Original Article

Prognosis of immunotherapy for non-small cell lung cancer with *CDKN2A* loss of function

Lu Zhao[1#], Xiao Zhou[2#], Hui Li[3], Tiejun Yin[3], Yueqiang Jiang[3]

[1]Department of Thyroid and Breast Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [2]Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [3]Department of Geriatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Contributions: (I) Conception and design: Y Jiang; (II) Administrative support: Y Jiang; (III) Provision of study materials or patients: L Zhao, X Zhou; (IV) Collection and assembly of data: L Zhao, X Zhou; (V) Data analysis and interpretation: L Zhao, X Zhou, H Li, T Yin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yueqiang Jiang, MD. Division of Geriatric Oncology, Department of Geriatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Jiefang Road No. 13, Wuhan 430030, China. Email: jyqwh@163.com.

Background: Immunotherapy has been widely used to treat non-small cell lung cancer (NSCLC) but is only effective in 20% of patients. Cyclin-dependent kinase inhibitor 2A (*CDKN2A*) is an important tumor suppressor gene, and its loss of function (LOF) is quite common in NSCLC. Pre-clinical studies suggest *CDKN2A* LOF promotes immune evasion; however, the results in relation to NSCLC are controversial, and debate continues as to the effect of *CDKN2A* LOF on immunotherapy.

Methods: In this study, we collected the data of 49 *CDKN2A* LOF and 173 *CDKN2A* wild-type NSCLC consecutive patients treated by any line of immunotherapy. Through immunohistochemical (IHC) and immunofluorescent (IF) staining, we analyzed the *CDKN2A* predominant transcription protein $p16^{INK4A}$ in the *CDKN2A* LOF and *CDKN2A* wild-type NSCLC patients. Using Kaplan-Meier curves, we also examined the relationship between *CDKN2A* LOF and immunotherapy.

Results: The IHC and IF staining results showed that most *CDKN2A* LOF patients were $p16^{INK4A}$ negative, while most *CDKN2A* wild-type patients were $p16^{INK4A}$ positive. In the LOF group, five patients had partial responses, 35 had stable disease, and nine had progressive disease after the first evaluation of immunotherapy. The LOF group had a median progression-free survival (PFS) time of 4.67 months, while the wild-type group had a median PFS time of 8.63 months [hazard ratio (HR): 0.54; 95% confidence interval (CI): 0.38–0.77; P<0.001]. The LOF group had a median overall survival (OS) time of 9.07 months, while the wild-type group had a median OS time of 21.37 months (HR: 0.42; 95% CI: 0.29–0.61; P<0.001).

Conclusions: Our study revealed that *CDKN2A* LOF NSCLC patients treated with immune checkpoint inhibitor (ICI) mono-therapy or combined therapy had a worse prognosis than those with *CDKN2A* wild-type NSCLC. However, our study also suggested that ICI could work quite effectively in selective *CDKN2A* LOF patients.

Keywords: *CDKN2A*; loss of function (LOF); immunotherapy; non-small cell lung cancer (NSCLC); prognosis

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Introduction

Non-small cell lung cancer (NSCLC), which mainly includes adenocarcinoma (ADC) and squamous cell carcinoma (SCC), accounts for about 75–80% of all lung cancers, and is the most deadly malignancy worldwide (1). The wide usage of tyrosine kinase inhibitors (TKIs) has greatly improved the prognosis of patients with driving gene mutations, such as epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) mutations; however, the rest of NSCLC patients are driving gene negative, which means that more than half of ADC and most SCC patients cannot benefit from targeted TKIs (2).

Fortunately, for patients without a driving gene mutation, immune checkpoint inhibitors (ICIs), such as the programmed death-1 (PD-1) or its ligand (PD-L1) inhibitor, offer hope. However, research has shown that immunotherapy is only effective in 20% of such patients, which narrows down the prescription of PD-1 (or PD-L1) greatly (3). It is often suggested that PD-L1 expression level, microsatellite instability status, and high tumor mutation burden (TMB-H) can be used to predict the effect of immunotherapy in NSCLC patients; however, research should be conducted to identify the other underlying mechanisms to determine why some patients are sensitive to immunotherapy, while others are not sensitive and are even resistant to immunotherapy.

Cyclin-dependent kinase inhibitor 2A (*CDKN2A*) is an important tumor suppressor gene. Its loss of function (LOF), which mainly includes a gene mutation and loss of copy number (LCN), is quite common in lung ADC (4) (occurring in about 8% of patients) and SCC (occurring in about 22% of patients) (5). *CDKN2A* can transcribe and then translate into two proteins (i.e., $p16^{INK4A}$ and $p14^{ARF}$), of which the former is predominant. Both of these two proteins function in the cell cycle and can cause cell-cycle arrest or cell senescence (6). It appears likely that *CDKN2A* LOF is detrimental to immunotherapy, as many pre-clinical studies suggest that cell-cycle dysregulation in tumor cells promotes immune evasion (7,8). However, due to controversial results in NSCLC patients, debates continue, as research has shown that while sometimes *CDKN2A* LOF does not counteract the effect of immunotherapy, other times, it is harmful to immunotherapy (9,10).

In this study, we collected the data of *CDKN2A* LOF and *CDKN2A* wild-type NSCLC consecutive patients treated by any line of immunotherapy at our Tongji hospital. All the patients tested negative for the common driving gene mutations, such as the *EGFR* or *ALK* mutations. Using these data, we sought to identify the characteristics of *CDKN2A* LOF in NSCLC and determine the effect of *CDKN2A* LOF on immunotherapy. We present this article in accordance with the REMARK reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1017/rc).

Highlight box

Key findings

- Immunotherapy functions less effectively in cyclin-dependent kinase inhibitor 2A (*CDKN2A*) loss of function (LOF) non-small cell lung cancer (NSCLC) patients than *CDKN2A* wild-type NSCLC patients. However, it also works quite effectively in selective *CDKN2A* LOF patients.

What is known and what is new?

- Immunotherapy only functions in about 20% of *NSCLC* patients. As one of most frequent mutation genes, *CDKN2A* LOF plays a controversial role in the effect of immunotherapy in NSCLC.
- Immunotherapy could work effectively in *CDKN2A* LOF patients.

What is the implication, and what should change now?

- Both *CDKN2A* LOF and wild-type NSCLC patients should also be prescribed immune checkpoint inhibitors.

Methods

Patients

All the patients were retrospectively recruited for this study from Tongji Hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Tongji Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology (No. TJ-IRB20231236). Written informed consent for the use of all clinical data were provided by patients or their direct relatives. Specifically, we consecutively collected the data of *CDKN2A* LOF NSCLC patients and *CDKN2A* wild-type NSCLC patients from February 2018 to February 2022. These patients were all stage IV before the commencement of the initial treatment. All the patients received any line of immunotherapy, with or without chemotherapy, radiotherapy, or targeted therapy.

Pathologic confirmation

Pathologic specimens of the included patients were collected either by surgery or core-needle biopsy, and were then

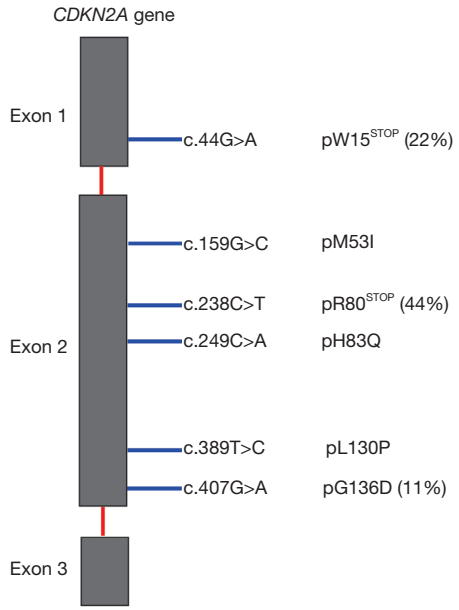

Figure 1 *CDKN2A* mutations in NSCLC patients. *CDKN2A*, cyclin-dependent kinase inhibitor 2A; NSCLC, non-small cell lung cancer.

stored at the Pathologic Department of Tongji Hospital waiting further analysis. Hematoxylin-eosin staining was performed to verify the diagnosis of lung cancer, and if possible, subtypes of lung cancer (e.g., lung ADC or SCC) were confirmed. Additionally, immunohistochemical (IHC) and immunofluorescent (IF) staining of $p16^{INK4A}$ (Abcam, Shanghai, China) was also performed. Specifically, for the IHC staining, three sections per patient were stained with a mouse anti-$p16^{INK4A}$ monoclonal antibody (dilution: 1:400) using a standardized procedure detailed in the instructions of Abcam website. For the IF staining, three sections per patient were stained with same mouse anti-$p16^{INK4A}$ monoclonal antibody (dilution: 1:100) following the instructions provided as the same above.

DNA extraction and sequencing

Genomic DNA samples were subjected to whole exon sequencing according to standard protocols, and this sequencing was performed by the Novogene Corporation (Beijing, China) using the Agilent SureSelectV6 Human All Exon Kit; the sequencing was performed using Illumina HiSeq-nova instruments.

Statistical analysis

STATA (version 12.0) was used to analyze all the data in this study. An analysis of variance and chi-squared (χ^2) test were carried out to compare different clinical features among different groups based on a two-way statistical analysis. Progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier curves. A P value ≤0.05 was considered statistically significant.

Results

Basic information of NSCLC patients treated by immunotherapy

From February 2018 to February 2022, we collected the data of 49 *CDKN2A* LOF NSCLC patients undergoing any line of ICI, of whom 18 had mutations and 31 had LCNs. The main mutation types were $pR80^{STOP}$ (8/18), $pW15^{STOP}$ (4/18), and pG136D (2/18) (*Figure 1*). Most mutations occurred in exon 2 of the *CDKN2A* gene. The LCN coefficients ranged from 0.10–0.70 (mean: 0.49). We also collected the data of 173 *CDKN2A* wild-type NSCLC patients treated with ICIs. The basic information of all the patients is set out in *Table 1*. In general, all the patients including those with *CDKN2A* LOF NSCLC and *CDKN2A* wild-type NSCLC, were stage IV at the time of the initial treatment. In terms of their pathologic histology, most patients had ADC, and less than 20% had SCC. Most of these patients were prescribed ICIs as their first-line treatment concurrently, with or without chemotherapy, or targeted therapy, such as anti-angiogenic therapy. The ICI regimens included pembrolizumab, nivolumab, sintilimab, toripalimab, tislelizumab, and camrelizumab. Notably, no patient had more than 50% PD-L1 expression in the *CDKN2A* LOF group, and only 4 of the 173 patients (2%) had more than 50% PD-L1 expression in the *CDKN2A* wild-type group. However, 10% (5/49) of the patients in the *CDKN2A* LOF group had a high tumor mutation burden (TMB-H), and the ratio was the same in the wild-type group.

Effects of ICI in NSCLC patients with CDKN2A LOF

In our 49 *CDKN2A* LOF NSCLC patients, there are 18 mutations and 31 LCNs. First, we tested $p16^{INK4A}$ expression, which is the predominant transcription and

Table 1 Basic information of the *CDKN2A* LOF and *CDKN2A* wild-type patients

Characteristics	*CDKN2A* LOF (n=49)	*CDKN2A* wild type (n=173)	P value
Age (years)	62 [41–69]	64 [39–73]	0.71
Gender			0.41
Male	31	98	
Female	18	75	
Histology			0.29
ADC	42	139	
SCC	6	31	
Other	1	3	
ECOG before ICI			0.65
>2	4	11	
≤2	45	162	
Smoking history	29	93	0.50
Combined therapy	47	169	0.50
TMB-H	5	19	0.88
PD-L1			0.35
≥50%	0	4	
≥1%, <50%	15	39	
<1%	34	130	
First-line ICI	38	142	0.47

CDKN2A, cyclin-dependent kinase inhibitor 2A; LOF, loss of function; ADC, adenocarcinoma; SCC, squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; ICI, immune check inhibitor; TMB-H, high tumor mutation burden; PD-L1, programmed death ligand 1.

translation protein of the *CDKN2A* gene, in all the patients (*Figure 2A*). As expected, the IHC and IF staining results showed that most *CDKN2A* LOF patients (36/49) were $p16^{INK4A}$ negative. Conversely, most *CDKN2A* wild-type patients (129/173) were $p16^{INK4A}$ positive (P<0.001) (*Figure 2B*). Additionally, $p16^{INK4A}$ was expressed in both the cytoplasm and nucleus in the *CDKN2A* wild-type group.

We then examined the effects of immunotherapy in the *CDKN2A* LOF group (*Figure 2C*). In total, five patients achieved partial response (PR), 35 achieved stable disease (SD), and nine had progressive disease (PD) after the first evaluation after ICI therapy (*Figure 2D*). Specifically, in one SCC patient with both *CDKN2A* $pR80^{STOP}$ and TMB-H, ICI worked effectively for 3 years as a second-line therapy after first-line concurrent radio-chemotherapy. Additionally, one patient was prescribed ICI therapy combined with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor as a second-line therapy, which worked effectively for about 10 months. However, there were also nine PD patients after 2 to 3 months of first-line ICI therapy, one of whom had super PD and died shortly into the 3rd month after receiving the first dose of ICI. Taken together, though these results indicated that *CDKN2A* might promote PD when the patients are treated with immunotherapy, *CDKN2A* might also work effectively in selective NSCLC patients treated with ICI.

Clinical outcomes of CDKN2A LOF compared to CDKN2A wild type in NSCLC patients treated with ICI

We also sought to examine the effects of ICI therapy in the *CDKN2A* LOF group compared to the *CDKN2A* wild-type group. Using the Kaplan-Meier method, we determined that the median PFS of the LOF group was 4.67 months,

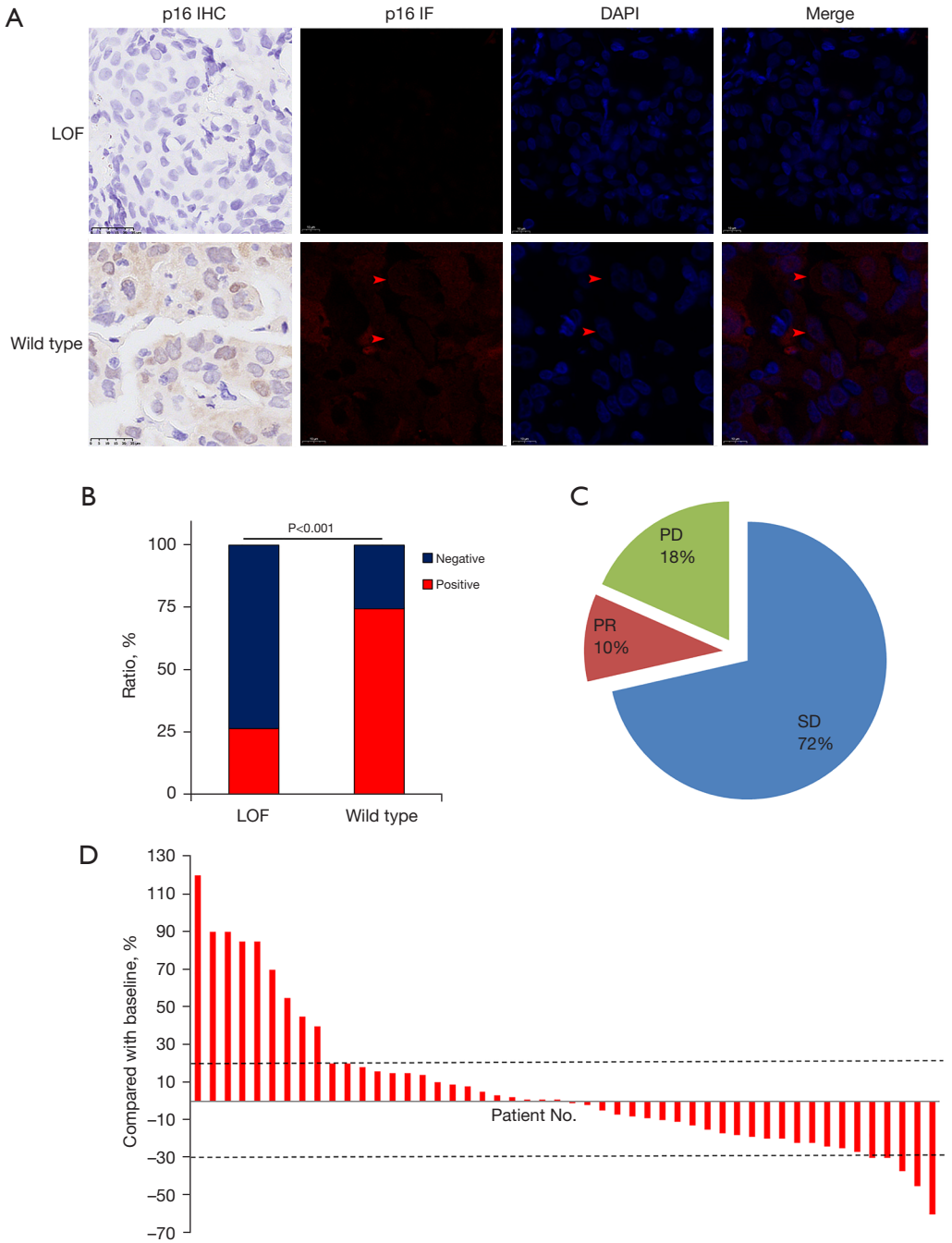

Figure 2 Relationship between *CDKN2A* LOF and immunotherapy. (A) Representative image of p16 IHC and IF staining in *CDKN2A* LOF and *CDKN2A* wild-type patients. The red arrows indicate p16 positive cells. (B) The ratio of p16 IHC staining in the *CDKN2A* LOF and *CDKN2A* wild-type patients. (C) The ratio of the effect of immunotherapy in the *CDKN2A* LOF patients. (D) Detailed effect of immunotherapy of every patient in the *CDKN2A* LOF group. LOF, loss of function; IHC, immunohistochemical; IF, immunofluorescent; PR, partial response; SD, stable disease; PD, progressive disease; *CDKN2A*, cyclin-dependent kinase inhibitor 2A.

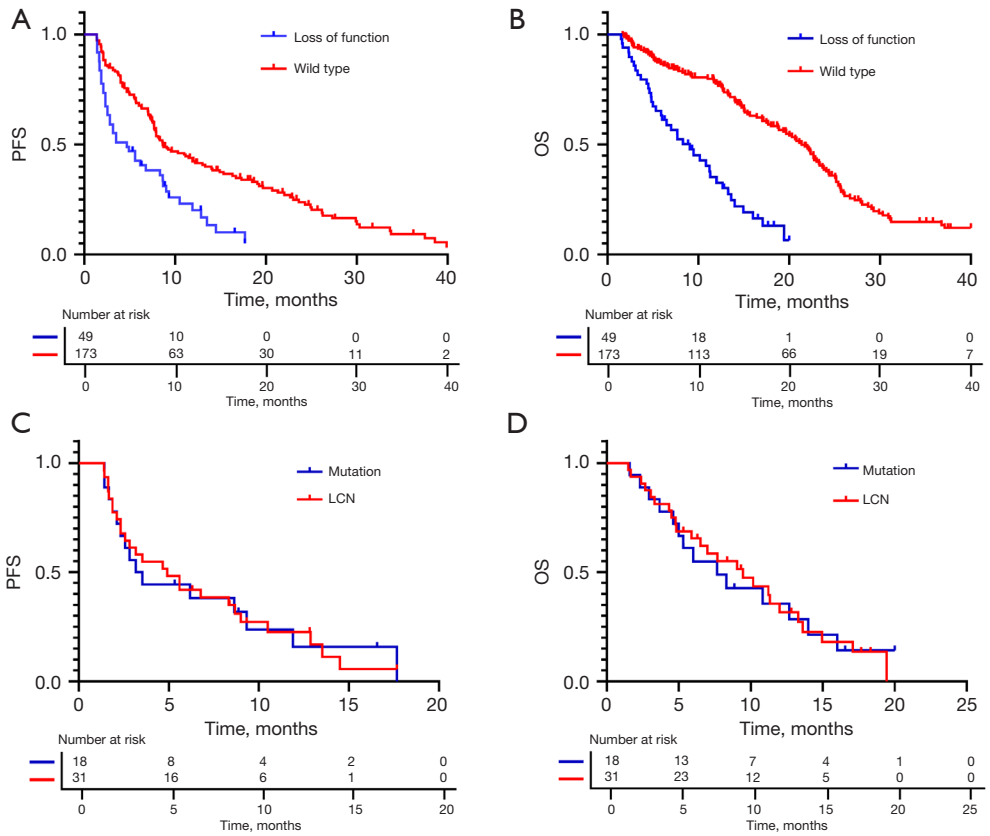

Figure 3 Kaplan-Meier curves of *CDKN2A* LOF and wild-type patients. (A) PFS curves of *CDKN2A* LOF and *CDKN2A* wild-type patients. (B) OS curves of *CDKN2A* LOF and wild-type patients. (C) PFS curves of *CDKN2A* mutation and LCN. (D) OS curves of the *CDKN2A* mutation and LCN. PFS, progression-free survival; OS, overall survival; LCN, loss of copy number; LOF, loss of function; *CDKN2A*, cyclin-dependent kinase inhibitor 2A.

while that of the wild-type group was 8.63 months [hazard ratio (HR): 0.54; 95% confidence interval (CI): 0.38–0.77; P<0.001] (*Figure 3A*). Meanwhile, *CDKN2A* LOF also had a negative effect on OS (*Figure 3B*). The median OS of the *CDKN2A* LOF group was 9.07 months and that of the *CDKN2A* wild-type group LOF was 21.37 months (HR: 0.42; 95% CI: 0.29–0.61; P<0.001). We also conducted a subgroup analysis to compare the *CDKN2A* mutation to LCN in the *CDKN2A* LOF group (*Figure 3C,3D*). As expected, there was no statistically significant difference in terms of PFS and OS between these two subgroups, which indicates that both the *CDKN2A* LCN and mutation may exert the same function in immunotherapy in NSCLC.

Discussion

In our study, *CDKN2A* LOF was common in the NSCLC patients, and the *CDKN2A* LOF patients had a worse prognosis than the *CDKN2A* wild-type patients treated by ICI mono-therapy or combined therapy. However, it is still difficult to determine whether or not patients with *CDKN2A* LOF are suitable for ICI, as the results also suggested that some selective patients in the LOF group could have PR or achieve SD following ICI treatment.

CDKN2A is a well-known tumor suppressor gene, and it is a very common alteration, second only to that of tumor suppressor protein 53 (*P53*) in all cancers (6). *CDKN2A* LOF is associated with most common tumors, including breast cancer, colorectal cancer, and melanoma (11-13). It has been reported that the *CDKN2A* germline mutation could work as a driving gene in melanoma (such as pM53I and pS56I) (14), and breast cancer (such as pA148T) (15). *CDKN2A* LOF is also one of the most frequent alterations in NSCLC. *CDKN2A* LOF has been reported in up to 10% of ADC patients and more than 20% of SCC patients (4,5). In patients with the *EGFR* mutation, *CDKN2A* LOF

could also work as a secondary resistance mechanism to TKIs (16). However, until now, there was no evidence to suggest that *CDKN2A* could work as a driving gene in NSCLC, especially in ADC. Interestingly, *CDKN2A* LOF was shown to drive small cell lung cancer tumorigenesis in a mouse model (17).

CDKN2A can transcribe and then translate to both $p16^{INK4A}$ and $p14^{ARF}$; the former is predominant, mainly works in the G1/S phase, and inhibits CDK4/6 and then causes cell cycle arrest (6). CDK4/6 inhibitors, such as palbociclib and abemaciclib, have been widely and successfully used to treat hormone positive late-stage breast cancer patients. Many clinical trials have used CDK4/6 inhibitors in NSCLC patients with *CDKN2A* LOF. In a phase II clinical trial, 29 patients with *CDKN2A* LOF received palbociclib; these patients had a medium PFS of 8.1 weeks, and one achieved a PR and six achieved SD (18). However, the CDK4/6 inhibitor single regimen has only been shown to have limited effects in treating NSCLC. It has been reported that CDK4/6 inhibitors up-regulate PD-L1 expression and promote $CD8^+$ T cell memory formation (19). A clinical trial is being conducted that combines ICI therapy with the CDK4/6 inhibitor (20) (NCT02079636); however, the results of that study have yet to be published. In one of our patients, the single CDK4/6 inhibitor did not work initially, but later worked effectively when combined with ICI therapy for about 10 months.

Due to the results to date, controversy remains as to whether ICI should be prescribed to patients with *CDKN2A* LOF. In one study, ICI therapy improved the prognosis of melanoma patients with the germline or somatic *CDKN2A* mutation, compared to those with *CDKN2A* wild-type melanoma, with 6 out of the 19 patients achieving a complete response (21). However, a study by the American Society of Clinical Oncology in 2019, which included only 20 patients, reported that *CDKN2A* LOF could act as a potential molecular signature for hyper-PD in advanced NSCLC, meaning that *CDKN2A* could directly cause super PD (22). However, no additional data have been collected to confirm this conclusion.

In our *CDKN2A* LOF patients, 40 of 49 achieved disease control by immunotherapy (five achieved a PR and 35 achieved SD); however, 9 of the 49 patients had PD, and one patient had super PD. However, this evidence does not directly prove that *CDKN2A* directly causes PD or even super PD. Another study reported that *CDKN2A* LOF is one of the reasons NSCLC patients become resistant to ICI (10). However, in that study, the authors only compared *CDKN2A* LOF to *CDKN2A* wild-type patients undergoing ICI treatment, and the authors did not directly compare the usage of ICI with no ICI inside *CDKN2A* LOF patients. A cohort study of six kinds of solid tumors reported that *CDKN2A* LOF had no relationship with the effectiveness of ICI therapy in NSCLC (9). In our study, ICI therapy achieved a better effect in the *CDKN2A* wild-type group than the LOF group; however, ICI therapy also worked effectively in the LOF group, with most of the patients achieving disease control at the time of their first evaluation of ICI. Based on our data, it is difficult to determine whether *CDKN2A* is a resistance mechanism or even promotes super PD in patients receiving ICI treatments.

This study had some limitations. First, it lacked a head-to-head comparison of treatment with ICI or no ICI inside *CDKN2A* LOF patients. This is the direct evidence to show the effect of ICI on *CDKN2A* LOF patients. Second, because some patients achieved a PR or SD following ICI therapy in the *CDKN2A* LOF group, it is necessary to identify which patients are suitable for ICI among the *CDKN2A* LOF patients. Third, while our data demonstrates that the *CDKN2A* mutation functions the same as the *CDKN2A* LCN, our study only collected the data of 18 *CDKN2A* mutations, which limits the interpretation of our entire results.

Conclusions

This study demonstrated that ICIs function less effectively in *CDKN2A* LOF than *CDKN2A* wild-type NSCLC patients. However, it is still difficult to determine whether or not patients with *CDKN2A* LOF are suitable for ICI, as our findings also suggest that ICI could work quite effectively in selective *CDKN2A* LOF patients.

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Footnote

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Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1017/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Tongji Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology (No. TJ-IRB20231236). Written informed consent for the use of all clinical data was provided by patients or their direct relatives.

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