LAY ABSTRACT

Identifying predictive biomarkers for novel antibody-drug conjugates

Background and Importance of Research: Stage IV breast cancer remains a critical challenge, but advancements in the design and development of a class of therapies known as antibody-drug conjugates (ADCs) have ushered in a new era of hope. These therapies are designed to deliver cancer-killing agents directly to tumor cells, minimizing damage to normal tissues and potentially improving patient outcomes. However, a significant hurdle in the use of ADCs is the inability to predict which patients will respond favorably to each specific ADC and to understand why some patients eventually develop resistance to these treatments.

Research Goals and Objectives: The main goal of our research is to innovate and refine the methods by which we predict responses to ADC therapies in patients with advanced breast cancer. This is made possible by great advancements in techniques able to quantitate with high sensitivity the amount of certain proteins on the tumor cells surface, as well as by techniques able to read the genetic code of cancer cells to identify therapeutic vulnerabilities. By developing new diagnostic tests that can predict treatment outcomes with ADCs before treatment begins, and by investigating the mechanisms through which resistance to these drugs occurs, we aim to significantly enhance the effectiveness of treatment protocols, concomitantly minimizing the risk for unnecessary side effects.

Detailed Methods: To achieve our goals, we will employ a series of state-of-the-art techniques to analyze tumor samples from patients before and after they receive ADC treatment. This includes using two distinct highly sensitive assays to measure levels of Trop2 and HER2, proteins on cancer cells that are targeted by the drugs sacituzumab govitecan and trastuzumab deruxtecan, respectively. We will examine how the expression of these proteins on tissue samples collected before treatment initiation correlates with patient responses to treatment. Concomitantly, we will study genetic changes in the tumors that may signal the development of drug resistance. This will be done both on tissue samples collected before and after treatment with ADCs, as well as by leveraging advances in the profiling of the genetic code of the tumor from a simple blood draw (i.e. liquid biopsy).

Our analyses will first focus on patients that have received treatment with ADCs at Dana-Farber Cancer Institute, aiming to develop thresholds of expression to be subsequently validated in additional cohorts of patients. The validation will occur leveraging the study samples of patients that participate to three clinical trials currently ongoing at Dana-Farber, dubbed the “SATEEN”, “DATO-Base” and “TRUDI” trials. All of these studies involve patients with advanced forms of breast cancer, who will be treated with ADCs, with the aim to improve outcomes for patients with a high unmet need.

Potential Benefits and Impact: The implications of our research are far-reaching. By identifying biomarkers that indicate how patients will respond to ADCs, and by understanding the genetic basis of resistance, we can help oncologists tailor treatment strategies to individual patients, thereby increasing the chances of successful outcomes. This personalized approach could transform the standard of care for patients with advanced breast cancer, especially those who have few treatment options available due to the nature of their disease or previous treatment failures. Moreover, we hope that our results will enable for a new era of clinical development of ADCs, with patients enrolled and treated in clinical trials only if they are predicted to have high chance of benefitting from a particular ADC, as suggested by a validated assay.

Clinical Application and Future Directions: Our findings will be rigorously tested in multiple clinical trials designed to validate these new biomarkers and refine treatment protocols. Successful outcomes from these trials could lead to new treatment guidelines that utilize ADCs more effectively, improving survival rates and quality of life for patients with metastatic breast cancer. Furthermore, our research could pave the way for similar strategies in other types of advanced cancer, potentially changing the landscape of cancer treatment.

Concluding Thoughts: This project is not just about enhancing existing treatments—it's about improving the way we approach cancer therapy to provide real, tangible benefits to patients facing one of the most challenging diagnoses in medicine. With these advancements, we hope to bring new hope and better health to individuals battling metastatic breast cancer.