Inference of evolutionary tumor-immune dynamics to predict treatment strategies in BRAF-mutant melanoma

Over 91,000 new cases of melanoma will be diagnosed this year. While 91.8% patients will survive 5 years post-diagnosis, many of the tumors eventually metastasize, claiming more than 9,000 lives annually. Identification of the BRAF V600E mutation, occurring in ~50% of patients with cutaneous melanoma, has lead to development of targeted therapies. Initial response to inhibitors of BRAF and its downstream target, MEK, affects growth of 70% tumors. However, these responses are not durable and usually within a year patients relapse. Melanoma relapses are currently treated with immunotherapy regimens based on immune checkpoint inhibition that aims to reactivate immune cells to attack the tumor. Despite some outstanding responses to anti-PDL1 or anti-CTLA4, the overall response rate is low. A recent Phase 1 trial of combination of BRAF/MEK inhibitors [BRAF/MEKi] and immunotherapy showed that the therapy may be effective, although it yielded excessive toxicity. Thus, designing rational combinations of drugs and dosing schedules remains a critical medical need and should be informed by evolutionary principles.
Hypothesis: We hypothesize that by *in silico* modeling the dynamics of tumor-immune cell interactions during treatment, we will optimize adaptive therapy for melanoma in a patient-specific manner.
Impact: Integration of available knowledge into functional models of cancer-immune reactivity can identify patients who will be benefit from immunotherapy first and then [BRAF/MEKi]. Our models will also inform a new clinical trial design to test intervallic administration of [BRAF/MEKi] and immune therapies to improve survival of melanoma patients.
Aim 1. *To integrate immune-phenotypic signatures of BRAF-mutant melanoma patients into mathematical models to determine initial treatment selection*.
We hypothesize that tumors may be prone to react to checkpoint blockade therapy especially when T-cells, even inactive, are infiltrating the tumor or localized in tertiary lymph nodes (TLS) at the tumor edge. Currently, some patients respond better to [BRAF/MEKi] upfront, followed by immunotherapy, but it is unclear which patients could fare better on immunotherapy as a first line of treatment. To answer that, we will measure the spatial localization of T cells and TLS in melanoma biopsies from patients before immunotherapy. The data (IHC for immune markers, PD-L1 and an RNAseq-derived chemokine signature) will inform the compartment model, where compartments represent zones around the TLS, designed to predict the immunotherapy outcome.
Melanomas have high mutation rate, thus high potential to produce many “neoantigens” that could be recognized by T cells to induce an immune response under immunotherapy. We will use patient-blood-derived T-cell receptor repertoire to predict temporal changes in immune activity using an agent based model (ABM) of T-cell clonality. Since the choice of most beneficial treatment ([BRAF/MEKi] vs. immunotherapy) as the first line of therapy for individual patients may vary, our model will help stratify patients to maximize responses.

Aim 2. *Personalize evolutionary therapy of [BRAF/MEKi] and immunotherapy in patients to improve survival as compared to standard of care.*
We will use an ordinary differential equation model (ODE) of tumor response dynamics, reflecting competition between BRAF/MEKi sensitive and resistant cells as well as tumor-immune interactions to predict optimal scheduling of targeted treatment and immunotherapy. The ODE model will be parameterized with sequential patient-specific data (CT scans & lactate dehydrogenase levels) as well as output of the ABM, which relies on T-cell receptor repertoire, tetramer flow and circulating tumor DNA. These data will be derived from an active clinical trial. The ODE will be used for *in silico* clinical trials that generate patient-specific evolutionary therapy schedules.

Supporting clinical trial design:
In parallel with this pilot proposal, a concurrent clinical trial will be initiated, which will provide data for current proposal. In this pilot trial, we will explore overall survival in 20 patients with advanced BRAF-mutant melanoma treated with a BRAF/MEK-inhibitor therapy – encorafenib and binimetinib. Ten patients will be switched to ipilimumab/nivolumab immunotherapy at time of disease progression on CT imaging per RECIST 1.1 criteria. Ten patients will be switched to ipilimumab/nivolumab therapy based on a mathematical model that optimizes maximum benefit from BRAF-targeted therapy, prior to developing resistance to treatment, and potential resistance to immunotherapy. CT scans and brain MRIs will be obtained every 8 weeks while on study. All statistical analyses will be descriptive.