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REVIEW

Neoadjuvant PD-1 Blockade in Non-Small Cell Lung Cancer: Current perspectives and Moving Forward

Kanako Shinada, Shuji Murakami

Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan

Correspondence: Shuji Murakami, Department of Thoracic Oncology, Kanagawa Cancer Center, 2-3-2 Nakao, Asahi-ku, Yokohama, Kanagawa, 241-8515, Japan, Tel +81-45-520-2222, Email murakamis@kcch.jp

Abstract: Perioperative therapy for non-small cell lung cancer has been studied extensively in a bid to improve overall survival, as approximately half of the patients with surgically resectable tumors at the time of diagnosis relapse. In recent years, immune checkpoint inhibitor therapies, such as the anti-programmed death 1/programmed death-ligand 1 (PD-1/PD-L1) blockade, have contributed to achieving an improved overall survival of patients with advanced stage lung cancer. Thus, the development of this treatment strategy has considerable potential to precipitate a breakthrough in cancer immunotherapy. PD-1/PD-L1 blockade has several potential immunological benefits when used as a neoadjuvant therapy. However, there are concerns associated with this neoadjuvant therapy. Many studies have reported its efficacy, but there is limited evidence regarding the long-term survival of patients. Similarly, it is unclear whether existing biomarkers are adequate for monitoring the prognosis of patients, or if new biomarkers are required. In this article, we present recent reports on neoadjuvant PD-1/PD-L1 blockade therapy and discuss its future challenges.

Keywords: non-small cell lung cancer, NSCLC, neoadjuvant, immune checkpoint inhibitor, ICI, programmed death 1, PD-1, programmed death ligand 1, PD-L1

Introduction

Approximately 30% of patients with lung cancer are eligible for surgical resection.[1,2] For early-stage (stage I–IIIA) non-small cell lung cancer (NSCLC), surgical resection is the mainstay of treatment.[3,4] However, even with complete resection, there are high rates of recurrence and metastasis.[5] This is probably due to the presence of distant micrometastases;[6,7] therefore, systemic treatment is important for improving the prognosis of NSCLC.

In some trials comparing neoadjuvant and adjuvant chemotherapy, the survival benefit was not demonstrated between these two strategies;[8,9] however, unlike in the adjuvant setting, the completion rate of chemotherapy in the neoadjuvant setting was maintained without increasing toxicity. Neoadjuvant chemotherapy thus has some advantages over adjuvant chemotherapy. Neoadjuvant therapy can generate the possibility of resection in patients with large tumors that are considered inoperable at diagnosis or in tumors that are connected to major organs. This is also expected to reduce the incidence of micrometastases. These are expected to increase the possibility of complete resection. Furthermore, it allows rapid assessment of tumor and surrounding tissue response to treatment.

Conversely, the disadvantages of neoadjuvant chemotherapy include the following; risk of missing the opportunity for resection in patients whose tumors progressed without response to chemotherapy, the possibility of difficulty in continuing subsequent treatment including surgery due to adverse events, and, in the worst case, the possibility of treatment-related death in the worst case.

In recent years, cancer immunotherapy targeting immune checkpoints, such as the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) signaling pathway, and molecular targeted therapy have dramatically improved the prognosis of patients with advanced NSCLC.[10–14] However, the role of immune checkpoint inhibitors (ICIs) in the early

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stages is poorly understood. Neoadjuvant PD-1/PD-L1 blockade therapy is also a topic of interest, and the results of clinical trials have been reported. The next section reviews the merits and feasibility of neoadjuvant PD-1/PD-L1 blockade regimens and discusses the perioperative treatment of immunotherapy as well as future problems and perspectives.

Preclinical Effect of Neoadjuvant Immune Checkpoint Inhibitors

To activate the anticancer immune response and destroy cancer cells, a series of stepwise events called the cancer-immunity cycle must be initiated. The released neoantigens created by oncogenic processes are captured and processed by dendritic cells.[15] Subsequently, dendritic cells migrate to the draining lymph nodes to prime and activate effector T-cell responses against cancer-specific antigens.[16,17] Therefore, draining lymph nodes are assumed to be the first lymph nodes to which cancer cells metastasize from the primary lesion, as well as the lymph nodes necessary for the activation of local tumor immunity. A potential advantage of neoadjuvant immunotherapy is the stimulation of effective systemic immunity. This means that it could potentially be effective in eradicating residual metastatic disease after surgical removal of the primary tumor.

In a study of metastatic breast cancer in mouse models, a group of mice receiving neoadjuvant or adjuvant Treg depletion before tumor resection had significantly improved long-term survival.[18] Immune analyses indicated that the number and proportion of tumor-specific CD8+ T cells increased when immunotherapy was administered to the primary tumor and/or regional lymph nodes.[18] These data suggest that the neoadjuvant setting is an optimal window of opportunity to prime an antitumor immune response and eliminate micrometastases.

Endpoint for Neoadjuvant Therapy

The aim of surgery is to offer curative resection, while that of perioperative treatment is to increase the cure rate. Therefore, the gold standard endpoint for perioperative treatment is overall survival (OS). OS is simple to measure, easy to interpret, and its measurement is unbiased; however, some of the disadvantages of this endpoint are the need for long-term follow-up, which is required before results are obtained, and a large number of patients are required to detect statistically significant prolongation and are affected by post-relapse treatment, which can prolong survival. OS is simple to measure, easy to interpret, and its measurement is unbiased; however, some of the disadvantages of this endpoint are the need for long-term follow-up. A large number of patients are required to detect statistical differences and are affected by post-relapse treatment, which may prolong survival. In clinical studies with long study periods, the use of surrogate endpoints is necessary to accelerate treatment evaluation. In trials of adjuvant cytotoxic chemotherapy involving patients with NSCLC, the correlations between disease-free survival (DFS) and OS were very good; therefore, DFS could be used as a valid surrogate endpoint.[19] There is insufficient evidence that DFS could become the surrogate endpoint for OS in neoadjuvant chemotherapy; however, for the above reasons, as with adjuvant trials, DFS and event-free survival (EFS) have been proposed as surrogate endpoints for OS in recent neoadjuvant trials.

In neoadjuvant studies, it is possible to evaluate short-term therapeutic effects using surgical specimens. Pathologic complete response (pCR), defined as the absence of any remaining active tumor cells, is one of the pathological endpoints. Several neoadjuvant trials in breast cancer patients have shown that pCR is strongly associated with EFS and OS; therefore, pCR has been approved as a surrogate endpoint for breast cancer.[20,21] Compared with the pCR rate in breast cancer patients receiving neoadjuvant therapy, the pCR rate of cisplatin-based neoadjuvant chemotherapy in lung cancer patients is approximately 10% or lesser. Some studies have indicated that pCR can be proposed as a meaningful research endpoint for NSCLC neoadjuvant therapy;[22] however, the low frequency of pCR limits its application as a surrogate endpoint.

The most important feature of chemotherapy in operable patients is the ability to pathologically evaluate the efficacy of the treatment. Major pathologic response (MPR), defined as a ≤10% portion of surviving tumor cells after neoadjuvant therapy, is a new pathological evaluation method. MPR was observed more frequently than pCR. Compared with patients with >10% surviving tumor cells, patients with ≤10% surviving tumor cells had significantly prolonged long-term OS (5-year OS: 40% vs 85%; P<0.0001) and DFS (5-year DFS: 35% vs 78%; P<0.001).[23] The validity of MPR in relation to ICI therapies, as with pCR, remains under investigation, and MPR is currently the endpoint of many ongoing trials of

neoadjuvant ICIs. A prognostic comparison with postoperative administration has not been performed, and it is not known which of them prolongs OS. However, there is a possibility that MPR and pCR may reduce the extent of resection, at least in cases where large diameter lesions are reduced to the extent that they can be operated on. In fact, many ICIs neoadjuvant studies have adopted pCR and MPR as endpoints.

Clinical Trials of Neoadjuvant ICI for NSCLC

The treatment of patients with resectable NSCLC has shown improved clinical outcomes with neoadjuvant PD-1/PD-L1 blockade therapy. Several PD-1/PD-L1 blockades are used as monotherapy in combination with chemotherapy and in combination with anti-CTLA-4-antibodies. The trial results are summarized in Table 1 and Table 2.

ICI Monotherapy

The first pilot trial of neoadjuvant PD-1 blockade for early-stage NSCLC was evaluated preoperatively for two cycles of nivolumab, a PD-1 blockade, in 21 patients. The primary end points of this study were safety and feasibility. This study showed that neoadjuvant nivolumab therapy could be a feasible and safe strategy with a low rate of severe adverse events and no treatment-related surgical delay. The rate of any grade of adverse event (AE) was 23%, and a grade ≥3 AE was pneumonia. Although only two (10%) of 21 patients obtained partial response on CT images, nine (45%) of the 20 patients who had undergone resection had an MPR and two patients (10%) had pCR.[24] This result was sufficient to suggest an effect of preoperative ICI, but indicated that CT evaluation does not accurately reflect the pathological response and that it is difficult to predict treatment efficacy using preoperative CT evaluation.

Lung Cancer Mutation Consortium 3 (LCMC3) is a multicenter Phase II trial that recruited 181 patients with resectable NSCLC (stage IB–IIIB). Patients were administered atezolizumab for two cycles prior to surgery. Of the study participants, 43% (66/155) were downstaged following atezolizumab treatment, but 19% (29/155) of patients were upstaged. Unfortunately, unresectability was detected in 29 (16%) patients. The MPR and pCR were 7 and 20%, respectively. A grade 3 AE was observed in 5% of patients.[25,26] Although this study showed that neoadjuvant atezolizumab monotherapy was well tolerated with no new safety signals, the rate of unresectable preoperative treatment is a concern for ICI monotherapy, especially in trials involving more advanced stages.

The IONESCO study included 46 patients with stage IB (≥ 4 cm), stage II, stage IIIA, non-N2 disease and resectable NSCLC. Patients received neoadjuvant treatment with durvalumab for three cycles. The mean MPR rate was 18.6% (8/43). The 1-year OS rate was 89.7%, and the 12-month DFS rate was 78.2%.[27] Impressively, the DFS rate at 12 months in patients with an MPR was 100%, but that in patients without an MPR was significantly lower (77.1%). This result showed that MPR was significantly associated with DFS.

NEOSTAR (NCT03158129) is a phase II randomized trial of neoadjuvant nivolumab or nivolumab + ipilimumab followed by surgery in 44 patients with operable NSCLC. The nivolumab + ipilimumab arm met the pre-specified primary endpoint threshold of six MPRs in 21 patients, achieving a 38% MPR rate (8/21). In 37 patients resected during the trial, nivolumab and nivolumab + ipilimumab produced MPR rates of 24% (5/21) and 50% (8/16), respectively. Compared with nivolumab, nivolumab + ipilimumab resulted in higher pCR rates (10% versus 38%) and fewer viable tumors (median 50% versus 9%). Grade 3–5 AEs were reported in 13% (3/23) of the patients in the nivolumab arm and 10% (2/21) of the patients in the nivolumab + ipilimumab arm.[28] The pathologic response was better with dual ICI combination therapy than with ICI monotherapy, and trAEs did not seem to differ significantly. However, despite the influence of comorbidities, fewer patients underwent surgery with combination therapy. Therefore, these results should be evaluated with caution.

ICI and Cytotoxic Chemotherapy

The NADIM is an open-label, multicenter, single-arm, phase II trial in which patients with stage IIIA N2 NSCLC received neoadjuvant treatment with paclitaxel and carboplatin plus nivolumab for 3 cycles before surgical resection, followed by adjuvant intravenous nivolumab monotherapy for 1 year.[29] The primary endpoint was progression-free survival. At 24-months, it was 77.1% [95% CI, 59.9–87.7]). Their pathological results showed an 86% MPR and 71% pCR with downstaging in 93% of the cases. Forty-three (93%) of the 46 patients had trAEs during neoadjuvant treatment,

Table 1 Trials with Some or All Results Reported

Trials	Reporter	Phase	Stage	n	Neoadjuvant Therapy	Adjuvant Therapy	MPR% (n)	pCR% (n)	ORR* % (n)	PFSor EFS or DFS**	Grade3 or Above trAE % (n)	R0 Surgery % (n)
Forde et al[24]	2018	2	I-IIIA	21	2 cycles of nivolumab		45.0 (9/20)	10.0 (2/20)	9.5 (2/21)	PFS at 18months 73.0%	4–5% pneumonia	95.2 (20/21)
LCMC3[26]	2021	2	IB-IIIB	181	2 cycles of atezolizumab		20.4 (30/147)	6.8 (10/147)	6.9 (11/159)	NR	16.60%	82.3 (149/181)
IONESCO[27]	2020	2	IB-IIIA	46	3 cycles of durvalumab		NR	NR	8.7 (4/46)	DFS at 18months 69.7%	0.00%	89.1 (41/46)
TOP1501[39]	2022	2	IB-IIIA	30	2 cycles of Pembrolizumab	4 cycles of Pembrolizumab	28.0 (7/25)	NR	NR	NR	NR	88.0 (22/25)
NEOSTAR[28]	2021	2	I-IIIA	30	3 cycles of nivolumab vs nivolumab plus ipilimumab	Chemotherapy 17 (46%) [11 (Nivo), 6 (Nivo plus Ipi)] Radiation therapy 4 (11%)	21.7 (5/23) vs 38.1 (8/21)	8.7 (2/23) vs 28.6 (6/21)	21.7 (5/23) vs 19.0(4/21)	Not reached with both groups	4.3% pneumonitis, pneumonia, hypoxia, and hypermagnesaemia vs 4.8% diarrhea, hyponatramia	95.7 (29/30) vs 81.0 (17/21)
NADIM[29]	2020	2	IIIA	46	3 cycles of nivolumab plus paclitaxel plus carboplatin	Nivolumab for 12months (37/46)	82.9 (34/41)	63.4 (26/41)	76.1 (35/46)	PFS at 24months 77.1%	30.4 (6.5% increased lipase, 6.5% febrile neutropenia)	89.1 (41/46)
SAKK 16/14[40]	2020	2	IIIA	68	3 cycles of cisplatin plus docetaxel followed by 2 cycles of durvalumab	Durvalumab for 12months	61.8 (34/55)	18.2 (10/55)	58.2 (39/67)	EFS at 12 months 73.3%	NR	NR
NADIMII[30]	2022	2	IIIA	87	3 cycles of platinum doublet chemotherapy vs 3 cycles nivolumab plus platinum doublet chemotherapy	Nivolumab for 6months (for R0 patients)	71 (35/45)	36.8 vs 6.9	NR	OS 85.3% at 24 months vs 64.8%	NR	NR
CheckMate-816[31]	2021	3	IB-IIIA	358	3 cycles of platinum doublet chemotherapy vs 3 cycles nivolumab plus platinum doublet chemotherapy		8.9 (16/179) vs 36.9 (66/179)	2.2 (4/179) vs 24.0 (43/179)	37.4 (67/179) vs 53.6 (96/179)	NR	NR	58.7 (105/179) vs 69.3 (124/179)

Abbreviations: MPR, Major pathological response; pCR, pathological complete response; ORR, objective response rate; PFS, progression free survival; EFS, event-free survival; DFS, disease-free survival; trAE, treatment-related adverse events; R0, R0 resection indicates a microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed; NR, Not reported.

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Table 2 Ongoing Trials

Trials	NCT	Phase	Stage	n	Neoadjuvant Therapy	Adjuvant Therapy	Primary Endpoints
KEYNOTE-671	NCT03425643	3	II, IIIA, selectedIIIB (T3-4N2)	786	4 cycles of pembrolizumab or placebo, plus platinum doublet chemotherapy	Pembrolizumab or placebo for 39 weeks	EFS and OS
IMpower030	NCT03456063	3	II, IIIA, selected IIIB (T3N2)	450	4 cycles of atezolizumab or placebo, plus platinum doublet chemotherapy	Atezolizumab or placebo for 48 weeks	EFS
AEGEAN	NCT03800134	3	IIA-IIIB	800	4 cycles of durvalumab or placebo, plus platinum doublet chemotherapy	Durvalumab or placebo for 12 months	pCR and EFS
CheckMate-77T	NCT04025879	3	IIA-IIIB (T3N2)	452	4 cycles of nivolumab or placebo, plus platinum doublet chemotherapy	Nivolumab for 12 months	EFS
NeoCOAST	NCT03794544	2	I(>2cm)-IIIA	80	1 cycle of durvalumab vs durvalumab plus oleclumab vs durvalumab plus monalizumab vs durvalumab plus danvatirsen	Not applicable	MPR

and 14 (30%) had trAEs of grade 3 or worse; however, none of the adverse events were associated with surgery delays or deaths. The most common grade 3 or worse trAEs were increased lipase (3 [7%]) and febrile neutropenia (3 [7%]). Despite being a trial of more advanced patients, none of the patients withdrew due to disease progression. This first clinical study to explore the combination of chemotherapy and immunotherapy in resectable stage NSCLC showed that this combination was a well-tolerated neoadjuvant therapy.

NADIM II is an open-label, randomized, two-arm, phase II trial that enrolled patients with resectable clinical stage IIIA to receive nivolumab plus chemotherapy (paclitaxel and carboplatin) or chemotherapy only for three cycles as neoadjuvant treatment followed by surgery. The primary endpoint was pCR by blinded independent pathological review (BIPR) in the intent-to-treat (ITT) population. The MPR rate was 52% in the nivolumab plus chemotherapy arm and 14% in the chemotherapy arm. Definitive surgery occurred in 91% of the patients treated with nivolumab plus chemotherapy and 69% in the chemotherapy arm. Surgery was mainly cancelled due to disease progression at 1 and 4 points in the nivolumab plus chemotherapy and chemotherapy arms, respectively. The pCR rate was 36.8% in the nivolumab plus chemotherapy arm versus 6.8% in the chemotherapy arm (P = 0.0068).[30] PD-1/PD-L1 blockade combination therapy seems to achieve higher MPR and pCR compared to monotherapy trials and higher pCR compared to chemotherapy. Moreover, it is less unresectable than monotherapy due to disease progression.

Phase III Clinical Trial

CheckMate816 enrolled patients with resectable stage IB (≥4 cm) to IIIA NSCLC who received nivolumab plus platinum-based chemotherapy or platinum-based chemotherapy alone, followed by resection. In this study, approximately 60% of the patients had stage IIIA disease. The primary endpoints were EFS and pCR. The secondary endpoints were OS, MPR, and time to death or distant metastases.[31] Definitive surgery was performed in 83% of patients in the nivolumab and chemotherapy arm and 75% in the chemotherapy arm. In addition, 28 (15.6%) and 37 (20.7%) patients in the nivolumab plus chemotherapy and chemotherapy groups, respectively, failed to achieve definitive surgery because of disease progression or other reasons during neoadjuvant therapy. The pCR rate was 24.0% in the nivolumab plus chemotherapy arm and 2.2% in the chemotherapy arm (odds ratio [OR] 13.94, 99% CI 3.49 to 55.75; p<0.0001). The median EFS was 31.6 months in the nivolumab plus chemotherapy arm and 20.8 months in the chemotherapy arm (hazard ratio [HR] 0.63; 97.38% CI 0.43 to 0.91; P=0.005). By stage, patients with stages IB-II had an HR of 0.87, and

those with stage IIIA had an HR of 0.54, showing a more pronounced effect in stage IIIA. The MPR rate was 36.9% in the nivolumab plus chemotherapy arm and 8.9% in the chemotherapy arm. AEs of any cause occurred in 92.6% of the patients in the nivolumab-plus-chemotherapy group and 97.2% of those in the chemotherapy group. The incidence of grade 3 or 4 trAEs was 33.5% and 36.9%, respectively. The most common grade 3 or 4 trAEs were neutropenia (8.5% with nivolumab plus chemotherapy and 11.9% with chemotherapy alone) and decreased neutrophil counts (7.4% and 10.8%, respectively).

Initially, of the 773 patients enrolled in the trial, 227 (29.3%) did not meet the criteria and were excluded. Thus, the patients were selected for the clinical trial. In addition, 28 (15.6%) and 37 (20.7%) patients in the nivolumab plus chemotherapy and chemotherapy groups, respectively, failed to achieve definitive surgery because of disease progression or other reasons during neoadjuvant therapy, which cannot be ignored.

Ongoing Study

KEYNOTE-671 (NCT03425643) is a double-blind Phase III trial that enrolled patients with resectable stage IIB/IIIA NSCLC. Patients were randomized in a ratio of 1:1 to receive neoadjuvant chemotherapy (cisplatin with gemcitabine [squamous histology] or pemetrexed [non-squamous histology]) combined with either pembrolizumab or placebo for four cycles, followed by surgery, adjuvant pembrolizumab, or placebo for 13 cycles. The primary end points were EFS and OS. The secondary endpoints were MPR, pCR, safety, and quality of life. The expected primary completion date is January 2024.

IMpower 030 (NCT03456063) is a global double-blind randomized study of patients with resectable stage II, IIIA, or select IIIB (T3N2) NSCLC Patients were randomized to receive atezolizumab plus platinum-based chemotherapy vs placebo plus platinum-based chemotherapy. The primary endpoint was EFS, and the secondary endpoints were pCR, MPR, OS, and DFS. The expected primary completion date is November 2024.[32]

AEGEAN (NCT03800134) is a phase III randomized, double-blind, placebo-controlled, international, multicenter study of eligible patients with stage IIA to IIIB NSCLC (cancer > 4 cm or positive lymph nodes). In this study, 802 patients were randomized to receive durvalumab before resection, durvalumab or placebo plus chemotherapy for 4 cycles, and up to 12 cycles of durvalumab or placebo after resection. The primary endpoints were pCR and EFS, while the primary secondary endpoints were MPR, DFS, OS, safety, and quality of life. The EFS results were not shown in the interim analysis of this study. The expected primary completion date is January 2024.

CheckMate 77T (NCT04025879) is a Phase III, randomized, double-blind study that evaluates neoadjuvant nivolumab versus chemotherapy followed by adjuvant nivolumab. Patients with resectable stage IIA-IIIB (T3N2 only) NSCLC were randomized to receive neoadjuvant nivolumab plus platinum-based doublet chemotherapy followed by resection and adjuvant nivolumab or neoadjuvant placebo plus platinum-based doublet chemotherapy followed by resection and adjuvant placebo. The primary endpoint was EFS; secondary endpoints included OS, pCR, MPR, safety, and tolerability. The expected primary completion date is May 2023.

・PD-1 blockade with other antibody therapies

NeoCOAST (NCT03794544) is a Phase II, open-label, randomized trial evaluating neoadjuvant durvalumab alone or in combination with the novel agents oleclumab (MEDI9447, an anti-CD73 monoclonal antibody), monalizumab (IPH2201, a humanized immunoglobulin (IgG) 4 monoclonal antibody), and danvatirsen (AZD9150, an antisense oligonucleotide designed to down-regulate expression of signal transducer and activator of transcription 3 protein) in patients with resectable stage I [T>2 cm] - IIIA NSCLC. The primary endpoint was MPR after treatment with neoadjuvant durvalumab, alone or in combination with novel agents. The secondary endpoints were the feasibility of tumor resection surgery within 14 days of the end of the 4-week treatment period, safety, pCR, pharmacokinetics, and immunogenicity. Good results have been reported for chemoradiation therapy for NSCLC.[33] They reported that combination therapy with oleclumab, monalizumab, and danvatirsen resulted in higher MPR rates than durvalumab monotherapy.

Biomarker of Response for Neoadjuvant Immune Checkpoint Inhibitors

Tumor PD-L1 protein expression is already known to be an important indicator and has been widely applied in clinical practice, especially in advanced NSCLC. Some studies have shown that a higher tumor mutational burden (TMB) is

associated with greater clinical benefit from PD-1/PD-L1 blockade; TMB levels are associated with improved PD-1/PD-L1 blockade efficacy, independent of PD-L1 expression.[34]

In a pilot study,[24] after nivolumab administration, the tumor was infiltrated by liquid containing CD8+ and PD-1+ immune cells, and some of the infiltrating immune cells expressed PD-L1. In a follow-up study of the LCMC3, the secondary endpoints of MPR rate in patients with a PD-L1 tumor proportion score (TPS) of <1%, 1–49%, and ≥50% at screening were 11% (6 of 53), 5% (1 of 20), and 33% (15 of 45), respectively. In an analysis of data from 111 patients, the baseline PD-L1 TPS was found to correlate significantly with pathological response ($R = -0.37$; $P < 0.001$).[25] In NEOSTAR, fewer viable tumor cells were also found in resected specimens with pretherapy tumor PD-L1 expression ≥1% than in tumors with PD-L1 expression <1%. In contrast, post-therapy tumor PD-L1 expression was not associated with a response, and no significant differences were noted in the percentage of malignant cells expressing PD-L1 between pre- and post-therapy tumors treated with nivolumab or nivolumab + ipilimumab. These results suggest that PD-L1 may be a marker of efficacy in the treatment of early-stage and advanced lung cancer.[28] For combination trials of ICI and chemotherapy, CM816 results show pCR rates of 17%, 24%, and 45% (PD-L1<1%, 1–49%, ≥50%), respectively. The hazard ratio for EFS was also better in the PD-L1≧50% group, as mentioned below.[31]

Pretreatment levels of circulating tumor DNA (ctDNA) are a potential early indicator of disease recurrence after surgery.[35,36] An exploratory analysis of the NADIM trial (NCT03081689) found that pretreatment ctDNA is a useful prognostic marker for neoadjuvant nivolumab and chemotherapy for stage IIIA NSCLC. In this trial, PD-L1 expression and TMB were not found to be associated with PFS or OS. Patients with a total mutation allele frequency (MAF) <1% for ctDNA in pretreatment samples had significantly better PFS and OS than those with MAF >1%. For the prediction of PFS, the adjusted C statistic was 0.68 (95% CI, 0.51–0.84) for ctDNA with mutation allele frequency <1%. The C statistic for clinical effect was 0.61 (95% CI, 0.45–0.78), indicating that higher MAF was a better predictor of improved PFS. Similarly, for OS, the adjusted C statistic was 0.85 (95% CI, 0.72–0.99) for mutation allele frequencies <1%. The clinical effect was 0.68 (95% CI, 0.44–0.93), indicating that MAF is a better predictor of OS improvement.[35]

In CheckMate816, the level of ctDNA could be evaluated in 89 patients The percentage of patients with ctDNA clearance was higher with nivolumab plus chemotherapy (56%; 95% CI, 40–71) than with chemotherapy alone (35%; 95% CI, 21–51). EFS was longer in patients with ctDNA clearance than in those without ctDNA clearance in both the nivolumab plus chemotherapy group (HR for disease progression, disease recurrence, or death, 0.60; 95% CI, 0.20–1.82) and the chemotherapy alone group (HR, 0.63; 95% CI, 0.20–2.01). The percentage of patients with a pCR was higher among those with ctDNA clearance than among those without ctDNA clearance in both treatment groups.[31]

Perspectives

Based on the CheckMate-816 data, nivolumab in combination with chemotherapy as a neoadjuvant treatment for resectable NSCLC was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in March 2022. The application has been submitted to the Pharmaceuticals and Medical Devices Agency, and it may not be long before nivolumab becomes available in the clinical setting for neoadjuvant therapy in Japan. Nivolumab was first approved as a neoadjuvant drug combined with chemotherapy for early-stage NSCLC, and this move is a significant step for treatment in this setting. Many trials targeting neoadjuvant chemotherapy in patients with clinical stage IB or higher disease have been conducted. Depending on the results, other PD-1/PD-L1 inhibitors are expected to undergo trials. Combining immuno-oncology with surgery has become a new standard of care and has potentially improved OS in early-stage disease for the first time in decades.

Considering that the pathologic response to neoadjuvant ICI therapy has been reported to be high, patients with large tumors or lymph node metastases who are unsuitable for initial definitive surgery are candidates for surgery. However, for patients with early-stage disease or patients whose disease may be inoperable if their tumor increases slightly (eg, T3 or N1-2), there is a risk of inoperability due to disease progression or AEs during neoadjuvant therapy. Chemoradiation followed by durvalumab consolidation therapy is currently the standard strategy for such patients; however, it is unclear whether neoadjuvant ICI therapy followed by surgery or chemoradiation and durvalumab thereafter is more appropriate. It remains difficult to predict the efficacy of neoadjuvant ICI therapy. Selection of treatment targets using biomarkers will be an important perspective in neoadjuvant ICI therapy. Appropriate biomarkers will help determine ideal candidates for

this treatment strategy rather easily. PD-L1, an established biomarker for advanced NSCLC, is being considered as a biomarker for neoadjuvant ICI therapy; however, its association with efficacy varies among studies.

Biomarker studies of perioperative therapy can be performed on surgical specimens, thus alleviating the barriers of collecting only small size of biopsy specimens and the problems of tumor heterogeneity, which are controversial in many advanced lung cancers. It is important both clinically and medically to identify patients in whom ICI is more effective.

Patients with high PD-L1 expression may be more likely to benefit from neoadjuvant therapy, but there are no data on patients with low PD-L1 expression or driver gene mutations in preoperative testing or other patients who were excluded from this trial, and there is insufficient evidence to recommend the use of neoadjuvant therapy.

What is the permissible level of trAEs or immune-related AEs (irAEs)? The PD1/PD-L1 blockade causes irAEs, which are thought to be T-cell mediated autoimmunity and/or inflammation and may be cytokine-related. In clinical trials with neoadjuvant PD-1/PD-L1 blockade, the distinctions between trAE and irAE were vague in each trial.[37,38] Should we take measures such as discontinuation of treatment if the incidence of AE is grade 3 or higher? It is better to continue treatment for relatively mild side effects or to discontinue treatment immediately and switch to surgery when even minor side effects appear. The answer to these questions remains unclear.

In the absence of a clear indicator, a difficult decision must be made regarding the number of AEs to tolerate before proceeding with the treatment.

Conclusion

Clinical trials of neoadjuvant PD-1/PD-L1 blockade treatment have shown a pathological response and prolonged EFS. TrAEs are generally tolerable. Especially in patients with stage III disease who are difficult to treat with surgery due to their large tumor size and lymph node metastasis, neoadjuvant treatment is beneficial because it makes resection possible. However, it also has the potential to cause patients to lose the opportunity for surgery due to disease progression or make it difficult to continue treatment due to severe AE. It is important to make an appropriate decision to stop neoadjuvant treatment when it is ineffective.

To improve the cure and survival rate for NSCLC, the combination of various drugs, antibodies, tyrosine kinase inhibitors, and other therapies such as surgery and radiation are expected breakthroughs in the future.

In early-stage cancers, as in advanced cancers, it is important to determine the treatment strategy based on molecular diagnosis, histology, and stage. Neoadjuvant therapy requires a disease management team made up of experts in oncology, surgery, pathology, and more. We expect to provide our patients with the latest findings and make efforts to improve treatment outcomes.

Disclosure

The authors report no conflicts of interest in this work.

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