Recent Advances in the Treatment of Malignant Astrocytoma

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Abstract

Malignant gliomas, including the most common subtype, glioblastoma multiforme (GBM), are among the most devastating of neoplasms. Their aggressive infiltration in the CNS typically produces progressive and profound disability—ultimately leading to death in nearly all cases. Improvement in outcome has been elusive despite decades of intensive clinical and laboratory research. Surgery and radiotherapy, the traditional cornerstones of therapy, provide palliative benefit, while the value of chemotherapy has been marginal and controversial. Limited delivery and tumor heterogeneity are two fundamental factors that have critically hindered therapeutic progress. A novel chemoradiotherapy approach, consisting of temozolomide administered concurrently during radiotherapy followed by adjuvant systemic temozolomide, has recently demonstrated a meaningful, albeit modest, improvement in overall survival for newly diagnosed GBM patients. As cell-signaling alterations linked to the development and progression of gliomas are being increasingly elucidated, targeted therapies have rapidly entered preclinical and clinical evaluation. Responses to therapies that function via DNA damage have been associated with specific mediators of resistance that may also be subject to targeted therapies. Other approaches include novel locoregional delivery techniques to overcome barriers of delivery. The simultaneous development of multiple advanced therapies based on specific tumor biology may finally offer glioma patients improved survival.

Introduction

Primary CNS tumors arise in more than 41,000 people in the United States annually, and account for 1.35% of all cancers, and 2.2% of all cancer-related deaths. Worldwide, approximately 176,000 cases of CNS cancer are diagnosed per year with an estimated annual mortality of 128,000. Glial tumors represent 42% of all primary CNS neoplasms, and over three quarters are malignant. Malignant gliomas remain one of the greatest challenges in oncology today. In a recent population-based study, overall survival of patients with newly diagnosed glioblastoma multiforme (GBM), the most common malignant glioma, was 42.4% at 6 months, 17.7% at 1 year, and 3.3% at 2 years, despite access to state-of-the-art surgery, imaging, radiotherapy, and chemotherapy. Furthermore, the incidence of malignant gliomas may be increasing, particularly among the elderly, and the elucidation of pathogenic or predisposing factors remains a high priority, as these are largely unknown.

Emerging Molecular-Clinical Correlates

Malignant gliomas, like most aggressive cancers, exhibit aberrant proliferation, diminished apoptosis, avoidance of both external growth control and immunoregulation, and striking rates of de novo and acquired resistance to therapeutic intervention. An enigmatic and unique behavioral feature, however, is a nearly absent rate of metastatic dissemination beyond the CNS, despite highly robust invasive and angiogenic capabilities. Another distinguishing characteristic is marked histopathologic and genetic heterogeneity across and within tumors.

Many molecular genetic abnormalities associated with phenotypic features are being increasingly characterized and include multiple abnormalities that span several critical regulatory arenas, such as genomic instability, cell cycle control, and intra- and intercellular communication via signal transduction pathways.

Disruption of p53 function, a key regulator of genomic stability, occurs frequently in malignant glioma due to either direct mutation or loss, p14^ARF^ mutation, or human double-minute 2 (HDM2) amplification. Additional genetic abnormalities contribute to dysregulation of cell cycle control, including CDK4 amplification or loss of either RB1, p16^INK4A^ or P15^INK4B^, due to either inactivating mutation or promoting hypermethylation.

Malignant gliomas also frequently exhibit abnormalities of signal transduction pathways that control key cellular processes including proliferation,
angiogenesis, apoptosis, and invasion. Dysregulation of the PI3K/AKT pathway, the most prominent abnormal signaling cascade, is associated with adverse outcome and has been linked with two primary, triggering genetic defects. First, increased activity of growth factor receptor tyrosine kinases (TKIs), due to receptor overexpression, amplification, or mutation, can increase PI3K/AKT activity. The most common abnormally active growth factor TKIs in malignant gliomas include the epidermal growth factor receptor (EGFR), platelet derived growth factor receptor (PDGFR), c-kit, and insulin-like growth factor–1 receptor (IGF1R). The most common EGFR mutation in malignant glioma, EGFRvIII, is created by intragenic deletion of exons 2 to 7, and exhibits ligand independent, constitutive signaling. A second genetic defect linked with aberrant PI3K/AKT signaling is loss of the tumor suppressor gene, and negative regulator of AKT, phosphatase, and tensin homolog deleted on chromosome 10 (PTEN), which occurs in approximately 30% of GBM tumors. Traditionally, GBMs are classified into either primary or secondary subtypes based on clinical and genetic features (Fig 1), although morphologic and microscopic characteristics of both subtypes are indistinguishable. Primary GBMs, which account for 95% of cases, arise de novo after a short clinical history, typically affect older patients, exhibit a male predominance, and frequently display aberrant PI3K/AKT signaling due to EGFR overexpression or PTEN loss. In contrast, secondary GBMs are relatively rare, arise from pre-existing lower grade gliomas, are more commonly seen in younger patients, exhibit a female predominance, and are characterized at the molecular level by mutation of TP53 and RB1, as well as either amplification or increased expression of PDGFR. Of note, a recent population-based analysis revealed that the most common genetic abnormality in newly diagnosed GBM patients is loss of the distal region of chromosome 10q. This finding occurs with equal frequency among both primary and secondary GBMs. Furthermore, in this extensive analysis, loss of distal 10q was the only genetic abnormality shown to confer a negative prognosis independent of clinical factors.

**MULTIMODALITY THERAPY: HISTORICAL PERSPECTIVE**

Patient prognosis has been based on clinical factors historically. The Radiation Therapy Oncology Group (RTOG) utilized a recursive partitioning analysis of 1,578 patients enrolled on three consecutive RTOG studies to define six prognostic patient subsets by algorithmic integration of age, histology, mental status, symptom duration, degree of surgery, and neurologic deficit. Recently, gene-expression and proteome-profiling analyses have been explored as strategies to more accurately predict prognosis, although such approaches will clearly require validation in prospectively followed and uniformly treated patients.

Surgery and radiotherapy (XRT), traditional cornerstones of malignant glioma therapy, provide palliative survival benefit. Until recently, the benefit of additional chemotherapy has been negligible for most patients, with survival under 12 months for newly diagnosed GBM patients, and only 2 to 3 years for those with WHO grade 3 malignant gliomas such as anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and mixed anaplastic gliomas. Two fundamental factors have critically hindered therapy responsiveness historically, and remain major obstacles for current and future treatments. The first critical factor is limited delivery. The blood brain barrier (BBB), although disrupted in regions of macroscopic tumor, is more intact in regions of microscopic tumor infiltration, and stringently limits CNS access based on chemical constitution and size. In addition, BBB efflux proteins, such as P-glycoprotein...
and ABCG2, known to actively pump chemotherapeutics from the CNS, have more recently been shown to affect molecular therapeutics such as imatinib mesylate and gefitinib. Additional factors limiting CNS tumor delivery include dysfunctional tumor vasculature, leading to relative hypoxia and diminished responsiveness to cytotoxic therapy, as well as elevated intratumoral interstitial pressures.

A second critical determinant of therapy efficacy is marked cellular and genetic heterogeneity across, and within, these tumors. Malignant gliomas, in particular GBM, have been long associated with striking histologic heterogeneity. Another measure of tumor heterogeneity—cell surface protein expression—varies dramatically among and within tumors. Furthermore, molecular defects, many of which are now being targeted by cutting edge therapies, also exhibit striking patterns of heterogeneity across and within tumors. Thus, inter- and intratumoral heterogeneity likely represents an evolved defense mechanism of malignant gliomas, that not only poses a significant therapeutic challenge, particularly in the monotherapy setting, but also complements the prevalent, additional de novo and acquired resistance mechanism frequently exhibited by these tumors including O6-alkylguanine-DNA alkyltransferase (AGT), nucleotide excision repair, and deficiency of mismatch repair. Furthermore, recently identified CD133 (AGT), nucleotide excision repair, and deficiency of mismatch repair. Additionally, the evaluation of TMZ among newly-diagnosed GBM, as well as the impact on future progress.

**Temozolomide: A New Standard of Care**

Temozolomide (TMZ), a second generation imidazotetrazine derivative, methylates specific DNA sites, the most critical being the O6 position of guanine. Nucleotide mismatch between complementary strands triggers continuous cycles of futile mismatch repair, that in turn, ultimately induce apoptosis. Several characteristics make TMZ an attractive therapeutic for brain tumor patients including that it (1) readily crosses the BBB and achieves CSF concentrations that are approximately 40% of plasma; (2) is nearly100% bioavailable after oral dosing; (3) does not require hepatic metabolism for activation; (4) exhibits dose-linear pharmacokinetics with little intersubject or intrasubject variability; and (5) is associated with generally mild and predictable toxicity.

Promising initial results (Table 1) led to accelerated approval of TMZ in 1999 for the treatment of recurrent AA in the United States, and approval in Europe for the treatment of recurrent AA and GBM, as well as the evaluation of TMZ among newly-diagnosed GBM patients. In the first such study, 17 of 33 patients with newly-diagnosed and untreated GBM (51%) achieved a radiographic response following TMZ administered before conventional XRT (200 mg/m2/d for 5 days every 28 days for up to four cycles). Three subsequent, open-label studies, enrolling a total of 767 patients, were recently performed to evaluate a novel combinatorial approach that included continuous, oral TMZ dosing administered concurrently with XRT, followed by monthly cycles of adjuvant TMZ (Table 2). The pivotal, randomized phase III study, conducted by the European Organization for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups (EORTC trial 22,981/26,981) and the National Cancer Institute of Canada Clinical Trials Group (NCIC trial CE.3), enrolled 573 patients from 85 centers in 15 countries over 19 months. The rationale for administering TMZ concurrently with XRT includes: (1) in vitro and in vivo synergy; (2) two-fold increase in TMZ dose-intensities; and (3) the potential to more effectively deplete AGT.

Initially a single arm, two-center pilot phase II study was performed, followed by two randomized, two-arm, open-label studies. All three studies administered the same TMZ dosing schedule during XRT (75 mg/m2/d for 42 consecutive days). Adjuvant TMZ, prescribed for six monthly cycles, was administered according to the standard dosing schedule (150-200 mg/m2/d for five days every 28-day cycle) in the Stupp pilot and EORTC/NCIC studies, while the Athanassiou study used a more intensive adjuvant TMZ schedule (150 mg/m2/d on day 1 through 5 and 14 to 19 of each 28 day cycle). Of note, patients enrolled on the Athanassiou study had poorer clinical features compared with patients enrolled on the other two studies. Importantly, however, patient characteristics were comparable between arms of each randomized study.

Compliance with prescribed therapy was good across the studies, reflecting the limited toxicity of the treatment regimens. The most common adverse effects associated with TMZ administration were hematologic (Table 2). Severe infections were infrequent and additional, nonhematologic toxicities were mild to moderate in most cases and included nausea/emesis, rash, constipation, and fatigue. Adjuvant TMZ discontinuation or dose modification was required in 8% to 25%, and 40% to 60% of patients received six cycles. Although not described in any of these studies, two concerning recent reports

| Table 1. Outcome With Temozolomide in Recurrent Patients at First Relapse* |
|---------------------------------|----------|----------|----------|
| **Histology**                     | **Anaplastic Astrocytoma/Anaplastic Oligoastrocytoma** | **Glioblastoma Multiforme** |
| **Temozolomide Arm**       | **Procarbazine Arm** |
| **(n = 112)**                     | **(n = 113)** |
| % of Patients With Radiographic Response | % of Patients With Radiographic Response | % of Patients With Radiographic Response |
| Complete                      | 8        | 0        | 0        |
| Partial                       | 44       | 5.3      | 5.4      |
| Stable disease                | 44       | 40.2     | 27.4     |
| Median PFS, weeks             | 21.6     | 12.4     | 8.3      |
| 6 months PFS                  | 46       | 21       | 8        |
| 12 months PFS                 | 24       | NA       | NA       |

Abbreviations: PFS, progression-free survival; NA, not available.

*Administered at 150-200 mg/m2/day x 5 days every 28 days.
describe severe myelosuppression in a subset of patients treated with TMZ concurrently during XRT.121,122

TMZ improved outcome on all three chemoradiotherapy studies although lower survivals were observed on the Athanassiou study, probably reflecting the comparatively poorer patient characteristics. The median overall survival for patients treated with TMZ was significantly better than that achieved with XRT alone on both randomized studies. In addition, the difference in survival between patients treated with XRT compared with TMZ/XRT-TMZ widened with time from diagnosis. The 18-month survival rate on the Athanassiou study was 25% for patients treated with TMZ/XRT-TMZ compared with only 5% survival for those treated with XRT alone. Similarly, the 24-month survival rate on the phase III EORTC/NCIC study was 27% for the TMZ/XRT-TMZ group compared with only 10% for the XRT group. Furthermore, evaluation of outcome on these studies relative to established prognostic features suggests that TMZ improves outcome in nearly all patient subsets. Of note, patients with poor performance status were the only subset treated with TMZ/XRT-TMZ who did not achieve a statistically significant improvement in OS in the EORTC/NCIC study.

The combined data from these trials indicates that the TMZ/XRT-TMZ regimen should be considered a new standard of care for newly diagnosed GBM patients. However, a number of issues require clarification if we are to effectively build on these results. First, a better understanding of this regimen’s mechanism of activity, particularly the interaction of TMZ with XRT, is clearly needed. Second, what is the relative value of each TMZ component to the overall TMZ/XRT-TMZ regimen? In particular, does adjuvant TMZ benefit all or only some patients beyond that of TMZ with XRT? The fact that outcome was poorer among patients treated on the EORTC/NCIC study with XRT alone, despite TMZ administration to most patients at relapse, suggests that TMZ during XRT is a particularly important component of the TMZ/XRT-TMZ regimen. A related controversy is whether the data from the GBM chemoradiotherapy studies should be extrapolated to define a new standard of care for newly diagnosed grade 3
malignant glioma patients. The results of two RTOG studies may help resolve this controversy.

Although the chemoradiotherapy GBM study results are highly significant and provide an important step forward, the overall benefit achieved with the TMZ/XRT-TMZ regimen, is modest. Specifically, median progression-free survival for patients treated with TMZ/XRT-TMZ on the pivotal EORTC/NCIC study was under 7 months, and OS was under 15 months. Clearly we still have a long way to go. Two additional courses of action may lead to additional incremental advances. First, modifications of the TMZ/XRT-TMZ regimen should be explored that may heighten its efficacy. Potential options to do so include alternative dosing schedules,\textsuperscript{119,120} longer durations of therapy,\textsuperscript{123} strategies to enhance delivery, and the addition of agents with complementary mechanisms of antitumor activity such as additional cytotoxics, targeted therapeutics (discussed in the section Targeted Therapies: Current Focus of Clinical Development), and locally administered agents (also discussed in the section Advances in Locoregional Therapy).

A second important step is the determination of biologic factors that identify subsets of patients with predictable response (or lack thereof) to TMZ/XRT-TMZ. An example of a biomarker predictive of treatment response is chromosomal 1p and 19q tumor deletion among anaplastic oligodendroglioma patients.\textsuperscript{124} While much work remains to develop biomarkers that can reliably predict response among malignant glioma patients, one clearly important modulator of TMZ response is O\textsuperscript{6}-alkylguanine-DNA alkyltransferase (AGT).

### AGT: The Next Hurdle

AGT is a critical DNA repair protein also referred to as O\textsuperscript{6}-methylguanine-DNA-methyltransferase (MGMT) which removes chloroethylation or methylation damage from the O\textsuperscript{6} position of DNA guanines, thereby protecting normal cells from exogenous carcinogens, and similarly protecting tumor cells from alkylating and methylating chemotherapeutic agents.\textsuperscript{125} AGT levels vary significantly across and within tumor types.\textsuperscript{126,127} Methylation of CpG islands within the AGT promoter is an epigenetic factor that can diminish AGT transcription and expression.\textsuperscript{91} AGT levels can be most readily measured by either immunohistochemistry or by a methylation-specific PCR assay.\textsuperscript{128-130}

Friedman et al initially implicated AGT in TMZ responsiveness among malignant glioma patients.\textsuperscript{92} In a series of 36 newly diagnosed patients, including 33 with GBM, the response rate to TMZ was 60% among patients with low-level AGT (detected by immunohistochemistry in < 20% of cells) compared with only 9% among patients with high-level AGT (present in ≥ 20% of tumor cells). Similarly, following Carmustine (BCNU) chemotherapy, Estellar noted a radiographic response in 12 (64%) of 19 malignant glioma patients with methylated AGT compared with only 1 (4%) of 28 patients with unmethylated AGT.\textsuperscript{91} Two subsequent, prospective studies demonstrate that AGT methylation is associated with better survival among malignant glioma patients treated with TMZ (Table 3).\textsuperscript{93,94} Of note, in these studies, the Kaplan-Meier survival curves for patients with methylated and unmethylated AGT become particularly divergent after 12 months of follow-up. Furthermore, these studies suggest that tumor AGT status is an independent predictor of outcome following therapy with alkylator-based chemotherapy, because AGT status does not correlate with established clinical prognostic factors.

Therefore a looming, fundamental question is whether tumor AGT status should ultimately direct treatment of newly diagnosed GBM patients. Although results to date suggest that AGT status is an important biomarker for TMZ responsiveness, these findings require further validation in additional prospective analyses. One important factor supporting such validation is that less than half of all samples analyzed in the landmark Hegi study\textsuperscript{94} were informative of AGT status. In addition, controversy exists regarding the optimal technique to assess tumor AGT status. Validated, commercially-available, PCR-based AGT methylation assays are not yet approved for clinical use, and may be technically challenging. Furthermore, inactivation of AGT transcription can occur by cytosine methylation of discrete regions of CG dinucleotide islands\textsuperscript{129} and additional study may be required to identify which methylation regions are most predictive of potential gene silencing. Immunohistochemical techniques are more widely available, but may be less reliable since external factors such as glucocorticoids, XRT, and genotoxic agents, can influence AGT expression.\textsuperscript{131,132} Therefore, pending validation of AGT testing in additional, prospective GBM clinical trials, and the development of a validated,

| Table 3. Summary of MGMT Methylation Status and Clinical Outcome in Malignant Glioma |
|-----------------|-----------------|-----------------|
|                | Esteller\textsuperscript{91} (AA and GBM) | Hegi\textsuperscript{93} (GBM only) | Hegi\textsuperscript{94} (GBM only) |
|                | No. % | No. % | No. % |
| Chemotherapy administered | Carmustine | Temozolomide | Temozolomide |
| Tumors with MGMT methylation | 19/47 40 | 26/38 68 | 92/206 45 |
| Study arm | — | — | XRT/TMZ |
| Overall survival at 18 months | | | |
| Methylated MGMT | NA | 62 | NA |
| Unmethylated MGMT | NA | 8 | NA |
| Overall survival at 24 months | | | |
| Methylated MGMT | 100 | NA | 23 |
| Unmethylated MGMT | 30 | NA | < 2 |

Abbreviations: MGMT, O\textsuperscript{6}-methylguanine-DNA-methyltransferase; AA, anaplastic astrocytoma; GBM, glioblastoma multiforme; NA, not available.
commercially available assay, it is premature to routinely incorporate AGT status in directing GBM therapy.

Although it appears clear that TMZ should be an integral component of therapy for patients with low AGT tumors, two fundamental questions remain. First, can the TMZ/XRT regimen be successfully modified to improve outcome for good prognosis patients (defined by either low AGT or methylated AGT) knowing that the median survival for this patient subset is under 22 months following treatment with TMZ/XRT-TMZ? Second, should TMZ be excluded in the treatment of patients with high AGT or unmethylated AGT, particularly given its cost and potential toxicity? One potential strategy to ameliorate AGT-mediated chemoresistance is to incorporate TMZ into therapeutic regimens that include AGT inactivating agents, such as O\(^{\text{\textregistered}}\)-benzylguanine. In addition, given the heterogeneity of AGT expression within individual tumors, a portion of the overall tumor burden may be AGT deficient and therefore TMZ sensitive. It is reasonable therefore to consider TMZ for AGT positive patients in combinatorial regimens that include agents that are either AGT suppressing, or are unaffected by AGT. Clearly additional studies are required to address these important issues.

**ADVANCES IN LOCOREGIONAL THERAPY**

The rationale for locoregionally administered therapies for malignant glioma patients is based on three fundamental factors. First, locally administered therapeutics may circumvent the BBB and thus potentially achieve higher intratumoral concentrations than are achievable following systemic administration. Second, systemic exposures associated with locoregional therapies are typically minimal, leading to less systemic toxicity. Third, since the majority of malignant gliomas recur at the primary tumor site, locoregional therapies may improve local control and thus improve overall outcome.

Gliadel, the initial locoregional therapy approved for malignant glioma patients, provides sustained delivery of BCNU from a controlled release, biodegradable polymer placed around the resection perimeter at surgery. Double-blind, randomized, placebo-controlled studies demonstrate that Gliadel improves survival for patients with either recurrent GBM or newly diagnosed malignant glioma. These encouraging results have led to additional investigations. In a recent phase I study, the maximum tolerated dose of BCNU delivered via biodegradable polymer was determined to be 20%, approximately five times greater than that utilized in the current formulation. Ongoing studies are evaluating the clinical activity of a higher concentration, BCNU polymer preparation. In addition, studies have confirmed that Gliadel can be safely combined with systemically administered agents, such as TMZ. Furthermore, the polymer delivery approach is currently being adopted to investigate delivery of a wide variety of additional therapeutic agents including alternative chemotherapeutics, angiogenesis inhibitors, radiosensitizers, immunomodulators, and cytokines.

Another locoregional strategy is the delivery of increased radiation to the tumor bed. One approach—stereotactic radiosurgery—has been shown to not improve outcome in a randomized phase III study. Another approach, brachytherapy with \(125\text{I}\)-beads implanted into the resection cavity, has improved outcome compared with historical controls, but is associated with a high rate of radiation necrosis requiring surgical debulking. A third approach, the administration of an aqueous solution of organically bound iodine-125 ([Iotrex [sodium 3-((125)I)-iodo-4-hydroxybenzenesulfonate]; Cytyc Corp, Marlborough, MA) to deliver low-dose-rate radiation via a temporarily inflated balloon catheter following resection (GliaSite), is undergoing evaluation in advanced clinical trials. Radioimmunotherapy, another innovative approach designed to enhance peritumoral radiation delivery, utilizes radiolabeled, monoclonal antibodies against tumor-associated antigens administered regionally. A number of potentially exploitable, tumor-associated antigens have been identified, but the most extensively evaluated is tenasin, a hexabrachion extracellular matrix protein widely overexpressed in malignant glioma tissue, but not expressed in normal brain. Additional molecular targets currently under investigation for antibody-toxin, antibody-chemotherapeutic agent, or radioimmunotherapy include glycoprotein neuroendocrin B, MRP3, a member of the multidrug resistance family, the gangliosides 3’-isolM1 and 3’-isoLD1, the insulin growth factor receptor and wild type and variant III epidermal growth factor receptor. Encouraging survival benefit has been noted in single arm studies evaluating the administration of radiolabeled antitenascin MAb into the resection cavity of newly diagnosed and recurrent malignant glioma patients, with a low rate of radiation necrosis requiring surgical debulking. Randomized studies are planned to further evaluate radioimmunotherapy approaches.

The use of convection enhanced delivery (CED) is another innovative locoregional therapeutic intervention currently being widely evaluated for malignant glioma patients. CED utilizes microinjection catheters strategically placed with stereotactic guidance in the peritumoral region to gradually infuse a therapeutic over 3 to 5 days. By applying a consistent, pressure-gradient, CED can overcome limitations associated with diffusion and elevated intratumoral interstitial pressures and potentially deliver therapeutic agents homogeneously into clinically significant volumes of distribution (Fig 2A). A variety of therapeutics have been evaluated including chemotherapeutics, liposomal gene vector particles and tumor-targeting toxin conjugates. Tumor-targeting toxin conjugates represent a novel development that are particularly well-suited for CED (Fig 2B). These genetically engineered agents, composed of a tumor cell receptor ligand conjugated to a highly potent toxin moiety (Table 4), have been associated with encouraging long-term survivals. Large, multicenter, randomized clinical trials are ongoing to further define the role of toxin conjugates delivered via CED.

**TARGETED THERAPIES: CURRENT FOCUS OF CLINICAL DEVELOPMENT**

Cancer cells frequently exploit critical molecules and signal transduction pathways to drive aberrant proliferation, invasion, angiogenesis, and survival. Molecularly targeted agents are being developed as potential, selective inhibitors of these molecules and pathway components. Several such agents have confirmed antitumor benefit and are currently integrated into treatment algorithms for a variety of cancers, including imatinib (Bcr-Abl, platelet-derived growth factor, and c-KIT inhibitor for chronic myelogenous leukemia and gastrointestinal stromal tumors), bevacizumab (humanized anti-vascular endothelial growth factor monoclonal antibody for
colorectal cancer), erlotinib (epidermal growth factor receptorinhibitor for lung cancer), and trastuzumab (Her-2-neu monoclonal antibody for breast cancer). The role of molecular targeted agents for malignant glioma patients remains to be determined. On the one hand, malignant gliomas harbor a wide array of molecular defects, yielding a large number of potentially exploitable, therapeutic targets (Fig 3; Table 5). On the other hand, given the diversity and number of molecular defects in these tumors, as well as the known redundancy and cross-talk between aberrant signal transduction pathways, one would predict that inhibition of a single target is unlikely to have a major, durable antitumor effect for most malignant glioma patients. Results of first generation clinical trials, conducted to evaluate a wide array of molecular targeted agents as monotherapeutics, support this prediction. In fairness, however, additional factors may have also contributed to the limited activity observed in these trials, including impaired CNS delivery, altered pharmacokinetic metabolism due to concurrently administered medications, such as CYP3A-inducing antiepileptics, and inadequate intratumoral concentration to effectively inhibit the intended target.

Nonetheless, subsets of patients have derived encouraging clinical benefit in some trials. For example, eight (20%) of 41 patients responded to the EGFR tyrosine kinase inhibitor (TKI) erlotinib in a...
The emergence of temozolomide as an effective therapy for malignant glioma patients, and the development of innovative therapies designed to circumvent treatment resistance, augment delivery, and block critical, tumor associated targets, marks a new era in neuro-oncology. The nihilism from 30 years of diligent, dedicated research failing to impact patient survival, is gradually giving way to a budding, cautious optimism that we are indeed on the verge of meaningful strides for patients with these tumors. Critical challenges persist. An immediate question is how to most effectively build on the activity demonstrated in the TMZ/XRT-TMZ chemoradiotherapy trials. Can we take advantage of our growing knowledge of the impact of TMZ resistance mechanisms, such as AGT, to better identify patient subsets for more effective treatment? Finally, the fundamental challenges posed by limited effective delivery and tumor heterogeneity, must be overcome if additional progress is to be realized. Locoregional therapeutics and molecularly-targeted therapies represent strategies that may help overcome these longstanding hurdles. Additional exploration of these important issues, through ongoing laboratory and clinical research, will no doubt continue to move us forward.

### Table 5. Partial Listing of Tumor Targeting Agents in Preclinical and Clinical Development for Patients With Malignant Glioma

<table>
<thead>
<tr>
<th>Target</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Gefitinib (ZD1839)</td>
<td>EGFR</td>
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<td>Erlotinib (OSI-774)</td>
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<td>Lonafarnib (SCH66336)</td>
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<td>2ME2 (Panzem; 2-methoxyestradiol)</td>
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<td>Histone Deacetylase Inhibitor</td>
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<td>Depsipeptide (FK228)</td>
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<td>Suberoylanilide hydroxamic acid</td>
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<td>Hsp90 Inhibitor</td>
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<tr>
<td>17-AAG(17-allylamino-geldanamycin)</td>
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<td>Integrin (avβ3 and avβ5) inhibitor</td>
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Abbreviations: VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; PKC, protein kinase C; VEGF, vascular endothelial growth factor.
TREATMENT OF MALIGNANT ASTROCYTOMA

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Reardon et al
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Authors’ Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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