Title

CTIM-24. RANDOMIZED TRIAL OF NEOADJUVANT VACCINATION WITH TUMOR-CELL LYSATE INDUCES T CELL RESPONSE IN LOW-GRADE GLIOMAS

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INTRODUCTION: Glioblastoma is an aggressive brain tumor with a median survival of 14.6 months. We have no standard treatment for relapse and known options have limited effect. Novel treatments are necessary to improve survival and quality of life. METHODS: We present our trial; phase II open label, two-armed translational study of Nivolumab and Bevacizumab for recurrent GBM, who have failed Stupp's regimen. Patients are included in two arms depending on the possibility of salvage neurosurgical resection. Both arms receive Nivolumab and Bevacizumab administrated every second weekend, and the surgical arm also receive Nivolumab 7 days prior surgery. Forty-four patients were included by January 2021; 20 in each arm (four screen-failures). In the surgical arm, 20 fresh tumor samples as well as paired tissue from primary tumor were available. Tumor infiltrating lymphocytes (TILs) and tumor digest were produced in vitro from recurrent settings. Young TILs were expanded from fresh tumor fragments after minimal-culture, whereas rapidly expanded TILs (REP TILs) were obtained after massive expansion. By intracellular cytokine staining, we investigated the TIL reactivity after exposure to autologous tumor digest in order to evaluate whether the TILs were tumor-reactive, non-reactive or bystanders. RNA and whole exome sequencing were available before and after treatment. RESULTS: Material from 19 patients was analyzed (one out of the 20 collected biopsies was limited in size, therefore no tumor digest could be produced). Four out of 19 TIL samples showed tumor reactivity after exposure to the autologous tumor digest. Tumor reactivity was ranged between 1,2 to 13,6 tox% in CD8+ TILs and between 2,8 to 10,9 tox% in CD4+ TILs. By flowcytometry we found, IgG4+ CD3+ TILS from tumor biopsies, meaning that Nivolumab were found in the brain. Currently controls are included to evaluate these results. CONCLUSIONS: Updated results will be presented at SNO.

CTIM-23. EVIDENCE OF T CELL ACTIVATION AND INTRATUMORAL NIVOLUMAB-PRESENCE IN GLIOBLASTOMA PATIENTS TREATED WITH NIVOLUMAB AND BEVACIZUMAB

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Glioblastoma (GBM) is an aggressive brain tumor with a dismal prognosis. Salvage neurosurgical resection is performed if possible and GBM patients are hereafter treated with Stupp's regime as standard treatment in the primary setting. However, after relapse, treatment in the recurrent setting shows very limited effect. We are monitoring the immune system of patients participating in a phase II clinical trial, where patients with recurrent GBM receive Nivolumab and Bevacizumab, treatments blocking PD1 and VEGF, respectively. The clinical trial consists of two arms. Arm A includes patients where surgical removal of the tumor is possible, and arm B includes patients who are only able to receive medical treatment. Arm A has received Nivolumab 7 days prior to surgery. Single cells suspension was produced from the resected tumors and blood samples was collected from patients through the course of treatment, wherefrom PBMCs (peripheral blood mononuclear cells) were purified. All samples were immunophenotyped using multi-color flow cytometry, to identify and follow the distribution of various immune cell types, and determine their expression of activating and inhibitory molecules over the course of treatment, in the periphery and in the tumor. An activated subset of T cells was characterized by CD103 (tissue residence), CD39 (antigen exposure) and CD69 (cytotoxicity). Such T cell populations were significantly enriched in the tumor. Importantly, we could demonstrate the presence of Nivolumab in the tumor, using an anti-IgG4 antibody to detect Nivolumab binding to T cells. We observed IgG4 positive T cell in the tumor digest, suggesting T cells binding Nivolumab are present in the tumor. Additional data analysis will be performed prior to the conference. With this we hope to gain further knowledge of the immune system's role in tumor clearance in the brain and the impact of immunotherapy hereupon.

CTIM-24. RANDOMIZED TRIAL OF NEOADJUVANT VACCINATION WITH TUMOR-CELL LYSATE INDUCES T CELL RESPONSE IN LOW-GRADE GLIOMAS

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BACKGROUND: The prognosis of WHO grade II low-grade gliomas (LGG) is varied with potential for long survival.Given their relatively intact immune system and slow growth rate, vaccines are an attractive treatment strategy for LGG in an attempt to defer more toxic treatments. The goals of this pilot study were to evaluate safety and immunological effects of vaccination with GBM6-AD, an allogeneic glioblastoma stem cell line lysate, with poly-ICLC in LGG. METHODS: Eligible patients were ≥ 18 years old, ≥ 70 KPS, with recurrent LGG or imaging consistent with LGG, and amenable to resection. Patients were randomized to vaccine prior to surgery (Arm 1) or not (Arm 2) and all received adjuvant vaccine. Co-primary outcomes were safety and immune response in the tumor, with exploratory outcomes of survival and immunologic effects in peripheral blood. RESULTS: A total of 17 eligible patients were evaluable – nine into Arm 1 and eight into Arm 2. Median age was 33 years, with median time from initial diagnosis of 4.7 years (0 – 20). Two patients (11.8%) previously received radiotherapy and seven (41.2%) prior systemic therapy. No dose limiting toxicities or grade 3 AEs were observed. Neoadjuvant vaccination induced up regulation of type-1 cytokines and chemokines in peripheral blood, and CD8+ T cell clones that reacted to the vaccine were also detected in the tumor. Median follow-up time from first post-operative vaccine was 20.8 months with median PFS of 11.0 months and time to change in therapy of 23.7 months. Of the six patients to receive additional treatment, three had second surgery only one confirming malignant progression to anaplastic oligodendroglioma. CONCLUSION: Treatment was well-tolerated with no regimen-limiting toxicity. GBM6-AD plus poly-ICLC induced effector $CD8^+$ T cell response in peripheral blood and enables some vaccine-reactive $CD8^+$ T cells to migrate into the TME. Further investigation is warranted.

CTIM-25. A RANDOMIZED PHASE 3 STUDY OF NIVOLUMAB OR PLACEBO COMBINED WITH RADIOTHERAPY PLUS TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA WITH METHYLATED MGMT PROMOTER: CHECKMATE 548

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BACKGROUND: Novel therapies are needed in newly diagnosed glioblastoma as nearly all patients experience recurrence following standard-of-care radiotherapy (RT) + temozolomide (TMZ), including patients with tumors with methylated *MGMT* promoter, a positive prognostic factor and predictor of benefit with TMZ. Here, we report the final analysis of progression-free survival (PFS), overall survival (OS), and safety from an international randomized, single-blind phase-3 study of nivolumab (NIVO)+RT+TMZ in patients with newly diagnosed glioblastoma with methylated/indeterminate *MGMT* promoter (CheckMate 548; NCT02667587). METHODS: Patients (N=716) aged ≥ 18y were randomized 1:1 regardless of tumor PD-L1 expression to NIVO (240 mg