therapy of GBM. Like T cells, NK cells can be genetically modified to express chimeric antigen receptors (CARs) that recognize tumor-associated cell surface antigens and mediate selective recognition and specific lysis of cancer cells, thereby overcoming endogenous resistance mechanisms in tumor cells. In two previous phase I clinical trials, the continuously expanding human NK cell line NK-92 has been safely applied as an allogeneic cell therapeutic with clinical responses observed in some of the cancer patients treated. To extend this specificity, the ErbB2-specific CAR-carrier NK cell line NK-92/5.28.z carries a codon-optimized CAR (CAR 5.28.z) based on ErbB2-specific antibody FRP5 and CD28 and CD3ζ signaling domains. ErbB2 protein levels have been reported in a significant proportion of GBM tumors and were correlated with impaired survival. We have previously demonstrated potent antitumor activity of NK-92/5.28.z cells in vitro and in orthotopic GBM models in vivo, suggesting adoptive transfer of these cells as a promising new approach for immunotherapy of ErbB2-positive glioblastoma and other ErbB2-expressing cancers. Based on the convincing preclinical data, we consequently designed the CAR2BRAIN trial, a monocentric phase I dose finding trial investigating the safety and tolerability of NK-92/5.28.z cells in patients with recurrent glioblastoma. The NK-92/5.28.z cells will be repeatedly injected through a Hickman reservoir into the resection cavity or the tumor margin in a dose escalation part of the trial the highest cell number which can be applied safely will be established (maximum tolerated dose = MTD). We plan to escalate the dose up to 1x10⁷ cells per injection in four injections. After determination of the MTD, up to twelve injections will be given to establish safety of prolonged treatment. Distribution of the injected NK-92/5.28.z cells in the brain, the cerebrospinal fluid and the blood will be monitored. Furthermore, the immune reaction triggered against the target antigen ErbB2 as well as ErbB2-independent immune reactions will be characterized.

P04.06 PD-L1 EXPRESSION IS ASSOCIATED WITH WILD TYPE IDH, IMMUNE RESPONSE AND DNA DAMAGE IN MALIGNANT GLIOMAS

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BACKGROUND: Immune-checkpoint inhibition is a promising new approach for glioma therapy. Currently, immune-checkpoint inhibition is being evaluated for glioblastoma in different clinical trials. Since the molecular mechanism of PD-L1 regulation in gliomas is largely unknown, the present study was initiated.

METHODS: Genomic data of 50 patients (Department of Neurosurgery, Freiburg) and publically available level 3 TCGA (https://tcga-data.nci.nih.gov/tcga/) data were used for analysis. Genome and transcriptome data were analysed in an individually designed R-pipeline including biocductor (www.biocductor.org) R-packages. Weighted Gene Co-Expression Network (WGCNA) analysis (WGCNA) was used for additional network analysis.

Patients were stratified according to the IDH1/2 mutation, the ATRX/P53 mutation status (https://cancer.gov/tcga/) and publically available TCGA (https://tcga-data.nci.nih.gov/tcga/) data were used for analysis. Genome and transcriptome data were analysed in an individually designed R-pipeline including biocductor (www.biocductor.org) R-packages. Weighted Gene Co-Expression Network (WGCNA) analysis was used for additional network analysis.

Patients were stratified according to the IDH1/2 mutation, the ATRX/P53 mutation status and publically available TCGA (https://tcga-data.nci.nih.gov/tcga/) data were used for analysis. Patients were stratified according to the IDH1/2 mutation, the ATRX/P53 mutation status and publically available TCGA data were used for analysis. Patients were stratified according to the IDH1/2 mutation, the ATRX/P53 mutation status and publically available TCGA data were used for analysis.

RESULTS: Genomic data of 50 patients (Department of Neurosurgery, Freiburg) and publically available level 3 TCGA data were used for analysis. Genome and transcriptome data were analysed in an individually designed R-pipeline including biocductor (www.biocductor.org) R-packages. Weighted Gene Co-Expression Network (WGCNA) analysis was used for additional network analysis. Patients were stratified according to the IDH1/2 mutation, the ATRX/P53 mutation status and publically available TCGA data were used for analysis. Patients were stratified according to the IDH1/2 mutation, the ATRX/P53 mutation status and publically available TCGA data were used for analysis.

CONCLUSION: Both PD-L1 and PD-L2 expression are linked to immune response (via IFNγ) and DNA damage (DTX3L, marker of DNA damage) with a strong PD-L1 expression. Both modules share an inflammatory disease. In an active demyelinating plaque, previous metastatic lesions were smaller and exhibited less intense annular enhancement. This finding is consistent with the concept that the active demyelinating lesion is less advanced than the metasitic one. The MRI changes seen in the active lesion were consistent with the possible demyelinating nature. The patient was completely whitin one month. She denied other neurological symptoms and image were resolved.

P04.07 RELAPSE IN A PAUCISYMPTOMATIC FORM OF MULTIPLE SCLEROSIS IN A PATIENT TREATED WITH NIVOLUMAB

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INTRODUCTION: The successful clinical application of immune checkpoint-blockade therapies, as anti-CTLA-4, anti-PD1 and anti-PDL2 antibodies, is changing the way to treat patients with cancer. Nivolumab is an anti-PD-1 antibody with promising efficacy in a broad of neoplasias. During treatment with these antibodies, a unique set of toxicities occur called immune-related adverse events (irAEs), including infrequent neurological effects, which present a case of relapse in a paucisymptomatic form of multiple sclerosis in a patient treated with nivolumab.

PATIENTS AND METHODS: A 42 year-old-woman was diagnosed of locally advanced lung adenocarcinoma EGFR wt, no ALK-translocation on October 2014. She received treatment with carboplatin-pemetrexed with concomitant radiotherapy. On May 2015, the patient progressed with adrenal, lung and cerebral metastases. She received loco-regional radiotherapy and was enrolled in a clinical trial with docetaxel and ganetespib. However after 3 cycles, she showed cerebellar progression treated with radiosurgery.

In previous brain MRI, multiple white matter hypodensities compatible with demyelinating disease were observed. When questioned, the patient related a dizziness episode several years ago, resolved spontaneously and completely within one month. She denied other neurological symptoms and neurological examination was normal. Therefore, Nivolumab was initiated through an expanded access program.

One week after the beginning of nivolumab, the patient presented progressive diplopia and gait instability. Bilateral ptosis and internuclear right ophthalmoplegia, right limbs dysmetria ant ataxic gait compatible with brainstem affection was found in neurological examination.

RESULTS: An urgent MRI was performed with suspicion of tumoral progression versus inflammatory disease in the context of previous lesion with post-radiotherapy sequelae.

FLAIR and T1-gadolinium WI showed a new lesion with incomplete annular enhancement in anterior and right pontine-medulla junction, suggesting an active demyelinating plaque. Previous metastatic lesions were small and exhibited less intense annular enhancement. The patient was hospitalized and a cycle of 1 gr of methylprednisolone IV per day for five days was administered. Four weeks after, the clinical picture and new lesion image were resolved.

CONCLUSIONS: Clinicians must perform a complete anamnesis focused in autoimmune disorders in patients who will be treated with anti-PD1. They must be aware of the irAEs, their variable presentations and management, to avoid complications or false progression disease. In our opinion, it can be reasonable weigh the potential benefits of PD-1 therapy against the life-threatening malignancy against the risk of exacerbating an underlying inflammatory disease. Relapse in multiple sclerosis has not been reported before during nivolumab treatment.

P04.08 NEUROLOGICAL ADVERSE EVENTS ASSOCIATED WITH THE IMMUNE CHECKPOINT INHIBITORS: REVIEW OF THE LITERATURE AND CHARACTERIZATION OF THE NEUROLOGICAL PATTERN

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INTRODUCTION: Immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1 and anti-PD-L1 antibodies) constitute a promising class of cancer treatment which, in addition, is associated with several immunological side effects (irAEs). Common grade 3/4 irAEs include dermatitis, enterocolitis, hepatitis and hypophysitis. Much less characterized are the neurological complications (irAEs), which have been reported in less than 1% of patients. To better define the neurological presentation of these irAEs, we reviewed the literature reporting neurological disorders associated with immune checkpoint inhibitors.

MATERIALS AND METHODS: A systematic search of literature, up to February 2016, mentioning irAEs in patients treated with immune checkpoint inhibitors was conducted in PubMed database. Eligible studies included the case reports and the prospective trials (phase II and III). Patients with brain metastases or tumor meningitidis and the cases of typical myositis, uveitis and hearing loss without neurological disorders were excluded.

RESULTS: A total of 67 patients having irAEs were described in case reports (32 cases) or in clinical trials (35 cases). In the clinical trials (38 trials, involving 9227 treated patients), the overall incidence of all-grade irAEs was 3.4% and 3.1% for the patients treated respectively with anti-CTLA4 and anti-PD1. Grade 3/4 irAEs included more than 60% of these irAEs. Overall incidence of high-grade irAEs was 0.5% for the anti-CTLA-4 group and 0.2% for the anti-PD-1 group. When the type of neurological disorder was mentioned, lymphocytic meningitidis and myasthenic syndromes were the most frequently reported (44% and 25% respectively). In the case reports, the most common irAEs related to CTLA-4 blockade included Guillain Barré syndromes (n=3) and other radiculoneuropathies (n=5), meningoradiculitis (n=5), myasthenia gravis (n=4) and less frequently lymphocytic meningitis (n=2), encephalitis (n=2) and myelitis (n=2). Anti-PD-1 irAEs were mostly associated with central nervous system toxicity: encephalitis (n=2), cerebral vasculitis (n=1) and PRES (n=1). Occurrence of irAEs was associated with tumor response in 29/32 patients. The median time of onset of irAEs was 6 weeks (1–21) and 7 weeks (1–74) with anti-CTLA-4 and anti-PD1-treatments, respectively. In almost all cases the outcome was favorable.