increasing both its specificity and sensitivity of detecting one or multiple antigen(s) (Ag) simultaneously. As such, IHC has become an affordable, powerful, and readily available means for the identification of candidate biomarkers (mostly lineage markers) in formalin-fixed, paraffin-embedded (FFPE) tissue samples. Pathologists are now asked to "quantify" expression levels of differential prognostic markers –at microscopic level – using this arguably "non-quantitative" technique. Conventionally, histological grading relies mainly on manual counting of positively immunostained cells, a labour intensive protocol that may be associated with subjectivity, intra- and inter- observer variation and reproducibility issues. The subjectivity and lack of reproducibility has prompted the use of computer-assisted or fully automated image analysis technologies. Digital image acquisition systems are becoming commonplace and as such, the demand for complex assessments of digital images of histological slides must be matched with quantitative platforms. In this study, we aim to introduce a computer-assisted image-computing platform that is both accurate and efficient in quantification of isolated and heterogeneous candidate biomarkers in glioblastoma.

IMAGING

PS2 – 196

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Investigating the Spatial Agreement Between Pre-Operative Functional MRI and Intra-Operative Direct Cortical Stimulation

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Pre-operative functional magnetic resonance imaging (fMRI) has emerged as valuable clinical tool to help surgically manage patients diagnosed with brain tumours. Surgical decision-making may be significantly improved through the provision of fMRI, however its clinical usage is contingent on the level of agreement with direct cortical stimulation (DCS). While previous studies have been undertaken to investigate the spatial agreement between fMRI and DCS, the influence that various factors may have on fMRI sensitivity and specificity is not fully clear. Thus, in a group of eight brain tumour patients who underwent pre-operative fMRI followed intra-operative DCS during an awake craniotomy procedure, we measured the agreement between the two brain mapping techniques looking at the influence of behavioural task, statistical threshold, and task standardization. Results: There were significant differences between motor and language mapping, where agreement was better for the former. Sensitivity and specificity shared an inverse relationship with increasing fMRI threshold, and were significantly reduced in the case where tasks were not standardized. Lastly, false positive occurrences were identified as the dominate source of error in comparison to false negative occurrences. Conclusion: Thus, the results from this work suggest that fMRI can predict intraoperative findings with good accuracy, however, sources of variability may significantly reduce the quality of fMRI data at the single-subject level. Neurosurgeons should carefully evaluate fMRI data with these considerations prior to its inclusion in the surgical-decision making process.

CLINICAL POSTER VIEWING SESSION III
11 JUNE 2016 ~ 1000 - 1045

GLIOMA CLINICAL

PC3 – 151

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Toca 5: A Phase 2/3 Randomized, Open-Label Study of Toca 511, a Retroviral Replicating Vector, Combined with Toca FC versus Standard of Care in Patients Undergoing Planned Resection for Recurrent Glioblastoma (GBM) or Anaplastic Astrocytoma (AA) (NCT02414165)

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Recurrent GBM and AA have a dismal prognosis and a high unmet need for effective therapies. Toca 511 (vocimagene amiretrorepvec) is an investigational retroviral replicating vector that encodes the transgene cytosine deaminase (CD). Toca 511 selectively infects, persists and spreads in tumor. Subsequent oral administration of 5-fluorocytosine (Toca FC) produces 5-fluorouracil (5-FU) by CD within infected cells. 5-FU kills cancer cells and myeloid derived suppressor cells, inducing robust antitumor immune responses in animal models. Clinical data from phase 1 trials are consistent with this mechanism of action, and show extended survival compared to historical controls. Toca 5 is a multicenter, randomized, open-label Phase 2/3 trial of Toca 511 and Toca FC versus standard of care administered to patients undergoing resection for first or second recurrence of GBM or AA. Phase 2 will enroll 170 patients. Primary endpoint is overall survival (OS). Key secondary endpoints are safety, objective response rate, clinical benefit rate, progression-free survival, and landmark OS. Key inclusion criteria are age 18-75 years, histologically proven GBM or AA, measurable disease preoperatively of less than 5cm, candidate for equal or greater 80% resection of enhancing tumor based on pre-operative evaluation, and KPS equal or greater to 70. Assays for immune monitoring will be performed and molecular profiling of resected tumor samples will be correlated efficacy.

PC3 – 152

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Impact of Extent of Resection Upon Outcome in Newly Diagnosed Glioblastoma: A Study in the Molecular Era

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For decades, debate has persisted regarding the role of surgical resection in newly diagnosed glioblastoma. There is increasing evidence that extent of resection (EoR) is an independent prognostic factor. Previous work has proposed the inclusion of EoR in a risk stratification algorithm but does not incorporate

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account recent advances in the molecular characterization of tumours. We set out to investigate the effect of EoR on overall survival (OS), and to develop a stratification algorithm incorporating both EoR and modern molecular markers for prognostication. HYPOTHESIS: Greater EoR is independently associated with improved OS. METHODS: We examined 190 consecutive cases of histopathologically confirmed newly-diagnosed glioblastoma who were operated upon between January 1, 2012 and December 31, 2014. Variables including age, sex, postal code, KPS, tumour location, presenting symptoms, treatment history, date of progression, date of reoperation, as well as MGMT, IDH, 1p/19q codeletion, and ATRX status were recorded. Preoperative and postoperative MRIs were reviewed and volumetric tumour burden will be analyzed and EoR will be calculated. RESULTS: Preliminary EoR calculations (n=18) show a positive correlation between EoR and OS. CONCLUSION: A correlation exists between EoR and OS, although multivariable analysis is planned to exclude potential confounders. MRI review, chart review including molecular marker analysis and EoR calculations are ongoing.

PC3 – 154

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Phase I/II Study of VAL-083 in Patients with Recurrent Glioblastoma

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Glioblastoma (GBM) is the most common brain cancer. Resistance to front-line systemic therapy with temozolomide (TMZ) is correlated with O6-methylguanine-DNA-methyltransferase (MGMT) expression. Second-line treatment with bevacizumab has not improved overall survival. Dianhydrogalactitol (VAL-083) is a bi-functional alkylating agent that has MGMT-independent cell-kill activity against GBM cell-lines and cancer stem cells in vitro. VAL-083 crosses the blood-brain barrier and showed promise against CNS tumors in prior NCI-sponsored clinical trials. The goal of this clinical trial is to determine appropriate VAL-083 dosing for advancement to Phase III trials as a new treatment for recurrent GBM. METHODS: Patients must have recurrent GBM following surgery, radiation, TMZ and bevacizumab. Phase I: Open-label, single-arm, dose-escalation study. Patients received VAL-083 on days 1,2,3 of a 21-day cycle, until reaching MTD. Phase II: Additional patients enrolled at MTD to further assess safety and outcomes. RESULTS: Phase I: 29 patients were enrolled across 9 dose cohorts (1.5-50 mg/m2/d). 40mg/m2/d was confirmed as MTD. Myelosuppression was mild; no drug-related serious adverse events were reported at doses up to 40mg/m2/d. Dose limiting G4 thrombocytopenia was observed at higher doses. Platelet nadir occurred around day 20 and resolved rapidly and spontaneously. A dose-related survival improvement was observed. Pharmacokinetic analyses show 1-2h plasma terminal half-life; average Cmax 781ng/mL at 40mg/m2/d. Phase II: 14 patients were enrolled at 40mg/m2/d. To date, safety observations in Phase II are consistent with Phase I. CONCLUSIONS: VAL-083 at 40mg/m2/d exhibits a favorable safety profile and dose-related trend toward clinically meaningful improved survival in refractory GBM patients.

PC3 – 155

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Phase II Study of Dianhydrogalactitol in Patients with MGMT-Unmethylated, Bevacizumab-Naïve Recurrent Glioblastoma

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Glioblastoma (GBM) is the most common brain cancer. Most GBM tumors have unmethylated promoter status for O6-methylguanine-DNA-methyltransferase (MGMT); a validated biomarker for MGMT protein-expression and ensuing temozolomide-resistance. Second-line treatment with bevacizumab has not improved overall survival (OS). Dianhydrogalactitol (VAL-083) is a bi-functional alkylating agent targeting N7-Guanine, thus MGMT-independently inducing interstrand cross-links, DNA double-strand breaks and cell-death in GBM cell-lines and cancer stem cells. VAL-083 is currently in Phase I/II clinical trial for recurrent GBM, post-TMZ and post-bevacizumab. In this Phase II clinical trial, the main goal is to assess the 9-month OS in MGMT-unmethylated, recurrent, bevacizumab-naive GBM. RATIONALE: The vast majority of GBM patients experience recurrent/progressive disease within a year from initial diagnosis and median survival after recurrence is 3-9 months. Chemotherapy regimens for these patients are lacking and there is a significant unmet medical need. Given VAL-083's novel alkylating mechanism, promising clinical benefit, and favorable safety profile, a trial studying VAL-083 in MGMT-unmethylated recurrent GBM is warranted. METHOD: Randomized, non-comparative biomarker-driven Phase II clinical trial in MGMT-unmethylated GBM patients at first recurrence/progression, prior to bevacizumab. 48 patients will be randomized to receive VAL-083 or "standard-of-care" salvage drug lomustine. 32 patients will receive VAL-083 40mg/m2/day on days 1,2,3 of a 21-day cycle. 16 patients will receive lomustine 90 mg/m2/day on day 1 of a 42-day cycle. Patients will be followed until death or for at least 9 months from enrollment, whichever occurs earlier. Survival will be compared to the BELOB trial for recurrent MGMT-unmethylated GBM patients treated with lomustine.

PC3 – 164

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Urban-Rural Residence and Brain Cancer Survival in Canada (1996-2008)

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Disparities in cancer survival rates have been identified for rural patients in Canada and are thought to be due to inequities in access to care. The objective was to perform the first examination of urban and rural brain cancer survival in Canada. Methods: A population-based retrospective cohort study was performed using Canadian Cancer Registry data for patients diagnosed with a primary brain cancer from 1996-2008. Seven major brain cancer histology groups used were glioblastoma, diffuse astrocytoma, glioma (not otherwise specified), oligodendroglioma, anaplastic astrocytoma, oligoastrocytic tumours, and anaplastic oligodendroglioma as categorized by the Central Brain Tumor Registry of the United States (CBTRUS). Kaplan-Meier (KM)

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