COLUMBIA UNIVERSITY MEDICAL CENTER

Study of PD-1 inhibitors Pembrolizumab and Nivolumab in Participants with Recurrent or Progressive Gliomas

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Gliomas are the most common primary brain tumor in adults with an estimated annual incidence of over 15,000 cases a year in the United States (CBTRUS, www.cbtrus.org). Despite advances in neuroimaging, neuroanesthesia, and neurosurgical techniques, the prognosis of patients with newly diagnosed glioblastomas treated by surgical resection alone remains dismal with a median survival of 4 to 6 months. To date, radiotherapy has proven to be the most effective treatment for glioblastomas extending median survival to 8 to 12 months. Although adjuvant chemotherapy with temozolomide prolongs median survival to 14 months, almost all patients eventually develop tumor progression. Furthermore, once patients have tumor progression, conventional chemotherapy has not shown to prolong survival. Once the primary modalities of treatment - surgery, chemotherapy, and radiation therapy - have failed, the prognosis for patients with recurrent disease is poor with median survival of 8 months from the diagnosis of recurrent disease (Clarke JL et al. Neuro-Oncol 2011; 13:1118).

Glioblastoma is well known for its capacity to interfere with effective antitumor immune response by tumor mediated immunosuppression. Gliomas are known to express PD-L1, which plays an important role in tumor immune evasion by negatively regulating T-cell functions by engagement with PD-1; glioblastomas have the highest expression of PD-L1 compared to lower grade astrocytomas and oligodendrogliomas (Wilmotte R et al. Neuroreport 2005;16:1081; Wintterle S et al. Cancer Res 2003;63:7462). Interestingly, PD-L1 expression is associated with tumor suppressor PTEN loss, which is a common molecular hallmark of glioblastomas (Parsa AT et al. Nat Med 2007; 13:84). Morever, glioma stem cells, a small subset of cells with more malignant properties such as tumorigenesis, radioresistance and chemoresistance, often express PD-L1 (Yao Y et al. Neuro-Oncol 2009;11:757). Glioma stem cells, through PD-L1, seem to inhibit T-cell proliferation and activation, induce regulatory T cells and trigger T-cell apoptosis (Wei J et al. Clin Cancer Res 2010;16:461).

Antibodies that block the interaction between PD-1 and PD-L1 preferentially release the cytotoxic function of tumor-specific T cells, leading to antitumor effects. Initial studies of anti-PD1 antibodies nivolumab and pembrolizumab and anti-PD-L1 antibody BMS936559 showed significant antitumor activity in patients with advanced melanoma, lung carcinoma and renal cell carcinoma, validating the PD-1/PD-L1 axis as an anticancer therapeutic target. PD-L1 tumor expression may correlate with the likelihood of response to anti-PD1 inhibitors.

Previous clinical studies have demonstrated that a decrease in the proportion of T regulatory lymphocytes and an increase in the CD8 cytotoxic lymphocytes was associated with improved outcome in response to immunotherapy in glioma. Yet, attributing such changes to the mechanism of action of the therapy and assessing their relevance to specific targeting of tumor antigens remains unproven. Whole-repertoire amplification and high-throughput sequencing of the T cell receptors (TCRseq) in a lymphocyte population (e.g., intratumoral and peripheral blood), provides quantification of the abundance of individual TCRs in both the blood and tumor tissue, and allows changes such as the restoration of proliferation and cytotoxic activity to be attributed to those TCR specificities.

In both the mouse model and in human samples, our collaborators in Dr. Bruce and Dr. Canoll laboratories have used pan-repertoire amplification of the complementarity-determining region 3 (CDR3) of the TCR-alpha and TCR-beta chains, which has become commercially available in recent years, developed a library preparation pipeline based on reverse transcription of RNA from peripheral blood mononuclear cells (PBMC) or cryofrozen tumor tissue, thus comparing TILs to the peripheral T cell populations without the artifacts intrinsic to tissue dissociation protocols. With collaborators in the Department of Systems Biology, an innovative computational pipeline which leverages long read length and sequence error handling for unprecedented inclusivity in whole-repertoire analysis of clinical samples was developed. With these tools, we have characterized the peripheral and TIL repertoires, using entropy-based statistics to quantify the degree of antigen-driven clonal expansion in those populations. Such metrics, coupled with traditional assays of T cell function, promise to differentially identify the T cells whose survival and diversity are most affected by local or systemic anti-PD1 treatment.

1) The primary objective is to compare high-throughput sequencing of the T cell receptors (TCRseq) in the lymphocyte population in the peripheral blood before and after patient exposure to pembrolizumab or nivolumab.

Secondary Objectives

2) To obtain exploratory information about the anti-tumor activity of pembrolizumab or nivolumab based on objective response rate, progression-free survival and overall survival.

3) To obtain exploratory data regarding the relationship between clinical outcome and tumor molecular features (PTEN loss, PD-L1 tumor expression, PD-L1/2 tumor microenviroment expression) and whole-repertoire amplification and high-throughput sequencing of the T cell receptors (TCRseq) in a lymphocyte population (peripheral blood).

Past and Present Funding:

This study is being done using internal Columbia grants. Medications are being covered through patients' medical insurances. Funding from Keep Punching would help cover the costs of the high-throughput sequencing of the T cell receptors (TCRseq) in the lymphocyte population in the peripheral blood (Approximately $1,000.00 per sample).