CASE STUDY

SAPIENT

Discovery of biomarker to predict immunotherapy related autoimmunity

Immunotherapy has transformed the treatment of solid organ cancers, rapidly becoming a first line therapy with transformative durable response.

While immunotherapies have favorable toxicity profiles compared to traditional chemotherapies, immunotherapy is associated with the development of immune-related adverse events (irAEs), an autoimmune condition incited by activation of the immune system.

THE CHALLENGE

Severe iRAEs that occur in major organs can be life-threatening and limit use of immunotherapy agents, making early prediction of such risks critical to patient safety. **20% to 60% of patients receiving immune checkpoint inhibitors (ICIs) will experience severe irAEs that can limit therapeutic continuation of treatment.**[1]

[1] Shah P, Punekar SR, Pavlick AC. *Melanoma Res.* 2021, 1;31(3):242-248

These adverse events have profound influence on the overall outcomes associated with checkpoint inhibitor drugs. There is a pressing need to identify reliable biomarkers that further elucidate how immunotherapies modify existing immune responses to disease, predict toxicities, and help to guide the treatment and management of at-risk patients.

In this study, Sapient set out to discover a robust, specific circulating biomarker that identifies individuals who are at risk for severe autoimmune events in the setting of ICI.

THE METHODOLOGY

Sapient profiled blood samples taken from **over 300 patients in several independent clinical trials** who had received checkpoint inhibitor drugs for a variety of solid tumors.

STUDY SCALE

300+
human blood samples

50K+
circulating factors captured across the group of samples

Using our proprietary rapid liquid chromatography-mass spectrometry (rLC-MS) systems, we analyzed **over 50,000 molecules** across the group of samples and identified a singular biomarker that identifies individuals at risk for severe iRAEs to immunotherapy.

Across the different clinical trials and regardless of the type of ICI administered, we found that individuals who do not develop an autoimmune reaction or have mild symptoms have no change in the biomarker level in their blood over time. However, individuals who **develop a severe iRAE –** particularly one that is significant enough to necessitate discontinuation of treatment – have **drastic changes in circulating biomarkers** that precede the development of ICI related autoimmunity.

Cross-validation of these observations confirmed the association of the circulating biomarker with tissue toxicity **in preclinical models** of ICI related autoimmunity. Within Sapient's Human Biology Database, we have been able to map how this singular biomarker **associates not only with immunotherapy-induced autoimmunity, but also traditional autoimmune diseases,** including lupus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD).

Using data from hundreds of thousands of human biosamples – from individuals who have been followed an average of 10-30 years for longitudinal outcomes – we found people with low levels of the biomarker relative to those with high levels

FAST FACTS

THE METHODOLOGY

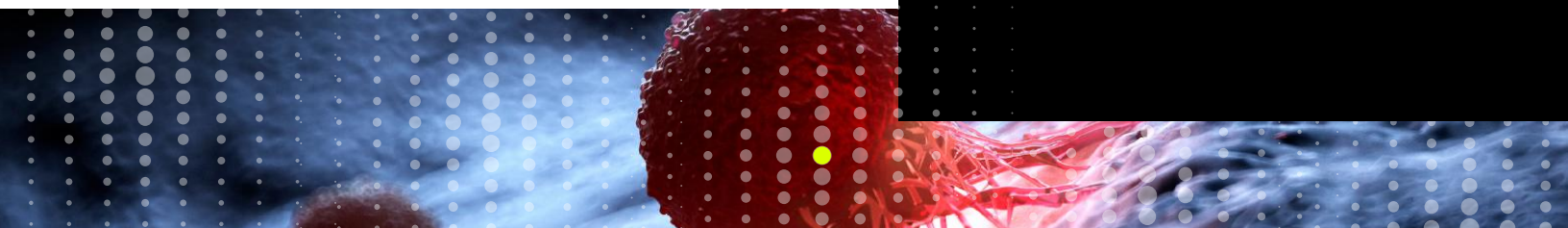
- Analyzed >50,000 molecules in >300 human blood samples, gathered from several independent clinical trials, via Sapient's rLC-MS systems
- Performed biocomputational prioritization to identify a singular key biomarker that drastically changes in individuals that develop severe immunotherapy related autoimmunity
- Cross-validated the key biomarker in preclinical models of autoimmunity
- Cross-referenced the biomarker in Sapient's proprietary Human Biology Database comprised of data from >100,000s of human biosamples

THE BIOMARKER FINDINGS

- Represents a robust biomarker of safety in the setting of immunotherapy
- Associates with non-drug related autoimmunity
- Identifies those individuals who are likely to develop an autoimmune disease over a 10-year period
- Is mechanistically related to immune cell activation

THE VALUE

- In development as a safety biomarker for immunotherapy
- In development as a therapeutic for autoimmune diseases



of the biomarker are **nearly twice as likely to develop an autoimmune disorder over a 10-year period.** Biomarker levels altered quite early in the disease process.

Our database further reveals potential mechanisms underlying the association between this circulating biomarker and autoimmunity, and suggests direct activation of particular immune cell populations.

THE IMPACT

This new biomarker has been cross validated in independent human clinical trials and preclinical models to be a **robust biomarker of safety in the setting of immunotherapy.** Not only does it elucidate the relation of drug-induced autoimmune reactions relative to immunotherapy, but also of non-drug related autoimmunity by **understanding the underlying mechanisms that give rise to this relationship.** In fact, the biomarker is currently being **developed both as a safety biomarker as well as a therapeutic.**

These findings **demonstrate the value of Sapient's approach** to rapidly deliver discoveries in tandem with actionable insights that progress drug development pipelines. The framework can be easily applied to many other therapeutic areas to answer similar questions.

WANT TO DISCOVER MORE?

Our scientists can share further data insights on this biomarker for immunotherapy or discuss how we can apply our methodology to your project.

Schedule call: discover@sapient.bio

Visit: sapient.bio/immunotherapy

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