

Selected Brain Tumor Related Abstracts from ASCO 2008
(Edited by Hong Lan)
Summary Table

Term	Description
mPFS	medium progression free survival
PFS6	6-month progression free survival
mOS	medium overall survival
OS6	6-month survival rate
1yrOS	1 year survival rate
2yrOD	2 year survival rate
mTTP	medium time to progression

2008 Data

AbstractNumber	Treatment	NumberOfPatients	PatientCatagory	Outcome
13014	Accelerated RT/Temodar	28	New GBM	mPFS=6m, PFS6=48%, OS1yr=48%, OS2yr=8%.
2051	AMG-102	20	Recurrent GBM	Response rate = 30%
13010	Avastin + chemo	34	Recurrent GBM	PSF6=25%, mTTP=4m, mOS=7.5m.
2021	Avastin + CPT-11	35	Recurrent GBM	PFS6=43%, OS6=74%, 2yrOS=15%.
2023	Avastin + CPT-11	44	Recurrent GBM	mPFS=5.2m, mOS=9.0m.
13000	Avastin + CPT-11	54	Recurrent high grade glioma	mPFS=5m, mOS=9m.
2074	Avastin + daily Temodar	32	Recurrent GBM	Response rate = 75%
13008	Avastin + Tarcevar	25	Recurrent GBM	PFS6=24%; Response rate = 48%.
13007	Avastin 4 mg/kg	44	Recurrent GBM	Response rate = 84%; Median duration of PR =3m.
2011	CDX-110 + Temodar	21	New GBM with EGFRvIII	mPFS=16.6m, mOS not reached.
2017	cetuximab	55	recurrent high-grade glioma	mPFS=1.9m, mOS=5.0m, PFS6=10%, OS6=40%
2056	cetuximab + Avastin + CPT-11	32	Recurrent GBM	mTTP=6m; no better than Avastin + CPT-11
2077	cetuximab + RT/Temodar	17	New GBM	1yrOS=87%, PFS6=81%, PFS1yr=37%.
2005	Enzastaurin vs CCNU Phase III	397	Recurrent GBM	Enzastaurin not superior than CCNU
2079	Fotemustine	43	Recurrent GBM	PFS6=21%, mOS=6.0m.
2088	gefenitib + rapamycin	18	Recurrent GBM	Response rate = 44%
13018	Nimustine + teniposide	35	Recurrent GBM	PFS6=28%, mOS=7m, OS1yr=14%.
2067	Pre-radiation ACNU-CDDP	87	New GBM	mOS=16m,
2015	Sagopilone	38	Recurrent GBM	PFS6=9%.
2008	Switching Chemo with Avastin	44	GBM progressed on Avastin	mPFS=1.3m, PFS6=2%; not good at all
2014	Talampanel + RT/Temodfar	72	New GBM	mOS=17.9m.
2062	Tarceva + rapamycin	27	Recurrent GBM	Modest antitumor activity
2016	Tarceva + RT/Temodar	97	New GBM	Not better than RT/Temodar (disappointing)
2022	Temodar + VP-16	27	Recurrent GBM	"encouraging radiographic response"
2010	Temodar 50mg/m2 daily	120	GBM failing standard Temodar	PFS6=7%-35%.
2044	Temodar 7/7 + indomethacin	41	New GBM	mPFS=7.6m, PFS6=69%, 1ryOS=70%
2042	Vaccine to cytomegalovirus	21	New GBM	mOS>20m.

2007 Data

AbstractNumber	Treatment	NumberOfPatients	PatientCatagory	PSF6-Month	
12521	AP12009	95	RecurrentGBM	NotReported(18mOS21%-24%)	
2003	Avastin+CPT11	35	RecurrentGBM		43%
2077	Avastin+CPT11	27	RecurrentHighGradeGlioma		46%
2078	Avastin+CPT11	22	RecurrentGBM	NotReported(mTTP3months)	
2001	AZD2171	30	RecurrentGBM		28%
2002	EMD121947	81	RecurrentGBM		16%
2000	EMD121947+Temodar	52	NewGBM		65%
2005	Erlotinib	54	RecurrentGBM		12%
2024	Erlotinib+Carboplatin	20	RecurrentGBM	NotReported(mTTP15.2wks)	
2066	ICE	42	RecurrentGBM		37%
12508	ICE	32	RecurrentGBM		31%
2055	Imatinib+Hydroxyurea	30	NonProgressionGBM		60%
2056	Imatinib600mg	20	RecurrentGBM		52%
2032	Temodar150mg7/7	64	RecurrentGBM		44%
2031	Temodar150mg7/7vsDaily50mg	51	NewGBM	mPFS6.8monthfor150vs3.8monthfor50	
2067	Thalidomide+Procarbazine	18	RecurrentGBM	NotGood(mTTP2.1months)	
2004	Vorinostat	68	RecurrentGBM		23%

Enzastaurin (ENZ) versus lomustine (CCNU) in the treatment of recurrent, intracranial glioblastoma multiforme (GBM): A phase III study.

Abstract No: 2005

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2005)

Author(s): H. A. Fine, V. K. Puduvalli, M. C. Chamberlain, A. F. Carpentier, L. Cher, W. P. Mason, M. J. van den Bent, S. Hong, D. Thornton, W. Wick

Abstract: Background: ENZ, an oral serine/threonine kinase inhibitor, targets PKC and AKT pathways to induce tumor cell apoptosis and suppress proliferation and angiogenesis. This phase III, multicenter, open-label study compared efficacy and safety of ENZ vs. CCNU in patients (pts) with recurrent, intracranial GBM (WHO grade IV). Methods: Pts were stratified by age, KPS, and disease recurrence, and randomized 2:1 to receive 6-week cycles of 500 mg ENZ daily (1,125-mg loading dose day 1) or CCNU (100-130 mg/m² on day 1). Treatment continued until disease progression or occurrence of unacceptable toxicity. Assuming a 45% improvement in PFS of ENZ over CCNU, 397 pts were to be enrolled to provide 80% power to achieve statistical significance at a one-sided level of 0.025. Enrollment was terminated at 266 pts after a planned interim analysis for futility. Results: Pt (N=266) characteristics were balanced between arms. Median PFS [HR=1.28 (0.97, 1.70)], OS [HR=1.2 (0.88, 1.65)] and 6 month PFS rate were not different between arms. As of 12/18/07, 3 pts are on ENZ therapy for >1 year. Pts with KPS 90-100 had significantly better PFS and OS with CCNU compared to ENZ. The incidence of adverse events (AEs) was similar in both arms; however, 62% in the CCNU arm were drug-related vs 44% in the ENZ arm. Four pts discontinued ENZ due to drug-related serious AEs (erysipelas, aortic thrombosis, cerebral hemorrhage, and convulsion). Eleven (7%) pts on ENZ died (4 due to AEs, 1 of which was drug-related). In the CCNU arm, all 4 (5%) deaths were disease-related. Grade (Gr) 3-4 hematological toxicities were significantly higher for CCNU (p <0.001). No anemia, neutropenia, or leukopenia occurred on ENZ, and only 1 pt had thrombocytopenia vs. 21 on CCNU. There were no significant differences in grade 3-4 nonhematological toxicities between arms. Conclusions: ENZ had a better toxicity profile but was not superior to CCNU in pts with recurrent GBM.

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

Abstract No: 2008

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2008)

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

Abstract: 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.

The temozolomide RESCUE study: A phase II trial of continuous (28/28) dose-intense temozolomide (TMZ) after progression on conventional 5/28 day TMZ in patients with recurrent malignant glioma.

Abstract No: 2010

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2010)

Author(s): J. R. Perry, W. P. Mason, K. Belanger, P. Kavan, D. Fulton, J. Easaw, S. Kirby, D. Macdonald, C. Shields, J. Pouliot

Abstract: Background: The combination of radiation with temozolomide (TMZ) 75 mg/m² x 6 weeks + adjuvant TMZ 150-200 mg/m² given 5 days out of 28 (5/28) is the standard of care for glioblastoma multiforme (GBM). However, many patients (pts) progress during or after first-line therapy and second-line regimens are only modestly active. Continuous dosing and dose intensification decrease levels of O-6-methylguanine-DNA methyltransferase (MGMT), which has been associated with TMZ resistance. Altering the schedule of TMZ and dose intensification may re-induce chemosensitivity. Methods: After REB-approved informed consent, pts with high-grade glioma who failed the standard TMZ 5/28 adjuvant regimen received continuous dose-intense TMZ 50 mg/m² for 28 days out of 28 (28/28) for up to one year. The primary endpoint was 6-mo progression-free survival (PFS). The trial used a two-stage design in which at least 1 of the first 15 pts enrolled in each group needed to achieve 6-mo PFS before the next stage was initiated Results: 120 pts were enrolled at 11 centers. Patients were divided into four cohorts: GBM patients failing during the first 3-6 months of adjuvant therapy (B1); GBM patients failing after more than 6 months of therapy (B2); GBM patients who recurred after stopping treatment (B3); and anaplastic glioma pts (A). Median age overall was 52 yrs (25-73 yrs). The majority (66%) were male. ECOG performance status was 0 in 47%, and 1 in 53%. An interim analysis was performed on the first 60 patients. The 6-mo PFS rates were 23% (B1), 7% (B2), 35% (B3), and 53% (A). Nausea and vomiting was observed in less than 5% of patients. Other toxicities were rare. Progressive lymphopenia was observed in some pts but no related clinically significant events have been reported. Prophylaxis for Pneumocystis carinii pneumonia was not required. Conclusions: Continuous dose-intense TMZ 50 mg/m² given on a 28/28 day schedule is active and well tolerated after failure of the conventional 5/28 day regimen. Efficacy compares favorably to other commonly used second-line agents. Continuous dose-intense TMZ may represent an ideal regimen for use in combination with other agents such as the new targeted therapies.

Effect of EGFRvIII-targeted vaccine (CDX-110) on immune response and TTP when given with simultaneous standard and continuous temozolomide in patients with GBM.

Abstract No: 2011

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2011)

Author(s): J. H. Sampson, G. E. Archer, D. D. Bigner, T. Davis, H. S. Friedman, T. Keler, D. A. Mitchell, D. A. Reardon, R. Sawaya, A. B. Heimberger

Abstract: Background: Conventional therapies for GBM fail to target tumor cells exclusively. Immunologic targeting of tumor-specific gene mutations may allow more precise eradication of neoplastic cells. The epidermal growth factor receptor variant III (EGFRvIII) is a consistent and

immunogenic mutation that is not expressed in any normal tissues, but is widely expressed in GBMs and other neoplasms making it an attractive target for active immunotherapy. Methods: A phase II multicenter clinical trial was undertaken to assess the immunogenicity and efficacy of an EGFRvIII-specific peptide vaccine in patients with newly-diagnosed, EGFRvIII+ GBM in combination with simultaneous standard or continuous temozolomide (TMZ). After resection and radiation/TMZ (75 mg/m²/d), consecutive cohorts received subsequent monthly cycles of 200 mg/m² (N=13) or continuous 100 mg/m² (N=8) TMZ simultaneous with intradermal vaccinations with an EGFRvIII-specific peptide (PEPvIII) conjugated to keyhole limpet hemocyanin (KLH) until tumor progression or death. Results: 21 patients were enrolled. There was one allergic reaction, but no other SAEs. There were no significant differences in vaccine immunogenicity ($p > 0.999$; binomial proportions), PFS ($p = 0.7979$; log-rank), or OS ($p = 0.7728$; log-rank) between TMZ regimens. Although TMZ induced grade II lymphopenia in 53.8% of patients, the co-administration of TMZ with the EGFRvIII vaccine (CDX-110) results in strong sustained immune responses to EGFRvIII in 100% (95%CI: 0.72, 1.00) of evaluated patients. Median PFS was 16.6 months (95%CI: 9.1, 22.7). Median survival has not been reached. The survival of the vaccinated patients is better than a matched historical control group (14.3 months; 95%CI: 13.0, 16.2) ($p < 0.0001$; log-rank) and a subgroup treated with TMZ (15.2; 95%CI: 13.9, 20.5) ($p = 0.0078$) and is also equivalent to the results seen in patients vaccinated without simultaneous temozolomide ($p = 0.4108$; log-rank). Conclusions: CDX-110 peptide vaccination with standard of care temozolomide in patients with GBM appears very promising and is under investigation in a phase III, randomized clinical trial.

Phase II trial of talampanel in conjunction with standard radiation (RT) and temozolomide (TMZ) in patients with newly diagnosed glioblastoma (GBM).

Abstract No: 2014

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2014)

Author(s): S. A. Grossman, X. Ye, M. C. Chamberlain, T. Mikkelsen, T. T. Batchelor, S. Desideri, S. Piantadosi, H. A. Fine

Abstract: Background: Recent findings suggest that Ca²⁺-permeable AMPA receptors play a crucial role in the proliferation and mobility of GBM cells perhaps via activation of Akt. Talampanel is a well-tolerated, oral AMPA receptor inhibitor with good CNS penetration that has been studied in patients with refractory seizures and ALS. Methods: This NABTT CNS Consortium study was designed to estimate survival in adults with newly diagnosed GBM when talampanel was added to standard RT and TMZ and to estimate talampanel toxicity in this setting. RT and TMZ were administered as per the EORTC trial reported in 2005. Talampanel was initiated on the first day of RT, escalated from 35 to 75 mg tid in patients receiving enzyme inducing antiseizure drugs (+EIASD) and from 25 to 50 mg tid in -EIASD patients, and discontinued for toxicity or disease progression. Results: Seventy-two patients with newly diagnosed GBM were enrolled from 12/05 to 7/06. 17% were >70 years old, the median age was 60 (37-85), median KPS was 90 (70-100), and 23% had only a biopsy. Talampanel was well tolerated. Grade 3-4 potentially related toxicities included fatigue in 3 patients and febrile neutropenia, hypoxia, mucositis and rash each in 1 patient. Hematologic toxicity from TMZ (8 pts with neutropenia, 15 with thrombocytopenia) was split between + and - EIASD groups. To date, 42 of 72 pts (58%) have died. The median survival is 17.9 months (lower 95% confidence interval =14.5 months, upper yet undefined) with a minimum follow-up time of 18 months. The average time on talampanel was 5 months and 7 patients remain on talampanel for >19 months. Conclusions: Talampanel can be added to standard RT and TMZ without apparent added toxicity. The 17.9 month median survival in this 72 patient, multicenter study which contained elderly patients suggests that blocking AMPA receptors may be a useful strategy in GBM.

Updated survival data and a prognostic factor comparison with the EORTC study (median survival 14.6 months) will be presented.

Phase II trial of the epothilone analog sagopilone (ZK219477; ZK EPO) in patients with recurrent glioblastoma: Initial report of the EORTC study 26061.

Abstract No: 2015

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2015)

Author(s): R. Stupp, A. Tosoni, W. Taal, P. Hau, M. Campone, J. Gijtenbeek, M. P. Frenay, T. Gorlia, D. Lacombe, A. A. Brandes, on behalf of the EORTC Brain Tumor Group

Abstract: Background: Sagopilone is a fully synthetic analog of epothilone B. It inhibits microtubule depolarization and induces cell cycle arrest. Not a substrate for ABCB1, good penetration into normal brain is expected. In orthotopically implanted brain tumor models it has demonstrated antitumor activity. This early clinical trial aims at evaluating the efficacy of sagopilone in recurrent glioblastoma, the success rate as a composite of response or progression-free survival at 6 months [PFS-6] is the primary endpoint. Methods: Pts with measurable first recurrence or progressive disease after > 3 mo from the end of radiochemotherapy were eligible, if WHO performance status [PS] < 2, no significant co-morbidity and adequate hematological, liver and renal function tests. Sagopilone (16mg/m²) was administered as 3 h infusion every 3 wks. Response was assessed every 2 cycles (6 wks). Fleming's one stage design was selected assuming: P0, unacceptable success rate=8%; P1, target success rate=23%; if > 5 successes were observed in 35 evaluable pts, the drug would be considered interesting in this indication. Results: Between 12/2006 and 08/2007, 38 (36 eligible treated) pts from 7 institutions were enrolled: median age 57 yrs (range 20-76), PS was 0 in 14 pts, PS 1 in 17 pts and PS 2 in 6 pts. A total of 100 cycles were administered (median 2, range 1-6), main reason for treatment discontinuation was disease progression in 82%. Related toxicity (grade 3) was: leucopenia (2 pts), neutropenia (3 pts), fatigue (2 pts), neuropathy (1 pt). Grade 1 and grade 2 neuro-sensory toxicity was also reported in 35% and 5% of pts, respectively. No objective response was documented, 13 pts had disease stabilization as best response. Two pts achieved PFS-6, in 2 pts follow-up is too early. The current success rate is 5.7%, (95%CI 0.007-19.0), the actuarial PFS-6 is 9.4% (95% CI 2.5-22.0). Conclusions: The envisaged activity mark can not be reached. Hematotoxicity and neurosensory alterations are the main toxicities. Our results do not support further exploration of sagopilone at this dose and schedule in malignant glioma. This trial has been supported in part by an unrestricted grant of Bayer-Schering Pharma, Berlin, Germany.

A phase II trial (N0177) of erlotinib and temozolomide (TMZ) combined with radiation therapy (RT) in glioblastoma multiforme (GBM).

Abstract No: 2016

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2016)

Author(s): P. D. Brown, S. Krishnan, J. Sarkaria, W. Wu, P. Mischel, W. H. Yong, R. Arusell, R. B. Jenkins, J. C. Buckner, C. Giannini

Abstract: Background: EGFR amplification in GBMs is a common occurrence and is associated with treatment resistance. Erlotinib, a selective inhibitor of EGFR, was combined with TMZ and RT in a phase II trial for GBMs. Methods: Adult patients not taking enzyme-inducing anticonvulsants after resection or biopsy of GBM were treated with erlotinib (150 mg daily) throughout the treatment protocol until progression. Erlotinib alone was delivered for 1 week, then concurrent with TMZ (75 mg/m² daily) and RT (60 Gy), followed by up to 6 cycles of adjuvant TMZ (200 mg/m², daily x 5d, q28 d). The primary endpoint was survival at 1 year with a planned sample size of 93 patients. Results: 97 eligible patients were accrued with 8 patients

over 70 years old. By definition the primary endpoint was successfully met with over half the patients (61%) patients alive at 1 year and a median survival of 15 months. However, there was no sign of benefit when comparing N0177 with the radiation/TMZ arm of EORTC 26981: Recursive partitioning analysis (RPA) III 19 vs. 21 months, RPA IV 15 vs. 16 months, RPA V 8 vs. 10 months respectively (Mirimanoff JCO 2006). Presence of diarrhea and/or rash, EGFRvIII, p53, PTEN, combination EGFR and PTEN, and EGFR amplification status were not significantly ($p>.05$) predictive of survival. MGMT status was analyzable in only 27% of patients and was not predictive of survival probably due to small sample size. The median survival of patients older than 70 was 4.5 months ($p=0.001$). Grade 2+ rash (42%) and diarrhea (10%) were frequent adverse events. Conclusions: Although the primary endpoint was successfully met utilizing pre-TMZ era historic controls, there was no sign of benefit compared to TMZ era controls. Analyses of molecular subsets did not reveal cohorts of patients sensitive to erlotinib. Elderly patients did poorly even with combination therapy.

A multicenter stratified phase II study of cetuximab for the treatment of patients with recurrent high-grade glioma.

Abstract No: 2017

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2017)

Author(s): B. Neyns, J. Sadones, E. Joosens, F. Bouttens, L. Verbeke, J. F. Baurain, L. D'Hondt, C. Chaskis, A. Michotte, J. De Greve

Abstract: Background: An increased copy number and mutation of the epidermal growth factor receptor (EGFR) gene are frequently found in high-grade gliomas (HGG). We investigated the activity of the EGFR-blocking monoclonal antibody cetuximab for the treatment of patients (pts) with recurrent HGG following surgery, radiotherapy, and chemotherapy. Methods: Eligible adult pts were treated with cetuximab (400 mg/m² 2 h IV on d1 and weekly 250 mg/m² 1 h IV thereafter). Pts were stratified in 2 treatment arms according to the amplification status of the EGFR gene of their HGG (determined by fluorescence in situ hybridization on archival tumor material). Results: Between May 2005 and December 2007 a total of 55 pts with performance status 0-2 initiated treatment with cetuximab (28 pts with and 27 pts without an increased EGFR copy number, 17F/38M, median age 53 years [range 32-73]). Cetuximab was generally well tolerated. During a total of 689 treatment weeks the most frequent treatment-related adverse events were: skin toxicity (grade 2, n=12; grade 3, n=4), thrombocytopenia (grade 2, n=1; grade 3, n=2), confusion/diminished consciousness (grade 3, n=4 pt), lymphopenia (grade 4, n=1), infusion related allergic reaction (grade 2, n=1), intratumoral hemorrhage (grade 2, n=1), diarrhea (grade 2, n=1), and fatigue (grade 2, n=3). A dose reduction of cetuximab (to 200 mg/m² weekly) was necessary in 2 pts. After a median follow-up of 15 months, 11 pts are alive (5 are still receiving cetuximab) and 44 pts have died. The disease control rate was 35% (3 pts (5.6%) had a PR and 16 pts (29.6%) had SD) and 35 pts (64.8%) had PD. The median PFS was 1.9 months, median OS was 5.0 months. The 6-month PFS and OS rates were 10% and 40%, respectively. Whereas PFS was less than 5 months in the majority (n=49) of pts, a subgroup of 5 pts (9.2%) have a PFS on cetuximab of more than 9 months (range 9.5 to >16.5). No significant correlation was found between response, survival and EGFR copy number. Conclusions: Cetuximab as a single agent was safe and well tolerated in this population of pretreated patients with recurrent high-grade glioma. Durable disease control was observed in a small subgroup of patients. Mature results of this study will be available for presentation at the meeting.

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

Abstract No: 2021

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2021)

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

Abstract: 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.

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

Sub-category: Central Nervous System Tumors

Abstract No: 2022

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2022)

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

Abstract: 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.

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

Abstract No: 2023

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2023)

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

Abstract: 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<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.

Efficacy of a phase II vaccine targeting Cytomegalovirus antigens in newly diagnosed GBM.

Abstract No: 2042

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2042)

Author(s): D. Mitchell, G. E. Archer, D. D. Bigner, H. S. Friedman, D. Lally-Goss, J. E. Herndon, II, S. McGehee, R. McLendon, D. A. Reardon, J. H. Sampson

Abstract: Background: Conventional therapies for GBM fail to target tumor cells exclusively. Immunologic targeting of tumor-specific proteins may allow more precise eradication of neoplastic cells. The discovery (Cobbs, Harkins et al. 2002) and recent confirmation (Mitchell, Xie et al. 2007) that GBM, but not surrounding normal brain tissue, serves as a refuge for Cytomegalovirus (CMV) reactivation provides an unparalleled opportunity to subvert, as tumor-specific antigens, the highly-immunogenic viral proteins expressed by CMV. Methods: A phase II randomized, prospective clinical trial was undertaken to assess the immunogenicity and efficacy of targeting the immunodominant CMV integument protein, pp65, in patients with newly-diagnosed GBM using pp65-RNA transfected dendritic cells (DCs). After resection and radiation with concurrent TMZ (75mg/m²/d), patients received subsequent monthly cycles of TMZ (200 mg/m²) simultaneous with intradermal vaccinations and were randomized to receive an autologous lymphocyte transfusion (ALT) (3x10⁷/Kg) prior to vaccination. Subjects received vaccinations until there was evidence of tumor progression or death. Results: 21 patients were consented. 5 progressed during radiotherapy. There were no vaccine-related, reportable SAEs. TMZ therapy, however, induced grade 3 lymphopenia (500 cells/mL) in 70% of patients after the first TMZ cycle. After TMZ, immunosuppressive regulatory T cell (TReg)

(CD4+CD25++CD45RO+CD127- FOXP3+) levels increased from 5.2% (3.3-7.5) to 11.8% (6.9-13.8) (P=0.0004; paired t-test). One nearly complete response was observed. Median PFS was 12.5 months (CI95: 10.0, ∞). Overall median survival is undefined, but is >19.7 months. The group randomized to receive ALT has a significantly worse median survival (P=0.0354; log-rank). CMV-specific polyfunctional cellular and humoral immune responses are under evaluation, but preliminary results show that patients with GBM have CMV-specific immunologic deficiencies. Conclusions: CMV proteins may serve as novel, tumor-specific targets for immunotherapy in patients with GBM. Immunotherapy targeting CMV pp65 may improve survival and should be evaluated in randomized phase III trials.

Phase II study of AMG 102, a fully human neutralizing antibody against hepatocyte growth factor/scatter factor, in patients with recurrent glioblastoma multiforme.

Abstract No: 2051

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2051)

Author(s): D. A. Reardon, T. F. Cloughsey, J. J. Raizer, J. Laterra, D. Schiff, X. Yang, E. Loh, P. Y. Wen

Abstract: Background: The hepatocyte growth factor/scatter factor (HGF/SF) and its receptor c-Met are implicated in the pathogenesis of glioblastoma multiforme (GBM) through an autocrine pathway, potentially affecting cancer cell survival, invasion, migration, and angiogenesis. In this phase 2 study, AMG 102, a fully human, IgG2, neutralizing antibody that selectively targets HGF/SF, was administered to patients with recurrent GBM to assess its safety and efficacy. Methods: Patients with measurable disease and < 3 relapses or prior systemic therapies were treated with AMG 102 by infusion every 2 weeks (Q2W) until progression, intolerable adverse event, or consent withdrawal. The first 10 mg/kg cohort of 20 patients would be expanded to 40 patients if > 1 response (including minor responses) were observed at week 9. The primary efficacy endpoint is response rate by Macdonald criteria. Results: This report describes the first 20 patients who received AMG 102 at 10 mg/kg: 15 men, mean age 48 ± 12 years, mean 19 ± 10 months since diagnosis, median 2.5 (range, 1-3) prior systemic therapies. In 18 patients with available data, 1 patient had a confirmed partial response and remains on study after 227 days; 1 had a minor response but withdrew after 161 days due to peripheral edema. Two patients had stable disease; 1 withdrew after 219 days (peripheral edema), and the other withdrew after 88 days (deep vein thrombosis [DVT]); 14 patients had progressive disease. Five patients reported grade 3 or 4 treatment-related adverse events (AEs): peripheral edema (n = 2); hypophosphatemia (n = 3), and DVT (n = 1). Grade 1 or 2 treatment-related AEs reported in > 2 patients included nausea (n = 3), diarrhea (n = 2), fatigue (n = 5), dyspnea (n = 2), and dry skin (n = 2). No treatment-related deaths were reported. The dose cohort was opened to the next 20 patients at 10 mg/kg. Conclusions: AMG 102 appeared to be well tolerated at 10 mg/kg IV Q2W in this heavily pretreated population. These results, using a neutralizing antibody highly specific for HGF/SF, suggest that in patients with recurrent GBM, a subpopulation has disease that may be dependent on the c-MET:HGF/SF axis. The study is ongoing with 40 patients treated at 10 mg/kg IV Q2W.

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

Abstract No: 2056

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2056)

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

Abstract: 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.

Phase II trial of erlotinib plus sirolimus for recurrent glioblastoma multiforme (GBM).

Abstract No: 2062

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2062)

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

Abstract: Background: Erlotinib, an EGF receptor kinase inhibitor, has limited single-agent activity in recurrent GBM patients. The antiglioma activity of EGFR inhibitors is enhanced by inhibitors of the mammalian target of rapamycin (mTOR), such as sirolimus, in preclinical studies. Methods: This phase II study assesses the antitumor activity of erlotinib plus sirolimus among recurrent GBM patients. Eligibility criteria: histologically confirmed GBM; age >18 years; KPS > 70%; adequate hepatic, renal, and bone marrow function and lack of prior EGFR or mTOR-directed therapy. Patients not on enzyme-inducing anticonvulsants (EIAED; phenytoin, carbamazepine, oxcarbazepine and phenobarbital) receive 150 mg of erlotinib and 5 mg of sirolimus per day, while those on EIAED receive 500 mg of erlotinib and 10 mg of sirolimus per day. Patients are evaluated after every other 28-day cycle. The primary endpoint is 6-month progression-free survival. Results: To date 27 patients have enrolled with a median age of 53.2 years (range 39.9-69.1) and a median of 2 prior episodes of progressive disease (range, 1-3). Only 26% are on EIAED. Toxicities appear comparable for patients on and not on EIAED and most commonly include rash (grade 3, 8%; grade 2, 30%), nausea/emesis (grade 3, 4%; grade 2, 15%), mucositis (grade 2, 19%, grade 3, 4%), diarrhea (grade 2, 4%; grade 3, 7%) and hyperlipidemia (grade 2, 7%). There have been no grade 4 or 5 attributable events. Three patients discontinued therapy due to toxicities including persistent grade 2 thrombocytopenia (n=1) and grade 2 diarrhea/rash (n=2). Best responses to date include stable disease (n=9, 33%) and progressive disease (n=13, 48%). Four patients (15%) are too early and one patient is lost to follow-up. Four patients with stable disease continue on study therapy after 6, 2 (n=2) and 1 cycle, respectively. Conclusions: Combination of erlotinib and sirolimus has modest

toxicity and antitumor activity among unselected patients with recurrent GBM. Further accrual, treatment and follow-up are ongoing.

Pre-radiation chemotherapy with ACNU-CDDP in patients with newly diagnosed glioblastoma: A retrospective analysis.

Abstract No: 2067

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2067)

Author(s): C. Kim, J. Han, C. Park, S. Lee, D. Kim, S. Paek, D. Kim, D. Heo, I. Kim, H. Jung

Abstract: Background: We evaluated the benefit of pre-radiation chemotherapy with ACNU(nimustine) plus CDDP(cisplatin) for patients with newly diagnosed glioblastoma by retrospective analysis. Methods: A total of 151 patients were newly confirmed to have glioblastoma between January 2000 and December 2004. All patients underwent surgical resection; complete resection in 38(25.2%), incomplete resection in 73(48.3%), and biopsy in 40(26.5%). Pre-radiation chemotherapy using ACNU-CDDP was administered as an initial adjuvant management for 87(57.6%) patients (ACNU-CDDP group), radiation therapy was performed in 31(20.5%) patients (RT group) and the rest 33 (21.9%) patients were treated with other regimens or refused further treatment. Results: The median survival time was 13 months (95% CI, 11.29-14.71), and the overall survival rate was 54.0% at 1 year, 21.3% at 2 years. Difference of the median survival time between complete resection group and biopsy group, and between ACNU-CDDP group and RT group was significant (15.0 months vs 10 months, $p=0.028$; 16.0 months vs 12.0 months, $p=0.036$) in the univariate analyses. Even in the multivariate analysis, pre-radiation chemotherapy using ACNU-CDDP showed significant effect on survival prolongation (HR=0.628, $p=0.042$). Usage of temozolomide for adjuvant or salvage management also had independent significant positive effect on the survival (HR=0.511, $p=0.006$). Grade 3 and 4 hematologic toxicities occurred in 28 (32.1%) patient of ACNU-CDDP group. However, there was no treatment-related death. Conclusions: Pre-radiation chemotherapy with ACNU-CDDP as an initial management is independently beneficial in survival prolongation with tolerable treatment-related toxicities in patients with newly diagnosed glioblastomas.

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

Abstract No: 2074

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2074)

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

Abstract: 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.

Phase I/II study of cetuximab plus temozolomide as radiochemotherapy for primary glioblastoma (GERT)--Eudract number 2005-003911-63; NCT00311857.

Abstract No: 2077

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2077)

Author(s): S. E. Combs, D. Schulz-Ertner, C. Hartmann, T. Welzel, C. Timke, K. Herfarth, A. von Deimling, L. Edler, M. Platten, W. Wick, J. Debus

Abstract: Background: Glioblastomas (GB) are known to express high levels of EGFR; targeting of EGFR using cetuximab has proven to be a successful treatment. This phase I/II trial of radiochemotherapy (RCHT) with TMZ and cetuximab in patients with primary GB evaluates feasibility and toxicity. Methods: Seventeen patients with pathologically confirmed GB were included into this analysis. Radiotherapy (RT) is delivered with a median dose of 60 Gy, 5*2Gy/week. TMZ is prescribed concomitantly at a dose of 75mg/m², followed by 6 cycles of adjuvant TMZ. Cetuximab is applied as weekly infusions (loading dose 400 mg/m² on day 1, and concomitant with RT on days 8, 15, 22, 29, 36, 43 at 250 mg/m²). Fourteen patients were male and 3 patients were female. Median age at diagnosis was 48 years. Neurosurgical resections had been complete in 7, subtotal in 7, and a biopsy in 3 patients. O(6)-methylguanine DNA methyltransferase (MGMT) gene promoter methylation was investigated in the tumor tissue: 33% of the patients were MGMT-positive, and 66% were MGMT-negative. EGFR-analysis is currently being conducted. Treatment was initiated after a median of 15 days after primary diagnosis. Median follow-up time at the time of this analysis was 13 months. Results: RCHT with cetuximab is safe and well tolerated. Cetuximab-related side effects included acneiform rash. In one patient cetuximab infusions were discontinued after occurrence of bilateral pulmonary embolism in treatment week 7. One patient died in treatment week 4 after tumor progression and massive brain edema which could not be controlled by medication including high-dose steroids. In all other patients the scheduled 7 cycles of cetuximab could be applied. Overall survival (OS) was 87% at 12 months. No prognostic factors could be determined until now. Methylated MGMT was not associated with longer OS (p=0.22). Progression-free survival (PFS) was 81% at 6 months and 37% at 12 months. Methylated MGMT was not associated with longer PFS (p=0.59). No prognostic factors of PFS could be identified. Conclusions: Early data from trimodal therapy in GB patients with RT, TMZ and cetuximab indicate feasibility without an increased toxicity profile. PFS as well as OS appear to be very promising.

A phase II multicentric trial of fotemustine (FTM) in patients (pts) with recurrent/progressive glioblastoma after radiotherapy plus concomitant and/or adjuvant temozolomide: A GICNO (Gruppo Italiano Cooperativo di Neuro-Oncologia) study.

Abstract No: 2079

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2079)

Author(s): A. A. Brandes, A. Tosoni, E. Franceschi, E. Mazza, A. Santoro, M. Faedi, R. Labianca, R. Bertorelle, T. Perrone, E. Pesenti

Abstract: Background: No drug has yet been proven effective in patients with GBM at time of failure after standard radiotherapy plus concomitant and adjuvant temozolomide. Although nitrosoureas may be considered as the gold standard, no data are available in an homogeneously pre-treated population. Methods: Pts with recurrent/progressive GBM after > 3 mo from the end of radiochemotherapy received 3 weekly doses of FTM (75 mg/m² i.v.) followed, after a 5-week rest, by FTM (100 mg/m² i.v.) every 3 weeks for < 1 year; treatment

was suspended if disease progression or unacceptable toxicity was observed. The main endpoint was to ascertain progression-free survival at 6 months (PFS-6). According to Fleming's design, a sample size of 40 patients was planned assuming $P_0=0.10$, $P_1=0.25$, $\alpha=0.1$, $\beta=0.1$. Results: Between April 2005 and May 2006, 6 Italian GICNO network centers enrolled 43 pts (29 M, 14 F; median age 52 [range 34-68] years; median KPS 90, range 70-100). PFS-6 was 21% (SE 6.2%), 3 patients (7%) had partial response (PR), 15 (35%) disease stabilization (SD). Two out of 3 responsive pts are alive after 21 and 22.7 months, and 1 died after 15.5 months. Median survival time was 6 months (95%CI: 5-7). MGMT methylation status was determined in 34 pts (73.5%): 8 (23.5%) were methylated and 26 (76.5%) unmethylated. In methylated pts, disease control was significantly better than in unmethylated pts (75% vs 34.6%, $p=0.05$); however no significant difference in terms of PFS-6 and survival was observed. Grade 3-4 thrombocytopenia and neutropenia were observed in 25.6% and 30.2% of pts, respectively. Conclusions: The findings of this present trial, the first to analyze second-line nitrosourea treatment in a homogeneous population following standard treatment, may represent a new benchmark of nitrosourea activity. However, as disease control was not long-standing, alternative doses, schedules and drug-combinations should be evaluated in future studies. This trial has been supported by an unrestricted grant of Italfarmaco Pharmaceuticals, Milan, Italy.

A phase I trial of gefitinib and sirolimus in adults with recurrent glioblastoma multiforme (GBM).
Abstract No: 2088

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 2088)

Author(s): S. Phuphanich, J. Rudnick, R. Chu, J. S. Yu, K. L. Black

Abstract: Background: Glioblastoma multiforme (GBM) overexpresses the epidermal growth factor receptor (EGFR) and gefitinib is an EGFR tyrosine kinase inhibitor (TKI). The protein mammalian target of rapamycin (mTOR) also promotes GBM growth and rapamycin blocks the interaction of mTOR with its target proteins. Therefore, the novel therapeutic approach by combination of gefitinib (iressa), and sirolimus (rapamycin) should have a synergistic effect in treating GBM. A possible mechanism of EGFR TKI resistance may be targeted by mTOR antagonists. The primary objective is to evaluate the safety, toxicity of gefitinib and sirolimus with a secondary end point of determining time to tumor progression, overall survival and quality of life in recurrent GBM. Methods: Eligible patients aged 18 years or older with recurrent GBM, who were treated previously with surgery, radiation, chemotherapy with or without immunotherapy (vaccine) and KPS > 40% are eligible. Gefitinib is dosed at 500 mg/day with those receiving dexamethasone or enzyme inducing anti-epileptic drugs (EIAED) escalated to 1,000 mg/day. Sirolimus is dosed at 2 mg/day and adjusted to levels of 4-12 nanograms/ml. They were co-administered on a continuous oral daily dosing. Neurological exam, KPS, laboratory parameters and NCI CTC are initially obtained every 2 weeks and then monthly. MRI scans of the brain and FACT-Br are performed every two months. Results: To date 21 patients have enrolled and 18 are evaluable. There are 13 male and 5 female with a median age of 51.6 years (range 23-72 years), a median KPS of 60% (range 50-80%) and 12 patients were on EIAED. Diarrhea, rash and mucositis were the most common toxicities as expected. There were 3 patients with grade 3/4 non-hematological toxicities with rash, renal failure, hypotension, dyspnea, coagulopathy, and elevated LFT. One patient developed wound infection which was not related to these drugs. There were 2 (11%) minor response and 6 (33%) stable disease (range 1-18 months) with a clinical benefit of 44%. Conclusions: Oral daily co-administration of gefitinib and sirolimus is safe, tolerable in this heavily treated group of patients with modest antitumor activity. The median progressive free survival time and time to tumor progression is to be determined.

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

Abstract No: 13000

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 13000)

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

Abstract: 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.

A phase II trial of sunitinib in patients with recurrent high-grade glioma.

Abstract No: 13001

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 13001)

Author(s): C. Chaskis, J. Sadones, A. Michotte, M. Dujardin, H. Everaert, B. Neyns

Abstract: Background: High-grade gliomas (HGG) are characterized by neoangiogenesis and disruption of the blood-brain barrier. KIT, PDGFR- α and VEGFR2 are commonly amplified in HGG and represent an attractive therapeutic target. Sunitinib is a small molecule that inhibits the VEGFRs, FLT1, FLK1/KDR, PDGFR-a and -b, c-Kit, the FLT3 and RET kinases. We evaluated the effect of sunitinib in patients (pts) with recurrent HGG. Methods: Pts received a continuous oral daily dose of 37.5 mg sunitinib. Glioma dimensions, CNS edema and tumor perfusion were assessed by T2 and T1w(\pm Gd) MRI images. Cerebral blood flow (CBF) in the glioma and contralateral white and grey matter was assessed by T1-DCE- and T2*-DSC-based perfusion; lesion-to-normal-white matter CBF ratios (CBFr) were obtained. Uptake of 2-¹⁸F-Fluoromethyl-L-Phenylalanine was assessed by PET (FMP-PET). Results: Twelve pts have been enrolled since 1 July 2007 (median age 46 (range 36-71), M/F 10/2, KPS 90-80: 6 pts, 70-60: 6 pts). All pts had recurrent disease following surgery, radiation therapy and temozolomide. Initial diagnosis was low-grade glioma in 4 pts, anaplastic oligo-astrocytoma in 1 pt and glioblastoma in 7 pts. A total of 50 treatment weeks (range 2-15; 10 pts) were evaluated for toxicity. Worse toxicity per pt included febrile neutropenia (gr3, n=1; gr4, n=1), afebrile neutropenia (gr2, n=1), fatigue (gr2, n=2), thrombocytopenia (gr2, n=2; gr3, n=1), lymphopenia (gr3, n=1; gr4, n=1), elevated AP and GGT (gr2, n= 1), and hypertension (gr2, n=3). Hematological toxicity necessitated a dose reduction to 25 mg/day in all 3 pts who continued treatment beyond 4 wks. Nine pts were evaluable for response. One pt experienced neurological improvement, regression on MRI with reduced activity on FMP-PET and remains on treatment after 15 weeks. Two pts have SD after 4w and continued therapy. Six pts had PD within the first

4 weeks of treatment. CBFr was reduced in 4 out of 6 pts that were evaluated at present. Conclusions: Sunitinib 37.5 mg on a continuous daily basis reduces the CBFr in a majority of patients with recurrent high-grade gliomas. Tumor regression is less frequently observed. Hematological toxicity necessitated a dose reduction to 25 mg/day in a significant proportion of patients.

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. Abstract No: 13007

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 13007)

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

Abstract: 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.

Phase II study of bevacizumab and erlotinib in patients with recurrent glioblastoma multiforme. Abstract No: 13008

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 13008)

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

Abstract: 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.

Accelerated radiotherapy and temozolomide in adults with newly diagnosed glioblastoma multiforme: A pilot study.

Abstract No: 13014

Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 13014)

Author(s): D. N. Korones, M. Milano, P. Okunieff

Abstract: Background: Radiotherapy is the backbone of treatment for patients with newly diagnosed glioblastoma (GBM). Standard-of-care for this disease includes 6 weeks of once daily radiation to 60 Gy and temozolomide. We sought to improve upon this standard by intensifying the radiotherapy in conjunction with standard dosing of temozolomide. Methods: Patients were eligible for the study if they had newly-diagnosed GBM, were > 18 years of age, and had a WHO performance score of 0-2. Radiation was delivered in 1.6 Gy fractions twice a day, 6 hr between doses (4 weeks; total 64 Gy). The initial target volume included the contrast enhancing lesion and post-operative defect demonstrated on CT/MRI plus a 2.0 cm margin. All patients received temozolomide, 75mg/m²/d x 42 days during the 4 weeks of radiation and an addition 2 weeks beyond. A radiosurgery boost was allowed, but not required for patients with residual lesions < 4 cm. One month after completing the low dose temozolomide (6 weeks after radiation), patients received temozolomide, 200mg/m²/d x 5 days every 28 days for 12 cycles. Results: 28 patients have been enrolled, all with glioblastoma. Two patients stopped therapy due to fatigue following cycle 1 of post-radiation temozolomide. Median age was 57 years (34-77), and 82% were male. Four had a gross total resection, 14 subtotal resection, and 10 had only a biopsy. Only one patient had a radiosurgery boost. Of the 24 patients evaluable for response, 3 had a partial response, 17 had stable disease, and 4 had progressive disease. The median progression-free survival (PFS) was 5 mo (0-21 mo), and the 6 mo PFS was 44 %. Twelve of 25 (48%) evaluable patients were alive at 1 year, and only 2 of 25 (8%) at 2 years. Of the 26 MRI documented recurrences, 17 were local, 3 were outside the radiation field, 4 were satellite lesions, and one each was local + satellite lesion and local + an out-of-field recurrence. Study-related toxicity included one patient with prolonged cytopenia during low-dose temozolomide and one patient with varicella-zoster. Conclusions: We conclude that accelerated radiotherapy in conjunction with temozolomide does not result in a survival advantage for patients with newly diagnosed glioblastoma, and may be associated with an increased of out-of-field recurrences.

Nimustine plus teniposide in recurrent glioblastoma.

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Abstract: **Background:** There is no established standard chemotherapy for recurrent glioblastoma (GBM). In a previous trial (NOA-01), the combination of nimustine and teniposide showed efficacy in previously untreated GBM. After temozolomide has been established as the standard for primary therapy of GBM, nimustine and teniposide is now been used as a second or third line chemotherapy for recurrent GBM. However, there are no data on toxicity and efficacy of this regimen in recurrent GBM. **Methods:** In two neurooncological centers, all patients with recurrent glioblastoma who had received nimustine (90 mg/m², day 1/42) and teniposide (45-60 mg/m², days 1-3/42) chemotherapy were analyzed retrospectively for progression-free survival, overall survival and toxicity. **Results:** Thirty-five patients, median age 51 years (range 25-71), all of them pretreated with temozolomide were identified. The rate of progression-free patients at 6 months after initiation of therapy was 29%. The median overall survival after initiation of nimustine/teniposide was 7 months and 14% of patients survived 1 year or longer after diagnosis of recurrent disease. Grade 4 hematotoxicity according to the common terminology criteria for adverse events (CTCAE v 3.0) was observed in 12/35 patients (34%) and in 12/83 chemotherapy cycles (14%). No high-grade non-hematological toxicity was observed. **Conclusions:** These data support the efficacy of nimustine and teniposide combination chemotherapy in recurrent GBM. Nimustine and teniposide combination therapy is associated with a comparably high rate of high-grade hematotoxicity.