Gene-signature for Predicting Immune-Related Adverse Events (irAEs) After Immune Checkpoint Inhibitor (ICI) Treatment

A novel predictive biomarker to guide personalized immune checkpoint treatments after surgical removal of melanoma.

Technology

The Kirchhoff Laboratory at NYU has developed a model to predict the occurrence of severe immune-related adverse events (irAEs) in melanoma patients undergoing immune-checkpoint inhibitor (ICI) treatment post-surgery. The researchers analyzed gene expression profiles in circulating CD4+ and CD8+ T cells from 212 patients participating in the CheckMate-915 clinical trial, where patients received either nivolumab (NIVO) or a combination of ipilimumab and nivolumab (COMBO) after surgery. Their analysis identified a spleen-tyrosine kinase (SYK) related gene expression profile specific to CD4+ T cells in COMBO-treated patients, which was linked to severe irAEs. Building on this finding, they developed a prediction model that utilizes the expression of five SYK-related genes (*CD22*, *PAG1*, *CD33*, *HNRNPU*, and *FCGR2C*) alongside patient characteristics such as age, sex, and disease stage. Using the outcomes from the CheckMate-915 trial, the model accurately predicted severe irAE occurrences in approximately 60% of COMBO patients. Implementation of this predictive model will allow clinicians to assess patients after surgery, before administering ICIs, to develop personalized treatment strategies designed to reduce associated toxicities.

Background

Immune checkpoint inhibitors (ICIs) like ipilimumab (anti-CTLA4) and nivolumab (anti-PD-1) have transformed melanoma treatment. While they were initially developed for metastatic disease, ICIs are now applied to treat resectable disease both before surgery (neo-adjuvant) and after surgery (adjuvant), showing better outcomes in both scenarios compared to surgery alone. Despite these benefits, many patients experience severe immune-related adverse events (irAEs) due to ICI treatment. These complications can lead to conditions such as colitis, pneumonitis, autoimmune hepatitis, psoriasis, vitiligo, or erythema, often necessitating the use of immunosuppressive therapy or even discontinuation of the treatment. While managing these toxicities is generally accepted as a necessary trade-off to enhance survival in metastatic melanoma, their impact in the adjuvant setting presents a significant and costly clinical challenge. The novel predictive model developed by the Kirchhoff lab addresses this issue by providing a tool to anticipate adverse outcomes, allowing for treatment strategies to be adjusted proactively, potentially preventing severe toxicities before treatment begins.

Development Stage

Technology ID

KIR03-04

Category

Life Sciences/Diagnostics
Life Sciences/Therapeutics/Oncology
Life Sciences/Therapeutics/Immunoth
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The Kirchhoff lab is continuing to validate their predictive model on additional patient cohorts.

Applications

- Personalized, post-surgery treatment plans for melanoma patients.
- Development of ICI combination therapies based on newly identified role of SYK pathway in patients experiencing irAEs.

Advantages

- **Accurately predicts patient responses:** Predictive model can identify patients who will develop severe irAEs with 83% accuracy.
- **Personalized approach:** Model predicts the likelihood of ipilimumab and nivolumab causing irAEs, enabling personalized post-surgery treatment strategies.
- **Non-invasive procedure:** Gene-expression signature is characterized from PBMCs which can be collected by a non-invasive blood-draw.
- **Novel biomarkers**: SYK gene signature uncovers novel biomarkers that inform future research into disease biology underlying development of irAEs in certain patients.

Intellectual Property

NYU has filed a PCT patent application covering the method of determining patient risk of developing irAEs via SYK gene signature.

References

1. Monson KR, Ferguson R, Handzlik JE, et al. , https://pubmed.ncbi.nlm.nih.gov/39115425/