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Adaptive Clinical Trial Design to Address Acquired Resistance and Therapeutic Failure

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Abstract: One of the challenges facing immunotherapy as a durable therapeutic approach in a variety of metastatic cancers is the development of acquired resistance and subsequent therapeutic failure. Widespread clinical applicability of immunotherapy to solid tumors depends on the understanding of response and resistance mechanisms that are mediated by evolving interactions between the immune system and cancer cells. These dynamic interactions are increasingly being identified through longitudinal molecular analysis and immunological profiling and combine to produce an evolving measure of a patient's cancer-immune status. However, cancer immune dynamics have yet to be formally quantified and studied as an evolutionary process in the context of immunotherapy clinical trials. To address this, we propose a method to integrate high dimensional, heterogeneous, longitudinal patient-derived cancer and immunological clinical data sets to identify cancer immune dynamics as well as a control theoretic method to preemptively address the onset of resistance through the prediction and synthesis of actionable immunotherapy combination strategies. We apply these methods to genomic and immunological data collected from a patient with recurrent multifocal glioblastoma that elicited a complete response and eventually recurred while enrolled in City of Hope's ongoing IL13Rα2-targeting chimeric antigen (CAR) T cell trial for patients with recurrent glioblastoma. We show that dynamic treatment strategies are necessary for the control of tumors with high antigen heterogeneity and propose this as a framework by which to assess the effectiveness of adaptive clinical trial design and patient stratification for combination immunotherapy trials.

Bio: Vanessa Jonsson is an assistant research professor in the and Department of Hematology and Hematopoietic Cell Transplantation and leader of the Computational Immuno-Oncology group in the T Cell Immunotherapy Program at City of Hope. Her research program in computational biology focusses on the integration, mathematical modeling and analysis of large-scale, longitudinal genomic, transcriptomic and immunological data from clinical studies to inform and address the mechanisms of immune-resistant cancer progression. In 2015, Vanessa completed her PhD at Caltech, where she was advised by Richard Murray and David Baltimore. She is a principal investigator on a Parker Institute for Cancer Immunotherapy award to model the evolution of cancer immunity during immunotherapy trials and co-investigator on a California Institute of Regenerative Medicine (CIRM) award to study response and resistance in a phase I CAR T cell trial targeting malignant glioma. She is the recipient of the NIH and NCI career development award in clinical oncology (K12), with a focus on immuno-oncology.