The role of distinct co-mutation patterns with TP53 mutation in immunotherapy for NSCLC

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Abstract TP53 mutations was reported to be correlated to the efficacy of program death-1 (PD-1) and program death ligand-1 (PD-L1). The role of co-mutations of TP53 with other recurrently mutated genes in outcome of anti-PD-(L)1 treatment for non-small cell lung cancer (NSCLC) is unknown. Here we mined a previously generated dataset to address the effect of co-mutations on the progression free survival (PFS) of NSCLC patients. Non-synonymous mutations and clinical data of 240 NSCLC patients with anti-PD-(L)1 based therapy was downloaded from cBioPortal. Totally 206 patients received monotherapy and 34 patients received combination therapy. In 240 NSCLC patients, TP53 mutation rate was 59.2%. For the monotherapy cohort, TP53 mutated NSCLC patients have a significantly longer PFS (4.3 vs. 2.5 months, P = 0.0019) compared with TP53 wild type NSCLC patients. The same tendency was also observed in the combination therapy cohort, but the difference in PFS (6.3 vs. 5.4 months, P = 0.12) was not significant. Ever-smoker had a longer PFS compared to never-smokers (4.0 vs. 2.7 months). For further co-mutation analysis with TP53 including KEAP1 mutation (53/240, 22.1%), KMT2C mutation (26/240, 10.8%), STK11 mutation (56/240, 23.3%), EGFR mutation (28/240, 11.7%) and KRAS mutation (86/240, 35.8%). Patients with both TP53 plus KEAP1...
mutations in all 240 patients had a longer PFS compared with co-wild population (PFS 9.2 vs. 4.2 months, \(P = 0.012\)) when treated with PD-1/PD-L1 inhibitors. TP53 might be the dominating mutation correlating with longer PFS in PD-1/PD-L1 monotherapy. Different genes displayed distinct effect when co-mutated with TP53 in NSCLC patients.

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Introduction

Checkpoint as PD-1 and PD-L1 inhibitors have emerged as the most promising therapeutics for non-small-cell lung cancer (NSCLC) which could prolong the 5-year survival in those responders. However, the efficacy of checkpoint inhibitors in NSCLC was limited with an objective response rate of around 20%.

Identification of biomarkers with predictive power for the outcome of checkpoint inhibition could guide the clinical decision to employ checkpoint inhibitors. Currently, expression of PD-L1 and tumor mutation burden (TMB) are most widely investigated as biomarkers to predict the effect of checkpoint inhibitors. However, some PD-L1 negative and TMB low NSCLC populations could still respond to PD-1/PD-L1 antibodies. The complexity of some PD-L1 negative and TMB low NSCLC populations could still respond to PD-1/PD-L1 antibodies. The complexity of checkpoint inhibition has yet to be investigated.

TP53 is one of the well-studied genes in human. With another tumor suppressor gene CHEK2, p53 checks whether DNA mutations in a damaged cell can be repaired or the cell has to be destroyed. It was reported that TP53 mutation is independently correlated with longer OS in advanced NSCLC patients. This effect can be partially explained by the connection between TP53 and TMB. If the functionality of p53 is intact, the magnitude of mutations in cancer will be kept at minimal level. TP53 mutation was reported to significantly increase the expression of immune checkpoints and activated T-effector and interferon-signature and TP53/KRAS co-mutation NSCLC showed remarkable clinical benefit to PD-1 inhibitors in a small sampled study with 34 patients, which needs to be further confirmed.

The mutational landscape of cancer is rather complex. For NSCLC, there are many other recurrently mutated genes with mutation frequency above 10%. Examples include KRAS, KEAP1, STK11 and EGFR. KRAS mutations leads to hyperactivated downstream signaling controlling cell proliferation. KEAP1 is an important regulator of antioxidant response, determining the cellular outcome after exposure to oxidative stress. STK11 is a major modulator of lung cancer differentiation and metastasis. EGFR is an important receptor regulating RAS/MAPK, PI3K/AKT signaling pathways, and the target of EGFR-TKI (Tyrosine Kinase Inhibitor). EGFR mutations critically impacts the clinical outcomes of NSCLC patients.

It is not clear that how co-mutation of TP53 with oncogenes or other tumor suppressor genes influence the response of NSCLC patients to checkpoint inhibitors. Our study took advantage of a recently published cohort of NSCLC patients with mutation data and survival data after receiving either monotherapy using anti-PD-1/PD-L1 therapy or combination therapy of anti-PD-1/PD-L1 and anti-CTLA-4.

Specifically, this study aims to investigate the impact of co-mutation pattern on progression free survival of NSCLC patients.

Materials and methods

Data collection

Non-synonymous mutations and clinical data of 240 NSCLC patients with anti-PD-(L)1 based therapy was downloaded from cBioPortal. Patient samples were analyzed by MSK-IMPACT assay as previously described. Sequencing libraries were generated for a custom panel of 341 (56 patients, version 1), 410 (164 patients, version 2) and 468 (20 patients, version 3) genes. In total, 206 patients received monotherapy with PD-1/PD-L1 inhibitors and 34 patients received combination therapy with PD-1/PD-L1 inhibitor and anti-CTLA-4 therapy. All patients were enrolled in Memorial Sloan Kettering Cancer Center between April 2011 and January 2017.

Survival analysis

Survival analysis was performed with Kaplan–Meier method. Survminer was used to implement survival analysis. All plots were generated with R statistical programming environment. For each patient stratification method, survival curves were plotted for the monotherapy cohort, the combination therapy cohort and the complete patient cohort.

To determine single-cell mutation and double-gene mutation, only non-synonymous mutations were considered. Kaplan–Meier curves analysis of progression-free survival (PFS) were compared using the log-rank test.

Statistics

No statistical method was carried out to estimate the sample number. All reported \(P\) values are two-tailed, and for all analyses, \(P\) less than 0.05 is considered statistically significant, unless otherwise specified. Hazard ratios (HRs) were calculated by the Mantel–Haenszel test. Given that smoking acts as a possible treatment selection bias, we performed multivariable extended cox regression when accessing the effect of co-mutation.
Table 1: Patients characteristics.

| Item                          | number | mPFS (all) | logrank_P | HR | 0.95LCI | 0.95UCI | mPFS (mono) | logrank_P | HR | 0.95LCI | 0.95UCI | mPFS (combination) | logrank_P | HR | 0.95LCI | 0.95UCI |
|-------------------------------|--------|------------|-----------|-----|---------|---------|-------------|-----------|-----|---------|---------|---------------------|-----------|-----|---------|---------|
| Diagnosis                     | 18–60  | 3.13       | 0.39      |     |         |         | 3.05        | 0.91      |     | 0.915   | 0.73    | 1.4                 | 7.9       |     | 0.26    | 1.6     |
| Age                           | ≥60    | 3.50       |           |     |         |         | 3.07        | 0.74      |     | 0.738   | 0.78    | 1.4                 | 7.9       |     | 0.43    | 0.63    |
| Sex                           | Female | 122        | 3.07      | 0.54 |         |         | 3.23        | 1.1       | 0.83 | 1.4     | 0.78    | 1.4                 | 7.9       |     | 0.427   | 1.4     |
| Smoking                       | Male   | 118        | 3.50      |     |         |         | 3.3         | 0.0025    |     | 0.003   | 1.2     | 2.6                 | 11.83     |     | 0.93    | 0.43    |
|                              | Ever   | 193        | 4.00      | 0.031|         |         | 2.1         |           |     | 0.001   | 2.6     | 2.6                 | 11.83     |     | 0.93    | 0.43    |
|                              | never  | 47         | 2.67      |     |         |         | 0.032       |           |     | 0.003   | 1.2     | 2.6                 | 11.83     |     | 0.93    | 0.43    |
| Pathology                     | squamous cell carcinoma | 34 | 2.92 | 0.9782 | 0.981 | 1.01 | 0.67 | 1.5 | 3.23 | LUAD-LUSC: 0.8644 | 0.426 | 0.84 | 0.54 | 1.3 | 1.83 | LUAD-LUSC: 0.0709 | 0.043 | 0.96 | 1.04 | 15 |
|                              | adenocarcinoma | 186 | 3.50 | 0.9639 | 0.981 | 1.01 | 0.67 | 1.5 | 3.23 | LUAD-LUSC: 0.8644 | 0.426 | 0.84 | 0.54 | 1.3 | 1.83 | LUAD-LUSC: 0.0709 | 0.043 | 0.96 | 1.04 | 15 |
|                              | Others | 20         | 3.68 | 0.9639 | 0.535 | 0.84 | 0.47 | 1.5 | 2.52 | LUAD-LUSC: 0.8644 | 0.753 | 0.91 | 0.49 | 1.7 | 6.33 | LUAD-LUSC: 0.0709 | 0.043 | 0.96 | 1.04 | 15 |
| Lines of treatment            | 1 st   | 51         | 7.50 | 0.00046| 0.005 | 1.7  | 1.2  | 2.4 | 5.47 | LUAD-LUSC: 0.8644 | 0.201 | 1.3  | 0.86 | 2  | 4.33 | LUAD-LUSC: 0.0709 | 0.043 | 0.96 | 1.04 | 15 |
|                              | 2      | 189        | 2.73 | 0.00046| 0.005 | 1.7  | 1.2  | 2.4 | 5.47 | LUAD-LUSC: 0.8644 | 0.201 | 1.3  | 0.86 | 2  | 4.33 | LUAD-LUSC: 0.0709 | 0.043 | 0.96 | 1.04 | 15 |
| Detection panel               | IMPACT341 | 56   | 2.92 | 0.4389 | 0.401 | 0.87 | 0.63 | 1.2 | 3.17 | IMPACT341: 0.04389 | 0.035 | 0.69 | 0.48 | 0.97 | 6.33 |
|                              | IMPACT410 | 164  | 3.50 | 0.4389 | 0.401 | 0.87 | 0.63 | 1.2 | 3.17 | IMPACT341: 0.04389 | 0.035 | 0.69 | 0.48 | 0.97 | 6.33 |
|                              | IMPACT468 | 20   | 4.17 | 0.4389 | 0.238 | 0.68 | 0.36 | 1.3 | 6.03 | IMPACT341: 0.04389 | 0.038 | 0.5  | 0.26 | 0.96 | 3.43 |
| KEAP1                        | yes    | 53         | 2.80 | 0.53  | 0.538 | 0.9  | 0.64 | 1.3 | 2.5  | IMPACT341: 0.04389 | 0.777 | 0.95 | 0.67 | 1.4 | 5.43 |
|                              | no     | 187        | 3.50 | 0.17  | 2.9    | 0.002 | 0.39 | 1   | 4.17 | IMPACT341: 0.04389 | 0.11  |       |       |       | 22.43 |
| KMT2C                        | yes    | 26         | 7.33 | 0.049 | 0.052 | 0.62 | 0.39 | 1   | 4.17 | IMPACT341: 0.04389 | 0.11  |       |       |       | 22.43 |
|                              | no     | 214        | 3.17 | 0.17  | 2.9    | 0.002 | 0.39 | 1   | 4.17 | IMPACT341: 0.04389 | 0.11  |       |       |       | 22.43 |
| STK11                        | yes    | 56         | 2.54 | 0.23  | 0.229 | 1.2  | 0.88 | 1.7 | 2.47 | IMPACT341: 0.04389 | 0.21  |       |       |       | 9.10  |
|                              | no     | 184        | 3.80 | 0.17  | 2.9    | 0.002 | 0.39 | 1   | 4.17 | IMPACT341: 0.04389 | 0.11  |       |       |       | 9.10  |
| EGFR                         | yes    | 28         | 3.07 | 0.038 | 0.04  | 1.6  | 1   | 2.4 | 3.07 | IMPACT341: 0.04389 | 0.12  |       |       |       | 2.92  |
|                              | no     | 212        | 3.50 | 0.17  | 2.9    | 0.002 | 0.39 | 1   | 4.17 | IMPACT341: 0.04389 | 0.12  |       |       |       | 2.92  |
| KRAS                         | yes    | 86         | 3.43 | 0.83  | 0.824 | 0.97 | 0.72 | 1.3 | 0.37 | IMPACT341: 0.04389 | 0.56  |       |       |       | 4.38  |
|                              | no     | 154        | 3.30 |       | 2.8    | 0.002 | 0.49 | 0.85 | 4.00 | IMPACT341: 0.04389 | 0.56  |       |       |       | 4.38  |
| TP53                         | yes    | 142        | 4.27 | 0.0019| 0.002 | 0.64 | 0.49 | 0.85 | 4.00 | IMPACT341: 0.04389 | 0.008 | 0.67 | 0.49 | 0.9 | 5.43 |
|                              | no     | 98         | 2.47 |       | 2.47  | 0.002 | 0.49 | 0.85 | 4.00 | IMPACT341: 0.04389 | 0.008 | 0.67 | 0.49 | 0.9 | 5.43 |

Co-mutation patterns of TP53 mutation

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entire cohort of patients. For monotherapy of PD-1 and PD-
P-L1 inhibitors, only smoking status (3.3 vs. 2.1 months, 

\( P = 0.0025 \)) and \( TP53 \) mutation (4.0 vs. 2.5 months, 

\( P = 0.0078 \)) had significant effect on PFS.

Then we plotted the survival curve for both the mono-
therapy cohort and the combination cohort (Fig. 1). Pa-
tients were stratified based on the status of \( TP53 \) mutation. 
In 240 NSCLC patients, \( TP53 \) mutation rate was 59.2%.
Consistently, it was found that NSCLC patients with \( TP53 \) mutations had significantly longer PFS either using the 
monotherapy cohort or the entire cohort. For the mono-
therapy (PD-1, PD-L1) cohort, \( TP53 \) mutated NSCLC patients 
have a significantly longer PFS (4.3 months vs. 2.5 months, 

\( P = 0.0019 \)) compared with \( TP53 \) wild type NSCLC patients.
The same tendency was also observed in the combination 
therapy cohort, but the difference in PFS (6.3 months vs. 
5.4 months, \( P = 0.12 \)) was not significant due to limited 
number of patients. We focused on three recurrently 
mutated tumor suppressor genes: \( KMT2C, STK11 \) and \( KEAP1 \) (Table 2). Patients with co-mutation in \( TP53 \) and \( KMT2C 

have longer PFS (9.2 months vs. 2.5 months, \( P = 0.005 \)) 
compared with patients without \( TP53 \) and \( KMT2C \) mutations 
(Fig. 2). Co-mutations seemed to confer a favorable sur-
vival compared with the patients with only mutation in one 
gene. For co-mutation analysis, patients with \( TP53 \) and 
\( STK11 \) co-mutations have better PFS (3.3 months vs. 2.6 
months), but this was not statistically significant. Patients 
with mutant \( TP53 \) and wild type \( STK11 \) had significantly 
longer PFS (4.3 months vs. 2.6 months) as compared with 
patients with wild type \( TP53 \) and \( STK11 \). Similarly, in the 
case of \( TP53 \) and \( KEAP1 \) co-mutation, it seemed that \( TP53 
mutation was dominating the outcome of checkpoint inhi-
bition. \( KEAP1 \) mutation diminished the effect of \( TP53 
mutation.

We next checked the effect of \( KRAS \) co-mutation on the 
outcome of patients in response to checkpoint inhibitors 
(Fig. 3). We found that patients with co-mutation of \( TP53 
and \( KRAS \) had significantly longer PFS (5.8 months vs. 2.6 
months, \( P = 0.005 \)), as compared to patients harboring wild 
type \( TP53 \) and \( KRAS \). Patient with \( TP53 \) mutation and wild 
type \( KRAS \) had a median PFS of 3.6 months. When smoking 
factor is included in multivariate analysis, only the \( TP53/ 
KRAS \) co-mutation stood out as a significant factor 
(\( P = 0.024 \)). Finally, we evaluated the effect of co-
occuring \( TP53 \) and \( EGF \) mutations. Patients with 
mutated \( TP53 \) and wild type \( EGF \) had significantly longer 
PFS (4.3 months vs. 2.5 months, \( P = 0.001 \)) as compared 
with patients with wild type \( TP53 \) and \( EGF \), while patients 
with co-occurring \( TP53 \) and \( EGF \) mutations exerted no 
significant improvement of PFS (3.4 months vs. 2.5 months, 

\( P = 0.707 \)).

To sum up, we proposed a model to explain the effect of 
mutations in key driver genes on the sensitivity of ICI 
treatment (Fig. 4). The effect of individual gene could be 
additive or subtractive to \( TP53 \) mutations.

Results

In total, there were 206 patients who received mono-
therapy with PD-1/PD-L1 inhibitor and 34 patients who 
received combination therapy with PD-1/PD-L1 inhibitor 
and anti-CTLA-4 therapy. First, we evaluated the effect of 
all the patients’ characteristics on PFS (Table 1), and re-
sults showed that smoking status (4.0 vs. 2.7 months, 

\( P = 0.031 \)), lines of treatment (7.5 vs. 2.7 months, 

\( P = 0.00046 \)), \( TP53 \) mutation (4.3 vs. 2.5 months, 

\( P = 0.00019 \)), \( EGF \) mutation (3.1 vs. 3.3 months, 

\( P = 0.0038 \)) and \( KMT2C \) mutation (7.3 vs. 3.2 months, 

\( P = 0.049 \)) were significantly correlated with PFS in 
the entire cohort of patients. For monotherapy of PD-1 and PD-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{(A) Patients treated with monotherapy were 
stratified with \( TP53 \) mutation status. The survival curve was 
plored with PFS for the distinct group. Wild type \( TP53 \) is shown 
with blue and mutated \( TP53 \) is displayed with red. (B) Patients 
treated either with monotherapy or combination therapy were 
stratified with \( TP53 \) mutation status. The survival curve was 
plored with PFS for the distinct group. Wild type \( TP53 \) is shown 
with blue and mutated \( TP53 \) is displayed with red.}
\end{figure}

Discussion

Our study approached the problem of patient stratification 
in immune checkpoint inhibition by extensive data mining 
and re-analysis of a publicly available dataset, uncovering a 
complex interplay between recurrently occurring
# Table 2

| Sample Type   | log-rank P | COX P | rmsmoker_cox P | mPFS | log-rank P | COX P | rmsmoker_cox P | mPFS   |
|---------------|------------|-------|----------------|------|------------|-------|----------------|--------|
| TP53 mut, KEAP1 mut | 0.3480 | 0.1348 | 0.0370 | 1.09 | 0.0930 | 0.3252 | 0.1090 | 0.97 |
| TP53 mut, KEAP1 wild | 0.5283 | 0.2830 | 0.3280 | 1.09 | 0.3140 | 0.3489 | 0.0830 | 1.30 |
| TP53 wild, KEAP1 mut | 0.3480 | 0.1348 | 0.0370 | 1.09 | 0.0930 | 0.3252 | 0.1090 | 0.97 |
| TP53 wild, KEAP1 wild | 0.5283 | 0.2830 | 0.3280 | 1.09 | 0.3140 | 0.3489 | 0.0830 | 1.30 |
| TP53 mut, KMT2C mut | 0.3480 | 0.1348 | 0.0370 | 1.09 | 0.0930 | 0.3252 | 0.1090 | 0.97 |
| TP53 mut, KMT2C wild | 0.5283 | 0.2830 | 0.3280 | 1.09 | 0.3140 | 0.3489 | 0.0830 | 1.30 |
| TP53 wild, KMT2C mut | 0.3480 | 0.1348 | 0.0370 | 1.09 | 0.0930 | 0.3252 | 0.1090 | 0.97 |
| TP53 wild, KMT2C wild | 0.5283 | 0.2830 | 0.3280 | 1.09 | 0.3140 | 0.3489 | 0.0830 | 1.30 |
| TP53 mut, STK11 mut | 0.3480 | 0.1348 | 0.0370 | 1.09 | 0.0930 | 0.3252 | 0.1090 | 0.97 |
| TP53 mut, STK11 wild | 0.5283 | 0.2830 | 0.3280 | 1.09 | 0.3140 | 0.3489 | 0.0830 | 1.30 |
| TP53 wild, STK11 mut | 0.3480 | 0.1348 | 0.0370 | 1.09 | 0.0930 | 0.3252 | 0.1090 | 0.97 |
| TP53 wild, STK11 wild | 0.5283 | 0.2830 | 0.3280 | 1.09 | 0.3140 | 0.3489 | 0.0830 | 1.30 |
| TP53 mut, EGFR mut | 0.3480 | 0.1348 | 0.0370 | 1.09 | 0.0930 | 0.3252 | 0.1090 | 0.97 |
| TP53 mut, EGFR wild | 0.5283 | 0.2830 | 0.3280 | 1.09 | 0.3140 | 0.3489 | 0.0830 | 1.30 |
| TP53 wild, EGFR mut | 0.3480 | 0.1348 | 0.0370 | 1.09 | 0.0930 | 0.3252 | 0.1090 | 0.97 |
| TP53 wild, EGFR wild | 0.5283 | 0.2830 | 0.3280 | 1.09 | 0.3140 | 0.3489 | 0.0830 | 1.30 |
| TP53 mut, KRAS mut | 0.3480 | 0.1348 | 0.0370 | 1.09 | 0.0930 | 0.3252 | 0.1090 | 0.97 |
| TP53 mut, KRAS wild | 0.5283 | 0.2830 | 0.3280 | 1.09 | 0.3140 | 0.3489 | 0.0830 | 1.30 |
| TP53 wild, KRAS mut | 0.3480 | 0.1348 | 0.0370 | 1.09 | 0.0930 | 0.3252 | 0.1090 | 0.97 |
| TP53 wild, KRAS wild | 0.5283 | 0.2830 | 0.3280 | 1.09 | 0.3140 | 0.3489 | 0.0830 | 1.30 |

Our analysis suggested that co-mutation of TP53 and chemotherapy in a NSCLC patient with co-occurring mutations in common oncogenes and other tumor suppressor genes on the response to immune checkpoint inhibition. KMT2C is a gene frequently mutated in non-small cell lung cancer. Our analysis suggested that co-mutation of TP53 with KMT2C seemed to confer a favorable response of NSCLC patients to immune checkpoint inhibition. Co-occurring KMT2C mutations significantly enhanced the response of NSCLC patients to ICIs, serving as proof of principle that finer patient stratification is more informative to guide clinical decision. The other two tumor suppressor genes STK11 and KEAP1 analyzed in this study did not significantly alter the response profile of NSCLC patients to immune checkpoint inhibitors. There is still limited evidence to completely rule out roles played by those tumor suppressor genes, as functionality is always context dependent.

Recently, there was a case report documenting a durable response to combination therapy with PD-1 antibody and chemotherapy in a NSCLC patient with co-occurring TP53 and KRAS mutations. One potential explanation for this is that TP53 and KRAS double mutated patients had significantly higher expression of PD-L1 in their cancer samples. PD-L1 is a well-accepted biomarker to predict the sensitivity to immune checkpoint inhibition. EGFR mutations were shown to correlate with a worse response of patients to immune checkpoint inhibition.
Despite this, the effect of EGFR mutations might be context dependent. The negative effect of EGFR mutations and the positive effect of TP53 mutations seemed to neutralize each other, as double mutants were similar to double wild type. This suggested that the first line therapy for TP53/EGFR double mutated NSCLC patients should be TKIs. To sum up previously discussed points, it is clear that the mechanisms for a cancer gene mutation to alter the ICIs response are decoupled from its roles played in tumorigenesis as an oncogene or tumor suppressor gene.

Conclusions

Immune checkpoint inhibition has emerged as a promising cancer therapeutic that can induce durable clinical benefit in a subset of patients. However, many patients are insensitive to checkpoint inhibitors, while the mechanistic insights remain lacking. It’s urgent to develop a finer patient stratification method to guide clinical decision. As next generation sequencing had become routine in clinic to inform clinical decision regarding the use of targeted drugs, the mutation status of recurrently mutated genes analyzed in this study is generally available for cancer patients. Thus, future studies using a larger population of patients are merited to further confirm the effect of distinct co-mutation patterns on the response of NSCLC patients to immune checkpoint inhibition.

Author contributions

Ning Li and Xiaoyun Huang contributed to concept and design. Shuhang Wang and Miaomiao Jiang contributed to the literature search, data acquisition, data analysis, statistical analysis, manuscript preparation. Zuozhen Yang contributed to manuscript editing and manuscript review.

Conflict of interests

All authors declare no conflict of interest.

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