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ORIGINAL RESEARCH

Efficacy and Safety of the PD-1 Inhibitor Combined with Albumin-Bound Paclitaxel and Nedaplatin in Preoperative Neoadjuvant Therapy of Unresectable Stage III Lung Squamous Cell Carcinoma

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Aim: To investigate the efficacy and safety of preoperative neoadjuvant therapy (PD-1 inhibitor plus nab-PTX and nedaplatin) for resectable stage III lung squamous cell carcinoma (SCC) patients.

Methods: Patients with locally advanced lung SCC (stage IIIA, IIIB) who received PD-1 inhibitor combined with nab-PTX and NED between February 2019 and June 2021 in Weihai Municipal Hospital were included and underwent surgical treatment 4 weeks after 2–4 cycles neoadjuvant therapy. The rate of resection R0, the effective rate, the complete pathological remission rate (pCR) and the rate of major pathological remission (MPR) were observed.

Results: A total of 14 initially unresectable male patients with lung SCC were included and received neoadjuvant treatment after evaluation. Nine out of 14 patients (64.3%) experienced treatment-related adverse events (TRAE), among which 8 (57.1%) experienced grade (G) I–II TRAEs including nausea, vomiting, fatigue, constipation, elevated ALT and AST, hyperthyroidism, hypothyroidism, rash, granulocytopenia, and thrombocytopenia, and 1 (7.1%) experienced grade III–V TRAEs (G), including granulocytopenia and atelectasis. Thirteen patients (92.86%) achieved RECIST-assessed partial remission (PR), while 1 patient (7.14%) achieved stable disease (SD) on imaging assessment after neoadjuvant treatment and continued to be progression-free for 26 months. Of the 11 patients who underwent resection, all were alive and recurrence/progression-free. MPR and pCR were observed in 2 (18.18%) and 9 (81.82%), respectively. IHC results exhibited that all NSCLC patients exhibited positive PD-L1 expression (9/14, TPS ≥50% or greater; 5/14, 1% < TPS < 50%). Two were negative for ALK, EGFR, and ros-1, and the rest were not examined for driver oncogene mutation.

Conclusion: The neoadjuvant therapy of the PD-1 inhibitor combined with nab-PTX and NED demonstrated remarkable therapeutic efficacy and good safety on stage III lung SCC without increasing the risk of TRAE, mortality and surgery-related complications, or impede surgery feasibility.

Keywords: lung squamous cell lung cancer, neoadjuvant therapy, immunotherapy, complete pathological remission, pCR, major pathological remission, MPR

Introduction

Lung cancer is one of the most common malignancies and has the highest rate of cancer-related death.[1] Approximately 1.5 million new cases of lung cancer are diagnosed annually worldwide, of which approximately 80–85% are non-small-cell lung cancers (NSCLCs).[2,3] Surgery is considered the ideal option for treatment, but only about 20–25% of NSCLCs are suitable for potentially curative resection, the majority of which were at stage I–IIIA and only a few were at stage III B.[4–6] NSCLC has several types of pathologies, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, etc., among which lung squamous

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cell carcinoma is the second common subtype of NSCLC, accounting for approximately 20–30% of NSCLC and exhibiting distinctive histological and genetic characteristics. Surgical resection is often difficult, especially for stage III lesions. Neoadjuvant therapy is a promising approach to increase the chance of curative rates and improve long-term survival for patients with locally advanced-stage lung squamous cell carcinoma. It has been applied before surgery to achieve the purpose of tumor regression, increased ratio of R0 resection, and elimination of micrometastases, which finally benefits patient overall survival. Since nivolumab, the first immune checkpoint inhibitor (ICI), was approved as a second-line treatment in China for NSCLC in 2018, ICIs have played an increasingly important role in the treatment of NSCLCs without driver gene mutations.[7] ICIs alone or in combination with chemotherapy have become the standard regimen for first-line, second-line, and post-line treatment of NSCLCs.[8–12] Recently, neoadjuvant treatment for locally advanced lung squamous cell carcinoma with immunochemotherapy has been explored. In this study, our objective was to explore the feasibility and safety of the programmed cell death 1 (PD-1) inhibitor combined with nanoparticle albumin-bound paclitaxel (nab-PTX) and nedaplatin (NED) in preoperative neoadjuvant therapy for patients with unresectable stage III lung squamous cell carcinoma.

Patients and Methods

Patient Selection and Study Design

It was a single-centered retrospective study conducted at Weihai Municipal Hospital between February 2019 and June 2021. The inclusion criteria of the patients were as follows: 1) Patients with locally advanced-stage IIIA-B histologically confirmed (as defined by the eighth edition of the American Joint Committee on Cancer Tumor Node Metastases) lung squamous cell carcinoma; 2) Patients with chemotherapy naïve; 3) Patients >18 and <75 years old; 4) Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2; 5) Patients with normal organ function and adequate lung function for resection. Exclusion criteria included 1) patients with active autoimmune disease; 2) patients with ongoing systemic steroids (>10 mg daily equivalents of prednisone) or other immunosuppressive therapy; 3) patients with active concurrent malignancy; 4) patients with a history of symptomatic interstitial lung disease; 5) patients with preoperative chemotherapy and any previous PD-1 treatment.

This study protocol was approved by the Ethics Committee of the Weihai Municipal Hospital and followed the guidelines outlined in the Declaration of Helsinki. All patients also gave their written informed consent for this study.

Treatment Protocol

Neoadjuvant treatment consisted of PD-1 inhibitors combined with nab-PTX and NED. Pabolizumab (200 mg), cindilimab (200 mg), tirelizumab (200 mg) and carrelizumab (200 mg) were administered every 3 weeks for 1, 7, 3, and 3 patients, respectively. Besides, nab-PTX (260 mg/m^2) was administered on day 1 and 8, and NED (75 mg/m^2) was administered on day 1–2 or day 1–3 through intravenous infusion every 3 weeks. Three weeks was named a cycle. The treatment regimen was repeated for 2–4 cycles and continued until disease progression, the development of unacceptable adverse events, or the request of the patients to stop treatment. Lesions were evaluated every 2 cycles according to the results of imaging. Surgical treatment was performed 4 weeks after 2–4 cycles of treatments.

The primary endpoints were the efficacy and safety of the PD-1 inhibitors combined with nab-PTX and NED. Specifically, efficacy was defined by the resection rate R0, the effective rate, the complete pathological remission rate (pCR), and the rate of major pathological remission (MPR). Safety was defined by treatment-related adverse events (TRAE) according to common terminology criteria for adverse events (CTCAE) V.4.0.[13]

Study Evaluation

Before enrollment in the study, all patients underwent appropriate cancer staging, including pathologic assessment of mediastinal lymph nodes, as well as baseline contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) or PET-CT of the brain and chest. Mandatory pretreatment primary tumor core biopsy was performed. Repeat imaging was obtained 7 days before surgery to assess radiographic response to neoadjuvant therapy and reaffirm resectability. After neoadjuvant treatment, the radiographic response was assessed according to the Response Evaluation Criteria for Solid Tumors (RECIST)

Table 1 Baseline Demographics

Patient Number	Age (Years)	Gender	Smoking History (Cigarettes/Day)	Histology	Pre-Treatment
1	58	Male	Never	SCC	IIIA
2	62	Male	40 years, 20	SCC	IIIA
3	67	Male	20 years, 20	SCC	IIIB
4	59	Male	40 years, 20	SCC	IIIB
5	57	Male	Never	SCC	IIIB
6	57	Male	30 years, 40	SCC	IIIA
7	62	Male	40 years, 40	SCC	IIIA
8	70	Male	30 years, 20	SCC	IIIA
9	69	Male	40 years, 30	SCC	IIIB
10	66	Male	20 years, 40	SCC	IIIB
11	58	Male	30 years, 40	SCC	IIIA
12	62	Male	30 years, 10	SCC	IIIB
13	57	Male	20 years, 30	SCC	IIIB
14	57	Male	30 years, 40	SCC	IIIB

Abbreviation: SCC, squamous cell carcinoma.

(version 1.1.7). Resected primary tumors were evaluated for residual viable tumor on routine H&E-stained slides by attending pathologists.

Statistical Analysis

All data were analyzed with a cutoff date of June 2021. Data on demographical characteristics, efficacy, and safety were described and tabulated.

Results

Baseline Characteristics of the Patients

A total of 14 patients with locally advanced lung squamous cell carcinoma treated in the department of Oncology of Weihai Municipal Hospital from February 2019 to June 2021 were included in this study. All the 14 patients were male, with a median age of 68 years old (Table 1). After evaluation, lung squamous cell carcinoma in all 14 patients was not resectable prior to neoadjuvant treatment. Of the 14 patients, 6 had single-station mediastinal lymph node metastasis, 4 had multi-station lymph node metastasis, and 5 with lymph node fusion greater than 2 cm. According to the eighth classification of TNM, the stage T4 was determined in 5 patients with invasion of the pulmonary artery and 1 patient with invasion of the vertebral body. The functions of the liver and kidney, blood routine, and ECG were normal in all patients, with ECOG-PS $\leq$2.

Safety and Efficacy

Of all the 14 patients after the neoadjuvant treatment, 13 (92.9%) achieved radiographic partial remission; 11 (78.6%) underwent surgical treatment; 2 (14.3%) were still not suitable for surgical treatment after evaluation; 1 (7.1%) was suitable for surgical treatment after evaluation yet refused surgical treatment (Table 2). No patient discontinued study treatment due to TRAE. However, 9 out of 14 patients (64.3%) experienced TRAE, among which 8 (57.1%) experienced grade (G) I–II TRAEs including nausea, vomiting, fatigue, constipation, elevated ALT and AST, hyperthyroidism, hypothyroidism, rash, granulocytopenia, and thrombocytopenia, and 1 (7.1%) experienced grade III–V TRAE (G), including granulocytopenia and atelectasis (Table 3). Of the 11 patients who underwent surgical treatment, 1 experienced repeated atelectasis after pulmonary arterioplasty and 10 had no surgical complications. Immune-related adverse reactions included hypothyroidism in 1 patient and rash in 1 patient (Table 3). Of the 11 patients who underwent R0 resection, all were alive and without recurrence/progression at present (Figure 1).

Table 2 Radiographic, Pathologic and Molecular Response Characteristics

Patient Number	Radiographic Response	Pathologic Response	PD-L1 Expression Before Treatment (TPS %)
1	PR	pCR	50
2	PR	pCR	40
3	PR	pCR	90
4	PR	MPR	5
5	PR	pCR	90
6	PR	pCR	80
7	PR	pCR	90
8	PR	MPR	15
9	PR	pCR	80
10	PR	pCR	90
11	PR	pCR	50
12	PR	N/A	90
13	SD	N/A	2
14	PR	N/A	15

Abbreviations: PR, partial response; pCR, complete pathological response; MPR, major pathological remission; SD, stable disease; N/A, not applicable, TPS, tumor cell proportion score.

Table 3 Treatment-Related Adverse Events (TRAEs) (n = 14)

Toxicity	Grade I–II n (%)	Grade III–V n (%)
Nausea	6 (42.9)	0
Vomiting	2 (14.3)	0
Fatigue	5 (35.7)	0
Constipation	4 (28.6)	0
Elevated ALT	1 (7.1)	0
Elevated AST	1 (7.1)	0
Hyperthyroidism	1 (7.1)	0
Hypothyroidism	2 (14.3)	0
Rash	1 (7.1)	0
Granulocytopenia	3 (21.4)	1 (7.1)
Thrombocytopenia	1 (7.1)	0
Atelectasis	0	1 (7.1)

Genomic Analyzes and Pathological Evaluation

Of the 14 patients, 2 were negative for ALK, EGFR, and ros-1, and 12 were not tested for driver genes. Patient 13 with stable disease assessed by RECIST was unresectable after neoadjuvant treatment and continues to be progression-free for 26 months after neoadjuvant treatment (Table 2, Figure 1). However, Patient 14 who had partial response died 13 months after neoadjuvant treatment (Figure 1). Of the 11 patients who underwent R0 resection, MPR and pCR were observed in 2 (18.18%) and 9 (81.82%), respectively. We also performed immunohistochemical staining to detect the expression of PD-L1 in pretreatment biopsy samples obtained from 14 patients. As expected, IHC results exhibited that all NSCLC patients exhibited positive PD-L1 expression (9/14, TPS $\geq$ 50% or greater; 5/14, 1% < TPS < 50%). Interestingly, complete pathological response occurred in patients (9/11) with high PD-L1 expression (TPS: range 40% to 90%), while major pathological response occurred in 2 of 11 patients (TPS, 5% and 15%). These data suggest that pre-treatment tumor PD-L1 expression was positively correlated with pathologic response (Table 2). Radiographic, pathological, and molecular response characteristics are summarized in Table 2.

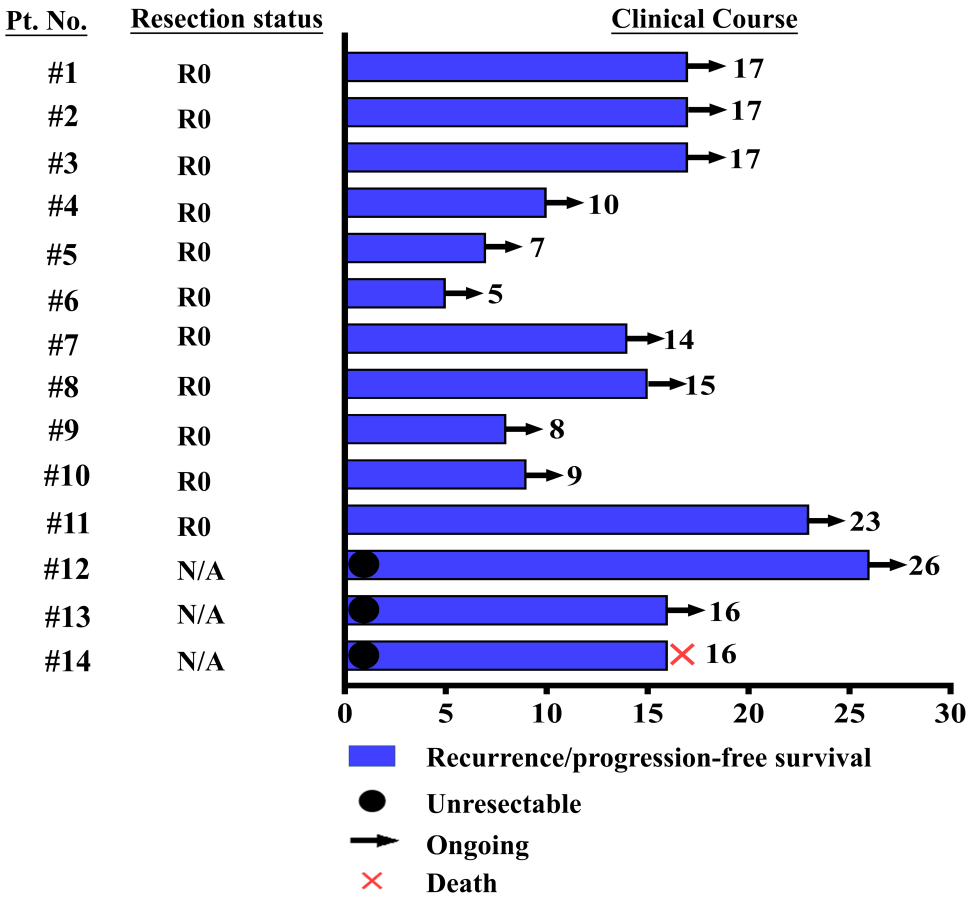

Figure 1 Swimmer-style clinical follow-up plot detailing the clinical course of all enrolled patients. Resection status is noted in the column to the right of the patient number and to the left of the clinical course outlined for that patient. R0 indicates a tumor that was radical resected. The clinical course describes the time following surgery or biopsy-confirmed primary disease progression.

Of the 14 patients, 13 (92.86%) achieved partial remission assessed with RECIST (PR), while 1 (7.14%) achieved stable disease (SD) on imaging evaluation (Table 3 and Figure 2).

Discussion

Lung squamous cell carcinoma accounts for 25–30% of NSCLC.[14] In clinical practice, resectable stage IIIA-B stage NSCLC patients are recommended to receive surgery and neoadjuvant therapy according to the NCCN and Chinese Medical Association lung cancer Diagnosis and Treatment Guidelines (2022 version). Numerous clinical evidence pointed out that neoadjuvant therapy (eg chemotherapy alone, sequential chemo-radiotherapy, concurrent chemoradiotherapy, induction chemotherapy and concurrent chemoradiotherapy, chemotherapy and concurrent targeted therapy or immunotherapy) could consider as a promising strategy for prolonging overall survival of resectable NSCLC patients and have becoming a hotly debated topic. Unfortunately, there is yet no consensus regarding the efficacy and safety of neoadjuvant therapy in resectable NSCLC patients and it still needs to be verified in a large number of lung cancer sample in future.

In this study, the ORR, PR, CR, pCR, and MPR rate of the PD-1 inhibitor combined with nab-PTX and NED in preoperative neoadjuvant therapy were 93%, 93%, 0%, 64%, and 14%, respectively, indicating good curative effects in patients with stage III lung squamous cell carcinoma. The PD-1 inhibitors involved in this study were pabolizumab, cindilizumab, tirelizumab and carrelizumab, the results of which in this study were consistent with each other. As a new paclitaxel, nab-PTX can be administered directly to patients without the pretreatment with corticosteroids and antihistamines. Compared to cisplatin, NED was similar in effective rate, but significantly fewer in side effects.[15]

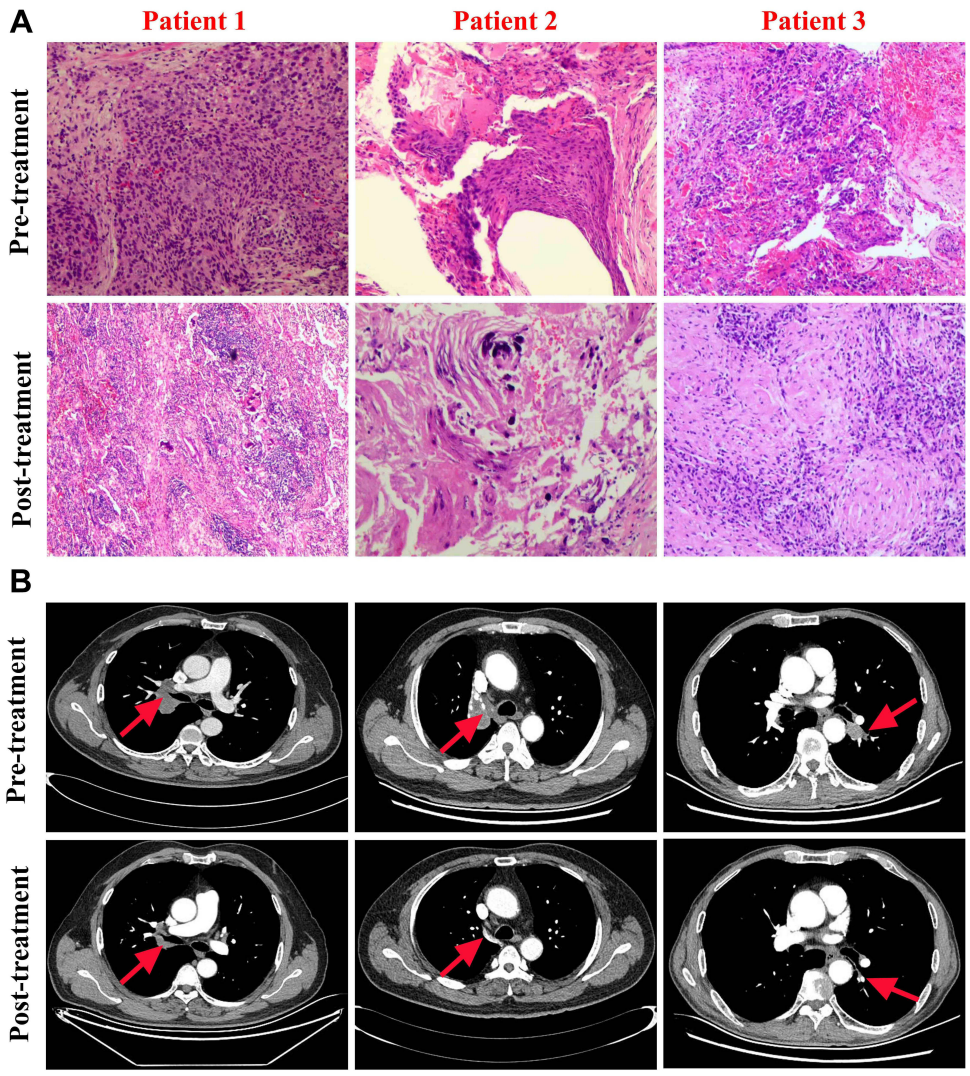

Figure 2 Pathologic (**A**) and radiographic (**B**) response to neoadjuvant therapy of the PD-1 inhibitor combined with NED and nab-PTX for patient (#1–3) with pathologic complete response (pCR). Red arrows indicate tumor mass.

As a distinct histologic subtype of NSCLC, lung squamous cell carcinoma has resulted in a median survival approximately 30% shorter than that of patients with other NSCLC subtypes due to its specific clinicopathologic characteristics, including older age, advanced disease at diagnosis, comorbid diseases, and central location of tumors. In addition, it is more likely to invade large blood vessels and shows more complex gene mutations. Unlike lung adenocarcinomas, patients with lung squamous cell carcinoma have not benefited from targeted therapies.[16] It remains a great challenge to manage advanced lung squamous cell carcinoma due to the rare established actionable genomic targets.[17] To date, only immunotherapy has evolved into a successful therapeutic strategy for patients with lung squamous cell carcinoma.[18]

Surgery has been considered the first option for resectable lung squamous cell carcinoma. All patients in this study were analyzed by the multidisciplinary team (MDT) and recognized as locally advanced unresectable lung squamous cell carcinoma prior to neoadjuvant therapy. In 2018, durvalumab obtained global approval for patients with unresectable stage III NSCLC whose disease had not progressed after concurrent chemoradiotherapy (CCRT) based on the results of the PACIFIC trial.[19] According to the guidelines of the Chinese Society of Clinical Oncology (CSCO), CCRT has been recommended as a first-line treatment for patients with lung squamous cell carcinoma, followed by the PD-1 inhibitor of

duvalizumab for consolidation treatment. However, CCRT must be performed in high-level centers by experienced technologists and the occurrence of radiation pneumonia cannot be ignored.

Fortunately, studies[20] have shown that neoadjuvant therapy alone or in combination with radiation therapy has potential to improve the rate of radical resection, eliminate micrometastasis, and reduce the risk of tumor recurrence in patients with initially inoperable localized NSCLC. Meta-analysis has concluded an absolute increase of 4–5% (from 40% to 45%) in overall 5-year survival as a benefit of neoadjuvant chemotherapy in the treatment of resected stage IB–IIIA NSCLC.[2,3] However, the survival increase was restricted to cases involving lymph nodes.[2] Furthermore, it is found that the overall benefit is limited, with various toxicities of neutropenia, anemia, nausea and vomiting, and so on,[2] indicating the curative effect of surgical treatment after neoadjuvant chemotherapy has entered the bottleneck stage. Thus, there is an urgent need for a better therapeutic treatment for lung squamous cell carcinoma in clinical practice.

ICIs in immunotherapy are monoclonal antibodies (mAbs) that target endogenous autoregulatory pathways to unleash antitumor immune responses. Recently, ICI alone or in combination with other ICIs or chemotherapy has demonstrated better survival benefits in first-line and second-line therapy than chemotherapy for advanced NSCLC.[8–12] Since the initial approval of nivolumab by the US Food and Drug Administration (FDA) for metastatic NSCLC after prior chemotherapy treatment with chemotherapy in 2015,[21] ICIs have become standard of care options in earlier lines of therapy, as components of combination regimens, and in unresectable stage III NSCLC. The FDA-approved ICIs for NSCLC include pembrolizumab,[22] nivolumab, ipilimumab,[23] atezolizumab, cemiplimab,[24] and durvalumab.[25] Recently, more and more studies have been carried out on neoadjuvant immunotherapy and its effects on stimulating the immune system, activating T cells before surgery, establishing immune memory, controlling micrometastases, identifying and killing residual cancer cells after surgery have been discovered, leading to great survival benefits among patients in the early stage of NSCLC. An open, single-center, phase IB study in China (ChiCTR - OIC 17013726 study) included 22 patients with resectable stage IA–IIIB lung squamous cell carcinoma to assess the effect of neoadjuvant immunotherapy with sindilimab, and the results of postoperative pathology showed that the MPR rate was 45.5%, of which 40% achieved pCR, without active tumor cells detected.[26] However, the role and indications of various ICIs in neoadjuvant therapy of NSCLC still need to be further confirmed by large-scale Phase III clinical studies.

However, immunotherapy alone for lung squamous cell carcinoma is limited in its curative effect and beneficiary population. Theoretically, immunotherapy combined with chemotherapy can further improve survival benefits. Drugs in chemotherapy could stimulate tumor cell mutations and release new tumor antigens, thus activating antitumor immunity and sending tumors to checkpoint blockade immunotherapies.[27] Platinum-based drugs were the most widely used chemotherapeutics in oncology, showing clinical efficacy against many solid tumors. As reported,[28] chemotherapy with platinum-based drugs could induce the immunogenic death of cancer cells through exposure to calreticulin and the release of ATP and the high mobility group protein box-1. Keynote 407 study evaluated the first-line therapeutic effect of pabolizumab combined with carboplatin and paclitaxel or nab-PTX in patients with previously untreated metastatic lung squamous cell carcinoma, and found that pembrolizumab plus chemotherapy resulted in significantly longer overall survival and progression-free survival than chemotherapy alone.[10] Besides, Impower-131 study showed that atezolizumab combined with chemotherapy significantly improved progression-free survival and overall survival compared with chemotherapy alone.[29] In addition, NADIM study[30] and checkmate-816 study[31] also showed that neoadjuvant immunotherapy combined with chemotherapy could effectively improve event-free survival (31.6 vs 20.8 months) and more resectable NSCLC patients achieve pCR (24% vs 2.2%) without increasing incidence of adverse events than chemotherapy alone.

Conclusion

Neoadjuvant therapy of the PD-1 inhibitor combined with NED and nab-PTX demonstrated remarkable therapeutic efficacy and good safety against unresectable stage IIIA, IIIB lung squamous cell carcinoma, showing few treatment-related adverse events without increasing the risk of surgical complications and mortality. Therefore, it is worth exploring further in clinical practice in the future.

Abbreviations

PD-1, programmed cell death 1; NED, nedaplatin; pCR, pathological remission rate; MPR, major pathological remission; SD, stable disease; NSCLCs, non-small-cell lung cancers; ICIs, immune checkpoint inhibitors; ECOG, Eastern Cooperative Oncology Group; PS, performance status; TRAE, treatment-related adverse events; CT, computed tomography; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria for Solid Tumors; CCRT, concurrent chemoradiotherapy; CSCO, Chinese Society of Clinical Oncology; FDA, Food and Drug Administration.

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Disclosure

The authors declare no conflicts of interest in this work.

References

1. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11(1):39–51. doi:10.1016/j.jtho.2015.09.009
2. Artal Cortes A, Calera Urquizu L, Hernando Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. *Transl Lung Cancer Res*. 2015;4(2):191–197. doi:10.3978/j.issn.2218-6751.2014.06.01
3. N M-a C Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet*. 2014;383(9928):1561–1571. doi:10.1016/S0140-6736(13)62159-5
4. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. *Nature*. 2018;553(7689):446–454. doi:10.1038/nature25183
5. Jasper K, Stiles B, McDonald F, et al. Practical management of oligometastatic non-small-cell lung cancer. *J Clin Oncol*. 2022;40(6):635–641. doi:10.1200/jco.21.01719
6. Arbour KC, Riely GJ. Systemic therapy for locally advanced and metastatic non-small cell lung cancer: a review. *JAMA*. 2019;322(8):764–774. doi:10.1001/jama.2019.11058
7. Wu YL, Lu S, Cheng Y, et al. Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced NSCLC: checkMate 078 randomized phase III clinical trial. *J Thorac Oncol*. 2019;14(5):867–875. doi:10.1016/j.jtho.2019.01.006
8. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078–2092. doi:10.1056/NEJMoa1801005
9. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol*. 2019;37(7):537–546. doi:10.1200/JCO.18.00149
10. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2040–2051. doi:10.1056/NEJMoa1810865
11. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627–1639. doi:10.1056/NEJMoa1507643
12. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373(2):123–135. doi:10.1056/NEJMoa1504627
13. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J Natl Cancer Inst*. 2014;106(9):dju244–dju244. doi:10.1093/jnci/dju244
14. Socinski MA, Obasaju C, Gandara D, et al. Current and emergent therapy options for advanced squamous cell lung cancer. *J Thorac Oncol*. 2018;13(2):165–183. doi:10.1016/j.jtho.2017.11.111
15. Tang LQ, Chen DP, Guo L, et al. Concurrent chemoradiotherapy with nedaplatin versus cisplatin in stage II-IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised Phase 3 trial. *Lancet Oncol*. 2018;19(4):461–473. doi:10.1016/S1470-2045(18)30104-9
16. Paik PK, Pillai RN, Lathan CS, et al. New treatment options in advanced squamous cell lung cancer. *Am Soc Clin Oncol Educ Book*. 2019;39:e198–e206. doi:10.1200/EDBK_237829
17. Satpathy S, Krug K, Jean Beltran PM, et al. A proteogenomic portrait of lung squamous cell carcinoma. *Cell*. 2021;184(16):4348–4371 e40. doi:10.1016/j.cell.2021.07.016
18. Karachaliou N, Fernandez-Bruno M, Rosell R. Strategies for first-line immunotherapy in squamous cell lung cancer: are combinations a game changer? *Transl Lung Cancer Res*. 2018;7(Suppl3):S198–S201. doi:10.21037/tlcr.2018.07.02
19. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379(24):2342–2350. doi:10.1056/NEJMoa1809697
20. Aghdam N, Lischalk JW, Marin MP, et al. Lobar gross endobronchial disease predicts for overall survival and grade 5 pulmonary toxicity in medically inoperable early stage non-small cell lung cancer patients treated with stereotactic body radiation therapy. *Front Oncol*. 2021;11:728519. doi:10.3389/fonc.2021.728519
21. Zhang Y, Wang F, Liu C, et al. Nanozyme decorated metal-organic frameworks for enhanced photodynamic therapy. *ACS Nano*. 2018;12(1):651–661. doi:10.1021/acsnano.7b07746
22. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540–1550. doi:10.1016/S0140-6736(15)01281-7

23. Paz-Ares LG, Ramalingam SS, Ciuleanu TE, et al. First-line nivolumab plus ipilimumab in advanced NSCLC: 4-year outcomes from the randomized, open-label, phase 3 CheckMate 227 part 1 trial. *J Thorac Oncol*. 2022;17(2):289–308. doi:10.1016/j.jtho.2021.09.010
24. Sezer A, Kilickap S, Gumus M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet*. 2021;397(10274):592–604. doi:10.1016/S0140-6736(21)00228-2
25. Gray JE, Villegas A, Daniel D, et al. Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC-update from PACIFIC. *J Thorac Oncol*. 2020;15(2):288–293. doi:10.1016/j.jtho.2019.10.002
26. Siemann DW, Hill RP, Bush RS. The importance of the pre-irradiation breathing times of oxygen and carbogen (5% CO2: 95% O2) on the in vivo radiation response of a murine sarcoma. *Int J Radiat Oncol Biol Phys*. 1977;2(9–10):903–911. doi:10.1016/0360-3016(77)90188-2
27. Pfirschke C, Engblom C, Rickelt S, et al. Immunogenic chemotherapy sensitizes tumors to checkpoint blockade therapy. *Immunity*. 2016;44(2):343–354. doi:10.1016/j.immuni.2015.11.024
28. Hato SV, Khong A, de Vries IJ, et al. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. *Clin Cancer Res*. 2014;20(11):2831–2837. doi:10.1158/1078-0432.CCR-13-3141
29. Jotte R, Cappuzzo F, Vynnychenko I, et al. Atezolizumab in combination with carboplatin and nab-paclitaxel in advanced squamous NSCLC (IMpower131): results from a randomized phase III trial. *J Thorac Oncol*. 2020;15(8):1351–1360. doi:10.1016/j.jtho.2020.03.028
30. Provencio M, Nadal E, Insa A, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, Phase 2 trial. *Lancet Oncol*. 2020;21(11):1413–1422. doi:10.1016/S1470-2045(20)30453-8
31. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386(21):1973–1985. doi:10.1056/NEJMoa2202170