How mutation load and neoantigens affect CTLA-4 and immunotherapy response in melanoma

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Introduction

Melanoma is a dangerous skin cancer that spreads quickly and is mainly caused by UV exposure. Immunotherapy, especially CTLA-4 inhibitors like ipilimumab, has become a powerful treatment. However, not all patients benefit equally. This study explores whether melanoma patients with higher mutation and neoantigen loads have better immune responses and longer survival after CTLA-4 therapy.

Research Question: Do patients with more mutations and neoantigens respond better to CTLA-4 immunotherapy?

Hypothesis: Yes — higher mutation and neoantigen loads help activate the immune system and improve survival outcomes.

Materials and Methods

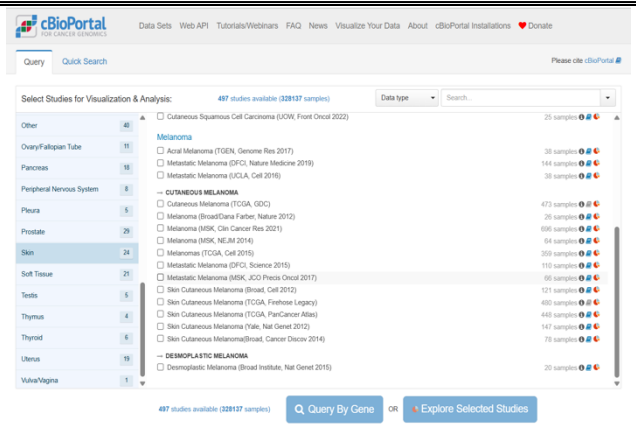
Data for this study were obtained from the SKCM_MSKCC_2014 melanoma dataset available on cBioPortal (Cerami et al., 2012).

The following measures were taken:

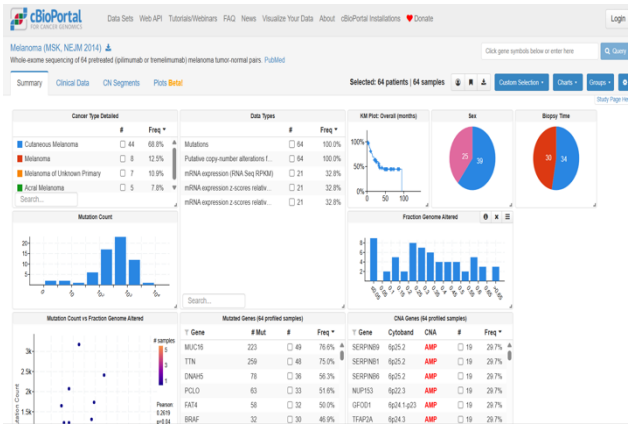
- Mutation load (the number of tumor mutations)
- Neoantigen load (mutations predicted to trigger immune response)
- Survival data after CTLA-4 therapy

These variables were compared to determine whether higher mutation and neoantigen loads correlate with better patient outcomes.

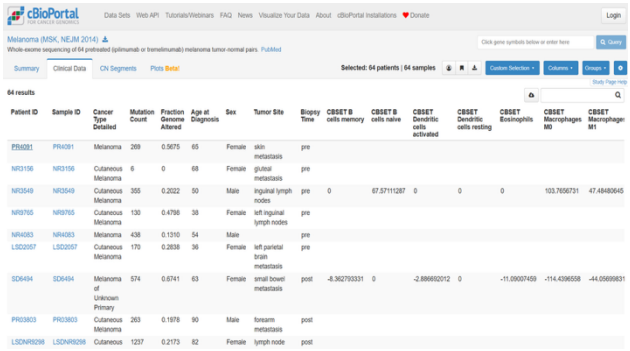
cBioPortal data from the SKCM_MSKCC_2014 melanoma study was used. Measured data points were mutation load (how many tumor mutations), neoantigen load (mutations that trigger immune response), and survival data after CTLA-4 therapy. These were then compared to see whether more mutations were correlated to better outcomes.



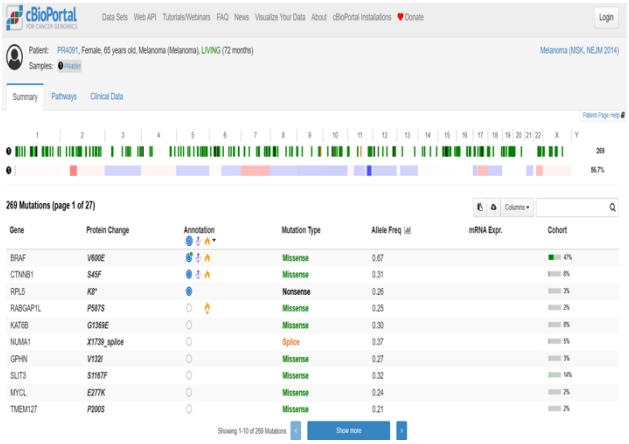
1: cBioPortal homepage where users can select specific cancer datasets.



2: This screenshot is a summary view from cBioPortal of the melanoma SKCM_MSKCC_2014 dataset.



3: Table view from cBioPortal showing individual melanoma patient data, including mutation counts, survival, and clinical features used for analysis.



4: Mutation overview of melanoma patients in cBioPortal, highlighting common genes affected and their frequencies.

Results

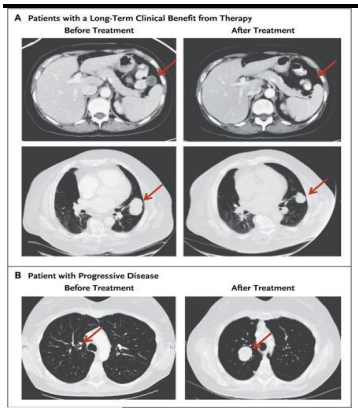


Figure 1 – Tumor Imaging Response
Panel A: Shows tumors shrinking in patients who responded to treatment.
Panel B: Shows no improvement in a patient with progressive disease.
Imaging confirms that some patients respond well while others do not. Also, early treatment matters.

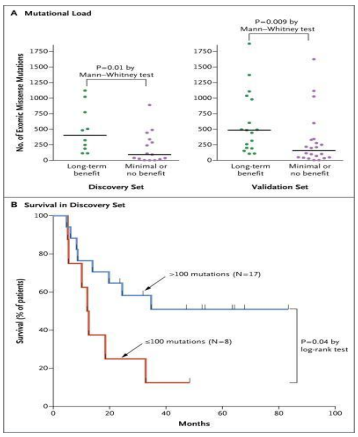


Figure 2 – Mutation Load and Survival
Panel A: Responders generally had more tumor mutations than non-responders.
Panel B: Patients with >100 mutations lived longer than those with fewer mutations.
High mutation load may enhance immune recognition of tumors.
Not all high-mutation patients had good outcomes—mutation load alone is not a perfect predictor.

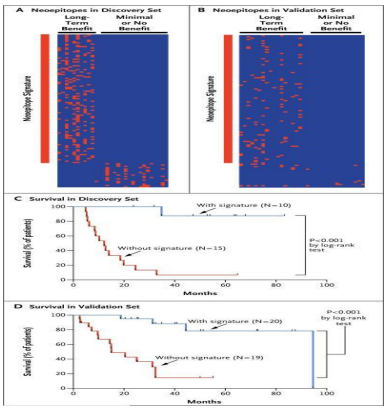


Figure 3 – Neoepitope Signature and Survival: Neoepitope Signature Predicts Benefit
Panels A & B: Patients with many neoepitopes (red dots) were more likely to benefit long-term.
Panels C & D: Those with the "signature" lived much longer.
A specific pattern of neoantigens helps predict who will respond well to CTLA-4 therapy.

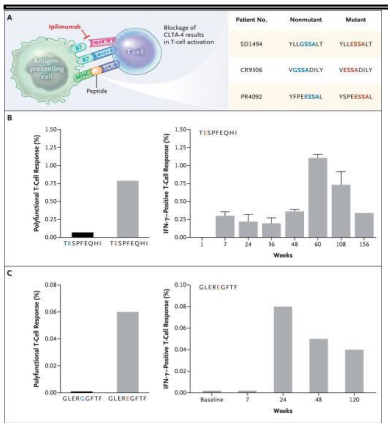


Figure 4 – T-Cell Activation by Neoantigens
Panel A: Ipilimumab blocks CTLA-4, enhancing T-cell activity.
Panels B & C: T cells responded more strongly to mutant peptides than to normal peptides.
The immune response to mutant peptides increased over time.
Tumor mutations can create novel targets that improve immune recognition.

Conclusion

Across all four figures, the data show that higher mutation load, abundant neoantigens, and specific neoepitope patterns are linked to better survival and stronger immune responses after CTLA-4 therapy. Imaging confirms that some patients respond well while others do not, highlighting that multiple biological factors influence outcomes.

Discussion

Results suggest that patients with higher mutation and neoantigen loads may benefit more from CTLA-4 immunotherapy, although the trend was not statistically significant. Some patients with higher loads lived longer, but mutation count alone is not a reliable predictor of response.

These findings are significant because they point to the potential of using genomic data to guide personalized treatment in melanoma. If validated in larger studies, mutation and neoantigen patterns could help identify patients more likely to benefit from CTLA-4 inhibitors, improving outcomes, and reducing unnecessary treatments. At the same time, the observation that some “non-responders” survived longer shows that current clinical labels do not fully capture survival differences.

Other factors—such as immune system activity, tumor aggressiveness, and biomarkers like LDH—likely play important roles. This suggests that treatment response depends on a combination of genomic and clinical features, not just mutation load.
Future work should involve larger patient cohorts and additional immune-related data, including T-cell activity, PD-1/PD-L1 expression, and tumor microenvironment characteristics. Such studies could build more accurate models to predict which patients will respond best. Ultimately, integrating genomic and immune information will help move melanoma care closer to precision medicine, where therapy is tailored to each patient’s unique biology.

References:

Cerami, E., Gao, J., Dogrusoz, U., Gross, B. E., Sumer, S. O., Aksoy, B. A., ... & Schultz, N. (2012). *The cBio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data*. Cancer Discovery, 2(5), 401–404. https://doi.org/10.1158/2159-8290.CD-12-0095
Accessed via: https://www.cbioportal.org/study/summary?id=skcm_mskcc_2014

Snyder, A., Makarov, V., Merghoub, T., Yuan, J., Zaretsky, J. M., Desrichard, A., Walsh, L. A., Postow, M. A., Wong, P., Ho, T. S., Hollmann, T. J., Bruggeman, C., Kannan, K., Li, Y., Elipenahli, C., Liu, C., Harbison, C. T., Wang, L., Ribas, A., Wolchok, J. D., & Chan, T. A. (2014). Genetic basis for clinical response to CTLA-4 blockade in melanoma. *The New England Journal of Medicine, 371*(23), 2189–2199. https://doi.org/10.1056/NEJMoa1406498