The DCCC Brain Tumor Center

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Tumor reactivity after neoadjuvant Nivolumab for recurrent Glioblastoma

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References:
(1) Readon et al.; Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma, The CheckMate 143 Phase 3 Randomized Clinical Trial
(2) Cloughesy T et al.; Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma
(3) Donia M et al.; Characterization and comparison of 'standard' and 'young' tumor-infiltrating lymphocytes for adoptive cell therapy at a Danish translational research institution.

Background:

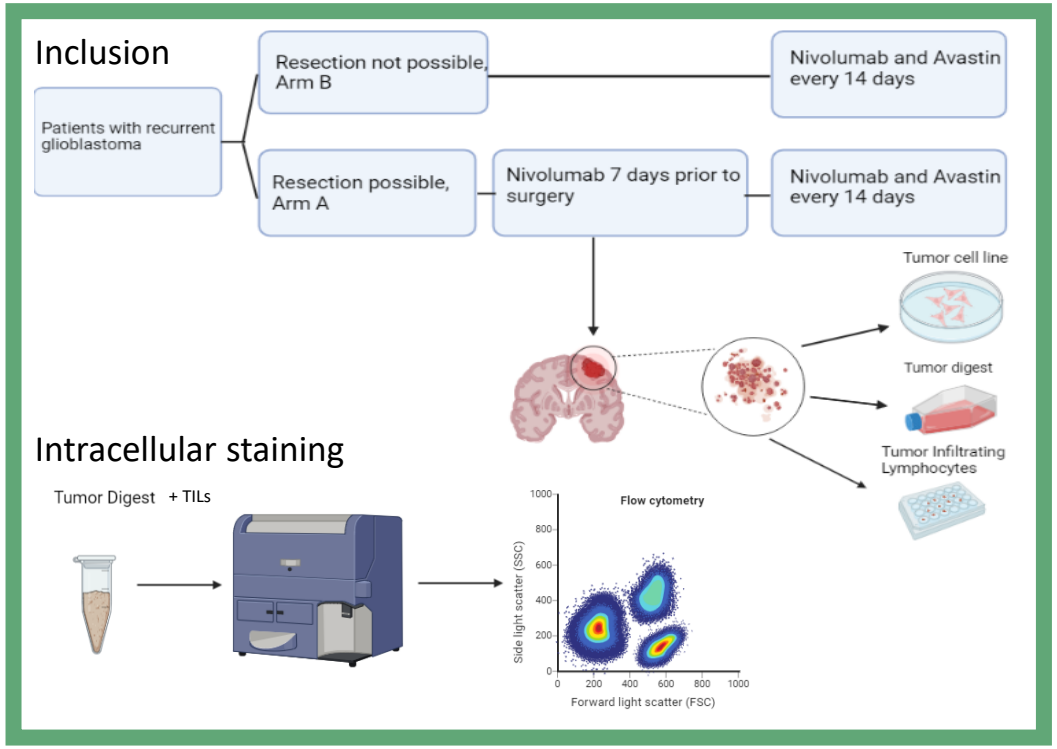
Expectations of Immunotherapy as a treatment for recurrent glioblastoma were sadly not meet in the checkmate 143 (1), however the Cloughesy et al. showed enhancement of the local and systemic anti-tumor immune response after treatment with neoadjuvant pembrolizumab (2). We still believe, that there are lessons to be learned from treating glioblastoma with neoadjuvant PD1/PDL-1 blockade. We combine PDL-1-inhibition with bevacizumab, as we speculate that the stabilization of the vessels among other will deliver the immunotherapy to the target.

Methods:

- Phase 2 trial; two-armed translational study of Nivolumab and Bevacizumab for recurrent GBM. Patients are included in two arms depending on the possibility of salvage neurosurgical resection.
- Forty-four patients were included by January 2021;
- 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 (3). 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.

Results:

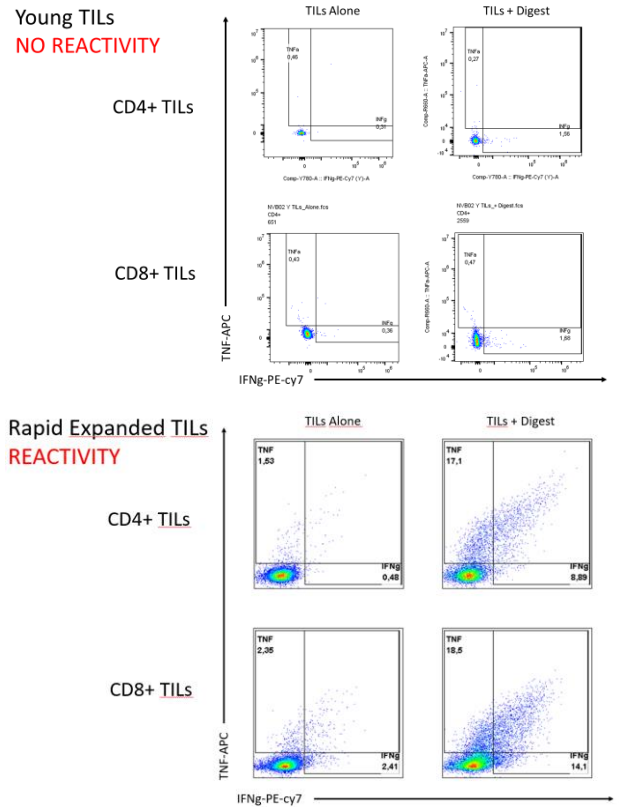
- Four out of 19 samples showed tumor reactivity after exposure to autologous tumor digest
- Tumor reactivity was ranged between 1,2 to 13,6 tox% in CD8+ TILs and between 2,8 to 10,9 tox% in CD4+ TILs.
- By flowcytometry we found, IgG4+ CD3+ TILS from tumor biopsies, meaning that Nivolumab were found in the brain.



Conclusions:

Interestingly, tumor reactivity was found for 3 patients in their rapid expanded TILs (tumor infiltrating lymphocytes), however, not in the young TILs. The rapid expanded TILs are produced with anti-CD3, meaning that only lymphocytes are present.
We could therefore speculate of an inhibitory factor in the tumor microenvironment.

Hot vs. Cold Tumor after Nivolumab



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