#3782: ROS1 mutation can serves as a potential efficacious predictor of immunotherapy in melanoma patients

Hucheng Liu[1], Dandan Fan[2] , Jin Zeng[1], Jun Xiao[1],. Yaoxu Chen[2], Mengli Huang[2].
[1]Department of Bone Oncology, the First Affiliated Hospital of Nanchang University； [2]The Medical Department, 3D Medicines Inc., Shanghai, P.R. China, Shanghai, China

Background

Melanoma is a serious skin cancer. Immune checkpoint inhibitors (ICIs) including atezolizumab, pembrolizumab, nivolumab, ipilimumab have shown durable responses and have been approved by FDA. However, ICIs demonstrate antitumor effects only in a fraction of patients, and research exploring the association between gene mutation and clinical benefit is limited. ROS1 mutation rate is high in melanoma. Studies have shown that ROS1 substitutions/indels correlated with higher TMB (Tumor Mutation Burden) and PD-L1+/TMB-H proportions than wild-type genotypes in non-small cell lung cancer (NSCLC), which means that the mutation of ROS1 gene may be related to the efficacy of immunotherapy in patients with NSCLC, but the association between ROS1 mutation and TMB or survival in melanoma is unknown.

Methods

The association between ROS1 mutation with TMB and survival data was analyzed in melanoma patients from the public immunotherapy-treated cohort called Melanoma.Allen2015.WES.110, which worked as training cohort while the validation cohort1 was retrieved from Pancancer.Samstein2018.NGS.1661 and validation cohort2 was from Melanoma.Hugo2016.WES.38. Wilcoxon test was used for the comparison of TMB. Overall survival (OS) analyses were conducted in the public cohort using Kaplan-Meier curves and log-rank tests. Statistical significance was set at p=0.05.

Results

In the training cohort, 18.2% (20/110) melanoma patients harbored ROS1 mutation. ROS1 mutation is associated with higher TMB (p<0.0001)(Figure 1). Survival analysis demonstrated that ROS1 mutation resulted in significantly longer OS (24.38 vs 7.65 months; HR, 0.55; p=0.046)(Figure 2) in melanoma patients treated with ICIs. While validation cohort1 showed that 19.7% (63/320) melanoma patients harbored ROS1 mutation and ROS1 mutation resulted in an increasing trend on TMB with strongly significant difference (p<0.0001) (Figure 3)and significantly longer OS (42 vs 41 months; HR, 0.55; p=0.026)(Figure 4). Besides, validation cohort2 also showed that ROS1 mutation resulted in an increasing trend on TMB with significant difference (p=0.036)(Figure 5) and significantly longer OS (NR vs 27.5 months; HR, 0.25; p=0.044) (Figure 6).

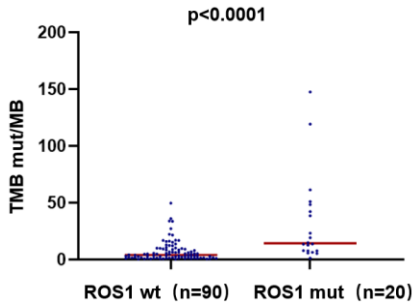

Figure 1. TMB classified by ROS1 mutations in training cohort

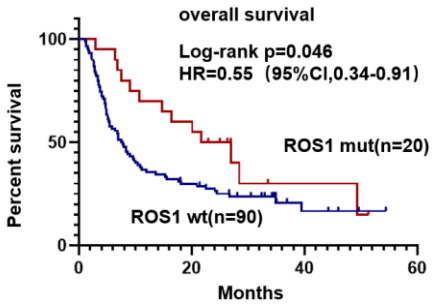

Figure 2 Kaplan-Meier curves of OS in patients with or without ROS1 mutations in training cohort.

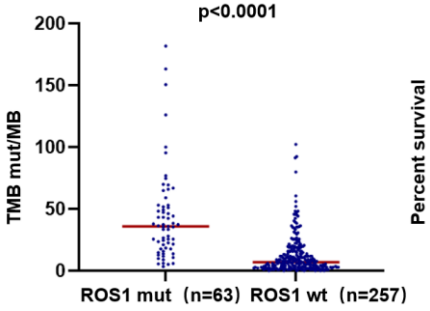

Figure 3. TMB classified by ROS1 mutations in validation cohort1

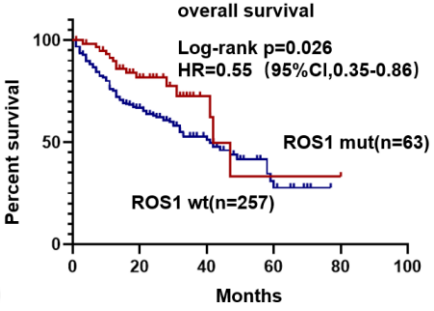

Figure 4. Kaplan-Meier curves of OS in patients with or without ROS1 mutations in validation cohort1

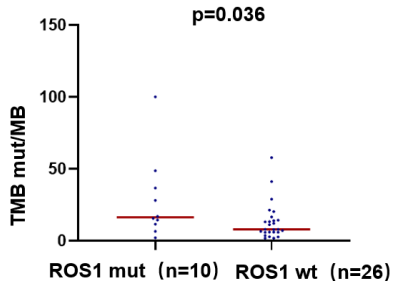

Figure 5. TMB classified by ROS1 mutations in validation cohort2

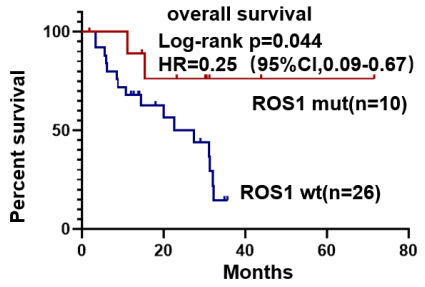

Figure 6. Kaplan-Meier curves of OS in patients with or without ROS1 mutations in validation cohort2

Conclusion

This study shows that ROS1 mutation is correlated with higher TMB in melanoma and serve as a predictive biomarker of ICI benefit in melanoma.