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NEURO-ONCOLOGY

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NEURO/MEDICAL ONCOLOGY

NO-001. LATE RELAPSES IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA TREATED WITH HHGH DOSE METHOTREXATE

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BACKGROUND: The treatment of patients with primary CNS lymphomas (PCNSL) has dramatically changed since the 1970's when whole brain radiation generated median survivals of about 12 months, significant neurotoxcity, and few long term survivors. High dose methotrexate (HD-MTX) monotherapy without radiation provides excellent response rates and 30% long term survivors without neurotoxicity. In general, relapses occur in the first two to four years after diagnosis and reports of very late relapses are rare. METHODS: Charts of all patients treated with HD-MTX monotherapy for newly diagnosed PCNSL between 1995 and 2012 at The Johns Hopkins Hospital were reviewed retrospectively. Patients with less than 5 years of follow-up data were excluded. First relapses over 10 years from diagnosis were identified and reviewed. RESULTS: Long-term follow-up data was available for 37 patients treated with HD-MTX monotherapy during this period. Four of 37 (11%) survived disease free for >10 years from initial diagnosis and maintain their excellent clinical status. All received methotrexate (8 gm/m^2) every two weeks until complete response and then monthly to complete one year of therapy. Two of these long survivors (50%) presented with new seizures 10.8 and 11.2 years after initial diagnosis. Imaging revealed recurrent intraparenchymal disease, re-biopsy confirmed PCNSL in one, and both responded very well to retreatment with high dose methotrexate and Rituximab. The other two patients remain relapse free 12 and 13.7 years after initial diagnosis. CONCLUSION: Very late relapses have occurred in 2 of 4 long term survivors. These observations suggest that PCNSL patients treated with HD-MTX who were considered "cured" may be at substantial risk for late recurrences. A concerted effort to follow patients with this rare disease is needed to determine the frequency of late recurrences. More information is needed to determine if the addition of rituximab or other therapies reduce late recurrence rates.

NO-002. CLINICAL AND DEMOGRAPHIC FEATURES OF ADULT PATIENTS WITH GLIOBLASTOMA (GB) PARTICIPATING ON CLINICAL TRIAL PROTOCOLS AT THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER (MDACC)

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BACKGROUND: GB is the most common primary brain tumor in adults and is associated with a universally poor prognosis. However, only 5-10% of patients are treated on clinical trials. METHODS: In this IRB-approved retrospective study, our neuro-oncology longitudinal database was screened for GB patients participating on a clinical protocol from 2007-2012. 618 adult patients (age > 18) were identified. RESULTS: 510 patients had primary GB. Median age was 54 years (18–83). 333 patients with a primary GB were consented for a newly diagnosed protocol (NDP). Median overall survival (OS) for these patients was 22.2 months and median progression free survival (PFS) was 11.6 months. Median OS for patients on a recurrent GB protocol (RP) was 21.7 months from time of diagnosis. 34% (114/333) of patients on a NDP enrolled in a RP. Fewer patients on a NDP receiving dose dense temozolomide therapy enrolled on a RP than those receiving standard dose temozolomide (56/124, 45% versus 47/75, 62%). 51% (147/288) of patients enrolled on a RP were previously enrolled on a protocol. Factors were significantly associated with OS were age (HR 1.02; $p = 0.002$), KPS at presentation (HR 0.98; $p = 0.028$), extent of resection (HR 1.2; $p < 0.001$), active tobacco use (HR 1.6; $p = 0.043$), and location of radiation therapy (MDACC versus outside facility; HR 1.4; $p = 0.003$). Location of surgery was not associated with a difference in OS. CONCLUSIONS: While GB patients have a poor prognosis, patients who enroll in clinical trials at MDACC have an overall better prognosis than historical controls, which is consistent with other studies. Caution should be taken when interpreting efficacy from single institution single arm clinical trials. Location of radiation therapy may represent an important variable associated with survival and requires additional investigation. Comparisons with patients who were protocol eligible but not enrolled in a protocol may provide additional insights.

NO-003. A MULTICENTER PHASE I/II STUDY OF THE BCNU IMPLANT (GLIADEL® WAFER) FOR JAPANESE PATIENTS WITH MALIGNANT GLIOMAS?LONG-TERM FOLLOW UP (NPC-08 STUDY GROUP)

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Carmustine (BCNU) implants (Gliadel® wafer) for the treatment of malignant gliomas were shown to enhance overall survival in comparison to placebo in controlled clinical trials in the United States and Europe. A prospective, multicenter phase I/II study involving Japanese patients with malignant gliomas was performed to evaluate the efficacy, safety, and pharmacokinetics of BCNU implants. The study enrolled 16 patients with newly diagnosed malignant gliomas and 8 patients with recurrent malignant gliomas. After the insertion of BCNU implants (8 sheets maximum, 61.6 mg BCNU) into the removal cavity, various chemotherapies (including temozolomide) and radiotherapies were applied. After placement, the overall survival rates (OS) was evaluated the subsequent period until 36 months. In patients with newly diagnosed malignant gliomas, the OS at 36 months were 62.5%. In the GBM subgroup ($n = 9$), the OS at 36 months were 44.4% and the median overall survival were 20.2 months (605 days). In the non-GBM subgroup ($n = 7$), the OS at 36 months was 85.7%. In patients with recurrent malignant gliomas, the median overall survival was 12.0 months (361 days), and the progression-free survival rate at 6 months was 37.5%. There were no grade 4 or higher adverse events noted due to BCNU implants, and grade 3 events were observed in 5 of 24 patients (20.8%). Whole blood BCNU levels reached a peak of 19.4 ng/mL approximately 3 hours after insertion, which was lower than 1/600 of the peak BCNU level recorded after intravenous injections. These levels decreased to less than the detection limit (2.00 ng/mL) after 24 hours. The results of this study involving Japanese patients are comparable to those of previous studies in the United States and Europe.

NO-004. PREOPERATIVE FACTORS IN PREDICTING ATYPICAL MENINGOMAS

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INTRODUCTION: Atypical meningiomas represent an ever-increasing proportion of all meningiomas. Prognostic factors and therapeutic strategy remain controversial due to little evidence from large case series. The aim of our study was to identify preoperatively any characteristics that can safely predict a more aggressive nature of these tumours. MATERIAL AND METHOD: This retrospective study includes all patients with atypical intracranial meningiomas who were operated at our Department between 2007 and 2011. Inclusion criteria included - age over 18 years, Grade 2 and 3 meningiomas including haemangiopericytomas. Patients were then followed up clinically and radiologically. Data collected: 1. clinical, (presenting symptoms and duration, exposure to radiotherapy) 2. preoperative radiological features (size, location, presence of necrosis or haemorrhage, oedema, bone invasion, cystic content and brain/tumour interface) 3. intraoperative findings and 4. histological characteristics (subtype, brain invasion). RESULTS: A total of 106 patients (with Grade 2 and Grade 3 meningiomas) undergoing 114 operations were analysed from a total of 544 patients with all types of meningiomas. The age ranged from 18-84 years (mean 56). Of these, there were 39 male

and 67 female. Headache was presenting feature in 16 patients (15.1%) whilst 20 (18.9%) were picked up on surveillance scanning. There were 32 recurrences (28.1%) and half (50%) were Grade 1 at original surgery. 17 cases had had previous radiotherapy (14.9%) and of these 14 (82.4%) had it as part of treatment of initial meningiomata. CONCLUSIONS: We failed to identify that any of the above features analysed were strongly predictive of a higher grade of meningioma. Parasaggital location and increased vascularity may be associated with atypical tumours, although larger studies are required to confirm above findings.

NO-005. IMPLICATIONS OF MGMT METHYLATION STATUS IN PITUITARY ADENOMA AND CORRELATION WITH MGMT PROTEIN EXPRESSION

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INTRODUCTION: It is well established that MGMT promoter methylation status predicts therapeutic response to Temozolomide (TMZ) in glioblastoma. However there are very limited studies describing the frequency of MGMT methylation status in pituitary adenoma. Knowledge of this would help stratify patients who could benefit from TMZ therapy in pituitary adenoma. AIM: To assess the frequency of MGMT methylation in pituitary adenoma and MGMT protein expression and correlate with clinical and pathological parameters including markers such as MIB-1 and p53. MATERIAL AND METHODS: Tumor tissues from 30 patients operated for pituitary adenoma were evaluated for MGMT promoter methylation status by methylation specific PCR method. MGMT protein expression was also analysed by immunohistochemistry. All tumors were also immunostained with MIB-1 and p53 antibodies. The results were correlated with clinical parameters. RESULTS: MGMT methylation status was noted in 40% of cases. Of these, MGMT methylation was found in 7 of 20 non functioning adenomas and 5 of 10 functioning adenomas. The MGMT methylation status correlated inversely with protein expression. Even though there was no correlation between patient age and MGMT methylation status ($p = 0.823$), it was noted that the frequency of methylation in younger patients between 10-29 yrs was found to be 12.5% and that in the older patients between 60-69 was 20%. Middle age patients with age between 30-59 showed a higher degree of MGMT methylation (64.7%). There was no correlation between MGMT methylation status and MIB-1 labeling ($P = 0.391$) or p53 expression($P = 0.709$). CONCLUSION: This is the first study from India showing MGMT promoter methylation status and protein expression in pituitary adenoma. Our study indicates that stratifying patients into different age groups may be taken into consideration for TMZ chemotherapy.

NO-006. RADIOGRAPHIC RESPONSE OF AN INCIDENTAL MENINGIOMA IN A PATIENT WITH GLIOBLASTOMA ON NovoTTF THERAPY

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NovoTTF therapy produces alternating electrical fields that disrupt tumor cell division. We report a patient who started NovoTTF therapy in a clinical trial for newly diagnosed glioblastoma and who also had an incidental meningioma distant from the glioblastoma site. After starting NovoTTF therapy, the patient presented significant and persistent radiographic response of the meningioma. Patient is a 44 year old woman who presented with an olfactory aura followed by a generalized seizure and a brain MRI showed a right anterior temporal intra-axial enhancing tumor and also a distant high-convexity right parietal extra-axial enhancing tumor with dural tail compatible with a meningioma. She underwent a gross total resection of the right temporal tumor which confirmed a glioblastoma. She then received standard 60 Gy of IMRT with temozolomide. Her right parietal meningioma remained stable in size (142 mm^2 on the largest perpendicular diameters) from the initial diagnosis to 3 months later, when she underwent her first post radiation/ temozolomide brain MRI scan. She then started NovoTTF therapy continuously and adjuvant temozolomide on a 5-day-on/23-day-off schedule. Her next brain MRI, 8 weeks after starting NovoTTF showed a reduction in the size of the right parietal meningioma to 82 mm^2 on the largest perpendicular diameters (42% reduction in size). Subsequent brain MRI scans done 16 weeks and 20 weeks after starting NovoTTF therapy showed further reduction of the incidental meningioma size to 60 mm^2 (58% reduction) and 56 mm^2 (60% reduction). Her glioblastoma has remained stable and she continues to be on both NovoTTF therapyand temozolomide. There are no FDA approved treatments for meningiomas and temozolomide is clearly not effective for meningiomas. Also, her meningioma is very far from the glioblastoma site and did not receive therapeutic levels of radiation. Finally, this degree of radiographic response is rarely seen in meningiomas and NovoTTF therapy warrants further study in meningiomas.

NO-007. IMPACT OF TREATMENT ON OUTCOME IN PATIENTS WITH GRADE II AND III GLIOMAS

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BACKGROUND: Molecular markers associated with both overall survival (OS) and progression free survival (PFS) in pts with Grade II/III gliomas have been identified, including 1P19Q codeletion (codel), IDHI mutation (MUT) vs wild type (WT), and PHH3 (mitosis) status. These molecular markers may help identify optimal treatment for pt subgroups. METHODS: Retrospective data was collected ($n = 440$), including age, gender, tumor grade, extent of resection, and initial treatment (observation (O), radiation (RT), radiation + chemotherapy (RTC), or chemotherapy alone(C)), and molecular markers. OS/PFS were estimated using the Kaplan-Meier method and compared using log-rank test. Cox proportional hazard models were applied to assess the effect on OS/PFS. RESULTS: Median OS is 11.4 years (95% CI 10.3, 13.1; 214 deaths). Predictors include gender, extent of resection, treatment, CODEL, MUT and MI. The median PFS was 5.3 years (95% CI 4.7, 6.4). Predictors of PFS include gender, extent of resection, treatment, CODEL, MUT and MI. In those treated with C or RTC, PCV was used in 53% and temozolomide in 38%. RTC is superior to RT for CODEL, MUT, low MI (PFS HR .330, $p = .0048$); for MUT, non-codel low MI (PFS HR .42, $p = .0048$, OS HR = .524 $p = .018$) and for WT (low MI) tumors (PFS HR = .312, $p = .03$; OS HR = .293, $p = .01$). Observation after surgery pts with non-codel, MUT, high MI tumors had a worse PFS outcome (HR 1.94, $p = .03$), but not OS. CONCLUSIONS: RTC as initial treatment provided improved outcome for pts with tumors with codel, or IDH mut with low MI, or IDH wt with low MI compared with RT alone. Pts with tumors with high MI despite MUT had early progression with observation, but had similar OS regardless of initial treatment, suggesting effective salvage treatments.

NO-008. ERIBULIN INDUCED NEUROPATHY IN A PATIENT WITH PREVIOUSLY UNDIAGNOSED CHARCOT-MARIE-TOOTH (CMT) DISEASE

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BACKGROUND: Neuropathy can be a dose-limiting toxicity with numerous chemotherapeutics, and may be particularly disabling in the setting of pre-existing inherited neuropathic disorders. Deleterious effects on inherited neuropathies have been well-documented with vincristine, platinum drugs and taxanes. The effects of other chemotherapeutic agents on these patients are more uncertain. METHODS: We report a case of a 69-year-old woman with follicular lymphoma, metastatic breast cancer (ER/PR + , HER2/neu-) and CMT who developed a disabling neuropathy after treatment with eribulin, a microtubule dynamics inhibitor. RESULTS: The patient was concurrently diagnosed with metastatic lobular breast cancer and follicular lymphoma. She was initially treated with rituximab, cyclophosphamide, vincristine and prednisolone for her lymphoma. Vincristine was discontinued after the first dose resulted in bilateral foot drop, which only partly recovered. Subsequently, she was treated for breast cancer with various single agents (e.g., letrozole, tamoxifen, exemestane, liposomal doxorubicin, capecitabine and paclitaxel) without substantial change in her neurologic status. Soon after initiation of eribulin for disease progression, she developed numbness in her hands and feet, followed by weakness of fingers extensors and dorsal extensors of the foot. The weakness progressed proximally to involve deltoids and hip flexors. She also developed hoarseness of voice, dysphagia and shortness of breath. Neurologic examination additionally revealed absent deep tendon reflexes and high arched feet. Neurophysiologic studies provided evidence for an inherited demyelinating neuropathy. Genetic testing revealed peripheral myelin protein 22 (PMP22) gene duplication confirming the diagnosis of CMT1A. The patient's symptoms slowly improved after discontinuation of eribulin.

CONCLUSION: As far as we know, this is the first reported case describing the adverse effects of eribulin on neuropathy in a patient with CMT. The case also highlights how pre-existing hereditary neuropathies can first surface in response to neurotoxic agents such as eribulin.

NO-009. SURVIVAL OUTCOMES WITH LOW-DOSE BEVACIZUMAB COMPARED TO STANDARD DOSE REGIMENS IN RECURRENT GLIOBLASTOMA

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BACKGROUND: Glioblastoma (GB), the most common and aggressive primary malignancy of brain, portends a dismal prognosis marked by rapidly progressive clinical deterioration. Bevacizumab (BV; Avastin), a US FDA approved humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has demonstrated significant efficacy in patients with recurrent GB at 10 mg/kg every 14 days either as a single agent or in combination with carboplatin or irinotecan. OBJECTIVE: This review compares the efficacy of low-dose BV (5mg/kg) administered as a single agent or in combination/tandem with other chemotherapies against survival expectations of standard dose/schedule. DESIGN: Retrospective cohort study. METHODS: A single institution retrospective review was conducted on all patients with recurrent GB treated from January 2009–May 2013. A subset of 48 patients with radiographically recurrent GB were placed on bevacizumab 5 mg/kg therapy every 2 weeks as a practice parameter. All patients had diagnostic surgery and temozolomide-based chemoradiation. The primary endpoint was median/mean overall survival (OS). RESULTS: Single-agent BV at 10 mg/kg or greater in patients with recurrent GB (control database): median OS 8.63 months (95%CI, 8.54–8.72 months). Review cohort: median OS 14 months (95%CI, 10-16 months); mean OS 19.2 months. Patients' first BV injection at >6 months from time of glioblastoma diagnosis was associated with a death hazard ratio of 2.27 ($p = 0.041$) using a multivariate Cox proportional hazards model. CONCLUSION: Our results suggest that administration of BV administered for treatment of rec/prog GB at 5 mg/kg every two weeks or less (in dose / frequency) is not inferior to standard dosing. There may be a survival advantage of low-dose (5 mg/kg) BV when compared against BV at 10 mg/kg every two weeks.

NO-010. RETROSPECTIVE STUDY OF TOXICITY PROFILE AND SURVIVAL BENEFITS OF INTRA-ARTERIAL CARBOPLATIN THERAPY IN RECURRENT HIGH GRADE GLIOMAS

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INTRODUCTION: Data from preclinical and clinical studies published over past decades have demonstrated activity of intra-arterial (IA) chemotherapy in high grade glial tumors. However, there are irrefutable potentials for significant hematologic and neurologic toxicities. In this retrospective review, we describe our experience in local disease control, survival benefit, and toxicity profile of IA carboplatin-based treatment of recurrent high-grade gliomas in combination with intravenous (IV) chemotherapy or bevacizumab. METHODS: A retrospective chart review was performed of patients ≥18 years-of-age treated with IA carboplatin for a recurrent glioblastoma at ANW's Neuro-Oncology program between Nov 2005 and May 2010. All patients received either of the two following regimens: (a) 400 mg/m^2 IA carboplatin every 4 weeks with 10 mg/kg bevacizumab every 2 weeks; (b) 400 mg/m^2 IA carboplatin with 660 mg/m^2 cytoxan cyclophosphamide and 400 mg/m^2 etoposide every 4 weeks. RESULTS: The study cohort comprised of 44 patients treated with IA carboplatin with 26 patients additionally receiving IV bevacizumab and 18 patients receiving cytoxan + etoposide. Median progression-free survival was 6.9 months and overall survival was 20.4 months with 4 surviving patients at 37.8 months or longer. Local complications included groin hematoma (n = 9), bleeding at the catheter insertion site (n = 4), and distant complications included transient visual blurring (n = 2). Most prevalent neurological complications noted were headaches (n = 26); focal seizures, generalized seizures, and transient confusion (n = 11). Two patients had strokes, both of which were deemed related to the chemotherapy procedure. Most of the patients (n = 36) reported nausea and/or emesis. One patient developed a perforated duodenal ulcer, requiring surgical intervention. CONCLUSION: IA chemotherapy with carboplatin is a relatively safe and well tolerated treatment in recurrent GBM patients demonstrating encouraging outcomes in terms of overall survival. Our data indicate that long-term survival may be achieved with this treatment regimen in a select group of patients.

NO-011. ISCHEMIC STROKE AS A POTENTIAL LATE TOXICITY OF CARMUSTINE WAFERS (GLIADEL®) COMBINED WITH RADIO-CHEMOTHERAPY: REPORT OF TWO CASES

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BACKGROUND: The use of Carmustine wafers (Gliadel®) as a first line treatment for malignant gliomas is associated with an increased risk of local complications such as cerebral edema, intracranial infections, cerebrospinal fluid leaks, hydrocephalus, cyst formation and seizures. These complications are well known and occur early on after Gliadel® implantation. OBSERVATION: We report 2 patients with as yet undescribed potential late onset vascular complications of Gliadel® implantation. The first patient, a 43-year old man, had a left temporal glioblastoma, treated with surgery and Gliadel® implantation followed by radio-chemotherapy according to the Stupp-protocol. One year after initial surgery, he presented with a severe ischemic stroke in the left middle cerebral artery territory. The second patient, a 47-year old woman, had a left frontal anaplastic oligodendroglioma treated with surgery, Gliadel® implantation and radio-chemotherapy. Five years and 5 months after initial surgery, she developed a left internal capsular ischemic stroke. DISCUSSION: Both strokes were unusual, occurring in relatively young patients with no known cardiovascular risk factors, in the same territory where the Gliadel® wafers had been implanted, suggesting a possible vascular toxicity of the combination of Gliadel® and radio-chemotherapy. Moreover, a vascular toxicity of Carmustine has already been described after intra-arterial administration. CONCLUSION: The purpose of this brief report is to warn clinicians about an additional potential late toxicity of the combination of Gliadel® implantation with radio-chemotherapy: ischemic stroke.

NO-012. BRAINSTEM VENOUS CONGESTION DUE TO DURAL ARTERIO-VENOUS FISTULA MIMICKING BRAINSTEM TUMORS

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Dural brainstem arterio-venous fistulas (dAVF) are exceedingly rare and not readily apparent with routine MRI studies. We present three cases of patients who were initially thought to have brainstem tumors and ultimately diagnosed with brainstem arterio-venous fistulas. Case 1 is a 54 year-old man who presented with headache and vertigo. Brain MRI revealed a FLAIR hyperintense in the medulla and pons involving the bilateral cerebellar peduncles with mass effect suggesting a brainstem glioma. MR Spectroscopy was inconclusive and PET scan was not FGD avid. On close review of his prior MRIs, there was vessel prominence around the fourth ventricle and an unusual amount of hemosiderin deposition in the bed of the lesion. Subsequent angiography revealed a dAVF. With this, it became clear that the FLAIR hyperintensity was due to venous congestion. The fistula was resected and the patient clinically and radiographically improved. Case 2 is a 67 yo man who presented with subacute diplopia and gait instability. MRI brain showed heterogenously enhancing expansile midbrain lesion extending to the thalamus with significant FLAIR hyperintensity and hemosiderin deposition in the midbrain lesions. Brain PET was not FGD avid. An angiogram was performed to investigate the possibility of hepatitis C associated vasculitis and revealed a dAVF. The fistula was resected and the patient improved. Case 3 is a 53 year-old man who presented with 4 months of gait difficulty. MRI brain demonstrated an expansile lesion within the medulla (R > L) hyperintense on T2/FLAIR with patchy enhancement. Given our recent experience with dAVFs, we pursued a MRA neck with/without contrast which revealed a prominent anterior spinal artery. Digital subtraction angiography confirmed the presence of a dAVF at the cervical medullary junction.These cases illustrate the importance of considering brainstem dural arterio-venous fistulas in the differential for brainstem expansile lesions. This is special important because brainstem tumors are often empirically treated without tumor tissue diagnosis.

NO-013. BEVACIZUMAB IN CHILDREN AND ADULTS WITH NEUROFIBROMATOSIS TYPE 2 AND SYMPTOMATIC VESTIBULAR SCHWANNOMAS

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Neurofibromatosis type 2 (NF2) is characterized by progressive bilateral vestibular schwannomas (VS) that commonly result in deafness. Compassionate use of bevacizumab (BEV) has been shown to improve hearing in some NF2 patients. We prospectively investigated the effect of BEV in patients with progressive hearing loss due to NF2-associated VS. Patients with NF2, aged >12 years, VS >1.5cm, and confirmed VS-associated hearing loss were enrolled at JHU, MGH and the NCI Pediatric Oncology Branch. Patients were given BEV 7.5mg/kg IV every 3wks for 1 year. Two evaluations were performed off drug to assess durability of response. The primary endpoint was hearing response defined as statistically significant increase in word recognition score (WRS) compared with baseline. 14 patients yielded >90% power to detect a response rate of 50%. Hearing was assessed at baseline, 13, 25, 49, 60 and 72 weeks. Adverse events (AE) were assessed every 3 weeks. 3D brain MRI for volumetric (>20% reduction defined as radiographic response) and functional assessment, whole body MRI, quality of life assessments and plasma biomarkers were collected. Fourteen patients, 10 female, median age 30 (range 14-79 yrs) were enrolled. All patients were evaluable; 16/18 completed all planned treatment. The target ear median baseline WRS was 53% (range 13-82%). 5/14 (36%; 95% CI13-65%) patients had a hearing response maintained for >3 continuous months with an average WRS of 57% at baseline and 85% at 6 months. Improvement in WRS was maintained at 3 and 6 months off BEV. No patients had hearing loss while on BEV. Radiographic response was seen in 6/14 patients (43%); 2 without hearing response. There were 86 AEs attributed as > possibly related to drug. Two were grade 3 (hypertension and ITP), but reversable. BEV was well tolerated and resulted in durable hearing response in 36% of patients with progressive hearing loss related to NF2.

NO-014. RANDOMIZED, PHASE IIIB TRIAL EVALUATING STANDARD-OF-CARE (SOC) THERAPY WITH/WITHOUT BEVACIZUMAB CONTINUATION BEYOND DISEASE PROGRESSION (PD) IN PATIENTS WITH GLIOBLASTOMA AFTER FIRST-LINE RADIOTHERAPY, TEMOZOLOMIDE AND BEVACIZUMAB (RT/T + BEV): TRIAL RATIONALE AND DESIGN

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Glioblastoma is associated with poor prognosis, severe neurological symptoms, cognitive deficits and impaired health-related quality of life (HRQoL). While the introduction of combined modality therapy (SOC) achieved extended survival, further advances are needed. Bevacizumab, an anti-vascular endothelial growth factor (VEGF) agent, is effective in newly diagnosed and recurrent glioblastoma, and is associated with stable/improved HRQoL and reduced corticosteroid requirements. Based on its mode of action, continuing bevacizumab through multiple lines of therapy may provide additional benefits, versus stopping bevacizumab at PD. A phase III study in colorectal cancer validated this approach, reporting longer progression-free (PFS) and overall survival (OS) when bevacizumab plus chemotherapy was continued beyond first PD, versus chemotherapy alone.[1] This strategy has not been previously investigated for glioblastoma. MO28347 is a randomized, double-blind, placebo-controlled, phase IIIb trial to evaluate continuous bevacizumab plus SOC beyond first PD after first-line RT/T + BEV. Eligible patients (newly diagnosed/histologically confirmed glioblastoma; target enrollment n = 510) will receive: first-line RT/T + BEV; T + BEV maintenance (x6); and single-agent bevacizumab until first PD (AVAglio regimen[2]). At PD, 300 eligible patients will be randomised to continue bevacizumab, or receive placebo, plus investigator's choice of second-line SOC (irinotecan/lomustine/carboplatin/fotemustine/temozolomide/best supportive care), with stratification based on: planned second-line SOC; performance status; time to PD during first-line treatment. At second PD, patients continue double-blind treatment and the investigator chooses third-line SOC. The primary endpoint is superiority in OS, from randomization to continuous bevacizumab plus SOC versus placebo plus SOC beyond first PD. Secondary endpoints include: PFS, 6-, 12- and 18-month OS, HRQoL, neurocognitive function and safety. Response will be assessed by modified Response Assessment in Neuro-Oncology Working Group criteria to minimize the impact of pseudoprogression. The wide SOC choice reflects clinical practice. Bevacizumab continued beyond PD has potential to improve survival in glioblastoma and provide a new treatment option.

1 Bennouna. Lancet Oncology;14:29-37,2013
2 Chinot. Neuro-Oncology:14;vi101-vi105(OT-03),2012

NO-015. PHASE I DOSE ESCALATING STUDY OF 2B3-101, GLUTATHIONE PEGYLATED LIPOSOMAL DOXORUBICIN, IN PATIENTS WITH SOLID TUMORS AND BRAIN METASTASES OR RECURRENT MALIGNANT GLIOMA

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BACKGROUND: Without active delivery across the blood-brain barrier (BBB) the efficacy of doxorubicin in brain tumors is limited. 2B3-101, glutathione PEGylated liposomal doxorubicin, has been developed as brain-targeted chemotherapy. In preclinical studies, 2B3-101 showed 5-fold enhanced doxorubicin brain-delivery versus pegylated liposomal doxorubicin (Doxil®). METHODS: Patients with either solid tumor brain metastases or recurrent malignant gliomas were treated with 2B3-101 by 90 min IV infusion q21d to assess (1) safety, tolerability and MTD (2) PK and (3) preliminary antitumor activity of 2B3-101, determined by brain MRIs and body CTs, according to RANO or RECIST criteria. Doses were escalated in cohorts of 3-6 patients. Three breast cancer patients received continued, parallel trastuzumab treatment. RESULTS: 28 patients received 2B3-101 at doses of 5-60 mg/m^2, without DLTs. 18 patients had brain metastases from solid tumors, and 10 patients had recurrent malignant gliomas WHO grade III (3) or IV (7). Twenty-seven patients received ≥ 3 prior therapies before 2B3-101. No cardiac or CNS toxicity was observed. At doses of ≥40 mg/m^2, adverse events ≥ grade II (CTCAE v.4.0) were: neutropenia (38%), thrombocytopenia (6%), mucositis (6%), and PPE (38%). Grade I-II infusion reactions were observed in 6/28 patients, being transient and manageable with standard treatments. Pharmacokinetic data showed non-linear exposure of 2B3-101 without signs of accumulation with repeat dosing. Due to one case of thrombocytopenia grade IV at 60 mg/m^2, this cohort was expanded to 6 patients. At doses of ≥40 mg/m^2, 9 of 16 patients demonstrated stable disease and 2 partial response after two cycles (brain metastases (n = 5), glioblastoma (n = 3) and grade III glioma (n = 3)). 2B3-101 also showed responses in extracranial disease. CONCLUSIONS: 2B3-101 is safe and well tolerated up to 60 mg/m^2 q21d in both brain metastases from solid tumors and recurrent malignant gliomas and demonstrates preliminary antitumor activity in the brain.

NO-016. DUAL PHASE I/II STUDY OF TH-302 AND BEVACIZUMAB IN RECURRENT GLIOBLASTOMA FOLLOWING BEVACIZUMAB FAILURE

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INTRODUCTION: Median progression free survival of glioblastoma patients who progress on bevacizumab and subsequently start a bevacizumab-containing regimen is 1.6 months. Preclinical studies have shown that

antiangiogenic treatment leads to increased hypoxia and invasiveness. TH-302 is a hypoxia-activated prodrug that once activated releases the DNA cross-linking agent Br-IPM. This study investigated TH-302 in combination with bevacizumab in patients with recurrent glioblastoma following bevacizumab failure. METHODS: Single center, dose-escalation, prospective study with single dose TH-302 (575 mg/m^2) or placebo administered pre-operatively, followed by postoperative combination therapy of bevacizumab at 10 mg/kg every 2 weeks and TH-302 dose escalated 240–480 mg/m^2 every 2 weeks (4 week cycle) until disease progression. Resected tumor tissue was evaluated for hypoxia induced pimonidazole adducts, endogenous CA-IX staining, gH2AX and TUNEL DNA damage biomarkers, and by metabolomic profiling. RESULTS: Nine patients underwent craniotomy and initiated TH-302 at doses of 240 to 480 mg/m^2 plus bevacizumab. No dose limiting toxicity (defined as occurring during Cycle 1) was reported. There were no grade 3 or 4 adverse events (AEs) observed at 240 mg/m^2, one grade 3 (skin ulceration) at 340 mg/m^2, and no grade 3 or 4 AEs observed thus far at 480 mg/m^2 in the third cohort. Of the initial nine patients treated, two patients achieved a partial response (PR) and five patients stable disease (SD) as best response by RANO criteria. One patient continues to have a response through his 19th cycle. The median progression-free survival is 3.1 months. Histological assessment of resected tumors demonstrated extensive areas of hypoxia. Partial least square discriminant analysis from MR-spectra showed significant differences in metabolites before treatment and at progression. CONCLUSIONS: No dose limiting toxicity has been observed at TH-302 doses of up to 480 mg/m^2 when combined with bevacizumab. Dose escalation is ongoing, with planned expansion at the MTD.

NO-017. CHARACTERISTICS OF LONG-TERM SURVIVORS IN GLIOBLASTOMA

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INTRODUCTION: Glioblastoma multiforme (GBM) remains a devastating disease with a dismal prognosis. Only 2–5% of patients are alive 3 or more years following diagnosis. Although improved overall survival (OS) has been associated with younger age, higher initial Karnofsky Performance Status (KPS), complete surgical resection, MGMT promoter methylation and IDH positivity, relatively little work has focused on unique signatures of long-term survivors (LTS). METHODS: In an effort to better understand underlying characteristics that may contribute to LTS, we examined 31 primary GBM patients with OS $\geq$ 3 years and compared them to a control cohort (OS $<$ 500 days (N = 162)). We evaluated tumor location, tumor size on MRI, the presence or absence of a cystic component at diagnosis (as distinct from central necrosis), extent of resection, KPS and patient age. RESULTS: No significant differences were observed with respect to tumor location, or tumor size at diagnosis between all cohorts. LTS displayed significantly higher initial KPS ($p = 0.0127$) and were more likely to be younger at diagnosis (mean age = 62.04 vs 53.10, $p = 0.00401$). A larger proportion of LTS received gross total resections (56.7% vs 24.8% control patients, $p = 0.0005$, Pearson Chi Square). As compared to a control cohort, LTS (N = 31) had a higher percentage of cystic tumors (45% and 24% respectively, $p = 0.0047$). In our entire cohort of patients (n = 267), including those with survival between 500 and 1095 days, those with imageable cysts also had statistically significant greater OS (log rank test, $p= 0.022$). CONCLUSION: To our knowledge, this analysis is the largest study to date of imaging characteristics and clinical features in long-term survivors of GBM. Our findings recapitulate previously identified attributes of LTS and demonstrate that cystic changes on pre-treatment MRI may also portend for long term survival. Further analysis of this population to elucidate if underlying phenotypic characteristics influence LTS is warranted.

NO-018. CSF RITUXIMAB CONCENTRATION AND EFFECT AFTER INTRATHECAL ADMINISTRATION OF RITUXIMAB IN CNS RELAPSE OF SYSTEMIC LYMPHOMA - RESULTS FROM THE PROSPECTIVE PHASE II HOVON 80 STUDY

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Rituximab is a monoclonal anti-CD20 antibody and does not cross the intact blood-brain barrier; CSF concentration after intravenous administration is 0.1-2% of the 400-500 ug/ml reported as serum concentration. In the prospective phase II HOVON 80 study, patients with CNS relapse of aggressive NHL were treated with intra-CSF rituximab combined with systemic R-DHAP and high-dose methotrexate followed by autologous stem cell transplantation (ASCT). CSF from these patients was investigated for rituximab concentration. METHODS: Intra-CSF rituximab was initially administered twice weekly and subsequently tapered. The first dose was 10 mg, subsequent doses 25 mg if no side-effects occurred. When possible CSF was collected before and one hour after the first two administrations; samples were examined for rituximab concentration, cell count and evidence of lymphoma. Patients in complete response were treated with ASCT after Busulfan/Cyclophosphamide conditioning. RESULTS: 33 patients were included and received intra-CSF rituximab, 18 had positive CSF. Three of the first 13 patients developed a transient, severely painful radiculopathy after the first 25 mg dose. Subsequently only 10 mg was given. For 17 patients 1-hour post-dose rituximab concentration was available. Median CSF rituximab concentration after 10 mg was 120 ug/ml,(range 35.5 - 539; n = 14); after 25 mg 272 ug/ml (range 47.8-1500; n = 3). Eight patients failed to clear the CSF from lymphoma after 4 weeks and were switched to MTX/ara-C/dexamethasone resulting in lymphoma clearance in 6. Five of 7 patients with elevated pre-dose cell count showed a cellular reduction of 36-63% within one hour of intra-CSF rituximab administration. PFS at one year was 19% (95%CI: 9-34%); OS 25% (95%CI: 12-40%). CONCLUSION: 20% of patients were still free from progression at one year. The MTD for intrathecal (lumbar) rituximab administration is 10 mg. Even at this dose higher CSF concentrations were found than after systemic administration and some, though limited, effect seemed present.

NO-019. A REGIONAL MULTI-CENTER RETROSPECTIVE STUDY OF TREATMENT PATTERNS AND CLINICAL OUTCOMES FROM 2000-2012 OF PATIENTS WITH PRIMARY CNS LYMPHOMA (PCNSL)

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INTRODUCTION: PCNSL is a rare tumor without a well-defined standard of care. Treatment with radiotherapy (RT) results in median overall survivals (OS) of 12-18 mos. The addition of methotrexate based chemotherapy (MBC) regimens to RT improved OS to 30-40 mos. but resulted in unacceptable neurotoxicity. Single arm studies in the 1990s of MBC without RT appeared to offer an alternative without compromising survival. Communities without a National Cancer Institute designated cancer center may have disparities in treatment when considering NCI recommended practices. This study was done to determine treatment patterns and outcomes for PCNSL in the Louisville, KY metro area from 2000–2012. METHODS: Data was collected by retrospective chart review on patients identified by ICD code from 3 major oncology practices in the metro Louisville area from 2000–2012. Exclusion criteria: age $<$ 18y, HIV positive, histology other than B-cell lymphoma, systemic lymphoma. RESULTS: Twenty-one patients were identified. Median age was 65y (range 30-90) all were Caucasian and median KPS was 80 (range 50-100). Male to female ratio was 1:1.3. Median OS for all patients was 19 mos. (range 1-155). Of 21 patients, 10/21 (47%) were offered treatment with MBC. Median age was 64y (range 43–71) and median OS was 22 mos. (range 1–155) Eleven of twenty-one patients (47%) were offered other therapies including RT or non-MTX based chemotherapies. Median age was 68 yrs. (range 30–90) and median OS was 5 mos. (range 2-150). Median OS for patients that received at least 4 cycles of MTX was 40 mos. (range 4–155).

CONCLUSION: MTX based therapies were offered to patients consistent with NCI standards. Patients able to receive this therapy had an improved survival. However a number of patients were treated with therapies considered less effective for PCNSL. Factors besides therapy choice may explain the survival disparity and warrant further investigation.

NO-020. A PHASE II STUDY OF ANTINEOPLASTONS A10 AND AS2-1 IN ADULT PATIENTS WITH RECURRENT GLIOBLASTOMA MULTIFORME BASED ON PROTOCOL BT-21

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Treatment of recurrent glioblastoma multiforme (GBM) creates one of the most difficult challanges in neuro-oncology. The aim of this presentation is to evaluate the responses and survival of 24 recurrent GBM patients and toxicity in all 33 eligible patients. The study accrued patients who developed disease progression during standard treatment within eight weeks from completion of radiation therapy (RT) and six weeks from chemotherapy. Forty candidates were registered but only 33 patients were eligible. The seven non-eligible patients received less than 28 days of treatment with Antineoplastons A10 and AS2-1. Among the eligible patients there were 24 cases of recurrent GBM that progressed during prior treatment, four patients with anaplastic astrocytoma and five persistent GBM. Previous treatment included surgery in all patients (18 had tumor resection, and 6 underwent biopsy only), chemotherapy in 75% of patients and radiation therapy in 88% of patients. Antineoplastons were administered intravenously every four hours (median dose of A10 10.7 g/kg/d and AS2-1 0.43 g/kg/d) until objective response was documented or until progression. The median duration of ANP treatment was 13.2 weeks ranging (4.6 - 80.3). Responses were assessed by MRI repeated every eight weeks, and or PET scan. Objective responses were determined in 16.7% of cases (complete response, and partial response in 8.3% each). Progression-free survival at six months was 25%. Overall survival is 39.3% at one year, 4.4% at two years, five and ten years. The treatment was well tolerated with reversible grades 3 and 4 toxicity including four cases of hypernatremia, two of fatigue, two of hypokalemia, and a single case of somnolence. There were no chronic toxicities. In conclusion, ANP is well tolerated and compares favorably to the current treatment for recurrent GBM.

NO-021. A PHASE II STUDY OF ANTINEOPLASTONS A10 AND AS2-1 IN PEDIATRIC RECURRENT DIFFUSE INTRINSIC PONTINE GLIOMA

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Brainstem gliomas (BSG) are rare tumors of which diffuse intrinsic pontine gliomas (DIPG) comprise a distinct group. Numerous trials have been conducted in DIPG without a proven pharmacological treatment benefit. Prior interim report on this phase II study of antineoplastons (ANP) A10 and AS2-1 provided data on 40 patients diagnosed with BSG. This report is focused on final results of 17 out of 40 patients diagnosed with recurrent pediatric DIPG (RPDIPG). The median age in this group was 8.8 years (range 4.5-18.5), with 9 females and 8 males. Previous treatment included radiation therapy (RT) in 15 patients, chemotherapy in 11 patients and surgery in 2 patients. At least eight weeks elapsed from initiation of ANP and previous RT and six weeks from chemotherapy with nitrosoureas. ANP was administered daily through a subclavian venous catheter via infusion pump. The median duration of treatment was 5.6 months. The median of average dosages of A10 was 8.8 g/kg/d and 0.40 g/kg/d of AS2-1. Responses were assessed by MRI repeated every eight weeks. In the RPDIPG group, a complete response (CR) was 6%, partial response (PR) 23.5%, and stable disease (SD) 23.5%. 6 month progression-free survival (PFS) was 35.3%. 1 year overall survival (OS) was 29.4%, 2 years 11.8%, and 5, 10 and 14 years 5.9%. One patient has OS and PFS of 14 years from the treatment start. Grade 4 toxicities including hypernatremia, hypokalemia and fatigue occurred in less than 18% of patients. Grade 3 fatigue, somnolence, skin allergy and urinary incontinence occurred in 6-12 %. There were no chronic adverse events. Responding patients experienced improved quality of life. The results suggest that ANP shows efficacy and an acceptable tolerability in patients with RPDIPG.

NO-022. GNAQ GENE MUTATION IN AN INTERMEDIATE-GRADE MELANOCYTIC TUMOR OF THE THORACIC SPINAL CORD

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Primary melanocytic tumors of the CNS are rare tumors arising from the melanocytes in the leptomeninges. These tumors range from focal, histologically benign tumors- melanocytomas, to malignant potentially disseminating melanomas. Between these 2 extremes lie tumors that show some histologic features suggestive of aggressive behavior but lack the overt cytologic atypia of melanomas and are therefore classified as intermediate-grade melanocytic tumors. We present a case of a 64-year-old gentleman who presented with a 1-year history of progressively worsening numbness in both lower extremities (LEs) ascending to the abdomen. This was associated with right LE weakness and foot drop. Examination revealed a sensory level at around T10 on the right. MRI of the thoracic-cord showed an enhancing lesion at T10-11 expanding the cord considerably with extensive syrinx formation extending up to the cervical-spine. A subtotal resection of the lesion followed by focal radiotherapy was performed with pathology consistent with an intermediate-grade melanocytic tumor due to the presence of brain invasion but with mitotic index of $<1/10$ hpf and Ki-67 of 1%. PET and a thorough dermatological examination excluded this to be a metastatic lesion. Molecular sequencing of the tumor demonstrated a mutation in exon 5 of the GNAQ gene resulting in the substitution of glutamine for leucine at codon 209 (nucleotide c.626A- $>$ T). No mutations were detected in exon 4 or 5 of the GNA11 gene. The BRAF V600E mutation was absent. GNAQ gene encodes a heterotrimeric G-protein α-subunit that leads to constitutive activation of the MAP kinase pathway. Recent literature has suggested that this mutation occurs frequently in primary melanocytic tumors of the CNS indicating it might be a future therapeutic target. Awareness of clinicopathological features and genetic alterations discussed may help in therapeutic decisions for these rare tumors since currently no consensus exists on the management of these tumors.

NO-023. ANTIEPILEPTIC DRUG EFFICACY IN GLIOBASTOMA PATIENTS (RedLANO 2013)

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INTRODUCTION: Epilepsy is a common symptom in patients with glial and neuro-glial tumors. METHODS: The study included data regarding 213 patients from the RedLANO follow-up registry. We recorded demographics, date of first seizure, anti-epileptic drugs (AED), initial dose of AED, time to next seizure, total seizures, dose adjustment for seizures, dose adjustments unrelated to seizure control, and main side effects. The relationship between epilepsy treatment and overall survival (OS) was evaluated. RESULTS: The patients' mean age was 53 years old and 56.8% were male. Eighty-seven (40.8%) were treated with levetiracetam (LEV), 23.6% were given other AED and 31% never use AEDs or such information was unknown. AED was used following partial/total resection in 75 cases and a biopsy was carried out in 33 cases; the difference between these groups was not statistically significant ($p = 0.19$). The requirement for using LEV and/or other AEDs was not greater in those aged over 60-yo ($p = 0.13$) amongst those having worse functional state ($p = 0.24$) or according to the localisation of the primary tumour ($p = 0.34$). Epileptic crises and the need for some type of medicament for controlling them were greater in those having primary GBs ($p = 0.004$). Mean time for the following crisis to be presented after AED had been begun was 9.9 days (SD + /- 6.3), being less for those receiving LEV ($p = 0.03$); mean crisis during the first 3 and 6 months was 2.9 and 4, respectively. Most patients treated with LEV ($N = 46$) required less than two adjustments compared to those treated with other AEDs ($p = 0.02$). Likewise, a smaller proportion of patients exposed to LEV required the use of some coadjuvant drug ($p = 0.04$). OS was significantly higher in the group treated with LEV compared to other AEDs (25.5 vs. 17.9-mo; $p = 0.047$). CONCLUSION: In our study patients treated with LEV had better control of epileptic crises and longer OS.

NO-024. GB-RedLANO REGISTRY 2013

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INTRODUCTION: The standard treatment for Glioblastoma (GB) achieved a 14.6-mo overall survival (OS) and a 26% survival at 2 years; advances in GB care resulted in a larger proportion of patients (pts) treated with bevacizumab after disease progression. METHODS: A bidirectional registry was designed to recorded a large series of GB pts (n = 213) treated in various institutions from Colombia throughout the last 5 years. We included the analysis of clinical characteristics and several outcomes as the response rate, progression free survival (PFS) and OS. RESULTS: The mean age was 53-yo (SD ± 14.4), 56.8% (n = 121) were male and 68/175 (32%) were placed in RTOG RPA V-VI classes. Most pts had primary GBs (n = 144), 21% had multicentric lesions and infiltration of the corpus callosum was documented in 16.4%. Biopsy, partial and complete resection were performed on 21%, 42% and 12% of patients, respectively; in the remaining 25% we could not establish the extent of the surgery. 80.3% of the pts received the Stupp platform, 8.5% the AVAglio schema, 9.9% palliative therapy and 1.4% were treated with other interventions. Response to first line therapy could be established in 191 pts (CR 13.4%; PR 36.1%; SD 13.6%; PD 29.8%). First line PFS was 6.1-mo (95%CI 3.9-12.3) and OS was 19.5-mo (95%CI 12.5-29.0). OS were greater for those suffering from secondary GBs ($p = 0.02$), for the group that had a lower RPA ($p = 0.022$), those <60-yo ($p = 0.04$) and those having MGMT+ ($p = 0.03$). In the same way, OS was significantly higher in pts treated with bevacizumab (2nd line and later; $p = 0.043$) and in those who achieved a partial or complete response after second and third line ($p = 0.002$ and $p = 0.009$, respectively). CONCLUSIONS: This study represented a comprehensive analysis of GB pts treated in Latin-America. The median PFS and OS obtained from this study are comparable to previous reports.

NO-025. USING PYRIMETHAMINE FOR REVERTING HIGH-GRADE GLIOMA PATIENTS' RESISTANCE TO BEVACIZUMAB

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INTRODUCTION: Cooper et al., noted that non-mesenchymal type glioblastomas (GB) become transcriptionally similar to the most aggressive neoplasias when necrosis levels increase, this being a notable manifestation following progression to bevacizumab. Such alterations are usually associated with high C/EVP-b and C/EVP-g expression in hypoxic cells from the perinecrotic niche. These two factors are strongly associated with STAT-3 expression. Takakura et al., found that pyrimethamine modulates STAT-dependent signalling routes, thereby reducing resistance to temozolamide (TMZ) via MGMT expression, the same as after bevacizumab has been used. MATERIALS AND METHODS: Data from RedLANO follow-up registry which included 213 patients was used for estimating the pyrimethamine efficacy as coadjuvant for bevacizumab after administering second and third line in Glioblastoma. Clinical characteristics, response rate, time to progression (TTP) and overall survival (OS) rate were compared between exposed and non exposed patients. RESULTS: Average age was 53 years-old and 56.8% of the subjects were male. Fifteen patients (7%) were given pyrimethamine (75 mg/day with folate support) after receiving bevacizumab. Pyrimethamine did not modify second or third line treatment response rate ($p = 0.36$ and $p = 0.33$, respectively) or TTP after bevacizumab began to be used ($p = 0.42$). However (and in spite of limited simple size), using pyrimethamine had a significant impact on OS following second line treatment (34 months pyrimethamine use versus 17.2 months non-use; $p = 0.01$). CONCLUSIONS: Using pyrimethamine on high-grade glioma patients following progression to bevacizumab seemed to modify OS, such finding supporting its prospective evaluation in clinical trials.

NO-026. SYSTEMIC BEVACIZUMAB (BEV) FOR LEPTOMENINGEAL DISEASE (LMD) FROM NON-SMALL CELL LUNG CANCER

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BACKGROUND: Bev is a monoclonal antibody against the vascular endothelial growth factor receptor that has activity in brain tumors. Previous studies show that bevacizumab may be safe and effective in brain metastases from non-small cell lung cancer (NSCLC), but there are little data in LMD. METHODS: We retrospectively reviewed patients with NSCLC treated with bev and selected patients treated with bev after the diagnosis of LMD and assessed their CNS response and survival outcome. RESULTS: Thirteen patients were identified (7 males; ages 46-69). Six patients received bevacizumab at initial diagnosis of LMD; 5 patients after initial treatment with WBRT; 2 patients were continued on bev that had already been initiated. Eleven patients had previously or concurrently identified brain metastases. Five had received WBRT prior to the diagnosis of LMD; 7 received WBRT after the diagnosis of LMD; 1 patient had only spine disease. All 13 patients received chemotherapy while on bevacizumab (paclitaxel, pemetrexed, gemcitabine, vinorelbine, erlotinib, cisplatin, carboplatin, afatinib, and cetuximab; one patient each was treated with temozolomide, intrathecal cytarabine, and pulsed erlotinib). Eleven patients had an MRI at least 1 month after initiation of bev; 2 patients died within 35 days of treatment. Best CNS radiographic response by RECIST criteria of "non-target lesions" was CR in 18% (2/11), improved in 45% (5/11), and SD in 36% (4/11). Median overall survival (OS) after initiation of bev was 6.1 months (range 6 days to 35 months.) Treatment was well tolerated; grade I intracranial hemorrhage developed in 2 patients. CONCLUSIONS: This retrospective study, although limited, suggests bev may have activity in patients with NSCLC and LMD. The effect of the concurrent therapy as well as pseudoresponse seen with bev in GBM need consideration also. Future studies are warranted.

NO-027. ARE MENINGIOMAS AT HIGHER RISK OF THROMBOEMBOLISM THAN GLIOMAS? EARLY RESULT OF A PROSPECTIVE STUDY

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INTRODUCTION: Neurosurgical patients operated for meningiomas or gliomas carry a relatively high risk of thromboembolic phenomena (TEP). The exact incidence of TEP in this population of patients is not known and the data available in the literature are highly variable and uncertain. Pulmonary perfusion scintigram is a cost-effective method to diagnose pulmonary embolism (PE). Aim of this study was to prospectively assess the exact incidence of PE in patients operated for meningioma and glioma, performing pre- and post-operative pulmonary perfusion scintigrams (PPS). Secondary aim was the investigation of risk factors associated with TEP occurrence. PATIENTS AND METHODS: 42 patients were included in the study. 24 had histologically confirmed meningiomas, and 18 gliomas. All patients signed the informed consent for participating to the study; all of them underwent a pre-operative and a post-operative PPS in order to assess the occurrence of PE. Whenever PPS was doubtful of positive, then a CTangio scan of the lungs was performed. RESULTS: Meningioma and glioma patients had a median age of 65 (range 41-83) and 62 (range 35-73), respectively. Pre-operative PPS resulted as follows: negative in 41 patients, positive in one patient affected by glioma (bed ridden for neurological status). Post-operative PPS were positive in 4 patients operated for meningioma (16.7%), and in 4 operated for glioma (22.3%). No statistical difference

could be noted in PE occurrence between meningioma and gliomas ($p = 0.47$). CONCLUSIONS: This study confirms that neurosurgical patients operated for glioma or meningioma carry a high risk of PE. Neurosurgeon should be aware of this complication and favour early detection and preventive measures.

NO-028. SURGERY WITH INTRA-OPERATIVE NEUROPHYSIOLOGICAL MONITORING IN THE MANAGEMENT OF THALAMIC ASTROCYTOMAS

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INTRODUCTION: The thalamus is a deep-seated and crucial structure for the sensory-motor system. It has been longly considered a surgically inaccessible area due to the morbidity associated with surgical resections. In fact, astrocytomas of the thalamus usually undergo bioptic procedures followed by adjuvant treatments (if indicated). Intra-operative neurophysiological monitoring (IONM) allows safe and satisfactory resections of lobar gliomas. Considering the need of reliable specimens for the pathological diagnosis and that the extent of resection is positively associated with overall survival, aim of this study was to review the feasibility and outcome of a small series of patients with thalamic astrocytomas operated with the aid of IONM. PATIENTS AND METHODS: Five patients with thalamic astrocytomas (1 grade I, 3 grade III, 1 grade IV) underwent surgical resection with IONM. Two astrocytomas were in the dominant hemisphere. All patients performed pre-operative and post-operative neuropsychological assessment. IONM consisted in transcranial MEP monitoring (4 patients), cortical MEP monitoring (2 patients), direct electrical stimulation (5 patients), EEG (5 patients) and ECoG monitoring (2 patients). Anesthesia was totally intra-venous (propofol + remifentanyl) for all patients; 1 patients was operated following an asleep-awake protocol, 4 following an asleep-asleep protocol. RESULTS: None of patients suffered from permanent motor deficits; 2 patients had a transient hemiparesis requiring rehabilitation; 1 patients suffered a transient aphasia, and 1 patient had permanent aphasia. None of the patients had intra- or post-operative seizures. Resection was total in 1 case (grade I astrocytoma), subtotal in 1 case (grade IV astrocytoma) and partial in the other 3 cases with resection beyween 50 and 80% of the tumor volume. CONCLUSIONS: Surgical resection of thalamic astrocytomas appears meaningful and relatively safe when guided by IONM. Larger series of patients are required to confirm this preliminary data.

NO-029. LEPTOMENINGEAL ASSESSMENT IN NEURO-ONCOLOGY (LANO): A RANO PROPOSED MODEL OF EVALUATION IN LEPTOMENINGEAL METASTASIS

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BACKGROUND: Leptomeningeal metastasis (LM) currently lacks standardization with respect to response assessment. METHODS: A group of investigators with expertise in LM developed a proposal for evaluating patients treated with LM. RESULTS: The group proposes three basic elements in assessing response in LM; a standardized neurological examination, CSF cytology or flow cytometry and radiographic evaluation. The group recommends that all patients enrolling in clinical trials undergo CSF analysis (cytology in all cancers; flow cytometry in hematologic cancers), complete contrast-enhanced neuraxis MRI and radioisotope CSF flow studies (in patients treated with intra-CSF therapy only). In conjunction with the RANO neurological assessment working group, a standardized instrument was created for assessing the neurological exam in patients with LM. Response based on CSF cytology is considered when CSF converts from positive to negative and with a second confirmatory determination. CSF flow cytometry is a quantitative analysis that also utilizes a binary outcome, i.e. positive or negative. CSF cytology is not to be considered in isolation in evaluation of response of patients with solid tumors as patients with persistence of positive cytology may continue on treatment if clinically and radiographically stable or improved. In contrast, CSF flow cytometry (assessed in patients with hematologic cancers), if unresponsive, constitutes progressive (refractory) disease irrespective of neurological or radiological determination. The committee currently is unable to determine a method to quantify MRI abnormalities commonly associated with LM as the majority of lesions are non-measurable. Consequently radiographic assessment of LM is subjective, qualitative and graded as stable, progressive or improved. Similar to CSF cytology, radiographic disease progression in isolation i.e. stable CSF cytology and neurological assessment would not be defined as LM disease progression. CONCLUSIONS: RANO LM has proposed a method of response evaluation for patients with LM that will require further testing, validation and likely refinement with use.

NO-030. SALVAGE THERAPY WITH BRAF INHIBITORS FOR RECURRENT PLEOMORPHIC XANTHOASTROCYTOMA: A RETROSPECTIVE CASE SERIES

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BACKGROUND: Pleomorphic xanthoastrocytoma (PXA) is a World Health Organization (WHO) Grade 2 glioma that is uncommon (<1% all adult gliomas) and seen primarily in children and young adults. PXA has been demonstrated to manifest the V600E BRAF mutation in nearly 70% of all tumors, a mutation that constitutively activates the BRAF/MEK signaling pathway. OBJECTIVE: Assess response and toxicity of a BRAF inhibitor, vemurafenib, in recurrent PXA manifesting the V600E mutation. RESULTS: Four adults (2 males; 2 female: median age 45 years {range 34-53}) with surgery, radiation and alkylator refractory recurrent PXA demonstrating the BRAF mutation (V600E) were treated with vemurafenib (960 mg orally twice per day). A cycle of vemurafenib was defined as 4 weeks of continuous therapy. All patients had previous treatment with surgery (once in 1 patient; twice in 3 patients), radiotherapy (median dose 54 Gy) and alkylator-based chemotherapy (temozolomide in 4 patients; PCV in 1 patient). All toxicities seen were grade 2 and included arthralgia, photosensitivity, fatigue and nausea (1 patient each). The median number of cycles of therapy was 5 (range 2-10). Radiographic response was progressive disease in 1, stable disease in 2 and partial response in 1. Median progression free survival was 5 months (range 2-10 months). Median overall survival was 8 months (range 4-14 months). CONCLUSIONS: In this small series of select patients with recurrent PXA manifesting the BRAF V600E activating mutation, vemurafenib appears to have single agent activity with manageable toxicity. Confirmation in a larger series of similar patients is required.

NO-031. FINAL EFFICACY AND SAFETY RESULTS FROM AVAglio, A PHASE III TRIAL OF BEVACIZUMAB (BEV) PLUS TEMOZOLOMIDE (TMZ) AND RADIOTHERAPY (RT) IN NEWLY DIAGNOSED GLIOBLASTOMA

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INTRODUCTION: In AVAglio, a phase III, placebo-controlled trial in newly diagnosed glioblastoma, BEV significantly prolonged PFS (HR 0.64, 95% CI 0.55–0.74, $p < 0.0001$; median 10.6 vs 6.2 months), with associated clinical benefits: maintained HRQoL, functional independence (KPS ≥ 70), and diminished corticosteroid requirements. We report final overall survival (OS). MATERIALS AND METHODS: Patients ≥ 18 years with histologically

confirmed glioblastoma were randomized to BEV or placebo (10mg/kg, q2w) with TMZ (75mg/m^2/d x6wks) + RT (2Gy, 5d/wk x6wks) followed by 28 treatment-free days, then TMZ (150–200mg/m^2/d, 5d, q4w x6) with placebo or BEV (10mg/kg, q2w), then single-agent placebo or BEV (15mg/kg, q3w) until progression/unacceptable toxicity. Co-primary endpoints were investigator-assessed PFS and OS. Secondary endpoints included 1- and 2-year OS rates, safety, and HRQoL. Exploratory endpoints included corticosteroid use and KPS. RESULTS: Baseline characteristics were balanced between BEV + RT/TMZ (n = 458) and placebo + RT/TMZ (n = 463). Clinical cut-offs were 31-Mar-2012 for PFS and 28-Feb-2013 for OS. The co-primary endpoint, OS, was not met (HR 0.88, 95% CI 0.76–1.02; p = 0.0987), subgroup analyses were consistent. 1-year OS with BEV + TMZ/RT and placebo + TMZ/RT was 72% and 66%, respectively (p = 0.049); 2-year OS was 34% and 30%, respectively (p = 0.235). Subsequent-line therapy was administered in 57% (263/458) and 65% (299/463), and incorporated BEV (any line) in 14% (62/458) and 31% (144/463) of patients in the BEV + RT/TMZ and placebo + RT/TMZ arms, respectively. AEs were reported in 98.5% and 96.0% of patients (serious AEs were reported in: 38.5% vs 25.8%; grade ≥ 3: 66.2% vs 51.8%; grade ≥ 3 AEs of special interest to BEV: 31.6% vs 15.9%) in BEV + RT/TMZ compared with placebo + RT/TMZ. CONCLUSIONS: Addition of BEV to RT/TMZ resulted in a clinically meaningful and statistically significant improvement in PFS in patients with newly diagnosed GBM. OS did not reach statistical significance. Safety was consistent with known BEV side effects.

NO-032. SALVAGE PCV CHEMOTHERAPY FOR RECURRENT PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS: USEFUL IN DEFERRING RADIOTHERAPY

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BACKGROUND: Second-line treatment has not been established and there is no general consensus about the chemotherapy regimen with refractory or relapsed primary central nervous system lymphomas (PCNSLs) after high-dose methotrexate (HD-MTX) based first-line chemotherapy. We evaluated the safety and efficacy of salvage procarbazine, lomustine and vincristine (PCV) chemotherapy, a well-known and traditional regimen that is often used in malignant glioma, for PCNSLs treated in a single institute. MATERIALS AND METHODS: We retrospectively reviewed eight consecutive immunocompetent patients (five males/three females, mean age: 56 years) who received salvage PCV chemotherapy for refractory or relapsed PCNSL and two patients switched to PCV chemotherapy due to severe adverse effects of HD-MTX chemotherapy. Radiologic responses, survival and adverse effects were analyzed. RESULTS: Of the eight refractory or relapsed PCNSLs, three patients (37.5%) displayed radiologic complete response, one (12.5%) had a partial response and four (50%) displayed progressive disease after PCV chemotherapy. Median progression free survival (PFS) from first administration of PCV to relapse or last follow-up was 7 months (range 5-32 months) and median overall survival was 8 months (range 2-41 months). The two patients who were switched to PCV chemotherapy maintained the previous HD-MTX effect and showed PFS of 9 and 5 months from the beginning of PCV to relapse. The common side effects were thrombocytopenia, neutropenia and peripheral neuropathy. PCV chemotherapy was delayed in four patients because of grade III and IV myelosuppression. CONCLUSION: PCV chemotherapy may be an effective salvage regimen for a subset of refractory or relapsed PCNSLs after the HD-MTX based chemotherapy.

NO-033. PHASE 1 TRIAL OF BEVACIZUMAB PLUS TPI 287 IN ADULTS WITH RECURRENT GLIOBLASTOMA (GBM)

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BACKGROUND: With few effective treatment options for recurrent glioblastoma (GBM), TPI 287, a novel, first in class anti-microtubule agent designed to circumvent multidrug resistance (MDR) that also allows penetration across the blood-brain barrier was investigated in combination with bevacizumab in this patient population. The objective was to explore the dose for a Phase 2 adaptive randomization trial. METHODS: Patients with documented GBM at first relapse failing prior standard therapy were eligible for this Phase 1, dose-escalation part of the study of TPI 287 in combination with bevacizumab. TPI 287 was administered as a 1-hour IV infusion every 3 weeks and bevacizumab was administered as an IV infusion once every 2 weeks. As of May, 2013, a total of 6 subjects had been enrolled in the Phase 1 part of the trial. MRI's were obtained at the end of every other cycle; response was assessed using RANO criteria. RESULTS: Of the six enrolled subjects, two were withdrawn from study due to disease progression, and one for wound dehiscence (attributed to bevacizumab). Three remain on study in the 4th (N = 1) or 1st (N = 2) treatment cycle as of May, 2013. A DLT (Grade 4 ANC) occurred at 160 mg/m^2 TPI 287 + 10 mg/kg bevacizumab, and the Phase 2 dose has been determined to be 160 mg/m^2 TPI 287 + 10 mg/kg bevacizumab. In the first three subjects enrolled, there was 1 partial response (maintained through the 4th cycle), and stable disease (2 cycles). All subjects eligible for evaluation for efficacy showed tumor shrinkage by MRI. CONCLUSIONS: The activity of TPI 287 plus bevacizumab in patients with recurrent glioblastoma shows promise in this refractory population. The trial has reached its MTD and will now begin randomization at the Phase 2 dose. Data continues to mature and will be updated at the meeting.

NO-034. OROFACIAL DYSKINESIA: A POSSIBLE PARANEOPLASTIC DISORDER?

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BACKGROUND: Paraneoplasic syndromes are a subset of disorders that can precede or appear concomitantly with a systemic cancer. SCLC (small cell lung cancer) is most commonly associated with paraneoplastic neurologic syndromes. Identification of antibodies associated with these syndromes gives clues to the mechanism of interaction between the cancer and the immune system. CASE DESCRIPTION: We describe a 72 year old male diagnosed with SCLC. He received cisplatinum and etoposide and concomitant radiation therapy to the lung at the time of diagnosis. A few months later, he slowly started involuntary movements. He was not exposed to antipychotics, antiemetics, or antidepressants at any time. Two years after the diagnosis, his examination was notable for repetitive hand rubbing movements, shoulder shrugging, frequent blinking, and prominent tongue protrusion. He received three subsequent courses of cisplatinum and etoposide without any change in the involuntary movements. A recurrent pleural effusion developed, suspicious of recurrent malignancy. RESULTS: Serum and CSF paraneoplasic panels demonstrated a unique, unclassified neuronal antibody detected by immunofluorescence. All other paraneoplastic antibodies in a comprehensive panel were negative. DISCUSSION: Although rare, paraneoplastic neurological syndromes that cause basal ganglia syndromes are known to be associated with antibodies associated with encephalomyelitis, including CRMP/CV2 and others. In our patient these antibodies were negative, but an antibody directed against neuronal tissue was found. Although we cannot exclude effects of delayed cisplatinum toxicity, hyperkinetic movements are not a recognized complication of cisplatinum treatment. CONCLUSION: More research is needed to determine the immunopathogenesis and relationship between these antibodies and central or peripheral nervous system symptomatology. Increased awareness of neurologists and oncologists is warranted in the development of unusual neurological presentations in patients with systemic cancers.

NO-035. HD-METHOTREXATE/LIPOSOMAL CYTARABINE/RITUXIMAB FOR THE TREATMENT OF A PATIENT WITH SECONDARY CNS LYMPHOMA, LYMPHOMATOUS MENINGITIS AND NEUROLYMPHOMATOSIS

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OBJECTIVE: Improve survival in a patient afflicted with refractory systemic lymphoma spreading to brain, lymphomatous meningitis, and neurolymphomatosis. BACKGROUND: We describe a patient afflicted simultaneously with three forms of lymphoma who responded to therapy with high-dose methotrexate, intra-ventricular liposomal cytarabine, and rituximab. METHODS: A 23 year-old male six years after commencement of immunosuppression for living donor renal transplantation developed stage IV EBV(-) diffuse large B-Cell lymphoma. Responsive for twelve months after six cycles of R-CHOP, he presented with CNS progression in the right temporal lobe. After two cycles of intravenous (IV) methotrexate (HD-MTX, 8g/m2/biweekly) he developed bilateral arm weakness and diplopia. Treated empirically with IV solumedrol (1g/day x 3 days) for "inflammatory

neuropathy." MRI revealed C4-C6 dorsal root enhancement. Lumbar puncture(LP) fluid contained lymphoma cells staining for atypical cells. Intra-ventricular liposomal cytarabine (50mg/biweekly) was given along with oral prednisone, and Sirolimus was discontinued. Denervation within the right C5-6 myotomes, including paraspinal muscles was seen on EMG/NCS and PET CT confirmed avidity in the dorsal nerve roots of the C-spine consistent with lymphomatous infiltration. After negative studies for paraneoplastic disease, weekly IV rituxan (375mg/m2) for six weeks was added. RESULTS: The HD-MTX (total 8 cycles) and intra-ventricular liposomal cytarabine (4 doses) resulted in resolution of his MRI parenchymal brain disease and resolution of the CSF cytologic abnormalities. The patient had only transient improvement in strength and vision to IV solumedrol, but after rituximab, diplopia improved quickly and upper extremity weakness resolved as did PET CT avid C-spine dorsal nerve root enhancement. After autologous stem cell transplantation he remains in remission 21 months later with normal neurological exam and normal renal function. CONCLUSION: This is the first report of a patient with post transplant EBV (-) systemic lymphoma involving brain, CSF, and nerve roots treated successfully with methotrexate, intra-ventricular liposomal cytarabine, and rituximab therapy.

NO-036. BEVACIZUMAB SALVAGE THERAPY FOR GLIOBLASTOMA REFRACTORY TO MONOCLONAL ANTIBODIES TARGETING VEGF AND PDGF PATHWAY

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BACKGROUND: Glioblastoma is a highly vascular tumor and inhibition of VEGF signaling is an important therapeutic strategy. We report our experience with bevacizumab, a monoclonal antibody against VEGF ligand, following failure of other antiangiogenic agents. METHODS: We retrospectively identified patients with recurrent GBM refractory to IMC-3G3 or IMC-1121B who were treated with bevacizumab at Cleveland Clinic. IMC-3G3 and IMC-1121B are human monoclonal antibody, antiangiogenic agents which specifically binds to the human PDGF receptor alpha and VEGFR2 respectively. RESULTS: Six patients (four men; median age 55) received bevacizumab immediately after progression on IMC-3G3 or IMC-1121B. Four patients had previously received IMC-3G3 and two received IMC-1121B. Median Karnofsky score at bevacizumab initiation was 65 (range 60-90). Average number of previous therapies used was 3.1. Half of the patients received bevacizumab alone and rest half received bevacizumab in combination with lomustine or carboplatin. One third of patients had progressive disease, one third had stable disease and rest one third had partial response as their best response. Median progression free survival(PFS) and overall survival(OS) from bevacizumab initiation was 18.5 and 46 weeks. PFS at 6 months from bevacizumab initiation was 33%. Median OS from GBM diagnosis 121.8 weeks respectively. Overall bevacizumab therapy was tolerated well, with three grade 2 (DVT) and one grade 1(hypertension) events (CTCAEv3.0). CONCLUSION: Radiographic and survival outcomes with bevacizumab following progression after IMC-3G3 or IMC-1121B are similar to data from studies of bevacizumab as initial salvage therapy in these 6 patients. Prior exposure to other antiangiogenic agents may not preclude response to bevacizumab in selected patients.

NO-037. RISK OF SEIZURES FOLLOWING SURGICAL RESECTION OF NEWLY DIAGNOSED MENINGIOMAS

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BACKGROUND: The risk of seizures in patients with meningiomas is well recognized, but few studies focus on seizure outcomes after surgical resection. Determining which patients benefit from continued anti-epileptic drug (AED) therapy after surgery can be difficult. OBJECTIVE: We sought to identify characteristics predictive of post-operative seizures in newly diagnosed patients who underwent surgical resection of a meningioma. METHODS: Demographic and clinical variables were evaluated retrospectively as predictors of post-operative seizures, defined as occurring more than 14 days after surgery, in 149 patients with newly diagnosed meningiomas treated between 2006 and 2011. RESULTS: Median follow-up was 41 months (2-388). Forty-one (28%) patients experienced a pre-operative seizure and 50 (35%) a post-operative seizure. Of those 50, 28 (56%) were not on AEDs at the time of their seizure. In 29 (58%) patients, seizures occurred in the absence of recurrence. RT was part of the initial treatment in 18 (12%) patients; 5 (28%) developed seizures following RT. Male gender, higher grade (Grade II: hazard ratio [HR] 2.57, 95% confidence interval [CI] 1.44-4.57, $P = 0.001$; Grade III: HR 3.64, CI 1.31-10.12, $P = 0.013$), parietal location (HR 2.62, 95% CI 1.26-5.43, $P = 0.01$), pre-operative seizures (HR 5.41, 95% CI 3.08-9.50, $P < 0.001$), and post-operative RT (HR 6.17, 95% CI 3.33-11.46, $P < 0.001$) were significantly associated with an increased risk of post-operative seizures. Pre-operative seizures (HR 6.96, 95% CI 3.49-12.45, $P < 0.001$) and RT (HR 8.10, 95% CI 4.29-15.31, $P < 0.001$) were identified as independent predictors in a multivariable model, but tumor grade was not ($p < 0.24$). CONCLUSIONS: Pre-operative seizures predict an increased risk of post-operative seizures in patients undergoing surgical resection of meningiomas. These patients are most likely to benefit from continued treatment with anti-epileptic medications post-operatively. However, further investigations are needed to clarify the role of RT.

NO-038. UNCONFIRMED COMPLETE RESPONSE (CRU) IN PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)

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BACKGROUND: Following treatment for PCNSL, many patients display minor residual enhancement on MRI, often characterized as CRu or partial responses. The prognostic meaning of such findings is unknown. METHODS: Retrospective review of PCNSL patients who had residual contrast enhancement (<1cm) between 01/2001-04/2013. RESULTS: We reviewed 231 patients diagnosed with PCNSL of whom 24 (10%) had minor residual enhancement in MRI. 12 were men and median age was 59 (range, 19-72 years). Fourteen patients (58%) were enrolled onto clinical trials. All patients were treated with rituximab, methotrexate, vincristine and procarbazine (R-MVP) as induction regimen. Consolidation regimen was cytarabine in 8 patients, high-dose chemotherapy followed by autologous bone marrow transplant in 8, low-dose WBRT followed by cytarabine in 4, high-dose WBRT in 2; one patient had progression of disease and another did not receive further treatment due to other comorbidities. All patients had a small enhancing abnormality after completion of induction chemotherapy with R-MVP (after a median of 7 cycles); 18/24 also had some T1 pre-contrast hyperintense abnormality. One patient died post-transplant, one had progression of disease and two had other comorbidities and were lost to followup. 20 patients had an MRI done after consolidation (19/20 completely off steroids), 18/20 had persistent small enhancing abnormalities and 2/20 had complete resolution. Brain FDG-PET was performed in 6/18; none showed hypermetabolism. In these 18 patients, median follow up was 33m, median PFS and OS have not been reached. Long-term follow-up MRI showed resolution of the enhancing abnormality in 13 patients, at a median time of 7 months. 1/18 patient had disease progression in a distant area and died, while another died due to treatment related complications. CONCLUSIONS: Patients who achieved CRu had a good prognosis. Enhancing abnormalities in the MRIs decreased and eventually resolved in long-term follow up.

NO-039. PHASE 1 STUDY OF AN ONCOLYTIC POLIO/RHINOVIRUS RECOMBINANT (PVSRIPO) AGAINST RECURRENT GLIOBLASTOMA

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BACKGROUND: Convection-enhanced delivery (CED), sustained direct intracerebral infusion at slow flow rates, can overcome some delivery barriers limiting treatment of glioblastoma. PVSRIPO is the live attenuated, oral (SABIN) serotype 1 poliovirus vaccine containing a heterologous internal ribosomal entry site stemming from human rhinovirus type 2. PVSRIPO recognizes nectin-like molecule-5, oncofetal cell adhesion molecule and tumor antigen widely expressed ectopically in malignancy. We present an ongoing phase 1 study evaluating PVSRIPO delivered by CED. METHODS: Eligible are adult patients with recurrent supratentorial glioblastoma, with 1-5cm of measurable disease, ≥1cm away from the ventricles, 4 weeks after chemotherapy, bevacizumab or study drug, and with: adequate organ function; KPS ≥70%; and positive anti-poliovirus titer. PVSRIPO is delivered over 6.5 hours. Dose is escalated by increasing agent concentration, allowing flow-rate and infusion volume to remain constant. Two-step continual reassessment method is used for dose escalation, with one patient each treated on dose levels 1-4, and a possibility of 21 patients on dose level 5. RESULTS: Thus far, seven patients have been treated. No dose limiting toxicity was observed. Adverse events possibly

related to study include: hemiparesis (grade 3, n = 1; grade 1, n = 1), diarrhea (grade 2, n = 1), seizure (grade 2, n = 1); and one each of grade 1 fever, cough, nasal congestion, vomiting, headache, and lethargy. Patient #1 had failed bevacizumab and remains disease free more than 12 months post PVSRIPO. Three additional patients remain disease free at 11 + , 3+ and 2+ months post infusion. One patient came off study after 4 months for possible disease progression, later confirmed to be mostly therapeutic effect. Two bevacizumab failure patients died six months post-infusion after initiating Hospice care due to continued persistence of baseline neurologic limitations. CONCLUSION: Infusion of PVSRIPO via CED is safe thus far and encouraging efficacy results are observed. Updated results will be presented.

NO-040. NEUROIMAGING OF TREATMENT ASSOCIATED NEUROTOXICITY IN GLIOBLASTOMA PATIENTS

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INTRODUCTION: Cancer therapy in brain cancer patients may be associated with neurotoxic adverse effects, such as neurocognitive impairment. Preclinical studies suggest that injury to self-renewing populations of neural stem and progenitor cells and myelin forming cells may form the cell-biological basis for such neurocognitive symptoms. Imaging parameters of chemotherapy and radiation on normal brain structures have not been well defined. We here used high-resolution structural MRI to explore patterns of brain changes in glioblastoma (GBM) patients treated with radiation and chemotherapy. METHODS: We longitudinally examined neuroimaging parameters within germinal zones and non-tumor regions in a cohort of 14 GBM patients receiving standard fractionated radiation and concurrent daily temozolomide (TMZ) chemotherapy over six weeks, followed by up to 6 monthly cycles of TMZ. We constructed regions of interest (ROIs) within the lateral ventricles and temporal lobes/hippocampus on baseline MEMPRAGE images prior to treatment and used non-rigid co-registration to map these ROIs onto images collected subsequently across the treatment period. RESULTS: Subjects remaining on treatment beyond the 6-week chemoradiation period (12/14 = 88%) showed mean ventricular dilatation of 39.0% (SD: 22.0%; range: 6.8-67.1%) at final visit. Percent volume change was positively associated with duration of exposure to treatment, and was not associated with tumor volume changes. No significant changes were identified in hippocampal volume over time. DISCUSSION: We present evidence of significant long-term consequences of chemo-radiation on normal brain structure. Our findings highlight the need for further exploration of treatment-associated brain changes and their underlying pathophysiologic mechanisms. Prospective studies are ongoing to correlate imaging biomarkers of neurotoxicity with neurocognitive function in brain cancer patients.

NO-041. ACTIVITY AND SAFETY OF THE COMBINATION BEVACIZUMAB AND FOTEMUSTINE IN RECURRENT MALIGNANT GLIOMAS

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INTRODUCTION: Recurrent malignant gliomas have a dismal prognosis with a median survival of 4–6 months; although Bevacizumab has been showed to provide encouraging tumor responses and prolonged survival, no established chemotherapeutic regimens do exist. We performed an observational prospective study with the aim of evaluating activity and toxicity of Bevacizumab (BEV) in combination with Fotemustine (FTM) in this setting. MATERIALS AND METHODS: 26 pts [17 M, 9 F, median age 38 yrs (23-68), median KPS 80 (70-100)] were enrolled. Eighty-five percent have received only one previous line of CT, namely temozolomide concomitant with radiotherapy as well as adjuvant; 11% of pts have received two prior lines of CT. In the induction phase enrolled patients received BEV iv (10 mg/kg) every 2 weeks plus FTM (65 mg/mq) day 1-8-15 q28. In the maintenance phase we administered BEV associated with FTM triweekly cycles at 75 mg/m^2. MGMT gene promoter methylation status was evaluated in 19 (73%) pts. RESULTS: PR was observed in 8 (31%) pts, and SD in 8 (31%) pts (disease control rate: 62%). Ten pts (38%) presented clinical benefit. Median PFS and OS were 4 months (95% C.I.: 3.0–4.9) and 6 months (95% C.I.: 4.2–7.8), respectively. OS differed with regard to response: 10 months (95% C.I.: 3.8–16.2) for pts with PR; 7 months (95% C.I.: 4.5–9.5) for SD; 4 months (95% C.I.: 2.0–6.4) for pts with progressive disease. The most common adverse events (all grades) were neutropenia (23%), thrombocytopenia (15%), hepatic toxicity (11%). Toxicity probably associated with BEV included venous thromboembolism (8%), asymptomatic CNS hemorrhage (4%), proteinuria (2%) and a grade 2 gastro-intestinal perforation (2%). CONCLUSION: The combination of BEV and FTM in recurrent malignant glioma revealed a good activity in pts previously treated with CT, and the treatment was widely well tolerated.

NO-042. EXTENDED TREATMENT WITH TEMOZOLOMIDE PROLONGS PROGRESSION FREE SURVIVAL IN A PATIENT WITH ASTROCYTIC GLIOMATOSIS CEREBRI

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BACKGROUND: Gliomatosis cerebri (GC) is a rare diffusely infiltrating tumor which involves multiple areas of the brain and carries a poor prognosis, even after radiation and/or chemotherapy. We present a patient with primary astrocytic GC treated with Temozolomie (TMZ) alone who has progression- free survival (PFS) of more than 26 months. CASE HISTORY: The patient is a 55 years old woman who in February 2011 presented with complex partial seizures, mild expressive aphasia and mild right hemiparesis. MRI scan showed extensive infiltrating lesion involving both temporal lobes, thalami and most of the left hemisphere. Biopsy on 2/11/2011 was diagnostic for grade II infiltrating astrocytoma. The tumor was too extensive to consider radiation therapy. She started TMZ in March 2011 at 150 mg/m^2/day for 5 days every 28 days and improved neurologically with stable disease radiologically. She continues TMZ which she tolerates well, with only gade I fatigue and grade I lymphopenia. PFS is more than 26 months. DISCUSSION: Published reviews of GC reports median survival of 11 months for astrocytic tumors. Treatment with extensive radiation fields or WBRT carry high risk for toxicity. Clinical trials with TMZ up to 24 courses show median PFS of 16 months and OS 29 months, with best results for patients with oligodendroglial GC. Our patient with primary astrocytic GC continues TMZ beyond 24 courses with no significant toxicity and has no evidence of tumor progression. CONCLUSION: Extended treatment with TMZ may improve PFS and survival in some patients with gliomatosis cerebri.

NO-043. UNUSUAL CASE OF MULTICENTRIC GLIOBLASTOMA MULTIFORME WITH RECURRENCE IN THE OLFACTORY BULB

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BACKGROUND: Multicentric glioblastoma multiforme (GBM) is a rare occurrence (2.4-10% of GBMs), with no identifiable route of spread. To date there are no reports of involvement of the olfactory bulb. We present a patient with GBM with distant recurrence in the olfactory bulb. CASE HISTORY: The patient is a 57 years old man who in December 2011 presented with focal seizure with expressive aphasia. MRI scan showed necrotic mass in the left supplemental motor region. He had resection of the tumor on 1/10/2012; pathology was consistent with GBM. He had chemoradiation with Temozolomide and 12 courses of adjuvant Temozolomide with near complete response. In January and March 2013 MRI scans showed a new enhancing lesion in the left olfactory bulb, which increased in size. He had resection of the new tumor on 4/25/2013. Pathology was GBM, similar with the initial tumor, with adjacent incidental small meningioma. The patient is recovering well and will have additional therapy. There is no local recurrence of the initial tumor. DISCUSSION: Involvement of the olfactory bulb was described in animals injected with human GBM cells arising from subventricular zones (SVZ), which have highly invasive and migratory potential. Similarly, patients with tumors involving or in the proximity of neural cell zones such as SVZ have a higher risk to develop multifocal GBMs and distant recurrences. Our patient does not have evidence of tumor in the SVZ or other neural stem cell zones and no evidence of leptomeningeal spread of tumor. He appears to have true multicentric GBM. CONCLUSIONS: To our knowledge this is the first case report of a patient with multcentric GBM with olfactory bulb involvement.

NO-044. BEVACIZUMAB FOR RADIATION INJURY IN METASTATIC BRAIN TUMORS AND MENINGIOMAS

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BACKGROUND: Metastatic brain tumors and meningiomas are sometimes irradiated several times for the same tumor or the same region. In these tumors, delayed radiation injury occurred more frequently, because these patients survive longer than patients with glioblastomas. We treated radiation injury after radiotherapy for metastatic brain tumors and meningiomas with bevacizumab and evaluated its efficacy. MATERIALS AND METHODS: Eight patients were treated with bevacizumab between March 2012 and March 2013. Four patients had metastatic brain tumors and the rest of four patients had meningiomas. One patient underwent single stereotactic radiosurgery (SRS), three underwent 2 radiotherapies (RTs), and two underwent 3 RTs. IThe rest of patients had four and six RTs, respectively. All patients had an enhanced lesion with perifocal edema and were diagnoses as delayed radiation injury. The patients underwent 1 to 4 administrations of bevacizumab at a dose of 5 mg/kg in other week. RESULTS: In metastatic brain tumors, three patients improved their symptoms and perifocal edema reduced to 8%, 18%, and 11% of pretreatment edema after bevacizumab, respectively. One patient increased perifocal edema to 117% of pretreatment one after one administration of bevacizumab because of tumor enlargement. In meningiomas, three patients improved their symptoms and one did not. Perifocal edema reduced to 29%, 71%, 76%, and 95% of pretreatment edema after bevacizumab, respectively. There was no adverse event associated with bevacizumab. We compared reduction rates between metastatic brain tumors and meningiomas in addition to our cases who were reported previously. The response rate of perifocal edema associated with radiation injury in metastatic brain tumors is higher than those in malignant gliomas and malignant meningiomas (Mann Whitney, $p < 0.05$). CONCLUSION: Bevacizumab is effective on delayed radiation injury which has perifocal edema in metastatic brain tumors better than in meningiomas. The treatment indication of bevacizumab should be elucidated in the future.

NO-045. TEXTILOMA MIMICKING RECURRENT GLIOBLASTOMA: A CASE REPORT

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BACKGROUND: Although uncommon, materials used for dissection or to achieve hemostasis during neurosurgical procedures can cause an inflammatory reaction called textiloma that can mimic recurrent tumor. We report a case where advanced magnetic resonance (MR) imaging suggested tumor, further mimicking previous reports of clinical and conventional MR patterns of tumor progression. METHODS: A 61 year-old woman underwent an initial resection of a temporal lobe glioblastoma, followed by conventional chemoradiation, although maintenance temozolomide was stopped secondary to myelotoxicity. A nodular enhancing mass near to the surgical cavity was noted 10 months after diagnosis, leading to further evaluation with advanced MR imaging. RESULTS: Brain MRI with advanced imaging studies including MR Spectroscopy (MRS), and perfusion imaging by dynamic contract-enhanced (DCE), and dynamic contrast susceptibility (DSC) were performed. There was progressive enlargement of an enhancing nodule in the wall of the resection cavity. MRS demonstrated an elevated choline-to-creatine ratio (approximately 2:1), while the DSC imaging demonstrated a mild amount of leak with a corrected cerebral blood volume value of about 1.93, and negative enhancement integral value 1.67. DCE demonstrated mild vascularity and mild-to-moderate leak, with an elevated peak enhancement integral value of ~22%. These imaging findings suggested recurrent GBM rather than post-treatment change. The mass was resected. Pathologic review showed both textiloma and radiation necrosis. Recurrent glioblastoma was not identified. CONCLUSIONS: Although very unusual, textiloma should be considered in the differential diagnosis of any growing mass lesion close to a surgical bed. Reparative granulomata show many of the hallmarks of cancer, including neovascularization, rapid growth and high lipid turnover, making it difficult to distinguish such lesions from true neoplasm, even with advanced imaging, without resorting to histology. Advanced imaging performs best in distinguishing conventional post-treatment change from tumor recurrence. This case highlights the major influence of surgical technique on postoperative imaging appearance.

NO-046. RTOG 0825: PRIMARY OUTCOME RESULTS FROM A PHASE III RANDOMIZED, PLACEBO CONTROLLED TRIAL EVALUATING BEVACIZUMAB IN NEWLY DIAGNOSED GLIOBLASTOMA

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BACKGROUND: Concurrent chemoradiation followed by maintenance temozolomide is the standard of care for patients with newly diagnosed glioblastoma. Bevacizumab, a humanized monoclonal antibody against VEGF-A, is currently approved for recurrent glioblastoma. We performed a randomized trial to determine if the addition of bevacizumab improved overall (OS) or progression free survival (PFS) for newly diagnosed glioblastoma. METHODS: This phase III randomized, double-blinded, placebo controlled trial was conducted by the RTOG, NCCTG and ECOG. Adult patients with centrally confirmed glioblastoma were treated with chemoradiation. Experimental treatment began with week 4 of radiotherapy and continued through six to twelve cycles of maintenance temozolomide chemotherapy. At disease progression, treatment could be unblinded; patients could then initiate or continue a bevacizumab regimen. The trial was designed to detect hazard reductions of 25% for OS and 30% for PFS, the two co-primary endpoints, with the addition of bevacizumab. Symptom, QOL and neurocognitive testing was performed in the majority of pts. Secondary analyses evaluated impact of MGMT methylation status and prognostic 9-gene signature status. RESULTS: From 978 registered pts, 637 were randomized. Inadequate tissue ($n = 105$) and blood on imaging ($n = 40$) were key reasons for non-randomization. There was no difference between arms for OS(median 16.1 vs.15.7 months, HR:1.13). PFS was extended for bevacizumab (7.3 vs.10.7 months, HR:0.79). Neither the 9 gene signature nor MGMT status predicted selective benefit for bevacizumab treatment. There was an increased rate of hypertension, thromboembolic events, intestinal perforation and over time, worse symptom burden, quality of life, and cognitive function with bevacizumab. CONCLUSIONS: First-line use of bevacizumab did not improve OS for glioblastoma. PFS was prolonged but did not reach the preset level of significance. The cross-over study design suggests that use of bevacizumab in recurrent disease provides equivalent survival outcomes and delays the risk of bevacizumab-associated toxicities. Support: U10 CA21661, U10 CA37422 and Genentech, Inc.

NO-047. RADIOGRAPHICALLY LOCALIZED BIOPSIES REVEAL INTRA-TUMORAL HETEROGENEITY AND PERITUMORAL-SPECIFIC SUBTYPES IN HIGH-GRADE GLIOMA

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BACKGROUND: Advances in comparative genetic and molecular analysis have uncovered patterns of gene expression and genetic alternations in glioblastoma, and led to the recognition of clinically significant tumor subtypes. Current analyses are predicated on biopsy specimens taken from within the contrast enhancing margins of glioblastoma, without radiographic localization of the biopsy site. Analysis of tissue sampled from both peritumoral, non-contrast enhancing tissue as well as contrast enhancing tumor would provide insight into intra-tumoral heterogeneity and its correlation with radiographic phenotype. Characterization of tumorigenic tissue that is not surgically resected has clinical implications for tumor recurrence. OBJECTIVE: This study investigates the intra-tumoral molecular and genetic differences present in radiographically distinct regions in glioblastoma, and clinical implications

regarding tumor behavior and identification of potential therapeutic targets. METHODS: In 11 patients with high-grade glioma, multiple stereotactic-guided biopsies were obtained prior to surgical debulkingfrom radiographically distinct regions including areas of contrast enhancement and areas of adjacent peritumoral FLAIR-intense tissue. RNA was extracted from flash frozen samples and sent for high-throughput RNA-sequencing with a portion reserved for histologic analysis. Bioinformatic analysis was performed using Tuxedo Suite, MATLAB and ClaNC. RESULTS: Samples taken from the FLAIR-intense regions in 10/11 patients were found to have a proneural subtype. The contrast enhancing regions of these 10 tumors were found to be proneural in 5 cases, mesenchymal in 4 cases, and classical in 1 case. DISCUSSION: The FLAIR-intense region of high-grade glioma demonstrates predominance for the proneural subtype even when contrast-enhancing tissue has a different subtype. The presence of multiple subtypes in individual tumors and the prevalence of proneural subtype in tissue adjacent to contrast enhancing tumor that is not normally surgically removed has clinical implications for characterization of recurrent tumors and identification of targets for adjunctive therapy.

NO-048. GLIOBLASTOMA TREATMENT PATTERNS AND OUTCOMES AND RESOURCE USE IN THE UNITED STATES

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BACKGROUND: Treatment of glioblastoma (GB) remains a challenge because of the lack of effective therapies and poor patient outcomes. OBJECTIVES: Describe GB treatment patterns and outcomes in the United States. METHODS: This was a retrospective, observational, online chart-abstraction study in which participating oncologists contributed charts from real-world clinical practice. Patients were ≥18 years of age with a diagnosis of primary or secondary GB confirmed by biopsy on or after 01 Jan 2010. Patient information was restricted to those who received both first- and second-line therapies and collected for at least the 3-month period after initiation of second-line systemic therapy or until death. Analyses were descriptive and included Kaplan-Meier analyses from initiation to end of second-line therapy, discontinuation due to disease progression, or death. RESULTS: 160 physicians, 46.9% with teaching hospital affiliation, contributed to a study sample of 503 patient charts. During first-line therapy, patients were most commonly treated with oral temozolomide (70.2%) or oral temolozamide-bevacizumab combination therapy (8.7%). During second-line therapy, patients were most commonly treated with bevacizumab monotherapy (58.1%), bevacizumab-irinotecan combination therapy (16.3%), or irinotecan monotherapy (5.8%). Median duration of second-line therapy was 92.5 days, time to disease progression was 100 days, and median survival was 137.5 days. Physicians most frequently reported disease progression as the reason for ending first- (57.3%) and second-line (28.6%) therapies. Supportive care utilization was more frequent in first- versus second-line therapy. Overall, frequently used resources included steroids (79.3% of patients), antiepileptics (49.1%), and narcotic opioids (46.7%). Disease symptom management was the main reason for GB-related emergency room use (52.9%); GB-related treatment was the main reason for inpatient hospitalization (43.3%). CONCLUSIONS: The majority of patients were treated with temozolomide during first-line therapy and bevacizumab monotherapy or combination therapy during second-line therapy. Healthcare resource-use patterns differ systematically across first- and second-line therapies.

NO-049. SUNITINIB IN PATIENTS WITH BRAIN METASTASES FROM METASTATIC RENAL CELL CARCINOMA (mRCC) – FINAL RESULTS FROM A GLOBAL EXPANDED ACCESS TRIAL

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BACKGROUND: With the introduction of targeted agents, mRCC patients live longer, but more patients develop brain metastases. mRCC patients with brain metastases were excluded from pivotal trials of sunitinib, an oral multitargeted tyrosine kinase inhibitor approved in 2006. From 2005–2007, >4,500 patients enrolled in a sunitinib mRCC global expanded access trial. We report final efficacy and safety data for patients with brain metastases from mRCC allowed entry in this trial (preliminary results; Gore et al, Cancer 2010). METHODS: 338 patients ≥18 years with treatment-naïve/previously treated mRCC and brain metastases received sunitinib 50 mg/day on a 4-weeks-on/2-weeks-off schedule or 37.5 mg/day continuously. Previous radiotherapy was allowed. Tumor measurements were scheduled per local practice and measured using RECIST. Safety was assessed regularly. Objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse events (TRAEs) are reported. Brain-specific response was not analyzed. Analyses included all patients with ≥1 dose. RESULTS: Baseline characteristics of brain metastases patients were comparable to all patients. Median treatment cycles was 3 (range, 1–50). Of 324 RECIST-evaluable patients, 3 (1%) had complete response and 27 (8%) partial response. ORR was 9%. Median PFS was 5.3 months (95% CI: 4.3–5.6) and median OS was 8.2 months (95% CI: 7.4–9.6). 94 patients (28%) had AEs leading to sunitinib withdrawal. The most common any-grade TRAEs were diarrhea (36%), fatigue (33%), nausea (29%), mucosal inflammation and decreased appetite (both 27%), vomiting (23%), asthenia and dysgeusia (both 22%), and stomatitis (21%). The most common grade 3/4 TRAEs were fatigue (9%), asthenia and thrombocytopenia (both 6%), neutropenia and anemia (both 5%), and hand-foot syndrome and hypertension (both 4%). CONCLUSIONS: Among 338 mRCC patients with brain metastases, patients with traditionally limited treatment options and poor prognosis, safety with sunitinib was comparable to the overall mRCC population, with encouraging efficacy.

NO-050. SARCOMA BRAIN METASTASES

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INTRODUCTION: Many systemic cancers do not regularly metastasize to the CNS, and there is very little data to guide treatment of these lesions. We report our experience in 21 patients with brain metastases from sarcoma. MATERIALS AND METHODS: All patients were treated surgically at our Neurosurgery department between 1996 and 2012 were retrospectively reviewed. Gliosarcoma, sarcoma of the head and neck with local extension into the brain, and metastatic sarcoma to the spine were excluded. The medical, radiological, surgical, pathological, and follow-up clinical records from these patients were reviewed. RESULTS: Mean age was 49.6 ± 14.2 years (range, 25-75) at the time of diagnosis of brain metastases. Fifteen patients had known history of sarcoma, most commonly in the extremities. All of these patients were treated previously with systemic chemotherapy and radiation therapy. The mean pre-operative KPS was 84 ± 13.5. The mean ± SD maximal tumor diameter was 4.9 ± 1.7cm. All tumors had exhibited heterogeneous enhancement with relatively mild surrounding edema. Most of the patients (81%) underwent gross-total-resection. Fifteen patients had received post-operative radiotherapy (71.4%). Nine (66.7%) patients underwent whole brain radiation therapy (WBRT), six (40%) received stereotactic-radiosurgery (SRS) and one (6.7%) received fractionated-stereotactic-radiosurgery (FSR). There was one patient (4.7%) who died within one week after surgery. The median overall survival of our patients was 6 months (range 2 to 28 months). Nine patients (42.9%) had experienced tumor recurrence within four months from the first operation. At the time of recurrence multiple brain metastases developed in seven patients. Local recurrence was observed in two patients. Four patients underwent re-craniotomy for resection of the symptomatic recurrent tumor. CONCLUSIONS: Gross total resection and subsequent radiation therapy was a well-tolerated therapy in the management of patients with metastatic sarcoma to the brain. This treatment may preserve their neurological function. However, most of the patients developed progressive new brain disease.

NO-051. SURVIVAL OUTCOMES OF PATIENTS WITH RECURRENT ANAPLASTIC GLIOMA TREATED WITH BEVACIZUMAB

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INTRODUCTION: Bevacizumab is approved by the FDA for use in recurrent glioblastoma. There is little data regarding survival outcome in recurrent anaplastic glioma (anaplastic oligodendroglioma, anaplastic astrocytoma and anaplastic oligoastrocytoma) treated with bevacizumab. We examined the survival outcome of patients with recurrent anaplastic glioma treated with bevacizumab in comparison with those treated with other chemotherapeutic

agents. METHODS: In this retrospective chart review derived from our longitudinal database, we identified patients with recurrent anaplastic glioma evaluated between 2006 and 2011, who were treated with bevacizumab alone or with bevacizumab-containing regimens, and those who were not treated with bevacizumab during the course of their disease. Data was analyzed to determine overall survival (OS) and progression free survival (PFS) from time of treatment initiation. RESULTS: A total of 140 patients with recurrent anaplastic glioma (34 anaplastic oligodendroglioma, 83 anaplastic astrocytoma and 23 anaplastic oligoastrocytoma and anaplastic infiltrative glioma) were identified, of whom 97 received bevacizumab and 43 received other chemotherapeutic agents. There was no significant difference in PFS between patients who received bevacizumab in comparison to those who received other chemotherapeutic agents (4.9 months versus 7 months, respectively, $P = 0.3$). However, OS was significantly higher in patients treated with other chemotherapeutic agents when compared to those treated with bevacizumab (17.6 months versus 11.4 months, respectively, $P = 0.04$). CONCLUSION: This retrospective study showed that the use of bevacizumab in patients with recurrent anaplastic glioma was not associated with an improvement in PFS, and may be associated with a poorer OS.

NO-052. PHASE II TRIAL OF DOSE-DENSE 1 WEEK ON/1 WEEK OFF TEMOZOLOMIDE FOR PATIENTS WITH RECURRENT HIGH GRADE GLIOMA

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BACKGROUND: The authors performed a phase II trial to evaluate the safety and efficacy of a dose dense 7-days-on/7-days-off schedule of temozolomide in patients with recurrent high grade gliomas (HGG). METHODS: Sixty eligible patients with recurrent HGG received temozolomide at 150 mg/m^2/day on days 1-7 and 15-21 per 4 week cycle. Primary endpoint was 6 month progression-free survival (PFS-6). Secondary and exploratory objectives included overall survival (OS) and investigation of whether methylation status of O^6-methylguanine DNA methyltransferase (MGMT) promoter within tumor tissue predicted more favorable outcomes. RESULTS: All patients had undergone radiotherapy with concurrent and adjuvant temozolomide at initial diagnosis. Thirty eight patients (63%) had been treated for 1 or more prior recurrences, and 48% of patients had failed prior bevacizumab therapy. Imaging response (complete response + partial response) was observed in 2 patients (3.3%). Among patients with glioblastoma ($N = 40$), PFS-6 was 10%, with median OS of 21.6 weeks. PFS-6 for grade III glioma patients ($N = 20$) was 50%, and median OS was 100.6 weeks. There were trends towards longer PFS and OS with MGMT promoter methylation (log-rank, $p = 0.06$, $p = 0.07$). Bevacizumab-naïve patients had significantly longer PFS and OS than patients with previous exposure (median PFS 10.7 vs. 7.6 weeks, log-rank $p < 0.001$, median OS 94.6 vs. 19.3 weeks, log-rank $p < 0.001$). Most common toxicity was myelosuppression. Grade 4 hematotoxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) was seen in 7 patients (12%). Grade 3 toxicity was observed in 33 patients (55%). Toxicity prompted discontinuation of therapy in 3 patients. CONCLUSIONS: The regimen was well tolerated and appears to have modest activity in this heavily pretreated population including prior treatment with temozolomide and bevacizumab. Results were particularly favorable for bevazicumab-naïve and grade 3 patients. This dose-dense regimen may be more active in tumors with MGMT promoter methylation.

NO-053. A DIRECT COMPARISON OF RESPONSE ASSESSMENTS IN A PHASE II CLINICAL TRIAL OF WT1 PEPTIDE VACCINATION; MACDONALD, RECIST AND RANO CRITERIA

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The phase II clinical trial against recurrent gliomas revealed that WT1 peptide vaccination is safe and effective (Izumoto, Hashimoto et al., J Neurosurg, 2008). At the SNO meeting in the last year, we also presented the result of phase I WT1 trial in combination with temozolomide for newly diagnosed glioblastomas. It is known to be difficult to determine clinical response by only enhancing MRI, as we have "pseudo-progression or -response". In fact, we have reported that methionine PET was more accurate than enhancing MRI, when assuming survivals (Chiba, Hashimoto et al., J Neurosurg, 2012). At this time, we compared Macdonald (MD), RECIST and newly proposed RANO criteria to know what is the best surrogate of overall survival (OS). In 50 patients with a diagnosis of recurrent glioblastoma enrolled in the phase II trial of WT1 vaccination, we conducted MRI evaluation 3 times during the trial. Although we had originally used RECIST according to the protocol, each evaluation was re-assessed by MD, RECIST and RANO, yielding a total of 450 assessments (50 patients x 3 times x 3 criteria). Kaplan-Meier analysis was performed in each criterion between CR/PR/SD group and PD group at the last MRI evaluation. The consistency rate of clinical response of CR/PR/SD/PD was 80.0% (120/150), 94.0% (141/150) and 76.7% (115/150), when we compared MD and RECIST, MD and RANO, RECIST and RANO respectively. The difference of OS between CR/PR/SD and PD group was largest when we used RANO, and those were 14.5 and 8.3 months in MD, 12.1 and 8.4 months in RECIST, 23.7 and 8.3months in RANO ($p = 0.0021$). In conclusion, an assessment by RANO was the best surrogate of OS in this trial. We might have shown the possibility of RANO usage in the future clinical trial including immunotherapy against gliomas.

NO-054. ELUCIDATING GLIOBLASTOMA REGIONAL EDEMA AND HYPOXIA CHANGES INDUCED BY ANTI-ANGIOGENIC TREATMENT THROUGH MATHEMATICAL MODELING COMBINED WITH CLINICAL IMAGING

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Glioblastoma multiforme (GBM) is the most aggressive primary brain tumor with a median survival of 14 months despite rigorous treatment protocols. As increased vascularity is a defining characteristic for these tumors and is necessary for invasive growth, there is a push for using anti-angiogenic therapies. Anti-angiogenic treatments are known to, at least transiently, normalize the tumor vasculature and restore the blood brain barrier while pruning small leaky vessels. Researchers understand that vascular normalization likely impacts the efficacy of MR imaging, but it is also hypothesized that this process re-oxygenates the tumor since GBMs preferentially co-opt the existing vasculature over recruiting new vessels. While this has major implications for combination therapies, no major studies have been done validating tumor re-oxygenation following anti-angiogenic treatment. In this work, we explore the re-oxygenation hypothesis using a mathematical model of GBM growth combined with clinical imaging data available in GBM patients receiving anti-angiogenic therapy. Previously, we have developed a spatio-temporal biomathematical model for glioma proliferation and invasion incorporating the role of the angiogenic cascade, which has already been seen to predict patient-specific functional PET images of hypoxia. To investigate the effects of anti-angiogenic treatment on the hypoxic regions of the tumor, we simulated multiple tumors, defined by different growth kinetics, and subjected each to anti-angiogenic treatment. Treatment was simulated by reducing the available angiogenic factors, akin to the action of bevacizumab, and by increasing the current vasculature's efficiency. Model results showed that all tumors would experience a decrease in their hypoxic cell population, consistent with imaging data in both the experimental and clinical setting. The model further predicts that tumors with lower proliferation rates would receive the fastest re-oxygenation. These results suggest a potential predictive tool for patient-specific differential benefit/response to anti-angiogenics.

NO-055. EFFICACY OF BEVACIZUMAB FOR GLIOBLASTOMA AT FIRST VERSUS SUBSEQUENT RECURRENCE - A SINGLE-INSTITUTION RETROSPECTIVE ANALYSIS

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BACKGROUND: Bevacizumab is FDA-approved for the treatment of recurrent glioblastoma, but relative efficacy at first vs subsequent recurrence has yet to be clearly defined. METHODS: In this single-institution retrospective analysis, we identified 106 glioblastoma patients who were treated with a bevacizumab-containing regimen at recurrence between 2003 and 2012. Kaplan-Meier estimates and the log-rank test were used to assess time to progression and survival from each recurrence. RESULTS: Median age for the entire cohort of 106 patients was 58 years, with median KPS of 80 at both initial diagnosis and first recurrence. Overall survival for the entire cohort was 25.7 months. Median survival from first recurrence for patients treated with bevacizumab at first recurrence ($n = 64$) was 15.1 months (95% CI: 8.6-22.8), and 15.1 months (13.3-24.3) for patients treated with bevacizumab

at subsequent recurrence (n = 42). Time to progression from first recurrence (TTP_{first}) was 9.8 mo (6.0-12.9) for patients treated with bevacizumab vs 2.8 months (2.1-4.2) for patients who did not receive bevacizumab, a statistically significant difference ($p < 0.0001$). Time to progression from the inception of bevacizumab (TTP_{bev}) was 8.6 mo (5.1-11.5) for patients treated with bevacizumab at 2nd or later recurrence, which was not a statistically significantly difference ($p = 0.71$) compared to patients treated with bevacizumab at first recurrence. CONCLUSIONS: Although the interval between first and second recurrence was significantly longer for patients who received bevacizumab at first recurrence compared to patients who received bevacizumab at subsequent recurrence, survival from first recurrence for these two cohorts was similar. Although this analysis is limited by its *post-hoc* nature, these results suggest that treatment with bevacizumab can be deferred without obvious adverse impact on survival.

NO-056. WHOLE BRAIN RADIOTHERAPY (WBRT) COMBINED WITH CONCOMITANT OR SEQUENTIAL INTRATHECAL LIPOSOMAL CYTARABINE (DEPOCYTE) IN THE TREATMENT OF LEPTOMENINGEAL METASTASES – A RETROSPECTIVE SAFETY ANALYSIS

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BACKGROUND: Treatment of leptomeningeal metastases (LM) includes intra-CSF chemotherapy combined with radiotherapy. At present, little is known on toxicity of combination therapies. We performed a retrospective safety analysis for the combination of intrathecal liposomal Cytarabine (DepoCyte) either given concomitantly or sequentially with WBRT in patients with LM. METHODS: Thirty patients with LM [median age 59 years (43-80)] diagnosed either by positive CSF cytology, MRI or both were treated with combined WBRT and liposomal Cytarabine; 24 patients concomitantly and 6 sequentially. RESULTS: WBRT was administered to a median total dose of 38,4 Gy. In total, 150 cycles of liposomal Cytarabine were applied every 2 weeks (50 mg) and oral Dexamethasone was given as prophylaxis against chemically-induced meningitis. According to the RTOG-toxicity criteria, acute reactions during WBRT were observed in 7 patients (sequential 16,7%; 1/6, concomitant 25,0%; 6/24) including alopecia, dermatitis, nausea/vomiting and mucositis. Adverse events (CTCAE criteria ≥Grade 3) following liposomal Cytarabine administration were seen in 23 patients (sequential 40,0%; 6/15 cycles, concomitant 37,0%; 50/135 cycles). These toxicities included headache, seizures, sensory/motor neuropathy, dizziness, nausea/vomiting and chemically-induced meningitis. Median time to progression in patients treated concomitantly was 49 days and median overall survival 126 days compared to 20 days and 65 days in the sequential group. SUMMARY: In this retrospective safety analysis, limited by unbalanced patients groups (135 concomitant vs. 15 sequential cycles), concomitant WBRT and intrathecal liposomal Cytarabine was fairly well tolerated and not associated with increased toxicity over sequential WBRT/liposomal Cytarabine. The risk of chemically-induced meningitis, which occurred twice in the concomitant group, however, will deserve particular attention in future investigations.

NO-057. OUTCOME PREDICTION IN PATIENTS WITH GLIOBLASTOMA USING IMAGING, CLINICAL AND GENOMIC BIOMARKERS: FOCUS ON THE NON-ENHANCING COMPONENT OF THE TUMOR

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Traditionally focus of treatment planning as well as response assessment and patient prognosis has been based on evaluation of contrast-enhancing component (CEL) in glioblastomas. The peri-CEL phenotype of the tumor also contains important information which is indicative of tumor invasiveness and aggressiveness. The purpose of this study was to examine role of morphologic imaging features and rCBV of the non-enhancing component (NEL) of GBM, with clinical features and genomic biomarkers in predicting patient survival. Forty-five patients who had DSC T2* MR perfusion data, and a detailed imaging assessment available from The Cancer Imaging Archive (TCIA) were included. Relative cerebral blood volume of the NEL ($rCBV_{NEL}$) was also measured. Molecular and clinical predictors of survival were obtained from The Cancer Genome Atlas (TCGA). Morphologic, physiologic imaging features along with clinical and genomic markers were assessed with respect to both overall and progression-free survival. We found that worsening overall survival (OS) (log-rank $P = 0.0145$) and progression-free survival (log-rank $P = 0.0223$) are each associated with increasing rCBV measures in the NEL. $rCBV_{NEL}$ is a unique and independent imaging predictor of survival retaining its association with survival in models containing other imaging parameters, clinical parameters, or genomic features. For both OS and PFS, $rCBV_{NEL}$ was consistently the top predictor with KPS, age at diagnosis, and NEL crossing the midline as also important. A multivariable model containing $rCBV_{NEL}$, age at diagnosis, and KPS is able to separate patients into groups with median survival differences of 1.3 years. Increasing blood volume in the NEL is associated with poor OS as well as poor progression-free survival in patients with a diagnosis of GBM. This association is independent of traditional prognostic predictors. Further exploration of the NEL region is warranted to potentially direct adjuvant treatment direct at residual NEL component following resection of the CEL.

NO-058. A PHASE II STUDY OF ANTINEOPLASTONS A10 AND AS2-1 (ANP) IN CHILDREN WITH HIGH-GRADE GLIOMA (PROTOCOL BT-06)

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There are no standard treatment recommendations for patients with high grade glioma after recurrence. New therapies are required for patients whose tumor recurs after first-line treatment. This single-arm, two stage, interventional Phase II study evaluated the efficacy and safety of ANP in children with high grade glioma. All patients had failed standard therapy including surgery, radiation, and chemotherapy. Nineteen patients were enrolled in the study (safety population) and twelve patients with a median age of 9.7 years, ranging in age from 1 to 17.5 years, who met eligibility criteria, were evaluated. The majority of subjects (11/12) were Caucasian and 7 (58%) were female. Half of the patients were diagnosed with glioblastoma, 42% with anaplastic astrocytoma, and one with rhabdoid tumor. Previous treatment included surgery in all patients (8 had tumor resection, and the 4 underwent biopsy only), chemotherapy in all patients and radiation therapy in 10 patients. At least 8 weeks elapsed between initiation on ANP and previous radiation and 6 weeks for chemotherapy with nitrosoureas. Antineoplastons were administered intravenously every four hours (median dose of A10 10.7 g/kg/d and AS2-1 0.43 g/kg/d) until objective response was documented or until progression. The median duration of antineoplastons treatment was 31.7 weeks (range 11 to 120 weeks). Responses were assessed by gadolinium-enhanced MRI repeated every 8 weeks. A complete response and partial response was documented in 4/12 (33%), stable disease in 3/12 (25%). Progression free survival at six months was 58% and overall survival at one year was 46%. One patient (8%) is still alive, 8 years post-treatment. All Grade 3 and 4 toxicities (two hypernatremia's and one decrease of neutrophils) were reversible. There were no chronic toxicities. It is concluded that antineoplastons show efficacy with an acceptable profile in this cohort of patients with recurrent high-grade glioma.

NO-059. Rab27a CONFERED STRONG WORSE PROGNOSIS, GRADE PROGRESSION ASSOCIATION AND SUBTYPE PREFERENCE IN GLIOMAS

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BACKGROUND: Rab27a belongs to the small GTPase superfamily, Rab family. The protein is membrane-bound and may be involved in protein transport and small GTPase mediated signal transduction. Mutations in this gene are associated with Griscelli syndrome type 2. However, the prognostic and molecular features of gliomas with Rab27a expression is still unclear. METHODS: We applied whole genome mRNA expression microarray data of 220 glioma samples from Chinese Glioma Genome Atlas (CGGA) database (http://www.cgga.org.cn) as discovery set. In this 220 gliomas set, 97 WHO Grade?gliomas, 34 WHO Grade III gliomas and 89 WHO IV Grade gliomas were analyzed by Kaplan-Meier method. For validating the protein expression of Rab27a, we detected another 96 glioma samples by Immunohistochemistry. Three additional datasets were obtained as validation sets. Gene ontology (GO) analysis and gene set variation analysis (GSVA) were used for functional

annotation of Rab27a in 89 WHO Grade IV gliomas. RESULTS: Rab27a was significantly associated with grade progression as well as the high mortality of every grade glioma in the discovery set. Rab27a also showed a Mesenchymal subtype, G3 subtype and Isocitrate Dehydrogenase 1 (IDH1) wild-type preference and migration association. 3 validation datasets showed similar findings. Rab27a showed a higher expression status in gliomas than that in normal brain tissues and increased along with grade progression of gliomas. CONCLUSION: Rab27a expression was significant associated with grade progression and worse prognosis in every grade gliomas, suggesting Rab27a as a novel biomarker with potential important therapeutic implications.

NO-060. EFFECT OF NEOADJUVANT TEMOZOLOMIDE UPON VOLUME REDUCTION AND RESECTABILITY OF DIFFUSE LOW-GRADE GLIOMA

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OBJECTIVE: Maximal safe resection is associated with prolonged survival in patients with low-grade glioma (LGG). Historically, upfront temozolomide produces partial response rates of 10-30% and minor response rates of 14-48% in LGG. It has been suggested that neoadjuvant temozolomide may provide sufficient tumor shrinkage to facilitate aggressive surgical debulking (Duffau 2006, Blonski 2011, Blonski 2013). We examined the impact of temozolomide upon reduction of LGG volume and maximum safe surgical resection. METHODS: We retrospectively identified 20 adult patients with biopsy-proven LGGs, treated initially with temozolomide. All tumors were deemed not totally resectable prior to initiation of chemotherapy. Median number of four-week temozolomide cycles was 12 (range, 2-16). Volumetric 3D (calculated from serial FLAIR images) and Macdonald 2D tumor measurements were obtained prior to treatment and at 3 months post-treatment. The anticipated extent of resection (aEOR) at the 2 time points was measured based on anatomical limitations, calculated as: (total tumor volume - unresectable tumor volume)/total tumor volume. Eloquent cortex, deep structures, and corpus callosum were considered unresectable. RESULTS: Mean tumor volume was 68.4 cm^3 pre-treatment and 49.5 cm^3 at 3 months post-treatment. The mean change from baseline was significant 3 months after treatment at -32.5% ($p < 0.001$). Mean 2D pre-treatment area was 28.6 cm^2 and 23.2 cm^2 at 3 months post-treatment. The 2D change was also significant, with mean change of -17% ($p < 0.001$). Five percent had partial response; 40% minor response; 45% stable disease; and 10% progressive disease by Macdonald criteria. Mean pre-treatment aEOR was 67.2% and 71.5% at 3 months post-treatment. The mean change from baseline was 4.3% ($p = 0.10$). CONCLUSIONS: Our findings demonstrate significant volumetric and 2D reduction of LGG with temozolomide. Although this tumor shrinkage might facilitate radical surgical resection in some cases, our data failed to show statistically significant improvement in aEOR.

NO-061. LONG-TERM SURVIVAL IN PATIENTS WITH BRAIN METASTASES: A RETROSPECTIVE ANALYSIS

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OBJECTIVE: To assess long-term survival in patients with BM and to identify predictors of improved overall survival (OS). METHODS: A mono-center analysis of long-term survival (defined as survival >24 months) including all cancer patients with BM treated surgically at our institution between 2000-2012, was performed. Prognostic factors for survival were examined. RESULTS: In total, 53 of 507 patients (10.5%) were defined to be long-term survivors. 36 (68%) had an OS > 36 months. The mOS was 54 months. Primary tumors were: 7 malignant melanomas, 14 bronchial, 10 urothelial, 9 breast and 8 gastrointestinal carcinomas, as well as 6 others. Patients with breast cancer had the longest mOS (66 months), whereas patients with gastrointestinal cancer had the shortest mOS (35.6 months). 33 patients suffered from systemic metastases (SM) with the highest frequency related to bronchial carcinoma. BM occurred in long-term survivors most commonly in the frontal lobe. The patientś mOS with SM was non-inferior compared to those without SM (64 vs. 60 months). In patients with SM, the median time of relapse was significantly shorter than in those without SM (35.5 vs. 60.5 months). 43 patients had a single BM (mOS 54 months), 10 had multiple BM (mOS 48 months), ($p > 0.05$). 33 patients (62%) underwent one surgical resection, 11 (20%) had two and 9 (18%) three surgeries or more. 23 patients (43%) had no radiation therapy (RT), 20 (37.7%) had a one-time RT, the rest received at least 2 RT. In most cases, RT was admitted as whole-brain RT, followed by salvage RT. The multivariate analysis revealed two independent prognostic factors for long-term survival: primary tumor histology and BM location. CONCLUSIONS: Despite the dismal prognosis of patients with BM, 10.5% of our patients in this series were long-term survivors. Favorable factors were histology of the primary tumor, BM location and consequent treatment.

NO-062. HISTOPATHOLOGICAL AND MOLECULAR GENETIC STUDY OF MENINGIOMAS - EXPERIENCE FROM A TERTIARY CARE CENTRE IN INDIA

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BACKGROUND: Meningiomas are the commonest benign CNS tumors. However, significant fraction of these tumors recurs, irrespective of WHO grade. To date, no molecular marker is available for prognostication or prediction of recurrence in meningiomas. OBJECTIVES: To study histopathological features and molecular alterations in meningiomas and correlate the results with clinicopathological features. METHODS: Meningioma cases were retrieved from the Neuropathology database, and reviewed. Clinical data was noted, Fluorescence in situ hybridization (FISH) for chromosomes 1p36 and 14q32 performed, Progesterone receptor (PR) status, p53 protein expression, and MIB-1 labelling index assessed. RESULTS: 8796 CNS tumors were received over a 10-year period, of which 17% were meningiomas. Eighty-four cases with adequate tissue were analyzed. Of these, 64 were convexity tumors (30 grade I, 21 grade II, 13 grade III); 20 were petroclival (all Grade I; 10with gross total resection (GTR), 10 with sub-total resection (STR)). Additionally, 15 recurrent meningiomas were analyzed with their corresponding primary tumors. Isolated 1p36 deletion was seen in 20% grade I, 28.5% grade II and 30% grade III convexity meningiomas. One case (grade III) showed isolated 14q deletion. 1p/14q co-deletion was seen in none of grade I, 28.5% grade II and 30% grade III meningiomas. 20% petroclival tumors with STR showed 1p/14q co-deletion; none with GTR showed co-deletion. Majority of recurrent meningiomas (all grades) showed 1p/14q co-deletion in both primary and recurrent tumors. PR immunoreactivity was less frequent in grade III tumors as compared to other grades. Most cases were immunonegative for p53. CONCLUSION: Combined 1p/14q deletion is seen in high grade meningiomas, and PR immunoreactivity decreases with tumor grade, suggesting their use as surrogate markers for tumor grading. Presence of 1p/14q codeletion in a substantial proportion of unresectable Grade I petroclival meningiomas and majority of recurrent meningiomas suggests that it can be used as a marker for prognostication and prediction of recurrence.

NO-063. HISTORICAL BENCHMARKS FOR MEDICAL THERAPY TRIALS IN SURGERY AND RADIATION REFRACTORY MENINGIOMA: A RANO REVIEW

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BACKGROUND: The outcome of surgery and radiation refractory meningiomas treated with medical therapies is poorly defined. Limitations of data interpretation include small patient numbers, selection bias, inclusion of mixed histologic grades and stages of illness, and WHO criteria changes. This analysis of the literature aims to define outcome benchmarks for future clinical trial design. METHODS: PubMed literature search performed for all English publications on systemic therapy for meningioma. All reports were evaluated for number of patients, histologic grade, prior therapy, overall survival (OS), progression-free survival (PFS), PFS rate at 6 months (PFS-6), and radiographic response. RESULTS: 47 reports were identified and divided by histology; studies that treated patients who failed radiation and surgery were selected. The only outcome measure reproducible across studies was PFS-6, which was summed from the studies of interest to arrive at a single historical benchmark. WHO I MENINGIOMA: A variety of agents (hydroxyurea, temozolomide, irinotecan, interferon-α, mifepristone, octreotide analogues, and tyrosine kinase inhibitors (TKI) including imatinib, erlotinib, and gefitinib) were included from retrospective studies, pilot study, phase II study,

exploratory arm of phase II studies, and phase III study. None of these studies reported clinically significant activity. The summed PFS-6 rate was 25.8% (range 0-54%). WHO II and III MENINGIOMA: These reports included hydroxyurea, megestrol acetate, octreotide analogues, bevacizumab, and TKIs. However, the overall numbers are very low. The summed PFS-6 rate was 14% (range 0-44%). CONCLUSIONS: Even after evaluation of the available literature, the clinical course of recurrent surgery and radiation refractory meningioma remains unclear. PFS-6 is the most discernible endpoint, despite large confidence intervals. This analysis would recommend that for future trials in surgery and radiation refractory meningioma, WHO grade I meningioma should be powered against a PFS-6 rate of 26%, and WHO grade II/III meningiomas powered against a PFS-6 of 14%.

NO-064. PRIMARY BRAIN TUMOUR AS SECOND NEOPLASMA IN PATIENTS WITH EXTRACRANIAL CANCER HISTORY

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INTRODUCTION: Metastases are most frequent CNS tumours. Currently prevail oncologic origins as lug, breast, colorectal cancers have already several advanced treatment strategies. Evident progress on this field brightens up expectation of these patients. In case of neurological disorders the patient should undergo MRI of brain. Rationale of surgery, whole-brain or stereotactic radiotherapy, or chemotherapy is set up. Recently, we have encountered misdiagnosed primary malignant brain tumours in patients with oncologic history, which formerly admitted to surgery with brain metastases. Aim of our study is evaluated an incidence of concurrent cancers, relations between former cancer staging and primary brain tumour evaluation, and also appreciation of treatment efficiency. METHOD: From January 2007 to December 2012 we prospectively followed up patients with concurrent history both of extracranial cancers and primary brain tumours. Tumour samples were undertaken histological, imunohistochemical and cytogenetic investigations. Regarding primary brain tumours patient preferably had standard oncologic treatment and scheduled regular MRI and clinic examination during postoperative period. RESULTS: Limited number of these patients has been selected. Prognosis was depended on staging of extracranial cancer and performance status. If these patients would be able to pass standard oncologic treatment (concomitant chemo-radiotherapy, adjuvant chemotherapy) of primary malignant brain tumour, they did not find survival distinctions to compare with no extracranial cancer history patients. For right treatment strategy it is mandatory to eliminate misdiagnose of brain metastases and primary malignant brain tumours. Current imagine techniques are not able to distinguish primary from secondary brain tumours. It is important to mentioned, that part of patients has administered various chemotherapy regimes of extracranial cancers. Its influence on evolution primary brain tumours is not clear. Support in part by grant of IGA of Ministry of Health, Czech Republic No. NT11065-5/5/2010. Support in part by grant of IGA of Ministry of Health, Czech No. NT13581-4/2012(86-91).

NO-065. TUMOR TREATING FIELDS (TTFIELDS) IN RECURRENT GBM. AN UPDATED SUBGROUP ANALYSIS OF THE PHASE III DATA

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NovoTTF-100A (Novocure Ltd.) is an anti-mitotic therapeutic device which delivers low intensity, alternating electric fields (Tumor treating fields - TTFields). These fields interfere with cell division during metaphase and anaphase. This portable device was investigated in a prospective, randomized clinical phase III trial (n = 237) and showed that NovoTTF-100A was equivalent in efficacy with better quality of life and lower toxicity compared to active chemotherapy (including bevacizumab) in patients with recurrent glioblastoma. The device has been approved by the FDA for the treatment of recurrent GBM based on this data. We performed a subgroup analysis using a Cox Proportional Hazards model after the most recent update of the trial database. As expected, older age, biopsy only, larger tumor size, and lower KPS were associated with shorter survival. Interestingly, in certain subgroups the effect of NovoTTF-100A appeared superior to that of cytotoxic chemotherapy and bevacizumab. These included bevacizumab failures (n = 44; median OS = 6 vs. 3.3 months respectively, p = 0.01), prior low grade gliomas (n = 21; median OS = 25.3 vs. 7.7 months respectively, p = 0.049) and KPS = >80 (n = 161; median OS = 7.9 vs. 6.1 months, respectively, p = 0.045). In addition, higher compliance with NovoTTF-100A use was associated with a statistically significant increase in survival (log rank test for trends p = 0.039). Patients aged < = 60 years used the device more than those >60 years of age (80% vs. 74% compliance, respectively, p = 0.043). Accordingly, patient aged <= 60 years showed a survival trend in favor of NovoTTF-100A compared to chemotherapy (n = 168; median OS = 7.4 vs. 6.2 months, respectively, p = 0.063). In conclusion, this post hoc subgroup analysis suggests certain patient and tumor characteristics which may be associated with better response to NovoTTF-100A treatment. These results should be viewed as hypothesis generating analyses to guide future investigations of this novel treatment modality.

NO-066. ETANTR A BIOLOGICALLY ELUSIVE TUMOR WITH CLINICAL AND RADIOGRAPHICAL HETEROGENITY- MD ANDERSON CANCER CENTER EXPERIENCE

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INTRODUCTION: Embryonal Tumors with Abundant Neuropil and True Rosettes (ETANTR) is a recently recognized rare variant of CNS tumors in children with less than 60 cases being reported. The prognosis is dismal and the rarity of this tumor has precluded development of treatment guidelines. METHODS: Retrospective chart review identified 4 cases of ETANTR since 2006 at our institution. We present their demographics, including radiographical heterogeneity and treatment outcome. RESULTS: The ages ranged from 2 to 6 years. One lesion was in the frontal area with extension into the orbit, 2 presented as pontine tumors and the other as an isolated spinal lesion with recurrences in the same area. All of them had pathological features of ETANTR but one of the pontine lesions had a medulloepithelioma component. Pontine tumors received focal radiation and adjuvant therapy. The fronto-parietal based lesion was treated initially with high dose chemotherapy and on recurrence received radiation with concurrent chemotherapy after surgical debulking. The patient with an isolated spinal lesion at L5 behaved uniquely with short interval local recurrences and proved refractory to surgery, radiation and adjuvant chemotherapy. Children with pontine lesions died within a year of diagnosis, and those with supratentorial and spinal lesions were alive at last follow-up of 11 and 20 months after diagnosis. CONCLUSION: This study describes the first case of an ETANTR presenting as a multiply recurrent isolated spinal lesion and also a rare variant of ETANTR with a medulloepithelioma component. The heterogeneity of this rare entity as seen in this small case series and the elusive biology of these tumors has impeded development of therapeutic guidelines. A comprehensive genomic and proteomic evaluation is now pursued at our institution for such rare tumors, which will hopefully enable to better understand the oncogenic driver molecules and profile targeted therapy against these tumors.

NO-067. ICE AS A SALVAGE THERAPY IN MULTIPLY RECURRENT INTRACRANIAL MALIGNANT GERM CELL TUMOR

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INTRODUCTION: Recurrence of intracranial malignant germ cell tumor (IMGCT) carries a poor prognosis especially those who receive craniospinal radiation (CSI) during their initial treatment. No clear therapeutic guidelines exist with recurrence after salvage with high-dose chemotherapy (HDC) and autologous stem cell rescue (ASCR). Here we describe an 8 year male with multiply recurrent MGCT who continues to respond well with ICE (Ifosfamide, Carboplatin, Etoposide) as a salvage therapy. CASE REPORT: At 6 years of age he presented with two weeks history of headache, and was found to have a large suprasellar mass and elevated alpha-fetoprotein (AFP). A complete resection was

achieved and pathology of the tumor was consistent with a MGCT. He was treated with ICE chemotherapy followed by CSI with a boost to the tumor bed and went into complete remission (CR). 4 months later he developed isolated recurrence at the T4 area with elevated AFP. He underwent HDC followed by ASCR and went into CR. Four months later, recurrence in the T4 area was again noted, for which he underwent therapy with gemcitabine and oxiplatin but continued to progress after 3 cycles. He was then started with ICE chemotherapy and following 2 cycles significant improvement of the tumor with normalization of tumor markers was noted. Clinically he remains unremarkable without any symptoms as he continues to receive this therapy. CONCLUSION: Dismal prognosis and therapeutic challenges remain with recurrences of IMGCT with few molecular targets being identified. Also the optimal HDC regimen as a salvage strategy is unknown. ICE based chemotherapy could be used for early recurrences and might be better tolerated than HDC regimens. The need to evaluate the biology of these relapsed tumors using a combined genomic and proteomic analysis is imperative and being pursued at our institution to profile targeted therapy.

NO-068. A PHASE 1/2 SAFETY AND PRELIMINARY EFFICACY STUDY OF SONIDEGIB (LDE225), A HEDGEHOG PATHWAY INHIBITOR, IN PEDIATRIC AND ADULT PATIENTS WITH RELAPSED OR REFRACTORY MEDULLOBLASTOMA AND OTHER SOLID TUMORS

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Aberrant Hedgehog pathway activation is linked to the pathogenesis of many human cancers, including medulloblastoma. Sonidegib blocks the Hedgehog pathway by selective inhibition of Smoothened, a positive regulator of Hedgehog signaling. Final phase 1 data for sonidegib in children with advanced solid tumors and preliminary phase 2 data in pediatric and adult patients with relapsed/refractory medulloblastoma are presented. Phase 1 dose escalation was performed in children (aged $\geq$ 12 months and $<$ 18 years) according to a Bayesian design starting at 372 mg/m^2 once daily (QD). Fifty-nine patients (38 with medulloblastoma) with a median age of 12 (range 2-17) years were treated in the phase 1 portion. The only dose-limiting toxicity observed was a grade 4 creatine phosphokinase elevation (at 372 mg/m^2). The recommended phase 2 dose was established as 680 mg/m^2. Systemic exposures were consistent with previously reported exposures in adults. In the phase 2 portion, patients ($\geq$ 12 months) with relapsed/refractory medulloblastoma were treated at previously established recommended clinical doses (adults: 800 mg QD; children: 680 mg/m^2). In the phase 2 portion, 12 adult patients with medulloblastoma have been treated. Of 50 medulloblastoma patients treated in both phases, three complete responses (CRs; 372 mg/m^2, 425 mg/m^2, 800 mg QD) and one partial response (PR; 800 mg QD) were observed. Analysis of tumor samples from 37 medulloblastoma patients using the RT-PCR-based five-gene Hedgehog signature assay showed that the patients with CRs and one patient with PR had Hedgehog-activated tumors. One adult and one pediatric patient with Hedgehog-activated tumors had stable and progressive disease, respectively. No responses were observed in the remaining 30 patients who were determined to be Hedgehog-non-activated. One sample was not analyzed due to assay failure. These data show promising efficacy of sonidegib in patients with Hedgehog-activated relapsed/refractory medulloblastoma. The phase 2 study is ongoing.

NO-069. A PHASE 3, MULTICENTER, OPEN-LABEL, RANDOMIZED, CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF ORAL SONIDEGIB (LDE225) VERSUS TEMOZOLOMIDE IN PATIENTS WITH HEDGEHOG PATHWAY-ACTIVATED RELAPSED MEDULLOBLASTOMA

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At present, no standard salvage therapy exists for patients with relapsed medulloblastoma, and the rate of long-term disease control with current therapies is low. Gene expression profiling studies have identified a medulloblastoma subgroup characterized by aberrant activation of the Hedgehog pathway. Sonidegib blocks the Hedgehog pathway by selective inhibition of Smoothened, a positive regulator of Hedgehog signaling. In several phase 1 studies of sonidegib, Hedgehog activation status, as determined by a five-gene Hedgehog signature assay, was associated with durable tumor responses in patients with relapsed medulloblastoma. In this phase 3, multicenter, open-label study (NCT01708174), temozolomide-naive patients with Hedgehog pathway-activated medulloblastoma who have relapsed following standard therapy, including radiotherapy, will be eligible for randomization (2:1; sonidegib:temozolomide) stratified by age ($<$ 18 years versus $\geq$ 18 years). A non-randomized part of the trial allows sonidegib treatment for patients who have had prior therapy with temozolomide or for children ($\leq$ 6 years) who are not candidates for radiotherapy or have declined radiotherapy due to concerns of potential long-term neurocognitive toxicities. For patients randomized to receive temozolomide, an optional one-way crossover to sonidegib will be allowed following documented disease progression. Patients will receive an oral suspension of sonidegib (600 mg for adults, 500 mg/m^2 for children) once daily or temozolomide (150-200 mg/m^2) for 5 sequential days every 4 weeks until documented disease progression, intolerable toxicity, withdrawal of consent, death, or discontinuation for any other reason. The primary endpoint of this study is overall response rate. Secondary endpoints include progression-free survival, duration of response, overall survival, safety, pharmacokinetics, and effects of sonidegib on Hedgehog pathway biomarkers. This study represents an example of the use of predictive biomarkers and the implementation of personalized medicine to accelerate the development of new therapies for childhood cancers.

NO-070. SURVIVAL BENEFIT OF LEVETIRACETAM IN GLIOBLASTOMA TREATMENT: A PROSPECTIVE, SINGLE CENTER, AND SINGLE ARM STUDY

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Although the inhibition O-6-methylguanine-DNA methyltransferase (MGMT) by levetiracetam (LEV) was established in vitro, the survival benefit of LEV has not been studied clinically. This study was performed to assess survival benefit of LEV as a chemo-sensitizer of temozolomide for glioblastoma patients compared with that of other anti-convulsant such as valproic acid (VPA). A total of 38 consecutive patients who underwent concomitant chemoradiotherapy for primary supratentorial glioblastoma and were administered LEV before adjuvant chemotherapy with temozolomide was prospectively collected. Forty-two consecutive patients taking VPA with same disease and chemoradiotherapy protocol were enrolled as a control group. The distributions of gender, age, extended lesion, Karnofsky performance scale (KPS) score, extent of removal and methylation status of MGMT promoter were not different between LEV and control group. The median progression-free and overall survival (PFS and OS) of the LEV group (9.3 months (95% CI, 7.3 – 11.3) and 25.7 months (95% CI, 21.1 – 30.3), respectively) were significant longer than those of the control group (6.5 months (95% CI, 5.6 – 7.4) and 16.4 (11.8 – 21.0), respectively) ($p = 0.019$ and 0.027, respectively). Significant prognostic factors for OS of the all the 80 patients were preoperative KPS score ($p = 0.027$; HR = 0.360), the methylation status of MGMT promoter ($p = 0.002$; HR = 0.203), and LEV ($p = 0.004$; HR = 0.244) in the multivariate analysis. LEV may present survival benefit in glioblastoma patients who receive temozolomide-based chemotherapy compared with other anti-epileptic drug such as VPA. Prospective randomized study is needed.

NO-071. SEIZURE CONTROL IN LOW-GRADE GLIOMA PATIENTS AFTER TREATMENT WITH TEMOZOLOMIDE

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OBJECTIVES: Seizures are a common symptom in low-grade glioma (LGG) patients, negatively influencing quality of life if uncontrolled. Besides antiepileptic drugs (AEDs), various antitumor treatment modalities may contribute to a reduction in seizure frequency. The aim of this study was to determine the effect of temozolomide chemotherapy on seizure frequency and identify factors associated with post-treatment seizure control. METHODS: Adult patients with supratentorial LGG who received chemotherapy with temozolomide as initial treatment or for progressive disease in two hospitals (VUmc Amsterdam; MCH The Hague) between 2002 and 2012 were retrospectively reviewed. RESULTS: One hundred and twenty-six patients were included in this series with a mean follow-up of 30.9 months; 110 (87%) of the 126 patients had at least one seizure before the start of temozolomide therapy. Uncontrolled seizures in the 3 months preceding chemotherapy were present in 68 of 110 (62%) patients with epilepsy. Six months after start of temozolomide 38% had uncontrolled seizures. A $>$ 50% reduction in seizure frequency occurred in 31 of 110 (28%) of the patients; none of these developed early tumor progression within 6 months and in 18 of 31 patients (58%) a seizure reduction after 6 months occurred without an increase or switch in AED use. Five of 110 patients with epilepsy (5%) developed increased seizure frequency after 6 months; 4 of these 5 patients showed early tumor progression. Ninety patients (82%) developed tumor progression during follow-up with a median progression-free survival of 12.0 months. Increased seizure frequency was present in 28 of 90 patients (31%) that developed tumor progression after temozolomide treatment. CONCLUSION: Chemotherapy with temozolomide contributes to an improvement in seizure control in a substantial part of LGG patients. Increased seizure frequency is associated with tumor progression, particularly when developing shortly after the start of temozolomide.

NO-072. VISUAL FIELD DEFECT RELATED TO TEMOZOLOMIDE

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INTRODUCTION: Temozolomide (TMZ), an oral alkylating chemotherapeutic agent, is essential part of the standard treatment of malignant glioma. Toxicity data derived from clinical studies with different dosing regimens of TMZ show an acceptable safety profile with major adverse events including hematologic and gastrointestinal toxicity and increased risk of opportunistic infections. The incidence of late neurocognitive deficits related to TMZ is low. In rare cases visual disturbances have been reported. METHODS: A 54-year old woman underwent resection of a left frontal oligodendroglioma WHO grade II in 1994 and surgery for recurrent tumor in 2012. RESULTS: A diagnosis of oligodendroglioma WHO grade III was made. On the 2nd postoperative day the patient developed right sided visual loss with temporal hemianopia; an immediate cranial MRI showed no space-occupying lesion and no ischemia. 7 months later, following fractionated radiotherapy with concomitant daily TMZ and during adjuvant monthly TMZ thereafter, right visual field defect became concentric within 1 week. Visual evoked potentials (VEP) showed a markedly increased P100 latency mainly on the right side. CSF analysis was normal. Carotid artery stenosis was excluded by extracranial and transcranial Doppler investigation. Follow-up examination 4 months after TMZ discontinuation revealed slight improvement of the ocular symptoms and partial recovery of the VEP abnormalities. A 5 day steroid pulse therapy with prednisolone 1 g daily intravenously was not effective. CONCLUSIONS: This is the first description of visual field deterioration in the context of chemotherapy with TMZ. However, the pathogenetic mechanism remains to be elucidated.

NO-073. LONG TERM FOLLOW UP AFTER THE TREATMENT OF ADULT INTRACRANIAL OR INTRASPINAL PRIMARY PURE GERMINOMA

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We report 16 adult patients with primary pure germinoma from a single institution followed over 2 to 19 years and we performed a retrospective analysis of treatment outcome. METHODS: 14 patients are males and 2 are females. Median age at diagnosis is 22.3 (range 19-40); 13 had a single lesion (10 pineal region, 3 suprasellar, thalamus, or T-spine); and 3 had multifocal lesions; 13 had tissue diagnosis and 3 were diagnosed based on imaging and tumor markers. 12 of 16 patients were treated with radiation alone; 4 were treated with radiation and neo-adjuvant chemotherapy with carboplatin and etoposide. Radiation therapy included 3 WBRT, 7 regional radiation to the tumor, and 6 ventricular radiation followed by boost to the tumor. RESULTS: Median follow-up is 7.5 years (range 2 -19). Two patients were lost follow up after 2 and 15 years. For the other 14, median progression free survival (PFS) is 5.7 years (range 4.5 months to 19 years). All patients are alive. 5-years PFS rate is 70% (7/10). Five of 14 patients had recurrence. At diagnosis, these patients received regional radiation therapy (3) or a combination of conventional radiation (2) to the entire ventricles (3600 cGy) followed by a stereotactic radiotherapy boost to the tumor (1800cGy). There was no recurrence in patients who received WBRT or regional radiation therapy with neo adjuvant chemotherapy. CONCLUSION: Although recurrences are uncommon in our patient series, it seems to occur only in the group of patients who received regional or ventricular radiation plus tumor boost therapy. Although regional radiation therapy is preferable to whole brain radiation therapy for this young population of patient, perhaps combinatory treatments should be considered for more durable effects.

NO-074. PROGNOSTIC VALUE OF MOLECULAR PHENOTYPES IN ANAPLASTIC GLIOMA PATIENTS WITH PROLONGED ADMINISTRATION OF TEMOZOLOMIDE

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BACKGROUND: High grade gliomas have dismal prognosis despite multimodal treatments. We retrospectively investigated the prognostic impact of the histo- molecular phenotypes in adult patients with recurrent anaplastic gliomas who received prolonged administration of Temozolomide. METHODS: In 87 patients who were diagnosed as recurrent anaplastic gliomas between March 2004 and June 2010, fifty eight patients were enrolled in this study. 21 patients had anaplastic oligodendroglioma (AO), 18 patients anaplastic oligoastrocytoma (AOA), 19 patients anaplastic astrocytoma (AA). All patients underwent surgical resection or biopsy and involved-field radiotherapy as primary treatment. At recurrence, patients were treated with 150-200 mg/m2 of TMZ on days 1 through 5 in 28-day cycles until disease progression. We evaluated correlations between 1p/19q deletions, O6-methylguanine DNA methyltransferase (MGMT) promoter methylation, isocitrate dehydrogenase (IDH)-1 genotyping, other clinico- histological findings and treatment outcome. RESULTS: During mean follow-up period of 44.6 months, 33 patients were alive (56.9%). Median survival from recurrence was 39.7 months (95% CI, 22.7-56.7 months). Time to progression from administration of Temozolomide was 6.4 months (95% CI, 5.0-7.8 months). Univariate analysis demonstrated that presence of only IDH1 mutation was closely associated with treatment response (8.4 vs. 3.8 months, $p = 0.015$). Oligodendroglial subtype, 1p/19q deletion status, or MGMT promoter methylation status were not independent variables for determining the treatment outcome of Temozolomide. CONCLUSION: In the recurrent anaplastic gliomas, Temozolomide showed relatively good treatment outcome regardless of MGMT methylation status or histological types. In particular, the presence of IDH1 mutation has more powerful prognostic variable on the response to Temozolomide and survival.

NO-075. GENOME SEQUENCING OF SHH MEDULLOBLASTOMA PREDICTS AGE-DEPENDENT RESPONSE TO SMOOTHENED-INHIBITION AND RATIONAL THERAPEUTIC COMBINATIONS

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PURPOSE: Smoothened (SMO)-inhibitors have recently entered clinical trials for SHH-driven medulloblastoma (SHH-MB). Early evidence suggests that even within this molecularly defined patient subgroup response to therapy is highly variable. To better understand the mechanism(s) of

primary resistance to conventional SMO-inhibitors and identify other pathways cooperating aberrant SHH signaling, we conducted a comprehensive next-generation study of 130 SHH medulloblastomas obtained from patients between 0 and 49 years of age. METHODS: Tumor and blood DNA of 61 SHH-MBs (38 pediatric [<18 years of age] and 23 adult [≥18]) were subjected to whole-genome or whole-exome sequencing. Two independent non-overlapping replication cohorts (43 pediatric and 26 adult) were sequenced for at least ~400 prioritized candidate genes. Gene expression (n = 103), DNA copy number (n = 266), and DNA methylation (n = 109) data complemented this integrative genomics approach. SHH-MB xenograft models with different underlying genotypes were used to evaluate response to SMO inhibition and other drugs. RESULTS: Three age-related subgroups exhibiting highly discriminate genomic profiles were identified. Mutations in the SHH-pathway involved PTCH1 (young children and adults), SUFU (infants, including germline), and SMO (adults). Children (10-17 years) harbored excess downstream MYCN and GLI2 amplifications, and frequent TP53 mutations, often in the germline, all of which were exceedingly rare in infants and adults. Functional assays demonstrated that SHH-MB harboring a PTCH1 mutation was responsive to SMO inhibition, whereas those harboring a MYCN amplification or SUFU mutation were not. CONCLUSIONS: Our data shows that (i) most adults but only half of the pediatric patients with SHH-MB will respond to SMO inhibition as predicted by molecular analysis of the primary tumor, (ii) tumor predisposition (Gorliń s Syndrome in infants and Li-Fraumeni-Syndrome in older children) is highly prevalent in patients with SHH-MB, and (iii) recurrent mutations in additional pathways suggest rational combination therapies including epigenetic modifiers and PI3K/AKT-inhibitors, especially in adults.

NO-076. A CASE REPORT: PRIMARY GLIOBLASTOMA OF THE PINEAL

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OBJECTIVE: To describe a rare case of primary glioblastoma of the pineal. BACKGROUND: While glioblastoma is the most common primary tumor of the CNS, it is rarely implicated as the primary tumor of the pineal. We describe a 69-year-old previously healthy female who was transferred to our facility for management of hydrocephalus. She initially presented to an outside hospital with symptoms of lethargy which quickly progressed to confusion and impaired balance. CT scan of the head at that time revealed enlarged ventricles and a calcified mass in the pineal region. Physical examination on presentation revealed a patient who was slow to respond, right-sided dysmetria on finger to nose and was unable to ambulate. METHODS: Patient underwent an MRI of the brain that revealed a contrast-enhancing lesion in the pineal gland with mass effect upon the cerebral aqueduct with resultant hydrocephalus. Patient subsequently underwent a left frontotemporal burr hole craniostomy for MRI-guided needle biopsy of pineal mass and an endoscopic third ventriculocisternostomy. Patient was started on radiation therapy with adjunctive chemotherapy, temozolomide. After completing radiation therapy the patient will undergo a repeat MRI of the brain. RESULTS: Surgical pathology report revealed positive MGMT methylation and immunohistochemistry and histological features consistent with glioblastoma. Patient's course is ongoing. CONCLUSION: Based on a literature review, since 1972 there have been 19 cases of pineal glioblastoma, including this one. Signs and symptoms of hydrocephalus secondary to cerebral aqueduct obstruction and eye movement impairment are most common presentations. Although imaging modalities such as CT and contrast MRI are important in the initial evaluation, final diagnosis is made on histologic basis. Albeit rare in the pineal region, this case along with others previously described, continues to remind us that glioblastoma should be considered as part of the differential diagnosis when evaluating mass lesions in this location.

NO-077. RASSF3 CANDIDATE TUMOR SUPPRESSOR INDUCES APOPTOSIS AND G1-S CELL CYCLE ARREST VIA p53, AND ITS DEPLETION CONTRIBUTES TO EMT

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Ras-association domain family (RASSF) was reported as tumor suppressor. The smallest member of this family RASSF3 also reported to have tumor suppressive function. RASSF3 renders MMTV/neu transgenic mice resistant to mammary tumor development. According to Cancer Genome Anatomy Project, the expression of RASSF3 was lower in some cancer tissues compared with normal tissues, supporting that RASSF3 also functions as a tumor suppressor, but it remains to be studied how RASSF3 suppresses tumor formation. We have here studied the basal characters of RASSF3. RASSF3 induces apoptosis in HCT116 cells. RASSF3 depletion attenuates UV- and VP16-induced apoptosis. RASSF3-induced apoptosis is decreased in p53-negative HCT116 cells. RASSF3 also induces G1/S arrest in U2OS cells, whereas RASSF3 knockdown promotes cell cycle progression and reduces UV- and VP-16-induced-G1/S arrest. However, in RASSF3- depleted U2OS cells, RASSF3 does not induce G1/S arrest. RASSF3 depletion decreases p53 protein expression, which is recovered by MG132 treatment, but not mRNA expression, suggesting that RASSF3 stabilizes p53 at protein level. RASSF3 depletion impairs DNA repair after UV- and VP-16-induced DNA damage and results in the polyploidy in U2OS cells. RASSF3 depletion decreases E-cadherin in A549 cells and increases fibronectin, vimentin, CTGF and PAI-1 to induce epithelial to mesenchymal transition. RASSF3-depleted A549 cells migrate with the higher motility in the wound healing assay and grow more rapidly in 3D matrigel assay. And the similar findings which supported that RASSF3 functions as a tumor suppressor were obtained in U87MG cells. All these findings indicate that RASSF3 functions as a tumor suppressor by regulating apoptosis and the cell cycle with p53-depedent mechanisms.

NO-078. A RETROSPECTIVE STUDY OF OUTCOMES IN OLDER PATIENTS WITH LOW-GRADE GLIOMAS

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INTRODUCTION: In adults, low-grade gliomas (LGG) are primarily World Health Organization grade II and are less common in older patients than malignant gliomas. As a result, clinical behavior, treatment parameters, and prognostic factors are not well defined. To further evaluate LGG in older adults, we conducted a multi-institution retrospective review assessing patient and tumor characteristics to measure progression-free survival (PFS) and overall survival (OS). METHODS: Northwestern University and The University of Washington databases were queried for patients > 50 years of age with a diagnosis of grade II glioma between the dates of January 1, 2000 and December 2012. Patient medical records were reviewed and data relevant to diagnosis, treatment and outcomes were collected. PFS and OS and with respect to these prognostic factors were calculated. Log-rank test and multivariate proportional hazards models were calculated for multiple tumor characteristics. RESULTS: A total of 36 patients with histopathologic diagnosis of LGG were identified. There were 15 female and 21 male patients with median age of 56 (range 50-84). Of the 36 patients, 9 had contrast enhancement on MRI, 1 had Ip19q co-deletion and 5 had an IDH1 mutation. At five years, 29 patients had disease progression (5 year PFS = 21%, median PFS = 17 months) and 20 patients had died (5 year OS = 44%, median OS = 48 months). From the log-rank test, there was a statistically significant improvement in OS for patients who possessed greater extent of resection and midline shift at diagnosis. There was a trend towards significance in improved OS in those patients with IDH mutation. CONCLUSION: This study demonstrates the aggressive pattern of LGG in older patients. Treatment following surgical resection should be considered; ongoing studies should clarify the most appropriate treatment after surgery (radiation and/or chemotherapy).

NO-079. A PILOT TRIAL EXPLORING THE PREDICTIVE VALUE OF EXCISION REPAIR CROSS COMPLEMENTING 1 (ERCC1) TESTING IN HIGH GRADE GLIOMA (HGG) PATIENTS TREATED WITH CARBOPLATIN AND BEVACIZUMAB

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BACKGROUND: The overexpression of ERCC1 protein is thought to cause resistance to platinum-based chemotherapy by correcting DNA damage. HGG patients with low ERCC1 levels are hypothesized to have increased sensitivity to carboplatin. Carboplatin is sometimes combined with bevacizumab for recurrent HGG management. The usefulness of ERCC1 protein by Immunohistochemistry (IHC) to predict carboplatin sensitivity in patients with glioma is unknown. We examined whether ERCC1 by IHC as performed by Caris diagnostics correlated with progression free survival greater than 4 months in recurrent HGG patients treated with carboplatin and

bevacizumab. METHOD: A pilot retrospective study was conducted in 17 patients with recurrent HGG who were treated with carboplatin and bevacizumab who had also had ERCC1 testing on their paraffin embedded tumor tissue. We examined the correlation between ERCC1 presence and progression free survival ≥ 4 months (4mPFS) on carboplatin and bevacizumab. RESULTS: Six out of 17 patients had low levels of ERCC1 by IHC and 3 of those achieved 4mPFS. Out of the 11 patients with higher levels of ERCC1, 10 reached 4mPFS. A significant association was not found between ERCC1 result and benefit from carboplatin and bevacizumab (Fisher's test, $p = 0.099$). Furthermore, the odds ratio of 0.118 (0.002 to 2.07) for ERCC1 predicting 4mPFS indicates that the presence of ERCC1 leans towards a negative correlation with benefit from carboplatin and bevacizumab. CONCLUSION: Based on a very small sampling of glioma patients, there was no correlation between low ERCC1 level by IHC and progression free interval in HGG patients treated with bevacizumab and carboplatin. These results are similar to a recent study published in NEJM (2013 Mar 21) that showed no correlation between ERCC1 levels and survival in NSCLC treated with cisplatin, despite earlier suggestions that ERCC1 could predict response to platinum-based agents.

NO-080. PHASE II STUDY OF PANOBINOSTAT IN COMBINATION WITH BEVACIZUMAB FOR RECURRENT GLIOBLASTOMA

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BACKGROUND: Bevacizumab is frequently used to treat recurrent GBM, but responses are generally not durable. Panobinostat is a histone deacetylase inhibitor with anti-neoplastic and anti-angiogenic effects in GBM and may work synergistically with bevacizumab. We conducted a multicenter phase II trial of panobinostat in combination with bevacizumab in patients with recurrent GBM. METHODS: Patients with recurrent GBM were treated with oral panobinostat 30 mg three times per week, every other week, in combination with bevacizumab 10 mg/kg every other week. The primary endpoint was PFS6 and the study was powered to discriminate between a 35% and 55% PFS6 rate (85% power at an alpha level of 0.07). A planned interim analysis specified suspension of accrual and careful data review if 12 or more of the first 21 patients accrued to the study progress within 6 months of initiating treatment. RESULTS: At interim analysis, the study did not meet criteria for continued accrual and the study was closed. A total of 24 patients with GBM were accrued prior to study closure. Median age was 53 (range 22-66), median KPS was 85% (60%-100%), and median number of prior recurrences was 1 (range 1-3). PFS6 rate was 30.4% [95% CI 12.4%, 50.7%], median PFS was 5 months [95% CI 3 months, 9 months], and median OS was 9 months [95% CI 6 months, 19 months]. Radiographic responses by RANO criteria included 7 PR (29.2%), 14 SD (58.3%), and 3 PD (12.5%). The most common grade 3 or higher toxicities included hypophosphatemia (12.5%), thrombocytopenia (12.5%), lymphopenia (8.3%), neutropenia (8.3%), and ALT elevation (8.3%). There was one grade 4 CNS hemorrhage (4.2%) and one grade 4 pulmonary embolism (4.2%). CONCLUSIONS: Although reasonably well-tolerated, the addition of panobinostat to bevacizumab in recurrent GBM may not significantly improve PFS6 compared to historical controls of bevacizumab monotherapy.

NO-081. WHO GRADE II MENINGIOMA SURVIVAL AFTER GROSS TOTAL RESECTION: A 23-YEAR SINGLE INSTITUTION EXPERIENCE

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OBJECTIVE: The role of adjuvant radiation in patients with WHO grade II (atypical) meningioma who undergo gross total resection at initial presentation is not clearly defined. This study evaluated the progression free and overall survival of patients with atypical meningioma stratified by adjuvant post-operative radiation versus observation. METHODS: The Mayo Clinic Department of Pathology database utilized to identify adult patients who underwent surgery for newly identified WHO grade II meningioma at Mayo Clinic, Rochester between 1988 and 2011, and had tumor tissue available for review. Clinical and radiographic data were retrospectively reviewed. Overall and progression-free survival were quantified via Kaplan-Meier analysis. RESULTS: A total of 102 patients met study inclusion criteria. Of these, 80 underwent surgeon-defined gross total resection (GTR), 11 near gross total resection, 10 subtotal resection and one had biopsy only. In the GTR group, 17 received post-operative adjuvant external beam radiation while the remaining 63 were observed until progression. The median progression free and overall survival of the entire GTR cohort was 9.7 years and 12.1 years, respectively. The median overall survival for the GTR followed by adjuvant external beam radiation therapy group was 8.6 years versus 12.1 years for the GTR followed by observation group ($p = 0.5192$). The median progression free survival for the GTR followed by adjuvant external beam radiation therapy group was 6.9 years versus 9.7 years for the GTR followed by observation group ($p = 0.6107$). CONCLUSION: This retrospective analysis of the Mayo Clinic, Rochester experience of newly diagnosed atypical meningioma treated with gross total resection offers evidence suggesting that close observation with serial imaging and deferring radiation therapy is non-deleterious to survival outcomes.

NO-082. THE JOURNEY BEGINS: IMPLEMENTATION OF A NOVEL SURVIVORSHIP CARE DELIVERY MODEL AT THE TIME OF DIAGNOSIS FOR PATIENTS WITH A PRIMARY BRAIN TUMOR

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The National Comprehensive Cancer Network states that cancer survivorship begins at time of diagnosis and includes patient, family, caretakers, and friends who are affected by the diagnosis. Despite this, many current models of survivorship care include only patients who have completed treatment. As part of a Midwestern Comprehensive Cancer Center, our neuro-oncology clinic has implemented a novel survivorship care delivery model that includes newly diagnosed primary brain tumor patients via nurse practitioner survivorship visits in coordination with the primary neuro-oncologist. Utilizing a multi-disciplinary approach, the goal of survivorship care is to maximize quality of life and empowerment through (a) early identification and management of symptoms and distress (physical, social, psychological, spiritual), (b) patient education, (c) facilitation of communication among care providers, and (d) navigation of resources. Survivorship visits are scheduled within three weeks of diagnosis, at specific time points in the disease trajectory, and as needed for distress management. Patients complete a validated distress screening questionnaire at regular intervals to measure the most common and distressing concerns which triggers appropriate supportive care referrals. A personalized education notebook provides information regarding diagnosis, treatment modalities, symptom management, and available supportive care services. A calendar is used to track symptoms, medication/chemotherapy schedules, and appointments. A pedometer and "walking challenge" are incorporated to promote general well-being and reduce fatigue. Through the electronic medical record an "After Visit Summary" is generated at the conclusion of each visit which provides an updated, chronological treatment summary. In addition, written summaries are sent to all treatment team members including the primary care provider to promote a partnership of care. Challenges include lack of clinic space and time to accommodate multiple disciplines, distance travelled by patients, and lack of evidence based guidelines. Future considerations include development of clinical practice guidelines, reliable metrics for evaluation, and expanded services for caregivers.

NO-083. OLIGODENDROGLIOMAS AND MIXED OLIGOASTROCYTOMAS HAVE A HIGH INCIDENCE OF PSEUDOPROGRESSION FOLLOWING CHEMORADIOTHERAPY

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INTRODUCTION: Pseudoprogression (PsP) is a common radiologic phenomenon that occurs shortly after gliomas are treated with chemotherapy and radiation. The contrast enhancement that develops—which is thought to be due to a robust inflammatory response to treatment—is challenging to distinguish from early tumor progression and a diagnostic dilemma in neuro-oncology. PsP is known to occur in oligodendroglioma (OG) and oligoastrocytoma (OA), but the frequency with which it occurs has not been well characterized. PATIENTS AND METHODS: A retrospective analysis was

performed on all OG and OA in a database of patients with brain tumors that underwent resection of their tumor since 1998. Eighty-eight cases met inclusion criteria (9 low grade OG, 19 low grade OA, 26 anaplastic OG, and 34 anaplastic OA), and their patient data was analyzed to determine the rate of PsP and early progression. RESULTS: The rate of PsP for the entire cohort was 19% while the rate of early progression was 7%. For low grade gliomas, the rate of PsP was 29% while the rate of early progression was 0%. For anaplastic OG/OA, the rate of PsP was 15% while the rate of early progression was 10%. CONCLUSION: Following therapy, low grade OG/OA develop PsP at a high rate but rarely develop early progression. Anaplastic OG/OA also develop PsP at a high rate but early progression is a common occurrence in these high grade gliomas.

NO-084. IDH1 EXPRESSION CORRELATES WITH INCIDENCE OF PREOPERATIVE SEIZURES IN PATIENTS WITH LOW-GRADE GLIOMAS

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BACKGROUND: The isocitrate dehydrogenase 1 (IDH1) R132H mutation is the most common mutation in low-grade gliomas, and has been reported in 70-80% of WHO grade II gliomas, an incidence similar to that of tumor associated epilepsy (TAE). The IDH1 mutation leads to the accumulation of 2-hydroxyglutarate (2HG), a metabolite, which bears a close structural similarity to glutamate, an excitatory neurotransmitter that has been implicated in the pathogenesis of epilepsy and TAE. We hypothesized that expression of mutated IDH1 may play a role in the pathogenesis of TAE in low grade gliomas. METHODS: Patients with WHO grade II gliomas were analysed for the presence of the IDH1-R132H mutation using immunohistochemistry. The expression of IDH1 mutation was semi-quantified using open-source biological-imaging analysis software. RESULTS: When the expression of cells staining positive for the IDH1-R132H was semi-quantified in 30 consecutive patients with WHO grade II gliomas, the percentage of positive cells was found to be higher in patients with TAE compared to those without (median and IQR: 25.3% (8.6-53.5) vs. 5.2% (0.6-13.4), $p = 0.03$). CONCLUSIONS: Increased expression of the IDH1-R132H mutation was found to correlate with the presence of preoperative seizures in low-grade gliomas.

NO-085. HER2 TARGETED THERAPIES AND LEPTOMENINGEAL DISEASE

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Leptomeningeal disease (LMD) carries a dismal prognosis with limited therapies. We describe two patients with Human Epidermal Growth Factor Receptor 2 (HER2) positive malignant cells in cerebrospinal fluid (CSF) who experienced significant clinical benefit from HER2 targeted treatment. PATIENTS/METHODS: Case 1: 52 year-old woman with HER2 positive metastatic breast cancer who developed brain metastasis (BM) 4 years after diagnosis and LMD 2 years later while on lapatinib. She was treated with intrathecal (IT) and intravenous (IV) trastuzumab and IT topotecan. Case 2: 37 year-old man with HER2 positive, epidermal growth factor receptor (EGFR) wild type lung adenocarcinoma, who developed LMD 6 months after diagnosis. He was treated with lapatinib, IV trastuzumab and IT topotecan. RESULTS: Case 1: BM, CSF and blood showed atypical cells with both HER2neu amplification and heterozygous deletion of EGFR by FISH; CSF revealed atypical cells with amplification of HER2neu in 15/3763 (0.4%) and gains of HER2neu in 56/3763 (1.548%), while 1.1 % cells showed polysomy/monosomy of HER2neu. Concurrently, mononuclear cells in blood displayed similar amplification of HER2neu in 39/3205 (1.2%) of cells consistent with circulating tumor cells (CTCs). Baseline CSF demonstrated malignant cells co-expressing GLUT1, cytokeratin and amplification of HER2neu. Eighteen months from LMD diagnosis there remains a complete radiographic, cytological and molecular response with absence of malignant cells with HER2neu amplification in CSF and blood. Case 2: Baseline CSF and CTCs showed malignant cells with HER2neu amplification. He had a transient clinical and cytological response with treatment. CONCLUSIONS: This is the first reported case with sustained clinical, radiologic and molecular response to IT trastuzumab in HER2 positive breast cancer and LMD. We also report a unique case of HER2 positive lung adenocarcinoma with LMD and response to combination therapy. HER2 targeted therapies should be considered in patients with HER2 positive LMD.

NO-086. THINKING OUTSIDE THE BOX: INTRACTABLE SEIZURES IN THE GLIOMA PATIENT, IS SEIZURE SURGERY THE ANSWER?

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The incidence of seizures in the brain tumor population can be as high as 70%. For most patients, surgery and treatment of the tumor with radiation and/or chemotherapy along with anticonvulsant medication results in good seizure control. However, more than 15% of patients will still have intractable seizures that significantly impair their quality of life. Patients with low grade tumors have the highest incidence of seizures but a better overall prognosis with survival averaging from five to fifteen years. Should we be more aggressive in treating these patients who have a potentially terminal diagnosis? "Tumor" surgery and "seizure" surgery have different approaches and outcomes. Tumor surgery targets the tumor not the seizure focus which often lies outside the boundary of the tumor. In these patients with intractable seizures who are in remission or in need of a second surgery for recurrence, an extensive evaluation in an Epilepsy Monitoring Unit and eventually a second "seizure" surgery may be a reasonable option. A presentation of case studies will be used to further illustrate the process of patient selection and actual patient outcomes.

NO-087. IMPROVEMENT IN VISUAL FIELDS AFTER TREATMENT OF INTRACRANIAL MENINGIOMA WITH BEVACIZUMAB

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BACKGROUND: Meningiomas display variable degrees of vascularity and produce angiogenic factors, including vascular endothelial growth factor (VEGF). Bevacizumab, a humanized monoclonal antibody targeting the VEGF pathway, has been proposed in the treatment of recurrent or progressive meningiomas resistant to standard therapy with resection and radiotherapy. METHODS: We describe a 57 year-old man who presented in 2004 with progressive cognitive difficulties and personality changes. MRI brain showed an extra-axial mass in the left frontotemporal lobe in close proximity to the left optic nerve. He underwent gross total resection. Pathology revealed a WHO Grade I meningioma. Given the location of the tumor, adjuvant therapy was deferred and the patient was monitored with annual MRIs. He had tumor recurrence in 2007 in the resection bed and left sphenoid greater wing, with extension through the left orbital canal. Resection was performed but he continued to progress radiographically, despite treatment with involved-field radiotherapy, two cycles of PTK787, and gamma-knife radiosurgery. In April 2012, he developed worsening vision in his left eye. Humphrey visual field (HVF) testing OS revealed a drop in mean deviation (MD) from -1.83 dB to -16.65 dB compared to November 2011. Previous mild inferior arcuate depression had progressed to involve all but the superior nasal quadrant. The patient was started on biweekly bevacizumab at 10 mg/kg. After three cycles of bevacizumab, he reported improved vision. HVF testing showed significant improvement in MD to -3.70 dB and MRI revealed minimal interval decrease in the size of the meningioma. CONCLUSIONS: This is the first report of bevacizumab producing a meaningful and measurable functional improvement in a patient with recurrent meningioma. This result is encouraging and mimics previously described data confirming positive effects of bevacizumab on hearing in patients with progressive vestibular schwannomas. Further exploration of anti-angiogenic therapies for recurrent or progressive meningioma is warranted.

NO-088. GLIOBLASTOMA AND LEPTOMENINGEAL DISSEMINATION

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OBJECTIVE: To evaluate patients with glioblastoma (GB) treated at MD Anderson Cancer Center who developed leptomeningeal dissemination (LMD) to estimate its incidence and assess the impact of treatment. BACKGROUND: Studies reporting the incidence of LMD in patients with GB are rare; only case reports and small case series have been published. Consequently, there are no established standards of care for these patients. DESIGN/METHODS: Analysis was performed on 591 patients treated on clinical trials for GB from 2006-2012. The diagnosis of LMD was made by either imaging or positive cerebrospinal fluid cytology. A total of 21 patients

were identified (3.6%) and an additional 15 patients with known LMD were further evaluated to determine treatment and outcome. RESULTS: LMD developed in 3.6% of the clinical trial cohort. Median overall survival from the time of LMD diagnosis was 13.5 weeks. Median survival from LMD diagnosis varied by treatment: patients provided palliative care had a median survival of 4.4 weeks (n = 5), radiotherapy alone 9.5 weeks (n = 2), chemotherapy alone 15.5 weeks (n = 16), and chemotherapy plus radiation 23 weeks (n = 10). 1 patient had not started treatment and 2 were lost to follow up. Twelve patients had prior treatment with bevacizumab (33%), however this did not appear to impact survival as the median survival in this group (15 weeks) was equal to patients not receiving prior bevacizumab. CONCLUSIONS: LMD remains an uncommon event in patients with GB. The outcomes after LMD were poor, but patients treated most aggressively with chemotherapy and radiation had the longest median survival following diagnosis of LMD. However, treatment decisions based on patient status may create bias. As with other cancers, improvements in treatments and prolongation of survival may lead to an increased incidence. Given the overall poor outcomes even with aggressive treatment, better therapeutic approaches are needed for GB patients with LMD.

NO-089. LONG-TERM SURVIVAL (OVER 13 YEARS) IN A CHILD WITH RECURRENT DIFFUSE PONTINE GLIOSARCOMA: A CASE REPORT

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Pediatric gliosarcoma (GS) is a rare variant of glioblastoma multiforme. The authors describe the case of an unusual pontine location of GS in a 9-year-old male who was initially diagnosed with low-grade astrocytoma (LGA), successfully controlled for four years. Subsequently his brain tumor transformed into a GS. His prior treatments included: subtotal tumor resection three times, standard radiation therapy, and gamma knife procedure twice. His LGA was treated with a standard chemotherapy regimen of carboplatin and vincristine and his GS with high-dose thiotepa with stem cell rescue and temozolomide. Unfortunately, he developed disseminated disease with more than four lesions including a tumor involving 80% of pons. Upon presentation at our clinic, he had a rapidly progressing disease. He received treatment with antineoplastons (ANP) A10 and AS2-1 for 6 years and 10 months under Special Exception to our phase II protocol BT-22. During his treatment with ANP, his tumor stabilized, then decreased and ultimately did not show any metabolic activity. The patient's response was evaluated by MRI and PET scans. His pathology diagnosis was confirmed by outside pathologists and his response to the treatment was reviewed by outside radiologists. He experienced only a single incidence of serious, but reversible, toxicity from ANP (Grade 4 hypernatremia) and there was no chronic toxicity. His condition gradually improved and currently he complains only of residual neurological deficit from his operations. He achieved a complete response, and his overall and progression-free survival is in excess of 13 years. This report indicates that it is possible to obtain long-term survival of a child with a highly aggressive recurrent GS with diffuse pontine involvement with currently available investigational treatment.

NO-090. TEMSIROLIMUS SUPPRESSES MENINGIOMA GROWTH IN MOUSE MODELS

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In the present study, we evaluated activity of the mTORC1 (mammalian target of rapamycin 1) pathway in meningiomas and mTORC1 inbititors in meningioma cell lines and mouse models. Tissue microarrays containing 53 meningiomas of all WHO grades were stained with antibodies against phosphorylated p70S6K, which is the accepted consensus marker for mTORC1 kinase activity. Moreover, phosphorylation of the second downstream target, 4EBP1, of mTOR and Akt were assessed. In 25 tumors mRNA and protein levels of the above proteins were analyzed. Malignant and syngenous meningioma cell lines differing in merlin expression were used to measure the sensitivity towards mTORC1 inhibitors in methyl-tetrazolium and BrdU-assays. To measure the suitability of temsirolimus in vivo, mice carrying either subcutaneous xenografts of malignant IOMM-Lee meningioma cells or intracranial xenografts of IOMM-Lee or malignant KT21 meningioma cells were treated daily with 20 mg/kg temsirolimus (i.p.), beginning three days after tumor inoculation, and compared to controls. It could be shown that the mTORC1 pathway was active in meningiomas of all WHO grades. All cell lines exhibited a dosage-dependent growth inhibition by temsirolimus and everolimus, slightly diminished by merlin loss. As estimated over three weeks using external measurement via calliper rule, the growth of subcutaneous meningiomas was reduced by about 70% in temsirolimus-treated animals ($p < 0.01$). A nearly identical quantitative reduction of tumor growth occurred in the orthotopic mouse models, as determined by MRI ($p < 0.01$). Reduced tumor volumes after defined time periods were paralleled by a reduced Ki67 mitotic index ($p < 0.05$). A reduction of mTORC1 activity in the treated tumors could be suggested from western blots of the relevant phosphorylated proteins, but was less evident than the tumor-inhibiting effect of temsirolimus. These results suggest that temsirolimus may be a beneficial tool to slow down tumor recurrence after incomplete meningioma resection.

NO-091. DOES TIME TO FIRST PROGRESSION (TTP) IMPACT POST-PROGRESSION SURVIVAL IN GLIOBLASTOMA (GBM) IN THE TEMOZOLOMIDE (TMZ) TREATMENT ERA?

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BACKGROUND: In general, the prognosis of patients (pts) with GBM is poor but also variable. The prognostic impact of TTP on post-progression survival (PPS) in GBM pts receiving concurrent chemoradiotherapy (CRT) and adjuvant TMZ has not been assessed. METHODS: We reviewed outcomes of GBM pts treated at Princess Margaret Cancer Centre, Toronto in the TMZ treatment era. Baseline demographics, treatment received, TTP, and overall survival (OS) were analyzed. RESULTS: 505 adult GBM pts with documented TTP were followed from 01/04-12/11. Median (med) age at diagnosis was 58 years, 303 (60%) were males, 474 (94%) had performance status (PS) 0-2, 404 (80%) had partial/subtotal resection and 385 (76%) received CRT followed by TMZ. Recorded TTP for 214 (42%) pts was ≤6 months (mo), for 233 (46%) pts was 6 to 18 mo and for 58 (12%) pts > 18 mo. For each of these TTP groups, the 2 year PPS was 9.3% (95%CI 5.4-14.6), 9.9% (95%CI 5.9-15.0) and 38.6% (95%CI 21.6-55.3) respectively (Trend test $P < 0.001$) and the 5 year PPS was 3.3% (95%CI 0.9-8.5), non-evaluable and 25.7% (95%CI 9.9-45.1) respectively (Trend test $P < 0.001$). There was significant association of TTP groups with age (ANOVA $P < 0.001$), PS (Fisher's exact test $P < 0.001$), extent of surgery (Fisher's exact test $P < 0.001$), and treatment received (Chi-square test $P < 0.001$). Med OS from diagnosis for TTP at ≤6 mo, 6 to 18 mo, >18 mo was 7.3 mo (95%CI 6.3-8.8), 15.2 mo (95%CI 14.5-16.9) and 50.6 mo (95%CI 36.6-82.4) respectively (Log-rank test $P<0.001$). CONCLUSION: Patients who progress > 18 mo after their initial treatment for GBM had significantly greater 2- and 5-year PPS as well as OS. This is informative for pts, caregivers and health care providers in optimization of care.

NO-092. LUNG ADENOCARCINOMA METASTASIS TO SCALP AND SKULL: CASE REPORT AND LITERATURE REVIEW

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BACKGROUND: Lung adenocarcimoma initially metastasizing to the scalp and skull is a rare entity. We report such a case and review the literture. CASE REPORT: A 61 year old female noticed a small left-sided scalp mass and gradually developed accompanying mild headache. She was neurologically intact. Computerized tomography (CT) of the head revealed a subtle mass in the subcutaneous soft tissues of the left frontal convexity. Magnetic resonance imaging (MRI), performed three months later, demonstrated significant growth of the lesion which now involved both the soft tissue and underlying skull. Dimensions were 1.2 × 4.3 × 3.5 cm. Total body bone scan revealed a metabolically active lesion of the left frontal bone with no other abnormalities. Radiographic differential favored sarcoma, fibrosarcoma, plasmacytoma, and lymphoma. Metastasis was also considered but felt to be less likely. The patient underwent biopsy and subsequent resection of the lesion, followed by cranioplasty. At the time of surgery the lesion had grown through the bone and dura to impinge on the brain. Pathological examination showed a moderately differentiated adenocarcinoma characterized by large irregularly shaped acini embedded in a desmoplastic stroma with a mixed acute and chronic inflammatory infiltrate. Mitotic figures were encountered. The

neoplastic cells were immunopositive for CK 7 and TTF-1 (nuclear), and immunonegative for CK 20, all features in keeping with adenocarcionoma. Mutation of EGFR was not detected. Further body imaging, including CT scanning of the thorax/abdomen/pelvis, revealed a soft tissue mass in the left upper lobe of the lung, with extensive hilar adenopathy, consistent with a lung primary. She underwent radiation therapy and chemotherapy with cisplatin and vinblastine. DISCUSSION: Review of the literature did not reveal other reported cases of lung adenocarcinoma metastatic to scalp and skull. This case will be reviewed in the context of other primary tumors metastatic to scalp and skull.

NO-093. LONG-TERM TOXICITY OF BEVACIZUMAB IN PATIENTS WITH NEUROFIBROMATOSIS 2

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INTRODUCTION: Bevacizumab treatment has been associated with durable tumor shrinkage and hearing improvement in neurofibromatosis 2 (NF2) patients with progressive vestibular schwannomas. While the long-term toxicity of bevacizumab has been studied in cancer patients, the toxicity in this younger population has not yet been documented. In this report, we describe the time course of two common bevacizumab-related toxicities, hypertension and proteinuria, in patients with NF2. METHODS: We reviewed the medical records of all NF2 patients treated with compassionate care bevacizumab at our institution. Hypertension was defined as a systolic blood pressure of $\geq$140 or a diastolic blood pressure $\geq$90 according to JNC 7 guidelines. Proteinuria was measured semi-quantitatively by urine dipstick. Time-to-
event analyses were performed for both hypertension and proteinuria. RESULTS: 33 patients were included in the study (16 men, median age 28 years, range 12-76). The median duration of treatment was 36.6 months (range, 3-66 months). Among 26 patients without baseline high blood pressure, 14 (54%) became newly hypertensive during treatment; the median time to hypertension was 13 months. No patients developed refractory hypertension or required treatment holds for hypertension. Among 29 patients with zero urine protein documented at baseline, 18 (62%) developed 1+ proteinuria and 14/29 (48%) developed 2+ proteinuria. The median time to 1+ proteinuria was 24 months, and median time to 2+ proteinuria was 32 months. 8 patients required treatment holds for proteinuria (median length 3.2 months [range, 1-8 months]). One patient with persistent proteinuria underwent renal biopsy which revealed chronic thrombotic microangiopathy. CONCLUSION: In our cohort of NF2 patients, extended use of bevacizumab was associated with manageable toxicity in the first year of treatment. While on average, hypertension occurred earlier, most toxicity-related drug interruptions were due to proteinuria. Prospective studies of bevacizumab should examine the optimal dosing schedules to minimize long term toxicity.

NO-094. IMMUNOCHEMOTHERAPY WITH RITUXIMAB AND METHOTOREXATE WITH DEFERRED RADIOTHERAPY FOR NEWLY DIAGNOSED PRIMARY CNS LYMPHOMA (PCNSL) IN THE ELDERLY

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BACKGROUND: High-dose methotrexate (HD-MTX)-based chemotherapy with whole brain irradiation (WBRT) improves the prognosis of PCNSL. However, the high neurotoxicity rates observed, especially in the elderly, raised interest in chemotherapy-only treatments. Withholding radiotherapy substantially decreases the risk of neurotoxicity, however, disease control may be compromised. Therefore, developing novel treatment for the elderly patients is crucial. To assess the efficacy and toxicity of induction immunochemotherapy with rituximab (RIT) and HD-MTX, maintenance chemotherapy with HD-MTX and deferred WBRT in the treatment of elderly PCNSL patients, we conducted a retrospective analysis. METHODS: Newly diagnosed elderly PCNSL patients (median age: 74 years) received biweekly RIT/ HD-MTX (375 mg/m^2/dose; 3.5g/m^2/dose) for 6 cycles followed by monthly RIT/MTX for 2 cycles (induction) and then were treated differently according to radiological response. With CR patents, HD-MTX was continued with every 3 months (maintenance) for 2 years. For PD patients, immunochemotherapy was interrupted and WBRT initiated immediately. Patients with PR and SD were treated with alternative chemotherapy with temozolomide and/or stereotactic radiotherapy. RESULTS: Nineteen patients were treated with the RIT/HD-MTX regimen. In 17 patients suitable for radiographic evaluation, 64.7% (11/17) had a CR, 17.6% (3/17) had a PR, and 17.6% (3/17) had a PD. The median PFS was 24.3 months and median OS was 29 months for the entire cohort. Grade III-IV toxicities were observed in 6 of 19 patients and included neutropenia in 10.5%, thrombocytopenia in 5.2%, pneumonia in 10.5%, and elevation of aminotransferases in 5.2%. Patients achieving a CR after induction immunochemotherapy ($n = 13$) had a significantly longer OS (not reached) and PFS (not reached) than patients with less than CR ($n = 6$) (OS: 15.3 months; PFS: 7.8 months) ($P < .01$). CONCLUSIONS: The RIT/HD-MTX regimen and maintenance chemotherapy with HD-MTX seems to play a favorable role (e.g. improvement in PFS) in elderly PCNSL patients with mild toxicity.

NO-095. PROGNOSTIC MARKERS AND SURVIVAL IN A CONTEMPORARY SERIES OF GLIOBLASTOMAS TREATED AT A SINGLE CENTRE

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INTRODUCTION: Combined multimodality treatment of glioblastomas has improved outcomes in the last decade. Improvements in surgical techniques as well as radiochemotherapy has contributed to this. We reviewed our data of consecutive patients treated on a uniform protocol over the last 5 year period. METHODS: 104 consecutive patients with GBMs were analysed. Routine clinical, surgical, radiological and treatment details were recorded. Progression-free and overall survivals were calculated. Univariate and multivariate analysis was performed to assses the role of known prognostic markers as well relation of the tumor to the subventricular zone(SVZ) areas. RESULTS: There were 66 males and 38 females (mean age 55 yrs, median KPS 70). Gross total excision could be achieved in 71.2%. 61.5% had subventricular zone(SVZ) involvement . These tumors were less likely to be gross-totally resected ($p = 0.001$) and more likely to progress ($p = 0.042$). 71.2% completed radiotherapy and 41.4% could complete adjuvant temozolomide. Progression was detected in 57.7%. Median follow up of the survivors was 23.4 months. Median PFS and OAS were 6.9 and 9.9 months respectively. In the radiotherapy group, median OAS was 12.9 months, and this further increased to 19.2 months for those who had received adjuvant temozolomide ($p < 0.001$). Univariate analysis yielded RPA class to be prognostically significant for OAS ($p = 0.001$) as well as PFS ($p = 0.05$). KPS and age were significant for OAS ($p = 0.012$ and 0.007 respectively) but not for PFS. Though not statistically significant, the median OAS and PFS for those with SVZ involvement was much lower as compared to that for those without SVZ involvement [7.8 v/s 12.3 and 6.8 v/s 12 months respectively]. CONCLUSIONS: Multimodality treatment (surgery and chemoradiotherapy) significantly improves outcomes in glioblastomas. Young patients with better KPS and tumors not involving the subventricular zone are likely to do better.

NO-096. GLIOBLASTOMA RECURRENCE: IMPACT OF THE MOLECULAR PROFILE

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GBM is the most frequent primary tumor of the central nervous system. This highly malignant neoplasm remains incurable despite substantial advances in the current therapeutic modalities. When it presents as multifocal disease, median survival is as low as 6 months. This poor outcome is mostly due to high recurrence rates, for which single agent treatment generally proves to be unsuccessful. We report the case of a 58 years old, right handed female. She was diagnosed in October 2009 with a multifocal primary GBM. She presented with three enhancing lesions on MRI and initially underwent subtotal resection of the largest lesion located within the right frontal lobe. Pathological findings revealed the tumor's MGMT gene promoter region to be mainly methylated. The IDH1was not mutated, and the EGFR was amplified. Four months after initial GBM diagnosis, following the completion of adjuvant radiotherapy with concomitant Temozolomide, the patient experienced disease progression while on maintenance TMZ. Subsequently, she was enrolled in a clinical study involving combined treatment with investigational Afatinib and TMZ. Since, her disease has shown significant regression on MRI scans

and has remained stable over 3 years of follow-up. Moreover, the patient's performance status maintained stable with KPS > 90 throughout the course of treatment. This report describes a dramatic and sustained clinical and radiographic response in a patient with a recurrent multifocal GBM. Although pseudoprogression cannot be definitively excluded and that this GBM was not IDH1 mutated, this patient surpassed the overall median survival by 6 folds. Studies are now looking at basing treatment of recurrent GBM on molecular profile. The EGFR amplification of this patient might explain the response to combined treatment with Afatinib and TMZ. We are currently attempting to perform a micro-array gene analysis to better assess the genetic signature associated with this exceptional good response to treatment.

NO-097. MULTIDRUG IMMUNOCHEMOTHERAPY (R-MPV-A) FOR NEWLY DIAGNOSED AND RECURRENT PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS

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BACKGROUND: High-dose methotrexate (HD-MTX) monotherapy, standard chemotherapy for primary CNS lymphoma (PCNSL), achieves CRs at only 20 – 30% despite a high initial response rate, necessitating full dose of whole brain radiotherapy (WBRT) which may cause symptomatic neurotoxicity. We analyzed efficacy of an intensive induction multiagent immunochemotherapy (R-MPV-A; rituximab, HD-MTX, procarbazine, vincristine, and HD-AraC) with reduced dose or deferral of radiotherapy for CR cases. PATIENTS AND METHODS: Among 88 PCNSL patients (age 19 – 79, ave 62; KPS med 60) treated in our institution since 2000, 61 cases treated with HD-MTX monotherapy (M group) were compared with 9 treated with R-MPV (R group). Four patients were also treated with salvage R-MPV at progression. RESULTS: In M group, there were 18% CR, 56% PR and 7% PD as best response; PD rate increased to 35% at the end of HD-MTX cycle before radiotherapy. In contrast, responses to R-MPV were 75% CR and 25% PR; final responses being 75% CR, 12.5% PR, and 12.5% PD. While most patients received post-induction WBRT (56/61 in M and 5/6 cases in R), reduced dose (24Gy) was applied at a higher frequency in R group (8/56 cases in M vs. 3/5 cases in R). In 4 patients treated with R-MPV at recurrence (one patient for two relapses), three treated at the first relapse achieved CR (2) or PR (1), with PFS 6, 6, and >7 months; one at the second relapse had a CR and PFS > 6 month; and one at the forth relapse had SD which lasted for 1 month. CONCLUSIONS: Induction R-MPV-A resulted in high rates of both CR and subsequent reduction of WBRT than HD-MTX monotherapy, suggesting the possibility of improving survival and functional outcomes. Additionally, R-MPV may be active against recurrent PCNSL with a high CR rate and relatively durable remission.

NO-098. CORRELATION BETWEEN GENETIC ALTERATIONS AND CLINICAL PROGNOSIS IN GRADE III GLIOMA

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PURPOSE: Glioma is a CNS tumor resulting from accumulation of genetic alterations. Whole genome analysis clarifying the correlations between genetic abnormalities and clinical features in gliomas may provide a new strategy for determining prognosis and treatment of glioma patients. In this study we analyzed the correlation between some genetic abnormalities and prognosis in the patients with grade III gliomas. PATIENTS AND METHODS: We examined genomic alterations of whole chromosome in 117 grade III gliomas (anaplastic astrocytoma (AA) 35, anaplatic oligo-astrocytoma (AOA) 44, anaplastic oligodendroglioma (AO) 38) using an Snip-microarray and analyzed the correlations between genetic alterations and prognosis. We focused on several genetic alterations such as loss of heterozygosity (LOH) of chromosome 10, 1p, 19q, amplifications sites of PDGFRA, EGFR and LOH of CDKN2B locus on chromosome 9p21, p53 locus on 17p13, RB locus on 13q14. IDH1 mutation was also examined by direct sequencing method. RESULTS: Overall survival and progression-free survival were prolonged in AO patients compared with AOA or AA patients. Both univariate and multivariate analysis statistically showed that PDGFRA amplification and LOH of chromosome 10q and 13q14 were dismal prognosis factor in grade III gliomas. 9p21 (CDKN 2B locus) and 17p13 (p53 locus) LOH are genetic alterations frequently confirmed in grade III gliomas, however, there was no correlation between their LOH status and prognosis. IDH1 mutation was confirmed in 70% of the patients with 1p/19q LOH and 46% of the patients without 1p/19q LOH. There was no difference of prognosis between the group with IDH1 mutation and without IDH1 mutation in the patients with 1p19q LOH. However, it was better prognosis factor in the patients without 1p19q LOH. CONCLUSION: Although there are various genetic alterations, common genetic alterations were observed in grade III gliomas, whole genome analysis was very useful for the prognostic information.

NO-099. INTRACRANIAL GERM CELL TUMOR IN ASSOCIATION WITH MARFAN'S SYNDROME

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BACKGROUND: Intracranial germ cell tumors account for ≤3% of pediatric CNS tumors. We present a case of this rare malignancy in a patient with Marfan's syndrome. OBSERVATION: A 20-year-old right-handed male presented with two weeks of marked gait instability, anxiety, frequent headaches, and difficulty looking upward. His history was notable for Marfan's syndrome, also present in his father and brother. He had met all childhood neurologic developmental milestones appropriately. His medications included citalopram and lorazepam, recently initiated for anxiety. There was no family history of neurologic disease. On physical examination, he appeared Marfanoid. He was alert and fully oriented. His calculation, language and comprehension were intact. He had difficulty spelling 'WORLD' backwards. Pupils were 4-mm, minimally reactive to light, and not reactive on convergence. He had limited up-gaze and conjugate gaze skew on primary and left lateral gaze. Facial strength and sensation were intact. On finger-nose-finger examination there was dysmetria. He demonstrated a positive Romberg sign and marked truncal ataxia. MRI revealed an enhancing 3.3-by-2.5-cm cystic mass in the region of the pineal gland, creating severe hydrocephalus involving the lateral and third ventricles. Biopsy revealed a pineal germinoma with immunohistochemistry positive for OCT 3/4 and SALL4 and negative for PLAP, AFP, and β-HCG. DISCUSSION: The pineal location is the most common site of intracranial germ cell tumors. Hydrocephalus is a common finding with such tumors, as is the Parinaud's syndrome of neuro-ophthalmalogic changes seen in our patient. Ataxia and behavioral changes seen in our patient are rarer manifestations of pineal involvement. On MRI, intracranial germinomas are enhancing and T2-hyperintense. Tumor tissue is essential for histopathologic diagnosis. Treatment consists of radiation therapy, with ongoing trials evaluating the utility of chemotherapy in conjunction. To our knowledge, this is the first report of CNS germinoma in a patient with Marfan's syndrome.

NO-100. AN OPEN-LABEL, MULTI-CENTER, PHASE II STUDY OF PATUPILONE (EPO906), IN THE TREATMENT OF RECURRENT OR PROGRESSIVE BRAIN METASTASES IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

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OBJECTIVE: To evaluate the efficacy of patupilone in NSCLC patients with progressive brain metastases. BACKGROUND: There are limited

chemotherapy options for NSCLC patients with progressive brain metastases. Patupilone is a microtubule targeting cytotoxic agent, known to cross the blood-brain barrier with activity in a phase I/II study of NSCLC patients. DESIGN/METHODS: NSCLC patients, ≥18 years and KPS ≥50, with radiographically-proven brain metastases that had progressed after chemotherapy, surgery and/or radiation were eligible. Patients with extracranial metastases in >3 organ sites including the primary tumor were excluded. Patients received patupilone at a dose of 10mg/m2 intravenously every 3 weeks. A multinomial 2-stage design was used. The primary endpoint was a combination of early progression rate (progression or death within cycle 1 [EPR]), and response rate (progression-free for 3 cycles [RR]). The drug would be considered active if EPR ≤40% and RR ≥20% (alpha = 10%, power 85%). RESULTS: Fifty patients were enrolled; 25 in each stage. Median age was 60 years (range, 33-74), 42% were women. Forty-nine (98%) patients had received prior radiation, 22 (44%) surgery, and 16 (32%) chemotherapy for brain metastases. Median number of cycles delivered was 2 (range 1-13). RR was 36% (95% CI 20-50%), and EPR 26% (95% CI: 10-40%). Mean AUC(0-tau) for Cycles 1 and 3 were 1544 and 1978 ng.h/mL, respectively. The median time to progression was 4.1 months (95% CI, 1.7–6.5mo) and median overall survival was 8.8 months (95% CI, 5.3–12.9mo). The most frequent grade 3–4 adverse events (AE) were diarrhea (24%), hypokalemia (8%), pulmonary embolism (8%), peripheral neuropathy (4%), sepsis (4%), and neutropenia (4%). All patients discontinued the study drug; 31 (62%) for disease progression and 13 (26%) for AE. Thirty-two deaths occurred; 25 from brain metastases. CONCLUSION: Patupilone has activity in NSCLC with brain metastases with a manageable side-effect profile. Study supported by Novartis.

NO-101. THE NEUROLOGIC ASSESSMENT IN NEURO-ONCOLOGY (NANO) SCALE: A TOOL TO ASSESS NEUROLOGIC FUNCTION FOR INTEGRATION IN THE RADIOLOGIC ASSESSMENT IN NEURO-ONCOLOGY (RANO) CRITERIA

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BACKGROUND: The Macdonald criteria and RANO criteria define radiologic parameters to classify therapeutic outcome among malignant glioma patients. While both scales specify that clinical status must be incorporated for overall assessment, neither provides specific parameters to do so. Furthermore, both scales prioritize clinical status over radiology in that response requires at least stable clinical status, while clinical deterioration is sufficient to declare progression. We hypothesized that a standardized metric to measure neurologic function will permit better overall response assessment in neuro-oncology. METHODS: An international group of neuro-oncologists convened bi- weekly for the past year to draft the Neurologic Assessment in Neuro-Oncology (NANO) criteria as an objective and quantifiable metric of neurologic function evaluable during a routine office examination. RESULTS: The NANO scale is a quick, clinician-friendly, and quantifiable evaluation of eight relevant neurologic domains based on direct observation/testing conducted during routine office visits. The score defines criteria for domain-specific and overall scores of response, progression, stable disease and not assessed. A given domain will be scored non-evaluable if it cannot be accurately assessed due to pre-existing conditions, co-morbid events, and/or concurrent medications. CONCLUSION: The NANO criteria aims to provide a more detailed and objective measure of neurologic function than currently exists. These criteria are designed to enable a consistent evaluation of neurologic function which will facilitate comparison across clinical trials and therapeutic interventions. Implementation and validation of these criteria are planned, and future modifications are anticipated for further optimization.

NO-102. PHASE II STUDY OF MONTHLY PASIREOTIDE LAR (SOM230C) FOR RECURRENT OR PROGRESSIVE MENINGIOMA: FINAL RESULTS

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BACKGROUND: No medical therapy for recurrent meningioma has proven effective, yet a subset of these tumors recur after surgery and radiation therapy. A pilot study of sustained-release somatostatin for recurrent meningioma yielded promising results (Chamberlain et al. Neurology, 2007; 69: 969-73). Pasireotide LAR is a long-acting somatostatin analog with higher affinity for most somatostatin receptor subtypes than octreotide. METHODS: This was an open-label phase II trial of monthly pasireotide LAR 60 mg intramuscularly in patients with recurrent or progressive meningioma. Patients were stratified by histology (benign [WHO grade 1] meningiomas compared to atypical [grade 2] and malignant [grade 3] meningiomas). Treatment cycles were 28 days. Restaging MRIs were performed every 3 cycles and response was assessed using Macdonald criteria. RESULTS: Eighteen patients with atypical/malignant meningiomas (arm A) and 16 with benign tumors (arm B) were accrued. Arm A had median age 59 (range 39-74), 8 men (44%), median KPS 80 (range 60-100), 17 (94%) with previous radiation therapy, and 11 (61%) showed high octreotide uptake. Arm B had median age 52 (range 36–81), 9 men (56%), median KPS 90 (range 70-100), 11 (69%) with previous radiation therapy, and 12 (75%) showed high octreotide uptake. There were no radiographic responses. Twelve patients in each group achieved stable disease (Arm A: 67%, Arm B: 75%). In Arm A, PFS6 was 11% and median PFS 15 weeks (95% CI: 8-20). In Arm B, PFS6 was 43% and median PFS 26 weeks (10-67). Toxicity was mild except for grade 3 hyperglycemia in 5 (15%) patients, grade 4 hyperglycemia in 1 (3%) patient, grade 3 amylase in 1 (3%) patient, and grade 3 lipase in 2 (6%) patients. Octreotide uptake did not predict PFS. CONCLUSIONS: Pasireotide LAR has minimal activity in recurrent meningiomas. Other somatostatin agonists may prove more effective.

NO-103. PHASE II TRIAL OF TRIPLE RECEPTOR TYROSINE KINASE RECEPTOR INHIBITOR NINTEDANIB IN RECURRENT HIGH-GRADE GLIOMAS

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BACKGROUND: Bevacizumab is FDA-approved for patients with recurrent GBM. However, the median response duration is only 4 months. Potential mechanisms of resistance include upregulated FGF signaling and increased PDGF-mediated pericyte coverage. Nintedanib is an oral, small-molecule tyrosine kinase inhibitor of PDGFR α/β, FGFR 1/3, and VEGFR 1-3 that may overcome resistance to prior anti-VEGF therapy. METHODS: This was an open-label, phase II trial in adults with first or second recurrence of GBM, stratified by prior bevacizumab. The primary endpoint was PFS6 in the bevacizumab-naive arm (arm A) and PFS3 in the post-bevacizumab arm (arm B). A Simon two-stage design was employed. Up to 10 anaplastic glioma (AG) patients were accrued to each arm in exploratory cohorts. RESULTS: Twenty-two patients enrolled in Arm A and 14 in Arm B. Accrual to both arms was stopped after the first stage due to futility. Arm A included 12 GBMs (55%), 13 patients with one prior regimen (59%), and median age 54 years (range 28–75). Arm B included 10 GBMs (71%), one patient with one prior regimen (7%), and median age 52 years (range 32-70). Median KPS overall was 90 (range 60-100). There were no responses. In Arm A (GBM only), PFS6 was 0%, median PFS 28 days (95% CI: 26–93), and median OS 6.1 months (6.1-7.3). In Arm B (GBM only), PFS3 was 0%,

median PFS 28 days (23–28), and median OS 2.8 months (1.0-6.9). In Arm A (AG only), PFS6 was 0% and median PFS 28 days (27–73). In Arm B (AG only), PFS3 was 0% and median PFS 35.5 days (28–56). Rare grade >3 toxicities included transaminase elevation, hypophosphatemia, hypertension, and abdominal pain. Two participants died during therapy, one from thromboembolism and one from colon perforation. CONCLUSIONS: Nintedanib is not active against recurrent high-grade glioma, regardless of prior bevacizumab therapy.

NO-104. A META-ANALYSIS OF SURVIVAL IN LEPTOMENINGEAL METASTASIS IN MELANOMA, LUNG, AND GASTROINTESTINAL CARCINOMA

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BACKGROUND: Leptomeningeal metastasis (LM) or the seeding of tumor cells to the leptomeninges or CSF occurs in 1-8% of patients with cancer, and is most commonly associated with melanoma, breast and lung carcinoma. The median survival is 4-12 weeks, and has not changed over the past several decades. There are few studies on primary tumor-specific LM survival to help guide treatment decisions. Different cancers have varying pathogenesis, and systemic treatments vary significantly. We postulated that LM also differs based on primary tumor type and likely impacts survival. METHODS: We conducted a meta-analysis of current survival data available on LM from specific carcinomas including lung, gastrointestinal (GI) and melanoma to determine average survival based on primary tumor type, histology and molecular characteristics. Publications on LM from 1/1/07-7/1/12 were identified. 37 studies and 1296 patients were included. RESULTS: We found that there was no significant difference between overall survival of patients with LM from lung (18 weeks; n = 338), GI (11 weeks; n = 65) or melanoma (8 weeks; n = 189) compared to composite mean survival of LM of 17 weeks (n = 1671; p= 0.76, 0.42, 0.17 respectively). In patients with lung cancer, there was a significantly longer survival in case reports compared to retrospective cohort trials (OS = 66 weeks, $p < 0.01$). Additionally, there was a significant effect of lung cancer histology; patients with NSCLC had a significantly longer survival than those with SCLC (NSCLC =19 weeks, SCLC = 8 weeks $p < 0.05$). Patients with known EGFR mutations had a tendency toward improved survival compared to all lung cancer LM (OS = 49 weeks versus 32.2 weeks, p = 0.05). CONCLUSIONS: This data suggests that there may be an effect of histology and EGFR status on survival in lung cancer LM. Prospective trials should report survival in light of histology and molecular characteristics to more clearly examine this possibility, and help guide treatment decisions.

NO-105. CLINICAL AND MOLECULAR CHARACTERISTICS OF NEWLY DIAGNOSED GLIOBLASTOMAS WITH IDH1 MUTATION AND CORRELATION OF IDH1 MUTATIONS WITH PROGNOSIS

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PURPOSE: Isocitrate dehydrogenase (IDH) 1 mutations have been reported to be associated with favorable prognosis in patients with newly diagnosed glioblastomas. However, IDH1 mutations are confounded with other favorable factors, such as younger age, frontal lobe involvement, oligodendroglial component, and MGMT promoter methylation, which may influence the prognosis. The aim of this study was to characterize newly diagnosed glioblastomas with IDH1 mutations (GBM-Mut) clinically and molecularly, and to determine the prognostic impact of IDH1 mutations. PATIENTS AND METHODS: We investigated 135 patients with newly diagnosed glioblastomas treated at National Cancer Center, Tokyo, whose IDH1 status could be assessed by immunohistochemistry. MGMT promoter methylation, p53 mutations, and 1p/19q deletions were analyzed by pyrosequence, direct sequence, and multiplex ligation-dependent probe amplification, respectively. RESULTS: IDH1 mutations were detected in 8 of 135 patients (5.9%). Younger age (40 vs 62 y.o., p = 0.0002), more frequent oligodendroglial component (37.5% vs 5.1%, p = 0.0097) and longer survival time (43.8 vs 16.2 months, p = 0.0081) were significantly correlated with patients with GBM-Mut compared to those with wild-type IDH1 (GBM-Wt). Genetically, 4 GBM-Mut had p53 mutations, and 2 had 1p/19 codeletions. MGMT promoter methylation was detected in 4 of 6 GBM-Mut. Furthermore, on the multivariate analysis of 85 patients who were between 18-70 years-old and initially treated with chemo-radiation therapy, frontal lobe involvement (Hazard ratio (HR) 0.45, p = 0.0054), postoperative KPS (HR 0.37, p = 0.0043), and MGMT promoter methylation (HR 0.28, p = 0.0012) were correlated with longer survival time, but not IDH1 mutations (HR 0. 55, p = 0.38). CONCLUSION: The clinical and molecular features of GBM-Mut may differ from those of GBM-Wt. IDH1 mutations were not independent prognostic factor, due to confounding with other favorable factors in patients with newly diagnosed glioblastomas.

NO-106. PRELIMINARY TRIAL OF MEBENDAZOLE IN PATIENTS WITH RECURRENT HIGH-GRADE GLIOMAS

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OBJECTIVE: Mebendazole is an antiparasitic agent with a well-established side effect and safety record in humans, and has shown preclinical anticancer activity in various types of cancer cells, including glioblastoma. This is a preliminary trial to determine the safety and efficacy of mebendazole for the treatment of recurrent high-grade gliomas. METHODS: Thirteen patients with high-grade gliomas had previously failed standard therapy (surgery followed by adjuvant radiotherapy and temozolomide) and had clear evidence of tumor progression. All patients had received a mebendazole with oral dose of 800 mg/day, combined with cimetidine 800mg/day to increase serum mebendazole concentrations. The primary end point of the study was to determine the safety. Treatment response was evaluated clinically and by MR imaging. RESULTS: Median age was 62 years, and 11 patients with glioblastoma, and 3 with anaplastic astrocytoma. Dose escalations to maximum of 4200 mg/day were applied for 3 GBM patients. No dose-limiting non-CNS toxicity has been encountered. The acute adverse reactions were grades I -II nausea, vomiting, diarrhea, and liver dysfunction, but they were all relieved after symptomatic treatment. The toxicity of more than grade?III was not observed. Of the 13 patients, 10 had received continuously with monthly temozolomide treatments, but 3 had not received any treatments other than mebendazole. Median mebendazole treatment period was 18 weeks. Four had complete response, 3 had stable disease, and 6 had progressive disease. The median time to progression was 16 weeks. CONCLUSION: The preliminary results demonstrate that mebendazole for recurrent high-grade glioma appears to be safe and effective. The further follow-up is required to determine the long-term outcomes.

NO-107. MULTICENTER RANDOMIZED PHASE II TRIAL OF METHOTREXATE AND TEMOZOLOMIDE VERSUS METHOTREXATE, PROCARBAZINE, VINCRISTINE AND CYTARABINE FOR NEWLY-DIAGNOSED PRIMARY CNS LYMPHOMA (PCNSL) IN THE ELDERLY: AN ANOCEF / GOELAMS INTERGROUP STUDY

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BACKGROUND: Elderly PCNSL patients are not candidates for radiotherapy and therefore establishing an optimal methotrexate-based regimen is crucial. This prospective multicenter study conducted in 13 French institutions tested two promising methotrexate-based chemotherapy regimens in elderly PCNSL patients. METHODS: Patients with histologically confirmed newly diagnosed PCNSL (age ≥60, KPS ≥40) were randomized to receive three 28-day cycles of methotrexate ($3.5g/m^2$ D1 and D15) and temozolomide (100-150mg/m2 D1-5 and 15-19) [MT arm] or 3 cycles of methotrexate ($3.5g/m^2$ D1 and D15), procarbazine $100mg/m^2$ (D1-7) and vincristine ($1.4mg/m^2$ D1 and 15), with cytarabine consolidation ($3g/m^2$/d X2d) [MPV-A arm]. Neither arm included radiotherapy; prophylactic G-CSF and corticosteroids (methylprednisolone 60mg/d D1-5) were given to both arms. The primary endpoint was PFS (one-stage Fleming design; $\alpha = 5\%$; $\beta = 10\%$). RESULTS: Accrual has been completed (N = 98 patients

randomized and 95 analyzed (MT: N = 48; MPV-A: N = 47)]. Pre-treatment characteristics were well balanced between the arms (all patients: median age = 72, range 60-85; median KPS= 70, range 40-100). In the MPV-A arm, the CR rate = 62% (vs 45% in MT arm [p = 0.11]), objective response rate = 82% (vs 71%; p = 0.23), median PFS = 9.5m (vs 6.1m; HR = 1.14; 95%CI 0.72-1.81; p = 0.6) and median OS= 31m (vs 13.8m; HR = 1.4; 95%CI 0.84-2.34; p = 0.2). The incidence of grades 3-4 toxicities was 72% in the MPV-A vs 71% in the MT arm. Quality of life evaluation (QLQ-30) showed an improvement in all 6 domains tested over time (P = 0.01-0.0001) with no differences observed between the two arms. Baseline cognitive impairment (MMSE >24 vs ≤24) predicted OS (p = 0.04). CONCLUSIONS: This is the first randomized PCNSL study testing two different methotrexate-based combination regimens. In this elderly population, toxicities and quality of life were similar in both arms, and all efficacy endpoints tended to favor the MPV-A arm. The MPV-A regimen is recommended for further development in PCNSL.

NO-108. TEMOZOLOMIDE FOLLOWED BY HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT (HDC-ASCT) FOR NEWLY DIAGNOSED ANAPLASTIC OLIGODENDROGLIOMA (AO): CAN RADIOTHERAPY BE DEFERRED?

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BACKGROUND: Combined PCV chemotherapy and radiotherapy improves overall survival (OS) in AO, as demonstrated in two randomized trials. However, the role of chemotherapy without radiotherapy remains undefined, and alternative regimens such as temozolomide have not been prospectively tested. We investigated a chemotherapy-only approach in newly-diagnosed AO consisting of temozolomide followed by HDC-ASCT, with the intent of deferring radiotherapy. METHODS: In this multicenter phase II study, patients with newly-diagnosed AO were treated with temozolomide (200mg/m2 X5/28 days) X6 cycles. Patients with a response or stable disease after 6 cycles were offered HDC-ASCT with thiotepa (250mg/m2/d x3) and busulfan (3.2 mg/kg/d X3), then followed radiographically. Primary endpoint was 2y-progression free survival (PFS), N = 40. RESULTS: Accrual has been completed, with 41 patients enrolled. Median age= 44y; median KPS = 90; median baseline MMSE = 30. Tumor 1p/19q co-deletion was present in 32 patients, absent in 7, unknown in 2. Twenty-eight patients completed temozolomide chemotherapy, and 20 eventually received HDC-ASCT. The HDC-ASCT was in general well tolerated, with no toxic deaths. In the intent-to-treat (ITT) population, the median OS was not reached (median follow-up: 37m); estimated ITT 2y-OS = 85%(95% ci 69-94) and 5y-OS = 79%(ci 55-90). The ITT median PFS was not reached; 2y-PFS= 73%(ci 51-86) and 5y-PFS = 51%(ci 26-72). The selected patients who underwent HDC-ASCT survived longer (p = 0.002), with no deaths observed so far, and 2y-PFS = 93% (ci 59-98). Patients with 1p/19q co-deletion were more likely to undergo transplant (p = 0.003) and achieved longer PFS (p = 0.007) and OS (p = 0.008). In the codeleted group: 2y-PFS = 82% (ci 58-93), 5y-PFS = 57% (ci 27-78), and 2y-OS = 5y OS= 96% (ci 76-99). CONCLUSION: This is the first prospective trial testing a chemotherapy-only, temozolomide based treatment for newly-diagnosed AO. Our results suggest this treatment is feasible in 1p/19q codeleted tumors and associated with promising efficacy, with survival results that to date are similar to patients receiving PCV/radiotherapy upfront.

NO-109. CLINICAL AND RADIOGRAPHIC RESPONSE IN A PATIENT WITH BRAIN METASTASIS FROM OVARIAN CANCER TREATED WITH BEVACIZUMAB

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The antiangiogenic agent bevacizumab has shown potential efficacy in the treatment of ovarian cancerr both as first-line and salvage agent in addition to chemotherapy. However, no ongoing trials or reports have been published on its use as treatment for brain metastasis from ovarian cancer. We present the case of a 75 year old female diagnosed with ovarian cancer in 2008. She was treated after surgery with 6 cycles of standard chemotherapy. She remained in remission until May 2010 when she complained of dizziness and was diagnosed to have an enhancing lesion at the right occipital lobe presumed as metastasis; no other masses were found elsewhere. Stereotactic radiosurgery was performed with resolution of the symptom. On December 2010, there was occurrence of left-sided weakness. Neuro-imaging revealed increased in size and vasogenic edema of the right occipital mass. Craniotomy and tumor excision was done with note of clinical improvement. Histologic diagnosis was metastatic adenocarcinoma of ovarian origin. She was followed with interval MRI every 3 months. MRI and MR perfusion studies 10 months later revealed tumor recurrence. Bevacizumab was initiated at 400 mg every 2 weeks for 1 year from January to December 2012. Interval imagings done every 2 months showed sustained complete response. No signs and adverse effects were observed during treatment. However, tumor recurrence was noted 3 months after being off Bevacizumab last March 2013. Bevacizumab was then restarted at a dose of 400 mg every 2 weeks. Presently, the patient remains asymptomatic; follow-up imaging is yet to be done at the time of abstract submission. CONCLUSION: Bevacizumab appears to be a feasible treatment to ovarian metastasis. Further studies are warranted to confirm this potential application.

NO-110. CHLOROQUINE RESPONSE IN GLIOBLASTOMA PATIENTS

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INTRODUCTION: Chloroquine (a pentanediamine used for treating Plasmodium) has been shown to induce apoptosis by activating p53, promoting autophagy and inhibiting the PI3K/AKT pathway in high-grade glioma cell lines. Sotelo et al., demonstrated that adding chloroquine to conventional treatment improved overall survival (OS) in glioblastoma (GB) patients. METHODS: A bidirectional registry was designed to recorded a large series of GB pts (n = 213) treated in various institutions from Colombia throughout the last 5 years. We performed an indirect efficacy analysis considering Chloroquine as a coadjuvant to the platform proposed by Stupp et al. Clinical characteristics and several outcomes as the response rate, progression free survival (PFS) and OS were evaluated. RESULTS: The mean age was 53-yo (SD ± 14.4), 56.8% (n = 121) were male and 68/175 (32%) were placed in RTOG RPA V-VI classes. 67 patients were exposed to chloroquine and it was not used on the rest of the cohort (n = 146). Using Chloroquine did not affect the initial treatment response rate (p = 0.52) but modify positively such outcome in second line (p = 0.006). In the same way Chloroquine did not modify TTP during the first line treatment (p = 0.42). OS was 19.5 months (95%CI 12.5-29.0), outcome that was not modified in favour of the chloroquine-exposed group (17.4 months vs. 20.5 months non-use; p = 0.69). However, in patients with MGMT promoter methylation treated with chloroquine median OS was 20.8-mo (CI95% 17-24) versus 12.7-mo (CI95% 4.6-20) (p = 0.04) for those unmethylated. CONCLUSIONS: Adding chloroquine did not lead to a positive effect on OS in the general population. However, it is worth noting that using this drug significantly modified OS in MGMT+ group and response after introducing bevacizumab. Further good-quality prospective studies are required for defining chloroquine's real value as part of the treatment for GB patients.

NO-111. CONTINUOUS LOW-DOSE TEMOZOLOMIDE (50 MG/MQ 1 WEEK ON/1 WEEK OFF) IN THE TREATMENT OF NEWLY DIAGNOSED LOW GRADE GLIOMAS

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Recent studies have reported an interesting activity of temozolomide chemotherapy with standard schedule in patients affected by LGG of different histology treated in different stage of disease. This phase II study was designed in 2006 to explore the activity of a low dose of temozolomide (50 mg/mq) given for 1 week on and 1 week off for the treatment of newly diagnosed LGG requiring treatment for the presence of negative prognostic factors such as residual tumors after surgery or biopsy, age higher than 40 years, neurological deficits or uncontrolled epilepsy. No previous chemotherapy or signs

of anaplastic progression with enhancing areas at MRI were allowed. Main objectives included evaluation of activity with objective response rate, PFS at 12 and 24 years and toxicity. Fourteen patients were enrolled (6 grade II astrocytomas and 8 oligos or mixed) and 167 cycles of chemo-therapy were delivered (median = 12). 1p-19q co-deletion was present in 9 cases. 14 patients are evaluable for objective response with 4 Minor response (28%) and 10 Stable Disease. 5 patients (38%) presented partial or complete seizures control. 6 patients presented early progression (median PFS = 7 months) and the study was stopped. No haematologic or gastro-toxicity more than grade 1 was reported. After 6 years of follow up we observed 4 deaths in pts without codeletion and IDH1 mutation. 4 patients (all presenting codeletion and IDH1 mutation) are free of progression. Conclusions: continuous administration of a low dose of temozolomide shows interesting activity with objective response, clinical benefit and long term survival in low grade glioma presenting 1p-19q codeletion and IDH1 mutation.

NO-112. MAKING NEOPLASTIC MENINGITIS DIAGNOSABLE – A SIMPLE, VERSATILE, POWERFUL ALTERNATIVE TO CONVENTIONAL TECHNIQUES

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INTRODUCTION: Neoplastic meningitis (NM) is a devastating oncologic complication that remains elusive to diagnose. As systemic treatments improve, NM is becoming an important cause of relapse and death. Three independent diagnostic tools constitute the standard of care for detecting this disease: neuroaxis MRI, CSF cytology and neurologic examination. Though the sensitivity and specificity of each method alone is poor, the three in combination increase the detection rate of NM. We compared this combination of imaging, cytology and examination (ICE) to CellSearch enumeration of tumor cells in the CSF (CSFTCs). METHODS: We compared the clinical triad (ICE), the current "gold" standard, to CSFTC detection in patients with breast cancer and NM: a total of 66 encounters in 13 patients. If any one of imaging, cytology or neurologic examination was suggestive of NM this was defined as a positive result. The modified CellSearch system enumerated malignant cells in the CSF and a standard cut off of >= 5 was used to define the presence of NM. RESULTS: The sensitivity and specificity of CSFTC testing were 82.4% [95%CI 66.5-91.7] and 93.8% [95%CI 80.0-98.3] respectively. The positive likelihood ratio was 13.2 [95%CI 3.4-50.9] and the negative likelihood ratio was 0.19 [95%CI 0.091-0.39]. These likelihood ratios translate into a profound enhancement in diagnostic yield. If the suspicion of NM (pre-test probability) is 50% then the post-test probability with a positive CSFTC test is 93.0% and the post-test probability with a negative CSFTC test is 15.8%. Charges for performing a brain MRI, cytology and a clinic visit total $5260 at our institution. CellSearch testing costs $280 per sample. CONCLUSIONS: CSFTC testing dramatically improves the diagnosis of NM compared with conventional MRI, CSF cytology, and neurologic examination and appears more cost effective. This new technique should allow earlier detection and more accurate monitoring of treatment response.

NO-113. USE OF HIGH-DOSE METHOTREXATE (HD-MTX) IN LEPTOMENINGEAL METASTASIS (LM) IN PATIENTS WITH BREAST CANCER

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INTRODUCTION: LM is a devastating complication of breast cancer, with dismal prognosis. Prior studies suggested that HD-MTX may be effective in patients with brain and leptomeningeal metastases. METHODS: We reviewed patients with breast cancer and LM who received HD-MTX between 01/2000-03/2012. RESULTS: A total of 63 women (median age: 49y, range 40-63) received a median of 2 (range 1-12) HD-MTX treatments. Triple-negative hormonal status was documented in 15 (24%) patients. Her2 was positive in 20 (32%) patients, negative in 35 (55%), unknown in 8 (13%). ER and/or PR were positive in 43 (68%) and unknown in 4 (6%). HD-MTX dose was 3.5 g/m^2 in 56 patients and 2-3 g/m^2 in 7. Forty-five (71%) patients received HD-MTX as first treatment for LM and 18 (29%) as second or later line of treatment, for progression of LM. Thirty-one (49%) received HD-MTX only; 11 (18%) also received intrathecal chemotherapy and 21 (33%) received radiotherapy for palliation prior to initiation of HD-MTX (whole-brain: 6, spinal: 6, both: 9). The median overall survival (medOS) was 3m; 1y-OS = 14% (95%CI 7-24). The median progression-free survival (PFS) was 1.4m; 6m and 12m PFS was 3% (95%CI 4-19) and 3% (95%CI 2-15) respectively. For 45 patients treated at initial LM diagnosis, the medOS = 3.5m (range 0.7-37), with 6 (13%) patients stable for ≥ 6m. Among the 18 patients who received HD-MTX for recurrent LM, the medOS from initiation of HD-MTX was 3m (range 2.6-41), and 5 (28%) were stable ≥ 6m. For the entire group, grades 3-4 hematologic toxicities developed in 11 patients and non-hematologic toxicities in 1. There were no differences in survival according to age, hormonal status and first line vs later line of treatment. CONCLUSION: In this breast cancer population, HD-MTX was well tolerated but no survival benefit was observed in unselected patients.

NO-114. A CASE OF MALIGNANT GEMISTOCYTIC ASTROCYTOMA WITH SYNCHRONOUS GLIOBLASTOMA

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INTRODUTION: Gemistocytic astrocytomas (GA) are typically indolent CNS lesions defined under the WHO classification as grade II neoplasia. The natural course of this disease includes a predilection for malignant transformation and, to date, limited analyses of these tumors have yielded evidence for differential genetic and pathological profiles that may underlie this behavior. We submit here a case of biopsy-proven GA and synchronous GBM. Antedating reviews have speculated an occurrence rate of 2.4% for multi-focal gliomas and rates for histopathologically distinct, multi-centric lesions are exceedingly lower. The contemporary literature is sparse for cases of either that involve GA. PRESENTATION: A fifty-five year old Caucasian male presented with a six-month history of dysphagia followed by weakness and neck pain. Examination revealed a weak gag, quadriparesis, and a C3-4 sensory level. MRI of the brain and spine demonstrated T2 signal changes with white matter in the right frontal lobe, cervico-medullary junction (CMJ), and at C3-4. MRS of the frontal mass demonstrated an elevated choline peak. Infectious, autoimmune, and metastatic workup was negative. SURGICAL INTERVENTION AND PATHOLOGY: This patient underwent stereotactic biopsy of the supratentorial lesion and histological analysis revealed globoid cells. Autopsy confirmed the presence of a frontal GA, WHO grade III, and a WHO grade IV glioma at the CMJ based on high MIB-1 labeling index, necrosis, and microvascular proliferation. CONCLUSION: We propose a case of a synchronous, malignant, multi-centric glioma based on radiographic and pathologic appearance per se as well as lack of demonstration of continuity between these two white matter lesions. However, previous theories have suggested a role for micro-migration of neoplastic cells, and more in depth genetic profiling could help to delineate either similar clonal populations that would indicate a multi-focal lesion in different stages of malignant progression or disparate populations that would espouse our working theory.

NO-115. RETROSPECTIVE STUDY OF USING CARMUSTINE OR LOMUSTINE WITH BEVACIZUMAB IN RECURRENT GLIOBLASTOMA PATIENTS WHO HAVE FAILED PRIOR BEVACIZUMAB

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BACKGROUND: Patients with recurrent glioblastoma have a dismal prognosis. There are no known effective treatments once patients progress on a bevacizumab-containing regimen. We explored the efficacy of adding the alkylating agents lomustine or carmustine to bevacizumab in patients who progressed on an initial bevacizumab-containing regimen. METHODS: In this retrospective study, adult patients with histologically confirmed glioblastoma (W.H.O. grade IV astrocytoma) who were treated with lomustine or carmustine in combination with bevacizumab as a second or third bevacizumab regimen were identified from an institutional pharmacy database. Overall survival (OS) and progression-free survival (PFS) were assessed from time of treatment initiation. The Kaplan-Meier method was used to provide median point estimates and time specific rates. RESULTS: Thirty patients were identified (23 males) with a median age of 48.0 years (range 24-78). The median PFS (mPFS) for patients on their first bevacizumab-containing regimen, explicitly without lomustine or carmustine, was 114 days. Of 30 patients, 17 received lomustine (n = 15) or carmustine (n = 2) with bevacizumab as their second bevacizumab-

containing regimen, and 13 received lomustine (n = 11) or carmustine (n = 2) as their third bevacizumab-containing regimen. The median number of prior failed regimens was 3 (range 2-5). From initiation of a bevacizumab regimen with lomustine or carmustine, the mPFS was 44 days, and the median OS was 100 days. With respect to toxicity, 8 patients (27%) had grade 3-4 thrombocytopenia, 3 patients (10%) had grade 3-4 hypertension, 2 (7%) patients had grade 3 neutropenia, and 1 patient (3%) had grade 3 lymphopenia. Four patients (13%) required treatment termination due to toxicity. CONCLUSION: The addition of lomustine or carmustine to bevacizumab after a patient has already progressed on a bevacizumab-containing regimen does not appear to provide benefit and is associated with additional toxicity.

NO-116. A RETROSPECTIVE REVIEW OF PATIENTS WITH RECURRENT GLIOBLASTOMA (GBM) TREATED WITH BEVACIZUMAB (AVASTIN), LOMUSTINE (CCNU) AND SIROLIMUS (RAPAMUNE)

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Radiotherapy and temozolomide in GBM has prolonged the median overall survival (OS) to 14.6 months but is not curative. Lomustine is an oral nitrosourea alkylating agent. Sirolimus inhibits a protein kinase complex known as mTORC1 (mammalian target of rapamycin) and has antitumor activity in PTEN- deficient glioblastoma patients. Medical records of Bevacizumab-failure recurrent GBM patients who initiated treatment by January 1, 2009 and completed treatment by March 15th 2013 are being evaluated. Group A includes patients treated with Bevacizumab, Lomustine and Sirolimus and Group B includes patients treated with Bevacizumab and Lomustine without Sirolimus. Thus far 600 of the 2000 planned records have been evaluated of which there are 15 patients in Group A and 22 patients in Group B. Bevacizumab dose ranged from 5-10mg/kg every 2 weeks. The dose of CCNU ranged from 67.5-110mg/m2 every 6 weeks and the usual sirolimus dose was 3 mg Monday, Wednesday and Friday. Of 37 patients there are 26 males and 11 females. The median age is 53, median KPS is 80 and the median number of prior chemotherapy failure is 3. The most common adverse events in both group include grade 2–4 fatigue, proteinurea and grade 2–4 thrombocytopenia. One patient developed pulmonary fibrosis after 7 cycles of lomustine and other discontinued treatment after 8 cycles due to liver dysfunction. Fatigue was more prominent in Group- A. Two patients discontinued Sirolimus due to intolerance. The median progression free survival (PFS) for group A is 2.8 months (95% CI: 1.6 to 6.3).The median PFS for group B is 1.8 months (95% CI: 0.8 to 10.03). In heavily pretreated recurrent GBM patients Bevacizumab and Lomustine with or without Sirolimus was safe and tolerable. The median PFS is moderate. Updated results will be presented but Group A seems to have better median PFS.

NO-117. COMBINED IMMUNO-CHEMOTHERAPY FOR PRIMARY CNS LYMPHOMA: A SINGLE INSTITUTION EXPERIENCE

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BACKGROUND: Elderly patients with primary central nervous system lymphoma (PCNSL) are at increased risk of developing delayed neurotoxicities following radiation-containing regimens, such as the DeAngelis regimen. Few studies have evaluated alternative regimens without radiation therapy (RT), and these have shown limited efficacy. This study aims to evaluate the safety and effectiveness of an immuno-chemotherapy regimen as an alternative treatment to methotrexate (MTX)-based regimens with RT for elderly patients. METHODS: This was a retrospective, observational case-series of elderly patients treated for PCNSL at the Cancer Therapy & Research Center in San Antonio, TX from 2008 to 2013. Eligible patients included adults >60 years old with an ICD-9-CM code for PCNSL and treatment with induction rituximab plus MTX, vincristine, and procarbazine (R-MVP) for the first cycle. MVP was given for four more cycles, followed by maintenance temozolomide (TMZ). Patients were evaluated for tolerability, response, and one-year progression free survival (PFS). RESULTS: Eight patients met inclusion criteria. Patients had a median age of 67 years and 50% were male. Median baseline mini-mental status exam was 27 and median prognostic score was 2. Median duration of follow-up was 472 days. Approximately 86% of patients experienced a response following induction (partial response: 75%). Of these, 85% continued to respond throughout maintenance therapy (progression: 14%). One-year PFS approximated 75%. Therapy was well tolerated; three patients required dose-delay or adjustment due to severe adverse effects (e.g., acute renal failure, thrombocytopenia). No neurologic sequelae attributable to therapy were identified in treated patients. CONCLUSIONS: R-MVP followed by maintenance TMZ was well tolerated and effective in older PCNSL patients. Patients demonstrated response rates similar to current methotrexate/RT-based therapies with the majority remaining progression free one year following treatment inititation. Further studies are needed to evaluate the long-term effects of the regimen.

NO-118. PRE-OPERATIVE CHEMOTHERAPY: A NEW OPTION FOR LOW GRADE GLIOMAS IN ELOQUENT AREAS?

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INTRODUCTION: Recent studies suggested total/near total resection to be significantly associated with increased survival in LGGs. This study was aimed at prospectively evaluating whether preoperative chemotherapy with temozolomide can reduce tumor infiltration as detected by Diffusion Tensor MR Imaging (MR-DTI), thus improving surgical resectability. METHODS: Patients with LGG after biopsy or partial resection at previous surgery, who progressed clinically (seizures) and/or radiologically, were treated with one-week on/one-week off temozolomide and monitored every three months with volumetric FLAIR and with MR-DTI. DTI changes were assessed by histogram analysis and Functional Diffusion Maps and compared with volumetry and clinical response. RESULTS: 20 patients with histological diagnosis of LGG were enrolled from 2008 to 2013. 15/20 males, median age 30.5 years, median KPS 90. Tumors were located in fronto-parietal lobes in 13/20 (left in 11, right in 2) with insula involvement in 7/20 (left in 4, right in 3). Indications for chemotherapy were: large residual tumor in 14/20 (seizures in 12/14) and radiological progression in 6/20 (seizures in 2/6). Eighteen of 20 patients are evaluable for response. Median number of cycles was 7 (range 4-12). Response by volumetric FLAIR was: MR in 10/18, SD in 7/18 and PD in 1/18. In all patients significant changes in diffusion patterns were observed after three months ($p < 0.05$). After six months these changes became more significant ($p < 0.01$). Twelve out of 15 patients had a significant reduction of seizure frequency: they had significant improvement on DTI even with volumetric SD. A second surgery was performed after 6 cycles of temozolomide in 10/15 and near-total resection was obtained in 5/15 (33%). CONCLUSION: This preliminary analysis shows that preoperative chemotherapy can allow a total/near-total resection at second surgery in a subset of patients. DTI changes may be an early signature for response, correlating with clinical response better than conventional MRI.

NO-119. SAFETY RESULTS FROM AVAglio, A PHASE III RANDOMIZED STUDY OF BEVACIZUMAB (BEV) PLUS STANDARD COMBINATION TEMOZOLOMIDE (TMZ) AND RADIOTHERAPY (RT) IN NEWLY DIAGNOSED GLIOBLASTOMA (GBM)

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INTRODUCTION: In the AVAglio study, BEV significantly prolonged PFS and positively impacted measures of clinical benefit in patients with newly diagnosed glioblastoma. Here we report the incidence of adverse events of special interest (AESIs; on-target, class-specific BEV toxicities): arterial thrombotic events (ATEs), wound healing complications (WHC), cerebral hemorrhage, and gastrointestinal perforations (GIP). METHODS: Patients with histologically confirmed glioblastoma received TMZ ($75mg/m^2/d$) + RT (2Gy, 5d/wk) + placebo or BEV (10mg/kg, q2w) x6 wks, 28 treatment-free days, maintenance TMZ ($150–200mg/m^2/d$, d1-5, q4w), placebo or BEV

(10mg/kg, q2w) x6 cycles, then single-agent placebo or BEV (15mg/kg, q3w) until progression/unacceptable toxicity. AEs and AESIs for BEV were monitored for ≤90 days and ≤6 months after last treatment dose, respectively. RESULTS: Overall incidences of AESIs (all grades) were increased with BEV versus placebo (72.6% [28.7% grade ≥3; 7 patients grade 5] vs 44.3% [15.2% grade ≥3; 3 patients grade 5]). ATEs were increased with BEV (5.0% [4.1% grade ≥3]) versus placebo (1.6% [1.3% grade ≥3]). While 42% (8/19) of the grade ≥3 ATEs with BEV occurred in patients ≥65 years, all grade ≥3 ATEs with placebo occurred in patients <65 years. Most ATEs were classified as stroke events: 16/23 (BEV) versus 6/7 (placebo). Cerebral hemorrhage rates were similar (2.6% BEV vs 2.2% placebo); WHCs were more frequent with BEV than placebo (3.7% [1.5% grade ≥3] vs 2.2% [0.7% grade ≥3]). All grade ≥3 WHCs were related to the craniotomy site and most resolved with treatment. GIP was reported for 1.7% (BEV) and 0.2% (placebo) of patients, and included one fatal large intestine perforation (BEV). CONCLUSIONS: Addition of BEV to RT/TMZ achieved a significant PFS benefit and was well tolerated, with expected and manageable, on-target, class-specific toxicities. There was a small increase in fatal complications that did not offset the clinical benefit achieved.

NO-120. NEOADJUVANT CHEMOTHERAPY AND STAGED REMOVAL OF CHEMOSENSITIVE GLIOMA BASED ON PREOPERATIVE MOLECULAR DIAGNOSIS BY IMAGING CHARACTERISTICS

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INTRODUCTION: Neoadjuvant chemotherapy (NAC) is the common treatment strategy in many cancers. Tumor removal following reduction of the tumor volume by NAC could provide greater chance of complete removal and better functional sequela. If chemosensitivity of tumor is predicted by imaging characteristics, neoadjuvant approach could be designed preoperatively. METHOD: We analyzed 55 gliomas of WHO grade 2-3 resected at Fujita Health University from 2001 to 2013 to see if any correlation between genetic characteristics (IDH1 mutaion, 1p19q codeletion) and imaging (CT, MRI) feature (calcification, gray matter involvement, surface localization, contrast enhancement). RESULTS: Tumor calcification was observed in 58.3% of codeleted gliomas and 6.5% of non-codeleted tumors, gray matter involvement (GMI) in 95.8% of codeleted and 48.4% of non-codeleted, surface localization (SL) in 79.2% of codeleted and 19.4% of non-codeleted, contrast enhancement in 25% of codeleted and 54.8% in non-codeleted. Presence of calcification, GMI, and SL were significantly correlated with 1p19q codeletion. CASE STUDY: A 44 year-old man presented with seizure, and showed a large tumorous lesion in the right medial frontal lobe. There was calcification on CT, and GMI/SL was confirmed on MRI, and those preoperative imaging characteristics suggested chemosensitivity of the tumor. The posterior margin of the tumor was bordered by the pyramidal tract. To reduce the risk of injuring the motor fibers, partial removal was intentionally performed after discussion of the potential benefit and risk of surgery as well as the neoadjuvant approach. The tumor showed 1p19q codeletion, and the second-look, total removal was performed after tumor shrinkage by neoadjuvant temozolomide. CONCLUSION: Preoperative molecular diagnosis based on imaging characteristics renders a designed, staged removal of chemosensitive gliomas. This new strategy might be beneficial in some portion of those tumors, since it could reduce the risk of surgery and might provide greater chance of complete removal.

NO-121. HIGH-DOSE METHOTREXATE FOR METASTATIC BREAST CANCER TO THE CENTRAL NERVOUS SYSTEM

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INTRODUCTION: The prognosis for patients with metastatic breast cancer to the brain or leptomeninges is poor. Methotrexate (MTX) is an active agent in the treatment of breast cancer & penetrates the central nervous system (CNS) at high doses and rapid rate of infusion. METHODS: We performed an IRB approved retrospective review of patients treated with CNS metastases from breast cancer treated at Northwestern between 8/1/2003 and 6/30/2011. Demographic data collected included date of breast cancer diagnosis, time to CNS metastases, Karnofsky performance status (KPS), HER-2 and hormone receptor status, radiographic response to MTX, progression-free survival (PFS) & overall survival (OS). RESULTS: 33 patients met criteria for inclusion. All patients were women with a median age of 48. Median number of doses administered was 4 (range 1-10) and dose was 3.5 gm/m^2. Median PFS and OS were 3.4 months (m) and 4.1 m. When evaluating for correlative factors, patients with KPS ≥ 70 had a PFS and OS of 4 m and 7.7 m. Those with KPS < 70 had a median PFS & OS of 1.3 m. Patients with ER/PR negative disease had median PFS/OS of 4.1 m/6.2 m (Her2−) and 4.0 m/8.9m (Her2+) and ER/PR positive disease had median PFS /OS of 3.4 m/4.3 m (Her2−) and 3.4 m/3.6 m (Her2+). Response rates were: 1 complete response, 3 partial responses, & 12 stable disease. 9 patients had disease progression. Most common toxicities were anemia (33%), hypokalemia (27%), mucositis (18%) & thrombocytopenia (12%). CONCLUSION: HD-MTX, while a treatment option, has limited activity in CNS metastasis from breast cancer. Patients that were ER/PR negative trended towards better PFS & OS. Patients with KPS < 70 may not warrant treatment given short survival.

NO-122. TREATMENT OF MALIGNANT GLIOMAS WITH AN ENERGY RESTRICTED KETOGENIC DIET: CASE REPORT AND LITERATURE SUMMARY

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INTRODUCTION: Based on animal models and several case reports, ketogenic diet (KD) has been proposed as an alternative therapy for treatment of malignant glioma.. This report documents our experience with an IRB approved, Clinical Trials registered (#NCTO1535911) treatment protocol to evaluate a calorie restricted ketogenic diet (CRKD) protocol as a single modality treatment for patients with progressive glioblastoma multiforme (GBM). METHODS: RKD with Ketocal® at 20-25 Cal/Kg was initiated during hospitalization where blood glucose and ketone levels could be monitored during AM and PM. RESULTS: A 55 year-old man with recurrent GBM following standard therapy was enrolled in this CRKD trial. Initial treatment with Ketocal® decreased his PM blood glucose to <80mg/dl, and increased his PM ketones to >3mM (our protocol's target concentrations). However, his AM glucose was still >80mg/dl and his AM ketones decreased to <3mM. Because of the low palatability of the Ketocal®, the patient was switched within the first week out of the hospital to a ketogenic regular food diet with a 3:1 ratio of fat to proteins and carbohydrates. His PM ketones remained > 3mM but his AM ketones were <3mM. However, his AM and PM glucose increased to > 80mg/dl. After 4 weeks of the CRKD treatment, the patient's disease progressed and he withdrew from the study. DISCUSSION: Most of the glioma patients treated with KD reported previously could not consistently maintain blood glucose below 80mg/dl. In most of these patients the CRKD was combined with one of the standard treatment modalities. At least 2 patients were in CR while others had documented disease progression after stopping the CRKD. CONCLUSION: The mixed results for CRKD in patients with malignant gliomas support the need for further evaluation of CRKD as a treatment modality for malignant gliomas.

NO-123. STUDY OF CHROMOSOME 9q GAIN, NOTCH PATHWAY REGULATORS AND TENASCIN-C IN EPENDYMOMAS

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BACKGROUND: Ependymomas are relatively uncommon tumours of the central nervous system, which arise from the ependymal lining of the ventricles and spinal canal. The molecular changes leading to ependymal oncogenesis are not completely understood. We examined chromosome 9q33-34 gain, potential oncogenes at this locus (Notch-1 & Tenascin-C) and Notch pathway target genes (Hes-1, Hey-2 & C-myc) in ependymomas by Fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC), respectively, to assess if they have any correlation with clinical characteristics. MATERIALS AND METHODS: 50 cases of ependymoma were retrieved and clinicopathological data obtained. FISH for 9q gain and IHC for Notch-1, its target gene protein (Hes-1, Hey-2 and C-myc) expression, and Tenascin-C (TN-C) was performed. Results obtained were correlated with clinicopathological parameters. RESULTS: FISH study revealed significant chromosome 9q gain in ependymomas of adult onset (age >18 years) and spinal cord origin. Notch-1 showed significantly more frequent immunohistochemical expression in supratentorial and anaplastic ependymomas. TN-C expression was

significant in intracranial, childhood (age <18 years) and anaplastic ependymomas. Out of three Notch pathway target gene proteins (Hes-1, Hey-2 and C-myc), Hes-1 and C-myc expression showed a significant correlation with anaplastic and adult onset ependymomas, respectively. CONCLUSIONS: Different pathogenetic mechanisms are involved in ependymomas in adults and children, and also in tumors located at different sites. Newer targeted therapies should therefore be developed keeping these clinicopathological subgroups in mind. As Notch -1 and TN-C immunoexpression correlates with higher tumor grade, these markers may be utilized as adjuncts in diagnosis, and to help predict aggressiveness in ependymomas.

NO-124. PREDICTION OF PRIMARY GLIOBLASTOMA RECURRENCE BY CLINICAL AND MOLECULAR FACTORS

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Recurrence of glioblastoma is almost unavoidable. Therefore, the ability to predict the recurrence pattern and timing would be highly useful for understanding their malignant clinical course. However, there are few studies on such clinical and molecular factors. Here, we conducted a retrospective study to identify factors associated with glioblastoma recurrence. We analyzed clinical (age, sex, KPS, Ki67 labeling index, extent of resection, ventricular entry) and genetic (IDH1, 7p, 9p, 10q, MGMT and CD133 expression) factors for correlation with the pattern (either distant or local recurrence) and the timing of initial recurrence. 112 patients of primary glioblastoma were investigated, and of them 99 suffered recurrence. The pattern of recurrence was distant in 22 patients and local in 77 patients. Factors to predict the pattern of recurrence, CD133 expression was significantly higher and 9p homozygous deletion was significantly frequent in distant than in local recurrence ($p = 0.0002$ and 0.045, respectivly). Next, factors to predict the timing of recurrence, high CD133 expression, high Ki67LI, and 9p homozygous deletion were associated with shorter time to distant recurrence (TTD), whereas low CD133 expression and total resection were with shorter time to local recurrence (TTL). In multivariate analyses, high CD133 expression remained as independent poor prognostic factor of TTD (Hazard ratio HR 2.9, 95% CI 1.1-7.8, $P = 0.038$). In conclusion, among factors analyzed, the expression of CD133 may be a predictor of the pattern and timing of primary glioblastoma recurrence.

NO-125. COMBINATION OF BEVACIZUMAB AND EVEROLIMUS IN PATIENTS WITH REFRACTORY, PROGRESSIVE INTRACRANIAL MENINGIOMA: UPDATED RESULTS FROM A PHASE II TRIAL OF THE SARAH CANNON RESEARCH INSTITUTE

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BACKGROUND: High levels of VEGF correlating with increased peritumoral edema and increased levels of pAkt expression are reported in meningioma patients. Mouse models predict inhibition of growth with mTORC1 inhibitors by abrogating the PI3K/AKT pathway. Everolimus, an mTORC1 inhibitor in combination with bevacizumab has demonstrated activity in kidney cancer and in GBM. This phase 2 multicenter study evaluated the combination of everolimus and bevacizumab in patients with refractory meningioma. METHODS: Adults with recurrent meningioma (WHO grade 1-3) following standard treatments with surgical resection (if possible) and radiation therapy, received everolimus 10 mg PO daily and bevacizumab 10 mg/kg IV on Days 1 and 15 of 28-day cycles. Patients were evaluated for response after every 2 cycles of treatment; patients continued treatment until radiographic or symptomatic progression. RESULTS: 18 patients were enrolled from 1/2010 to 1/2012; this analysis includes 17 patients. The median age was 59 years (range 29-84). 24% of patients had grade I meningioma, 41% grade II, 24% grade III and grade was unknown in 2 patients. Median number of cycles was 8 (range 1-28); 2 patients (12%) remain on treatment. Stable disease was the best response in 88% of the patients. A significant number of these patients had experienced progressive disease prior to starting treatment. Common reasons for discontinuation included: disease progression, 6 (35%); toxicity, 2 (12%); intercurrent illness, 2 (12%); patient request, 2 (12%). Median PFS was 22 months (95% CI 4.5 - 26.8 months) and was similar for patients with WHO grade I vs grade II and III tumors (17.5 vs 22.0 months). Hematological toxicity was rare; the common non-hematologic toxicities of any grade were hypercholesterolemia, mucositis, and fatigue. CONCLUSIONS: The combination of everolimus and bevacizumab was tolerable, and 15 patients (88%) had stable disease for durations of 2-28 months. Follow-up is continuing.

NO-126. ANAPLASTIC LYMPHOMA KINASE (ALK) POSITIVE CENTRAL NERVOUS SYSTEM (CNS) METASTASES FROM NON SMALL CELL LUNG CANCER (NSCLC)

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The ALK-EML4 rearrangement in NSCLC creates a recognized oncogenic driver with high response rates to the tyrosine kinase inhibitor (TKI) crizotinib. The characteristics of CNS metastases and their response to crizotinib in ALK-rearranged NCSLC is unknown. We reviewed NSCLC patients with florescence in-situ hybridization (FISH) positive ALK rearrangement and CNS metastases at Memorial Sloan-Kettering Cancer Center. 29 patients (11 men, 38%) were identified, with a median age at initial CNS diagnosis of 50 (range 25-80). Brain metastases developed a median of 11 months (IQR 0.3-22) after NSCLC diagnosis, and were present at the initial cancer diagnosis in 10 (34%). 10 patients (34%) had >4 brain lesions at initial CNS diagnosis. Median initial Karnofsky Performance Scale (KPS) score at diagnosis of brain metastases was 80% (range 60-100). Leptomeningeal metastases developed following brain metastases in 6 patients (21%), at a median of 27 (range 20-82) months from cancer diagnosis. Initial CNS-directed treatment included chemotherapy in 10 (34%), radiation followed by chemotherapy or TKI in 10 (34%), radiation only in 5 (17%), surgery followed by chemotherapy or radiation in 3 (10%), and palliative care in 1. Median time to CNS progression from initial CNS therapy was 7.2 months (IQR 5.8-29.8mo). With a median follow-up of 17 months, median OS from diagnosis of brain metastases and leptomeningeal disease were 38 months and 105 days, respectively. In 17 patients who received crizotinib after diagnosis of CNS disease, partial response (PR), stable disease and progression were noted in 7 (41%), 5 (29%) and 5 respectively; however only 2 patients with PR received crizotinib without closely sequential chemotherapy or radiation. Median CNS PFS from crizotinib initiation in the 17 evaluable patients was 5.8 months (IQR 3.7-9.7mo). Survival with brain metastasis in ALK-rearranged NSCLC may be prolonged with selected therapy, and crizotinib may have therapeutic activity.

NO-127. CLINICAL ASPECTS OF TUMOR- VERSUS NON-TUMOR-RELATED STATUS EPILEPTICUS: A RETROSPECTIVE COHORT STUDY

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OBJECTIVE: Status epilepticus (SE) is a neurological emergency with substantial morbidity and mortality. Clinical observations suggest that SE due to a brain tumor is associated with increased severity and sequelae compared to SE due to other causes. We studied the association between the cause of SE (brain tumor versus other causes) on the one hand and duration of SE, duration of postictal signs, irreversible morbidity and mortality on the other. METHODS: Observational retrospective single-center cohort study of 94 consecutive adult patients with SE. The primary outcome measures were the duration of the SE and the occurrence and duration of postictal neurological deficit. Secondary outcome measures were SE-associated long-term morbidity and mortality. We analyzed the relationship between cause of SE and the outcome measures by means of Poisson regression. RESULTS: We found that tumor-related SE ($n = 50$) was associated with a higher risk than non-tumor related SE ($n = 44$) for postictal neurological deficit (adjusted risk ratio (ARR) 2.00; 95% confidence interval (CI), 1.22 to 3.28), duration of postictal signs beyond 24 hours (ARR 2.67; 95% CI, 1.19 to 6.01) and of irreversible sequelae after SE (ARR 3.97; 95% CI 1.42 to 11.01). Overall

SE-associated mortality was low (4%) and was comparable for the two groups. CONCLUSIONS: In comparison to SE by other causes, tumor-related SE is associated with more and longer postictal neurological deficits as well as more frequent irreversible sequelae. The relationship between characteristics of SE and the occurrence of tumor progression will be discussed. Future studies should focus on whether patients with tumor-related SE may benefit from a specific therapeutic approach.

NO-128. THE ROLE OF NATURAL KILLER (NK) CELLS IN PREDICTING PSEUDO-PROGRESSION (PsdPG) VS TRUE PROGRESSION (TP) IN HIGH-GRADE GLIOMAS

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BACKGROUND: PsdPg is the phenomenon of increased contrast enhancement, increased perfusion and high choline/creatine ratio seen in patients with high-grade glioma, after treatment with radiation/temozolomide. It occurs in 10-31% of patients and resolves 3-6 months after radiation. It is difficult to distinguish it radiographically from TP. PsdPg may be linked to a more effective anti-tumor response. Levels of circulating CD56 + NK cells, which are important mediators of anti-tumor immunity, may provide a useful surrogate marker for disease activity. METHODS: We recently reported a trial where a high rate of pseudo-progression was seen (Jeyapalan, AJCO 2013). Ten of these patients had T-cell panels monitored weekly during concurrent chemo-radiation and then twice a month during adjuvant treatment with temozolomide. We identified two groups of patients: PsdPg only (4) and PsdPg followed by TP (6). RESULTS: In the group with PsdPg only, the percentage of CD56+ NK cells increased by 2-3 fold (median 2.6, range 1.4-21.4) approximately one month before detection of PsdPg by imaging and then decreased with resolution of PsdPg. In the second group, CD56+ NK levels increased by two-fold (median 1.89, range, 1.2-3.4), also prior to radiographic detection of PsdPg. Prior to development of TP on imaging, CD56 + NK levels increased threefold (median 2.9, range 1.8-6.5), continuing to remain high until death. The difference in the increased median levels of CD56 + NK cells in the second group, from PsdPg to TP, was not statistically significant ($p = 0.106$, paired t-test). CONCLUSIONS: CD56 + NK cells may be a promising early predictor of both PsdPG and TP. Stable or decreasing CD56 + NK levels, on longitudinal blood tests, may provide a better indicator of PsdPG vs. TP than radiographic data. There was a trend to significance of CD56 + NK cells being higher in TP vs. PSDPG. We are now validating this data in a larger patient population.

NO-129. DYNAMIC ^{18}FET-PET IDENTIFIES PATIENTS AT RISK FOR MALIGNANT TRANSFORMATION IN NEWLY DIAGNOSED LOW GRADE ASTROCYTOMAS

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PURPOSE: The clinical course of gliomas WHO grade II (low grade gliomas, LGG) varies considerably depending on the histological subtype, biomarkers, patient's age and tumor location. In order to identify further imaging factors which might be associated with outcome, we investigated the value of dynamic ^{18}FET-PET in newly diagnosed LGG. METHODS: 83 patients with newly diagnosed LGG and dynamic FET-PET prior to histopathological assessment were retrospectively investigated. FET-PET analysis comprised a qualitative visual classification of lesions (FET-negative vs. FET-positive), the assessment of semi-quantitative parameters (maximal and mean tumor uptake, biological tumor volume) and a kinetic analysis (increasing vs. decreasing time-activity-curve (TAC)). PET parameters were correlated with progression-free and overall survival (PFS and OS) and with time to malignant transformation (TTM). RESULTS: Histopathological analyses revealed 59 astrocytomas WHO II and 24 oligodendroglial LGG WHO II. During follow-up (median time 37 months), 32/83 patients experienced tumor progression, of whom 20 presented with malignant transformation. Median PFS was 39.2 months, median TTP was not yet reached (mean 58.2 months). None of the semiquantitative parameters was associated with the clinical outcome; FET-negative LGG did not have a better prognosis than FET-positive gliomas. In contrast, patients with a decreasing TAC had a significantly shorter PFS and TTM in astrocytomas ($p \leq 0.001$), but not in oligodendrogliomas. CONCLUSIONS: FET-negative LGG should not be considered as slowly growing gliomas with low metabolic activity. Decreasing TAC was shown to be associated with an unfavourable prognosis in astrocytomas WHO II. Thus, dynamic acquisition of ^{18}FET-PET might help to identify more aggressive tumors in order to optimize a personalized treatment.

NO-130. IDENTIFICATION AND QUANTIFICATION OF CSF MALIGNANT CELLS BY THE CELLSEARCH TECHNOLOGY IN PATIENTS WITH LUNG CANCER LEPTOMENINGEAL METASTASIS

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BACKGROUND: Lung cancer is the second cause of leptomeningeal metastases (LM), representing the evolution of about 5% of lung neoplasms. The diagnosis can be obtained with the detection of malignant cells in cerebrospinal fluid (CSF) or concomitant suggestive neurological symptoms and gadolinium-enhanced MRI signs but both lack effectiveness. We adapted the CellSearch VERIDEX technique (CS), already used in detection of circulating tumor cells (CTCs) in blood, in order to detect and enumerate malignant cells in CSF (CTCSFs) of patients with lung cancer and suspicion of LM. METHODS: We analysed the CSF of lung cancer patients presenting with LM suspicion by both cytology and CS. This last tehchnique consists in immunomagnetic enrichment and immunofluorescent identification of cells permitting visualization and enumeration of carcinomatous cells expressing EpCAM markers. The CSF was collected on traditional tubes for cytology (1 ml) and on preservative CellSave® tubes for the analysis on CS (4 ml). RESULTS: 8 patients suspected with LM benefited from a lumbar punction. The average CSF cell count was 9,3/mm3 (range : 0–24/mm3). Proteinorachia was elevated in 6 cases on 10 (range : 0,24-18,3 g/L) and glycorachia was lowered in 2 cases on 10 (range : 0,19-2,01 g/L). 3 samples on 10 found CTCSFs with standard cytology whereas 6-7 samples on 8 could observe and quantify CTCSFs with CS. DISCUSSION: The CS provides a semi-automated analysis allowing the detection and quantification of CTCSFs, improving the sensibility in comparison with standard cytology, often limited by the preanalytical conditions. It also permits precise quantification that could be useful for the follow-up of the patients during and after treatment.

NO-131. PROGNOSTIC FACTORS FOR SURVIVAL IN PATIENTS WITH CEREBRAL LOW-GRADE GLIOMA

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OBJECTIVE: The management of low-grade gliomas (LGGs) still remains controversial, although some physicians advocate early and extensive surgery or early radiation therapy. In particular, prognostic factors for survival should help the strategy of treatment for patients with LGG, but the importance of them remains a matter of discussion. The purpose of this study was to validate prognostic factors for survival in patients with LGG. METHOD: A consecutive series of 58 patients underwent initial treatments for cerebral LGG in our institute between 1983 and 2012. All data were retrospectively analyzed from the aspect of baseline characteristics, pathological findings, genetic change, surgical treatments, adjuvant therapies, and survival time. Cox multivariate analysis was performed to determine the prognostic factors for survival. RESULTS: There were 40 patients with WHO grade II astrocytoma (DA), 14 patients with oligodendroglioma (OG), and 4 patients with oligodendroastrocytoma (OA) diagnosed on initial surgery. Median survival was 166 months (95% CI, 49.14-282.86) in all patients. Median survival of patients with DA was 84 months (95% CI, 0-198.96) while that of patients with OG was 258 months (95% CI, 197.19-318.81). Overall survival was significantly better with gross total resection than biopsy or partial removal ($p = 0.017$, log-rank test). Multivariate analysis on all patients showed prognostic value for histology (OG vs DA and OA, HR 0.097 [95% CI 0.010-0.908], $p = 0.041$), tumor size (<6cm vs >6cm, HR 0.146 [95% CI 0.040-0.532], $p = 0.004$) and IDH (isocitrate dehydrogenase)-mutation (positive vs negative, HR 0.248 [95% CI 0.070-0.877], $p = 0.030$). CONCLUSION: For patients with LGG, gross total surgical removal was recommended as first intention therapy. Tumor histology, size and IDH-mutation status are important predictors for prolonged overall survival in patients with LGG.

NO-132. MALIGNANT HUMORAL HYPERCALCEMIA (MHH) ASSOCIATED WITH A WHO GRADE II MENINGIOMA IN BRAIN AND LUNG: A CASE REPORT AND REVIEW OF THE LITERATURE

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Malignant hypercalcemia (MH) is relatively common in solid tumors (20-30%). However, it is rare with CNS malignancies. The most common etiology of (MH) is tumor secretion of parathyroid hormone related protein (PTHrp) with osteolytic bone metastasis being second. PTHrP is a normal gene product expressed in a wide variety of tissues and its secretion is regulated by the extracellular calcium concentration (Ca 2+) in both normal and malignant tissues. Meningiomas have been reported to express PTHrP (1). No cases have been reported of MH in a patient with meningioma. 71 yo WM had GTR + external beam radiation for grade II frontal meningioma in 2007. PMH; localized prostate cancer. Physical exam was normal. In January of 2012 surveillance CT revealed pleural based nodules and biopsy confirmed meningioma. March 2013 patient (pt) presented with increasing pulmonary metastasis as well as calcium 11.6 mg/DL. Evaluation revealed no other systemic disease including bone metastasis. Serum PTH was low and PTHrP was elevated on multiple occasions consistent with (MHH). Hydrea 20mg/ kg/day was started. Pt initially declined bisphosphonate therapy and attempted to control (Ca 2+) with oral fluids. PTHrP and (Ca 2+) remained elevated, chest xray stabilized. May 2013 zolendronic acid 4 mg was administered and (Ca2+) returned to normal. Both brain and lung meningioma showed no PTH expression. PTHrP staining is pending. The majority of meningiomas are benign and spread locally. Metastatic disease occurs rarely. The only reported cases of hypercalcemia and meningioma have been in pts with primary hyperparathyroidism and/or MEN syndrome. This case represents the first of (MHH) in a pt with a meningioma. We postulate that it may be related to the extensive amount of meningioma which he has in his lung. (1)Chattopadhyay N, Evliyaglu C, Heese O, Carroll R, Sanders J, BlackP, Brown EM. Regulation of secretion of PTHrP by Ca(2+)-sensing receptor in human astrocytes, astrocytomas, and meningiomas. Am J Physiol Cell Physiolo.2000 Sep;279(3):C691-9.

NO-133. CHANGES IN THE PROGESTERONE-, ESTROGEN-, HER2/NEU-RECEPTOR STATUS AND THE PROLIFERATION MARKER Ki-67 IN METASTASIZED BREAST CANCER: DISCORDANCE RATES AND TIME TO PROGRESSION IN BRAIN METASTASIS

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Estrogen receptor (ER), progesterone receptor (PgR), human EGF receptor 2 (Her2), and Ki-67 are important predictive and prognostic markers for making effective treatment decisions. Out of 90 patients with breast cancer brain metastasis in our tumor tissue bank from 2001 to 2012, there were 23 consecutive patients from whom both, the primary lesion and the brain metastasis were operated in our hospital. Patients with spinal metastasis were excluded from this study. The lesions were resected and ER, PgR, Her2 and Ki-67 were evaluated by immunostaining and molecular techniques including FISH. In addition, number and location of the brain metastasis were evaluated. Moreover, samples from our tumor bank are currently analyzed for novel biomarkers with regard to brain metastasis formation. The median age of the patient cohort was 56 $\pm$ 9 years at first diagnosis. At that time 85% of the patients who developed a brain metastasis later on already had lymph node involvement. The Ki-67 proliferation index increased significantly from a mean of 21% at primary tumor site to 60% at relapse ($p < 0.001$). Most patients developed one single brain metastasis at diagnosis (74%), but 26% had multiple brain metastasis. The localisation of the filiae was mainly either the cerebellum (39%) or fronto-temporal (43.5%). The hormone receptor positive rate from the primary tumor to recurrence decreased from 43% to 17% and from 43% to 26% for ER and PgR, respectively. On the other hand, the rates of Her2+ tumors increased from 45% to 86%. 22% of all cases were triple negative. ER and PgR decreased while Her2 and Ki-67 increased due to relapse. Interestingly, there was a doubling of Her2+ cases in the relapse situation. Therefore, we presently analyze different target genes to further understand this mechanism. These findings could get important for making effective treatment in the era of targeted therapies.

NO-134. THE EFFECT OF FIELD STRENGTH ON GBM RESPONSE IN PATIENTS TREATED WITH NOVOCURE-TTF

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NovoTTF is a portable device that delivers intermediate frequency alternating electric fields through transducer arrays arranged on the scalp. The device is being studied for newly-diagnosed GBM and has been FDA-approved for recurrent GBM. The fields are believed to interfere with formation of the mitotic spindle as well as affect polar molecules at telophase, thus preventing cell division. Kirson et al. demonstrated that 200Hz fields delivered in multiple planes are optimal for cytotoxicity. The position of four arrays is unique and optimized based on the patient's imaging. We present three patients in whom the fields were adjusted at recurrence and the effects of each adjustment. We believe there may be a higher risk of TTF failure on the edges of the field where the field strength may be lower. The first patient underwent subtotal resection, radiation with Temozolomide (TMZ), and then began TTF with metronomicTMZ. She had good control for nine months, however, new bifrontal lesions developed, and her fields were adjusted with radiographic response. Over the next five months, her tumor burden increased and death was preceded by a right insular recurrence. A second patient underwent two resections followed by XRT/TMZ and TTF/TMZ. Six months later, two new distal lesions were noted and he underwent further resection with adjustment of his fields. He has remained stable over the past year on TTF and Avastin. A third patient on TTF/TMZ remained stable for two years but developed a small, slow growing enhancing lesion which was resected, and his fields were adjusted accordingly. Interestingly, the pathology showed giant cell GBM with multiple syncitital-type cells. Based on these observations, we believe that field strength may play a role in "out of field" recurrences and that cells which don't respond to TTF may adapt to avoid the effects of TTF by changing size.

NO-135. ^{11}C METHIONINE-PET FOR DETECTION AND EARLY RE-INTERVENTION OF LOW GRADE GLIOMA RECURRENCE

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Grade II or III 1p/19q co-deleted gliomas respond to radiation or chemotherapy, and remain stable for a long time. In general, regrowth of the tumor is slow, typically indicated by gradual increase of the FLAIR-high area on MRI over several months, and diagnosis of recurrence and hence the decision of re-intervention can be difficult. We have used 11C methionin-PET (MET-PET) to monitor the recuurence. For 51 patients with Grade II and III gliomas (25 with 1p/19q co-deletion, 26 without), MET-PET was obtained annually or when increase of the FLAIR-high lesion was indicated. In 11 cases (8 co-deleted, 4 non co-deleted), MET-PET demonstrated increased uptake12-64 months (median 34 m) following the initial treatment, and 8 of those had a surgically resectable MET-PET "hot" lesion that was resected. Histological examination of the resected tissue confirmed recurrence in all 8 cases. The 1p/19q co-deleted tumors demonstrated strong uptake in all 8 cases, and 1 case with 10q loss and 1 "triple negative", i.e. mIDH -, TP53 mut-, 1p/19q codel - case also showed dense uptake at the recurrent lesion. MET-PET is a useful modality to detect tumor recurrence in its early stage, that would allow more effective treatment for recurrent low grade glioma, especially 1p/19q co-deleted gliomas showing slower growth in general.

NO-136. OLIGODENDROGLIAL TUMORS: A SINGLE INSTITUTION EXPERIENCE

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OBJECTIVES: Management of oligodendrogliomas remains controversial, particularly the timing and extent of surgery and the optimal sequence of radiotherapy and chemotherapy. This is a retrospective study of our experience in a single institution. METHODS: All cases of oligodendrogliomas (low grade and anaplastic) were reviewed, correlating outcomes with several variables of possible prognostic values. Fifty-one patients were treated between 1992 and 2012 in our hospital. RESULTS: There were 43 (84%) low grade oligodendrogliomas (LGO) and 8 (15%) anaplastic oligodendrogliomas(AO). The majority were located in the frontal lobe. All patients had undergone an initial surgical procedure: gross-total resection in 23 (53%), and biopsy only in 4 cases (9%). Twenty-seven (63%) LGO and 25% patients of AO had 1p/19q co-delection. Fourteen (32,6%) patients received adjuvant radiotherapy (RT) in LGO and in 75% of AO. Upfront chemotherapy (CT) was administered in 5 cases (12%) of LGO and in 6 cases (75%) of AO. Two cases were treated with only chemotherapy. The median overall survival (OS) was 14,9

years (y) (5,5-24,3) for LGO and 3,5y (2,35-2,67) for AO. There were differences that did not reach the statistical significance in favour of a more extended surgery (P= 0,442) and 1p/19q codelection:14,9 vs 18,4y (p = 0,442). The median progression free survival in LGO was 8,011y (5,4-10,5) and 2,77y (0,77-4,76) in AO. In LGOs, at the time of first progression, we found MRI enhancement in 8 cases (19%). After the first progression the main option of treatement was surgical resection, in second or third progression, chemotherapy. The majority of cases with chemotherapy were treated with temozolomide. CONCLUSIONS: This retrospective review confirms the indolent but progressively fatal nature of LGOs. A more extended surgery and 1p/19q codelection was correlated with a better prognosis althought did not reach a statistical significance in our study. AO is a more agressive and infrequent disease.

NO-137. INNOVATIVE MOLECULAR IMAGING IN CHILDREN WITH DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG): THE ROLE OF 89-ZIRCONIUM LABELED BEVACIZUMAB

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INTRODUCTION: Molecular imaging offers the possibility to study target-expression and drug-distribution in a non-invasive manner. A disease that benefits from this approach is diffuse intrinsic pontine glioma (DIPG); a childhood malignancy with a dismal prognosis, resistant to all kinds of systemic (chemo)therapy. Vascular endothelial growth factor (VEGF) may be a potential treatment-target. Our aim was to study this target by studying the tumor-uptake and biodistribution of VEGF-A-inhibitor bevacizumab labeled to 89-zirconium (^{89}Zr) in DIPG patients. METHODS: Three patients received ^{89}Zr 0.9MBq/kg-bevacizumab 0.1mg/kg i.v., with a maximum of 37MBq/5mg i.v. Whole-body PET-CT scans (GeminiTF64 PET/CT scanner, Philips) were performed 1, 72 and 144 hours post-injection (p.i.). ^{89}Zr uptake-analysis was performed by calculating the standardized uptake values (SUV) of the defined volume-of-interest (VOI). VOIs of organs and aorta were determined on CT, whereas the VOIs of the whole tumor and its gadolinium-enhancing part were drawn on a co-registered T1-contrast MR-image of the brain. RESULTS: ^{89}Zr-bevacizumab uptake was observed in the contrast-enhancing part of the tumor in two patients at 72 and 144 p.i., while the third tumor was negative for both contrast-enhancement and ^{89}Zr-bevacizumab uptake. In the patient with the highest uptake, SUVs of the contrast-enhancing part were 12.5 and 16.8 at 72 and 144 hours, respectively, compared to 0.84 and 2.42 of the whole tumor. Apart from contrast-enhancing tumor regions, lungs, liver and kidneys had relatively high bevacizumab uptake. CONCLUSION: ^{89}Zr-bevacizumab only targeted contrast-enhancing parts of the tumor, or even none, in these DIPG patients. This is in concordance with previous reports that VEGF production is mostly present in hypoxic and necrotic areas of the tumor, but might also be a sign that large molecules only reach tumor-parts where the blood-brain barrier (BBB) is disrupted. In DIPG, with usually an intact BBB, the benefit of bevacizumab therapy could therefore be limited.

NO-138. CLINICAL CHARACTERISTICS AND OUTCOME OF PAPILLARY GLIONEURONAL TUMOR, ROSETTE-FORMING GLIONEURONAL TUMOR OF THE FOURTH VENTRICLE AND GLIONEURONAL TUMOR WITH NEUROPIL-LIKE ISLANDS-UPDATE OF AN ONGOING INTERNATIONAL INDIVIDUAL PATIENT DATA META-ANALYSIS

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BACKGROUND: In 2007 the group of neuronal and mixed neuronal-glial tumors (NGT) of the WHO Classification of Brain Tumors was expanded by two entities (WHO I): the papillary glioneuronal tumor (PGNT) and the rosette-forming glioneuronal tumor of the fourth ventricle (RGNT). Further, the glioneuronal tumor with neuropil-like islands (GNTNI) (WHO II/III) was added to the section of anaplastic astrocytomas. All entities are infrequent, thus data on clinical features and prognosis is still scarce. METHODS: Web of Science, EMBASE and Pubmed were searched with predefined search terms for cohort studies and case series. Individual patient data was extracted. RESULTS: Sixty-nine cases of PGNT, 26 of GNTNI and 85 of RGNT met the inclusion criteria. Median age at diagnosis was 23 years (range 4-75) for PGNT, 40 years (range 2-65) for GNTNI and 27 years (range 6-79) for RGNT. 99% of PGNT and 69% of GNTNI were located supratentorial, 30% of GNTNI were in the spinal cord, 88% of RGNT were found in the posterior fossa. Complete resection was reported in 7 GNTNI- (27%), 53 PGNT-(77%) and 37 RGNT-patients (44%). Adjuvant therapy was more likely to be given after incomplete resection. Patients (7x GNTNI, 3x PGNT, 0x RGNT) were treated with chemo- or radiotherapy (11x GNTNI, 7x PGNT, 3x RGNT) as primary therapy. Follow-up data was available for 131 cases. After a median follow-up time of 1.5 years (range 0.2-25) across all patients 2-year progression-free survival rates were 44 $\pm$ 12% for GNTNI, 82 $\pm$ 6% for PGNT and 100% for RGNT. 2-year overall-survival 95 $\pm$ 5%, 98 $\pm$ 2%, 100% respectively. CONCLUSIONS: As predicted by WHO grading PGNT and RGNT seems to be related with a more favorable prognosis than GNTNI. International collection of all available data is necessary to identify risk factors and and to develop risk-adapted therapeutic standards.

NO-139. MULTIMODAL TREATMENT OF ADULTS WITH CNS PRIMITIVE NEUROECTODERMAL TUMORS/ PINEOBLASTOMAS ACCORDING TO THE PEDIATRIC HIT 2000 PROTOCOL

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BACKGROUND: Central nervous system primitive neuroectodermal tumors (CNS-PNET) and pineoblastomas (PBL) occur only sporadically in adulthood, therefore the knowledge on clinical outcome and the efficacy as well as toxicity of chemotherapy is limited. METHODS: Patients aged $\geq$ 21 years were included in the observational arm of the prospective pediatric multicenter trial HIT 2000. Following surgery, craniospinal radiotherapy and either maintenance or sandwich chemotherapy were recommended. Craniospinal radiotherapy was normo- (35.2 Gy; tumor region, 55.0 Gy; metastasis, 49.6 Gy) or hyperfractionated (40.0 Gy; tumor bed, 68.0 Gy; metastasis, 50-60 Gy). Maintenance chemotherapy consisted of eight courses of vincristine, lomustine, and cisplatin after craniospinal radiotherapy. Sandwich chemotherapy included two cycles of postoperative chemotherapy (vincristine, cyclophosphamide, methotrexate, carboplatin, etoposide and in case of metastasis intraventricular methotrexate) followed by craniospinal irradiation, and four courses of maintenance chemotherapy. RESULTS: Seventeen patients (CNS-PNET, n = 7; PBL, n = 10), median age 30.0 years, were eligible for the analysis. Eight patients had a postoperative residual disease and three patients metastatic dissemination. The median follow-up of 10 surviving patients was 41 months. The estimated rates for 3-year progression-free survival (PFS) and overall survival (OS) were 68% $\pm$ 12% and 66% $\pm$ 13%, respectively. Both chemotherapeutic (maintenance, n = 6; sandwich, n = 8) protocols did not differ in their PFS and were feasible, with some evidence that the sandwich chemotherapy might be slightly more toxic. **Conclusion:** Combined chemo- and craniospinal radiotherapy is feasible in adults with CNS-PNET/PBL. It remains to be further assessed, whether survival rates can be improved by multimodal treatment concepts. Large registries with standard recommendations for diagnostic procedures need to be established. The collection of tumor tissue would provide a great opportunity to perform biological studies with the aim to adequately classify these rare tumors and to identify novel therapeutic targets.

NO-140. RESULTS OF ADULTS TREATED FOR METASTATIC MEDULLOBLASTOMA USING THE PEDIATRIC PROTOCOL HIT 2000. A PROSPECTIVE MULTICENTER OBSERVATIONAL STUDY

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BACKGROUND: Little is known about the efficacy and toxicities of adults with metastatic medulloblastoma treated with intensive chemotherapy in addition to radiotherapy, as frequently applied in pediatric protocols. PATIENTS AND METHODS: Twenty-three patients, diagnosed from November 2001 to July 2009, and treated in 18 institutions, were eligible. After surgery, 14 patients received the same treatment as older children and adolescents with metastatic medulloblastoma within the HIT 2000 trial (sandwich strategy: postoperative chemotherapy, hyperfractionated craniospinal radiotherapy (2 × 1 Gy/d, 40 Gy craniospinal, 60 Gy posterior fossa, 68 Gy tumor bed, 50-60 Gy boost to metastatic deposits), and maintenance chemotherapy), and 9 adults were treated according to the HIT'91 maintenance strategy (postoperative craniospinal radiotherapy (1 × 1.6 Gy, 35.2 Gy craniospinal, 55.2 Gy posterior fossa, 50 Gy boost to metastatic deposits), and maintenance chemotherapy). RESULTS: At a median follow-up of 3.99 years, the 4-year event-free survival (EFS) and overall survival (OS) (± standard error, SE) rates of 23 adults (median age: 30.7 years) with metastatic medulloblastoma were 47% ± 12% and 91% ± 6%, respectively. Survival rates were similar in both treatment groups (HIT'91 maintenance strategy, n = 9; sandwich strategy, n = 14). In our cohort, the OS rates differed between patients with classic medulloblastoma (n = 11; 4-year OS 91% ± 9%), desmoplastic medulloblastoma (n = 10; 4-year OS 100%) and adults with large cell / anaplastic medulloblastoma (n = 2; 4-year OS 0%) (p = 0.033). Treatment induced toxicities consisted mainly of neurotoxicity (~ 50% of patients, ≥ °II), followed by hematotoxicity, and nephrotoxicity/ototoxicity. Hematotoxicity and ototoxicity were slightly more frequent in patients treated according to the sandwich strategy. CONCLUSIONS: Our results confirm that treatment of adults with metastatic medulloblastoma according to the pediatric protocol HIT 2000 is feasible, toxicity acceptable, and survival rates achieved by both chemotherapeutic protocols are slightly inferior to that obtained in older children and adolescents with metastatic disease.

NO-141. ROLE OF MEANING IN THE PATIENT EXPERIENCE OF NEUROLOGIC CANCER

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BACKGROUND: The drive to find meaning in life is a motivational force that provides personal significance in life. Finding meaning is important when coping with existential and physical distress of cancers of the nervous system, and ascribed meaning may influence the person's quality of life (QOL). An individual's sense of coherence (SOC) may influence both meaning and QOL. Furthermore, symptoms experienced may affect meaning, creating a dynamic interaction between meaning and the experience of neurologic cancer that may vary over the disease course. METHODS: A review of the literature was conducted for the purpose of examining relationships between various concepts, including meaning and symptoms, meaning and quality of life (QOL), and between QOL and sense of coherence (SOC) in patients with any cancer. FINDINGS: Twenty-six studies were identified and included in this analysis. Thirteen studies examined the relationship between meaning and symptoms. Ascribed meaning was found to influence the number of symptoms and individual symptoms including fatigue, pain intensity and interference, and mood. Ten studies explored the relationship of meaning and QOL, and found that meaning influenced and was influenced by QOL. Two studies indicated that spirituality is related to QOL with spiritual concern associated with negative QOL. Finally, five studies were reviewed relating to SOC and QOL. All showed that SOC was predictive of QOL, and was more highly related early in the disease process. CONCLUSIONS: Understanding the role of meaning in the experience of patients with a neurologic cancer will allow clinicians to better evaluate symptoms and apply interventions. Based on this review, a conceptual model, "The Role of Meaning in Serious Illness" which may be applied to patients with neurologic cancer has been developed. The model provides a framework to investigate the relationships between meaning and the patient experience.

NO-142. EPIGENETIC SILENCING OF KAZALD1 CONFER A BETTER PROGNOSIS AND ASSOCIATE WITH MALIGNANT TRANSFORMATION/PROGRESSION IN GLIOMA

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In an attempt to analyze more profoundly aberrant DNA methylation in glioma, we applied a large cohort methylation microarray including 119 glioma samples. 6 genes were screened out through SAM (Significance anlaysis of microarrays), survival cox-regression and so on condition. They were ADCY1, KAZALD1, KLF4, SLMAP, TETRAN and TP53INP1. KAZALD1 was the oncogene we interested in. KAZALD1?also known as IGFBP-rP10, belongs to the IGFBP family. We found that KAZALD1 was hypomethylated in high-grade glioma (anaplastic gliomas and glioblastomas) compared to low-grade glioma (astrocytoma, oligodendrocytoma and oligoastrocytoma) using methylation microarray ($p < 0.001$). Immunohistochemistry (IHC) of 91 glioma samples showed KAZALD1 expression score of high grade glioma samples were higher than those score of low-grade ($p < 0.001$). In high-grade gliomas, overall survival (OS) was shorter for patients with KAZALD1 hypomethylation or overexpression than those without. Decreased KAZALD1 expression in glioma inhibited cell proliferation and invasion both in vitro and in vivo. On the basis of these observations and the results from subset analysis, it is reasonable to conclude that KAZALD1 promoter hypomethylation is an important prognostic biomarker in glioma. KAZALD1 promoted glioma malignant progression through invasion and proliferation.

NO-143. RAB34 IDENTIFIED AS A PROGRESSION AND PROGNOSIS ASSOCIATED BIOMARKER IN GLIOMA

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OBJECTIVE: To explore the expression pattern, prognostic value and functional role of RAB34 in glioma patients, we analyzed the data from Chinese Glioma Genome Atlas (CGGA) and other two datasets. METHODS: RAB34 expression was evaluated from low grade to high grade in 220 glioma patients of CGGA. We therefore analyzed RAB34 expression in two validated datasets. Gene ontology (GO) analysis and gene set variation analysis (GSVA) were used for functional annotation of RAB34. RESULTS: The expression levels of RAB34 were related to glioma grade progression and inversely correlated with overall survival both in low grade and high grade glioma patients. GO and GSVA analysis showed that RAB34 sets related to migration were significantly enriched in the cases with RAB34 high expression. Person correlation analysis identified that genes including MMP-11, HSPB1, IGFBP2, HSPA6, IGFBP5, MMP19 were positive correlated with RAB34. CONCLUSIONS: The expression of RAB34 is related to glioma grade progression and confers a poor prognosis both in low and high grade glioma patients.

NO-144. PILOT STUDY TO DETERMINE THE EFFECT OF SULFASALAZINE ON GLIOMA GLUTAMATE LEVELS MEASURED BY MRS

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BACKGROUND: Seizures are a common symptom of gliomas and increase patient morbidity. Recent preclinical evidence suggests that gliomas initiate seizures through release of the neurotransmitter glutamate (GLU) via the cystine/glutamate antiporter "System x_c^-"(SXC). Sulfasalazine (SAS), an FDA-approved drug used in the treatment of Crohn's disease, has been shown to block SXC. METHODS: The goal was to non-invasively quantify tumor-associated GLU in patients with glioma and determine the utility of the SXC-inhibitor SAS as a biomarker for SXC function through detection of peritumoral GLU changes. Patients were scanned before and after receiving an oral dose of SAS. Single voxel MRS was acquired at baseline, 1hr, 2hrs, 3hrs,

24hrs, and 30 days after initial dose, using the same imaging parameters. To minimize variability, images of voxel placement from the first imaging session were used as a guide for subsequent sessions. RESULTS: Overall, 5 patients have been enrolled. Of the 4 that have been imaged, 3 patients showed a marked reduction in GLU + Glutamine (Glx) within 1 to 3 hours following initial SAS administration (mean Glx decrease: 21.3%) and 1 patient showed no acute change. Interestingly, the 3 participants with an acute Glx decrease also showed a delayed Glx increase 24h post SAS administration; however, this delayed response was not observed in the patient with no acute change. This Glx "rebound" seen in the 3 patients is of higher magnitude than the acute decrease (mean Glx increase: 36.3% vs. mean Glx decrease: 21.3%). Although the mechanism behind this delayed increase is not yet understood, it may provide a better signal with which to identify those patients with SXC activity. CONCLUSIONS: This preliminary data indicates that tumor-associated GLU can be quantified by MRS and the reduction of peritumoral GLU upon SAS administration supports the use of SAS as a marker of SXC function.

NO-145. PHASE II TRIAL OF THE PHOSPHATIDYINOSITOL-3 KINASE (PI3K) INHIBITOR BUPARLISIB (BKM120) IN RECURRENT GLIOBLASTOMA: AN IVY FOUNDATION EARLY PHASE CLINICAL TRIALS CONSORTIUM STUDY

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BACKGROUND: The PI3K pathway is activated in most GBMs and represents a potential therapeutic target. Buparlisib is an oral, pan-Class I PI3K inhibitor that enters the brain at therapeutic concentrations, and inhibits the growth of U87 tumors and human glioma tumor spheres in vivo. METHODS: Phase II study of buparlisib in recurrent GBM patients with activation of the PI3K pathway (mutation, homozygous deletion or loss by IHC of PTEN, PIK3CA or PIK3RI mutations, or detectable pAKT). Additional eligibility criteria: 1st or 2nd relapse, > 18 yrs, KPS > 60, controlled blood glucose, and no EIAED. Patients received BKM120 100mg daily. The study consisted of 2 concurrent parts. Part 1 included up to 15 patients who received BKM120 for 8-12 days prior to surgery. Patients underwent FDG-PET and pharmacokinetic (PK) studies and tumor obtained for drug concentrations and pharmacodynamic effects. Part 2 involved up to 50 patients with unresectable GBM treated with BKM120. Primary endpoint was PFS6. RESULTS: To date 9 patients have been enrolled into Part 1, 41 into Part 2 (9 women, 41 men; median age 54 yrs [29-79]). Treatment was well-tolerated with no grade 4 toxicities. Grade 3 toxicities were asymptomatic lipase elevation (5), rash (4), hyperglycemia (3), fatigue (2), and 1 each of depression, elevated ALT, hypophosphatemia, thrombocytopenia and lymphopenia. Analysis of surgical tumor specimens (Part 1) showed reduction of pAKT by IHC. Genotyping of tumor specimens is ongoing. To date 17 patients had only pAkt, 31 had PTEN loss by IHC. Of the first 32 patients who underwent whole exome sequencing, there were 4 PIK3CA mutations, 2 PIK3R1 mutations, and 10 PTEN mutations. CONCLUSIONS: Buparlisib is generally well-tolerated in recurrent GBM patients and achieves adequate tumor concentration to inhibit pAkt. Final PK and efficacy data, and correlation of outcome with tumor genotype will be presented.

NO-146. OBJECTIVE RESPONSE IN RECURRENT GLIOBLASTOMA FROM ADJUVANT NOVOTTF-100A AND TCCC AFTER TEMOZOLOMIDE AND BEVACIZUMAB FAILURE

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NovoTTF-100A is a novel, FDA-approved treatment for recurrent glioblastoma. It works by perturbing tumor cells during mitosis resulting in aneuploidy, asymmetric chromosome segregation and cell death. Clinical trial data have shown equivalent efficacy when compared to salvage chemotherapies, including bevacizumab, and responders had lower dexamethasone requirement and higher rate of prior low-grade histology. We report response in a 56-year-old woman with recurrent glioblastoma after failure of adjuvant temozolomide, PLX-3397 and bevacizumab. Baseline MRI revealed a 5.5 cm × 3.6 cm right frontal glioblastoma with extensive dural invasion and an extracranial tumor mass measuring 2.4 cm × 1.9 cm. She was then placed on NovoTTF-100A. Bevacizumab was restarted and her daily dexamethasone was weaned from 6 to eventual discontinuation. The 4-week interval MRI showed minimal change. However, after 6 weeks of adjuvant NovoTTF-100A and TCCC (6-thioguanine, lomustine, capecitabine and celecoxib), repeat MRI demonstrated partial response and shrinkage of both intracranial and extracranial tumors to 4.6 cm × 2.8 cm and 1.5 cm × 1.4 cm, respectively. Tumor perfusion measured by arterial spin labeling had decreased to undetectable level. After another 8 weeks of treatment with bevacizumab, NovoTTF-100A, capecitabine and celecoxib, repeat head MRI showed no change in tumor size and tumor perfusion remained low. This case illustrates the possibility of achieving a response by the combination of NovoTTF-100A, cytotoxic chemotherapy, COX-2 inhibiton and immune recovery.

NO-147. SAFETY ANALYSIS OF BEVACIZUMAB PLUS NOVOTTF-100A IN PATIENTS WITH RECURRENT MALIGNANT GLIOMAS

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PURPOSE: Both bevacizumab and the NovoTTF-100A device are treatments approved by the FDA for recurrent glioblastoma. We examined our single-institution experience in using this combination for patients with recurrent malignant gliomas. METHODS: We identified retrospectively the side effects experienced by patients while on both bevacizumab and NovoTTF-100A. Overall survival was also tabulated from initiation of this combined modality treatment. RESULTS: There were 14 men and 6 women. Their median age was 54 (range 29-76). All had Karnofsky Performance Status of 60 or above. Fourteen patients received NovoTTF-100A after failure of bevacizumab treatment while the other 6 received both treatments concurrently. The median duration of bevacizumab plus NovoTTF-100A treatment was 2.3 (95%CI 1.8-4.7) months. There were 2 patients who experienced electric shock burns, 3 patients developed scalp rash (2 moderate and 1 severe), 4 patients experienced liquefied hydrogel from the arrays as a result of high ambient temperature during summer months, 2 experienced vivid dreams of applying the arrays and 3 removed the arrays during periods of sleep or confusion. Only one patient required NovoTTF-100A treatment interruption because of severe scalp rash. No hemorrhage into the malignant glioma or thromboembolism was seen in this cohort. From the time of initiation of bevacizumab plus NovoTTF-100A treatment, the Kaplan-Meier median overall survival was 5.6 (95%CI 4.2-N/A) months. CONCLUSION: No additive or synergistic side effects were observed when patients were treated with both bevacizumab and NovoTTF-100A. Further evaluation in a prospective manner would be needed to evaluate both side effects and efficacy of this treatment combination.

NO-148. RELATIONSHIP BETWEEN OVERALL SURVIVAL AND PROGRESSION-BASED ENDPOINTS IN BEV-INCLUDED RECURRENT GLIOBLASTOMA MULTIFORME TRIALS

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BACKGROUND: Progression free survival (PFS) or PFS rate at specific time points are widely used in phase II clinical trials testing novel agents for recurrent glioblastoma (rGBM). However, the associations between progression-based endpoints and survival have not been evaluated after Bevacizumab (Bev) became the standard therapy for rGBM.METHODS: Datasets from 4 Bev-including phase II clinical trials in rGBM (n = 265, 3 single armed and 1 randomized trials) were pooled and analyzed to evaluate the endpoint correlation between PFS and OS using landmark analyses and weighted linear regression. A control arm was constructed by sampling without replacement from the Bev alone arm from the randomized trial for each of the single armed trial to mimic randomized trial. Treatment

effects on PFS based endpoints and OS (hazard ratio or odd ratio) were estimated and analyzed to evaluate the trial level correlation between PFS based endpoints and OS using weighted linear regression. Sensitivity analyses were conducted by repeating above simulation 100 times. RESULTS: For patient level correlation, the estimated hazard ratio of death in the landmark analysis at 4 and 6 months are 3.6 (95%CI, 2.3 to 5.5, p-value < 0.0001) and 4.2 (95%CI, 2.3 to 7.6, p-value < 0.0001), respectively. For arm level correlation, the R^2 from weighted linear regression between PFS rate at 4 and 6 month and OS at 12 month are 0.62 and 0.89, respectively. For treatment effect correlation, the R^2 between HR_{os} and OR_{pfs_6} ranges from 0.17 to 0.8, and the R^2 between HR_{os} and HR_{pfs} ranges from 0.5 to 0.9 based on 100 simulated data sets. CONCLUSIONS: PFS and OS correlated closely at the patient and the arm levels. Consistent association between treatment effects on OS and PFS based binary endpoints is not supported by simulated data in this study, even though PFS as time-to-event endpoint looks more promising.

NO-149. REPEATED RECURRENCE OF PILOCYTIC ASTROCYTOMAS IN ADULT PATIENTS

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In general, pilocytic astrocytoma is a slow growing tumor with a benign clinical course within the pediatric population. Tumor recurrence after the surgery is relatively rare and adjuvant radiotherapy can prolong progression free survival period. To evaluate the frequency and clinical course of recurrence of pilocytic astrocytoma in adult patients, we performed a retrospective analysis for this tumor. In our cohort of 12 patients, there were 3 (25%) recurrence with the median time to recurrence being 6 months. All patients underwent second surgical resection due to symptomatic progression. Two recurrent patients underwent adjuvant radiotherapy or chemotherapy. But all three patients showed second recurrence with median time to second recurrence being 4 months. Malignant transformation was observed in one patient. In conclusion, the clinical course of pilocytic astrocytoma in adult patient is not benign with a potential of recurrence and malignant transformation.

NO-150. PREGNANCY AND BRAIN TUMORS

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BACKGROUND: Advances in the treatment of brain tumors have resulted in an overall improvement in prognosis for these patients. There is an increasing number of young women with brain tumors with sustained periods of disease control, who are now considering pregnancy. The aim of this study was to provide data about pregnancy outcomes and the influence of pregnancy on progression and survival. DESIGN/METHODS: In this IRB approved retrospective study, the MDACC Neuro-Oncology longitudinal database was screened for female patients with gliomas who were pregnant during the course of their illness. 34 patients were identified and extensive reviews were performed to determine the patient's clinical course and pregnancy outcome. RESULTS: 15 patients presented with a brain tumor while they were pregnant (5–30 weeks of pregnancy). Pregnancy was terminated only in 2 patients and the rest delivered healthy babies, despite treatment with surgery and radiation. 23 patients became pregnant after diagnosis (range 2–90 month; mean- 27 month). 5 patients had grade 1 tumors and remained stable during and after pregnancy. 44% (8/18) of the patients with grade 2/3 gliomas that became pregnant during the course of their illness had tumor progression during or immediately after pregnancy. CONCLUSIONS: Although retrospective, these results suggest that patients with grade 2/3 gliomas who become pregnant during the course of their illness may be at increased risk for tumor progression. This potential risk should be discussed in women of childbearing potential. Conversely, in women diagnosed with gliomas while pregnant, if the risk of delaying treatment with chemotherapy is not high, it is reasonable to consider maintaining the pregnancy. Given the importance of this issue, a registry or larger scale studies are needed to generate a consensus approach.

NO-151. GLIOBLASTOMA MULTIFORME IN SIBLINGS WITH BIALLELIC MSH6 MUTATIONS: A CASE REPORT AND REVIEW OF THE LITERATURE

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BACKGROUND: Biallelic germline mutation of the mismatch repair (MMR) gene MSH6 is characterized by increased risk of childhood neoplasia, including hematological, bowel and brain malignancies. We report the clinical and molecular characterization of glioblastoma in a patient with biallelic MSH6 germline mutations to reveal the biology and to discuss treatment challenges and consider innovative therapy. CASE REPORT: A 14-year-old female presented with headache, nausea and vomiting over a several week period. A head CT revealed a bifrontal mass, with follow-up MRI showing multifocal abnormalities, including a bifrontal non-enhancing lesion, suggestive of multifocal glioma. Family history was significant for a brother who had been diagnosed with colon cancer and glioblastoma who had died of his disease a few months later. The patient and the brother are homozygous for MSH6 mutations. The patient had worsening of her headaches, with repeat MRI showing tumor progression with marked contrast enhancement, necrosis, mass effect and ventriculomegaly. The patient underwent emergent debulking; pathology confirmed glioblastoma. Molecular testing showed TP53, IDH1, and PIK3CA mutations, and immunostaining showed increased expression of platelet derived growth factor receptors α and β and epidermal growth factor receptor (EGFR). A spine MRI and lumbar puncture were negative for disease. Irradiation with vorinostat was initiated and tolerated well. Temzolomide was not recommended based on literature reports of resistance and increased mutagenesis in MSH6 mutation-bearing patients. The patient will commence to consolidation immunotherapy with cytotoxic T cell against EGFR then after. CONCLUSION: A literature review on brain tumors in MMR deficiency families shows that they are treatment-resistant and lead to early death. Limited data are available on the use of chemotherapy in the treatment of MMR. Additional data about disease course, relevant biomarkers, and treatment outcomes are needed to further understanding and improve of therapy for children with MMR deficiency and brain tumors.

NO-152. PROGRESSIVE DISSEMINATED SUPRATENTORIAL PRIMITIVE NEUROECTODERMAL TUMOR (SPNET) POST-CHEMORADIATION TREATED WITH COMBINED CHEMOTHERAPY AND TARGETED AGENT

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BACKGROUND: Supratentorial primitive neuroectodermal tumor (SPNET) is the second common pediatric embryonal tumor with more dismal outcome compared to medulloblastoma (MB). SPNET is treated as MB with surgery, radiation and chemotherapy. We report a patient with disseminated SPNET who failed chemoradiotherapy and was salvaged with combined approach using chemotherapy and target agent. CASE REPORT: This is an eleven year-old male presented initially with headaches and vomiting for few weeks, brain MRI revealed right multifocal enhancing tumors. He underwent subtotal resection and pathology was anaplastic PNET. Cerebrospinal fluid (CSF) was positive for malignant cells. He commenced to chemoradiotherapy with vincristine, carboplatin and craniospinal irradiation. Post-irradiation MRI revealed disease progression. He was started on chemotherapy with temozolomide, irinotecan and cyclophosphamide. Follow up MRI revealed shrinkage of the SPNET and progression of spinal and leptomeningeal disease. His CSF was remarkable for malignant cells, which stained positive for platelet derived growth factor receptor (PDGFR). Molecular studies of the primary tumor revealed TP53 and kinase insert domain receptor mutations. Dasatinib was added to his treatment and following MRI revealed further regression of primary tumor and disappearance of spinal and LMD, as well as negative CSF study. The patient received five cycles of the treatment which were tolerated well with marked improvement in his quality of life. He has minimal residual disease and is scheduled for high dose chemotherapy with stem cell rescue. DISCUSSION: Recurrent or progressive SPNET is an aggressive disease with dismal outcome and no effective standard treatment post chemo-radiation. PDGFR pathways are significantly up-regulated in metastatic medulloblastoma, suggesting therapeutic role. Linking pathway deregulation with sensitivity to therapeutics that target components of the pathway provides an opportunity to make use of these oncogenic pathway signatures to guide the use of targeted therapeutics with the hope of more effective and less toxic therapy.