## Title

NCOG-20. GENETIC MARKERS AND CLINICAL CHARACTERISTICS RELATED TO NEUROCOGNITIVE OUTCOMES OF PEDIATRIC BRAIN TUMOR PATIENTS



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paired samples t-tests were conducted to compare neurocognitive functioning. **RESULTS:** There was a significant effect on language functioning across time, Wilks' Lambda = .112, F (2,3) = 11.919, p = .037. A paired samples t-test indicated a significant difference in the scores between 3 (M=97.8, SD=8.47) and 6 (M=89.60, SD=7.60) months; t(4)=4.954, p=.008. All neurocognitive scores will be presented. Other cognitive domains and all emotional ratings were nonsignificant for effects across time. **CONCLUSIONS:** Although still within the average range, there was a negative trend in language functioning between 3 and 6 months. It will be important to further compare these results to individuals undergoing standard therapy alone. This study was supported by an Investigator-Initiated Trial grant from Biogen, and by the Massey Cancer Center.

### NCOG-19. NEUROCOGNITIVE OUTCOMES OF EORTC BRAIN TUMOR GROUP STUDY 26101 PHASE III TRIAL COMPARING THE COMBINATION OF LOMUSTINE AND BEVACIZUMAB WITH LOMUSTINE ALONE IN GLIOBLASTOMA PATIENTS WITH FIRST PROGRESSION

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**BACKGROUND:** Despite prolonged PFS, EORTC study 26101 showed that combined treatment of lomustine (LOM) plus bevacizumab (Bev) does not confer an OS advantage over LOM alone. Here we report in detail the outcomes on neurocognitive functioning (NCF) of these patients. **METHODS:** NCF using Hopkins Verbal Learning Test (Free Recall, Delayed Recall, and Delayed Recognition), Trail Making Test (TMT A/B), and Controlled Oral Word Association Test (COWA) was evaluated at baseline and every 12 weeks. Minimal compliance for analyses was set at 60%. The Reliable Change Index (RCI) was calculated for each test outcome to define NCF change over time. **RESULTS:** NCF assessment was performed at baseline in 288 LOM+Bev patients and 149 LOM patients (randomization ratio 2:1). Compliance in both arms dropped from 94.5% at baseline to 61.4% at week 36. The primary analysis compared NCF scores at last disease assessment before or at 36 weeks in patients who had at least one NCF assessment after baseline between treatment arms. No statistically significant differences were found at baseline and follow-up in NCF between treatment arms and the RCI was not indicative for a clinically significant neurocognitive decline over time in a specific treatment arm. Poorer NCF was significantly correlated with poorer overall health, quality of life, and WHO performance status. Poorer NCF outcome was also associated with steroid use at baseline and tumors >40 mm. Except for TMT-A and TMT-B, NCF tended to be lower in patients with first reported target lesion in the left hemisphere. NCF in all domains were significantly linked to OS in univariate, but not in multivariate Cox regression analyses. **CONCLUSION:** NCF of patients with progressive glioblastoma using lomustine is similar to that of patients using lomustine plus bevacizumab and there is no evidence of accelerated NCF decline in either treatment regimen at the group level.

### NCOG-20. GENETIC MARKERS AND CLINICAL CHARACTERISTICS RELATED TO NEUROCOGNITIVE OUTCOMES OF PEDIATRIC BRAIN TUMOR PATIENTS

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Pediatric brain tumors affect more than 50,000 children in the US with nearly 5,000 new diagnoses annually. Although neurocognitive outcomes for this population show lower scores when compared to population means, there is great variability among individuals. In the current study, we aim to investigate the impact of cognition-related genes, *KLOTHO*, *ApoE4*, *BDNF*, *COMT*, and *KIBRA*, on neurocognitive outcomes in pediatric brain tumor patients. Utilizing an existing cohort of pediatric brain tumor patients from a diverse brain tumor population, we performed single nucleotide polymorphism (SNP) genotyping for *KLOTHO*, *ApoE4*, *BDNF*, *COMT*, and *KIBRA*. Neurocognitive evaluations were completed for these same patients at baseline and follow-up intervals, using validated, computer-based CogState batteries. Mixed modeling was done to correlate individual SNPs with neurocognitive outcomes over time, adjusting *a priori* for time from radiation, age at diagnosis, hydrocephalus, seizures, chemotherapy/radiation exposure, sex, tumor type, and tumor location. Lowess smoothing regression was done to assess the impact of individual genes SNPs on neurocognition. Ninety-seven patients were included in the analyses (54 males; median age at diagnosis 7 years). Medulloblastoma was the most frequent diagnosis (29%). Time from radiation, hydrocephalus at diagnosis, and seizures at diagnosis most consistently impacted neurocognition across neurocognitive test batteries (as based on statistical significance at p-value<0.05 across gene SNPs and testing batteries). Using smoothing regression, *ApoE4* carrier status consistently negatively impacted neurocognitive function over time, as seen by decreasing neurocognitive scores over time across all batteries. Time from radiation and hydrocephalus and/or seizures at diagnosis illustrated statistically significant impacts on neurocognitive outcomes of pediatric brain tumor patients. *KLOTHO*, BDNF, *COMT*, and *KIBRA* did not appear to impact neurocognition; however, *ApoE4* warrants further investigation as a possible predictor of neurocognitive outcomes. Our study highlights factors that may be of importance in anticipatory guidance and potentially, treatment-planning for children with brain tumors.

## NEURO-IMAGING

### NIMG-01. DIFFUSION MRI PHENOTYPES PREDICT OVERALL SURVIVAL BENEFIT FROM ANTI-VEGF MONOTHERAPY IN GLIOBLASTOMA AT FIRST OR SECOND RELAPSE

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Anti-VEGF therapies remain controversial in the treatment of recurrent GBM. In the current study we demonstrate that recurrent GBM patients with a specific diffusion MR imaging signature have an OS advantage when treated with anti-VEGF therapy at first or second recurrence. These findings were then validated using data from a separate trial. **METHODS:** A total of 258 patients with recurrent GBM and diffusion MRI from the monotherapy arms of 5 separate phase II clinical trials were included. Data from 4 trials were used as training data and a fifth for validation: 1) cediranib (NCT00035656); 2) bevacizumab (BRAIN Trial, AVF3708g; NCT00345163); 3) cabozantinib (XL184-201; NCT00704288); 4) aflibercept (VEGF Trap; NCT00369590); and 5) bevacizumab or lomustine (BELOB; NTR1929). Apparent diffusion coefficient (ADC) double-Gaussian histogram analysis was performed prior to therapy to estimate "$ADC_L$", the mean of the lower ADC distribution. Pre-treatment $ADC_L$, enhancing volume, and clinical variables were tested as independent prognostic factors for OS. **RESULTS:** The coefficient of variance in double baseline $ADC_L$ measurements was 2.5% and did not significantly differ (P=0.454). An $ADC_L$ cut-off value of 1.24 $um^2$/ms produced the largest OS differences between patients (HR~0.5), with an $ADC_L$>1.24 $um^2$/ms resulting in better OS. Training and validation data confirmed baseline $ADC_L$ as an independent predictive biomarker for OS in all anti-VEGF therapies (P<0.05), but