hours per day) improve survival outcomes as observed in GBM clinical trials. The results of this patient survey indicate that the improved size, weight and convenience of the second generation Optune® System help patients comply with daily treatment duration goals.

P09.24 THE GERMLINE MUTATION PIK3R1MET326ILE CORRELATES WITH THE LEVELS OF CYSTEINE<->RICH PROTEIN 61 AND POOR PROGNOSIS OF GLIOBLASTOMA

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Despite advances in treatment, glioblastoma remains a lethal brain tumor. Efforts to identify prognostic molecular biomarkers for glioblastoma have intensified, and we previously reported that the median progression-free survival (PFS) and overall survival (OS) of patients with high levels of cysteine-rich protein 61 (CCN1/CYR61) are significantly shorter compared with those with low levels of CCN1. To identify the molecular mechanisms that regulate the expression of CCN1 in glioblastomas, we analyzed tumor samples from 42 patients with glioblastoma. Next-generation and Sanger sequencing techniques revealed that the PIK3R1Met326Ile mutation was significantly more frequent in patients with high vs low levels of CCN1 (9/22, 40.9% vs 2/20, 10.0%; respectively). Moreover, this mutation was identified in the corresponding blood samples. Univariate analysis of Kaplan-Meier survival data revealed that high levels of CCN1 and the presence of the PIK3R1Met326Ile mutation were significantly associated with PFS ($p=0.0003$ and 0.0191 , respectively) and that age, high levels of CCN1, and the presence of the PIK3R1Met326Ile mutation were significantly associated with OS ($p=0.0016$, 0.0019 and 0.0057 , respectively). Multivariate analysis identified age >65 years and the presence of the PIK3R1Met326Ile mutation as prognostic factors for OS (HR=3.533 [1.519-8.220], $p=0.003$) and (HR=2.712 [1.187-6.198], $p=0.018$, respectively). We conclude that the germline mutation PIK3R1Met326Ile correlates with the levels of CCN1 and poor prognosis of glioblastoma.

P09.25 IDENTIFYING THE CORRECT PATIENT (PT) POPULATION FOR ABT414: BIOMARKER ASSAYS FOR EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) IN PTS WITH GLIOBLASTOMA (GBM)

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AIM: Aberrant EGFR signaling plays a vital role in GBM oncogenesis. ABT414 comprises an EGFR targeted antibody conjugated to the toxic agent monomethylauristatin F. An open label, 3 arm, phase I study (NCT01800695) is underway to evaluate 3 different ABT414 regimens in GBM. To understand the population most suited for ABT414 therapy, assays measuring EGFR gene amplification/protein overexpression, and the presence of EGFRvIII mutation have been developed. **METHODS:** Total EGFR and EGFRvIII expression were measured with reverse transcription polymerase chain reaction (RT-PCR). EGFR gene amplification was detected with fluorescence in situ hybridization (FISH) using 2 probes: Vysis locus specific identifier EGFR probe and Vysis chromosome enumeration probe (CEP) 7 probe. FISH utilized Ratio of EGFR to CEP 7 to identify locus specific EGFR gene amplification. Total EGFR protein expression was analyzed via immunohistochemical (IHC) using Dako pharmDx™ IHC assay. Relative expression of total EGFR and presence of EGFRvIII mRNA were determined with quantitative RTPCR. Tumor tissues from 89 pts were used for these tests. **RESULTS:** IHC and RTPCR confirmed expression of EGFR mRNA and protein are correlated in GBM tissue samples (Spearman correlation is -0.86, $P = 0.0026$). A strong association between EGFR gene amplification and mRNA overexpression was observed. EGFRvIII mRNA was detected almost exclusively in cases with EGFR amplification. Thus far, EGFR amplification has been confirmed in 23/29 pts tested. All 6/6 pts with confirmed objective radiographic responses by Response Assessment in NeuroOncology criteria displayed EGFR gene amplification, whereas only 5/6 pts had total EGFR mRNA overexpression using RTPCR. EGFRvIII expression by RTPCR was detected in 4/6 pts. **CONCLUSIONS:** Assays were developed to characterize

EGFR gene amplification, EGFR mRNA and protein expression, EGFRvIII status, and used to characterize EGFR status of GBM samples from pts treated with ABT414 in ongoing phase I trial. When comparing EGFR status to pt outcome, EGFR amplification by FISH had strongest association with objective radiographic responses.

P09.26 FET PET RADIOMICS - DIAGNOSIS OF PSEUDOPROGRESSION IN GLIOBLASTOMA PATIENTS BASED ON TEXTURAL FEATURES

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INTRODUCTION: The differentiation of pseudoprogression (PsP) from tumor progression (TP) in glioblastoma patients is difficult on the basis of standard MRI alone. Textural feature analysis as part of the concept of radiomics offers a quantitative method to describe tumor heterogeneity and gains increasing interest in the field of neuro-oncology. In our study, we investigated the potential of textural features of O-(2-[¹⁸F]fluoroethyl)-L-tyrosine (FET) PET to discriminate between PsP and TP in glioblastoma patients. **MATERIALS AND METHODS:** Twenty-three newly diagnosed glioblastoma patients with MRI findings suspicious for TP within 12 weeks after completion of chemoradiation with temozolomide underwent an additional dynamic FET PET scan. Volumes-of-interest were defined on summed images from 20-40 min post-injection (p.i.) by a 3-dimensional auto-contouring process using a tumor-to-brain ratio (TBR) of 1.6 or more. For each lesion, TBRs and the time-activity curves (TACs) of the FET uptake were determined. The TACs were used to evaluate the dynamic FET PET parameters time-to-peak (TTP), slope (slope of linear regression line 20-50 min p.i.) and intercept (intercept of linear regression line with y-axis). Additionally, 39 textural parameters were calculated using the software LifeX (lifexsoft.org). The diagnostic accuracy of TBRs, TTP, slope, intercept, and textural parameters to discriminate between PsP and TP was evaluated using ROC analyses. In order to further increase the diagnostic accuracy, parameters were combined using linear logistic regression for classification of PsP and TP. **RESULTS:** Fourteen patients had a clinico-radiological diagnosis of TP and nine patients had PsP. The FET PET parameters TBRmean, TBRmax, TTP and intercept yielded a diagnostic accuracy to discriminate between PsP and TP of 79%, 79%, 58%, 63%, respectively. The dynamic FET PET parameter slope yielded the highest diagnostic accuracy of 83% to discriminate between PsP and TP. Two textural features showed a comparable accuracy of 79%. The diagnostic accuracy could not be increased by combination of parameters. **CONCLUSIONS:** Textural features yielded a comparable diagnostic accuracy for diagnosis of pseudoprogression in glioblastoma patients in comparison with static and dynamic FET PET parameters. Textural features might yield additional valuable information for this highly relevant clinical problem and should be further evaluated in larger cohort prospective studies.

P09.27 EFFECTIVENESS OF ANTIANGIOGENIC DRUGS (ADS) IN GLIOBLASTOMA (GBM) PATIENTS (PTS): A METANALYSIS OF RANDOMIZED CLINICAL TRIALS (RCTs)

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BACKGROUND: GBMs are highly vascularized tumors and various ADs have been investigated in clinical trials showing unclear results. We performed this metanalysis to evaluate the effectiveness of ADs, in terms of progression-free survival (PFS) and overall survival (OS), as first or second-line therapy and their association with chemotherapy in GBM PTS. **METHODS:** the authors searched relevant published and unpublished RCTs analyzing ADs versus chemotherapy in GBM PTS from 2000 to January 2016 in MEDLINE, WEB OF SCIENCE, ASCO, ESMO and SNO databases. **RESULTS:** sixteen RCTs (9 with bevacizumab, 2 cilengitide, 1 enzastaurin, 1 dasatinib, 1 vandetanib, 1 temsirolimus, 1 cediranib) were identified including 4566 PTS. All trials showed no improvement in OS with a pooled HR of 1.02 (95% CI 0.93-1.1; $p = 0.7$). The use of bevacizumab (BEV) did not improve OS; indeed, the pooled HR for OS for BEV studies (9 studies, 2752 PTS) was 0.98 (95% CI 0.89-1.08; $p = 0.7$); 6 RCTs (2084 PTS) analyzed BEV as first-line and the pooled HR for OS was 1.02 (95% CI 0.88-1.19; $p = 0.8$); 3 RCTs studied BEV as second-line therapy and the pooled HR for OS was 0.95 (95% CI 0.77-1.17; $p = 0.6$). No improvement of OS was shown when BEV was associated with chemotherapy (2588 PTS) with a pooled HR of 0.99 (95% CI 0.88-1.11; $p = 0.8$). Seven RCTs with a different AD demonstrating no improvement of OS versus standard treatment with a pooled HR of 1.05 (95% CI 0.89-1.23; $p = 0.5$). 14 RCTs (4349 PTS)

were analyzed for PFS and the use of ADs showed a statistically longer PFS with a pooled HR of 0.73 (95% CI 0.62-0.86; $p < 0.01$); However, among ADs, only bevacizumab (2752 PTS) demonstrated an improvement of PFS; indeed, the pooled HR for PFS for BEV studies was significant at HR = 0.6 (95% CI 0.5-0.7; $p < 0.01$), both alone (HR = 0.6; CI 95% 0.44-0.82; $p < 0.01$) or in combination to CT (HR = 0.6; 95% CI 0.4-0.7; $p < 0.01$), both as first-line treatment (HR = 0.65; 95% CI 0.52-0.83; $p < 0.01$) or in recurrent disease (HR = 0.51; 95% CI 0.43-0.61; $p < 0.01$). CONCLUSIONS: ADs did not improve OS in GBM PTS, both as first or second-line treatment. Among ADs, only BEV demonstrated a PFS benefit both as single agent or in combination with chemotherapy, both as first or second-line treatment.

P09.28 MGMT PROMOTER METHYLATION STATUS IN GLIOBLASTOMA (GBM) PATIENTS: A QUANTITATIVE PYROSEQUENCING APPROACH AND ITS PROGNOSTIC ROLE

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BACKGROUND: MGMT gene promoter methylation status is acknowledged as a prognostic factor and predictive marker for temozolomide (TMZ) treatment. Although MGMT status determined by pyrosequencing was showed to correlate with progression free survival (PFS) and overall survival (OS), it is still unclear a cut-off value that discriminates between methylated and unmethylated patient (pts) and its correlation with the patient clinical outcome. MATERIALS AND METHODS: We analyzed the tissue samples from 128 PTS diagnosed with GBM from November 2009 to December 2015. All PTS underwent treatment with RT + TMZ and had an ECOG-PS 0-2. Methylation percentage for each sample was obtained by calculating the average methylation of all 10 CpG sites (75-84) of MGMT promoter by pyrosequencing analysis. PTS with 0-6% of methylation were classified as unmethylated (UM), PTS with 7-24% as low methylated (LM) and PTS with $\geq 25\%$ as high methylated (HM). 25% was the median value of methylation of our PTS having $>6\%$ of methylation. RESULTS: Median age was 60 yrs (range 25-84), 60.9% were male, 74.2% had an ECOG PS 0-1, 50.8% underwent radical surgery, 85 PTS were dead at the time of analysis. 75 PTS were UM, 26 PTS were LM and 27 PTS were HM. On univariate analysis HM, LM and UM showed a PFS of 15.8, 10 and 9.1 ms, respectively ($p=0.1$). OS was 38.7, 21 and 18.8ms ($p=0.06$). On multivariate analysis UM and LM PTS had a statistically lower PFS vs HM PTS (HR=2.57; $p=0.001$; HR=2.5; $p=0.007$, respectively) and statistically lower OS (HR=3.47; $p<0.001$; HR=2.63; $p=0.016$; respectively). No significant difference was showed between UM and LM PTS in terms of PFS and OS, both on univariate and multivariate analyses. CONCLUSIONS: MGMT promoter methylation status determined by pyrosequencing analysis may correlate to PFS and OS. We found a cut-off of 25% of methylation which determined two sub-groups of PTS having different clinical outcome; in particular, HM PTS had a significant longer PFS and OS.

P09.29 ANAPLASTIC ASTROCYTOMA (AA) AND GLIOBLASTOMA (GBM): A REAL-LIFE EXPERIENCE IN PADUA NEURO-ONCOLOGY CENTER

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BACKGROUND: various prospective clinical trials on high-grade gliomas were performed in the last years but patient (PTS) characteristics and outcome may be different in real clinical practice. We performed a retrospective analysis to evaluate the real-life experience in Padua Neuro-Oncology center. MATERIALS AND METHODS: retrospectively, we reviewed the medical records of PTS admitted to our observation from June 2010 to June

2015 with a diagnosis of AA or GBM. We analyzed clinical outcome with prognostic factors. RESULTS: we analyzed 592 PTS with a diagnosis of CNS primary tumor. Among these, we enrolled 395 PTS: 33 (8.4%) with a histological diagnosis of AA, 293 (74%) with a histological diagnosis of GBM and 69 (17.4%) with a radiological diagnosis of GBM. At diagnosis, median age was 63.2 (range 24-88), 61.8% were male; 80% of PTS had an ECOG PS 0-2. Among PTS who underwent surgery, 48% had a radical surgery; 279 PTS (70.6%) performed RT in association to chemotherapy. 17% of PTS performed a second surgery at relapse and 45% a second-line treatment. MGMT was analyzed in all PTS who underwent surgery: it was methylated in 38.7% of PTS, IDH1 was mutated in 6%. GBM PTS with ECOG PS 0-2 and >2 had a median OS of 21.1 and 7.2ms, respectively. GBM PTS with met and unmet MGMT had a mOS of 22.7 and 13.7ms ($p=0.005$). AA PTS with met and unmet MGMT had a mOS of 29.5 and 16.6ms ($p=0.03$). Considering all high-grade gliomas, PTS with met MGMT + wtIDH1 reported a mOS of 23.1ms, PTS with metMGMT + wtIDH1 had a mOS of 20.9ms and PTS with unmetMGMT + wtIDH1 showed a mOS of 12.6ms ($p<0.001$). On multivariate analysis, ECOG PS 0-2 (HR=0.6), radical surgery (HR=0.7), methylated MGMT (HR=0.5) and PTS receiving a second-line chemotherapy (HR=0.7) were positive prognostic factors in terms of OS. CONCLUSIONS: in our real-life experience most PTS underwent surgery, performed a radiation therapy in association to chemotherapy and nearly half of PTS performed a second-line chemotherapy, although a subset of PTS had a poor performance status. However, we reported a good clinical outcome demonstrating the importance of molecular characterization in these PTS. Type of surgery, ECOG PS, MGMT methylation and lines of chemotherapy were independent prognostic factors.

P09.30 ABCB1 GENOTYPE PREDICTIVE FOR SURVIVAL IN GLIOBLASTOMA TREATED WITH RADIOTHERAPY AND CONCOMITANT TEMOZOLOMIDE

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INTRODUCTION: Standard treatment for newly diagnosed glioblastoma (GBM) patients is surgery followed by radiotherapy (RT) and temozolomide (TMZ) given concomitant and adjuvant. Tumor MGMT methylation status has been identified as predictive for response to TMZ. Also other factors are believed to influence TMZ effect. We examined the role of different single nucleotide variants (SNV:s) of ABCB1, a transmembrane drug transporter, for survival for GBM patients receiving RT concomitant with TMZ. PATIENTS AND METHODS: Genomic samples from patients with GBM who received RT+TMZ concomitant was analyzed for SNV:s of ABCB1, namely variants G1199A, C1236T, G2677T_A and C3435T and correlated to overall survival (OS). ABCB1 was determined using DNA mainly from blood. RESULTS: For a cohort of 97 patients treated between 2004 and 2014, 67% were male and 46% were over 60 years, 67% had radical surgery. For SNV G1199A median OS for variant G/G was 18.2 months versus 11.6 months for those with G/A ($p=0.012$), while the other SNV:s showed no significant correlation to survival. For those with methylated MGMT, for SNV G1199A median survival was 6.0 months compared to 23.4 months for G1199G. In multivariate analyses MGMT status and G1199A SNV were both independent factors for survival ($p=0.00$ and 0.04 respectively). CONCLUSION: For GBM patients receiving RT concomitant with TMZ the ABCB1 SNV G1199A could be a new treatment predictive factor. Expansion of the cohort to 200 patients is ongoing and a confirmatory cohort of 100 patients from Copenhagen will be analyzed. Updated results will be presented.

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P09.31 THE PROGNOSTIC VALUE OF SYSTEMIC INFLAMMATORY INDICES IN RECURRENT GLIOMA TREATED WITH BEVACIZUMAB

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