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**Title: The addition of stereotactic body radiation therapy as an immune stimulator to a multimodal immunotherapeutic approach in oligometastatic NSCLC patients**

Lung cancer is the leading cause of cancer-related death worldwide with non-small-cell lung cancer (NSCLC) being the most common subtype, accounting for approximately 85% of lung cancers. The addition of immune checkpoint inhibition (pembrolizumab) to standard-of-care has been the most recent improvement in NSCLC in patients with high PD-L1 expression (monotherapy) or no alterations of EGFR, ALK or ROS (combination with platinum-based chemotherapy). Despite these advances in the field, less than 20% of non-selected patients with advanced NSCLC will benefit from durable disease control.

Our research group has initiated several phase I clinical trials in which autologous, non-manipulated CD1c (BDCA-1)<sup>+</sup> myeloid dendritic cells (myDCs) isolated from the blood are injected intratumorally with the purpose of reinvigorating the cancer immunity cycle. These myDCs are injected together with supplementary immune stimulatory compounds, such as immune-checkpoint inhibitors (NCT03707808) or oncolytic viruses (NCT03747744). Our early promising observations from these trials encouraged us to explore additional modalities that could synergize with immune checkpoint blockade. Hypofractionated stereotactic body radiation therapy (SBRT) has been shown to result in the release of tumor antigens, reduction of the immunosuppressive capacities of the tumor microenvironment (TME), induction of immunogenic cell death, ... Moreover, it has been shown *in vitro* that radiotherapy-induced immunogenic cell death can induce DC maturation and activation, providing a clear rationale to combine unmanipulated myDC vaccination with SBRT.

We have set up a phase II clinical trial to assess the efficacy of SBRT in combination with intratumoral myDC vaccination and immune checkpoint inhibition in oligometastatic NSCLC patients refractory to pembrolizumab. This project furthermore contains a translational aspect wherein we aim to follow up tumor transformation and changes in peripheral blood mononuclear cells (PMBCs) over time by analyzing sequential biopsies/blood draws. Additionally, antigen specificity and T-cell repertoire will be compared in responder versus non-responder patients. Lastly, the effects on the cellular and molecular characteristics of the TME following SBRT will be investigated.

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