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CNS Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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CME Certified

CNS Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Brain tumors are a diverse group of neoplasms arising from different cells within the central nervous system (CNS) or from systemic tumors that have metastasized to the CNS. Primary brain tumors include a number of histologic types with markedly different tumor growth rates and are divided into anaplastic gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma) and glioblastoma multiforme (GBM) based on their histopathologic features. Despite treatment, the median survival for anaplastic oligodendroglioma is two to three years, and patients with GBM can succumb to their disease within a year of the onset. Thus, clinical education regarding standard and evolving best-practice therapeutic management of these neoplasms is essential to improving patient outcomes. To bridge the gap between research and patient care, this issue of *CNS Cancer Update* features one-on-one discussions with leading neuro-oncologists and neurosurgeons. By providing information on the latest research developments in the context of expert perspectives, this activity assists medical oncologists with the formulation of state-of-the-art clinical management strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES

- Identify strategies to distinguish between true disease progression and radiographic pseudoprogression in patients with glioma who have undergone chemoradiation therapy.
- Apply advances in imaging and neuropathology to diagnose, prognosticate and measure response to therapy for patients with CNS tumors.
- Use the results of new clinical studies for CNS tumors to improve patient outcomes.
- Recall the results of existing and emerging research on interstitial chemotherapy for patients with Grade III or IV gliomas.
- Integrate palliative management initiatives to improve quality of life for patients with brain tumors.
- Develop evidence-based clinical management strategies for recurrent or progressive GBM.
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate.

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INTERVIEW

Timothy F Cloughesy, MD

Dr Cloughesy is Professor, Director of the Neuro-Oncology Program and Director of the Henry Singleton Brain Cancer Research Program at the David Geffen School of Medicine at UCLA in Los Angeles, California.

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Track 1 **Case discussion:** A 48-year-old man with glioblastoma multiforme (GBM) undergoes subtotal resection followed by chemoradiation therapy and neurosurgery for presumed disease progression after headaches and a worsening MRI scan one week later

Track 2 Prognostic and predictive significance of MGMT promoter methylation status in GBM

Track 3 Pseudoprogression after chemoradiation therapy for GBM

Track 4 **Case discussion:** A 65-year-old man regains functional status with bevacizumab treatment for progressive GBM after chemoradiation therapy and a complicated clinical course in the intensive care unit with acute respiratory distress syndrome and a pulmonary embolism after neurosurgery

Track 5 Consideration of bevacizumab for patients with GBM on anticoagulation therapy

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Track 18 Mechanism of action of cilengitide

Select Excerpts from the Interview

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DR LOVE: Would you discuss the updated data from the BRAIN study that you presented at ASCO 2010?

DR CLOUGHESY: The BRAIN study evaluated patients with recurrent glioblastoma. Patients were randomly assigned to either bevacizumab alone or bevacizumab and irinotecan. No control arm of chemotherapy alone was included, and patients randomly assigned to receive bevacizumab alone had the opportunity to cross over to bevacizumab and irinotecan at disease progression. The initial data showed significant benefits in response rates, six-month progression-free survival and overall survival when compared to historical controls. At ASCO 2010 we presented durability of survival data (Cloughesy 2010; [1.1]).

I believe these are impressive data, but it is difficult to determine a comparator as we have not had many successful therapies. A number of historical studies showed a 12-month overall survival rate in the range of 20 to 25 percent, so the BRAIN study data indicating a 12-month overall survival of 38 percent are encouraging. The follow-up also demonstrated that many of the patients continue to fare well much further out. In addition, no difference was observed between the two arms, and one takeaway is that bevacizumab is carrying the majority of the weight rather than irinotecan.

1.1

BRAIN Phase II Study: Updated Survival Data Among Patients Receiving Bevacizumab or Bevacizumab and Irinotecan for Recurrent Glioblastoma

	Bevacizumab (n = 85)	Bevacizumab + irinotecan (n = 82)
12-month survival	38%	38%
18-month survival	24%	18%
24-month survival	16%	17%
30-month survival	11%	16%

Cloughesy T et al. *Proc ASCO* 2010;**Abstract 2008**.

We also updated the safety data from the BRAIN study at ASCO 2010 (Cloughesy 2010; [1.2]). No change was evident in the safety signal from the original evaluation through July 2008. The rate of hypertension is about the same as previously reported, and it is interesting to note that it is lower on the irinotecan arm. Relative dehydration may occur because of decreased fluid intake among patients on the irinotecan arm, and that might have affected the different rates of hypertension in the two groups. The rate of Grade III or higher cerebral hemorrhage was also low, in the range of zero to one percent. Overall, I believe we are all more comfortable using bevacizumab in the setting of brain tumors.

DR LOVE: In your practice, at what point do you incorporate bevacizumab into the clinical management of glioblastoma multiforme (GBM)?

DR CLOUGHESY: I tend to limit its use to the recurrent setting, except in a few clinical situations for which I may bring it in earlier. For example, if a patient who has recently undergone neurosurgery is having a difficult time

1.2

BRAIN Phase II Study: Updated Safety Data Among Patients Receiving Bevacizumab or Bevacizumab and Irinotecan for Recurrent Glioblastoma

	Bevacizumab	Bevacizumab + irinotecan
Hypertension		
All grades	39.3%	29.1%
Grade ≥III	10.7%	3.8%
Cerebral hemorrhage		
All grades	3.6%	3.8%
Grade ≥III	0%	1.3%
Venous thromboembolism		
All grades	3.6%	11.4%
Grade ≥III	3.6%	10.1%
Arterial thromboembolism		
All grades	4.8%	3.8%
Grade ≥III	3.6%	2.5%
Gastrointestinal perforation		
All grades	0%	2.5%
Grade ≥III	0%	2.5%

"The incidence of selected adverse events in the updated safety data was consistent with that previously reported, and no new safety signals were identified."

Cloughesy T et al. *Proc ASCO* 2010;**Abstract 2008**.

with radiation therapy and experiences a mass effect with swelling, I try to salvage with up-front bevacizumab. Some patients obtain a real benefit from bevacizumab in this setting.

Tracks 10-11

DR LOVE: Would you discuss the current data on the up-front use of bevacizumab for GBM?

DR CLOUGHESY: Up-front use of bevacizumab for glioblastoma has been evaluated in several studies (Lai 2009; Shih 2010). In the Phase II trial presented by my group at ASCO 2009 (Lai 2009), 70 patients with newly diagnosed GBM received radiation therapy/bevacizumab and temozolomide.

We observed that patients in the bevacizumab group experienced progression-free survival of approximately 13 months. However, almost all of the patients in the control group went on to receive bevacizumab at disease progression. Thus the overall survival was not different between the two groups. So it is not clear if it is better to use it up front or in the recurrent setting.

Ongoing, randomized, blinded Phase III studies (1.3) are evaluating the role of bevacizumab in the up-front management of GBM. These trials are well designed and should be able to demonstrate the effect of bevacizumab, when used in the up-front setting, on overall survival and progression-free survival.

1.3

Ongoing Phase III Trial Evaluating the Role of Bevacizumab in the Up-Front Management of Glioblastoma Multiforme (GBM)

Protocol ID: RTOG-0825 **Target Accrual:** 942

Eligibility: Newly diagnosed GBM, surgical resection within the past three to five weeks

* Radiation therapy (IMRT or 3D conformal) is administered five days a week for six weeks. † Temozolomide is administered PO daily for up to seven weeks. Four weeks after completion of concomitant temozolomide/radiation therapy, oral temozolomide is administered in the adjuvant setting on days one through five of 28-day cycles for up to 12 cycles. ‡ Bevacizumab or matching placebo is administered at 10 mg/kg q2wk starting in week four of concomitant temozolomide/radiation therapy and continues until the end of adjuvant temozolomide.

www.clinicaltrials.gov, September 2010.

Tracks 16-17

DR LOVE: Can you comment on clinical research on the use of cilengitide in the treatment of GBM?

DR CLOUGHESY: Cilengitide is an integrin receptor inhibitor, and although its actual mechanism is unclear, it is supposed to have an effect that could limit the invasion of the tumor. It might also have a direct antitumor effect. The side effects are minimal, so it could be combined with many different kinds of agents.

In the recurrent setting, the Phase II studies showed an interesting effect on survival with the higher 2,000-mg cilengitide dose (Fink 2010; Reardon 2008; [1.4, 1.5]). The survival with this higher dose was nine months, and in the group that received 500 mg the survival was closer to six or seven months.

1.4

Efficacy of Two Dose Levels of Cilengitide in Recurrent Glioblastoma: A Randomized Phase II Study

	500 mg/d (n = 41)	2,000 mg/d (n = 40)
Radiographic response	5%	13%
Time to disease progression, median	7.9 wk	8.1 wk
Six-month progression-free survival	10%	15%
Overall survival, median	6.5 mo	9.9 mo
	Hazard ratio = 0.70, $p = 0.15$	

Reardon DA et al. *J Clin Oncol* 2008;26(34):5610-7.

In the up-front setting, we are waiting on a large EORTC-sponsored Phase III study (1.6), which is evaluating the role of cilengitide in conjunction with temozolomide and radiation therapy among patients with GBM with methylated MGMT promoter status. ■

1.5

Long-Term Survival Rates with Cilengitide at Two Dose Levels in Recurrent Glioblastoma: 54-Month Follow-Up

	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	54 mo
500 mg/d	58.5%	22.0%	12.2%	12.2%	9.8%	4.9%	2.4%	2.4%	2.4%
2,000 mg/d	65.0%	37.5%	27.5%	22.5%	17.5%	15.0%	12.5%	10.0%	5.0%

Overall survival rates were consistently higher with cilengitide 2,000 mg than with the lower dose, although the study was not powered to detect a significant difference between the two doses.

Fink K et al. *Proc ASCO* 2010;**Abstract 2010**.

1.6

Phase III Study Evaluating the Role of Cilengitide in the Up-Front Management of Glioblastoma Multiforme (GBM)

Protocol IDs: EORTC 26071-22072, CENTRIC **Target Accrual:** 504

Eligibility: Newly diagnosed GBM, proven methylated MGMT gene promoter methylation status

www.clinicaltrials.gov, September 2010.

SELECT PUBLICATIONS

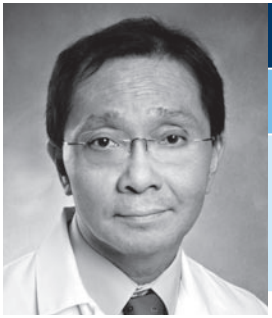
Cloughesy T et al. **Updated safety and survival of patients with relapsed glioblastoma treated with bevacizumab in the BRAIN study.** *Proc ASCO* 2010;**Abstract 2008**.

Fink K et al. **Long-term effects of cilengitide, a novel integrin inhibitor, in recurrent glioblastoma: A randomized phase IIa study.** *Proc ASCO* 2010;**Abstract 2010**.

Lai A et al. **Phase II trial of bevacizumab in combination with temozolomide and regional radiation therapy for up-front treatment of patients with newly diagnosed glioblastoma multiforme.** *Proc ASCO* 2009;**Abstract 2000**.

Reardon DA et al. **Randomized phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme.** *J Clin Oncol* 2008;26(34):5610-7.

Shih KC et al. **Phase II trial of radiation therapy/temozolomide/bevacizumab followed by bevacizumab/everolimus in the first-line treatment of glioblastoma multiforme (GBM).** *Proc ASCO* 2010;**Abstract 2075**.



INTERVIEW

Patrick Y Wen, MD

Dr Wen is Director of the Center for Neuro-Oncology at Dana-Farber/Brigham and Women's Cancer Center and Professor of Neurology at Harvard Medical School in Boston, Massachusetts.

Tracks 1-13

Track 1 Pivotal Phase II trial of bevacizumab for recurrent GBM

Track 2 Infiltrating pattern of relapse after bevacizumab in GBM

Track 3 Efficacy and safety of XL184 in recurrent GBM

Track 4 Radiographic artifact versus durable response with bevacizumab in GBM

Track 5 Six-month progression-free survival as a clinically meaningful endpoint in recurrent GBM

Track 6 Pseudoprogression versus true disease progression after chemoradiation therapy for GBM

Track 7 Clinical trials of cediranib in GBM

Track 8 Perspective on the use of bevacizumab for patients with brain metastases

Track 9 Antiedema versus antitumor effect of VEGF inhibitors in GBM

Track 10 Approach to integrating bevacizumab in the treatment algorithm for recurrent GBM

Track 11 Risk-benefit ratio of bevacizumab for patients with GBM receiving anticoagulation for thromboembolism

Track 12 **Case discussion:** A 48-year-old woman with GBM experiences disease recurrence with an infiltrating pattern of relapse after a clinically meaningful response to bevacizumab

Track 13 Mesenchymal phenotype as a distinct aggressive vascular subtype of GBM

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you discuss the novel multitargeted tyrosine kinase inhibitor XL184, which is being evaluated in GBM?

DR WEN: The interest in this class of drugs is tremendous. XL184 in particular inhibits not only VEGFR2 but also MET and RET. We presented initial Phase II results with two doses of XL184 for patients with recurrent GBM at ASCO 2010 (Wen 2010a; [2.1]). The original Phase II dose garnered from the Phase I studies was 175 mg, but that dose was toxic. Dose reduction to 125 mg daily was better tolerated, patients remained on treatment longer and results were more favorable. Response rates were approximately 30 percent, which

2.1 **Efficacy of XL184 for Recurrent Glioblastoma Multiforme**

	Prior anti-angiogenic therapy			
	No		Yes	
Cohort	XL184 175 mg N = 34	XL184 125 mg N = 37	XL184 175 mg N = 12	XL184 125 mg N = 22
Median PFS	16 weeks	16 weeks	NR	7.9 weeks
ORR, n (%)	7 (21)	11 (30)	1 (8)	0

PFS = progression-free survival; NR = not reported; ORR = overall response rate

- XL184 shows encouraging clinical activity in patients with recurrent glioblastoma.
  - Clinical activity was observed in both populations of patients with anti-angiogenic-naïve and pretreated disease.
- XL184 at the dose of 125 mg demonstrated improved tolerability compared to the 175-mg dose while retaining clinical activity.
  - Fewer treatment interruptions and lower rates of permanent discontinuation were observed at the lower dose.

Wen PY et al. *Proc ASCO* 2010a;**Abstract 2006**.

compares favorably with bevacizumab, and the six-month progression-free survival rate was approximately 26 percent.

In terms of side effects, patients exhibited hypertension, fatigue and some diarrhea. Another troublesome toxicity with this class of drugs is hand-foot syndrome, which often results in the need to reduce the dose. It's possible that further dose reduction of XL184 might be useful because it is a potent inhibitor of the VEGF receptor. Thus, a lower dose would probably still be effective.

I believe another important characteristic of VEGF receptor inhibitors is that by blocking VEGF you significantly decrease the edema around these tumors. It's a feature of all of these drugs that allows you to significantly reduce steroid use, and that is of real benefit to patients.

Track 6

DR LOVE: Would you describe the phenomenon of pseudoprogression, which patients can experience after chemoradiation therapy for GBM?

DR WEN: Pseudoprogression can occur after patients have completed six weeks of radiation therapy with temozolomide. In approximately 40 percent of patients, the post-therapy scan at week four will appear worse. Approximately half of the time this is because of true tumor progression, but the other half of the time it's because of radiation therapy effects. Delineating between the two is extremely difficult.

This phenomenon occurs mainly in the first three months after radiation therapy, although occasionally it can occur later. A recent publication proposes that within the first three months of radiation therapy, patients should not

automatically be assumed to be experiencing disease progression based solely on the scan (Wen 2010b).

Track 7

DR LOVE: What are the current data with cediranib in GBM?

DR WEN: Cediranib is a potent pan-VEGF receptor inhibitor with some inhibitory activity against PDGF. It doesn't inhibit MET at all. We reported a Phase II study of cediranib for recurrent GBM (Batchelor 2010; [2.2]).

When this trial was initiated, the cediranib dose was 45 mg/day, but that dose was difficult for patients to tolerate. A dose reduction to 30 mg/day was better tolerated. I believe the most striking side effect with the lower dose was hypertension, which was prominent. It was treatable but often required more than one antihypertensive agent.

Combining cediranib with radiation therapy is also of interest. Preclinical data suggest this class of agents might potentiate radiation therapy, thus the rationale for using it with radiation therapy for brain metastases (Eichler 2010). Some trials are also evaluating cediranib with radiation therapy and temozolomide for newly diagnosed glioblastoma (NCT00662506, NCT01062425).

2.2 Phase II Study of Cediranib for Patients with Recurrent Glioblastoma

	Alive and progression free at six months (APF6)	Partial response (by MRI three-dimensional measurements)
Cediranib (N = 31)	25.8%	56.7%

"Potential advantages of cediranib relative to bevacizumab include oral bioavailability; a shorter half-life (22 hours v 21 days), which should allow more rapid clearance of drug in the event of serious toxicity such as hemorrhage; multiple tyrosine kinase targets and the ability to target intracellular VEGF receptors.

We observed that cediranib treatment results in a radiographic response proportion, APF6 proportion, median PFS and median OS that compare favorably with data from historical controls.

These data are also comparable to data obtained in phase II studies of bevacizumab in this patient population. The frequency of drug discontinuation due to toxicity was low and comparable to other anti-VEGF therapies. The safety profile of cediranib in patients with glioblastoma was acceptable, and there were no CNS hemorrhages or increased risk of thromboembolic complications."

Batchelor TT et al. *J Clin Oncol* 2010;28(17):2817-23.

Track 8

DR LOVE: What is your perspective on the use of anti-VEGF therapies, specifically bevacizumab, for patients with brain metastases?

DR WEN: When bevacizumab was first administered in this setting, the concern was that its use would cause brain metastasis bleeding. Meta-analyses are now evaluating patients on trials who either developed brain metastases while receiving bevacizumab or were allowed to enroll on bevacizumab trials with known brain metastases.

The risk of hemorrhage in these patients is low — on the order of one or two percent (Rohr 2009; [2.3]). I believe that for most patients with brain metastases bevacizumab is a safe agent. For patients with brain metastases who exhibit many symptoms and for whom no other interventions are available, bevacizumab may be helpful. ■

2.3

Rates of Cerebral Hemorrhage with Bevacizumab in Patients with Brain Metastases from Various Solid Tumors: A Retrospective Analysis of (A) 13 Phase II or III Trials, (B) the ATHENA and SAiL Trials and (C) Two Open-Label Studies for Patients with Treated CNS Metastases

Data set	Patients with CNS metastases	Rates of cerebral hemorrhage	
		Bevacizumab	No bevacizumab
A	Bevacizumab (n = 91), no bevacizumab (n = 96)	3.29%	1.04%
B	N = 321	0.93%	—
C	N = 131	0.80%	—

- Risk of cerebral hemorrhage does not appear to be disproportionately high for patients who have received bevacizumab.
- Patients with CNS metastases should not, in general, be excluded from bevacizumab therapy.

Rohr UP et al. *Proc ASCO* 2009;**Abstract 2007**.

SELECT PUBLICATIONS

Batchelor TT et al. **Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma.** *J Clin Oncol* 2010;28(17):2817-23.

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Eichler AF et al. **A phase I study of cediranib plus whole-brain radiation therapy in patients with brain metastases from non-small cell lung cancer.** *Proc ASCO* 2010;**Abstract TPS177**.

Friedman HS et al. **Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma.** *J Clin Oncol* 2009;27(28):4733-40.

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Wen PY et al. **Phase II study of XL184 (BMS 907351), an inhibitor of MET, VEGFR2, and RET, in patients (pts) with progressive glioblastoma (GB).** *Proc ASCO* 2010a;**Abstract 2006**.

Wen PY et al. **Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group.** *J Clin Oncol* 2010b;28(11):1963-72.

INTERVIEW

Jon D Weingart, MD

Dr Weingart is Professor of Neurosurgery and Oncology at Johns Hopkins School of Medicine in Baltimore, Maryland.

Tracks 1-9

Track 1 **Case discussion:** A 55-year-old man with GBM undergoes gross total resection with adjunctive carmustine wafer followed by chemoradiation therapy

Track 2 Implementation of the carmustine wafer implantation

Track 3 Challenges of carmustine wafer implantation in the community setting

Track 4 **Case discussion:** A 63-year-old man with recurrent GBM receives combination therapy with bevacizumab and temozolomide

Track 5 Pace and duration of clinical benefit with bevacizumab in recurrent GBM

Track 6 **Case discussion:** A 58-year-old man with GBM undergoes gross total resection and radiation therapy and is diagnosed with a quiescent tumor after undergoing a second neurosurgical resection six months later

Track 7 Clinical significance of quiescent tumors

Track 8 Global improvement in GBM survival during the past two decades

Track 9 Role of neurosurgery versus radiation therapy in patients with brain metastases

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: How do you approach the use of BCNU (carmustine) wafer implants for the treatment of GBM?

DR WEINGART: At our institution, if we know that the likelihood is high in terms of obtaining a gross total resection of the enhancing tumor at surgery, we discuss the use of carmustine wafers with the patient before surgery.

In the retrospective study of carmustine wafers, among patients who received carmustine wafers followed by concomitant temozolomide and radiation therapy and then temozolomide alone for six months, the median survival was approximately 21 months (McGirt 2009).

DR LOVE: Would you describe the technical procedure involved in the implantation?

DR WEINGART: It's quite straightforward. The wafers look like little disks the shape and size of a dime. The surgeon places them along the wall of the tumor cavity and then applies Surgicel® to hold them laterally against the tumor cavity wall. Altogether the procedure is accomplished in approximately 10 minutes, and hemostasis has already occurred.

Certain nuances must be considered when implanting the wafers. A small incision in the brain may expand into a large cavity — this is not the best case. The best-case scenario is a resection cavity that resembles the shape of an ice cream scoop.

Ideally, you have a wide opening on the surface to facilitate the implantation. You're not causing bleeding by inserting them. Also, an inflammatory response occurs around the wafers. When an inflammatory response is hindered due to closure of the cortical surface, increased swelling and a need for extended use of steroids may occur.

DR LOVE: Have you observed any other complications — for example, any systemic chemotherapy-type effects?

DR WEINGART: No measurable carmustine is detectable in the bloodstream. The agent is all localized. The infection risk is no different than that associated with surgery without the use of carmustine wafers. It's good to have a dural closure that's fairly tight because wound healing in the different randomized studies has been an issue in patients with leaking spinal fluid. It is not known whether this is associated with the carmustine in the spinal fluid.

DR LOVE: How often are carmustine wafers used in community-based practice? This doesn't seem to be a commonly used treatment.

DR WEINGART: That is correct. Part of the reason is that you must discuss the use of carmustine wafers with the patient before surgery. My guess is that neurosurgeons in community practice are not following up with these patients after surgery, when the patients are referred to their oncologists.

Track 5

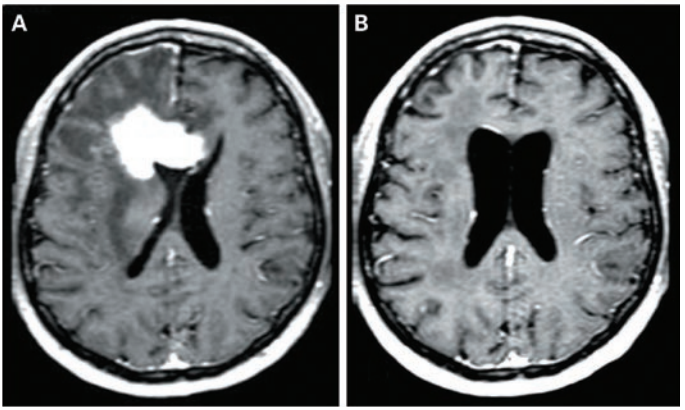
DR LOVE: What have you observed with bevacizumab in the treatment of GBM?

DR WEINGART: The use of bevacizumab improves MRI scans (3.1), and patients are able to receive lower doses of steroids, which improves their quality of life. Patients feel better, and sometimes their neurological deficits improve. It's a short-term benefit lasting three to six months at best. Then, when the tumor progresses, symptom progression often occurs before disease progression is noted on MRI. Of course, if bevacizumab is stopped, the MRI often rapidly appears abnormal.

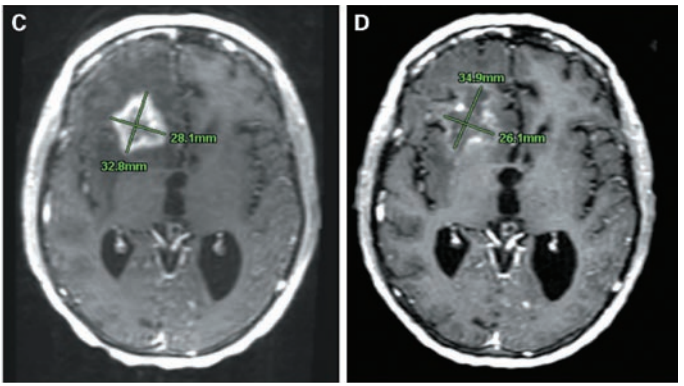
We tend to continue the use of bevacizumab in the setting of disease progression if symptoms are worsening or if the flare abnormality worsens. If you pull back on bevacizumab, patients may experience disease progression quickly. ■

3.1

MRI-Documented Response to Treatment with Bevacizumab* in Patients with Recurrent Glioblastoma



Patient 1: (A) Before treatment; (B) After three months of treatment without concomitant corticosteroid therapy



Patient 2: (C) Before treatment; (D) Partial response by Levin criteria versus stable disease by cross-sectional diameters (Macdonald criteria)

* Patients received bevacizumab 10 mg/kg every 14 days on a 28-day cycle.

Kreisl TN et al. *J Clin Oncol* 2009;27(5):740-5.

SELECT PUBLICATIONS

Kreisl TN et al. **Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma.** *J Clin Oncol* 2009;27(5):740-5.

McGirt MJ et al. **Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme.** *J Neurosurg* 2009;110(3):583-8.

INTERVIEW

David M Peereboom, MD

Dr Peereboom is Associate Professor in the Department of Medicine at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University and Director of Clinical Research at Cleveland Clinic Taussig Cancer Institute's Brain Tumor and Neuro-Oncology Center in Cleveland, Ohio.

Tracks 1-17

Track 1 **Case discussion:** A 60-year-old woman with an oligodendroglioma treated with surgery and adjuvant temozolomide 10 years previously followed by multiple systemic treatments undergoes external beam radiation therapy after developing focal seizures

Track 2 Classification and natural history of primary brain tumors

Track 3 Prognostic and predictive significance of 1p/19q deletion in anaplastic oligodendroglioma

Track 4 Use of bevacizumab in oligodendroglioma

Track 5 Effect of brain radiation therapy on cognitive function

Track 6 Ongoing clinical trials of temozolomide and/or radiation therapy for patients with 1p/19q codeleted oligodendroglioma

Track 7 **Case discussion:** A 28-year-old man with right-frontal GBM undergoes surgical resection followed by enrollment on a clinical trial of radiation therapy/temozolomide and erlotinib followed by multiple systemic regimens for recurrent progressive disease

Track 8 Secondary glioblastoma as a distinct subtype of GBM with a different biology

Track 9 Investigating change in intensity or pattern of chronic low-grade headaches

Track 10 **Case discussion:** A 51-year-old man with relapsed gliosarcoma develops a pulmonary embolism eight to 10 weeks after initiation of bevacizumab

Track 11 Gliosarcoma: A subset of GBM with spindle-like morphology

Track 12 Management of venous thromboembolism in patients with gliomas

Track 13 Tolerability of bevacizumab in GBM

Track 14 Pros and cons of bevacizumab versus bevacizumab/irinotecan for recurrent GBM

Track 15 Evaluation of bevacizumab as front-line therapy for GBM

Track 16 Palliative issues among patients with GBM

Track 17 Importance of immediate neurosurgical evaluation and biopsy of suspected central nervous system lymphoma

Select Excerpts from the Interview

Tracks 14-15

DR LOVE: What are your thoughts about the use of bevacizumab or irinotecan/bevacizumab for GBM?

DR PEEREBOOM: Bevacizumab is FDA approved for recurrent glioblastoma, and two clinical trials (Cloughesy 2010; [1.1, page 4]; Friedman 2009; [4.1]) have evaluated, in a randomized fashion, bevacizumab with or without irinotecan. These studies have demonstrated an improvement in progression-free survival but no improvement in overall survival when irinotecan is added to bevacizumab. Toxicity is increased with the combination, and much debate has taken place in the neurooncology community as to whether irinotecan should be used in combination with bevacizumab.

My bias is not to use the combination but rather to use bevacizumab as a single agent because I believe that in this patient population quality of life is probably at the top of the list as far as goals we are trying to accomplish. The addition of irinotecan puts a dent in patients' quality of life.

DR LOVE: What about clinical research in the up-front setting?

DR PEEREBOOM: A number of Phase II trials have evaluated bevacizumab in the up-front management of GBM. The preliminary findings from these small, single-institution studies appear encouraging. The important ongoing clinical trial is RTOG-0825 (1.3, page 6), in which patients are randomly assigned to radiation therapy/temozolomide with or without bevacizumab. This is a placebo-controlled study that will be enrolling approximately 1,000 patients.

I believe the results of this trial will answer the important question of whether up-front bevacizumab produces an improvement in survival, progression-free survival and quality of life. With well-informed patients I discuss the fact that at some point in the course of the illness bevacizumab will probably become part of their therapy. We do not know yet if using it up front is better than using it at the time of disease progression.

4.1

Randomized Phase II Trial: Bevacizumab Alone or in Combination with Irinotecan in Recurrent Glioblastoma

	Bevacizumab	Bevacizumab/ irinotecan
Overall response rate	28.2%	37.8%
Six-month progression-free survival	42.6%	50.3%
Overall survival	9.2 months	8.7 months

Friedman HS et al. *J Clin Oncol* 2009;27(28):4733-40.

Tracks 3, 6

DR LOVE: What is the significance of 1p/19q deletion in anaplastic glioma?

DR PEEREBOOM: Patients with anaplastic glioma with 1p/19q deletion have long survival rates and good sensitivity to chemotherapy and radiation therapy.

This codeletion is mediated by a translocation of 1p and 19q. At this point, the function of this translocation is not understood. The important fact, I believe, is that in this subset of high-grade gliomas, patients may not need to undergo radiation therapy at the time of diagnosis. And, although no trials have examined cognitive and quality-of-life issues, when we take one approach or the other my bias for such patients would be to delay radiation therapy.

DR LOVE: Are any clinical trials evaluating treatment for this subset?

DR PEEREBOOM: A large randomized trial is ongoing for patients with anaplastic gliomas with 1p/19q codeletion (4.2). The trial has three arms: radiation therapy alone, radiation therapy with temozolomide and temozolomide alone. This trial will teach us how to best approach this group of patients. ■

4.2

Phase III Trial Evaluating Temozolomide Alone versus Radiation Therapy Alone versus Temozolomide/Radiation Therapy in the Up-Front Management of 1p/19q Codeleted Anaplastic Glioma

Protocol IDs: NCCTG-N0577, EORTC-26081 **Target Accrual:** 488

Primary endpoint: Overall survival

Eligibility

- Histologically confirmed 1p/19q codeleted anaplastic glioma
- Mandatory central pathology review
- Surgery within three months

R

- Radiation therapy alone*
- Radiation therapy + temozolomide†
- Temozolomide alone‡

* Radiation therapy is administered five days a week for six weeks. † Oral temozolomide is administered on days one through seven for six weeks. Beginning four weeks after completion of concurrent chemoradiation therapy, patients receive adjuvant oral temozolomide once daily on days one through five, q28d for six to 12 courses. ‡ Oral temozolomide is administered once daily on days one through five, q28d for 12 courses.

www.clinicaltrials.gov, October 2010.

SELECT PUBLICATIONS

Cairncross JG et al. **Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas.** *J Natl Cancer Inst* 1998;90(19):1473-9.

Cloughesy T et al. **Updated safety and survival of patients with relapsed glioblastoma treated with bevacizumab in the BRAIN study.** *Proc ASCO* 2010;**Abstract 2008**.

Friedman HS et al. **Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma.** *J Clin Oncol* 2009;27(28):4733-40.

Kim JW et al. **Relationship between radiological characteristics and combined 1p and 19q deletion in World Health Organization grade III oligodendroglial tumours.** *J Neurol Neurosurg Psychiatry* 2010;[Epub ahead of print].

Vredenburgh JJ et al. **Bevacizumab plus irinotecan in recurrent GBM.** *J Clin Oncol* 2007;25(30):4722-9.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following regimens was not a "randomized treatment arm" in the Phase II BRAIN study in recurrent GBM?**
   a. Single-agent bevacizumab
   b. Single-agent irinotecan
   c. Bevacizumab/irinotecan combination

2. **Which of the following regimens showed a relative superiority in two-year survival in the Phase II BRAIN study?**
   a. Single-agent bevacizumab
   b. Bevacizumab/irinotecan
   c. Regimens a and b were essentially equivalent at two years

3. **During a retrospective evaluation of carmustine wafer with temozolomide and radiation therapy versus carmustine wafer alone and radiation therapy, the combination of carmustine wafer and temozolomide improved overall survival by approximately _____.**
   a. 14 months
   b. Nine months
   c. One month

4. **In which of the following clinical settings is the REGAL study investigating cediranib?**
   a. Up-front management of GBM
   b. Bevacizumab-naïve, recurrent GBM
   c. Bevacizumab-refractory GBM

5. **Which of the following agents is a multi-targeted tyrosine kinase inhibitor?**
   a. Bevacizumab
   b. Cilengitide
   c. XL184
   d. None of the above

6. **In a retrospective analysis of studies of bevacizumab for patients with CNS metastases from various solid tumors, the rate of cerebral hemorrhage was _____.**
   a. Less than five percent
   b. 10 to 12 percent
   c. 22 percent

7. **What is the typical time frame for the occurrence of pseudoprogression in GBM?**
   a. Within 24 hours of initial surgery
   b. Within four to 12 weeks of radiation therapy
   c. Within 12 months of finishing adjuvant temozolomide

8. **The combination of bevacizumab and irinotecan has demonstrated _____ compared to bevacizumab alone for recurrent GBM.**
   a. Improved efficacy
   b. Increased toxicity
   c. Both improved efficacy and additional toxicity

9. **Which of the following is true regarding patients with anaplastic glioma with 1p/19q codeletion?**
   a. Prolonged survival
   b. Good sensitivity to chemotherapy
   c. Good sensitivity to radiation therapy
   d. All of the above

10. **Which of the following statements about pseudoprogression is correct?**
    a. Pseudoprogression can occur within six weeks of the completion of radiation therapy and temozolomide
    b. Distinguishing pseudoprogression from true progression is easily accomplished by viewing post-treatment scans
    c. Pseudoprogression and true progression have equally bad prognoses, so differentiating between them is not of any significance

11. **What is the mechanism of action of cilengitide?**
    a. VEGF inhibition
    b. Cytotoxicity
    c. Integrin receptor inhibition

Post-test answer key: 1b, 2c, 3b, 4b, 5c, 6a, 7b, 8b, 9d, 10a, 11c

EDUCATIONAL ASSESSMENT AND CREDIT FORM

CNS Cancer Update — Issue 2, 2010

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Pseudoprogression after chemoradiation therapy for malignant gliomas	4 3 2 1	4 3 2 1
Activity of bevacizumab in recurrent GBM	4 3 2 1	4 3 2 1
Clinical trials of bevacizumab as initial therapy for GBM	4 3 2 1	4 3 2 1
Interstitial chemotherapy with the carmustine wafer in front-line GBM	4 3 2 1	4 3 2 1
Ongoing clinical studies with the oral pan-VEGF tyrosine kinase inhibitor cediranib in recurrent GBM	4 3 2 1	4 3 2 1
ASCO 2010 data with the multikinase inhibitor XL184 in recurrent GBM	4 3 2 1	4 3 2 1
Mechanism of action of cilengitide	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Identify strategies to distinguish between true disease progression and radiographic pseudoprogression in patients with glioma who have undergone chemoradiation therapy. . . . . 4 3 2 1 N/M N/A
- Apply advances in imaging and neuropathology to diagnose, prognosticate and measure response to therapy for patients with CNS tumors.. . . . . 4 3 2 1 N/M N/A
- Use the results of new clinical studies for CNS tumors to improve patient outcomes. . . . . 4 3 2 1 N/M N/A
- Recall the results of existing and emerging research on interstitial chemotherapy for patients with Grade III or IV gliomas. . . . . 4 3 2 1 N/M N/A
- Integrate palliative management initiatives to improve quality of life for patients with brain tumors. . . . . 4 3 2 1 N/M N/A
- Develop evidence-based clinical management strategies for recurrent or progressive GBM. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate. . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ☐ Yes, I am willing to participate in a follow-up survey.
- ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Timothy F Cloughesy, MD	4 3 2 1	4 3 2 1
Patrick Y Wen, MD	4 3 2 1	4 3 2 1
Jon D Weingart, MD	4 3 2 1	4 3 2 1
David M Peereboom, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

Name: ..... Specialty: .....

Professional Designation:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other .....

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Telephone: ..... Fax: .....

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Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at CME.ResearchToPractice.com.

CNSU210

CNS Cancer™ UPDATE

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U P D A T E

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