Genomic signature of poor outcome in elderly melanoma predicts immunotherapy response.

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Problem

Which melanoma patients are at highest risk, and which will respond best to IT?

Melanoma incidence and mortality particularly affects elderly patients.

85% of melanoma deaths occur in patients older than 60, and age is a powerful independent predictor of outcome.

The genomic characteristics driving melanoma in the aged population have not been previously investigated.

Elderly patients benefit from immune checkpoint inhibitor therapies, and there are currently no accepted predictors of for these costly therapies in the adjuvant or advanced disease stages.

Methods

Data was obtained from TCGA for all clinical and mutation information for metastatic melanomas.

Old was defined as >60 and young <55, alternative cut-offs were investigated with similar results.

Multiple Cox regression analysis on TCGA data showed age as the strongest predictor of survival.

MAF files were analysed to find hypermutation spots and perform driver gene identification.

Genes were sequentially removed according to impact on survival to define core 4-gene driver set.

Validation cohorts were collected from France and Spain with sequencing data in relevant genes.

Survival from MSK-IMPACT was analysed from published data to determine effect of gene mutations with TMB in immunotherapy-treated melanoma patients.

Summary

Elderly melanoma patients are the population at highest risk of death and disease progression.

Melanoma in the elderly has specific and biologically relevant molecular characteristics and driver mutations which differentiate them from younger melanomas.

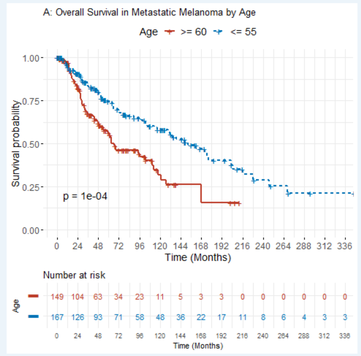
Stratifying old patients by 4-gene set of driver mutations with TMB is associated with survival benefit in immunotherapy-treated patients.

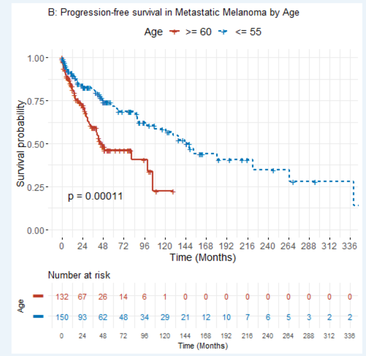
Our study demonstrates that stratifying patients by age will allow improved discrimination of prognosis and association with response to treatment.

Enrolling patients with high genetic risk of poor outcome and improved rate of immunotherapy response using a simple 4-gene signature with TMB can be easily translated into clinical practice.

Risk

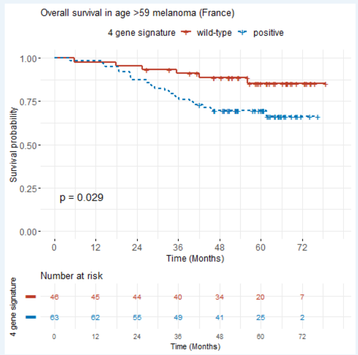
Older patients (age >60) at significantly higher risk of death and disease progression than younger patients (age <55) and have more mutations. Data from TCGA.

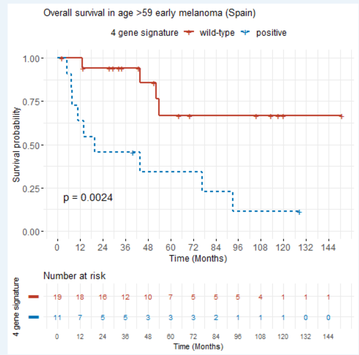




Genomics

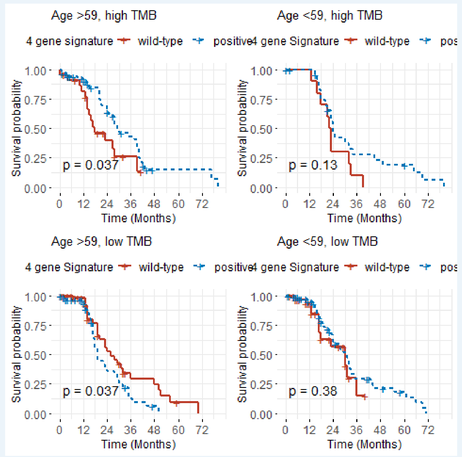
Older patients' mutations cluster at spots of hypermutation, and a group of driver mutations accurately predicts survival across independent cohorts from France and Spain.





Response

Stratifying mutations & TMB identify patients who survive longer on immunotherapy (MSK-IMPACT).



We have undertaken a comprehensive genomic analysis of age-specific molecular characteristics in metastatic cutaneous melanoma and discovered a core set of 4 driver genes (identified using oncodriveCLUST) that when mutated in older patients is a powerful predictor of poor outcome. We validated these findings in international independent primary melanoma replication cohorts. This signature stratifies patient prognosis more accurately than the current staging guidelines from early to late stages, making it relevant to immediate clinical practice.