

# Radiotherapy and Radiosensitizers in the Treatment of Glioblastoma Multiforme

Julie E. Chang, MD, Deepak Khuntia, MD, H. Ian Robins, MD, and Minesh P. Mehta, MD

Dr. Chang is Assistant Professor in the Department of Medicine, Section of Hematology and Oncology, at the University of Wisconsin School of Medicine and Public Health, in Madison; where Dr. Khuntia is Assistant Professor in the Department of Human Oncology; Dr. Robins is Professor in the Departments of Medicine, Neurology, and Human Oncology; and Dr. Mehta is Chairman and Professor in the Department of Human Oncology.

Address correspondence to:  
Julie E. Chang, MD, Department  
of Hematology/Oncology, University of  
Wisconsin CSC H4/534, 600 Highland  
Avenue, Madison, WI 53792;  
E-mail: jc2@medicine.wisc.edu.

## Keywords

Glioblastoma multiforme, radiotherapy,  
radiosensitizers

**Abstract:** Effective treatment of glioblastoma multiforme (GBM) is complicated by multiple factors, including the diffusely infiltrative nature of the disease, which limits complete surgical resection; the difficulty in overcoming the blood-brain barrier with systemic therapies; and the challenge of identifying novel means of treating the residual hypoxic tumor cells that are relatively resistant to radiotherapy (RT) and chemotherapy. Clear survival advantages have been demonstrated with postresection RT to doses of 5,000–6,000 cGy, but further attempts at dose escalation over 6,000 cGy have resulted in increased toxicity without a survival benefit. In an effort to improve local control of tumor and limit toxicity to normal brain tissue, novel imaging techniques (eg, chemical shift imaging) are being explored in order to better define RT fields. Brachytherapy and stereotactic radiosurgery are effective therapies for relapsed GBM but have undefined roles outside of clinical trials in treating newly diagnosed GBM. Stereotactic RT may have a survival advantage in subgroups that have undergone a gross total resection and have favorable (recursive partitioning analysis class IV) disease. In contrast, experience with hyperfractionated RT in GBM has shown that survival outcomes may actually be unfavorable in certain patient subgroups. Novel means of delivering RT, including radioimmunotherapy, have demonstrated efficacy with acceptable toxicity. Systemic agents are being explored as potential radiosensitizers, with the recent emergence of temozolomide as a model radiosensitizing agent having a positive impact on survival. Ongoing investigations are evaluating temozolomide in combination with other systemic agents, and additional agents (eg, motexafin gadolinium, mammalian target of rapamycin inhibitors, farnesyltransferase inhibitors) have shown promising activity in combination with RT.

Approximately half of the 18,000 new cases of central nervous system neoplasms diagnosed annually in the United States will be categorized as glioblastoma multiforme (GBM). GBM represents the most aggressive subgroup of malignant gliomas, with a median survival of six months following surgical resection alone, and less than 10% of patients surviving for two years after diagnosis. The average survival of patients has improved to 10–12 months with radiation and chemotherapy, but little improvement has been seen in the number of long-

**Table 1.** Case Series of Radiotherapy in Treatment of Glioblastoma Multiforme

Reference	Treatment	N	Radiation Dose	Survival Rates (%)	
				1 Year	2 Year
Bouchard et al <sup>15</sup>	S	125	5,000–6,000 cGy	32	7
	S + RT			39	20
Uihlein et al <sup>16</sup>	S	27	≤6,000 cGy	5	0
	S + RT	28		29	10
Stage and Stein <sup>17</sup>	S	13	3,500–6,500 cGy	15	8
	S+RT	22		41	6
Kramer <sup>18</sup>	S+RT	55	5,000–6,500 cGy	15	NR
Sheline <sup>11,12</sup>	S	50	5,000–5,500 cGy	8	NR
	S+RT	40		24	

NR=not reported; RT=postresection radiotherapy; S=surgery (resection).

term survivors.<sup>1-3</sup> However, several significant advances have been made in the treatment of GBM over the last 40 years, primarily with the use of radiotherapy (RT). There is clear evidence through randomized trials supporting the benefit of postresection RT,<sup>4-7</sup> and other novel means of delivering RT to achieve optimal dose intensification are being explored. This review focuses on the evolution of RT in the treatment of GBM, with the goal of providing a better understanding of the advances made and avenues of further research in the treatment of this devastating disease.

### Establishing Postresection RT as the Standard of Care

#### Early Nonrandomized Case Series

Although indirect data comparisons suggest that superior outcomes are associated with more complete tumor resections,<sup>8-11</sup> the need for adjuvant postsurgical therapy has long been realized given the infiltrative nature of GBM, which makes complete surgical resection impossible without profound and unacceptable neurologic morbidity. Early experience with postresection RT in the treatment of GBM was limited primarily to single-institution case series, many of which, prior to the 1960s, reported unimpressive results. However, most patients in these case series received low doses of RT (≤2,000 cGy) that were later determined to be subtherapeutic.<sup>12-15</sup> The first large case series suggesting a survival advantage with postresection RT was reported by the Montreal Neurology Institute, in which patients received an average total dose of 5,000–6,000 cGy (Table 1).<sup>16</sup> Importantly, this case series

included a central pathology review, which likely reduced bias from mislabeling anaplastic astrocytoma or other lower-grade gliomas as GBM.

Other case series published in the 1960s and 1970s also suggested a survival advantage with postresection RT (Table 1).<sup>11,12,15-18</sup> Although interpretation of these data is limited by the nonrandomized nature of the reports, inconsistent classification of malignant gliomas, and variances in doses of RT, survival trends with postresection RT were favorable.

#### Randomized Trials

The Brain Tumor Study Group (BTSG; later renamed the Brain Tumor Cooperative Group [BTCG]) initiated several randomized studies beginning in the 1970s that established postresection RT as the standard of care in the treatment of GBM (Table 2). The first of the initial three studies (BTSG 66-01) randomized patients with newly diagnosed malignant gliomas postresection to mithramycin or no chemotherapy, with whole-brain radiotherapy (WBRT) allowed but not randomized.<sup>4</sup> Ultimately, 55% of patients received WBRT, with approximately half receiving 3,000 or more cGy. The study found no significant difference in median survival between patients treated with mithramycin or no chemotherapy, but patients receiving adjunctive WBRT were found to have a statistically significant survival advantage (8.4 vs 3.5 months;  $P<.05$ ). When outcomes were evaluated with WBRT at doses of either less than 5,000 or 5,000 or more cGy, there was a trend toward improved survival favoring patients treated at higher doses of WBRT, but even patients receiving lower doses

**Table 2.** Randomized Studies of Postresection Radiotherapy in Glioblastoma Multiforme

Trial	N (% GBM)	Treatment	Median Survival, months	P value
BTSG 66-01 <sup>4</sup>	96 (85%)	No radiotherapy	3.5	<.05*
		WBRT <5,000 cGy	7.7	
		WBRT ≥5,000 cGy	8.4	
BTSG 69-01 <sup>5</sup>	222 (90%)	BSC (no radiotherapy)	3.1	.001 <sup>†</sup>
		WBRT 5,000–6,000 cGy	8.4	
		WBRT + BCNU	8.0	
		BCNU (no radiotherapy)	4.3	
BTSG 72-01 <sup>6,7</sup>	358 (84%)	CCNU (no radiotherapy)	7.2	NR
		WBRT 6,000 cGy	8.4	
		WBRT + BCNU	11.9	
		WBRT + methyl-CCNU	7.2	

BCNU=carmustine; BSC=best supportive care; GBM=glioblastoma multiforme; NR=not reported; WBRT=whole-brain radiotherapy.

\*P value comparing all patients receiving various doses of WBRT versus patients not receiving adjunctive WBRT.

<sup>†</sup>P value comparing patients receiving WBRT ± BCNU versus patients receiving BSC.

of WBRT had improved survival compared with those not receiving WBRT.<sup>4</sup>

The results from BTSG 66-01 led to a subsequent study in which RT was a randomized therapy. BTSG 69-01 randomized patients postresection to receive best supportive care or chemotherapy (BCNU [carmustine]) with or without WBRT. All therapeutic modalities showed superiority compared with best supportive care in terms of overall survival. The investigators also noted a significantly greater percentage of patients in the WBRT plus BCNU group surviving at 18 months compared with the group receiving RT alone ( $P=.01$ ).<sup>5</sup>

A follow-up study to BTSG 69-01 was performed to further evaluate the role of nitrosoureas plus RT (BTSG 72-01).<sup>6,7</sup> Patients received postresection WBRT with or without a nitrosourea (BCNU or methyl-CCNU); those who received BCNU plus WBRT had the longest median survival. Results from BTSG 72-01 confirmed the survival advantage for adjuvant RT previously reported, and both BTSG 69-01 and 72-01 showed a trend toward improved survival at 18 months in patients who received chemotherapy (BCNU) plus RT. Although the benefit of postresection RT was felt to be clearly established by the results of BTSG 69-01 and 72-01, the benefit of chemotherapy remained in question.<sup>5-7</sup>

## Defining Optimal Radiotherapy Dose and Delivery

### Optimal Radiation Doses in GBM

A subsequent publication by the BTSG evaluated the combined results from BTSG 66-01, 69-01, and 72-01,<sup>4,7</sup> with particular consideration given to whether dose escalation of RT improved survival outcomes.<sup>19</sup> In the evaluable group of 621 patients (86% with GBM), survival data were reported for subgroups based on the dose of WBRT received. Poor median survival times of 4.2 and 3.1 months were reported for patients treated with less than 4,500 cGy or no RT, respectively. Median survival durations of 6.5, 8.4, and 9.8 months were reported for patients treated with 5,000, 5,500, and 6,000 cGy, respectively. There was progressive improvement in survival with RT doses of 5,000 cGy or more, with a statistically significant difference between the groups receiving 5,000 and 6,000 cGy ( $P=.004$ ). Of importance, there was no significant difference in toxicity observed between the 5,000- and 6,000-cGy treatment groups.<sup>19</sup>

Given these results suggesting improved survival with RT doses of 5,000 cGy or greater,<sup>19</sup> interest then focused on further dose escalation of RT. Salazar and colleagues evaluated doses ranging from 6,000 to 8,000 cGy in three

**Table 3.** Median Survival in RTOG 74-01/ECOG 1374<sup>22</sup>

Treatment	N	Median Survival, months	
		Overall	GBM Subgroup
WBRT (6,000 cGy)	141	9.3	8.7
WBRT (6,000 cGy) + boost (1,000 cGy)	103	8.2	7.7
WBRT (6,000 cGy) + BCNU	156	9.7	7.8
WBRT (6,000 cGy) + methyl-CCNU + dacarbazine	138	10.1	9.2

BCNU=carmustine; GBM=glioblastoma multiforme, WBRT=whole-brain radiotherapy.

dose levels of WBRT with or without a local boost.<sup>20</sup> Over half of the patients randomized to the highest dose level received total RT doses of 7500 cGy or more. The study also included a retrospective cohort treated with more conventional doses of WBRT (5,000–5,500 cGy). Median survival in the highest level dose group was 13 months, compared with 9.8 months in the next highest dose level group and 7 months in the retrospective cohort treated with conventional doses of WBRT. The survival difference between the highest dose level group and the conventional dose group was statistically significant ( $P<.05$ ), but involved comparison with a retrospective cohort. Differences between consecutive dose levels of RT were not statistically significant, and survival curves for all dose groups were superimposable by 2 years.<sup>20</sup>

Within this same study, autopsy data were reported from 40% of the study patients, including ten autopsies from the highest dose level group.<sup>20</sup> Autopsy specimens clearly showed areas of viable tumor in the irradiated areas of patients receiving the highest doses of RT, indicating that tumor eradication was not achieved with doses of 7,000–8,000 cGy. In addition, marked radiation effect was seen microscopically in normal tissue at the periphery of tumor. Given the high risk:benefit ratio of RT doses exceeding 6,000 cGy suggested by these autopsy findings, further investigation of escalated RT doses in GBM was undertaken with caution.

In an effort to define the optimal dosing for postresection RT with or without chemotherapy, Chang and colleagues reported results from an intergroup trial evaluating standard WBRT to 6,000 cGy compared with escalated doses of RT.<sup>21,22</sup> This phase III trial included four treatment arms: 1) WBRT (6,000 cGy), 2) WBRT plus 1000 cGy boost, 3) WBRT plus BCNU, and 4) WBRT plus methyl-CCNU and dacarbazine. In contrast to the study by Salazar and associates,<sup>20</sup> this trial included a randomized arm receiving standard doses of WBRT. Essentially, escalation of RT above 6,000 cGy or the addition of chemotherapy did not significantly improve

survival outcomes beyond conventional doses of WBRT (Table 3), and subset analysis of patients with GBM revealed almost superimposable survival curves ( $P=.59$ ) among the treatment groups. Consistent with what had been reported previously in BTSG 69-01 and 72-01, the addition of concurrent BCNU did not significantly improve overall or median survival, with the exception of a trend toward improved survival among a subgroup of patients less than 60 years of age, and a trend toward improved survival at 18 months. In this study, the 18-month survival rate among patients 40–60 years old was 10.3% for 6,000 cGy RT versus 30.9% for 6,000 cGy RT plus BCNU.<sup>21,22</sup>

## Optimal Field Design

### *Whole-brain Versus Involved-field RT*

Traditionally, WBRT was utilized for the treatment of GBM primarily because of concerns that GBM may be multicentric in a significant number of cases and that available neuroradiologic techniques were relatively inaccurate in localizing the extent of disease.<sup>23-26</sup> However, subsequent data have suggested that multicentric involvement with GBM is relatively uncommon. For example, Hochberg and Pruitt reported results of serial computed tomography (CT) scans and correlative autopsy data in 35 GBM patients.<sup>25</sup> In this report, GBM was found to relapse within a 2-cm margin of the primary site in 90% of cases, and only 6% of patients treated with RT were found to have multicentric disease at autopsy. In addition, multiple studies have demonstrated that there is an upper limit to the WBRT dose in terms of both necrosis and cognitive dysfunction.<sup>27,28</sup> Given the toxicity associated with escalated doses of WBRT and the observed local failure pattern with recurrence, interest subsequently focused on maximizing dose intensification of therapy to the tumor and surrounding margin.

Beginning in the early 1970s, interest was generated in comparing outcomes of WBRT with involved-field RT

(IFRT), with IFRT defined as radiotherapy administered to the tumor and to the tissue within a 3-cm radius surrounding the tumor.<sup>29-32</sup> In a retrospective review of 127 patients receiving RT for treatment of GBM, Onoyama and colleagues reported nearly identical 1-year survival rates with IFRT compared with WBRT.<sup>29</sup> Ramsey and Brand compared two randomized groups of GBM patients treated with WBRT (median dose=4,400 cGy) or IFRT (median dose=5,300 cGy), noting improved survival outcomes in patients treated with higher doses delivered to a limited field.<sup>30</sup> In BTOG 80-01, patients with GBM were randomized to receive WBRT to a dose of 6,020 cGy or WBRT 4,300 cGy followed by IFRT to 1,720 cGy. Survival differences between the RT groups were not significantly different.<sup>27</sup> Based on these data suggesting comparable outcomes with WBRT and IFRT, IFRT has become the standard of care in the treatment of GBM.

### *Imaging Techniques in RT Field Design*

Limitations still exist with delivering RT in the treatment of GBM. Although CT and magnetic resonance imaging (MRI) have improved the ability to deliver IFRT, these imaging modalities are not reliable indicators of active or microscopic regions of tumor. Therefore, novel imaging techniques are under investigation as a means of more effectively targeting areas of tumor. One such technique is magnetic resonance spectroscopy imaging (MRSI; also termed chemical shift imaging), which provides information about tumor activity based on levels of cellular metabolites (eg, choline, creatine, N-acetylaspartate, and lactate). MRSI relies on the detection of alterations in these metabolite levels in predicting areas of occult disease; theoretically, targeting these areas of occult disease may decrease the rates of local relapse.<sup>33</sup>

Graves and colleagues performed a retrospective study in which the prognostic value of MRSI was explored in patients with high-grade gliomas treated with gamma-knife radiation.<sup>34</sup> Patients without MRSI activity outside the areas of MRI contrast enhancement had significantly better outcomes than patients with MRSI activity outside the region of MRI contrast enhancement. In a study of 34 patients with high-grade gliomas, Pirzkall and colleagues found metabolically active tumors outside the region of enhancement ( $\leq 28$  mm) on T2-weighted MRIs in 88% of patients. Interestingly, MRIs in general predicted a larger volume of microscopic disease by 50% or more compared with MRSI, suggesting that targeted RT based on results of anatomic versus metabolic imaging would likely be of significantly different sizes and locations.<sup>33</sup>

Additional imaging modalities under investigation include positron emission tomography (PET) using methyl-11C-L-methionine (MET) and 3-iodine-123 ( $I^{123}$ )

- $\alpha$ -methyl-tyrosine single-photon emission tomography (IMT-SPECT).<sup>35,36</sup> Experience using IMT-SPECT in 30 patients with unresected gliomas found that the IMT region of abnormality was 69% greater than the region of enhancement on T1-weighted contrast MRI imaging.<sup>37</sup> One particular limitation of these imaging modalities is their inability to differentiate areas of active tumor cells from necrosis. Although these novel imaging techniques are of ongoing interest, they have yet to become a standard diagnostic approach in the evaluation and treatment of GBM.

### **Dose Intensification Approaches: Brachytherapy, Radiosurgery, and Hyperfractionation**

In an effort to improve outcomes in GBM, various strategies aimed at improving the local dose intensification of RT have been explored. Such strategies have included alternative means of delivering RT (brachytherapy, radiolabeled antibodies, radiosurgery), alternative dosing schedules (accelerated and hyperfractionated RT), and the use of radiosensitizing agents.

#### *Brachytherapy*

Interstitial delivery of RT (ie, brachytherapy) directs RT to a well-defined tumor bed, thereby sparing normal brain tissue from the toxicity of high-dose RT and theoretically allowing for treatment of even RT-resistant hypoxic tumor cells.<sup>38-40</sup> Significant prior research has evaluated different means of delivering interstitial brachytherapy, leading to debate as to whether isotopes should be permanently or temporarily implanted and which radioisotopes are best suited for treatment of gliomas.

Some of the earliest reports of brachytherapy in the 1980s focused on patients with local relapse of brain tumors who had previously received RT.<sup>39-43</sup> Later, focus shifted to using brachytherapy as a local boost with IFRT in cases of newly diagnosed GBM.<sup>44-48</sup> A Northern California Oncology Group study (NCOG 6G-82-2)<sup>44</sup> reported a remarkable median survival of 20.5 months in newly diagnosed GBM patients treated with iodine-125 ( $I^{125}$ ) implants following 6,000 cGy IFRT. Some criticisms of the NCOG trial are that a comparison group receiving IFRT alone was not included and only patients with smaller, more peripherally located, tumors were enrolled. In addition, 38 patients of the original cohort of 67 had been excluded after demonstrating no response to IFRT. Therefore, although this NCOG study observed the best survival outcomes ever reported by the NCOG<sup>44,49</sup> or the BTOG (longest median survival= $\sim 12$ -13 months),<sup>27,50</sup> it is likely that the NCOG experience with brachytherapy represents a subpopulation of GBM patients with favor-

**Table 4.** Brachytherapy in Newly Diagnosed Glioblastoma Multiforme

Trial	N	Treatment	Median Survival, months
NCOG 6G-82-2 <sup>44</sup>	29*	IFRT 6,000 cGy I <sup>125</sup> implants	20.5
Lapierre et al <sup>45</sup>	63	IFRT to 5,000 cGy I <sup>125</sup> implants	13.8
		IFRT to 5,000 cGy	13.2
BTCG 87-01 <sup>38</sup>	270	I <sup>125</sup> implants (6,000 cGy) + BCNU	15.8
		IFRT to 6,020 cGy + BCNU	13.7

BCNU=carmustine; IFRT=involved-field radiotherapy.

\*Survival outcomes reported for 29 of the original cohort of 67 patients; 38 patients were excluded after failing to respond to IFRT.

able outcomes based on tumor size, location, and initial response to IFRT.

In contrast, Laperriere and colleagues in a Canadian study failed to demonstrate a significant survival advantage with I<sup>125</sup> implants following standard IFRT to 5,000 cGy.<sup>45</sup> However, the interpretation of these results is limited by the suboptimal doses of IFRT administered. More recently, BTCG 87-01 evaluated survival in newly diagnosed malignant glioma patients treated with the combination of BCNU and either IFRT or brachytherapy.<sup>38</sup> Median survival was not significantly different between the groups, and no survival advantage was observed on subgroup analysis of the patients with GBM (Table 4).<sup>38</sup>

In summary, despite the favorable results reported in single-arm studies using brachytherapy as part of initial therapy for GBM, randomized studies comparing brachytherapy with standard IFRT have failed to show a significant survival difference. In addition, brachytherapy requires invasive procedures for placement. Complications may occur during placement and potentially during later removal of the isotopes, and isotopes that shift in position after placement may require surgical intervention. For example, Laperriere and colleagues reported 15 complications (eg, neurologic decline requiring high-dose steroids, intracerebral bleeding, exacerbation of seizures, infection, and arterial occlusion) in the relatively small cohort of 63 patients who underwent brachytherapy.<sup>45</sup> With the current lack of evidence to support brachytherapy in the treatment of newly diagnosed GBM, its role in clinical practice outside of a clinical trial is primarily limited to the setting of recurrent disease.

#### ***GliaSite Radiation Therapy System***

The GliaSite Radiation Therapy System (Cytec) received Food and Drug Administration approval in 2001 as a

novel means of brachytherapy delivery for the treatment of high-grade gliomas. The GliaSite device is placed at the time of tumor debulking with an expandable balloon that is temporarily filled with radioactive I<sup>125</sup> liquid through a subcutaneous reservoir. The balloon reservoir of the GliaSite system adheres to the walls of the resection cavity, allowing homogenous dosing of radiation to the surrounding brain tissue.<sup>51</sup> Potential advantages with GliaSite include the ability to deliver a more homogenous dose distribution to tissue at risk in the resection cavity, the need for only a single operative procedure for placement (which generally parallels resection of disease), and the possibility of lower risk for infection due to limited percutaneous access to the brain.<sup>51-53</sup>

A multicenter study by the NABTT (New Approaches to Brain Tumor Therapy) Central Nervous System Consortium investigating GliaSite in the treatment of recurrent malignant gliomas determined that the GliaSite system delivers brachytherapy safely and efficiently. Patients in the NABTT study received 4,000–6,000 cGy to the target volume via the GliaSite system, and a median survival of 12.7 months was observed in this population with recurrent disease.<sup>54</sup> Based on these results, ongoing studies are being carried out to further evaluate the efficacy of the GliaSite system in newly diagnosed and recurrent high-grade gliomas.

#### ***Radioimmunotherapy***

Another novel means of delivering local therapy involves the use of radiolabeled antibodies targeting malignant brain tissue. Investigators at Duke University have been studying the efficacy of an iodine-131–labeled murine antitenascin monoclonal antibody (<sup>131</sup>I-m81C6) in the treatment of newly diagnosed and recurrent brain tumors. Tenascin is an extracellular matrix glycoprotein expressed

ubiquitously in multiple tumor types, including high-grade brain gliomas, but not in normal brain tissue. The murine monoclonal immunoglobulin G2b (81C6) binds to an epitope within tenascin, resulting in inhibition and delay of cell growth.<sup>55-57</sup> Administration of <sup>131</sup>I-m81C6 involves direct injection of the agent into the resection cavity at the time of tumor debulking.<sup>55,58,59</sup>

A phase II study of newly diagnosed glioma patients treated with <sup>131</sup>I-m81C6 followed by conventional IFRT and chemotherapy reported a median survival of 20 months, with a median survival of 18 months in the subgroup of patients with GBM.<sup>60</sup> A more recent study of <sup>131</sup>I-m81C6 in cases of recurrent malignant brain tumors reported a median survival of 15 months in a subgroup of patients with GBM and gliosarcoma.<sup>55</sup> This phase II experience yielded survival results comparable to or more favorable than what had been reported in other salvage therapies (including temozolomide [TMZ; Temodar, Schering], stereotactic radiosurgery, interstitial chemotherapy, and brachytherapy).<sup>61-63</sup> In addition, rates of radionecrosis in the phase II trials of <sup>131</sup>I-m81C6 were lower than rates observed with other methods of boost radiotherapy.<sup>55</sup> However, these survival results and rates of neurotoxicity must be interpreted in light of the overall good performance status of the patient groups analyzed (ie, Karnofsky performance status >80 in >90% of patients). In addition, the fixed millicurie dosing was observed to lead to a wide range of radiation doses delivered to the 2-cm resection margin, which could explain the low rates of neurotoxicity observed.<sup>55</sup> Nevertheless, the results to date with this method of radioimmunotherapy are promising; a phase III study at Duke University using patient-specific dosimetry planning and antibody dosing in patients with newly diagnosed and recurrent gliomas is ongoing.

### **Stereotactic Radiosurgery**

Radiosurgery involves the precise delivery of high-dose radiation, generally in a single treatment.<sup>64</sup> Although radiosurgery was first administered to a patient in 1968, skepticism over the technology and cost constraints resulted in slow generalized acceptance of this technology.<sup>65</sup> Classically, radiosurgery was delivered with a gamma knife device using cobalt-60 sources, but more recently, similar radiosurgery dose distributions have been achieved with a linear accelerator.<sup>66</sup> With the advances in hardware along with the introduction of linear accelerator-based radiosurgery in the 1980s, radiosurgery has become commonplace in the management of brain metastasis and recurrent gliomas.

Stereotactic radiosurgery (SRS) involves the use of numerous beamlets of radiation aimed precisely at an immobilized target to deliver high-dose radiation. Although no single beamlet carries significant energy,

a large dose is deposited at the intersection of these beamlets, with a steep dose fall-off outside the target. As tumor size increases, this fall-off becomes shallower, and typically radiosurgery becomes prohibitive with tumors in excess of 4–5 cm.<sup>67</sup> Because SRS involves a higher dose per treatment, there is increased biologic effect on the normal tissues, which may influence the development of late side effects.<sup>68</sup> As a result, single-fraction radiosurgery must be precisely delivered to minimize the dose to normal structures.

Several early retrospective reports of SRS in the setting of recurrent gliomas suggested a survival advantage with SRS.<sup>69-71</sup> For example, retrospective data from the University of Maryland comparing survival data in GBM patients treated with IFRT followed by SRS as a local boost or SRS at the time of progression found that median survivals favored the group receiving an SRS boost (25 vs 13 months;  $P=.0335$ ).<sup>69</sup> RTOG 93-05 evaluated SRS in a randomized study of 203 patients with GBM who received either conventional IFRT (6,000 cGy) plus BCNU or SRS prior to IFRT plus BCNU.<sup>72</sup> In this study there were no significant differences in median survival (13.5 months for SRS vs 13.6 months for conventional IFRT), 2-year overall survival, quality-of-life deterioration, or cognitive decline.<sup>72</sup> Therefore, outside the setting of a clinical trial, there is no clearly defined role for the administration of SRS in the treatment of newly diagnosed GBM.

### **Stereotactic Radiotherapy**

Stereotactic radiotherapy involves precisely targeted fractionated radiation treatment, often delivered at higher doses per fraction over several treatments. This is in contrast to radiosurgery, in which high doses are typically given in a single treatment. RTOG 98-03 investigated escalated doses of stereotactic radiotherapy in newly diagnosed GBM, with patients receiving IFRT to 4,600 cGy followed by a stereotactic radiotherapy boost to total doses of 6,600–8,400 cGy. The acute and late toxicity data in this population were promising, with no difference in late RT-related grade 3 or 4 toxicities at the escalated dose levels of RT, and similar percentages of patients at each dose level requiring second resections.<sup>73</sup>

Subsequently, the RTOG reported its phase II experience with administering accelerated RT with weekly stereotactic conformal boosts in 76 patients with newly diagnosed GBM (RTOG 00-23).<sup>74</sup> During the course of standard RT to 5,000 cGy, patients received four weekly fractionated stereotactic RT boosts (500 cGy or 700 cGy per fraction), for a total cumulative dose of 7,000–7,800 cGy. Although reported toxicities were manageable, the median survival of 12.5 months was not improved compared with the RTOG historical database.<sup>74,75</sup> However, a trend for improved survival was observed in subgroups of

**Table 5.** Hyperfractionated and Accelerated Radiotherapy in Glioblastoma Multiforme

Trial	N	Treatment	Median Survival, months
EORTC <sup>78</sup>	66	200 cGy thrice daily to: 4,200 cGy 4,800 cGy 5,400 cGy 6,000 cGy	8.7
Lutterbach et al <sup>79</sup>	149	150 cGy thrice daily to 5,400 cGy	8.8
Neider et al <sup>80</sup>	126	130 cGy twice daily to 7,800 cGy	7–10
		150 cGy twice daily to 6,000 cGy	
Prados et al <sup>81</sup>	231	AHFRT ± DFMO 160 cGy twice daily to 7,040 cGy	8.6–9.8
		Standard RT ± DFMO 180 cGy daily to 5,940 cGy	
RTOG 83-02 <sup>82</sup>	786	HFRT 120 cGy twice daily to: 6,480 cGy 7,200 cGy 7,680 cGy 8,160 cGy	10.8–12.7*
		AHFRT 160 cGy twice daily to: 4,800 cGy 5,440 cGy	
RTOG 90-06 <sup>83,84</sup>	712	HFRT + BCNU 120 cGy twice daily to 7,200 cGy	19.8 <sup>†</sup>
		Conventional RT + BCNU: 200 cGy daily to 6,000 cGy	21.9 <sup>†</sup>

AHFRT=accelerated hyperfractionated radiotherapy; BCNU=carmustine; DFMO=difluoromethylornithine; HFRT=hyperfractionated radiotherapy.

\*Subgroups with GBM treated with HFRT at higher doses of 7,680 and 8,160 cGy had better survival than GBM patients treated with AHFRT.

<sup>†</sup>Survival data reported in GBM subgroup ≤50 years old (P=.05).

patients undergoing gross total resection (median survival 16.1 vs 12.0 months; P=.19). In addition, a subgroup of patients classified as having more favorable disease according to a recursive partitioning analysis (RPA) model proposed by Curran and colleagues were noted to have an improved median survival (14.7 months for RPA class IV patients versus 11.3 months for the overall study group; P=.15).<sup>74,75</sup>

***Hyperfractionated and Accelerated Radiotherapy***

Hyperfractionation of radiotherapy involves the more frequent administration of RT doses to achieve several theoretical advantages, including reduction in the late effects of RT injury and prevention of tumor repopulation between treatments.<sup>76</sup> In addition, small doses of

RT given more than once daily may produce a redistribution of proliferating tumor cells that results in some tumor cells entering an RT-sensitive stage. In summary, hyperfractionated radiotherapy (HFRT) offers the potential advantage of giving higher cumulative doses of RT without significant additional toxicity.<sup>76,77</sup>

Much of the experience with HFRT in GBM has not suggested a survival advantage compared with standard doses and fractionation of RT. For example, the European Organization for the Research and Treatment of Cancer (EORTC) reported its experience with administering accelerated HFRT to doses of 4,200–6,000 cGy in 200-cGy fractions three times daily. An overall median survival of 8.7 months was observed, with no differences in survival noted among any of the dose levels admin-

istered.<sup>78</sup> Several other investigators reported similar results with accelerated HFRT failing to achieve significant improvements in median survival over conventional IFRT (Table 5).<sup>79-81</sup>

In contrast, data from RTOG 83-02 suggested a promising role for HFRT in the treatment of GBM.<sup>82</sup> Patients were randomized to either HFRT or accelerated HFRT (AHFRT), with median survivals of 10.8–12.7 months reported (Table 5). However, survival outcomes in the subgroup of patients with GBM receiving higher HFRT doses of 7,680 and 8,160 cGy were superior to the survival outcomes observed in patients in the AHFRT group.<sup>82</sup>

RTOG 90-06 was initiated specifically to address whether higher doses of HFRT offered benefit over standard doses and fractionation of RT in GBM. In this phase III study patients were randomized to HFRT (120 cGy twice daily to 7,200 cGy) plus BCNU versus conventional RT (6,000 cGy) plus BCNU.<sup>83,84</sup> Ultimately, there was no survival advantage seen in the HFRT group and, in fact, the outcome in the conventional RT group was superior for patients 50 years of age or older (median survival of 21.9 months vs 19.8 months;  $P=.05$ ); this trend was also observed on subgroup analysis of patients with GBM.<sup>83,84</sup>

### Radiosensitizers: Hypoxic Sensitizers, S-Phase Sensitizers, and Novel and Targeted Agents as Sensitizers

Another strategy to improve the local dose intensification of radiation is the use of systemic agents, typically chemotherapy agents or targeted agents, to enhance the efficacy of RT. Here we describe the previous experience with potential radiosensitizers ultimately found to be ineffective, as well ongoing experience with promising radiosensitizing agents (Table 6).

**Hypoxic Sensitizers: Imidazoles, RSR13, Tirapazamine**  
**Imidazoles** The nitroimidazole compounds metronidazole and misonidazole are orally administered agents able to achieve good penetration of the blood-brain barrier. In a small randomized trial, Urtasun and colleagues initially reported a survival advantage with the use of metronidazole,<sup>85</sup> but other trials have failed to duplicate a similar benefit (Table 7).<sup>86-89,93</sup> Similarly, a survival advantage with misonidazole first reported by the Vienna Study Group in 1981 was no longer significant by the time of its updated report in 1984.<sup>90,91</sup> Subsequently, a double-blind randomized trial conducted by the Medical Research Council found no difference in median survival between patients treated with RT to 4,500 cGy in combination with either misonidazole or placebo.<sup>92</sup>

**RSR13** RSR13 (efaproxiral) showed early promise as a radiosensitizing agent with a novel mechanism of action. As a synthetic allosteric modifier of hemoglobin, RSR13 noncovalently binds to the hemoglobin tetramer and decreases the hemoglobin-oxygen binding affinity, resulting in an increase in tissue  $PO_2$ . In contrast to other hypoxic radiosensitizing agents, the hypothesized radiation-enhancing effect of RSR13 does not rely on direct diffusion of the agent into a tumor cell.<sup>94</sup> Results of a phase III study of RSR13 plus WBRT versus WBRT alone in brain metastases from solid tumors demonstrated the greatest benefit of RSR13 in the subgroup of patients with metastatic breast cancer.<sup>95,96</sup> In GBM, phase II data with RSR13 plus IFRT demonstrated a median survival of 12.3 months, with 1-year and 18-month survival rates of 54% and 24%, respectively.<sup>97</sup> However, a subsequent phase III study in brain metastases from breast cancer (the ENRICH trial) comparing RSR13 plus WBRT versus WBRT alone failed to demonstrate a survival advantage with RSR13. The disappointing results from the ENRICH trial have called into question the value of RSR13 as a radiosensitizing agent.

**Tirapazamine** Tirapazamine is a bioreductive agent with enhanced toxicity for hypoxic cells.<sup>98</sup> An attractive feature of this agent is its unique margin of safety, with a large differential between lower doses required to damage hypoxic cells and much higher doses needed to exhibit toxicity to normally oxygenated cells. A phase II trial of two dose levels of tirapazamine given with standard IFRT to 6,000 cGy in newly diagnosed GBM (RTOG 94-17) observed median survivals of 10.8 and 9.5 months. In comparing survivals among the tirapazamine-treated patients with matched RPA class controls from the RTOG database, no significant improvement in survival outcomes with the addition of tirapazamine was noted.<sup>75,99</sup>

### S-Phase Sensitizers

**Halogenated Pyrimidines** Halogenated pyrimidines are incorporated into the DNA of dividing cells due to their biochemical similarity to thymidine. After being incorporated, cells are much more susceptible to single-strand breaks from radiation-induced free radicals and have an impaired ability to repair DNA.<sup>100-102</sup> Early clinical trials focused on intra-arterial infusion of bromodeoxyuridine (BrdU), but later it was determined that prolonged intravenous infusion could achieve radiosensitization equivalent to intra-arterial administration with fewer complications.<sup>103</sup>

Phase I and II studies evaluating continuous infusion of iododeoxyuridine with hyperfractionated RT reported median survivals of 11–15 months.<sup>101,104,105</sup> In another

(Continued on page 907)

(Chang et al, continued from page 902)

**Table 6.** Experience with Radiosensitizers in Glioblastoma Multiforme

Agent	Activity superior to RT?	Comments
<b>Hypoxic sensitizers</b>		
Imidazoles	No	Negative double-blind, placebo-controlled randomized trial
RSR13	No*	Phase II experience with RSR13 + RT in GBM favorable; drug development discontinued due to negative phase III data in brain metastases
Tirapazamine	No	Phase II data no better than RTOG database historical controls
<b>S-phase sensitizers</b>		
Halogenated pyrimidines	No	Some comparisons with RTOG database suggested benefit to BrdU, but no randomized study proving benefit
<b>Cytotoxic agents</b>		
Camptothecans	No	Data with topotecan no better than IFRT alone; newer camptothecans (eg, irinotecan) unproven to date
Platinums	No	Phase III data with cisplatin/RT vs RT alone showed no difference in outcomes
Taxanes	No	Phase II data no better than historical controls; interference with taxane metabolism by anticonvulsants may have influenced outcomes
Temozolomide	Yes	Phase III data showing survival advantage with TMZ + RT followed by adjuvant TMZ
<b>Novel agents</b>		
Motexafin gadolinium	Potential	Preliminary phase II data promising in GBM
Antiangiogenesis agents (thalidomide, bevacizumab)	Potential	Ongoing phase II studies with RT + bevacizumab and thalidomide
<b>Targeted therapies</b>		
Tamoxifen	No	Phase II data no better than historical controls
Anti-EGFR (gefitinib, erlotinib)	No	Gefitinib studies in GBM no better than RT alone; ongoing studies evaluating erlotinib + RT + TMZ
mTOR inhibitors (temsirolimus, RAD001)	Potential	Role for CCI-779 and RAD001 undefined; promising objective responses with both agents
Farnesyltransferase inhibitors (tipifarnib)	Potential	Modest activity in relapsed GBM; role as a radiosensitizer undefined
Imatinib	Potential	Phase II data in recurrent GBM with modest activity; role as a radiosensitizer undefined

GBM=glioblastoma multiforme; IFRT=involved-field radiotherapy; RT=radiotherapy; RTOG=Radiation Therapy Oncology Group; TMZ=temozolomide.

\*Inactivity as a radiosensitizer proven only in brain metastases.

report, the NCOG observed an improvement in progression-free survival among a subgroup of patients receiving higher cumulative doses of BrdU.<sup>106,107</sup> This observation led to a subsequent single-institution trial at The University of Texas M. D. Anderson Cancer Center investigating significantly higher doses of BrdU concurrent with hyperfractionated RT.<sup>102</sup> Unfortunately, median survival was

not improved at 12–13 months, and significant toxicities were observed with the escalated dose of BrdU.

The NCOG later published data comparing survivals from pooled patient data within the NCOG (patients treated with BrdU + RT)<sup>106</sup> with a similar population of patients from the RTOG database (patients not receiving BrdU).<sup>22,89,108</sup> Overall, this combined data analysis reported

**Table 7.** Experience with Imidazole Radiosensitizers in Gliomas

Study	N	RT Dose	Imidazole	Median Survival, weeks	P value
Urtasun et al <sup>85</sup>	15	3,000 cGy	—	15	<.02
	16	3,000 cGy	MNZ	26	
Urtasun et al <sup>86</sup>	19	5,800 cGy	—	26	NS
	23	3,900 cGy	MISO	27	
	17	3,900 cGy	MNZ	19	
Bleehan et al <sup>87</sup>	20	5,656 cGy	—	36	NS
	18	4,352 cGy	—	31	
	17	4,352 cGy	MISO	39	
EORTC <sup>93</sup>	81	4,950 cGy	Placebo	46	NS
	82	4,950 cGy	MISO	45	
RTOG 78-01 <sup>88</sup>	54	6,000 cGy	MISO	39	—
RTOG 79-18 <sup>89</sup>	146	6,000 cGy	—	55	0.35
	147	6,000 cGy	MISO	46	
Vienna Study Group <sup>91</sup>	27	6,650 cGy	—	43	>.08
	18	6,650 cGy	MISO	60	
MRC <sup>92</sup>	195	4,500 cGy	Placebo	36	0.7
	188	4,500 cGy	MISO	33	

MISO=misonidazole; MNZ=metronidazole; NS=not statistically significant; RT=radiotherapy.

a median survival of 16.9 months for the NCOG patients who had received BrdU compared with 9.8 months for the RTOG control group ( $P<.0001$ ).<sup>106</sup> However, there were many limitations with this comparison, including wide variations among RT fractions, total RT dose, use of chemotherapy, and use of other potential radiosensitizers. A randomized phase III study would be needed to clearly establish a potential role for BrdU in the treatment of GBM.

#### **Radiosensitizing Agents: Cytotoxic Chemotherapy Agents**

**Topotecan** Camptothecins are systemic agents able to effectively penetrate the blood-brain barrier and are hypothesized to act as radiation sensitizers by preventing DNA repair through inhibition of the topoisomerase I enzyme.<sup>109,110</sup> Previous experience in phase I and II trials of newly diagnosed and relapsed GBM patients has shown responses with single-agent topotecan.<sup>111,112</sup>

RTOG 95-13 evaluated topotecan (Hycamtin, GlaxoSmithKline) as a radiosensitizer in newly diagnosed GBM, but the reported median survival of 9.3 months

was not significantly different from matched historical controls in the RTOG database.<sup>113</sup> Other camptothecins (eg, irinotecan [Camptosar, Pfizer]) may prove more effective than topotecan. Some early experience with irinotecan in recurrent gliomas has shown promise,<sup>114</sup> and ongoing trials are being considered with irinotecan and newer camptothecins.<sup>115</sup> Recent data with the combination of irinotecan and the vascular endothelial growth factor (VEGF) inhibitor bevacizumab (Avastin, Genentech) showed a response rate of 64% in patients with recurrent gliomas.<sup>115</sup>

**Platinum Agents** Preclinical studies with platinum agents have suggested that these chemotherapeutic drugs are able to inhibit the repair of radiation-induced damage and potentially exert a direct cytotoxic effect on glioma cells.<sup>116,117</sup> Although some early experience with platinum agents concurrent with RT in GBM suggested a benefit,<sup>118</sup> a phase III intergroup trial comparing continuous-infusion cisplatin in combination with RT with conventional RT found no significant difference in survival between the groups.<sup>119</sup>

**Taxanes** Based on preclinical studies showing activity of paclitaxel as a radiosensitizing agent in malignant glioma cell lines,<sup>120-122</sup> the RTOG performed a phase II study (RTOG 96-02) evaluating the feasibility and efficacy of conventional RT and concurrent weekly paclitaxel in newly diagnosed GBM.<sup>121</sup> An objective response was observed in 23% of the patients, with an observed median survival of 9.7 months. Despite this promising response rate, the median survival was not improved compared with historical controls from the RTOG database.<sup>121</sup> However, the concurrent use of anticonvulsant therapy in essentially all GBM patients may have contributed to escalated rates of paclitaxel metabolism, and the potential of paclitaxel as a radiosensitizing agent may have been unevaluable.

**Temozolomide** TMZ is a novel alkylating agent with activity in primary and recurrent gliomas,<sup>123-126</sup> with preclinical data demonstrating additive or even synergistic activity in combination with RT.<sup>127-129</sup> Several multicenter phase II trials had previously established the efficacy of TMZ in the treatment of relapsed GBM,<sup>63,130</sup> with additional data demonstrating the feasibility of administering TMZ prior to and concurrent with RT.<sup>131,132</sup> However, Stupp and colleagues reported groundbreaking data in their phase III trial showing a survival benefit with concurrent TMZ and RT compared with conventional RT alone.<sup>133</sup> In this study, patients with newly diagnosed GBM received TMZ 75 mg/m<sup>2</sup>/day for 6–7 weeks during RT followed by 6 months of adjuvant therapy. The rationale for daily dosing of TMZ was based on previous experience showing that resistance to TMZ appears to be mediated in part through the DNA repair enzyme O-6-methylguanine DNA methyltransferase (MGMT). MGMT levels are virtually depleted with continuous exposure to TMZ, leading to interest in daily dosing schedules, particularly during RT.<sup>134</sup>

In the Stupp study, median survivals of 14.6 and 12.1 months were reported for the TMZ-plus-RT versus RT-alone groups, respectively. Two-year survival again favored the combination of TMZ plus RT (26% vs 10% for RT alone).<sup>133</sup> A retrospective analysis of tissue samples from both arms of the study generated intriguing data, including additional data to support the role of MGMT in determining resistance to chemotherapy and RT.<sup>135</sup> Among the 92 assessable cases with evidence of MGMT promoter methylation (ie, transcriptionally inactive and not producing the DNA repair enzyme MGMT), a statistically significant improvement in survival was observed in patients receiving TMZ plus RT compared with RT alone (21.7 vs 15.3 months, respectively;  $P=.007$ ). Approximately 60% of patients in the control arm received TMZ at recurrence and survival among these patients with pro-

moter methylation was significantly better than for patients with an unmethylated promoter (overall survival 15.3 vs 11.8 months, respectively).<sup>135</sup>

Data from a German study by Combs and colleagues confirmed the RT-potentiating effect of TMZ.<sup>136</sup> In this study patients received a lower dose of TMZ (50 mg/m<sup>2</sup>/day) concurrent with standard IFRT to 6,000 cGy without the administration of adjuvant TMZ. The overall median survival of 19 months was comparable to survival data reported by Stupp and associates, suggesting that the most significant benefit with TMZ is gained from its activity as a radiosensitizer and further suggesting that even low doses have clinically significant activity with lower rates of toxicity.<sup>136</sup> Although the Stupp and Combs studies demonstrate the first new therapeutic strategy in GBM with a survival advantage in several decades, the survival gain is modest and there is clearly room for improvement in management of GBM. Ongoing trials are investigating TMZ in combination with other novel chemotherapy agents, targeted agents, and radiosensitizing agents.

#### ***Radiosensitizing Agents: Novel Agents***

**Motexafin Gadolinium** Motexafin gadolinium (MGd) is a metallotetraphyrin that catalyzes the oxidation of intracellular-reducing metabolites and generates reactive oxygen species. These reactive oxygen species selectively concentrate in tumor cells and promote apoptosis, and tumor cells that have taken up MGd are visualized by MRI due to the paramagnetism of gadolinium.<sup>137,138</sup> Initial interest with MGd centered on its use in treatment of brain metastases.<sup>139-141</sup> A later phase III study (the SMART trial) in brain metastases from solid tumors did not demonstrate a survival advantage with WBRT plus MGd compared with WBRT alone, but did demonstrate a statistically significant difference in time to neurologic progression favoring MGd within a subgroup of lung cancer patients.<sup>142</sup> The most recent follow-up data from the SMART trial showed promising results favoring MGd in terms of time to neurologic progression following randomization (15.4 vs 10.0 months;  $P=.12$ ) or following the diagnosis of brain metastases (15.5 vs 10.2 months;  $P=.05$ ). Among the subgroup of 348 patients treated in North America where time from diagnosis to randomization tended to be shortest (60% of patients randomized within 2 weeks of diagnosis), the time to neurologic progression significantly favored MGd (24.2 vs 8.8 months;  $P=.004$ ).<sup>143</sup>

Similarly, experience with MGd in gliomas shows promise. A phase I dose escalation study in GBM reported an impressive median survival of 17.3 months.<sup>144</sup> A subsequent phase II study treated 25 newly diagnosed GBM patients concurrently with MGd and RT, and the median

survival had not been reached after a median follow-up of 8.1 months.<sup>145</sup>

**Antiangiogenesis Agents** Gliomas are among the most angiogenic of solid tumors, with overexpression of multiple angiogenic factors, including VEGF and basic fibroblast growth factor.<sup>146-149</sup> In vitro studies with multiple malignant cell lines exposed to the VEGF inhibitor SU5416 found greater-than-additive effect when VEGF inhibition was combined with RT.<sup>150</sup>

The antiangiogenic properties of thalidomide (Thalomid, Celgene) have made it an agent of particular interest in malignant gliomas. Initial experience with thalidomide as a single agent in the setting of recurrent GBM showed thalidomide to be well tolerated.<sup>151</sup> A more recent report evaluated thalidomide given concurrently with RT to 6,000 cGy, with over half of patients also receiving adjuvant TMZ.<sup>147</sup> A time to progression of 8.4 months and an overall survival of 24 months was observed in the group receiving thalidomide plus TMZ. An ongoing prospective double-blind phase II trial is underway to further evaluate the efficacy of this combination of agents.<sup>147</sup>

Other antiangiogenic agents (eg, the thalidomide analog lenalidomide [Revlimid, Celgene]) and anti-VEGF agents (eg, bevacizumab, AZD2171, sorafenib [Nexavar, Bayer]) are being evaluated in the treatment of GBM.<sup>152,153</sup> As described above, promising results were reported recently with the combination of bevacizumab and irinotecan in recurrent GBM.<sup>115</sup>

#### **Radiosensitizing Agents: Targeted Therapies**

Multiple genetic abnormalities have been described in GBM, including amplification and mutation of the epidermal growth factor receptor (*EGFR*) gene, loss of the tumor suppressor gene *P TEN*, overexpression of platelet-derived growth factor (PDGF) receptor  $\alpha$ , and mutation of the gene encoding the tumor protein p53.<sup>154-159</sup> Ongoing recognition of these genetic abnormalities has led to a rapid increase in the development of small molecular inhibitors with the ability to specifically target these amplified or aberrant pathways. Experience with several of these agents, particularly when administered concurrently with radiotherapy, is described below.

**Tamoxifen** Proliferation of high-grade gliomas appears to be at least partially dependent on the activation of protein kinase C (PKC)-mediated pathways, which play a crucial role in signal transduction,<sup>160,161</sup> and several preclinical studies have demonstrated that PKC inhibition enhances the effects of ionizing radiation.<sup>162-165</sup> The RTOG recently reported its experience in GBM with the PKC inhibitor tamoxifen at high doses of 80 mg/m<sup>2</sup> administered daily concurrent with conventional RT. Ultimately, median

survival was found to be 9.7 months, which was not significantly different from historical controls in the RTOG database.<sup>164</sup> However, as tamoxifen is well tolerated and has the convenience of oral dosing, it remains an agent of ongoing potential interest, particularly as part of treatment regimens combined with other targeted agents to achieve the goal of multilevel intracellular signaling blockade.

**EGFR Inhibitors** Multiple preclinical models have demonstrated increased radiosensitivity with EGFR inhibition.<sup>166,167</sup> Chakravarti and colleagues reported their experience with several malignant glioma cell lines with strong overexpression of EGFR found to be resistant to both RT and BCNU.<sup>168</sup> Interestingly, the sensitivity to subsequent radiotherapy and BCNU was found to be restored among these radiation- and chemotherapy-resistant cell lines following EGFR inhibition with the agent AG1478.<sup>168</sup>

In phase I and II studies of the EGFR/tyrosine kinase inhibitor gefitinib (Iressa, AstraZeneca) in relapsed GBM, there was no evidence of improvement in median time to progression or survival, although several patients were noted to have prolonged responses or periods of stable disease.<sup>169</sup> Similarly, phase II testing of gefitinib in cases of newly diagnosed GBM following standard RT did not find improvement in overall or progression-free survival, and EGFR amplification was not associated with improved overall or progression-free survival.<sup>170</sup> The role of gefitinib as a radiosensitizing agent in newly diagnosed GBM was investigated in RTOG 0211, in which patients received gefitinib concurrently with RT followed by gefitinib maintenance until the time of relapse. A median progression-free survival of 5.1 months was observed and the reported median survival of 11.0 months was not significantly improved from historical controls.<sup>171</sup>

The EGFR/tyrosine kinase inhibitor erlotinib (Tarceva, Genentech/OSI) is a particularly attractive targeted agent given its activity against both wild-type EGFR and the most common mutant form of EGFR, EGFR-vIII.<sup>172</sup> Previous experience with erlotinib in relapsed GBM showed promising activity,<sup>173,174</sup> which led to further trials investigating erlotinib in combination with RT and other chemotherapy agents (eg, TMZ).<sup>175,176</sup> The North Central Cancer Treatment Group recently published its phase I experience with erlotinib given concurrently with RT followed by maintenance erlotinib until progression. In a preliminary report, the median time to progression was 6 months, with a median survival of 12.8 months.<sup>176</sup> However, given the results reported by Stupp and coworkers<sup>133</sup> showing improved survival with TMZ given concurrently with RT in GBM, the protocol was amended to include TMZ in combination with erlotinib. Accrual is ongoing, and the combination of the two radiosensitizing agents shows promise in further improving patient outcomes.

**mTOR Inhibitors** Temsirolimus (Torisel, Wyeth) is an analog of the immunosuppressant agent sirolimus (rapamycin), which has an established role in organ anti-rejection therapy. Temsirolimus forms a complex that interacts with the mammalian target of rapamycin (mTOR) kinase, resulting in inhibition of key signal transduction pathways necessary for cell-cycle progression.<sup>177,178</sup> The mTOR kinase is downstream of PI3K in the PI3K/Akt signaling pathway, and this pathway may be activated by several factors, including ligand binding to EGFR and mutations of the tumor suppressor gene *PTEN*, which is affected by mutations/deletions in 30–40% of GBM cases.<sup>154,156,179</sup>

A phase II study of patients with recurrent GBM treated with weekly temsirolimus noted no objective responses to therapy but did find that 36% of patients had evidence of regression on neuroimaging. Although the median overall survival (4.4 months) and time to progression (2.3 months) did not yield impressive results, a trend toward improved time to progression was noted in patients with regression on imaging versus nonresponders (5.4 vs 1.9 months, respectively).<sup>179</sup> In another phase II study of weekly temsirolimus in recurrent GBM, two partial responses and 20 stabilization-of-disease responses were observed. However, the duration of responses was disappointing, with a median time to progression of only 2.1 months.<sup>178</sup>

Another mTOR inhibitor, RAD001 (Novartis), was recently tested in combination with the EGFR inhibitor gefitinib in patients with metastatic prostate cancer and GBM.<sup>180,181</sup> Nineteen patients with recurrent GBM were treated with gefitinib and escalating doses of RAD001, with 17 of the patients enrolled at the time of their second or greater recurrence. Partial responses were observed in 26% of patients, with a median progression free survival of 2.6 months.<sup>181</sup> Although response durations were generally short, the observed responses in refractory, recurrent disease are promising with this regimen utilizing two well-tolerated targeted agents.

**Farnesyltransferase Inhibitors** *Ras* gene mutations are prevalent in multiple tumors and have been implicated in tumorigenesis. *Ras* acts as an intermediate G protein in multiple pathways in the complex system of cell-signaling, which directs cell growth, membrane activity, and apoptosis. Farnesyltransferase is involved in the post-translational modification of the *Ras* protein to convert it into a functionally active proto-oncogene product.<sup>182,183</sup> Farnesyltransferase inhibitors (FTIs) have been shown to inhibit growth of multiple tumors, presumably by blocking *Ras*-mediated cell signals.<sup>182,184,185</sup>

The synthetic FTIs tipifarnib (R111577) and lonafarnib (SCH66336) have demonstrated positive results in preclinical studies using brain tumor models.<sup>186,187</sup> Recent experience with R111577 showed modest activity in

patients with recurrent gliomas (n=33), with three partial responses and 2 patients with stable disease exceeding 6 months.<sup>188</sup> Experience with R111577 administered prior to standard RT in newly diagnosed GBM followed by maintenance therapy until progression did not result in any measurable responses.<sup>189</sup> Ongoing approaches to incorporating FTIs into treatment of GBM have included concurrent administration with TMZ, with encouraging preliminary results.<sup>190</sup> Multiple studies investigating the role of FTIs in GBM are actively accruing.

**Imatinib** Upregulation of the platelet-derived growth factor (PDGF) occurs frequently in GBM.<sup>191</sup> Imatinib mesylate (Gleevec, Novartis) is a potent small molecule inhibitor of the *BCR-ABL* receptor tyrosine kinase that also exhibits inhibitory effects on the PDGF receptor. Although imatinib generally has poor penetration of the blood-brain barrier, in vitro activity of imatinib as a radiosensitizer has been reported in glioma cell lines.<sup>192</sup> Phase II testing of imatinib by the NABTC and EORTC in recurrent gliomas showed modest activity.<sup>193,194</sup> Ongoing studies in GBM are investigating the efficacy of imatinib combined with TMZ and hydroxyurea.<sup>195,196</sup>

## Conclusion

Although the overall survival of patients with GBM has not improved dramatically in the last several decades, there have clearly been advances in the treatment of GBM. Radiotherapy has consistently shown survival benefits following surgical resection. Agents such as TMZ have shown modest survival advantages in combination with RT and serve as important examples of progress being made in the treatment of GBM. Ongoing research with novel imaging techniques may allow for better targeting of RT to areas of occult tumor, and new techniques of delivering RT will continue to be explored as a means of improving local dose intensification. With the advent of targeted therapies, rational combinations of chemotherapy and targeted agents for treatment of GBM are being developed based on the unique biologic profile of this tumor. Through this complex process of evaluating multiple agents for activity in GBM, the recursive partitioning analysis proposed by Curran and colleagues<sup>75</sup> based on a large patient population in the RTOG database has emerged as a powerful comparative tool against which future treatment regimens and novel agents can be assessed. Appropriate use of this recursive partitioning analysis will allow for rapid identification of promising treatment strategies, in turn enabling the dedication of time and resources to agents that show clear benefit in the treatment of GBM. In addition, other novel means of treating GBM with chemotherapy (systemic and interstitial chemotherapy) in the newly diagnosed and relapsed settings are being actively explored,

and a complete discussion of progress made in that area is beyond the scope of this review. These multiple avenues of research in GBM show significant promise for future translation into substantial gains in patient outcomes.

## References

- Grossman SA, Batarra JF. Current management of glioblastoma multiforme. *Semin Oncol*. 2004;31:635-644.
- Jelsma R, Bucy PC. Glioblastoma multiforme, its treatment and some factors affecting survival. *Arch Neurol*. 1969;20:161-171.
- Enam SA, Rock JB, Rosenblum ML. Malignant gliomas. In: Berger MS, Bernstein M, eds. *Neuro-oncology: The Essentials*. New York, NY: Thieme; 2000:309-318.
- Walker MD, Alexander E Jr, Hunt WE, et al. Evaluation of mitomycin in the treatment of anaplastic gliomas (BTSG 66-01). *J Neurosurg*. 1976;44:655-667.
- Walker MD, Alexander E Jr, Hunt WE, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas (BTSG 69-01). *J Neurosurg*. 1978;49:333-343.
- Walker MD, Strike TA. An evaluation of methyl-CCNU, BCNU, and radiotherapy in the treatment of malignant gliomas. *Proc Am Assoc Cancer Res*. 1976;17:163-167.
- Walker MD, Green SB, Byar DP, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery (BTSG 72-01). *N Engl J Med*. 1980;303:1323-1329.
- Hess KR. Extent of resection as a prognostic variable in the treatment of gliomas. *J Neurooncol*. 1999;42:227-231.
- Simpson JR, Horton J, Scott C, et al. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. *Int J Radiat Oncol Biol Phys*. 1993;26:239-244.
- Fadul C, Wood J, Thaler H, et al. Morbidity and mortality of craniotomy for excision of supratentorial gliomas. *Neurology*. 1988;38:1374-1379.
- Sheline GE. Conventional radiation therapy of gliomas. In *Recent Results in Cancer Research. Gliomas: Current Concepts in Biology, Diagnosis, and Therapy*. New York, NY: Springer-Verlag; 1975:125-134.
- Sheline GE. Radiation therapy of brain tumors. *Cancer*. 1977;39:873-881.
- Schultz MD, Wang CC, Zininger GF, et al. Radiotherapy of intracranial neoplasms. *Prog Neurol Surg*. 1968;2:318-370.
- Lindgren M. Roentgen treatment of gliomata. *Acta Radiol*. 1953;40:325-334.
- Bouchard J, Peirce CB. Radiation therapy in the management of neoplasms of the central nervous system, with a special note in regard to children: twenty years' experience 1939-1958. *Am J Roentgenol Rad Ther Nuc Med*. 1960;84:610-628.
- Uihlein A, Colby MY Jr, Layton DD, et al. Comparisons of surgery and surgery plus irradiation in the treatment of supratentorial gliomas. *Acta Radiol Ther Phys Biol*. 1966;3:67-78.
- Stage WS, Stein JJ. Treatment of malignant astrocytomas. *Am J Roentgenol Rad Ther Nucl Med*. 1974;120:7-18.
- Kramer S. Radiation therapy in the management of malignant gliomas. In *Cancer of the Central Nervous System: Seventh National Cancer Conference Proceedings*. Philadelphia: J.B. Lippincott Company; 1973:823-826.
- Walker MD, Stryke TA, Sheline GE. An analysis of dose-effect relationship in the radiotherapy of malignant gliomas. *Int J Radiat Oncol Biol Phys*. 1979;5:1725-1731.
- Salazar OM, Rubin P, Feldstein ML, et al. High dose radiation therapy in the treatment of malignant gliomas: final report. *Int J Radiat Oncol Biol Phys*. 1979;5:1733-1740.
- Chang CH, Horton J, Schoenfeld D, et al. Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas: a joint Radiation Therapy Oncology Group and Eastern Cooperative Oncology Group study. *Cancer*. 1983; 52:997-1007.
- Nelson DF, Diener-West M, Horton J, et al. Combined modality approach to treatment of malignant gliomas - re-evaluation of RTOG 7401/ECOG 1374 with long-term follow-up: a joint study of the Radiation Therapy Oncology Group and the Eastern Cooperative Oncology Group. *NCI Monograph*. 1988;6:279-284.
- Concannon JB, Kramer S, Berry R. The extent of intracranial gliomata at autopsy and its relationship to techniques used in radiation therapy of brain tumors. *Am J Roentgenol Radium Ther Nucl Med*. 1960;84:99-107.
- Salazar OM, Rubin P, McDonald JV, et al. Patterns of failure in intracranial astrocytomas after irradiation: analysis of dose and field factors. *Am J Roentgenol*. 1976;126:279-292.
- Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. *Neurology*. 1980;30:907-911.
- Salazar OM, Rubin P. The spread of glioblastoma multiforme as a determining factor in the radiation treated volume. *Int J Radiat Oncol Phys*. 1976;1:627-637.
- Shapiro WR, Green SB, Burger PC, et al. Randomized trial of three chemotherapy regimens and two radiotherapy regimens in postoperative treatment of malignant glioma. Brain Tumor Cooperative Group Trial 80-01 (BTCC 80-01). *J Neurosurg*. 1989;71:1-9.
- Marks JE, Baglan RJ, Prasad SC, et al. Cerebral radionecrosis: incidence and risk in relation to dose, time, fractionation and volume. *Int J Radiat Oncol Biol Phys*. 1981;7:243-252.
- Onoyama T, Abe M, Yabumoto E, et al. Radiation therapy in the treatment of glioblastoma. *Am J Roentgenol*. 1976;126:481-492.
- Ramsey RG, Brand WN. Radiotherapy of glioblastoma multiforme. *J Neurosurg*. 1973;39:197-202.
- Caldwell WL, Aristizabal SA. Treatment of glioblastoma multiforme: a review. *Acta Radiol Ther Phys Biol*. 1975;14:505-512.
- DeSchryver A, Greitz T, Forsby N, et al. Localized shaped field radiotherapy of malignant glioblastoma multiforme. *Int J Radiat Oncol Biol Phys*. 1976;1:713-716.
- Pirzkall A, McKnight TR, Graves EE, et al. MR-spectroscopy guided target delineation for high-grade gliomas. *Int J Radiat Oncol Biol Phys*. 2001;50:915-928.
- Graves EE, Nelson SJ, Vigneron DB, et al. A preliminary study of the prognostic value of proton magnetic resonance spectroscopic imaging in gamma knife radiosurgery of recurrent malignant gliomas. *Neurosurgery*. 2000;46:319-326.
- Moskin M, Ericson K, Hindmarsh T, et al. Positron emission tomography compared with magnetic resonance imaging and computed tomography in supratentorial gliomas using multiple stereotactic biopsies as reference. *Acta Radiol*. 1989;30:225-232.
- Ogawa T, Shishido F, Kanno I, et al. Cerebral gliomas: evaluation with methionine PET. *Radiology*. 1993;186:45-53.
- Grosu AL, Weber W, Feldmann HJ, et al. First experience with I123-alpha-methyl-tyrosine spect in the 3-D radiation treatment planning of brain gliomas. *Int J Radiat Oncol Biol Phys*. 2000;47:517-526.
- Selker RG, Shapiro WR, Burger P, et al. The Brain Tumor Cooperative Group NIH Trial 87-01: a randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine. *Neurosurgery*. 2002;51:343-357.
- Gutin PH, Leibel SA, Wara WM, et al. Recurrent malignant gliomas: survival following interstitial brachytherapy with high activity iodine-125 sources. *J Neurosurg*. 1987;67:864-873.
- Gutin PH, Phillips TL, Wara WM, et al. Brachytherapy of recurrent malignant brain tumors with removable high-activity iodine-125 sources. *J Neurosurg*. 1984;60:61-68.
- Gutin PH, Hosobuchi Y, Phillips TL, et al. Stereotactic interstitial irradiation for the treatment of tumors. *Cancer Treat Rep*. 1981;65(suppl 2):103-106.
- Hosobuchi Y, Phillips TL, Stupar TA, et al. Interstitial brachytherapy of primary brain tumors: preliminary report. *J Neurosurg*. 1980;53:613-617.
- Bernstein M, Laperriere N, Glen J, et al. Brachytherapy for recurrent malignant astrocytoma. *Int J Radiat Oncol Biol Phys*. 1994;30:1213-1217.
- Gutin PH, Prados MD, Phillips TL, et al. External irradiation followed by an interstitial high activity iodine-125 implant "boost" in the initial treatment of malignant gliomas: NCOG study 6G-82-2. *Int J Radiat Oncol Biol Phys*. 1991;21:601-606.
- Laperriere NJ, Leung PMK, McKenzie S, et al. Randomized study of brachytherapy in the initial management of patients with malignant astrocytoma. *Int J Radiat Oncol Biol Phys*. 1998;41:1005-1011.
- Loeffler JS, Alexander E, Hochberg FH, et al. Clinical patterns of failure following stereotactic interstitial irradiation for malignant gliomas. *Int J Radiat Oncol Biol Phys*. 1990;19:1455-1462.
- Prados MD, Gutin PH, Phillips TL, et al. Interstitial brachytherapy for newly diagnosed patients with malignant gliomas: the UCSF experience. *Int J Radiat Oncol Biol Phys*. 1992;24:593-597.
- Hitchon PW, VanGilder JC, Wen BC, et al. Brachytherapy for malignant recurrent and untreated gliomas. *Stereotact Funct Neurosurg*. 1992;59:174-178.
- Levin VA, Wara WM, Gutin PH, et al. Initial analysis of NCOG 6G82-1: Bromodeoxyuridine (BUdR) during irradiation followed by CCNU, procarbazine, and vincristine (PCV) chemotherapy for malignant glioma. *Proc Am Soc Clin Oncol*. 1990;9:91.
- Deutsch M, Green SB, Strike TA, et al. Results of a randomized trial comparing BCNU plus radiotherapy, streptozocin plus radiotherapy, BCNU plus hyperfractionated radiotherapy, and BCNU following misondazole plus radiotherapy in the postoperative treatment of malignant gliomas (BTSG 77-02). *Int J Radiat Oncol Biol Phys*. 1989;16:1389-1396.
- Frankel R, Stubbs J, Dillehay D, et al. Pre-clinical evaluation of a novel device for delivering brachytherapy to resected brain tumor cavity margins. *Int J Radiat Oncol Biol Phys*. 1999;45(suppl 1):319-320.
- Monroe JI, Dempsey JF, Dorton JA, et al. Experimental validation of dose calculation algorithms for the GSite RTS, a novel 125I liquid-filled balloon brachytherapy applicator. *Medical Physics*. 2001;28:73-85.
- Dempsey JF, Williams JA, Stubbs JB, et al. Dosimetric properties of a novel brachytherapy balloon applicator for the treatment of malignant brain tumor resection-cavity margins. *Int J Radiat Oncol Biol Phys*. 1998;42:421-429.
- Tatter SB, Shaw EG, Rosenblum ML, et al. An inflatable balloon catheter and liquid 125I radiation source (GliaSite Radiation Therapy System) for treatment of recur-

- rent malignant gliomas: multicenter safety and feasibility trial. *J Neurosurg.* 2003;99:297-303.
55. Reardon DA, Akabani G, Coleman E, et al. Salvage radioimmunotherapy with murine iodine-131-labeled antitenascin monoclonal antibody 81C6 for patients with recurrent primary and metastatic malignant brain tumors: phase II study results. *J Clin Oncol.* 2006;24:115-122.
56. Ventimiglia JB, Wikstrand CJ, Ostrowski LE, et al. Tenascin expression in human gliomas cell lines and normal tissues. *J Neuroimmunol.* 1992;36:41-55.
57. Zalutsky MR, Moseley RP, Coakham HB, et al. Pharmacokinetics and tumor localization of 131I-labeled anti-tenascin monoclonal antibody 81C6 in patients with gliomas and other intracranial malignancies. *Cancer Res.* 1989;49:2807-2813.
58. Bigner DD, Brown MT, Friedman AH, et al. Iodine-131-labeled antitenascin monoclonal antibody 81C6 treatment of patients with recurrent malignant gliomas: phase I trial results. *J Clin Oncol.* 1998;16:2202-2212.
59. Cokgor I, Akabani G, Kuan CT, et al. Phase I trial results of iodine-131-labeled antitenascin monoclonal antibody 81C6 treatment of patients with newly diagnosed malignant gliomas. *J Clin Oncol.* 2000;18:3862-3872.
60. Reardon DA, Akabani G, Coleman RE, et al. Phase II trial of murine 131I-labeled antitenascin monoclonal antibody 81C6 administered into surgically created resection cavities of patients with newly diagnosed malignant gliomas. *J Clin Oncol.* 2002;20:1389-1397.
61. Masciopinto JE, Levin AB, Mehta MP, et al. Stereotactic radiosurgery for glioblastoma: a final report of 31 patients. *J Neurosurg.* 1995;82:530-535.
62. Shrieve DC, Alexander E III, Wen PY, et al. Comparison of stereotactic radiosurgery and brachytherapy in the treatment of recurrent glioblastoma multiforme. *Neurosurgery.* 1995;36:275-284.
63. Yung WK, Albright RE, Olson J, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer.* 2000;83:588-593.
64. Leksell L. The stereotaxic method and radiosurgery of the brain. *Acta Chir Scand.* 1951;102:316-319.
65. Leksell, L. Stereotactic radiosurgery. *J Neurol Neurosurg Psychiatry.* 1983;46:797-803.
66. Steiber VW, Bourland JD, Tome WA, et al. Gentlemen (and ladies), choose your weapons: Gamma knife vs. linear accelerator radiosurgery. *Technol Cancer Res Treat.* 2003;2:79-86.
67. Kubsad SS, Mackie TR, Gehring MA, et al. Monte Carlo and convolution dosimetry for stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys.* 1990;19:1027-1035.
68. Mehta MP. The physical, biologic, and clinical basis of radiosurgery. *Curr Probl Cancer.* 1995;19:265-329.
69. Nwokedi EC, DiBiase SJ, Jabbour S, et al. Gamma knife stereotactic radiosurgery for patients with glioblastoma multiforme. *Neurosurgery.* 2002;50:41-47.
70. Hall WA, Djililian HR, Sperduto PW, et al. Stereotactic radiosurgery for recurrent malignant gliomas. *J Clin Oncol.* 1995;13:1642-1648.
71. Lederman G, Arbit E, Odaimi M, et al. Recurrent glioblastoma multiforme: potential benefits using fractionated stereotactic radiotherapy and concurrent taxol. *Stereotact Funct Neurosurg.* 1997;69:162-174.
72. Souhami L, Seiferheld W, Brachman D, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. *Int J Radiat Oncol Biol Phys.* 2004;60:853-860.
73. Werner-Wasik M, Seiferheld W, Michalski J, et al. Phase I/II conformal three-dimensional radiation therapy dose escalation study in patients with supratentorial glioblastoma multiforme: report of the Radiation Therapy Oncology Group 98-03 protocol. *Proc Amer Soc Ther Rad Onc (ASTRO).* 2004;60(Suppl 1):163-164.
74. Cardinale R, Won M, Choucair A, et al. A phase II trial of accelerated radiotherapy using weekly stereotactic conformal boosts for supratentorial glioblastoma multiforme (RTOG-0023). *J Clin Oncol.* 2005;23(18S):1511.
75. Curran WJ Jr, Scott CB, Horton J, et al. Recursive partitioning analysis of prognostic factors in three radiation therapy oncology group malignant gliomas trials. *J Natl Cancer Inst.* 1993;85:704-710.
76. Thames HD Jr, Withers HR, Peter LJ, et al. Changes in early and late radiation responses with altered fractionation: implications for dose-survival relationships. *Int J Radiat Oncol Biol Phys.* 1982;8:219-226.
77. Symonds RP. Recent advances: radiotherapy. *Br Med J.* 2001;323:1107-1110.
78. Gonzales DG, Menten J, Bosch DA, et al. Accelerated radiotherapy in glioblastoma multiforme: a dose searching prospective study. *Radiother Oncol.* 1994;32:98-105.
79. Lutterbach J, Weigel P, Guttenberger R, et al. Accelerated hyperfractionated radiation therapy in 149 patients with glioblastoma multiforme. *Radiother Oncol.* 1999;53:49-52.
80. Neider C, Nestle U, Ketter R, et al. Hyperfractionated and accelerated-hyperfractionated radiotherapy for glioblastoma multiforme. *Radiat Oncol Investig.* 1999;7:36-41.
81. Prados MD, Wara WM, Sneed PK, et al. Phase III trial of accelerated hyperfractionation with or without difluoromethylornithine (DFMO) versus standard fractionated radiotherapy with or without DFMO for newly diagnosed patients with glioblastoma multiforme. *Int J Radiat Oncol Biol Phys.* 2001;49:71-77.
82. Werner-Wasik M, Scott CB, Nelson DF, et al. Final report of a phase I/II trial of hyperfractionated and accelerated hyperfractionated radiation therapy with carmustine for adults with supratentorial malignant gliomas: Radiation Therapy Oncology Group study 83-02. *Cancer.* 1996;77:1535-1543.
83. Curran WJ Jr, Scott CB, Yung WK, et al. No survival benefit of hyperfractionated (HFX) radiotherapy (RT) to 72.0 Gy and carmustine versus standard RT and carmustine for malignant gliomas patients: preliminary results of RTOG 90-06. *Proc Amer Soc Clin Oncol.* 1996; Abstract 280.
84. Scott CB, Curran WJ, Yung WK, et al. Long term results of RTOG 90-06: a randomized trial of hyperfractionated radiotherapy (RT) to 72.0 Gy & carmustine vs. standard RT & carmustine for malignant gliomas patients, with emphasis on anaplastic astrocytoma (AA) patients. *Proc Amer Soc Clin Oncol.* 1998; Abstract 1546.
85. Urtasun R, Band P, Chapman JD, et al. Radiation and high-dose metronidazole in supratentorial glioblastomas. *N Engl J Med.* 1976;294:1364-1367.
86. Urtasun R, Feldstein ML, Partington J, et al. Radiation and nitroimidazoles in supratentorial high grade gliomas: a second clinical trial. *Br J Cancer.* 1982;46:101-108.
87. Bleehan NM, Wiltshire CR, Plowman PN, et al. A randomized study of misonidazole and radiotherapy for grade III and IV astrocytoma. *Br J Cancer.* 1981;43:436-442.
88. Carabell SC, Bruno LA, Weinstein AS, et al. Misonidazole and radiotherapy to treat malignant glioma: a phase II trial of the Radiation Therapy Oncology Group (RTOG 78-01). *Int J Radiat Oncol Biol Phys.* 1981;7:71-77.
89. Nelson DF, Schoenfeld D, Weinstein AS, et al. A randomized comparison of misonidazole sensitized radiotherapy plus BCNU and radiotherapy plus BCNU for treatment of malignant gliomas after surgery; preliminary results of an RTOG study (RTOG 79-18). *Int J Radiat Oncol Biol Phys.* 1983;9:1143-1152.
90. Kogelnik HD, Kärcher KH, Szepesi T, et al. High-dose irradiation and misonidazole in the treatment of malignant gliomas: a preliminary report. *Prog Radio-oncol.* 1981;11:189-195.
91. Stadler B, Kärcher KH, Kogelnik HD, et al. Misonidazole and irradiation in the treatment of high-grade astrocytomas: further report of the Vienna Study Group. *Int J Radiat Oncol Biol Phys.* 1984;10:1713-1717.
92. A study of the effect of misonidazole in conjunction with radiotherapy for the treatment of grades 3 and 4 astrocytomas. A report from the Medical Research Council (MRC) Working Party on misonidazole in gliomas. *Br J Radiol.* 1983;56:673-682.
93. EORTC Brain Tumor Group. Misonidazole in radiotherapy of supratentorial malignant brain gliomas in adult patients: a randomized double-blind study. *Eur J Cancer Clin Oncol.* 1983;19:39-42.
94. Teicher BA, Ara G, Emi Y, et al. RSR13: effects on tumor oxygenation and response to therapy. *Drug Dev Res.* 1996;38:1-11.
95. Suh J, Stea B, Nabid A, et al. Standard whole brain radiation therapy (WBRT) with supplemental oxygen (O<sub>2</sub>), with or without RSR13 (efaproxiral) in patients with brain metastases: results of the randomized REACH (RT-009) study. *Proc Am Soc Clin Oncol.* 2004; Abstract 1534.
96. Shaw E, Scott C, Suh J, et al. RSR13 plus cranial radiation therapy in patients with brain metastases: comparison with the Radiation Therapy Oncology Group Recursive Partitioning Analysis Brain Metastases Database. *J Clin Oncol.* 2003;21:2364-2371.
97. Kleinberg L, Grossman SA, Carson K, et al. Survival of patients with newly diagnosed glioblastoma multiforme treated with RSR13 and radiotherapy: results of a phase II New Approaches to Brain Tumor Therapy CNS Consortium safety and efficacy study. *J Clin Oncol.* 2002; 20:3149-3155.
98. Zeman EM, Brown JM, Lemmon MJ, et al. SR-4233: a new bioreductive agent with high selective toxicity for hypoxic mammalian cells. *Int J Radiat Oncol Biol Phys.* 1986;12:1239-1242.
99. Del Rowe J, Scott C, Werner-Wasik M, et al. Single-arm, open-label phase II study of intravenously administered tirapazamine and radiation therapy for glioblastoma multiforme. *J Clin Oncol.* 2000;18:1254-1259.
100. McGinn CJ, Shewach DS, Lawrence TS. Radiosensitizing nucleosides. *J Natl Cancer Inst.* 1996;88:1193-1203.
101. Freese A, O'Rourke D, Judy K, et al. The application of 5-bromodeoxyuridine in the management of CNS tumors. *J Neuro-Oncol.* 1994;20:81-95.
102. Groves MD, Maor MH, Meyers C, et al. A phase II trial of high-dose bromodeoxyuridine with accelerated fractionation radiotherapy followed by procarbazine, lomustine, and vincristine for glioblastoma multiforme. *Int J Radiat Oncol Biol Phys.* 1999;45:127-135.
103. Goffinet DR, Brown JM. Comparison of intravenous and intra-arterial pyrimidine infusion as a means of radiosensitizing tumors in vivo. *Radiology.* 1977;124:819-822.
104. Kinsella TJ, Collins J, Rowland J, et al. Pharmacology and phase I/II study of continuous intravenous infusions of iododeoxyuridine and hyperfractionated radiotherapy in patients with glioblastoma multiforme. *J Clin Oncol.* 1988;6:871-879.
105. Sullivan FJ, Herscher LL, Cook JA, et al. National Cancer Institute (phase II) study of high-grade glioma treated with accelerated hyperfractionated radiation and iododeoxyuridine: results in anaplastic astrocytoma. *Int J Radiat Oncol Biol Phys.* 1994;30:583-590.
106. Phillips TL, Levin VA, Ahn DK, et al. Evaluation of bromodeoxyuridine in glioblastoma multiforme: a Northern California Cancer Center phase II study. *Int J Radiat Oncol Biol Phys.* 1991;21:709-714.

107. Levin VA, Prados MD, Wara WM, et al. Radiation therapy and bromodeoxyuridine chemotherapy followed by procarbazine, lomustine, and vincristine for the treatment of anaplastic gliomas. *Int J Radiat Oncol Biol Phys.* 1995;32:75-83.
108. Curran WJ Jr, Scott CB, Weinstein AS, et al. Survival comparison of radiosurgery-eligible and -ineligible malignant glioma patients treated with hyperfractionated radiation therapy and carmustine: a report of Radiation Therapy Oncology Group 83-02. *J Clin Oncol.* 1993;11:857-862.
109. SmithKline Beecham Pharmaceuticals Investigator Brochure. Topotecan SK&F 104864-A; 1994.
110. Blaney SM, Cole DE, Balis FM, et al. Plasma and cerebrospinal fluid pharmacokinetic study of topotecan in nonhuman primates. *Cancer Res.* 1993;53:725-727.
111. MacDonald D, Cairncross G, Stewart D, et al. Phase II study of topotecan in patients with recurrent malignant glioma. *Ann Oncol.* 1996;7:205-207.
112. Kadota RP, Stewart CF, Horn M, et al. Topotecan for the treatment of recurrent or progressive central nervous system tumors — a Pediatric Oncology Group phase II study. *J Neurooncol.* 1999;43:43-47.
113. Fisher B, Won M, MacDonald D, et al. Phase II study of topotecan plus cranial radiation for glioblastoma multiforme: results of Radiation Therapy Oncology Group 9513. *Int J Radiat Oncol Biol Phys.* 2002;53:980-986.
114. Friedman HS, Castellino RC, Elion GB, et al. Schedule-dependent activity of irinotecan plus BCNU against malignant glioma xenografts. *Cancer Chemother Pharmacol.* 2000;45:345-349.
115. Vredenburgh JJ, Desjardins A, Herndon JE II, et al. Bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF), and irinotecan for treatment of malignant gliomas. *J Clin Oncol.* 2006;24(18S): Abstract 1506.
116. Coughlin CT, Richmond RC. Biologic and clinical developments of cisplatin combined with radiation: concepts, utility, projections for new trials, and the emergence of carboplatin. *Semin Oncol.* 1989;16(Suppl 6):31-43.
117. Peterson K, Harsh G IV, Fisher PG, et al. Daily low-dose carboplatin as a radiation sensitizer for newly diagnosed malignant gliomas. *J Neurooncol.* 2001;53:27-32.
118. Glass J, Silverman CL, Axelrod R, et al. Fractionated stereotactic radiotherapy with cis-platinum radiosensitization in the treatment of recurrent, progressive, or persistent malignant astrocytoma. *Am J Clin Oncol.* 1997;20:226-229.
119. Grossman S, O'Neill A, Grunnet M, et al. Phase III study comparing three cycles of infusional BCNU/Cisplatin followed by radiation with radiation and concurrent BCNU for patients with newly diagnosed supratentorial glioblastoma multiforme (ECOG 2394-SWOG 9508). *Proc Am Soc Clin Oncol.* 2000; Abstract 612.
120. Tischler RB, Schiff PB, Geard CR, et al. Taxol: a novel radiation sensitizer. *Int J Radiat Oncol Biol Phys.* 1992;22:613-617.
121. Langer CJ, Ruffer J, Rhodes H, et al. Phase II Radiation Therapy Oncology Group trial of weekly paclitaxel and conventional external beam radiation therapy for supratentorial glioblastoma multiforme. *Int J Radiat Oncol Biol Phys.* 2001;51:113-119.
122. Tischler RB, Geard CR, Hall EJ, et al. Taxol sensitizes human astrocytoma cells to radiation. *Cancer Res.* 1992;52:3495-3497.
123. Newlands ES, Blackledge GR, Slack JA, et al. Phase I trial of temozolomide (CCRG 81045; M&B 39831; NSC 362856). *Br J Cancer.* 1992;65:287-291.
124. Newlands ES, O'Reilly SM, Glaser MG, et al. The Charing Cross Hospital experience with temozolomide in patients with gliomas. *Eur J Cancer.* 1996;32:2236-2241.
125. O'Reilly SM, Newlands ES, Brampton M, et al. Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumours. *Eur J Cancer.* 1993;29:940-942.
126. Stupp R, Gander M, Leyvraz S, et al. Current and future developments in the use of temozolomide for the treatment of brain tumours. *Lancet Oncol.* 2001;2:552-60.
127. Wedge SR, Porteous JK, Glaser MG, et al. In vitro evaluation of temozolomide combined with irradiation. *Anticancer Drugs.* 1997;8:92-97.
128. van Rijn J, Heimans JJ, van den Berg J, et al. Survival of human glioma cells treated with various combinations of temozolomide and x-rays. *Int J Radiat Oncol Biol Phys.* 2000;47:779-784.
129. Hirose Y, Berger MS, Pieper RO. p53 affects both the duration of G2/M arrest and the fate of temozolomide-treated human glioblastoma cells. *Cancer Res.* 2001;61:1957-1963.
130. Brada M, Hoang-Xuan K, Rampling R, et al. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. *Ann Oncol.* 2001;12:259-266.
131. Gilbert MR, Friedman HS, Kuttlesch JF, et al. A phase II study of temozolomide in patients with newly diagnosed supratentorial malignant gliomas before radiation therapy. *Neuro-oncol.* 2002;4:261-267.
132. Stupp R, Dietrich P-Y, Kraljevic SO, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. *J Clin Oncol.* 2002;20:1375-1382.
133. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352:987-996.
134. Friedman HS, McLendon RE, Kerby T, et al. DNA mismatch repair and O6-alkylguanine-DNA alkyltransferase analysis and response to temodar in newly diagnosed malignant gliomas. *J Clin Oncol.* 1998;16:3851-3857.
135. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005;352:997-1003.
136. Combs SE, Gurwien S, Schulz-Ertner D, et al. Temozolomide combined with radiation as first-line treatment in primary glioblastoma multiforme: phase I/II study. *J Clin Oncol.* 2004;22(14S): Abstract 1531.
137. Rodrigus P. Motexafin gadolinium: a possible new radiosensitizer. *Expert Opin Investig Drugs.* 2003;12:1205-1210.
138. Magda D, Lepp C, Gerasimchuk N, et al. Redox cycling by motexafin gadolinium enhances cellular response to ionizing radiation by forming reactive oxygen species. *Int J Radiat Oncol Biol Phys.* 2001;51:1025-1036.
139. Carde P, Timmerman R, Mehta MP, et al. Multicenter Phase Ib/II trial of the radiation enhancer motexafin gadolinium in patients with brain metastases. *J Clin Oncol.* 2001;19:2074-2083.
140. Viala J, Vanel D, Meingan P, et al. Phases Ib and II multidose trial of gadolinium tetrophyrin, a radiation sensitizer detectable at MR imaging: preliminary results in brain metastases. *Radiology.* 1999;212:755-759.
141. Rosenthal DI, Nurenberg P, Becerra CR, et al. A phase I single-dose trial of gadolinium tetrophyrin (Gd-Tex), a tumor selective radiation sensitizer detectable by magnetic resonance imaging. *Clin Cancer Res.* 1999;5:739-745.
142. Mehta MP, Rodrigus P, Terhaard CHJ, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *J Clin Oncol.* 2003;21:2529-2536.
143. Mehta MP, Gervais R, Chabot P, et al. Motexafin gadolinium (MGd) combined with prompt whole brain radiation therapy (RT) prolongs time to neurologic progression in non-small cell lung cancer (NSCLC) patients with brain metastases: results of a phase III trial. *Proc Am Soc Clin Oncol.* 2006;24: Abstract 7014.
144. Ford JM, Endicott T, Alger JR, et al. A Phase I dose escalation trial of motexafin gadolinium as a radiation sensitizer in patients with newly diagnosed glioblastoma multiforme. *Int J Radiat Oncol Biol Phys.* 2001;51:205.
145. Suh J, Mehta M, Chang E, et al. Phase II trial of motexafin gadolinium (MGd, Xcytrin®) and cranial radiation in newly diagnosed glioblastoma multiforme (GBM). *Int J Radiat Oncol Biol Phys.* 2002;54(suppl 1): Abstract 2061.
146. Plate KH, Breier G, Weich HA, et al. Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo. *Nature.* 1992;359:845-848.
147. Baumann F, Bjeljac M, Kollias SS, et al. Combined thalidomide and temozolomide treatment in patients with glioblastoma multiforme. *J Neurooncol.* 2004;67:191-200.
148. Kaur B, Tan C, Brat DJ, et al. Genetic and hypoxic regulation of angiogenesis in gliomas. *J Neurooncol.* 2004;70:229-243.
149. Chan AS, Leung SY, Wong MP, et al. Expression of vascular endothelial growth factor and its receptors in the anaplastic progression of astrocytoma, oligodendroglioma, and ependymoma. *Am J Surg Pathol.* 1998;22:816-826.
150. Geng L, Donnelly E, McMahon G, et al. Inhibition of vascular endothelial growth factor receptor signaling leads to reversal of tumor resistance to radiotherapy. *Cancer Res.* 2001;61:2413-2419.
151. Marx GM, Pavlakis N, McCowatt S, et al. Phase II study of thalidomide in the treatment of recurrent glioblastoma multiforme. *J Neurooncol.* 2001;54:31-38.
152. Teo SK. Properties of thalidomide and its analogues: implications for anti-cancer therapy. *AAPS J.* 2005;7(suppl 1):E14-E19.
153. Butowski NA, Sneed PK, Chang SM. Diagnosis and treatment of recurrent high-grade astrocytoma. *J Clin Oncol.* 2006;24:1273-1280.
154. Hurtt MR, Moosy J, Donovan-Peluso M, et al. Amplification of epidermal growth factor receptor gene in gliomas: histopathology and prognosis. *J Neuropathol Exp Neurol.* 1992;51:84-90.
155. Hidalgo M, Rowinsky EK. The rapamycin-sensitive signal transduction pathway as a target for cancer therapy. *Oncogene.* 2000;19:6680-6686.
156. Wang SI, Puc J, Li J, et al. Somatic mutations of PTEN in glioblastoma multiforme. *Cancer Res.* 1997;57:4183-4186.
157. Crul M, de Klerk GJ, Beijnen JH, et al. Ras biochemistry and farnesyl transferase inhibitors: a literature survey. *Anticancer Drugs.* 2001;12:163-184.
158. Sebt SM, Hamilton AD. Farnesyltransferase and geranylgeranyltransferase I inhibitors and cancer therapy: lessons from mechanism and bench-to-bedside translational studies. *Oncogene.* 2000;19:6584-6593.
159. Reardon DA, Wen PY. Therapeutic advances in the treatment of glioblastoma: rationale and potential role of targeted agents. *Oncologist.* 2006;11:152-164.
160. Baltuch GH, Dooley NP, Villemure JG, et al. Protein kinase C and growth regulation of malignant gliomas. *Can J Neurol Sci.* 1995;22:264-271.
161. Mastroianni L, Farah JO, Puzilli F, et al. Tamoxifen modulation of carboplatin cytotoxicity in a human U-138 glioma cell line. *Clin Neurol Neurosurg.* 1998;100:89-93.
162. Chumura SJ, Mauceri HJ, Sunil A, et al. Decreasing the apoptotic threshold of tumor cells through protein kinase C inhibition and sphingomyelinase activation increases tumor killing by ionizing radiation. *Cancer Res.* 1997;57:4340-4347.
163. Tsuchida E and Urano M. The effect of UCN-01 (7-hydroxystaurosporine), a potent inhibitor of protein kinase C, on fractionated radiotherapy or daily chemotherapy of a murine fibrosarcoma. *Int J Radiat Oncol Biol Phys.* 1997;39:1153-1161.
164. Robins HI, Won M, Seiferheld WF, et al. Phase 2 trial of radiation plus high-dose tamoxifen for glioblastoma multiforme: RTOG protocol BR-0021. *Neuro-oncol.* 2006;8:47-52.

165. Muanza T, Shenouda G, Souhami L, et al. High dose tamoxifen and radiotherapy in patients with glioblastoma multiforme: a phase IB study. *Can J Neurol Sci.* 2000;27:302-306.
166. Lammering G, Valerie K, Lin PS, et al. Radiosensitization of malignant glioma cells through overexpression of dominant-negative epidermal growth factor receptor. *Clin Cancer Res.* 2001;7:682-690.
167. Krishnan S, Rao RD, James CD, et al. Combination of epidermal growth factor receptor targeted therapy with radiation therapy for malignant gliomas. *Front Biosci.* 2003;8:e1-e13.
168. Chakravarti A, Chakladar A, Delaney MA, et al. The epidermal growth factor receptor pathway mediates resistance to sequential administration of radiation and chemotherapy in primary human glioblastoma cells in a RAS-dependent manner. *Cancer Res.* 2002;62:4307-4315.
169. Lieberman FS, Cloughesy T, Fine H, et al. NABTC phase I/II trial of ZD-1839 for recurrent malignant gliomas and unresectable meningiomas. *J Clin Oncol.* 2004;22(14S): Abstract 1510.
170. Uhm JH, Ballman KV, Giannini C, et al. Phase II study of ZD1839 in patients with newly diagnosed grade 4 astrocytoma. *J Clin Oncol.* 2004;22(14S): Abstract 1505.
171. Chakravarti A, Berkey B, Robins HI, et al. An update of phase II results from RTOG 0211: a phase I/II study of gefitinib with radiotherapy in newly diagnosed glioblastoma. *J Clin Oncol.* 2006;24(18S): Abstract 1527.
172. Vogelbaum MA, Goldlust S, Kanner A. The EGFR tyrosine kinase inhibitor tarceva (OSI-774) shows activity against both wild-type and mutant EGFR function. *Neuro-Oncol.* 2003;4: Abstract ET-47.
173. Yung A, Vredenburgh J, Cloughesy T, et al. Erlotinib HCL for glioblastoma multiforme in first relapse, a phase II trial. *J Clin Oncol.* 2004;22(14S): Abstract 1555.
174. Raizer J, Abrey L, Wen P, et al. A phase I trial of OSI-774 (Tarceva) in patients with recurrent malignant gliomas on enzyme inducing anti-convulsants: a North American Brain Tumor Consortium Trial. *Neuro-Oncol.* 2005;7:320. Abstract 154.
175. Prados MD, Lamborn KR, Chang S, et al. Phase 1 study of erlotinib HCL alone and combined with temozolomide in patients with stable or recurrent malignant glioma. *Neuro-Oncol.* 2006;8:67-78.
176. Krishnan S, Brown PD, Ballman KV, et al. Phase I trial of erlotinib with radiation therapy in patients with glioblastoma multiforme: results of North Center Cancer Treatment Group protocol N0177. *Int J Radiat Oncol Biol Phys.* 2006;65:1192-1199.
177. Hidalgo M, Rowinsky EK. The rapamycin-sensitive signal transduction pathway as a target for cancer therapy. *Oncogene.* 2000;19:6680-6686.
178. Chang SM, Wen P, Cloughesy T, et al. Phase II study of CCI-779 in patients with recurrent glioblastoma multiforme. *Invest New Drugs.* 2005;23:357-361.
179. Galanis E, Buckner JC, Maurer MJ, et al. Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: a North Central Cancer Treatment Group study. *J Clin Oncol.* 2005;23:5294-5304.
180. Shaffer DR, Abrey L, Beekman K, et al. A phase I/II trial of RAD 001 with gefitinib in patients with castrate metastatic prostate cancer and glioblastoma multiforme. *J Clin Oncol.* 2006;24(18S): Abstract 14520.
181. Nguyen TD, Lassman AB, Lis E, et al. A pilot study to assess the tolerability and efficacy of RAD-001 (everolimus) with gefitinib in patients with recurrent glioblastoma multiforme (GBM). *J Clin Oncol.* 2006;24(18S): Abstract 1507.
182. Sebt SM. Blocked pathways: FTI's shut down oncogene signals. *Oncologist.* 2003;8(suppl 3):30-38.
183. Zhang FL, Casey PJ. Protein prenylation: molecular mechanisms and functional consequences. *Annu Rev Biochem.* 1996;65:241-269.
184. Sebt SM, Hamilton AD. Farnesyltransferase and geranylgeranyltransferase I inhibitors and cancer therapy: lessons from mechanism and bench-to-bedside translational studies. *Oncogene.* 2000;19:6584-6593.
185. Caponigro F. Farnesyl transferase inhibitors: a major breakthrough in anticancer therapy? *Anticancer Drugs.* 2002;13:891-897.
186. Pollack IF, Bredel M, Erff M, et al. Inhibition of Ras and related G-proteins as a therapeutic strategy for blocking malignant glioma growth: preclinical strategies in a nude mouse model. *Neurosurgery.* 1999;45:1208-1215.
187. Bredel M, Pollack IF, et al. Inhibition of Ras and related G-proteins as a therapeutic strategy for blocking malignant glioma growth. *Neurosurgery.* 1998;43:124-131.
188. Cloughesy TF, Kuhn J, Wen P, et al. Phase II trial of R115777 (Zarnestra) in patients with recurrent glioma not taking enzyme inducing antiepileptic drugs (EIAED): a North American Brain Tumor Consortium (NABTC) report. *Proc Am Soc Clin Oncol.* 2002;21: Abstract 317.
189. Lustig RA, Mikkelesen T, Lesser G, et al. Pre-irradiation R115777 (Zarnestra) in patients with newly diagnosed glioblastoma multiforme and residual enhancing disease. *J Clin Oncol.* 2005;23(16S): Abstract 1518.
190. Gilbert MR, Gaupp P, Liu V, et al. A phase I study of temozolomide and the farnesyl transferase inhibitor lonafarnib (Sarazar, SCH66336) in recurrent glioblastoma. *J Clin Oncol.* 2006;24(18S): Abstract 1556.
191. Jendrossek V, Belka C, Bamberg M. Novel chemotherapeutic agents for the treatment of glioblastoma multiforme. *Exp Opin Investig Drugs.* 2003;12:1899-1924.
192. Holdhoff M, Kreuzer KA, Appelt C, et al. Imatinib mesylate radiosensitizes human glioblastoma cells through inhibition of platelet-derived growth factor receptor. *Blood Cells Mol Dis.* 2005;34:181-185.
193. Wen PY, Yung W, Lamborn K, et al. Phase I/II study of imatinib mesylate (ST1571) for patients with recurrent malignant gliomas (NABTC 99-08). *Neurooncol.* 2004;6:384. Abstract TA-63.
194. Raymond E, Brandes A, Van Oosterom A, et al. Multicentre phase II study of imatinib mesylate in patients with recurrent glioblastoma: an EORTC/NDDG/BTG Intergroup study. *J Clin Oncol.* 2004;22(14S): Abstract 1501.
195. Dresemann G, Hosius C, Nikolova Z, et al. Imatinib plus hydroxyurea in pretreated non-progressive glioblastoma – a single center phase II study. *J Clin Oncol.* 2006;24(18S): Abstract 1583.
196. Sathornsumetee S, Reardon DA, Quinn JA, et al. An update on phase I study of dose-escalating imatinib mesylate plus standard-dosed temozolomide for the treatment of patients with malignant glioma. *J Clin Oncol.* 2006;24(18S): Abstract 1560.