



Team Progress Updates

SU2C–Dutch Cancer Society Translational Research Team: “Prospective Use of DNA-Guided Personalized Cancer Treatment”



The team is investigating how changes in the tumor DNA of patients can be used to predict sensitivity to specific anti-cancer agents. This requires detailed analysis of the alterations in large numbers of genes in tumors and then studies of patient responses to specific cancer drugs. The results will enable doctors to make far more educated choices for the treatment of individual patients, leading to greater therapeutic benefit while reducing the toxicity of drugs that are not effective.

The research team asks patients to provide biopsies before and two months after the start of their treatment regimens. DNA is isolated from these biopsies and analyzed for mutations in 2,000 potentially informative genes. Genetic changes are correlated with treatment outcomes, and DNA profiles are generated that can predict whether patients with breast or colorectal cancer will respond to specific treatments. By linking the clinical data to the genetic data of the tumor and utilizing all available information on the biology of that cancer, doctors can further refine patient selection criteria for a specific treatment.

The four major aims of the project are as follows:

1. Identify DNA-based biomarkers of response to neo-adjuvant chemotherapy +/- neratinib in breast cancer through analyses of biopsies from the trial.
2. Generate genomic selection criteria for patients with KRAS wild type colorectal tumors to improve the outcome of anti-EGFR antibody treatment using genomic analyses of metastases for a cancer mini-genome of genes.
3. Deliver systems biology tools to analyze alterations in the cancer mini-genome to refine patient selection criteria for individualized treatment.
4. Identify DNA and RNA-based biomarkers of response to chemotherapy + atezolimumab in metastatic lobular breast cancer.

The team has reported the following progress:

Aim 1:

The Team reached agreement with the ISPY consortium to exchange genomic data for the neratinib treated patients. This agreement allows the Team to perform an integrated genomic analysis of the response to neratinib, based on gene expression, proteomic and mutation data.

Aim 2:

This part of the project was amended in such a way that paired biopsies of EGFR treated patients were not included (after suggestions made by the SU2C review team). Analyses will be performed on





Team Progress Updates

the pretreatment biopsies as described below under 1.4. The remainder of the duration of the project's time and resources will be devoted to immunotherapy (see also aim 4)

Aim 3:

The Team has developed and published several new tools (see under 1.4 for a complete overview) to better predict drug responses of cancer cells. They have developed a multilevel mixed effects model to improve the precision of the half-limiting dose (IC₅₀) estimates by simultaneously employing all dose-responses across all cell lines and drugs, rather than using a single drug-cell line response. The new estimates are highly concordant with the currently used Bayesian model when the data are well behaved. Otherwise, the multilevel model is clearly superior. The Team concludes that the multilevel model yields a significant reduction of extreme IC₅₀ estimates, and an increase in precision. The model also runs faster.

Aim 4:

The Team has identified a subset of lobular breast tumors that are expected to respond to checkpoint immunotherapy. This is based on a gene expression classifier developed by the molecular diagnostic company Agendia Ltd, in collaboration with the Netherlands Cancer Institute. The protocol for a study with the Roche checkpoint blockade antibody atezoluzumab ("GELATO") has been approved by both Agendia and Roche, and funding has been secured from these two companies.