INTERVIEW

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Tracks 1-18

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

Track 6 Genome analysis in GBM by The Cancer Genome Atlas (TCGA) research network

Track 7 BRAIN study: Bevacizumab versus bevacizumab and irinotecan for recurrent GBM

Track 8 Role of bevacizumab in recurrent and front-line GBM

Track 9 Bevacizumab-associated adverse events in GBM

Track 10 Emerging role of bevacizumab in front-line GBM

Track 11 Relapse and prognosis after bevacizumab failure in GBM

Track 12 Emerging efficacy results of XL184, an oral tyrosine kinase inhibitor, in GBM

Track 13 XL184-associated adverse events

Track 14 REGAL study: Cediranib in combination with lomustine for recurrent GBM

Track 15 Challenges of response assessment in recurrent GBM

Track 16 Cilengitide as an investigational agent in front-line GBM

Track 17 Cilengitide as an investigational agent in recurrent GBM

Track 18 Mechanism of action of cilengitide

Select Excerpts from the Interview

Tracks 7-8

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**.