166P: Integrated Analysis Reveals *TP53* Mutation as a Biomarker of Anti-PD-1/PD-L1 Treatment for *EGFR*-Mutant Lung Adenocarcinoma Patients

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Background

On one hand, the clinical benefits of immunotherapy are limited for unselected *EGFR*-mutant lung adenocarcinoma (LUAD) patients and conventional biomarkers like PD-L1 and TMB are not sufficient for these patients. On the other hand, *EGFR*-mutant patients with *TP53* mutation experience significantly inferior prognosis of EGFR-TKIs than patients without *TP53* mutation. Therefore, the subsequent systemic treatment strategy for these patients would be even more important. Several studies have reported *TP53* mutation as a biomarker for immunotherapy among *EGFR*-wildtype LUAD and the mechanism underlying the better clinical outcomes of *TP53*-mutant patients from immunotherapy was due to higher PD-L1 expression, higher TMB and higher proportion of activated immune cell infiltration. However, the predictive value of *TP53* mutation of immunotherapy among *EGFR*-mutant patients after resistance to EGFR-TKIs remains unclear.

Methods

A retrospective study was conducted to explore the predictive value of *TP53* in clinical outcomes of anti-PD-1/PD-L1 treatment.

An intergrated analysis of genomic and transcriptomic data from TCGA database and immunohistochemistry (IHC) results of paired samples at baseline and after resistance to EGFR-TKIs of the local cohort were conducted to explore the changes in tumor microenvironment (TME).

Results

A total of 42 *EGFR*-mutant LUAD patients were included in the retrospective study. The median progression-free survival (PFS) of *TP53*-mutant patients was significantly longer than that of *TP53*-wildtype patients (6.7 vs. 2.6 months; $p = 0.003$). Multivariate Cox regression analysis revealed that *TP53* mutation was independently associated with superior PFS (HR, 0.38; 95%CI, 0.17-0.84; $p = 0.016$).

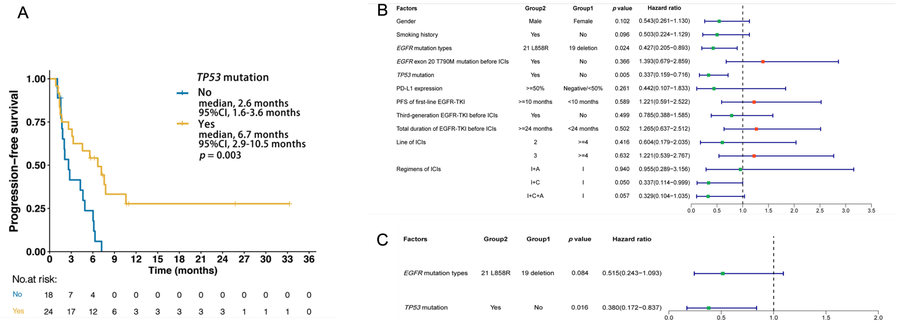

Fig 1. PFS of PD-1/PD-L1 inhibitors for *EGFR*-mutant LUAD patients. (A) PFS of all patients stratified by *TP53* mutation status; (B) Association between clinical factors and PFS analyzed by univariate Cox proportional hazards regression analysis; (C) Multivariate Cox proportional hazards regression analysis. Abbreviations: A, anti-angiogenesis; C, chemotherapy; I, immunotherapy; ICI, immune checkpoint inhibitor.

A total of 43 sensitive *EGFR*-mutant LUAD patients from TCGA database were included into this study. There was no significant difference in the median TMB between *TP53*-mutant and *TP53*-wildtype patients (mutant vs. wildtype: 1.3 muts/Mb vs. 1.1 muts/Mb; $p = 0.274$). There was also no significant difference in the median *PD-L1* (*CD274*) expression between *TP53*-mutant and *TP53*-wildtype patients [mutant vs. wildtype: $\log_2$(FPKM), 1.3 VS. 0.8; $p = 0.172$]. Analyzed by CIBERSORT, the fractions of 22 tumor infiltrating immune cells (TIICs) in each sample were determined. There were no significant differences in fractions of all these 22 TIICs between *TP53*-mutant and *TP53*-wildtype groups.

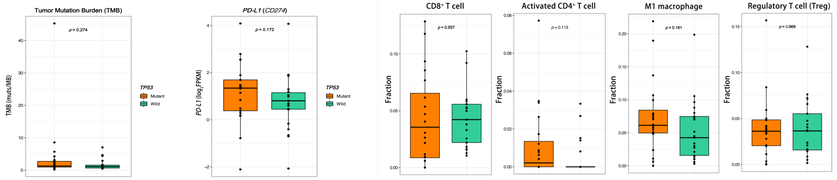

Fig 2. TMB, *PD-L1* (*CD274*) expression and fractions of TIICs of *EGFR*+ LUAD patients classified by the *TP53* mutation status.

Twenty paired tissue samples of *EGFR*-mutant LUAD patients before EGFR-TKI treatment and after resistance to EGFR-TKIs were included into this study. There were no significant differences in TIICs between *TP53*-mutant and *TP53*-wildtype patients in both baseline and re-biopsy samples. However, analysis of 20 paired samples indicated that the median density of $CD8^+$ T cell increased significantly during EGFR-TKI treatment only in *TP53*-mutant patients (re-biopsy vs. baseline: 14.6 vs. 3.2; $p = 0.008$), not in *TP53*-wildtype patients (21.9 vs. 13.6; $p = 0.422$).

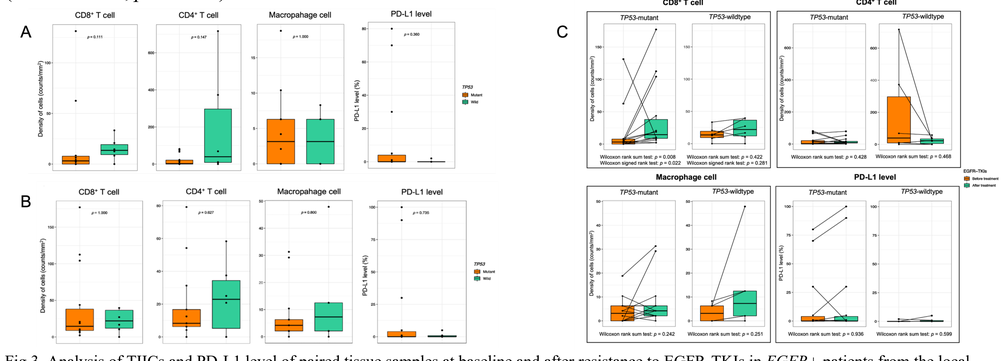

Fig 3. Analysis of TIICs and PD-L1 level of paired tissue samples at baseline and after resistance to EGFR-TKIs in *EGFR*+ patients from the local cohort classified by TP53 mutation status. (A) Baseline samples; (B) Re-biopsy samples; (C) Paired analysis.

Conclusion

TP53 mutation is an independent predictive factor of superior efficacy of anti-PD-1/PD-L1 treatment among *EGFR*-mutant LUAD patients, which may result from the trend to be more inflamed in TME during EGFR-TKI treatment in *TP53*-mutant patients.