subtypes showed that M1 was enriched with neural subtype-specific genes. Using the gene expression data from four fetal neuronal stem cell lines and 13 GBM-derived neural stem (GNS) cell lines, we found that M1 was also enriched for genes that are up regulated in GNS. CONCLUSIONS: These results provide empirical support for a unique gene network influencing GBM invasive margins and illustrate how systems-level analyses can reveal relationships between invasion-associated genes in GBM.

P08.17 TARGETING DEVELOPMENTAL PROTEINS AS A NOVEL TREATMENT IN GliOBLASTOMA
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INTRODUCTION: HOX genes are essential developmental genes that pattern the body during embryonic development, but are dysregulated in numerous cancers, including glioblastoma. The HOX genes are expressed at varying levels in glioblastoma cells, and are highly expressed in glioma stem cells. HXR9, a small hexapeptide designed to inhibit HOX-PBX binding, has been shown to be cytotoxic in a variety of solid tumour models. We aimed to evaluate whether HXR9 is a potential glioblastoma treatment.

METHODS: HOX and PBX expression were determined using quantitative RT-PCR and western blot analysis. Glioma cell lines were enriched for glioma stem cells and these were assessed for stem cell marker expression using immunofluorescence techniques. Patient-derived glioma samples were then treated with HXR9, and cell viability was determined by MTS assay. Mode of death was assessed using annexin V/7-AAD and caspase 3/7 Glo assays. The anti-proliferative and anti-migratory properties of HXR9 were then determined using a BrdU incorporation assay and transwell migration assays, respectively.

RESULTS: Glioma cell lines showed elevated HOX and PBX expression when compared to normal astrocytes, with glioma stem cells exhibiting the highest expression levels. Patient-derived samples showed similar HOX and PBX dysregulation when compared to matched adjacent tissue. HXR9 showed dose dependent cytotoxicity in all cell lines, with glioma stem cells having the greatest sensitivity. Patient-derived glioma stem cells were shown to be the most sensitive with IC50 values less than half of the most sensitive cell line. The mechanism of cell death was determined to be apoptosis via annexin V/7-AAD and Caspase 3/7 Glo assays. Cells treated with an IC25 dose of HXR9 exhibited a marked reduction in proliferation and migration, without causing apoptosis. All assays were performed with a control peptide CXR9, which differs from HXR9 by only a single amino acid. CXR9 was shown to have no cytotoxic, anti-proliferative or anti-migratory potential.

CONCLUSION: HOX and PBX genes are aberrantly expressed in glioblastoma cells, with glioma stem cells, either artificially produced or patient-derived, showing the highest expression levels. This aberrant expression is also seen in patient derived tissue. HXR9 has a potent cytotoxic potential and can target glioma stem cells, which are widely accepted to be the most malignant and resistance glioma cell subtype. Glioma cell sensitivity to HXR9 in vivo are to follow.

P08.18 LC-MS-BASED GENOME-WIDE PROFILING OF GliOBLASTOMA METABOLIC SUBCLONES AND FUNCTION METABOLISM WITHIN THE INVASIVE REGION
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INTRODUCTION: Glioblastoma multiforme (GBM) demonstrates a heterogeneous genetic landscape resulting from dynamic competition between tumour subclones to survive selective pressures within the tumour microenvironment, including gradients in oxygen and nutrients. Improvements in metabolite identification and metabolome coverage have led to increased interest in clinically relevant applications of metabolomics. Here, we use liquid chromatography–mass spectrometry (LC-MS) as an analytical method to extract tumour metabolic heterogeneity, as a direct functional readout of the adaptive responses of tumour subclones to the tumour microenvironment.

MATERIALS AND METHODS: Multi-region surgical sampling during gross tumour resection was performed on five adult GBM patients based on pre-operative MRI scans and administration of 5-aminolevulinic acid to assist in the fluorescent identification of the invasive region. Metabolites extracted from tumour fragments were assessed through LC-MS-based metabolite profiling, followed by putative assignment of metabolite identifications based on retention times and exact masses of authentic standards. One-way ANOVA (FDR<0.05) and OPLS-DA were used for significant feature selection.

RESULTS: Putative identifications were made for a total of 787 metabolites. A class distinction between non-invasive and invasive regions of GBM was shown to be clear and statistically significant for both regions when compared to normal adjacent tissue. A total of 787 candidate features showed clear separation of tumour regions based on polar metabolite profiles with R2 and Q2 values of 0.854 and 0.528, respectively. Clustering analysis of hydrophobic metabolites only revealed class distinction between invasive tumour regions and the invasive region. Metabolic pathway assignments revealed the majority of significantly altered metabolites between the tumour core and invasive region to be associated with purine and pyrimidine metabolism.

CONCLUSIONS: This proof-of-principle study is the first to assess intra-tumour metabolic heterogeneity through LC-MS-based metabolite profiling of multi-region biopsies. Bioinformatic integration of the GBM metabolome and lipodrome has highlighted the invasive region to be biologically distinct compared to tumour core and revealed drug-targetable metabolic pathways associated with purine and pyrimidine metabolism that may sustain invading glioma cells. Integration of transcriptomic and metabolomic data sets to reveal metabolic associations with TCGA GBM subtypes will be discussed.

P08.19 EFFICACY OF A NOVEL ANTIBODY-DRUG CONJUGATE (ADC), ABT-414, AS MONOTHERAPY IN EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) AMPLIFIED, RECURRENT GliOBLASTOMA (GBM)
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BACKGROUND: Recurrent GBM (rGBM) has dismal prognosis. Almost 50% GBM tumors harbor amplified (amp) EGFR. ABT-414 is a tumor specific ADC combining an antibody targeting a unique conformation of EGFR (ABT-906) to a micromolecular cytotoxic, monomethyl auristatin F (MMAF).

RESULTS: We report the safety and efficacy of ABT-414 monotherapy at recommended phase 2 dose (RPTD) in EGFR amp, rGBM.

METHODS: MI2-336 (NCT01800695) is an open-label, phase 1, 3-arm study: Arm A (ABT-414+radiation/temozolomide (TMZ) in newly diagnosed GBM), Arm B (ABT-414+TMZ in GBM as adjuvant therapy, or in rGBM) and Arm C (ABT-414 monotherapy in rGBM). Each arm had an escalation cohort to determine the RPTD and an expansion cohort to establish the safety and preliminary efficacy at RPTD. Results of Arm C expansion cohort at 1.25 mg/kg RPTD (IV infusion) are shown here. Eligible patients (pts) were adults with KPS score ≥70, EGFR amp (confirmed centrally), rGBM, normal end-organ function and no prior bevacizumab.

RESULTS: As of January 7, 2016, 48 EGFR amp, rGBM pts were treated in this cohort. The median age was 59 years (range, 35–80). Most pts had prior therapies: 40% had 1, 48% had 2, 10% had ≥3 prior therapies. Most common treatment emergent adverse events (TEAEs) (≥25% pts) were blurred vision (60%), headache, photophobia (29% each), dry eye, eye pain, fatigue (27% each). The most common serious AE (>1 pt) was seizure (8%). Grade 3/4 TEAEs (>1 pt) were keratitis (15%), corneal epithelial microcysts (8%), hemaparas, hyperglycemia, muscular weakness, seizure (6% each), blurred vision, ulcerative keratitis (4% each). No dose-limiting toxicities were reported. Best RANO responses of 44 pts with complete data were: 2 partial responses, 18 stable disease, 24 progressive disease. The 6-month progression-free survival (PFS6) estimate was 30% [95% CI, 17–44].

CONCLUSIONS: ABT-414 monotherapy, at 1.25 mg/kg RPTD, displayed frequent yet reversible ocular toxicities. An encouraging tumor stability/response and PFS6 were observed in this highly refractory EGFR amp, rGBM. A global randomized phase 2 study of ABT-414, alone or with TMZ, vs. TMZ or lomustine, is underway in EGFR amp, rGBM (NCT02343406).