

Avastin

1. Introduction: About Avastin

Avastin is a biologic antibody designed to specifically inhibit the VEGF protein that plays an important role in the development and maintenance of blood vessels, a process known as angiogenesis. VEGF is a potent activator of angiogenesis throughout the lifecycle of a tumor. By inhibiting VEGF Avastin is designed to interfere with the blood supply to a tumor, which is thought to be critical to a tumor's ability to grow and spread in the body (metastasize). For more information on angiogenesis, visit <http://www.gene.com>.

Avastin is indicated for the first- and second-line treatment of metastatic colorectal cancer in combination with intravenous 5-FU-based chemotherapy and for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel.

2. Indications & Usage

Metastatic Colorectal Cancer

AVASTIN[®], in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.

Non-Small Cell Lung Cancer

AVASTIN[®], in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer.

Metastatic Breast Cancer

AVASTIN[®], in combination with paclitaxel, is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

The effectiveness of Avastin in metastatic breast cancer is based on an improvement in progression-free survival. Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.

Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Avastin in breast cancer.

3. Safety Information

Gastrointestinal (GI) perforation: Treatment with Avastin can result in the development of a potentially serious side effect called GI perforation. In clinical trials, these events occurred throughout the course of treatment and in some cases resulted in fatality. Avastin therapy should be permanently stopped in people with GI perforation.

Wound healing complication: Treatment with Avastin can lead to slow or incomplete wound healing (for example, when a surgical incision has trouble healing or staying closed). In some cases, this event resulted in fatality. Avastin therapy should be permanently stopped in patients with wound healing complications that require medical treatment. The appropriate waiting time between stopping treatment with Avastin and having surgery has not been determined.

Hemorrhage: Some people receiving Avastin with chemotherapy for lung cancer experienced hemoptysis (a severe bleeding problem at the site of the tumor). In some cases, this event resulted in fatality. People with recent hemoptysis should not receive Avastin.

In clinical trials, additional serious side effects in patients receiving Avastin with chemotherapy included non-GI fistula formation, strokes or heart problems (blood clots), hypertensive crisis (severe hypertension), reversible posterior leukoencephalopathy syndrome (nervous system and vision disturbances), neutropenia (a reduced white blood cell count that may increase the chance of infection), nephrotic syndrome (a sign of severe kidney malfunction), and congestive heart failure. The most common adverse events seen in patients receiving Avastin with chemotherapy across all studies were weakness, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, loss of appetite, mouth sores, constipation, upper respiratory infection, nosebleeds, difficulty breathing, skin irritation, and proteinuria (a possible sign of kidney malfunction).

4. Avastin (bevacizumab) in the Treatment of Brain Tumours

(Note: Abstracts listed are from ASCO 2008)

4.1 Efficacy

4.1.1 In the USA, Avastin in combination with irinotecan, is already regarded as the de facto standard treatment for recurrent or refractory GBM. In addition, some neuro-oncologists in the US, including Dr Howard Fine at the NIH, are routinely prescribing Avastin as monotherapy (single agent) for recurrent GBM.

4.1.2 In Nov 2008 Genentech submitted an application for a supplemental BLA to the FDA for Avastin in the treatment of recurrent GBM. The application is to be considered for accelerated approval by the FDA. The principal supporting data for the application is provided by the Phase II clinical trial (BRAIN) which evaluated Avastin as a single agent or in combination with irinotecan (CPT-11) chemotherapy (refer ASCO 2008 Abstract 2010b below). Roche/Genentech are planning to initiate a Phase III clinical trial for Avastin in newly diagnosed GBM in 1H 2009.

4.1.3 To summarise the efficacy data, the current benchmark survival data for patients undergoing salvage therapy (chemotherapy) for recurrent GBM is:

Objective Response Rate:	6%
Median PFS:	9 weeks
6 Month PFS:	15%
Median OS:	25 weeks

The Phase II study conducted at Duke achieved the following results:

Objective Response Rate:	57%
Median PFS:	24 weeks
6 Month PFS:	46%
Median OS:	42 weeks
6 Month OS:	77%
2 Year OS:	15%

The Phase II BRAIN clinical trial achieved the following results:

Avastin Only Arm

Objective Response Rate:	20%
6 Month PFS:	35.1%
Median OS:	42 weeks

Avastin plus Irinotecan Arm

Objective Response Rate:	32.9%
6 Month PFS:	50%

Median OS: 58.5 weeks

4.1.4 The above efficacy data show a significant improvement in both PFS and OS for Avastin over the existing benchmarks for recurrent GBM. The results for recurring anaplastic glioma are even more encouraging. It is on the strength of these results that Genentech is applying for accelerated FDA approval in recurrent GBM and the Phase III clinical trials for newly diagnosed GBM are being initiated.

Abstract No: 2010b

A phase II, randomized, non-comparative clinical trial of the effect of bevacizumab (BV) alone or in combination with irinotecan (CPT) on 6-month progression free survival (PFS6) in recurrent, treatment-refractory glioblastoma (GBM).

Author(s): T. F. Cloughesy, M. D. Prados, P. Y. Wen, T. Mikkelsen, L. E. Abrey, D. Schiff, W. K. Yung, Z. Maoxia, I. Dimery, H. S. Friedman

Conclusions: Both the PFS6 and OS of >9 months with BV alone or with CPT provides encouraging evidence of significant activity in this poor prognosis population. In addition, the reduction in corticosteroid use has the potential to provide benefit to patients.

Abstract No: 2021

Update on survival from the original phase II trial of bevacizumab and irinotecan in recurrent malignant gliomas.

Author(s): S. A. Wagner, A. Desjardins, D. A. Reardon, J. Marcello, J. E. Herndon, II, J. A. Quinn, J. N. Rich, S. Sathornsumetee, H. S. Friedman, J. J. Vredenburgh

Conclusions: The combination of bevacizumab and irinotecan provides a clinically meaningful treatment option for patients with recurrent malignant gliomas.

Abstract No: 2023

A retrospective single institutional analysis of bevacizumab and chemotherapy versus non-bevacizumab treatments for recurrent glioblastoma.

Author(s): P. Nghiemphu, C. Graham, W. Liu, T. Than, A. Lai, R. Green, R. M. Elashoff, T. F. Cloughesy

Conclusions: Bevacizumab in combination with chemotherapy can be a more effective treatment for recurrent glioblastoma and warrants further randomized prospective studies to determine its effect on survival. Bevacizumab also has more effect in those with older age and might reflect biological differences in glioblastoma in different age groups, and biological correlates should also be considered.

Abstract No: 13007

Bevacizumab (B) plus irinotecan (I) in progressive multiple pretreated and temozolomide (T) refractory glioblastoma multiforme (GBM): A single center experience using a low dose regimen.

Author(s): A. Dresemann, A. Hobbold, G. Dresemann

Conclusion: B plus I seems to be the most effective regimen for induction of objective response in multiple pretreated GBM pts with excellent toxicity profile. Efficacy of the low dose regimen was comparable to other published regimen. Confirmation is required. A following maintenance treatment should be considered.

4.1.5 The detailed mechanism of action of Avastin in brain tumours is a matter for some speculation. Studies have indicated that Avastin normalises tumour vasculature but there is debate over whether this process facilitates or inhibits drug delivery to the tumour tissue. If Avastin facilitates drug delivery then it may be worthwhile maintaining Avastin but with a different chemotherapy once a patient progresses on Avastin plus irinotecan. The role of a second chemotherapy in combination with Avastin has been studied in clinical trials but with disappointing results so far.

Abstract No: 2008

Role of a second chemotherapy in recurrent malignant glioma patients who progress on a bevacizumab-containing regimen.

Author(s): E. Quant, A. D. Norden, J. Drappatz, A. Ciampa, L. Doherty, D. LaFrankie, S. Kesari, P. Y. Wen

Conclusions: Patients with malignant gliomas who progress following treatment with a bevacizumab-containing chemotherapeutic regimen generally respond poorly to a second chemotherapy combined with bevacizumab. Other therapeutic options should be considered for these patients.

4.1.6 Avastin is also being tried as a first line treatment in combination with other cytotoxic chemotherapies, most notably temozolomide, and other targeted agents, including other monoclonal antibodies (cetuximab) and tyrosine kinase inhibitors (erlotinib).

Abstract No: 2022

Phase II study of bevacizumab and etoposide in patients with recurrent malignant glioma.

Author(s): J. N. Rich, A. Desjardins, S. Sathornsumetee, J. J. Vredenburgh, J. A. Quinn, S. Gururangan, A. H. Friedman, H. S. Friedman, D. A. Reardon

Conclusions: Combination of bevacizumab and etoposide is well tolerated in recurrent MG patients and is associated with encouraging radiographic response. Further accrual, treatment and follow-up are ongoing.

Abstract No: 2056

A phase II trial with cetuximab, bevacizumab, and irinotecan for patients with primary glioblastomas and progression after radiation therapy and temozolamide.

Author(s): U. Lassen, B. Hasselbalch, M. Sørensen, M. Holmberg, S. Hansen, M. Kosteljanetz, H. Laursen, H. S. Poulsen

Conclusions: The CBI regimen was well tolerated, with encouraging response rates, including 1 CR. However, the efficacy of the combination seems to be similar to BI alone, therefore is further evaluation of this regimen not planned.

Abstract No: 2074

Bevacizumab and daily temozolomide for recurrent glioblastoma multiforme (GBM).

Author(s): R. Maron, J. J. Vredenburgh, A. Desjardins, D. A. Reardon, J. A. Quinn, J. N. Rich, S. Gururangan, S. A. Wagner, M. E. Salacz, H. S. Friedman

Conclusions: Daily temozolomide and bevacizumab is an active regimen against recurrent GBM and has acceptable toxicity. Daily temozolomide is a good platform for combination regimens.

Abstract No: 13008

Phase II study of bevacizumab and erlotinib in patients with recurrent glioblastoma multiforme.

Author(s): S. Sathornsumetee, J. J. Vredenburgh, J. N. Rich, A. Desjardins, J. A. Quinn, A. E. Mathe, S. Gururangan, A. H. Friedman, H. S. Friedman, D. A. Reardon

Conclusions: Combination of bevacizumab and erlotinib is safe and well tolerated in recurrent GBM patients. It is associated with promising radiographic response and encouraging survival benefit.

4.2 Areas Of Concern

4.2.1 Despite the encouraging clinical benefits shown in the latest clinical trials there remain some doubts about Avastin treatment in brain tumours, principally regarding the toxicity and possible side effects of treatment. Toxicity concerns include slow wound healing, gastrointestinal perforation, blood clots and brain hemorrhaging. Despite these concerns, most patients faced with the grim prognosis of a recurring GBM accept the associated safety risk and opt to undergo treatment.

Abstract No: 13010

A single institution's experience with bevacizumab and cytotoxic chemotherapy in progressive malignant glioma.

Author(s): T. M. Mayer, J. Lacy, J. Baehring

Conclusions: Overall, our results confirm the efficacy and safety of bevacizumab in combination with chemotherapy in patients with progressive malignant glioma. Although the TTF and OS were less than previously reported with bevacizumab/irinotecan, this was an unselected and heavily pretreated patient population with 50% of patients having received >1 prior chemotherapy regimen.

Abstract No: 13011

Combination of bevacizumab plus irinotecan in recurrent malignant gliomas (MG): A retrospective study of efficacy and safety.

Author(s): M. J. Gil Gil, M. Martinez-Garcia, G. Reynes, E. Costas, C. Fernández-Chacón, S. Pernas, M. Benavides, A. Herrero, J. Perez-Martin, C. Balañá, Grupo Español de Neuro-Oncología Médica

Conclusion: Our experience suggests that the combination of bevacizumab plus irinotecan in recurrent MG improves the RR, PFS and OS when compared with historical figures. However, this regimen is not free of severe toxicity (TEC and severe cognitive impairment) and requires a careful selection of patients. A phase 3 trials to validate this combination is needed.

4.2.2 Of perhaps greater concern is the possible side effect that Avastin treatment might promote tumour invasiveness or induce a more aggressive tumour phenotype on recurrence. Related to this concern is the suggestion that Avastin produces a good radiographic response but does not actually reduce tumour mass. This concern is highlighted by reports that in other cancers Avastin increases progression free survival (PFS) but not overall survival (OS).

Abstract No: 2028

Patterns of relapse and prognosis after bevacizumab (BEV) failure in recurrent glioblastoma (GBM).

Author(s): A. B. Lassman, F. M. Iwamoto, P. H. Gutin, L. E. Abrey

Conclusions: A multifocal tumor/gliomatosis cerebri pattern of recurrence/progression is common following treatment with BEV for GBM, and is correlated with poor KPS and short survival. Treatments after BEV failure may provide only transient tumor control.

Abstract No: 13000

Bevacizumab therapy in recurrent high grade glioma: Impact on local control and survival.

Author(s): A. Narayana, S. Raza, J. G. Golfinos, G. Johnson, E. A. Knopp, D. Zagzag, I. Fischer, P. Medabalmi, P. Eagan, M. L. Gruber

Conclusion: Bevacizumab therapy improves the survival in recurrent high grade glioma. A possible change in the invasiveness of the tumor following therapy is worrisome and needs to be closely monitored.

Abstract No: 13013

Retrospective analysis of patterns of recurrence seen on MRI in patients with recurrent glioblastoma multiforme treated with bevacizumab plus irinotecan.

Author(s): R. M. Zuniga, R. Torcuator, T. Doyle, J. Anderson, R. Jain, J. Orley, M. Rosenblum, T. Mikkelsen

Conclusions: Although bevacizumab effectively inhibits angiogenesis, there are patients who recur despite stable areas of gad-enhancement. This has been observed by an increase in FLAIR signals without corresponding increased areas of enhancement. Tumor recurrence in patients with inhibited angiogenesis may recur via cooption of pre-existent vasculature. The inclusion of non-enhanced MRI sequences as part of criteria to assess GBM recurrence may be warranted. A larger prospective study is required in order to build upon the understanding of the pattern of recurrence in patients with GBM.

List of ASCO 2008 Abstracts featuring Avastin

Abstract No: 2008

Role of a second chemotherapy in recurrent malignant glioma patients who progress on a bevacizumab-containing regimen.

Author(s): E. Quant, A. D. Norden, J. Drappatz, A. Ciampa, L. Doherty, D. LaFrankie, S. Kesari, P. Y. Wen

Background: Bevacizumab is a humanized VEGF monoclonal antibody with promising activity in recurrent glioblastomas, alone and in combination with irinotecan. Patients who progress on this regimen are frequently maintained on bevacizumab and the concurrent chemotherapeutic agent is changed. The benefit of this therapeutic strategy is unknown.

Methods: We retrospectively reviewed the clinical features and radiologic studies of 44 patients with recurrent malignant glioma who progressed on a bevacizumab-containing regimen and were then treated with an alternate bevacizumab-containing regimen. All patients received bevacizumab 10 mg/kg IV every 2 weeks. As the initial bevacizumab-containing regimen, 37 patients received irinotecan, 4 bevacizumab alone, 1 temozolomide and 2 carboplatin. As a second bevacizumab-containing regimen, 32 patients received carboplatin, 6 irinotecan, 2 BCNU, 1 CCNU, 1 etoposide, 1 erlotinib/rapamycin and 1 erlotinib. There was no limit on the number of prior therapies. Clinical characteristics and outcomes were reviewed. Tumor progression was determined by a combination of clinical status and radiographic changes.

Results: Patient characteristics were 28 male, 16 female; median age 49 years (range 22-72); median KPS prior to receiving both regimens 70 (range 60-100 with first regimen and 40-100 with second regimen); median prior chemotherapy regimens including the first bevacizumab-containing regimen was 3 (range 2-5). Median PFS on first bevacizumab-containing regimen was 123.5 days. 6 month PFS was 33%. Median PFS on the second bevacizumab-containing regimen was 40 days (range 14 to 359 days). 6 month PFS was 2%. The number of grade 3/4 adverse events was similar between the two groups (7 with the first regimen and 8 with the second regimen).

Conclusions: Patients with malignant gliomas who progress following treatment with a bevacizumab-containing chemotherapeutic regimen generally respond poorly to a second chemotherapy combined with bevacizumab. Other therapeutic options should be considered for these patients.

Abstract No: 2010b

A phase II, randomized, non-comparative clinical trial of the effect of bevacizumab (BV) alone or in combination with irinotecan (CPT) on 6-month progression free survival (PFS6) in recurrent, treatment-refractory glioblastoma (GBM).

Author(s): T. F. Cloughesy, M. D. Prados, P. Y. Wen, T. Mikkelsen, L. E. Abrey, D. Schiff, W. K. Yung, Z. Maoxia, I. Dimery, H. S. Friedman

Background: Effective 2nd-line therapies are absent in GBM leading to poor survival. VEGF upregulation is implicated in GBM tumorigenesis. In a single-arm PhII trial of BV + CPT in recurrent GBM, activity was demonstrated, warranting further investigation of clinical benefit of BV alone, and in combination with CPT (Vredenburgh J, JCO 2007).

Methods: From June 2006 to Feb 2007, 167 patients (pts) with recurrent GBM were randomized 1:1 to BV (10 mg/m² q 2 wks) (Arm 1, n=85) or BV + CPT (340 mg/m² if enzyme-inducing anti-epileptic drugs (AEDs) and 125 mg/m² for non-AEDs) (Arm 2, n=82), stratified by KPS: 70-80, 90-100, and relapse (1st or 2nd). The co-primary endpoints were PFS6

(defined at 24-weeks) and objective response rate (ORR) determined by an independent radiology facility (IRF), with secondary endpoints of safety, PFS, and duration of response determined by IRF, and overall survival. The trial provided approximately 80% power to detect 13% improvement in PFS6 from an assumed rate of 15%, and 90% power to detect 13% improvement in ORR from assumed rates of 5% (Arm 1) and 10% (Arm 2) (2-sided significance level of 0.025).

Results: Clinical outcomes are shown in Table 1. Median OS was based on 61.2% of deaths for BV alone and 67.1% of deaths for BV+CPT. One intracranial hemorrhage occurred in Arm 1 (Gr 1; 1.2%) and one in Arm 2 (Gr 4; 1.3%) during planned treatment period. The dose of corticosteroid required diminished from baseline to cycle 4 (Table 1). Benchmarking OS to that in a national GBM database is ongoing. Å in KPS and neurocognitive function from baseline, and post-progression response will be presented.

Conclusions: Both the PFS6 and OS of >9 months with BV alone or with CPT provides encouraging evidence of significant activity in this poor prognosis population. In addition, the reduction in corticosteroid use has the potential to provide benefit to patients.

Randomized Subjects	BV (n=85)	BV + CPT (n=82)
Median OS months (95% CI)	9.7 (8.2-11.8)	8.9 (7.8-11.9)
PFS6 % (97.5% CI)	35.1 (23.2-47.0)	50.2 (36.6-63.8)
ORR % (97.5% CI)	20 (12.7-29.5)	32.9 (23.4-43.5)
Treated Subjects	BV (n=84)	BV + CPT (n=79)
Grade \geq 3 toxicities, %	47.6	67.1
Grade 5 AEs, %	2.4	1.3
BV discontinuation due to AEs, %	3.5	13.9
Corticosteroid dose (mg/kg)	BV (n=84)	BV + CPT (n=79)
N, Mean (SD)		
Day 1	44, 7.3 (7.37)	46, 8.0 (4.96)
Day 42	41, 5.0 (5.59)	44, 7.5 (5.71)
Day 84	34, 3.1 (2.80)	34, 4.7 (3.68)
Day 126	21, 2.7 (3.13)	21, 3.9 (2.60)
Day 168	12, 1.1 (1.04)	15, 4.4 (4.13)

Abstract No: 2021

Update on survival from the original phase II trial of bevacizumab and irinotecan in recurrent malignant gliomas.

Author(s): S. A. Wagner, A. Desjardins, D. A. Reardon, J. Marcello, J. E. Herndon, II, J. A. Quinn, J. N. Rich, S. Sathornsumetee, H. S. Friedman, J. J. Vredenburgh

Background: Recurrent grade III-IV malignant gliomas have a dismal prognosis and effective salvage therapies are limited.

Methods: From 4/05-2/06, a phase II trial was conducted at Duke University using bevacizumab and irinotecan in patients with recurrent malignant gliomas. 2 cohorts were enrolled that included 33 grade III and 35 grade IV patients. The first cohort received bevacizumab at 10mg/kg plus irinotecan (dose based on patient's anticonvulsant) every two weeks. The second cohort received bevacizumab at 15mg/kg every 21 days and irinotecan on days 1, 8, 22, and 29.

Results: Overall response rates for both grade III and IV were 59% (grade III 61%, grade IV 57%). 6 month PFS and OS for grade III were 59% and 79% and for grade IV 43% and 74% respectively. In 12/07, we evaluated all patients enrolled in the trial to determine the 2 yr OS. From the 2 cohorts, 22% (15/68) of the patients are still alive (11 grade III, 4 grade IV). For the grade IV patients, the 2yr OS is 15%. All four of the grade IV patients completed 9 cycles of therapy. Two (2/4) progressed (8mo and 17mo) and both reinitiated bevacizumab and irinotecan with radiographic response. The other two have been progression free since the end of treatment (11mo and 18mo). Surprisingly, both of these patients had only partial resections at the time of diagnosis. For the grade III patients, the 2 yr OS is 33%. All but one patient has progressed; ranging from 1 to 14 months. 4 patients are currently on bevacizumab-based therapy. 1 on carboplatin, 2 on etoposide and 1 on bevacizumab alone for radiation necrosis. The remaining patients are on metronomic temozolomide (2), etoposide (1), and a phase I clinical trial (2). 2 patients are currently being followed off therapy. The one patient who did not progress only received a partial cycle on study and had to discontinue secondary to TTP and has been off treatment for the last 21 months.

Conclusions: The combination of bevacizumab and irinotecan provides a clinically meaningful treatment option for patients with recurrent malignant gliomas.

Abstract No: 2022

Phase II study of bevacizumab and etoposide in patients with recurrent malignant glioma.

Author(s): J. N. Rich, A. Desjardins, S. Sathornsumetee, J. J. Vredenburgh, J. A. Quinn, S. Gururangan, A. H. Friedman, H. S. Friedman, D. A. Reardon

Background: Bevacizumab (BV), a neutralizing monoclonal antibody to vascular endothelial growth factor (VEGF), has demonstrated remarkable radiographic response and promising survival benefit in combination with irinotecan in patients with recurrent glioblastoma multiforme (GBM). In this study, we evaluate the efficacy of bevacizumab when combined with etoposide, a topoisomerase inhibitor, in patients with recurrent malignant glioma (MG).

Methods: Recurrent patients with no more than three prior episodes of recurrence are eligible, while those with prior BV treatment or prior intracranial hemorrhage are excluded. The primary outcome measure is 6 month progression-free survival. BV is dosed at 10 mg/kg intravenously every other week. Etoposide is orally administered daily (50 mg/m²) for days 1-21 of each 28-day cycle.

Results: Fifty-three patients have enrolled including 27 with GBM, 16 with anaplastic astrocytoma, 8 with anaplastic oligodendroglioma and 2 with malignant pleomorphic xanthoastrocytoma. The median age is 48.7 years (range, 25.2-71.2), and patients have had a median of 2 prior progressions (range, 1-3) and 2 prior therapeutic agents (range, 1-7). The most common significant toxicities include neutropenia (grade 3, n=8; grade 4, n=1), thrombosis (grade 3, n=2, grade 4, n=2; grade 5, n=1), hyponatremia (grade 3, n=3) and infection (grade 3, n=2). Two patients developed grade 1 intracranial hemorrhage. Best responses to date include complete response (n=1; 2%); partial response (n=9; 17%), stable disease (n=34; 60%); progressive disease (n=3; 6%). Six patients are too early to assess.

Conclusions: Combination of bevacizumab and etoposide is well tolerated in recurrent MG patients and is associated with encouraging radiographic response. Further accrual, treatment and follow-up are ongoing.

Abstract No: 2023**A retrospective single institutional analysis of bevacizumab and chemotherapy versus non-bevacizumab treatments for recurrent glioblastoma.**

Author(s): P. Nghiemphu, C. Graham, W. Liu, T. Than, A. Lai, R. Green, R. M. Elashoff, T. F. Cloughesy

Background: Bevacizumab, a monoclonal antibody to vascular endothelial growth factor, has been shown to be effective in the treatment of recurrent glioblastoma in combination with chemotherapy compared to historical controls but not in randomized trials.

Methods: We conducted a retrospective analysis of all patients treated at our institution for a recurrent glioblastoma to compare patients who received bevacizumab versus a control group of patients. We compared progression free survival (PFS) and overall survival (OS) between the two groups, and also compared these factors based on the age and performance status within each group. We also analyzed the impact of bevacizumab on quality of life by comparing change in performance status.

Results: We identified 44 patients who received bevacizumab, and 79 patients who have not been treated with bevacizumab. There is a statistically significant improvement in PFS in the bevacizumab treated group, but only a trend toward better survival. Patients of older age (≥ 50) and poor performance status ($KPS \leq 80$) have significantly better PFS when treated with bevacizumab, and bevacizumab-treated older patients have significantly increase OS. Patients treated with bevacizumab also maintained their functional status longer than the control group.

Conclusions: Bevacizumab in combination with chemotherapy can be a more effective treatment for recurrent glioblastoma and warrants further randomized prospective studies to determine its effect on survival. Bevacizumab also has more effect in those with older age and might reflect biological differences in glioblastoma in different age groups, and biological correlates should also be considered.

	Bev	Control	p value
No	44	79	
Age	54	55	0.86
KPS	82	82	0.8
Recurrence (%)			
1st	50	100	
2nd	32	0	
3rd	18	0	
PFS (mos)			
all (n)	4.25 (44)	1.82 (79)	0.01
age <50 (n)	4.01 (15)	2.01 (28)	0.85
age ≥ 50 (n)	4.60 (29)	1.87 (51)	0.0002
KPS >80 (n)	3.83 (24)	1.84 (36)	0.16
KPS ≤ 80 (n)	4.60 (20)	1.87 (43)	0.04
OS (mos)			
all	9.01	6.11	0.08
age <50	10.83	6.88	0.74
age ≥ 50	8.31	6.11	0.02
KPS >80	9.22	8.05	0.61
KPS ≤ 80	9.01	4.74	0.08
Time to KPS change (days)	252	120	0.006

Abstract No: 2026**Effect of bevacizumab (BEV) and irinotecan (CPT-11) on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in glioblastoma (GBM) patients.**

Author(s): A. Desjardins, D. P. Barboriak, J. E. Herndon, II, J. Marcello, D. A. Reardon, J. A. Quinn, J. N. Rich, S. Sathornsumetee, H. S. Friedman, J. J. Vredenburgh

Background: DCE-MRI can determine vascular permeability using Ktrans, a volume transfer constant of contrast agent between blood plasma and the extravascular extracellular space. We report a phase II trial to determine the correlation between vascular permeability and radiographic response in GBM patients treated with irinotecan and bevacizumab.

Methods: Eligibility included 20 patients with recurrent GBM. Both agents were given every 14 days; bevacizumab at 10 mg/kg IV, and irinotecan at 340 mg/m² for patients on enzyme inducing antiepileptic drugs (EIAED) and 125 mg/m² for patients not on EIAED. Radiographic responses were assessed every 6 weeks. DCE-MRIs were performed before administration of chemotherapy, one day after treatment and after the first cycle. The primary endpoint was to examine the effect of bevacizumab and irinotecan treatment on vascular permeability as measured by percent change from baseline in Ktrans.

Results: All 20 patients were enrolled, with a median age of 49.5 years. Best responses include one patient with complete response, nine with partial response (response rate=50%), nine patients with stable disease, and one with disease progression. A 6-month progression-free survival (PFS) of 65% and a 6-month overall survival (OS) of 85% were observed. Changes in Ktrans value were highly correlated with the percentage decline in tumor volume from baseline to end of cycle one (Spearman's rank correlation = 0.47; p=0.04). Using a two-sided t-test, borderline significant difference in mean Ktrans at 24 hours between responders and non-responders was obtained at six weeks (p=0.05). No DCE MRI measures at either 24 hours or 6 weeks were determined as predictors of PFS and OS. Fifteen patients discontinued therapy due to disease progression and two patients discontinued treatment due to toxicity (wound healing, n=1; pulmonary embolism, n=1).

Conclusions: The utilization of DCE-MRI to determine a reduction in vascular permeability following a combination of bevacizumab and irinotecan is feasible and correlates with the degree of tumor volume decrease, but does not predict survival in this small study.

Abstract No: 2028**Patterns of relapse and prognosis after bevacizumab (BEV) failure in recurrent glioblastoma (GBM).**

Author(s): A. B. Lassman, F. M. Iwamoto, P. H. Gutin, L. E. Abrey

Background: BEV has shown promise for recurrent GBM in phase II trials. However, the patterns of relapse and prognosis of patients (pts) with GBM following BEV have not been studied systematically. This may have important implications for efficacy analysis of post-BEV therapies.

Methods: We reviewed departmental databases to identify pts with recurrent GBM treated with BEV on or off clinical trials following IRB approval of this study. Pts who discontinued BEV for progressive disease (PD) were included. Records were assessed for post-BEV outcomes.

Results: There were 21 pts (14 men, 7 women; median age 53 yrs, range 30-80) who discontinued BEV for PD. The median number of recurrences prior to starting BEV was 1 (range, 1-2). Patients received BEV alone (n=1) or in combination with irinotecan (n=10), hypo-fractionated re-irradiation (hyRT) (n=8), temozolomide (n=1) or temozolomide plus hyRT (n=1). The median overall survival (OS) after stopping BEV was 2.5 months (95% CI, 1.6 to 5.9); 15 patients have died. At the time BEV was discontinued, seven pts had local recurrence

(initial site of disease) whereas 14 had recurred in a multifocal tumor/gliomatosis cerebri pattern. Median KPS at recurrence for those with a local pattern was 70 (range, 70-90) compared to a median of 60 (range, 40-80) in patients with a multifocal pattern ($p < 0.001$). Multifocal tumor/gliomatosis pattern of relapse was associated with increased risk of death (Hazard Ratio [HR]=13, 95% CI: 1.7- 101, $p=0.01$) compared to local relapse. $KPS \leq 60$ at the time of BEV failure was also associated with increased risk of death (HR=11, 95% CI: 2.3-49, $p=0.002$). Additional tumor directed therapy following BEV failure was given to 11 pts (8 chemotherapy, 2 resection and chemotherapy, 1 resection). Median PFS for the therapy after BEV failure was 2.3 months (95% CI: 0.7 to 4), median OS was 4.5 months (95% CI:1.4-NR), and 6 month-PFS was 0%.

Conclusions: A multifocal tumor/gliomatosis cerebri pattern of recurrence/progression is common following treatment with BEV for GBM, and is correlated with poor KPS and short survival. Treatments after BEV failure may provide only transient tumor control.

Abstract No: 2056

A phase II trial with cetuximab, bevacizumab, and irinotecan for patients with primary glioblastomas and progression after radiation therapy and temozolamide.

Author(s): U. Lassen, B. Hasselbalch, M. Sørensen, M. Holmberg, S. Hansen, M. Kosteljanetz, H. Laursen, H. S. Poulsen

Background: Recent data has shown that bevacizumab (B) and irinotecan (I) induces significant responses in recurrent GBM. Primary GBM is very often associated with amplification of EGFR (40-50%) and alterations in the EGFR gene. In vivo experiments have shown that cetuximab (C) increases apoptosis, decreases cell proliferation and decrease vascular endothelial growth factor expression in EGFR-amplified GBM cells in vitro. The use of the combination of C and I has shown a significantly higher response rate compared to irinotecan as monotherapy in colorectal cancer. In addition, adverse events (AE) have been acceptable and the BOND-2 study has shown the feasibility of combining C, B and I. In this phase II study we examine the safety and efficacy of CBI in recurrent GBM.

Methods: Patients (pts) with recurrent GBM after standard primary treatment (surgery/biopsy, followed by radiotherapy and temozolamide) were included after signed informed consent and standard inclusion criteria. The pts received C 400 mg/m² on day 1, followed by weekly C 250 mg/m²; B 10mg/kg every other week (first 10 pts received 5 mg/kg) and I 125 mg/m² in pts not treated with enzyme inducing antiepileptic drugs (EIAED) or 340 mg/m² in pts treated with EIAED, every other week. Evaluation was performed according to MacDonald criteria with MRI every 8 weeks and safety according to CTCAE v.3.0.

Results: A total of 32 pts were included between August 2006 and January 2008. After safety analysis of the first 10 pts B was increased from 5 to 10 mg/kg and this regimen was well tolerated. 3 pts experienced grade III-IV allergic reaction during first C administration despite pre-medication. In January 2008, 27 were evaluable for response. One CR and 8 PR were observed (RR 33%) and 5 pts (19%) had minor responses (25-50% regression and clinical improvement). Median TTP was 24 weeks. Five pts had thromboembolic complications.

Conclusions: The CBI regimen was well tolerated, with encouraging response rates, including 1 CR. However, the efficacy of the combination seems to be similar to BI alone, therefore is further evaluation of this regimen not planned.

Abstract No: 2074**Bevacizumab and daily temozolomide for recurrent glioblastoma multiforme (GBM).**

Author(s): R. Maron, J. J. Vredenburgh, A. Desjardins, D. A. Reardon, J. A. Quinn, J. N. Rich, S. Gururangan, S. A. Wagner, M. E. Salacz, H. S. Friedman

Background: The survival for patients with recurrent GBM is dismal, with < 10% alive at two years. GBMs are highly vascular tumors. The more vascular endothelial growth factor (VEGF) a GBM contains, the worse the prognosis. An antibody to VEGF improved survival in a xenograft model of GBM. Bevacizumab is a humanized antibody to VEGF and was active against recurrent GBM when combined with irinotecan. Daily temozolomide may overcome resistance to 5-day temozolomide by depleting MGMT.

Methods: The trial combined daily temozolomide at 50 mg/m²/day with bevacizumab at 10 mg/kg every 14 days for patients with recurrent GBM. Thirty-two patients with recurrent GBM were enrolled between 07/18/07-09/02/07, all had received radiation therapy and 20/32 (63%) progressed to 5-day temozolomide.

Results: The treatment had acceptable toxicity with one patient with grade 4 hemorrhagic pancreatitis, and one patient with grade 5 pneumocystis carinii pneumonia. There was no > grade 3 hematologic toxicity, and no CNS hemorrhages. Twelve patients (37.5%) had a partial response, another 12 (37.5%) had stable disease, and 8/32 (25%) had progressive disease. Eighteen of the 32 patients remain on study. Two patients requested to come off study secondary to fatigue.

Conclusions: Daily temozolomide and bevacizumab is an active regimen against recurrent GBM and has acceptable toxicity. Daily temozolomide is a good platform for combination regimens.

Abstract No: 13000**Bevacizumab therapy in recurrent high grade glioma: Impact on local control and survival.**

Author(s): A. Narayana, S. Raza, J. G. Golfinos, G. Johnson, E. A. Knopp, D. Zagzag, I. Fischer, P. Medabalmi, P. Eagan, M. L. Gruber

Background: Anti-angiogenic agents have recently shown impressive radiological responses in high grade glioma. However, it is not clear if the responses are related to vascular changes or due to anti-tumoral effect. We report the mature results of a retrospective study of bevacizumab based therapy in recurrent high grade gliomas.

Methods: Fifty four patients with recurrent high grade gliomas received therapy with Bevacizumab at 10 mg/kg every two weeks for four doses in an 8 week cycle along with Irinotecan at 125 mg/m². Treatment evaluation was done with neurological examination, conventional magnetic resonance and perfusion imaging subsequently. The survival was calculated from the time of starting bevacizumab based therapy. Results: The median progression free survival (PFS) and overall survival (OS) were 5 (95% confidence interval, 1.0-6.9) and 9 (95% confidence interval, 7.5-10.5) months respectively. Radiological responses following therapy were noted in 72.2% of cases. The Patients who received > 2 cycles of bevacizumab based therapy had a PFS and OS of 7 and 11 months compared to 3.5 and 5 months for the patients who received < 2 cycles of therapy (p=0.02 and P<0.0001) respectively. Neither the grade of the tumor nor the surgical resection prior to therapy had an impact on survival. Although the predominant pattern of relapse was local, twelve patients (22.2%) failed as diffuse disease.

Conclusion: Bevacizumab therapy improves the survival in recurrent high grade glioma. A possible change in the invasiveness of the tumor following therapy is worrisome and needs to be closely monitored.

Abstract No: 13007

Bevacizumab (B) plus irinotecan (I) in progressive multiple pretreated and temozolomide (T) refractory glioblastoma multiforme (GBM): A single center experience using a low dose regimen.

Author(s): A. Dresemann, A. Hobbold, G. Dresemann

Background: Standard treatment consisting of surgery, irradiation plus concomitant and following T is established in GBM with median survival of 15.6 months, indicating the need for further effective treatment. In several phase II studies B plus I showed impressive objective response rates (>50%) in pre-treated GBM pts with low toxicity rate, duration of response, however, was moderate. Therefore B plus I might be an effective induction regimen for T resistant GBM patients as basis for further treatments. In colo-rectal cancer a lower dose of B plus I was effective therefore B and I dose was reduced.

Methods: From December 2006 to October 2007, 44 pts with progressive GBM resistant to T were treated with B 4 mg/kg body weight intravenously (iv) followed by I 80 mg/m² iv repeated every 2 weeks. ECOG performance status (PF) was 0-2 in 43 pts, 3 in 1 patient. MRI scans were required at baseline (no haemorrhage was allowed) after 4 weeks and afterwards every 6 weeks. Treatment was given until progressive disease (PD) or intolerable toxicity occurred.

Results: All 44 pts were eligible for toxicity and efficacy, median follow up was 7 months, 33 pts were male, 11 female, median age was 45 years (21-79), 32 pts had primary GBM, 12 pts secondary GBM. All pts had prior irradiation (56-60 Gy) 4 pts 4 prior chemotherapy regimens, 11 pts 3, 22 pts 2 and 7 pts T only. The only patient with PF 3 died of clostridium sepsis during grade IV leucopenia after the first treatment, 1 patient developed grade III leucopenia and 2 pts grade III thrombopenia, 1 patient grade III pneumonia, 2 pts asymptomatic intracerebral bleeds requiring treatment delay and 1 patient grade III fatigue. In 22 pts a partial response (PR) was achieved, in 15 pts disease stabilization for at least 2 months, 7 pts showed primary PD. Median duration of PR was 3 months (2-8), best MRI response was achieved after 4 to 8 weeks of treatment. Data will be updated.

Conclusion: B plus I seems to be the most effective regimen for induction of objective response in multiple pretreated GBM pts with excellent toxicity profile. Efficacy of the low dose regimen was comparable to other published regimen. Confirmation is required. A following maintenance treatment should be considered.

Abstract No: 13008

Phase II study of bevacizumab and erlotinib in patients with recurrent glioblastoma multiforme.

Author(s): S. Sathornsumetee, J. J. Vredenburgh, J. N. Rich, A. Desjardins, J. A. Quinn, A. E. Mathe, S. Gururangan, A. H. Friedman, H. S. Friedman, D. A. Reardon

Background: Bevacizumab, a neutralizing monoclonal antibody to vascular endothelial growth factor (VEGF), has demonstrated promising radiographic response and promising survival benefit in combination with irinotecan in patients with recurrent glioblastoma multiforme (GBM). Erlotinib, an EGFR tyrosine kinase inhibitor, has shown anti-tumor activity in some glioma patients. Combination of bevacizumab and erlotinib has demonstrated safety and efficacy in several solid malignancies. In this study, we evaluate the combinatorial efficacy of bevacizumab and erlotinib in patients with recurrent GBM

Methods: Twenty-five patients with recurrent GBM were enrolled. The primary outcome measure is 6 month progression-free survival. Radiographic response, pharmacokinetics and correlative biomarkers are secondary outcome measures. Patients are stratified based on concurrent use of enzyme-inducing anticonvulsants (EIA). Bevacizumab is dosed at 10 mg/kg intravenously every two weeks. Erlotinib is orally administered daily with 200 mg/day for patients not on EIA and 650 mg/day for patients on EIA.

Results: With a median follow-up of 32.3 weeks, the 6 month progression-free survival rate was 24%. Twelve patients (48%) achieved radiographic response. This treatment combination was well-tolerated. Common side effects include those previously seen with erlotinib therapy such as rash, diarrhea, mucositis and fatigue. One ischemic stroke and one asymptomatic intracerebral hemorrhage were observed.

Conclusions: Combination of bevacizumab and erlotinib is safe and well tolerated in recurrent GBM patients. It is associated with promising radiographic response and encouraging survival benefit.

Abstract No: 13010

A single institution's experience with bevacizumab and cytotoxic chemotherapy in progressive malignant glioma.

Author(s): T. M. Mayer, J. Lacy, J. Baehring

Background: A recent phase II study with bevacizumab/irinotecan indicated that this combination may represent one of the most active treatments in patients with progressive glioma (Vredenburgh JJ, et al. Clin Cancer Res. 2007;13:1253-1259.). However, limited published experience regarding use of bevacizumab for CNS tumors raises concerns regarding toxicity, particularly with respect to hemorrhage and thromboembolism.

Methods: We performed a retrospective analysis of 36 patients with progressive malignant glioma after prior resection, chemotherapy and radiation who were treated with bevacizumab at our institution. Patients were evaluated for bevacizumab related adverse events, time to treatment failure (TTF), and overall survival (OS). Two patients who progressed or died prior to completion of 4 cycles of bevacizumab were analyzed for adverse events only.

Results: Patient characteristics: median age 50 (range 24-76); 22 glioblastoma multiforme and 14 other progressive gliomas; 18 prior chemotherapy with temozolomide only and 18 temozolomide plus other salvage chemotherapy. Regimens included: 1 bevacizumab alone, 31 bevacizumab + irinotecan, and 4 bevacizumab + carboplatin. Bevacizumab dose ranged from 5-10mg/kg, typically given every 2 weeks. In 34 patients who received ≥ 4 cycles of bevacizumab (median 8, range of 4-23 cycles), median TTF and OS were 16 and 30 weeks. Six patients are still being actively treated at the time of this analysis. Progression free survival at 6 months was 25%. In the 36 total patients there was 1 arterial thrombotic event, specifically MI (2.8%), 4 venous thrombotic events (11.1%), and 5 intracranial hemorrhages, but only 3 were clinically significant (8.3%).

Conclusions: Overall, our results confirm the efficacy and safety of bevacizumab in combination with chemotherapy in patients with progressive malignant glioma. Although the TTF and OS were less than previously reported with bevacizumab/irinotecan, this was an unselected and heavily pretreated patient population with 50% of patients having received >1 prior chemotherapy regimen.

Abstract No: 13011**Combination of bevacizumab plus irinotecan in recurrent malignant gliomas (MG): A retrospective study of efficacy and safety.**

Author(s): M. J. Gil Gil, M. Martinez-Garcia, G. Reynes, E. Costas, C. Fernández-Chacón, S. Pernas, M. Benavides, A. Herrero, J. Perez-Martin, C. Balañá, Grupo Español de Neuro-Oncología Médica

Background: Recurrent MG have poor prognosis and low response rates to available treatments. Following data from Vredenburt's phase II trial (pro ASCO 2005) some centres began to treat recurrent MG with bevacizumab and irinotecan. The aim of this study is to confirm efficacy and safety of this combination in non-selected consecutive patients (pts).

Methods: Data from 6 Spanish hospitals was collected retrospectively. All pts were > 18 years, had to sign an informed consent and to present: histological documented MG; progression after radiation and temozolomide; measurable disease on MRI; have received at least 3 infusions of treatment schedule: Irinotecan 125mg/m² and bevacizumab 10 mg/kg every 2 weeks for a maximum of a year. Response rate (RR) was determined by MRI (performed every 6 cycles) using McDonald criteria. Progression free survival (PFS) and overall survival (OS) were calculated by Kaplan Meier method.

Results: From August 2006 to October 2007, 44 consecutive pts (28 Glioblastoma, 11 Anaplastic Astrocitoma & 5 Anaplastic Oligoastrocitoma) were treated with this combination. Median age: 53 years (25-73). Median number of prior chemotherapy: 2 (1-4). Six cases had received irinotecan previously. Median KPS: 70% (60-100). Median Barthel Index: 100% (55-100). 26 pts received dexamethasone with median dosage: 4 mg (1-18). 29 were taking a non enzyme-inducing antiepileptic drug. Median cycles received: 9 (4-23) Toxicity grade 3-4: Asthenia in 6 pts; thrombocytopenia 1; neutropenia 1; mucositis 2 pts; thromboembolic complications (TEC) 3 pts, skin 1, haemorrhage out of CNS 2 pts and severe cognitive impairment 4 cases. Efficacy: 25 pts had response (4 complete response); 12 pts stable disease \geq 3 months and 7 progression as best response. RR was 56.8% (95% CI [41-71.6]) Mean follow-up: 5.8 months (1.6-16.2). Mean PFS was 7.4 months (4,6-10,1). OS was 9.8 months (6.8-12.8).

Conclusion: Our experience suggests that the combination of bevacizumab plus irinotecan in recurrent MG improves the RR, PFS and OS when compared with historical figures. However, this regimen is not free of severe toxicity (TEC and severe cognitive impairment) and requires a careful selection of patients. A phase 3 trials to validate this combination is needed.

Abstract No: 13013**Retrospective analysis of patterns of recurrence seen on MRI in patients with recurrent glioblastoma multiforme treated with bevacizumab plus irinotecan.**

Author(s): R. M. Zuniga, R. Torcuator, T. Doyle, J. Anderson, R. Jain, J. Orley, M. Rosenblum, T. Mikkelsen

Background: Glioblastoma multiforme (GBM) is characterized by diffuse parenchymal infiltration and regional angiogenesis. Bevacizumab, an anti-VEGF recombinant humanized monoclonal antibody, has shown remarkable response to treatment rates in patients with recurrent GBM. The best way to assess tumor recurrence via MRI studies has yet to be determined. We have observed the development of distant and new foci of increased FLAIR signals that do not correlate with changes seen on gadolinium-enhanced sequences (Gd-MRI).

Methods: We retrospectively analyzed Gd-MRI and FLAIR MRI sequences of 24 patients who demonstrated either focal (a new enhancing lesion or FLAIR signal < 2 cm from the original tumor), distant (new focus > 2 cm outside original tumor) or both focal and distal recurrence while treated with bevacizumab and irinotecan.

Results: Ten patients (10/24) demonstrated only focal recurrence, one patient (1/24) only distant recurrence (to cerebellum) and nine patients (9/24) both focal and distant recurrences on Gd-MRI. Four patients (4/24) did not show any recurrence on Gd-MRI. These patients only presented with clinical decline and FLAIR changes. Ten patients (10/24) demonstrated only focal recurrence, two patients (2/24) only distant recurrence (both in the cerebellum) and twelve patients (12/24) revealed both focal and distant recurrence on FLAIR (3 to midbrain) sequences. There was concordance of 87% (20/23) in distal only and focal only recurrences on Gd-MRI and FLAIR. Twenty-one percent (5/24) of patients with recurrence seen on FLAIR involved the posterior fossa without concordant findings on Gd-MRI sequences.

Conclusions: Although bevacizumab effectively inhibits angiogenesis, there are patients who recur despite stable areas of gad-enhancement. This has been observed by an increase in FLAIR signals without corresponding increased areas of enhancement. Tumor recurrence in patients with inhibited angiogenesis may recur via cooption of pre-existent vasculature. The inclusion of non-enhanced MRI sequences as part of criteria to assess GBM recurrence may be warranted. A larger prospective study is required in order to build upon the understanding of the pattern of recurrence in patients with GBM.

List of SNO 2008 Abstracts featuring Avastin

CB-12. MEDIATORS OF GLIOBLASTOMA INVASION DURING ANTI-VEGF TREATMENT

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The growth of highly aggressive glioblastoma tumors depends on angiogenesis is regulated by a balance of pro- and anti-angiogenic factors. Vascular endothelial growth factor (VEGF) has been identified as the most critical molecule involved in this process. Currently, several different strategies are being employed to target the VEGF and VEGFR signal transduction pathway in these tumors. Although anti-angiogenic therapy appears to be effective in blocking vascular permeability and slowing tumor growth, some studies have demonstrated that one mechanism of tumor escape from this therapy is via vessel co-option, which results in tumor infiltration into the normal brain. In the present study, we evaluated the effect of antiangiogenic treatment on glioma cell invasion in vitro. Glioma cells that secrete high levels of VEGF and have minimal or no in vitro or in vivo invasion were selected. In the selected cell lines, the influence of increasing doses of the anti-VEGF monoclonal antibody bevacizumab (Avastin) on transwell migration was tested. We also measured the total levels (using western blotting) and activity (using zymography) of invasion-related proteins matrix metalloproteinase (MMP)-2 and MMP-9 using conditioned, serum-free media from control and treated cells. The levels of total secreted proteins were also evaluated using an antibody array. The transwell migration of U87 and the glioma cancer stem cell NSC23 increased after treatment with bevacizumab compared to migration in IgG-treated control cells. In agreement with the increased invasion observed, the activity of MMP-2 (in both cell lines) and MMP-9 (in U87 cells) was higher after treatment in a concentration-dependent manner. A dose-dependent increase in MMP-2 and MMP-9 protein levels was also observed in U87 cells after treatment. Results from the antibody array demonstrated that both cell lines had increased levels of bFGF, TIMP-1, and TIMP-2 after bevacizumab treatment. However, some proteins were differentially secreted by U87 and NSC23 cells: the levels of angiogenin and IL-1alpha were higher in U87 glioblastoma cells but lower in NSC23 cells. Similarly, the levels of IL-6 and IL-8 were decreased in U87 cells, although this trend was not observed in NSC23 cells. **We conclude that anti-angiogenic treatment induces invasion in U87 and NSC23 cells. Although the levels of invasion-related proteins, such as MMP-2, TIMP-1, and TIMP-2, increased after treatment of both cell lines, the invasive process may also be regulated by the secretion of other growth factors and cytokines. These findings suggest that alternate pathways that are induced by anti-angiogenic treatment are involved in tumor invasion in these cell lines. The mechanisms leading to enhanced tumor invasion after anti-angiogenic therapy is under investigation.**

CB-54. PHENOTYPIC CHANGES INDUCED BY ANTI-VEGF TREATMENT—A LINK TO RESISTANCE MECHANISMS IN ANTI-ANGIOGENIC THERAPIES?

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BACKGROUND: Neoangiogenesis is a feature of malignant tumors, including WHO grade IV gliomas. Thus, antiangiogenic therapies are promising adjuvant treatment modalities. Initial clinical and pre-clinical studies have shown that antiangiogenic therapies using anti-vascular endothelial growth factor (VEGF) antibodies (e.g.,

bevacizumab; trade name, Avastin) are capable of improving progression-free survival in patients with some solid tumors. However, increasing data show that in spite of continuing anti-VEGF therapy, resistance phenomena resulting in secondary re-angiogenesis can occur after a transient reduction and normalization of tumor vascularization. Thus, alternative signaling molecules may be involved in escaping anti-VEGF therapies.

METHODS: Human glioma cell lines U87, U373, and U251; brain-derived endothelial cell lines; and freshly isolated CD31-positive endothelial cells from malignant glioma were treated with bevacizumab for different time periods. Cell growth, expression of the lymphangiogenic growth factors VEGF-C and -D, and cellular response to these factors were investigated.

RESULTS: Bevacizumab treatment did not reduce proliferation in a short time in any group, but it did decrease proliferation by approximately 10% after longer periods (12 days) of treatment. All cell lines showed significant upregulation of VEGF-D at a protein level after the longer time period. Even more, cells developed reactivity to VEGF-C and -D by increasing proliferation while being unreactive to these substances before bevacizumab treatment. VEGFR3 expression did not increase significantly; however, the phosphorylation of VEGFR3 by VEGF, VEGF-C, and VEGF-D was enhanced in cells treated with bevacizumab. The intracellular response to VEGF, VEGF-C, and VEGF-D changed in a cell-type-specific manner, with a shift from Erk1/2 to p38 and SAP/JNK phosphorylation.

CONCLUSION: Treatment with anti-VEGF antibodies in glioma leads to a phenotypic change with the upregulation of VEGF-D and an increased reactivity to VEGF-C and -D, accompanied by intracellular changes in signal transduction. This may represent an escape mechanism of the tumor in anti-angiogenic therapy.

ET-44. SYSTEMIC ADMINISTRATION OF VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) ANTIBODY (BEVACIZUMAB) INCREASES THE ANTI-TUMOR ACTIVITY OF TEMOZOLOMIDE AGAINST INTRACRANIAL GLIOMA

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PURPOSE: Tumor angiogenesis is mediated by tumor-secreted angiogenic growth factors that interact with their surface receptors expressed on endothelial cells. Vascular endothelial growth factor (VEGF) and its receptor play an important role in vascular permeability and tumor angiogenesis. Temozolomide (TMZ) is a DNA methylating agent that has shown promising anti-tumor activity in recent clinical trials against high-grade gliomas, metastatic melanoma, and brain lymphoma. In this study, we tested whether systemic administration of bevacizumab (Avastin), a monoclonal antibody against VEGF, could enhance the efficacy of TMZ against glioblastoma multiforme in the brain.

EXPERIMENTAL DESIGN: An orthotopic xenograft of the human U87 cell line (105) was implanted in nude mice with the coordinate (A, 10; L, -3; D, -3). Animals were treated with TMZ (100 mg/kg intraperitoneally) 1 Avastin (200 mg/mouse) using

a schedule of TMZ for 5 days 1 Avastin 2 times a week or Avastin 1 TMZ for 5 days 1 Avastin 2 times a week. The efficacy of drug treatment was assessed by the increase in mouse survival.

RESULTS: Combined treatment of TMZ 1 Avastin significantly increased survival in tumor-bearing mice with respect to untreated controls or to groups treated with either TMZ or Avastin only. Interestingly, systemic administration of Avastin shortly before TMZ administration significantly increased survival compared to TMZ 1 Avastin.

CONCLUSIONS: *These data indicate that systemic administration of Avastin significantly enhances the anti-tumor efficacy of TMZ against glioblastoma multiforme.*

ET-51. ACTIVITY OF BEVACIZUMAB AGAINST NF2-RELATED VESTIBULAR SCHWANNOMAS

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Vestibular schwannomas (VS) and meningiomas are benign tumors that comprise 35%-40% of all brain tumors. Currently, there are no well-tolerated agents that produce disease stabilization or regression. Neurofibromatosis 2 (NF2) is characterized by the presence of multiple schwannomas, meningiomas, and ependymomas; new treatments are desperately needed. Previous studies have shown that sporadic VS express significant levels of vascular endothelial growth factor (VEGF). In this study, we expand those findings to include both sporadic and NF2-associated schwannomas. Using formalin-fixed, paraffin-embedded archival specimens (22 sporadic and 21 NF2-associated), we studied vascular patterning, quantified parameters of vessel morphology (number, size, and distribution), and analyzed angiogenic molecules, including VEGF, vascular endothelial growth factor 2 (VEGFR2), neuropilin-2, PDGFR-alpha, and PDGFR-beta. Both vessel density and mean vessel diameter were significantly greater in VS and meningiomas than in normal nerve. VEGF was expressed uniformly by tumor cells and was bound to endothelium in 75% of NF2 vestibular schwannomas. VEGFR2, the receptor commonly associated with active tumor angiogenesis, was found in only 31% of vessels in schwannomas. These findings suggest that the VEGF angiogenic pathway is activated in these tumors. Therefore, we treated 6 NF2 patients at risk of complete hearing loss because of progressive vestibular schwannomas with bevacizumab, an anti-VEGF antibody, at a dose of 5 mg/kg every 2 weeks. This group included 3 women and 3 men with a median age of 23 years. Tumor response was monitored clinically by serial audiology and magnetic resonance imaging scanning. The primary endpoint was the composite of radiographic response and hearing response on the affected side. A radiographic response was defined as a decrease in tumor volume of .5 20%, and a hearing response was defined as a statistically significant increase in word recognition score. Five of the 6 patients met the primary endpoint within 3 months of starting treatment. Four patients experienced tumor shrinkage of . 20%, and 4 patients had improvement in word recognition. The improvement in word recognition was clinically significant for some patients (patient 2, 7% to 96%; patient 3, 36% to 68%; patient 4, 0% to 14%; patient 5, 78% to 90%). Overall, treatment with bevacizumab was well tolerated. One patient required port removal because of infection. No patients discontinued treatment due to progressive disease or toxicity. No patients became hypertensive, and no episodes of bleeding or thrombosis were noted. No clinical or laboratory toxicity higher than grade 1 was reported. These preliminary clinical data demonstrate for the first time a medical therapy that can

significantly improve word recognition in NF2 patients with chronic hearing loss. We believe that a clinical trial of bevacizumab is warranted in selected patients with NF2 who are not candidates for standard therapy. Additional work is needed to understand the biology of angiogenesis in benign tumors.

MA-02. OPTIC NEUROPATHY IN PATIENTS WITH MALIGNANT GLIOMAS TREATED WITH BEVACIZUMAB

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INTRODUCTION: Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor, has recently been studied for both initial treatment and recurrence of malignant gliomas. Initial data indicate that patients show an increased response rate as well as an increase in progression-free survival compared with historical controls. Despite these promising data, isolated reports have emerged of acute optic neuropathy in a small subset of patients with malignant gliomas treated with bevacizumab.

METHODS: Using clinical records from 2005 to 2008, we identified adult patients with glioblastoma treated with bevacizumab who developed acute optic neuropathy. Four institutions participated in this study: the University of Virginia, UCLA, Columbia University, and Rush University. The age at diagnosis, sex, radiation therapy data, the chemotherapeutic regimen (including the bevacizumab dosing schedule), ophthalmologic records, laboratory values, and magnetic resonance imaging (MRI) were assessed.

RESULTS: Five patients were identified, including one man and four women. The mean age at diagnosis was 54 years (range, 37–68). After surgical resection of a glioblastoma, all patients received fractionated radiation therapy with concomitant temozolomide. One patient received bevacizumab at initial diagnosis, and the other four received the drug at recurrence. The mean radiation doses to the optic chiasm, left optic nerve, and right optic nerve were 5,509.7 cGy, 4,344.3 cGy, and 3,679.8 cGy, respectively. The mean time from the end of radiation therapy to the onset of visual symptoms was 11.5 months (range, 8–15.5). The patients completed a mean of 10.4 doses (range, 3–18) of bevacizumab before the onset of visual symptoms. Visual loss subsequently developed unilaterally in three patients and bilaterally in two patients. MRI from one of the former patients displayed left optic nerve enhancement, and another patient displayed parenchymal gliomatosis. MRI from one of the latter patients displayed bilateral optic nerve enhancement and evidence of parenchymal gliomatosis. A post-mortem pathologic specimen of the patient with left optic nerve enhancement displayed no evidence of tumor infiltration. Cerebrospinal fluid analysis was performed in four patients and showed no evidence of demyelinating disease or meningeal gliomatosis. The mean time from visual symptom onset to no light perception in at least one eye was 1.7 months (range, 0.5 months–4.5 months).

CONCLUSIONS: A small subset of glioblastoma patients treated with standard chemoradiation therapy has developed optic nerve dysfunction following treatment with bevacizumab. Patients receiving bevacizumab should be followed closely to clarify whether this complication represents drug-related optic neuropathy, coincidental radiation optic neuropathy, or an unusual bevacizumab-related pattern of tumor failure.

MA-11. REFRACTORY CEREBROSPINAL FLUID LEAK WITH FATAL OUTCOME IN TWO PATIENTS WITH RECURRENT MALIGNANT GLIOMAS WHO WERE TREATED WITH BEVACIZUMAB AND IRINOTECAN AFTER GLIADEL WAFER PLACEMENT

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The Gliadel wafer (GW) is approved by the FDA for the treatment of patients with malignant gliomas. Recently, the combination of bevacizumab and irinotecan has been shown to have a significant response in recurrent malignant gliomas. Cerebrospinal fluid (CSF) leak is a known adverse event associated with GW, and it is generally treated successfully with medical and surgical interventions. However, using bevacizumab after GW placement can potentially complicate the wound healing process, leading to a higher rate of difficult-to-treat CSF leaks. We report two cases of patients who underwent a second surgical resection for recurrent malignant gliomas with implantation of GW. They both received bevacizumab-irinotecan combination 4 weeks after surgery and presented shortly thereafter with CSF leak leading to severe infectious complications. Despite aggressive medical and surgical interventions, the condition of both deteriorated and they died subsequently. **CSF leak appeared to have a worse outcome when an anti-angiogenic agent, like bevacizumab, is incorporated into the treatment of patients who undergo GW placement. With the emergence of new anti-angiogenic agents for the treatment of recurrent malignant gliomas, a longer waiting period might be needed to allow for better wound healing. Further studies are needed to clarify the safety of combining GW with anti-angiogenic agents.**

MA-12. BRAINSTEM AND CEREBELLAR INVOLVEMENT IN POSTERIOR REVERSIBLE LEUKOENCEPHALOPATHY FOLLOWING BEVACIZUMAB

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Bevacizumab is a vascular endothelial growth factor (VEGF)-receptor inhibitor used to treat various cancers. There have been few reports of posterior reversible leukoencephalopathy following its use. Here, we report two cases involving the brainstem and cerebellum.

CASE 1: A 47-year-old woman diagnosed with colon cancer presented with a 2-day progressive history of headache, unsteady gait, nausea, and vomiting 2 weeks after her tenth cycle of chemotherapy (5-fluorouracil, oxaliplatin, and bevacizumab). She had no prior history of hypertension. The physical examination showed a blood pressure of 188/113 mmhg, left upper motor neuron facial nerve palsy, and ataxic gait. Cerebrospinal fluid analysis showed seven lymphocytes only, total protein 79 mg/dl, and glucose 51 mg/dl. A magnetic resonance imaging (MRI) contrast study of the brain showed non-enhancing extensive leukoencephalopathy of the posterior frontal, parieto-occipital, and cerebellar white matter with obstruction of the fourth ventricle from mass effect. Her blood pressure was controlled and her symptoms and ventricular obstruction resolved.

CASE 2: A 71-year-old woman diagnosed with colon cancer developed gait dysfunction and recurrent falls 4 weeks after completing her course of chemotherapy (bevacizumab, irinotecan, and 5-fluorouracil). She had no history of hypertension and

denied other neurological symptoms. Her blood pressure was 200/88 mmhg and examination showed only an ataxic gait. A lumbar puncture was not done. An MRI contrast study of the brain showed non-enhancing leukoencephalopathy of bilateral posterior periventricular white matter, cerebellar hemispheres, and the brainstem. Her symptoms improved with blood pressure control. A repeat MRI of the brain showed complete resolution of white matter changes seen on the earlier scan.

DISCUSSION: Reversible posterior leukoencephalopathy has been observed in various clinical scenarios in the setting of hypertensive encephalopathy. The pathophysiology is speculated to be an abnormality in the autoregulatory capacity of the brain vasculature during sustained blood pressure elevation. Extravasation of fluid from the intravascular space may be related to an underlying endothelial dysfunction. 1, 2 Bevacizumab is a recombinant humanized monoclonal antibody that binds to VEGF.3 Damage to the blood-brain barrier by immunosuppressive agents is believed to play a role in the predisposition to reversible leukoencephalopathy. To our knowledge, involvement of the brainstem after the use of bevacizumab has only been reported once.4 We report two cases of brainstem and cerebellar involvement and one case of fourth ventricle obstruction. **Reversible posterior leukoencephalopathy may manifest during or after the course of treatment with bevacizumab. Physicians should be aware of this potential idiosyncratic neurological complication as its use increases.**

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MA-17. BEVACIZUMAB SALVAGE THERAPY FOLLOWING PROGRESSION IN HIGH-GRADE GLIOMA PATIENTS TREATED WITH VEGF RECEPTOR TYROSINE KINASE INHIBITORS

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PURPOSE: Agents that target the vascular endothelial growth factor (VEGF) pathway are being used with increasing frequency in patients with recurrent high-grade glioma. The effect of more than one anti-angiogenic therapy given in succession has not been established. Therefore, we reviewed cases of recurrent high-grade glioma in which bevacizumab, a monoclonal antibody (MAb) that binds circulating VEGF-A, was given to patients who had tumor progression despite therapy with VEGF receptor tyrosine kinase inhibitors (R-TKi).

EXPERIMENTAL DESIGN: Seventy-three cases in which patients with recurrent high-grade gliomas had received VEGF R-TKi (cediranib, sorafenib, pazopanib, or sunitinib) as part of phase I or II clinical trials were retrospectively reviewed. Of the 73 patients, 24 progressed and subsequently received bevacizumab 1/-

irinotecan immediately after R-TKi. Those who stopped R-TKi therapy for reasons other than disease progression (i.e., adverse events) and those who received a treatment that did not include bevacizumab were excluded from the analysis. In the 24 patients who received bevacizumab at the time of disease progression, we assessed median time to progression on R-TKi and bevacizumab treatment, 6-month progression-free survival, and best radiographic response using MacDonald criteria. In addition, overall survival and toxicities of therapy are reported.

RESULTS: During TKi therapy, 5/24 patients (21%) had a radiographic partial response to treatment. The 6-month progression-free survival was 16.7% and the time to progression was 16 weeks. Grade 3 or 4 toxicities were seen in 13 of 23 patients (54%). Subsequently with bevacizumab salvage therapy, 5 of 24 patients (21%) had a radiographic partial response. The 6-month progression-free survival was 12.5% and the time to progression was 8 weeks. Six of 24 patients had grade 3 or 4 toxicities (25%). Two patients discontinued bevacizumab because of grade IV adverse events (bowel perforation (1), pulmonary embolism (1)). The median overall survival was 91 weeks (range, 55–166), whereas the median overall survival after starting bevacizumab was 22 weeks.

CONCLUSION: Bevacizumab retains modest activity in high-grade glioma patients who progress on VEGF receptor tyrosine kinase inhibitors. However, the 6-month progression-free survival of 12.5% of the patients in this cohort indicates that durable tumor control is not achieved for most patients.

MA-18. SOLITARY MALIGNANT FIBROUS TUMOR: RESPONSE TO BEVACIZUMAB AND IRINOTECAN

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BACKGROUND: Solitary fibrous tumors (SFTs) are uncommon intracranial tumors that radiographically resemble meningiomas. SFTs are usually treated with surgical resection and external beam radiation therapy (EBRT), but there is no effective drug treatment for recurrent disease. We report the radiological and clinical response of a patient treated with bevacizumab and irinotecan.

CASE HISTORY: A 48-year-old man initially presented in April 2004 with headaches, disorientation, short-term memory loss, and behavior changes. A magnetic resonance imaging (MRI) scan revealed a left para-falcine enhancing extra-axial mass invading the anterior superior sagittal sinus, with erosion through the frontal bone in the midline. He underwent craniotomy with total resection; pathology was consistent with malignant solitary fibrous tumor. No further therapy was given, and in June 2005, tumor recurred at the primary site and he underwent resection and EBRT. In July 2006, he had worsening memory loss, concentration, and irritability, as well as two generalized tonic-clonic seizures. An MRI scan at that time revealed new heterogeneous enhancement of the posterior margin of the surgical bed, with extensive intraventricular enhancement and a left midline shift. He reported sleep/wake cycle disturbances, hallucinations, anhedonia, and difficulty with activities of daily living. The patient's neurological exam was normal, with the exception of mild ptosis of the right eye lassitude, inattentiveness, and flattened affect. Cognitive testing using the MMSE scored 30/30. Positron emission tomography of his chest, abdomen, and pelvis showed no evidence of metastatic disease. Areas of increased uptake in the right frontal lobe corresponded with the most recent MRI. The patient was started on bevacizumab and irinotecan. Each 6-week cycle consisted of bevacizumab at 5 mg/kg on days 1 and 22 and irinotecan at 125 mg/m² on days 1, 8,

22, and 29. There were no dose delays for myelosuppression or gastrointestinal toxicity. MRI after two cycles of chemotherapy demonstrated radiological response by MacDonald criteria, and after seven cycles, there was no residual contrast-enhancing tumor. Unfortunately, the frontal lobe dysfunction did not improve. The patient became increasingly somnolent and dependent for care. An MRI scan demonstrated widespread white matter FLAIR hyperintensity, but no contrast-enhancing tumor. Chemotherapy was discontinued in November 2007. In February 2008, disease recurred at the original primary site, and the family chose hospice care.

CONCLUSIONS: Bevacizumab and irinotecan may be an active regimen for SFTs. It is unclear whether bevacizumab exacerbated leukoencephalopathy attributed to prior EBRT.

MA-21. BEVACIZUMAB PLUS IRINOTECAN IN PROGRESSIVE TEMOZOLOMIDE-REFRACTORY GLIOBLASTOMA MULTIFORME: A SINGLE-CENTER EXPERIENCE USING A LOW-DOSE REGIMEN

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BACKGROUND: First-line treatment for glioblastoma multiforme (GBM) consisting of surgery, irradiation plus concomitant and following temozolomide has been established, resulting in a median survival time of 15.6 months, indicating the need for further effective treatment. In several phase II studies, bevacizumab plus irinotecan showed impressive objective response rates (. 50%) in pre-treated GBM patients with a low toxicity rate. Duration of response, however, was moderate. Therefore, bevacizumab plus irinotecan might be considered as an effective induction regimen for temozolomide-resistant progressive GBM as a basis for further treatments. In colorectal cancer, a lower dose bevacizumab plus irinotecan was effective and it is not known whether the higher and much more cost-intensive dose used in progressive GBM really is necessary and whether the dose should be increased because of enzyme-inducing anticonvulsive drugs (EIAED). Therefore, we reduced the dose of bevacizumab and irinotecan.

METHODS: From December 2006 to October 2007, 44 patients with progressive GBM resistant to temozolomide were treated with bevacizumab 4 mg/kg body weight intravenously followed by irinotecan 80 mg/m² intravenously repeated every 2 weeks. ECOG performance status was 0–2 in 43 patients and 3 in one patient. MRI scans were required at baseline (no hemorrhage was allowed) after 4 weeks and afterwards every 6 weeks. Treatment was given until progressive disease or intolerable toxicity occurred. Stratification included EIAED.

RESULTS: All 44 patients were eligible for toxicity and efficacy, the median follow up time was 7 months, 33 patients were male, 11 female, the median age was 45 years (range, 21–79), 32 patients had primary GBM, and 12 patients had secondary GBM. All patients had prior irradiation (56–60 Gy): four patients had four prior chemotherapy regimens, 11 patients had three, 22 patients had two, and 7 patients had temozolomide only. Forty-three patients had ECOG performance status of 0–2, one patient had 3. The patient with a performance status of 3 died of clostridium sepsis during grade IV leucopenia after the first treatment. One patient developed grade III leucopenia and two patients grade III thrombopenia, one patient grade III pneumonia, two patients asymptomatic intracerebral bleeds requiring treatment delay, and one patient grade III fatigue. In 22 patients, a partial response was achieved, in 15 patients disease stabilization for at least 2 months, and seven patients showed primary progressive disease. The median duration of partial response was 3 months (range, 2–8), and the best magnetic resonance imaging response was achieved after 4 to 8 weeks of treatment. The data will be updated.

CONCLUSION: Bevacizumab plus irinotecan seems to be the most effective regimen for induction of objective response in multiple pre-treated GBM patients with an excellent toxicity profile. Efficacy of the low-dose regimen was comparable to other published regimens and seems to be independent from the use of EIADS. In targeted therapy, the principle of maximum-tolerated dose might not necessarily be identical with the optimal treatment dose, which might be lower. Confirmation is required. A following maintenance treatment should be considered.

MA-27. ROLE OF A SECOND CHEMOTHERAPY IN RECURRENT MALIGNANT GLIOMA IN PATIENTS WHO PROGRESS ON A BEVACIZUMAB-CONTAINING REGIMEN

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OBJECTIVE: Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) that has efficacy in recurrent malignant gliomas, particularly in combination with irinotecan. However, responses are rarely durable. Continuation of bevacizumab in combination with another chemotherapeutic agent may demonstrate some activity.

METHODS: We conducted a retrospective review of 54 patients with recurrent malignant gliomas who progressed on a bevacizumab containing regimen and were then treated with an alternate bevacizumab containing regimen. All patients received bevacizumab 5–10 mg/kg intravenously every 2 weeks alone or in combination with an additional chemotherapeutic agent, such as irinotecan, carboplatin, carmustine, lomustine, temozolomide, etoposide, or erlotinib. There was no limit on the number of prior therapies. Clinical characteristics and outcomes were reviewed. Tumor progression was determined by a combination of clinical status and radiographic changes.

RESULTS: Patient characteristics were 33 men, 21 women; median age 50 years (range, 23–72); median KPS 80 before the first bevacizumab-containing regimen and 70 prior to the second regimen; median prior chemotherapy regimens, including the first bevacizumab-containing regimen 3 (range, 2–5). The median progression free survival on the first bevacizumab-containing regimen was 124 days (95% CI: 87–154). The 6-month progression-free survival rate was 33%. The median progression-free survival time on the second bevacizumab containing regimen was 37.5 days (95% CI: 34–42). The 6-month progression-free survival rate was 2%. Ten patients on the first regimen and 12 patients on the second regimen suffered grade 3 or 4 toxicities.

CONCLUSIONS: Patients with malignant gliomas who progress despite a bevacizumab-containing regimen do not respond favorably to a second bevacizumab-containing chemotherapeutic regimen.

MA-34. RETROSPECTIVE ANALYSIS OF CARBOPLATINUM AND BEVACIZUMAB CHEMOTHERAPY IN PATIENTS WITH RECURRENT GLIOMA

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BACKGROUND: Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, has shown good response rates when given with irinotecan in patients with recurrent malignant glioma. The diarrhea and fatigue associated with irinotecan, and its limited activity against gliomas as a monotherapy, led us to offer patients carboplatinum in combination with bevacizumab, since carboplatinum has some activity in recurrent glioma.

METHODS: Carboplatinum and bevacizumab was given to patients with malignant glioma (WHO grade III or IV) who had recurred following radiation therapy and temozolomide chemotherapy. Patients were advised of the investigational nature of the chemotherapy combination and the known risks of treatment, including the risk of intracranial hemorrhage, bowel perforation, hematologic toxicity, and allergic or idiosyncratic reactions, and all consented to treatment. The retrospective analysis was approved by our institutional review board. We analyzed our data in April 2008 after 56 patients had been treated. Patients received bevacizumab at 5 mg/kg every 2 weeks and carboplatinum at 5–6 AUC every 4 weeks. Carboplatinum was given after bevacizumab. Hematologic parameters were monitored weekly, and MRI scans were done every 8 weeks (every two cycles). Charts were reviewed to assess progression-free survival, overall survival, and response rates.

RESULTS: Fifty-six patients were treated. The mean age was 53.3 ± 12.1 years. Thirty-five were male (62.5%). Thirty-eight had glioblastoma, and 18 had anaplastic (WHO grade III) tumors. At the time of the analysis, 35 patients had progressed and 21 had not. Twenty nine patients had died, and all deaths followed tumor progression. The progression-free survival rate was 43.6% at 6 months, and 32.3% at 1 year. The median progression-free survival time was 168 days (24 weeks) (95% CI: 115–495 days). The overall survival rate at 6 months was 61.3%. The median overall survival time was 257 days (36.7 weeks) (95% CI: 155–295 days). A subgroup analysis showed no significant difference in overall survival for patients with grade III and grade IV tumors ($p = 0.1832$; log rank test). Progression-free survival was not significantly different between those with grade III and IV tumors. Significant toxicities included the following: allergic reactions (1), retro-peritoneal bleeding (1), stroke (1), radiographic tumor bleeding (1), radiographic leptomeningeal spread (5), grade 4 neutropenia (1), pneumonia (1), wound dehiscence (1), and pulmonary emboli (1). The response rates and recurrence patterns are being analyzed and will be reported at the meeting.

CONCLUSIONS: Combination therapy with bevacizumab and carboplatinum is well tolerated and active in patients with recurrent malignant glioma. Progression-free survival and overall survival were similar to those seen with other bevacizumab-containing regimens and appear better than the results seen with older salvage regimens. In particular, the 6-month progression-free survival rate of 43.6% is better than most historical series. The toxicity of the combination was acceptable. The patients who had a response to treatment improved neurologically and enjoyed an apparent improvement in their quality of life, although this was not formally assessed. This pilot data warrants a larger prospective trial, with formal quality of life assessments.

MA-37. CALCIFICATION IN HIGH-GRADE GLIOMAS TREATED WITH BEVACIZUMAB

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INTRODUCTION: Calcification is a rare phenomenon in high-grade glioma and has not been previously cited in primary glioblastoma.

METHODS: We report our experience with 45 patients with progressive high grade glioma who were treated with biochemotherapy consisting of bevacizumab and cytotoxic agent. Among 15 patients treated for 6 or more months, 11 had at least one computed tomography scan performed, and all patients had serial MRIs for tumor evaluation. We observed an unexpected phenomenon of calcification in these CT scans. A search of our Neurooncology/Neurosurgery database from 1995 to 2007 for calcifications in long-term survivors of more than 500 patients with primary glioblastoma was performed to be used as a comparative denominator group.

RESULTS: Forty of the 45 patients treated with biochemotherapy had recurrent or progressive glioblastoma, three patients had anaplastic oligodendroglioma, and two patients had anaplastic astrocytoma. Fifteen (33%) of these patients were treated for 6 months or more. In six of these patients treated for an extended period of time, we observed an unexpected phenomenon of calcification, in some cases quite extensive. Of patients treated less than 6 months, only one patient with anaplastic oligodendroglioma had calcification on CT scan; the calcification was evident, at a lesser degree, before treatment with bevacizumab.

DISCUSSION: Although tumor calcification is a recognized phenomenon in low-grade glial tumors, particularly oligodendrogliomas, calcification has not been previously cited in glioblastomas.

CONCLUSION: Calcification in high grade glial tumors (and specifically glioblastoma) treated with bevacizumab is a previously unrecognized finding. We speculate that these changes may occur at a microvascular level and represent a unique, perhaps organ-specific, phenomenon associated with anti-angiogenic therapy for brain tumors.

MA-41. SAFETY AND EFFICACY OF BEVACIZUMAB AND ERLOTINIB FOR RECURRENT GLIOBLASTOMA PATIENTS IN A PHASE II STUDY

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BACKGROUND: In glioblastoma (GBM), overexpression of the epidermal growth factor receptor (EGFR), a key mediator of cell survival, proliferation and angiogenesis, occurs in most tumors, while prolific overexpression of vascular endothelial growth factor (VEGF), is universal. Concurrent targeting of EGF and VEGF receptors has synergistic activity in GBM xenograft models and other solid tumors. Recently, bevacizumab, a neutralizing VEGF monoclonal antibody, has demonstrated significant single-agent anti-tumor activity among patients with recurrent GBM, which appears to be enhanced by concurrent cytotoxic chemotherapy. We performed a single-arm, phase II study to evaluate the efficacy of bevacizumab and erlotinib in patients with recurrent GBM.

METHODS: The primary endpoint was 6-month progression-free survival. Radiographic response, pharmacokinetics, and correlative biomarkers were the secondary endpoints. Erlotinib was orally administered daily at 200 mg/day for patients not on enzyme-inducing anticonvulsants (EIAC) and 500 mg/day for patients on EIAC. All patients received 10 mg/kg bevacizumab intravenously every 2 weeks. The key eligibility criteria included age 18 years or older; KPS of 60 or higher; more than 4 weeks from prior surgery, XRT, or chemotherapy. Patients with either more than 3 prior progressions, requirement for therapeutic anti-coagulation or acute hemorrhage on pretreatment imaging were excluded.

RESULTS: Twenty-five recurrent GBM patients with a median of 2 prior progressions were enrolled, including 10 (40%) on EIAC. Rash, mucositis, diarrhea, and fatigue were common but mostly grade 2. Serious side effects were rare and included single patients who developed either intestinal perforation, arterial thrombosis, pulmonary embolism, or nasal septal perforation. Six patients have completed more than 6 months of therapy, including three who continue on therapy over 1 year. Twelve patients (50%) achieved radiographic response, 10 (42%) achieved stable disease, and 2 (8%) progressed.

CONCLUSIONS: Among heavily pre-treated recurrent GBM patients, bevacizumab and erlotinib are tolerated and associated with an encouraging anti-tumor benefit.

MA-42. BEVACUZIMAB AND TEMOZOLOMIDE FOR PATIENTS WITH RECURRENT MALIGNANT GLIOMAS

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INTRODUCTION: Bevacizumab is a recombinant humanized antibody inhibitor of vascular endothelial growth factor (VEGF), a key factor in tumor angiogenesis. Temozolomide is a cytotoxic alkylating agent that penetrates well in the central nervous system (CNS). Both have shown activity against malignant glioma, a disease with inevitable recurrence after primary therapy with resection, radiation to 60 Gy, and temozolomide.

METHODS: Nine patients with recurrent glioma confirmed on magnetic resonance imaging (MRI) were treated with bevacizumab 10 mg/kg every other week and daily temozolomide 50 mg/m² in 12 cycles of 28 days. One patient had an optic glioma, one had anaplastic astrocytoma, two had anaplastic oligodendroglioma, and five had glioblastoma multiforme. Patients could not have evidence of CNS hemorrhage on imaging and required at least a 4-week interval from previous treatment with resection or radiation. Tumor response was measured by contrast-enhanced MRI.

RESULTS: Forty-four infusions of bevacizumab with temozolomide have been administered, with only one patient experiencing grade 1 weakness and another patient experiencing grade 1 elevations in blood pressure. Follow-up times ranged from 2 to 10 months. Three patients received bevacizumab only. One patient had a minor response, one patient had a complete response, and an added patient had a partial response. Other patients are pending imaging.

CONCLUSION: Bevacizumab and temozolomide for treatment of recurrent glioma is well tolerated. Survival data are pending, although radiographic response rates appear encouraging.

MA-43. LOCKED-IN SYNDROME FROM HIGH-GRADE GLIOMA – POSSIBLE ROLE OF BEVACIZUMAB

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Locked-in syndrome (LIS) is a devastating condition caused most often by ischemic stroke or hemorrhage, affecting the corticospinal, corticopontine, and corticobulbar tracts in the brainstem. The term was coined by Plum and Posner in 1966 to describe the state of quadriplegia and anarthria with preserved consciousness. Other causes of LIS include trauma, pontine abscess, brainstem tumors, central pontine myelinolysis, toxins, and heroine abuse. Only one case report describing LIS resulting from direct invasion of the brainstem by tumor (lymphoma) exists in the literature. To our knowledge, association of LIS with high-grade glioma has not been reported. A 28-year-old man was diagnosed with pleomorphic xanthoastrocytoma with anaplastic features 22 months before presentation. The tumor was located in the right parietal lobe. Recurrence occurred within 4 months following initial gross total resection, and the second resection identified glioblastoma. The patient received standard therapy with radiation and concomitant temozolomide with adjuvant temozolomide for six cycles. He was then found to have a subependymal nodule in the left frontal lobe and received focal therapy with Gamma knife. Cerebrospinal fluid (CSF) analysis and entire spine magnetic resonance imaging (MRI) failed to demonstrate evidence of distant metastases. The patient started bevacizumab and irinotecan and completed two cycles. Because of significant toxicity (fatigue and nausea), irinotecan was replaced with carboplatin. He received one dose without significant improvement and then developed new symptoms: gait ataxia, double vision, and difficulty swallowing. His MRI scan identified extensive and progressive FLAIR changes involving both hemispheres and ventral brainstem with leptomeningeal enhancement. MRI spectroscopy was suggestive of tumor. His initial neurologic examination identified decreased alertness, dysarthria, right sixth nerve palsy, left incomplete third nerve palsy, twelfth nerve palsy, depressed gag reflex, hyperactive jaw jerk, and severe gait ataxia. The patient was admitted to the neurology service where his condition worsened rapidly and he required intubation for airway protection. He was found to have aspiration pneumonia and pulmonary embolism. His CSF analysis (x3) failed to identify malignant glioma cells. Interestingly, Epstein-Barr and varicella zoster (VZV) virus DNAs were found in the CSF, and the patient was started on acyclovir for VZV meningoencephalitis. Subsequent testing demonstrated negative viral titers. Multiple neurological examinations off sedation were performed independently by two neurologists. He was found to be alert with eyes open. He had down-gaze (looked down to command intermittently), he was able to blink (intermittently to command), his horizontal eye movements were limited and nystagmus was present, but he had no facial movement. He was quadriplegic with diminished tone and asymmetric hyperreflexia. The patient remained ventilator-dependent. Tumor-directed therapies were limited and thought not to be beneficial to the patient at his disease stage, and thus efforts were focused on comfort care. **This is the first reported case demonstrating diffuse growth of a high-grade glioma producing locked-in syndrome in a patient treated with bevacizumab. Diagnostic challenges, including pathological verification of leptomeningeal gliomatosis, and co-existing presumed VZV encephalitis will be discussed. Since it was recently recognized that bevacizumab can alter patterns of recurrence in malignant gliomas, this report is very timely and contributes to our knowledge about the possible deleterious effects of anti-angiogenic therapies in this malignancy.**

MA-44. A PHASE II TRIAL WITH CETUXIMAB, BEVACIZUMAB AND IRINOTECAN FOR PATIENTS WITH PRIMARY GLIOBLASTOMAS AND PROGRESSION AFTER RADIATION THERAPY AND TEMOZOLOMIDE

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BACKGROUND: Recent data has shown that a combination of bevacizumab and irinotecan induces significant responses in recurrent glioblastoma multiforme (GBM). Primary GBM is frequently associated with amplification (40–50%) and/or mutations (20–60%) of the epidermal growth factor receptor (EGFR). Moreover, GBM tumors are known to be highly vascularized, and pronounced tumor vascularity is significantly correlated with poor survival. In vivo experiments have shown that cetuximab increases apoptosis, decreases cell proliferation, and decreases vascular endothelial growth factor expression in EGFR-amplified GBM cells in vitro. The use of the combination of cetuximab and irinotecan has shown a significantly higher response rate compared to irinotecan as monotherapy in colorectal cancer. In addition, adverse events (AE) have been acceptable and the BOND-2 study has shown the feasibility of combining cetuximab, bevacizumab, and irinotecan (CBI). In this phase II study, we examined the safety and efficacy of CBI in recurrent GBM.

METHODS: Patients with recurrent GBM after standard primary treatment (surgery/biopsy, followed by radiotherapy and temozolomide) were included after signed informed consent and standard inclusion criteria. The patients received cetuximab 400 mg/m² on day 1, followed by weekly cetuximab 250 mg/m²; bevacizumab 10 mg/kg every other week (the first 10 patients received 5 mg/kg); and irinotecan 125 mg/m² in patients not treated with enzyme-inducing anti-epileptic drugs (EIAED) or 340 mg/m² in patients treated with EIAEDs every other week. Evaluation was performed according to the MacDonald criteria with magnetic resonance imaging every 8 weeks and safety according to CTCAE v.3.0.

RESULTS: Thirty-two patients were included between August 2006 and February 2008. After safety analysis of the first 10 patients, bevacizumab was increased from 5 to 10 mg/kg, and this regimen was well tolerated. Three patients experienced grade III-IV allergic reaction during first cetuximab administration despite premedication. In March 2008, 27 were evaluable for response. One complete response and eight partial responses were observed (RR 33%), and five patients (19%) had minor responses (25–50% regression and clinical improvement). The Median TTP was 24 weeks. Five patients had thromboembolic complications.

CONCLUSION: The CBI regimen was well tolerated, with encouraging response rates, including one complete response. However, the efficacy of the combination seems to be similar to the combination of bevacizumab and irinotecan alone; therefore, further evaluation of this regimen is not planned. An update on survival data, including progression-free survival at 6 months and toxicity data, will be presented at the meeting.

MA-48. SALVAGE CONCURRENT CHEMOTHERAPY WITH BEVACIZUMAB FOR RECURRENT MALIGNANT GLIOMAS PREVIOUSLY TREATED WITH BEVACIZUMAB AND IRINOTECAN

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BACKGROUND: Recurrent malignant glioma confers a grave prognosis with a median survival of 25 weeks for glioblastoma multiforme and 47 weeks for AA. The combination of bevacizumab and irinotecan is well tolerated and active against progressive malignant gliomas, with radiographic response rates of at least 50% and a median PFS of 24 weeks. At further recurrence, continuing bevacizumab and changing the chemotherapy agent is one therapeutic option. However, there is limited experience published in the literature on the efficacy of continuing bevacizumab after progression when combined with irinotecan.

METHODS: We retrospectively reviewed 12 patients with recurrent malignant gliomas who all received irinotecan and bevacizumab after initial progression with adjuvant temozolomide. These patients were continued on bevacizumab but with addition of another chemotherapeutic agent. Data were collected from the Hermelin Brain Tumor Center Database to determine the clinical and radiologic outcomes.

RESULTS: Eleven patients who were treated with irinotecan and bevacizumab for progression showed initial partial response. One patient showed stable disease. These patients eventually recurred with a median time to progression of 8.6 months. At progression, nine of 12 patients were continued on bevacizumab with temozolomide given 21 days on and 7 days off. Two patients were elected to be treated with bevacizumab and carboplatin while the remaining patient was given bevacizumab and BCNU. One patient treated with bevacizumab and carboplatin showed stable radiologic follow-up. Another patient treated with bevacizumab and temozolomide initially showed stable disease after one cycle but eventually progressed. The rest of the patients (10/12) progressed with a short median time to progression of only 1.7 months. All patients showed clinical decline except for one who remained stable despite significant imaging progression. Seven patients died shortly after progression with the salvage treatment.

DISCUSSION: Norden et al first reported their initial experience with 23 patients who progressed on bevacizumab and irinotecan. They were continued on bevacizumab and most were treated with concurrent carboplatin with no objective radiographic response. We tend to maintain bevacizumab even though patients showed progression for two reasons: one is the fear of rebound phenomenon once bevacizumab is discontinued and the other is that the optimal chemotherapy agent to combine with bevacizumab is unclear. The use of temozolomide at an alternate dose-intensified schedule is an attractive option considering the convenience and safety profile of this drug. It is also one of the treatment arms in the RTOG 0625, which makes it a logical choice as a replacement chemotherapy agent once the patient progressed on bevacizumab and irinotecan. In our series of 12 patients with recurrent malignant gliomas who failed bevacizumab and irinotecan, maintaining bevacizumab and changing the concurrent chemotherapy failed to show any clinical or radiographic benefit. Furthermore, this subset of patients had a very short median time to progression of 1.7 months.

CONCLUSION: There are limited data on the efficacy of treatment options for patients who have failed treatment with bev/cpt-11. Our experience concurs with the generally held belief that bev/cpt-11 failure portends an aggressive progressive disease course and few remaining options for successful palliative treatment.

MA-49. BEVACIZUMAB PLUS SINGLE-AGENT CHEMOTHERAPY FOR RECURRENT EPENDYMOMA

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Two chemotherapy-naïve patients with ependymoma were treated with bevacizumab plus single-agent chemotherapy in the recurrent setting after the failure of surgery and radiation therapy. Patient 1, a 22-year-old woman with occipital ependymoma, was initially treated with tumor resection only; the first recurrence was treated with repeat resection showing anaplastic ependymoma, followed by regional radiation therapy (5,940 cGy); the second recurrence was treated with stereotactic radiosurgery (2,500 cGy); the third recurrence was treated with temozolomide at 150–200 mg/m²/day for 5 days every 28 days plus bevacizumab at 5 mg/kg every 2 weeks. She achieved a partial response with a time to progression (TTP) of 253 days. Patient 2, a 52-year-old man with fourth ventricular ependymoma, was initially treated with tumor resection and regional radiation therapy; the first recurrence was treated with carboplatin AUC 5.5 every 28 days plus bevacizumab at 5 mg/kg every 2 weeks. He achieved a complete response with a TTP of 195 days. Tumor progression occurred in both patients as diffuse non-enhancing infiltration on T2-weighted magnetic resonance images. After tumor progression, bevacizumab was continued in conjunction with sequential trials of other chemotherapy agents. Patient 1 did not respond to carboplatin (TTP, 26 days), achieved a partial response to etoposide (TTP, 341 days), and is now being treated with CCNU. Patient 2 did not respond to temozolomide or etoposide and died with a survival time of 650 days. Bevacizumab when combined with single-agent chemotherapy may have activity in recurrent ependymoma and deserves further study.

MA-50. TEMOZOLOMIDE PLUS BEVACIZUMAB FOR RECURRENT SUPRASELLAR PILOCYTIC ASTROCYTOMA

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Two patients with recurrent suprasellar pilocytic astrocytoma (PA) were treated with temozolomide at 150–200 mg/m² for 5 days every 28 days plus bevacizumab at 5 mg/kg biweekly (temozolomide plus bevacizumab). Patient 1, a 30-year-old woman, had been initially treated at age 6 for PA with VP shunt, tumor resection, and regional radiation therapy (5,040 cGy); the first recurrence was at age 26. After biopsy confirmation of PA, she was treated with carboplatin AUC 5.5 for 12 cycles and had disease stabilization. Her second recurrence was treated with temozolomide plus bevacizumab and she achieved a partial response with a marked reduction in contrast-enhancing tumor volume and improvement of a visual field deficit. Treatment with bevacizumab was stopped when symptomatic intratumoral hemorrhage with visual loss occurred after 505 days of treatment; temozolomide was continued for two more cycles. Patient 2, a 44-year-old woman, underwent initial biopsy; postoperative tumor progression was treated with fractionated stereotactic radiation therapy (5,220 cGy); further symptomatic tumor progression immediately following

radiation therapy was treated with ongoing temozolomide plus bevacizumab (currently 348 days). This patient also achieved a partial response, with marked reduction in contrast-enhancing tumor volume and improvement of extra-ocular movements. **Temozolomide plus bevacizumab may have activity in recurrent PA after failure of radiation therapy and deserves further investigation.**

MA-55. A RETROSPECTIVE ANALYSIS OF PATIENTS WITH RECURRENT HIGH-GRADE GLIOMAS TREATED WITH BEVACIZUMAB WITH OR WITHOUT IRINOTECAN: THE MOFFITT CANCER CENTER EXPERIENCE

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INTRODUCTION: Recurrent glioblastomas (GBM) have very poor outcomes despite aggressive therapy. Although there is no standard of care for recurrent GBM, the combination of bevacizumab and irinotecan has been shown to have activity against these tumors. In addition to recurrent GBMs, bevacizumab plus irinotecan may also have activity against recurrent anaplastic gliomas (AG). We evaluated the responses of bevacizumab plus irinotecan in recurrent GBM patients and compared them to those for recurrent AG patients.

METHODS: We conducted a retrospective analysis of 33 recurrent high-grade glioma (HGG) (GBM and anaplastic glioma) patients followed at Moffitt Cancer Center from September 2006 to April 2008 treated with bevacizumab alone or in combination with irinotecan. HGG histologies included GBM, anaplastic astrocytomas (AA), anaplastic oligodendrogliomas (AO), and anaplastic oligoastrocytomas (AOA). Progression-free survival (PFS) and overall survival (OS) were analyzed and correlated with respect to specific prognostic variables, including histology, age, gender, Karnofsky performance status (KPS), extent of resection, and number of prior therapies.

RESULTS: Thirty-three percent (11) of the patients were female and 67% (22) were male. The median age was 51 years (range, 21–72). The median KPS was 80 (range, 60–100). Twenty-three (70%) patients had GBM, six (18%) had AA, two (6%) had AO, and two (6%) had AOA. Five (15%) patients had a gross total resection (GTR), 21 (64%) had a subtotal resection (STR) and seven (21%) had biopsy only. The median number of prior therapies was two (range, 1–7). At the time of analysis, 21 (64%) patients had progressed and 12 (36%) patients had died. No prognostic variable was significantly associated with PFS or OS. From time of progression prior to initiation of bevacizumab, the median PFS time for all patients (95% CI) was 6 months (range, 4.6–8.1) and the median OS time was 12 months (range, 8.7–13.0). From time of progression prior to initiation of bevacizumab, the median PFS time for GBM patients was 6 months, whereas the median PFS of AG patients was 6.2 months. The median OS time for GBM patients from before initiation of bevacizumab was 12.9 months and 8.7 months for AG patients. The median OS time from time of initial diagnosis was 45.2 months for GBM patients and 80.2 months for AG patients. The addition of irinotecan to bevacizumab did not significantly affect outcome.

CONCLUSIONS: The outcomes of our GBM patients compare favorably with those of prior study patients treated with bevacizumab and irinotecan. However, the median OS time of the AG patients from initiation of therapy was lower than that of GBM patients. **This finding suggests that the benefit of bevacizumab with irinotecan may not benefit recurrent AG patients as much as recurrent GBM patients.** However, our sample size is too small to draw definitive conclusions. A prospective phase II clinical trial may help determine the efficacy of bevacizumab in recurrent AG patients.

MA-60. BEVACIZUMAB FACILITATES UP-FRONT CHEMORADIATION IN POOR-RISK PATIENTS WITH GLIOBLASTOMA MULTIFORME BY CAUSING TUMOR SHRINKAGE AND IMPROVING NEUROLOGICAL FUNCTION

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Poor postoperative neurological function due to mass effect and perilesional edema often limits the ability of patients with glioblastoma multiforme to tolerate standard radiation therapy (RT) and temozolomide (TMZ). We retrospectively analyzed the records of 19 patients with poor or declining neurological function due to bulky tumors whom we treated with bevacizumab in the up-front setting in an attempt to improve patients' ability to tolerate chemoradiation. The average age was 62; 10 patients were male, 9 were female. All patients received TMZ at 75 mg/m²/day for 42 days, followed by 150–200 mg/m² for 5 days every 28 days; bevacizumab was given at a dose of 5 mg/kg biweekly. Bevacizumab was initiated prior to RT for six patients, concurrently with RT for four patients, and after completion of RT for six patients; three patients received bevacizumab without any RT. Fourteen of the 19 patients were able to receive standard regional RT (6,000 cGy); two received a short course of RT; one declined RT, and two died before RT could be initiated. All patients had low pre-treatment Karnofsky performance status (KPS) (average, 62%; range, 30–80) and/or severe deficits (hemiparesis, amnesia) attributable to bulky disease despite high-dose dexamethasone (average, 15.3 mg daily). Clinical exams and magnetic resonance scans were obtained, when possible, at the end of the first treatment cycle of TMZ in which bevacizumab had been added. Five patients died before follow-up clinical examination. Of the 14 patients who could be examined, the average immediate follow-up KPS was 84%; 79% of patients had improvement of KPS (range of improvement, 0–60). In these 14 patients, the average dexamethasone dose requirement was reduced from 15 mg prior to treatment to 7.5 mg immediately after the first treatment cycle (1–3 doses of bevacizumab) and to 2.5 mg at the lowest dose. Of 17 patients with post-bevacizumab magnetic resonance scans, 65% showed a partial response, 24% a minor response, and 11% stable disease. Two patients had pulmonary embolism requiring anticoagulation. No cerebral hemorrhages occurred. Time to progression could not be reliably measured for the cohort because of the five early deaths without imaging data. The median survival time for the entire group was 334 days. The 6-month progression-free survival rate was 60%. Recurrence often took the form of diffuse non-enhancing tumor resembling gliomatosis cerebri. Five patients were treated for tumor recurrence, four patients received irinotecan plus bevacizumab; and one received carboplatin plus bevacizumab. The median time to progression for those five patients was 138 days (range, 24–231). The addition of bevacizumab to standard chemoradiation in patients with GBM with large cerebral tumors and poor neurological function lead to tumor shrinkage in the majority of patients, rapidly improved neurological function, reduced steroid requirements, and allowed most patients to complete definitive RT.

MA-63. PHASE II STUDY OF BEVACIZUMAB PLUS IRINOTECAN IN CHILDREN WITH RECURRENT MALIGNANT GLIOMA AND DIFFUSE BRAINSTEM GLIOMA—A PEDIATRIC BRAIN TUMOR CONSORTIUM STUDY (PBTC-022)

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A phase II study of bevacizumab (BVZ) plus irinotecan (CPT-11) was initiated in children with recurrent malignant glioma (MG) (stratum A) and brainstem glioma (BSG) (stratum B) to estimate rates of sustained (lasting 8 weeks or more) responses and toxicity to this combination. Eligible patients received two doses of single-agent BVZ given intravenously (10 mg/kg) 2 weeks apart followed by intravenous CPT-11 (125 mg/m² or 250 mg/m² based on enzyme-inducing anticonvulsant use) and then BVZ plus CPT-11 every 2 weeks until progressive disease, unacceptable toxicity, or a maximum of 2 years. Correlative studies included T1 dynamic contrast-enhanced permeability imaging, FDG-PET scan of the brain, BVZ pharmacokinetics, and estimation of changes in VEGF-R2 phosphorylation (pVEGF-R2) by Western blot analysis in peripheral blood mononuclear cells (PBMC) following single-agent BVZ. Between October 2006 and January 2008, 30 evaluable patients [stratum A (n = 14, median age 15.9 years), and stratum B (n = 16, median age 8.7 years)] have been enrolled in this study. No sustained responses have been observed thus far in either stratum. The median times to progression were 9 weeks (range, 7–32) and 9 weeks (range, 3.5–35) for stratum A (n = 9) and B (n = 10), respectively. Toxicities related to BVZ included fatigue (7), hypertension (7), CNS ischemia (2), asymptomatic CNS hemorrhage (4), epistaxis (3), proteinuria (3), neutropenia (1), and pancreatitis (1). A significant reduction in PBMC pVEGF-R2 occurred in patients following BVZ exposure. Enrollment is currently open for stratum A only and final results of responses for this stratum and other correlative studies will be reported.

MA-65. TREATMENT OF CHILDREN WITH RECURRENT OR PROGRESSIVE HIGH-GRADE GLIOMAS WITH IRINOTECAN, TEMOZOLOMIDE, AND BEVACIZUMAB

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BACKGROUND: Children with recurrent high-grade gliomas have a dismal outcome with a median progression-free survival (PFS) of 3 months. No chemotherapy regimen has been clearly shown to yield a survival advantage. Adults with recurrent high-grade gliomas treated with irinotecan and bevacizumab had a 63% response rate and a median PFS of 23 weeks in a recent publication. There is no published pediatric data on response rates in patients with high-grade glioma treated with irinotecan, bevacizumab, and temozolomide.

METHODS: We retrospectively reviewed the records of seven children less than 21 years of age with recurrent or progressive WHO grade III-IV gliomas who were treated with irinotecan, temozolomide, and bevacizumab.

RESULTS: Five patients had grade III glioma (anaplastic astrocytoma) and two had grade IV glioma (glioblastoma multiforme). Five patients had a partial surgical resection and two patients had a gross total resection at presentation. Prior treatment included irradiation for six patients and temozolomide for 5–9 months in all patients. Additional chemotherapy that was used in different patients included CCNU, carboplatin, vincristine, irinotecan, etoposide, and myeloablative chemotherapy with autologous hematopoietic stem cell rescue. Five patients developed recurrent disease and two patients developed progressive disease (PD) on these therapies,

which consisted of contrast-enhancing lesions in four patients and non-contrast-enhancing lesions on magnetic resonance imaging (MRI) (confirmed by MR spectroscopy) in three patients. The recurrence was local in three patients, distant in one patient, and distant and local in one patient. These patients were then treated with salvage therapy with temozolomide (50–75 mg/m² daily for 5 days repeated every week), irinotecan (20 mg/m² daily for 5 days a week for 2 weeks repeated every month in one patient or 125 mg/m² given either once every 2 weeks or weekly for 4 weeks in six patients) and bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) for 4–73 weeks. There was one complete response and one mixed response (contrast-enhancing disease resolved but a new distant non-enhancing lesion developed). Two patients continued to have stable disease at 49 weeks and 73 weeks, respectively. Three patients had progression without any response. The median PFS time was 10 weeks. Contrast-enhancing disease responded or remained stable in four patients, whereas non-enhancing disease progressed in all four patients. New distant non-contrast-enhancing lesions developed in three patients while receiving this therapy. Side effects included hypertension in one patient due to bevacizumab, diarrhea in four patients due to irinotecan, vomiting in three patients, grade 3 neutropenia in one patient, and grade 1 thrombocytopenia in one patient.

CONCLUSION: This regimen was tolerated well. The PFS time in our cohort is much shorter than what has been reported in adults. **Similar to the adult data, there was effective suppression of contrast-enhancing disease, absence of responses in non-contrast enhancing disease, and development of distant non-contrast-enhancing recurrences on this regimen.**

MA-69. FEASIBILITY AND TOLERABILITY OF BEVACIZUMAB IN 16 PEDIATRIC PATIENTS WITH INTRACRANIAL TUMORS

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BACKGROUND: Bevacizumab (BV), a monoclonal antibody against vascular endothelial growth factor (VEGF), has proven anti-cancer activity in a number of solid tumors. Regarding intracranial tumors, concern exists with respect to intratumoral hemorrhage associated with BV. We report the tolerability and feasibility of a compassionate use of BV treatment in 16 pediatric patients with intracranial tumors.

PATIENTS AND METHODS: We retrospectively analyzed 16 children (11 male, 5 female) with intracranial tumors. The diagnoses were glioblastoma WHO[°]IV (1), diffuse intrinsic pons glioma (1), medulloblastoma (2), supratentorial primitive neuroectodermal tumor (2), anaplastic astrocytoma WHO[°]III (1), anaplastic ependymoma WHO[°]III (1), atypical teratoid rhabdoid tumor (1), CNS non-germinomatous germ cell tumor (1), pilomyxoid astrocytoma (2), pilocytic astrocytoma (2), clear cell meningioma (1), and metastatic alveolar soft part sarcoma (1). Except for one patient (no parental consent for chemotherapy), all patients received BV for recurrence/progression of their disease. The median age at the start of BV treatment was 9.6 years (range, 1.5–18). The dose ranged from 5 to 10 mg/kg (median, 8.18) and was administered intravenously every 2–4 weeks. A total of 255 BV courses were administered (median per patient, 16; range 2–46). Except for one, all patients received additional chemotherapy or oral four-drug anti-angiogenic metronomic therapy concomitant to BV.

RESULTS: BV was well tolerated by most of our patients. Although all patients had large tumors ranging in size from 2.5 cm to 8 cm in diameter, no thrombosis or

intratumoral hemorrhage occurred. BV-related adverse effects were observed in 8 of 16 patients and consisted of severe hypertension requiring discontinuation of BV followed by antihypertensive treatment for 4 months (1), mild hypertension (2), moderate proteinuria (1), mild proteinuria (2), and impairment of wound healing (2).

CONCLUSIONS: In contrast to reports in adult patients with high-grade gliomas, no tumor hemorrhage was observed in any of our 16 pediatric patients. However, further prospective studies with more patients are warranted.

MA-73. BEVACIZUMAB IN COMBINATION WITH TEMOZOLOMIDE AND RADIATION THERAPY FOLLOWED BY BEVACIZUMAB, TEMOZOLOMIDE, AND IRINOTECAN FOR NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME

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BACKGROUND: Adding temozolomide to radiation therapy improves the survival of patients with glioblastoma multiforme (GBM). However, most patients die within 2 years of diagnosis. The combination of bevacizumab and irinotecan has demonstrated activity and acceptable toxicity in recurrent GBM. This study aims to improve the survival of newly diagnosed GBM patients by incorporating an anti-angiogenic agent with radiation therapy and temozolomide and by adding a topoisomerase I inhibitor and an anti-angiogenic agent to temozolomide post-radiation therapy. Adding bevacizumab and irinotecan may overcome the resistance mediated by MGMT.

METHODS: Patients receive standard radiation and temozolomide at 75 mg/m²/day, with bevacizumab at 10 mg/kg every 14 days beginning a minimum of 28 days post-operatively. Following the completion of radiation therapy, patients receive six cycles of bevacizumab, temozolomide, and irinotecan. Each cycle is 28 days. Bevacizumab is given at a dose of 10 mg/kg on days 1 and 15, temozolomide at 200 mg/m² on days 1–5, and irinotecan at 125 mg/m² for patients not on an enzyme-inducing antiepileptic drug (EIAED) and 340 mg/m² for patients on an EIAED on days 1 and 15.

RESULTS: Forty-six of the planned 75 patients have been enrolled between August 15, 2007, and May 12, 2008. Thirty patients have completed radiation therapy. No patient had to stop radiation therapy. Two patients developed grade 3 and another patient grade 4 thrombocytopenia necessitating holding the temozolomide. Four patients had a deep venous thrombosis requiring anti-coagulation. There were no other grade 3 or 4 toxicities, including no wound dehiscence during radiation and for 2 weeks afterwards. Twenty-seven patients are currently receiving bevacizumab, temozolomide, and irinotecan. Two patients developed grade 3 or 4 thrombocytopenia and one grade 3 neutropenia. There was one grade 1 wound dehiscence requiring holding the bevacizumab for two doses. There have been four progressions, two of whom died. Two other patients withdrew consent; one citing severe fatigue and the other had grade 3 diverticulitis. There have been no toxic deaths.

CONCLUSION: Adding bevacizumab to temozolomide and radiation therapy and temozolomide with irinotecan is tolerable. Further follow-up is required to determine whether the goal of 60% overall survival at 16 months is met.

MA-79. BEVACIZUMAB IS ACTIVE AS A SINGLE AGENT AGAINST MALIGNANT GLIOMAS: A CASE SERIES

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Bevacizumab is a humanized monoclonal antibody designed to inhibit VEGF. Fourteen adult patients with grades III and IV malignant gliomas were divided into three groups. Group A (n 5 7) received bevacizumab only, group B (n 5 7) received bevacizumab and salvage chemotherapy, and group C (n 5 6) included patients in groups A or B with multiple recurrences who received salvage chemotherapy before bevacizumab. Tumor response and progression were evaluated by serial magnetic resonance imaging of the brain. All patients in group C showed tumor progression within 3 months. On the other hand, 57% and 43% of patients in groups A and B, respectively, showed no progression at 6 months. Furthermore, 29% of patients in groups A and B showed a complete radiological response, defined as a less than 1-cm enhancement in all three dimensions. None of the patients developed intracranial hemorrhage. **We concluded that bevacizumab is active as a single agent against malignant gliomas. Possible additional benefits from chemotherapy may be below the resolution of this study.**

MA-80. INITIAL EXPERIENCE OF BEVACIZUMAB AND IRINOTECAN FOR DIFFUSE BRAINSTEM GLIOMA

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INTRODUCTION: Brainstem gliomas have been reported to make up 2.4% of all intracranial tumors in adults. Common clinical presentation can be summarized as constituting a triad of cranial nerve deficits, long tract signs, and ataxia. Magnetic resonance imaging (MRI) is the diagnostic test of choice, and typically, biopsy and/or surgery are not required to diagnose or treat diffuse intrinsic pontine or tectal gliomas. Brainstem gliomas have relatively poor prognoses with an overall median survival time of 44 to 74 weeks. The best results have been attained with hyperfractionated focal radiation therapy, which is the cornerstone of treatment. The role of chemotherapy for typical brainstem gliomas upfront or at relapse is unclear. Recently, there have been published reports on the use of irinotecan and bevacizumab for patients with recurrent supratentorial malignant gliomas showing significant radiographic response with improved progression-free survival. In this paper, we report our experience with irinotecan and bevacizumab in a patient with diffuse brainstem glioma.

METHODS: We reviewed the medical record of a 43-year-old woman with diffuse brainstem glioma from the Hermelin Brain Tumor Center Database. She presented in 2006 with progressive headaches, hoarseness, dysphagia, and ataxia. An MRI scan with gadolinium demonstrated a diffusely enlarged pons extending into the medulla with minimal area of contrast enhancement. Biopsy was not recommended, and she was treated with fractionated radiotherapy for 54 Gy concurrent with temozolomide. She was maintained on temozolomide given five times daily on a 28-day schedule. Post-radiotherapy MRI showed progression with note of increased FLAIR signals.

She was started on adjuvant temozolomide but was discontinued after one cycle because of progressive clinical decline. The patient was then started on irinotecan and bevacizumab given intravenously once every 2 weeks.

RESULTS: The patient was noted to have shown objective clinical improvement of her symptoms after only two treatments. She was seen at this time with mild clinical improvement. The patient can now slowly ambulate with improving dysphagia but with persisting diplopia. An MRI scan showed slight worsening with development of new enhancement in the brainstem. However, we elected to continue treatment on the basis of her improving clinical status. She continued to show dramatic clinical improvement with the treatment. Eight months after starting treatment, the patient complained only of intermittent diplopia and is independent with all daily activities. An interval MRI scan showed continuing decreased FLAIR signals as well as the degree of contrast enhancement. Irinotecan was discontinued after eight cycles because of fatigue and neutropenia. Bevacizumab was continued as the single agent with note of continuing radiographic response and stable clinical status. Bevacizumab was electively discontinued 1 year after starting treatment. A recent MRI scan showed no evidence of progression. The patient is doing well with no new neurologic symptoms.

DISCUSSION: Conventional chemotherapy appears to be ineffective in diffuse pontine gliomas. The reason for the lack of response to even high-dose chemotherapy is unknown. It may be due to poor blood-brain barrier penetration, innately resistant tumors, and a multidrug resistance-like brainstem pump. At present, however, there is no proven effective chemotherapy for diffuse pontine glioma. The decision to treat this patient with bevacizumab and irinotecan was based on her declining clinical status and the positive experience with the use of this combination drug for patients with supratentorial malignant gliomas. In this patient, we observed clinical benefit and sustained radiographic response typically seen among patients with supratentorial malignant gliomas.

CONCLUSION: Bevacizumab and irinotecan may have a role in the treatment of patients with diffuse brainstem glioma.

MA-83. SAFETY AND EFFICACY OF BEVACIZUMAB AND METRONOMIC, ORAL ETOPOSIDE FOR RECURRENT GLIOBLASTOMA PATIENTS IN A PHASE II STUDY

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BACKGROUND: Bevacizumab, a neutralizing VEGF monoclonal antibody, has significant single-agent anti-tumor activity among recurrent glioblastoma (GBM) patients, which is enhanced by concurrent chemotherapy. In addition to direct cytotoxicity, protracted, daily (metronomic) chemotherapy may exert an anti-angiogenic effect. We performed a single-arm, phase II study to evaluate the efficacy of bevacizumab and metronomic, oral etoposide, a topoisomerase II inhibitor, in patients with recurrent GBM.

METHODS: The primary endpoint was 6-month progression-free survival. Radiographic response and safety were secondary endpoints. Etoposide was orally administered daily at 50 mg/m² for 21 days followed by a 7-day rest. All patients received 10 mg/kg bevacizumab intravenously every 2 weeks. Key eligibility criteria included age of 18 years or older, KPS of 60 or higher, and more than 4 weeks from prior surgery, XRT, or chemotherapy. Patients with either more than three prior

progressions, requirement for therapeutic anti-coagulation or acute hemorrhage on pre-treatment imaging were excluded.

RESULTS: Twenty-five recurrent GBM patients with a median of two prior progressions were enrolled. Fatigue (33%, grade 2) and neutropenia (33%, grade 2; 26%, grade 3; 3%, grade 4) were the most common toxicities. Serious events included grade 4 thrombosis in two patients (6%) and grade 4 neutropenia in one patient. One patient experienced an asymptomatic (grade 2) central nervous system hemorrhage. With a median follow-up of 47 weeks, the 6-month progression-free survival rate was 44% (95% CI, 26–62%). Seven patients (26%) achieved a radiographic response, 19 (70%) achieved stable disease, and one (4%) progressed.

CONCLUSIONS: Among heavily pre-treated recurrent GBM patients, the combination of bevacizumab and metronomic etoposide is safe and associated with encouraging survival and radiographic response.

MA-92. RADIOGRAPHIC CHARACTERISTICS OF BEVACIZUMAB-TREATED MALIGNANT GLIOMAS

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BACKGROUND: In phase II clinical trials, bevacizumab has demonstrated efficacy in the treatment of recurrent malignant gliomas. This monoclonal antibody could induce tumor regression on contrast images of magnetic resonance imaging (MRI), but clinical observations suggested that an increase in hyperintensity on FLAIR or T2 signals may occur before progression on contrast sequences.

OBJECTIVE: To retrospectively review the serial imaging characteristics of recurrent malignant glioma treated with bevacizumab-based therapy at Columbia University Medical Center between 2005 and 2008.

METHODS: Fifty-six patients treated with bevacizumab-based therapies were reviewed for clinical and imaging responses and outcomes. Pre- and post-treatment brain MRIs were reviewed using volumetric measurements. The RECIST criteria were used to measure radiographic response.

RESULTS: Our study cohort included 37 men and 19 women. The median age was 58 years. Forty-one of the 56 patients had progression of disease by the study cut-off date. The median follow-up time was 18 months. Sixty-eight percent of patients received at least one dose of concurrent cytotoxic chemotherapy, including 66% who were treated with CPT11 and 2% treated with temozolomide. The median duration of response to bevacizumab was 18.8 weeks. After two cycles of bevacizumab, there was a 43% response rate (19% with a greater than 50% decrease in tumor size, 25% with a 25–50% decrease), and 50% of patients had stable disease. All patients had a response on FLAIR signal (28% with greater than 50% and 53% with 25–50%). Of 28 patients who had progressed and had scans available for review, 17.9% had evidence of an increase of hyperintensity on T2 or FLAIR imaging at least 2 months before progression of disease defined by contrast scans. This increase in FLAIR hyperintensity occurred at least 4 weeks before the development of neurological symptoms in 80% of these patients. Overall, the 6-month progression-free survival rate was 35.2%, and the 6-month overall survival rate was 68%. The median overall survival time was 18 months. Patients who exhibited progression on FLAIR images first had a median survival time of 16 months, whereas patients who had concurrent progression on contrast and FLAIR images had a median survival time of 27 months.

DISCUSSION: This series showed that an increase in FLAIR hyperintensity may herald clinical and contrast imaging progressions. Our results suggested that the survival of those who first progressed on FLAIR may be shorter, but a larger study cohort is necessary for formal analyses. This unique pattern of progression may suggest aggressive proliferation of invasive tumor behind an intact blood-brain barrier, or it could signify an early increase of tumor-related edema.

MA-94. THE RISK OF RECURRENT DEEP VENOUS THROMBOSIS/PULMONARY EMBOLUS (DVT/PE) AND THE SAFETY OF THERAPEUTIC ANTICOAGULATION FOR DVT/PE IN GLIOMA PATIENTS RECEIVING BEVACIZUMAB BASED THERAPY: THE CENTRAL NEURO-ONCOLOGY GROUP (CNOG) EXPERIENCE

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BACKGROUND: Bevacizumab is an important treatment option for gliomas and possibly for cerebral radiation necrosis. Bevacizumab administration is associated with a small risk of deep venous thrombosis and pulmonary embolus (DVT/PE) and bleeding, including intracranial hemorrhage (ICH). Of concern is whether the risk of ICH from bevacizumab is increased when therapeutic anticoagulation (AC) is concurrently administered to treat glioma patients with a DVT/PE and whether bevacizumab administration is associated with recurrent DVT/PE.

METHODS: We retrospectively reviewed our experience of glioma patients treated with bevacizumab who also had a DVT/PE managed with therapeutic AC. We determined the frequency of recurrent DVT/PE and of bleeding, including ICH.

RESULTS: Eighteen patients were diagnosed with DVT/PE during (10) or before (8) bevacizumab treatment and were treated with therapeutic AC while bevacizumab was continued. Bevacizumab doses were 10 mg/kg (16) or 5 mg/kg (2) intravenously biweekly in each patient (range, 2–36 infusions). Bevacizumab was combined with chemotherapy in each patient. Low molecular weight heparin (LMWH) was the most commonly used AC. Bevacizumab and AC were given concurrently in 16 patients. In two others, LMWH was held temporarily before and after bevacizumab infusions. A vena cava filter was placed in two patients before bevacizumab administration. There were no recurrent episodes of DVT/PE at last follow-up. Bleeding during AC and bevacizumab administration included ICH, hemoptysis, epistaxis, and Mallory-Weiss tear (one each).

CONCLUSION: The combination of bevacizumab and therapeutic AC in this setting appears relatively safe. The rate of ICH does not appear to be higher than the natural history of this disease, but our numbers are too small to state this confidently. There were no instances of recurrent DVT/PE. Additional options to consider in this patient population for (a) prevention of ICH is temporarily holding AC around bevacizumab infusions, and (b) for prevention of PE, in those patients with DVT only, is placement of a vena cava filter, but the need for these is unproven.

PA-07. EXPRESSION OF PHOSPHORYLATED VEGFR2 RECEPTOR IN HIGH-GRADE GLIOMAS

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OBJECTIVE: Vascular endothelial growth factor (VEGFR) is a key mediator of angiogenesis in high-grade gliomas. It effects vascular proliferation mainly through binding to its tyrosine kinase receptor VEGFR-2. The goal of this study was to correlate the expression of phosphorylated (active) VEGFR-2 with overall survival and assess its utility as predictive biomarker in patients treated with anti-angiogenic therapy using bevacizumab.

MATERIALS AND METHODS: The study included 117 high grade glioma patients (anaplastic–12, glioblastoma–105), of which 29 underwent adjuvant treatment with bevacizumab-based therapy. Paraffin embedded tissue sections of all cases were stained with anti-pVEGFR2 antibody (Tyr1214; Neomarkers, Fremont, CA). Staining in endothelial cells and tumor cells was scored separately as either absent or present. Pertinent clinical data was collected from the participating institutions.

RESULTS: Focal or diffuse expression of pVEGFR2 was observed within tumor cells in 73/117 cases. In contrast, endothelia were positive for pVEGFR2 in 40/117 cases. The median overall and 1-year survival for the entire group were 14.6 months and 64%, respectively. The median survival in patients with pVEGFR2 expression in tumor alone, endothelia alone, or both were 13.6, 18, and 14 months, respectively (compared to 12 months in those without any pVEGFR2 expression;p5ns). In the subgroup of patients treated with bevacizumab, expression of pVEGFR2 was not predictive of overall survival.

CONCLUSION: We demonstrated that the VEGFR2 signalling cascade was activated not only in endothelial cells, but also in tumor cells in high grade glioma. This may indicate additional functions of the VEGFR2 signalling pathway besides angiogenesis. We found no correlation between pVEGFR2 expression in endothelial or tumor cells and overall survival. Studies on larger patient cohorts are needed to further evaluate the predictive value of pVEGFR2 expression in patients treated with bevacizumab.

PA-27. CONCERNS ABOUT ANGIOGENESIS INHIBITION AS TREATMENT FOR HIGH-GRADE ASTROCYTOMAS

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In contrast to the generally optimistic view of the potential of angiogenesis inhibitors as a treatment for GBM, we have come to realize, based on our preclinical and clinical experiences, that some unique features of GBM may impede antiangiogenic treatment. While the extensive central vascular part of GBM is responsive to angiogenesis inhibition, the invading and migrating tumor cells at the tumor rim seem far more resistant. Cooption of preexistent vessels by migrating tumor cells allows a

unique escape from antiangiogenesis treatment. Expression of VEGF-A by tumor cells is sufficient for Blood Brain Barrier (BBB) disruption, leading to edema and contrast enhancement on MRI. Vascular normalization by angiogenesis inhibitors has a marked effect on peritumoral brain edema, on symptoms of raised ICP, and on MRI contrast enhancement. In our clinic, recurrent and primary GBM patients showed impressive response to bevacizumab treatment. In total, 31 patients were treated, of which 90% showed some evidence of clinical or radiological improvement (T1, T2, FLAIR, DCEMRI, or DSC-MRI). Unfortunately, these effects were not lasting, due to the progression of invading and migrating tumor parts, as was documented by MRI and histological examination of resected tumor material and autopsy specimens from 4 of our bevacizumab-treated patients. Vessel cooption and tumor cell migration into the other hemisphere were observed in a bevacizumab-treated patient that died of GBM progression. **Although angiogenesis inhibition reduces edema and other symptoms quickly and strongly, the direct antitumor effects seem to be limited. In fact, in our murine models, the invasive GBM phenotype was even enhanced by angiogenic inhibitors. Additionally, restoration of the BBB by angiogenic inhibition may even antagonize antitumor treatment by reducing GBM drug penetration. Recently, we did prove this in mice treated with temozolomide and antiangiogenic treatment. In conclusion, the high vascularity of the brain, the infiltrative growth of GBM, and the BBB are unique features of this tumor type that give cause for concern about the role of angiogenesis inhibition as a treatment for GBM.**

RO-20. TREATMENT OF RADIATION NECROSIS WITH BEVACIZUMAB

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In 2007, we published a study of bevacizumab combinations in patients with high-grade gliomas and observed that those patients with radiation necrosis seemed to respond better than expected to VEGF depletion by bevacizumab (Gonzalez J, Kumar AJ, Conrad CA, Levin VA. *Int J Rad Oncol Biol Phys* 2007;67:323–326), with 8 of 8 patients with radiation necrosis improving with respect to a decrease in capillary permeability (Gd contrast enhancement), regional edema (T2 FLAIR), and daily dexamethasone requirement. From this study, we hypothesized that since radiation necrosis is associated with cytokine release and what appears to be the increased leakiness of small blood vessels, local VEGF release must be taking place. This led to our hypothesis that an anti-VEGF agent, such as bevacizumab, will reduce postradiation damage (necrosis) to the central nervous system and, hopefully, help limit neurological signs and symptoms due to radiation necrosis. To further support this contention and to determine the length of clinical and radiographic improvement following bevacizumab, we initiated a randomized placebo-controlled study that required 16 randomized patients. While we cannot present the results of a complete study at this time, we would like to present a spectrum of patients with radiation necrosis and their diverse MRI and clinical responses to bevacizumab and the implications of this therapy for future irradiated patients. Specifically, we present MRI data that includes axial T2*, diffusion tensor imaging with ADC mapping, coronal 3D T1 post-Gd, and DCE. In addition, we obtained a quality of life assessment (MDASI), neurological assessment, steroid dependency, and formal neurocognitive testing. Based on our results to date, we conclude that bevacizumab

is the most powerful modern treatment for radiation necrosis in the CNS, and its use deserves serious consideration.

RO-37. BEVACIZUMAB CHANGES LOCAL MICROVASCULAR PERFUSION OF GLIOBLASTOMA WITHIN 48 HOURS OF TREATMENT

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Data from human studies in gliomas have documented radiographic changes as early as 7 days after treatment with bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF). Dynamic CT perfusion is a valuable tool for assessing stroke, and its application to grade gliomas and to differentiate radiation necrosis from recurrent tumor is under investigation. We treated a 56-year-old man with recurrent glioblastoma using bevacizumab (10 mg/kg i.v.) and irinotecan (125 mg/m²) and assessed the patient's initial response to therapy with dynamic CT perfusion before therapy, at 24 hours, and at 48 hours. The parameters were cerebral blood volume (CBV, mL/100 g), cerebral blood flow (CBF, mL/100 g/minute), and mean transit time (MTT, second). The first region of interest (ROI1) was the contrast-enhancing area. The second ROI (ROI2) was peritumoral vasogenic edema. We drew mirror ROIs on the contralateral hemisphere as controls and to calculate relative values (rCBV, rCBF, and rMTT). ROI1 had higher rCBV, rCBF, and rMTT before treatment; all these variables decreased in 24 hours, and at 48 hours, rCBV decreased 48% and rCBF decreased by 38%. ROI2 had lower rCBV and rCBF and higher rMTT. At 48 hours after bevacizumab, rCBV increased 68% and rCBF more than 100%. rMTT increased in both ROIs at that time. **These results suggest that bevacizumab changes intra- and peritumoral perfusion as early as 24 hours after treatment. Such changes are evident visually on color maps as well as on quantification. Dynamic CT perfusion could be a useful tool to investigate the effect of antiangiogenic drugs in glioblastomas.**

RO-51. IMAGING GLIOBLASTOMA PROGRESSION DURING ANTI-VEGF THERAPY

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BACKGROUND: High-grade gliomas can infiltrate into normal brain parenchyma along white-matter tracts and perivascular spaces. Diffusion tensor magnetic resonance imaging (DTI) is sensitive to water diffusion along axonal fibers and can detect alteration in white matter. Infiltrative tumors decrease white-matter tract diffusion anisotropy secondary to peritumoral edema and tumor cells. However, edematous regions are not always infiltrated with tumor cells, and using fractional anisotropy (FA) can lead to a false estimate of tumor infiltration. Hence, reduction of vascular permeability and peritumoral edema by antiangiogenic agents may allow better delineation of infiltrative tumor and assessment of treatment response with sequential evaluation of FA.

METHODS: We retrospectively evaluated 10 patients with recurrent glioblastomas receiving bevacizumab therapy using serial assessments of precontrast T1-weighted, T2-weighted, T1-postgadolinium, and DTI MR imaging before and after bevacizumab treatment. Radiographic response assessment of treatment outcome was based on standard MacDonald criteria. We acquired DTI images with b51200, and 27 were diffusion gradient; we analyzed the DTI data using a custom program developed

using Matlab. Regions of interest (ROIs) were drawn, and FA values were obtained in the peritumoral fiber tracts surrounding the contrast-enhancing area. We calculated the relative anisotropy index (RAI) according to the method described by Price et al. (2003).

RESULTS: A total of 85 scans were analyzed, with the first postbevacizumab MRI scan performed between 6 and 8 weeks and the second one at approximately 12–16 weeks after the initiation of therapy (week 0). Patients with progressive disease demonstrated a reduction in the peritumoral RAI, those with stable disease had a slight decrease in the RAI, and partial responders had a borderline mixed response. However, the peritumoral RAI unequivocally increased in patients with a complete response. In this group, there was a significant correlation between the change from the baseline to the second posttreatment RAI measurement and duration on anti-VEGF therapy (Spearman -0.72 ; $P,0.05$). No association was observed in comparison to the first posttreatment RAI measurements.

CONCLUSION: Although this study evaluated a small number of patients, an unequivocal increase in RAI in complete responders suggested a relative lack of tumor infiltration in peritumoral white matter tracts and may serve as a prognostic factor. FA could be a sensitive measure of the type of response to antiangiogenic treatment and could be a useful tool for assessing tumor progression. DTI analysis could thus provide important information about tumor infiltration into peritumoral regions in patients on antiangiogenic therapy.