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Brain metastases (BM) are an increasing challenge. Insight in the pathology of the brain metastatic cascade, and in particular in the characteristics of the BM initiating cells can help to identify new treatment targets. PHK26 membrane dye was used in stably GFP expressing human breast cancer to differentiate slow from fast cycling cells by membrane signal intensity changes using multiphoton laser scanning microscopy, both in vitro and in vivo. The heterogeneous population of fast and slow cycling cells as well as resting cells was injected intracardially and followed with in vivo repetitive multiphoton laser microcopy via a chronic intracranial window. Here, slow cycling cells, representing only 16% of the entire cell population, were the only ones that mastered all steps of the brain metastatic cascade (0% marcometastasis formation after intravascular arrest of fast cycling cells vs. 6.15% marcometastasis formation after intravascular arrest of slow cycling cells; $p<0.001$), namely intravascular arrest, extravasation, perivascular survival, and marcometastasis outgrowth. These 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 up-regulation of N-Myc down regulated gene (NDGR1). 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 is a characteristic of slow cycling cells, and is a pivotal molecular precondition 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/BCB 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-cancer 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 LRP-1 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/m^2 q3w. HER2+ patients were allowed to continue trastuzumab +/- pertuzumab for systemic disease control. Intracranial (IC) response was assessed by Gd-MRI using CNS RECIST 1.1 and extracranial response was evaluated per RECIST 1.1.

RESULTS: Median age was 47.5 (26–76) years. Safety profile was similar to that of paclitaxel with myelosuppression as the predominant toxicity. Patients received a median of 6 (1–29) prior therapies for breast cancer, including 86% with prior taxane treatment. To treat their BM, 84% had prior cranial surgery and/or radiation, and 18% of the patients had prior systemic therapies. Clinical benefit (best IC PR + SD) was seen in 71% of the patients. Best IC response in the efficacy population included 8/58 (14%) patients with PRs [3 (5%) confirmed PRs] and 33/58 (57%) with SD. For evaluable patients with LC, best IC responses included 5/23 (22%) PRs [2 (9%) confirmed PRs] and 12/23 (52%) SDs. Importantly, Kaplan-Meier estimated median OS was 34.6 weeks (95% CI 24.1–40.9) for patients with LC from first ANG1005 treatment. Improvement of clinical symptoms post-ANG1005 treatment was seen, including in patients with LC. Completed extracranial tumor assessments in 30 evaluable patients with extracranial lesions showed 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.

CONCLUSIONS: Anti-tumor activity with 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 positive and triple negative breast cancer. BM are associated with high morbidity and mortality due 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 (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 Jimt1 br (human breast cancer), stably expressing green or red fluorescent protein. I.v. Rhodamin 6G dye injection before imaging was used to visualize thrombocytes in thrombus formation and FITC labeled anti-vWF was used to visualize vWF fibers in vivo.

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 to 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 outgrowth to a clinically relevant macrometastasis.

CONCLUSION: Thrombus formation seems to facilitate extravasation of brain metastasis 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.

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