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Immunotherapy in Early and Locally Advanced Stage Non-small Cell Lung Cancer

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ABSTRACT

Non-small cell lung cancer (NSCLC) is important for public health as it is one of the major causes of cancer-related deaths worldwide. The use of immunotherapy in NSCLC is becoming increasingly widespread. Immunotherapies are currently used in metastatic stages, as well as in earlier stages, in light of new studies. In our article, we aimed to summarize and compare neoadjuvant, perioperative, and adjuvant immunotherapy studies and their results in patients diagnosed with early and locally advanced NSCLC. Although there are no studies comparing neoadjuvant, perioperative, or adjuvant immunotherapy head-to-head, which treatment strategy is superior is one of the most important problems we encounter in clinical practice. Studies have shown that good results are obtained from both perioperative and neoadjuvant immunotherapy in patients who develop a pathological complete response (pCR). However, in patients without a pCR, the results indicate that perioperative immunotherapy is superior to neoadjuvant immunotherapy. Biomarkers such as circulating tumor DNA and baseline four-gene inflammatory score will be used to facilitate follow-up of patients and individualize treatment strategies in the future. Nowadays, perioperative immunotherapy and chemotherapy studies come to the fore for patients diagnosed with operable or potentially operable NSCLC. For inoperable locally advanced NSCLC, adjuvant immunotherapy is a valuable option after definitive chemoradiotherapy.

Keywords: Lung cancers, immunotherapy, neoadjuvant, perioperative, adjuvant

Introduction

Lung cancer is one of the leading causes of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases [1]. The primary treatment for NSCLC is surgery if possible. However, disease recurrence is observed in 45-55% of operable patients [2]. These high recurrence rates increase the importance of neoadjuvant and adjuvant therapies.

After studies conducted with adjuvant cisplatin-based doublet chemotherapies yielded different results, the LACE meta-analysis published in 1995 evaluated the data of 4584 patients from 5 studies. The overall survival (OS) benefit was found to be 5.4% and the disease-free survival (DFS) benefit was 5.8% [3]. Subsequently, a large meta-analysis was performed with data from 13 studies in neoadjuvant therapy. As a result of this meta-analysis, it was shown that platinum-based doublet chemotherapy was superior to surgery in terms of OS when given neoadjuvant [4]. Another large meta-analysis, neoadjuvant chemotherapy was compared with adjuvant chemotherapy. It was observed that the benefit obtained from chemotherapy was the same in terms of OS in neoadjuvant and adjuvant settings [5]. In light of these studies, there has been no change regarding neoadjuvant and adjuvant treatment of NSCLC for many years.

As immune checkpoint inhibitors (ICIs) were observed to significantly prolong survival data in the metastatic stage, the use of immunotherapy in studies shifted towards adjuvant, neoadjuvant and perioperative periods [6]. ICIs are IgG type

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antibodies that act by showing an antagonistic effect against programmed death 1/programmed death ligand 1 (PD-1/PD-L1) or cytotoxic T-lymphocyte-associated protein 4. While ICIs can be used alone, it is known that they provide additional immunomodulatory activity when used with chemotherapy [7]. Chemotherapy causes tumor cells to die and thus release tumor-derived antigens into the microenvironment. This situation increases the immune response to the tumor and the effectiveness of ICIs [8]. Based on these data, ICIs were first used as adjuvants in the postoperative period. Subsequently, the effectiveness of its use in combination with chemotherapy was evaluated through neoadjuvant and perioperative studies. As an outcome, it emerged as a potent option in an essential field for NSCLC treatment [9].

The advantages of giving immunotherapy to an unoperated patient include strong antigenic effect because the primary tumor is still in place and the lymphatic system has not been changed by surgery yet. Tumor antigens are usually presented to cytotoxic T cells in the lymph nodes. From here, cytotoxic T cells and memory T cells spread throughout the body. While the T cell clones formed against the tumor are responsible for the effectiveness of immunotherapy on tumor tissue and micrometastases, memory T cells ensure that this effect is maintained. Neoadjuvant and perioperative immunotherapy are thought to provide benefits by increasing the strength of this immune activity [10,11].

The survival benefit of definitive concurrent or sequential chemoradiotherapy (CRT) in patients with inoperable locally advanced NSCLC is limited. The 5-year OS in stage 3A, stage 3B and stage 3C patients was 36%, 26% and 13%, respectively [12]. It has been shown that the use of maintenance immunotherapy after CRT in patients who have received definitive treatment provides significant improvements in these survival data [13]. It is certain that neoadjuvant, perioperative, or post-CRT maintenance immunotherapy options will be discussed in these patient groups that we currently consider unresectable.

Adjuvant Immunoterapy

While the recurrence rate in patients who undergo surgery is approximately 45% in stage 1B, it can reach up to 70% in stage 3 patients. For this reason, adjuvant treatment is essential in operated NSCLC. However, it is known that cisplatin-based adjuvant chemotherapy has a very modest OS contribution [3]. It has been shown that adding adjuvant immunotherapy to standard chemotherapy provides a significant contribution to OS. The main advantage of preferring adjuvant treatment is surgical removal of the primary tumor without delay. It is known that in neoadjuvant studies, at least 20% of patients cannot undergo surgery at all [14]. Adjuvant treatment can be started at more flexible times during the postoperative period. For these reasons, patients can tolerate the treatment more easily [15,16]. Adjuvant chemo-immunotherapy hypothetically eliminates micrometastases and circulating tumor cells at a time when tumor burden is reduced by surgery [17]. There may be longer recovery times following surgery. Thus, an effective treatment strategy can be developed [18].

Many adjuvant ICI studies have been designed to prove the hypothetical benefits mentioned above. IMpower-010 is one of them. IMpower-010 is a phase 3, open-label, randomized study. 1280 patients with R0 resection, stage 1B (≥4 cm)-stage 3A (TNM 7th edition) and ECOG performance score 0-1 were included in the study, and 1005 patients were randomized. Patients were divided into two arms: one receiving 16 cycles of atezolizumab 1200 mg, and the other receiving best supportive care after standard cisplatin-based adjuvant chemotherapy. IMpower-010 is important because it is the first adjuvant immunotherapy study that has been shown to demonstrate improvement in DFS. While evaluating the data, we focused on patients with stage 2-3A. Patients were stratified according to PD-L1 status. Five-year follow-up results were published in 2024. DFS contribution is especially evident in the PD-L1 ≥1% group. In the intent-to-treat (ITT) population (stage 1B-3A), median DFS was 65.6 months in the atezolizumab arm and 47.8 months in the control arm. Hazard ratio (HR): 0.85 [95% confidence irterval (CI): 0.71-1.01], p value: 0.07. In all randomized patients in stage 2-3A, median DFS was 57.4 months/40.8 months; HR: 0.83 (95% CI: 0.69-1.00). In patients with PD-L1 ≥1%, median DFS was 68.5 months versus 37.3 months and HR: 0.70 (95% CI: 0.55-0.91). In patients with PD-L1 ≥50%, DFS was not reached (NR)/41.1 months. HR: 0.48 (95% CI: 0.32-0.72). Although there was a numerical difference between the two groups in the general population, there was no statistically significant difference. However, it was seen that there was a significant DFS difference starting from the PD-L1 ≥1% group, and it was more evident among PD-L1 ≥50% patients. Median OS was NR in the atezolizumab arm in PD-L1 ≥1%, patients, while it was 87.1 months in the control arm. HR: 0.77 (95% CI: 0.56-1.06). However, in PD-L1 ≥50% patients, the median OS was NR/87.1 months, with an HR of 0.47 (95% CI: 0.28-0.77). Grade 3 or higher side effects were seen in 22% of atezolizumab patients, and 12% were observed in the opposite arm. Of note, a significant difference in OS was only achieved in patients with PD-L1 ≥50% [19,20].

Another significant adjuvant ICIs study is KEYNOTE-091/PEARLS. The phase 3 randomized study included 1177 patients who underwent surgery for NSCLC, stage 1B-3A. Adjuvant pembrolizumab was started within 3-12 weeks after adjuvant platinum-based chemotherapy. Patients who started pembrolizumab by week 12 after surgery and did not receive adjuvant chemotherapy were included in the study. One arm received pembrolizumab every 21 days for 18 cycles, while the other arm received placebo. No crossover was allowed. Median DFS was 53.6 months in the immunotherapy arm and 42 months in the placebo arm. HR: 0.76 (95% CI: 0.60-0.89). In patients with PD-L1 1-49%, the HR was 0.67 (95% CI: 0.48-0.92) in terms of DFS. Unexpectedly, no statistically significant difference was seen between the two arms in patients with PD-L1 ≥50% (HR: 0.82). The median was NR in either arm. However, the pembrolizumab arm demonstrated numerically superior results compared to the placebo arm. In the subgroups, patients receiving ICIs without adjuvant chemotherapy, stage 3 patients, and patients with squamous cell carcinoma pathology were seen to have worse outcomes.

The median was also NR OS in the study. There was a significant benefit in terms of DFS in the ITT population and PD-L1 1-49% patients, but the lack of a statistically significant difference in patients with PD-L1 ≥50% presents a contrast. The reason for this discrepancy may be the difference in patient populations between the IMpower-010 study and the KEYNOTE-091/PEARLS study. At the same time, this may be because, in KEYNOTE-091/PEARLS, there were patients who received adjuvant ICIs without receiving adjuvant chemotherapy, and the rate of stage 3A patients was higher. Additionally, the immaturity of some data may have caused this discrepancy [21].

The adjuvant BR-31 study included patients with stage 1B-3A NSCLC. The study was designed as a Phase 3, double-blind study. Patients who received adjuvant platinum-based doublet therapies after surgery were then given durvalumab or placebo for 1 year. No significant difference in DFS was found between the two arms in patients with PD-L1 ≥1% and PD-L1 ≥25% [22]. In addition to the current studies, the adjuvant ANVIL study of nivolumab and the MERMAID 1 and 2 durvalumab studies are still ongoing [23-25]. Adjuvant ICI trials are summarized in Table 1.

Neoadjuvant and Perıoperative Immunoterapy

There is no clinical study comparing neoadjuvant ICIs with adjuvant ICIs in patients with NSCLC. However, the OpACIN study conducted in patients with stage 3 malignant melanoma showed a stronger immune response and greater T cell expansion with immunotherapy given in the neoadjuvant period [26,27]. It is known that immunotherapy given in the neoadjuvant period while the primary tumor remains in situ creates a stronger immune response. It is thought that this response creates a more permanent effect against circulating tumor cells and micrometastases [28]. Since the patient's performance status was better before the operation, treatment compliance was observed to be higher. In addition, another advantage of neoadjuvant ICIs includes the R0 resection rates and increased surgical success associated with the reduction in tumor size [29,30].

The concepts of pathological complete response (pCR) and major pathological response (MPR), which are thought to contribute to survival, are frequently used in neoadjuvant or perioperative, ICI studies. In pathological evaluation, no remaining viable tumor cells were defined as pCR, and ≤10% remaining viable cells were defined as MPR [31].

The most well-known study planned solely as a neoadjuvant study is CheckMate 816. Stage 1B-3A EGFR and ALK negative patients diagnosed with NSCLC were included in the study. One arm received 3 cycles of neoadjuvant nivolumab and chemotherapy every 21 days, while the control arm received 3 cycles of chemotherapy alone. The primary endpoints were pCR and event-free survival (EFS), and the secondary endpoints were MPR and OS. After neoadjuvant treatment, definitive surgery could be performed in 83.2% of the patients in the nivolumab + chemotherapy arm, while this rate was 77.8% in the control arm. Surgery could not be performed in 15.6% of the patients in the nivolumab + chemotherapy arm. When the reasons for not being able to undergo surgery in these patients were examined, it was observed that 6.7% of the patients could not be operated on due to disease progression, 1.1% due to treatment side effects, and 7.7% due to other reasons. Other reasons were the refusal of surgery by patients and the performance status or lung capacity of patients not being suitable for surgery. Median surgery time was 185 minutes in the experimental arm and 213.5 minutes in the control arm. A complete response was achieved in 24% of patients in the nivolumab + chemotherapy arm, while the complete response rate was 2.2% in the control arm. Again, MPR was 36.9% in the nivolumab + chemotherapy arm and 8.8% in the control arm. No significant difference was found only in terms of pCR in never smokers. The nivolumab + chemotherapy arm was superior in all other subgroups, such as PD-L1, age, and pathological type. Median EFS was 31.6 months in the experimental arm and 20.8 months in the control arm, with a HR of 0.63. When examined according to stage, the greatest EFS contribution was in stage 3A patients, with an HR of HR: 0.54. In stage 1B and 2, the contribution to EFS was not statistically significant. Non-squamous histology was associated with a better clinical outcome. While there was a significant contribution to EFS in the PD-L1 ≥1% group (HR: 0.41), there was no statistically significant difference in the PD-L1 <1% group. OS data is not available yet [32].

Table 1. Characteristics of adjuvant immunotherapy trials

Adjuvant trial	Phase	Stage	N	Treatment	Primary endpoint	HR in terms of DFS		
						ITT	PD-L1 ≥1%	PD-L1 ≥50%
IMpower-010	3	1B-3A	1280	CT + atezolizumab/ placebo	DFS	0.85 (95% CI: 0.71-1.01)	0.70 (95% CI: 0.55-0.91)	0.48 (95% CI: 0.32-0.72)
KEYNOTE-091/ PEARLS	3	1B-3A	1177	CT + pembrolizumab/ placebo	DFS	0.76 (95% CI: 0.60-0.89)	PD-L1 1-49% 0.67 (95% CI: 0.48-0.92)	0.82 (95% CI: 0.54-1.20)
Adjuvant BR-31	3	1B-3A	1219	CT + durvalumab/ placebo	DFS	0.89 (p=0.21)	0.99 (p=0.93)	-
ANVIL	3	1B-3A	903	CT + nivolumab/ placebo	DFS, OS	-	-	-

HR: Hazard ratio, DFS: Disease free survival, OS: Overall survival, CT: Chemotherapy, ITT: Intent-to-treat population, N: Sample size, PD-L1: Programmed death 1/programmed death ligand 1, CI: Confidence interval

The CheckMate 816 study included an exploratory arm in which 3 courses of neoadjuvant nivolumab plus ipilimumab were administered, while 3 courses of neoadjuvant chemotherapy were given in the control arm. Chemotherapy or radiotherapy was allowed in the adjuvant phase. These data were published in 2025. Two hundred and twenty-one patients were randomized 1:1. Median EFS was determined as 54.8 months in the nivolumab plus ipilimumab arm and 20.9 months in the control arm. The relationship between EFS and baseline four-gene inflammatory score (calculated by *STAT1, LAG3, CD8A, CD274,* genes) was examined. While there was no relationship between the baseline four-gene inflammatory score and EFS in patients who developed MPR, it was seen that, patients who developed pCR and had higher scores had significantly better EFS (HR: 0.45). pCR was observed as 20.4% in the nivolumab plus ipilimumab arm and 4.6% in the control arm. The MPR was 28.3% in the ICIs arm and 14.8% in the contralateral arm. OS data are immature, but 3-year OS data are 73% in the ICIs arm and 61% in the control arm. Grade 3-4 drug-related adverse events were seen in 14% of the ICIs arm and 36% of the control arm. Recurrence rates after definitive surgery were 23% and 44%, respectively. Recurrence rates with brain metastases were 2% and 13% [33].

LungMate 002 is a phase 2 neoadjuvant immunotherapy study, conducted with 50 patients with stage 2-3 disease. Toripalimab and chemotherapy was given for 2 to 4 cycles. After the operation, 27.8% of the patients achieved pCR and 55.6% achieved MPR [34]. In addition, TD-FOREKNOW is a phase 2 neoadjuvant immunotherapy study. It was conducted with 88 patients, with stage 3A and 3B disease. One arm received 3 cycles of camrelizumab plus chemotherapy and the other arm received 3 cycles of chemotherapy. The sentence needs to be rewritten for logical consistency and clarity, such as: 'After the procedure, the patients were monitored in the recovery room'. After the operation, pCR was 32.6% compared to 8.9%, and MPR was 65.1% compared to 15.6%, demonstrating the superiority of the (immunotherapy + chemotherapy) arm. In terms of EFS, HR: 0.13 was achieved in patients with pCR, while HR: 0.84 was achieved in patients without pCR [35].

NADIM II is a phase 2, perioperative immunotherapy study. Stage 3A and 3B; 86 patients were randomized 2:1. One arm received 3 cycles of nivolumab + carboplatin + paclitaxel, and the other arm received only carboplatin + paclitaxel. Postoperatively, nivolumab was continued every 28 days for 6 months in the immunotherapy arm. pCR was 37% in the immunotherapy arm and 7% in the control arm. The MPR was 57% compared to 14%, indicating a significant difference between the two groups. Downstaging occurred in 69.8% of the patients in the immunotherapy arm. The median PFS was NR in the immunotherapy arm, while it was 18.3 months in the control arm (HR: 0.47). 93% of the immunotherapy arm underwent surgery, while only 69% of the control arm underwent surgery. PFS and OS have been linked to baseline and changes in levels of ctDNA [36,37].

KEYNOTE-671 is a randomized, double-blind, phase 3 study. Seven hundred and eighty six patients with stage 2-3B NSCLC were randomized 1:1. The experimental arm received 4 cycles of neoadjuvant pembrolizumab + chemotherapy every 21 days. The control arm received 4 cycles of placebo + chemotherapy. The experimental arm received 13 cycles of postoperative pembrolizumab every 21 days. The primary endpoints of the study were EFS and OS. The secondary endpoints were pCR and MPR. The median EFS was NR in the pembrolizumab arm. The median EFS was 17 months in the placebo arm. HR: 0.58 (95% CI: 0.46-0.72) and p value: 0.00001. There was no statistically significant difference in EFS between patients with PD-L1 <1 and never smokers. In other subgroups, the ICI arm was significantly superior to the control arm. In terms of OS, the pembrolizumab arm did NR the median. In the placebo arm, the median OS was 45.5 months. HR: 0.73 (95% CI: 0.54-0.99) and p value: 0.02124. pCR was seen in 18.1% of patients in the ICI arm and 4% in the control arm. MPR was 30.2% vs 11%. In terms of EFS, the HR was 0.33 in patients with pCR, while the HR was 0.69 in patients without pCR. Regarding EFS, patients with MPR had an HR of 0.54, whereas those without MPR had an HR of 0.73 [38].

CheckMate 77T is a perioperative immunotherapy study that included patients with stage 2A (>4 cm)-3B NSCLC. Four hundred and sixty one patients without anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR) mutations, ECOG 0-1, were randomized 1:1 in the study. Patients were stratified according to their histological diagnosis and PD-L1 status. The ICI arm received 4 cycles of nivolumab and chemotherapy every 21 days, while the control arm received 4 cycles of placebo and chemotherapy. Among the patients who underwent surgery afterwards, nivolumab was continued for 1 year in the ICI arm. The primary endpoint was defined as EFS. The secondary endpoints were pCR and MPR. While 78% of the patients in the ICI arm underwent definitive surgery, 77% in the control arm underwent the procedure. Only 60% of the patients in both arms could complete the neoadjuvant and adjuvant processes. While the median EFS in the control arm was 18.4 months, the median EFS in the ICI arm was NR. HR: 0.58 (0.42-0.81) and p value: 0.00025. When the subgroups were examined, there was no significant difference among stage 2 patients, while there was a significant difference among stage 3 patients. Again, there was no difference in terms of EFS in the PD-L1 <1% group, while there was a significant difference in the PD-L1 ≥1% group. There was no difference EFS between the two arms in non-smokers. The ICI arm was seen to be superior in both single-station, and double-station N2 patients. pCR was detected in 25.3% of the patients in the ICI arm and 4.7% of the control arm. Again, the MPR rates were 35.4% and 12.1%. There was no difference regarding pCR in never smokers. The ICI arm was superior to the control arm in terms of pCR in all other subgroups. In terms of EFS, HR was 0.33 in patients with pCR and 0.79 in patients without pCR. Regarding EFS, patients with MPR had an HR of 0.40, whereas those without MPR had an HR of 0.85 [39].

Neotorch is a phase 3 study. Five hundred patients with stage 2-3 NSCLC were randomized 1:1 in a clinical trial. Patients with

EGFR and ALK mutations were excluded from the study. In the ICI arm, he received 3 cycles of toripalimab + chemotherapy as neoadjuvant and then another cycle of toripalimab + chemotherapy as adjuvant, and 13 cycles of toripalimab every 21 days. In the control arm, they received 3 cycles of placebo + chemotherapy as neoadjuvant, and then another cycle of placebo + chemotherapy as adjuvant and 13 cycles of placebo. pCR was 24.8% in the ICI arm and 1% in the control arm. MPR was 48.5% and 8.4%, indicating results for two different conditions or metrics. EFS at 24 months was 64.7% in the ICI arm and 38.7% in the control arm. In terms of EFS, HR: 0.59 in patients with PD-L1 <1%, HR: 0.31 in patients with PD-L1 ≥1-49%, and HR: 0.31 in patients with PD-L1 ≥50% were found. Squamous cell disease patients had a better outcome than non-squamous cell disease patients [40].

The AEGEAN study is a phase 3 perioperative ICI study. 802 patients with Stage 2A-3B were randomized 1:1. The ICI arm received 4 cycles of durvalumab + chemotherapy, then underwent surgery, and received 1 year of adjuvant durvalumab. The control arm received 4 cycles of placebo + chemotherapy, followed by surgery and received placebo for 1 year. While EFS did NR the median in the ICI arm, the median EFS in the control arm was 25.9 months. The HR (HR: 0.68). pCR was 17.2% in the ICI arm and 4.3% in the control arm. MPR was found to be 33.3% in the ICI arm and 12.3% in the opposite arm. OS data have not yet reached the median [41].

Although there are no studies comparing neoadjuvant or perioperative immunotherapy, which treatment strategy is superior is one of the most important problems we encounter in clinical practice. It is observed that very good EFS results were obtained in the CheckMate 816, CheckMate 77T, KEYNOTE-671, and Neotorch studies in patients with pCR. However, in patients without pCR, the HR in the CheckMate 816 study was 0.84, while the HR in the CheckMate 77T, KEYNOTE-671, and Neotorch studies was 0.73, 0.69, and 0.53, respectively. This situation indicates that perioperative immunotherapy is superior to neoadjuvant immunotherapy, especially in patients without pCR. Biomarkers such as ctDNA and baseline four-gene inflammatory score will be used to facilitate follow-up of patients and individualize treatment strategies in the future. Neoadjuvant and perioperative ICI studies are summarized in Table 2.

Immunoterapy Strategies in Inoperable Locally Advenced NSCLC

Among locally advanced NSCLC patients, some are considered inoperable. Patients with multiple N2 lymph node involvement, bulky lymph nodes, N3 involvement, or with vascular invasion are considered to have inoperable locally advanced disease. However, with the emergence of neoadjuvant and perioperative immunotherapy studies, some patient groups previously considered inoperable have begun to be evaluated

Table 2. Characteristics of neoadjuvant and perioperative immunotherapy trials

Trial	Phase	Stage	N	Trial design / Treatment	Primary endpoint	pCR rate	MPR rate	EFS	OS
CheckMate 816	3	1B-3A	358	Neoadjuvant Neoadjuvant CT + nivolumab	pCR, EFS	24% vs. 2.2%	36.9% vs. 8.9%	31.6 m vs. 20.8 m HR: 0.63	-
LungMate 002	2	2-3	50	Neoadjuvant Neoadjuvant CT + toripalimab	Safety, MPR	27.8%	55.6%	-	-
NADIM II	2	3A-3B	86	Perioperative Neoadjuvant CT + nivolumab, adjuvant nivolumab after surgery	PFS	36.8% vs. 6.9%	52.6% vs. 13.8%	PFS: NR vs. 18.3 m HR: 0.47	NR vs. NR HR: 0.43
KEYNOTE-671	3	2-3B	786	Perioperative Neoadjuvant CT + pembrolizumab, adjuvant pembrolizumab after surgery	EFS, OS	18.1% vs. 4%	30.2% vs. 11%	NR vs. 17 m HR: 0.58 p<0.00001	NR vs. 45.5 m HR: 0.73 p: 0.02124
CheckMate 77T	3	2A-3B	461	Perioperative Neoadjuvant CT + nivolumab, adjuvant nivolumab after surgery	EFS	25.3% vs. 4.7%	35.4% vs. 12.1%	NR vs. 18.4 m HR: 0.58	-
Neotorch	3	2A-3B	406	Perioperative Neoadjuvant CT + toripalimab, adjuvant durvalumab after surgery	EFS, MPR	24.8% vs. 1%	48.5% vs. 8.4%	NR vs. 15.1 m HR: 0.40	NR vs. 30.4 m HR: 0.62
AEGEAN	3	2A-3B	802	Perioperative Neoadjuvant CT + durvalumab, adjuvant durvalumab after surgery	EFS, pCR	17.2% vs. 4.3%	33.3% vs. 12.3%	NR vs. 25.9 m HR: 0.68	-

HR: Hazard ratio, EFS: Event free survival, OS: Overall survival, PFS: Progression free survival, CT: Chemotherapy, N: Sample size, pCR: Pathologic complete response, MPR: Major pathologic response, NR: Not reached, m: Month, vs: Versus

as potentially operable [42]. Operability for patients diagnosed with NSCLC is a frequently discussed topic soon. However, the results of adjuvant immunotherapy after definitive CRT inoperable patients are noteworthy.

The PACIFIC trial is a phase 3 randomized trial. In the study, 709 patients were randomized in a 2:1 ratio. All patients received ≥2 cycles of platinum-based doublet chemotherapy and definitive radiotherapy. The ICI arm then received durvalumab for up to 1 year, while the control arm received placebo. Median PFS was 16.8 months in the ICI arm and 5.6 months in the control arm (HR: 0.52). At the beginning of the study, participants were stratified into groups of <25% and ≥25% in terms of PD-L1. When the subgroups were examined, an EFS benefit was observed in both groups in the ICI arm in terms of PD-L1. No benefit was shown in the subgroups, only in EGFR-positive patients [43]. The 5-year follow-up data were then published in 2022. Median OS was 47.5 months in the ICI arm and 29.1 months in the control arm (HR: 0.72). The 5-year OS was 42.9% vs 33.4%. Five-year PFS was 33.1% in the ICI arm and 19% in the control arm. When subgroups were evaluated according to OS data, no OS contribution was shown in the PD-L1 <25% group. Subsequently, it was re-stratified as <1% and ≥1% according to PD-L1. While no OS contribution was shown in the PD-L1 <1% group, adjuvant durvalumab was shown to contribute to OS in patients with PD-L1 ≥1%. Grade ≥3 side effects were seen in 30% in the ICI arm and 26% in the opposite arm [13].

Conclusion

In adjuvant ICIs studies, a contribution to OS was observed in patients with PD-L1 ≥50% in IMpower-010. OS contribution was shown in patients with PD-L1 ≥1% in KEYNOTE-091/PEARLS, but not in patients with PD-L1 ≥50%. At the same time, the contribution of adjuvant durvalumab to EFS could not be shown in the Adjuvant BR-31 study. However, the contribution of pCR, MPR, EFS, and OS in favor of ICIs in all groups in neoadjuvant and perioperative studies is remarkable. We see that OS and EFS contribution cannot be assessed in the adjuvant ICIs studies in some cases. The superior results of neoadjuvant and perioperative studies compared to neoadjuvant and perioperative studies are better than adjuvant studies can be attributed to the continuation of the antigenic effect of the primary tumor in the neoadjuvant phase and the stronger immune response associated with this effect. At the same time, the immune system is not suppressed by surgery, and the structure of the lymphatic system is not disrupted, both of which are in favor of neoadjuvant ICIs. Today, perioperative ICIs have come to the forefront for patients with operable or potentially operable NSCLC diagnosis, especially stage 3. For inoperable locally advanced NSCLC, adjuvant durvalumab after definitive CRT is a valuable option.

Ethics

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., Concept: Y.D., Design: Y.D., Literature Search: A.K., S.K., Writing: A.K.

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