

# Balancing Benefit and Risk: Managing Immunotherapy Side Effects in Melanoma

Watch a Melanoma Research Alliance presentation by Alexandra-Chloe Villani about immunotherapy side effects in this skin cancer.

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In recent years, [immunotherapy](#) has revolutionized melanoma treatment, offering new hope to patients with advanced disease. However, these powerful treatments can sometimes trigger immune-related adverse events (irAEs) that affect various organs. Understanding, predicting, and managing these side effects has become crucial in melanoma care.

## The Immunotherapy Revolution

During her presentation at MRA's 2025 Melanoma > Exchange Patient Forum, Dr. Alexandra-Chloé Villani, a scientific researcher at Massachusetts General Hospital (MGH), shared valuable insights about the delicate balance between effective treatment and managing potential complications.

Certain types of immunotherapies work by removing checkpoints, or “brakes,” from the immune system, allowing them to recognize and attack cancer cells. Dr. Villani emphasized that this immunotherapy approach fundamentally differs from other therapies because it does not target anything specific to the tumor. Instead, it unleashes the body's own immune response. “This is a good news story,” Dr. Villani reassured the audience.

“Since immune checkpoint inhibitors were approved for melanoma in 2011, this class of drugs has been approved for 109 indications across different cancer types.”

Dr. Villani's presentation focused on how immune checkpoint inhibitors work and why they sometimes cause side effects. She explained that these immune checkpoint molecules typically serve essential protective functions in the body by:

- Slowing down immune responses to prevent damage to healthy tissues.
- Helping the immune system distinguish between the body's own healthy cells and foreign cells

so it doesn't attack the healthy cells.

- Preventing excessive immune responses once infections or allergic reactions are resolved.

Melanoma cells can exploit these protective mechanisms by expressing molecules that tell T cells not to attack them. Checkpoint inhibitor drugs block this deception, allowing T cells to recognize and destroy cancer cells. However, by interfering with these protective mechanisms without a tool for modulation, these treatments can sometimes lead to side effects. Immunotherapy does not work for everyone, and different checkpoint inhibitors are often combined to improve their effectiveness.

### Understanding Immune-Related Adverse Events

Depending on the dose and combination of immunotherapy drugs, up to 90% of patients on these therapies may develop some form of side effect. These can range from mild skin rashes to potentially life-threatening inflammation of organs such as the heart, lungs, or nervous system. Dr. Villani noted that side effects are becoming increasingly relevant as immunotherapy, such as immune checkpoint inhibitors, expands beyond treatment of metastatic disease to adjuvant and neoadjuvant settings. "The consideration of risk-to-benefit ratio is a whole different story if you are in a curative or preventive setting," she explained.

Dr. Villani shared the story of David, a 64-year-old businessman whose melanoma journey inspired her work and the work of her colleagues at MGH in this field. David initially responded well to immunotherapy for metastatic melanoma but later had severe complications. First, he developed pneumonitis (lung inflammation), then colitis (colon inflammation), and finally inflammation of his nerves. Despite aggressive treatment with steroids and other immunosuppressive medications, David's condition worsened, and he ultimately passed away. His autopsy revealed no remaining cancer cells, as the treatment had effectively eliminated his melanoma, but his organs showed extensive inflammation from an over-activated immune system.

This case highlighted several important aspects of managing immunotherapy side effects:

- The need for multidisciplinary care teams with expertise across different organ systems.
- The importance of developing better treatment solutions for side effects beyond broad immunosuppression.
- The necessity for more research to understand why some patients develop multiple different toxicities while others have none.

## Timing and Types of Side Effects

Most checkpoint inhibitor immunotherapy-related side effects occur within the first six months of treatment, although some can develop later or be chronic. Dr. Villani presented data showing that different side effects tend to emerge at different time points:

- Skin reactions often occur first.
- Gastrointestinal and liver issues typically follow.
- Endocrine problems such as thyroid dysfunction may develop later.

Some side effects resolve completely with proper management, while others, particularly those that affect endocrine organs such as the thyroid or pancreas, may cause permanent damage requiring lifelong hormone replacement therapy. This underscores the importance of early detection of side effects and intervention.

Chronic side effects from immunotherapy, which can affect up to 43% of patients, were previously underreported for several reasons: They can occur months after treatment ends, early clinical trials focused on patients with limited survival time, side effects were often confused with other health problems, and until October 2024, there wasn't even an official medical billing code to track these problems in health care systems.

## Building Solutions: The Severe Immunotherapy Complications Service

In 2017, Dr. Villani in partnership with Dr. Kerry Reynolds and colleagues established the [MGH Severe Immunotherapy Complications \(SIC\) Service](#) to address these challenges. This multidisciplinary team includes oncologists, specialists from various departments (gastroenterology, pulmonary, cardiology, etc.), nurses, and researchers collaborating to provide comprehensive care for patients who experience immunotherapy complications. The team also conducts research to better understand the root causes of these toxicities, with the goal of developing improved treatments to better prevent and manage them.

The service operates in both inpatient and outpatient settings with established protocols for patient care, research sample collection, and data analysis. Dr. Villani described how this integrated approach has improved patient outcomes and accelerated research efforts.

"It takes a village to make this happen," she explained, describing a case where over 14 specialists and researchers worked together to rapidly diagnose and treat a patient with muscle and joint inflammation. The team was able to not only provide excellent clinical care but also collect tissue samples, which led to important scientific insights.

## Advancing Science Through Research

To improve the treatment of immunotherapy side effects, doctors need several key advances: tools to quickly distinguish side effects from opportunistic infection or melanoma progression, methods to predict which patients will develop specific side effects, and more targeted treatments that go beyond steroids (which can possibly reduce the melanoma-fighting response). Because these side effects do not appear in laboratory mice, researchers need partnerships with patients and families to collect samples and understand the root causes and ultimately develop better treatments that don't require stopping the life-saving melanoma immunotherapy.

Dr. Villani's work focuses on understanding the biological mechanisms behind different types of immune-related side effects. Her lab uses cutting-edge single-cell genomics technology to analyze affected tissues at high levels of detail.

She compared this approach to analyzing a fruit salad, where each piece of fruit represents an individual cell. "Traditional methods would be like blending the entire fruit salad into a smoothie and analyzing the average content." Using this new single-cell genomics technology is like emptying the bowl onto a table, organizing and regrouping each piece of fruit based on similarity, and examining its quality (healthy versus rotten).

This detailed analysis allows researchers to:

- Identify the specific types of immune cells that drive inflammation in each organ.
- Determine whether similar mechanisms are at work across different types of toxicities.
- Discover potential biomarkers that might predict which patients are at risk to develop toxicities.
- Find targeted treatment approaches to address side effects without diminishing the anti-cancer effects.

Dr. Villani shared that her team has already made significant discoveries about the mechanisms driving heart inflammation (myocarditis) and colon inflammation (colitis) in patients receiving immunotherapy. They found that the biology driving anti-tumor responses differs from that causing heart inflammation, suggesting that it may be possible to separate the beneficial effects of treatment from the harmful ones.

"This work is really important in terms of setting the next phase," she noted. "With this big data approach, we can define targets that could be followed up on in clinical trials."

## Looking Ahead: Challenges and Opportunities

Despite the progress made, significant challenges remain. Dr. Villani highlighted several areas where further work is needed:

- Establishing larger patient cohorts to validate findings and discover predictive biomarkers for patients at risk of developing side effects.
- Developing better classification systems and terminology to distinguish these side effects from anti-tumor immune response (i.e. treatment efficacy).
- Securing funding for research on toxicity management, which often receives less attention than developing new cancer treatments.
- Building partnerships between patients, clinicians, and researchers to advance understanding.

“I personally believe that the future of improving efficacy is by mitigating these side effects, so that we can keep patients on these drugs safely for a longer time,” Dr. Villani stated.

She emphasized that patients could play a crucial role by reporting symptoms promptly to their health care providers. Early intervention is key, because side effects are generally easier to manage when caught early.

## The Road Forward

Dr. Villani concluded by reminding the audience that despite the challenges, immunotherapy — in particular immune checkpoint inhibitors — represents a tremendous advancement in cancer treatment. The goal is to make these life-saving treatments safer and more effective for more patients.

The field is making significant progress toward understanding and managing immune-related side effects through integrated clinical care, innovative research approaches, and collaboration between patients and medical professionals. This work promises to further transform the treatment landscape for melanoma and many other cancers, allowing more patients to benefit from these powerful therapies with fewer complications.

By raising awareness about immunotherapy side effects and supporting research efforts to address them, the melanoma community can help ensure that it reaches its full potential as a cornerstone of cancer treatment.

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