for U87, U137, U251, and T98G, respectively. However, if combined with LEV(40μg/ml) for 72 hours, the sensitivity of glioma cell lines to TMZ was significantly increased (P < 0.05), the IC50 were 208.91 ± 25.64μmol/l, 272.3 ± 18.67μmol/l, 272.3 ± 18.67μmol/l, and 272.3 ± 18.67μmol/l for U87, U137, U251 and T98G, respectively. The MGMT expression was negative in cell lines, U87, U137 and U251, but positive in cell lines T98G.

CONCLUSION: Leviteracetam can significantly increase TMZ anti-tumor activity against glioma cell lines especially to those MGMT negative gliomas.

P08.43 BEVCIZUMAB DISCONTINUATION AND BEVCIZUMAB RE-CHALLENGE IN GLOBLASTOMA PATIENTS
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BACKGROUND AND OBJECTIVE: In glioblastoma (GBM) patients who benefit from bevacizumab, it is unknown how long this treatment should be continued and whether it may be safely stopped. The aim of the present study was to describe the outcome of 36 responding GBM patients in whom bevacizumab was discontinued in the absence of tumour progression.

MATERIAL AND METHODS: We retrospectively reviewed the characteristics of GBM patients who received bevacizumab (10mg/kg every 2 weeks) either as first-line treatment in association with temozolomide radiochemotherapy (n=13) or at recurrence (n=23) in association to temozolomide, CCNU or irinotecan. In all of the patients, bevacizumab was discontinued while they had achieved a partial (63%) or a complete response (37%) according to RANO criteria. Reasons for bevacizumab discontinuation were physician’s decision in 80% of cases and toxicity in 20% of cases.

RESULTS: In patients treated with first-line bevacizumab (median number of infusions = 4, range 1 to 44), median time to progression and median survival after bevacizumab discontinuation, were 11.8 months and 29 months, respectively. In patients treated with bevacizumab at recurrence (median number of infusions = 10, range 2 to 36), median time to progression and median survival after bevacizumab discontinuation were 6.9 months and 15 months, respectively. In none of the patients, rebound tumor recurrence upon bevacizumab discontinuation was observed. At the time of tumor progression, 22 patients were re-treated with bevacizumab with a 53% response rate and a median progression-free survival of 6 months.

CONCLUSION: In responding patients, bevacizumab may be discontinued without rebound recurrence and a prolonged response may be observed in the absence of prolonged treatment. At the time of tumor progression, previously responding patients may benefit from bevacizumab re-challenge.

P08.44 PHASE II STUDY OF HYPOFRACTIONATED RADIATION THERAPY WITH CONCOMITANT AND ADJUVANT TEMOZOLOMIDE FOLLOWING SURGICAL RESECTION FOR PATIENTS WITH NEWLY DIAGNOSED GLOBLASTOMA: PRELIMINARY EVALUATION
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INTRODUCTION: The current standard treatment for glioblastoma multiforme (GBM) has led a median, overall survival (OS) of 14.6 months, a 2-year progression-free survival (PFS) of 11% and a 2-year OS of 27.2%. The predominantly local failure pattern indicates the need to intensify local treatment. Radiation therapy dose escalation did not result in an improvement of tumor local control and patient survival. Hypofractionation could be an attractive alternative approach of dose intensification compared to dose escalation with conventional fractionation. It uses a higher dose per fraction to increase the biological effective dose, while shortening the overall treatment time. The aim of this phase II study is to evaluate safety and feasibility of hypofractionated RT in addition to chemotherapy, concomitant and adjuvant, following surgical resection, in patients with newly diagnosed GBM.

METHODS AND MATERIALS: From September 2013 to February 2016, 120 patients with newly diagnosed GBM were enrolled. This is a preliminary evaluation of the first 49 patients treated. Inclusion criteria were presence of GBM in patients aged >70 years with KPS ≥80, histopathologically confirmed of GBM or WHO grade III glioma IDH1 wild type and no codeletion 1p/19q, estimated survival ≥ 3 months, tumor or surgical cavity ≤ 10 cm in its greatest diameter (including FLAIR area). All patients underwent surgical resection followed by hypofractionated radiation therapy, concomitant and adjuvant chemotherapy with temozolomide. The total dose prescribed was 60 Gy/ 4 Gy fraction/15 fractions (BEDp 84, Gy) on surgical cavity and eventual postoperative residual tumor.

RESULTS: The majority of patients had KPS ≥80, histopathologically confirmed of GBM or WHO grade III glioma IDH1 wild type and no codeletion 1p/19q, estimated survival ≥ 3 months, tumor or surgical cavity ≤ 10 cm in its greatest diameter (including FLAIR area). All patients evaluated have carried out the treatment as planned and no interruption or severe toxicity occurred. At the last observation time 15 (30.6%) patients are alive and 34 (69.4%) dead. The median, 1- and 2-year PFS were 14.9 months, 63% and 13.7%; the median, 1 and 2 years Disease-specific survival (DSS) were 16.2 months, 76.5% 22.9%. Patients with age < 60 years, KPS 90–100, complete surgical resection, MGMT methylated status had better outcome with a median, 1 and 2 years DSS of 22.5 months, 85.7%; 22.4 months, 92%, 30%; 20.3 months, 86.9%; 35%; 20.3 months, 76.2%, 38% respectively.

CONCLUSIONS: Hypofractionated radiation therapy is a safe and feasible treatment for patients with newly diagnosed glioblastoma.

PO8.45 MIBEFRADIL DIHYDROCHORIDE WITH HYPOFRACTIONATED RADIATION FOR RECURRENT GLOBLASTOMA: PRELIMINARY RESULTS OF A PHASE I DOSE ESCALATION TRIAL

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INTRODUCTION: Recurrent Glioblastoma Multiforme (GBM) has limited treatment options and the prognosis is poor. Our group recently performed a high-throughput screen for novel drugs which could inhibit tumor correlate with that required for tumor cell radiosensitization in vitro. We screened 300 compounds for the presence of drug in situ using LC/MS, in both T1-post contrast and FLAIR regions of disease. These levels in the translational sub-study. Of note, we detected drug levels in biopsies specifically from T1-post contrast and FLAIR regions of disease; as identified by intraoperative MRI. Inclusion criteria included histologically proven GBM progressive or recurrent following RT and temozolomide. Patients received mibefradil, which was co-administered with RT over a 17 day period at 200 mg/day. Promising tumor activityagainst glioma cell lines especially to those MGMT negative but positive in cell lines T98G. however, if combined with LEV(40μg/ml) for 72 hours, the sensitivity of glioma cell lines to TMZ was significantly increased (P < 0.05), the IC50 were 208.91 ± 25.64μmol/l, 272.3 ± 18.67μmol/l, 272.3 ± 18.67μmol/l, and 272.3 ± 18.67μmol/l for U87, U137, U251 and T98G, respectively. The MGMT expression was negative in cell lines, U87, U137 and U251, but positive in cell lines T98G.

CONCLUSION: Leviteracetam can significantly increase TMZ anti-tumor activity against glioma cell lines especially to those MGMT negative gliomas.

backbone.
approximately 15 months following standard of care therapy. However, 10% survival at 5 years was observed in a randomized phase III study. At GBM recurrence, the addition of bevacizumab (BEV), a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), resulted in a 3–4 month prolongation of progression-free survival (PFS) without improving overall survival (OS). A 45-year-old female who underwent surgery for left fronto-temporal WHO grade II astrocytoma associated with a 1253 bp insertion and missense mutations, and seed explantation 9 months later, was diagnosed with MGMT methylated GBM on the occasion of partial tumor resection in 2010 followed by radiotherapy plus concomitant and adjuvant temozolomide (TMZ) chemotherapy, which was stopped after 4 months due to recurrence of a left temporal tumor cyst and recurrent cyst within 1 month. TMZ treatment causing prolonged thrombocytopenia was discontinued after 1 additional cycle. Immediately after this cycle, the patient experienced left median cerebral artery stroke resulting in right hemianopia, Broca’s aphasia and severe hemiparesis of the right side. Three months later, BEV 10 mg/kg i.v. q4d was initiated, shortly interrupted for abdominal herniotomy in 2012, and continued for 3 years. Since 2014, concurrent low molecular weight heparin was given because of right lower limb deep venous thrombosis suspicion. Whereas GBM progression had not been detected for 2 years during anti-VEGF therapy, methotrexate PET MRI 6 months after BEV discontinuation revealed left temporal tumor recurrence. Rechallenge with BEV was initiated and the patient remained in stable clinical and radiographical condition for 15 months. The case highlights the potential utility of salvage therapy in a patient at high risk to develop chemotherapy-induced myelotoxicity. Long-term survival (>3 years after diagnosis) in GBM has been attributed to patient-derived rather than tumor-derived factors. To our knowledge, this is the first description of a late term-ontherapy with BEV for GBM and ongoing therapeutic response to single-agent BEV rechallenge in a patient with recurrent secondary GBM.

P08.47 DIANHYDROGALACTITOL (VAL-083) CAUSES BIFUNCTIONAL ALKYLATION LEADING TO IRREVERSIBLE DNA DOUBLE-STRAND BREAKS, S/G2 PHASE CELL-CYCLE ARREST AND TUMOR CELL DEATH IN AN MGMT INDEPENDENT MANNER OFFERING A UNIQUE TREATMENT PARADIGM FOR GBM

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Glioblastoma (GBM) is the most common brain cancer. Systemic therapy with temozolomide or nitrosoureas is often ineffective due to the activity of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase (MGMT). Patients with recurrent GBM have limited treatment options and a poor outcome. Dianhydrogalactitol (VAL-083) is a bifunctional alkylating agent that rapidly induces interstrand DNA cross-links targeting N7 of guanine leading to cell cycle arrest and apoptosis due to DNA double-strand breaks. VAL-083 readily crosses the blood-brain barrier and accumulates in brain tumor tissue and has shown activity in NCI-sponsored clinical trials against CNS tumors, including GBM and medulloblastoma. We have previously shown that VAL-083’s cytotoxic activity is independent of MGMT in contrast to temozolomide and nitrosoureas. We have also demonstrated VAL-083 is active against GBM cancer stem cells (CSCs) and acts as a radiosensitizer in GBM CSCs, in vitro. We have also previously shown that VAL-083 cdc571695 circumvents cisplatin-resistance and is less dependent on p53 activity than cisplatin suggesting a distinct mechanism of action for VAL-083. We recently completed enrollment of a Phase III clinical trial in the United States for recurrent GBM in patients who have failed temozolomide and bevacizumab (clinicaltrials.gov identifier: NCT01478178). Separate clinical trials are planned in GBM patients with high expression of MGMT both in recurrent bevacizumab-naive GBM patients (clinicaltrials.gov identifier: NCT02717962) and in newly diagnosed GBM patients utilizing MGMT promoter methylation as a validated biomarker for patient selection. Here we report new insights into VAL-083 mechanisms of action by showing that VAL-083 rapidly induces interstrand DNA cross-links leading to irreversible S/G2 cell-cycle arrest and cell death caused by replication-dependent DNA damage. VAL-083 pulse-treatment leads to persistent phosphorylation of DNA double-strand break (DBS) sensors ATM, single-strand DNA-binding Replication Protein A (RPA32), and histone variant H2AX. After 10 months in culture, following a standard protocol for inducing chemo-resistance, cancer cells remained sensitive to VAL-083 at low M concentrations. Taken together, these results support a unique mechanism of action for VAL-083 in retrospectively selected GBM patients not easily acquired by cancer cells.

Tumors with histological features of pilocytic astrocytoma but with increased mitotic activity and additional high grade features (i.e. microvascular proliferation, necrosis) have been designated anaplastic pilocytic astrocytomas (APA). Patients with such tumors are thought to have an unfavorable clinical outcome. The status of APA as a separate entity has not yet been established and molecular features have only partially been elucidated. We analyzed a large retrospective series of 98 cases with histological features of APA by genome wide DNA methylation profiling, copy number analysis, targeted sequencing and, in a subset, panel sequencing. Unexpected biallelic clonal clustering analysis of 450K methylation data together with over 250 reference cases of 13 established glioma classes (glioblastoma, astrocytoma, oligodendroglioma, pleomorphic xanthoastrocytoma, pilocytic astrocytoma, ganglioglioma, dysembryoplastic neuroepithelial tumor and diffuse leptomeningeal glioneuronal tumor) revealed a heterogeneous group of tumors. We identified the expression of a distinct methylation cluster comprising 73 APA (“APA core group”). Most of the remaining cases clustered into other tumor classes. The median age of the APA core group was 43 years with only 6/69 (9%) cases occurring in pediatric patients. 56/67 (84%) were located in the cerebellum. The most frequent molecular alterations were deletions of CDKN2A/B (64/73, 87%) followed by alterations of the MAPK pathway (19/24, 79%, mostly NFI mutations and BRAF fusions) and loss of ATRX (31/67, 46%). Outcome analysis confirmed an overall median survival of 22/28 (43%) patients deceased (median survival 13 months). In summary, APA is characterized by increased patient age, predominant cerebellar location, frequent MAPK pathway alterations, CDKN2A/B deletion, ATRX loss and unfavorable prognosis.

P08.49 THE VALUE OF NEUROCOGNITIVE TESTING IN MULTIMODAL RESPONSE ASSESSMENT IN PATIENTS WITH Glioblastoma multiforme

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BACKGROUND: Due to several possible clinical and radiological pitfalls in response assessment, Tumorboard decision (TB) in patients with glioblastoma can sometimes be challenging. Early detection of recurrence in glioblastoma multiforme (GBM) is a crucial factor for a prompt and effective second line therapy. Standard MRI sequences are the main diagnostic tool for follow up and the diagnosis of possible tumor recurrence. Additional MRI sequences, such as MRT-Perfusion and MRI-Perfusion imaging, or 18F-FET-PET (PET) imaging, may provide useful information in ambiguous GBM imaging. We were interested in answering the question, whether additional neurocognitive assessment (NA) is in line with imaging results, as well as the TB. METHODS: We consecutively enrolled twenty-five patients with histological diagnosis of newly diagnosed GBM from 2010 to 2015 in a retrospective pilot study, counting for eighty-one (n=81) multimodal follow up (FU) test results. All patients were selected after receiving consecutive FU, comprising of MRI, PET and NA, using basically NeuroCogFX as neuropsychological test battery. Results were analysed for statistically significant correlations among themselves and over time. A consistency analysis was performed to demonstrate the impact of the presence or absence of the abnormalities.