The role of immunotherapy in neoadjuvant treatment of non-small cell lung cancer—a narrative review

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Background and Objectives: Immune checkpoint inhibitors (ICIs) have undoubtedly reversed the paradigms of treatment of non-small cell lung cancer (NSCLC) in stage III and IV of the disease, and the intention is to transfer good experience from advanced stages into the resectable disease. Their role in the perioperative setting was investigated through trials with mono-immunotherapy and in combination with chemotherapy. The aim is to obtain an overview of data on immunotherapy in the neoadjuvant setting, as detailed as possible from available studies of earlier phases.

Methods: We searched the database PubMed, Google Scholar as well as the clincaltrials.gov database for data on clinical trials researching ICIs efficacy in neoadjuvant treatment of NSCLC. The search included the timeframe before August, 31st 2023. Only articles available in English were included.

Key Content and Findings: ICI therapy in the neoadjuvant setting has been researched trough several clinical trials, whether as monotherapy or in combination with chemotherapy. The results are promising and suggest a significant benefit of neoadjuvant chemoimmunotherapy compared to neoadjuvant chemotherapy, with good tolerability. The up do date data are still too immature to reach final conclusions about perioperative treatment, especially regarding overall survival (OS), but the approval of nivolumab/paclitaxel/carboplatin chemoimmunotherapy as the standard of neoadjuvant treatment sufficiently demonstrates the strength of the results so far.

Conclusions: New findings on neoadjuvant immunotherapy suggest an advantage of ICIs and chemotherapy combination regimens in terms of efficacy and safety over current standards of care, but many key questions still remain unanswered. However it is safe to presume that upcoming trial results will make further changes in everyday standard of care.

Keywords: Non-small cell lung cancer (NSCLC); immunotherapy; neoadjuvant therapy; immune checkpoint inhibitors (ICIs)

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Introduction

Background

Lung cancer is one of the most common malignancies and the most common cause of death from malignant disease in men and women worldwide (1,2). Even more than in other cancer sites, in the last few years we have witnessed great progress in the treatment of non-small cell lung cancer (NSCLC), where immunotherapy with immune checkpoint inhibitors (ICIs) is the main carrier of this positive shift (3).

The vast majority of immunotherapy studies in lung cancer relate to stage IV disease where dozens of larger, randomized clinical studies have shown the benefit of immunotherapy in the treatment of NSCLC, whether as monotherapy or in combination with chemotherapy, either as first-line or in previously treated patients (4). Great progress has also been made in the treatment of unresectable stage III NSCLC, where the addition of immunotherapy to chemoradiotherapy, as shown in the PACIFIC trial [overall survival (OS) 47.5 *vs.* 29.1 months, hazard ratio (HR) 0.72], has significantly contributed to disease control time and prolonged survival (5).

The broader goal of treating any cancer, including lung cancer, is to make a diagnosis at an early stage of the disease, where there is a chance of achieving complete cure with surgery. According to current data, about 18% of lung cancers are detected in the localized phase of the disease, while an additional 22% are cases with spread to regional lymph nodes, of which about 50% are potentially resectable (6). However, despite the limited stage of the disease at the time of diagnosis, the 5-year OS of patients with stage I and II lung cancer is only about 59%. Over 40% of patients experience a relapse within 5 years, most often in terms of distant metastases (6).

Today's standard of care for treating stage I–IIIA disease is surgical resection. Based on the results of randomized trials and real world data, adjuvant or neoadjuvant chemotherapy is combined with surgical treatment, with the aim of achieving better control of disease recurrence. Unfortunately, the benefit of 5-year survival by adding adjuvant chemotherapy is only about 5% (7,8).

Adjuvant chemotherapy after surgical resection of NSCLC definitely holds its place in the treatment algorithm, primarily thanks to clinical studies conducted in the mid-2000s. Thus, the IALT (9), JBR.10 (10) and ANITA (11) studies compared the adjuvant use of cisplatin and vinorelbine in patients with resected NSCLC and showed a certain benefit of the use of chemotherapy compared to follow-up (HR 0.86, 0.69 and 0.80, respectively). Adjuvant paclitaxel and carboplatin also led to a improvement in survival in patients with stage IB resected disease (HR 0.83) (12).

Further studies have shown the benefit of treatment with combinations of cisplatin and gemcitabine and cisplatin and docetaxel for squamous cell and cisplatin and pemetrexed for non-squamous cell carcinomas (13,14). Finally, the LACE meta-analysis established adjuvant chemotherapy as standard-of-care in resected NSCLC, with vinorelbine and cisplatin as a preferred combination (7).

Plenty of hope has been placed in neoadjuvant therapy, as several retrospective studies have shown superiority over adjuvant treatment: a 2020 study by Xu *et al.* showed a benefit in OS of patients receiving neoadjuvant therapy over those treated with adjuvant chemotherapy (5-year OS 56.2% *vs.* 33.0%, P=0.006), while another study compared neoadjuvant and adjuvant chemoradiotherapy in over 1,700 patients (5-year OS rate: 38.1% *vs.* 26.3%; HR 0.74; P<0.001) (15,16). Only a few retrospective studies and no phase III study have been published about a direct comparison of outcomes of induction versus adjuvant chemotherapy delivery in stage IIIA (N2) patients and the proper timing still remains an unsolved question (17,18).

In treatment of lung cancer, ICIs typically target one of two signalling pathways: programmed death/programmed death ligand 1 (PD-1/PD-L1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). These pathways, in the physiological environment, serve to control lymphocyte proliferation and differentiation (CTLA-4) or to regulate the T-cell response to a particular cell (PD-1), while tumours use them to avoid an immune response (19).

Several drugs that block these pathways have been tested, in monotherapy or as dual therapy, in clinical studies, where their efficacy in the treatment of metastatic melanoma, NSCLC and renal cell carcinoma has been demonstrated (20,21).

The rationale behind the use of immunotherapy preoperatively is to improve the outcome of surgical treatment. Stimulation of the immune system should lead to disease control until the surgery itself, and possible downstaging, allowing time for preoperative preparation, reducing the probability of tumor (micro)metastasis (22). Compared to exclusively adjuvant treatment, the analysis of resected material after neoadjuvant immunotherapy enables additional analyzes of the tumor immune microenvironment, which can be useful in further research—an opportunity which the application of immunotherapy in the metastatic and advanced stages does not provide (23). Furthermore, there is also an economic issue—the eventual application of only a few cycles of immunotherapy preoperatively would have a lower cost than adjuvant immunotherapy applied for at least a year (19).

To compare neoadjuvant and adjuvant immunotherapy in NSCLC, preclinical models were constructed, where the results showed a significantly higher survival rate in animals receiving PD-1 and CTLA-4 inhibitor neoadjuvant, compared to adjuvant and single agent treatment, respectively (24). This, together with the well-known

Table 1 Research details

Items	Specification
Date of search	April 10th, 2023; August 31st, 2023
Databases and other sources searched	PubMed, Google Scholar, Clincaltrials.gov
Search terms used	Non-small cell lung cancer, resectable disease, neoadjuvant chemotherapy, adjuvant chemotherapy, immune checkpoint inhibitors, PD-1, PD-L1, neoadjuvant immunotherapy
Timeframe	Up to August 31, 2023
Exclusion criteria	Articles not available in English
Selection process	Data search was performed independently by all co-authors and discussed together between all of them

PD-1, programmed death protein 1; PD-L1, programmed death ligand 1.

benefit of immunotherapy in the metastatic and locally advanced stage, has motivated the design of clinical studies to investigate neoadjuvant immunotherapy.

Objectives

The aim of this paper is to investigate the current knowledge about immunotherapy in the neoadjuvant setting, highlight the basic clinical studies that led to this knowledge and gain an impression of the main challenges in further research of neoadjuvant immunotherapy treatment. There are several available review articles that analyze the results and issues of neoadjuvant immunotherapy (20,21,24), but considering the recently published results of important studies, we believe that our analysis provides new insight into the knowledge surrounding this topic. We present this article in accordance with the Narrative Review reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-23-15/rc).

Methods

A review of literature published in the PubMed and Google Scholar databases was made and papers on the topic of neoadjuvant immunotherapy, the content of whom is available in English, were taken into account. Emphasis is placed on completed phase II clinical studies and their results, as well as data available on ongoing phase III studies from Clinicatrials.gov. Technical data on research details are shown in *Table 1*.

Literature overview

Neoadjuvant immunotherapy—phase II studies

The first data from a clinical study are available from Ford *et al.*, where patients with stage I–III NSCLC received two cycles of adjuvant nivolumab, followed by surgery which was performed in 20 of 21 originally involved patients. A major pathological response (MPR) has been observed in 45% of them, and a complete pathological response in 10%. The response correlated with tumor mutational burden (TMB), but not with PD-L1. Further analysis of detectable tumour-specific T cells in peripheral blood suggested a possibility of long-lasting immune response (25).

In the LCMC-3 trial, with 181 patients who received two cycles of neoadjuvant atezolizumab, 88% underwent surgery. MPR was 21% and pathological complete response (pCR) was 7%. Here, a good response correlated with PD-L1 expression over 50%, and not TMB (26).

The NEOSTAR phase 2 study involved 44 patients, 23 of whom received 2 cycles of nivolumab, and 21 received ipilimumab in addition to the 1st cycle of nivolumab, followed by one cycle of nivolumab alone. Thirty-nine patients underwent surgery: 21 in the nivolumab group, of whom 24% achieved MPR, and 16 in the nivo + ipi group, where the MPR was observed in 50% of the cases.

pCR showed similar treatment—related diversity, namely 9% and 29%, respectively, suggesting the benefit of dual therapy, although with a broad 95% CI (18–62%). According to radiological evaluations, ORR was 22% in the nivolumab population and 19% after nivolumab + ipilimumab.

Table 2 Neoadjuvant immunotherapy trials

Study name	ICI agent	N (total/resected)	MPR (%)	TRAEs (%), any grade	TRAEs (%), grade 3 or higher
Checkmate-159 (25)	Nivolumab (2 cycles)	21/20	45	23	5
LCMC III (26)	Atezolizumab (1 cycle)	181/160	20.4	56	5
IONESCO (30)	Durvalumab (3 cycles)	43/41	18.6	33.3	0
NCT17013726 (28)	Sintilimab (2 cycles)	40/37	40.5	52.5	10
NEOSTAR (27)	Nivolumab + ipilimumab (2 cycles)	44/39	50	–	10

ICI, immune checkpoint inhibitor; MPR, major pathological response; TRAEs, treatment related adverse events.

Table 3 Phase II neoadjuvant immunotherapy + chemotherapy trials

Study name	Study design	Phase	N (total/ resected)	MPR/CPR (%)	TRAEs (%) any grade/ TRAE grade 3 or higher
COLUMBIA (32)	Atezolizumab + nab-paclitaxel + carboplatin (2 cycles)	II	30/26	57/33	93/50
SAKK 16/14 (33)	Cisplatin + docetaxel (3 cycles; sequential durvalumab 2 doses; adjuvant durvalumab 12 months	II	67/55	34/10	100/88
NADIM (34)	Nivolumab + paklitaksel + carboplatin (3 cycles); adjuvant nivolumab 12 months	II	46/46	85/71	14/3

MPR, major pathological response; CPR, complete pathologic response; TRAE treatement related adverse event.

In 11% patient, progression in lymph node size was monitored, but the resection material showed granulomatous infiltration with no signs of tumor invasion (27).

Gao *et al.* tested sintilimab through 2 cycles of neoadjuvant therapy in a cohort of 40 patients with stage I–III NSCLC. Thirty-seven underwent radical surgery (92.5%), 40.5% achieved MPR, and complete pathologic response (CPR) was observed in 8.1% of them. Interestingly, all samples monitored for MPR were squamous NSCLC. Patients were monitored by positron emission tomography/computed tomography (PET/CT) before the start of the study and immediately before surgery, and a decrease in standardized uptake values (SUV) correlated with pathological remission (P<0.0001) (28).

In the PRINCEPS study, 43 patients received one cycle of atezolizumab, and all underwent radical surgery. Tumour tissue analysis did not show MPR in any of the cases, and there were no visible responses according to the RECIST criteria either (29). Durvalumab was also tested as a neoadjuvant agent in the IONESCO study, but the enrolment was stopped because of excessive 90-day postoperative mortality, which was reportedly not related to direct durvalumab toxicity. Nevertheless, the results showed that all of the patients with a MPR were alive 12 months after surgery, compared to 11% in the control arm (30). The date are summarized in *Table 2*.

Neoadjuvant chemoimmunotherapy

Chemotherapy and radiotherapy can enhance antitumor immunity in several different ways, for example by inducing immunogenic cell death and modulating immune cells in the tumor microenvironment, thus enhancing the effect of immunotherapy (31). The combination of chemo—and immunotherapy therapy is nowadays a treatment standard in advanced-stage NSCLC, providing a rationale for exploration in adjuvant and neoadjuvant settings.

Several phase II trials have by now investigated anti PD-1/PD-L1 immunotherapy in combination with chemotherapy as neoadjuvant agents (*Table 3*).

In the COLUMBIA trial, 30 patients with stage IB–IIIA NSCLC were enrolled, to receive up to four cycles of neoadjuvant atezolizumab plus carboplatin and nab-paclitaxel. 86% underwent surgery with R0 resection, with a MPR in 57% (17 patients). Compared to those who did not show MPR, the median disease-free survival (DFS) was 34.5 *vs.* 14.3 months respectively, but still without statistical significance. Side effects of grade 3 and 4 related

Table 4 Phase III and a 2-arm phase II neoadjuvant immunotherapy + chemotherapy trials

Study name	Study design	Phase	N (total/resected)	EFS
NADIM II (35)	Paclitaxel + carboplatin +/– nivolumab (3 cycles)	II (2 arms)	86 (57 treatment *vs.* 29 control)/ 53 (93%) *vs.* 20 (69%)	PFS: 67.2% *vs.* 40.9% at 24 months; HR 0.47
CheckMate 816 (36)	Nivolumab + platinum doublet *vs.* platinum doublet (3 cycles)	III	358 (179 treatment *vs.* 179 control/ 149 (83.2%) *vs.* 135 (75.4%)	31.6 *vs.* 20.8 months; HR 0.68, P<0.001
Keynote 671 (37)	Pembrolizumab/placebo + cisplatin-doublet (4 cycles); adjuvant pembrolizumab for 13 cycles q3 weeks in treatment arm	III	797 (397 treatment *vs.* 400 control)/ 325 (82.1%) *vs.* 317 (79.4%)	NR *vs.* 17 months; HR 0.58, P<0.001

EFS, event-free survival; PFS, progression-free survival; HR, hazard ratio; NR, not reached.

to chemotherapy, primarily neutropenia, were observed in about 50% of patients, without grade 5 events (32).

In the NADIM trial, which included 46 participants who were treated with nivolumab and paclitaxel-carboplatin for 3 cycles, only patients with stage IIIa–N2 NSCLC were enrolled. All patients received neoadjuvant nivolumab for 12 months. All of the patients were eligible for surgery and no R1/2 resections were observed. MPR was observed in 35 (85%) patients (95% CI: 71–94%), CPR in 25 (71%) and downstaging in 38 (93%) of them. The median follow-up was 13.8 months and DFS 12 months (95% CI: 84–99%). Only 14 cases (30%) had treatment—related adverse events grade III, none of which caused a delay in surgical treatment (34).

The NADIM II trial, a two-arm phase 2, multi-center trial, enrolled 86 patients with both IIIA and IIIB NSCLC 93% of whom underwent surgery in the experimental arm and 69% in the control arm. The primary endpoint, a complete pathological response was observed in 37% and 7% of the patients, respectively. The estimates of OS were 85.0% in the experimental group and 63.6% in the control group (HR 0.43; 95% CI: 0.19 to 0.98) (35).

The SAKK 16/14 phase 2, single-arm trial, included 67 patients with stage IIIA NSCLC, with N2 involvement, proven by PET CT scan and confirmed with invasive mediastinal staging [mediastinoscopy or endobronchial ultrasound (EBUS)]. Fifty-five (85% patients underwent resection, the most common reasons for surgery ineligibility being disease progression (n=6, 8.9%) and toxicity (3, 4.4%). The radiological preoperative assessment showed an ORR after chemotherapy of 43% [3% complete response (CR) and 40% partial response (PR)] and of 58% after durvalumab (7% CR and 52% PR). MPR was observed in 34 of 55 patients (62%, 95% CI: 48–75%), with 10 (18%) showing a CPR. Nodal downstaging was shown in 37 (67%) of resected specimens, 26 (47%) of them showing a pN0 stage.

Phase III trials

The first phase III trial which presented results is CheckMate 816, a randomised trial of neoadjuvant nivolumab + chemotherapy *vs.* chemotherapy alone, which enrolled 358 stage IB (tumour size >4 cm)–IIIA patients, 179 in each group. Definitive surgery rates were 83% with nivolumab + chemo (n=149) *vs.* 75% with chemo (n=135). Reasons for not performing surgery were disease progression (12 and 17 patients, respectively), adverese events (AEs) (2 pts/arm), or other (14 and 19 pts, respectively; including patient refusal, unresectability).

The median event-free survival (EFS) was 31.6 months (95% CI: 30.2 *vs.* not reached) with nivolumab plus chemotherapy and 20.8 months (95% CI: 14.0 to 26.7) with chemotherapy alone. The percentage of patients with a pathological complete response was 24.0% (95% CI: 18.0% to 31.0%) and 2.2% (95% CI: 0.6% to 5.6%), respectively (OR 13,94; 99% CI: 3.49 to 55.75%; P<0.001). The HR for death was 0.57 (99.67% CI: 0.30 to 1.07) and did not meet the criterion for significance at the first interim analysis (36).

Results of the Keynote 671 study, which compared neoadjuvant chemotherapy with a combination of neoadjuvant chemotherapy and pembrolizumab, followed by 1-year pembrolizumab or placebo were recently published. A total of 797 patients (397 in the pembrolizumab and 400 in the placebo group) were enrolled and an MPR occurred in 30.2% of the participants in the pembrolizumab group and in 11.0% of those in the placebo group (difference, 19.2 percentage points; 95% CI: 13.9 to 24.7; P<0.0001). A significant DFS was observed (31.6 *vs.* 20.8 months; HR 0.68, P<0.001), but no difference in OS was observed at the first interim analysis (37).

The AEGEAN study was investigated neoadjuvant durvalumab in combination with chemotherapy versus chemotherapy alone. Patients on the durvalumab arm

received durvalumab for 12 months after surgery. The results are not mature compared to other phase III trials, but available data suggest an EFS benefit from combination treatment (38). The data are summarized in *Table 4*.

Discussion

A huge breakthrough has been made in the past couple of years regarding perioperative ICI therapy—from initial phase 2 studies that indicated a positive effect of neoadjuvant ICI treatment, to several large phase 3 studies, due to which neoadjuvant chemoimmunotherapy was included in the guidelines for NSCLC treatment (39).

Perhaps it can be argued that the initial phase II research on immunotherapy in the neoadjuvant setting raised more questions than they had been answered. The basic issues included the choice of patients, i.e., biomarkers to guide this choice, the timing of treatment and the choice of drug(s), whether in combination therapy or immunotherapy alone.

The biomarkers most commonly explored in relation to PD-1/PD-L1 inhibitors are TMB and PD-L1 expression, which have so far shown uneven predictability in early-stage NSCLC. In NEOSTAR, PD-L1 expression was associated with a MPR rate, in contrast to Forde *et al.*, LCMC 3 and NADIM. Furthermore, in Forde *et al.* TMB was also associated with MPR, but not in LCMC3 (25,27,40). Lymphocyte clonality in peripheral blood, which was associated with MPR, could suggest longer DFS, but in reality no clinical data are available.

The significance of MPR and CPR as surrogate markers is still controversial and they are only used as a standard for assessing the effect of neoadjuvant treatment due to its practicality. Their causal connection with DFS, progression-free survival (PFS) and OS has not been directly proven. CheckMate 816 has shown that a higher pCR was associated with an improvement in EFS (HR 0.84) (36). What we have learned is that NAICI has good tolerability (25-30) and the addition of chemotherapy does not appear to cause any unexpected AEs (31-34). The main problem with NAICI is the one that is also present with classic neoadjuvant chemotherapy—the risk of disease progression to inoperable during treatment. What further complicates this problem is the fact that radiological evaluations according to RECIST criteria, especially in borderline cases, often do not provide an accurate assessment of disease progression. In LCMC3 10% patients were rendered inoperable after radiological evaluation, and in Forde *et al.* radiological response did not correlate with MPR. In NEOSTAR, radiological "upstaging" due to granulomatous lymph node enlargement was observed, luckily not causing surgery denial (27). Adverse events related with NAICI toxicity did not appear to cause any major delays in surgical treatment, especially compared to NACT data. In-surgery complications, conversion rates of video-assistant thoracoscopies to open thoracotomies and postoperative complications were also tolerable, in comparison to NACT (25-27).

The question of safety of the combination neoadjuvant chemoimmunotherapy is probably resolved by the new results of the studies NADIM II, CheckMate 816 and Keynote 671, where the data speak in favor of a higher percentage of operated patients in the groups that received neoadjuvant combination therapy, compared to those treated with chemotherapy alone. However, as neoadjuvant chemotherapy is less used in standard clinical practice compared to adjuvant and bearing in mind completed (41,42) and upcoming studies of adjuvant chemoimmunotherapy, it remains to be seen whether the overall benefit of the neoadjuvant approach compared to adjuvant will be demonstrated. While NAICI is probably justified in stage IIIA and IIIB, the question of the justification of the application of any neoadjuvant therapy in stage II, and thus NAICI, also remains unanswered.

CheckMate 816 is still the only large study in which patients did not automatically receive adjuvant immunotherapy (36). Keynote 671 (37) and AEGEAN (38) are designed so the patients in the treatment arm, regardless of operative staging, also receive an immunotherapy agent for one year. Whether this will lead to a benefit in clinical outcomes and how it will affect the degree of AEs remains to be seen, but surely such different designs make it even more difficult to answer the question about the best treatment approach.

Conclusions

Neoadjuvant immunotherapy in lung cancer treatment is a hot topic, but to be approached with caution. Hitherto data encourage further investigation and several ongoing major phase III trials should answer some of the questions—which patients will benefit from this treatment, when will be the right time to administer it in the course of treatment, whether to combine anti PD-1/PD-L1 and anti CTLA-4 or anti PD-1/PD-L1 and chemotherapy? Should adjuvant/maintenance immunotherapy tip the scale of benefit? Are we going to be able to "copy" at least some of the vast experience from advanced NSCLC treatment, and maybe,

acquire some new insights from resected tumour specimen analyses, which will reveal new, better biomarkers, deficient in every stage of NSCLC?

An exciting period awaits in terms of further research into the limits of immunotherapy. We surely will have to wait for some time for the definitive results, given the need for long-term follow-up after surgical resection and neoadjuvant/adjuvant therapy. But that quasi-pessimism is a reflection of our high expectations of the new therapeutic implications and benefits of immunotherapy in resectable NSCLC.

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