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PD60-03

Mutation in TP53 as Potential Marker of Clinical Benefit From PD-1/PD-L1 Blockade Immunotherapy in Advanced Urothelial Carcinoma

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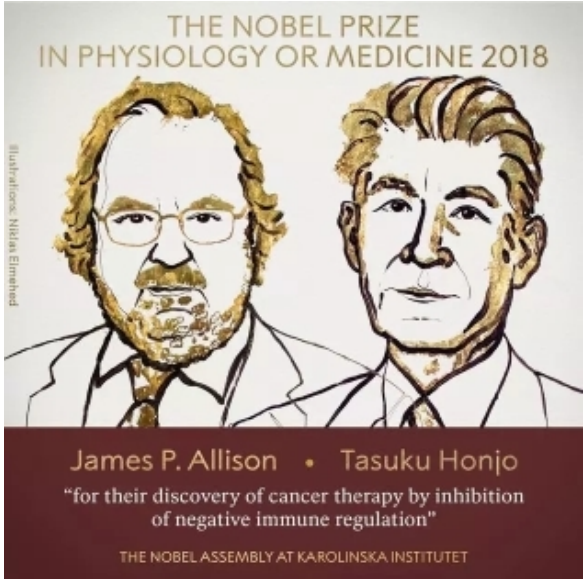
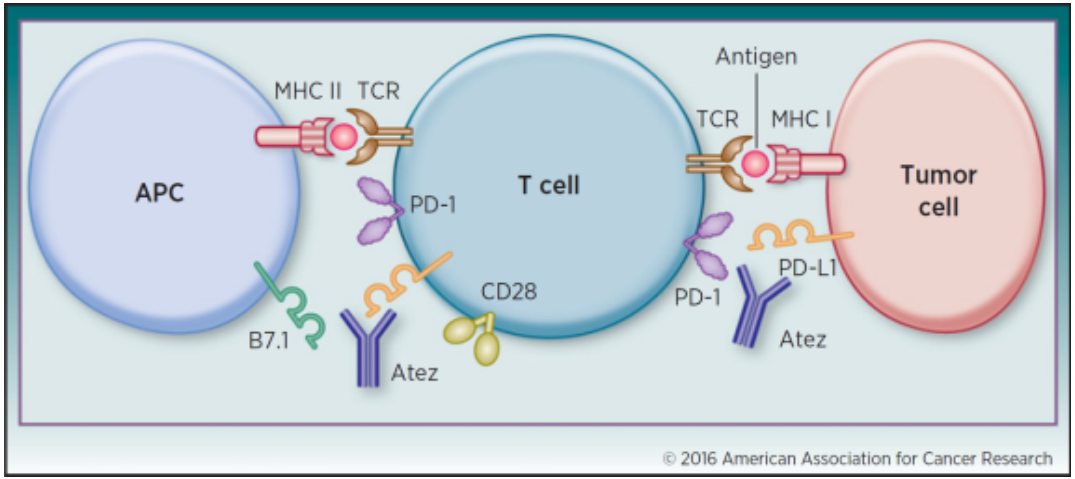
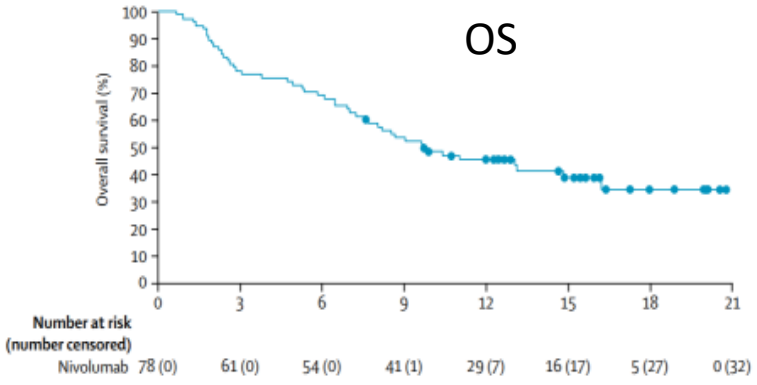
Background:

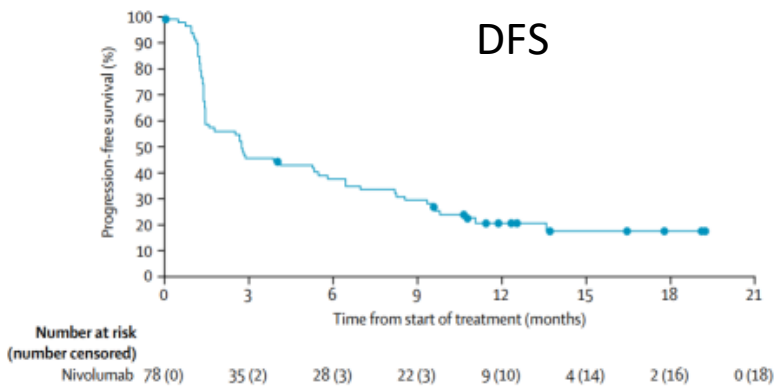




Reference: Brant A Inman, et al. Atezolizumab: A PD-L1-Blocking Antibody for Bladder Cancer. Clin Cancer Res. 2017, 23(8):1886-1890.

Background:





Nivolumab (anti- PD-1) was associated with a substantial and durable clinical response in previously treated patients with locally advanced or metastatic urothelial carcinoma

Reference: Sharma P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol 2016;17:1590-1598.

However:

1. Only 15% to 24% of treated patients with metastatic urothelial carcinoma could respond to immunotherapy

2. The understanding of predictive biomarkers to discern patients who could benefit from immunotherapy remains an ongoing challenge.

3. TP53 mutation status is associated with clinical response to immunotherapy in lung adenocarcinoma, but the association in metastatic urothelial carcinoma in still unknown.

Reference: ZY Dong, et al. Potential Predictive Value of TP53 and KRAS Mutation Status for Response to PD-1 Blockade Immunotherapy in Lung Adenocarcinoma. Clin Cancer Res. 2017: 23(12):3012-3024.

Methods:

1. We performed an integrated analysis based on multiple-dimensional types of data, including clinical trial follow-up data, genomic and transcriptomic data.
2. Cohorts of bladder cancer patients treated with immunotherapy were retrieved from cBioPortal for CANCER GENOMICS.
3. Gene set enrichment analysis was performed to associate the potential signature of genes with the TP53 mutation status.

Reference: Samstein RM, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet. 2019: 51(2):202-206.

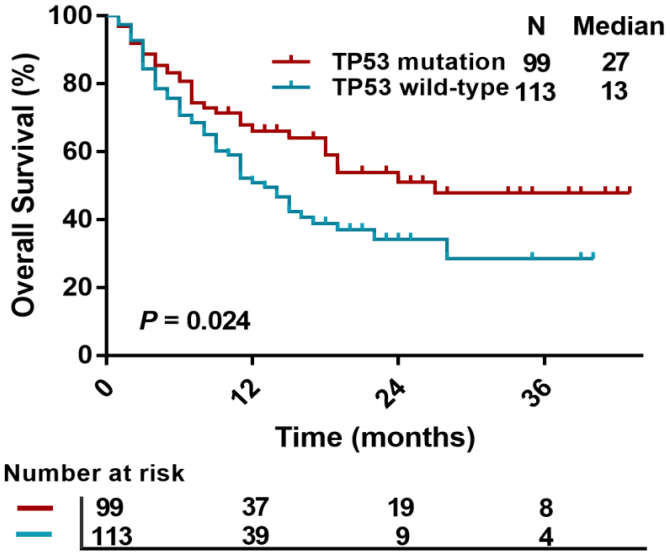
Results:

Table 1. Demographic, clinical and pathological information of the Immunotherapy cohorts.

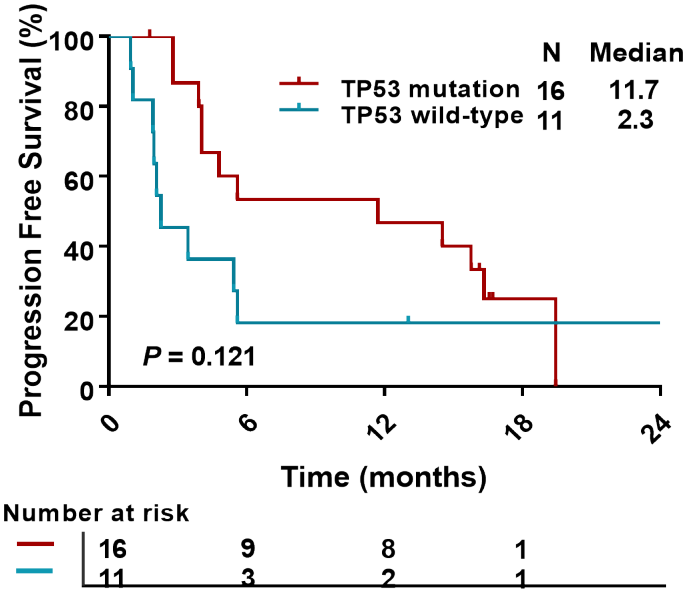
	MSKCC cohort	Dana-Farber cohort
No. of patients	212	27
Age(year)		
Mean	67.4	65.2
Gender		
Male	163(76.9%)	19(70.4%)
Female	49(23.1%)	8(29.6)
Drug type		
anti-PD-1/PD-L1	189(89.2%)	26(96.3%)
anti-PD-1/PD-L1+CTLA-4	23(10.8%)	1(3.7%)
Tumor type		
Primary	123(58.0%)	0
Metastasis	89(42.0%)	27(100%)
Liver	13(6.1%)	/
Lung	15(7.1%)	/
Lymph node	29(13.7%)	/
Pelvis	7(3.3%)	/
Others	25(11.8%)	/
Vital status		
Living	119(56.1%)	12(44.4%)
Deceased	93(43.9%)	15(55.6%)
TP53 status		
Mutation	99(46.7%)	16(59.3%)
Wild type	113(53.3%)	11(40.7%)

Results:

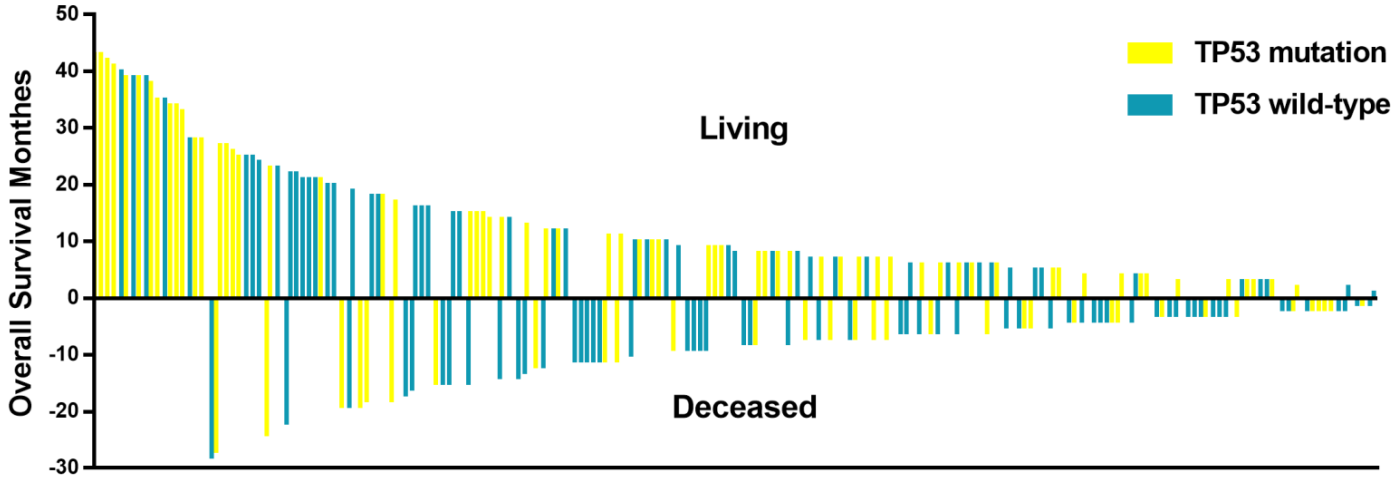
MSKCC cohort



Dana-Farber cohort



Results:

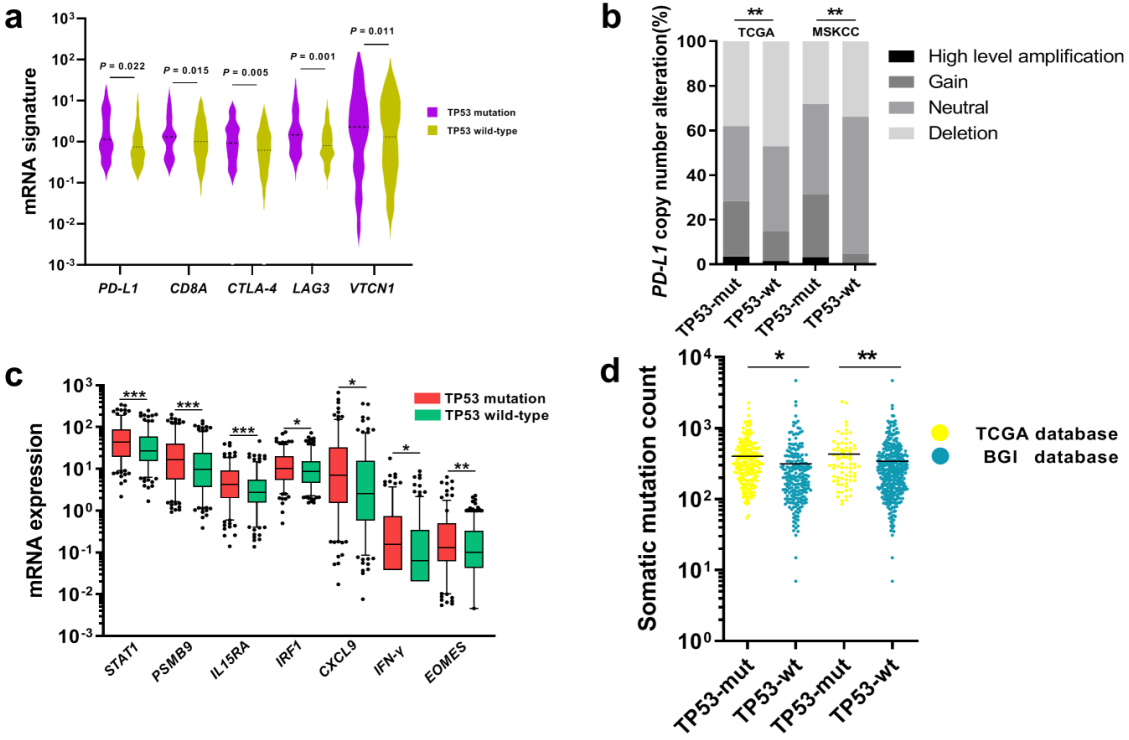

50
40
30
20
10
0
-10
-20
-30
Overall Survival Monthes
Living
Deceased
TP53 mutation
TP53 wild-type

Results:

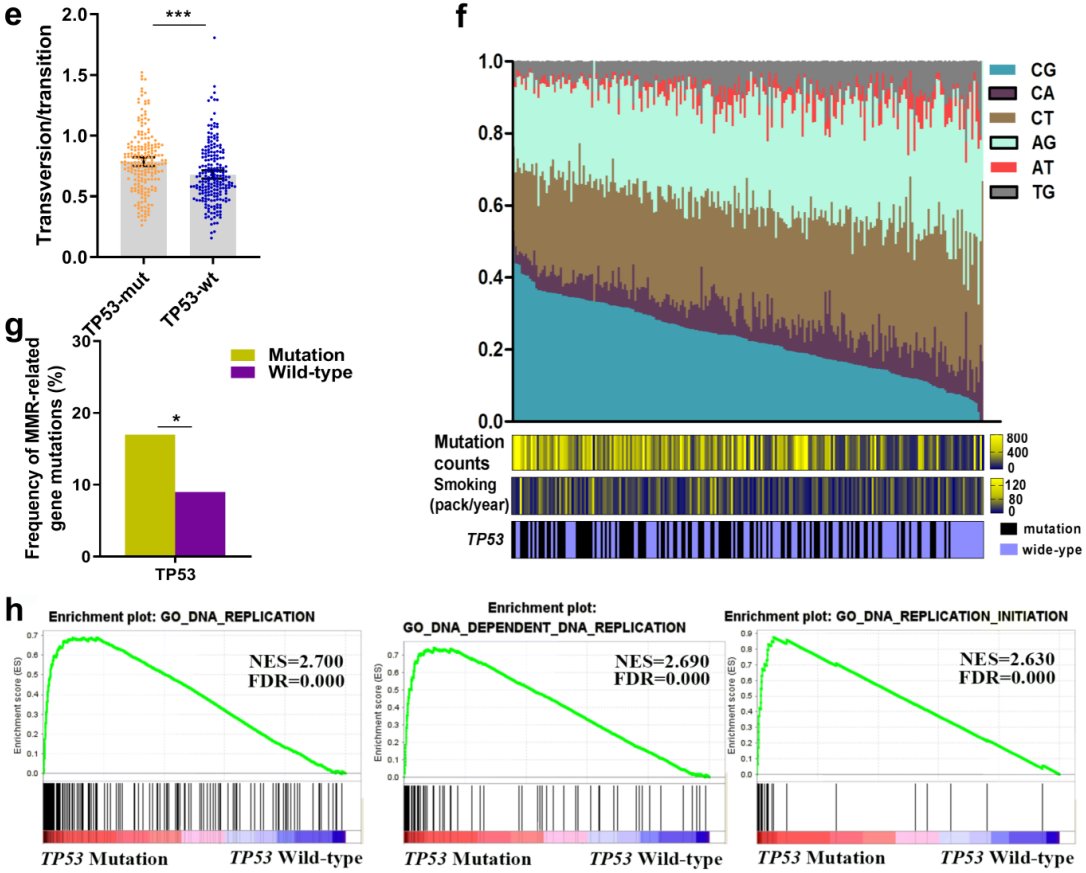
Table 2. Univariable and Multivariable Cox Analyses of Overall Survival

	Univariable Cox analysis				Multivariable Cox analysis		
Parameter	HR	95% CI	P		HR	95% CI	P
Age	0.999	0.980 to 1.018	0.915				
Sex	1.146	0.666 to 1.971	0.623				
Tumor purity	1.006	0.996 to 1.016	0.226				
Drug type: anti-PD-1/PD-L1 vs anti-CTLA4+PD-1/PD-L1	1.237	0.656 to 2.333	0.511				
Primary site : bladder/urethra vs upper tract	1.019	0.609 to 1.706	0.943				
Metastasis :	1.527	1.015 to 2.296	0.042		1.492	0.992 to 2.245	0.055
liver vs no	3.399	1.749 to 6.605	<0.001				
lung vs no	1.365	0.642 to 2.898	0.419				
lymph node vs no	0.946	0.476 to 1.879	0.873				
pelvis vs no others vs no	0.949 1.869	0.339 to 2.652 1.038 to 3.367	0.920 0.037				
TP53 mutation vs wide-type	0.625	0.410 to 0.952	0.029		0.638	0.418 to 0.972	0.037

Results:


a
mRNA signature
P = 0.022
P = 0.015
P = 0.005
P = 0.001
P = 0.011
TP53 mutation
TP53 wild-type
PD-L1
CD8A
CTLA-4
LAG3
VTCN1
b
PD-L1 copy number alteration(%)
TCGA
MSKCC
High level amplification
Gain
Neutral
Deletion
TP53-mut
TP53-wt
TP53-mut
TP53-wt
c
mRNA expression
TP53 mutation
TP53 wild-type
STAT1
PSMB9
IL15RA
IRF1
CXCL9
IFN-γ
EOMES
d
Somatic mutation count
TCGA database
BGI database
TP53-mut
TP53-wt
TP53-mut
TP53-wt

Results:


e
Transversion/transition
2.0
1.5
1.0
0.5
0.0
***
TP53-mut
TP53-wt
f
1.0
0.8
0.6
0.4
0.2
0.0
CG
CA
CT
AG
AT
TG
Mutation counts
800
400
0
Smoking (pack/year)
120
80
0
TP53
mutation
wide-ype
g
Frequency of MMR-related gene mutations (%)
30
20
10
0
*
TP53
Mutation
Wild-type
h
Enrichment plot: GO_DNA_REPLICATION
NES=2.700
FDR=0.000
Enrichment score (ES)
TP53 Mutation
TP53 Wild-type
Enrichment plot:
GO_DNA_DEPENDENT_DNA_REPLICATION
NES=2.690
FDR=0.000
Enrichment score (ES)
TP53 Mutation
TP53 Wild-type
Enrichment plot: GO_DNA_REPLICATION_INITIATION
NES=2.630
FDR=0.000
Enrichment score (ES)
TP53 Mutation
TP53 Wild-type

Conclusions:

1. TP53 mutation status is independently associated with improved survival from immunotherapy in patients with urothelial cancers.

2. Mutation of TP53 in urothelial cancers facilitates $CD8^+$ T-cell infiltration, activates T-effector and boosts PD-L1 expression.

3. Additional investigations are warranted to evaluate the mechanisms that link TP53 mutations and immunotherapy response.

Statements:

1. **Competing interests**
   The authors declare that they do not have any conflicts of interest related to this study.

2. **Acknowledgement**
   We appreciate the free access of multiple-dimensional types of data retrieved in this study from cBioPortal for CANCER GENOMICS.

3. **Founding**
   No.

Thank you very much!