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Phase II trial of bevacizumab in combination with temozolomide and regional radiation therapy for up-front treatment of patients with newly diagnosed glioblastoma multiforme. A. Lai, P. Nghiemphu, R. Green, L. Spier, S. Peak, S. Phuphanich, L. Feltenzacher, T. Koleska, J. Poldi, T. Cloughesy; UCLA, Los Angeles, CA; Kaiser Permanente Southern California, San Diego, CA; Kaiser Permanente Northern California, Redwood City, CA; Cedars-Sinai, Los Angeles, CA; Kaiser Permanente, Vallejo, CA.

Background: Bevacizumab (BV) is a humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF). Based on the promising activity of BV in the treatment of recurrent glioblastoma, we are conducting a phase II trial to determine whether up-front treatment with newly diagnosed GBM with BV may be more advantageous than withholding BV until recurrence. In this trial, we evaluate the safety and efficacy of BV combined with standard of care radiation (RT) and temozolomide (TMZ) and radiation (RT) for newly-diagnosed GBM. Methods: This is a phase II trial with a 10-patient pilot and 60-patient expansion phases. Newly-diagnosed GBM patients with no prior treatments are eligible. Primary outcome measure is overall survival; the secondary outcome measure is TTP and 12-month survival. Therapy began between 3–5 weeks of surgery with BV (10 mg/kg every 2 weeks), TMZ (75 mg/m2 daily), and external beam RT (30 x 200 Gy) on the same day. After completion of radiotherapy, patients are then placed on a maintenance phase of BV (10 mg/kg every 2 weeks) and TMZ (150–200 mg/m2 5 out of every 28 days) until progression or 24 months in which patients are then maintained on BV only. Results: 70 of 70 projected GBM patients have been enrolled between August 2006 and November 2008 at UCLA and Kaiser Permanente (KP) (Northern and Southern California). All patients had resections to ensure that frozen tissue (~100 mg) was collected. The median age was 57.4 years (range 26–77). 57% of patients had KPS 80–100 and 43% KPS 70–79. Most frequent CTC grade 3–4 toxicities occurring in >5% of patients included ischemic stroke, pulmonary embolus, wound break down, bleeding/perforation, and renal dysfunction. Isolated cases of retinal detachment and optic neuropathy have also been observed. As of now, 35/70 patients are off study (26 due to progression and 9 due to SAE). Preliminary TTP by Kaplan-Meier analysis is promising compared to that of a UCLA/KP control group of patients that received the conventional RT/TMZ regimen. Conclusions: Addition of BV to the standard regimen of TMZ and RT for newly-diagnosed GBM is well-tolerated and shows promising efficacy. More detailed analysis of safety and efficacy will presented.

A phase II study of chemoradiation followed by adjuvant temozolomide and regional radiation therapy for up-front treatment of patients with newly diagnosed glioblastoma. A. M. Salazar, X. Ye, New Approaches to Brain Tumor Therapy: A CNS Consortium; University of Alabama at Birmingham, Birmingham, AL; Oncovir, Inc., Washington, DC; University of Pennsylvania, Philadelphia, PA; Cedars-Sinai Medical Center, Los Angeles, CA; University of Pennsylvania, Philadelphia, PA; University of Alabama at Birmingham, Birmingham, AL; Hospital of the University of Pennsylvania, Philadelphia, PA.

Background: Polyinosinic-polycytidylic (poly-ICLC), is a double-stranded RNA that stimulates a variety of host defense mechanisms including T-cell and natural killer cell activation, cytokine release and specific anti-viral and anti-filoviral properties. The objective of this study was to determine the safety and efficacy of poly-ICLC when added to adjuvant treatment for newly diagnosed glioblastoma. Methods: Newly diagnosed patients ≥ 18 years with histologically proven glioblastoma received standard external beam radiation with concurrent low-dose temozolomide (TMZ) (75 mg/m2) followed by adjuvant cycles of TMZ for 5 days (150–200 mg/m2) (week 1) then intramuscular injections of poly-ICLC (20 mcg/kg) 3 times a week (weeks 2–8; total 21 injections) with week 9 off and no limit to the number of adjuvant cycles (TMZ + poly-ICLC). Imaging evaluations were performed before each cycle. Results: There were 97 patients enrolled (60 men); median age 56 yrs (range 21–85); median KPS 90 (range 60–100). Fourteen patients did not start adjuvant treatment (5 patient request and 4 investigator withdrawal, 2 progressive disease, 1 death, 1 toxicity; 1 other). The most frequent CTC grade 3–4 toxicities occurring in >5% of subjects at least possibly related to poly-ICLC were leukopenia (20%), lymphopenia (14%), anemia (12%), nausea and vomiting (10%), and SGPT (9%) or alkaline phosphatase (7%) elevation. Two deaths during adjuvant treatment were considered unlikely related to poly-ICLC. To date 71 of 97 patients have survived at least 12 months from diagnosis. The estimated median survival for the entire cohort is 15.5–19.3 months. Overall survival for the cohort at 12 months was 73.2% (95% CI: 63%-82%) and at 18 months 47.4% (95% CI: 37–58%). For only those subjects 18–70 years old, overall survival at 18 months was 51.8% (95% CI: 41–63%). This is compared with EORTC 26981/22981 that reported an 18 month overall survival of 39.4% (95% CI: 33.8–45.1).

Conclusions: The addition of poly-ICLC to the standard regimen for newly diagnosed GB is well-tolerated. Survival data at 12 and 18 months suggest increased efficacy compared to chemoradiation with adjuvant TMZ only.
Background: Glioblastomas (GBM) frequently have EGFR amplification/mutations and inactivation of PTEN. Although single agent EGFR and mTOR inhibitors have limited activity, combinations of these agents may be more effective.

Methods: The North American Brain Tumor Consortium (NABTC) conducted a phase I/II study of erlotinib and temsirolimus in recurrent GBM. Eligibility criteria included histologically proven GBM and anaplastic gliomas (AG), radiologic progression, KPS ≥ 60, adequate bone marrow reserve, and organ function. There was no limit on the number of prior relapses for phase I and no more than two prior relapses for phase II. Patients must not be receiving enzyme-inducing antiepileptic drugs. The dose of erlotinib was 150 mg/d in phase I and titrated up to maximum of 200mg/d in phase II depending on tolerability. Patients initially received temsirolimus 50 mg i.v. once weekly and the dose adjusted based on toxicities. Escalation was performed in groups of three. MTD was defined as the dose with 1/6 or fewer patients with dose-limiting toxicities (DLTs). Primary endpoint for the phase II component was PFS6. Results: In phase I, 17 patients were enrolled (15 GBM; 2 AG); median age 54 years (26–74); median KPS 90 (range 60–100); median prior relapses 1 (range 0–3). The MTD was determined to be 150 mg of erlotinib daily combined with 15 mg of temsirolimus weekly. DLs were rash, mucositis, and liver function abnormalities. In phase II, 14 patients were enrolled (13 GBM; 1 AG); median age 47 years (20–72); median KPS 90 (range 60–100); median prior relapses 1 (range 1–3). Six patients discontinued therapy as a result of toxicities. For GBM patients, there was no PR, 30% SD, and PFS6 was 12.5%. For AG patients there was 12.5% PR, 12.5% SD, and PFS6 was 6.25%. Conclusions: The combination of erlotinib and temsirolimus was associated with a higher than expected incidence of toxicities and had minimal activity in recurrent MG.

2006

Oral Presentation, Sat, 3:00 PM - 6:00 PM

Phase I/II study of sorafenib and temsirolimus for patients with recurrent glioblastoma (GBM) (NABTC OS-02). Y. Y. Wen, T. Cloughesy, J. Kuhn, K. Lamborn, L. E. Abrey, F. Lieberman, T. T. Robbins, J. Wright, M. D. Prados, M. Gilbert; Dana-Farber Cancer Institute, Boston, MA; UCLA, Los Angeles, CA; UT, San Antonio, San Antonio, TX; DFCI, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; University of Pittsburgh Medical Center, Pittsburgh, PA; University of Wisconsin, Madison, WI; National Cancer Institute, Bethesda, MD; M. D. Anderson Cancer Center, Houston, TX

Background: The activity of targeted molecular therapy with single agents has been disappointing in GBM. Combination therapy simultaneously targeting both the PI3K/Akt/mTOR and the MAP kinase pathway may be more effective.

Methods: The North American Brain Tumor Consortium (NABTC) conducted a phase I/II study of sorafenib (VEGFR/PDGFR/raf inhibitor) in combination with temsirolimus (mTOR inhibitor) in recurrent GBM. Eligibility criteria included histologically proven GBM, radiologic progression, ≥ 18 yrs old, KPS ≥ 60, adequate bone marrow reserve, and organ function. There was no limit on the number of prior relapses for phase I and no more than two prior relapses for phase II. No enzyme-inducing antiepileptic drugs were allowed. Dose-finding was conducted using a 3+3 design and the MTD was defined as the dose with DLTs in 1/6 or fewer patients. The primary endpoint for the phase II component was PFS6 (p0 = 15%; p1 = 35%). A 2-stage design was used. If p ≤ 4 of the initial 19 patients achieved PFS6, an additional 14 patients would be accrued for a total of 33 patients. Results: In phase I, 17 patients were enrolled. Median age 50 years (35–69); median prior chemotherapy 1 (1–3). The initial doses were sorafenib 200 mg bid and erlotinib 100 mg q.d. The initial dose was 1/6 evaluable patients had a DLT (grade 3 thrombocytopenia). Other DLTs included transaminits, hypertension, hypophosphatemia, and increased lipase. Pharmacokinetic studies showed no alterations in sorafenib PK, but no accumulation of erlotinib, suggesting a drug-drug interaction with sorafenib altering erlotinib metabolism or clearance. In phase II, 19 patients were accrued to stage I. Median age 51 years (30–75); median prior chemotherapy 2 (1–3). Phase II toxicity and outcome data are not yet mature but will be available at the time of presentation. Conclusions: This combination was moderately well-tolerated. MTD was below other combination phase I studies. Sorafenib affected the PK of erlotinib preventing drug accumulation. Phase II toxicity and outcome data will be reported.

2007

Oral Presentation, Sat, 3:00 PM - 6:00 PM

Safety of bevacizumab in patients with metastases to the central nervous system. U. P. Rohr, S. Augustus, S. F. Lasserre, P. Compton, J. Huang; F. Hoffmann-La Roche, Basel, Switzerland; Genentech, Inc., South San Francisco, CA

Background: The background rate of CNS hemorrhage (CH) in cancer patients with brain metastases not receiving bevacizumab (BV) treatment is 5%–29%, depending on tumor type. Patients with CNS metastases were routinely excluded from most BV late-stage clinical trials, following the occurrence of CH without BV use. Available safety information in BV-treated patients with CNS metastases has been reviewed to determine whether the exclusion of these patients from trials is still justified. Methods: A retrospective exploratory analysis was conducted using safety data from three datasets: A) 13 randomized controlled phase II or III trials (RCTs); B) Two ongoing open-label trials MO19391 (ATHEMA) and MO19390 (SAIL). While patients with known CNS metastases, based on imaging or clinical signs and symptoms, were excluded from trial A and B datasets, patients who were found to have CNS lesions had either unrecognized CNS metastases at study entry or had developed these during the trial; C) 2 ongoing open-label studies AVF3752g and AVF3671g in patients with NSCLC, where inclusion of patients with treated CNS metastases was allowed. Incidence of CH in patients with brain metastases was quantified in each dataset. Results: A) In 13 RCTs, with a total of 8443 patients with locally advanced, unresectable, or metastatic breast, renal, pancreatic, colorectal cancer, or NSCLC, brain metastases were identified. Incidence of CH in patients with brain metastases was 1.2% (91/7533); CH in patients with CNS metastases, out of 3,252 patients with known CNS metastases, was 0.33% (11/3336). B) CH incidence was 0.35% (6/1749) in patients with brain metastases not receiving BV treatment during the trial.; C.) 2 ongoing open-label studies AVF3752g and AVF3671g in patients with NSCLC, where inclusion of patients with treated CNS metastases was allowed. Incidence of CH in patients with brain metastases was 1.2% (91/7533). Conclusions: The background rate of CH without BV use is low, and appears consistent with historical rates of CH in patients with primary and metastatic CNS tumors.
Biomarkers in tumor vasculature could provide novel targets for novel therapies. The combination of bevacizumab and irinotecan demonstrated increased survival and improved tumor control via a "normalized" tumor vasculature. Prior studies of this combination demonstrated high radiographic response and 6-month progression free (mPFS) rates. This study was designed to determine the efficacy and safety of this combination in recurrent GBM.

Results: Full enrollment (57) was achieved, median age was 57, median KPS was 80; all had prior radiation and temozolomide treatment. The 6m-PFS rate was 37% (95% CI: 24–50%), with 21 of 57 patients (37%) without progression after the first 6 months. The 1-year PFS was 26% (95% CI: 16–36). Treatment-related grade 3/4 toxicities included thrombocytopenia (17%), leucopenia (17%), and neutropenia (10.3%). Grade 3/4 hypertension (3.5%) was noted. A total of 39 patients (68%) had an experienced grade 3/4 hematologic toxicity. The 18% reduction in the daily dose resulted in a 19% decrease in the concentration of total gimatecan in plasma prior to administration of the fifth daily dose (56.00 ± 23.45 vs. 45.20 ± 20.96 mg/mL) and a 33% decrease in the AUC for dose 5 (8.01 ± 4.8 vs. 5.33 ± 4.2 mg·h/mL). Only one patient had a partial radiographic response by the modified Macdonald criteria and stable disease as the best response in 13 patients. All other patients had progressive disease after two cycles of therapy. Only three patients (12%) were progression-free at 6 months, and the 1-year OS was 7% (95% CI: 0.7, 17.0).

Conclusions: Treatment with single-agent gimatecan 1.0 mg/m²/day for 5 days, repeated every 28 days showed minimal efficacy.
Phase II study of bevacizumab and nitrosourea in patients with recurrent malignant glioma: A multicenter Italian study. R. Soffietti, R. Rudy, E. Trevisan, E. Picco, D. Guarneri, M. Caroli, M. Fabrini, V. Scotti; Univ and S. Giovanni Battista Hospital, Torino, Italy; University of Milano, Milano, Italy; University of Pisa, Pisa, Italy

Background: Bevacizumab (BV) has shown a promising activity in recurrent malignant gliomas (MG) in combination with irinotecan. Few data are available on the combination of bevacizumab (BV) and fotemustine (FTM) which is effective in recurrent gliomas 41.5%). Median time to maximal response was 1 month. Steroids response rate (2 CR and 9 PR) was 35% (glioblastomas 33%, anaplastic glioblastomas and 9 anaplastic gliomas) are evaluable for response. Overall from April 2008 to December 2008, 34 patients were enrolled and 31 (22 newly diagnosed anaplastic oligodendroglial tumors.

Methods: In this ongoing phase II study patients with MG recurrent after surgery, radiation therapy, and temozolomide are eligible. The treatment consists of an inductive phase with BV at 10 mg/kg intravenously on day 1 and fotemustine (FTM) (a nitrosourea with elevated lipolipic properties) at 75 mg/m² intravenously on day 1 and 8, followed after a 3-week interval by a maintenance phase with BV at 10 mg/kg i.v. and FTM 75 mg/m² i.v. every 3 weeks until tumor progression or unacceptable toxicity. Patients undergo clinical and MRI assessment 1 month after the start of treatment and thereafter every 2 months. Monitoring of CBV with perfusion MRI is performed in selected centers. The co-primary endpoints are objective response rate (ORR), based on Mc Donald's criteria (CR + PR) and progression-free survival at 6 months (PFS6), with secondary endpoints of safety time to tumor progression (TTP) and overall survival. Results: From April 2008 to December 2008, 34 patients were enrolled and 31 (22 glioblastomas and 9 anaplastic gliomas) are evaluable for response. Overall response rate (2 CR and 9 PR) was 35% (glioblastomas 33%, anaplastic gliomas 41.5%). Median time to maximal response (not reached) were reduced in 50% of patients. Sixteen of 31 patients progressed with a TTP of 2.6 months (1–8.5). Patterns of progression were local in 10/16, and 10/16 had SD. Median TTP was longer following CT&RT (sequential or concurrent) than CT alone (7.6 vs. 3.6 years, respectively). GBM have high concentrations of vascular endothelial growth factor (VEGF), higher levels are associated with poorer prognosis.

Conclusions: Combination of bevacizumab and fotemustine in recurrent malignant gliomas is safe and promising. Updated results, monitoring of CBV with perfusion MRI, and correlations between MGMT promoter methylation and response/outcome will be presented.

Retrospective analysis of outcomes among more than 1,000 patients with newly diagnosed anaplastic oligodendrogliom tumors. A. B. Lassman, Oligodendroglioma Study Group; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Treatment of anaplastic oligodendrogliomas is controversial. Early results of randomized trials suggest chemotherapy (CT) with procarbazine-lomustine-vincristine (PCV) before or after radiotherapy (RT) improves progression-free but not overall survival (OS) versus RT alone. It is unknown if CT alone or CT & RT outcomes with PCV are similar. Methods: We retrospectively identified adults with newly diagnosed anaplastic oligodendroglioma (AO) or oligoastrocytoma (OA) seen at 17 medical centers from 1991–2007 exclusive of phase III or bone marrow transplant trials. Data were updated January 1, 2009. Survivals were estimated by Kaplan-Meier method and compared with log-rank. Results: There were 1054 patients: 594 men, 460 women; median age 42 (18–88); 661 with AO, 443 with OA. Treatment was: observation (82%, 8%), RT alone (n = 210, 20%), RT then chemotherapy (283, 27%), RT + CT concurrently (116, 11%), CT alone (205, 19%), CT then RT (137, 13%), or other (19, 2%). Median time to progression (TTP) and OS were 2.8 and 6.5 years, respectively, with median follow up of 4.1 years (0.03–20.8) on surviving patients (n = 560, 53%). 1p19q co-deletion was observed in 292 (48%) and no deletion in 232 (38%) of 606 tested tumors. Co-deletion predicted longer median TTP (4.4 vs. 1.9 years for no deletion, p = 0.0002) and OS (8.4 vs. 3.3 years, p < 0.0001). Median TTP was longer following CT&RT (sequential or concurrent) than CT alone (3.7 vs. 2.6 years, p = 0.0007), but median OS did not differ (6.6 vs. 7.1 years, p = 0.8). Co-deletion was more common with CT alone than CT&RT (p = 0.0001). Although restricting to patients co-deletion to the co-deletion cohort yielded analogous results (median TTP 7.2 vs. 3.8 years, p = 0.011; OS 7.9 vs. 10.4 years, p = 0.26). Median TTP was longer following PCV alone (7.6 years, n = 17) than TMZ alone (3.3 years, n = 65) with co-deletion (p < 0.002); median OS was also longer (not reached, vs. 7.1 years), but did not reach statistical significance (p = 0.07 log-rank). Conclusions: 1p19q co-deletion predicted improved outcome. Treatment strategies varied widely. CT alone did not appear to shorten OS versus CT&RT. PCV may be superior in efficacy to TMZ. Multivariate analyses and additional 1p19q testing are in progress.
2016

Poster Discussion, Sat, 8:00 AM - 12:00 PM

Bevacizumab in combination with temozolomide in the adjuvant treatment of newly diagnosed glioblastoma multiforme: Preliminary results of a phase II study. M. K. Nicholas, R. V. Lucas, J. Arzbacher, N. Paleologos, H. Krouwer, M. Malkin, A. Omar, N. A. Vick; University of Chicago, Chicago, IL; NorthShore University Health System, Evanston, IL; Regional Cancer Center, Waukesha Medical Hospital, Waukesha, WI; Medical College of Wisconsin, Milwaukee, WI

Background: Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor. Current standard treatment consists of fractionated radiotherapy (RT) with daily oral temozolomide (TMZ) chemotherapy followed by 6 months of adjuvant TMZ chemotherapy. Median survival is 14.3 months. Because GBM is characterized by accelerated cell proliferation and produces high levels of vascular endothelial growth factor (VEGF), attempts to better control the disease with targeted antiangiogenesis therapies are underway. Here, we report preliminary safety and tolerability data of bevacizumab (BV) when added to monthly TMZ chemotherapy. Methods: Subjects received standard regional RT to a dose of 60 Gy in 30 fractions with daily concurrent TMZ (75 mg/m2) within 3–5 weeks of diagnosis. Four weeks after RT/TMZ, subjects received 5 consecutive daily TMZ doses (150–200 mg/m2) administered every 28 days. BV (10 mg/kg) was given every 14 days. Treatment continued until complete or progressive disease or unacceptable toxicity occurred. Results: 42 of 48 planned subjects were enrolled as of 12/30/08. Twenty-three remained on study. Of these, 4 were receiving RT/TMZ, 18 were receiving TMZ/BV and 1 was delayed post-RT/TMZ due to local wound infection. Nineteen were off-study, e.12 of whom off-study early. New safety events included BV withdrawal (n = 2), toxicity during RT/TMZ (n = 3) and post-RT/TMZ progression (n = 6). Seven subjects progressed while receiving TMZ/BV. Twenty-six of the 42 enrolled received at least one 28-day cycle of TMZ/BV (range 1–16 cycles). Duration of treatment, inclusive of RT/TMZ, ranged from 27 to 523 days. Best radiographic responses of evaluable subjects, using MacDonald criteria were: 5 complete, 9 partial, 13 stable and 7 progressive disease. Of those taken off study, 13 were due to disease progression. Of those removed from study due to toxicity, none were unexpected and only 1 (a GI bleed) occurred during the TMZ/BV phase. A statistician’s analysis of responses and survival is pending. Conclusions: The co-administration of TMZ/BV following RT/TMZ for newly diagnosed GBM is safe and well-tolerated.

2017

Poster Discussion, Sat, 8:00 AM - 12:00 PM

Bevacizumab in combination with radiotherapy plus concomitant and adjuvant temozolomide for newly diagnosed glioblastoma: Update progression-free survival, overall survival, and toxicity. M. L. Gruber, S. Raza, D. Gruber, A. Narayana; NYU Clinical Cancer Center, New York, NY; New York University Medical Center, New York, NY; New York University School of Medicine, New York, NY

Background: Prognosis of glioblastoma (GBM) is very poor. Standard treatment includes surgical resection (SR), radiation (RT), concomitant and adjuvant chemotherapy with temozolomide (TMZ). Our objective is to assess the treatment efficacy, safety and survival in patients with newly-diagnosed GBM treated with RT, TMZ, and bevacizumab in the upfront management. Methods: From 2006–2008, 51 eligible patients (age ≥18, KPS >70) with newly-diagnosed GBM divided into two groups. Group A (n = 20) was treated with RT (60 Gy) and concomitant TMZ (75 mg/m2 daily for 42 days) with bevacizumab (10 mg/kg every 2 weeks), 29 days following surgery, followed by up to six cycles of adjuvant TMZ (150 mg/m2 daily x 7d, q28 with bevacizumab at 10 mg/kg days 8 and 22 of each 28 day cycle. Group B (n = 31) received similar treatment without bevacizumab. Both groups were followed up until tumor progression (PFS). Recurrence was defined according to MacDonald Criteria. The end points were PFS, overall survival (OS) and toxicity. Results: Median bevacizumab infusions were 12 (4–32). Median follow-up was 14 months for both groups. 6 months PFS survival in Group A was 77.5% and in Group B was 51.6%. Median PFS in Group A was 17 months compared to 7 months in Group B (p < 0.0001, HR = 0.26). Median OS has not been reached in Group A and was 17 months in Group B. One and two year OS were 83% and 57% in Group A compared to 72% and 6.5% in Group B (p = 0.02). Post-RT and temozolomide toxicities include thrombocytopenia (1 patient; Gr 3 and fatigue (3 patient;Gr 3), bevacizumab related toxicities with RT include leg ulcer with cellulitis (1 patient; Gr 3) and pulmonary embolism with thrombocytopenia (1 patient;Gr 4), hypotension (2 patients; Gr 1), and asymptomatic blood products on MRI (2 patients). Conclusions: Bevacizumab has demonstrated efficacy, acceptable toxicity, improved PFS and OS in the upfront management of GBM.

2018

Poster Discussion, Sat, 8:00 AM - 12:00 PM

Phase II trial of radiation therapy/temozolomide followed by temozolomide/sorafenib in the first-line treatment of glioblastoma multiforme (GBM). R. E. Lamar, D. R. Spigel, H. A. Burris, T. M. Markus, M. Kuzur, T. Ervin, S. Fichtel, F. A. Greco, J. D. Hainsworth; Tennessee Oncology, Nashville, TN; Sarah Cannon Research Institute, Nashville, TN; Florida Cancer Specialists, Ft. Myers, FL; South Texas Oncology and Hematology, San Antonio, TX

Background: Anti-angiogenesis agents have recently shown activity in the treatment of patients (pts) with GBM. We added sorafenib, a multi-targeted TKI, to the standard first-line treatment of patients with GBM. We added sorafenib, a multi-targeted TKI, to the standard first-line treatment of patients with GBM. We added sorafenib, a multi-targeted TKI, to the standard first-line treatment of patients with GBM. We added sorafenib, a multi-targeted TKI, to the standard first-line treatment of patients with GBM. We added sorafenib, a multi-targeted TKI, to the standard first-line treatment of patients with GBM. Methods: Twenty-six of the 42 enrolled received at least one 28-day cycle of TMZ/BV (range 1–16 cycles). Duration of treatment, inclusive of RT/TMZ, ranged from 27 to 523 days. Best radiographic responses of evaluable subjects, using MacDonald criteria were: 5 complete, 9 partial, 13 stable and 7 progressive disease. Of those taken off study, 13 were due to disease progression. Of those removed from study due to toxicity, none were unexpected and only 1 (a GI bleed) occurred during the TMZ/BV phase. A statistician’s analysis of responses and survival is pending. Conclusions: The co-administration of TMZ/BV following RT/TMZ for newly diagnosed GBM is safe and well-tolerated.

2019

Poster Discussion, Sat, 8:00 AM - 12:00 PM


Background: The mammalian target of rapamycin (mTOR) functions within the PI3K/Akt signaling pathway as a critical modulator of cell survival. We previously demonstrated that GBM is characterized by vascular permeability factor (VPF)/vascular endothelial growth factor (VEGF) overexpression and high levels of vascular endothelial growth factor (VEGF), attempts to better control the disease with targeted antiangiogenesis therapies are underway. Here, we report preliminary safety and tolerability data of bevacizumab (BV) when added to monthly TMZ chemotherapy. Methods: Subjects received standard regional RT to a dose of 60 Gy in 30 fractions with daily concurrent TMZ (75 mg/m2) within 3–5 weeks of diagnosis. Four weeks after RT/TMZ, subjects received 5 consecutive daily TMZ doses (150–200 mg/m2) administered every 28 days. BV (10 mg/kg) was given every 14 days. Treatment continued until complete or progressive disease or unacceptable toxicity occurred. Results: Between April 2007 and July 2008, 45 pts were enrolled. The median age was 54 years; 30 pts (67%) had previous partial or complete surgical resection. 39 pts (87%) completed concurrent RT/temozolomide therapy, while 6 pts were removed from treatment (PD 4, toxicity 1, intercurrent event 1). 39 pts began treatment with temozolomide/sorafenib; 3 have completed all planned treatment, 8 remain on treatment, and 28 stopped treatment early (PD 22, toxicity 2, intercurrent event 1, pt decision 3). Best responses to date as follows: CR, 1 pt (2%); PR, 5 pts (11%); stable disease, 22 pts (49%); progression disease, 2 pts (4%); immune mediated adverse events, 2 pts (4%); and grade 5 toxicity, 1 pt (2%). The median PFS for pts who received at least 1 dose of sorafenib is also 6 months. The median overall survival is 16 months (95% CI, 7.2–NR months). Grade 3/4 toxicity during temozolomide/sorafenib was uncommon; 7 pts (16%) required dose reductions of sorafenib during their treatment course. Conclusions: The addition of sorafenib to standard treatment with RT/temozolomide is feasible and well tolerated by most pts. Preliminary efficacy is similar to standard therapy; updated results will be presented.
Phase II and pharmacogenomics study of enzastaurin plus temozolomide and radiation therapy in patients with glioblastoma multiforme or gliosarcoma.

N. A. Butowksi, K. Lamborn, S. Chang, E. Hsieh, A. Fedoroff, R. Parvataneni, S. Nicol, A. Liepa, D. Thornton, M. Prados; University of California, San Francisco, San Francisco, CA; Eli Lilly, Indianapolis, IN

Background: ENZ, an oral serine/threonine kinase inhibitor, suppresses signaling through PCSKβ and the PI3K/AKT pathways to induce apoptosis, reduce proliferation, and suppress angiogenesis. The pharmacogenomic signature of this single-arm phase II trial was overall survival (OS). Secondary objectives included progression-free survival (PFS), safety, PK/PD, and patient-reported outcomes (PROs). A concurrent PGx project assessed the value of pretreatment and radiation response molecular signatures as predictors of outcome. Immunofluorescence spectroscopy (MRS) was also evaluated during treatment for its value in predicting OS.

Methods: Patients enrolled with newly diagnosed GBM/GS and KPS ≥60. Treatment started <5 weeks after diagnosis with RT 60 Gy given over 6 weeks and TMZ 75 mg/m² given daily during RT and then at 200 mg/m² from days 1–5 of a 28-day cycle. ENZ 250 mg/day was given orally daily during RT and adjuvantly. Planned treatment duration was 1 year. PGx parameters were: MGMT promoter methylation, mismatch repair status, PKC isoforms, pERK, pCREB, EGFR, PTEN, GSK3β, ser9 VEGF, and pS6. MRS was performed at baseline and at scheduled intervals. Changes in molecular signatures and imaging while on treatment to survival were estimated using Kaplan-Meier and proportional hazards models. Analyses included phase I patients at ENZ 250 mg/day.

Results: From September 2007 to November 2008, 60 phase II patients enrolled; 21 completed RT and eight patients withdrew. Two of the three patients, the dose was increased by 50% in the next cohort (neutropenia or thrombocytopenia). In the absence of a DLT in at least one-third of patients, the dose was increased by 50% in the next cohort. of the three patients, the dose was increased by 50% in the next cohort.

Conclusions: The combination of ENZ plus TMZ during and following RT was well tolerated and may be an active regimen in GBM. This study represents the future of neuro-oncology clinical trial design by employing a novel multi-kinase inhibitor while concurrently studying novel imaging and molecular techniques that may predict efficacy.

Targeting brain tumor stem cells using a bispecific antibody directed against CD133+ and EGFRvIII+. A. Wong, S. Mitra, P. Gupta; Stanford University Medical Center, Stanford, CA

Background: Using the marker CD133, cancer stem cells (CSCs) have been demonstrated for glioblastomas (GBMs) and medulloblastomas. However, CD133 is also present on normal neural stem cells. EGFRvIII is a tumor specific EGF receptor. We hypothesized that a recombinant bispecific antibody directed against CD133 and EGFRvIII would be a highly specific reagent for brain tumor stem cells (BTSCs) that target glioblastoma multiforme (GBM) cells with reduced toxicity. EGFRvIII is a constitutively activated and immunogenic mutation not expressed in normal tissues, but widely expressed in GBM and other neoplasms. The cancer vaccine CDX-110 is composed of an EGFRvIII-mimetic peptide sequestering Th, lymphopenia. Grade 1 thrombocytopenia was seen in eight patients and one-third of patients were grade 1 fatigue, grade 1 nausea, and grade 1–2 vomiting. Twenty-five of 54 patients progressed immediately after RT and 17 progressed after one or more adjuvant cycles; five discontinued due to toxicity; four withdrew from trial. Treatment was well tolerated. The only toxicities seen in more than one-third of patients were grade 1 fatigue, grade 1 nausea, and grade 1–2 lymphopenia. Grade 1 thrombocytopenia was seen in eight patients and grade 3 lymphopenia in five patients. OS, PFS, PROs, PGx, and imaging findings will be reported.

Results: From September 2007 to November 2008, 60 phase II patients enrolled; 21 completed RT and eight patients withdrew. Two of the three patients, the dose was increased by 50% in the next cohort (neutropenia or thrombocytopenia). In the absence of a DLT in at least one-third of patients, the dose was increased by 50% in the next cohort.

Conclusions: The combination of ENZ plus TMZ during and following RT was well tolerated and may be an active regimen in GBM. This study represents the future of neuro-oncology clinical trial design by employing a novel multi-kinase inhibitor while concurrently studying novel imaging and molecular techniques that may predict efficacy.

Epidermal growth factor receptor variant III (EGFRvIII) vaccine (CDX-110) in GBM.

A. B. Heimberger, G. E. Archer, D. A. Mitchell, D. D. Bigner, R. J. Schmitting, J. E. Herndon II, T. Davis, H. S. Friedman, T. Keler, D. A. Reardon, J. H. Sampson; University of Texas M. D. Anderson Cancer Center, Houston, TX; Duke University Medical Center, Durham, NC; Celdex Therapeutics, Philadelphia, PA

Background: Unlike conventional therapies for GBM, immunologic targeting of tumor-specific gene mutations allows precise eradication of neoplastic cells with reduced toxicity. EGFRvIII is a constitutively activated and immunogenic mutation not expressed in normal tissues, but widely expressed in GBM and other neoplasms. The cancer vaccine CDX-110 is composed of an EGFRvIII-mimetic peptide sequestering Th, lymphopenia. Grade 1 thrombocytopenia was seen in eight patients and one-third of patients were grade 1 fatigue, grade 1 nausea, and grade 1–2 vomiting. Twenty-five of 54 patients progressed immediately after RT and 17 progressed after one or more adjuvant cycles; five discontinued due to toxicity; four withdrew from trial. Treatment was well tolerated. The only toxicities seen in more than one-third of patients were grade 1 fatigue, grade 1 nausea, and grade 1–2 lymphopenia. Grade 1 thrombocytopenia was seen in eight patients and grade 3 lymphopenia in five patients. OS, PFS, PROs, PGx, and imaging findings will be reported.

Results: From September 2007 to November 2008, 60 phase II patients enrolled; 21 completed RT and eight patients withdrew. Two of the three patients, the dose was increased by 50% in the next cohort (neutropenia or thrombocytopenia). In the absence of a DLT in at least one-third of patients, the dose was increased by 50% in the next cohort.

Conclusions: The combination of ENZ plus TMZ during and following RT was well tolerated and may be an active regimen in GBM. This study represents the future of neuro-oncology clinical trial design by employing a novel multi-kinase inhibitor while concurrently studying novel imaging and molecular techniques that may predict efficacy.

A phase I study of ABT 510 and concurrent temozolomide and radiotherapy for patients with newly diagnosed glioblastoma multiforme.

M. Keegan, J. Pivash, J. M. Markert, G. V. Gillespie, H. Kuo, S. Meleth, C. L. Gladson, L. B. Nabor; University of Alabama at Birmingham, Birmingham, AL

Background: ABT-510 (Abbott Laboratories, Abbott Park, IL, USA) is a Thrombospondin-1 (TSP-1) mimetic drug with anti-angiogenic properties. This phase I dose escalation trial was designed to study the maximum tolerated dose (MTD) of ABT 510 when used concurrently with temozolomide (TMZ) and radiotherapy (RT) in patients newly diagnosed glioblastoma multiforme (GBM). Methods: A total of 23 patients with newly diagnosed, histologically verified GBM were enrolled between April 2005 and January 2007, after obtaining written consent. The study was approved by the University of Alabama at Birmingham (UAB) Institutional Review Board. Four cohorts with three patients in each, receiving subcutaneous ABT 510 injection at doses of 20, 50, 100, and 200 mg/day were studied. The starting dose was primarily based on preclinical findings from animal studies and phase I studies on healthy subjects and cancer patients. Treatment plan included 10 weeks of induction phase (TMZ and RT with ABT 510) followed by a maintenance phase (ABT 510 and TMZ) of 14 cycles each consisting of 28 days. Patients were monitored with brain MRI along with laboratory values for dose limiting toxicities (DLT) defined as grades 3–4 non-hematological toxicities and grade 4 hematological toxicities (neutropenia or thrombocytopenia). In the absence of a DLT in at least two of the three patients, the dose was increased by 50% in the next cohort of patients. Therapy was discontinued if 14 maintenance cycles were completed, disease progression occurred, or if the patient requested withdrawal. Disease progression and survival statistics were analyzed. Results: During this trial, 23 of 24 DLT were not observed even after the dose was increased to 200 mg/day, hence, the last cohort was expanded to include 4 patients. A MTD was not defined. The median time to tumor progression (TTP) was 220 days and the median overall survival was 422 days. Gene expression analysis of the tumor pathology will be performed to evaluate the relationship between the expression of TSP-1, TSP-2, and patient response to the drug.

Conclusions: ABT 510, at subcutaneous doses up to 200 mg/day, is tolerated well with concurrent TMZ and RT in patients with newly diagnosed GBM.
Background: Recent studies suggest that anti-angiogenic therapies may be effective in patients with glioblastoma multiforme (GBM), a highly vascular tumor. We have previously demonstrated that angiotensin-(1–7) [Ang-(1–7)], an endogenous heptapeptide with anti-angiogenic properties, significantly reduced the serum-stimulated growth of three human glioblastoma cell lines which contained mRNA for the AT_1 receptor. We now provide the first evidence that Ang-(1–7) markedly decreases the proliferation and growth of human glioblastomas in vivo using a xenograft model. Methods: Aghamic mice with tumors resulting from injection of human U87 glioblastoma cells were treated for 18 days with saline or 1000 μg/kg Ang-(1–7), delivered by subcutaneous injection every 12 h. Results: The average volume of the tumors from mice treated with the heptapeptide was approximately 3-fold less than the size of the tumors from control animals (586.1 ± 94.5 mm³ vs 1845.5 ± 238.1 mm³; n = 6, p < 0.05). Further, the tumors from mice injected with Ang-(1–7) weighed almost 50% less than the tumors from mice treated with saline (1.31 ± 0.12 g. vs. 2.45 ± 0.23 g; n = 6, p < 0.05). The Ang-(1–7)-mediated reduction in tumor growth was associated with a significant decrease in immune-reactive Ki67, a proliferation marker. In addition, a marked down-regulation of cyclooxygenase 2 (COX-2), prostaglandin E synthase (PGES-1) and vascular endothelial growth factor (VEGF) was observed in tumors from Ang-(1–7)-injected mice compared to saline-treated controls (COX-2: 1.00 ± 0.06 vs 0.55 ± 0.07 relative gene expression; PGES-1: 1.03 ± 0.08 vs 0.40 ± 0.06; VEGF: 1.05 ± 0.07 vs. 0.59 ± 0.09; n = 6, p < 0.05) with no effect on COX-1 or PGI synthase mRNA. Conclusions: These results suggest that Ang-(1–7) may reduce the concentration and ratio of proliferative and anti-proliferative prostaglandins to decrease glioblastoma growth as well as attenuate angiogenesis through a reduction in VEGF. Thus, Ang-(1–7) may be a new, first-in-class small molecule inhibitor for the treatment of glioblastoma, providing combination therapy as a selective COX-2/PGES-1 and angiogenic inhibitor, targeting a specific AT_1 receptor.
2028 Poster Discussion, Sat, 8:00 AM - 12:00 PM
Role of IκBα as a negative regulator of EGFR and a molecular determinant of prognosis in glioblastoma multiforme. M. Bredel, J. Renfrow, A. Yadav, A. Alvarez, D. Lin, D. Scholtens, X. He, J. Chandler, A. Scheck, G. Harsh; Northwestern University, Chicago, IL; Barrow Neurological Institute, Phoenix, AZ; Stanford University, Stanford, CA

Background: Glioblastoma multiforme is a complex disease that involves the deregulation of overlapping signaling pathways. Constitutive activation of the epidermal growth factor receptor (EGFR) is a single-across tumor clear factor-κB (NF-κB) has been broadly associated with various human cancers, including glioblastomas, and their therapy resistance and may be due to cross-coupling with other oncogenic pathways, such as epidermal growth factor signaling. Methods: Multidimensional analysis involving gene and protein data for the modulation of markers in response to affercept and to identify potential predictive markers. Results: Plasma samples were collected from 31 of 32 enrolled patients at baseline, 24 hours and every 2–4 weeks until progression. Urine samples were collected at baseline and every 4 weeks. Levels of 41 circulating factors were measured using suspension bead multiplex assays (BioRad) or ELISA. Free VEGF and PIGF levels were determined following sample immunodepletion. Baseline and changes in marker levels over time were correlated with response and progression using logistic regression and Cox proportion hazard models. Results: Treatment with affercept resulted in significant increases in total VEGF and PIGF at 24 hours and 28 days in both patients receiving aflibercept (p = 0.001). However, free PIGF levels rose over time and by 28 days were 45-fold higher than baseline (p < 0.001). Additional modulation of free PIGF levels in GBM (p = 0.011) and decreases in urinary VEGF and MIP1β (p = 0.001). At 28 days, levels of IL-1β were significantly decreased (p = 0.02) while SCGFβ and urinary VEGF levels increased (p < 0.02). Baseline biomarker levels between response groups (PD, SD, and PR), patients with lower levels of GRα, β-catenin, and SCGFβ and higher levels of free VEGF were more likely to have a PR (p < 0.05). Conclusions: In recurrent glioblastoma, affercept resulted in rapid and sustained decreases in free VEGF levels. Although greater than 95% of PIGF remained bound, free PIGF levels significantly increased over time. Treatment significantly modulated multiple cytokine and angiogenic factor levels, with striking increases in MIF and SCGFβ. Potential biomarkers predictive of response to affercept include GRα, HGF and SCGFβ.

2029 Poster Discussion, Sat, 8:00 AM - 12:00 PM
Circulating cytokine and angiogenic factors as predictive biomarkers of glioblastoma response to affercept (VEGF Trap). Y. Piao, J. V. Heymach, B. Bekele, K. Campathausen, P. Y. Wen, J. Liu, W. K. Yung, J. De Groot; UT M. Anderson Cancer Center, Houston, TX; NCI, Bethesda, MD; Dana-Farber Cancer Institute, Boston, MD

Background: Affercept is a recombinant fusion protein that scavenges both vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). While in children medulloblastoma comprises the most common malignant brain tumor, it accounts for only 1% of intracranial malignancies in adults. The infrequent incidence of the disease has been the impediment to the question, whether these tumors are the same in adults and children in terms of biological and clinical peculiarities. Methods: Array-CGH was performed for a total 34 adult medulloblastoma samples (>18 years) and results were compared with data from 101 pediatric patients. Selected genomic regions were further investigated by FISH analysis in an independent cohort of 415 samples (112 adult and 303 pediatric). All 146 adult patients received a standard treatment regimen consisting of tumor resection, irradiation of the neuroaxis with 36 Gy, a boost of 20~23 Gy to the posterior fossa, and eight cycles of vincristine, lomustine, and cisplatin. To identify novel prognostic markers, DNA copy-number information was correlated with survival data using log rank and chi-square tests. Results: Copy-number gains of chromosome 1q73 as well as high-level amplifications of CDK6 were identified as significant adverse prognostic markers in adult medulloblastoma. Apart from one exception, CDK6 amplifications were only observed in adult patients (9% in adults versus 0.2% in children), whereas amplifications of MYC or MYCN were significantly overrepresented in the pediatric cohort, but when present were also associated with dismal prognosis in adults. Monosomy of chromosome 6, in contrast to the pediatric cohort, was significantly associated with better survival in adult medulloblastoma, although nuclear β-catenin accumulation was detected in most cases (r = 0.68). Based on these results, we propose a molecular staging system for adult medulloblastoma: i) cases with oncogene amplification (10% of cases, 5-year OS = 0%); ii) cases with chromosome 1q73 gain without oncogene amplification (25% of cases, 5-year OS = 35%); and iii) cases without oncogene amplification or 1q7 gain (65% of cases, 5-year OS = 92%).

Conclusions: We report on the largest cohort of adult medulloblastoma investigated for genomic imbalances to date. We propose a model for the molecular risk stratification of adult medulloblastoma comprising five distinct genomic risk groups with significantly different survival and tumor biology.
Conclusions: demonstrated an antigen-specific cytotoxic T-cell response to at least one (ranging from 26 to 115 weeks). Of 15 patients tested to date, six patients courses of dendritic cell vaccines demonstrate zero grade 3 /4 toxicities patients, 15 males and five females, were enrolled between November toma progression free survival correlated with CTL response. bioactivity of a TAA-pulsed dendritic cell vaccine for patients with glioblas- gated into dendritic cells in culture, pulsed with tumor peptide, and then ible fashion using epitopes of HER-2, TRP-2, gp100, MAGE-1, IL13R study is to use tumor associated antigens (TAA) known to be expressed on gliomas and pulse dendritic cells with these antigens in an MHC compat- on enzyme inducing anti-epileptic drugs. Anti-vascular endothelial growth factor (VEGF) agents are hypothesized to work synergistically with chemotherapy and radiation (RT). Vatalanib (MW 347, T1/2 4.6 h) is an oral, pan-VEGFR tyrosine kinase inhibitor that has shown clinical activity in patients with recurrent glioblastoma. Methods: This randomized phase II clinical trial assessed the effects of daclizumab in the context of the cancer vaccine, CDX-110, which is comprised of an EGFRvIII-specific peptide sequence linked to KLH. EGFVIII is a constitutively activated and immunogenic mutation not expressed in normal tissues, but widely expression in GBMs and other neoplasms. In patients with newly-diagnosed, EGFVIII+ GBM, after resection and radiation/ TMZ, patients received CDX-110 vaccinations biweekly x 3, then monthly until tumor progression in combination with TMZ (200 mg/m² x 5/28 days). Half the patients were randomized to receive dacarbazine (1mg/Kg x 1) at the first vaccine. The others received saline in a double-blinded fashion. Results: There were no drug related SAEs. EGFRVIII-specific immune responses were generated in all patients, and all immune responses were sustained or enhanced during subsequent TMZ cycles. Preliminary analysis (n = 4) suggests that dacarbazine reduces Treg (CD4+CD25+CD45RO+FOXP3+) numbers (change 82.4 ± 7.1% from baseline (p = 0.01; t-test) without reducing overall CD8+ or CD4+ T-cell counts. Treg decreased only 3.1 ± 11.0% after vaccination in the same treated group during the same interval. Prelimi- nary analysis (n = 4) also suggest that dacarbazine enhanced EGFRVIII- specific immune responses (p = 0.01; t-test) and enhanced the titer of cytotoxic EGFRVIII-specific IgG1 antibody compared to the saline treated group (p = 0.003; t-test) and compared to previously vaccinated patients who did not receive dacarbazine (p = 0.0015; t-test). TTP and OS survival in both arms has not been reached. Conclusions: Daclizumab may enhance Treg cells in patients with GBM. TMZ and dacarbazine may enhance EGFVIII-targeted immune responses despite lymphodepletion. These combinations are currently under further investigation.

Conclusions: This phase I study demonstrated the feasibility, safety, and bioactivity of a TAA-pulsed dendritic cell vaccine for patients with glioblas- toma progression free survival correlated with CTL response.
A phase I study of temozolomide (TMZ) and RAD001 in patients (pts) with glioblastoma multiforme (GBM). W. P. Mason, M. MacNeil, J. Easaw, L. McIntosh, Z. Lwin, E. Chen, E. E. Eisenhauer; Princess Margaret Hospital, Toronto, ON, Canada; Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; Tom Brown Cancer Centre, Calgary, AB, Canada; NCIC Clinical Trials Group, Kingston, ON, Canada

**Background:** The mTOR protein kinase is a critical step in the PI3K/Akt/PTK signaling pathway. RAD001 exerts antiproliferative and antiangiogenic effects by inhibiting mTOR. This phase I trial was designed to determine the maximum tolerated dose(s) (MTD) and recommended phase II dose(s) of RAD001 in combination with TMZ in patients with GBM. Patients receiving enzyme-inducing anti-epileptic drugs (EIAEDs) and those not receiving EIAEDs (NEIAEDs) were studied separately.

**Methods:** Enrollment was restricted to pts with proven GBM, either newly diagnosed following completion of radiotherapy with concurrent TMZ, or at first progression. TMZ was administered at a starting dose of 150 mg/m² for 5 days every 28 days, and RAD001 was administered continuously at a starting dose of 2.5 mg orally on a daily schedule starting on day 2 of cycle 1 in 28-day cycles (maximum 10 mg daily unless PK interaction shown). Response was evaluated every 2 cycles. Pharmacokinetics (PK) of TMZ and RAD001 were determined during cycle 1.

**Results:** To date, 16 NEIAEDs and 9 EIAEDs pts have been enrolled and received 79 and 58 cycles respectively. The majority of pts (20/23) were newly diagnosed in the NEIAEDs group at dose level 2 (RAD001 2.5 mg, TMZ 200 mg/m²) 3 of 4 pts had cycle 2 delays and dose reduction. TMZ burnout suppression in the NEIAEDs cohort without DLTs; RAD001 PK at this dose level was comparable to 10 mg RAD001 with TMZ 150 mg/m² because no additional DLTs were observed in 6/14 evaluable pts after 4 weeks of sunitinib, 5/19 pts were enrolled at this dose level; further escalation in this group will depend on delays and dose reduction of TMZ because of myelosuppression (neutropenia [gr 3, n 1], afebrile- [gr 2, n 1], and 3) and febrile neutropenia (gr 3, n 1), diarrhea (gr 2, n 1), and 1), thrombocytopenia (gr 2, n 4), anemia (gr 2, n 1), hypertension (gr 2, n 10), mucositis (gr 3, n 1), afibrosis (gr 2, n 3), and febrile neutropenia (gr 3, n 1; gr 4, n 1), thrombocytopenia (gr 2, n 4; gr 3, n 1; gr 4, n 1), and lymphocytopenia (gr 2, n 2; gr 3, n 4). Decrease in CBV, T1w, and T2w signal, and increase in DWI signal was observed in 61/62 evaluable pts after 4 weeks of sunitinib, 5/11 evaluable pts had SD; T1+Gd after 8 weeks. Sunitinib was associated with a marked clinical improvement with a reduction in the tumor metabolism in the tumor population.

**Conclusions:** Sunitinib at a continuous daily dose of 37.5 mg has a transient antiangiogenic effect in pts with recurrent HGG but is of insufficient clinical benefit to warrant further investigation as a single agent.

**2038**

General Poster Session (Board #A14), Sun, 8:00 AM - 12:00 PM

Phase II trial of sunitinib malate in patients with temozolomide refractory recurrent high-grade glioma. B. Neven, C. Chaskis, M. Dujardin, H. Eversaert, J. Sadones, N. N. Nuppen, A. Michotte; UZ Brussel, Brussel, Belgium; University of Helsinki, Helsinki, Finland

**Background:** High-grade gliomas (HGG) are characterized by neo-angiogenesis. Sunitinib is a small molecule tyrosine kinase inhibitor that inhibits multiple receptors (including VEGFR, PDGFR, and c-KIT). We investigated sunitinib for the treatment of patients (pts) with temozolomide (TMZ) refractory recurrent glioblastoma (GBM). Methods: Pts were recruited according to a pre-specified inclusion criteria. This was a 2-stage phase II design and planned to evaluate a daily dose of 37.5 mg sunitinib. T1+Gd and T2 weighted MRI images were obtained after 4 and 8 weeks of sunitinib and 8 weeks thereafter. We assessed the antangiogenic effect by calculating the cerebral blood volume (CBV) and cerebral blood flow (CBF) from dynamic susceptibility (DSC) based perfusion MRI and determined during cycle 1.

**Results:** To date, 16 NEIAEDs and 9 EIAEDs pts have been enrolled and received 79 and 58 cycles respectively. The majority of pts (20/23) were newly diagnosed in the NEIAEDs group at dose level 2 (RAD001 2.5 mg, TMZ 200 mg/m²) 3 of 4 pts had cycle 2 delays and dose reduction. TMZ burnout suppression in the NEIAEDs cohort without DLTs; RAD001 PK at this dose level was comparable to 10 mg RAD001 with TMZ 150 mg/m² because no additional DLTs were observed in 6/14 evaluable pts after 4 weeks of sunitinib, 5/19 pts were enrolled at this dose level; further escalation in this group will depend on delays and dose reduction of TMZ because of myelosuppression (neutropenia [gr 3, n 1], afebrile- [gr 2, n 1], and 3) and febrile neutropenia (gr 3, n 1), diarrhea (gr 2, n 1), and 1), thrombocytopenia (gr 2, n 4), anemia (gr 2, n 1), hypertension (gr 2, n 10), mucositis (gr 3, n 1), afibrosis (gr 2, n 3), and febrile neutropenia (gr 3, n 1; gr 4, n 1), thrombocytopenia (gr 2, n 4; gr 3, n 1; gr 4, n 1), and lymphocytopenia (gr 2, n 2; gr 3, n 4). Decrease in CBV, T1w, and T2w signal, and increase in DWI signal was observed in 61/62 evaluable pts after 4 weeks of sunitinib, 5/11 evaluable pts had SD; T1+Gd after 8 weeks. Sunitinib was associated with a marked clinical improvement with a reduction in the tumor metabolism in the tumor population.

**Conclusions:** Sunitinib at a continuous daily dose of 37.5 mg has a transient antiangiogenic effect in pts with recurrent HGG but is of insufficient clinical benefit to warrant further investigation as a single agent.

**2039**

General Poster Session (Board #A13), Sun, 8:00 AM - 12:00 PM

Feasibility and phase I trial of tandutinib in patients with recurrent glioblastoma. J. G. Supko, S. A. Grossman, D. M. Peereboom, S. Chowdhary, G. J. LessPelt, B. Nabors, T. Mikkelson, S. DeSideri, T. T. Batkefer; Massachusett's General Hospital, Boston, MA; Johns Hopkins University, Baltimore, MD; Cleveland Clinic, Cleveland, OH; Moffitt Cancer Center, Tampa, FL; Wake Forest University, Winston-Salem, NC; University of Alabama, Birmingham, Birmingham, AL; Henry Ford Hospital, Detroit, MI

**Background:** Platelet-derived growth factor signaling is important in glioma growth and PDGFR-B expression has been identified on glioblastoma cells in glioblastoma specimens. Methods: We report the results of a feasibility and phase I study of tandutinib (MNL518), an orally bioavailable, quinazoline-based inhibitor of type III receptor tyrosine kinases including PDGFR-ß, FLT-3, and c-KIT, in patients with recurrent glioblastoma (GBM) conducted in the New Approaches to Brain Tumor Therapy (NABTT) consortium.

**Results:** A feasibility study was conducted in 6 recurrent GBM patients in whom resection was clinically indicated. These patients received tandutinib 500-mg BID for 7 days prior to resection. In these patients, the drug was measured in tumor tissue and plasma samples obtained shortly before and after the resection by LC/MS. The mean ± SD concentration of tandutinib in tumor tissue was 7.2 ± 3.2 μM and the mean ratio of its concentration in brain tumor to plasma was 9.6 ± 7.7. A phase I study was conducted in 19 patients to determine the MTD in this recurrent GBM population with sequential assessment of the following dose levels: 500-, 600-, and 700-mg BID. Four patients were replaced due to early withdrawal unrelated to toxicity. Dose limiting toxicities were observed in 1/6 patients at 500-mg BID (grade 3 phospho-c-KIT and grade 3 vomiting), and in 1/3 patients at 600-mg BID (grade 3 vomiting) and 1/3 patients at 700-mg BID (grade 4 thrombocytopenia). 600-mg BID was declared the MTD and a phase II study has been initiated at this dose level.

**Conclusions:** The mean brain tumor to plasma ratio of tandutinib in GBM patients receiving 500-mg BID exceeded the estimated threshold ratio of 0.33 that was considered as being necessary to achieve local cytotoxic concentrations in brain tumors. The MTD of tandutinib in the recurrent GBM population is 600-mg BID. A phase II trial has been initiated at this dose level.
2040 General Poster Session (Board #A16), Sun, 8:00 AM - 12:00 PM

Pazopanib and lapatinib in patients with relapsed malignant glioma: Results of a phase I/II study. S. N. Frenzlas, M. D. Groves, J. Bariu, D. Harris, D. Reardon, M. C. Curtis, A. B. Suttle, B. Ma, J. J. Lager, J. S. de Bono; The Royal Marsden Hospital, Sutton, United Kingdom; M. D. Anderson Cancer Center, Houston, TX; Royal Marsden Hospital, Sutton, United Kingdom; Duke University Medical Centre, Durham, NC; GlaxoSmithKline, Research Triangle Park, NC

Background: Pazopanib (paz) is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-kit; and lapatinib (lap) is an oral tyrosine kinase inhibitor of EGFR (ErbB1) and HER-2 (ErbB2). Combination of VEGFR, PDGFR, and ErbB1 inhibitors may provide synergistic antitumor activity in malignancies with high VEGF expression. It is unknown if there is a tolerable dose of pazap/lap (mg, daily unless specified) of 200/1500 (N paz/lap combination has a manageable safety profile with a preliminary

Target of 0.5

Efficacy of intracerebral inoculations of G207 to patients suffering from GBM, mOS was 7.4 months, in patients suffering from relapsed AA, mOS was 9.25 months. 20 serious adverse events occurred in this study, only 3 were variable ranging from 3 to 24 hours. The mean area under the plasma concentration-time curve (AUC) ranged from 0.07 to 0.65 μg x hr/ml. Conclusions: CpG-ODN are immunostimulating oligodeoxynucleotides containing CpG motifs. When injected locally, they can induce tumor rejection in animal models. In a phase I clinical trial, intra-tumoral infusions of CpG-ODN are well tolerated at doses up to 20 mg. This multicenter phase II trial was designed to study the efficacy and tolerance of a local treatment by CpG-ODN in patients with recurrent glioblastoma. Patients: With recurrent GBM occurring at least three months after radiotherapy and previously treated with one at least regimen of chemotherapy received 20mg CpG-ODN (Cpg-28) by convection-enhanced delivery. The percentage of patients without tumor progression at 6 months after inclusion was the primary endpoint. Secondary endpoints were tolerance, survival, and radiological response. Results: Thirty-four patients were enrolled in two centers and thirty-one patients received the treatment. The 6-months progression free survival (PFS) was 19%. One partial response and 3 minor responses were observed. Eight patients (24%) were alive after 1 year, and 5 patients (15%) were alive 2 years after inclusion. The median overall survival was 29 weeks. Treatment was usually well tolerated. Among 6 patients studied, the pharmacokinetic profile of CpG-28 in the blood was heterogeneous. CpG-28 reached up to 79 ng/mL at the initial dose schedule produces measurable changes in perfusion MRI parameters which correlate with clinical response. Perfusion MRI parameters appear to correlate with clinical response to TMZ and are consistent with angiogenic inhibition.

2042 General Poster Session (Board #A18), Sun, 8:00 AM - 12:00 PM


Background: G207 is a doubly mutated (deletion of both γ134.5 loci, insertional inactivation of UL39) herpes simplex virus (HSV)-1. Safety and efficacy of intracerebral inoculations of G207 in patients with recurrent malignant gliomas have been demonstrated in previous clinical trials. Methods: In this phase I clinical trial, a total of 1 x 10^7 plaque forming units (pfu) G207 were administered by five stereotactic injections at the initial dose schedule produces measurable changes in perfusion MRI parameters which correlate with clinical response. Perfusion MRI parameters appear to correlate with clinical response to TMZ and are consistent with angiogenic inhibition.

Conclusions: The phase I/II trial of intracerebral administration of CpG oligonucleotide for patients with recurrent glioblastoma. R. Uru, A. Carpenter, P. Metellus, M. Barrie, Y. Meng, F. Laigle-Donadey, A. Tili, O. Chinot, A. F. Carpentier; Hôpital Avicenne, Bobigny, France; Hôpital Lariboisiere, Paris, France; Hôpital La Timone, Marseille, France; Hôpital Pitié-Salpêtrière, Paris, France; Hôpital Pitié-Salpêtrière, Paris, France; AGEPS, Paris, France

Background: CpG-ODN are immunostimulating oligodeoxynucleotides containing CpG motifs. When injected locally, they can induce tumor rejection in animal models. In a phase I clinical trial, intra-tumoral infusions of CpG-ODN in glioblastoma patients were well tolerated at doses up to 20 mg. This multicenter phase II trial was designed to study the efficacy and tolerance of a local treatment by CpG-ODN in patients with recurrent glioblastoma. Patients: With recurrent GBM occurring at least three months after radiotherapy and previously treated with one at least regimen of chemotherapy received 20mg CpG-ODN (Cpg-28) by convection-enhanced delivery. The percentage of patients without tumor progression at 6 months after inclusion was the primary endpoint. Secondary endpoints were tolerance, survival, and radiological response. Results: Thirty-four patients were enrolled in two centers and thirty-one patients received the treatment. The 6-months progression free survival (PFS) was 19%. One partial response and 3 minor responses were observed. Eight patients (24%) were alive after 1 year, and 5 patients (15%) were alive 2 years after inclusion. The median overall survival was 29 weeks. Treatment was usually well tolerated. Among 6 patients studied, the pharmacokinetic profile of CpG-28 in the blood was heterogeneous. CpG-28 reached up to 79 ng/mL at the initial dose schedule produces measurable changes in perfusion MRI parameters which correlate with clinical response. Perfusion MRI parameters appear to correlate with clinical response to TMZ and are consistent with angiogenic inhibition.
A phase II trial of single-agent bevacizumab given every 3 weeks for recurrent malignant gliomas. J. J. Raizer, S. Grimm, L. Rice, K. Muro, J. Chandler, C. Tellez, A. L. Mellot, S. Newman, M. K. Nicholas, M. Chamberlain; Northwestern University Feinberg School of Medicine, Chicago, IL; Northwestern University, Chicago, IL; University of Chicago, Chicago, IL; University of Washington, Seattle, WA

**Background:** Increasingly target specific agents are used in the treatment of malignant gliomas (MG). Among targeted agents, bevacizumab appears most promising and when combined with CPT-11. As CPT-11 has limited activity in recurrent MG, a single agent phase II trial of bevacizumab given every 3 weeks in with recurrent MG was performed. **Methods:** All patients (pts) had to sign an IRB informed consent except six pts who were treated at a different site in a similar fashion. All pts had to have at least one relapse with the first sixteen required to have two relapses before protocol implementation. **Inclusion criteria required > 18 year of age, KPS > 60, on a non-enzyme inducing anticouvantil, adequate bone marrow, liver and renal function, and normal urine protein and creatinine. MRI with perfusion was done at baseline (if patient consented) and then every 6 weeks. Patients were assessed using Macdonald criteria and continued on trial until tumor progression or toxicity. Treatment was bevacizumab 15 mg/kg every 3 weeks. **Results:** 61 patients (35 male; 26 female; 50 GBM, 5 AA, 6 AO/AOA) with a median age of 51 were treated. Median number of doses given was 4 (range 1–18). PFS-6 was 32% (median PFS was 3.9 m; median OS was 6.6 m). Best radiographic response included OR CR, 25% PR and 50% SD. Grade 3+ toxicities were non-fatal intracranial hemorrhage (1), fatal GI perforation (1), DVT (1), fatigue (4), rectal bleeding (1), weakness (1), and lack of drive (1). **Conclusions:** Bevacizumab as a single agent given every 3 weeks at 15 mg/kg is effective and safe for recurrent MG. The observed PFS-6 and OS is lower than reported bevacizumab regimens administered every 2 weeks; this difference may be related to patient selection.

Bevacizumab plus etoposide among recurrent malignant glioma patients: Phase II study final results. D. Reardon, A. Desjardins, J. J. Vredenburgh, S. Gururangan, K. B. Peters, J. A. Northfelt; Duke University Medical Center, Durham, NC

**Background:** Significant therapeutic benefit has been observed among recurrent malignant glioma (MG) patients treated with bevacizumab (BV), a neutralizing monoclonal antibody to vascular endothelial growth factor (VEGF) with or without chemotherapy. In this study, we evaluate the efficacy of BV plus etoposide (E), a topoisomerase inhibitor, among recurrent MG patients. **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 (6-PFS). 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-nine patients (GBM, n = 27; grade 3 MG, n = 32) with a median of 2 prior progressions have enrolled. With a median follow-up of 45 weeks, median overall survival (OS) for GBM and grade 3 MG patients were 46 and 47 weeks, while the 6-PFS is 44% and 40.6%, respectively. The most common toxicities were neutropenia (41%), fatigue (22%), and infection (20%) and were grade 2 in most cases. One patient developed grade 1 intracranial hemorrhage and 1 patient had a grade 4 GI perforation. **Conclusions:** Combination of bevacizumab and etoposide is well tolerated among recurrent MG patients and is associated with encouraging anti-tumor benefit. Accrual is complete and an update of further treatment and follow-up will be presented.

Bevacizumab plus erlotinib for recurrent malignant gliomas. S. Sathornsumetee, A. Desjardins, J. J. Vredenburgh, J. N. Rich, S. Gururangan, A. H. Friedman, H. S. Friedman, D. A. Reardon; Duke University Medical Center, Durham, NC

**Background:** Bevacizumab (B), a neutralizing VEGF monoclonal antibody, has anti-glioma activity as single agent and in combination with cytotoxic therapy. Erlotinib (E), an EGFR tyrosine kinase inhibitor, may exhibit anti-tumor activity in some malignant glioma (MG) patients. B plus E was associated with clinical benefit in several solid tumors. We performed a single-arm, phase II study to evaluate the efficacy of B and E in patients with recurrent MG. **Methods:** The primary endpoint was 6-month progression-free survival (PFS-6). Pharmacokinetics and correla- tive biomarkers were secondary endpoints. E was orally administered daily at 200 mg/day for patients not on enzyme-inducing anticouvanants (EIA) and 500 mg/day for patients on EIA. All patients received 10 mg/kg of B intravenously every two weeks. Key eligibility criteria included: age ≥ 18 years; KPS > 60; > 4 weeks from prior surgery, XRT or chemotherapy. Patients with either > 3 prior progressions, requirement for therapeutic anti-coagulation or acute hemorrhage on pre-treatment imaging were excluded. **Results:** Fifty-six patients with recurrent MG (n = 24 for glioblastoma multiforme [GBM] and n = 32 for anaplastic gliomas [AGs]) were assessable for outcome. The PFS-6 rates were 25% for GBM and 50% for AGs. There was no survival difference between EIA and non-EIA groups. Rash (54% grade 1–2 and 38% grade 3) was the most common side effect. Nausea, diarrhea, and fatigue were common but mostly grade 1–2. Serious side effects were rare and included two patients with pulmonary embolism, single patients with either intestinal perforation, ischemic stroke, gastric bleeding, or nasal septal perforation. Pharmacokinetic and tissue biomarker profiles are in preparation. **Conclusions:** Among heavily pretreated recurrent MG patients, bevacizumab plus erlotinib is tolerated and associated with encouraging anti-tumor benefit.

XL184 is a potent orally bioavailable inhibitor of MET, RET, KIT, and VEGFR2. Elevated levels of VEGFR2 and its ligand VEGF are found in GBM, and elevated levels of MET and KIT are correlated with poor outcomes. We performed a phase II study of bevacizumab plus erlotinib for recurrent malignant gliomas. 2045 General Poster Session (Board #B5), Sun, 8:00 AM - 12:00 PM

**Methods:** The primary endpoint was 6-month progression-free survival (PFS-6). Primary objectives are 6-month progression-free survival (PFS6) and safety. Secondary objectives include response rate (per MacDonald Criteria), duration of response, overall survival, pharmacodynamic and pharmacokinetic parameters, vascular imaging, and changes in steroid usage. **Results:** As of January 6, 2009, all 46 pts have been enrolled. At least 1 post-baseline tumor assessment at 4 weeks was available for 26 pts. Of these, 17 pts had not received prior therapy with an anti-angiogenic agent, whereas 9 pts had received prior therapy with bevacizumab (n = 6), vandetanib (n = 2), or VEGF-TRAP (n = 1). Safety: 6 pts have experienced a total of 9 possibly related grade 3/4 AEs including increased troponin I and myocarditis (n = 1); dehydration, nausea, and fatigue (n = 1); elevated ALT (n = 1); pulmonary embolism (n = 2); and CNS hemorrhage (n = 1). 24/46 (52%) pts have required a dose interruption or reduction due to AEs or SAEs. Baseline characteristics included representative biomarkers are reduced in tumor burden. 1 pt with prior vandetanib therapy has experienced a best radiologic response of < 50% reduction in tumor burden. 1 pt with prior vandetanib therapy has experienced a best radiologic response of > 50%. Of the 4 pts with > 6 months follow-up, 3 remain on study with a sustained radiologic response. **Conclusions:** XI L184 at a dose of 175 mg PO qd, has demonstrated substantial activity in pts with recurrent glioblastoma, with PFS and response rates to be reported.

Combination of bevacizumab and etoposide is well tolerated among recurrent MG patients. 2046 General Poster Session (Board #B6), Sun, 8:00 AM - 12:00 PM

**Methods:** The primary endpoint was 6-month progression-free survival (PFS-6). Secondary objectives are 6-month progression-free survival (PFS6) and safety. **Results:** As of January 6, 2009, all 46 pts have been enrolled. At least 1 post-baseline tumor assessment at 4 weeks was available for 26 pts. Of these, 17 pts had not received prior therapy with an anti-angiogenic agent, whereas 9 pts had received prior therapy with bevacizumab (n = 6), vandetanib (n = 2), or VEGF-TRAP (n = 1). Safety: 6 pts have experienced a total of 9 possibly related grade 3/4 AEs including increased troponin I and myocarditis (n = 1); dehydration, nausea, and fatigue (n = 1); elevated ALT (n = 1); pulmonary embolism (n = 2); and CNS hemorrhage (n = 1). 24/46 (52%) pts have required a dose interruption or reduction due to AEs or SAEs. Baseline characteristics included representative biomarkers are reduced in tumor burden. 1 pt with prior vandetanib therapy has experienced a best radiologic response of < 50% reduction in tumor burden. 1 pt with prior vandetanib therapy has experienced a best radiologic response of > 50%. Of the 4 pts with > 6 months follow-up, 3 remain on study with a sustained radiologic response. **Conclusions:** XI L184 at a dose of 175 mg PO qd, has demonstrated substantial activity in pts with recurrent glioblastoma, with PFS and response rates to be reported.
2048 General Poster Session (Board #810), Sun, 8:00 AM - 12:00 PM Use of neurovascular imaging in GBM patients (pts) to quantify early physiologic changes after treatment with XL184, an inhibitor of multiple receptor tyrosine kinases: Results from a phase II study. A. G. Sorenson, D. Jenning, M. Wang, O. Andronesi, P. Chen, M. Prados, P. Wen, E. Jackson, S. Cha, J. deGroot; Massachusetts General Hospital, Boston, MA; UCSF, San Francisco, CA; Dana-Farber Cancer Institute, Houston, TX; University of California, San Francisco, San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA.

Background: Treatment of recurrent glioblastoma by targeting VEGF has gained recent attention. Bevacizumab (bev) or cediranib block VEGF signaling which is detectable within one day by MRI; early changes on MRI may correlate with clinical outcome. XL184 is a potent orally bioavailable inhibitor of FLT3, VEGF, and RET. Preliminary data in GBM (Muller et al. ASCO, 2014) showed strong effects on tumor vasculature which is qualitatively different than that observed with other antiangiogenic agents. Methods: A multi-center phase II study of XL184 in 46 pts with relapsed or progressive GBM with primary endpoints of 6-month progression free survival and safety is fully enrolled. Vascular neuroimaging including DCE-MRI, CBV/CBF, diffusion, and magnetic resonance spectroscopy (MRS) is performed in these GBM pts treated with XL184. Lesion volumes are also calculated. Assessments are at baseline and every 4 weeks post first dose. Results: As of January 1, 39 pts have undergone imaging. In all 9 pts with imaging available at Day 28, decreases in tumor size were seen on post-Gd T1 (mean drop 51%, SD 31%, p = 0.03 by t-test) and FLAIR MRI (mean drop 33%, SD 43%, p = 0.003) which was consistent with a rapid effect. 11 of 14 pts T1 volume decrease was visible on Day 1 (mean drop 20%, SD 12%, p = 0.01), consistent with the rapid changes seen with VEGF inhibition. Two of 3 pts with no Day 1 decrease in enhancing lesion volume were bev-pretreated. Pts treated with other VEGF inhibitors (vandetanib, VEGF-TRAP) responded similarly to naive pts at Day 1 and 28. Assessment of Ktrans in 5 pts showed a 79% decrease (SD 13%, p = 0.04). MRS from 3 pts showed an increase of the NAA/Choline ratio (10–100%) between the baseline and Day 28 scans, and a decrease in lipid signal (50–100%), consistent with inhibition of tumor progression. Conclusions: Treatment with XL184 results in significant decreases in lesion volume and Ktrans at Day 1 and even greater decreases at Day 28, suggestive of biological activity in GBM.

2050 General Poster Session (Board #812), Sun, 8:00 AM - 12:00 PM Influence of expression of EGFR and PTEN on outcome in patients with primary glioblastoma treated with standard radiochemotherapy and cetuximab: Interim analysis from the GERT-Protocol. S. E. Combs, C. Hartmann, J. Welzel, A. von Deimling, J. Debus, M. Platten, W. Wick, T. Gaiser; University of Heidelberg, Heidelberg, Germany; University Hospital of Heidelberg, Heidelberg, Germany.

Background: The epidermal growth factor receptor (EGFR) is commonly amplified, overexpressed, and mutated in glioblastoma (GBM). Anti-EGFR treatment has been shown to have significant benefit in patients with glioblastoma multiforme (GBM) with EGFRvIII expression in presence of PTEN expression, suggesting a prognostic role of EGFRvIII expression. We determined molecular biomarkers and correlated these with outcome in the GERT trial. Methods: To date, 39 patients were treated with the GERT protocol (Combs SE et al., 2019) evaluating radiochemotherapy (RCHT) with temozolomide (TMZ) and weekly CTX. Pretreatment paraffin-embedded tumor tissue of 32 patients was available for molecular analysis. Twenty-three patients were male, 9 were female. Median age was 49 years. We analyzed amplification of EGFR, expression of EGFR, EGFRvIII, the tumor-suppressor PTEN and (6)-methylguanine DNA methyltransferase (MGMT) gene promoter methylation. Results: Median follow-up was 12 months. Overall survival (OS) at 12 and 24 months was 89% and 42%. Progression-free survival (PFS) was 76% and 45% at 6 and 12 months, respectively. MGMT promoter hypermethylation was detected in 18/32 tumors. Methylated MGMT did not impact PFS or OS (p = 0.48 and p = 0.08). Data on EGFR copy number of 31/32 tumors showed EGFR gene amplification in 11 tumors. EGFR protein expression was found in 23/32 patients. EGFR-amplification did not impact PFS or OS (p = 0.56; p = 0.3). In the 13/32 patients with EGFR expression, this was also not associated with significant increase in PFS or OS (p = 0.05). 8/32 tumors showed PTEN loss, but only 3 patients (2%) had un-methylated MGMT. EGFRvIII protein expression was seen in 5/32 patients, only in tumors with EGFR amplification. Expression of EGFRvIII did not influence PFS (p = 0.26) or OS (p = 0.09). Reduced PTEIN (22/32) did not influence PFS or OS (p = 0.27; p = 0.85). Outcome was not associated with coexpression of EGFRvIII and PTEN (p = 0.15). Conclusion: Expression of EGFRvIII was associated with significant increase in PFS after RCHT with TMZ and CTX. EGFR-amplification, reduction of PTEN expression, and coexpression of EGFRvIII were not impact PFS or OS. Randomized data in the primary treatment of GBM might help identify patients for anti-EGFR therapies.

2049 General Poster Session (Board #811), Sun, 8:00 AM - 12:00 PM Correlative tumor molecular profiling and plasma biomarker analysis in a phase II study of XL184 in patients with progressive or recurrent glioblastoma multiforme (GBM). S. DePrimo, B. Wu, S. Huang, R. Bautista, B. Cancilla, V. Vysotskaja, J. De Groot, M. Prados, R. Bulfer, P. Wen; Exelixis, Inc., South San Francisco, CA; University of Texas M. D. Anderson Cancer Center, Houston, TX; Dana-Farber Cancer Institute, Boston, MA; University of California, San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA.

Background: XL184 is an oral inhibitor of MET, RET, KIT, and VEGFR-2 with potent antitumor effects in preclinical models of GBM. Clinically, elevated levels of MET, KIT, VEGFR-2, and VEGF-A are found in GBM, where MET and KIT levels correlate with poor prognosis. XL184 –201 is a fully humanized GBM study in which patients were screened for archival tumor and serial plasma samples. The encouraging clinical activity of XL184 in this study is the subject of a separate abstract. Methods: Tumor profiling focused on genomic alterations prevalent in GBM, reflecting dysregulation of key signaling pathways (Pathway 2008: 455:1061), or XL184 targets. Plasma samples were analyzed with ELISA assays. Correlation of results with clinical outcomes is a secondary objective of study XL184 –201. Results: Tumor genotyping assessments included EGFR and KIT copy number; PTEN, PIK3CA, PIK3R1, and NF1 sequencing, as well as MGMT and PTEN promoter methylation. Results from the first 12 cases indicate that these molecular biomarkers may be useful for selecting patients for XL184 treatment. Conclusions: Plasma biomarkers confirm pharmacodynamic activity of XL184 in advanced GBM where marked clinical activity has been observed. Upon completion analysis of a full set of biological samples and with mature clinical data, predictive markers for clinical activity of XL184 will be evaluated.
2052 General Poster Session (Board #B14), Sun, 8:00 AM - 12:00 PM
Hematologic adverse events associated with temozolomide (TMZ). J. L. Villano, N. Letarte, J. M. Yu, A. R. Shakir, L. Bressler; University of Illinois at Chicago, Chicago, IL

Background: Secondary acute myeloid leukemia (AML) is reported to occur in 3%-10% of patients treated with alkylating agents for Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, ovarian cancer, breast cancer, and multiple myeloma. The incidence of secondary AML is greatest at 5–10 years after treatment. In general, this effect is often followed by the development of a myelodysplastic syndrome (MDS). TMZ is a pro-drug of methyl-triazeno-imidazole-carboxamide (MITC), an alkylating metabolite of dacarbazine. Chemotherapy induced aplastic anemia is usually dose-related versus an idiopathic mechanism. A small number of fatal cases of TMZ-induced aplastic anemia have been reported. The FDA, in a Drug Safety Newsletter, described 18 cases of aplastic anemia reported between 1999 and 2006. TMZ use in brain tumors and in melanoma is increasing, with little known on the incidence of severe hematologic adverse events. Methods: We searched the FDA MedWatch database for TMZ and obtained all entries submitted to the FDA from November 1, 1997 to September 3, 2008. We also obtained the number of aplastic anemia cases reported from Schering Plough’s Global Pharmaco-vigilance department, as of December 13, 2007. Results: During this time period, 5,127 reports (on any side effect) on 3,490 patients were submitted to MedWatch. Among these patients, we identified 140 cases that we labeled as major hematologic adverse events: agranulocytosis (8 cases), aplasia (42), aplastic anemia (52), leukemia (26), MDS (6), and lymphoma (6). Gender was reported in 133 cases. Of these, 56 were male and 77 were female. The overall mean age in cases of major hematologic adverse events was 54 years. Schering Plough reports 25 cases of aplastic anemia and estimates the frequency to be 10.22 per 100,000 patients exposed to TMZ. Conclusions: TMZ’s major hematologic adverse event profile seems to differ compared with other alkylating chemotherapy. Aplastic anemia is a significant concern with TMZ use and should be disclosed to patients. Risk of leukemia/MDS from our review may also be significant, but length of follow-up is insufficient and the real risk is likely still unknown.

2053 General Poster Session (Board #B15), Sun, 8:00 AM - 12:00 PM
MGMT methylation status as a prognostic factor in anaplastic astrocytomas. A. Tosoni, E. Franceschi, M. Ermani, A. Bacci, L. Volpin, L. Lombardo, G. Ravenna, G. Pinna, R. Poggi, A. A. Brandes; Bellaria Maggiore Hospital, Bologna, Italy; Bellaria Maggiore Hospital, Bologna, Italy; Azienda Ospedale Università, Padova, Italy; Ospedale Civile, Vicenza, Italy; Azienda Ospedaliera, Verona, Italy; Policlinico, Modena, Italy

Background: MGMT methylation status has often been found to be an important prognostic factor in human glioma patients (pts). However, further data on the epigenetic feature are needed before its role in rare diseases such as anaplastic astrocytomas (AA) can be established. Methods: A retrospective analysis was made on a database of 139 AA pts followed prospectively from January 1995 and August 2008. We evaluated only pts who met the following inclusion criteria: age >18 years; PS 0–2; histological diagnosis of AA; postoperative radiotherapy (RT) and chemotherapy (CT). MGMT status was determined with methylation specific PCR. The study aim was to evaluate the role of MGMT methylation status in AA. The log-rank test was employed to evaluate the significance of the prognostic variables. Results: 80 pts (m/f: 46/34, median age: 41 years, range: 18–71 years) were enrolled. MGMT was assessable in 71 of 80 pts (88.8%), being methylated in 30 (42.9%), and unmethylated in 41 (57.7%) pts. Median PFS was 48.6 months (95% CI: 33.8–63.4), median OS 192 months (95% CI: 129–254) and survival 328 months (95% CI: 29–163) and 38 months (95% CI: 18–57.2) in MGMT-methylated and unmethylated pts, respectively (p = 0.09). At univariate analysis, complete resection (p = 0.02), age (p = 0.002), and KPS (p = 0.003) were significantly correlated with PFS. At multivariate analysis only age remains an independent prognostic factor together with age in AA. This datum should provide the background to improve the therapeutic index with temozolomide concurrent with and adjuvant to RT in AA.

2054 General Poster Session (Board #B18), Sun, 8:00 AM - 12:00 PM
Bevacizumab and irinotecan for recurrent oligodendroglial tumors. S. Talibbert, L. A. Vincent, B. Granger, Y. Marie, C. Carpentier, R. Guillevin, A. Bellanger, D. Psimaras, M. Sanson, J. Delatour; Salpetriere Hospital, Paris, France; Faculté Pierre et Marie Curie Paris VI, Paris, France

Background: Treatment with a regimen of bevacizumab/irinotecan has been shown to be effective in recurrent grade 3 and 4 gliomas, but the effect of this regimen against recurrent oligodendroglial tumors has not been specifically studied. Methods: The bevacizumab/irinotecan regimen was retrospectively evaluated in a consecutive series of 25 patients with recurrent oligodendroglial tumors. All patients had failed previous treatment with radiation therapy and at least one line of temozolomide chemotherapy. Bevacizumab (10 mg/kg) and irinotecan (125 or 340 mg/m²) according to the antiepileptic regimen) were delivered every 14 days. Response was measured clinically and on monthly MRI. Results: The objective response rate was 72% (20% complete response, 52% partial response). After a median follow-up (from the first cycle) of 310 days (95% CI, 47–499), the median progression-free survival was 174 days (95% CI, 116–342), and the median OS was 32 months (95% CI, 217 not reached). The 6-month progression-free survival was 42 % (95% CI, 26% to 67%). Among the 20 patients who progressed at the time of the analysis, the radiological pattern of progression was atypical in seven patients with an isolated multifocal or diffuse spread of the FLAIR signal, or an isolated meningeal spread or FLAIR abnormalities preceding contrast-enhance- ment recurrence. Among the 10 patients who are still alive, two are still on follow-up since 6 months with a complete response after, respectively, 10 and 12 months of treatment. Among the 17 patients in whom the status of the main molecular alterations of gliomas could be evaluated (searching for deletions of chromosomes 1p, 19q, 9p, 10q, and amplification of EGFR, MDM2, CDK4), no relation could be found between the response rate and the type of genetic change (including 1p-19q co-deletion). The profile of tolerance was fair, with treatment discontinuation in 20% of patients. Intratumoral hemorrhages occurred in six patients (24%), but the treat- ment had to be discontinued because of symptomatic bleeding in only one patient (4%). Conclusions: This regimen is effective in recurrent oligoden- droglomas, and the overall tolerance is acceptable.

2055 General Poster Session (Board #B19), Sun, 8:00 AM - 12:00 PM
Phase II trial of temozolomide (TMZ) followed by myeloablative chemotherapy with autologous peripheral blood progenitor cell rescue (APBPCR) for newly diagnosed anaplastic oligodendroglioma: An Oligodendroglioma Study Group trial. T. J. Kaley, J. J. Raizer, N. Paleologos, T. Kewalramani, S. Grimm, D. El Nokal, J. G. Cairncross, E. Abrey; Washington Alzheimer Cancer Center, New York, NY; Northshore Memorial Hospital, Chicago, IL; Evanston Hospital, Evanston, IL; Lahey Clinic Medical Center, Burlington, MA; Massachusetts General Hospital , Boston, MA; University of Calgary , AB, Canada

Background: Treatment of anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytomas (AOA) is controversial. Radiotherapy (RT) remains the standard therapy, but not without toxicity. Exploiting the chemosensitivity of these tumors using myeloablative chemotherapy with APBPCR is a potential strategy to defer RT. We previously reported results using induction PCV chemotherapy; subsequently the induction regimen was changed to temozolomide (TMZ) which is reported here. Methods: Patients were treated with six cycles of TMZ at 200mg/m² on standard 5/28 day schedule. MRI was performed after three cycles and then after six cycles. Patients with surgical gross total resection who maintained response or patients who responded to temozolomide (CR or PR defined as >50% reduction in tumor) were eligible for myeloablative chemotherapy with thiotepa 250mg/m²/day for three days followed by busulfan 3.2mg/kg/day for three days, followed by APBPCR. 1p/9q status was analyzed prospectively; however, patients were enrolled without regard to deletion status. Results: 19 patients (16 AO, 2 AOA, 1 low-grade oligodendroglioma with radiographic features suggestive of high-grade tumor) with a median age of 42 (28–56) and KPS of 90 (70–100) were enrolled. 13 patients had co-deletion of 1p/19q; 2 had intact 1p/19q; 1 pt had biopsy without genetic analysis. Eleven patients underwent APBPCR; 10 patients either maintained surgical CR (9) or had a response to TMZ (1) and went on to transplant; one surgical CR pt refused transplant. Six patients were ineligible for transplant because of best response of SD (2), PD (2), or 1p deletion (1). Eleven patients were undergoing receiving induction TMZ. Median progression-free (PFS) and overall survival (OS) have not been reached at a median follow-up of 20 months. 2 of the 10 patients who underwent APBPCR recurred, one at 16.1 and one at 34.2 months. No veno-occlusive disease was observed during transplant and no treatment-related deaths occurred. Conclusions: TMZ followed by myeloabla- tive chemotherapy with APBPCR can be safely administered to newly diagnosed AO patients.
2056 General Poster Session (Board #820), Sun, 8:00 AM - 12:00 PM
Neurocognitive function in patients with glioblastoma multiforme in first or second relapse treated with bevacizumab in the BRAIN study, J. S. Wefel, T. Cloughesy, J. Zazzali, J. Y. H. S. Friedman, for the BRAIN Investigators; M.D. Anderson Cancer Center, Houston, TX; UCLA School of Medicine, Los Angeles, CA; Genentech, Inc., South San Francisco, CA; Duke University, Durham, NC

Background: Patients with glioblastoma multiforme (GBM) suffer from neurocognitive decline due to both the disease and its treatment. We analyzed changes in neurocognitive function of patients with recurrent GBM who participated in the BRAIN study, a phase II, multicenter, randomized, noncomparative clinical trial which assessed the efficacy and safety of bevacizumab alone or in combination with irinotecan.

Methods: Eighty-five patients who participated in the bevacizumab-only group of the BRAIN study were assessed with the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test parts A (TMTA) and B (TMTB), and the Controlled Oral Word Association (COWA) test. Assessments were conducted at baseline and then every 6 weeks while patients remained on study drug, up to 52 weeks. Changes in neurocognitive function from baseline to Week 6 was categorized as improved, stable, or declined, using the reliable change index. Changes were confirmed at the next assessment, when available. Results were not adjusted for practice effects.

Results: Between 93 and 98% of patients completed each test at baseline and Week 6. The majority of patients demonstrated stable performance on each test at Week 6, relative to baseline. With COWA word list A, 180–256 patients demonstrated improved performance on one or more tests at Week 6.

Conclusions: Preliminary results suggest that the majority of patients with recurrent GBM who were treated with bevacizumab alone in the BRAIN study demonstrated improved neurocognitive function during the first 6 weeks of treatment. Changes across tasks and associations with measures of clinical efficacy, patient characteristics, and concomitant medications will be explored.

2058 General Poster Session (Board #96), Sun, 8:00 AM - 12:00 PM
Prognostic significance of early changes in the apparent diffusion coefficient that occurs after treatment of patients with glioblastoma multiforme with bevacizumab, M. Paldino, A. Desjardins, H. S. Friedman, J. J. Vredenburgh, D. P. Barboriak; Duke University Medical Center, Durham, NC

Background: To determine the prognostic significance of changes in parameters derived from diffusion tensor imaging (DTI) that occur in response to combination chemotherapy with the antiangiogenic agent bevacizumab (BEV) in patients with recurrent glioblastoma multiforme (GBM). Methods: Sixty-eight patients (10 men, 58 women; age range 32–72 years) with recurrent GBM underwent serial 1.5T MRI imaging. Axial single-shot echo planar DTI (TR/TE 6000/100; flip angle 90 degrees; voxel: 1.72 x 1.72 x 5mm; b value of 1000 sec/mm²; 12 directions) was obtained on scans performed 3 days and 1 day prior to and 1 day after initiation of therapy with BEV and irinotecan (CPT-11). Clinical follow-up and survival status was documented up to 20 months after the date of initial MR imaging. Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) maps were aligned to whole brain contrast-enhanced 3D FLAIR and 3D FLAIR image volumes (1 mm isotropic voxels) using a rigid body normalized mutual information algorithm. Based on two pre-treatment scans, the 95% confidence limits for change (95%CL) in ADC and FA were calculated in volumes of tumor-related contrast-enhancement (TRE) and FLAIR signal abnormality (FA). A patient was considered to have a change in FA or ADC after therapy if the difference between the pre- and post-treatment values was greater than the 95% CL for that parameter. Progression was defined on contrast-enhanced MRI using MacDonald criteria by neuro-oncologists blinded to the DTI findings. Survival was compared using the log rank test. Results: DTI detected a change in ADC within FSA after therapy in three patients (p < 0.0012) and progression free (p < 0.015) survival than those with no change. Median survival in the patient group with a change in ADC was 24.7 (95% CI [17.3, 39.4]) weeks and 56.4 (95% CI [41.7, 90]) weeks in those patients with no change. Conclusions: In patients with GBM treated with BEV and CPT-11, a change in ADC after therapy in areas of FSA is associated with decreased survival. Parameters derived from DTI may, therefore, potentially serve as early markers of treatment failure in patients with GBM.

2057 General Poster Session (Board #65), Sun, 8:00 AM - 12:00 PM
The infiltrative, diffuse pattern of recurrence in patients with malignant gliomas treated with bevacizumab. L. Potthast, S. Chowdhary, E. Pan, D. Yu, W. Zhu, S. Brem; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: There is no standard of care for recurrent gliomas; however, bevacizumab is often used as a salvage chemotherapy regimen. A diffuse, infiltrative pattern of recurrence, as evidenced by MR imaging, was seen manifesting as disease or progression in patients with GBM, in combination with subependymal spread. Methods: We conducted a retrospective analysis of 40 recurrent glioma patients followed at Moffitt Cancer Center from September 2006 through December 2008 treated with bevacizumab alone or in combination with irinotecan. Histologies included glioblastoma (GB), anaplastic astrocytoma (AA), anaplastic oligodendrogliomas (AOA), and low-grade astrocytomas. Rate of diffuse, infiltrative recurrence, progression free survival (PFS) and overall survival (OS) were analyzed and correlated with respect to specific prognostic variables.

Results: 38% (15) of the patients were female and 63% (25) were male. The median (range) age was 51 (20–72) years. The median (range) KPS was 80 (50–100). Twenty-six (65%) patients had GB, 8 (20%) AA, 2 (5%) AO, and 3 (8%) AOA and 1 (3%) had LGA. Five (13%) patients had a gross total resection (GTR), 23 (58%) a subtotal resection (STR) and 12 (30%) had biopsy only. The median (range) number of prior therapies was 2 (1–7). At time of analysis 28 (70%) patients had died. Incidence of diffuse, infiltrative recurrence was seen in 8 (20%) of patients (95% CI: [9%, 36%]). This recurrence seems to be negatively associated with patient age (p = 0.015) and male patients are at a higher risk of recurrence (OR: 5.0). 

Conclusions: There appears to be an increase in a diffuse, infiltrative pattern of recurrence among recurrent glioma patients treated with bevacizumab as a salvage regimen. In our experience, this appears most prevalent in patients less than 50 years of age. It is unclear why the disparity among this subset of patients occurs, however, we hypothesize that this may once again highlight the distinct tumor biology among young glioma patients. The impact of this observation on clinical decision making on whether to utilize bevacizumab in young recurrent glioma patients warrants further investigation.

2059 General Poster Session (Board #37), Sun, 8:00 AM - 12:00 PM
Correlation of serum urokinase plasminogen activator (uPA) to progression of recurrent malignant glioma during bevacizumab treatment: A marker of invasive phenotype and a candidate for monitoring therapy. O. L. Chinot, F. Boudouresque, C. Bequet, M. Barrie, A. Thiebaut, M. Maffa, D. Autran, L. Ouafik; CHU Timone, Marseille, France

Background: Identification of circulating markers that predict tumor response or reflect progression is of crucial importance when using antiangiogenic agents. However, to date, no such parameters have been identified particularly for bevacizumab, for which, recently, increasing data have supported a role in patient with recurrent malignant glioma. Methods: Serial serum levels of VEGF, VEGF-R2, FGF, SDF-a, urokinase plasminogen activator (uPA), plasminogen activator inhibitor type I (PAI-1), and metalloprotease type 9 (MMP9) were determined in a cohort of 32 patients treated with bevacizumab and irinotecan for recurrent malignant glioma. Samples were collected at the start of treatment and then at 4 weeks intervals until progression. Serum levels were measured using an enzyme-linked immunosorbent assay. Progression was defined by MacDonald’s criteria, modified by integrating increase of infiltration as measured on MRI by Flair sequence. All subjects were followed for PFS and OS. Cox model analysis is used for correlation between markers and clinical outcome.

Results: This preliminary analysis is restricted to pre-treatment (D0; n = 32), day 30 (D30; n = 27), and at progression time (DP; n = 15). None of the pre-treatment serum level (n = 32) significantly affect PFS or OS although uPA and MMP9 tend to influence OS. Decrease of median level of all serum markers except PAI1 and VEGF-R2 is observed from D0 to D30 under bevacizumab therapy, but only uPA and FGF variations tend to impact clinical outcome. From D30 to DP, increase of uPA is correlated to PFS (p = 0.028) while the observed increase of FGF and SDF-a fail to reach significant correlation to PFS and OS. Conclusions: Increase of uPA serum level appear to be correlated to disease progression for patients with recurrent malignant glioma treated with bevacizumab and may reflect the invasive phenotype of glioma progression. Serum uPA may help in assessing treatment response under bevacizumab and warrant further studies.
TTP and OS were 6.5 (95% CI: 2.7–10.2) and 9.4 (95% CI: 6.3–12.6) months. Five patients achieved radiographic response (5–10 mg/kg) every other week was combined with cytotoxic agents: four women and two men, with a median age of 29 years (range, 20–65). Prior treatment included RT in all and temozolomide in four. Bevacizumab (5–10 mg/kg) every other week was combined with cytotoxic agents: irinotecan (3), carboplatin (2), or temozolomide (1). Five patients achieved partial response (83%); one patient the disease was stable. Median TTP and OS were 6.5 (95% CI: 2.7–10.2) and 9.4 (95% CI: 6.3–12.6) months, respectively, with a median follow up of 18.7 months for the two surviving patients. One additional patient is initiating bevacizumab mono-therapy (not included in this analysis). **Conclusions:** Bevacizumab has efficacy in the treatment of recurrent ependymoma. Prospective study is warranted.

**Methods:** Twenty-five eligible patients were enrolled with median age 57 years (range 29–81) and median Karnofsky performance status (KPS) score 90 (range 60–100). Sixteen patients (64%) received gefitinib or gefitinib in patients with recurrent meningiomas. A. D. Norden, J. J. Raizer, K. R. Lamborn, L. E. Abrey, S. M. Chang, M. R. Gilbert, T. F. Cloughesy, M. D. Prados, F. Liebermann, P. Wen; Dana-Farber Cancer Institute, Boston, MA; Northwestern University, Chicago, IL; University of California, San Francisco, San Francisco, CA; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Texas M. D. Anderson Cancer Center, Houston, TX; University of California, Los Angeles, Los Angeles, CA; University of Pittsburgh, Pittsburgh, PA

**Background:** No effective treatment is available for recurrent meningiomas when surgical and radiation options are exhausted. The epidermal growth factor receptor (EGFR) is often over-expressed in meningiomas and may promote tumor growth. In open-label, single arm phase II studies of the EGFR inhibitors gefitinib (NABTC 00–01) and erlotinib (NABTC 01–03) for recurrent malignant gliomas, we included exploratory subsets of recurrent meningioma patients. We have pooled the data and report the results here. **Methods:** Patients with recurrent histologically confirmed meningiomas and no more than two previous chemotherapy regimens were treated with gefitinib 500 mg/day or erlotinib 150 mg/day until tumor progression or unacceptable toxicity. **Results:** Twenty-five eligible patients were enrolled with median age 57 years (range 29–81) and median Karnofsky performance status (KPS) score 90 (range 60–100). Sixteen patients (64%) received gefitinib or gefitinib in meningiomas and a (5 consecutive days), once every 4 weeks, defined as a single cycle. **Results:** There were six patients, four women and two men, with a median age of 29 years (range, 20–65). Prior treatment included RT in all and temozolomide in four. Bevacizumab (5–10 mg/kg) every other week was combined with cytotoxic agents: irinotecan (3), carboplatin (2), or temozolomide (1). Five patients achieved partial response (83%); one patient the disease was stable. Median TTP and OS were 6.5 (95% CI: 2.7–10.2) and 9.4 (95% CI: 6.3–12.6) months, respectively, with a median follow up of 18.7 months for the two surviving patients. One additional patient is initiating bevacizumab mono-therapy (not included in this analysis). **Conclusions:** Bevacizumab has efficacy in the treatment of recurrent ependymoma. Prospective study is warranted.

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**Efficacy and tolerability of intrathecal liposomal cytarabine for central nervous system embryonal tumors.** S. Partap, A. P. Murphy, H. Vogel, P. D. Barnes, M. S. Edwards, P. G. Fisher; Stanford University, Stanford, CA

**Background:** Liposomal cytarabine (DepoCyt) is a sustained-release intrathecal (IT) preparation of cytarabine, formulated by encapsulating the drug in spherical aqueous chambers within a lipid matrix. While proven effective in lymphomatous meningitis, this drug has shown some activity in medulloblastoma (MB) with spinal metastases in largest single institution studies.

**Methods:** We reviewed all patients at our institution treated with liposomal cytarabine for primary central nervous system (CNS) embryonal tumors (MB, primitive neuroectodermal tumor (PNET), and atypical teratoid rhabdoid tumor (ATRT)).

**Results:** A cohort of 17 patients were treated with liposomal cytarabine at diagnosis of CNS embryonal tumor (2 PNET, 3 ATRT) or relapse (12 MB [7 average-risk, 5 high-risk]; nine had leptomeningeal metastases. Drug was dosed at 2 mg/kg up to 50, every 2 weeks to monthly, along with dexamethasone. Concurrent systemic chemotherapy was given in 16 patients. Median age at first dose was 10.8 years (range 0.9 to 27.9 years). A total of 102 doses were administered (lumbar IT 76, Ommaya intraventricular 36) with a mean of six treatments (range 1–16). Only three administrations were associated with adverse effects of arachnoiditis or headache; no dose reductions were required. Median overall survival from relapse was 11.8 months. All six evaluable patients with malignant cerebrospinal fluid (CSF) cytology and treated with at least two doses cleared their spinal fluid (mean 3 doses, range 1–5). No patient developed malignant CSF cytology while receiving liposomal cytarabine. Ten patients developed progressive disease and died, with only one later recurrence in the spinal fluid. Seven patients remain alive (4 initial and 3 relapse) with five in continuous complete remission (2 ATRT) for a median 13.7 months from first liposomal cytarabine. Conclusions: Liposomal cytarabine was well tolerated and easily administered. All patients with neoplastic meningitis cleared malignant cells from their spinal fluid after treatment with IT liposomal cytarabine and systemic chemotherapy. One-third of our cohort remains in remission from otherwise fatal diagnoses. Our findings warrant a phase II trial of liposomal cytarabine in newly diagnosed or recurrent CNS embryonal tumors.

**Extraneural metastasis of medulloblastoma.** A. Mazloom, A. H. Zangeneh, B. S. Teh, A. C. Paulino; Methodist Hospital System, Houston, TX

**Background:** Medulloblastoma is the most common childhood intracranial tumor to spread extraneurally. Information regarding prognostic factors and best therapeutic approach of extraneural metastasis (ENM) of medulloblastoma is mostly limited to case reports. The purpose of this study was to perform a comprehensive literature review and analysis of reported cases dealing with ENM to identify the characteristics, prognostic factors, optimal treatment modalities, and survival of these patients.

**Methods:** A PubMed search of English language articles from 1963–2007 was performed, yielding 47 articles with 119 patients. Factors analyzed included age, time interval to ENM, CNS involvement at the time of ENM, treatment, and outcome. Results: Location of ENM included bone in 84%, bone marrow in 27%, lung in 6%, liver in 6%, and lymph nodes in 15%. Of patients with available data regarding location of RT after ENM, 87% of patients received this treatment to the site of ENM. The 1-year disease free survival (DFS) and overall survival (OS) after the diagnosis of ENM was 35% and 42%, respectively. The 1-year OS for patients with and without radiotherapy (RT) after ENM was 58% and 35%, respectively (p = 0.019). For patients without CNS involvement at the time of ENM the 1-year OS for those treated with and without RT was 82% and 51%, respectively (p = 0.030), however RT did not significantly improve OS for those with CNS involvement. ENM in the lung or liver was found to be a negative prognostic factor (p = 0.002). 1-year OS of patients with time interval to ENM of <18 months was 25% while those with time interval greater than 18 months was 61% (p = 0.001). Conclusions: Negative prognostic factors for patients with ENM include CNS involvement at the time of ENM, lung or liver involvement, and duration to ENM <18 months. Patients without CNS involvement who received RT after ENM had an OS and DFS benefit compared to those not receiving RT.
A retrospective survival analysis of whole brain radiotherapy (WBRT) for brain metastases at Mount Vernon Cancer Centre (MVCC). P. J. Mulholland, M. Assoku, P. Sasienski; University College London Hospital and Mount Vernon Cancer Centre, London, United Kingdom; CRUK, Wolfson Institute, Barts & Queen Mary University, London, United Kingdom

Background: The primary purpose of this retrospective study was to determine the survival of patients with brain metastases following WBRT with regards to the influence of tumor type. Methods: From treatment records we identified 1,926 patients with brain metastases from solid tumors who were treated with WBRT at MVCC between February 1992 and March 2008. Dates of death were sourced from records at MVCC, the Cancer Registry and GP practices. Results: We obtained dates of death for patients with lung (n = 804), breast (n = 457), colorectal (n = 129), skin (n = 119), kidney (n = 82) and unknown (n = 124) cancers. 42 patients were excluded from analysis as their tumor types were unspecified. A heterogeneous group of 169 patients with a variety of other primary tumor types were also excluded from our primary analyses. 22% of the patients died within the first month following WBRT and only 2.4% remained alive at 2 years. Log-rank analysis of age < 65 versus ≥ 65 demonstrated improved survival for the former for the colorectal, lung, and skin tumor types (p = 0.0048, 0.0001, and 0.0456 respectively). This relationship did not reach significance for the breast, unknown primary, and renal cancer groups (p = 0.14, 0.13, and 0.06 respectively). With the exception of colorectal cancer, the analysis of the effect of treatment on survival did not reveal recent improvements in survival for patients with brain metastases. An improvement in survival was experienced by the colorectal subgroup treated after March 2006 (HR = 0.51 95% CI 0.27- 0.96). Conclusions: Our data validate an age as an important prognostic factor for many tumor types with notable exceptions for as of now yet undetermined reasons. Metastasis to the brain is a late stage feature of colorectal malignancy. The survival of the majority of patients undergoing WBRT for brain metastases is poor and with the possible exception of colorectal cancer, has not improved over the last decade.

1st site Age n % survival 95% Conf 4 months 6 months 12 months
Breast <65 335 39% 33-44% 24% 19-28% 11% 8-14%
≥65 122 31% 23-39% 20% 13-27% 11% 6-17%
Colorectal <65 68 35% 24-47% 19% 11-29% 0% 0%
≥65 61 15% 7-25% 10% 4-19% 0% 0%
Kidney <65 53 43% 30-56% 30% 19-43% 21% 11-32%
≥65 29 24% 11-41% 21% 8-37% 10% 3-24%
Lung <65 414 37% 33-42% 22% 19-27% 6% 4-9%
≥65 390 22% 18-26% 13% 10-16% 5% 3-8%
Skin <65 70 33% 22-44% 17% 9-27% 6% 2-13%
≥65 49 16% 8-28% 4% 1-12% 6% 3-9%
Unknown 1* <65 50 38% 25-51% 18% 9-30% 6% 2-15%
≥65 74 24% 15-35% 16% 9-25% 5% 2-12%

2070 General Poster Session (Board #B5), Sun, 8:00 AM - 12:00 PM

Background: The incidence of PCNSL is increasing and is highest in those ≥65 years of age. Systemic chemotherapy (CT) ± radiotherapy (RT) improves survival, but treatment related toxicity is greatest in this population. The optimal treatment has yet to be determined. The aim of this study was to characterize the patient demographics with PCNSL and to identify outcomes related to treatment. Methods: We identified patients ≥65 years of age treated for PCNSL from 1986 to 2008. Charts were reviewed for demographics, treatment details, tumor progression, and survival. Approval for this study was obtained from the IRB at MSKCC. Results: 174 patients were identified with a median age of 72 years (range: 65–89). 60% of patients had a stereotactic biopsy for diagnosis; 93% had a histologic or cytologic diagnosis. 14% of patients had evidence of systemic involvement with detailed staging evaluation. 82% of patients received a high-dose methotrexate (3.5g/m2) regimen, only 13% did not receive CT. Among the patients who received CT, 76% had a radiographic response (CR+PR), 3% had stable disease while 12% progressed. Only 26% had RT as part of initial therapy. CR rate to initial therapy was 67%, 52% of these patients eventually relapsed. Median time to progression was 24 months (range: 1-91). Among the patients who relapsed, 85% received salvage therapy consisting of CT (n = 42), RT (n = 14), or both (n = 7) while 15% received no further treatment. 48% of patients had a CR or PR to salvage therapy while 26% had PD; the remainder were not evaluated. Median overall survival for the entire cohort was 25 months (range: 0.5 to 177+) with a 3-year survival of 36%. 17% developed late treatment-related neurologic toxicity. Administration of RT was associated with the development of neurotoxicity (p < 0.0001). 36% of patients received no further treatment. 17% developed late treatment related toxicities. Conclusion: Our results suggest a production of CXCL13 within the CNS of CNS lymphoma patients which decreases with response to therapy. Thus, CXCL13 may represent a marker for further diagnostic and prognostic studies.

2071 General Poster Session (Board #D6), Sun, 8:00 AM - 12:00 PM
CXCL13 and CXCL12 in central nervous system (CNS) lymphoma patients. L. Fischer, A. Koriel, S. Pfeiffer, P. Kiewe, H. Volk, H. Cakirgul, T. Widmann, L. Thiel; Charité Universitätsmedizin Berlin, Berlin, Germany; University Hospital Saarland, Homburg, Germany

Background: Homing of malignant lymphocytes to the CNS may play a role in the pathogenesis of CNS lymphoma. Recently, the expression of the chemokine receptors CXCR4 and CXCR5 as well as their chemokine ligands CXCL12 and CXCL13 by tumor cells in primary CNS lymphoma (PCNSL) has been demonstrated. In this study, we evaluated CXCL12 and CXCL13 in cerebrospinal fluid (CSF) and serum of patients with CNS lymphoma. Methods: Samples from 30 patients with CNS lymphoma (23 with PCNSL and seven with secondary CNS lymphoma) and 40 controls (10 patients with other CNS malignancies and 30 without a malignant CNS disease) were examined. CXCL12 and CXCL13 concentrations were measured using enzyme-linked immunosorbent assays. The grade of brain blood barrier (BBB) disruption was estimated by the CSF/serum albumin ratio. Results: CNS lymphoma patients and controls did not differ in CXCL12 serum and CSF levels. Serum levels of CXCL13 were generally lower. CXCL13 CSF levels, however, were high only in CNS lymphoma patients but not in controls (p < 0.0001). Chemokine levels in CSF and serum did not correlate. In CNS lymphoma CXCL13 concentration in CSF correlated with BBB disruption (R = 0.66, p = 0.003). Elevated CSF levels of CXCL12 and CXCL13 were measured in seven CNS lymphoma patients decreased in five patients which responded to chemotherapy, and increased in two with lymphoma progression. Conclusions: Our results suggest a production of CXCL13 within the CNS of CNS lymphoma patients which decreases with response to therapy. Thus, CXCL13 may represent a marker for further diagnostic and prognostic studies.
2072 General Poster Session (Board #07), Sun, 8:00 AM - 12:00 PM
Combination immunochemotherapy followed by reduced dose (rd) whole brain radiation therapy (WBRT) in an expanded cohort of patients with newly diagnosed primary central nervous system lymphoma (PCNSL). L. J. Abery, D. Corea, J. Yahaolom, J. Raizer, S. Grimm, R. Lai, D. Schiff, B. Grant, E. M. C. Development, St. Vincent’s Medical Center, New York, NY; Northwestern University, Chicago, IL; Columbia University, New York, NY; University Of Virginia, Charlottesville, VA; University of Vermont, Burlington, VT.

Background: High-dose methotrexate (M)-based chemotherapy combined with WBRT has improved survival in patients with PCNSL. However, disease recurrence and treatment-related neurotoxicity are significant problems in this population. The prospective use of the treatment protocol used in this study was extended and previously described this feasibility. This study was addressed to assess the long-term outcome of this approach in an expanded cohort.

Methods: Patients were treated with R-MPV (d1 R 500mg/m2; d2 M 3.5gm/m2; vincristine 1.4mg/m2; d1–7 procarbazine 100 mg/m2/d on odd-cycles). Patients with a PR after five cycles received two additional cycles. Patients with a CR received rdWBRT (2530CqGy), otherwise patients received standard WBRT (4500CqGy). Patients then received two cycles of Ara-C 3gm/m2. Prospective neuropsychological evaluations were performed at baseline, before WBRT, and every 6 months thereafter.

Results: From October 2002 to September 2008, 50 patients were enrolled (22 female, 28 male), median age 59.5 years (range 30–79 years). Due to neutropenia in two of the first five patients, all subsequent patients received G-CSF. 42 patients were assessable for response (4 patients died due to progressive disease prior to completing the first cycle of treatment, 4 patients – treatment ongoing). 33 patients (79%) had a CR, of whom 29 received rdWBRT (3 refused, 1 died). At median follow-up of 3 years for survivors the median OS has not been reached and the estimated 2-year OS is 68%. Patients treated with rdWBRT have a median follow up of 38 months: 21 (72%) are alive with no evidence of disease, seven (24%) relapsed, and one died of unknown causes. Eight of 21 (38%) who are alive from progressive disease prior to completing the first cycle of treatment, 4 patients – treatment ongoing). 33 patients (79%) had a CR, of whom 29 received rdWBRT (3 refused, 1 died). At median follow-up of 3 years for survivors the median OS has not been reached and the estimated 2-year OS is 68%. Patients treated with rdWBRT have a median follow up of 38 months: 21 (72%) are alive with no evidence of disease, seven (24%) relapsed, and one died of unknown causes. Eight of 21 (38%) who are alive from progressive disease prior to completing the first cycle of treatment, 4 patients – treatment ongoing). 33 patients (79%) had a CR, of whom 29 received rdWBRT (3 refused, 1 died). At median follow-up of 3 years for survivors the median OS has not been reached and the estimated 2-year OS is 68%.

Conclusions: Prolonged follow-up of an expanded cohort of patients treated with immunochemotherapy followed by rdWBRT for patients with an initial CR continues to support our initial conclusions that this approach results in excellent disease control with no observed treatment-related neurotoxicity.

2074 General Poster Session (Board #11), Sun, 8:00 AM - 12:00 PM

Background: Neurofibromatosis 1 (NF1), NF2, and schwannomatosis are a unique patient population. Although pediatric and adult ependymomas are associated with NF1, NF2, and schwannomatosis. In addition, WBMRI may prove useful in situ hybridization validated observed genetic events. Results: Gene expression profiling segregated tumors by site and identified disease subgroups within each anatomical region (4 ST, 4 PF, 1 SP). miRNA expression profiles identified these same subgroups, indicating that they are biologically distinct. Subgroup-specific gene expression profiles were dictated by proliferation, development, and polyplody pathways. Genes and miRNA expression were validated, of which 80 displayed copy number drive expression. These genetic alterations targeted specific cellular functions (e.g., cell adhesion, cell cycle, metabolic, development), and pathways (e.g., NOTCH, EPHRIN, TP53). Our cohort also included five sample sets consisting of primary tumors and at least two corresponding relapses. Genomic analysis of these tumors identified large chromosomal alterations as well as focal losses and gains associated with disease relapse. Conclusions: We present a highly comprehensive view of the ependymoma genome, including 80 previously unrecognized candidate TSG and oncogenes that may afford diagnostic and therapeutic targets.

2075 General Poster Session (Board #010), Sun, 8:00 AM - 12:00 PM
A comprehensive view of the structure and expression of the ependymoma genome at presentation and relapse. K. D. Wright, V. Rand, S. E. Leary, S. Mack, B. Coyle, Y. Gillespie, J. Allen, M. D. Taylor, R. Grundy, J. R. Gilbertson; St. Jude Children’s Research Hospital, Memphis, TN; New York University, New York, NY; Northwestern University, Chicago, IL; Columbia University, New York, NY; University Of Virginia, Charlottesville, VA; University of Vermont, Burlington, VT.

Background: Although pediatric and adult ependymomas are associated with NF1, NF2, and schwannomatosis. In addition, WBMRI scan is a powerful tool to evaluate the number, size, and distribution of internal tumors. The prevalence of internal tumors is not known because current estimates are partly by developmental regulatory genes and partly by large chromosomal suppressor syndromes.

Methods: We performed WBMRIs in subjects with NF1, NF2, or schwannomatosis as part of an IRB-approved research study. Each subject was imaged from head to ankles in the supine position over a period of 10–20 min. The median number of tumors in affected individuals was 5 (range, 1 to 63 tumors). Overall, the legs harbored the greatest number of tumors (33%), followed by the trunk/abdomen (27%) and head/neck (7%). Only 40% of internal tumors were classified as plexiform. The legs were imaged the most (50%), followed by the trunk/abdomen (27%), head/neck (7%), and thoracic spine (3%). The number of tumors per patient ranged from 15–30 points, and patients were divided into three groups (14–18, 19–23, and 24–27 points). In the test group, the 6-month OS rates were 98% for those with 19–23 points, and 78% for those with 20–25 points, and 78% for those with 26–30 points (p < 0.0001). The corresponding OS rates in the validation group were 72%, 72%, and 73%, respectively (p < 0.0001).

Conclusions: WBMRIs can be a powerful tool to evaluate the number, size, and distribution of internal tumors in patients with neurofibromatosis. This technique provides unique phenotypic information for genetic studies on NF1, NF2, and schwannomatosis. In addition, WBMRIs may prove useful in identifying individual patients at high risk for complications (such as neurologic dysfunction or malignant transformation) due to heavy internal tumor burden and in determining the efficacy of antitumor drugs in this unique patient population.
2076 General Poster Session (Board #013), Sun, 8:00 AM - 12:00 PM

Functional pathway mapping of human glioblastoma multiforme and brain metastases for patient tailored therapy. M. Khalil, J. Wulfkuhle, H. Filimore, J. Deng, L. Liotta, E. Petricoin III, J. Watson, B. Broadus; George Mason University, Manassas, VA; Virginia Commonwealth University, Richmond, VA; Virginia Commonwealth University/Inova Campus, Falls Church, VA

Background: Genome scanning analysis of human glioblastoma multiforme (GBM) has suggested that this form of cancer is a protein pathway disease. Since genomic analysis cannot directly predict an analysis of protein pathway activation is required. With the current focus on targeted translational therapeutic modalities, a functional understanding of the GBM signaling repertoire is critical, and yet largely unknown. Methods: Twelve patients were included in this study including two primary GBMs (one recurrent) and two brain metastases (1 breast and 1 lung). Pure tumor cell populations were obtained from fixed frozen tissue sections using Laser Capture Microdissection. Protein pathway mapping was performed using Reverse Phase Protein Microarrays (RPMA) whereby the activity of 85 key signaling proteins was quantitatively measured at once. Unsupervised and supervised analysis was used to explore pathway activation. Results: Unsupervised hierarchical clustering of all tumors in the study set revealed largely patient-specific signaling portraits yet also identified distinct pathway subsets. The two metastatic tumors clustered separately and distinctly from the GBMs. The GBM specimens clustered according to pathway activity. Statistical analysis demonstrated significant correlations between certain phosphorylated endpoints detected and overall survival. Phosphorylation of coflin (S3) was associated with shorter survival time, while Akt-Ser473 phosphorylation (S3) was associated with longer overall survival. Conclusions: This study represents the first comprehensive proteomic analysis of human GBM pathway mapping to date. Since certain pathway biomarkers are themselves being targeted by current investigational therapies, the ability to map pathway activation and identify critical pathway biomarkers can lead to targeted therapeutics tailored to each patient’s tumor. The ability to segregate short from long-term survivors according to protein pathway activation is promising.

2077 General Poster Session (Board #014), Sun, 8:00 AM - 12:00 PM

Effect of the combination of retinoic acid and rapamycin on cerebellar granule cell and medulloblastoma proliferation. T. R. Gershon, A. Shirazi, A. M. Kenney; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Cerebellar granule cell precursors (CGCPs) are neuroblasts that proliferate in early postnatal life and may become transformed, giving rise to medulloblastoma. The proliferation of CGCPs is driven by mitogenic signals including Sonic Hedgehog (SHH), and growth factors that activate the mammalian target of rapamycin (mTOR). Dysregulation of these intercellular signal pathways promote medulloblastoma formation. We propose that microenvironmental signals that down-regulate the response of CGCPs to mitogens may inhibit medulloblastoma growth. Retinoic acid (RA) is an endogenous signaling molecule with potent anti-neoplastic effects. We investigated whether SHH, mTOR, and RA signaling pathways interact to regulate CGCP and medulloblastoma proliferation. Methods: We measured proliferation in cultured CGCP explants and the CGCP-derived murine medulloblastoma cell line PZp53 using quantitative phosphohistone-H3 immunocytochemistry. We examined the effects of adding to culture medium SHH, the mTOR inhibitor rapamycin, and all trans-RA (ATRA) in specific combinations. We compared CGCPs from wild type animals to CGCPs from mice with constitutive mTOR activation due to TSC2 mutation. Results: A minimum concentration of 1uM ATRA inhibited SHH-driven CGCP proliferation measurably but incompletely, while 10uM ATRA caused widespread necrosis. CGCPs from TSC2 mutant animals, in which mTOR was constitutively active, were 50% less effected by 1uM ATRA than wild type CGCPs. PZp53 medulloblastoma cells were relatively resistant to ATRA, tolerating 10uM ATRA but the persistent proliferation of rapamycin was decreased but did not eliminate PZp53 proliferation. The combination of rapamycin and ATRA, however, acted synergistically, suppressing proliferation >90%. This suppression persisted at 10-fold lower drug concentrations. Conclusions: CGCPs and CGCP-derived medulloblastoma cells integrate signals transmitted by SHH, mTOR, and RA pathways. These signaling pathways can be manipulated by pharmacologic agents in combinations that confer dramatically enhanced antineoplastic effect. We are investigating the molecular basis of the synergy of rapamycin and ATRA. We plan to test the combination in xenografts and ultimately in patients with medulloblastoma.

2078 General Poster Session (Board #015), Sun, 8:00 AM - 12:00 PM

A placebo-controlled study investigating the dexamethasone-sparing effects of corticorelin acetate in patients with primary or metastatic brain tumors and peritumoral edema. L. O. Recht, L. Mechtler, S. Phuphanich, A. Hormigo, V. Hines, R. Milsted, P. C. O’Connor, R. P. Ryan, E. T. Wong; Stanford University Medical Center, Palo Alto, CA; Dent Neurologic Institute, Amherst, NY; Cedars-Sinai Medical Center, Los Angeles, CA; Memorial Sloan-Kettering Cancer Center, New York, NY; Celtic Pharma, New York, NY; Celtic Pharma London, United Kingdom; Beth Israel Deaconess Medical Center, Boston, MA

Background: Corticorelin acetate (CrA) is a synthetic peptide formulation of corticotropin-releasing factor, which is associated with significant short- and long-term adverse events (AEs). Steroid-specific treatment-emergent AEs (TEAEs) were also evaluated. A maximum dex dose reduction of 50% by week 2 and maintain the maximum possible reduction of the dexamethasone (dex) dose without knowledge of their patients’ prior treatment regimen in the controlled feeder studies. During this extension study, patients’ dex doses and adverse events were monitored monthly; neurologic function and clinical status were recorded 3 monthly. For this analysis, data up to October 17, 2008, are reported from this ongoing study. Results: Of the 110 patients enrolled, 47 (43%) reduced their dex dose to zero and 67 (61%) were able to reduce their dose to ≤1 mg/day. At entry to this extension study, the daily baseline dex dose was lower for patients who had previously received CrA (3.9 mg; n = 51) than for those who had received CrA previously (5.9 mg; n = 59). At the end of this study, 8 (15%) of 84 patients remained on study for ≤6 months; 27 patients for ≥12 months, 5 patients for ≥2 years; 31 patients remain on study. Conclusions: The efficacy and safety data for this study support the development of CrA in patients with primary or secondary brain tumors and peritumoral edema.

2079 General Poster Session (Board #017), Sun, 8:00 AM - 12:00 PM

A long-term open-label extension study examining the steroid-sparing effects of corticorelin acetate in patients with cerebral tumors. L. Mechtler, E. T. Wong, A. Hormigo, S. Pannullo, V. Hines, R. Milsted, P. C. O’Connor, R. P. Ryan, L. Recht, Dent Neurologic Institute, Amherst, NY; Beth Israel Deaconess Medical Center, Boston, MA; Memorial Sloan-Kettering Cancer Center, New York, NY; New York-Presbyterian Hospital/Weill Cornell, New York, NY; Celtic Pharma London, United Kingdom; Stadium Medical Center, Stanford, CA

Background: Corticorelin acetate (CrA) is a synthetic peptide formulation of corticotropin-releasing factor, which is an ongoing clinical trial as a treatment for peritumoral edema. The objective of this study was to evaluate the long-term safety, tolerability and steroid-sparing potential of CrA in patients with primary or secondary brain tumors and peritumoral edema. Methods: Patients from two randomized double-blind controlled studies who received either CrA (CrA-CrA group) or placebo (PLA) (PLA-CrA group) were permitted to receive open-label CrA 1 mg SC bid after participation in the initial studies. Treating physicians were requested to attempt and maintain the maximum possible reduction of the dexamethasone (dex) dose without knowledge of their patients’ prior treatment regimen in the controlled feeder studies. During this extension study, patients’ dex doses and adverse events were monitored monthly; neurologic function and clinical status were recorded 3 monthly. For this analysis, data up to October 17, 2008, are reported from this ongoing study. Results: Of the 110 patients enrolled, 47 (43%) reduced their dex dose to zero and 67 (61%) were able to reduce their dose to ≤1 mg/day. At entry to this extension study, the daily baseline dex dose was lower for patients who had previously received CrA (3.9 mg; n = 59) than for those who had previously received CrA (5.9 mg; n = 59). At the end of this study, 8 (15%) of 84 patients remained on study for ≤6 months; 27 patients for ≥12 months, 5 patients for ≥2 years; 31 patients remain on study. Conclusions: These findings indicate that CrA is safe and well-tolerated, and may enable substantial reduction or cessation of dex therapy for many patients with cerebral tumors.

2086 Central Nervous System Tumors
A randomized, double-blind study comparing corticorelin acetate with dexamethasone in patients with primary malignant glioma who require increased dexamethasone doses to control symptoms of peritumoral brain edema. W. R. Shapiro, L. Mechtler, L. Cher, H. Wheeler, V. Hines, R. Milsted, P. C. O’Connor, R. P. Ryan, L. Recht; Barrow Neurological Institute, Phoenix, AZ; Dent Neurologic Institute, Amherst, NY; Cancer Services, Austin Health, Australia; Northern Specialist Center, St Leonards, Australia; Celtic Pharma, New York, NY; Celtic Pharma, London, United Kingdom; Stanford Medical Center, Stanford, CA

Background: Corticorelin acetate (CrA) is a synthetic peptide of corticotropin-releasing factor, undergoing clinical trials as a treatment for peritumoral edema in patients with cerebral tumors. This study compared CrA therapy vs an increase in dexamethasone (dex) dose (+4 mg) for controlling symptoms in primary glioma patients with a subacute exacerbation.

Methods: In addition to their prestudy dex dose, patients were randomized to receive CrA 1 mg bid SC or control (+4 mg dex PO) for 8 weeks. Patients were evaluated at baseline and during weeks 1 and 2 for their neurologic status, Karnofsky Performance Score (KPS), and continuing dex requirements. The primary endpoint was response, defined as no post-baseline increase in dex dose >4 mg for >1 day, stable or improved KPS; and ≥25% improvement in 10-item Neurological Examination Score during weeks 1 and 2. Dex therapy requirements were also evaluated. The study aimed to enroll 120 patients, but was terminated with only 37 patients (20 CrA, 17 control) due to slow recruitment. Results: Formal statistical analyses were not undertaken due to the small sample size. The treatment groups had similar demographic and baseline disease characteristics. Despite the small numbers, the data suggest that CrA treatment had similar efficacy to increased dex: (1) The proportions of responders were similar (CrA 3/20; control 3/17); (2) Comparable proportions of patients completed 8 weeks’ treatment (CrA 16/20; control 12/17); (3) After randomization of blinded study drug (CrA or dex 4 mg), dex dosing remained stable for most patients in each arm (CrA 12/20; control 11/17); (4) The mean daily dex dose was 3 mg in the CrA arm and 7 mg in the control arm. There was a lower incidence of cushingoid symptoms in the CrA arm (CrA 1/20, control 3/17). Patients in the CrA arm reported more injection site erythema and flushing vs. the control arm. CrA was well tolerated and no patient withdrew from the trial because of CrA side effects. Conclusions: CrA may be of value in managing patients with cerebral tumors who have subacute exacerbations of their symptoms, without needing to increase their dex dose.
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