Review Article

Neoadjuvant immunotherapy in non-small cell lung cancer: a narrative review on mechanisms, efficacy and safety

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Background and Objective: Immune checkpoint inhibitors and immunotherapy have been shown to improve survival rates, especially in non-small cell lung cancer (NSCLC) patients. More recently, several trials have evaluated the clinical roles of immunotherapy as neoadjuvant settings for NSCLC. There trials suggested that neoadjuvant immunotherapy may effectively reduce the risk of the local recurrence and metastasis of cancer, and significantly improved overall survival and cure rates. Here we conducted a review to summarize the possible mechanism, clinical development, and research progress of neoadjuvant immunotherapy in NSCLC.

Methods: Relevant articles for this review were retrieved from Google Scholar, Clinicaltrials.gov., and PubMed using the terms "non-small-cell lung cancer", "NSCLC", "neoadjuvant", "immunotherapy", "immune checkpoint inhibitors", "mechanisms", and "toxicity". The primary focus was placed on clinical studies and conference abstracts measuring the safety and efficacy of neoadjuvant immunotherapy in NSCLC until May 2022.

Key Content and Findings: After reviewing the preclinical and clinical trial, the preclinical study showed that neoadjuvant immune checkpoint inhibitor promotes antitumor immunity through the enhancement of T cell effector function and the induction of long-term memory. The initial results of preliminary early-phase trials suggested that neoadjuvant immunotherapy is a promising therapeutic strategy for resectable NSCLC patients, with long-term response and modest toxicity, many of these regimens are currently being evaluated by randomized phase III trials. In addition, the major pathologic response of neoadjuvant immunotherapy ranged up to 45% in these studies when used alone, and up to around 83–86% when used in combination with chemotherapy, therefore it has been seen as a rather potent tumor debulking agent.

Conclusions: Neoadjuvant immunotherapy has been shown to be a novel integral component of NSCLC care. However, there are also several research questions that requires further investigation, such as the side effects, the optimally treated patients, and the time of preoperative immunotherapy.

Keywords: Neoadjuvant; immunotherapy; immune-checkpoint inhibitors; non-small cell lung cancer (NSCLC)

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Introduction

According to Global Cancer Observatory (GLOBOCAN) 2020, lung cancer, which is also the 2nd most commonly diagnosed malignancy, is the leading cause of cancer-related death worldwide (1). The National Cancer Center of China estimated that there would be 549,800 (24.6%) new cases of lung cancer and 454,700 (29.71%) deaths from lung cancer in 2016 in China (2). Among all new lung cancer diagnoses, approximately 85% are non-small cell lung cancer (NSCLC) (3). Surgery is the main treatment option for patients with early stage NSCLC, and the surgery followed by adjuvant chemotherapy is the most common treatment for patients with locally advanced resectable NSCLC. Complete surgical resection is curative for some NSCLC patients; however, 25–70% of patients will eventually relapse after complete resection (4). It has been shown that platinum-based adjuvant chemotherapy can increase the 5-year survival rate of patients marginally by 4–8% (5-7). Among the eligible patients who received surgery and adjuvant therapies, it has been reported that 20–30% of stage I, 50% of stage II, and 60% of stage IIIA patients died within 5 years (8).

In 2021, the phase-III IMpower010 study (NCT 02486718) reported the first results on the use of adjuvant immunotherapy in the treatment of stage IB–IIIA NSCLC (9). After treatment with adjuvant platinum-based chemotherapy plus adjuvant atezolizumab, the patients with completely resected stage II–IIIA NSCLC showed significant improvements in terms of disease-free survival (DFS) compared to those who received the best supportive care after adjuvant chemotherapy treatment. The IMpower010 study changed the landscape of adjuvant treatment in NSCLC therapy and led to the approval of adjuvant atezolizumab by the Food and Drug Administration for resected NSCLC patients with programmed death-ligand 1 (PD-L1) ≥1%.

Neoadjuvant therapy has the potential to improve the survival of resectable NSCLC patients. Defined originally as systemic therapy (hormonal therapy or chemotherapy), neoadjuvant therapy has been extended from being administered before local treatment, to include radiation therapy which is given before surgery. Compared to adjuvant therapy, neoadjuvant therapy has a number of advantages, including better tolerability, and an ability to reduce the tumor burden before surgery and provide early treatment for micro-metastasis (10,11).

In recent years, immune checkpoint inhibitors and immunotherapy have been shown to improve survival rates, especially in NSCLC patients (12). By blocking the cancer-derived inhibitory signal on effector T cells, and removing residual cancer cells and small lesions, immunotherapy drugs, including programmed cell death 1 (PD-1), PD-L1, and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), can prevent tumor recurrence and metastasis. In advanced and metastatic settings, immunotherapy has been added to NSCLC treatment, and has become an integral component of standard care. In addition, due to the sustained elevated tumor-specific immune response, neoadjuvant immune checkpoint inhibitors have been shown to be more effective than adjuvant immune checkpoint inhibitors in eliminating distant metastases on a pre-clinical level (13). Similarly, combined neoadjuvant immunotherapy also appears to be more effective than adjuvant therapy in a murine model (14).

To date, many clinical trials have reported promising results and others are underway. Here, we conducted a review to summarize the possible mechanism, clinical development, and research progress of neoadjuvant immunotherapy in NSCLC. Additionally, we present some unresolved issues, including the immune-related adverse events in various organs induced by immune checkpoint inhibitors, efficacy prediction, how to screen the optimally treated patients of neoadjuvant immunotherapy, end points setting, and the time of preoperative immunotherapy. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1192/rc).

Methods

To complete this review, we conducted a literature search to identify relevant articles, using databases, including Google Scholar, Clinicaltrials.gov., and PubMed. We also included abstracts from major clinical conferences, including world conferences on lung cancer, such as the conferences of International Association for the Study of Lung Cancer (IASLC), European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and American Association for Cancer Research. The primary focus was placed on clinical studies and conference abstracts measuring the safety and efficacy of neoadjuvant immunotherapy in NSCLC until May 2022. The following search terms were used in the literature search: “NSCLC”, “non-small-cell lung cancer”, “lung cancer”, “neoadjuvant”, “immunotherapy”, “mechanisms”, “checkpoint inhibitors”, and “toxicity”. In this review, we only included articles and abstracts published in English. The results of the various

Table 1 The search strategy summary

Items	Specification
Date of search	May 31, 2022
Database and other sources searched	Google Scholar, Clinicaltrials.gov., and PubMed
Search terms used	NSCLC [all fields] OR non-small-cell lung cancer [all fields] OR lung cancer [all fields] OR neoadjuvant [all fields] OR immunotherapy [all fields] OR mechanisms [all fields] OR checkpoint inhibitors [all fields] OR toxicity [all fields]
Timeframe	Articles and abstracts were published from October 1998 to May 2022
Inclusion and exclusion criteria	English-language articles include clinical trials, abstracts from major clinical conferences, reviews and cited literatures
Selection process	Lan Shao and Guangyuan Lou conducted the selection independently. The consensus was obtained through their discussion

relevant studies and trials were summarized narratively. Information used to write this review was collected from the sources listed in *Table 1*

Mechanism of neoadjuvant immunotherapy for NSCLC

Under the neoadjuvant treatment approach, cancer immunotherapies are administered after the identification of the primary tumor. Presently, there is only limited evidence of the superior efficacy of neoadjuvant immunotherapy compared to adjuvant immunotherapy. It is widely accepted that the presence of a full tumor mass at the start of immunotherapy enables the induction of an extensive and strong T-cell response (15).

Reinvigorated tumor-specific cluster of differentiation (CD)8^+ T cells, which can kill the existing tumor and recirculate into the blood, may re-expand after the administration of cancer immunotherapy. Additionally, the release of new tumor antigens can be caused by an existing tumor-specific T-cell response (16). Antigen-presenting cells (APC) can present these new tumor antigens to prime naïve T cells, which have tumor specificity against distinct tumors. Following primary tumor resection, the tumor-specific $CD8^+$ T cells that present at the metastatic sites and those that remain circulating have an increased T-cell: tumor ratio, which could result in the destruction of the remaining tumor tissue. After the clearance of the tumor, a stable pool of tumor-specific $CD8^+$ T cells may remain (13). Research has shown that following neoadjuvant immunotherapy in mice, all of the immune responses have been observed to remain for the remainder of the lives of the surviving mice (17,18).

Additionally, in some cases, the peripheral expansion of T-cell clones, which was not detected in the primary tumor on treatment, has also been observed following neoadjuvant immunotherapy (15,19). There are two possible explanations for this. First, it may be that there were already expanded T-cell clones present in the primary tumor, but the baseline readouts were below the detection limit (15). Second, it may be that immediately following treatment, a proliferative burst occurred in the immunodominant T-cell clones. By enabling the generation of new tumor-specific $CD8^+$ T cells and iterative revolutions of the cancer immunity cycle, the proliferative burst promoted epitope spreading (20,21).

Thus, increasing the anti-tumor effect of the autoimmune system and reducing tumor-induced immunosuppression benefit the immune checkpoint inhibitors. Motivation for the clinical evaluation of neoadjuvant immunotherapy has been fueled by these encouraging preclinical findings.

Clinical studies of neoadjuvant immunotherapy in NSCLC

There has been an explosion of recent and ongoing trials evaluating the effect of neoadjuvant immunotherapy on NSCLC. In 2018, Forde *et al.* performed a pilot study (NCT02259621) to examine the effect of neoadjuvant nivolumab (a PD-1 inhibitor) in 21 patients with untreated, surgically resectable early (stage I, II, or IIIA) NSCLC (22). Of the 21 patients, 20 received 2 preoperative doses of nivolumab every 2 weeks. The primary end points of the study were the safety and feasibility of the treatment. The results showed that 9 [45%, 95% confidence interval (CI):

23–68%] of 20 the patients achieved a major pathologic response (MPR). Neoadjuvant treatment-related adverse events (TRAEs) were observed in 5 patients, but only 1 patient experienced grade ≥3 pneumonia. There were no treatment-related surgical delays, and the median interval between administration of the 2nd dose of nivolumab and surgery was 18 days [interquartile range (IQR) 11–29 days].

Subsequently, Gao *et al.* found similar results for resectable NSCLC patients who received 2 cycles of neoadjuvant sintilimab (a PD-1 inhibitor) (23). In this phase-Ib study (ChiCTR-OIC-17013726), 40 patients with stage IA–IIIB NSCLC received 2 doses of sintilimab, and 37 patients underwent radical resection. Among the 37 patients, 15 patients (40.5%, 95% CI: 24.8–57.9%) achieved an MPR and 6 patients (16.2%, 95% CI: 6.2–32.0%) achieved a pathologic complete response (pCR). Immunotherapy-related adverse events (AEs) were observed in 21 patients (52.5%), of whom 4 patients (10%) experienced a grade ≥3 adverse event, and 1 patient experienced a grade 5 adverse event. The findings of Forde *et al.* and Gao *et al.* (22,23) demonstrated that there was a substantial expansion of CD8 cells in the resected tumors and post-surgery peripheral blood. Before and after surgery, blood sampling for tumor-specific CD8+ T cells is correlated with patients' responses to therapy, which may provide a potential biomarker for neoadjuvant immunotherapy (24,25).

In 2021, a large multicenter phase-II trial (LCMC3, NCT0292730) analyzed the effect of 2 cycles of neoadjuvant atezolizumab (PD-L1 inhibitors) in 181 patients with stage IB–IIIA (selected IIIB) NSCLC (26). Of the 181 patients, 159 (88%) underwent surgical resection, and the median time from the end of the neoadjuvant therapy to surgery was 22 days. Excluding 8 patients who had driver mutations (7 had epidermal growth factor receptor (EGFR), 1 had anaplastic lymphoma kinase (ALK), and 0 had MPR), 20.4% (95% CI: 14–28%) achieved an MPR and 6.8% (95% CI: 3–12%) achieved a pCR. TRAEs of any grade were observed in 56% of the patients, but only 5% of these were grade ≥3 TRAEs. Immunotherapy-related AEs were only observed in 24.3% of the patients, and only 2.2% of these were grade ≥3 TRAEs. In another phase-II clinical trial (PRINCEPS, NCT02994576) by Besse *et al.*, neoadjuvant atezolizumab was used to treat 30 patients with resectable clinical stage IA (≥2 cm)–IIIA, non N2 NSCLC (27). Among the patients, 4 (14%) achieved an MPR and 12 (41%) had <50% residual tumor cells. Further, a metabolic response (a variation of maximum standardized uptake value (SUV_{max}), ^{18}F-FDG PET/CT) was observed. This study also sought to examine the safety of neoadjuvant atezolizumab, and only 1 patient suffered from the grade 1 TRAE of parietal pain related to surgery.

At the ESMO Virtual Congress 2020, Eichhorn *et al.* presented a phase-II clinical trial (NEOMUN, NCT03197467) in which neoadjuvant pembrolizumab (a PD-1 inhibitor) was used to treat patients with resectable NSCLC stage II/IIIA (28). The patients received 2 cycles of pembrolizumab before surgery. Among the patients, 4 (27%) achieved an MPR. Additionally, 5 patients (33%) suffered from grade 2–3 TRAEs.

In addition, Wislez *et al.* presented the interim results of another phase-II trial (IONESCO, NCT03030131), which analyzed the administration of neoadjuvant durvalumab (a PD-L1 inhibitor) (29). In total, 46 eligible patients with stage IB–IIIA, non-N2, resectable NSCLC were included in this study, of whom, 43 underwent surgery. The primary endpoint was the rate of complete surgical resection (R0), which was achieved in 90% (41/43) of the patients who underwent surgery. The pathologic analysis showed that 18.6% of the patients achieved an MPR, and 7% achieved a pCR. No grade 3–5 immunotherapy-related AEs were observed.

The results of the above-mentioned studies examining the use of neoadjuvant immune-checkpoint inhibitors in resectable NSCLC patients are summarized in *Table 2*. The common findings include generally high resection rates, encouraging pathological regression rates, and an overall manageable toxicity profile.

Clinical studies of combination neoadjuvant immunotherapy in NSCLC

Trials that analyze the effect of immune-checkpoint inhibitor combinations have been conducted to further explore the potential of neoadjuvant immunotherapy in treating NSCLC. In 2021, Cascone *et al.* published the outcomes of a phase-II randomized NEOSTAR trial (NCT03158129) in which 44 patients with operable NSCLC were treated with neoadjuvant nivolumab or nivolumab plus ipilimumab (anti-CTLA-4) followed by surgery (30). Of the 44 patients, 41 completed the planned neoadjuvant therapy, and 37 received surgery. Of the 37 patients who underwent resection, 24% (5/21) and 50% (8/16) of the patients achieved an MPR in the nivolumab arm and the nivolumab plus ipilimumab arm, respectively. The pCR rate of the nivolumab plus ipilimumab arm

Table 2 Clinical trials with reported results for neoadjuvant immunotherapy in NSCLC

Regimen	Study	Time	Phase	Sample size	MPR (%)	pCR (%)	TRAEs (%)	
							Any grade	Grade ≥3
Nivolumab (22) (2 cycles)	NCT02259621	2018	II	20	45	15	23	4.5
Sintilimab (23) (2 cycles)	NCT17013726	2020	II	37	40.5	16.2	52.5	10
Atezolizumab (26) (2 cycles)	NCT02927301 (LCMC3)	2021	II	147	20.4	6.8	56	5
Atezolizumab (27) (1 cycle)	NCT02994576 (PRINCEPS)	2020	II	29	14	0	3	0
Pembrolizumab (28) (2 cycles)	NCT03197467 (NEOMUN)	2020	II	15	27	13	53	33
Durvalumab (29) (3 cycles)	NCT03030131 (IONESCO)	2020	II	43	18.6	7	–	–

NSCLC, non-small cell lung cancer; MPR, major pathologic response; pCR, pathologic complete response; TRAE, treatment-related adverse event.

(38%) was higher than that of the nivolumab arm (10%). The results indicated that combination neoadjuvant immunotherapy enhances pathologic responses, tumor immune infiltrates, and immunologic memory compared to single-agent immunotherapy. Compared to known safety profiles of nivolumab and nivolumab plus ipilimumab, no new safety signals were observed. Grade 3–5 TRAEs were reported in 13% (3/23) of the patients treated with nivolumab and 10% (2/21) of the patients treated with nivolumab plus ipilimumab.

Reuss *et al.* performed another phase-Ib/II clinical trial (NCT02259621) evaluating a combination immunotherapy of neoadjuvant nivolumab plus ipilimumab in 9 patients with resectable stage IB (≥4 cm)–IIIA NSCLC (31). Of the 6 patients who underwent resection, a pCR was observed in 2 (33%) of the 6 resected tumors, without any MPR and 6 (67%) of the 9 patients did not experience a TRAE of any grade, but 3 (33%) experienced grade 3 TRAEs.

Clinical studies of neoadjuvant immunotherapy combined with chemotherapy and radiotherapy in NSCLC

Anti-tumor immunity can be enhanced by chemotherapy and radiotherapy in various ways, including by modulating the immune cells and inducing immunogenic cell death in the tumor microenvironment (32). To examine whether the benefits of immunotherapy can be improved by its concurrent use with radiotherapy or chemotherapy, trials are being developed based on the activity of immune-checkpoint inhibitors in metastatic NSCLC.

Neoadjuvant immunotherapy combined with chemotherapy

In 2020, Shu *et al.* first developed a multicenter, single-arm, phase-II trial (NCT02716038) of atezolizumab in combination with carboplatin and nab-paclitaxel as a neoadjuvant treatment before surgical resection (33). A total of 30 patients with stage IIIA NSCLC were enrolled in the study. Of the 30 patients, 29 (97%) underwent surgery, and 26 (87%) underwent successful R0 resection. Of the 30 patients, 17 (57%; 95% CI: 37–75%) achieved an MPR, and 33% (95% CI: 19–51%) achieved a pCR. The most common grade 3–4 TRAEs were mainly chemotherapy related, and 50% of patients suffered from neutropenia.

Subsequently, Provencio *et al.* conducted another open-label, multicenter, single-arm, phase-II trial (NADIM, NCT03081689) in which neoadjuvant nivolumab with carboplatin and paclitaxel, followed by adjuvant intravenous nivolumab monotherapy for 1 year was used to treat resectable NSCLC (34). It should be noted that there was some positive selection in this study; approximately 50% of the patients had better prognosis stage IIIA (cT1 or cT4N0) disease. In total, 46 patients with stage IIIA (N2 or T4N0) NSCLC were enrolled in the study. Of the 41(89%) patients who underwent resection, MPR was achieved in 83% (95% CI: 68–93%) of patients, of whom 63% (95% CI: 62–91%) achieved a pCR. The 2-year progression-free survival [intent-to-treat (ITT) population], which was the primary endpoint of the study, was 77.1% (95% CI: 59.9–87.7%). In terms of toxicity, 43 (93%) of the 46 patients suffered from TRAEs during neoadjuvant treatment, and 14 (30%) patients suffered from grade ≥3 TRAEs. None of the

Table 3 Clinical trials with reported results for neoadjuvant immunochemotherapy in NSCLC

Regimen	Study	Time	Phase	Sample size	MPR (%)	pCR (%)	TRAEs (%)	
							Any grade	Grade ≥3
Atezolizumab + nab-paclitaxel + carboplatin (33) (2 cycles)	NCT02716038	2020	II	26	57	33	93	50
Nivolumab + paclitaxel + carboplatin (34) (3 cycles)	NCT03081689 (NADIM)	2020	II	41	83	63	93	30
Cisplatin + docetaxel (3 cycles) followed by durvalumab (35) (2 cycles)	NCT02572843	2020	II	55	60	18.2	–	12.9
Nivolumab + cisplatin + pemetrexed/gemcitabine (36) (3 cycles)	NCT03366766	2020	II	13	85	39	–	15
Toripalimab + carboplatin + pemetrexed/nab-paclitaxel (37) (3 cycles)	NCT04304248 (NeoTPD01)	2021	II	30	66	50	–	9
Pembrolizumab + nab-paclitaxel + carboplatin (38) (2 cycles)	N/A	2021	N/A	37	65	54	–	13.5
Camrelizumab + nab-paclitaxel + cisplatin (39) (2 cycles)	NCT04338620	2020	III	7	86	57	–	–
Avelumab (4 cycles) + cisplatin/ carboplatin and gemcitabine/pemetrexed (3 cycles) (40)	NCT03480230	2020	II	11	27	9	–	27
Ipilimumab (2 cycles) + paclitaxel and cisplatin/carboplatin (3 cycles) (41)	NCT01820754	2018	II	13	15	15	69	38
Nivolumab + platinum doublet (3 cycles) (42)	NCT02998528 (CheckMate 816)	2021	III	179	36.9	24	–	33.5

NSCLC, non-small cell lung cancer; MPR, major pathologic response; pCR, pathologic complete response; TRAE, treatment-related adverse event.

AEs were associated with surgery delays or deaths.

Similarly, at the ESMO Virtual Congress 2020, Rothschild *et al.* presented the findings of their phase-II clinical trial (SAKK 16/14, NCT02572843) in which standard neoadjuvant cisplatin and docetaxel combined with neoadjuvant durvalumab was used to treat patients with stage IIIA (N2) NSCLC (35). In total, 68 patients were enrolled in the study. Of the 55 (80.9%) patients who underwent resection, an MPR was achieved in 60% of the patients, of whom 18.2% achieved a pCR. The 1-year event-free survival (EFS), which was the primary endpoint of the study, was 73.3% (90% CI: 60.1–82.7%). In terms of toxicity, 12.9% of the patients suffered from grade 3–4 AEs, which were attributed to the neoadjuvant durvalumab. The findings of several related studies that used neoadjuvant chemoimmunotherapy to treat NSCLC are detailed in *Table 3*.

Upon review, the MPR and pCR rates reported for immunotherapy only range from 14–45% and 0–16.2% (33-42). Conversely, the MPR and pCR rates reported for the combination therapy of chemotherapy and neoadjuvant immunotherapy range from 15–86% and 9–63%, respectively (33-42). Further, there is evidence that the combination therapy may lead to increased anti-tumor activity (33-42). However, given the high rates of AEs and TRAEs related to these treatments, immunochemotherapy may be less tolerated than immunotherapy alone. Following the promising results of the early phase chemoimmunotherapy studies, many of the regimens are currently being evaluated by randomized phase III trials.

In 2021, Forde *et al.* (42,43) conducted an open-label, phase-III trial (CheckMate 816, NCT02998528) of patients with resectable stage IB to IIIA NSCLC to compare the efficacy and safety of neoadjuvant nivolumab plus chemotherapy (3 cycles) to chemotherapy alone (3 cycles). The result showed that the median EFS was 31.6 months (95% CI: 30.2 months–not reached) in the nivolumab plus chemotherapy group and 20.8 months (95% CI:

14.0–26.7 months) in the chemotherapy alone group. The pCR rate was 24.0% (95% CI: 18.0–31.0%) in the nivolumab plus chemotherapy group as compared with 2.2% (95% CI: 0.6–5.6%) in the chemotherapy alone group. The MPR rates were 36.9% and 8.9% in the nivolumab plus chemotherapy group and chemotherapy alone group, respectively. Grade 3–4 surgery-related AEs were reported to be 33.5% and 36.9% for the nivolumab plus chemotherapy group and the chemotherapy alone group, respectively. Based on the CheckMate 816 trial results, nivolumab plus chemotherapy was approved for use in the United States as a neoadjuvant treatment for patients with resectable NSCLC.

Additionally, several investigator-initiated phase-II clinical trials are pending or ongoing, such as NCT03800134 (AEGEN, Durvalumab + platinum doublet), NCT03425643 (Keynote671, pembrolizumab + cisplatin doublet), NCT03456063 (IMpower030, atezolizumab + platinum doublet), NCT04025879 (CA209-77T, nivolumab + platinum doublet), and NCT04379635 (BGB-A317-315, tislelizumab + platinum doublet).

Neoadjuvant immunotherapy combined with radiotherapy

As another treatment, radiotherapy is suggested and is currently being evaluated to determine whether it can be used in the neoadjuvant setting in combination with immunotherapy. In 2021, Altorki *et al.* (44) published the results of a single-center, randomized, controlled, phase-II trial (NCT02904954) comparing neoadjuvant durvalumab therapy alone to neoadjuvant durvalumab plus stereotactic radiotherapy in patients with early stage NSCLC. The study included 60 patients with potentially resectable early stage NSCLC. The results of the study showed that the MPR rate was significantly improved in the neoadjuvant durvalumab plus stereotactic radiotherapy group (53.3% *vs.* 6.7%). Of the 16 patients who received neoadjuvant durvalumab plus stereotactic radiotherapy and achieved an MPR, 50% achieved a pCR. Grade 3–4 AEs were observed in 5 (17%) of the 30 patients in the durvalumab monotherapy group and 6 (20%) of the 30 patients in the durvalumab plus radiotherapy group.

Additionally, a number of clinical studies are currently ongoing or pending, including NCT03871153, NCT03694236, NCT03237377, and NCT03446911. These studies will provide more important information on the efficacy and safety of neoadjuvant immunotherapy combined with radiotherapy in the treatment of NSCLC.

Conclusion and future directions

Neoadjuvant immunotherapy has proven to be a novel integral component of NSCLC care. The promising results of early clinical trials demonstrate that it is a safe and feasible approach that merits further study. However, there are also several research questions that require further investigation. Immune checkpoint inhibitors can induce the immune-related adverse events (irAEs) in various organs. The immune related organs, including intestine, thyroid, skin and liver, are the main attacked organs (45,46). Compared with traditional chemotherapy and targeted therapy, neoadjuvant immunotherapy may destroy the primary tumor vascularization and microenvironment causing problems following surgery, such as delaying surgery and increasing the risk of intraoperative complications (47,48). Screening the patients who can benefit from neoadjuvant immunotherapy and finding the appropriate biomarkers to predict the curative effect will seem to be the important objective. Until now, PD-L1 expression and tumor mutation burden (TMB) are the main biomarkers of immune checkpoint inhibitors which have been confirmed by clinical trials (49,50). However, the application of PD-L1 expression or TMB as a biomarker of response in NSCLC remains to be further confirmed. In addition, although OS is the standard endpoint in early-stage NSCLC, most of the neoadjuvant immunotherapy trials has not included it as a primary endpoint. Because it will take numerous years to obtain the mature data for the NSCLC trials with OS as the primary endpoint, thus resulting enormous cost of drug development and significant long time till potential drug approval (51). MPR or pCR seems to be the most often surrogate for OS when using neoadjuvant immunotherapy in NSCLC, but its accuracy should be tested by long-term survival data. At present, there is still lack of a uniform endpoint in the ongoing studies. Many researches showed that the time span of preoperative immunotherapy may affect the long-term survival. To date, 2–4 cycles of neoadjuvant therapy are the adopted design for most studies. To reduce the incidence of irAEs and improve immune activity, shortening the duration of neoadjuvant therapy has proven to be effective. However, how many cycles of immunotherapy should be used as neoadjuvant therapy and what is the most reasonable dosage, these are the specific questions that need further exploration. Questions remain as to how to determine the best approach for each patient. Ultimately, in

deciding the optimal approach, the arbiter remains overall survival; however, data on overall survival are lacking in both adjuvant and neoadjuvant immunotherapy trials. Thus, decisions will largely need to be guided by patient choice, the ease of surgery, and disease presentation.

For resectable NSCLC, the standard of care may be revolutionized in the future by the use of neoadjuvant immunotherapy alone or combined with other therapies. Thus, we eagerly await the results of the ongoing randomized trials that seek to determine if and how this original approach can be optimally used to treat patients with NSCLC.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1192/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1192/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved.

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