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Nivolumab plus ipilimumab for elderly Chinese patients with advanced non-small cell lung cancer

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Abstract

Background

Elderly Chinese patients with advanced non-small cell lung cancer (NSCLC) often refuse chemotherapy due to the risk of intolerable grade 3–4 adverse events. This study aimed to evaluate the efficacy and safety of nivolumab plus ipilimumab in elderly patients with advanced NSCLC.

Methods

We retrospectively analyzed data from elderly patients with advanced NSCLC treated with nivolumab plus ipilimumab as initial or second-line therapy between May 2022 and December 2023 at The Tenth Affiliated Hospital, Southern Medical University, China. Tumor response and treatment toxicities were assessed based on the Response Evaluation Criteria in Solid Tumors version 1.1 criteria and National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Results

A total of 5 elderly patients were included, with a median age of 82 years. All patients received nivolumab plus ipilimumab until disease progression, unacceptable toxicity, or unwillingness to continue treatment. The objective response rate (ORR) and disease control rate (DCR) were both 100%, and the median progression-free survival (PFS) was not reached. Treatment-related adverse events were generally mild, with the most common being pruritus (80%), rash (40%), and fatigue (40%). No grade 3 or higher toxicities were observed.

Conclusions

Nivolumab plus ipilimumab may provide durable ORR in elderly Chinese patients with advanced NSCLC, regardless of PD-L1 expression, with generally tolerable toxicities compared to standard chemotherapy.

Introduction

Lung cancer remains one of the most prevalent and deadly cancers worldwide, particularly in elderly populations. It is the leading cause of cancer-related deaths, with non-small cell lung cancer (NSCLC) accounting for approximately 80–85% of all cases [1]. While significant progress has been made in the treatment of NSCLC, survival outcomes for advanced-stage disease remain poor, especially for elderly patients who often present with coexisting health conditions and are underrepresented in clinical trials. Historically, chemotherapy has been the mainstay of treatment for advanced NSCLC, but it provides limited long-term survival benefits, particularly for elderly patients.

Recent advancements in immunotherapy, particularly immune checkpoint inhibitors (ICIs), have transformed the treatment landscape for advanced NSCLC. Drugs targeting the programmed cell death protein 1 (PD-1) and programmed cell death protein-ligand 1 (PD-L1) pathway have demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) of NSCLC compared to chemotherapy [2, 3]. In several pivotal phase III trials, such as CheckMate 017 and CheckMate 057 study, nivolumab has been shown to provide superior PFS and OS in patients with advanced NSCLC, including those patients aged 65 years and older [4–6].

In particular, nivolumab plus ipilimumab, a combination therapy targeting both PD-1 and cytotoxic T-lymphocyte antigen-4 (CTLA-4), has demonstrated enhanced efficacy in various cancer types, including NSCLC [7]. The CheckMate 227 trial, which evaluated nivolumab plus ipilimumab in a first-line setting, reported significant improvements in OS compared to chemotherapy, with 5-year survival rates of 24% in patients with PD-L1 expression ≥ 1% [8]. These benefits were observed regardless of PD-L1 status, with long-term durable responses being achieved, even in patients who discontinued treatment due to adverse events [9]. Importantly, this combination therapy was associated with a manageable safety profile, and immune-mediated adverse events were typically resolved with appropriate management.

However, while these findings are promising, the specific impact of nivolumab plus ipilimumab in elderly Chinese patients, particularly those aged 70 and older, remains less well-defined. Studies such as CheckMate 171 and CheckMate 153, which include elderly cohorts, showed that nivolumab-based therapies were well-tolerated in this population [10, 11]. Thus, this study aims to evaluate the efficacy and safety of nivolumab plus ipilimumab in elderly Chinese patients with advanced NSCLC, with the hypothesis that this combination will offer clinically significant benefits in terms of OS, PFS, and quality of life, similar to the outcomes observed in younger cohorts.

Methods

Patient Selection

This retrospective study included elderly patients (aged ≥65 years) with advanced NSCLC who were treated with nivolumab plus ipilimumab as either first- or second-line therapy. Eligible patients were treated between May 2022 and December 2023 at The Tenth Affiliated Hospital, Southern Medical University (Dongguan People's Hospital), China. The inclusion criteria were as follows: patients ≥60 years old; reluctant to receive chemotherapy; with histologically or cytologically confirmed stage IIIb or IV lung adenocarcinoma or squamous cell carcinoma per the International Association for the Study of Lung Cancer (IASLC) 8th edition of Tumor Node Metastasis (TNM) staging; without oncogenic driver gene mutations; with at least one measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria; with normal organ function and performance status (PS) score less than 2. The exclusion criteria were as follows: patients with small cell carcinoma or neuroendocrine carcinoma, including mixed carcinoma; harboring oncogenic driver gene mutations; with carcinomatous meningitis, spinal cord compression; pregnant or breastfeeding women; with any other uncured active malignancies,

excluding cases of cured basal cell carcinoma, cervical carcinoma in situ, or superficial bladder cancer; with a condition that the investigator deemed to potentially interfere with the conduct or outcome of the study.

Treatment Schedule

This retrospective study was conducted in accordance with the Declaration of Helsinki. Elderly NSCLC patients were treated with nivolumab (3mg/kg, Q2W) plus ipilimumab (1mg/kg, Q6W), with dose adjustments made based on clinical assessments. Treatment was administered until disease progression, the occurrence of unacceptable toxicity, or voluntary discontinuation by the patient. Patient responses were evaluated according to RECIST v1.1. Toxicities were recorded and categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Data Collection

The clinical data of patients were recorded carefully at baseline. Additionally, tumor responses were evaluated based on the RECIST criteria, where objective response rate (ORR) was defined as the rate of complete response (CR) and partial response (PR). Disease control rate (DCR) was defined as the rate of CR, PR and stable disease (SD) without progression. PFS was defined as the time from the initiation therapy to either disease progression or death, with patients who were alive and without progression at the time of the last follow-up being censored. The relationship between toxicities and the administered treatment was assessed. Throughout the study period, all clinical data were meticulously monitored to ensure accuracy and completeness. The final follow-up date for this study was March 27, 2024.

Statistical Analysis

Descriptive statistics were used to analyze baseline characteristics and response rates. The incidence of toxicity was summarized based on recorded adverse events. All statistical analyses were performed using SPSS version 25 (IBM Corp, Armonk, NY, USA).

Results

Baseline Characteristics and Treatment

This study evaluates the clinical outcomes of nivolumab plus ipilimumab in elderly Chinese patients with advanced NSCLC. The median age of the cohort was 83 years, ranging from 62 to 84 years. Smoking history was present in four of the five patients, while one patient was a non-smoker. All participants had a performance status (PS) score of 1, indicating they were fully active with only mild disease-related symptoms. Regarding histology, four patients had squamous cell carcinoma (SQC) and one had adenocarcinoma (ADC). Disease staging varied, with two patients diagnosed with stage IVB, one with stage IVA, one with stage IIIB, and one with stage IV. PD-L1 expression was assessed, revealing that four patients had negative PD-L1 expression, and one had 75% PD-L1 expression. Gene mutations included

PIK3CA (in two patients), KRAS G12D, TP53, and RB1 (in one patient), and KRAS G12C, TP53, and CDKN2A (in one patient), while one patient had no gene mutations detected. All patients had previously received two lines of immunotherapy prior to starting nivolumab plus ipilimumab. The treatment regimen for all patients was nivolumab combined with ipilimumab, and treatment started between May 2022 and December 2023. The best response observed in all five patients was partial response (PR), demonstrating the efficacy of nivolumab plus ipilimumab in this elderly cohort with advanced NSCLC.

Efficacy

The efficacy of nivolumab plus ipilimumab in elderly Chinese patients with advanced NSCLC was evaluated in five male patients, with a median age of 82 years (range: 62–84 years). Among the cohort, three patients had squamous cell carcinoma (SQC), and two had adenocarcinoma (ADC). All patients received nivolumab plus ipilimumab, with three cases treated as first-line therapy and two as second-line therapy. PD-L1 expression was assessed in three patients, and only one patient exhibited positive expression (75%). Notably, one patient with brain metastases had undergone whole-brain radiation therapy (WBRT) prior to treatment. The ORR and DCR were both 100%, with all five patients achieving a PRas their best treatment outcome. The median PFS was not reached, indicating durable responses across the cohort. Only one patient experienced disease progression after 18.8 months of treatment, while the remaining four patients continued to show sustained responses at the last follow-up date. Treatment-related adverse events were generally mild, further supporting the tolerability of this regimen in elderly NSCLC patients. These findings underscore the potential of nivolumab plus ipilimumab as an effective and well-tolerated therapeutic option for elderly patients with advanced NSCLC, regardless of PD-L1 expression or prior lines of therapy.

Safety

The safety profile of nivolumab plus ipilimumab in elderly Chinese patients with advanced NSCLC was favorable, with treatment-related adverse events generally mild and manageable. The most common toxicities observed were pruritus (80%), rash (40%), and fatigue (40%). Other adverse events included hypothyroidism, decreased appetite, insomnia, anemia, leukopenia, and elevated creatinine, each occurring in one patient during the treatment period. Importantly, none of the patients experienced grade 3 or higher toxicities, indicating that the regimen was well-tolerated in this population. This safety data suggests that nivolumab plus ipilimumab can be administered effectively in elderly NSCLC patients without significant risk of severe adverse events, supporting its use as a viable therapeutic option for this challenging demographic.

Discussion

Previous study investigated the clinical outcomes and toxicities of ICI monotherapy for elderly cancer patients. In 2021, data on the clinical efficacy and toxicity analysis were released [12]. A total of 928 elderly cancer patients aged 80 and above were screened from 18 international centers between 2010 and 2019. Patients received monotherapy with PD-1 antibody therapy (86.9%), PD-L1 antibody therapy

(8.5%), and CTLA-4 antibody therapy (4.6%), respectively. There were 345 cases of NSCLC. The results showed that the ORRs for these patients were 32.2%. The median PFS and OS were 6.7 and 10.9 months, respectively. The results also showed that ICI monotherapy was effective in patients aged 85 years, 85–89 years, and ≥ 90 years in NSCLC patients, with no significant difference in efficacy among different age groups.

The use of dual ICIs, specifically combining nivolumab with ipilimumab, has shown significant promise in improving OS and PFS in advanced NSCLC. However, the clinical outcomes and toxicities of nivolumab with ipilimumab for elderly Chinese patients still need to be clarified. Our study demonstrates that nivolumab plus ipilimumab offers a promising therapeutic strategy for elderly Chinese patients with advanced NSCLC, achieving a 100% ORR and DCR without severe adverse events. These findings highlight the potential of dual immune checkpoint inhibition to provide durable clinical benefits in this challenging population. Compared to the CheckMate 227 trial, which showed improved OS with nivolumab plus ipilimumab over chemotherapy in patients with metastatic NSCLC, our study observed higher ORR and DCR in elderly Chinese patients. This difference may be attributed to variations in patient selection criteria and treatment protocols. Notably, our study found that PD-L1 expression did not significantly impact treatment outcomes, suggesting that this combination therapy could be beneficial regardless of PD-L1 status.

However, the impact of immunosenescence, which refers to the decline in immune system function with age, remains a significant concern regarding the efficacy and safety of immune checkpoint inhibitors. Older adults are particularly vulnerable to immune-related adverse events (irAEs) due to age-related changes in the immune system, including a reduced ability to mount effective immune responses [13]. It is thought that while the combination of nivolumab and ipilimumab has been associated with durable responses, elderly patients, especially those over 75, may experience a diminished benefit due to immunosenescence. Nevertheless, our study suggests that while nivolumab plus ipilimumab is well tolerated in elderly Chinese patients, treatment-related adverse events were generally mild, with no grade 3 or higher toxicities observed.

The clinical significance of our findings lies in the potential of nivolumab plus ipilimumab as a viable treatment option for elderly Chinese patients who may not be suitable candidates for chemotherapy. The favorable safety profile observed in this study, with no severe toxicities, supports the use of this combination therapy in elderly NSCLC patients, particularly for those who are frail or have comorbid conditions that preclude the use of more aggressive treatments. Notably, the durable clinical responses seen in our cohort suggest that this regimen could be a better alternative to chemotherapy, which often presents a higher risk of severe side effects in older patients.

However, our study has several limitations. The small sample size and retrospective design limit the generalizability of the results. Furthermore, the short follow-up period prevents a comprehensive assessment of long-term survival outcomes and late-onset adverse events. The lack of a control group also hinders our ability to directly compare the efficacy and safety of nivolumab plus ipilimumab to other

treatment regimens. Future prospective, randomized clinical trials with larger cohorts and extended follow-up are needed to confirm these findings and provide more robust data on the long-term efficacy and safety of dual immune checkpoint inhibition in elderly Chinese patients with advanced NSCLC.

In conclusion, our study adds to the growing body of evidence supporting the use of nivolumab plus ipilimumab in elderly Chinese patients with advanced NSCLC. The combination therapy appears to offer durable responses with a manageable safety profile, making it a promising treatment option for elderly patients who are unable to tolerate traditional chemotherapy. However, further studies, including those that incorporate comprehensive geriatric assessments, are necessary to optimize treatment strategies and better understand the role of immunotherapy in this challenging patient population.

Abbreviations

NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; PFS, progression-free survival; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein-ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen-4; ORR, objective response rate; CR, complete remission; PR, partial remission; IASLC, International Association for the Study of Lung Cancer (IASLC); TNM, Tumor Node Metastasis; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PS, performance status; SQC, squamous cell carcinoma; ADC, adenocarcinoma; WBRT, whole-brain radiation therapy; irAEs, immune-related adverse events.

Declarations

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Author Contributions

KJL, LXH and SYC conducted the experiment and participated in drafting and revising the manuscript. SYC did the statistical work. ZHL and JJ designed and supervised the process of whole study. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work presented in the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of The Tenth Affiliated Hospital, Southern Medical University (Dongguan People's Hospital) was conducted according to the Declaration of Helsinki. All patients provided informed written consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Clinical trial number

Not applicable.

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Table

Table 1 Clinicopathologic characteristics of NSCLC patients treated with nivolumab plus ipilimumab.

Patient ID	P1	P2	P3	P4	P5
Sex	Male	Male	Male	Male	Male
Age (Years)	83	62	84	82	75
Smoking	No	Yes	Yes	Yes	Yes
PS score	1	1	1	1	1
Pathology	SQC	ADC	SQC	SQC	ADC
Stage	□B	□A	□B	IVA	IVB
PD-L1 expression	Negative	Negative	2%	Negative	75%
Gene mutation	PIK3CA	KRAS G12D□ TP53□RB1	None	PIK3CA□TP53□ CDKN1A	KRAS G12C□TP53□ CDKN2A
Lines of treatment	2	2	1	1	1

Abbreviations: PS, performance status; SQC, squamous cell carcinoma; ADC, adenocarcinoma; PD-L1, programmed cell death protein-ligand 1.

Figures

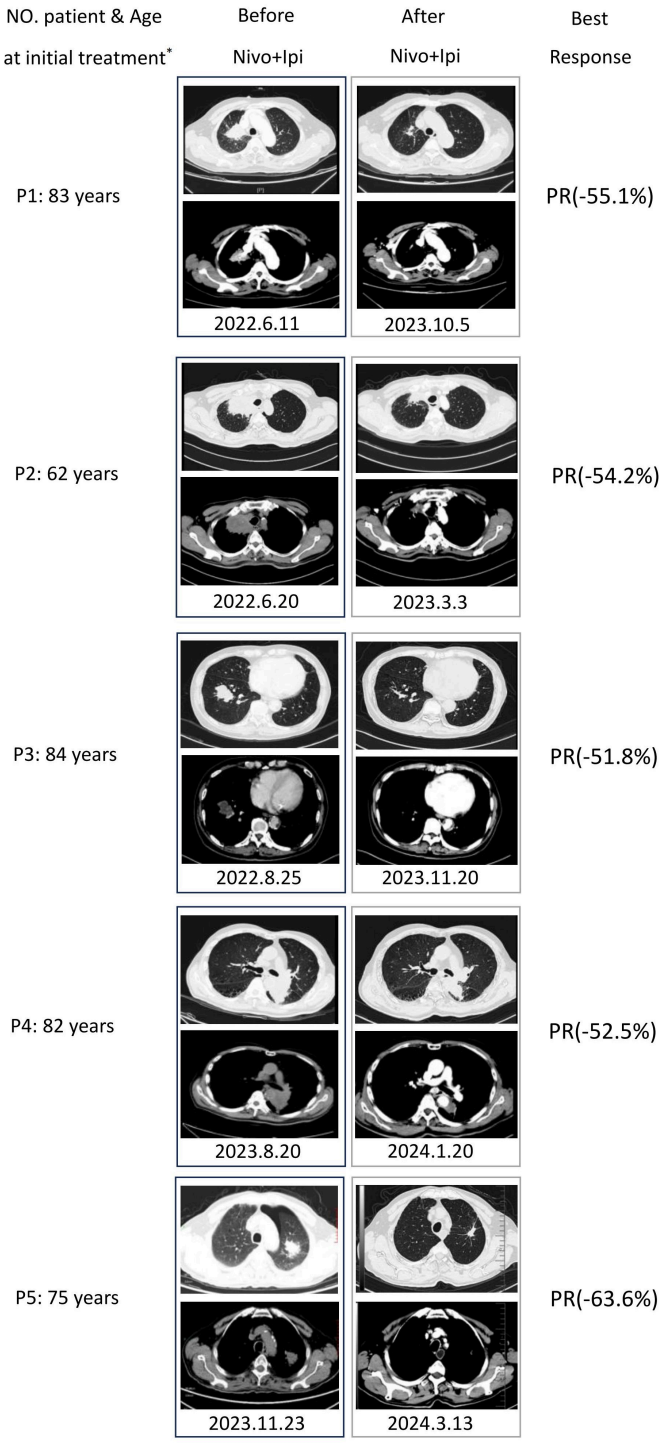


Figure 1

The efficacy of nivolumab plus ipilimumab in elderly Chinese patients.

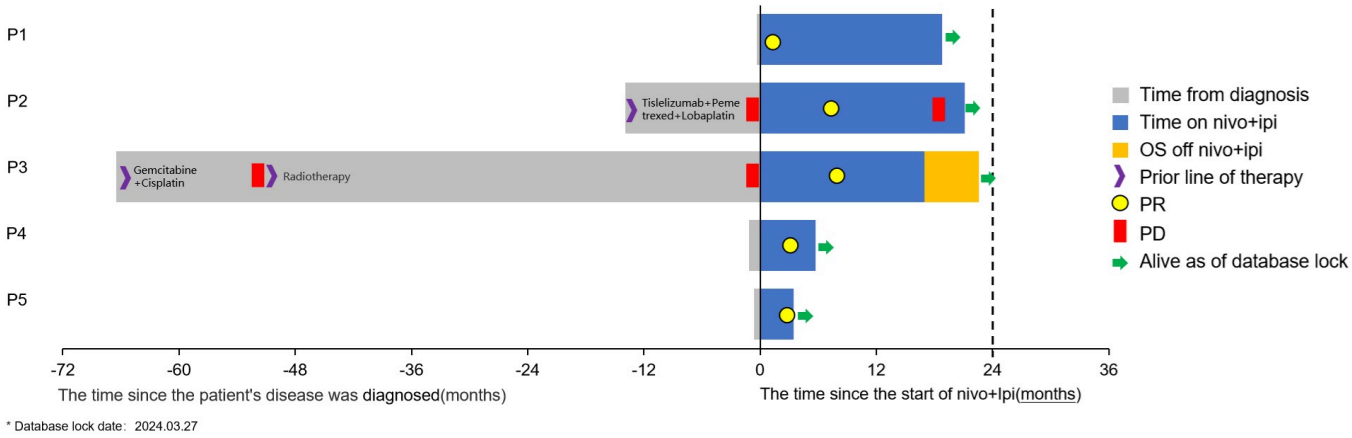


Figure 2

Treatment duration of of nivolumab plus ipilimumab in elderly Chinese patients.