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Abstract: This study aims to evaluate the outcomes of neoadjuvant chemotherapy with immunotherapy in patients with non-small cell lung cancer (NSCLC) within a real-world context. We analyzed medical records from January 2022 to August 2023, focusing on individuals aged 18 and older diagnosed with resectable NSCLC who received neoadjuvant chemoimmunotherapy prior to surgical intervention. The cohort comprised 56 patients, predominantly smokers (95%) and male (74%), with 80% presenting at stage III. Of the participants, 44 underwent surgery, with 95% receiving lobar resection. Clinical assessments via PET-CT imaging revealed an 86% rate of response or disease stabilization, while pathological evaluations showed complete and major pathological responses in 61% of cases. This real-world data supports the safety and efficacy of incorporating immune checkpoint inhibitors in the neoadjuvant treatment of NSCLC, followed by surgical resection.

Keywords: Neoadjuvant; Chemotherapy; Immunotherapy; Non-Small Cell Lung Cancer; Resection surgery; Real-world clinical outcomes

1. Introduction

Lung cancer is one of the most common diagnosed malignancy worldwide [1,2]. In the United States, 238,340 new cases of lung cancer were documented, nonetheless 127,070 deaths were reported representing the high morbidity and mortality of this disease [3]. More than two-thirds of the cases are diagnosed in individuals over the age of 65-70, while roughly up to 5% are diagnosed in individuals under 40-45 years old. The heightened morbidity and mortality rates associated with NSCLC arise from its frequent diagnosis at progressive stages. Nearly 65-70% of patients are diagnosed in advanced stages (III/IV) [4-7]. This late detection at an advanced stage of an aggressive tumor, with variety of phenotypes and acquired resistance to treatment, attributes to the poor prognosis of lung cancer in the majority of cases [3,4].

Lung cancer is histologically divided into small cell lung cancer, which comprises approximately 15-20% of cases, and non-small cell lung cancer (NSCLC) which accounts for almost 80-85% of cases [4-7]. Diagnosis of NSCLC is further subtyped into three main categories: adenocarcinoma (45-50% of cases), large-cell carcinoma (10-15% of cases), squamous cell carcinoma (30-35% of cases) and almost 5% others [4]. The TNM system classifies and categorizes different stages of the disease [4]. NSCLC treatment is contingent upon cancer stage and patient health. Understanding staging is crucial for determining whether tumor removal is viable. Tumors at stages I and II, which are diagnosed in almost 32% of non-metastatic resectable lung cancer patients, signify localized disease. These early stages are usually eligible for resection without metastatic concerns, while stages IIIC and IV preclude resection. Stages IIIA presents a unique situation: T3N0M0 tumors are resectable, but T3N2M0 tumors are not [3,5,6]. The 5-year survival rate for clinical stage IA1 and IIB were reported to be 92% and 53% respectively [5,6]. However, for locally advanced stage III lung cancer that accounts for 25% of the patients, the 5-year survival rate range is 13-36% [5,6]. Among 70% of resectable stage IB-IIIA patients, recurrence was observed both loco-regionally and distantly (33% and 67% respectively) at median follow-up of 4.5 years [8,9].

Systemic treatment strategies for resectable NSCLC follow three main approaches. The preoperative approach administers neoadjuvant systemic therapy prior to surgery. The postoperative approach applies first surgery and then systemic therapy. The third approach of perioperative therapy combines both pre and postoperative modalities, i.e. systemic therapy, followed by the surgery and later another round of systemic therapy [2,10]. Immunotherapy consensus for early-stage NSCLC patients has recently been published [11]. Neoadjuvant chemotherapy administered to NSCLC patients was shown to have improved progression free survival (PFS) by addition of immunotherapeutic agent, Nivolumab, an immune checkpoint inhibitor. Phase I/II and phase III clinical trials NADIM II and Checkmate 816, respectively, demonstrated the effectiveness of this combination therapy [2,10,12]. The impressive results of the phase III Checkmate 816 trial have made a revolution in the treatment of resectable disease NSCLC, and the neoadjuvant chemotherapy/immunotherapy (CT/IO) has become a crucial part of the multi-disciplinary treatment of this disease [13].

Adjuvant therapy goal is to minimize the risk of relapse by eradicating minimal residual disease [14]. Patients with completely resected stage IB-IIIA NSCLC disease had documented recurrence in 33 % of cases (out of 831 patients in France, Germany and UK). 68% of them had distant metastasis involvement [15,16]. The risk of distant metastases was higher than local and regional risk, indicating the need for earlier improved systemic control, such as preoperative neoadjuvant effective therapy [17]. Lung cancer disease was shown to have low response rate to standard of care chemotherapy and radiation in addition to challenging treatment for metastases [4,18]. Adjuvant chemotherapy has increased overall survival rate by 5% [13]. However, NSCLC Meta-analysis Collaborative Group publication on neoadjuvant chemotherapy found that it led to a 5% increase in 5-year survival benefit [19]. These clinical outcomes have called for development of better adjuvant treatments.

Clinical trials KEYNOTE 91 and IMpower 010 report novel treatment approaches, by administration of immunotherapy [20-22]. Standard of care treatment for patients diagnosed with metastatic NSCLC incorporates immune checkpoint inhibitors (ICIs) [7]. Nivolumab, an immune checkpoint inhibitor, blocks PD-L1, a protein which is expressed by tumor cells, thus enables T cells to kill the cancer cells [23]. Nivolumab was approved by the Food and Drug Administration in 2022

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for adult NSCLC patients as part of a neoadjuvant setting in combination with platinum-doublet chemotherapy [7]. ICIs administered both at neoadjuvant and adjuvant venues display their efficient mode of action by better clinical outcome than without immunotherapy [7]. Neoadjuvant immunotherapy triggers a T cell anti-tumor response, aiming to reduce its size before surgery [7,10]. This may lead to resection surgery of smaller magnitude i.e. lobectomy vs pneumonectomy. In addition, the pathologic response evaluates the neoadjuvant treatment on tissue removed during the operation [14]. Adjuvant immunotherapy objective is to eliminate undetectable “micro metastatic” residual tumor cells, that may exist in lymph nodes, blood vessels or lymphatic vessels after surgery [10].

In the perioperative approach, the role of adjuvant therapy is to prevent recurrence by inducing anti-metastatic environment [7]. KEYNOTE-671 clinical trial results describe pembrolizumab administration in perioperative setting, both as a neoadjuvant agent combined with chemotherapy and as an adjuvant agent for early NSCLC [24]. This potent immune checkpoint blocker had improved event free survival and pathological complete response (pCR) in comparison to neoadjuvant therapy modality.

The aim of the study was to check the efficacy of the combination of neoadjuvant therapy on major pathological response (MPR), which is defined as less than 10% residual viable tumor after neoadjuvant therapy and pCR, defined as no viable residual tumor.

2. Materials and Methods

2.1. Study Design

This is a real-world retrospective multicenter observational study. Fifty-six NSCLC patients’ data, retrieved from medical records files of nine medical centers in Israel, composed the study cohort.

2.2. Patients Enrolled

Inclusion criteria were 18 years of age or older, the patients diagnosed with lung cancer NSCLC diagnosed in early stages (IB-IIIA), All Eastern Cooperative Oncology Group (ECOG) performance-status scores of 0 to 4 (on a 4-point scale, with higher scores indicating increasing disability) were included. Each of the studied patients was presented to and discussed with a multidisciplinary medical team when admitted to the Medical Centers Oncology Institute as per the standard protocol. This team included medical oncologist, a thoracic surgeon, a pulmonologist, a pathologist, an imaging physician, a nuclear medicine physician, and a radiation oncologist. The multidisciplinary team evaluates the patient’s status, pathology findings, and imaging reports after which. Each patient was assigned a primary physician who is oncology specialist being responsible for the treatment plan. The patients received neoadjuvant treatment of combined chemotherapy and immunotherapy with nivolumab followed by resection surgery. The patients included in the study had not received any previous systemic therapy for any other oncologic disease.

The exclusion criteria comprised in other treatment regimens and the presence of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations within the tumor.

Each institutional review board (IRB) approved the study. The IRB waived patients’ consent due to the retrospective nature of the study.

2.3. Treatment Administered

The planned systemic treatment consisted of platinum-based chemotherapy with nivolumab 360 mg in 3 weeks intervals up to 3 cycles in total.

2.3.1. Non-Squamous Lung Cancer Patients Received 3 Cycles of Chemotherapy of the Physician’s Choice

Cisplatin (75 mg per square meter of body-surface area) or carboplatin (area under the concentration–time curve, 4-5 mg per milliliter per minute, depending on the performance status), plus pemetrexed (500 mg per square meter), plus nivolumab at a fixed dose of 360 mg every 3 weeks.

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Prior to pemetrexed treatment, premedication of folic acid, vitamin B12, and glucocorticoids was administered to all patients.

2.3.2. Squamous Cell Carcinoma Lung Cancer Patients Received 3 Cycles of Chemotherapy of the Physician's Choice

Cisplatin (75 mg per square meter of body-surface area) or carboplatin (area under the concentration–time curve, 6.5 or 4 mg per milliliter per minute, depending on the performance status), plus paclitaxel (175 mg per square meter) or gemcitabine (1000 mg per square meter, on days 1 and 8) plus nivolumab at a fixed dose of 360 mg every 3 weeks.

2.4. Surgery

All patients underwent a positron emission tomography-computed tomography (PET-CT) imaging for disease restaging purpose, 3 weeks following the last dose of neoadjuvant treatment. The multidisciplinary team held a discussion prior to the decision for surgery. The Response Evaluation Criteria in Solid Tumors (RECIST) served for disease evaluation by the treating physician [25]. Surgery was performed 4-8 weeks after last dose of neoadjuvant therapy cycles.

A board certified thoracic surgeons performed all of the surgeries in a minimally invasive fashion. Standard surgery included lobar resection with mediastinal lymph node dissection. Patients' admission either to the intensive care unit or to the thoracic surgery unit following the surgery depended on the complexity of the procedure and the hospital protocols. Two weeks after discharge, the thoracic surgery clinic followed up the patients. Follow-ups continued both by the thoracic surgeon and by the oncologist.

2.5. Molecular Profiling

Next generation sequencing (NGS) genetic testing performed on biopsy samples for the following oncogenes: epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS proto-oncogene 1 (ROS-1). As well, programmed death ligand 1 (PD-L1), microsatellite instability and tumor burden were evaluated.

Immunohistochemistry assessed PD-L1 protein expression. Tumor proportion score (TPS) calculated the percentage of viable tumor showing membrane staining [26].

2.6. Data Analysis

Descriptive statistics calculated frequency (n) and percentage for all the parameters of the study. Median and range present the age, follow-up and days in hospital variables. Fisher's exact test assessed the association between PD-L1 status and the response to treatment.

3. Results

3.1. Patient Characteristics

Fifty-six patients have been included in the study (Table 1). Median follow-up duration was 10 months (range 3-17 m). Median age of the study cohort participants was 65 years old, 74% were male. Seventy percent of patients reported current smoking.

Fifty-one percent of lung cancer tumors had a histological type of adenocarcinoma. Stage III disease had 80% prevalence in the study cohort.

All samples had undergone molecular profiling. Analysis of oncogenes ALK, ROS, and EGFR were negative. PD-L1 analysis was performed in 48 patients, 70% scored >1%. Other co-mutations detected were KRAS, STK11, p53 and BRCA.

Table 1. Demographic and clinical characteristics of the study population (*n*=56).

Characteristic	Frequency (*n*)	Percentage (%)
Age, (years), median [range]	65 [51-79]	
Gender		

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Female	15	26
Male	41	74
Background conditions	43	77
COPD*/IHD*	34	56
Smoking Habits		
Current	39	70
Past	10	18
Light	4	7
Never	3	5
Follow-up (months), median [range]	10 [3-17]	
Histology		
Adenocarcinoma	29	52
Squamous cell carcinoma	22	39
Other	5	9
Disease Stage		
IIB	11	20
IIIA	35	62
IIIB	10	18
Molecular profile of EGFR, ALK, ROS1-Performed	56	100
TMB*-Performed	42	75
MSI*-Performed	41	73
PD-L1*-Performed	48	86
Time till results (days), median [range]	8 [4-22]	
PD-L1 expression level		
> 1%	34	70
< 1%	14	30
Other mutations checked		
KRAS	3	5
STK11	1	2
P53	3	5
BRCA	1	2

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; IHD, Ischemic Heart Disease; EGFR, Epidermal Growth Factor Receptor; ALK, anaplastic lymphoma kinase; ROS, Ros-Proto Oncogene1; PD-L1, Programmed Death Ligand 1; TMB, Tumor Mutational Burden; MSI, Micro Satellite Instability; KRAS, Kirsten Rat Sarcomas Viral Oncogene; STK, Serine/Threonine Kinase 11; BRCA, Breast Cancer Gene. Notes: [a]PD-L1 score < 1% is considered negative. [b]PD-L1 score >1% is considered positive.

3.2. Treatment

3.2.1. Neoadjuvant Therapy

Taxol® (paclitaxel) and Alimta® (pemetrexed) are the most common administered platinum-based drugs to 48% and 46% of cases respectively (Table 2).

Table 2. Treatment: Platinum based chemotherapy used in the study population (*n*=56).

Platinum-based Combination	Patients *n* (%)	No. of cycles (No. of patients, percentage)
Paclitaxel	27 (48)	1 (2 patients, 4%)
Pemetrexed	26 (46)	2 (1 patient, 2%)
Gemcitabine	2 (4)	3 (40 patients, 70%)
Etoposide	1 (2)	4 (13 patients, 23%)

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Twice as many patients reported adverse events of any grade, following chemotherapy (n=38) than by immunotherapy (n=17) (Table 3). Most adverse events were described as Grades 1,2. Nonetheless, three patients needed to discontinue the treatments.

Table 3. Treatment reported Toxicity and adverse events *n* (%).

Treatment	Any Grade	Grades 1,2	Grades 3,4
Chemotherapy, *n* (%)	38 (68%)	31 (81%)	7 (18%)
Immunotherapy, *n* (%)	17 (30%)	15 (88%)	2 (12%)
Dose change			
Dose interruption	3 (5.17%)		
Dose reduction	1 (1.72%)		
Discontinuation	3 (5.17%)		
Adverse events[a]			
Diarrhea	13 (23%)	11(84%)	2 (15%)
Nausea/Vomiting	14 (25%)	14 (100%)	
Weakness	29 (52%)	25 (86%)	4 (13%)
Neuropathy	11 (20%)	9 (82%)	2 (18%)
Thyroid	14 (25%)	13 (93%)	1 (7%)
Skin	12 (21%)	12 (100%)	

Notes: [a]Any grade adverse events rates were calculated as percentage of total cohort *n=56*. Grades 1,2 and Grades 3,4 toxicity rates were calculated as percent of "Any Grade" category.

3.3. Response to Treatment

Post treatment staging was done using PET-CT. Response to treatment was detected in 40 (72%) of patients while tumor progression was evident in 8 (14%) of cases (Table 4). All the non-responders were evaluated as disease progression either stage IIIB (n=5) or non-operable stage IIIA (n=3). These patients' expressed a progressive disease as locally progression however without distant metastasis. 4 out of 48 responders were not operated due to patients' refusal and loss of follow-up. Among the 44 operated patients, Complete pathological response was found in 16/44 (36.4%), major pathological response was found in 11/44 (25%) and Partial pathological response in 17/44 (38.6%), (Table 4). There is no statistical differences at the response to treatment rate according to type of histology, TMB and gender p=0.68, p=0.67 and p=0.67 respectively.

Table 4. Clinical description of surgery and response to treatment.

Procedure	Patient frequency *n*, (Percentage %)
Surgery	44 (78%)
Thoracoscopy	42 (42/44, 95%)
Open surgery	2 (2/44, 5%)
Resection	
Lobectomy	43 (98%)
Pneumonectomy	1 (2%)
Days in hospital, median [range]	4 [2-29]
Complications	5 (5/44, 11%)
Prolong air leak	3 (3/44, 6%)
Pneumonia	1 (1/44, 2%)
Surgical site infection	1 (1/44, 2%)
Clinical response by PET-CT	
Complete response	6 (11%)
Partial response	34 (61%)
Stable disease	8 (14%)

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Tumor progression	8 (14%)
Surgery	44 (79%)
Pathological response	
Complete response	16 (36.4%)
Major pathologic response	27 (61.4%)

Abbreviations: PET-CT, positron emission tomography-computed tomography; n, number.

3.4. Surgery

Forty-four of the patients' cohort medical records files documented surgery data (Table 4), (four patients refused surgery for personal reasons). Minimally invasive thoracoscopic surgery was performed in 42/44 (95%) of cases. Lobar resection was performed in 43/44 patients (98%) and pneumonectomy was done in 1 patient (2%). All tumors were resected with appropriate margin (R0). Post-surgery complications were recorded in 5/44 (11%) patients, of them three had prolong air leak (6%), one had pneumonia (2%) and one had surgical site infection (2%).

Analysis of the association between PD-L1 status and the treatment response, using Fisher's exact test, compared the rates of the responders (n=48) and non-responders (n=8) in the current study. 17% of responders and 75% of non-responders presented a negative PD-L1 status (p-value = 0.0019). Conversely, 69% of responders and 12.5% of non-responders expressed a positive PD-L1 status, (p-value = 0.004). Of note, 14% of responders and 12.5% of non-responders had unknown PD-L1 status. These findings underscore the significance of PD-L1 status as a predictive biomarker for treatment response, emphasizing its potential utility in guiding therapeutic decisions for patients undergoing immunotherapy. Descriptive statistics in terms of median, percentages and ranges calculated to the whole parameters in the study. Median and ranges present to age, follow-up time and days in hospital variables. Fisher's exact test assessed to test the association between smoking status, histology, gender, PD-L1 and TMB according to response to treatment rate. P<0.05 was consider as significant, (Table 5).

Table 5. Table 5. The clinical biomarker for response by Fisher's exact test.

	No Response; *n*=8	Response; *n*=48	*P*-value
PD-L1 status			
Negative[a]	6/8 (75%)	8/48 (17%)	0.0019
Positive[b]	1/8 (12.5%)	33/48 (69%)	0.004
Unknown	1/8 (12.5%)	7/48 (14%)	1.00
Smoking status			
Current and past	3/8 (37.5%)	46/48 (95.8%)	0.0003
Light and never	5/8 (62.5%)	2/48 (4.2%)	0.0003
Histology			
Adenocarcinoma	4/8 (50.0%)	25/48 (52.1%)	0.68
Squamous cell carcinoma	2/8 (25.0%)	20/48 (41.7%)	0.68
Other	1/8 (12.5%)	3/48 (6.3%)	0.68
TMB status			
High (over 10 Mut/Mb)	5/8 (62.5%)	11/35 (31.4%)	0.67
Low (under 10 Mut/Mb)	3/8 (37.5%)	24/35 (68.6%)	0.67
Gender			
Male	5/8 (62.5%)	36/48 (75.0%)	0.67
Female	3/8 (37.5%)	12/48 (25.0%)	0.67

Abbreviations: n, number; PD-L1, Programmed death-ligand 1; TMB, Tumor Mutational Burden; Mut/Mb , mutations per megabase. Notes: [a]PD-L1 score < 1% is considered negative. [b]PD-L1 score >1% is considered positive.

4. Discussion

Lung cancer stands is the foremost cause of cancer-related deaths worldwide, claiming an estimated 1.8 million lives in 2020. Traditionally, the standard treatment for resectable NSCLC involved lobectomy followed by systemic adjuvant therapy. However, recent research has highlighted the benefits of neoadjuvant combination therapy (chemo-immunotherapy), ushering in a new perspective. Neoadjuvant treatment presents an alternative avenue to enhance survival rates in patients with resectable NSCLC. This approach offers several potential advantages, including tumor downstaging, early management of micrometastases, facilitating complete resection and improved tolerability. Nevertheless, the utilization of neoadjuvant chemotherapy for resectable NSCLC remains as the backbone [27,28].

The current study investigated patients, diagnosed with advanced but resectable NSCLC. The present research aimed to assess the efficacy of the combination therapy ie chemo-immunotherapy, in real-world data. Treatment of early stage NSCLC is complex and involves several modalities due to variety of factors such as genetic mutations and other clinical biomarkers. [29].

Following major clinical trials and approval by the FDA, the NCCN guidelines [Version 1.2024] for Non-Small Cell Lung Cancer recommend perioperative systemic therapy for patients who are candidates for immune checkpoint inhibitors. The NCCN guidelines provide neoadjuvant and adjuvant updates on an ongoing basis [30,31]. Nivolumab and platinum-doublet chemotherapy are suggested for neoadjuvant modality. Pembrolizumab and cisplatin-based doublet therapy followed by surgery and then continue as single-agent adjuvant therapy [30,31].

Early stages of NSCLC are treated by pre-surgery approach, resection, and post-operative therapy. CheckMate 77T and KEYNOTE 671 trials [24], report that perioperative, tri-phasic treatment improved survival benefit. KEYNOTE 671 clinical trial included multimodality approach of both neoadjuvant and adjuvant therapies. These treatments used immune checkpoint inhibitor pembrolizumab and provided more benefits than a single modality approach [24]. Immunotherapy reached wide international consensus for NSCLC. Addition of immunotherapy, eg nivolumab as an agent in neoadjuvant treatment along with platinum-based chemotherapy to NSCLC patients, presented in the current study are in line with the published results of the clinical trials [12,32]. The present real-world outcomes of nine medical centers in Israel demonstrated 36% pathological complete response which is comparable to NADIM II trial result from hospitals in Spain having achieved 37% pathological complete response. Moreover, the sample size of the study cohort was similar, i.e. 56 patients were included in the Israeli study and 57 were found eligible in Spain [12].

We observed higher rates of partial clinical responses (36%) and major pathological responses (25%) compared to those reported in clinical trials. This difference may be attributed to the fact that 82% of our patients were in stages IIB and IIIA. Additionally, over 70% of our patients tested positive for PD-L1, which is known to be a surrogate marker for a better response to immunotherapy; this is higher than the 55-60% positivity rates typically reported in clinical trials. Furthermore, 70% of our patients were current smokers, a group known to generally have better responses to immunotherapy compared to former or never smokers. A systematic review and meta-analysis support this, showing that overall response rates to immunotherapy were significantly higher in current and former smokers compared to never smokers (36% vs. 26% vs. 14%; $p=0.02$), with even greater differences among patients with PD-L1 tumor proportion score (TPS) ≥50% (current smokers 58% vs. never smokers 19%; $p=0.03$), [32].

A recurrence rate of 23.6% has been reported for patients with pathologic complete response after neoadjuvant therapy for locally advanced NSCLC [17]. Pathologic complete response is observed upon no finding of viable tumor cells neither at the primary tumor site and lymph nodes [33]. Provencio et al reported treatment of stage III NSCLC with perioperative approach which included a neoadjuvant step of nivolumab and platinum-based chemotherapy; followed by surgery and an adjuvant therapy of nivolumab for 6 months [12]. This clinical trial (NADIM II) resulted in 37% of patients presenting a pathological complete response and longer survival than chemotherapy. That study showed evidence of the synergistic effect of immunotherapy combined with chemotherapy [12].

Currently, there are four main therapies that may be utilized as neo-adjuvant or perioperative treatments, pembrolizumab from KEYNOTE-671 trial [24], nivolumab from CheckMate 816 trial [13], toripalimab from Neotorch trial [33], and durvalumab from AEGEAN trial. Several notable differences emerge upon comparing the current study results with findings from other four main trials assessing the efficacy of neoadjuvant chemo-immunotherapy (Table 6). The present study observed a pathologic complete response (PCR) rate of 36%. Contrarily, the CheckMate 816 trial, which administered chemotheapy plus nivolumab for 3 cycles, reported a PCR rate of 24%. The AEGEAN trial, employing chemotherapy plus durvalumab for 4 cycles, reported a PCR rate of 17.2%. Similarly, the KEYNOTE-671 trial, utilizing chemotherapy plus pembrolizumab for 4 cycles, reported a PCR rate of 18.1%. Notably, the Neotorch trial, combining chemotherapy plus toripalimab for 3 cycles, reported a PCR rate of 24.8%. Regarding the rate of major pathologic response (MPR), the present study reported a high rate of 61%. In comparison, the CheckMate 816 trial reported a MPR rate of 36.9%, the AEGEAN trial reported 33.3%, the KEYNOTE-671 trial reported 30.2%, and the Neotorch trial reported 48.5%.

In terms of the incidence of Grade ≥3 adverse events related to immunotherapy, the current study reported a rate of 12%. In contrast, the Neotorch trial reported a significantly higher rate of 63.4%, adverse events, nevertheless, 0.5% fatal adverse events relate to toripalimab administration. The CheckMate 816 trial reported a rate of 33.5% adverse events; however, without treatment-related deaths. AEGEAN trial reported a rate of 42.4% adverse events, and 5.7% of fatal adverse events related to durvalumab administration. The KEYNOTE-671 trial reported a rate of 12.6% adverse events, with 1% death attributed to adverse events. In the current study, 5.17% of the cases discontinued the treatment due to adverse events. This rate was lower compared to the AEGEAN trial (12%), the Neotorch trial (9.4%), the KEYNOTE-671 trial (12.6%), and the CheckMate 816 trial (10.2%). In addition in our study, the rate of treatment discontinuation was 5.17%, which is much lower than it was observed in clinical trials (10-12%). This reduced rate may be attributed to the clinical experience of our treatment team and their heightened awareness of the need for close monitoring, gained through extensive use of immunotherapy and chemo-immunotherapy. Promptly diagnosing and effectively managing adverse events likely contributed to better patient outcomes and reduced the need for discontinuation.

Table 6. Comparing the current study results with findings from other trials.

Study	PCR Rate (%)	MPR Rate (%)	Grade ≥3 AE (%)	Treatment Discontinuation (%)	Reference
Current Study	36	61	12 (no death)	5.17	
CheckMate 816	24	36.9	33.5 (no death)	10.2	13
AEGEAN	17.2	33.3	42.4 (5.7% death)	12	35
KEYNOTE-671	18.1	30.2	12.6 (1% death)	12.6	24
Neotorch	24.8	48.5	63.4 (0.5% death)	9.4	34

Abbreviations: PCR, pathologic complete response; MPR, major pathologic response; AE, adverse events. .

The limitations of the current study are attributed to the retrospective and multicenter nature of the investigations. Medical records file collection showed that out of 56 patients eligible as per inclusion criteria, 44 had undergone surgery procedure, which reduced the sample size of the study cohort. Another limitation is that the majority of the study population consisted of stages II and III patients, without inclusion of stage I patients. This could potentially impact the results of the study, considering that patients with more advanced disease may derive greater benefit from such an approach. Another limitation is that the study is retrospective in nature. Retrospective studies rely on data collected from past records, which may introduce biases or limitations in data collection and analysis.

Future directions in lung cancer treatment research could comprise of molecular assays developed for biomarkers as predictors of specific targeted therapies encompassing all stages of NSCLC.

5. Conclusions

The current study demonstrates the advantages of neoadjuvant chemo-immunotherapy for NSCLC patients with resectable disease. These findings align with a recently published clinical trial report, reinforcing the efficacy of neoadjuvant chemo-immunotherapy followed by surgery. Importantly, the approach was found to be safe and feasible, with no significant complications reported.

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