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**Title: Characterization of the response of glioblastoma to intrathecal immune checkpoint blockade to rationally design combination therapies**

Glioblastoma is the most common brain tumor with a very bad prognosis. The glioblastoma tumor microenvironment is highly immunosuppressive with downregulation of HLA molecules on tumor cells, increased activation of regulatory T cells, decreased T cell function, expression of immunosuppressive cytokines and the expression of immune checkpoint molecules such as CTLA-4 and PD-1. The presence of these immune checkpoints CTLA-4 and PD-1 has prompted the testing of intravenous immune checkpoint inhibitors in these patients but showed low activity.

Therefore we decided to start a phase I clinical trial (GliTIpNi) to explore the intratumoral and intracavitary administration of anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) in recurrent glioblastoma patients. This treatment regimen proved to be feasible and safe with a low incidence of immune-related adverse events. Although preliminary, the overall survival of these patients compares favorably with an historical control cohort of Belgian recurrent glioblastoma patients treated with a VEGF inhibitor. Longitudinal follow up of the cerebrospinal fluid of these patients showed increased protein levels and increased leukocyte counts which is indicative of an ongoing immune reaction.

In this project, we aim to unravel the immune response induced by intratumoral/intracavitary immune checkpoint blockade. Single-cell RNA sequencing will provide a high-dimensional picture of the induced T cells which will guide more in depth analysis of certain T cell characteristics. In order to evaluate whether the T cells are tumor-specific instead of bystanders, we will investigate their clonality and epitope specificity. The cerebrospinal fluid will be analyzed for cytokine/chemokine and ct-DNA content. Altogether, when comparing these determinants in responder and non-responder patients, we anticipate to identify specific traits in non-responders that can be used to guide the design of combinatorial therapeutic approaches.

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