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REGION

The DCCC Brain Tumor Center

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Tumor reactivity for patients treated with Nivolumab and Bevacizumab for recurrent Glioblastoma

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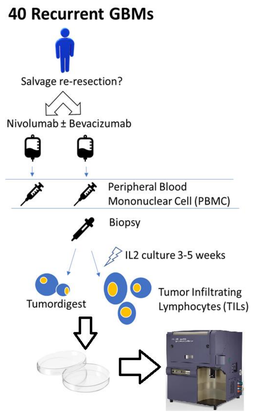
Abstract

Introduction:
Glioblastoma multiforme (GBM) is an aggressive brain tumor with a poor prognosis. Receiving the standard of care, the median survival is 14.6 months [1]. We have no standard treatment for relapse and known options have limited effect. Novel treatments are necessary to improve survival and especially quality of life.

Methods:
We present our translational study; a phase II open label, two-armed translational study of Nivolumab and Bevacizumab for recurrent GBM, who have failed Stupp's regime [1]. 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 in order to obtain post-surgical specimens for analysis. 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 [2].

Results:
We investigated by intracellular cytokine staining the TIL reactivity after exposure to autologous tumor digest in order to evaluate whether the TILs were tumor-reactive or bystanders. Material from 19 patients was analyzed (one out of the 20 collected biopsies was limited in size, and no tumor digest could be produced). Four out of 19 TIL samples showed tumor reactivity after exposure to the autologous tumor digest. Though meaning that 15 patients showed no tumor reactivity. Tumor reactivity was ranged between 2 tox% in CD8+ TILs and from 10 to x% in CD4+ TILs. Tumor reactivity data from the surgical arm will be further analyzed in relation with the available WES and RNAseq data from biopsies collected before and after Nivolumab. However, these analyses are pending.



References:
1. Stupp R et al.: Lancet Oncol 2009, 10(5): 459-466
2. Donia M, Junker N, Ellebaek E, Andersen MH, Straten PT, Svane IM. Characterization and comparison of 'standard' and 'young' tumour-infiltrating lymphocytes for adoptive cell therapy at a Danish translational research institution. Scand J Immunol. 2012;75(2):157-67.

Material and Methods

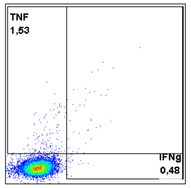
An Open-Label, Phase II, two armed study of Nivolumab and Bevacizumab for recurrent GMB after Stupp's regime (2 Gy x 30 plus concomitant and adjuvant temozolomide [1]);

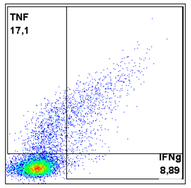
- Patients: 40 patients with recurrent GBM;
  - Arm A: Salvage re-resection possible
  - Arm B: Salvage re-resection not possible
- Samples: PBMC (Peripheral Blood Mononuclear Cell), TILs (Tumor Infiltrating Lymphocytes), tumordigest.
- Investigate biomarkers, TMB (tumor mutation burden) and neoepitope load
- WES (mutations, mutational load), RNA seq (fusion, alternative splicing), expression array (subtyping: neural, mesenchymal, classical) and CytoScan HD (somatic copy number alterations)
- T-cell reactivity analysed by interleukin-measurering, Olink

Recruitment

- 1 site; Rigshospitalet, Copenhagen
- Enrollment; October 2018 – January 2021
- Total of 40 patients:
  Arm A: Salvage re-resection possible
  Arm B: Salvage re-resection not possible

Tumor reactivity after Nivolumab





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