ONGOING CLINICAL TRIALS

OT-01. IS SURGERY AT PROGRESSION A PROGNOSTIC MARKER FOR IMPROVED 6-MONTH PROGRESSION-FREE SURVIVAL OR OVERALL SURVIVAL FOR PATIENTS WITH RECURRENT GLIOBLASTOMA?

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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 intervention 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 difference 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 do 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

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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 preliminary activity in adults with recurrent GBM. Preclinical studies have also demonstrated that vorinostat can overcome resistance to agents currently used against recurrent GBM, such as isotretinoin and carboplatin. We hypothesized that vorinostat could overcome isotretinoin-resistance and synergize with carboplatin to target gliomas. We report the results of the Phase I study of combinations of these agents preceding an adaptive randomized 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 + 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, thrombocytopenia, pulmonary embolism, elevated AST (DLT), and hypertriglyceridemia (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/m^2/d $\times$ 21 d) and Arm 2 (carboplatin, AUC 6; isotretinoin, 100 mg/m^2/d $\times$ 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/m^2/d $\times$ 21d; carboplatin, AUC 5) and has accrued 2 patients. The best response has been stable disease in 12 patients; 4 patients achieved 6-month progression-free survival (PFS). CONCLUSIONS: The combinations of vorinostat, isotretinoin, and carboplatin were well tolerated; the MTD has been established for Arms 1 and 2 and is expected to be determined shortly in Arm 3. Preliminary evidence of activity has been seen in these heavily pretreated patients, and the multicenter adaptive randomized Phase II study will open for accrual shortly.

OT-03. PHASE I DOSE ESCALATION TRIAL OF VANDETANIB WITH FRACTIONATED RADIOSURGERY IN PATIENTS WITH RECURRENT MALIGNANT GLIOMAS

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PURPOSE: To determine the maximium tolerated dose (MTD) of vandetanib with SRS in recurrent malignant gliomas. PATIENTS & METHODS: Patients with recurrent malignant glioma and T1-enhancing recurrent tumor of <6 cm were eligible. Vandetanib was administered 7 days before SRS and continued until dose-limiting toxicity (DLT) or disease progression. The vandetanib 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 hematologic toxicity. RESULTS: Thirteen patients gave informed written consent, 10 patients were treated on the protocol, and 9 patients had follow-up data. Characteristics of the 10 treated patients were: 7 men, 3 women; median age, 40 years (range, 22–72); 7 patients had glioblastoma (GBM), 3 had anaplastic astrocytoma (AA); median prior 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). One of 6 patients in the first cohort developed a grade 3 DLT of pulmonary embolism and hemathorax. The trial was stopped when two of the four patients enrolled to the second cohort developed 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

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PURPOSE: To improve survival and quality of life for young children newly diagnosed with medulloblastoma and other primitive neuroectodermal 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 41 participating institutions. All patients were to receive five induction cycles (vincristine, cisplatin, cyclophosphamide, etoposide, 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, carboplatin, and etoposide) rescued with autologous hematopoietic cells. The initial Induction Regimen D was replaced midway through the study by Regimen D2, in which cyclophosphamide and methotrexate doses were attenuated due to inordinate toxicities.

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 localized (M0) patients, 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: 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. Among other PNET cases, the induction response was: CCR 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 D 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-05. A PILOT STUDY OF BEVACIZUMAB-BASED THERAPY IN CHILDREN AND YOUNG ADULTS WITH NEWLY DIAGNOSED HIGH-GRADE GLIOMAS AND DIFFUSE INTRINSIC PONTINE GLIOMAS

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BACKGROUND: Outcomes for children with high-grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG) remain poor. The combination of bevacizumab and irinotecan is commonly used for adults with recurrent HGG, and ongoing trials are now investigating bevacizumab as a radiosensitizer for adults newly diagnosed with HGG. The safety and feasibility of this approach in the pediatric population has not yet been reported. METHODS: An institutional pilot study of a bevacizumab-based regimen in children and young adults (ages, 3–29 years) with newly diagnosed HGG or DIPG was initiated. For the HGG stratum, chemoradiotherapy consisted of bevacizumab (10 mg/kg; Days 22, 36) and temozolomide (75–90 mg/m^2/day; 42 days) concurrent with conformal irradiation, and maintenance chemotherapy consisted of twelve 28-day courses of bevacizumab (10 mg/kg; Days 1, 15), irinotecan (125 mg/m^2; Days 1, 15) and temozolomide (150 mg/m^2/day; Days 1–5). Patients with DIPG received the above 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 therapy due to toxicity (prolonged grade 4 myelosuppression attributable to temozolomide). No other patient required dose reductions or treatment delays of >1 week. Therapy-related grade 3 toxicities included neutropenia (1) and hypertension (1). No intracranial bleeding or wound infections have been observed. Three patients have experienced disease progression (2 DIPG during maintenance courses 4 and 5; 1 HGG after chemoradiotherapy). Gene expression profiling, genome-wide integrity analyses, telomerase activity, and hTERT/hTERC expression studies in tumor and peripheral blood mononuclear cells are being conducted in consenting patients. Early MR perfusion/diffusion changes are being reviewed to assess correlation with response. Enrollment continues for both strata. CONCLUSIONS: A bevacizumab-based regimen is feasible and tolerable in newly diagnosed children and young adults with HGG and DIPG.

OT-06. PHASE II TRIAL OF VORINOSTAT IN COMBINATION WITH BORTEZOMIB IN RECURRENT GLIOBLASTOMA MULTIFORME: A NORTH CENTRAL CANCER TREATMENT GROUP STUDY

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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 400 mg orally daily for 14 days of a 21 day cycle, while bortezomib was administered at a dose of 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11 of the cycle. A total of 37 patients were treated: 16/37 (43%) had received prior bevacizumab. Treatment was well tolerated: ≥ grade 3 nonhematologic toxicities occurred in 12/37 (32.4%) patients and consisted mainly of fatigue (5/37; 13.5%) and neuropathy (2/37; 5.4%); ≥grade 3 hematologic toxicity occurred in 16/37 (43.2%) patients and consisted of thrombocytopenia (13/37; 35.1%), lymphopenia (2/37; 5.4%) and neutropenia (2/37; 5.4%). An interim efficacy analysis was conducted after 34 patients were enrolled and followed for 6 months. The trial failed to meet the predetermined interim analysis efficacy rule with 0/34 patients being progression-free at 6 months. Only 1 patient achieved a partial response according to the MacDonald criteria. The median time to progression (TTP) for all patients was 1.39 months (range, 0.5–5.6 months). Patients who had received prior bevacizumab therapy had a median TTP of 1.29 months versus 1.72 months for patients who had not received prior bevacizumab. Median overall survival (OS) was 2.4 months. Based on the results of this Phase II study, further evaluation of the vorinostat/bortezomib combination in GBM patients is not recommended.

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

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BACKGROUND: The use of single-agent bevacizumab (BEV) improves the objective response rate in 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-Br). METHODS: This clinical trial is ongoing, with an accrual goal of 30 subjects. Patients are treated with 10-mg/kg BEV in combination with 100-mg/m^2 TMZ every 2 weeks; this regimen is continued until tumor progression or unacceptable toxicity occurs. Complete patient evaluations are conducted every 4 weeks and magnetic resonance imaging (MRI) scans are done every 8 weeks. FACT-Br 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 5 CNS hemorrhage in a patient who had discontinued the study due to tumor progression. CONCLUSIONS: The combination of BEV and TMZ given bi-monthly 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 S9811

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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 unresectable, measurable, histologically proven benign meningioma; progressive tumor or progressive neurologic deficit at >1 year after radiation therapy (RT); prior RT; having had no prior cytotoxicities; being 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 5% null hypothesis response probability vs. 20%, with 90% power; the 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, 25%–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 (5/7 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 progressive unresectable 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

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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/m^2/day for 5 consecutive days every 28 days), the optimal therapy is unknown. Resistance to temozolomide is partially mediated by the DNA repair enzyme O^6-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/m^2/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

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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 chemotherapy and targeted molecular agents, no effective drug 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 then at the beginning of every third cycle. 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. Toxicity 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

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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/m^2/day administered intravenously for 2 consecutive days every 4 weeks). All patients previously had been treated with surgery, temozolomide, and radiotherapy. 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 other cycle. Treatment responses 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 (2 grade 3). Twelve patients died from disease progression, 3 patients are alive and on alternative therapy, and 1 patient continues on study. The PFS6 was 6.25%. CONCLUSION: Bendamustine was reasonably well tolerated but failed to meet the study's prespecified endpoint of a 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 (GBM)

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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 of KDR, PDGFR, and c-kit that may provide more 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 $\geq$6 weeks before study entry. Patients treated with enzyme-inducing antiepileptic drugs, prior non-BEV VEGF-directed therapies, concurrent anticoagulation therapy, and other significant cardiovascular conditions were not elible 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-naïve arm. Applying modified Macdonald criteria, only one patient has achieved a partial response in the BEV-naïve arm. Four additional patients (2 BEV-naïve and 2 BEV-resisitant) 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-naïve 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

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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 glioma cells. Supported by promising preclinical and early 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, muticenter 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 centralized neuroimaging review. Overall survival served as a secondary endpoint, with quality-of-life and safety as additional parameters. RESULTS: Between August 2008 and March 2010, the targeted total study population of 150 patients was enroled at 10 sites. A prespecified analysis of the first cohort of 75 patients who had a minimum follow-up of 12 months showed no specific toxicity of nimotuzumab and an unsuspicious safety profile; neither rash, conjunctivitis, nor mucositis were reported. It is too early to determine the treatment efficacy in the overall group; however, molecular markers such as MGMT status and EGFR expression levels are currently being determined. CONCLUSION: The intravenous administration of OSAG-101 for newly diagnosed glioblastoma has been proven safe and free of additional toxicity when added to standard radiochemotherapy. The interim analysis has not been able to determine efficacy yet without correlation to molecular markers.

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)

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BACKGROUND: Metronomic TMZ schedules have been proposed as salvage therapy for recurrent malignant glioma (MG) with the goal of targeting angiogenesis and overcoming the chemoresistance mediated 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/m^2) until progression. A Simon 2-stage design was used; the primary endpoint was 6-month progression-free survival (PFS) (promising: 20%, nonpromising: 5%, 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; 16 were women). The MGMT promoter was methylated in 5 patients, unmethylated in 18, and not available in 24. In addition to standard chemoradiotherapy with TMZ, previous treatments included BEV (17 patients), other cytotoxic agents (9), and experimental targeted therapies (8). In the GBM group, 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, $P = 0.02$). In the AA/AO group, 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 ANTINEOPLASTONS A10 AND AS2-1 (ANP) IN ADULT PATIENTS WITH RECURRENT MIXED GLIOMAS

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The purpose of this study was to evaluate the efficacy and toxicity of antineoplastons 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 magntic 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 of 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 survivals (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. The 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

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A subgroup of 98 patients with cerebral tumors (GBM, n = 46; other primary cerebral tumors, n = 33; cerebral metastases, n = 19) who had received hCRF through all Phase III studies (NTI 0302, 0303, and 0501) 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 with GBM. 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 hCRF 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 hCRF on cerebral tumors.

OT-17. A PROSPECTIVE STUDY OF CONCURRENT CARBOPLATIN AND RADIATION THERAPY (CTRT) FOLLOWED BY ADJUVANT CHEMOTHERAPY IN PATIENTS WITH HIGH-RISK MEDULLOBLASTOMA

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AIM: To assess the role of concurrent carboplatin and radiation therapy (CTRT) followed by adjuvant chemotherapy (AC) in patients with high-risk medulloblastoma (HRM) for improving event-free survival (EFS). METHODOLOGY: Newly-diagnosed 3- to 21-year-old HRM patients have been prospectively accrued since July 2004. Within 6 weeks of surgery, all patients underwent CTRT, including craniospinal radiation (CSI; 35 Gy/21#) with tumor bed boost (19.8 Gy/11#) with 35-mg/m^2/day carboplatin 5 days a week for 15 doses (during 3 weeks of CSI), followed by 6 cycles of 4-weekly adjuvant chemotherapy (using 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% each were M1 and M2, and 30.8% were M3. At the end of CTRT, 23 (88.5%) are in complete response (CR), 2 (7.7%) are in partial response (PR), 1 (3.8%) has radiologic stable disease, and none of the patients has had progression on CTRT. 26 patients were started on AC, 19 of whom have completed treatment. Two patients are still on AC, 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 are in CR (EFS - 65%) and 5/26 (19.2%) 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 CTRT followed by AC is feasible with manageable toxicities for children presenting with HRM 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

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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 meningeoma (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/m^2 irinotecan every 14 days (2 treatments = 1 cycle). Evaluation was carried out every 8 weeks using magnetic resonance imaging (MRI) and McDonald response criteria. Treatment was continued until disease progression or death. RESULTS: Patients received a median of 4.5 cycles. Best responses to treatment for glioblastoma were 0% CR, 26 % PR, and 70% SD and for grade 3 gliomas 8% CR, 11% PR, and 46 % SD. For nonglioma diagnoses, the best responses were 17% CR, 0 % PR, and 83% SD. Median PFS for all patients was 23 weeks and for glioblastomas was 26 weeks. Side effects included mild (grade ≤2) fatigue and nausea. Seven patients experienced serious (grade ≥3) thromboembolic or bleeding events. DISCUSSION AND CONCLUSION: The combination of bevacizumab and irinotecan is well tolerated and moderately efficacious in glioblastoma and other recurrent brain tumors. A majority of patients achieve at least disease stabilization with this treatment. The median PFS of 23 weeks compares favorably with historic results.

OT-19. A PHASE I/II STUDY OF VORINOSTAT PLUS DAILY TEMOZOLOMIDE AND BEVACIZUMAB IN THE TREATMENT OF PATIENTS WITH RECURRENT MALIGNANT GLIOMA

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BACKGROUND: We report a phase I study to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of vorinostat (V), an oral histone deacetylase inhibitor (HDACi), when combined with daily temozolomide and bevacizumab among recurrent malignant glioma (MG) patients. A planned Phase II component of this study will incorporate the MTD established 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/m^2) 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 HDACi 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 have 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 5 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

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BACKGROUND: The conjugation of paclitaxel to a poly-L-glutamic acid polymer forms PPX, which has an increased radiation enhancement factor. In esophageal adenocarcinoma, PPX and concurrent radiation (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/m^2 and daily TMZ 75 mg/m^2 for 6 weeks with concomitant RT (200 cGy, 5 d/wk for a total dose of 60 Gy). Adjuvant chemotherapy with TMZ (200 mg/m^2/d × 5 d), 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, 15 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 myelosuppresion: 3/14 (21.4%) patients had an asymptomatic grade IV thrombocytopenia. The Data Safety Monitoring Group decreased the PPX dose to 40 mg/m^2/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 (5/24, 20.8%): 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 BLOOD OF GLIOMA PATIENTS TREATED WITH TEMOZOLOMIDE

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BACKGROUND: Glioblastoma patients are currently treated by surgery, radiotherapy, and concomitant and adjuvant temozolomide (TMZ). TMZ is converted to monomethyl triazeno imidazole carboxamide (MTIC) at physiological pH, which is responsible for the methylation of the DNA guanine adducts. We have completed a Phase II trial assessing the influence of neoadjuvant presurgical treatment of glioma patients with the administration of a daily dose of 75 mg/m^2 of TMZ for 14 days prior to surgery. METHODS: Blood was drawn from patients at days 1 (control), 7, 14, 21, and 42. Surgery was performed on day 14 and TMZ was orally administered immediately before surgery. On the day of surgery, blood was drawn at 2, 4, 6, 8, 10, and 12 hours after TMZ administration (n = 7). Tumor and normal-tissue samples were collected from patients enrolled in the trial. We have evaluated plasma and tissue TMZ and MTIC levels in these samples. RESULTS: Plasma TMZ and MTIC levels peaked 2 hours after TMZ administration. Variable levels of TMZ and MTIC were observed in plasma samples, especially 2 hours after TMZ administration. A rapid decay of TMZ and MTIC levels was observed in all patients with no measurable detection 24 hours post-TMZ administration. We were unable to detect TMZ or MTIC in brain tumor (n = 28) and normal brain tissues (n = 5) resected 4 hours after TMZ administration. CONCLUSIONS: TMZ and MTIC plasma levels peaked 2 hours after TMZ administration and maximum variability in these levels was also observed at this time point. We were unable to detect TMZ and MTIC in brain tumor or normal brain tissues 4 hours after TMZ administration. These results suggest it may be more appropriate to assess TMZ-induced guanine N7 and O6 methylation as downstream targets of TMZ efficacy rather than tissue levels of TMZ and MTIC.

OT-22. PHASE III SAPPHIRE STUDY IN HIGH-GRADE GLIOMAS: TARGETED THERAPY WITH TGF-BETA2 INHIBITOR TRABEDERSEN BASED ON RESULTS OF A RANDOMIZED PHASE IIB STUDY

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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 anaplastic astrocytoma (AA, WHO grade III) or glioblastoma multiforme (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 80 μM) or to 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 80-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 SAPPHIRE 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

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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. METHOD: The group consists of 32 neurosurgical 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 chemoradiotherapy was compared in the first clinical trial for astrocytoma grades 3/4 (JCOG 0305). ACNU-based chemoradiotherapy 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 started this April. The patients are enrolled in either postoperative temozolomide or temozolomide plus Interferon-beta arms and the overall survival is evaluated (JCOG 0911). A clinical trial for metastatic brain tumor is ongoing that compares the results of postoperative overall survival by whole brain radiotherapy with that of stereotactic radiotherapy (JCOG 0504). One more trial for primary CNS lymphoma (PCNSL) will be started. CONCLUSION: These results are expected to establish the standard therapy for malignant gliomas and the other malignant brain tumors, such as brain metastasis and PCNSL.

OT-24. HIGH SV2A EXPRESSION IN TUMOR AND PERITUMORAL TISSUE IN GLIOMA PATIENTS WITH EPILEPSY IS ASSOCIATED WITH HIGH EFFICACY OF LEVETIRACETAM

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OBJECTIVES: Epilepsy is a common symptom in patients with glioma. Many antiepileptic drugs are known to interact with anti-neoplastic drugs and corticosteroids. Levetiracetam 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 regarding 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 peritumoral tissue (if available) of the patients. RESULTS: Three 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

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BACKGROUND: Glioblastoma is the most common type, and highest grade, of brain tumor. Glioblastoma is also a highly vascular tumor, with angiogenesis driven by the expression or upregulation of vascular endothelial growth factor (VEGF) and its receptors in both endothelial and glioma cells. Therefore, targeting angiogenic signaling is a rational approach in treating glioblastoma. Cediranib is a highly potent oral VEGF-signaling inhibitor with activity against all three VEGF receptors. REGAL (NCT00777153) is a randomized, parallel-group, multicenter Phase III study comparing cediranib (as monotherapy and in combination with lomustine) with lomustine alone in patients with recurrent glioblastoma. METHODS: Eligible patients had to have had histologic or cytologic confirmation of recurrent glioblastoma, to have received one prior treatment with a temozolomide-containing regimen, and to have not received another VEGF-signaling inhibitor. Patients were randomized (2:2:1 ratio) to receive cediranib monotherapy (30 mg/day orally), cediranib (20 mg/day orally) + lomustine (110 mg/m^2 orally, once every 6 weeks), or lomustine (110 mg/m^2 orally, once every 6 weeks) + cediranib-matched placebo (20 mg/day orally). The primary endpoint was to determine the relative efficacy of cediranib (either as monotherapy or in combination with lomustine) compared with lomustine alone by independent central radiographic assessment of progression-free survival (PFS). Secondary endpoints included overall survival (OS), response rate, the proportion of patients alive and progression free at 6 months, assessment of the steroid-sparing effects of each treatment, time to deterioration of neurological status, change from baseline of disease-related neurological symptoms, and safety and tolerability. PFS and OS will be analyzed after approximately 230 progression events have occurred. A final analysis of OS will take place when 270 deaths have occurred. 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.

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)

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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) examines the effects of intensifying cilengitide in patients with an unmethylated O^6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter, which is associated with unresponsiveness to chemoradiotherapy (Hegi *et al.* NEJM 2005). 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 cilengitide intensification over 3 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 cilengitide 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 (SU011248) FOR RECURRENT MENINGIOMA

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BACKGROUND: Medical therapies for radiotherapy-refractory meningiomas are limited. Sunitinib malate (SU011248) is a small-molecule

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 hemangiopericytoma/hemangioblastoma (n = 10). Sunitinib 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 (PFS) rate, with secondary endpoints of radiographic response rate, safety, and progression-free and overall survival (OS). Exploratory objectives include analysis of tumoral 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 with malignant/atypical meningioma, 2 with benign meningioma, 4 with hemangiopericytoma, 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/vomiting (5), GI perforation (1), hypertension (3), prolonged QTc (2), dehydration (2), elevated ALT/AST/amylase/lipase (1 each), confusion (1), and gait difficulty (1). MR-perfusion imaging has demonstrated decreased perfusion after treatment in most patients. CONCLUSIONS: Sunitinib may be active in recurrent atypical/malignant meningioma patients who are not eligible for further surgery or radiotherapy. The toxicity of sunitinib in this population is concerning and needs further evaluation.

OT-28. A PHASE II TRIAL OF TEMOZOLOMIDE IN ELDERLY PATIENTS WITH GLIOBLASTOMA AND POOR PERFORMANCE STATUS (KPS < 70): PRELIMINARY RESULTS OF THE ANOCEF "TAG" TRIAL

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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/m^2/5 days every 4 weeks) for a maximum of 12 cycles or until progression. Radiotherapy was not administered. 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 objective 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

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BACKGROUND: Tuberous sclerosis (TS) is a potentially devastating disorder caused by mutations in *TSC1* or *TSC2* that result in constitutive mTOR activation. TS is characterized by hamartoma formation in multiple organs and disabling neurologic disorders, including epilepsy. Neuronal lesions include cerebral cortex abnormalities, called tubers, which are associated with seizures and subependymal nodules (SENs) that protrude into the ventricles. SENs can give rise to subependymal giant-cell astrocytomas (SEGAs), which develop in 5%–15% of patients with TS and represent a significant risk, including acute hydrocephalus. Neurosurgical resection is the current standard treatment for SEGAs. METHODS: This prospective Phase II study recruited 28 patients with SEGAs with evidence of serial growth (NCT00411619) between January 2007 and December 2008 and evaluated the effect of everolimus on SEGAs, SENs, and ventricular and tuber volume, in addition to changes in seizure frequency. Everolimus (3 mg/m^2/d orally) was titrated subject to tolerability to achieve target trough concentrations of 5–15 ng/mL. RESULTS: Median duration of treatment was 21.5 months (range, 4.7–34.4). Twenty-one patients (75.0%) experienced reductions in SEGA volume of ≥30% during the first 6 months. Mean reduction in left and right ventricular volume was 3.22 cm^3 and 3.15 cm^3, respectively, at month 6. No patient developed a new lesion and none required surgical resection or other therapy for SEGA. Mean reduction in tuber volume was 3.39 cm^3 from baseline to month 6. No change was evident in SEN volume. Among the 16 patients for whom 24-hour vEEG was available at baseline and at month 6, 9 showed reductions, 6 showed no change, and 1 had an increase. Percentage of patients experiencing seizures on a daily basis improved from 27% at baseline to 8% at month 6, based on caregiver observation. CONCLUSIONS: Everolimus offers patients with TS-associated SEGA a viable alternative to surgical resection.

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-Basanta , Robert A. Lustig , and Jay F. Dorsey ; University of Pennsylvania

BACKGROUND: HIV protease inhibitors (HPI) sensitize glioblastoma cells to radiation *in vitro* and *in vivo* via a proposed mechanism of Akt inhibition. We initiated a Phase I trial to determine the maximum tolerated dose (MTD) and the dose-limiting toxicities (DLT) of the HPI 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 temozolomide (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 nelfinavir 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 experienced a grade IV serious adverse event not related to the study. The recommended dose of nelfinavir mesylate in combination with radiation and temozolomide is 1250 mg orally twice daily. This regimen 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 GLIOBLASTOMA (GBM)

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BACKGROUND: EGFRvIII is a constitutively activated mutation of epidermal growth factor receptor (EGFR) expressed in ~25% of glioblastomas (GBMs) but absent in normal tissues. PF-04948568 is a vaccine containing a 13 amino acid sequence unique to EGFRvIII. The ACT III study was designed as a multicenter, randomized, open-label Phase IIb/III study in

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 ≤53% of patients will be progression-free at 5.5 months (Ho: 5.5PFR ≤ 53%) from first vaccination. METHODS: Eligible pts had gross total resection of newly diagnosed EGFRvIII+ GBM and successful completion of standard radiotherapy with concurrent TMZ. Vaccine was administered once a week ×3 before starting maintenance TMZ and monthly thereafter on day 21 of each TMZ cycle until disease progression. One interim analysis for futility was planned on the first 40 pts treated with PF-04948568. RESULTS: The study passed the interim analysis with 28 of 40 pts alive and progression free at 5.5 months (PFR [95% CI] = 70% [54%, 83%]) (ASCO 2010 abstract #2014.) The study was expanded to 65 pts. The study rejected the null hypothesis. Final results of the primary endpoint, as well as overall survival and overall progression-free survival (PFS) will be presented. The most common treatment-related adverse events (AEs) reported were local injection-site reactions that occurred in most pts. Reversible hypersensitivity reactions (all grades) occurred in 5% of pts, with 2 reactions being reported as serious, requiring discontinuation of PF-04948568. DISCUSSION: Vaccination with PF-04948568 was well tolerated in combination with maintenance TMZ in pts with newly-diagnosed fully resected GBM. The PFR at 5.5 months in this successful multicenter study is similar to that reported from the previous Duke/The University of Texas MD Anderson Cancer Center trial. Further study of 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)

Mariam 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 play a part in this carcinogenesis. 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. CONCLUSION: 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 ULTRAFRACTIONATED RADIATION THERAPY AND TEMOZOLOMIDE FOR NEWLY INOPERABLE GLIOBLASTOMA

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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. Three doses of 0.75 Gy spaced by at least 4 hours are delivered daily, 5 days a week for 6 consecutive weeks for a total of 67.5 Gy, and concomitant chemotherapy consisting of temozolomide is given at a dose of 75 mg/m^2, 7 days per week during the ultrafractionated radiotherapy. After a 4-week break, chemotherapy is resumed, with up to 6 cycles of adjuvant temozolomide every 28 days, according to the standard 5-day regimen. Tolerance and toxicity are the primary endpoints; survival and progression-free survival (PFS) are secondary endpoints. RESULTS: To date, 31 patients have been enrolled in this study; 21 men and 10 women, with a median age of 62, and a median Karnofsky Performance Status (KPS) of 80. The concomitant ultrafractionated radiotherapy–temozolomide has been well tolerated; no acute grade 3 and/or 4 central nervous system (CNS) toxicity has been observed. Stabilization responses at the end of irradiation were seen in 8 patients. The median survival from initial diagnosis was 9.5 months and 2 patients remain alive. The median PFS was 5.1 months. The overall survival (OS) rates at 18 and 24 months were 19% and 15%, respectively. CONCLUSIONS: Ultrafractionated radiation is safe and may prolong the survival of patients with glioblastoma. Further investigation is warranted and a trial associating ultrafractionation and temozolomide is ongoing.

OT-34. SURVIVAL AND TOXICITY UPDATE OF THE PHASE 2 TRIAL OF BEVACIZUMAB (BV) IN COMBINATION WITH TEMOZOLOMIDE (TMZ) AND RADIATION THERAPY (RT) 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, II, John P. Kirkpatrick, Henry S. Friedman, and James J. Vredenburgh; 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 6.9 and 15.9 months, respectively. Bevacizumab (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/m^2/day, with BV at 10 mg/kg every 14 days beginning 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/m^2 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/m^2 for patients not on an enzyme-inducing antiepileptic drug (EIAED) and at a dose of 340 mg/m^2 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 and the median OS is 21.2 months. One-year and 2-year OS are 79% and 45%, respectively. PFS rates at 1 and 2 years are 63% and 14%, respectively. For recursive partitioning analysis (RPA) class 3, 1-year OS was 100% and 2-year OS was 68%. For RPA class 4, OS dropped from 92% at 1 year to 39% at 2 years. Toxicities for all 125 enrolled patients included 1 CNS hemorrhage, 9 venous thromboembolisms, 2 wound dehiscences, 1 bowel perforation, 17 grade 4 hematologic toxicities, 1 secondary malignancy (AML), and 2 pneumonias of Pneumocystis jiroveci. 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 ASTROCYTOMA (AA)

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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 with centrally reviewed 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/m^2), and then 6 adjuvant 28-day cycles of either dose-dense (150 mg/m^2, days 1–7 and 15–21) or metronomic (50 mg/m^2, days 1–28) TMZ. Following completion of adjuvant TMZ, maintenance c-RA

(100 mg/m^2, days 1–21/28) was administered until disease progression. MGMT promoter methylation was assessed when possible. RESULTS: There were 30 patients enrolled from 8/2005–12/2009, 21 of whom were men, with a median age of 48.5 (range, 20 to 74 years). Median KPS was 90 (60–100). Eleven patients underwent gross total resection, 7 underwent subtotal resection, and 12 underwent biopsy. Twenty-seven had AA and 3 had AOA. MGMT was methylated in 6, unmethylated in 12, and unknown in 12. Thirteen were randomized to dose-dense and 17 to metronomic TMZ. Median time to progression was 25.2 months, with 16 patients censored. Median overall survival (OS) was 40.9 months, with a median follow-up duration of 29.3 months on 20 surviving patients. Early analysis demonstrated no significant difference in time to progression or OS between treatment arms. CONCLUSION: Median survival following chemoradiotherapy for anaplastic gliomas (AA or AOA) was 40.9 months. 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, Mikdat Kaya, and Can H. Yıldırım; 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 midline between the L2 and T11 levels. The patient's neurological exam was normal. Magnetic resonance imaging of the thoracic spine showed a posteriorly located lesion between the L2 and T11 levels that invaded both pedicles and the laminae and spinous processes of those vertebrae. The patient underwent surgery, and gross total tumor resection was accomplished. His postoperative period was uneventful. The histopathological diagnosis 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

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Cytomegalovirus (CMV) is a latent herpesvirus infecting approximately half of the world's population. Recent series 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 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 and pp65 nuclear staining, the 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 NEUROPIL AND TRUE ROSETTES: OLDEST REPORTED CHILD WITH A RARE CENTRAL NERVOUS SYSTEM TUMOR

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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 afflict very young children, has a female predominance, occurs primarily in the cerebral cortex, and carries a dismal prognosis. METHODS: A 5-year, 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 seemingly 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 connote 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 and more cases are reported. Our patient is receiving aggressive therapy including craniospinal 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

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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 50-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 cytopathology 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, cytopathology, 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

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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 biological markers, preoperative imaging,