BACKGROUND: Bevacizumab combined with chemotherapy is among the most frequently used treatments in recurrent glioblastoma, and patients who achieve response to bevacizumab have improved survival as well as quality of life. The aim of this study was to investigate transcriptional changes associated with response and resistance to bevacizumab therapy. MATERIAL AND METHODS: The study included 21 recurrent glioblastoma patients who were response evaluable and had biomarker assessable tumor tissue surgically removed both before bevacizumab treatment and at time of progression. Patients were grouped into responders (n = 7) and non-responders (n = 14). Gene expression profiling of formalin-fixed paraffin-embedded tumor tissue was performed using RNA-sequencing. Differentially expressed genes were identified by comparing pretreatment samples of responders with those of non-responders and by pairwise comparison of pre- and posttreatment samples in responders and non-responders, separately. False discovery rate adjusted p-values < 0.05 were considered significant. Significant genes were analyzed by functional data mining. RESULTS: There was no significant difference when comparing the transcriptional expression of responders and non-responders prior to initiation of bevacizumab therapy. In non-responders, we identified 1 differentially expressed gene using paired analysis of before and after treatment samples. In responders, this approach revealed 236 significantly differentially expressed genes (false discovery rate adjusted) of which 72 genes were down-regulated and 164 genes were up-regulated at time of progression. Genes differentially expressed in responders revealed a shift towards a more proneural and less mesenchymal phenotype at the time of progression. These transcriptional changes were found associated with a down-regulation of TGF-β family. CONCLUSION: Bevacizumab combination treatment is associated with significant transcriptional changes in responders but not in non-responders. This suggests that non-responders progress due to intrinsic resistance while responders progress due to acquired resistance to bevacizumab. Data suggests that responding glioblastomas undergoes a reverse mesenchymal shift at the time of recurrence, possibly related to down-regulation of TGF-β activity.

P08.07 MICRONRNA REGULATION OF INTRATUMOUR METABOLIC HETEROGENEITY IN GLOBLASTOMA MULTIFORME

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Glioblastoma multiforme (GBM) is the most aggressive and common malignant brain and central nervous system tumour. GBM adaptation to the diverse micro-environmental conditions, including varying degree of vasculature, nutritional supply, oxygen and pH levels, is reflected on its tumour microenvironment (TME) and metabolic heterogeneity. microRNA (miRNA) play a role in the regulation of gene expression and translation. They have been implicated in the regulation of metabolic pathways. Understanding the intratumour heterogeneity in miRNA expression will add an extra layer of complexity to the regulation of metabolic heterogeneity in GBM. The set of the differentially expressed miRNA in different regions of the GBM tumour can serve as therapeutic targets to selectively disrupt and destabilise dysregulated metabolic processes in GBM cells across a widespread area of the brain, whilst sparing normal brain cells that employ functional metabolic pathways.

P08.08 EXPRESSION LEVEL OF MRNAS ON CHROMOSOME 14q32.31 REGION CORRELATES WITH SURVIVAL OF GLOBLASTOMA PATIENTS

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BACKGROUND: The 54 miRNAs within the DLK-DIO3 genomic region on chromosome 14q32.31 (cluster 14 miRNAs) are organized into sub-clusters 14A and 14B. These miRNAs are down-regulated in glioblastomas and might have a tumor suppressive role. Any association between the expression levels of cluster 14 miRNAs with overall survival (OS) is undetermined.

METHOD: We randomly selected miR-433, belonging to subcluster 14A and 14B, both belonging to cluster 14 miRNAs, and assessed their role in vivo in glioblastoma cell lines. We also determined the expression level of cluster 14 miRNAs in tumor samples obtain from tumor bank tissues of 28 patients with newly diagnosed glioblastoma. We analyzed the association between cluster 14 miRNAs and OS.

RESULTS: Overexpression of miR-323-3p and miR-369-3p, but not miR-433, in glioblastoma cells inhibited their proliferation and migration in vitro studies. Bioinformatics analysis identified 13 putative target genes of cluster 14 miRNAs, and real-time RT-PCR validated these findings. Pathway analysis of the overexpressed transcripts identified neuroglin (glial growth factor) as the most enriched pathway. The expression level of cluster 14 miRNAs correlated with the patients’ OS. The median OS was 8 months for patients with high expression levels and 32.5 months for patients with low expression levels (HR = 0.37; 95% CI 0.12-0.64, P = 0.005).

CONCLUSIONS: The expression level of cluster 14 miRNAs correlates with OS, suggesting a role for cluster 14 miRNAs in promoting aggressive behavior of glioblastoma, possibly through neuroglin signaling.

P08.09 AXITINIB FOR THE TREATMENT OF PATIENTS WITH RECURRENT GLOBLASTOMA, FINAL RESULTS FROM A RANDOMIZED PHASE II CLINICAL TRIAL TRIMG

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BACKGROUND: vascular endothelial growth factor receptor (VEGFR) signal transduction mediates glioblastoma (GBM) associated neo-angiogenesis. The AXIG trial (NCT01562197) is a randomized clinical trial that initially investigated the activity of axitinib as a monotherapy (AXI-arm) versus physicians best alternative choice of therapy (Duerinck et al. JNO March 2016) and following amendment axitinib plus lomustine (Duerinck et al. ASCO AM 2016).

METHODS: an updated pooled analysis was made of the clinical outcome of all patients who initiated treatment with axitinib mono-therapy or axitinib in combination with lomustine in the AXIG trial.

RESULTS: between August 2011 and July 2015, a total of 78 pts were enrolled in the trial and initiated treatment with axitinib monotherapy (N: 50; AXI) or axitinib plus lomustine (N: 28; AXILOM). Median age was 55y [range 18–80], 50M/28F, 19, 29, 19, 7 and 4 pts had a WHO-PS of 0, 1, 2, 3 and 4 respectively. Baseline characteristics were well balanced between study arms. The AXIG trial (NCT01562197) is a randomized clinical trial that was initially investigated the activity of axitinib as a monotherapy (AXI-arm) versus physicians best alternative choice of therapy (Duerinck et al. JNO March 2016) and following amendment axitinib plus lomustine (Duerinck et al. ASCO AM 2016). All pts had failed prior surgery, RT and TMZ. Thirteen pts in the AXI-arm crossed-over at the time of progression (AXIseqLOM). Median OS of all patients who initiated treatment with axitinib mono-therapy or axitinib in combination with lomustine was well tolerated. AXILOM pts were at higher risk for grade 3/4 adverse events (most frequent gr3/4 AE on AXILOM vs AXI were: thrombocytopenia 3- vs 0 pts, hypertension 2 vs 2 pts, anemia 3 vs 3 pts).

From the overall survival of the tumour outcomes produced significantly (P< 0.001) more lactate than established GBM cell lines origi

neity in GBM. The set of the differentially expressed miRNA in different regions of the GBM tumour can serve as therapeutic targets to selectively disrupt and destabilise dysregulated metabolic processes in GBM cells across a widespread area of the brain, whilst sparing normal brain cells that employ functional metabolic pathways.

Understanding the intratumour heterogeneity in miRNA expression will add an extra layer of complexity to the regulation of metabolic heterogeneity in GBM. The set of the differentially expressed miRNA in different regions of the GBM tumour can serve as therapeutic targets to selectively disrupt and destabilise dysregulated metabolic processes in GBM cells across a widespread area of the brain, whilst sparing normal brain cells that employ functional metabolic pathways.

Understanding the intratumour heterogeneity in miRNA expression will add an extra layer of complexity to the regulation of metabolic heterogeneity in GBM. The set of the differentially expressed miRNA in different regions of the GBM tumour can serve as therapeutic targets to selectively disrupt and destabilise dysregulated metabolic processes in GBM cells across a widespread area of the brain, whilst sparing normal brain cells that employ functional metabolic pathways.