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Atezolizumab prolongs overall survival over docetaxel in advanced non-small-cell lung cancer patients harboring *STK11* or *KEAP1* mutation

Wei Nie[a*], Lu Gan[b*], Xin Wang[c,d,e*], Kai Gu[e], Fang-Fei Qian[a], Min-Juan Hu[a], Ding Zhang[f], Shi-Qing Chen[f], Jun Lu[a], Shu-Hui Cao[a], Jing-Wen Li[a], Yue Wang[a], Bo Zhang[a], Shu-Yuan Wang[a], Chang-Hui Li[a], Ping Yang[g], Mi–Die Xu[c,d,e], Xue-Yan Zhang[a], Hua Zhong[a], and Bao-Hui Han[a]

[a]Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China; [b]Department of Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; [c]Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China; [d]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; [e]Institute of Pathology, Fudan University, Shanghai, China; [f]The Medical Department, 3D Medicines Inc., Shanghai, China; [g]Department of Health Sciences Research, Mayo Clinic, Scottsdale, AZ, USA

ABSTRACT

Somatic mutations of *STK11* or *KEAP1* are associated with poor clinical outcomes for advanced non-small-cell lung cancer (aNSCLC) patients receiving immune checkpoint inhibitors (ICIs), chemotherapy, or targeted therapy. Which treatment regimens work better for *STK11* or *KEAP1* mutated (SKmut) aNSCLC patients is unknown. In this study, the efficacy of atezolizumab versus docetaxel in SKmut aNSCLC was compared. A total of 157 SKmut aNSCLC patients were identified from POPLAR and OAK trials, who were tested by blood-based FoundationOne next-generation sequencing assay. Detailed clinical data and genetic alterations were collected. Two independent cohorts were used for biomarker validation (n = 30 and 20, respectively). Median overall survival was 7.3 months (95% confidence interval [CI], 4.8 to 9.9) in the atezolizumab group versus 5.8 months (95% CI, 4.4 to 7.2) in the docetaxel group (adjusted hazard ratio [HR] for death, 0.70; 95% CI, 0.49 to 0.99; *P* = .042). Among atezolizumab-treated patients, objective response rate, disease control rate, and durable clinical benefit were higher when blood tumor mutation burden (bTMB) and PD-L1 being higher (biomarker 1, n = 61) or with *FAT3* mutation-positive tumors (biomarker 2, n = 83) than otherwise. The interactions for survival between these two biomarkers and treatments were significant, which were further validated in two independent cohorts. In SKmut patients with aNSCLC, atezolizumab was associated with significantly longer overall survival in comparison to docetaxel. Having *FAT3* mutation or high TMB and PD-L1 expression potentially predict favorable response in SKmut patients receiving atezolizumab.

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STK11; KEAP1; NSCLC; immune checkpoint inhibitor

Introduction

Immune checkpoint inhibitors (ICIs), which target programmed cell death receptor-1 (PD-1) or its ligand (PD-L1), have considerably improved the outcomes of advanced non-small-cell lung cancer (aNSCLC).[1–6] However, the response rate to ICI therapy remains relatively low (~20%); thus, the majority of aNSCLC patients could not benefit from this treatment.

Serine/threonine kinase 11 (STK11), also named liver kinase B1 (LKB1), is a tumor suppressor and plays a negative regulatory role over the mTOR pathway.[7] Kelch-like ECH-associated protein 1 (KEAP1) functions as a negative regulator of nuclear factor erythroid 2-related factor 2 (NRF2), and promotes transcription of genes encoding detoxifying enzymes and antioxidative stress proteins.[8,9] Somatic mutations in *STK11* and *KEAP1* are estimated to be present in approximately 20% of NSCLC patients.[10–12] Several lines of evidence suggested that *STK11* or *KEAP1* mutations might predict for lack of clinical benefit from ICIs.[13–15] For example, Negrao et al. suggested that *STK11* mutations were significantly correlated with shorter progression-free survival (PFS) in aNSCLC treated with ICIs.[14] Chen et al. found that tumors with *KEAP1* mutations had a significantly inferior overall survival (OS) comparing with the wild-type group in ICI-treated cohort.[15] *STK11* or *KEAP1* genetic alterations showed highly significant negative associations with the T cell-inflamed gene expression profile in NSCLC.[13] Therefore, it seems that *STK11* or *KEAP1* mutated (SKmut) patients with NSCLC have inhibitory tumor immune microenvironment and limited benefit from ICIs.[16–18]

In addition to immunotherapy, *STK11* and *KEAP1* mutations might promote resistance against chemotherapy and targeted therapy.[19–24] For example, Papillon-Cavanagh found that mutations in *STK11* or *KEAP1* were associated with poor outcomes with platinum-based chemotherapy and *EGFR* tyrosine kinase inhibitors.[22] We also demonstrated that NSCLC patients with *STK11* or *KEAP1* mutation could not derive benefit from docetaxel in our previous study.[25]

So far, no study compared ICIs with chemotherapy for patients with advanced NSCLC and SKmut. Thus, it is largely

CONTACT Mi-Die Xu xumd27202003@sina.com Fudan University Shanghai Cancer Center, Shanghai, China; Hua Zhong eddiedong8@hotmail.com Shanghai Chest Hospital, Shanghai 200030, China; Bao-Hui Han xkyyhan@gmail.com Shanghai Chest Hospital, Shanghai 200030, China.; Xue-Yan Zhang zxychest@163.com
*The authors contributed equally to this work.
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unknown which treatment could improve overall survival in these patients. Here, we used the clinical and genetic data from OAK and POPLAR trials to compare the efficacy of atezolizumab with docetaxel in SKmut aNSCLC patients. Additionally, we explored potential biomarkers to predict clinical benefit from atezolizumab.

Methods

Patient population

In our study, a total of 157 SKmut patients were identified from OAK and POPLAR trials (Figure 1). The OAK and POPLAR trials were open-label, multicentre, randomized controlled trials, which compared the efficacy and safety of atezolizumab versus docetaxel in patients with stage IIIB or IV NSCLC who had progressed after one to two previous chemotherapy regimens.[5,6] Atezolizumab was given as an intravenous 1200 mg fixed dose every 3 weeks; docetaxel was given intravenously at 75 mg/m2 every 3 weeks. Twenty SKmut aNSCLC patients from Van Allen & Rizvi cohort and 30 SKmut aNSCLC patients from Memorial Sloan Kettering Cancer Center (MSKCC) were enrolled for biomarker validation.[26–28] In addition, SKmut NSCLC patients without receiving immunotherapy from The Cancer Genome Atlas (TCGA) were included in this study to explore genetic and immune mechanism.

No institutional review board approval was required, for all the data was obtained from publicly available data sets, and no patient information can be identified.

Outcomes

The primary outcome was OS, which was defined as the time from the initial treatment to the date of death due to any cause. The secondary endpoints included PFS, objective response, and durable clinical benefit (DCB). PFS was defined as the

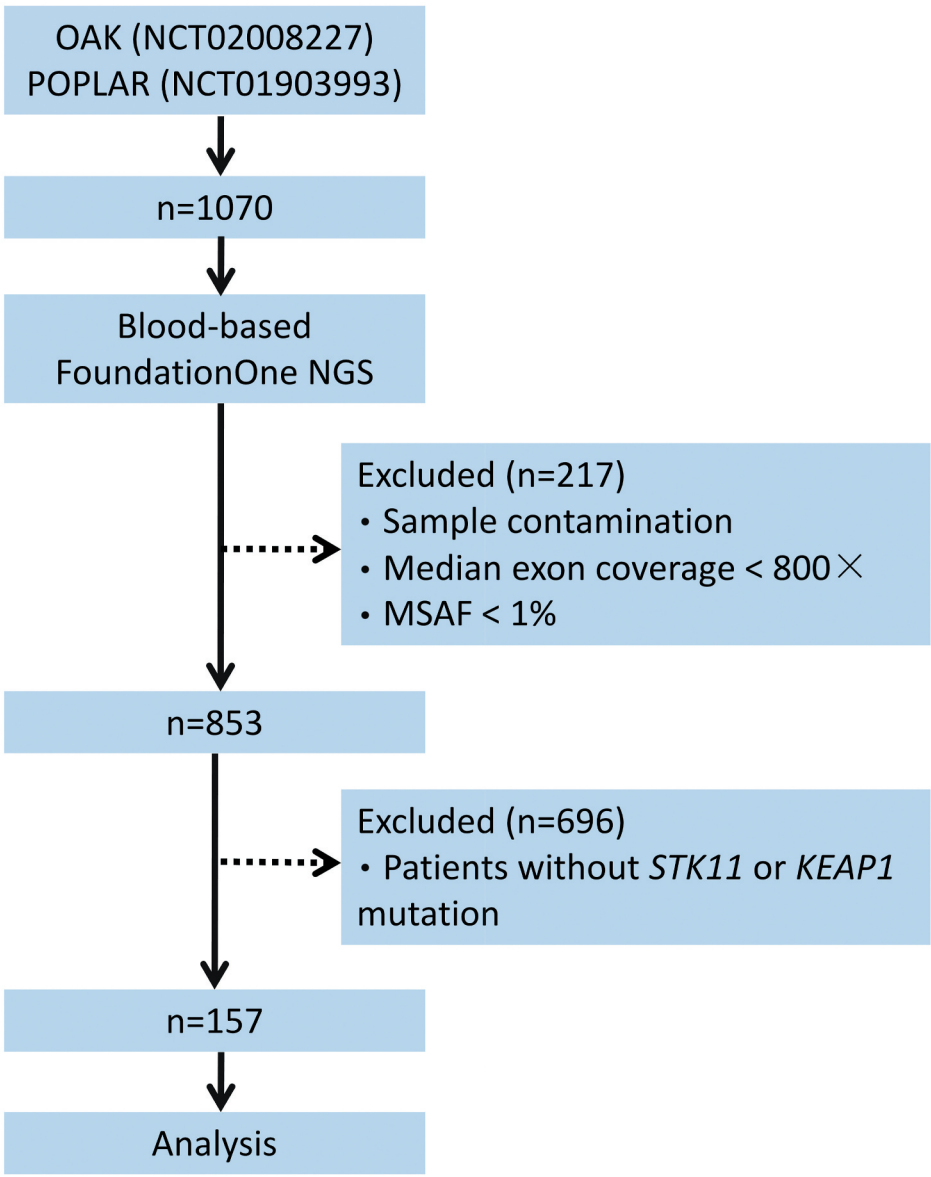

Figure 1. Process of patient selection.

time from the initial treatment to the date of the first documentation of objective tumor progression or death on study due to any cause, whichever occurred first. DCB was defined as PFS that lasted no less than 6 months, whereas no durable benefit (NDB) was defined as progression of disease within 6 months. The response of treatments was assessed by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[29,30]

Relationships between DCB and clinical variables and individual gene alterations were exploratory biomarker endpoints.

Genetic sequencing and PD-L1 immunohistochemistry

Blood-based FoundationOne CDx assay was performed through next-generation sequencing (NGS) in the POPLAR and OAK trials.[5,6,31,32] The Memorial Sloan Kettering Integrated Molecular Profiling of Actionable Cancer Targets (MSK-IMPACT) clinical sequencing assay was used in MSKCC cohort.[28] Whole-exome sequencing was performed in Van Allen & Rizvi cohort[26,27] and TCGA cohort. The calculation of blood-based tumor mutation burden (bTMB) and tissue-based TMB were described previously.[31,32] All loss-of-function alterations were considered deleterious, including deletions, nonsense mutations, and frameshift or splice site alterations. For missense mutations, the deleterious status of mutation was algorithmically determined by recurrent hot spot mutations and annotation of oncogenicity by OncoKB.[33,34]

PD-L1 expression was evaluated with the VENTANA SP142 PD-L1 immunohistochemistry assay (Ventana Medical Systems, Inc., Tucson, AZ, USA) in the POPLAR and OAK trials.[5,6] Strong PD-L1 expression was defined as TC3 or IC3 (≥50% PD-L1 on tumor cells or ≥10% PD-L1 on tumor-infiltrating immune cells). PD-L1 expression data was only collected from OAK trial. Several antibodies, which have largely been shown to be similar,[35] were used in MSKCC cohort, including 22C3 (DAKO), 28–8 (DAKO), and E1L3N (Cell Signaling, Danvers, MA).[28]

Estimation of the abundance of immune cell populations

To quantify the abundance of tumor-infiltrating immune cells, gene set variation analysis (GSVA) was performed.[36] The GSVA produces normalized enrichment scores ranging from −1 to 1, which represent the abundance of the immune cell population in the sample. A list of 16 immune cells was shown in eTable 1.

Immune-related genes expression

The association between different groups and immune-related genes was assessed. The immune gene list was mainly based on three published articles that summarized the genes related to activated T cells, immune cytolytic activity, and IFNγ release.[37–39] A list of 47 immune-related genes was shown in eTable 1. Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes pathway enrichment (KEGG) analyses to identify the pathways that may be regulated by differentially expressed immune-related genes were used. The KEGG pathways and GO terms regarding cellular component, molecular function, and biological process with P values and false discovery rates (FDRs) less than 0.05 were considered statistically significant.

Statistical analysis

Mann–Whitney U test was used to examine the difference between two groups. Fisher exact test was used to evaluate between-group differences for proportions. The Kaplan–Meier method was used to estimate OS and PFS. We estimated that a sample of 157 patients would provide the study with 66% power to detect a difference in treatment effect on the primary end point with the use of a log-rank test with a two-sided significance level of 5%. Between-group differences in OS and PFS were assessed with the use of a log-rank test. The univariate and multivariate Cox proportional hazards model was utilized to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the outcomes.

Univariable logistic regression was used to evaluate the association between DCB and the variables, with results presented as odds ratios (ORs) and 95% CIs. All reliable variables associated with DCB were entered into a multivariable model using forward stepwise binary logistic regression analysis (P = .05 included but P = .10 removed). Variables in the regression model were assessed for co-linearity using the variance inflation factor. The coefficients from the multivariable logistic regression model were used to calculate prediction score. The area under the curve (AUC) of the receiver operator characteristic (ROC) curve was computed using the predicted probability of DCB. The optimal cutoff point and different prediction score groups were determined by Youden's index.

Assessment of enrichment of binary molecular features (e.g., wild-type or mutant gene) with response (e.g., DCB versus NDB, partial response and stable disease versus progressive disease) and HR of survival (e.g., PFS and OS) was done with Fisher's exact test and Cox proportional hazards regression, respectively. Correction for multiple-hypothesis testing was conducted controlling for FDR by the Benjamini–Hochberg method.[40]

All P values were two-sided and $P < .05$ indicated statistical significance. Both types of effect sizes were reported with their 95% CIs. All analyses were conducted with R, version 3.6.1 (R Project for Statistical Computing) and SPSS version 22.0 (IBM, Armonk, NY).

Results

Clinical and genetic characteristics of the patient population

In OAK and POPLAR cohort, there was no significant difference on OS, PFS, bTMB, and PD-L1 expression between deleterious and non-deleterious SKmut aNSCLC patients receiving atezolizumab (eFigure 1). No significant difference of the degree of immune cells was observed between the deleterious and non-deleterious SKmut NSCLC patients from the TCGA database (eTable 2). Thus, we enrolled all SKmut aNSCLC patients whether deleterious mutation or not (n = 157). Clinical characteristics for the atezolizumab and docetaxel

groups were shown in eTable 3. No significant difference was observed, except for baseline sum of the longest diameters (P = .014).

The genomic mutational landscape of these patients categorized according to treatment was shown in eFigure 2. The locations of the *KEAP1* and *STK11* mutations were displayed in eFigure 3a. eFigure 3b correlates the distribution of genetic mutations detected in OAK and POPLAR cohort with the findings previously reported by TCGA Research Network, which analyzed tumor specimens from 177 SKmut NSCLC patients. Most genetic mutations in OAK and POPLAR cohort were similar to those in the TCGA analysis, although the mutation frequency of certain genes, including *DNMT3A* (P < .001), *CHEK2* (P = .039), *KRAS* (P < .001), and *LRP2* (P < .001), was higher or lower than that in TCGA cohort.

Primary and secondary outcomes

Compared with docetaxel, overall survival was better with atezolizumab in SKmut aNSCLC patients. The median OS of patients with atezolizumab was 7.3 months (95% confidence interval [CI], 4.8 to 9.9) and 5.8 months (95% CI, 4.4 to 7.2) for those with docetaxel (adjusted HR 0.70; 95% CI 0.49–0.99; P = .042; Figure 2a and eTable 4). In the subgroup analysis, SKmut aNSCLC patients with current smoking status, ECOG 0 point, non-squamous, larger tumor size, less number of metastatic site, or deleterious status showed a greater survival benefit with atezolizumab than with docetaxel (Figure 2b). Treatment with ICI was associated with improved outcomes in patients with *SMARCA4*-mutant NSCLC and mutations in *STK11* and *KEAP1* had the strongest association with *SMARCA4*-mutant tumors.[41] We thus assessed the interaction between *SMARCA4* status and treatments in SKmut aNSCLC patients and no significant result was found (interaction P = .900). Similar analysis was performed between *NRF2* status and treatments, and the interaction was also not significant (interaction P = .611). These results suggested that the overall result was not influenced by *SMARCA4* and *NRF2* mutation statuses.

Progression-free survival was similar between treatment groups (adjusted HR 1.03; 95% CI 0.66–1.60; P = .893; eTable 5). The proportions of patients with an objective response and DCB were also similar between treatment groups (eTable 5) and gene mutation groups (eTable 6).

Clinical variables and durable clinical benefit in patients receiving atezolizumab

PD-L1 expression and TMB are established biomarkers to predict benefit from ICIs in NSCLC.[28,31,42,43] However, the predictive role of PD-L1 and TMB on clinical benefit in SKmut patients with NSCLC remains unknown. The results of univariate and multivariate logistic regression analyses for DCB in patients receiving atezolizumab showed that PD-L1 and bTMB were related to DCB (eTable 7). These 2 variables had a variance inflation factor of less than 1.01, indicating a lack of multi-collinearity between them. The coefficients from the multivariable logistic regression model were used to calculate prediction score. Prediction score of DCB was distinguished from NDB with a ROC-AUC of 0.85 (95% CI 0.73–0.93) (eFigure 4a). The optimal cutoff point of prediction score for predicting DCB was 0.27, with a sensitivity of 78.6% and specificity of 85.1%. Clinical characteristics for the low and high prediction score groups are shown in eTable 8. Notably higher level of bTMB and frequency of strong PD-L1 expression were found in high prediction score group (eTable 8). In addition, DCB, objective response rate (ORR), and disease control rate (DCR) were significantly higher among patients with high prediction score receiving atezolizumab (eFigure 4b–d). More importantly, the interactions between prediction score and treatment were significant for OS (interaction P = .030; Figure 3a) and PFS (interaction

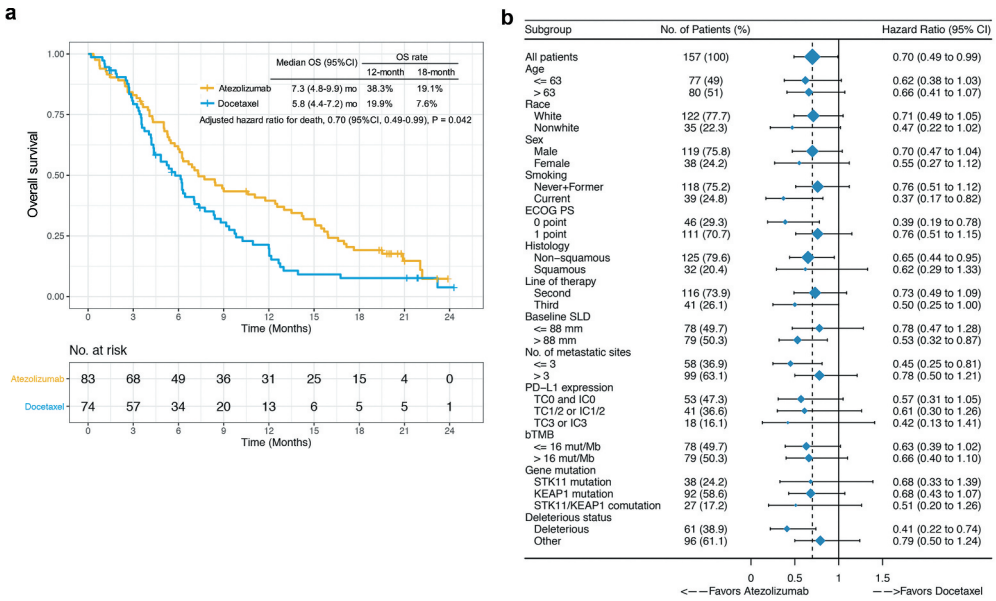

Figure 2. Overall survival (OS) and subgroup analysis. (a) Kaplan–Meier estimates of overall survival, according to treatment group. (b) Hazard ratios for overall survival in subgroups.

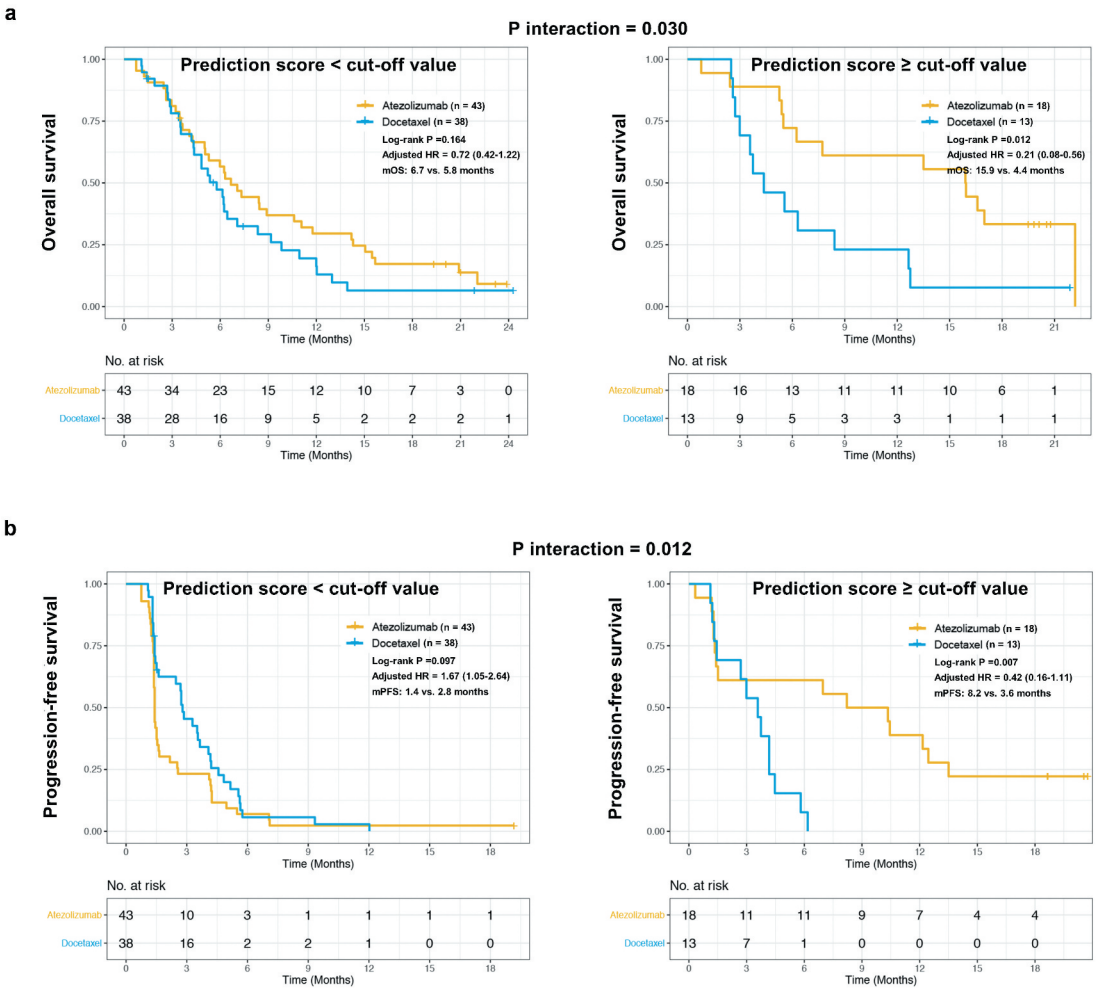

Figure 3. Predictive capacity for progression-free survival (PFS). (a) and overall survival (OS) (b) is stratified by treatment with atezolizumab vs docetaxel in patients with low and high prediction score in the OAK and POPLAR cohort.

P = .012; Figure 3b). We then tested the predictive value of this model in *STK11* and *KEAP1* mutated subgroups and only found the similar result in *STK11* mutant NSCLC patients (eTable 9).

The prediction model was also assessed in an independent cohort from MSKCC (n = 30; eTable 10). The AUC for the combination of TMB and PD-L1 was 0.73 (95% CI 0.54–0.88) (eFigure 5a). Significantly higher DCB was observed in high prediction score group (eFigure 5b). Additionally, high prediction score was associated with higher 1-year and 2-year OS rates (eFigure 5c) and significantly longer median PFS (eFigure 5d).

We then evaluated immune cell populations and immune-related genes expression in a TCGA data set of SKmut NSCLC patients (n = 177) who treated without ICIs. Patients with high TMB and PD-L1 had higher abundance of immune cells and higher expression of immune-related genes, compared with patients with low TMB or PD-L1 (eFigures 6 and 7). The KEGG pathway enrichment analysis found that differential immune genes were significantly involved in T helper cell differentiation and T cell receptor signaling pathways (eFigure 8A). The GO enrichment analysis indicated that these differential immune genes enriched immunological processes (eFigure 8B).

Individual gene alterations and durable clinical benefit in patients receiving atezolizumab

We next evaluated whether mutations in individual genes were associated with DCB of atezolizumab. The mutations of four genes, including *FAT3*, were enriched in DCB group (all FDR-adjusted P < .05; Figure 4a). SKmut patients with *FAT3* mutations had significant higher DCB rate (14/24, 58.3% vs. 3/59, 5.1%, P < .001; Figure 4b). Multivariable logistic regression model revealed that PD-L1 and *FAT3* mutation status were significantly associated with DCB (eTable 11). The AUC of PD-L1 and *FAT3* mutation status was not greater than that of *FAT3* mutation status (0.91 vs. 0.87, P = .352; Figure 4b). Importantly, *FAT3* mutation was associated with greater DCB irrespective of bTMB and PD-L1 status (Figure 4c and Figure 4d). In addition, *FAT3* mutation was associated with significantly higher ORR, DCR, and bTMB, but not with PD-L1 expression (eFigure 9 and eTable 12). Unsurprisingly, *FAT3* mutated SKmut

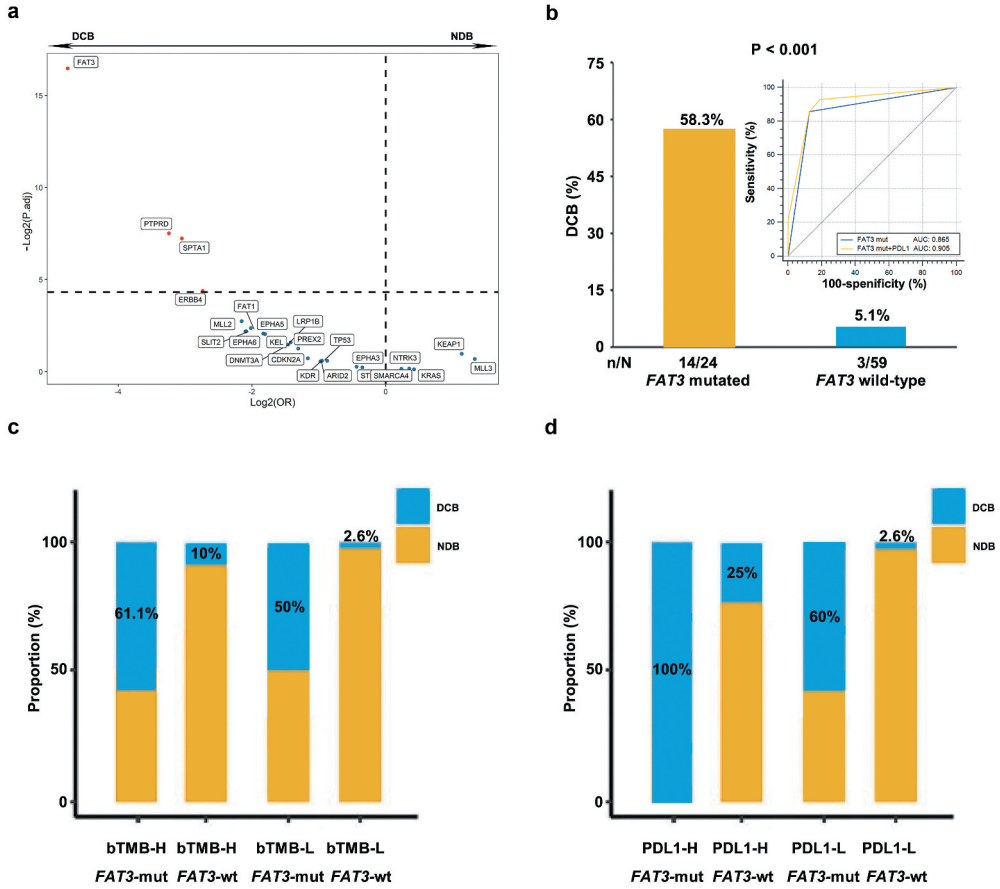

Figure 4. (a) Log2(OR) and – log2(FDR-*P* value) for enrichment of individual-altered genes in group comparison of DCB versus NDB. Only genetic mutations >10 were included in the analysis. (b) Comparison of DCB between patients with *FAT3* mutation and *FAT3* wild-type. ROC curves of *FAT3* mutation alone and the combination of *FAT3* mutation and PD-L1 to predict DCB in OAK and POPLAR cohort. (c–d) Histograms depicting proportions of patients who experienced DCB in different groups in OAK and POPLAR cohort, defined by bTMB status or PD-L1 expression and *FAT3* mutation status, as indicated. OR, odds ratio; FDR, false discovery rate; DCB, durable clinical benefit; NDB, no durable benefit; bTMB, blood-based tumor mutation burden; PD-L1, programmed death ligand 1.

patients with atezolizumab had significantly longer OS and PFS (both FDR-adjusted $P < .05$; Figure 5a and Figure 5b). Although treatment-*FAT3* interaction was not significant for OS (interaction $P = .128$; Figure 5c), the interaction was significant for PFS (interaction $P < .001$; Figure 5d), suggesting the predictive role of *FAT3* for atezolizumab benefit in SKmut aNSCLC patients. Again, we tested the predictive value of *FAT3* mutation in *STK11* and *KEAP1* mutated subgroups, and found similar results (eTable 13).

We then asked whether *FAT3* mutation could predict atezolizumab benefit in non-SKmut aNSCLC patients. We found that *FAT3* mutation was also associated with higher bTMB and not with PD-L1 expression in non-SKmut aNSCLC patients (eFigure 10A and 10B). However, the interaction between *FAT3* and treatment was not significant for OS and PFS (eFigure 10 C and 10D).

We validated our results using previously published dataset from Van Allen and Rizvi cohorts (eTable 14).[21,22] *FAT3* mutation was significantly correlated with higher DCB, but not with TMB and ORR (eFigure 11A-C). In addition, SKmut aNSCLC patients with *FAT3* mutation had significantly longer median PFS (adjusted HR 0.06; 95% CI 0.01–0.60; $P = .016$; eFigure 11D).

Among SKmut NSCLC cohort from TCGA database, *FAT3* mutated patients had higher TMB, compared with *FAT3* wild-type patients (eFigure 12A). However, PD-L1 expression and the degree of immune cells were similar between two groups (eFigure 12B and eTable 15). Since *FAT3* mutation was associated with the increased level of TMB, we hypothesized that *FAT3* mutated patients might have higher frequencies of concurrent DNA damage response (DDR) pathways mutations. In both TCGA and OAK+POPLAR cohorts, we found that DDR pathways mutations were more common in those with *FAT3* mutation (eFigure 13).

Discussion

The results of this study showed the superiority of atezolizumab over docetaxel as second-line treatment for advanced NSCLC with *STK11* or *KEAP1* mutation. Treatment with atezolizumab resulted in significantly longer overall survival than did standard chemotherapy. The longer overall survival with atezolizumab was observed across all subgroups analyzed and thus appeared to occur independently. In addition, *FAT3* mutation or combination of bTMB and PD-L1 was predictive of which SKmut aNSCLC patient received the most benefit

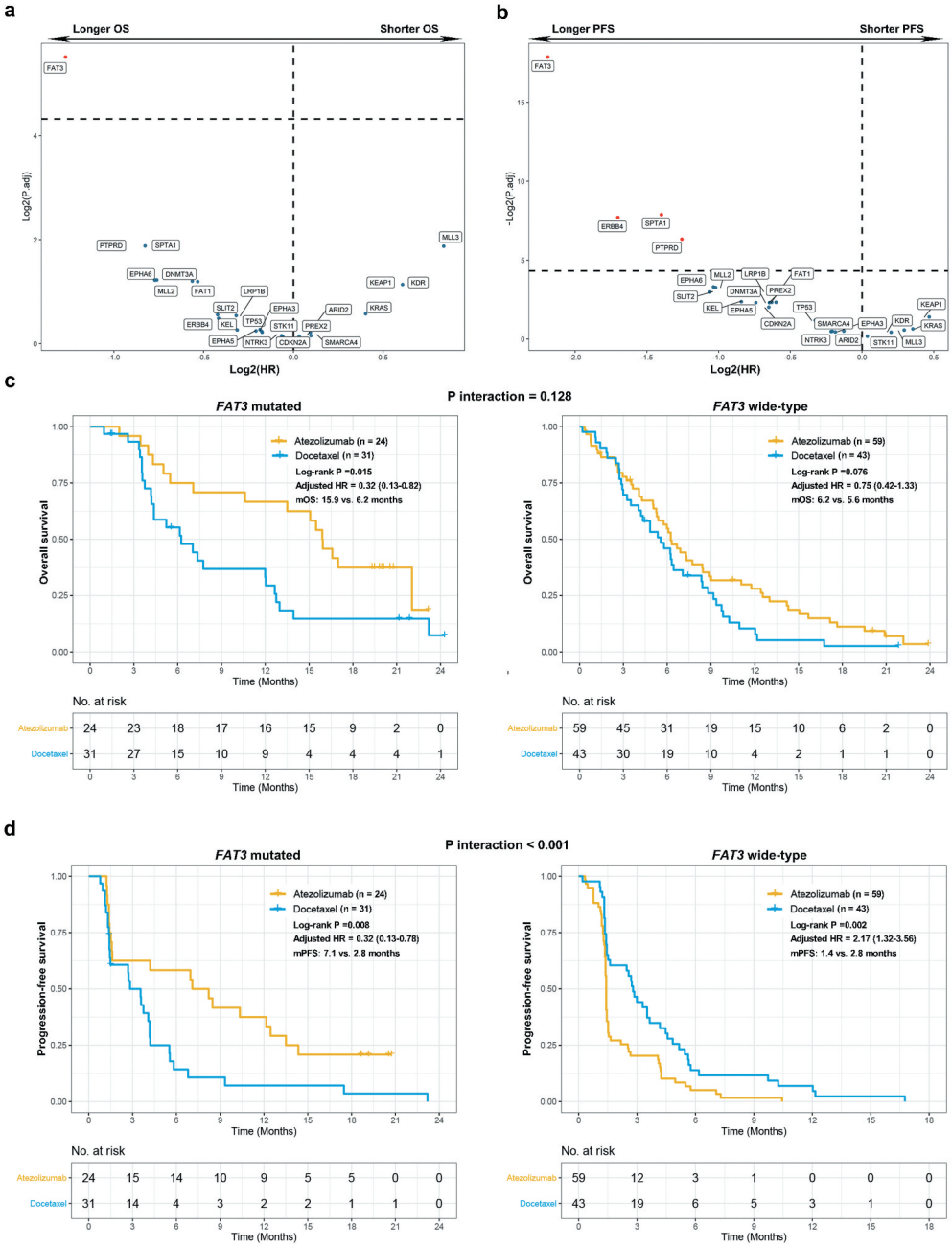

Figure 5. Hazard ratios (HRs) and – log2(FDR-*P* value) for enrichment of individual-altered genes associated with PFS (a) and OS (b). Predictive capacity for PFS (c) and OS (d) is stratified by treatment with atezolizumab vs docetaxel in *STK11* or *KEAP1* mutated patients with or without *FAT3* mutation in OAK and POPLAR cohort. FDR, false discovery rate; PFS, progression-free survival; OS, overall survival.

from atezolizumab therapy compared with treatment with docetaxel.

There might be two potential explanations for why atezolizumab could prolong overall survival for SKmut aNSCLC patients. Firstly, although most SKmut patients had cold tumor immune microenvironment,[13] our results showed that some SKmut patients still had immunologically 'hot' tumors and these patients might gain clinical benefit from ICIs treatment. Secondly, Cai et al. reported that *STK11* and *KEAP1* were the most commonly mutated genes with predicted neoantigens in lung adenocarcinoma,[44] suggesting the immunogenicity of SKmut NSCLC. Thus, if PD1/PD-L1 axis mediated immune escape in these tumors, immunotherapy with anti-PD-(L)1 antibody blockade could lead to favorable outcomes. Actually, we found high PD-L1 expression could predict DCB from atezolizumab in this study.

Recently, a real-world study indicated that *STK11* or *KEAP1* mutations were prognostic, not predictive, biomarkers for ICIs, and chemotherapy.[22] However, an exploratory analysis of KEYNOTE-042 showed that pembrolizumab monotherapy associated with superior outcomes than chemotherapy in SKmut NSCLC patients, which was consistent with our findings.[45] In addition, ICIs treatment could continue beyond disease progression if the investigator deemed the patient to be receiving clinical benefit in randomized control trials.[5,6,46,47] However, some physicians would stop ICIs treatment when

disease progression occurred in the real-world clinical practice. Therefore, these differences may affect the final outcomes of the SKmut aNSCLC patients.

In this study, we found a benefit to atezolizumab over docetaxel for OS, but not for PFS, suggesting that only a subset of patients could benefit from atezolizumab. Thus, it is important to find potential biomarkers. TMB value and PD-L1 expression have been demonstrated as actionable biomarkers for ICIs response in various tumor types, and each could identify a unique subgroup that gained benefit from ICIs.[28,48,49] In this study, we found that combination of two variables could select the ones who would derive the most clinical benefit from ICIs treatment, even in SKmut population. We also validated this result in another cohort. However, some pitfalls of TMB and PD-L1, such as lack of standardization, lack of validation of a cutoff, lack of adequate tissue, and dynamic changes,[50–52] would limit the clinical application of this model.

Fortunately, *FAT3* mutation was found to predict the response of ICIs treatment, which was also validated as a favorable surrogate biomarker in an independently published dataset. Fang and colleagues suggested that, compared with wild-type, cancer patients treated with ICIs with *FAT1* mutation had higher DCB and ORR.[53] *FAT1* is regarded as a tumor-suppressive gene and loss of *FAT1* in cells activates the Wnt signaling pathway.[54] *FAT3* is similar to *FAT1*, but it has not been well characterized to date. We observed a significant association between *FAT3* mutation and DDR pathways mutations and high TMB, which might be part of the reason in predicting superior outcomes in SKmut patients receiving atezolizumab. Interestingly, *FAT3* mutation could not predict clinical benefit in non-SKmut patients, suggesting that there might be an unknown mechanism between *FAT3* mutation and *STK11* or *KEAP1* mutation in predicting immunotherapeutic outcomes. Overall, the role of *FAT3* mutation as a predictive biomarker for ICIs treatment in this setting warrants further evaluation.

The prevalence of the molecular aberrations in this study was consistent with data reported by the TCGA.[12,55] The higher mutation frequencies of *DNMT3A* and *CHEK2* might be due to the high read coverage obtained and the alterations in white blood cells.[56] In the cases of *KRAS* and *LRP2*, the mutation frequencies were lower than that in the TCGA for unknown reasons. Skoulidis et al. suggested that lung adenocarcinoma patients with *STK11* and *KRAS* co-mutation showed significantly shorter PFS and OS with PD-1 axis blockade.[57] Although we could not assess this issue because of insufficient data, none of 5 patients with *STK11* and *KRAS* co-mutation had DCB in our cohort.

There were also some limitations to our study. First, the sample size of our study and validation cohorts was moderate, which might limit the power of conclusions. Second, and the results should be considered hypothesis generating rather than hypothesis testing since this was a retrospective study. Third, adverse events in different groups could not be assessed due to insufficient data. Fourth, *STK11* and *KEAP1* mutations are common in lung adenocarcinoma, but less in squamous NSCLC, especially for *STK11*. The inclusion of squamous carcinoma may introduce a source of bias. Fifth, *STK11* and *KEAP1* are located on the end of the short arm of chromosome 19.[58,59] Therefore, loss of both genes can occur by deletion of the short arm of this chromosome. Because no copy number variation data was available in this study, we cannot exclude effects of heterozygous loss of one or both genes after chromosome deletion or by loss of heterozygosity. Lastly, we could not get the data about which chemotherapeutic drugs were used in patients before treatment with atezolizumab or docetaxel. Thus, we could not assess whether the absence of response to any chemotherapy could predict the absence (or presence) of response to atezolizumab.

In conclusion, atezolizumab showed an overall survival benefit over docetaxel in previously treated aNSCLC patients with *STK11* or *KEAP1* mutation. Our study suggested that *FAT3* mutation or combination values of TMB and PD-L1 was predictive for the outcome of these patients with atezolizumab. The results need to be further explored with prospective studies.

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of supporting data

Datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Bao-Hui Han has consulted for AstraZeneca and Roche Pharmaceutical Company. He also received payment for speaking from AstraZeneca Pharmaceutical Company and Lily Pharmaceutical Company. All remaining authors have declared no conflicts of interest.

Authors' contributions

WN, LG, XW and MDX were involved in the literature search, figures, data collection, data analysis, and writing. KG, FFQ, MJH, DZ, SQC, JL, SHC, JWL, YW, BZ, SYW, FH, and CHL were involved in data collection. PY, XYZ, HZ, and BHH were involved in article review. WN, MDX, XYZ, HZ, and BHH were involved in the study design and writing.

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ORCID

Bao-Hui Han http://orcid.org/0000-0002-3950-3030

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