weeks after diagnosis and despite long-term neutropenia the patient was still clinically stable under nivolumab treatment and discharged with continued deescalated antimycotic treatment. A bone marrow biopsy revealed a further progression of AML relapse. After 3 weeks during follow-up mucormycosis was still clinically stable. Ten days later the patient developed fever up to 39.5°C, but refused to seek medical attention due to unfavorable prognosis of AML and died two days later from septic shock combined with disseminated intravascular coagulation.

Conclusions In immunocompromised hematological patients with invasive fungal infections, immune checkpoint inhibition is capable of reversing an infection-induced immunosuppressive phenotype. Therefore, it might complement the treatment of invasive fungal infections and should be evaluated in future clinical trials.

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P09.10 LOCAL IMMUNOTHERAPY OF BRAIN CANCER HARNESSING HIGH-RETENTION FC-FUSION CONSTRUCTS

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Background Glioblastoma is a highly aggressive cancer type and despite aggressive therapy, patients' survival remains poor. Immunotherapy of brain cancer is particularly difficult because of its location behind the blood-brain-barrier and the immunosuppressive tumour microenvironment. In order to (re-)activate the immune system, and reverse the local immunosuppression, we employ the pro-inflammatory cytokine interleukin 12 (IL-12). This highly potent immune-stimulatory agent is known for its anti-cancer effect. Unfortunately, IL-12 was found to induce severe toxicity when applied intravenously, impeding its way into clinics. Thus, currently the only valid therapeutic option is local application into the tumour site.

Materials and Methods Engineered proteins were expressed in HEK293T cells and purified by affinity chromatography. In vivo experiments were performed in glioma-bearing mice using intracranial injection of bioluminescent GL-261 cell line. Treatments were performed on day 21 and 28 post tumour injection through intracranial injection using a step-catheter modelling convection enhanced delivery in mice. Blood or tissue was analysed using immunohistochemistry, flow cytometry and ELISA.

Results Based on an IL-12-IgG fusion protein, we engineered a molecule for exclusively local therapy of brain cancer. We showed anti-cancer efficacy and increased tissue retention of the fusion molecule in glioma in mice. However, molecular analysis of treated tissue confirmed an upregulation of the immunosuppressive molecule PD-L1 in the tumour microenvironment. This means that, despite its efficacy, IL-12 induces an adaptive resistance mechanism, counteracting the therapeutic effect. We thus hypothesised that local IL-12 therapy combined with local blockade of the PD-1/PD-L1-axis would further improve therapeutic efficacy, while exclusively local administration would avoid increased side effects, which usually accompany combination immunotherapy. We showed significantly enhanced long-term survival of glioma-bearing mice treated with IL-12 therapy in combination with PD-L1 blockade compared to single or control treatments. In a next step, we engineered a novel, bifunctional molecule. Optimized for local application and minimized leakage into the systemic circulation, it combines immune-stimulation and checkpoint blockade in one entity. We showed anti-cancer efficacy and increased tissue retention in glioma in mice.

Conclusions The potent anti-cancer effect of the cytokine IL-12 can be used in therapy when applied locally into the brain tumour. Besides fusion to IgG, we introduced several specific modifications on the molecule, which are crucial to prevent systemic exposure and associated toxic side effects. To overcome the dampening of the immune reaction through induced PD-L1 expression, we introduced a combination therapy of IL-12 with a PD-L1-blocking antibody in a single molecule. We showed this combination superior to single treatments in the context of exclusively local brain tumour therapy.

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P09.11 TLR3 SUPPRESSES COLORECTAL CARCINOGENESIS, PRESUMABLY THROUGH UP-REGULATION OF T-CELL ATTRACTING CXC CHEMOKINES

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Background Toll-like-receptors (TLRs) are main components of the innate immune system which recognize endogenous or pathogen-associated molecular 'danger patterns'. Previous findings from us and others highlighted a role of TLRs in the formation of tumors. However, TLRs may have differing roles in immune and cancer cells, and the underlying mechanisms are still unclear. TLR downstream signaling is mediated by two adapter proteins; MyD88 (myeloid differentiation primary response gene 88) and TRIF (TIR-domain-containing adapter-inducing interferon-β). The MyD88-mediated signaling pathway is activated by all TLRs, except TLR3. We could show previously that it leads to the initiation of oncogenic, proliferative and pro-inflammatory responses in colorectal cancer. The endosomal receptor TLR3, in contrast, solely depends on TRIF. It recognizes viral, microbial and endogenous dsRNA leading to production of type-I interferon and chemokines, and induces apoptosis. The role of TRIF dependent TLR3 signaling in colorectal cancer is still disputed. Within this study, we show tumor-suppressive TLR3 functions prevailing over oncogenic effects in colorectal cancer.

Materials and Methods TLR3-deficient colon cancer cell lines were engineered by CRISPR-Cas9. Genetically modified mouse models were generated, based on a 'switch-on mutagenesis' approach, with global inactivation of Tlr3 or TRIF (Ticam1), allowing tissue specific re-expression based on Cre recombination. The mice were interbred with the Apc^{1638N} mouse model for digestive cancer. Furthermore, clinical significance of TLR3 expression levels was assessed in human colorectal cancer tissue samples from our clinic (n=81) and from TCGA datasets. A putative correlation between