ongoing clinical trials

OT-01. IS SURGERY AT PROGRESSION A PROGNOSTIC MARKER FOR IMPROVED 1-MONTH PROGRESSION-FREE SURVIVAL OR OVERALL SURVIVAL FOR PATIENTS WITH RECURRENT GliOMASTA?
J. L. Clarke 1 , Michele M. Ennis 2 , Kathleen R. Lamborn 1 , and Michael D. Prados 1

1UCSF; 2Quintiles

Historically, the North American Brain Tumor Consortium (NABTC) has used 6-month progression-free survival (PFS6) as the primary endpoint of Phase II clinical trials for recurrent glioma. Measurable disease has not been required and patients with recent surgeries have been eligible. In some trials, a subset of patients has received the trial agent before surgery to allow for the assessment of tumor uptake and biologic activity. With increased interest in targeted therapies, trials are now being designed to include only surgical candidates. When surgery is part of the trial, time-to-event is measured from the first post-surgery treatment. We compared PFS6 and overall survival (OS) for patients with glioblastoma (GBM) who underwent surgery at the time of progression to results for those who did not undergo surgery to evaluate the impact of surgical inter-vention on outcomes. All trials had similar entry criteria. Two data sets were analyzed. The first trial included 424 patients enrolled prior to 2003, of whom 65 had surgery (excluding biopsies) on study or within 30 days prior to registration. Analysis was stratified based on whether temozolomide was part of the protocol treatment regimen. No statistically significant differ-ence in PFS6 or OS was found (P > 0.4 for both analyses). These analyses were repeated for 246 patients on seven recent trials: 68 who had surgery while on the clinical trial, 35 who had surgery for disease progression but not as part of the trial, and 143 who did not have surgery at the time of pro-gression. PFS6 was 6%, 9%, and 6% for the 3 groups, respectively, with no difference in OS (P > 0.5 for both analyses). Conclusion: Results from two separate data sets indicate that PFS6 and OS results for patients having surgery at the time of disease progression are similar to the results for those who did not have surgery, allowing data from both types of patients to be combined in assessing the benefits of new treatments. Presented on behalf of the NABTC investigators.

OT-02. PHASE I STUDY OF VORINOSTAT COMBINED WITH ISOTRETINOIN AND CARBOPLATIN IN ADULTS WITH RECURRENT MALIGNANT GLIOMAS
Vinay K. Padowic 1 , Marla Penas-Prado 2 , Mark R. Gilbert 1 , Morris D. Groves 1 , Kenneth R. Hess 1 , Victor A. Levin 1 , John de Groot 1 , Howard Colman 1 , Charles A. Conrad 1 , Monica E. Loghin 1 , Kathy Hunter 1 , and W K. Yung 3
1The University of Texas MD Anderson Cancer Center; 2Hospital Doce de Octubre; 3University of Texas MD Anderson Cancer Center, Houston

BACKGROUND: Epigenetic processes, such as DNA methylation and histone acetylation, constitute novel therapeutic targets against glioblastoma (GBM). Vorinostat, a histone deacetylase inhibitor (HDACi), has shown pre-clinical and clinical activity against GBM and other solid tumors (PNET). METHODS: Between April 2003 and December 2005, 122 patients with recurrent GBM (Arm 1) or recurrent PNET (Arm 2) were treated in a standardized 3 arm phase II study due to open shortly. METHODS: Adults with recurrent malignant glioma, KPS ≥ 60, normal organ function, and no prior exposure to vorinostat; other HDAC inhibitors or carboplatin were enrolled into one of three arms. Arm 1: Vorinostat + Isotretinoin, Arm 2: Carboplatin + Isotretinoin, or Arm 3: Vorinostat + Isotretinoin + Carboplatin. Dose escalation was by a +3 design that defined the maximum tolerated dose (MTD) as the highest dose that caused dose-limiting toxicity (DLT) in <2/6 patients. RESULTS: Toxicities among the 27 evaluable patients enrolled to date include (Arm 1) neutropenia, thrombocyto-penia, pulmonary embolism, elevated AST (DLT), and hypertriglyceri-cidemia (DLT); (Arm 2) neutropenia, thrombocytopenia (DLT), and hypertriglyceridemia; (Arm 3) thrombocytopenia (DLT) and hypokalemia (DLT). The MTD has been identified in Arm 1 (vorinostat, 400 mg/d on days 1–7 and 15–21; isotretinoin, 100 mg/m²/d x 21 d) and Arm 2 (carbo-platin, AUC 6; isotretinoin, 100 mg/m²/d x 21 d). Arm 3 has undergone dose deescalation to level 2 (vorinostat, 300 mg/day on days 1–7 and 15–21; isotretinoin, 100 mg/m²/d x 21 d) and Arm 2 (carbo-platin, AUC 6; isotretinoin, 100 mg/m²/d x 21 d). The study drug was given orally once a day. A total SRS dose of 36 Gy was delivered over 3 consecutive days. A standard 3 + 3 design was used. The MTD was defined as the dose of vorinostat at which less than 33% of patients developed DLTs, defined by the CTCAE version 3.0 as any grade 3 or higher nonhematologic toxicity or grade 4 or higher hema-tologic toxicity. RESULTS: The first trial included 424 patients enrolled prior to 2003, of whom 65 had surgery (excluding biopsies) on study or within 30 days prior to registration. Analysis was stratified based on whether temozolomide was part of the protocol treatment regimen. No statistically significant differ-ence in PFS6 or OS was found (P > 0.4 for both analyses). These analyses were repeated for 246 patients on seven recent trials: 68 who had surgery while on the clinical trial, 35 who had surgery for disease progression but not as part of the trial, and 143 who did not have surgery at the time of progression. PFS6 was 6%, 9%, and 6% for the 3 groups, respectively, with no difference in OS (P > 0.5 for both analyses). Conclusion: Results from two separate data sets indicate that PFS6 and OS results for patients having surgery at the time of disease progression are similar to the results for those who did not have surgery, allowing data from both types of patients to be combined in assessing the benefits of new treatments. Presented on behalf of the NABTC investigators.

OT-03. PHASE I DOSE ESCALATION TRIAL OF VANDETANIB WITH FRACTIONATED RADIOTHERAPY IN PATIENTS WITH RECURRENT MALIGNANT GLIOMAS
Changlu Chen 1 , Denise Damek 1 , Arthur Liu 1 , Laurie E. Gaspar 2 , Allen Waziri 1 , Kevin Lillehei 1 , and Brian Kavanagh 1
1University of Colorado School of Medicine

PURPOSE: To determine the maximum tolerated dose (MTD) of vande-tanib with SRS in recurrent malignant gliomas. PATIENTS & METHODS: Patients with recurrent malignant glioma and T1-enhancing recurrent tumor of ≤ 6 cm were eligible. Vandetanib (400 mg once daily) was administered 7 days before SRS continued until dose-limiting toxicity (DLT) or disease progression. The vande-tanib doses for Cohorts 1, 2, and 3 were 100 mg, 200 mg, and 300 mg, respectively. The study drug was given orally once a day. A total SRS dose of 36 Gy was delivered over 3 consecutive days. A standard 3 + 3 design was used. The MTD was defined as the dose of vandetanib at which less than 33% of patients developed DLTs, defined by the CTCAE version 3.0 as any grade 3 or higher nonhematologic toxicity or grade 4 or higher hema-tologic toxicity. RESULTS: There patients gave informed radiotherapy (RT) dose, 60 Gy (range, 59.4–70); median interval since prior RT, 14.5 months (range, 7–123). Median time on vandetanib was 3 months (range, 1–11) and all patients received SRS per protocol. The median follow-up time from SRS was 4 months (range, 1–10 months). Six patients had the vorinostat in a grade 3 DLT of pulmonary embolism and hemarthrosis. The trial was stopped when two of the four patients entered to the second cohort devel-oped DLTs. CONCLUSION: Vandetanib MTD is 100 mg daily. This dose was well tolerated with 36 Gy SRS in recurrent malignant gliomas.

OT-04. HEAD START III: A PROSPECTIVE MULTINATIONAL PROTOCOL FOR NEWLY DIAGNOSED CNS EMBRYONAL TUMORS (MEDULLOBLASTOMA AND OTHER PRIMITIVE NEUROECTODERMAL TUMORS [PNET]) OF YOUNG CHILDREN WITH AN IRRADIATION-AVOIDING STRATEGY.
First report of response to and outcome of induction chemotherapy
Jonathan L. Finlay 1 , Kelley Hailey 1 , Gish Dhall 1 , Sharon Gardner 1 , Jeffrey Allen 3 , Albert Cornelius 4 , Randy Olsheski 1 , James Garvin 5 , Kamesh Pradhan 6 , Michael Eitz 6 , Stewart Goldman 6 , Mark Atlas 6 , Stephen Thompson 7 , Andreas Hirt 7 , Juliette Hukin 7 , Melanie Comito 8 , Salvatore Bertolone 9 , Joseph Torkildson 9 , Michael Joyce 9 , Christopher Moertel 10 , John Letterio 10 , Gloria Kennedy 20 , Andrew Walter 21 , Lingyun Ji 22 , and Richard Spottos 22
1Children’s Hospital Los Angeles, Los Angeles; 2Childrens Hospital of Oakland, Oakland; 3New York University Medical Center, New York; 4DeVos Children’s Hospital, Grand Rapids; 5Columbus Children’s Hospital, Columbus; 6Columbia Children’s Hospital, New York; 7Riley Children’s Hospital, Indianapolis; 8Phoenix Children’s Hospital, Phoenix; 9Children’s Hospital Los Angeles, Los Angeles; 10NYU Medical Center, New York; 11DeVos Children’s Hospital, Grand Rapids; 12Columbus Children’s Hospital, Columbus; 13Kosair Children’s Hospital, Louisville; 14Milton S. Hershey Medical Center, Hershey; 15Alfred I. Dupont Hospital, Wilmington; 16Children’s Memorial Hospital, Chicago; 17Children’s Hospital of Oakland, Oakland; 18University Children’s Hospital, Basel; 19UC Children’s Hospital, Vancouver; 20SUNY Upstate Medical University, Syracuse; 21Alfred I. Dupont Hospital, Wilmington

PURPOSE: To improve survival and quality of life for young children newly diagnosed with medulloblastoma and other primitive neuroectoder-mal tumors (PNET). METHODS: Between April 2003 and December 2009, 144 children who had been newly diagnosed with medulloblastoma (n = 93) and other central nervous system (CNS) PNETs (n = 51) were enrolled among the participating institutions. All patients were to receive five induction cycles (vincristine, cisplatin, cyclophosphamide, etopo-side, and high dose methotrexate in cycles 1, 3, and 5; vincristine, cyclophosphamide, oral etoposide, and temozolomide in cycles 2 and 4) followed by (in children without tumor progression) consolidation with myeloablative chemotherapy (thiotepa, carbo-platin, and etoposide) rescued with autologous hematopoietic stem cells. The initial Induction Regimen D was replaced away through the study by Regimen D2, in which cyclophosphamide and etoposide were administered only before SRS.

Abstracts
RESULTS: Ongoing pathology review revealed that, of 93 institutionally diagnosed medulloblastoma cases, 28 (30%) were nodular/desmoplastic and 11 (12%) were diffuse anaplastic disease. The extent of resection in loco-¯ cord was based upon magnetic resonance (MR) imaging, was gross total (R0) in 24/39 (62%). Disseminated disease (M1-3) was reported in 52/91 (57%). Among other PNET cases, the extent of resection in M0 patients was R0 in 14/25 (56%); M1-3 was reported in 25/50 (50%). Among medulloblastoma, the response to induction was bi-weekly (10 mg kg−1) with bevacizumab (10 mg kg−1) for 21 days of a 21 day cycle: Continuing Complete Response (CCR) in 20/92 (22%), Complete Response (CR) in 25/92 (27%), <CR in 26/92 (28%), Progressive Disease (PD) in 19/92 (21%), Toxic Death (TD) in 2/92 (2%), and Not Yet Evaluable in 1/92 (1%). Among PNET cases, the incidence of CR in: 10/50 (20%), CR in 8/50 (16%), <CR in 9/50 (18%), PD in 20/50 (40%), TD in 3/50 (6%), and pending in 1. Of medulloblastoma and other PNET patients, 67/93 (72%) and 27/50 (54%), respectively, proceeded to consolidation.

CONCLUSIONS: Similar induction response rates were observed in Regimens B and D2. A higher than expected proportion of Head Start III medulloblastoma/other PNET patients had R1 and/or M1-3 disease, and/or diffuse anaplastic histology. Nevertheless, the responses to induction chemotherapy and the proportion of patients who proceeded to myeloablative chemotherapy are consistent with prior Head Start studies.

OT-06. PHASE II TRIAL OF VORINOSTAT IN COMBINATION WITH BORTezOMIB IN RECURRENT Glioblastoma Multiforme: A NORTHERN CENTRAL CANCER TREATMENT GROUP STUDY

Brett R. Friday1, Jan Buckner3, S. Keith Anderson2, Caterina Giannini2, John Kugler1, Miroslaw Mazurczak4, Patrick Flynn5, Howard Gros6, Eduardo Pajon1, Kurt Jaeckle2, and Evangelia Galans1; 1SMDC Cancer Center; 2Mayo Clinic; 3Illinois CancerCare; 4Sioux Valley Clinic Oncology; 5Southwest Oncology Group; 6Wayne State University

Histone deacetylase (HDAC) inhibitor vorinostat has shown evidence of modest single-agent activity in glioblastoma multiforme (GBM). In preclinical studies, we have demonstrated significant synergistic cytotoxicity between HDAC inhibitors and proteasome inhibitors in GBM cell lines. We therefore conducted a Phase II trial to evaluate the efficacy of vorinostat in combination with the proteasome inhibitor bortezomib in patients with recurrent GBM. Patients who had received one or fewer regimens for progressive disease were eligible to participate; 6-month progression-free survival (PFS6) was the primary endpoint. Vorinostat was administered at a dose of 200 mg m−2; Days 1, 15) concurrent with conformal irradiation, and maintenance chemotherapy consisted of 12 28-day cycles of vorinostat (10 mg/kg; Days 1, 15), bortezomib (125 mg/m2; Days 1, 15) and temozolomide (150 mg/m2/day; Days 1–5). Patients with PFS6 received the same regimen without temozolomide. RESULTS: Eight patients have been enrolled (6 HGG; 2 DIPG), with a mean age of 17.5 years (range, 7–29). Median follow-up is 5.5 months (range, 0–11). The regimen has generally been well-tolerated. Only one patient discontinued treatment due to toxicity (prolonged grade 4 myelosuppression attributable to temozolomide). No other patient required dose reductions or treatment delays of >1 week. Treatment-related grade 3 toxicities included neutropenia (1) and hypertension (1). No intracra- nal bleeding or wound infections have been observed. Three patients have experienced disease progression (2 DIPG during maintenance courses 4 and 5; 1 HGG after chemoradiation). Gene expression profiling, genome-wide integrity analyses, telomerase activity, and hTERT expression studies in tumor and peripheral blood mononuclear cells are being conducted in consenting patients. Early MR perfusion/diffusion changes are being assessed to correlate with response. Enrollment continues for both strata. CONCLUSIONS: A bortezomib-based regimen is feasible and tolerable in newly diagnosed children and young adults with HGG and DIPG.

OT-07. PHASE II STUDY OF BI-WEEKLY TEMOZOLOMIDE PLUS BEVACIZUMAB FOR ADULT PATIENTS WITH RECURRENT Glioblastoma Multiforme

Michael A. Badruddoja1, Marjorie A. Pazzi1, Baldassarre Stea2, Patricia Lefferts3, Nancy Contreras3, Maria Bishop2, Joachim Seeger4, Raymond Carmody5, Naomi Rance2, Marco Marsella2, Kurt Schroeder1, and Abhay Sanan; 1Center for Neurosciences; 3University of Arizona; 5St. Mary’s Hospital

BACKGROUND: The use of single-agent bevacizumab (BEV) improves the outcomes of patients with progressive glioblastoma multiforme (GBM) following prior therapy. Metronomic/dose-dense temozolomide (TMZ) has been combined with BEV in the treatment of recurrent GBM; however, the optimal dosing of TMZ has not been defined. The combination of BEV and metronomic TMZ may not increase survival to levels above that found with the use of BEV alone. The purpose of this study was to determine the 6-month progression-free survival of patients with recurrent GBM treated with BEV plus bi-weekly dosing of TMZ. Secondary endpoints included radiographic response, evaluation of toxicity, analysis of tumor DNA (MGMT and a 9-gene assay), and functional assessment of cancer therapy for brain tumors (FACT-Bt). METHODS: This clinical trial is ongoing, with an accrual goal of 50 subjects. Patients are treated with 10-mg/kg BEV in combination with 100-mg/m2 TMZ every 2 weeks; this regimen is continued until tumor progres- sion or unacceptable toxicity occurs. Complete patient evaluations are conducted every 4 weeks and magnetic resonance imaging (MRI) scans are done every 8 weeks. FACT-Bt questionnaires are completed every 8 weeks. RESULTS: Preliminary data is presented here. Nine patients have been accrued thus far and 5 patients have been actively enrolled; 8 patients have shown a partial radiographic response and 1 patient was a nonresponder. Methylation of the MGMT gene was NOT detected in 7 subjects and is pending in the remaining 2. Grade 3 toxicities have included: encephalopathy (epileptic), deep vein thromboses, pulmonary emboli, and fatigue. There was one grade 3 CNS hemorrhage in a patient who had discontinued the study due to tumor progression. CONCLUSIONS: The combination of BEV and TMZ given bi-weekly is well-tolerated and may have efficacy in the treatment of recurrent GBM. Added safety and efficacy data will be reported as this Phase II study progresses.

OT-08. OBJECTIVE RESPONSE RATE OF UNRESECTABLE BENIGN MENINGIOMA TO HYDROXYUREA: SOUTHWEST ONCOLOGY GROUP PHASE II TRIAL 59811

Lode J. Swinnen1, Cathryn Rankin2, Elisabeth J. Rushing2, Laura F. Hutchins4, Denise M. Darnek1, and Geoffrey Barger2; 1Johns Hopkins University; 2Southwest Oncology Group Statistical Center; 3Airmed Forces Institute of Pathology; 4University of Arkansas; 5University of Colorado; 7Colorado Cancer Research Program

BACKGROUND: An effective drug would be valuable for patients with benign meningioma that is no longer amenable to resection or irradiation.
Objective responses have been reported with long-term hydroxyurea (HU) therapy, and activity has been demonstrated in benign meningioma primary explant cultures. The Southwest Oncology Group S9811 Phase II trial was designed to estimate the objective response rate of unresectable benign meningioma to that same HU regimen. METHODS: Inclusion criteria included having unsectable, measurable, histologically proven benign meningioma; progressive tumor or progressive neurologic deficit at >1 year after radiation therapy; having no prior cytotoxic therapy or targeted molecular agents; no effective local therapy; and age >18 years; having adequate hematologic reserve; and PS 0–2. 20-mg/kg/day HU was given orally for up to 2 years in the absence of progressive disease. Single-stage accrual of 38 patients would have allowed detection of a 3% null hypothesis response probability vs. 20% at 90% power; 28 eligible patients actually accrued provide 81% power. RESULTS: Twenty-nine patients were accrued onto the study over 7 years, with study closure due to slow accrual. One ineligible patient response assessment showed complete response + partial response in 0% (95% CI, 0%–12%); stable disease in 71% (95% CI, 51%–87%); progressive disease in 21% (95% CI, 8%–41%); and undetermined response in 7%. Median progression-free survival (PFS) was 27 months (95% CI, 12–80 months); 3-year PFS was 43% (95% CI, 23%–61%). Median overall survival (OS) is not yet available, but the 3-year OS was 79% (95% CI, 63%–94%). Seven patients were removed from the study because of toxicity (3/7 had hematologic toxicity). Toxicity was primarily hematologic: 11/28 (39%) had grade 3 and 2/28 (11%) had grade 4. Grade 3 nonhematologic toxicity was seen in 7/28 (25%) patients. CONCLUSIONS: Chronic HU therapy for patients with table benign meningioma resulted in an objective response rate of <12%. Whether the stable disease found in 71% of patients was the result of treatment cannot be determined from this Phase II study design.

OT-09. PHASE II STUDY OF DOSE-INTENSE TEMOZOLOMIDE IN RECURRENT GLIOBLASTOMA
Andrew D. Norden1, GlennLesser2, Samantha N. Hammond1, Jan Drapatz1, Camilo E. Faruqui1, Tracy T. Batchelor4, Eudocia C. Quant1, Rameen Beroukhim1, Debra LaFrankie1, Sandra Johnston1, Carrie Graham1, Fabio Iwamoto1, Joohee Sul1, John A. Butman1, and Howard A. Fine1

BACKGROUND: Survival among patients with glioblastoma (GBM) is poor, and the majority of patients relapse within 1 year. Among patients who progress on the standard schedule of temozolomide (150–200 mg/m²/day for 5 consecutive days every 28 days), the optimal therapy is unknown. Resistance to temozolomide is partially mediated by the DNA repair enzyme O6-methylguanine-DNA methyltransferase (MGMT). Since MGMT may be depleted by prolonged temozolomide administration, there is interest in whether dose-intense schedules of temozolomide can overcome MGMT-mediated resistance in patients with recurrent GBM. METHODS: This is a Phase 2, single-arm, multicenter study of temozolomide (75–100 mg/m²/day for 21 days of a 28-day cycle for up to 12 cycles). To be eligible, patients had to have histologically confirmed GBM in first recurrence following standard therapy, including at least 2 cycles of adjuvant temozolomide dosed in the standard fashion. The primary endpoint was 6-month progression-free survival. A planned subgroup analysis will compare participants whose tumors recurred during adjuvant temozolomide therapy to those whose tumors recurred after completion of the adjuvant temozolomide regimen. RESULTS: Forty-one participants have been accrued to date. Overall, the regimen has been well tolerated, with toxicity comparable to the standard temozolomide dosing regimen. Accrual continues, and updated results, including response, survival data, and correlation of clinical outcomes with tumor MGMT status, will be presented. CONCLUSIONS: Dose-intense temozolomide on a 21/28 day schedule is a safe regimen for patients with GBM in first recurrence. Updated efficacy results will be presented.

OT-10. PHASE II STUDY OF MONTHLY PASIREOTIDE LAR (SOM230C) FOR RECURRENT OR PROGRESSIVE MENINGIOMA
Samantha N. Hammond1, Andrew D. Norden1, Jan Drapatz1, Surasak Phuphanich2, David Reardon3, Eric T. Wong4, Scott R. Plotkin5, Brenna McNamara1, Karly David1, Myrna R. Rosenfeld5, and Patrick Y. Wen5

BACKGROUND: Patients with recurrent meningiomas who have exhausted surgical and radiation options have limited remaining treatment choices. Despite interest in treating such patients with cytotoxic chemotherapeutics and targeted molecular agents, no effective local therapy has emerged. Somatostatin receptors are expressed in nearly 90% of meningiomas, and somatostatin effectively inhibits meningioma cell growth in vitro. In a pilot study, 16 patients with recurrent meningiomas were treated with a sustained-release somatostatin preparation (Chamberlain et al. Neurology, 2007; 69: 969–73); nearly one-third of patients achieved partial response, toxicity was minimal, and the 6-month progression-free survival rate (PFS6) was 44%. Pasireotide LAR (SOM230C) is a long-acting somatostatin analog that has higher binding affinity for most somatostatin receptor subtypes than octreotide. Like octreotide, pasireotide is well-tolerated in most patients. METHODS: This is an open-label, single-arm, nonrandomized, phase II trial of monthly pasireotide LAR 60-mg administered intramuscularly in patients with recurrent or progressive intracranial meningioma. Patients are stratified based on histology (benign meningiomas compared to atypical and malignant meningiomas). Treatment cycles are 28 days in length, and treatment continues until progressive disease or unacceptable toxicity. Patients are examined at the beginning of cycles 1–3, at the midpoint of cycles 1 and 2, and at the end of cycles 1 and 2. Restaging magnetic resonance imaging (MRI) scans are performed every 3 cycles, and response is assessed using the Macdonald criteria. RESULTS: Twenty participants have been accrued, 17 (85%) of whom have atypical/malignant meningiomas. Treatment has been mild, with the exception of grade 3 hyperglycemia in 4 (20%) patients and grade 3 lipase, in the absence of clinical signs of pancreatitis, in 2 (10%) patients. Updated results, including response and survival data, will be presented. CONCLUSIONS: Pasireotide LAR is a well-tolerated somatostatin analog that is under investigation for heavily pretreated recurrent meningiomas. Efficacy results have yet to be determined.

OT-11. BENDAMUSTINE FOR RECURRENT GLIOBLASTOMA
Marc C. Chamberlain1, Carrie Graham1, Maciej Mrugala2, and Sandra Johnston; University of Washington, Fred Hutchinson Research Cancer Center

BACKGROUND: The treatment of recurrent glioblastoma (GBM) remains challenging, notwithstanding the recent approval of bevacizumab for this indication. Bendamustine has a bifunctional mechanism of action, penetrates the CNS, and does not show cross-resistance to other alkylators. METHODS: In a single-institution, open-label, prospective Phase 2 trial, patients with recurrent GBM were treated with bendamustine (100 mg/m²/day administered intravenously for 2 consecutive days every 4 weeks). All patients previously had been treated with surgery, temozolomide, and radiation therapy. The primary study endpoint was 6-month progression-free survival (PFS6) and the study design was a Simon 2-step, such that if 3 or more of the initial cohort of 16 patients manifested PFS6, an additional 14 patients would be enrolled. Complete blood counts were obtained bimonthly, clinical evaluations were performed monthly, and brain imaging was performed every 12 weeks. Treatment regimens were based upon Macdonald criteria. RESULTS: Sixteen patients (9 men; 7 women) entered onto trial with a median age of 53 years (range, 36–68) and median Karnofsky performance status of 90 (range, 70–100). Ten patients were treated at first relapse and 6 at second relapse (bevacizumab had failed 5 patients). A total of 17 cycles of bendamustine were administered, with a median of 1 (range, 1–6). Bendamustine-related toxicity was seen in 7 patients, lymphopenia in 5 (4 CTC grade 3; 1 grade 4), and thrombocytopenia in 2 (grade 2). Twelve patients died from disease progression, 3 patients are alive on alternative therapy, and 1 patient continues on study. The PFS6 was 62.5%. CONCLUSION: Bendamustine was reasonably well tolerated but failed to meet the study’s prespecified endpoint of PFS6 >19% and, consequently, does not appear to be active in adults with recurrent GBM.

OT-12. A PHASE II TRIAL OF SUNITINIB IN THE TREATMENT OF RECURRENT GLIOBLASTOMA
Terr N. Kreisl, P. Smith, Fabio Iwamoto, Joohee Sul, John A. Butman, and Howard A. Fine; National Institutes of Health

While the response rate for bevacizumab (BEV) in patients with glioblastoma (GBM) is high relative to other salvage regimens, durable disease
control remains elusive for the majority of patients, possibly due to activation of angiogenic factors other than vascular endothelial growth factor (VEGF). Sunitinib is an orally available multitarget tyrosine kinase inhibitor on vascular endothelial growth factor receptor, and c-KIT that way promoting broad-spectrum antiangiogenic activity. We designed a Phase II trial for recurrent GBM, stratified by prior exposure to BEV, in order to assess the safety and efficacy of 37.5-mg sunitinib administered on a continuous daily schedule. The primary endpoint for both cohorts was 6-month progression-free survival. Patients who progressed on BEV were eligible if their last treatment was ≥6 weeks before study entry. Patients treated with enzyme-inducing anti-epileptic drugs, prior non-BEV VEGF-directed therapies, concurrent antiangiogenic therapy, and other significant cardiovascular conditions were not eligible for the study. Radiologic and clinical evaluations were performed every 4 weeks. FDG-PET scans were evaluated at baseline and end of the first 4-week cycle as a correlative study. Twenty-eight patients have been enrolled to the BEV-resistant arm and 21 patients have been enrolled to the BEV-naive arm. Applying modified Macdonald criteria, only one patient has achieved a partial response in the BEV-naive arm. Four additional patients (2 BEV-naive and 2 BEV-resistant) had a significant reduction in contrast enhancement but did not meet the criteria for partial response. No patients have reached 6-month progression-free survival. Updated response, toxicity, and survival data will be presented. Preliminary results from this trial indicate that while sunitinib has activity in terms of radiographic response for some patients, disease control may be poor for patients with recurrent GBM who have had prior exposure to bevacizumab. Results in patients who are BEV-naive will be presented by the time of the meeting.

OT-13. CURRENT STATUS OF A PHASE III TRIAL OF NIMOTUZUMAB (ANTI-EGFR) IN NEWLY DIAGNOSED GLIOBLASTOMA

Manfred Westphal1, Oliver Heese2, M. Warmuth-Metz3, Torsten Pietsch4, Uwe Schlegel5, Jörg-Christian Tonn6, Johannes Schramm7, Gabriele Schackert8, A. Melms9, Hubertus Maximilian Mehdorn10, Volker Seifert6, Johannes Schramm7, Volker Seifert11, K. Geletneky12, D. Reuter13, and Ferdinand Bach13; 1UK Bochum; 6Neurosurgery, LMU, Munich; 7Neurosurgery, UK Bonn; 8Neurosurgery, University Dresden; 9Neurology, UK Tübingen; 10Neurosurgery, University Kiel; 11Neurosurgery, University Hospital Bochum; 12Neurosurgery, LMU, Munich; 13Neurosurgery, UK Bonn; 14Neurosurgery, University Dresden; 15Neurosurgery, UK Tübingen; 16Neurosurgery, University Kiel; 17Neurosurgery, University Frankfurt; 18Neurosurgery, UK Heidelberg; 19OncoScience AG, Wedel

RATIONALE: Epidermal growth factor receptor (EGFR) has been shown to be relevant to glioma by numerous approaches. It is a drug target for small-molecule tyrosine kinase inhibitors, targeted toxins, and monoclonal antibodies. Within the CNS, it has exquisite selectivity for high-grade glialoma cells. Supported by promising preclinical and clinical findings, we tested the therapeutic effect of a monoclonal antibody against EGFR (nimotuzumab) that had a lower affinity than cetuximab and that bound more specifically to highly overexpressing cells. METHODS: Nimotuzumab (OSAG-101) was tested in an open-label, randomized, multicenter Phase III trial in patients with newly diagnosed glioblastoma. OSAG-101 was administered by intravenous infusion (2 weekly infusions of 400 mg) in addition to the current standard radiochemotherapy, followed by biweekly infusions of 400 mg thereafter until progression. Patients with histologically confirmed glioblastoma were included and stratified for resection status. Patients under the age of 18 years and over 70 years were excluded. The primary endpoint was time to progression as determined by follow-up magnetic resonance imaging (MRI) scans. There were 400 mg/kg every 4 weeks. FDG-PET scans were evaluated at baseline and end of the first 4-week cycle as a correlative study. Twenty-eight patients have been enrolled to the BEV-resistant arm and 21 patients have been enrolled to the BEV-naive arm. Applying modified Macdonald criteria, only one patient has achieved a partial response in the BEV-naive arm. Four additional patients (2 BEV-naive and 2 BEV-resistant) had a significant reduction in contrast enhancement but did not meet the criteria for partial response. No patients have reached 6-month progression-free survival. Updated response, toxicity, and survival data will be presented. Preliminary results from this trial indicate that while sunitinib has activity in terms of radiographic response for some patients, disease control may be poor for patients with recurrent GBM who have had prior exposure to bevacizumab. Results in patients who are BEV-naive will be presented by the time of the meeting.

OT-14. PHASE II TRIAL OF CONTINUOUS LOW-DOSE TEMOZOLOMIDE (TMZ) FOR PATIENTS WITH RECURRENT MALIGNANT GLIOMA (MG) WITH AND WITHOUT PRIOR EXPOSURE TO BEVACIZUMAB (BEV)

Mustafa Khasraw, Lauren E. Abrey, Andrew B. Lassman, Adilia Hormigo, Craig Nolan, Igor T. Gavrilovic, Ingo K. Mellinghoff, Anne S. Reiner, Lisa DeAngelis, and Antonio M. Omsoro; MSKCC

BACKGROUND: Metronomic TMZ schedules have been proposed as salvage therapy for recurrent malignant glioma (MG) with the goal of targeting angiogenesis and overexpressing the chemoefronetransferred by O-6-methylguanine-DNA-methyltransferase (MGMT). METHODS: In this prospective Phase II study, patients with recurrent/progressive MG were treated with daily TMZ (50 mg/m2) until progression. A Simon 2-stage design was used; the primary endpoint was 6-month progression-free survival (PFS) (promising: 20%, nonpromising: 3%, alpha = 0.1, beta = 0.1, N = 37 planned GBM). Ten additional cases of recurrent anaplastic astrocytomas (AA) or oligodendrogliomas (AO) were included for exploratory analysis. RESULTS: Forty-seven patients were enrolled (glioblastoma [GBM]: 37; AA: 6; AO: 4; median age: 56 years; median KPS: 80). Sixteen were women. The MGMT promoter was methylated in 5 patients, unmethylated in 32. Nine patients (22%) had a significant reduction in 18F-FDG uptake in brain metastases, providing evidence of response. Updated 6-month PFS was 29% (95% CI, 13–47); median PFS was 2 months (CI, 1–6); median overall survival (OS): 7 months (CI, 4–9); objective response rate: 6%. GBM patients with prior BEV exposure fared worse than GBM patients with no BEV exposure (6-month PFS: 12% vs 48%, P = 0.007; median OS: 5 months vs 12 months; CI, 0.03–0.20). GBMs, 6-month PFS was 30% and median OS was 16 months (CI, 7–30). There was a trend towards shorter PFS in unmethylated patients (P = 0.06). CONCLUSIONS: The regimen was well tolerated in this heavily pretreated population. The primary endpoint was met, indicating that this treatment deserves further investigation. Although the increase in treatment efficacy in the overall GBM population was modest, results in non-BEV failures were particularly encouraging and comparable to BEV. Results in BEV failures are difficult to interpret due to lack of historic controls. This study highlights the need for stratification according to previous BEV exposure and for new historic controls for trials of recurrent MG.

OT-15. PRELIMINARY RESULTS OF A PHASE II STUDY OF ANTI-NEOPLASTONS A10 AND AS2-1 (ANP) IN ADULT PATIENTS WITH RECURRENT MIXED GLIOMAS

Stanislaw R. Burzynski, Robert A. Weaver, Tomasz J. Janicki, Gregory S. Burzynski, Barbara Szymkowiak, and Sherryll S. Acelar; Burzynski Clinic

The purpose of this study was to evaluate the efficacy and toxicity of anti-neoplasms A10 and AS2-1 (ANP) in adult patients with recurrent mixed gliomas. Thirteen of 20 patients enrolled were evaluable; 7 patients could not be evaluated due to an inadequate duration of treatment and lack of follow-up magnetic resonance imaging (MRI) scans. There were 4 women and 9 men. The median age was 38 (range, 29–54) and the median KPS score at baseline was 70 (range, 60–100). One patient had low-grade and twelve patients had high-grade mixed gliomas. All patients received chemotherapy, radiation therapy, and surgery prior to ANP, with the exception of 1 patient who received no chemotherapy or radiation therapy postsurgery. Patients received escalating doses of intravenous ANP six times daily. The median duration of treatment was 4.4 months; the median average dosages of A10 was 6.0 g/kg/d and of AS2-1 was 0.3 g/kg/d. ANP was well tolerated, with the most common side effects being urinary frequency, hypernatremia, dysgeusia, myalgias, nausea, and hypersensitivity. Serious (grade 3) toxicity (urinary frequency) was observed in only 1 patient and there were no grade 4 toxicities. Response to ANP was monitored by MRIs of the brain. The responses were as follows: complete response, 23%; partial response, 8%; stable disease, 23%; and progressive disease, 46%. Progression-free survival (PFS) at 1, 2, and 5 years were 31%, 23%, and 8%, respectively. Overall survivals (OS) from diagnosis and from start of treatment at 1, 2, and 5 years were 92% and 54%, 85% and 23%, and 46% and 8%, respectively. Preliminary results of our small study of adults with recurrent mixed gliomas revealed ANP to be very effective in resolving or stabilizing disease in more than 50% of treated patients as well as encouraging PFS and OS with minimal toxicity.
OT-16. LONG-TERM IMAGING DATA FROM HCRF PHASE III STUDIES DEMONSTRATE STABILITY OF CEREBRAL TUMORS AND PERITUMORAL EDEMA
Lazlo L, Mechtler T, Patrick C, O'Connor M, and Henk-André Kroon T; Dent Neurologic Institute; 2Celtic Pharma
A subgroup of 98 patients with cerebral tumors (GBM, n = 46; other primary or recurrent tumors, n = 33; cerebral metastases, n = 19) who received hCRT through all Phase III studies (NTI 302, 303, and 305) were retrospectively enrolled in a magnetic resonance imaging (MRI) study to evaluate the change from baseline of tumor volume (TV) and peritumoral brain edema (PBE). The TV was measured at the largest dimension on the postcontrast T1 weighted image. PBE was measured at the largest area on FLAIR imaging at each time point. Each was compared to the first available MRI or computed tomography (CT) data set. The quantitative assessments of changes in the TV and PBE regions were performed according to World Health Organization (WHO) criteria: Progressive Disease (PD) = +25% +100% or more; Stable Disease = +24% –50%; and Responder (R) = <51% –100%. Patients could meet more than one criterion during the study. Stable disease was the maximum TV response in 72% of subjects. The mean duration of stable TV was 58% of the observation time (mean, 5.8 months), with PD 38% (mean, 3.7 months), and R 4% (mean, 2.2 months). These proportions were similar in the primary and metastatic-disease subgroups and in patients who were and were not eligible. Stable PBE was the maximum response in 78% of patients. The mean duration of stable PBE was 65% of the observation time (6.3 months), of PD was 29% (mean, 4.1 months) and of R was 6% (mean, 7.6 months). As with TV, the proportions were similar in the primary and metastatic-disease subgroups and in GBM. These findings are notable in that treatment with hCRT was also associated with a concomitant 87.5% decrease in steroid requirements in study NTI0501. These findings are consistent with the postulated antiangiogenic mechanism of action of hCRT on cerebral tumors.

OT-17. A PROSPECTIVE STUDY OF CONCURRENT CARBOPLATIN AND RADIATION THERAPY (CCTR) FOLLOWED BY ADJUVANT CHEMOTHERAPY IN PATIENTS WITH HIGH-RISK MEDULLOBLASTOMA
Tushar Vora, Parma Kurkure, Brijesh Arota, Tejal Gupta, Vandana Dhamankar, Shipad Banavali, Aliasgar Moyaadi, Shirdhar Epari, Nikhil Merchant, and Rakshak Jalali; Tata Memorial Hospital
AIM: To assess the role of concurrent carboplatin and radiation therapy (CCTR) followed by adjuvant chemotherapy (AC) in patients with high-risk medulloblastoma (HMB) for improving event-free survival (EFS). METHODOLOGY: Newly-diagnosed 3- to 21-year-old HMB patients have been prospectively accrued since July 2004. Within 6 weeks of surgery, all patients underwent CCTR, including craniospinal radiation (CSI; 35 Gy/21#) with tumor bed boost (19.8 Gy/11#) with 35 mg/m2/day carboplatin 5 days a week for 15 doses (during 3 weeks of CSI), followed by 6 cycles of 4-weekly adjuvant chemotherapy including vincristine, cisplatinum, and cyclophosphamide) beginning 4 weeks post-CTRT. RESULTS: 26 patients have been accrued. Median age was 8.5 years (range, 4–17 yrs). M:F ratio was 3.1:1. M stage: 62% were M0, 3.8% M1 and 34.6% M2. Among evaluable patients, three achieved a complete response (CR) and 2 (7.7%) had progressive disease, 2 (7.7%) died from toxicity, and in 1 (3.8%), treatment was discontinued because of toxicity. At a median follow-up duration of 30 months (range, 2–51 months), 17/26 (65%) of patients have relapsed/progressive disease. During treatment, grade III-IV anemia was observed in 17%, neutropenia in 54%, and thrombocytopenia in 26%. 92% of patients had anorexia, 100% had nausea/vomiting, 71% developed mucositis, 70% had grade II-III radiation dermatitis, and 94% had alopecia. 21% of patients had febrile neutropenia and 57% required G-CSF support. During adjuvant chemotherapy, hematologic toxicity (grade III-IV) was observed in 85% of patients. CONCLUSION: Concurrent CCTR followed by AC is feasible with manageable toxicities for children presenting with HMB and the encouraging EFS of 65% may translate into higher cure rates.

OT-18. A PHASE II TRIAL WITH BEVACIZUMAB AND IRINOTECAN FOR PATIENTS WITH PRIMARY BRAIN TUMORS AND PROGRESSION AFTER STANDARD THERAPY
Soren M. Moller, Kirsten Grunnet, Henrik Schantz, Henrik Scholtz 1, MatsHolmberg, 4 Morten M. Sorensen, 1 Hans S. Poulsen, and Ulrik Lassen 1; 1Copenhagen University Hospital, Rigshospitalet; 2Odense University Hospital; 3Aarhus University Hospital; 4Aalborg University Hospital
INTRODUCTION: The combination of irinotecan and bevacizumab has shown efficacy in the treatment of recurrent brain tumors. A multicenter, phase II, nonrandomized study of 77 patients with various recurrent brain tumors was carried out. Primary endpoints were progression-free survival (PFS) and response rate. We included 77 patients with performance statuses of 0–2 with recurrent primary brain tumors. Diagnoses were glioblastoma multiforme (n = 32), anaplastic astrocytoma of World Health Organization (WHO) grade 3 (n = 13), anaplastic oligodendroglioma of WHO grade 3 (n = 8), anaplastic oligoastrocytoma of WHO grade 3 (n = 5), astrocytoma of WHO grade 2 (n = 8), oligoastrocytoma of WHO grade 2 (n = 2), ependymoma of WHO grade 3 (n = 2), gliosarcoma of WHO grade 3 (n = 2), medulloblastoma of WHO grade 4 (n = 1), prolactinoma (n = 1), Schwannoma of WHO grade 4 (n = 1), and medulloblastoma (n = 1). 95% of patients had received prior chemotherapy. MATERIALS AND METHODS: Patients were treated with 10-mg/kg intravenous bevacizumab and 125/340 mg/m2 irinotecan every 14 days (2 treatments = 1 cycle). Evaluated were the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of vorinostat (V), an oral histone deacetylase inhibitor (HDAC), which combined with daily temozolomide and bevacizumab among recurrent malignant glioma (MG) patients. A planned Phase II component of this study will incorporate daily temozolomide (TMZ) at the MTD identified by the Phase I component to evaluate the antitumor efficacy of this regimen among recurrent glioblastoma patients. METHODS: We employed a 3 + 3 dose escalation design to determine the MTD and DLT of V administered once daily for 7 days every other week (7 days on, 7 days off) for each 28-day cycle combined with daily temozolomide (50 mg/m2) and bevacizumab (10 mg/kg intravenously every 2 weeks). Dose levels of V included 200 mg and 400 mg. Key eligibility criteria: grade ≥ 3 MG that is progressive; age ≥ 18 years; KPS ≥ 70%; adequate organ function; and at least 4 weeks from either prior surgery or chemotherapy and 12 weeks from prior XRT. Exclusion criteria: grade ≥ 1 hemorrhage on pretreatment MRI; prior progressive disease or grade ≥ 3 toxicity to either daily temozolomide or bevacizumab; prior HDAC therapy; and concurrent warfarin. RESULTS: Nine patients have enrolled, including 5 at the 200-mg V dose level and 4 at the 400-mg V dose level. Seven patients had GBM and 2 had anaplastic astrocytoma. Five patients had progressed on prior 5-day temozolomide therapy. No DLTs or grade ≥ 4 toxicities occurred. Grade 3 toxicities included abdominal pain (n = 1) and hypertension (n = 1). The most frequent grade 2 event was fatigue (n = 6; 67%). Among evaluable patients, three achieved a complete response (CR) or partial response (PR) and 3 achieved stable disease. CONCLUSIONS: The combination of vorinostat plus daily temozolomide and bevacizumab is well tolerated in recurrent MG patients at the dose levels evaluated.
OT-20. PACLITAXEL POLIGLUMEX (PPX), TEMODAR (TMZ), AND RADIATION (RT) FOR NEWLY DIAGNOSED HIGH-GRADE GLIOMAS: A BROWN UNIVERSITY ONCOLOGY GROUP PHASE II STUDY

Surya Jayapalan 1, Maria Constantinous1, Devon Evans 2, Heinrich Elinzano 3, Brigid O’Connor 1, M. Yakub Puthawala 1, Mark Goldman 1, Adetukunbo Oyelese 1, Deus Celso 1, Thomas Dipetrillo 1, and Howard Safran 1
1Rhode Island Hospital; 2Maine Center for Cancer Medicine (MCCM)

BACKGROUND: The conjugation of paclitaxel to a poly-L-glutamic acid polymer forms PPX, which has an increased radiation enhancement factor. In ependymal adenocarcinoma, PPX and radiation therapy (RT) achieved a pathologic complete response of 30% (Safran, ASCO 2010). The primary objective of this study was to determine the safety of PPX with standard TMZ and RT for patients with high-grade gliomas. METHODS: Patients received weekly PPX 50 mg/m2 and daily TMZ 75 mg/m2 for 6 weeks with concomitant RT (200 cGy, 5 d/wk for a total dose of 60 Gy). Adjuvant chemotherapy with TMZ (200 mg/m2/d × 5 d × 5 repeated every 28 days, was started 1 month afterward and continued until evidence of disease progression. RESULTS: The study has accrued 24 out of 25 planned patients, 13 patients had glioblastomas (GBMs), 21 patients completed radiation (3 are ongoing). Due to thrombocytopenia, 2 patients received only 4 weeks of TMZ/PPX and 3 patients received 5 weeks. The main toxicity was myelosuppression: 3/14 (21.4%) patients had an asymptomatic grade IV thrombocytopenia. The Data Safety Monitoring Group decreased the PPX dose to 40 mg/m2/week and an additional 2/10 (20%) patients developed an asymptomatic grade 4 thrombocytopenia; 1 patient was also on aspirin/clopidogrel. Other hematologic grade 3/4 toxicities were: grade III thrombocytopenia (4/24, 16.7%), neutropenia (2/24, 8.3%), and lymphopenia (1/24, 4.2%). Treatment related nonhematologic grade 3/4 toxicities were: dehydration, anorexia, upper extremity pain, weakness, and elevated alkaline phosphatase. The median duration of follow-up was 7.75 months (range, 1–16 months). Fifteen patients were enrolled in the protocol for at least 6 months and 10 of them (67.7%) were progression free at 6 months. CONCLUSION: PPX with TMZ and concurrent radiation is an easily administered regimen for high-grade gliomas. The hematologic toxicities were asymptomatic and the 6-month progression-free survival (PFS) rate of 67.7% is encouraging. Results will be updated.

OT-21. DETECTION OF TEMOZOLOMIDE AND MTIC IN BRAIN TUMOR OR NORMAL BRAIN TISSUES 4 HOURS AFTER TMZ ADMINISTRATION

Mitsuhiro Anan, Mohamad Seyed Sadr, Jald Alshami, Carmen Sabau, Emad Seyed Sadr, Vincent Sui, Marie-Christine Guisot, Amir Samani, and Rolando Del Maestro; MNI - McGill University

BACKGROUND: Glioblastoma patients are currently treated by surgery, radiotherapy, and concomitant and adjuvant temozolomide (TMZ). TMZ is converted to the methyl triazeno imidazole carboxamide (MTIC) and hydrolyzes to the active metabolite, O6-methylguanine which is responsible for the methylation of the DNA genome adducts. We have completed a Phase II trial assessing the influence of neoadjuvant chemotherapy (CT) with concomitant and adjuvant temozolomide (TMZ). TMZ is converted to monomethyl triazeno imidazole carboxamide (MTIC) at physiologically relevant concentrations. We have also assessed the efficacy of TMZ in glioblastoma patients using PET imaging. The primary objective of this study was to determine the safety of PPX with standard TMZ and RT for patients with high-grade gliomas. The study has accrued 24 out of 25 planned patients, 13 patients had glioblastomas (GBMs), 21 patients completed radiation (3 are ongoing). The main toxicity was myelosuppression: 3/14 (21.4%) patients had an asymptomatic grade IV thrombocytopenia. The Data Safety Monitoring Group decreased the PPX dose to 40 mg/m2/week and an additional 2/10 (20%) patients developed an asymptomatic grade 4 thrombocytopenia; 1 patient was also on aspirin/clopidogrel. Other hematologic grade 3/4 toxicities were: grade III thrombocytopenia (4/24, 16.7%), neutropenia (2/24, 8.3%), and lymphopenia (1/24, 4.2%). Treatment related nonhematologic grade 3/4 toxicities were: dehydration, anorexia, upper extremity pain, weakness, and elevated alkaline phosphatase. The median duration of follow-up was 7.75 months (range, 1–16 months). Fifteen patients were enrolled in the protocol for at least 6 months and 10 of them (67.7%) were progression free at 6 months. CONCLUSION: PPX with TMZ and concurrent radiation is an easily administered regimen for high-grade gliomas. The hematologic toxicities were asymptomatic and the 6-month progression-free survival (PFS) rate of 67.7% is encouraging. Results will be updated.

OT-22. PHASE III SAPHIRE STUDY IN HIGH-GRADE GLIOMAS: TARGETED THERAPY WITH TGF-BETA INHIBITOR TRABEDERSEN BASED ON RESULTS OF A RANDOMIZED PHASE IIb STUDY

1University of Regensburg, Department of Neurology; 2University of Innsbruck, Department of Neurology; 3Sanjay Gandhi Post-Graduate Institute of Medical Sciences; 4Manipal Hospital, Manipal Institute for Neurological Disorders; 5Policy Research Neurosurgery Research Institute St. Petersburg; 6Military Medical Academy St. Petersburg; 7Samarra Medical Hospital; 8University of Regensburg, Department of Neurology, Regensburg; 9Antisense Pharma GmbH, Regensburg

INTRODUCTION: TGF-beta2 regulates key mechanisms of carcinogenesis, especially immunosuppression and metastasis. The antisense oligonucleotide trabedersen (AP 12009) is a TGF-beta2-specific inhibitor developed for the treatment of patients with highly malignant tumors such as recurrent or refractory high-grade glioma (HGG). METHODS: Clinical studies with trabedersen in HGG have included 3 phase I/II studies and one randomized, controlled, multinational dose-finding phase IIb study. These studies were performed in adult patients with recurrent/refractory high-grade glioma (GBM, WHO grade IV). Trabedersen was administered intratumorally by convection-enhanced delivery during a treatment period of about 6 months. RESULTS: In the phase IIb study, of 145 patients randomized to either one of the two doses of trabedersen (10 µM or 20 µM) or chemotherapy (TMZ or PCV), 134 patients (AA = 39; GBM = 95) received study medication. The highest efficacy was observed in AA patients treated with 10-µM trabedersen. In this group, the 14-month progression rate was 16.7%, which was lower than seen with 30-µM trabedersen (40.0%, P = 0.1534) or chemotherapy (58.3%, P = 0.0032). The 10-µM trabedersen group also had a 3-fold longer duration of response and a clearly longer median survival than chemotherapy (39.1 vs. 21.7 months, ns). In addition, promising efficacy data were observed in GBM, especially in patients not older than 55 years with Karnofsky Performance Statuses (KPS) >80% at baseline, who had a 24-month survival rate of 40% in the 10-µM trabedersen group vs. 13% in the chemotherapy group. Trabedersen generally had a good tolerability and safety profile. CONCLUSIONS: Trabedersen treatment showed a clear clinical benefit in recurrent HGG. Based on the Phase IIb results, the pivotal Phase III SAPHIRE study in patients with recurrent/refractory AA was started. Patient recruitment is ongoing. The primary endpoint is 2-year survival rate; secondary endpoints include overall survival, tumor response, quality of life, and safety.

OT-23. CLINICAL TRIALS FOR MALIGNANT BRAIN TUMORS CONDUCTED BY JCOG-BRAIN TUMOR STUDY GROUP

Yohei Maruyama 1, Takamasa Kayama 1, Toshihiko Wakabayashi 1, a and Ryo Nishikawa 3; 1National Cancer Center Hospital; 2Nagoya University; 3Sattama Medical University

PURPOSE: A multi-institutional cooperative study group for brain tumors (JCOG-Brain Tumor Study Group) was organized and conducted Phase II/III studies in order to establish the standard therapy for malignant brain tumors. METHODS: The group consists of 32 neurological institutions and has started clinical trials for malignant gliomas, metastatic brain tumors, and primary CNS lymphomas. These studies are supported by grants from the Ministry of Health, Labor, and Welfare, Japan. RESULTS: The efficacy of ACNU vs ACNU + procarbazine as a postoperative chemotherapy was compared in the first clinical trial for astrocytoma grades 3/4 (JCOG 0035), ACNU-based chemotherapy was effective. The median survival durations of glioblastoma patients were 16.8 months and 18.7 months; however, myelosuppression grades 3/4 were observed in more than 40% and 50% of the patients, respectively. Another trial for glioblastoma based on results of a randomized Phase IIb study (JCOG 0035) is planned. The primary target is a 2-year survival rate; secondary endpoints include overall survival, tumor response, quality of life, and safety.

PUBLIC DATABASE LINK: http://www.jco-g.org
OT-24. HIGH SV2A EXPRESSION IN TUMOR AND PERITUMORAL TISSUE IN GLIOMA PATIENTS WITH EPILEPSY IS ASSOCIATED WITH HIGH EFFICACY OF LETRIVACETAM
M. de Groot1,2, †3, J-J. Verhaak4,5, W. van den Bent6,9, T. Ten Kate-Franx7, and J.C. Reijnierse1,2,†
1Department of Neurology, VU University Medical Center; 2Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands; 3Department of (Neuro)Pathology, Academic Medical Center, Amsterdam, The Netherlands; 4DiaDEE Clinical Trials, Heemstede, The Netherlands; 5Department of Neurology, MC HagaLanden, The Hague, The Netherlands

OBJECTIVES: Epilepsy is a common symptom in patients with glioma. Many antiepileptic drugs are known to interact with anti-neoplastic drugs and corticosteroids. Letrivacetam does not have these interactions and benefits the majority of glioma patients. Unfortunately, not all patients are seizure free on levetiracetam. Synaptic vesicle protein 2A (SV2A) is the binding site for levetiracetam. Possibly, the expression of SV2A in brain tissue correlates with clinical response to levetiracetam. Selection of patients by using SV2A expression as a predictive tool might avoid unnecessary treatment with levetiracetam. We aimed to correlate SV2A expression in surgically removed tumor and peritumoral tissue of glioma patients suffering from epilepsy with the clinical response to levetiracetam. METHODS: Forty glioma patients with epilepsy were recruited. All patients had undergone surgery and were on levetiracetam monotherapy. Treatment with levetiracetam was carried out according to standardized guidelines. Clinical characteristics including patient, tumor, and epilepsy history were documented. Follow-up visits were scheduled at six months. Expression of SV2A was determined by means of immunohistochemistry on the surgically removed tumor tissue and the peritumoral tissue (if available) of the patients. RESULTS: Twenty-one patients were lost during follow-up: all three due to tumor progression. After six months, 21 patients (57%) were seizure-free, while six patients (16%) reported a reduction in seizure frequency of >50%. In six patients (15%) levetiracetam was not effective. Three patients (8%) had to switch to a different anti-epileptic drug due to adverse effects. Of the patients with high SV2A expression, 100% showed efficacy of levetiracetam and of the patients with low SV2A expression, 38.5% showed efficacy and 61.5% showed no efficacy (P < 0.01). CONCLUSIONS: Our results indicate that levetiracetam monotherapy is efficacious in reducing seizures in the majority of glioma patients suffering from epilepsy, and high expression of SV2A in tumor and peritumoral tissue appears to predict levetiracetam efficacy.

OT-25. THE EFFICACY OF CEDIRANIB AS MONOTHERAPY AND IN COMBINATION WITH LOMUSTINE COMPARED TO LOMUSTINE ALONE IN PATIENTS WITH RECURRENT GLIOBLASTOMA: A PHASE III RANDOMIZED STUDY
Tracy Batchelor1, Paul Mulholland2, Bart Neyns3, L. B. Nabors4, Mario Campone5, Anne Wick6, Warren Mason7, Tom Mikkleseen8, Suracek Phuphanich9, Lynn S. Ashby10, John F. DeGroot11,† H R Gattamaneni12, Lawrence M. Cher13, Mark A. Rosenthal14, Franz Payer15, John Xu16, QiLu Liu17, and Marthin van den Bent18
1Memorial Sloan-Kettering Cancer Center; 2Dana-Farber Cancer Institute; 3Centre Rene´ Gauducheau, Saint-Herblain, France; 4University of Alabama at Birmingham, Birmingham; 5Centre Rene´ Gauducheau, Saint-Herblain, France; 6University of Heidelberg, Heidelberg; 7Princess Margaret Hospital, Toronto; 8National Center for Cancer Research, NCI, Boston, MA; 9Marianne van den Berg, Buenos Aires, Argentina; 10Marianne van den Berg, Buenos Aires, Argentina; 11Memorial Sloan-Kettering Cancer Center, New York; 12Baylor Research Institute, Dallas; 13Henry Ford Health Systems, Detroit; 14Wake Forest University Health Sciences, Winston Salem; 15Monmouth Medical Center, Long Branch, NJ and Garden State Neurology & Neuro-Oncology, West Long Branch; 16Merck KGaA, Darmstadt; 17EMD Serono Inc, Rockland; 18Duke University Medical Center, Durham

Cediranib, a selective alphavbeta3/5 integrin inhibitor, exhibits concentration-dependent antitumor activity in patients with recurrent glioblastoma multiforme (Reardon et al. JCO 2008). CORE (Cediranib in subjects with newly diagnosed glioblastoma multiforme and unmethylated MGMT gene promoter: Safety run-in results from a randomized controlled phase II study (CORE)) is a Phase II, multicenter, open-label, randomized, controlled trial. The initial 6-week safety run-in (SRI) used a 3+3 design to evaluate stepwise cediranib intensification over three treatment groups: 3×/week, 4×/week and 5×/week. 2000-mg cediranib was administered intravenously over 1 hour in combination with standard therapy (radiotherapy (RT) and daily temozolomide (TMZ)), followed by twice weekly cediranib with standard therapy (TMZ cycles). Eligible adult patients had newly diagnosed, histologically-proven glioblastoma, unmethylated MGMT status, postoperative gadolinium-enhanced magnetic resonance imaging, Eastern Cooperative Oncology Group performance scores of 0–1, and stable or decreasing steroid dose. Twelve patients completed the SRI: no maximum tolerated dose was identified. The first two groups contained 3 patients each. One patient in the third group experienced a dose-limiting toxicity (DLT) of hepatobiliary disorder (hyperbilirubinemia, elevated AST/ALT) during the first 4 weeks of combination therapy, and this group was expanded to 6 patients. No further DLTs were observed. After >3 months of treatment, 1 further serious adverse event (SAE; pulmonary embolism) occurred, which was related to either cediranib or underlying disease. Four unrelated SAEs occurred in 2 patients. Observed AEs mainly reflected the underlying disease or known toxicities of TMZ/RT. The Safety Monitoring Board recommended proceeding with the randomized part as planned. These data support the use of an intensified regimen of cediranib (2000 mg, 5×/week combined with RT/TMZ) for the randomized (currently accruing) phase of CORE in patients with newly diagnosed glioblastoma with unmethylated MGMT status.

OT-26. CILENGITIDE IN PATIENTS WITH NEWLY DIAGNOSED GliOBLASTOMA MULTIFORME AND UNMETHYLATED MGMT GENE PROMOTER: SAFETY RUN-IN RESULTS FROM A RANDOMIZED CONTROLLED PHASE II STUDY (CORE)
Burt Nabors1, Karen Fink2, Tom Mikkleseen3, Michael Chan4, John Troshlein5, Sumal Raval6, Christine Hicking7, Jean Henslee-Downey8, Martin Picard9, and David Reardon10
1University Hospitals of Cleveland, Cleveland, OH; 2Baylor Research Institute, Dallas; 3Henry Ford Health Systems, Detroit; 4Wake Forest University Health Sciences, Winston Salem; 5Abbott Northwestern Hospital, Minneapolis; 6Monmouth Medical Center, Long Branch, NJ and Garden State Neurology & Neuro-Oncology, West Long Branch; 7Merck KGaA, Darmstadt; 8EMD Serono Inc, Rockland; 9Duke University Medical Center, Durham

Cilengitide, a selective alphavbeta3/5 integrin inhibitor, exhibits concentration-dependent antitumor activity in patients with recurrent glioblastoma multiforme (Reardon et al. JCO 2008). CORE (Cilengitide in subjects with newly diagnosed glioblastoma multiforme and unmethylated MGMT gene promoter: Safety run-in results from a randomized controlled phase II study) is an open-label, randomized, controlled trial. The initial 6-week safety run-in (SRI) used a 3+3 design to evaluate stepwise cilengitide intensification over three treatment groups: 3×/week, 4×/week and 5×/week. 2000-mg cilengitide was administered intravenously over 1 hour in combination with standard therapy (radiotherapy (RT) and daily temozolomide (TMZ)), followed by twice weekly cilengitide with standard therapy (TMZ cycles). Eligible adult patients had newly diagnosed, histologically-proven glioblastoma, unmethylated MGMT status, postoperative gadolinium-enhanced magnetic resonance imaging, Eastern Cooperative Oncology Group performance scores of 0–1, and stable or decreasing steroid dose. Twelve patients completed the SRI: no maximum tolerated dose was identified. The first two groups contained 3 patients each. One patient in the third group experienced a dose-limiting toxicity (DLT) of hepatobiliary disorder (hyperbilirubinemia, elevated AST/ALT) during the first 4 weeks of combination therapy, and this group was expanded to 6 patients. No further DLTs were observed. After >3 months of treatment, 1 further serious adverse event (SAE; pulmonary embolism) occurred, which was related to either cediranib or underlying disease. Four unrelated SAEs occurred in 2 patients. Observed AEs mainly reflected the underlying disease or known toxicities of TMZ/RT. The Safety Monitoring Board recommended proceeding with the randomized part as planned. These data support the use of an intensified regimen of cilengitide (2000 mg, 5×/week combined with RT/TMZ for the randomized (currently accruing) phase of CORE in patients with newly diagnosed glioblastoma with unmethylated MGMT status.

OT-27. PHASE II TRIAL OF SUNITINIB (SU11248) FOR RECURRENT MENINGIOMA
Thomas J. Kaley1, Patrick Y. Wen2, David Schif3, Sasan Karimi1, Lisa M. DeAngelis4, Craig P. Nolan5, Antonio O'Suoro6, Igor Gavrilovic7, Andrew Norden8, Jan Drapatz8, Benjamin W. Purwen8, Frank S. Lieberman8, Subramanian Harinaran8, Lauren E. Abrey9, and Andrew B. Lassman10
1Memorial Sloan-Kettering Cancer Center; 2Dana-Farber/Brigham and Women’s Cancer Center; 3University of Virginia Health Science Center; 4University of Pittsburgh Medical Center; 5Pfizer

BACKGROUND: Medical therapies for radiotherapy-refractory meningiomas are limited. Sunitinib malate (SU11248) is a small-molecule inhibitor of VEGFR, PDGFR, KIT, and FLT3 in addition to the general tyrosine kinase inhibition activity of SU11248. Beneficial effects of sunitinib (SUT) in recurrent meningioma have been previously reported in several phase I and II trials. However, no randomized controlled phase II study has been conducted for patients with recurrent meningioma. METHODS: This open-label, randomized, controlled trial was designed to evaluate stepwise sunitinib intensification over three treatment groups: 3×/week, 4×/week and 5×/week. 2000-mg sunitinib was administered intravenously over 1 hour in combination with standard therapy (radiotherapy (RT) and daily temozolomide (TMZ)). RESULTS: Between October 2008 and September 2009, 325 patients from 67 centers across 10 countries were randomized to study arms. Full results will be available for presentation at the meeting.
multiple tyrosine kinase inhibitor that targets the VEGF and PDGF receptors abundant in meningiomas. METHODS: We conducted a Phase II trial for patients with recurrent meningioma (WHO grades I–III, n = 40) or heman- giopericytoma/pagetoangioblastoma (n = 10). Sunnitinib is administered orally at 50 mg/day for days 1–28 of every 42 day cycle. Magnetic resonance imaging (MRI) scans are performed every cycle for the first two cycles and then every two cycles. The primary endpoint is the 6-month progression-free survival rate and secondary endpoints are radiographic response rate, safety, and progression-free and overall survival (OS). Exploratory objectives include analysis of tumor molecular characteristics and MRI-perfusion. RESULTS: To date, 37 patients (14 male) with a median age of 61 (range, 32–85 years) and median KPS of 80 have been enrolled, including 28 malignant/atypical meningioma, 2 with benign meningioma, 4 with heman- giopericytoma, and 3 with hemangioblastoma. For malignant/atypical meningioma patients (28), mPFS is 4.6 months and mOS has not been reached; 21 patients are alive and 3 remain on treatment. Initial radiographic responses in the meningioma patients have included 1 partial response (PR), 17 with stable disease (SD; some with a minor reduction in tumor size), 6 with progressive disease (PD), and 4 patients pending evaluation. The patient with PR subsequently suffered a fatal intratumoral hemorrhage. One patient with hemangiopericytoma with initial stable disease had an intratumoral hemorrhage at progression. Fifteen patients required dose reductions for toxicity. Grades 3 and 4 toxicities include cerebrovascular ischemia (1), myelosuppression (9), headache (4), fatigue (5), nausea/vomit- ing (3), asthenia (2), GI perforation (1), hypertension (3), prolonged QTc (2), dehydration (2), elevated ALT/AST/amylase/lipase (1 each), confusion (1), and gait dif- ficulty (1). MR-perfusion imaging has demonstrated decreased perfusion after treatment in most patients. CONCLUSIONS: Sunnitinib may be active in recurrent atypical malignant meningioma patients who are not eligible for further surgery or radiotherapy. The toxicity of sunnitinib in this popu-lation is concerning and needs further evaluation.

OT-28. A PHASE II TRIAL OF TEMOZOLOMIDE IN ELDERLY PATIENTS WITH GLOBLASTOMA AND POOR PERFORMANCE STATUS (KPS < 70); PRELIMINARY RESULTS OF THE ANOCEF “TAG” TRIAL
Jaime Gallego Perez-Larraya1, Jerome Honnorat2, Olivier Chinot3, "TAG" TRIAL STATUS (KPS < 70) is concerning and needs further evaluation. For further surgery or radiotherapy. The toxicity of sunitinib in this popu-lation is concerning and needs further evaluation. The postoperative KPS was 60 in 44 patients (63%) and below 60 in 26 patients (37%). During follow-up, 18 patients (25.7%) achieved a KPS ≥ 70, and 21 patients (30%) improved their score by at least 10 points. An objec-tive response was observed in 18 patients (26%). The toxicity profile was acceptable, with grade 4 neutropenia and neutropenic fever occurring in 5 patients. There were no treatment-related deaths. CONCLUSIONS: As the primary endpoint was reached, the trial was closed after 18 patients (12%) were enrolled. Twelve patients are evaluable for further analysis.

BACKGROUND: The correct management of glioblastoma (GBM) in elderly patients with a poor Karnofsky performance status (KPS < 70) has not been settled. A trial evaluating the effect of temozolomide alone in this population was undertaken. PATIENTS AND METHODS: Patients aged 70 years or older with newly-diagnosed GBM and a postoperative KPS < 70 were eligible for this multicenter prospective Phase II trial. The treatment consisted of temozolomide (150-200 mg/m²) every day for 5 weeks followed by 2 weeks of rest. Radiotherapy was not adminis-tered. RESULTS: Seventy patients (42 female and 28 male) with a median age of 77 (range, 70–87 years) were included between 07/07 and 02/09. The postoperative KPS was 60 in 44 patients (63%) and below 60 in 26 patients (37%). During follow-up, 18 patients (25.7%) achieved a KPS ≥ 70, and 21 patients (30%) improved their score by at least 10 points. An objec-tive response was observed in 18 patients (26%). The toxicity profile was acceptable, with grade 4 neutropenia and/or thrombocytopenia occurring in 5 patients. The rate of 6-month progression-free survival (PFS) was 29%, with a median PFS of 16 weeks (95% CI, 10–20). The rate of 6-month overall survival (OS) was 44%. The median OS was 25 weeks (95% CI, 19–28), comparing favorably with an expected 12–16 weeks from a purely supportive approach. CONCLUSION: In elderly patients with GBM and poor KPS, treatment with temozolomide has an acceptable safety profile. It is associated with an improvement of functional status in 30% of cases and appears to increase survival as compared to supportive care alone.

OT-29. EFFECT OF EVEROLIMUS ON TUBEROUS SCLEROSIS-RELATED LESIONS IN THE BRAIN
David N. Franz1, Darcy A. Krueger1, Marguerite M. Care1, SCLEROSIS-RELATED LESIONS IN THE BRAIN appears to increase survival as compared to supportive care alone. During follow-up, 18 patients (25.7%) achieved a KPS ≥ 70, and 21 patients (30%) improved their score by at least 10 points. An objec-tive response was observed in 18 patients (26%). The toxicity profile was acceptable, with grade 4 neutropenia and/or thrombocytopenia occurring in 5 patients. The rate of 6-month progression-free survival (PFS) was 29%, with a median PFS of 16 weeks (95% CI, 10–20). The rate of 6-month overall survival (OS) was 44%. The median OS was 25 weeks (95% CI, 19–28), comparing favorably with an expected 12–16 weeks from a purely supportive approach. CONCLUSION: In elderly patients with GBM and poor KPS, treatment with temozolomide has an acceptable safety profile. It is associated with an improvement of functional status in 30% of cases and appears to increase survival as compared to supportive care alone.

OT-30. A PHASE I TRIAL OF THE PROTEASE INHIBITOR NELFINAVIR AND CONCURRENT RADIATION AND TEMOZOLOMIDE IN PATIENTS WITH WHO GRADE IV Glioma
Michelle Alonso-Basanta1, Robert A. Lustig2, and Jay F. Dorsey1; University of Pennsylvania BACKGROUND: HIV protease inhibitors (PI) sensitize glioblastoma cells to radiation in vitro and in vivo via a proposed mechanism of Akt inhibi-tion. We initiated a Phase I trial to determine the maximum tolerated dose (MTD) and the dose-limiting toxicities (DLT) of the HIV nelfinavir mesylate in combination with concurrent radiation and temozolomide in WHO grade IV glioma. METHODS: The study was designed as an open-label Phase I/II study. Patients with pathologically confirmed grade IV glioma were eligible. A classic 3 + 3 study design was selected. Nelfinavir (625 or 1250 mg orally twice daily) was added to standard concomitant radiation (60 Gy) and temo-zolomide (75 mg/kg) beginning 7–10 days prior to chemoradiotherapy. After completion of concurrent nelfinavir mesylate and chemoradiotherapy, patients received standard adjuvant temozolomide. RESULTS: Six patients have been enrolled thus far and six patients have completed concurrent nelf-inavir mesylate and chemoradiotherapy. No DLTs were observed. Most common toxicities were grade I and II GI and endocrine toxicities, including diarrhea, transient LFT elevation, and hyperglycemia. One patient experi-enced a grade IV serious adverse event not related to the study. The rec-ommended dose of nelfinavir mesylate in combination with radiation and temozolomide (grade 2 GI toxicity weekly) demonstrates acceptable toxicities and is well tolerated. CONCLUSIONS: The preliminary results of our Phase I study with twice daily administration of up to 1250 mg of nelfinavir mesylate in conjunction with concomitant temozolomide and radiotherapy suggest that this treatment is feasible and safe. The planned Phase II portion of the trial is ongoing and patients are currently being recruited at the second dose level.

OT-31. FINAL ANALYSIS OF ACT III: A PHASE II TRIAL OF PF-04948568 (CDX-110) IN COMBINATION WITH TEMOZOLOMIDE (TMZ) IN PATIENTS (PTS) WITH NEWLY DIAGNOSED GLOBLASTOMA (GBM)
Rose K. Lai1, Lawrence D. Recht2, David A. Reardon3, Nina Paleologos4, Morris Groves5, Myrana R. Rosefeld6, Sandra Mirech7, Tom Davis8, Dmitri Pavlov7, Margaret A. Marshall7, and John Sampson9; 1Neurological Therapeutics; 2Stanford Cancer Center; 3The Preston Robert Tisch Brain Tumor Center at Duke University Medical Center; 4NorthShore University Health System; 5The University of Texas MD Anderson Cancer Center; 6Hospital of the University of Pennsylvania; 7Pfizer Global Research and Development; 8Celldex Therapeutics; 9Duke University Medical Center BACKGROUND: EGF-R II is a constitutively activated mutation of epi-dermal growth factor receptor (EGF-R) expressed in ~25% of glioblastomas (GBMs) but absent in normal tissues. PF-04948568 is a vaccine containing a 13 amino acid sequence unique to EGF-R II. The vaccine was designed as a multivalent, randomized, open-label Phase IIIb/II study in

Abstracts
the United States and was amended to a single-arm design after 14/16 patients (pts) randomized to the standard-of-care arm withdrew after notification of treatment assignment. The primary objective was to reject the hypothesis that 3% or fewer of patients with newly diagnosed GBM remain alive 16 months (H0: 5.5 PFS ≤ 53%) from first vaccination. METHODS: Eligible pts had a gross total resection of newly diagnosed EGBRvIII + GBM and successful completion of standard radiotherapy with concurrent TMZ. Vaccine was administered on day 1 and then weekly for 4 weeks, with a boost and then weekly thereafter for at least 18 months. A total of 21 evaluable pts were enrolled in this study and 16 were treated with the vaccine every 3 weeks, with a median follow-up of 16 months. RESULTS: The median PFS was 20 months and the median OS was 47 months. CONCLUSIONS: The vaccine in a randomized placebo-controlled trial is warranted.

OT-32. CHROMOSOMAL INSTABILITY AS A RISK FACTOR FOR THE DEVELOPMENT OF (MULTIPLE) BENIGN MENINGIOMAS (PILOT) Marjam Slot and S. M. Peerdeman; VU University Medical Center

The prognosis for patients treated with resection of WHO grade I meningioma is known to be variable. Nineteen percent develop a recurrent tumor or a second primary tumor within 10 years after gross total resection. There is strong evidence that ionizing radiation is an etiologic factor for the development of meningiomas. Those patients might already have had a premalignant field of tissue from whence new tumors can easily grow after radiation. We believe that patient-related factors that affect tumor formation can also play a role in this carcinogenic process. One of those factors is the congenital susceptibility to DNA damage, also known as chromosomal instability. We hypothesize that people with high chromosomal instability have a greater risk of developing multiple tumors in this premalignant field. METHODS: We included 20 patients with proven WHO grade I meningioma who had been operated on at our institution. Ten patients had a stable neurologic and radiologic status after 5 years of follow-up, and 10 patients had multiple meningiomas, recurrence of tumor, or proven growth within 5 years after surgery. For the patients in both groups we measured chromosomal instability using mutagen-sensitivity on lymphocytes. The chromosomal instability can be expressed as the number of chromatid breaks per cell (b/c ratio). The lymphocytes were exposed to damage-inducing material. When the b/c ratio was >1.0 after this exposure, the patient qualified as chromosomally unstable. RESULTS: Surprisingly, the number of chromatid breaks per cell was less than 1.0 for both patient groups. In other words, the chromosomal instability in both groups is very low. This is in contrast with what we had hypothesized. CONCLUSIONS: At this moment, we are still working on the results. When the calculations are done, we can hopefully identify whether constitutional chromosomal instability in a patient can be associated with the development of (multiple) meningiomas.

OT-33. TEMOFRAC A PHASE II TRIAL: CONCURRENT 3-TIMES-DAILY ULTRAFRINGATED RADIATION THERAPY AND TEMOZOLOMIDE FOR NEWLY INOPERABLE Glioblastoma

Patrick D. Beauchesne, Guillaume Faure, Georges Noel, Thierry Schmitt; 1Centre d’Aurore Montpellier; 2Centre Paul Papin Angers; 3Centre Guillaume Le Conquérant Le Havre

BACKGROUND: We are now conducting a Phase II clinical trial to determine the effect of a concurrent ultrafractionation regimen and temozolomide for inoperable glioblastoma patients. METHODS: A prospective, multicenter, Phase II study opened for accrual in February 2008. Patients over 18 years of age who are able to give informed consent and have histologically proven newly diagnosed, inoperable, and supratentorial glioblastoma are eligible. Entry criteria are: age ≤ 75 years, KPS ≥ 60, ≤ 3 days of steroids, ≤ 2 weeks since radiation therapy or surgery. RESULTS: Up to 30% of patients are operated on and then proceed to 3 times daily ultrafractionated radiation therapy and temozolomide every 28 days for 6 cycles. CONCLUSIONS: Ultrafractionated radiation therapy–temozolomide has been well tolerated; no accelerated progression was observed; moderate neurocognitive deficits were observed; median overall survival is 12 months, suggesting a clinically meaningful benefit over historical controls. Further investigation is warranted and a trial associating ultrafractionation and temozolomide is ongoing.

OT-34. SURVIVAL AND TOXICITY UPDATE OF THE PHASE II TRIAL OF BEVACIZUMAB (BV) IN COMBINATION WITH TEMOZOLOMIDE (TMZ) AND IRINOTECAN (CPT-11) FOLLOWED BY BV, TMZ, AND IRINOTECAN (CPT-11) FOR NEWLY DIAGNOSED Glioblastoma Multiforme (GBM) PATIENTS Annick Desjardins, David A. Reardon, Katherine B. Peters, James E. Herndon, IL, John P. Kirkpatrick, Henry S. Friedman, and James J. Vredenburg; Duke University Medical Center

BACKGROUND: Newly diagnosed glioblastoma multiforme (GBM) patients receiving temozolomide (TMZ) and radiation therapy (RT), followed by 6 monthly cycles of TMZ have median progression-free survival (PFS) and median overall survival (OS) rates of 21 and 15 months, respectively. BV has demonstrated a significant therapeutic benefit for recurrent GBM. This study aimed to evaluate the benefit of incorporating BV with RT and TMZ, and CPT-11 and BV to TMZ post-RT therapy for newly diagnosed GBM patients. METHODS: Patients received standard RT and TMZ at 75 mg/m2/week plus BV at 10 mg/kg every 28 days with BV continued for 2 years following at least 28 days postoperatively. Afterward, patients received 6 to 12 cycles of TMZ, BV, and CPT-11 (28-day cycle). TMZ was given at a dose of 200 mg/m2 on days 1–5, BV and CPT-11 were given on days 1 and 15; BV was given at a dose of 10 mg/kg and CPT-11 at a dose of 125 mg/m2 for patients not on an enzyme-inducing antiepileptic drug (EIAED) and at a dose of 340 mg/m2 for patients on an EIAED. RESULTS: For the first 75 patients enrolled, at a median follow-up of 23 months, the median PFS is 14.5 months. The OS is 19.1 months. RESULTS: For patients receiving 3 chemotherapy cycles, 1 bowel perforation, 1 grade 7 hematologic toxicity, 1 second malignancy (AML), and 2 pneumonias of Pneumocystis jirovecii. CONCLUSION: Adding BV to TMZ and RT followed by BV, TMZ, and CPT-11 is tolerable and efficacious. Updated survival and toxicity results for the whole group of 125 patients enrolled will be presented.

OT-35. RADIOTherAPy (RT) AND TEMOzoLOMIDE (TMZ) FOR ANAPLASTic ACsTROYcToMA (AA) Lakshmi Nayak, Katherine S. Panagopoulos, Lisa M. Deangelis, Lauren E. Abrey, and Andrew B. Lassman; Memorial Sloan-Kettering Cancer Center

BACKGROUND: Anaplastic astrocytomas (AA) are aggressive tumors with a median survival of 24–36 months. Combined radiotherapy (RT) and temozolomide (TMZ) is well established as the standard of care for newly diagnosed glioblastoma, but its applicability to anaplastic astrocytoma (AA) is controversial. We conducted a randomized Phase II study in malignant gliomas of RT + TMZ followed by either metronomic or dose-dense adjuvant TMZ, followed by cis-retinoic acid (c-RA). We previously reported results for the GBM cohort and now describe the outcomes for patients with anaplastic gliomas. PATIENTS AND METHODS: Following maximal surgical resection, patients were randomized to newly diagnosed AA or anaplastic oligo-astrocytoma (AOA), with an age ≥ 18, and KPS ≥ 60 were treated with concurrent RT (60 Gy over 6 weeks) + TMZ (75 mg/m2), and then 6 adjuvant 28-day cycles of either dose-dense (150 mg/m2, days 1–7 and 18–21) or metronomic (50 mg/m2, days 1–28) TMZ. RESULTS: Following completion of RT, 14% of TMZ-pretreated patients continued c-RA.
Patient follow-up and MGMT analysis continue. More mature results and multivariate analyses will be presented at the meeting.

PATHOLOGY

PA-01. POSTERIOR SPINAL COLUMN METASTASIS OF CLEAR CELL CARCINOMA OF THE LUNG

Erol Tasdemiroglu, Mikialart Kaya, and Can H. Yildirim; Kafkas University Medical Faculty

Clear cell carcinoma of the lung is extremely rare. A 48-year-old man presented with severe back pain and a subcutaneous mass located dorsally at the midsagittal plane of the T2 and T11 vertebrae. The patient’s neurological examination was normal. Magnetic resonance imaging of the thoracic spine showed a posteriorly located lesion between the T2 and T11 vertebrae that invaded both pedicles and the laminae and spinous processes of those vertebrae. The patient underwent surgery, and gross total tumor resection was accomplished. Histologically, this lesion was metastasis of clear cell carcinoma of the lung. Histopathology was confirmed with immunohistochemistry and computed tomography of the thorax.

PA-02. DETECTION OF CYTOMEGALOVIRUS PP65 AND IE-1 PROTEINS FROM GliOBLASTOMA MULTIFORME

Kenneth G. Lucas, Lei Bao, Richard Bruggeman, and Charles Specht; Penn State Hershey Medical Center

Cytomegalovirus (CMV) is a latent herpesvirus infecting approximately half of the world’s population. Recent studies have shown variable expression patterns of CMV in tumor specimens from patients with malignant glioma. We report the largest single-institution series to date on the expression of CMV pp65 and IE-1, 2 of the most immunogenic CMV proteins, on glioblastoma multiforme (GBM). In our series, 25 of 49 tumors were positive for pp65, and 8 of the 49 tumors were positive for IE-1. Of the 8 tumors that were positive for pp65 and IE-1, 7 were also positive for pp65. Not all cells within a given tumor that tested positive for pp65 or IE-1 had staining for these antigens, possibly reflecting variability in the infection of GBM cells. Although cells that are permissively infected by CMV, such as skin fibroblasts, have prominent IE-1 nuclear staining, CMV-positive GBM in this series generally had pp65 and IE-1 cytoplasmic staining. CMV pp65 and IE-1 nuclear staining was seen in approximately half of the GBM. These findings could be due to alterations in CMV life cycle and virus production within infected tumor cells, as reported by other groups. We infected GBM cell lines exogenously with laboratory strains of CMV and demonstrated that most tumor cells only had cytoplasmic staining, with some also having perinuclear localization of IE-1. These findings confirm that CMV proteins are present in a subset of GBM and suggest that CMV pp65 and IE-1 could be targeted in an immunotherapy strategy for GBM patients. Further studies are needed to better define the behavior of CMV-infected tumor cells and determine whether they can be recognized by CMV-specific T cells.

PA-03. EMBRYONAL TUMOR WITH ABUNDANT NEUROPIt AND TRUE ROSSETTES: OLDEST REPORTED CHILD WITH A RARE CENTRAL NERVOUS SYSTEM TUMOR

Jeffrey C. Murray, David J. Donahue, and Carlos A. Galliani; Cook Children’s Medical Center

INTRODUCTION: Pediatric central nervous system (CNS) embryonal neoplasms represent a unique group of primitive neuroectodermal tumors (PNETs) whose unifying features include poorly differentiated cells, the capacity to differentiate along multiple cell lineages, the propensity to disseminate throughout the neuraxis, and aggressive clinical behavior. PNETs are typically classified as medulloblastomas (cerebellar PNETs), CNS PNETs (other-location PNETs), or atypical teratoid/rhabdoid tumors. A novel embryonal tumor, the embryonal tumor with abundant neuropil and true rosettes (ETANTR), a rare PNET that has been reported in 29 children worldwide, has recently been characterized. ETANTR appears to affect primarily young children, has a female predominance, occurs primarily in the cerebral cortex, and carries a dismal prognosis. METHODS: A 5-year-old, 2-month-old girl presented with a several week history of headaches, ataxia, and photophobia. Examination revealed papilledema. Magnetic resonance imaging revealed a 5.1 cm × 7.4 cm × 6 cm poorly enhancing mass arising from the right lateral ventricle. Gross total resection was achieved, and there was no evidence of neuraxis metastases. RESULTS: Histopathology revealed a cellular lesion with features suggestive of ependymoma. However, abundant neuropil, ependymoblastoma true rosettes, nuclear pleomorphism, GFAP reactivity, vimentin reactivity, a high MIB-1, and retention of INI1 nuclear expression resulted in a diagnosis of ETANTR. CONCLUSIONS: ETANTR is now recognized as a distinct type of CNS embryonal tumor/PNET despite having only been reported in 29 children to date. As with all forms of CNS PNETs affecting children less than 3 years old, ETANTR appears to connotes a poor prognosis. Our case represents the oldest child with ETANTR yet reported, suggesting that the age spectrum may expand as more is understood about this disease. More cases are needed to be reported. Our patient’s treatment included craniopinal radiotherapy and chemotherapy. Her older age may portend a better prognosis, as has been observed in patients with other types of PNET.

PA-04. T-CELL RECEPTOR-GAMMA SUBUNIT GENE REARRANGEMENT ANALYSIS AS AN ADJUNCTIVE DIAGNOSTIC STRATEGY IN PRIMARY Meningeal T-CELL NON-HODGKIN LymphOMA

Nicholas A. Blondin1, Peli Hu2, Alexander Vortmeyer2, Joshua Hashbuni1, and Joachim Baehring2; 1 Yale-New Haven Hospital; 2 Yale University School of Medicine

Primary CNS lymphoma accounts for 3% of all primary brain neoplasms. The vast majority of these tumors are derived from the B-cell lineage. While meningeal involvement occurs in 5–20% of patients, primary meningeal manifestations are rare and pose a diagnostic challenge, especially in T-cell lymphomas. Radiographic features are nonspecific, and the sensitivity of morphology-based analysis and flow cytometry is insufficient. We used a multiplex polymerase chain reaction/capillary electrophoresis–based method to detect clonal rearrangements of the gene encoding the gamma subunit of the T-cell receptor in 2 patients with primary meningeal T-cell lymphoma. The first patient was a 22-year-old African-American man who initially presented with generalized seizures and was found to have a rapidly growing mass in the right temporal lobe. A brain biopsy revealed a monoclonal population of T-lymphocytes. The patient’s disease went into remission following chemotherapy and radiation therapy; however, the patient subsequently developed a biopsy-confirmed metastatic T-cell lymphoma lesion in the abdominal subcutaneous tissue approximately 15 months later. He later achieved a second remission with chemotherapy. The second patient was a 30-year-old Caucasian man who initially presented with headaches, a left abducens nerve palsy, and progressive left-sided radiculopathy. A lumbar puncture was performed, and while cerebrospinal fluid cytology and flow cytometry suggested a diagnosis of primary meningeal T-cell lymphoma, T-cell receptor-gamma gene rearrangement analysis confirmed the diagnosis without need for a brain biopsy. The patient achieved remission following treatment with chemotherapy. We will present the radiographic findings, cytology, flow cytometry, and molecular pathology methodology and data for these two cases. Clonality analysis based on rearrangement analysis of the gene encoding the gamma subunit of the T-cell receptor may be a useful adjunct to conventional diagnostic methods in patients with T-cell lymphoma of the nervous system.

PA-05. MOLECULAR MARKERS OF HYPOXIA, VASCULARITY, AND IMAGING TO PREDICT OUTCOMES OF PATIENTS WITH INTRACRANIAL MENINGIOMAS

Randy L. Jensen and Janet Lee; Huntsman Cancer Institute, University of Utah

BACKGROUND: Intracranial meningiomas, even those of a WHO grade I, have a wide variation in natural history. No fail-proof method for predicting recurrence and patient outcome currently exists. This study explored multiple factors including tumor vascularity markers, preoperative imaging,