Designing and evaluating evolutionary therapies for advanced progressive thyroid cancer

Background: In the U.S., thyroid cancer is the fifth most common cancer among women and the cancer growing fastest in incidence. Most patients have an excellent prognosis with a five-year survival rate > 98%. However, when advanced and metastatic (lymph nodes, lung, and bone are frequent metastatic sites), the five-year survival rate drops to around 56%. Mortality rates have changed little for several decades. Standard of care involves tyrosine kinase inhibitors (TKI). Because of the evolution of drug resistance, median time to progression or intolerable drug toxicity is about 18-20 months. Delaying the evolution of resistant clones and decreasing the toxicity profile of TKIs in patients with thyroid cancer should improve progression free survival and improve quality of life. Adaptive TKI therapy could be one such mechanism.

A phase 2 trial (MCC 19442, PI-Chung) has recently opened at Moffitt to apply an adaptive therapy to advanced-stage differentiated (DTC) and medullary (MTC) thyroid cancers, which develop in follicular and parafollicular cells, respectively. Based on the levels of distinct biomarkers for DTC and MTC, the current standard of care TKIs will be administered. The TKIs are Lenvatinib or Sorafenib in DTC and Cabozantinib or Vandetanib in MTC. Modeled after the previous prostate cancer trial with adaptive design, a TKI is administered until there is >50% reduction in the biomarker and is then withdrawn. The therapy resumes when the biomarker increases to the pre-treatment level. A separate international phase III trial on metastatic DTC (MCC 19818, Moffitt Site PI-Tarasova) proposes to evaluate the efficacy of Cabozantinib after patients have progressive disease on Lenvatinib or Sorafenib given standard continuous dosing, with the hope that cells do not have cross resistance with the preceding TKIs. Neither of these trials has been formally modelled mathematically or *in silico*.

We propose to provide the first eco-evolutionary model for advanced stage, metastatic thyroid cancer (both DTC and MTC) subjected to TKI therapies. We propose a core model built around a population ecology model that includes the cancer cells' intrinsic growth rate (r), carrying capacity (K), and therapy-induced mortality. The cancer cells possess a resistance strategy that mitigates mortality from therapy at the expense of reduced r or K. Little is known regarding TKI-specific mechanisms of resistance, the costs of resistance, or the distribution of resistance strategies found within the tumors. For this reason, the core model is intended to have general properties that can be modified and expanded to consider: 1) competition between sensitive and resistant cancer clones (competitive release adaptive therapy), 2) a monomorphic cancer clone whose resistance strategy evolves along a continuum (a novel perspective on adaptive therapy), 3) a vector of resistance strategies that may be specific or general to different TKIs (appropriate for trials that sequentially use multiple TKIs), and 4) spatially-explicit histologies and potential for combining TKI and immunotherapy within the tumor immune microenvironments.

We **hypothesize** that: i) the model will support the conclusion that an adaptive therapy based on a 50% trigger point will be non-inferior and likely superior to continuous TKI, ii) the extended model will show how an evolutionarily informed sequential use of two different TKIs will promote a more durable response than just one, especially when each TKI requires a different resistance strategy by the cancer cells (double bind adaptive therapy), and iii) using a patient's data to parameterize the model will permit a personalized resistance management plan.

Specific Aim 1. To develop and validate a core mathematical model of tumor progression and therapeutic response in advanced stage DTC and MTC. We will model the eco-evolutionary dynamics associated with a TKI monotherapy given continuous vs. adaptive dosing schedule. The model(s) will be parameterized using retrospective cohorts of DTC and MTC patients based on: i) the choice of TKI, ii) longitudinal biomarker levels, iii) available tumor specimens, and iv) tumor burdens determined by longitudinal radiographic scans. The model(s) will be validated using prospective cohorts treated under the adaptive trial (MCC 19442).

Specific Aim 2. To develop a core mathematical model of tumor progression and therapeutic response given a sequential therapy using two different TKIs. We will develop a model(s) of the eco-evolutionary dynamics associated with the continuous dosing schedule given a TKI monotherapy vs. a sequential therapy using two different TKIs in the retrospectively collected cohort. We will test the model(s) in the prospective cohort from treated MCC 19442 control arm and MCC 19818. In addition, we will develop a model(s) in patients with adaptive dosing schedule given a TKI monotherapy vs. a sequential therapy using two different TKIs in the prospectively collected cohorts from MCC 19442 experimental arm. We will apply machine learning data augmentation to use existing time-series data on biomarkers to generate much larger cohorts of virtual patients. Actual and virtual patients will provide unique patient parameterizations.

Specific Aim 3. To develop, validate, and test a core mathematical model of therapeutic response and its effects in the tumor immune microenvironment. We will model the eco-evolutionary dynamics associated with a TKI monotherapy given continuous vs. adaptive dosing schedule. The model(s) will be parameterized using retrospective cohorts of DTC and MTC patients based on: i) the choice of TKI, ii) longitudinal biomarker levels, iii) available tumor specimens, and iv) characterization of immune cells and hypoxia markers using multiplex immunohistochemistry. The model(s) will be validated using prospective cohorts treated under MCC 19442.