Stealthier mutanomes are induced after nivolumab immunotherapy

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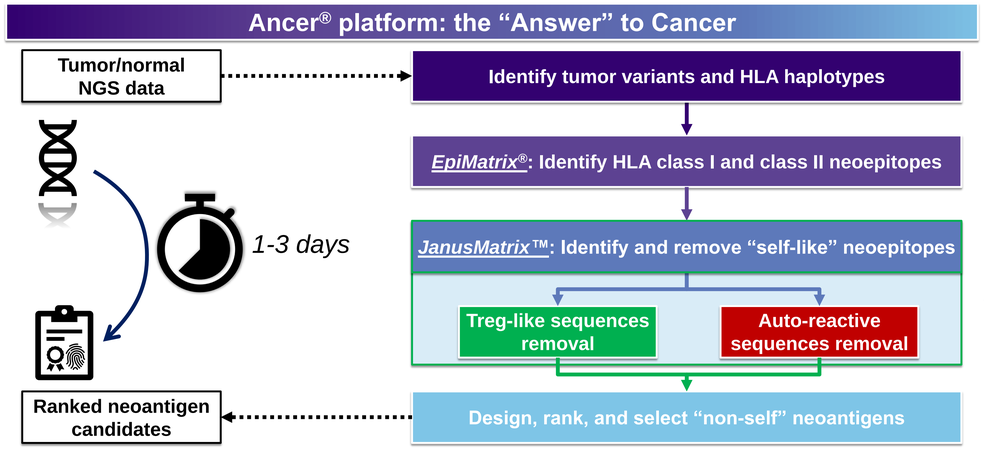
Overview

- **Hypothesis**: Tumor clones surviving checkpoint inhibition therapy harbor mutations more prone to immune avoidance.
- **Approach**: Tumors from melanoma patients collected **before and after** nivolumab immunotherapy (n=41) were analyzed with **Ancer, an advanced neoepitope screening platform** that combines proprietary machine learning-based **CD8 and CD4** epitope mapping tools with removal of **inhibitory Treg** epitopes.
- **Results**: **Mutations gained after nivolumab therapy are less immunogenic and more tolerogenic** compared to mutations found prior to therapy.
- **Response to therapy is associated with Ancer results.**
- **Summary**: Our Ancer analysis suggests that nivolumab therapy affects the immunogenicity and tolerance profiles of newly generated mutations in a manner that is **consistent with the concepts of immunoediting and immune camouflaging**.

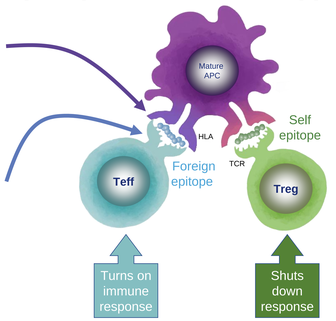
Background – Mutanome-Directed Cancer Immunotherapy Based on 20 Years of Experience in Epitope Mapping

Ancer® platform: the "Answer" to Cancer

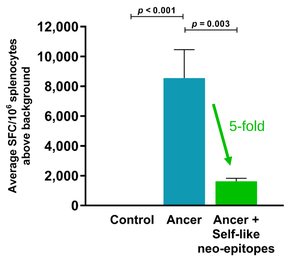


HLA binding predictions. ***EpiMatrix*** Class I an Class II predictions are respectively **95% and 74% accurate** [1].

Foreign vs self epitopes. Epitopes can be either effector (Teff) or regulatory (Treg). ***JanusMatrix*** has identified immunosuppressive epitopes in pathogens [2, 3, 4] and cancer mutanomes [5].

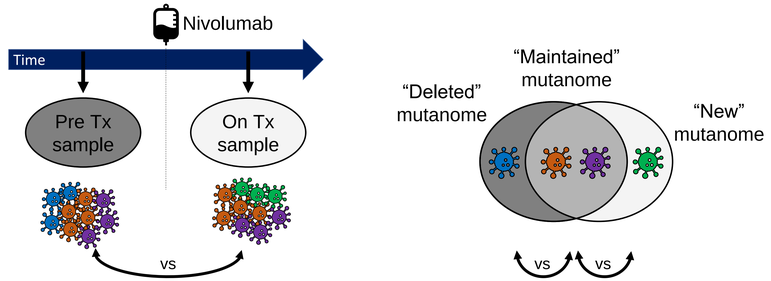


CT26 self-like neo-epitopes suppress IFNγ production to Ancer-CT26 vaccines



Approach – Ancer analysis of melanoma samples

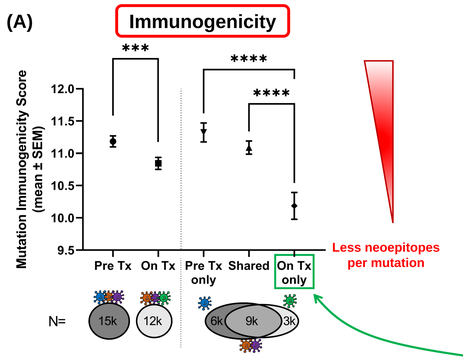
- Forty-one pairs of mutanomes collected before (*Pre*) and while on (*On*) nivolumab therapy were retrieved from [6].
- Pre and On mutanomes were compared to identify deleted, maintained, and newly acquired mutations.
- Immunogenic and tolerance potentials were calculated for all mutations with Ancer.

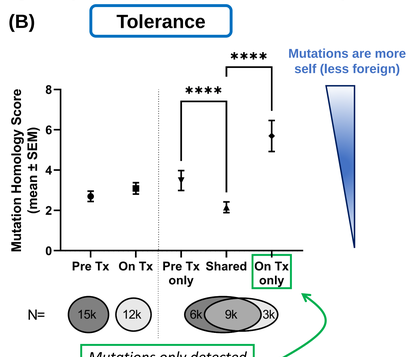


Simplification: one tumor clone = one mutation

Results – Post-therapy mutations are less immunogenic and more tolerogenic

- Mutations gained after nivolumab therapy are less immunogenic (A) and more tolerogenic (B).
- Tumors respond to immunotherapy by reducing their immunogenicity and by avoiding the immune system.

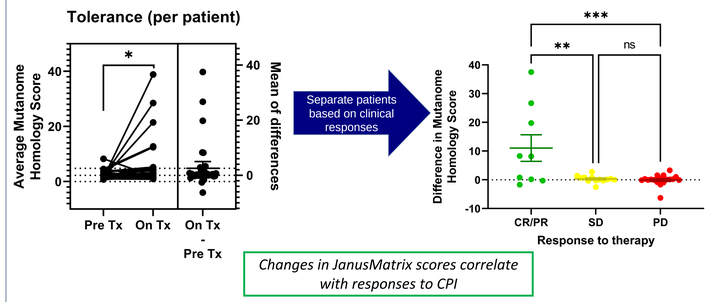




N = 41 paired Pre/On Tx samples. Mutations grouped across all patients.
Pre Tx vs On Tx: Mann-Whitney test. Pre Tx only vs Shared vs On Tx only: ANOVA (Krustal-Wallis, multiple comparisons)

Results – Association with response to therapy

- Tumors increase their tolerance potential (homology scores) after nivolumab therapy.
- Change in tolerance is associated with response to therapy.



41 paired Pre/On Tx samples. Samples paired by patient.
Pre Tx vs On Tx: paired t test. CR/PR vs SD vs PD: ANOVA (multiple comparisons)

Summary and Conclusions

- **This study demonstrates the utility of immunogenicity screening tools in the Ancer platform for streamlined designs of personalized cancer vaccines.**
- **Our Ancer analysis suggests tumors reduce their immunogenicity (less neoepitopes) and increase their tolerance potentials (mutations more likely to be tolerated) in response to nivolumab therapy. Mutations acquired after immunotherapy are more "stealth" than mutations found prior to therapy.**
- **These results highlight that identifying relevant mutations for precision immunotherapy (e.g. personalized vaccines) will become more difficult once patients are treated with a checkpoint inhibitor. Specialized tools, such as JanusMatrix are needed to correctly and quickly identify immunogenic mutations.**
- **Ancer can be employed to identify novel biomarkers associated with clinical responses. Ancer identified a tolerance signature specific to patients who respond to nivolumab, suggesting Ancer can be used to triage patients for immunotherapy clinical trials.**

References

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