Current Treatment Options in Adult Glioblastoma

a report by
Christopher E Pelloski, MD[1] *and* **Mark R Gilbert, MD**[2]

1. Assistant Professor, Departments of Radiation Oncology and Pathology; 2. Professor and Deputy Chair, Department of Neuro-oncology, University of Texas MD Anderson Cancer Center

DOI: 10.17925/OHR.2007.00.2.105

The purpose of this article is to review the current treatment options for patients with glioblastoma (GBM). The current standard of care involves maximal safe surgical resection followed by concurrent chemotherapy with radiation followed by adjuvant chemotherapy. Although level 1 evidence supports the use of this treatment, GBM remains incurable and most patients will succumb to the disease within two years of diagnosis. The need for better treatments has led to the development of numerous experimental agents that are currently in various phases of pre-clinical and clinical application. The new treatment approaches provide hope that significant treatment advances are likely, but will require a collaborative effort between laboratory-based and clinical investigators.

Demographics

GBM is the most common and malignant primary brain tumor. While it is more prevalent among older adults, it is a disease that afflicts people of all ages, races, and gender. Most series report a median age in the mid-50s.[1–3] There are no identifiable risk factors or social habits that induce GBM tumorigenesis. There are few cases of familial GBM, but it is a sporadic disease. Patients with certain genetic diseases such as neurofibromatosis, tuberous sclerosis, and Li Fraumeni syndrome have a much higher risk of developing malignant gliomas than the general population.

Survival and Risk Stratification

Most series report that the median survival from the time of diagnosis is approximately one year. The actuarial two-year overall survival is about 5–15%. Even in patients with the most favorable prognostic factors, the likelihood of surviving for any longer than two years is only 25%. The single most important prognostic factor in GBM is patient age. Although age has important implications with regards to issues of patient management (including the greater comorbidities and decreased reserve that preclude aggressive therapy), patient age seems to correlate with differences in tumor biology and pathogenesis. The classic concept of primary (*de novo*) and secondary GBM have strong associations with age. Typically, older patients are more likely to have primary GBMs, characterized by amplification of the epidermal growth factor receptor (EGFR) gene and a more aggressive clinical course. In these patients, large, debilitating tumors can arise within several months. Secondary GBMs are more often associated with younger patients who frequently have an established history of lower-grade gliomas (grade II–III). These tumors often display protein (p)53 accumulation on tumor sample staining, indicating mutation of the TP53 gene.

The patient's performance status is another factor. Most studies have correlated a higher performance status with improved prognosis. This may reflect both the patient's ability to tolerate treatment and the extent of tumor burden in the brain. The extent of resection has also been a statistically significant prognostic factor in some studies; however, this remains somewhat controversial. While a complete resection of the enhancing component of the tumor confers an improved overall survival time, no statistically well-powered randomized trial has been performed. Although the association between extent of resection and outcome has been shown in several series, this may reflect differences in tumor biology or patient performance status rather than the impact of tumor removal. The data supporting a sub-total resection over a biopsy are quite limited and inconclusive.

The evaluation of prognostic factors is important when considering treatment options for individual patients and critical when evaluating the efficacy of treatment regimens tested in clinical trials. Selection of patients with excellent prognosis may inappropriately skew the results so, compared with a 'typical' patient population, the new treatment appears (erroneously) effective. The impact of prognostic factors is so critical to the evaluation of new therapies that the Radiation Therapy and Oncology Group (RTOG) devised the recursive partitioning analysis (RPA) for malignant gliomas. This validated analysis was able to define six distinct groups of patients with malignant gliomas on the basis of tumor histology and additional clinical factors. The RTOG RPA[4] was recently simplified for GBM[5] and shares features similar to the European Organisation for Research and Treatment of Cancer (EORTC) classification schema (see *Table 1*).[6]

Christopher E Pelloski, MD, is an Assistant Professor in the Department of Radiation Oncology and the Department of Pathology at the University of Texas MD Anderson Cancer Center (MDACC). His clinical specialization and area of research regards malignancies of the central nervous system, specifically glioblastoma. Dr Pelloski is studying the secreted protein YKL-40. This research is designed to better understand the biology of the protein and translate this into novel therapeutic approaches.

Mark R Gilbert, MD, is Professor and Deputy Chair in the Department of Neuro-oncology at the University of Texas MD Anderson Cancer Center (MDACC). He is the principal investigator of the international phase III trial RTOG 0525, comparing a standard versus a dose-dense schedule of adjuvant temozolomide for newly diagnosed glioblastoma. He is a principal investigator in the North American Brain Tumor Consortium (NABTC) and Director of the Collaborative Ependymoma Research Network (CERN).

E: mrgilbert@mdanderson.org

Table 1: Original and Adapted Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Recursive Partitioning Analysis Class III–VI for Glioblastoma

RPA Class	RTOG (original) (1)	RTOG (modified) (2)	EORTC (adapted) (3)	Median OS	One-year OS	Three-year OS
III						
Age (years)	<50	<50	<50	17 months	70%	20%
Performance status	KPS 90–100	KPS 90–100	WHO PS 0			
IV						
Age (years)	<50	<50	<50			
Performance status	KPS <90	KPS <90	WHO PS 1–2			
	or	or	or			
Age (years)	≥50	≥50	≥50			
Performance status	KPS 70–100	KPS 70–100				
	Three months from time of			11.2 months	46%	7%
Treatment status	first symptom to start of treatment	G/STR	G/STR			
Mental status		Normal	MMSE 27			
			or			
Age (years)	≥50					
Mental status	Good neurological function					
Treatment status	G/STR					
V			V&VI*			
Age (years)	≥50	≥50	≥50			
Performance status	KPS 70–100	KPS 70–100				
Mental status	Neurological function that inhibits the ability to work	Neurological function that inhibits the ability to work	MMSE <27			
Treatment status	G/STR/biopsy only, followed by at least 54.4Gy radiotherapy	G/STR	Biopsy only			
			or	7.5 months	28%	1%
Age (years)	≥50	≥50				
Performance status	KPS <70	KPS <70				
Mental status	Normal	Normal				
			or			
Age (years)		≥50				
Performance status		KPS 70–100				
Mental status		Normal				
Treatment status		Biopsy only				

RTOG = Radiation Therapy Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; RPA = recursive partitioning analysis; OS = overall survival; PS = performance status; KPS = Karnofsky performance status; G/STR = gross/sub-total resection; MMSE = Mini-Mental Status Examination.
**The modified RTOG RPA combines classes V and VI as the outcomes are very poor in both.*

Surgery

Maximal Resection

Although not proved in a randomized phase III study, several studies do support maximal, safe surgical resection. For example, data from the University of Texas MD Anderson Cancer Center indicate that >98% resection of the enhancing component of the tumor results in the best outcome.[7] Interestingly, complete resection of the non-enhancing component does not result in a significant difference in survival and may increase post-operative morbidity.

Intra-operative Treatments

Local treatments can also be administered at the time of the surgical resection. For example, a biodegradeable polymer containing carmustine (BCNU) has been approved for placement along the walls of the tumor resection cavity for both newly diagnosed and recurrent GBM. The wafer will dissolve over two to three weeks, slowly releasing the carmustine into the cavity walls. Radioactive seed implants are also placed at the time of surgery; however, phase III studies do not demonstrate any survival benefit when this technique is used in combination with standard external-beam radiotherapy (EBRT).

A new brachytherapy device—a balloon catheter system that is inflated with radioactive liquid iodine—has been developed and is currently undergoing testing in clinical trials. The balloon conforms to the shape of the cavity and may deliver a more uniform dose of radiation to the tumor bed. No proof of improved efficacy has been reported. Finally, convection-enhanced delivery is undergoing extensive evaluation. Catheter placement into the brain parenchyma surrounding the tumor cavity followed by continuous delivery of treatment under pressure promotes diffusion of the treatment into areas of the tumor that were previously not reachable by systemic delivery because of the blood–brain barrier. Targeted agents such as antibody fragments and gene therapies are currently being studied using this delivery modality.

Post-operative Imaging

For an accurate evaluation of resection, a post-operative magnetic resonance imaging (MRI) scan is best obtained within 72 hours of surgery and preferably within 48 hours.[8] This avoids misinterpreting post-operative changes such as edema and hyperemia at the resection margin. These can be mistaken for residual tumor.

Radiation Therapy

RT has long been the mainstay of adjuvant treatment in GBM, with well-documented improvement of patient survival times from approximately 14 weeks with surgery and supportive care to 36 weeks with the addition of EBRT.[9–11] Although radiation has demonstrated efficacy, the dose, fractionation, target delineation, and use of concurrent agents have been part of an ongoing search for improvement. There have been several dose-escalation studies that have failed to reveal a survival advantage in doses above 60Gy. Furthermore, accelerated hyperfractionation, hypofractionation, and the use of Boron neutron capture have all failed to show any benefit. Collectively, from these studies, the standard dosing for GBM emerged as 60Gy at 1.8–2Gy per fraction.

GBM is a difficult disease to treat with radiation because, although it rarely metastasizes outside the central nervous system, it can infiltrate throughout the brain. Autopsy studies consistently show malignant cells that are a significant distance from the primary site.[12] However, despite this fact, more than 80% of tumors recur within the original tumor location. The radiation field remains restricted as studies demonstrated no survival improvement with whole-brain RT, but a higher incidence of treatment-induced brain injury compared with regional radiation. Therefore, the use of radiation is largely to reduce the tumor burden within the brain and to slow the disease process. In keeping with the goal of treating the areas with the highest concentration of tumor, it has been recognized that there are often significant numbers of tumor cells within the T2/fluid-attenuated inversion-recovery (FLAIR) abnormality on MRI.[13] However, the presence of T2/FLAIR abnormality may be the result of the mass effect created by these tumors, and discriminating areas of tumor from reactive or vasogenic edema may be difficult. As a result, the delineation of treatment volumes remains an area of debate. The RTOG recommends coverage of the whole T2/FLAIR signal with a 2cm margin, and this volume should be treated with 46Gy. The surgical cavity and, if present, residual enhancing tumor is given a 2.5–3cm margin and is boosted to a total dose of 60Gy.

Chemotherapy

Chemotherapy has been extensively evaluated in the treatment of patients with GBM, both as first-line therapy and for patients with recurrent disease. The studies that confirmed the benefit of RT failed to demonstrate any improvement in survival with the addition of nitrosourea chemotherapy (semustine, carmustine). In fact, a large meta-analysis requiring the analysis of over 3,000 patients comparing those who received radiation with chemotherapy with those receiving radiation alone demonstrated only a 6% improvement in the one-year survival rate.[14] Conventional chemotherapy for recurrent disease typically demonstrates a 5–15% objective response rate and a 15–25% six-month progression-free survival (PFS), suggesting that the objective responses are often not durable.

The Establishment of Temozolomide

The introduction of temozolomide (TMZ) has proved to be a significant advance in the treatment of patients with GBM. Initial studies in patients with recurrent or progressive disease demonstrated only modest efficacy, with an objective response rate of 5% and a six-month PFS rate of 21%.[15] In patients with newly diagnosed GBM, a phase II study showed a high response rate (48%), but these responses were not durable with the median PFS at 3.6 months.[16] However, TMZ demonstrates excellent oral bioavailablity, no significant drug–drug interactions, and no cumulative myelotoxicity. Therefore, it has been extensively investigated in combination with other cytotoxic chemotherapies and with cytostatic agents and signal transduction modulators. As shown in *Table 2*, some combinations suggest an enhancement of efficacy over TMZ alone. Studies testing combinations of cytotoxic and cytostatic agents continue.

Table 2: Combination Regimens with Temozolomide

Combination	Patients (n)	Objective Response (PR) (%)	Overall Response (PR and SD) (%)	PFS at Six Months (%)
IFNα 2b + TMZ[a]	33	9	67	22
Thalid + TMZ[b]	31	12.5		19
cRA + TMZ[c]	40	8	58	32
Marimastat + TMZ[d]	42	14	71	41
TMZ alone[e]	112	5	46	21

PR = partial response; SD = stable disease; PFS = progression-free survival; IFNa 2b = interferon alpha 2b; TMZ = temozolomide; Thalid = thalidomide; cRA = isotretonin.
a. Yung WKA, et al., Neuro-oncology, *1999, abstract 217.*
b. Groves MD, et al., J Neurooncol, *2007;81:271–7.*
c. Jaeckle KA, et al., Neuro-oncology, *2000;2:271, abstract 103.*
d. Groves MD, et al., Neuro-oncology, *2000;2:266, abstract 86.*
e. Yung WKA, et al., J Clin Oncol, *1999;17:2762–71.*

Until recently, no study had provided level 1 evidence of a benefit for chemotherapy in treating patients with GBM. The phase III clinical trial conducted by the EORTC and National Cancer Institute of Canada (NCIC) demonstrated, for the first time, that a chemotherapeutic agent could improve overall survival in GBM patients. In the experimental arm, the addition of TMZ 75mg/mg^2 daily, given concurrently with standard radiation (60Gy in 30 fractions), and adjuvant TMZ alone 150–200mg/mg^2 daily for six months improved the median survival from 12.1 to 14.6 months, but, more importantly, increased the long-term survivorship (>2 years, actuarial) from 10.4 to 26.5%. The unadjusted hazard ratio for death in the RT–TMZ group was 0.63 (95% confidence interval (CI) 0.52–0.75; p<0.001 by the log-rank test).[17]

Additionally, an analysis was performed on these data comparing patients in the two treatment groups (stratified by prognostic group) and determined by a recursive portioning analysis (RPA). Six distinct prognostic groups have been determined and patients with glioblastoma can be in class III–VI in order of worsening prognosis. Survival with combined RT/TMZ was higher in RPA class III, with a median survival time of 21 months and a 43% two-year survival rate, versus 15 months and 20% for RT alone (p=0.006). In RPA class IV, the survival advantage remained statistically significant, with median survival times of 16 and 13 months, respectively, and two-year survival rates of 28 and 11%, respectively (p=0.0001). In RPA class V, however, the survival advantage of RT/TMZ was of borderline significance (p=0.054).[6]

Additional efforts were made to determine whether benefit from the chemoradiation regimen could be predicted on the basis of a molecular marker

Table 3: List of Signal Transduction Modulators

Pathway(s)/Molecular Target(s)	Agents
PDGFR	Imatinib mesylate
EGFR	Gefitinib
	Erlotinib
	Cetuximab
	Nimotuzumab
Ras/MAPK pathway:	Tipifarnib
Farnesyl transferase inhibitors	Lonafarnib
PI3K/Akt/mTOR pathway	Sirolimus (rapamycin)
	Temsirolimus (CCI-779)
	Everolimus (RAD-001)
	AP 23573
	Perifosine (KRX-0401)
VEGF/VEGFR	Semaxanib (SU5416)
	Vatalanib (PTK787/ZK222584)
	Bevacizumab
	VEGF Trap
PKC and PKC-ß inhibitors	Tamoxifen
	Enzastaurin (LY317615)
Integrin antagonists	Cilengitide (EMD121974)
Proteasome inhibitors	Bortezomib
Matrix metalloproteinase inhibitors	Marimastat (BB-251)
	Metastat (COL-3)
	Prinomastat (AG3340)
Cyclooxygenase-2 inhibitors	Celecoxib
Histone deacetylase inhibitors	Depsipeptide (FK228)
	Vorinostat (SAHA)
EGFR, VEGFR2	AEE788
EGFR, VEGFR2	ZD6474 (Zactima)
VEGFR2, PDGFR, c-kit, FLT-3	SU 11248 (Sunitinib)
Raf, VEGFR, PDGFR	BAY 43-9006 (Sorafenib)
EGFR, ERBB2/HER2	GW572016 (Lapatinib)
VEGFR, PDGFR, c-Kit	GW786034 (Pazopanib)
VEGFR, PDGFR, c-Kit, Src, EphA2	BMS-354825 (Dasatinib)
c-Kit, PDGFR, FLT-3, CSF-1R	MLN 518

EGFR = epidermal growth factor receptor; PKC = protein kinase c; VEGFR = vascular endothelial growth factor receptor; PDGFR = platelet derived growth receptor factor; FLT-3 = FMS-related tyrosine kinase 3; CSF-1R = colony-stimulating factor 1 receptor.
Adapted from Penas-Prado M, Gilbert MR, Expert Rev Anticancer Ther, *2007;7:641–61.*

within the tumor sample. Prior studies had made a correlation between the expression of the methylguanine-DNA methyltransferase (MGMT) protein, as measured by immunohistochemical technique, and outcome with nitrosourea-based treatment of malignant gliomas. A correlation was also made between methylation (inactivation) of the promoter region of the MGMT gene and improved outcome with the TMZ-based chemoradiation regimen.[18] Determination of the methylation status of the promoter region of the MGMT gene was successful in 206 tumor samples from the EORTC trial.

Overall, there was a statistically significant improvement in both median survival and two-year survival rate for patients with methylated MGMT.[19] This suggests that MGMT methylation is a positive prognostic factor. Furthermore, those patients with promoter methylation of the MGMT gene who were treated with chemoradiation had an improved two-year survival rate compared with those patients with methylated MGMT promoter who received only radiation, suggesting that MGMT promoter methylation is also predictive of response to TMZ chemotherapy. Among those patients whose tumor contained a methylated MGMT promoter, a survival benefit was observed in patients treated with TMZ and RT; their median survival was 21.7 months (95% CI 17.4–30.4) compared with 15.3 months (95% CI 13.0–20.9) among those who were assigned to RT only (p=0.007 by the log-rank test). In the absence of methylation of the MGMT promoter, there was a smaller and statistically insignificant difference in survival between the treatment groups.[19]

The successor trial to the EORTC trial is currently accruing patients. This is an international collaborative effort involving the RTOG, the EORTC, and the North Central Cancer Treatment Group (NCCTG). The protocol, RTOG 05-25, enrols patients with newly diagnosed GBM. All patients receive conventional chemoradiation, and are then randomized to receive either standard-dose adjuvant TMZ of six to 12 months or TMZ using a dose-dense schedule of 100mg/m^2 on days one to 21 of a 28-day cycle. Stratification is performed factoring in both RPA prognostic class and MGMT gene promoter status. The latter stratification factor has mandated the submission of tumor tissue paraffin blocks for all patients. This material will provide the ability to perform additional molecular profiling that may enhance the understanding of glioma biology and aid discovery of new therapeutic targets.

Special Considerations

High-risk Patients

High-risk patients are defined as those with a poor performance status, large tumor burden that causes neurological dysfunction, or significant comorbid conditions that increase the risk of requiring brain tumor therapies. These factors often have a significant impact on prognosis. As high-risk patients have a short life expectancy, the use of tri-modality therapy (surgical resection, radiation, and chemotherapy) must be weighed against the potential toxicities, compromises, and quality of life. Often, these patients have extensive radiographic evidence of disease and the upfront surgical intervention is biopsy alone for diagnostic purposes. A hypofractionated radiotherapy regimen can be used in this setting (50Gy in 20 fractions), which trades off the risk of late toxicity with a shorter overall treatment time (six weeks instead of four) with no increased toxicity or apparent impact on survival.[20] Treatment of elderly patients (usually older than 70 years) with GBM remains controversial. Studies have demonstrated similar survival rates using either chemotherapy or radiation alone, although an adequately powered phase III study has not been reported. Recent data from the EORTC show that elderly patients with a Karnofsky Performance Score (KPS) >70 achieved a modest improvement in median overall survival—29.1 versus 16.9 weeks—with no detriment to their quality of life.[21] Furthermore, retrospective data from the University of Texas MD Anderson Cancer Center showed that RPA class V and VI patients who received RT had a 20% radiographic response rate and an approximately 90-week overall survival.[22] Randomized studies are planned to formally compare radiation with chemotherapy and chemoradiation with radiation alone in this age group. Typically, the decision to use radiation in patients with poor performance status and advanced age should take into account the patient's and family's wishes, expectations, and social situation. The logistics and time commitment of fractionated RT can compromise the quality of remaining life of the patient. The use of TMZ is frequently given in this palliative setting, although there are no phase III data to support this application. In many situations, supportive care alone can be used, and is appropriate if the patient and family decide to not pursue aggressive treatment.

Brainstem Glioma

Frequently, the diagnosis of brainstem glioma is made empirically via imaging studies, without the benefit of an actual tissue-based diagnosis. These lesions are diffuse and often show T2/FLAIR hyperintensity and/or contrast enhancement on MRI. For lesions in this location, the standard treatment is RT alone. Because the actual grade of the tumor is unknown, the brainstem should be treated to its tolerance dose. The gross tumor volume is defined by the T2/FLAIR and enhancement abnormalities. Since these tumors spread along white matter tracts, a radial margin of 0.5cm and a longitudinal margin of 2m is treated to within the tolerance dose of the brainstem (54Gy in 28 fractions). As described above, patients do not typically undergo a biopsy. However, despite the absence of phase III data to support the use of concurrent systemic or radiosensitizing agents, use of chemoradiation is increasing for the treatment of brainstem gliomas in adults.

Recurrent Tumors

Patients with GBM nearly always develop recurrent or progressive tumor growth. However, unlike patients with newly diagnosed disease, no level 1 evidence exists to guide therapy; therefore, treatment options and decisions are often determined by the specific clinical situation and treatment availability.

Re-operation

Most series report that approximately 20–40% of patients with recurrent GBM undergo re-resection of tumor at the time of recurrence. This varies by center and treatment provider. No formal guidelines exist to assist in the decision; however, patients with a local recurrence in non-eloquent brain regions are more likely to undergo a repeat tumor resection. This procedure can relieve mass effect and resolve issues related to increased intracranial pressure. In addition, the tissue can be analyzed to distinguish between treatment effect (necrosis) and active progressive tumor. Furthermore, the newly established tumor cavity permits use of a local therapy strategy such as placement of BCNU-containing biodegradable polymers or an intracavitary balloon for subsequent local radiation using brachytherapy.

Chemotherapy

Chemotherapy regimens are commonly used to treat patients with recurrent GBM. To date, no regimen has been proved in terms of efficacy by randomized clinical trials in order to become the established standard of care. A wide spectrum of therapeutic regimens have been tested, including single-agent cytotoxic chemotherapies, such as irinotecan (CPT-11), or combination regimens, such as irinotecan with TMZ. Objective response rates in recurrent GBM to cytotoxic regimens remain low (5–15%). More recently, six-month PFS rate has been used as a measure of efficacy, based on a statistical analysis that set a six-month PFS rate of 15% or less as an indication of low activity.[23]

Re-irradiation

Due to the success of TMZ, especially in its creation of more long-term survivors, the use of re-irradiation will become more common in clinical practice. This also creates an impetus for more careful delivery of radiation in the definitive setting. Stereotactic radiosurgery/RT can be used for small volumes of recurrence that appear within a short period of time, close to or within the previous high-dose region.[24] Specifically, tumors <4cm can be treated with stereotactic radiosurgery using 12–20Gy in a single fraction. For tumors >4cm, fractionated 3D-conformal or intensity-modulated radiation therapy (IMRT) can be used, but the dose and timing must be tailored to prevent radiation necrosis. Doses of 30–50Gy can be used, depending on the previous dose received by the volume. For tumors that recur within the 60Gy volume, 12–15 months are required between radiation courses. Tumors in the 50Gy region should have a period of 12 months between courses. Lastly, tumors outside of significant dose volumes can be treated three to six months after completion of the initial course.

Novel Agents

Patients with recurrent GBM often gain only minimal or modest benefit from conventional treatments. Therefore, there has been great interest in developing new treatment regimens for this group of patients. A wide variety of traditional cytotoxic chemotherapy agents such as cisplatin, carboplatin, procarbazine, and irinotecan have been tested. Most studies demonstrate only modest benefit, with objective response rates reported in the 5–15% range, and response is often not durable. More recently, signal transduction-modulating agents have been evaluated. As outlined in *Table 3*, a large number of new drugs have been synthesized with a limited number of specific pathway targets. To date, response to these drugs as single-agent therapy has been limited; however, combinations with cytotoxic therapies may prove to be more beneficial. Combinations of signal transduction modulators have recently been moved into clinical trials. Careful phase I testing has revealed that these strategies may have overlapping toxicities that were unanticipated from the general low toxicity of treatment with single agents. Currently, the efficacy of combination regimens using signal transduction modulators has not been determined, but is an area of active investigation.

Conclusions

Although the prognosis for patients with GBM remains guarded, there have been some recent advances in treatment that clearly demonstrate that multimodality therapy can improve outcome. The standard of care is to maximally debulk the tumor and follow this with concurrent chemotherapy and EBRT. This is followed by additional adjuvant chemotherapy. Despite this new standard of care, better treatments are needed. Currently, there are active investigations of signal transduction modulators along with extensive studies of tumor molecular profiles. These parallel investigations will ultimately result in individualized patient treatment. In this scenario, laboratory testing of tumor samples including molecular profiling will determine the optimal regimen, analogous to the use of tratuzumab in human epidermal growth factor (HER)2-positive breast cancer. The collaboration of laboratory scientists and clinical investigators holds great promise for future advances in treatment. ■

1. Kleihues P, Ohgaki H, *Neuro-oncol*, 1999;1(1):44–51.
2. Ohgaki H, et al., *Cancer Res*, 2004;64(19):6892–9.
3. Simmons ML, et al., *Cancer Res*, 2001;61(3):1122–8.
4. Curran WJ Jr, et al., *J Natl Cancer Inst*, 1993;85:704–10.
5. Shaw EG, et al., *Int J Radiat Oncol Biol Phys*, 2003;57:S135–6.
6. Mirimanoff RO, et al., *J Clin Oncol,* 2006;24:2563–9.
7. Lacroix M, et al., *J Neurosurg*, 2001;95:190–98.
8. Henson JW, et al., *Lancet Oncol*, 2005;6:167–75.
9. Kristiansen K, et al., *Cancer*, 1981;47:649–52.
10. Shapiro WR, et al., *J Neurosurg*, 1989;71:1–9.
11. Walker MD, et al., *N Engl J Med*, 1980;303:1323–9.
12. Halperin EC, et al., *Int J Radiat Oncol Biol Phys*, 1989;17:1347–50.
13. Wallner KE, et al., *Int J Radiat Oncol Biol Phy*, 1989;16:1405–9.
14. Fine HA, et al., *Cancer*, 1993;71:2585–97.
15. Yung WK, et al., *J Clin Oncol,* 1999;17:2762–71.
16. Gilbert MR, et al., *Neuro Oncol*, 2002;4:261–7.
17. Stupp R, et al., *N Engl J Med*, 2005;352:987–96.
18. Jaeckle KA, et al., *J Clin Oncol,* 1998;16:3310–15.
19. Hegi ME, et al., *N Engl J Med*, 2005;352:997–1003.
20. Chang EL, et al., *Int J Radiat Oncol Biol Phys*, 2003;56:519–28.
21. Keime-Guibert F, et al., *N Engl J Med*, 2007;356:1527–35.
22. Pelloski CE, et al., *Clin Cancer Res*, 2005;11:3326–34.
23. Wong ET, et al., *J Clin Oncol*, 1999;17(8):2572–8.
24. Kim HK, et al., *Am J Clin Oncol,* 1997;20:358–63.