The Predictive Value of *LATS1* Mutation for Immune Checkpoint Inhibitors Therapy in Bladder Cancer

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Background

- As a key regulator of hippo signaling pathway, LATS1 (large tumor suppressor 1) gene encodes a Ser/Thr protein kinase which plays a crucial role in cellular transformation and tumorigenesis.
- But it remains to be determined if LATS1 mutation may have true biologic relevance and can independently predict responses to immune checkpoint inhibitors (ICIs).
- Our research aims to elucidate its mutation association with ICI efficacy.

Methods

- In order to investigate the correlation between LATS1 mutation and ICI efficacy in the bladder cancer, we used cBioportal to collect clinical and mutation data of 215 ICI-treated bladder cancers from MSKCC cohort.
- Gene expression and WES data of 413 samples were obtained from the TCGA database for further analysis of the differences of potential biological mechanisms between LATS1-mutant and LATS1-wildtype tumors.
- Tumor mutation burden (TMB) was calculated as the total number of somatic non-synonymous mutations per megabase in both MSKCC and TCGA cohorts.
- CIBERSORT algorithm was applied to infer 22 human immune cell type proportions in TCGA advanced bladder cancers.

Results—Survival analysis

- Patients with LATS1 mutation had better OS in the MSKCC cohort (P = 0.023, HR = 0.23, 95%CI: 0.06-0.93). This link was still existing in the multivariate Cox regression analysis

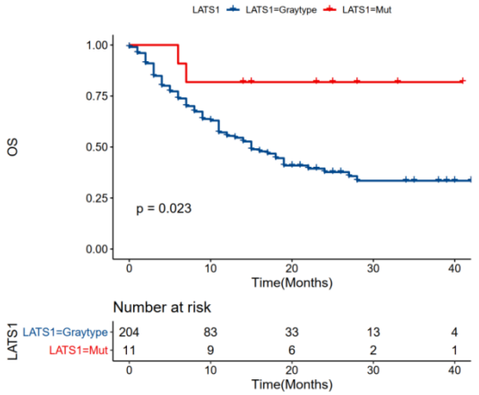

Fig.1 Kaplan-Meier estimates of overall survival

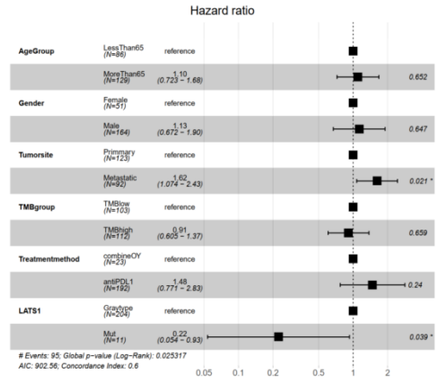

Fig.2 Multivariable analysis of MSKCC cohort

TMB

- In both of MSKCC and TCGA cohort, LATS1-mutant group had higher TMB than wildtype group (P<0.05)

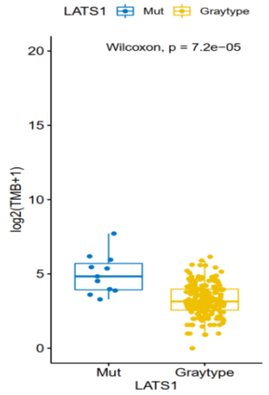

Fig.3 TMB level of LATS1 gene status in MSKCC cohort

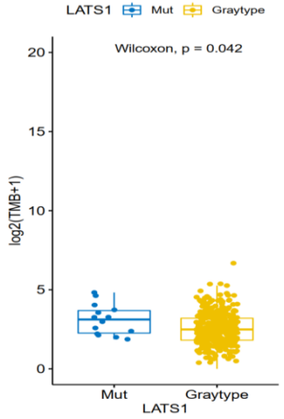

Fig.4 TMB level of LATS1 gene status in TCGA cohort

Immune microenvironment analysis

- Immune cell analysis showed that NK activated cells were abundant in the LATS1-mutant group (P = 0.05). This result indicated LATS1-mutant tumors had an activated antitumor immune microenvironment.

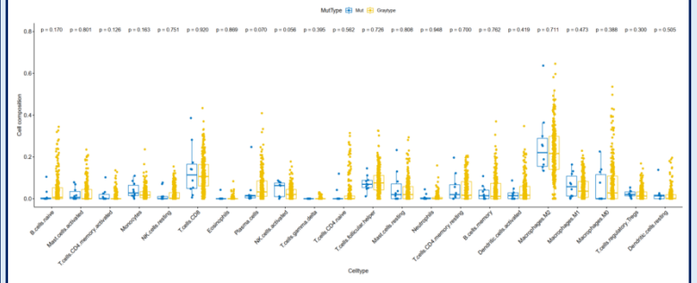

Fig.5 Boxplot depicting the infiltration of 22 immune cells in LAST1-Mut and LAST1-Wt tumors. CIBERSORT was used to calculate the infiltration degree of these immune cells.

Conclusion

- LATS1 mutations might be a potential biomarker to predict the efficacy of immunotherapy for bladder cancer.
- Considering the heterogeneity among the patients and other confounding factors, further prospective validation cohorts are warranted.

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