or radioisotopes and may represent other targeted treatment options for MGs (34). The administration of the mAb against tenascin-C, an extracellular matrix glycoprotein ubiquitously expressed by malignant gliomas, has also been evaluated in clinical trials (49,50). In a nonrandomized, phase II, dose-response clinical trial in patients (n = 33) with primary MGs, 131I-81C6 (Bradmer Pharmaceuticals, Toronto, Canada), a radiolabeled mAb targeting tenascin (an extracellular matrix protein present in MGs, but not in normal brain tissue), was injected directly into surgically created resection cavities followed by conventional external-beam radiotherapy and chemotherapy (49). This treatment strategy demonstrated a median survival of 86 weeks for patients with either anaplastic astrocytomas (n = 4) or AAs (n = 2). In patients with GBM (n = 27) a median OS of 79 weeks was observed (49). Therefore, 131I-81C6 increased the median survival of GBM patients compared with the standard Stupp regimen (49). Furthermore, histopathological analyses were conducted in patients (n = 28) treated with combined external-beam radiotherapy and a brachytherapy consisting of 131I-81C6 injected into surgically created resection cavities during brain tumor resections (50). Histological tissue classification outcomes included “proliferative glioma,” “quiescent glioma,” and “negative for neoplasm”. Median survival with tissue classified as proliferative glioma, quiescent glioma, and negative for neoplasm were 3.5, 15, and 27.5 months, respectively (50). Median survival in patients receiving a total radiation dose greater than 86 Gy)was 19 months, compared with 7 months for those receiving less than 86 Gy, thus suggesting that the total dose of radiotherapy was a significant predictor of sur-
vival ($P < 0.002$) (50). Therefore, additional clinical trials are warranted to determine the effectiveness of $^{125}$I-81C6 for the treatment of MGs.

TP-38 is a recombinant chimeric protein composed of transforming growth factor α combined with a mutated form of *Pseudomonas* exotoxin (51). Binding specificity of TP-38 for cells in the brain was demonstrated by the ability of non-radiolabeled TP-38 to block the binding of $^{125}$I-EGF to EGFR-expressing non–small cell lung cancer cell lines (51). TP-38 has also demonstrated toxicity to human glioma cell lines (51). However, in a pilot phase I clinical trial, TP-38 was associated with an inferior clinical response (52), compared with the Stupp regimen (18). Efficacy results of this pilot study (52) showed that after TP-38 administration, the median OS of patients ($n = 20$) with recurrent malignant brain tumors was 23 weeks. Median OS for patients with residual disease at the time of therapy was 18.7 wk, whereas for those without radiographic evidence of residual disease median survival was 32.9 weeks. Overall, 2 of 15 patients (14%) with residual disease at the time of therapy demonstrated radiographic responses. One patient (7%) had CR and another (7%) had a PR with $>50\%$ tumor shrinkage 34 weeks after TP-38 therapy (52).

However, interpretation of data from trials, such as those described above, is challenging because of methodological problems, mainly consisting of the small sample sizes enrolled and the open-label study design (48–50,52).

**Integrins**

Integrins are cell surface receptors that play important roles in tumor invasion (53). Cilengitide has demonstrated some efficacy against MGs in both a preclinical study (54) and in a nonrandomized phase I clinical trial of cilengitide (2400 mg/m$^2$) for treating 51 patients with MGs, including 37 with GBMs (55). Among the evaluable patients, 2 patients (4%) demonstrated CRs, 3 patients demonstrated PRs (6%), and 4 (8%) demonstrated stable disease. Considering these preliminary results, cilengitide appears to be a promising treatment agent against MGs, and therefore the final results of this study are awaited before definitive conclusions can be drawn. To our knowledge, a larger randomized phase II trial of cilengitide is currently ongoing in patients with newly diagnosed GBMs concurrent with radiation therapy.

**Histone Deacetylase Inhibitors**

Epigenetic changes to the genome through DNA methylation and covalent modification of the histones that form the nucleosome are key to maintenance of the differentiated state of the cell. Thus, inhibition of deacetylation, which is controlled by histone deacetylases, may lead to chromatin remodeling, up-regulation of key tumor repressor genes, differentiation, or apoptosis. Histone deacetylase inhibitors, by altering functional epigenetic modifications, are additional potential anticancer agents for the treatment of MGs.

Structurally diverse histone deacetylase inhibitors, including vorinostat and romidepsin (FK-228; Gloucester Pharmaceuticals, Cambridge, MA, USA) have demonstrated their ability to inhibit proliferation and induce differentiation and/or apoptosis of tumor cells in culture and in animal models (56), suggesting that treatment with vorinostat may enhance radiation-induced cytotoxicity in MGs (57).

**MONITORING RESPONSE TO MOLEULARLY TARGETED THERAPIES**

A critical issue that remains to be fully explored is the identification of the optimal method to evaluate the response and biologic activity of molecularly targeted therapies in gliomas (58). Because antiangiogenic therapy is acknowledged to be the most promising treatment approach against MGs, research has been focused in the development of objective methods to evaluate its efficacy.

**Pharmacodynamic Surrogate Markers**

Measurements of serum levels of VEGF and other angiogenic cytokines have been considered to provide useful information toward the monitoring of response of molecularly targeted therapies in solid tumors (58). This method is not applied in MGs, however, because the levels of VEGF are not increased in patients with MGs (59). Levels of VEGF and basic FGF in cerebrospinal fluid have been associated with brain tumor vascularity and patient survival (60). Therefore measurement of VEGF and basic FGF in cerebrospinal fluid may be a suitable method to clinically monitor the response to antiangiogenic therapy. In addition, the levels of circulating endothelial progenitor cells (CEPs) in the peripheral blood correlate with antiangiogenic drug activity (61), and therefore CEPs have been measured to clinically monitor response to antiangiogenic therapy (58). Results were conflicting, however, and therefore the significance of CEPs as pharmacodynamic markers to monitor antiangiogenic drug activity in MGs remains to be conclusively demonstrated.

**Radiological Functional Techniques**

Apart from the standard MRI imaging techniques, novel molecular imaging techniques—such as arterial spin labeling, perfusion MRI (62), $^1$H-magnetic resonance spectroscopy (63), and blood oxygenation level–dependent imaging (64)—have recently been shown to provide quantitative measurements of brain tumor perfusion. Single-photon emission computed tomography and positron emission tomography imaging have been recently applied in the clinical setting and may be sensitive quantitative techniques to objectively assess the efficacy of antiangiogenic therapy in MGs, providing some useful information (65). Recently, coupling of antibodies against αvβ3-integrin and the intercellular adhesion molecule-1, and the E-selectin adhesion molecule with paramagnetic liposomes or nanoparticles have been applied and assessed in experimental animal models to molecularly image angiogenesis (66,67). Overall, the significance of the above-mentioned techniques is...
mainly degraded by the preliminary or experimental results and the limited availability in the general setting. In any case, this issue of great importance warrants further study.

CONCLUSIONS

Various single-agent therapies, such as gefitinib and imatinib, that target growth and survival pathways have failed to demonstrate a significant survival benefit. Therefore, more effective therapies may be those that target multiple signaling pathways simultaneously by multi-targeted kinase inhibitors or combinations of kinase inhibitors that target single kinases. Additional clinical trials are required to elucidate whether multi-targeting strategies will improve survival rates in patients with MGs.

Pharmacokinetic evaluation of drugs is important to assess therapeutic drug levels and identify potential drug interactions. Important areas for additional pharmacodynamic research include the assessment of serum or tissue biomarkers, the elucidation of prognostic molecular markers, and the use of biomarkers to determine if the mechanism of drug action is appropriate to genetic alterations within individual tumors. Moreover, biological endpoints, such as measures of target inhibition, should be included in the design of clinical trials that evaluate standard or novel targeted therapies against MGs.

DISCLOSURE

We declare that the authors have no competing interests as defined by Molecular Medicine, or other interests that might be perceived to influence the results and discussion reported in this paper. No funding source had a role in the preparation of this paper or in the decision to submit it for publication.

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