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Association of Molecular Characteristics with Survival in Advanced Non-Small Cell Lung Cancer Patients Treated with Checkpoint Inhibitors

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Authors' contributions

DZ and RS conceived the study and participated in information collection, results analysis and wrote the manuscript. DZ, IM, HL, CC, JF collected the data and participated in data analysis. DZ, HL and CC performed bioinformatic and statistical analysis and YX helped in statistical models. PF, EM, MK, and KR contributed to the clinical database. PK, PL and AB aided data interpretation and manuscript revision. All authors read and approved the final manuscripts.

Credit Author Statement

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Declaration of Competing Interests

The authors declare that they have no competing interests relevant to this work

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The authors declare that they have no conflicts of interest relevant to this work.

Availability of data and materials

The results generated in this manuscript are included in the manuscript results section and supplemental files. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

The manuscript doesn't include any individual person's data.

Ethics approval and consent to participate

The study was approved by the ethics review boards and in accord with an assurance filed with and approved by the Department of Health and Human Services at City of Hope. This study was approved by the Institutional Review Board at City of Hope under IRB 18529 and was conducted according to the Declaration of Helsinki.

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Abstract

Objectives—Immune checkpoint inhibitors (ICIs) have changed the landscape of lung cancer therapy. However significant proportions of patients have primary or acquired resistance to ICIs. Molecular characterization is critical for patient selection and overcoming resistance to checkpoint inhibitors. The purpose of this study is to investigate the molecular characteristics associated with ICIs outcomes in advanced non-small cell lung cancer (NSCLC) patients.

Materials and methods—All advanced stage NSCLC patients at City of Hope who received ICIs (pembrolizumab, nivolumab, atezolizumab, and durvalumab) were identified retrospectively. Overall survival (OS, from the start of the ICIs), Pathology and information on genomic alterations (GAs) including next-generation sequencing (NGS) data, tumor mutation burden (TMB), and Programmed death-ligand 1 (PD-L1) levels were collected. Chi-square and Fisher's exact test, Log-rank test were used for comparison of demographics, and survival curves respectively. Univariate and multivariate COX proportional hazards model was used for survival analysis.

Results: 346 NSCLC patients were identified. Univariate and multivariate analysis found the association of OS with PD-L1 level ≥50% (Hazard ratio [HR], 0.19; 95% confidence interval [CI], 0.06–0.59; P<0.01), EGFR (HR 7.38; 95% CI, 1.15–47.42; P<0.05), and TET2 (HR 0.15; 95% CI, 0.03–0.90; P<0.05). The median OS was not reached [NR] for the 12 patients who had genomic alterations (GAs) in TET2 (12/108, 11%) versus (vs) 11.5 months in TET2 negative patients (98/108, 89%). Interestingly, GAs in TET2 and FANCA were mutually exclusive and patients who had GAs in FANCA gene (6%) had shorter OS (5.5 months vs 14.5 months, Log-rank test, P<0.05).

Conclusions: We described the clinical and molecular features of NSCLC patients treated with ICIs. The association of GAs in TET2 with longer OS and its mutual exclusivity with FANCA GAs were insightful for developing novel therapeutic strategies to improve ICIs outcomes in NSCLC.

Keywords

Lung cancer; molecular; next-generation sequencing (NGS); immune checkpoint inhibitors; TET2; FANCA; PD-L1; TMB; immunotherapy

Introduction

Immune checkpoint inhibitors (ICIs) are currently used as monotherapy or combination therapy in frontline and subsequent lines for metastatic lung cancer including adenocarcinoma, squamous cell carcinoma, and small cell lung cancer (SCLC) [1–5]. Furthermore, ICIs before or after surgery showed efficacy in patients with resectable disease, highlighting the potential of ICIs to improve outcomes in these patients and expand the use of ICIs in the neoadjuvant and adjuvant settings [6, 7]. Despite higher response rates, longer duration of response, and less toxicity of ICIs compared with chemotherapy, many lung

cancer patients have primary and acquired resistance to ICIs. Specifically, response rates to ICIs are ~20% for monotherapy and ~ 40% for combination therapy, but eventually, most patients have progression of disease [8, 9]. Therefore, clinical and molecular profiling to understand the underlying mechanisms behind response and resistance is needed for the selection of patients, and identification of novel therapeutic targets and strategies to improve the response to ICIs.

To date, programmed death-ligand 1 (PD-L1) protein expression is the only US FDA-approved biomarker to select metastatic lung cancer patients for first-line pembrolizumab monotherapy [10]. However, studies using nivolumab or atezolizumab monotherapy, and combination therapy with chemotherapy or ipilimumab, show responses to treatment regardless of the PD-L1 levels [1, 5, 11–13]. Analysis of 5-year survivors of nivolumab treated non-small cell lung cancer (NSCLC) patients showed that only 70% of the survivors had ≥ 1% PD-L1 expression at baseline, indicating that patients without PD-L1 expression may still have durable responses from ICIs [14]. Besides, FDA-approved immunohistochemistry (IHC) tests show variable concordance for evaluation of the PD-L1 expression, as indicated in the Blueprint project [15], there was poor reliability on immune cells PD-L1 scoring and different sensitivities between antibodies, which is further complicated by the inter- and intratumoral heterogeneity [16]. Exploratory analyses had shown tumor mutation burden (TMB) could be a potential predictive marker for ICIs in lung cancer as patients with higher TMB seemed to fare better when treated with nivolumab and ipilimumab combination therapy [17, 18]. However, larger datasets for confirmation and standardization of TMB thresholds across different platforms and samples (whole exon DNA sequencing versus (vs) targeted gene panel sequencing using tissues vs circulating tumor DNA) are needed [19].

Studies using next-generation sequencing (NGS) to identify genomic alterations (GAs) that drive response and resistance to ICIs appear promising. GAs in tumors could shape the immune microenvironment to affect the outcomes of checkpoint inhibitors [20]. The meta-analysis demonstrated no overall survival (OS) benefit for patients who had EGFR mutant tumors treated with ICIs compared with chemotherapy [21]. Lack of responses to ICIs in EGFR mutated patients was consistently observed in multiple studies [22, 23]. Co-mutation of KRAS and KEAP1/NFE2L2 was reported to be an independent prognostic factor with shorter OS [24]. GAs such as STK11/LKB1 mutations was identified as the genomic drivers for primary resistance to immune checkpoint inhibitors in KRAS-mutated lung adenocarcinoma [25]. It was also reported that increased expression of PD-L1 was associated with TP53 mutation and MET amplification [26]. However, the role of TP53 was not very prominent in other studies and KRAS mutations were not different in the overall population compared with patients who had durable clinical benefits [23, 27–29]. To date, correlations of GAs with ICIs outcomes in NSCLC vary between different cohorts; validation of the results in larger and different populations are needed. Furthermore, identifying specific mutations in patients who survived longer with ICIs will be helpful to explore signaling pathways important in tumor responses to ICIs and to develop novel therapeutic strategies. Therefore, in the present study, we used clinical and molecular information of 346 advanced NSCLC patients treated with ICIs including available NGS data to identify molecular features associated with overall survival.

Methods

Patients

Total 346 patients with advanced NSCLC in City of Hope, who received ICIs (pembrolizumab, nivolumab, atezolizumab, and durvalumab) in different settings including standard of care, compassionate use, and clinical trials, were identified retrospectively at the cutoff date of 11/8/2018. All lines of therapy were not available during analysis and the cohort includes a heterogeneous population of lung cancer patients who received immunotherapy. Demographic, clinical, and pathological information was collected with approval by the institutional review board (IRB) of City of Hope. Informed consent was waivered per IRB requirements since it was a retrospective observational study. Overall survival (OS, from the start of the ICIs) were calculated if available at the study time point.

Molecular information

The information of tumor GAs was extracted from the available clinical data including EGFR, ALK/ROS rearrangement, KRAS, TP53 and TMB from patients who had next-generation sequencing (NGS) using various platforms such as FoundationOne (Foundation Medicine, Cambridge, MA, USA), Caris (Caris life science, Phoenix, AZ, USA), Paradigm (Paradigm diagnostics, Phoenix, AZ, USA), Guardant360 (Guardant, Redwood City, CA, USA), Neogenomics (NeoGenomics Laboratories, Fort Myers, FL, USA) or targeted gene sequencing panels at City of Hope. TMB was reported by FoundationOne. PD-L1 (22C3) expression detected by paraffin IHC was reported as Tumor Proportion Score (TPS), which is defined as the percentage of viable tumor cells showing partial or complete membrane staining (≥ 1+) relative to all viable tumor cells present in the sample (positive and negative). Negative PD-L1 is defined as < 1% of viable tumor cells showing membranous staining.

Statistical analysis

The OS was defined from the start of ICIs until death due to any cause. The association of clinical and molecular features with OS was analyzed first by univariate COX proportional hazards model independently. Based on the results of the univariate analysis, clinically and biologically relevant features with statistical significance (cutoff P value 0.05) were selected for the multivariate COX proportional hazards model. TMB was categorized to low, intermediate, and high groups as reported by Foundation. PD-L1 expression was categorized as negative (<1%), 1% - <50% and ≥ 50%. The Kaplan-Meier method was used to estimate overall survival (OS) and the Log-rank test was used to compare the survival curves. Statistical analyses and data visualization were performed using GraphPad Prism 8 (GraphPad Software) and R (open source for statistical computing and data visualization). All tests were two-sided and $P<0.05$ was considered statistically significant. Lollipops diagram for TET2 gene and its mutations was generated using Lollipops application [30].

Results

Patient characteristics

The baseline characteristics of 346 patients were summarized in Table 1. The median age was 69 years (range 34–100) with 164 (47%) patients was age ≥ 70 and 182 (53%) were <70

years old at the treatment of ICIs. 160 (46%) were female and 186 (54%) were male. 102 (29%) were never smokers, 211 (61%) former smokers and 33 (10%) were current smokers. Histology included 257 (74%) adenocarcinoma, 67 squamous cell lung cancer (19%), and 22 (6%) other types (9 poorly differentiated tumors including non-small cell carcinoma, not otherwise specified (NSCC-NOS), 4 large cell lung cancer, 2 neuroendocrine tumors, 1 lung atypical carcinoid, 1 adenosquamous tumor, 1 basaloid squamous cancer, 1 mixed large cell with neuroendocrine tumor, 1 giant cell carcinoma, 1 mixed adenocarcinoma with large cell neuroendocrine tumor, and 1 adenoid cystic adenoid carcinoma). PD-L1 was tested in 212 patients: 72 (34%) were negative (<1%), 89 (42%) were ≥ 50%, 51 (24%) were 1% - <50%. TMB was reported in 52 patients (8 high, 26 intermediate, 18 low). EGFR was tested in 307 patients with 50 (16%) positive and 257 (84%) negative patients.

Univariate COX analysis revealed the association of OS with PD-L1 level ≥50% and the statistical significance was retained in the multivariate analysis (HR 0.19; 95% CI, 0.06–0.59; $P<0.01$). The median OS was NR for patients who had PD-L1 level ≥50% vs 12.2 months with PD-L1 level 1%−50% and 6.9 months with negative PD-L1 (Figure 1A). No statistical significance was found in age, gender, smoking status, TMB, histology associated with OS in the multivariate analysis.

Recurrently detected GAs and OS

Top detected GAs and the patients' clinical information (Figure 2) were sorted by the detected positive rate of GAs among tested patients (number of tested patients for each gene varied due to different gene panels in the testing platforms). TP53 ranked as the most frequently detected GAs (123 patients) with 50% positive rate in the 246 patients tested for TP53, followed by KRAS (84/301, 28%) and LRP1B (28/108, 26%). Univariate analysis showed statistically significant ($P<0.05$) association of OS with GAs in EGFR, FANCA, TET2 and CDKN2A/B loss (Hazard Ratio in Figure 2), which were included for the multivariate analysis. The association of OS with GAs in EGFR (HR, 7.38; 95% CI, 1.15–47.42; $P<0.05$) and TET2 (HR, 0.15; 95% CI, 0.03–0.90; $P<0.05$) was retained in the multivariate COX proportional hazards model, as indicated in Table 2. The median OS for patients who had EGFR GAs was 7.2 months and for patients who were EGFR negative, the median OS was 14.8 months (Figure 1B). CDKN2A/B loss (HR, 2.51; 95% CI, 1.27–4.96; $P<0.01$) and FANCA (HR, 2.69; 95% CI, 1.28–5.69; $P<0.01$) was associated with worse OS (Figure 3) in the univariate analysis but was not statistically significant in the multivariate analysis.

TET2 GAs

We found that TET2 GAs were associated with longer OS. As shown in Figure 2C, the median survival was not reached (NR) for the 12 patients who had GAs in TET2 among 108 patients tested for TET2 (positive rate 11%) compared with 11.5 months in the 96 negative patients (89%) (Log-rank test, $P<0.05$). Interestingly we found none of the patients were positive for GAs in both TET2 and FANCA. Shorter survival was found in patients who harbored FANCA GAs. The median survival was 5.5 months for the 8 patients who had GAs among 132 patients tested for FANCA (positive rate 6%) vs 14.5 months in the patients who tested negative (124/132, 94%) for FANCA GAs (Log-rank test, $P<0.05$). However, in the

multivariate analysis, there is no statistical significance in the association of FANCA GAs and OS. We summarized the information of patients who had GAs in TET2 (Table 3). Among the 12 positive patients, there were 8 lung adenocarcinomas, 2 NSCC-NOS, 1 lung squamous cancer, and 1 basaloid squamous lung cancer. All 12 patients had non-synonymous mutations and 4 of them had nonsense mutations. 3 mutations located in the oxygenase domain as shown in the Lollipops diagram (Figure S1).

Discussion

In this study, we investigated the clinical and molecular features associated with survival of NSCLC patients treated with ICIs at City of Hope. Consistent with previous studies [21], EGFR mutated patients (n=50, 16%) had worse OS (median, 7.2 months) compared with patients who were negative for EGFR GAs (median, 14.8 months) (multivariate COX analysis, HR, 7.38; 95% CI, 1.15–47.42; $P<0.05$). Longer OS (median, not reached) was observed in patients who had PD-L1 ≥50% than patients with PD-L1 1%−50% (median, 12.2 months) or negative PD-L1 (median, 6.9 months) (Log-rank test, $P< 0.01$). However, patients with PD-L1 level ≥50% likely received ICIs at first-line rather than later lines of therapy; thus, the results might be confounded by the lines of therapy. Detailed therapy information including previous tyrosine kinase inhibitors for EGFR mutated patients was not available for analysis, but for the OS analysis the OS was defined from the start of the immunotherapy rather than cancer diagnosis. Despite the heterogeneity of the study population, our findings are consistent with previous reports that patients with PD-L1 ≥50% fare better with ICIs and patients who had EGFR mutations had worse OS than patients who were EGFR negative treated with ICIs [10]. The underline mechanism of lack of benefits in EGFR mutated tumors remains unclear and a recent study of T cell receptor repertoire analysis showed that EGFR-mutated tumors had lower clonal T cell expansion compared with EGFR non-mutated tumors [31]. Our real-world experience with patient populations in different settings from clinical trials validated the role of PD-L1 level ≥50% and EGFR mutations in ICIs. The top 3 detected GAs in our cohort were TP53 (50%), KRAS (28%), and LRP1B (26%). None of these was associated with OS. STK11 mutations were reported to be associated with resistance to ICIs but no statistically significant association of STK11 mutations (31/243, 13%) with OS was detected in our cohort (Figure 2) [25]. We did not find an association of TMB with OS. This may be due to the limited sample size (n=52) for TMB analysis.

In univariate analysis, patients who had GAs in FANCA gene (8/132, 6%) had shorter OS (median, 5.5 months vs 14.5 months, Log-rank test, $P<0.05$) compared to patients who were negative (124/132, 94%). Worse OS was also found in CDKN2A/B loss (13/132, 10%) patients (7.1 months vs 14.7 months, Log-rank test, $P<0.05$) compared to patients who were negative (119/132, 90%) for CDKN2A/B loss in the univariate analysis but the results were not statistically significant in the multivariate analysis. Fanconi anemia complementation group A (FANCA) is a core component of Fanconi anemia complex and important for DNA damage (double-strand breaks) repair [32]. GAs in DNA damage response and repair genes including FANCA were reported to be associated with higher response rates to PD-1/PD-L1 in metastatic renal cell carcinoma[33]. Targeting DNA damage response proteins has been shown to increase PD-L1 expression and enhance the anti-tumor effect of PD-L1 blockade

in small cell lung cancer via the activation of the STING pathway [34, 35]. The worse survival of FANCA mutated patients treated with ICIs in our cohort might imply different mechanisms underneath. FANCA mutations were reported to cause adult immunodeficiency and be involved in impaired lymphomagenesis likely due to the accumulated DNA replication stress [36]. In our cohort, we had 18 patients (18/241, 7%, Figure 2) tested positive for BRCA2 GAs but there was no association with OS on ICIs with BRCA2 GAs. The role of GAs in DNA damage repair genes in ICIs outcomes warrants further studies in lung cancer.

Interestingly, we found longer OS (median, NR vs 11.5 months, $P<0.05$) in patients who had TET2 mutations and the statistical significance was confirmed in the multivariate COX model (HR, 0.15; 95% CI, 0.03–0.90; $P<0.05$). TET2 encodes the Ten-eleven translocation (TET) demethylase which is important in epigenetic modification by converting 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) with α-ketoglutarate (α-KG)-dependent hydroxylase activity and by recruiting acetylglucosamine transferase (OGT) enzyme for histones modifications to increase gene expression [37, 38]. TET2 inactivation was common in myeloid and lymphoid malignancies and its mutations were loss of function [39]. Loss of TET2 function has been shown to increase self-renewal and expansion and TET2 is a proposed tumor suppressor [40]. Interestingly, TET2 determines the fate of CD8+ T cells by promoting CD8+ T cell memory differentiation [41]. Recently, a single clone of chimeric antigen receptors (CARs)-T cell with disrupted TET2 and a hypomorphic mutation in the second TET2 allele induced complete remission of a chronic lymphocytic leukemia (CLL) patient and central memory phenotype of CAR-T cells were detected after 4.2 years [42]. In our cohort, all the GAs of TET2 identified in the 12 patients were non-synonymous mutations, with 4 of them nonsense mutations. Functions of these mutations were rarely reported but they are potentially pathogenic since they caused amino acid/protein changes. The role of TET2 mutations in solid tumors and ICIs outcomes is unclear. Ablation of TET2 in myeloid cells suppressed melanoma growth *in vivo* [43]. In primary breast cancer and colorectal cancer, upregulated TET2 with PD-L1 promoter hypomethylation as well as PD-L1 expression in peripheral blood contributed to immunosuppressive microenvironment compared with healthy donors and methylation patterns in tumor tissues were different from blood cells [44]. In our cohort, TET2 mutations were present in both lung adenocarcinoma and squamous histology and the PD-L1 level was tested in tumor cells not immune cells in lung cancer tissue samples. As listed in Table 3, the PD-L1 levels in the 12 TET2 positive patients ranged from ≥50% (n=4) to negative (n=4) with 2 patients no tested and 2 patients were 1% to<50%. TET2 mutations on the PD-L1 expression on immune cells in lung cancer are unclear. However, it is possible that the TET2 mutated tumors had altered epigenetics or metabolism and thus, modulated the tumor microenvironment and affected T cells function and anti-tumor responses. TET2 mutations were previously observed to be mutually exclusive with isocitrate dehydrogenase 1 and 2 (IDH1/2) mutations, as cytosolic IDH1 and mitochondrial IDH2 were important for α-KG production and TET dioxygenase activity [45]. To the best of our knowledge, mutual exclusivity of TET2 and FANCA mutations have not been reported. However, by querying public databases using cBioPortal, we found mutual exclusivity of TET2 GAs and FANCA GAs existed in the pan-cancer sequencing of 12089 samples that included MSK-IMPACT clinical sequencing cohort (n=10945), pan-lung

cancer cohort from TCGA (n=1144) (Figure S2) [46–49]. The underlying mechanisms for the mutual exclusivity of TET2 and FANCA GAs remain poorly understood. It is possible that TET2 could bind to the FANCA promoter and upregulate its gene expression as shown in diffuse large B cell lymphoma (DLBCL) [50]. TET2 mutations are not well characterized in NSCLC and ICIs, along with FANCA GAs. Our results of longer OS in patients who had TET2 mutations with ICIs and mutual exclusivity with FANCA GAs suggest further investigation of TET2, FANCA is warranted, and TET2 may be a therapeutic target for improving outcomes of NSCLC treated with ICIs.

Limitations

Despite the promising results, the present study does suffer from some caveats. First, it is a single institution study with a modest cohort for which NGS data were available. Second, it includes a heterogeneous population with different settings of ICIs used including monotherapy, combination therapy, and different lines of therapy. Third, we included results from different NGS platforms and the sample size for TMB analysis is small with only 52 patients. Finally, less than half of our patients were tested for TET2 (n=108), FANCA (n=132), CDKN2A/B (n=132) and the number of positive patients for TET2 (n=12), FANCA (n=8), CDKN2A/B (n=13) were limited. Analyzing larger datasets in the future would be helpful to explore the molecular features of ICIs outcomes in NSCLC. EGFR mutated patients would also need to be further evaluated in a future study to determine the effect of ICIs before, after, and concurrently with EGFR-TKIs.

Conclusions

We have summarized the clinical and molecular features of patients with NSCLC treated with ICIs. Our results validated the role of EGFR mutations and PD-L1 ≥50% in the outcomes of ICIs. We identified a novel association of TET2 mutations with longer OS and mutual exclusivity of mutations in TET2 and FANCA genes. Due to limited sample sizes and non-conforming NGS platforms, studies with a larger dataset and with different populations are warranted. Exploring the role of TET2, FANCA, CDKN2A/2B loss in NSCLC and ICIs appears a promising strategy to discern potential prognostic biomarkers for survival and to investigate novel targets for improving outcomes of NSCLC treated with ICIs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- 346 Lung Cancer patients including next generation sequencing data were analyzed
- EGFR mutations were associated with shorter overall survival
- PD-L1 ≥50% was associated with longer overall survival
- TET2 muations was associated with longer overall survival
- TET2 mutations were mutually exclusive with FANCA gene mutations.

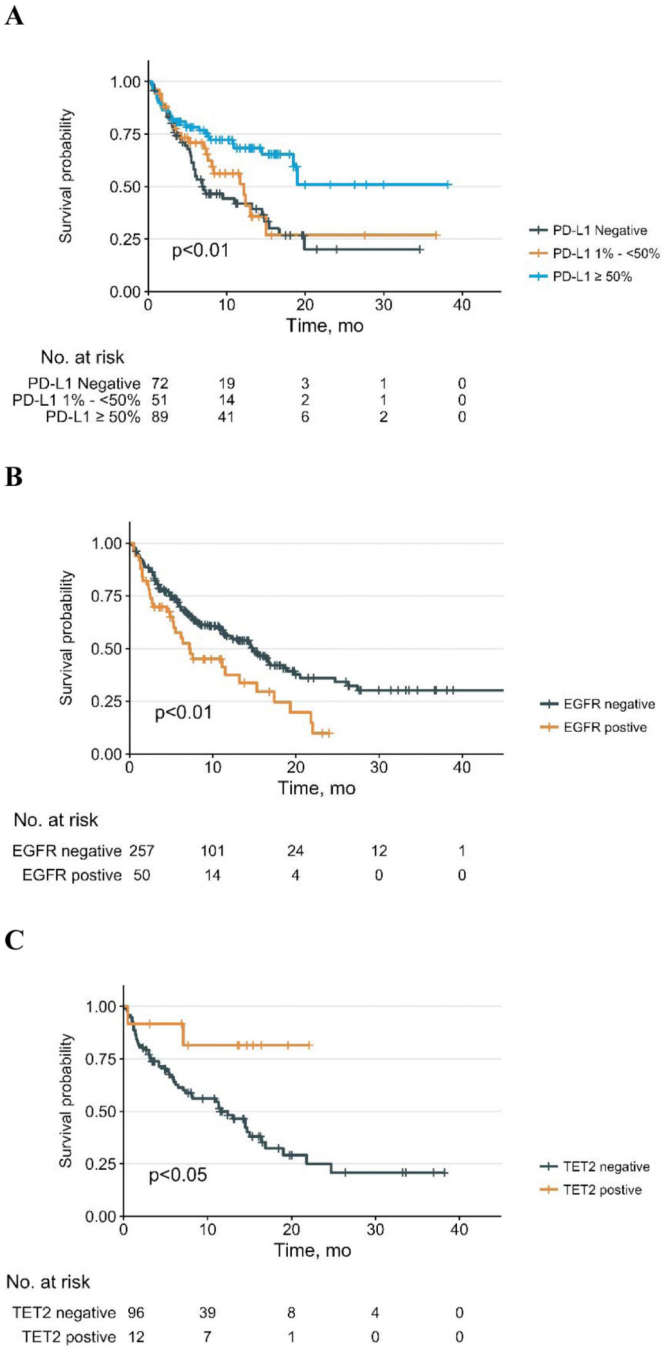

Figure 1: PD-L1, EGFR and TET2 genomic alterations (GAs) with overall survival (OS).
Survival curves of OS according to levels of PD-L1 (A), mutation status of EGFR (B), and TET2 (C). The Kaplan Meier curves and Log-rank tests were performed using R.

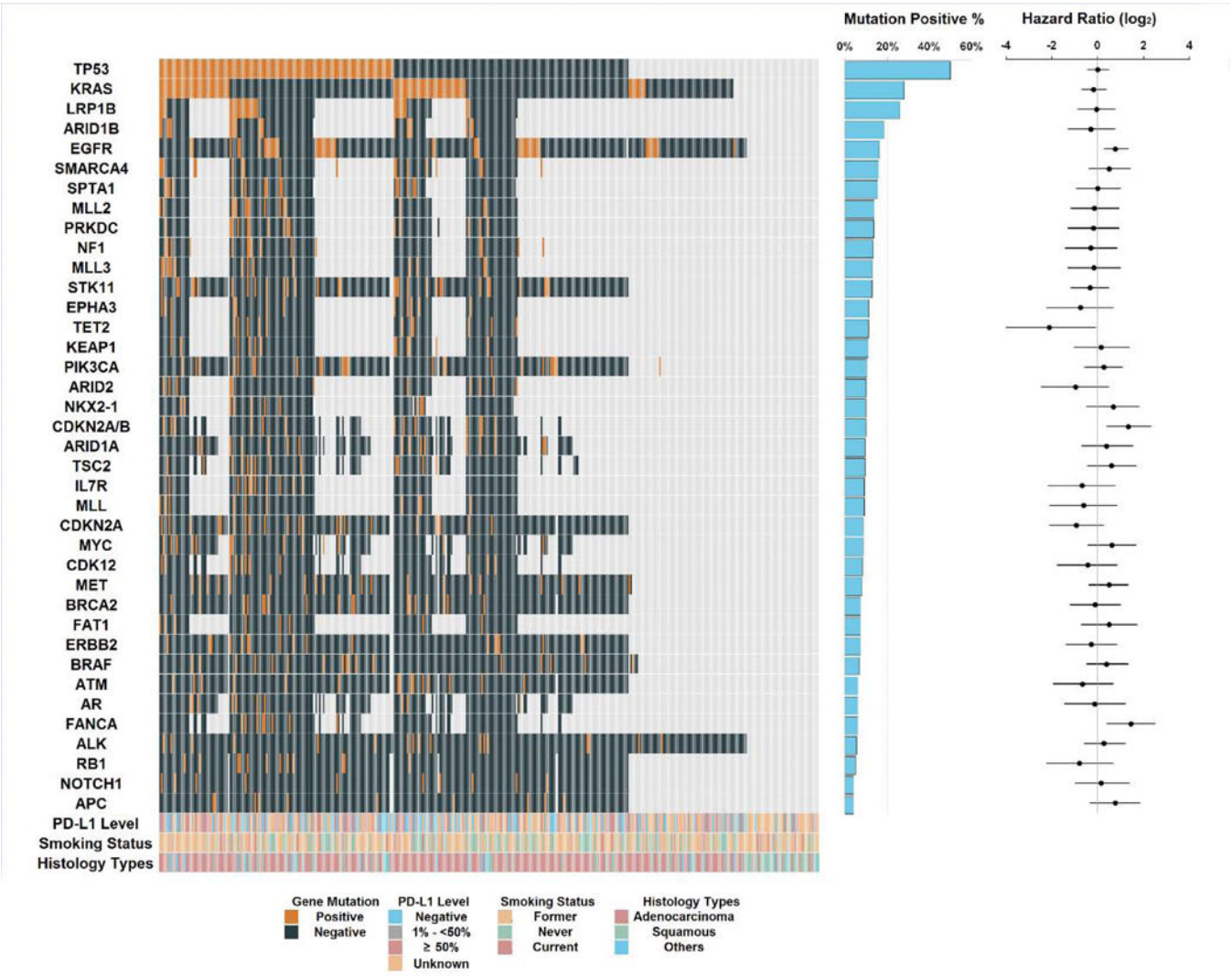

Figure 2. Top detected genomic alterations (GAs) and overall survival (OS)

Oncoplot showed clinical information and top detected genomic alterations in 346 patients sorted by the rate of positive patients among tested patients (Mutation Positive %) with results of Hazard Ratio (HR) and 95% confidence interval (CI) by univariate COX analysis of overall survival (OS). Statistical analyses and data visualization were performed in R (open source for statistical computing and data visualization).

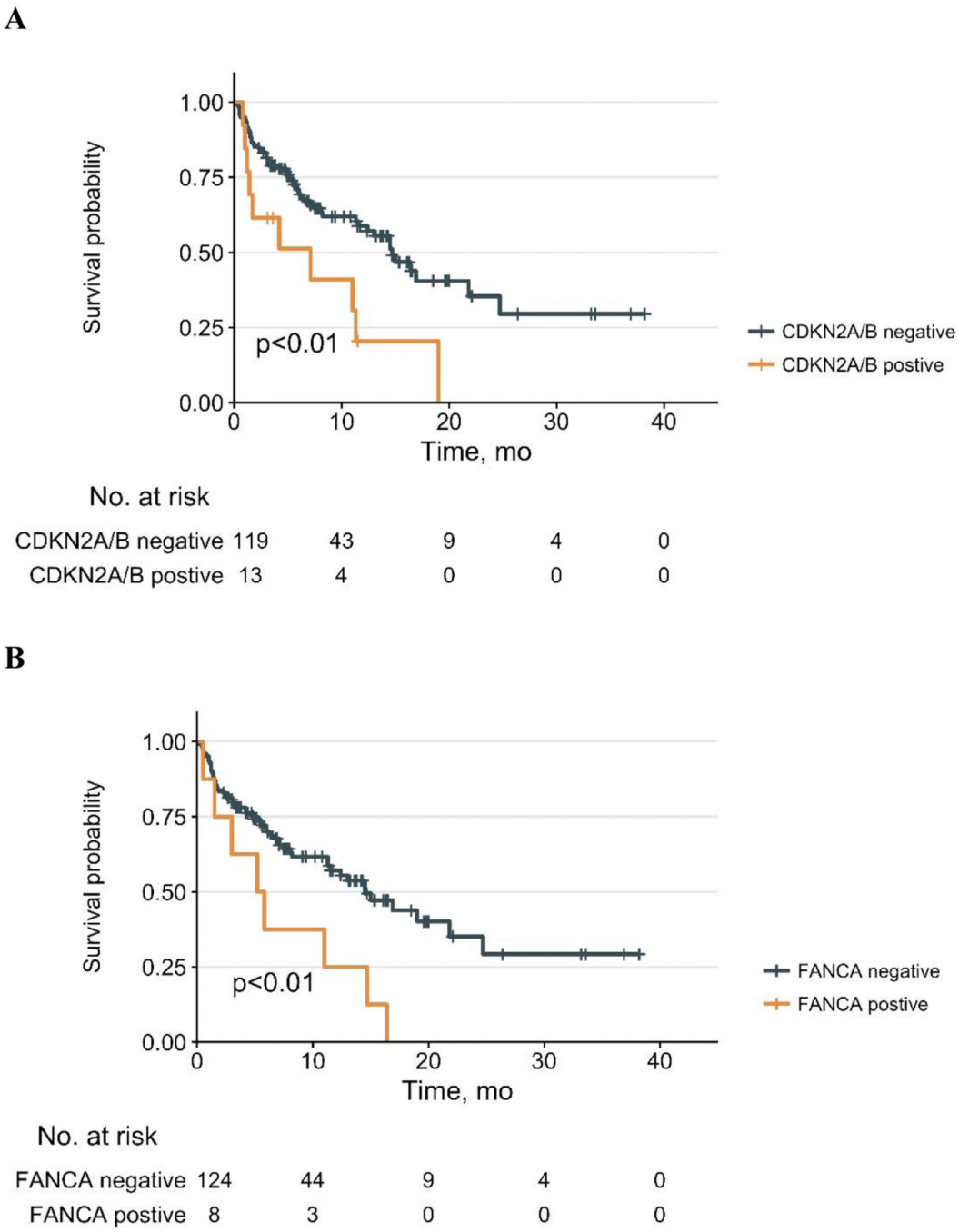

Figure 3: Overall survival (OS) with genetic alterations (GAs) of FANCA and CDKN2A/B.

Overall survival (OS) according to genomic alterations of CDKN2A/B loss (A) and FANCA (B). The Kaplan Meier curves and Log-rank teste were performed using R.

Table 1.

Baseline patient characteristics

Characteristics	No. (%)
Age, years, at ICIs	
< 70	182 (53)
≥ 70	164 (47)
Gender	
Women	160 (46)
Men	186 (54)
Smoking status	
Current	33 (10)
Former	211 (61)
Never	102 (29)
Histology	
Lung adenocarcinoma	257 (74)
Lung squamous	67 (19)
Others[a]	22 (6)
EGFR	
Positive	50 (16)
Negative	257 (84)
Total tested	307
PD-L1	
Negative	72 (34)
1%-<50%	51 (24)
≥50%	89 (42)
Total tested	212
TMB	
High	8 (15)
Interme ‘iat	26 (50)
Low	18 (35)
Total tested	52

[a]Others included 9 poorly differentiated lung tumors including non-small cell carcinoma, not otherwise specified (NSCC-NOS), 4 large cell lung cancer, 2 neuroendocrine tumors, 1 lung atypical carcinoid, 1 lung adenosquamous tumor, 1 basaloid squamous lung cancer, 1 mixed large cell with neuroendocrine tumor, 1 lung giant cell carcinoma, 1 mixed lung adenocarcinoma with large cell neuroendocrine tumor, and 1 lung adenoid cystic adenoid carcinoma.

Table 2.

Multivariate analysis of overall survival (OS)

All Cohort	HR (95% CI for	*P value
Age		
< 70	Reference	
≥ 70	1.46 (0.62 – 3.46)	0.3841
Gender		
Female	Reference	
Male	0.92 (0.41 – 2.04)	0.8321
Histology		
Adenocarcinoma	Reference	
Squamous	0.39 (0.08 – 1.82)	0.2291
Others	0.63 (0.11 – 3.70)	0.6081
Smoking Status		
Never	Reference	
Current	0.68 (0.17 – 2.68)	0.5773
Former	1.00 (0.35 – 2.88)	0.9988
PD-L1		
Negative	Reference	
1%-<50%	1.6’ (0.63 – 4.2)	0.3170
≥50%	0.19 (0.06 – 0.59)	0.0037
Genomic alterations		
CDKN2A/B	2.^ 5 (0.73 – 6.95)	0.1572
EGFR	‘ .38 (1.15 – 47.42)	0.0353
FANCA	2.31 (0.59 – 9.03)	0.2304
TET2	0.15 (0.03 – 0.90)	0.0381

*Multivariate COX proportional hazards model.

Table 3.

Information of patients tested positive for genomic alterations (GAs) in TET2

Information of the 12 patients tested positive for TET2 genomic alterations (GAs) including clinical information and features of PD-L1, TMB, EGFR, and TP53 mutations status.

Case	Age	Gender	Histology	Smoking	TET2	EGFR	TMB	TP53	PD-L1
1	62	Female	Adenocarcinoma	Never	E1151*	L858R, T790M	Unknown	P190L	1% to<50%
2	75	Male	NSCC-NOS NOS	Former	E263Q	Negative	High	R213*673-	≥50%
3	84	Male	Adenocarcinoma	Former	Q1389*	Negative	Intermediate	1G>A	Negative
4	83	Male	Adenocarcinoma	Never	R1966C	Negative	Unknown	Negative	1% to<50%
5	59	Male	NSCC-NOS	Never	Y1421fs*1	Amplification	High	375G>T	≥50%
6	78	Male	Squamous	Former	V386L	Negative Exon 19	Unknown	Negative	Unknown
7	43	Female	Adenocarcinoma	Former	S460F	deletion	Low	G302fs*4	Negative
8	72	Female	Adenocarcinoma	Former	y192H P1889L,	Negative	Intermediate	P152fs*18	Negative
9	74	Male	Adenocarcinoma	Former	subclonal*	Negative	Intermediate	Negative	≥50%
10	59	Female	Adenocarcinoma	Current	R1095T	Negative	Intermediate	Negative	≥50%
11	58	Male	Adenocarcinoma Basaloid	Never	S1039L	Negative	Unknown	Negative	Negative
12	68	Male	Squamous	Former	R96C, R1214Q	Negative	Unknown	Negative	Unknown