

Clinical challenges in neoadjuvant immunotherapy for non-small cell lung cancer

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Abstract

Immune checkpoint inhibitors (ICIs), a type of immunotherapy, have become one of the most important therapeutic options for first- and second-line treatment of advanced non-small cell lung cancer (NSCLC). Recent clinical studies have shown that immunotherapy can offer substantial survival benefits to patients with early-stage or resectable advanced NSCLC. However, considering the importance of timing when using ICIs and their associated adverse events (AEs), the advantages and disadvantages of using these agents need to be weighed carefully when deciding the use of a combined treatment. In addition, the inconsistency between imaging assessment and pathological results poses further challenges to the evaluation of efficacy of neoadjuvant immunotherapy. It is also important to develop new methodologies and discover suitable biomarkers that can be used to evaluate survival outcomes of immunotherapy and identify patients who would benefit the most from this treatment. In this review, we aimed to summarize previous results of ongoing clinical trials on neoadjuvant immunotherapy for lung cancer and discuss the challenges and future perspectives of this therapeutic approach in the treatment of resectable NSCLC.

Keywords: Non-small cell lung cancer; immune checkpoint inhibitor; immunotherapy; neoadjuvant therapy

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Introduction

Lung cancer has the highest morbidity and mortality among malignant tumors in the world, and non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases (1). Surgery, radiotherapy, and chemotherapy remain the standard treatment for early and locally advanced (resectable) NSCLC. Despite undergoing surgery and adjuvant radiotherapy and/or chemotherapy, some patients experience relapse and metastasis; and 20%–30% of patients with stage I, 50% with stage II, and 60% with IIIA NSCLC die within 5 years (2). Preventing tumor recurrence and improving the cure rate are the primary treatment goals for resectable NSCLC. Neoadjuvant therapy can increase the success rate of curative surgery by decreasing tumor volume and eliminating micrometastasis,

thereby reducing the risk of tumor recurrence (3). However, a meta-analysis of patients with stage IB–IIIA operable NSCLC showed that neoadjuvant chemotherapy could improve the 5-year survival rate by only 5% (4), and the incidence of adverse events (AEs) was higher (5). Therefore, new treatment methods are needed to reduce the risk of recurrence and improve survival in patients with NSCLC.

As a new milestone in cancer treatment, immune checkpoint inhibitors (ICIs), a type of immunotherapy, have had a profound impact on the treatment landscape of NSCLC. Compared with standard chemotherapy, ICIs alone or in combination with platinum-containing chemotherapy could improve the overall survival (OS) rate in patients with advanced NSCLC [programmed cell death-ligand 1 (PD-L1) positive, tumor proportion score

(TPS) $\geq 50\%$] by 15%–20% in the first-line treatment (6–8). In the second-line treatment, the 1-year survival in patients treated with ICIs was more than 10% higher than that in patients treated with chemotherapy (9,10). Furthermore, ICIs as a maintenance treatment after concurrent radiotherapy and chemotherapy also significantly prolonged OS in patients with locally advanced NSCLC [28.3 vs. 16.2 months, hazard ratio (HR): 0.53; 95% confidence interval (95% CI): 0.41–0.68] (11). It is increasingly believed that the earlier the application of immunotherapy, the greater its benefit. The relationship between neoadjuvant immunotherapy and surgery is synergistic and complementary. On the one hand, perioperative stress and inflammation caused by surgery will lead to immunosuppression, and the greater antigen load before the operation may associate with more fully mobilized of the immune system. On the other hand, the operation not only removes the tumor itself but also partially removes the tumor microenvironment that causes immunosuppression, which may result in a synergistic effect on the follow-up immunotherapy.

Preliminary data from various ongoing trials indicated that neoadjuvant immunotherapy may potentially improve survival rate in patients with resectable NSCLC. A meta-analysis of 252 patients from 7 studies showed that the major pathologic response (MPR) value and pathological complete response (pCR, absence of active tumor cells) rate in neoadjuvant immunotherapy were significantly higher than those in neoadjuvant chemotherapy [MPR: odds ratio (OR)=0.59; 95% CI, 0.36–0.98; pCR: OR=0.16; 95% CI, 0.09–0.27] (12). Immunotherapy has slow onset, long effective time, and special therapeutic response, such as pseudo-progression (PP), hyper-progression (HP), and mixed remission (13). Clinical research on neoadjuvant immunotherapy is in the preliminary stage, and there are still many problems to be addressed. For example, the end points used in clinical studies, which can be roughly divided into three categories according to the evaluation indicators: The first is the evaluation index of safety, such as the incidence of immune-related AEs (irAEs). In addition, the resection rate of surgery, incidence of surgical complications, and rate of surgical delay are also needed to consider in the clinical study of neoadjuvant immunotherapy. The second category is the evaluation index of the curative effect, which is also the most important endpoint in clinical research. The third type of evaluation index is the quality of life (QoL), which is measured by the Patient Reported Outcome (PRO), such as the QoL scale.

Through the safety, efficacy, and QoL evaluation, we achieve an omni-directional, objective, and sober understanding of the neoadjuvant treatment. This review aimed to summarize clinical research conducted on ICIs used as the neoadjuvant treatment of patients with early and locally advanced NSCLC and discuss existing problems and research prospects focus on the above aspects, in order to provide reference for clinical practice.

Neoadjuvant immunotherapy in resectable NSCLC

Immunotherapy, especially PD-1/PD-L1 antibodies, is a revolutionary breakthrough in anticancer treatments. At present, patients with advanced disease stage mostly benefit from immunotherapy and clinical trials. Can early disease stage patients also benefit from immunotherapy? For some patients, the answer is yes. Patients with resectable NSCLC can use PD-1 immunotherapy in the following settings: preoperative (neoadjuvant therapy), postoperative (adjuvant therapy), and perioperative (neoadjuvant therapy + adjuvant therapy). At present, a number of clinical trials have shown that neoadjuvant immunotherapy is safe and effective in the treatment of NSCLC (Table 1). A large number of phase III clinical studies are also underway.

Neoadjuvant monotherapy with immunotherapy

ICI monotherapy is a safe neoadjuvant therapy for NSCLC, and the MPR in the three clinical studies published so far was 17%–45%. CA209-159 is the first clinical trial on NSCLC neoadjuvant immunotherapy. The MPR (active tumor cells $\leq 10\%$) and 18-month recurrent-free survival rates were 45% and 73%, respectively (14). Recent data on the annual meeting of the American Society of Clinical Oncology showed that 15 of the 20 patients had no recurrence during a median follow-up of 34.6 months (15). The ChiCTR-OIC-17013726 study is an open, single-center, Ib phase study conducted in China, in which 22 patients with IA–IIIB resectable squamous NSCLC underwent surgery after receiving two cycles of Sintilimab. MPR rate was 45.5% (10/22), and 4 patients achieved pCR (16). Another phase II study on Atezolizumab neoadjuvant therapy for NSCLC patients (LCMC3 study) is the largest neoadjuvant immunotherapy study to date. A total of 180 patients who were newly diagnosed with Ib–IIIB (T3N2) resectable NSCLC were planned to be enrolled in the study. The results of the mid-term analysis showed that 90

Table 1 Early results of clinical trials on major neoadjuvant immunotherapy

Clinical trials	Phase	No. Stage (n)	Neo-adjuvant immunotherapy	Adjuvant treatment after surgery	Timing of surgery (weeks)	Primary endpoint	Treatment-related surgical delays/cancel (%)	AEs	References
CA209-159 (NCT02259621)	Ib	22	I-IIIA resectable NSCLC Nivolumab, 3 mg/kg; Q2W, 2 cycles	-	4	MPR, 45%; 18 months RFS, 73%	-	1 case of long-term irAE (skin, grade 3)	(14,15)
ChIctr-OIC-17013726	Ib	22	IA-IIIB resectable NSCLC Sintilimab; 200 mg; Q3W, 2 cycles	-	4	MPR, 45.5% pCR, 18.2%	-	-	(16)
LCMC3 (NCT02927301)	II	101	IB-IIIB (T3N2) resectable NSCLC Atezolizumab, 1,200 mg; Q3W, 2 cycles	-	6	MPR, 19% pCR, 5%	One case of delayed operation (grade 3 pneumonia)	2 cases of grade 5 AE, grade 3 and above AE 6% (6/101)	(17,18)
NADIM (NCT03081689)	II	46	IIIA (N2) resectable NSCLC Nivolumab, 360 mg, + carboplatin + paclitaxel; Q3W, 3 cycles	Nivolumab 240 mg Q2W for 4 months and 480 mg Q4W for 8 months	9	MPR, 85.36% pCR, 71.4%	-	1 case of grade 4 AE, grade 3 and above AE 8.8% (4/46)	(19)
SAKK 16/14 (NCT 02572843)	II	68	IIIA (N2) resectable NSCLC Cisplatin, 100 mg/m ² + docetaxel 85 mg/m ² ; Q3W, 3 cycles, followed by durvalumab 750 mg; Q2W, 2 cycles	Durvalumab 750 mg Q2W, for 12 months	13	1-year EFS rate, 73.3%, ORR, 44.8% after neoadjuvant chemotherapy and 59.7% after additional neoadjuvant immunotherapy	4 cases not undergoing surgery due to PD	-	(20,21)
NEOSTAR (NCT03158129)	II	44	I-IIIA (N2) resectable NSCLC Nivolumab (3 mg/kg, d 1, 15,29) ± ipilimumab (1 mg/kg, d1) 3 cycles	-	3-6	MPR, 17%/33%	-	Grade 3 and above AE: 24% (N: 16%, NI: 8%)	(22)
NCT02716038	II	30	IIIA Atezolizumab, 1,200 mg + nab-paclitaxel + carboplatin; Q3W, 4 cycles	-	12	MPR, 57%	-	Grade 3 and above AE: neutropenia 50% (15/30), increases ALT 7% (2/30), increases AST 7% (2/30), Thrombocytopenia 7% (2/30)	(23)

NSCLC, non-small cell lung cancer; MPR, major pathologic response; RFS, recurrent-free survival; pCR, pathological complete response; EFS, event-free survival; ORR, objective response rate; PD, progressive disease; AE, adverse event; irAE, immune-related AE; ALT, alanine aminotransferase concentration; AST, aspartate aminotransferase concentration.

of the 101 patients underwent surgical treatment, and the pathological remission rate in 38 patients (49%) was $\geq 50\%$. The MPR rate was achieved in 19% (15/77) of patients, of which 4 achieved pCR. According to the Response Evaluation Criteria in Solid Tumors (RECIST), the partial remission (PR) and stable disease (SD) rates were 7% (6/90) and 89% (80/90), respectively (17,18).

Neoadjuvant combination therapy

Chemotherapy can stimulate tumor cells to mutate and release new tumor antigens, thus activating the antitumor immune response and enhancing the sensitivity of tumors to ICIs (24,25). Previous studies have shown that platinum-containing drugs not only induced immunogenic death of tumor cells, but also reduced the expression of PD-L2 and enhanced the interaction between tumor and immune cells by inhibiting the Signal Transducer and Activator of Transcription (STAT) pathway (26). Chemotherapy can also normalize tumor blood vessels and reconstruct immune microenvironment by increasing the infiltration of dendritic cells and effector T cells. In a large-scale trial on ICIs combined with chemotherapy, combination therapy could exert the best therapeutic effect (6). ICI combined with chemotherapy is also the most effective neoadjuvant immunotherapy. In the NADIM study, patients with NSCLC were treated with three cycles of neoadjuvant therapy with nivolumab combined with chemotherapy, followed by surgery and sequential nivolumab therapy for 1 year. The MPR at mid-term analysis was 85.37% (35/41), and the pCR 60.98% (25/41). The PR and complete remission (CR) were 80.49% (33/41) and 7.3% (3/41), respectively (19). However, the results of this study remained controversial because the patients were treated with immunotherapy postoperatively as an adjuvant treatment. In addition, it is uncertain whether adjuvant immunotherapy should be administered after surgery or not and what is the ideal duration of adjuvant treatment. The appropriate methods of assessing survival benefits of neoadjuvant immunotherapy or adjuvant immunotherapy should be explored further.

The SAKK16/14 study explored a new adjuvant model of sequential immunotherapy in patients with stage IIIA (N2) NSCLC who were treated with neoadjuvant chemotherapy. The neoadjuvant treatment consisted of three cycles of cisplatin and docetaxel followed by two cycles of durvalumab (750 mg). Durvalumab was continued as an adjuvant therapy after surgery for 1 year. The primary end

point of this study was the event-free survival (EFS) rate. The objective response rate (ORR) was 44.8% (95% CI: 32.6–57.4) after neoadjuvant chemotherapy and 59.7% (95% CI: 46.4–71.9) after additional neoadjuvant immunotherapy. The 1-year EFS was 73.3% (90% CI: 62.5–81.4) (20,21). The 1-year EFS rate in patients with IIIA stage was 50% in previous studies, while that in this study was significantly higher; therefore, the chemotherapy sequential immunotherapy model in this study should be evaluated using a larger sample size to validate its exact benefits.

The combination of two different ICIs can increase the MPR of neoadjuvant therapy by 10%. The NEOSTAR study compared the efficacy of nivolumab (N) and nivolumab combined with ipilimumab (NI) as a neoadjuvant therapy; the overall MPR was 25% (17% in the N group and 33% in the NI group); the overall pCR was 18% (9% in the N group and 29% in the NI group). Compared with the single drug group, the double immunotherapy group could achieve a higher rate in T-cell proliferation, which may be the mechanism underlying higher efficacy of NI treatment (22). However, the proportion of patients with delayed/cancelled surgery in double ICI combined with neoadjuvant immunotherapy increased significantly (22,23), and the CheckMate-617 study of double ICI was terminated prematurely due to the occurrence of AEs and the unclear efficacy of this treatment.

Ongoing trials on neoadjuvant immunotherapy therapy

The current evidence shows that the MPR of neoadjuvant monotherapy with ICIs is between 19% and 45%, and the MPR of ICI-based neoadjuvant combination therapy is between 33% and 83%, but the sample sizes in the related studies were small and the exact regimen that should be given to patients needs to be further confirmed by phase III clinical studies. Keynote-671 (NCT03425643), IMpower-030 (NCT03456063), and AEGEAN (NCT03800134) were randomized, double-blind, phase III clinical trials, using pembrolizumab, atezolizumab, and durvalumab combined with platinum chemotherapy to compare the efficacy of chemotherapy alone as a neoadjuvant therapy for patients with resectable NSCLC. These studies continued using a single-dose immunotherapy after surgery for different periods of time. The CA209-77T (NCT04025879) evaluated the efficacy of nivolumab monotherapy and nivolumab combined chemotherapy as

neoadjuvant immunotherapy, while the Checkmate-816 (NCT02998528) evaluated the efficacy of nivolumab monotherapy, chemotherapy alone, and nivolumab combined with chemotherapy as a neoadjuvant immunotherapy. The results of these clinical studies may be helpful in evaluating the mechanism of ICI, in determining the optimal time between operations, and in predicting markers.

Safety of neoadjuvant immunotherapy

At present, the preliminary results of neoadjuvant immunotherapy showed that neoadjuvant immunotherapy was safe and effective for resectable NSCLC. The safety of neoadjuvant immunotherapy should take into account the incidence of irAEs, the rate of surgical delays/cancel, and the incidence of surgical complications.

Incidence of AEs related to neoadjuvant immunotherapy

Throughout the current clinical research on immunotherapy with the increasing application of immunotherapy, more and more AEs, and even some fatal AEs have been reported. Therefore, there is a certain risk of using immunotherapy as an adjuvant therapy. At present, LCMC3 study, that used the largest sample size of patients to date, included those with an incidence of treatment-related AEs (TRAEs) of grade 3 and above of 3%. There were two patients who had grade 5 AEs unrelated to treatment, including cardiac death and death due to progressive disease (PD) (17,18).

When evaluating AEs of immunotherapy, the particularity of immunotherapy should be taken into account. First, the AEs of immunotherapy have lagging effects, such as delayed adverse reactions (27). Of the 21 patients included in the CA209-159 study, 20 were able to undergo surgery as planned, and 1 underwent surgery after one course of nivolumab treatment due to the occurrence of grade 3 immune-associated pneumonia. Long-term irAEs occurred in one patient (grade 3 skin) (15). Second, the occurrence of irAEs may not depend on the treatment dose. Third, the standard Common Terminology Criteria for Adverse Events grading to determine the need for immunotherapy needs to be discussed further. Fourth, the superposition of drug toxicity in combined therapy must also be explored (28). The target organs of AEs of immunotherapy and chemotherapy are believed to be different; hence, the adverse reactions to combined therapy

usually do not increase, but double ICIs or ICIs combined with other immune agonists are often accompanied by an increase in irAEs, even leading to severe acute cytokine release syndrome (29). The NEOSTAR study showed that in the double ICI group, the incidence of grade 1–2 TRAEs was increased, such as rash (52% vs. 26%) and diarrhea (29% vs. 9%), but there was no significant difference in the overall incidence between two groups. There was no significant difference in grade 3–5 TRAEs between two groups, including bronchopleural fistula and death due to hormone therapy for pneumonia (one patient, grade 5, N group); grade 3 pneumonia, hypoxia, and hypermagnesemia (one patient in each, all in group N); and grade 3 diarrhea (one patient in NI group) (22).

For epidermal growth factor receptor (EGFR)-positive patients, the sequence of immunotherapy and targeted therapy requires special attention. The incidence of severe AEs increased significantly in EGFR-positive patients who were initially treated with immunotherapy followed by osimertinib (30). Osimertinib is a third-generation EGFR-TKI that has been approved for the first-line treatment in patients with EGFR-positive NSCLC. Although the mechanism of action is ostensibly different, a retrospective study on 126 patients with NSCLC showed that sequential treatment with ICI after osimertinib was associated with severe irAEs, and 15% (6/41) of the patients who were administered immunotherapy followed by targeted therapy developed grade 3–4 irAEs. The incidence of severe irAE was higher [24% (5/21)] in patients who were treated with ICIs recently (within 3 months) (30). In the LCMC3 study, EGFR/ALK+ patients had 40%–50% of pathological regression. Patients with potential negative predictors such as *EGFR* sensitive mutation/*ALK* fusion should carefully choose neoadjuvant immunotherapy, and decide whether to carry out targeted adjuvant therapy in the follow-up treatment.

Rate of surgical delays/cancellations and incidence of surgical complications

After neoadjuvant therapy, the pulmonary artery, vein and trachea may have varying degrees of fibrosis and increased fragility, which may increase the difficulty of operation (31). Among the cases of using neoadjuvant immunotherapy reported at present, there was only one case of delayed operation due to grade 1 hyperthyroidism in the LCMC3 study (17), and four patients not undergoing surgery due to PD in the SAKK 16/14 study (20,21), other

studies have not reported such delays (14,16,22,23,32,33). In addition, the incidence of operative complications was also low, with only two cases (1.2%) of fatal operative complications (postoperative cardiac death) (22); other complications included atrial arrhythmia (17), bronchopleural fistulas, and air leaks (22). META analysis of seven clinical studies showed that the combined OR values of TRAE, operative complications, and operative delay rate of neoadjuvant immunotherapy were 0.19, 0.41, and 0.03 respectively, which were significantly better than those in the neoadjuvant chemotherapy group (95% CI: 0.04–0.90, 0.22–0.75, 0.01–0.10, respectively). The average resection rate was 88.70%, which was similar to that reported in neoadjuvant chemotherapy (75%–90%, OR=7.61; 95% CI, 4.90–11.81) (12). However, the number of patients in the neoadjuvant immunotherapy group was small (20–40 patients), and the follow-up time was relatively short. The safety of neoadjuvant immunotherapy still needs to be verified further by large sample, multicenter, long-term follow-up clinical trials.

The cycle of neoadjuvant immunotherapy (timing of surgical intervention) has always been an unresolved issue. In a preclinical study, postponing or shortening the operation interval after a neoadjuvant therapy will cause the T cells to dysfunction and, thus, will significantly affect OS of the lung cancer mouse model (34). The clinical benefit may be greater if the operation is performed when the effect of T-cell activation is the strongest after ICI treatment. The results of two retrospective studies based on the National Cancer Database showed that patients who underwent surgery 8 weeks or later after diagnosis (delayed operation group) had higher perioperative mortality (30-day mortality: 2.9% vs. 2.4%, $P=0.001$) and shorter median OS (57.7 months vs. 69.2 months, $P<0.001$) (35). The 3-year survival rates in patients grouped according to the quartile of the interval between diagnosis and operation (<11 weeks, 11–16 weeks, and >16 weeks) were 59%, 58% and 52% ($P=0.0003$), respectively (36). These results suggest that delayed surgery may increase the risk of death; therefore, the formulation of the immunotherapy cycle is very important. In most clinical trials, neoadjuvant immunotherapy is administered in 2–3 cycles, and surgery is performed 4–9 weeks after the completion of treatment. In the SAKK16/14 study, five cycles of neoadjuvant therapy and a 13-week interval significantly increased the proportion of patients who lost surgical opportunities due to PD (20), which was consistent with the results of previous studies. Larger sample, multicenter clinical studies

are needed to further determine the optimal time interval of surgery for NSCLC patients after administering neoadjuvant immunotherapy.

Efficacy evaluation criteria and end point of neoadjuvant immunotherapy

The evaluation index of the curative effect includes indexes measured by time [progression-free survival (PFS), OS, duration of remission (DoR), etc.], and those evaluated by imaging or pathology (CR, PR, SD, PD, MPR, etc.). In addition, there are indicators based on the ratio of the above parameters, such as 1-year survival rate, ORR, and disease control rate (DCR).

Time-based evaluation index is the most commonly used end point in clinical studies, but the follow-up time is usually long. In order to accelerate the clinical transformation of new drugs, the evaluation criteria based on imaging or pathological tumor measurement have become the most commonly used end point in the study of neoadjuvant immunotherapy for various resectable tumors, in order to further shorten the follow-up time and improve the efficiency of clinical trials.

Efficacy index based on time

OS is still the most ideal end point for evaluating the prognosis in patients with resectable NSCLC, which is also the most classic gold standard in clinical research design. However, it takes a very long time to observe OS events, which requires conducting a clinical study that may take more than a decade. Disease-free survival (DFS) and treatment-free survival (TFS) are also ideal end points for immunotherapy because it considers patients who have long-term survival without disease progression, who benefit the most from immunotherapy (37). In clinical trials on neoadjuvant immunotherapy for lung cancer, the follow-up time was too short to obtain data on OS and DFS. The median OS and median PFS allow the pre-estimation of survival when 50% of patients experience a particular event (death or progression). However, this will not correctly assess the long-term benefits because it does not take into account the patients represented by the tail of the Kaplan-Meier survival curve (product-limit method) (38). Landmark survival rates at long-term time points can better identify the differences in survival benefits over time (28). Due to the tailing effect of immunotherapy, the landmark of OS rate needs to be selected very carefully, and mid-

term analysis can lead to the problem of premature blindness.

Evaluation index effect based on imaging

Patients with PP who continue to use immunotherapy may have a better chance of achieving long-term efficacy; therefore, traditional imaging evaluation criteria cannot accurately describe the efficacy of immunotherapy, and identifying new indicators for evaluating the efficacy of solid tumors is necessary.

Immune-related response criteria (irRC) are the first standard for evaluating the efficacy of immunotherapy on solid tumors (39), which introduced the concept of calculating measurable new lesions ($\geq 5 \text{ mm} \times 5 \text{ mm}$) into the original tumor load for the first time. For new lesions, the irRC indicate that as long as the total tumor load increases by less than 25%, it will not be classified as PD and will be reevaluated at least 4 weeks later, and can only be classified as PD if the tumor load increases by more than 25% twice in a row. Second, immune-related RECIST (irRECIST) (40) adopted a single diameter measurement, which has a lower dispersion and high repeatability than the double diameter measurement, especially when the changes in tumor size are small (41). Later, the immune RECIST (iRECIST) (42) introduced the concepts of unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD). The immune-modified RECIST (imRECIST) proposed in 2018 only calculated the baseline measurable lesions when evaluating PD (43). The purpose of these new evaluation criteria was to evaluate the efficacy of immunotherapy more accurately.

Evaluation index based on pathology

The inconsistency between radiographic response and pathological response is also a challenge in clinical practice posing challenges in detecting PP in this case or, in other words, of identifying patients who have actual pathological remission without radiographic response. The NEOSTAR data also prove this point. Only 60% of the patients who achieved MPR had “significant tumor reduction” on imaging data (22). Therefore, the use of ORR may underestimate the efficacy of ICIs as a neoadjuvant therapy. pCR is defined as the absence of invasive cancer cells in resected residual lesions and in all lymph node specimens. Studies have confirmed that pCR in neoadjuvant therapy studies can be used as a good alternative endpoint for OS (44). However, it is difficult to achieve pCR in NSCLC

(only about 4%) (45). A series of studies have confirmed that the MPR with a cutoff value of active tumor cells $\leq 10\%$ was consistent with DFS and OS of NSCLC neoadjuvant chemotherapy (46).

In current trials of immunotherapy as neoadjuvant therapy, MPR rather than ORR is regarded as the main criterion, which is consistent with the above view. The MPR rate in the NEOSTAR study was 25%, and the patients with MPR had higher ORR than patients without MPR (60% vs. 7%) (22). The NADIM study showed that there was a significant difference in PFS between patients with and without MPR (log rank $P=0.01$), and if the pathological remission was limited to pCR, the difference was more significant (log rank $P=0.0023$) (19). However, due to the lack of comparison between MPR and long-term survival indicators, the value of neoadjuvant immunotherapy in evaluating the efficacy of neoadjuvant immunotherapy needs to be further improved and confirmed. Different from the pathological response criteria (PRC), which uses the ratio of active tumor cells to all tumor cells in traditional chemotherapy, the immune-related PRC (irPRC) is modified to the ratio of the area of active tumor cells to the area of tumor bed (retraction bed + necrotic tissue + active tumor cells) (47). We look forward to obtaining the most updated OS in these data to clarify the relationship between MPR and OS in patients with lung cancer.

Evaluation index based on metabolic imaging

Regarding the mechanism, there is a correlation between the PD-1 pathway and the expression of glucose transporter-1 (GLUT1) and hypoxia-inducible factor-1 α (HIF-1 α) in NSCLC tissues (48), which may lead to the increase of glucose metabolism in tumor tissue and inhibit the energy uptake in local immune microenvironment, thus indirectly modulating the immune system (49). The consistency of standard uptake value (SUV) in positron emission tomography-computed tomography (PET-CT) and level of PD-L1 varies with tumor stages. There is a significant correlation between the SUV_{max} and the expression level of PD-L1 in patients with early-stage lung cancer who can undergo feasible segmental pneumonectomy (48).

The evaluation criteria associated with PET-CT mainly include the European Organization for Research and Treatment of Cancer (EORTC) criteria and PET response evaluation criteria in solid tumors (PERCIST), which has

been proved to be effective in evaluating the efficacy of immunotherapy (50). A study that classifies the immunophenotype of resected specimens shows that the results of PET-CT can predict survival after neoadjuvant therapy (49). At present, there are few studies on the evaluation of neoadjuvant immunotherapy of NSCLC by PET-CT. The ChIctr-OIC-17013726 study showed that there was a positive correlation between the changes in SUV and MPR. However, the baseline SUV did not show a correlation with MPR (16). The results of PRINCEPS study suggested that pathological remission did not influence the changes of SUVmax (51). Similar to ordinary CT, PET-CT also has pseudo-progression, which is related to increased sugar uptake by lymphocytes infiltrating the tumor (52). The price of PET-CT is relatively high, and its value as a clinical evaluation method of neoadjuvant immunotherapy remains to be further confirmed.

Exploration of people benefiting from neoadjuvant immunotherapy

In addition to predicting the long-term efficacy after surgery combined with neoadjuvant immunotherapy, it is also very important to predict the short-term efficacy after neoadjuvant immunotherapy (before surgery). The poor efficacy of neoadjuvant therapy or the occurrence of over-progression of the disease may make the resectable tumor unresectable and delay the timing of surgical treatment for patients. Therefore, predictive markers of efficacy are very important for identifying patients who may benefit from neoadjuvant immunotherapy in order to achieve accurate treatment.

Characteristics of tumor cells

The value of PD-L1 and tumor mutational burden (TMB) in predicting the efficacy of immunotherapy has been confirmed in large clinical studies. In the neoadjuvant therapy, CA209-159, and LCMC3 studies, there was no significant correlation between PD-L1 expression and MPR (14,15,18,53). In the NEOSTAR study, patients with higher PD-L1 before treatment were more likely to achieve an MPR, and those with PD-L1>1% had fewer residual tumors after treatment (20% vs. 80%) (22). The CA209-159 study showed a positive correlation between TMB and MPR (14,15); however, LCMC3 studies did not observe any relationship between TMB and MPR (18). The

NADIM study showed that there was no significant difference in PFS among different TMB groups, while the group with no specific mutation (*STK11*, *KEAP1*, *RBI*, *EGFR*) and higher TMB had longer PFS (19).

Immune microenvironment of tumor

The type, quantity, expression level of inhibitory molecules, activity (54), spatial distribution (55), and changes before and after treatment (56) of the immune cells in tumor immune microenvironment, are all important biomarkers for predicting the efficacy of immunotherapy (57). Ipilimumab neoadjuvant therapy can significantly activate CD4 and CD8 cells in a CD28-dependent manner and increase the frequency of CD4+ cell activation markers such as ICOS, HLA-DR, CTLA-4, and PD-1 (58). Patients who achieved MPR in the LCMC3 study were assessed for an increase in the proportions of natural killer cells and granulocyte subsets as well as a decrease in the proportion of monocyte subsets (18). The results of the NEOSTAR study showed that neoadjuvant immunotherapy with double ICI could induce local tumor CD3+ T-cell proliferation, T-cell diversity, and a significant increase in memory T cells (22). Parra *et al.* found that higher levels of tumor associated macrophages (TAMs) in NSCLC patients treated with neoadjuvant chemotherapy were associated with better survival outcomes (59). The histological indexes of surgical specimens reflect more of the role of immunotherapy alone. Therefore, the evaluation of the changes of IC expression in immune cells after operation can better evaluate the therapeutic response of neoadjuvant immunotherapy (60).

Markers of peripheral blood circulation

Circulating tumor DNA (ctDNA) may originate from necrotic or apoptotic tumor cells, circulating tumor cells, efflux secreted by tumor cells, and so on, which is also an important prognostic marker. The CA209-159 study showed that ctDNA clearance may be a potential predictor of treatment efficacy and can be used to monitor the recurrence of neoadjuvant immunotherapy (14,15). The detection of circulating tumor cells (CTCs) is more sensitive than ctDNA, and it can dynamically monitor the "evolution" of tumor cells (61). However, at the same time, the number of CTCs in early lung cancer is lower, and the technology of detection is more complicated, so it has not been widely used. Researches have shown that the prognosis of NSCLC patients whose PD-L1 expression of

CTC turns negative after 6 months of nivolumab treatment was better (62), so dynamic monitoring of PD-L1 expression in CTC is also a potential marker of neoadjuvant immunotherapy.

As the main component of tumor immunity, CD8+T cell counts were observed to increase synchronously in tumor tissues and peripheral blood circulation after neoadjuvant immunotherapy (14,53). Tumor-specific T cells in the blood have the potential to eradicate minimal lesions, reduce distal recurrence, and promote a more lasting anti-tumor immune response. The CA209-159 study showed that T-cell proliferation in the peripheral blood may be a potential predictor of the efficacy of neoadjuvant immunotherapy in patients with NSCLC and can be used to monitor recurrence (15). In the LCMC3 study, patients with MPR had the expansion of natural killer cells and granulocytes in peripheral blood, as well as the changes of dendritic cells, B cells, and T cells in lymph nodes (53). In the POPLAR study, it was found that patients with good response to immunotherapy had more specific T cells in their peripheral blood, and most of which were in a state of stimulation (63). Compared with tumor infiltrating lymphocyte, circulating immune cells are easier to monitor dynamically and they have certain clinical value.

Markers of HP

The incidence of HP after immunotherapy was between 4% and 29% (64). The occurrence of HP, like a poor immunotherapy response, may cause patients to lose the opportunity for surgery. Unfortunately, no predictors have been identified to predict HP so far. Older patients (13), and those diagnosed with more metastatic sites; higher number of tumor-infiltrating macrophages that co-express CD163, CD33, and PD-L1 (65); *MDM2/MDM4* gene amplification; or *EGFR* amplification, may have HP (66). At present, only a few clinical studies on neoadjuvant immunotherapy have been conducted, and there is no available study on HP. ctDNA may be a useful tool for predicting HP (67), which is expected to optimize the efficacy evaluation system of NSCLC neoadjuvant immunotherapy in the future, but still needs to be verified in a larger cohort.

At present, there is no evidence that molecular markers can predict the efficacy of neoadjuvant immunotherapy, and biomarker-based selection is not essential. The use of biomarkers for immunotherapy efficacy in early-stage NSCLC patients is still under exploration.

Conclusions

Generally speaking, neoadjuvant immunotherapy can achieve an ideal MPR rate and has the potential for continuous antitumor immunity, which shows good treatment prospects in patients with resectable NSCLC. Among the existing early results on the benefits of neoadjuvant immunotherapy, the MPR of ICI monotherapy and ICI combined with chemotherapy reached 45.5% and 85.36%, respectively, which was three times higher than the MPR of chemotherapy (68,69). However, some problems remain. The side effects of ICIs and the occurrence of PD or distant metastasis during neoadjuvant immunotherapy are the associated risks that must to be considered. The search for appropriate biomarkers for identifying patients who can benefit from neoadjuvant immunotherapy and those who may need adjuvant immunotherapy should be taken into consideration. At present, most of the clinical studies are exploratory, the sample sizes are small (approximately 20–40 patients), and the follow-up time is relatively short. Hence, future prospective, large sample, long-term follow-up studies are needed to further confirm the efficacy of neoadjuvant immunotherapy. Although the current results of the benefits of neoadjuvant immunotherapy are not satisfactory, there is still room for exploration.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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