RESULTS: The multivariate Cox model identified SUVmax [hazard ratio (HR) = 1.08, 95% confidence interval (CI): 1.03-1.15; p = 0.004] and MTVg [HR = 1.03, 95% CI: 1.007-1.057; p = 0.01] as prognostic for the risk of tumor progression. Using receiver operating characteristics model we identified the threshold values that stratified the patients into groups of high and low risk of progression. These were tested in a Kaplan-Meier univariate model which found MTVg, TLGg and MTVgM significant (log-rank test results 3.011 and p = 0.011, respectively). The combination of these predictors, MTVg identified patient subgroups of progression risk 66.6% vs 8.9%.

CONCLUSIONS: SUVmax and MTV of gradient- and muscle-based threshold are significant and objective predictors of meningioma progression following surgical resection. An early diagnosis and treatment failure can allow for salvage treatment options such as surgery or re-irradiation. Therefore, the quantifiers that our study identified as unfavorable prognostic factors can be used along with the clinical variables to select a group of patients who may benefit from a more intensive surveillance.

OS6.4 CEVOIREAL THERAPIE: COMBINATION OF EVEROLIMUS AND METASTASIS INITIATING CELLS IN PARANEOPLASTIC NEUROLOGICAL SYNDROMES WITH ONCONEURAL ANTIBODIES: RESULTS FROM THE IASON TRIAL IN PARANEOPLASTIC NEUROLOGICAL SYNDROMES WITH ONCONEURAL ANTIBODIES

INTRODUCTION: WHO grade II and III meningiomas in therapeutic failure are a real therapeutic challenge with a rate of progression-free survival at 6 months closed to 10%. The results of our in vitro studies have demonstrated an additive antiproliferative effect of octreotide and everolimus on meningiomas in primary culture. These results led us to test this combination in within the HRC K-2013 targeting meningioma with therapeutic failure despite multiple surgeries and radiation therapy.

MATERIALS AND METHODS: 20 patients were included in this two-center phase II study in 18 months. The eligibility criteria include meningioma with treatment failure after surgery and radiotherapy and radiological progression documented before inclusion. The expected duration of treatment is one year. The primary endpoint is the PFS6, but the PFS average, the rate of tumor growth, the overall survival and side effects will also be assessed. A central review of imaging is planned. The success criterion of this study is to observe a PFS6 ≥ 40%.

RESULTS: 20 patients were included in less than a year (18% grade I, grade II 70%, and 12% of grade III). To date, 78 cycles were performed. We note 3 cases of discontinuation for poor tolerance (1 case of 2 drugs discontinuation, 1 case of ocreotide discontinuation and 1 case of everolimus discontinuation), and 1 case of discontinuation for progression at 3 months. Among the 6 patients who continued combination therapy 6 months or more, the treatment was discontinued in 1 case for progression at 1 month and in 5 cases for tumor stability.

DISCUSSION: The rapid inclusion highlights a real medical need and the feasibility of this protocol. Tolerance of everolimus-octreotide combination seems acceptable on these preliminary results. Further analysis is required to precise the activity of this combination.

OS6.9 FAMILY CAREGIVERS’ LEVEL OF MASTERY PREDICTS SURVIVAL OF GLIOBLASTOMA PATIENTS

BACKGROUND: Para-neoplastic Neurological Syndromes (PNS) are severe immune-mediated complications of systemic cancer. The rarity of these disorders hampers the realization of prospective studies and treatment strategies mainly rely on retrospective reports. The mainstay of treatment remains the achievement of cancer remission, whereas immunotherapy has shown little or no additional benefit. Still, as literature reports isolated cases of clinical improvement following early intravenous immunoglobulin (IVIg) treatment, we decided to further evaluate the efficacy of IVIg in PNS with a prospective trial.

PATIENTS AND METHODS: IaSOON was a prospective, multicentric, open-label, non-comparative, phase II clinical trial designed to assess the efficacy of early IVIg treatment in patients with PNS and well-characterized onconeural antibodies (anti-Hu, anti-Yo or anti-CV2). A total of 17 patients were enrolled between November 2013 and December 2015 among 3 of the participating Centres (Paris, Lyon, Strasbourg). Patients received intravenous infusions of IVIg 2g/kg at a key IVIg E0 (0), following which the primary endpoint (modified Rankin Score at 3 months) was evaluated. Patients showing functional stability or improvement received 3 supplementary IVIg infusions, while patients showing clinical deterioration discontinued IVIg treatment.

RESULTS: Of the 17 patients enrolled, 9 had isolated peripheral involvement, 3 had isolated central involvement and 5 had mixed central and peripheral involvement. Fourteen patients had anti-Hu antibodies, 2 patients anti-CV2 and 1 anti-Yo antibodies. Thirteen patients had an associated neoplasm, which in 10 cases was a small cell lung cancer; in the remaining 4 patients no tumor was detected during follow-up. Mean delay from neurological symptom onset to the start of IVIg treatment was 2.8 months. Ten patients concomitantly received antitumoral treatments. At 3 months, 3 patients had improved, 3 patients had deteriorated and 7 patients had stabilized. Primary outcome could not be assessed in 4 patients: 2 patients died prematurely, 1 dropped out and 1 interrupted IVIg treatment after one cure due to cutaneous toxicity. At 6 months, 9 out of the 13 patients with cancer were still alive, 7 of which were in tumor remission.

CONCLUSIONS: IaSOON was the first prospective trial to assess the efficacy of IVIg treatment in patients with PNS. IVIg treatment was in general well tolerated and only one patient had serious toxicity resulting in treatment discontinuation. At 3 months, a higher proportion of patients improved compared to previous studies on IVIg. This could be the result of both the earlier IVIg administration in our series and the recent advances made in cancer care, allowing a faster achievement of tumor remission. The timeliness of treatment is probably a key factor to obtain a clinical response in PNS and this should be highly regarded by future studies.

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OS7.1 IDENTIFICATION AND CHARACTERIZATION OF BRAIN METASTASIS INITIATING CELLS

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OS7.8 FAMILY CAREGIVERS’ LEVEL OF MASTERY PREDICTS SURVIVAL OF GLIOBLASTOMA PATIENTS

BACKGROUND: Glioblastoma multiforme (GBM) is associated with a poor prognosis and patients rely heavily on family caregivers for physical and emotional support. The capability and mental health of family caregivers may influence their ability to provide care and affect patient outcomes. We aimed to investigate whether caregivers’ anxiety, depressive symptoms, burden and mastery influenced survival in a sample of patients newly diagnosed with GBM.

METHODS: Baseline data from caregiver-patient dyads participating in a NIH funded large, longitudinal study were used. Cox regression analyses were performed to determine whether caregiver anxiety (Profile of Mood States-Anxiety), depressive symptoms (Center for Epidemiologic Studies-Depression), burden (Caregiver Reaction Assessment), and feelings of mastery (Mastery Scale) predicted GBM patient survival time after controlling for known covariates (patient age, performance status, type of surgery, and postsurgical treatment).

RESULTS: In total, 88 caregiver-patient dyads were included. Median overall survival for the sample was 14.5 months (range 0–88 months). After controlling for covariates, mastery was predictive of patient survival. With each unit increase in mastery, there was a 16.1% risk reduction of patient death (95% confidence interval: 0.77–0.913, P<0.001).

CONCLUSIONS: Our results are among the first to explore the impact of family caregiving for GBM patients’ outcomes. If these results are supported in other studies, providing neuro-oncology caregivers with more structured support and guidance in clinical practice have the potential to improve caregivers’ feelings of mastery, influencing patients’ wellbeing for the better.
Brain metastases (BM) are an increasing challenge. Insight in the pathology of brain metastasic cascade, and in particular in the characteristics of the BM initiating cells may help to identify new treatment targets. PHK26 membrane dye was used in stably GFP expressing human breast cancer cells to visualize the extravasation of cancer cells across the blood-brain barrier (BBB). In vitro, slow cycling cells showed a high overlap with established markers for tumor stem-like cells, like Oct4/Sox2. Notch and WNT, and also (but less) with low 26S proteasome activity. Illumina gene expression profiling of slow versus fast cycling JIMT1 breast cancer cells revealed a regulated Wnt/β-catenin and Notch pathway with lower 26S proteasome. Knock down of NDRG1 resulted in complete inhibition of BM formation by preventing successful colonization of the perivascular niche. In conclusion, slow cycling cells resemble the population of BM initiating cells. Increased NDRG1 expression was a characteristic of slow cycling cells, and a pivotal molecular preconditon for successful BM formation that might serve as a potential target for BM prevention or treatment.

OS7.2 A PHASE II STUDY OF ANG1005, A NOVEL BBB/BBC PENETRATANT TAXANE IN PATIENTS WITH RECURRENT BRAIN METASTASES AND LEPTOMENINGEAL CARCINOMATOSIS FROM BREAST CANCER
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INTRODUCTION: Treatment options for brain metastases (BM) and leptomeningeal carcinomatosis (LC) are limited due to the inability of most anti-metastatic agents to cross the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCB). ANG1005 is a novel taxane derivative, consisting of 3 paclitaxel molecules covalently linked to Angiopep-2, a peptide designed to cross the BBB/BCB via the LDL receptor transport system and to penetrate malignant cells.

MATERIALS AND METHODS: Adult patients with measurable recurrent BM from breast cancer, with or without LC, were enrolled in this multicenter, open-label study (n=72 safety population; n=58 efficacy population). ANG1005 was administered IV at 600 mg/m2 q3w. HER2+ patients were allowed to continue trastuzumab +/- pertuzumab for systemic disease control. PHK26 patients were high risk of disease control in 90% of the patients [1 (3%) CR, 2 (7%) PRs and 24 (80%) SDs]. Furthermore, 93% of these patients with extracranial disease control had prior taxane therapy.

RESULTS: ANG1005 was seen both intracranially and extracranially. Response was notable in patients with LC, resulting in prolonged OS compared to historical control and improvement of clinical symptoms in these poor prognosis patients. The estimated median OS for the LC patients of 8 months following ANG1005 treatment, considerably exceeds the historical median of two months, if untreated, and 3 to 4 months, following aggressive therapy.

OS7.3 IMPACT OF PLATELETS AND COAGULATION FACTORS ON THE EARLY STEPS OF THE BRAIN METASTATIC CASCADE
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BACKGROUND: Brain metastases (BM) occur in up to 50% of patients suffering from metastatic malignant melanoma (MM), and up to 30% of those suffering from HER2+ and triple negative breast cancer. BM are associated with mortality and are the most common reason for patients being referred to limited treatment strategies. Therefore, a deeper understanding of the key factors involved in the brain metastatic cascade are needed to identify targets for preventive strategies. Platelets and the coagulation system are interesting candidates in this respect. However, the impact of thrombus formation and von Willebrand factor (vWF) factor fibers on the brain metastatic cascade has not been investigated so far.

METHODS: Multiphoton laser scanning microscopy (MPLSM) via a chronic cranial window in mice was used to investigate the single steps of BM formation after intracardial injection of A2058 and H1 (human melanoma) and Jum1 hr (human breast cancer), stably expressing green or red fluorescent protein. Intravenous thrombus formation in vivo was visualized in a fluorochrome labeled anti-vWF. BM formation was visualized using fluorescence in vivo imaging.

RESULTS: It was possible to establish the first long-term imaging method that allows to study the entire brain metastatic cascade and platelet / vWF accumulation simultaneously. More than 60% of tumor cells demonstrated platelet aggregation at the site of their arrest in brain microvessels, particularly just before the time point of extravasation. The ability to successfully extravasate and grow into a micrometastasis in the brain parenchyma was increased in cells with surrounding thrombus formation, indicating that early clot formation fosters several steps of the brain metastatic cascade. Ongoing experiments investigate the impact of vWF on extravasation and micrometastasis outgrowth. Finally, we will present data of how anticoagulants (heparin) and dual platelet inhibition can prevent extravasation into the brain and later on, growth of micrometastases.

CONCLUSION: Thrombus formation seems to facilitate extravasation of brain metastatic initiating cells and is therefore an early key factor of the brain metastatic cascade. Further experiments are on-going to investigate the potential of clot-inhibiting agents for BM prevention.

OS7.4 OUTCOME OF PATIENTS PRESENTING WITH BRAIN METASTASIS AS FIRST MANIFESTATION OF CANCER
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BACKGROUND: Patients with brain metastases (BM) as first manifestation of cancer represent up to 26% of all BM patients. We retrospectively explored the prognostic characteristics and outcome of such patients in a large tertiary care center.

METHODS: Patients presenting with BM in the absence of a prior cancer diagnosis were identified from the Brain Metastases Database, Medical University of Vienna. Clinical characteristics and overall survival time from diagnosis of BM to death or last follow up were retrieved by chart review. Graded prognostic assessment score (GPA) was calculated as previously published.