Analysis of PMS2 mutation as a potential biomarker for melanoma immunotherapy

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Background

- Several clinical trials have demonstrated that mismatch repair deficiency is significantly associated with long-term immunotherapy-related responses in malignancies treated with immune checkpoint inhibitors (ICIs).
- The protein encoded by PMS2 gene is a key component of the mismatch repair system. However, whether the PMS2 mutation status is associated with better survival benefit in ICIs treatment melanoma is still unclear.

Methods

- 418 melanoma samples derived from seven immunotherapy studies (http://www.cbioportal.org/), as discovery cohort, were used to evaluate association between PMS2 mutation and efficacy of immunotherapy.
- The predictive value of PMS2 was validated in 320 melanoma patients from MSKCC cohort (http://www.cbioportal.org/).
- TMB was calculated as the total count of nonsynonymous mutations in coding sequence.

Results

- In discovery cohort, longer overall survival (OS) was observed in the PMS2-mutant group (median OS: not reach, NR vs 22.7 months, HR= 0.13, 95% CI: 0.02 to 0.95, P = 0.018).

Overall survival

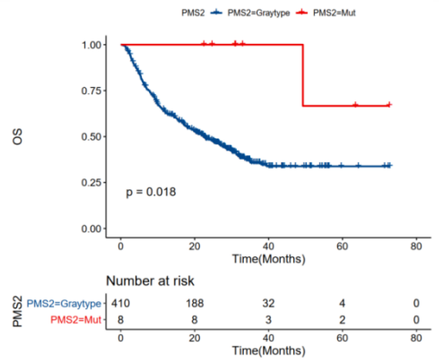

Fig.1 Kaplan-Meier estimates of overall survival in discovery cohort

- In validation cohort, PMS2-mutant patients achieved significantly longer OS (median OS: NR vs. 42.0 months, HR=0, 95% CI: 0.37 to 0.69, P=0.044).

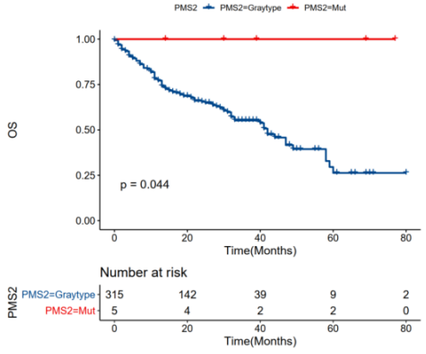

Fig.2 Kaplan-Meier estimates of Overall Survival in validation cohort

TMB

- In both of discovery and validation cohort, PMS2-mutant group had higher TMB than wildtype group.

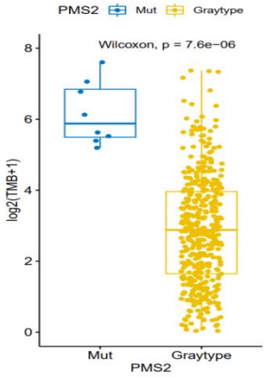

Fig.3 TMB level of PMS2 gene status in discovery cohort

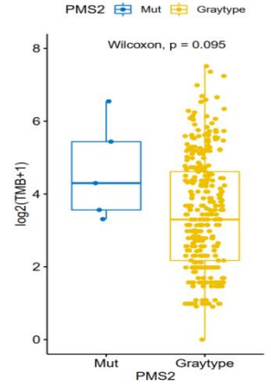

Fig.4 TMB level of PMS2 gene status in validation cohort

Multivariable analysis

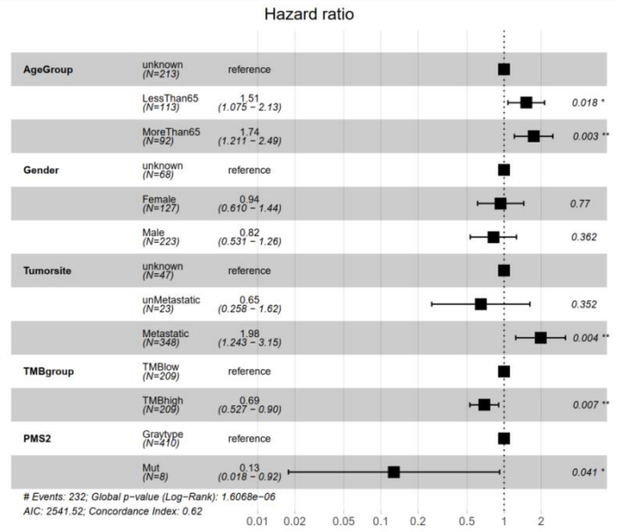

Fig.5 Multivariable analysis of discovery cohort

Conclusion

- PMS2 mutation is associated with high TMB in melanoma. Analysis of discovery and validation cohort data shows PMS2 mutation is associated with better OS in ICI-treated patients. These findings indicates that PMS2 mutation may serve as a potential predictive biomarker for ICIs in melanoma

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