OS03 CLINICALLY RELEVANT VULNERABILITIES OF CNS METASTASIS

OS03.4.A. IN VIVO DYNAMICS AND ANTI-TUMOR EFFECTS OF EP Carm-DIRECTED CAR T-CELLS AGAINST BRAIN METASTASES FROM LUNG CANCER
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BACKGROUND: Immune checkpoint (IO) therapy has changed the treatment landscape of metastatic cancer patients, however, treatment resistance is frequent. We aimed to characterize the inflammatory tumor microenvironment (TME) in brain metastases (BM) after IO to gain a deeper understanding of immunological escape mechanisms. MATERIAL AND METHODS: Solid cancer patients who had BM resection after IO progression (IO cohort) were retrospectively identified. We analyzed tumor-infiltrating immune cell subtypes (CD3+, CD8, CD45RO+ T-cells; CD20+ B-cells; and expression of immunomodulatory checkpoint molecules (PD-L1, PD-L2, LAG-3)) by immunohistochemistry. A control cohort of BM tissue samples without prior IO served for comparison (no IO therapy cohort, NIO). RESULTS: Twenty-eight IO patients (12/28, 42.9% females; 16/28, 57.1% males; median 61 years; 14/28, 50% lung cancer; 3/28, 17.9% melanoma; 4/28, 14.3% renal cell carcinoma; 3/28, 3.6% breast cancer; 4/28, 14.3% other cancer entities) and 57 NIO patients (28/57, 49.1% females; 29/57, 50.9% males; median 58 years; 33/57, 61.4% lung cancer; 9/57, 15.8% breast cancer; 4/57, 7.0% melanoma; 3/57, 5.3% renal cell carcinoma; 6/57, 10.5% other cancer entities) were included. IO patients had a median of one (range 0–4) systemic therapy prior line therapy prior to IO. Median time from last IO application until BM resection was 3.6 months (range 0.2–49.8 months). Patients received a median number of (range) 1 (0–56) IO application until BM. NIO patients (28/57, 50% PD-L1; 1/28, 7.1% CTLA-4; 4/28, 14.3% CTLA-4+PD-1; 3/28, 10.7% IO-chemotherapy). No statistically significant differences in the densities of investigated TILs or PD-L1 expression between the IO and the NIO cohort were observed. Patients of the IO cohort showed a significant correlation of PD-L1 with compared to the NIO cohort (57.1 vs. 42.1%, Chi-square, p < 0.05). Overall survival (OS) was similar in both cohorts, with a median OS of 11.0 months (range 5.0–17.0) in the IO cohort and 11.0 months (range 5.5–16.3) in the NIO cohort. CONCLUSIONS: Our findings show an upregulation of PD-L1 in BM occurring after prior IO therapy in the absence of other overt changes in the inflammatory microenvironment. Ongoing analyses in this cohort are investigating possible molecular driver of resistance by analyzing DNA methylation and gene expression profiles of pre- and post-IO tissue samples of the IO cohort to potentially gain insights on immunological IO resistance mechanisms in BM patients.

OS03.6.A. RITUXIMAB IN PRIMARY CNS Lymphoma - LONG TERM FOLLOW-UP OF THE PHASE III HOWON 105/ALLG H. 24 STUDY
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BACKGROUND: The efficacy of rituximab in Primary CNS Lymphoma (PCNSL) is still under debate. We performed an international randomized phase III study to investigate the efficacy of rituximab when added to methotrexate, BCNU, teniposide and prednisolone (MBVP) in PCNSL. The primary endpoint, event-free survival (EFS) at one year, was similar in both treatment groups and was previously reported (Bromberg et al, Lancet Oncology 2018; 19: 216–228). Here we present long-term follow up results after a median follow-up of 82 months. MATERIAL AND METHODS: between August 2010 and May 2016 200 newly-diagnosed, non-immunocompromised patients with PCNSL aged 18-70 years and WHO performance status 0-3 were randomized between treatment with MBVP chemotherapy (arm B) or without (arm A) rituximab. The rituximab was given weekly in the first MBVP cycle, fortnightly in the second (in total 6 rituximab administrations). Response patients received consolidation with high-dose cytarabine, and patients aged > 60 were subsequently treated with low-dose WBRT if OS/CrA in case of PR with an additional boost on the tumor. Patients > 60 were not irradiated. All patients gave written informed consent. RESULTS: The modified intention-to-treat (mITT) population consisted of 199 eligible patients, 55% were men. The primary endpoint, event-free survival (EFS) in the mITT population. Results at 5 years were 23% (17/74) and 36% (27/74) respectively, hazard ratio 0.85, 95% CI 0.57–1.28, p = 0.33 (adapted for age and WHO performance status). The progression-free survival (PFS) at one and five years was 58% (47-67) and 29% (21-39) (MBVP) and 65% (54-73) and 43%
Abstracts

OS05.5.A. GLOBLASTOMA-INSTUCTED MICROGLIA TRANSIT TO HETEROGENEOUS PHENOTYPIC STATES WITH DENDRITIC CELL-LIKE FEATURES IN PATIENT TUMORS AND PATIENT-DERIVED ORTHOTOPIC XENOGRAPHS
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BACKGROUND: A major contributing factor to Glioblastoma (GBM) development and progression is its ability to evade the immune system by creating an immune-suppressive tumor microenvironment (TME). GBM-TME development and progression is its ability to evade the immune system by generating a highly immunosuppressive tumor microenvironment (TME) and an impaired interferon-response signature in the tumor-peripheral cytotoxic T cell compartment. Comparing CD8+ T cells from the tumor periphery to GBM-associated CD8+ T cells of the same patient revealed CX3CR1+ and CX3CR1- CD8+ T cells with effector and memory phenotype, respectively, enriched in the GBM but lacking in the tumor periphery. Tumor-peripheral CD8+ T cells showed exhausted effector functions. CONCLUSION: Our analysis provides a large-scale dissection of GBM-associated cell types complemented by patient-matched PBMCs, serving as a high dimensional reference map of the human GBM TME.

OS05.5.B. MULTICOLOR FLOW CYTOMETRY TO DISCOVER LABEL-SAVING STRATEGIES FOR YIELDING QUALITY IMMUNOHISTOCHEMICAL DATA

BACKGROUND: A frequent problem in immunohistochemical labeling strategies is the need to include endogenous labeling for the blocking of Fab fragments expressing CD169 or CD68. This is usually achieved by including labeling for CD45 in the labeling protocol. Here, we describe a label-saving strategy for obtaining quality immunohistochemical labeling data which eliminates the need for endogenous labeling, yet still preserves all aspects of the quality of the labeling. CONCLUSION: We describe a label-saving strategy for obtaining quality immunohistochemical labeling data which eliminates the need for endogenous labeling, yet still preserves all aspects of the quality of the labeling.

OS05.6.A. MODIFICATION OF THE TUMOR MICROENVIRONMENT IN PATIENTS WITH GLIOBLASTOMA USING AUTOLOGOUS, GENE-THERAPEUTIC MODIFIED, GBM-TUMORIPOIETIC STEM CELL-BASED THERAPY: THE TEM-GBM STUDY (NCIT03866109)
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BACKGROUND: A major contributing factor to Glioblastoma (GBM) development and progression is its ability to evade the immune system by creating an immune-suppressive tumor microenvironment (TME) and an impaired interferon-response signature in the tumor-peripheral cytotoxic T cell compartment. Comparing CD8+ T cells from the tumor periphery to GBM-associated CD8+ T cells of the same patient revealed CX3CR1+ and CX3CR1- CD8+ T cells with effector and memory phenotype, respectively, enriched in the GBM but lacking in the tumor periphery. Tumor-peripheral CD8+ T cells showed exhausted effector functions. CONCLUSION: Our analysis provides a large-scale dissection of GBM-associated cell types complemented by patient-matched PBMCs, serving as a high dimensional reference map of the human GBM TME.

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