doi.org/10.36721/PJPS.2026.39.8.238.1

Neoadjuvant nivolumab plus chemotherapy in resectable NSCLC: A pharmacological outcome study

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Abstract: **Background**: Immune checkpoint inhibitors have transformed anticancer pharmacotherapy, with nivolumab demonstrating significant immunomodulatory potential when combined with cytotoxic agents. However, real-world pharmacological evidence regarding the safety, tolerability and biomarker-guided response of neoadjuvant nivolumab combined with platinum-based chemotherapy in resectable non-small cell lung cancer (NSCLC) remains limited. This study aimed to evaluate the pharmacological efficacy, safety profile and predictive biomarker associations of this combination regimen in clinical practice. **Methods**: A multicenter retrospective pharmacological outcome study was conducted in 58 patients with stage IB–IIIB resectable NSCLC who received four cycles of neoadjuvant nivolumab in combination with platinum-based chemotherapy. The primary pharmacodynamic endpoint was major pathological response (MPR), serving as a surrogate marker of drug efficacy. Secondary endpoints included pathological complete response (pCR), treatment completion rate, post-treatment surgical resectability and incidence of adverse drug reactions graded according to CTCAE v5.0. Programmed death-ligand 1 (PD-L1) expression and KRAS mutation status were evaluated as predictive biomarkers of drug response. **Results**: The median patient age was 60 years, with male predominance (70.7%). Adenocarcinoma was the most prevalent histological subtype (60.3%). High PD-L1 expression (≥50%) was observed in 31.5% of patients, while KRAS mutations were detected in 44.8%. Curative surgical resection was achieved in 77.6% of patients following neoadjuvant pharmacotherapy. MPR and pCR rates were 43.1% and 29.3%, respectively, with significantly higher response rates observed in patients exhibiting elevated PD-L1 expression. Grade ≥3 adverse drug reactions occurred in 17.2% of patients, with no treatment-related mortality, indicating an acceptable safety and tolerability profile. **Conclusion**: Neoadjuvant nivolumab combined with platinum-based chemotherapy demonstrates favorable pharmacological efficacy, manageable toxicity and biomarker-driven therapeutic response in resectable NSCLC under real-world clinical conditions. These findings support the role of personalized immunopharmacotherapy and reinforce the clinical relevance of biomarker-guided drug selection in modern pharmaceutical oncology.

Keywords: Common terminology criteria for adverse events (CTCAE v5.0); Immune checkpoint inhibitors; Kirsten rat sarcoma virus on oncogene homologue (KRAS); Major pathological response (MPR); Neoadjuvant chemoimmunotherapy; Nivolumab plus chemotherapy; Pathologic complete response (pCR); Programmed death ligand 1 (PD-L1) expression; Resectable non-small cell lung cancer (NSCLC)

Submitted on 20-01-2026 – Revised on 15-03-2026 – Accepted on 13-05-2026

INTRODUCTION

Background

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all cases (Jeon *et al*., 2025. Several studies published between 2020 and 2024 have further highlighted the increasing role of neoadjuvant chemoimmunotherapy in improving pathological response rates and surgical outcomes in resectable NSCLC, emphasizing the need to incorporate recent evidence into current clinical research. One of the major challenges in the treatment of NSCLC is that the disease is often diagnosed at advanced stages, thus curbing the time frame in which curative measures can still be given. Even in patients with early-stage, surgically resectable disease, which is estimated to comprise between 20% and 25% of all NSCLC diagnoses, the rates of relapse are still high (Cascone *et al*., 2025). Approximately 30%–55% of patients experience relapse and ultimately succumb to disease-specific mortality (Pirker *et al*., 2025).

Traditionally, the acceptable approach in the case of resectable NSCLC has been surgery followed by adjuvant chemotherapy. Though this has brought about a slight improvement in the outcome, the overall rates of survival are still not satisfactory (Liu *et al*., 2025). However, despite therapeutic advances over the past two decades, improvements in long-term survival remain limited. In early-stage disease, preventing recurrence remains a major clinical challenge. Systematic analysis of neoadjuvant chemotherapy alone showed a limited gain,

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with an estimated 5% absolute gain in 5-year survival rates. In addition, recent findings from several countries, including China, suggest that the response to preoperative chemotherapy may vary depending on genetic susceptibility, emphasizing the importance of a more efficient and holistic approach (Cai *et al*., 2025).

Immunotherapeutic rationale: Nivolumab and tumor microenvironment modulation

Significant advances in tumor immunology have changed how we can treat non-small cell lung cancer (NSCLC). In particular, the advent and use of immune checkpoint inhibitors (ICIs) have transformed the therapeutic landscape. Nivolumab is a fully human IgG4 monoclonal antibody targeting programmed cell death-1 (PD-1). Nivolumab re-establishes the function of effector T cells and induces long-lived and durable anti-tumor immune activity (Mandal *et al*., 2025). The ability of Nivolumab to improve overall survival rates and the quality of life of those with metastatic NSCLC has been confirmed in several phase III clinical trials (Forde *et al*., 2025).

Using nivolumab as a neoadjuvant therapy is supported by the biologic hypothesis that neoadjuvant ICI administration, while the primary tumor is still present, allows for enhanced presentation of neoantigens and priming of T cells to the tumor, which may cause systemic activation of the immune system and ultimately eliminate micro metastatic disease (Awada *et al*., 2025). The combination of neoadjuvant chemotherapy and immune checkpoint inhibitor (ICI) therapy may synergistically enhance antitumor effects. Chemotherapy promotes immunogenic tumor cell death and modifies the tumor microenvironment to facilitate immune cell infiltration and activation. Therefore, the immunological synergism between these two treatment models could lead to better oncological results when used together in the neoadjuvant setting (Jánváry *et al*., 2025).

The existing standard of care for those undergoing resectable NSCLC also involves the use of adjuvant therapy for those in Stages II to III, which offers an advantage of survival of 4%-5%. The advanced version of adjuvant therapies such as anti-EGFR and anti-ICI therapies is adding to the list of available treatments for those undergoing the disease (Sa-nguansai *et al*., 2025) The growing body of evidence increasingly supports the use of neoadjuvant immunotherapy prior to surgical resection.

Clinical Impact of neoadjuvant chemoimmunotherapy

The neoadjuvant chemo-immunotherapy technique has several theoretical and practical advantages over the adjuvant technique. The technique aids in the management of the systemic disease, offers functionality based upon the reduction brought about by the therapy and provides an evaluation of the effectiveness of the therapy based upon the pathologic response value. Moreover, the technique may improve the opportunity for reaching pathological complete response (pCR) or major pathological response (MPR); both have been shown to have noteworthy survival benefits (Cai *et al*., 2025; Loi *et al*., 2025).

These hypotheses have been proven in recent clinical studies. The phase II NADIM trial evaluated neoadjuvant nivolumab together with paclitaxel and carboplatin in first-line patients with stage IIIA NSCLC (Sidaway, 2025; Awad *et al*., 2025). The trial has shown impressive rates of pCR and promising event-free and overall survival outcomes with manageable toxicity. Later on, the phase III trial CheckMate 816 gave sound confirmation of these findings. Patients undergoing neoadjuvant nivolumab and platinum doublet chemotherapy showed a higher rate of pathologic complete response (pCR) and improved event-free survival (EFS) than chemotherapy alone median EFS of 31.6 months in the combination therapy group, as compared with 20.8 months in the chemotherapy group (hazard, ratio = 0.63; 95% CI, 0.43–0.91; p = 0.005) (Loi *et al*., 2025; Sidaway, 2025). Linked with more favourable post-surgical outcomes, including shorter surgery time and higher rates of minimal invasive resections. These data provide a standard shift in the treatment of patients with resectable NSCLC and a strong rationale for incorporating DCC in combination with other therapies to foundation for the integration of immunotherapy into neoadjuvant protocols in standard clinical settings.

Fortunately, the addition of nivolumab therapy did not increase the probability and severity of treatment-related adverse events and surgery could still be carried out easily. These key observations set the bar high for the management of resectable NSCLC and their study clearly showed why immune checkpoint inhibitors should now be considered a regular mode of treatment in the treatment plan.

Knowledge gaps in real-world evidence

Although immense progress had been made through paradigmatic RCTs such as NADIM trials, Check Mate 816 trials, KEYNOTE 671 trials and AEGEAN trials, an important drawback associated with these trials remains the fact that these trials had been performed under strictly controlled environments with “narrow patient entry criteria” or “narrow inclusion criteria” themselves (Cortellini *et al*., 2025).

These clinical trials usually enroll patients who represent a highly selected group of relatively young, people with good organ function, few comorbidities and good performance status (Kaufmann *et al*., 2025; Koçanoğlu *et al*., 2025; Casolino *et al*., 2025). By contrast, clinical practice usually involves more diverse and heterogeneous

populations that include older people and patients with multiple comorbidities or with biological characteristics that were excluded from participating in clinical trials. This limits the generalizability of clinical trial findings to routine clinical practice. Despite these advancements, real-world evidence on the effectiveness and safety of neoadjuvant chemoimmunotherapy in diverse patient populations remains limited (Janvary *et al*., 2025).

This disparity highlights the importance of real-world validation of treatment approaches assessed in trials. This issue takes on a special emphasis within the regions with variable genetics, health care systems and accessibility of innovative treatments to patients (Kaufmann *et al*., 2025; Krebs *et al*., 2025). In this regard, the role of real-world evidence will consist of filling the existing gap between the effectiveness and the efficacy of the approaches assessed with the goal of making appropriate treatment decisions.

Study objective

Lung cancer continues to be the main cause of cancer mortality and among these, NSCLC contributes largely to the patient population. In recent years, the management of patients with resectable NSCLC in the perioperative setting has been revolutionized by the use of immune checkpoint inhibitors, specifically anti-PD-1 monoclonal antibodies, namely nivolumab (Dennehy *et al*., 2025). However, the current evidence on the applicability, tolerability and efficacy of neoadjuvant chemoimmunotherapy in real-world settings remains limited.

To address this gap, the present multicenter study evaluates the real-world efficacy, safety and biomarker associations of neoadjuvant nivolumab combined with platinum-based chemotherapy in patients with resectable NSCLC (Zhao *et al*., 2025).

Through the analysis of real-world data from Turkish centres, the aim of this study is to provide valuable insights regarding the effectiveness of neoadjuvant immunotherapy approaches in a real-world setting outside the controlled trial setting. The end goal of the study would thus be to fill the gap that pervades today between research evidence and practical experience in a real-world setting to provide valuable information to clinicians regarding patient selection and treatment plans to optimize.

MATERIALS AND METHODS

Study design and setting

This study was designed as a retrospective multicenter observational cohort study conducted in two prominent oncology institutes in Turkey. The two institutes taking part in this research study are Acibadem Maslak Hospital and Şişli Hamidiye Etfal Training and Research Hospital. The two centres participated in this sampling because both are mainly operative in patients diagnosed and treated for thoracic cancers and have detailed records for analyses. The study aims to investigate outcomes associated with applying chemoimmunotherapy in patients given resectable NSCLC. The study also proposed to create a data set of patients based on the evaluation of existing records in the institution considering cases between January 2022 and March 2025 (Zhao *et al*., 2025) (Fig. 1).

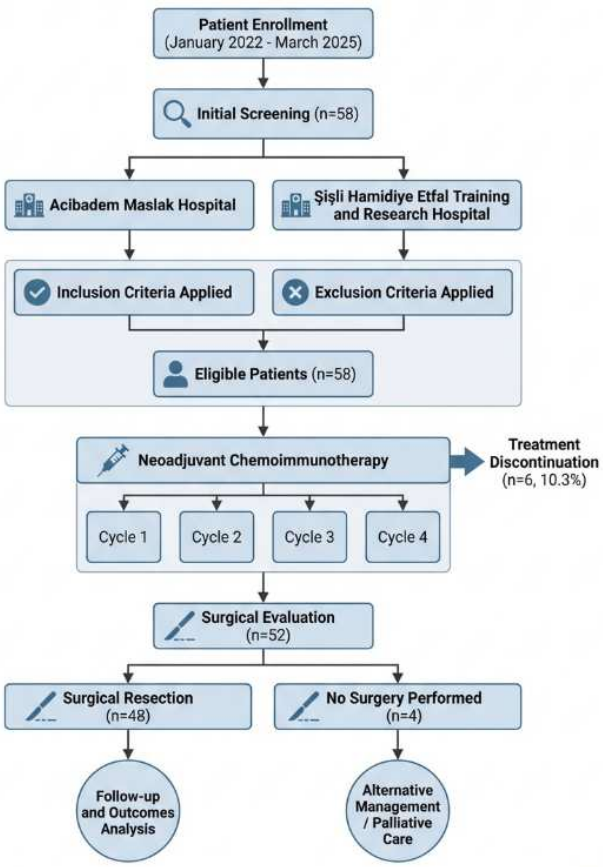

Fig. 1: Patient enrollment and treatment from January 2022 to March 2025.

Patient selection

A total of 58 patients with resectable NSCLC were enrolled in this analytical clinical study. To enter the trial, all patients had to meet certain criteria: 40-80 years old and histologically proven candidates with potentially resectable NSCLC stage IB to IIIB according to modern radiological and pathological criteria. The Multidisciplinary Thoracic Oncology Conference (MTOC) was designed to assess all possible candidates for performing surgery on patients after they have undergone neoadjuvant therapy.

Inclusion criteria: Patients were required to have received no prior systemic therapy and to be eligible for treatment

with platinum ± taxane–based chemotherapy in combination with immune checkpoint inhibitors (Liu *et al*., 2025; Zhao *et al*., 2025).

Exclusion criteria: Exclusion criteria included patients with contraindications to immune checkpoint inhibitors and those with a history of malignancy within the past 5 years that could interfere with the evaluation of treatment response to neoadjuvant therapy and subsequent surgery.
The purpose of this study was to evaluate the outcomes of a general group of patients diagnosed with resectable Stage IB to Stage IIIB NSCLC for effective and tolerable neoadjuvant chemotherapy plus immunotherapy compared to surgery with a therapeutic intent.

Treatment protocol
The CheckMate 816 protocol differs from the four cycles of platinum-doublet chemotherapy plus nivolumab used in this study. The difference in number of chemotherapy cycles was done to ensure maximum possible cytoreduction before surgery, according to institutional best practices and was therefore used in this study. Additionally, this extended neoadjuvant chemotherapy treatment conformed to the expected time frame for the treatment of patients with resectable NSCLC.

All 58 patients received a standardized neoadjuvant regimen consisting of four cycles of platinum-doublet chemotherapy combined with nivolumab administered at a fixed dose of 360 mg every three weeks. The type of platinum-doublet chemotherapy received was determined by tumor histology (Sidaway *et al*., 2025), either cisplatin/carbo or pemetrexed/paclitaxel. The choice of platinum agent and chemotherapy partner was dependent on histological subtype and the preference of the attending physician based on institutional guidelines. Typically, pemetrexed was used in the case of non-squamous histology and treatment involving squamous cell lung cancer tended to include paclitaxel. Nivolumab, a fully human PD-1 targeting antibody, was given at standard immunotherapy dosing every three weeks. All patients completed all four cycles according to the standardized protocol, followed by surgery after imaging review and comprehensive clinical evaluation, with curative intent.

Data collection
At both sites, a post hoc analysis was conducted using information obtained from the electronic medical record system. Baseline demographic information (age, sex, smoking history, cancers associated with other medical problems), tumor pathology information (type) and cancer stage were captured for all patients. PD-L1 level of expression and KRAS mutation status were collected when available because of their ability to serve as predictors of response to immunotherapy. A review of the surgical record provided data on what type of resections were used, the pathology of the tumour and whether or not the resections were complete. Timing of chemotherapy, initiation and conclusion of nivolumab and scheduling of surgery were also collected to examine adherence to protocol and the feasibility of treatment.

Endpoints and outcomes
Pathological complete response and major pathological response are the two main endpoints and were evaluated by the examination of the surgical specimen pathologically. Pathological complete response means no viable tumour cells can be found in either the primary tumour or the lymph nodes. Major pathological response means there were ≤ 10% viable tumour cells present in the primary tumour. These endpoints are reliable indicators of the long-term outcomes, including disease-free survival and overall survival, of the patients who received neoadjuvant treatment. The secondary analyses included treatment-related adverse events, graded according to the CTCAE version 5.0 and treatment completion rates (Loi *et al*., 2025). Events were characterized by their severity and type, with a focus on immune-related adverse events, hematologic toxicities and postoperative complications. Treatment completion was defined as the patient completing the full four-cycle neoadjuvant and undergoing surgical resection without significant delays, which showed acceptable safety profile and treatment possibilities.

Comparative analysis
In addition to a comparison of outcomes within our patient population treated in Turkey, a comparative analysis based on data provided by top-level referral centers across North America, Europe and the Middle East has been undertaken by our study (Zhang *et al*., 2025). Outcomes have thus been compared to published data from patient cohorts treated within the Mayo Clinic (n=26, USA), Guy's Cancer Centre (n=19, UK) and Israel's National Registry data set (n=56), each having received a regimen of neoadjuvantly administered chemoimmunotherapy given a platform including platinum-doublets + immune checkpoint inhibitors focused on the PD-1/L1 pathway. These centers were selected based on similar demographics, clinical characteristics and uniformity in the neoadjuvant treatment strategies. The major endpoints of interest for comparison across cohorts included pCR and MPR, incidence of grade ≥3 therapeutic adverse events and feasibility of proceeding to surgical resection.

This collaborative, cross-regional comparison was intended to assess the external validity and reproducibility of neoadjuvant nivolumab-containing regimens across varying healthcare systems and population subsets. The results add to an emerging body of standard evidence supporting the global applicability of chemoimmunotherapy protocols in resectable NSCLC, reinforcing their clinical utility beyond the restrictive

conditions of highly regulated randomized controlled trials.

Statistical analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (range), while categorical variables were presented as frequencies and percentages. Associations between variables were analyzed using chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant.

RESULTS

Patient demographics and baseline characteristics

In two thoracic oncology centers, 58 patients with resectable non-small-cell lung cancer (NSCLC) were treated with neoadjuvant chemoimmunotherapy (platinum-based chemotherapy and nivolumab). Most patients were between the ages of 40 and 80, with a median age of 59.5, consistent with the age distribution of NSCLC. The study population predominantly consisted of middle-aged and elderly patients (Fig. 2).

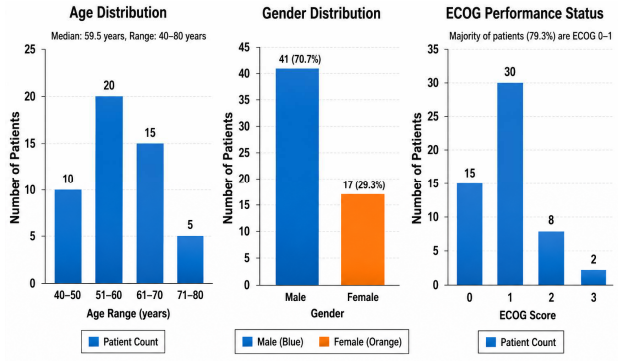

Fig. 2: Patient demographics and baseline characteristics.

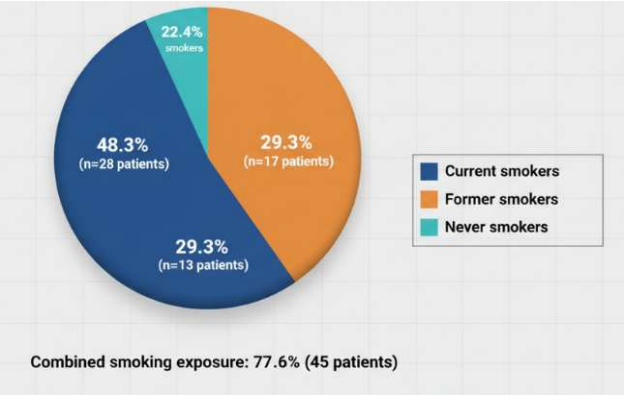

Fig. 3: Smoking history distribution

The majority of patients were male, with 41 males (70.7%) and 17 females (29.3%), highlighting the higher prevalence of tobacco use among men. With reference to the smoking history, 28 patients (48.3%) were active or current smokers at diagnosis, 17 (29.3%) were past or former smokers and 13 (22.4%) were never-smokers. Therefore, 77.6% of the cohort had a history of tobacco exposure, underscoring its well-established association with lung cancer pathogenesis (Fig. 3).

To determine patients' functional status at admission, the Eastern Cooperative Oncology Group (ECOG) performance status scale was used (Dennehy *et al*., 2025). Most patients had an ECOG score of 1 (n = 38, 65.5%), indicating mild symptoms but the ability to carry out daily activities independently. A smaller proportion of patients (n = 16, 27.6%) had an ECOG score of 0, indicating full activity without symptoms. Only 4 patients (6.9%) had an ECOG score of 2, indicating that they were symptomatic but capable of self-care and eligible for further systemic therapy and surgical intervention. These findings are presented in Fig. 2.

Tumor staging and histopathological characteristics

Most patients had borderline resectable presentation at initial clinical staging. Clinical staging was determined according to the TNM classification system for lung cancer (Rami-Porta *et al*., 2022). Clinical Staging IIIA was most common, with 28 patients (48.3%) meeting that criteria; Clinical Stage IIB had 18 patients (31.0%); Clinical Stage IIA had 7 patients (12.1%); and Clinical Stage IB had 5 patients (8.6%); finally, Clinical Stage IIIB was observed in 2 patients (3.4%) approved for neoadjuvant treatment and surgical treatments after institutional cross-functional assessment (Fig. 4).

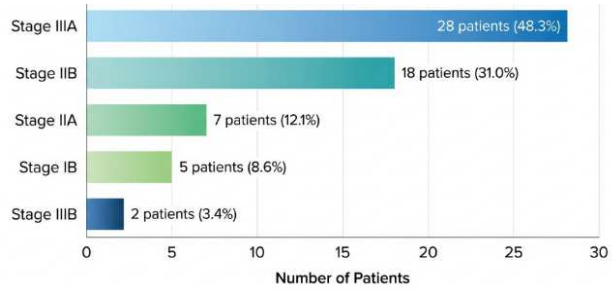

Fig. 4: Clinical Stage Distribution

Histopathological data indicate that there was a dominance of adenocarcinomas among the study sample, being present in 35 patients (60.3%). Squamous cell carcinoma represented 20 patients (34.5%) and non-small-cell lung carcinoma not otherwise specified (NOS) was represented by three subjects (5.2%). The results are consistent with current global epidemiologic trends, where adenocarcinoma is the most common type of NSCLC histology, especially among those with mixed or non-smoking histories (Fig. 5).

Among the patients sampled, 31% had a PD-L1 expression greater than or equal to 50% (n=18), while 37.9% exhibited an intermediate level of PD-L1 at an

expression range of 1%-49% (n=22) and the remaining 31% demonstrated low or non-existent PD-L1 expression (n=18). Because of these nearly equal distributions of patients among the three groups of active PD-L1 status, it became possible to conduct an indirect comparison of treatment efficacy based on grouping.

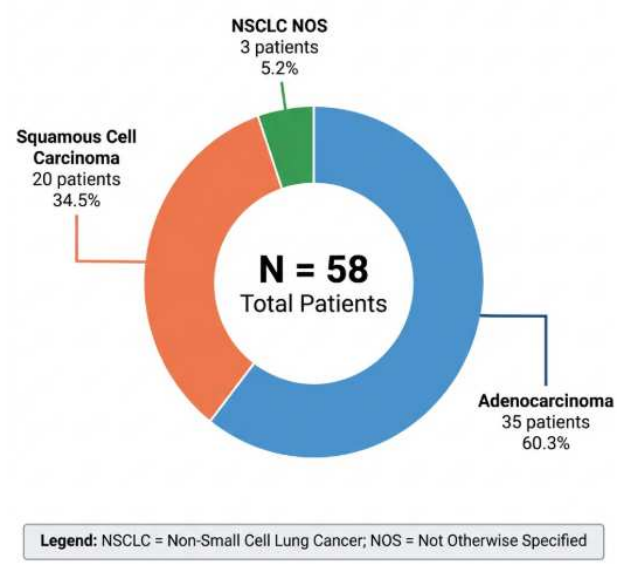

Fig. 5: Histological subtype distribution

As expected, patients belonging to the higher PD-L1 expressing group also had higher pathology response rates than patients in the other two non-high PD-L1 groups; however, because of the population size limitations, this finding could not be confirmed with a formal statistical test.

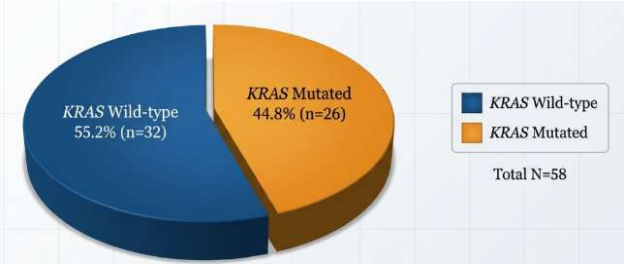

Fig. 6: KRAS mutation status distribution

KRAS mutations were detected in 44.8% (n=26) of this cohort, whereas 55.2% (n=32) had what is known as KRAS-wild-type. Overall, this study did not specifically analyse or report the outcomes based on KRAS mutational status, but given the prevalence of KRAS mutations within this study population, their established importance within NSCLC biology and the growing importance of KRAS mutations with regard to resistance mechanisms to immunotherapy, we can draw the conclusion that KRAS mutations play an important role in both NSCLC biology and in resistance mechanisms to immunotherapy (Fig. 6).

Neoadjuvant therapy completion

With a total of 58 patients who began neoadjuvant chemotherapy and immunotherapy, 45 were able to complete the recommended treatment schedule of four cycles of chemotherapy/nivolumab. Eleven patients (19.0%) stopped taking their medication after completing 2 cycles due to the effects of the medications on them or their decision to quit and two patients (3.4%) completed one cycle of medication before stopping. The results show that the majority of patients completed their full treatment cycle and did not experience severe treatment-limiting adverse effects, demonstrating the feasibility and tolerability of chemotherapy and immunotherapy in patients with resectable NSCLC who were eligible for surgery (Fig. 7).

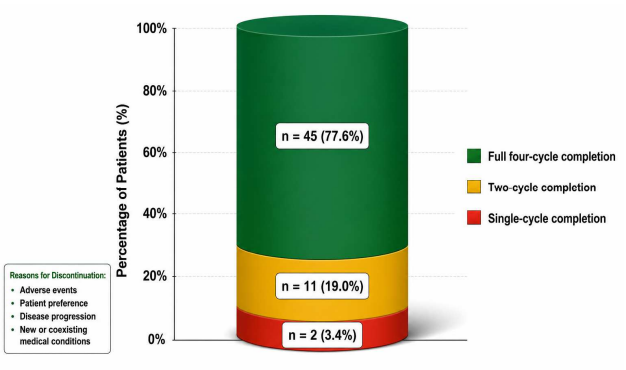

Fig. 7: Treatment completion rates

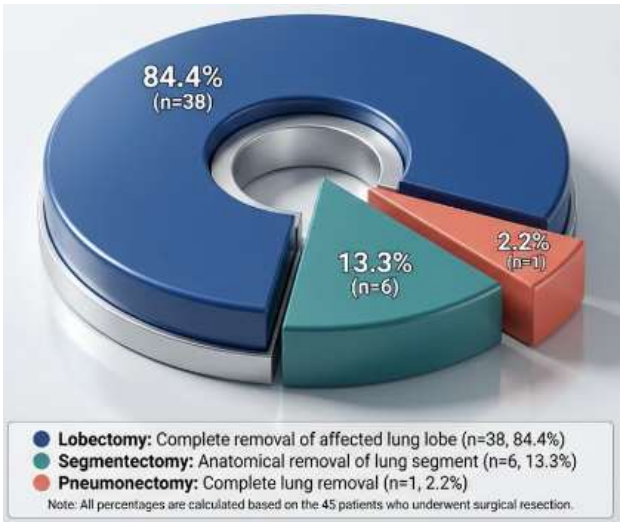

Fig. 8: Surgical procedure distribution

Surgical resection

Following neoadjuvant chemoimmunotherapy, 45 patients (77.6%) proceeded to surgical treatments with curative intent. The remaining 13 patients (22.4%) were unable to participate in the surgical resection because of tumor progression, reduction in performance status, or refusal by the patient. Of those patients who underwent surgery, lobectomy (removal of a lobe of lung) was performed on

38 of the 45 (84.4%), segmentectomy (removal of a segment of lung) was performed on 6 (13.3%) and one patient (2.2%) underwent pneumonectomy (removal of an entire lung) due to the location of the tumor in the central area of the lung where tumors usually occur. In every operation, systemic lymph node assessment was performed to provide accurate information about the final pathology and to decrease the chance of recurrence in the same area (Fig. 8).

Pathological complete response (pCR)

The histopathological assessment of surgically removed specimens from the lung and nearby lymph nodes indicated that a complete pathological response (defined as the absence of any viable tumor cells) occurred in 13/58 patients, which equates to 22.4%. The overall data from this analysis support the use of neoadjuvant-based chemotherapy combined with stimulatory drugs or immuno-biological agents (neoadjuvant chemoimmunotherapy) to achieve eradication of tumour in some patients who can be surgically treated for lung cancer that can be completely surgically removed (resectable non-small cell lung carcinoma or NSCLC). Furthermore, the complete pathological response rate that was seen in our group of patients is consistent with the rates reported in other studies and was comparable to rates reported in previous trials, including approximately 24% in the CheckMate 816 study, 37% in NADIM II and 36% in Israel. Importantly, this information validates the relevance of the clinical application of protocols developed in clinical trials in community-based practices. Importantly, while the patients analysed by way of Subgroup analyses were limited by the small sample size and lacked sufficient statistical power, it appeared that patients with a high level of PD-L1 positive status (>50%) had a higher average Complete Pathological Response than those who did not and was similar to the prior findings of the association of PD-L1 status with the potential for immunotherapy to be effective (Fig. 9).

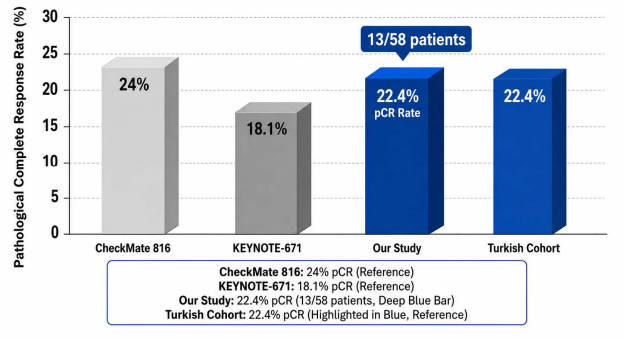

Fig. 9: Pathological complete response rate

Major pathological response (MPR)

Major pathological response (MPR), defined as ≤10% viable tumor cells in the primary tumor, was observed in 22 of 58 patients (37.9%). Although not all patients achieving MPR reached pCR, both response categories are clinically meaningful and complementary. The MPR rate in our cohort is comparable to rates reported in real-world datasets and prospective trials, including 61% in the Israeli registry and 83% in NADIM II. This reinforces the value of MPR as a potential and measurable therapeutic outcome in neoadjuvant NSCLC treatment protocols.

The results demonstrate the clinical relevance and potential to measure MPR outcomes in neoadjuvant NSCLC clinical trial settings (Fig. 10).

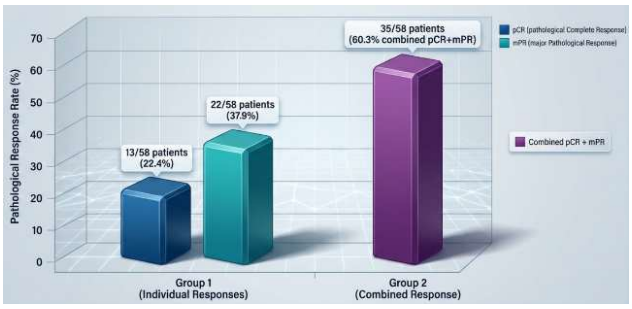

Fig. 10: Major Pathological Response Rate

Safety and treatment discontinuation

The researchers systematically evaluated the safety profile of the neoadjuvant chemotherapy and immune therapy in this study cohort. They found that 10 patients (17.2%) experienced Grade 3 or higher immune-related adverse events, predominantly consisting of pneumonitis, immune-mediated rashes and Grade 3–4 neutropenia. However, it should be noted that none of the treatments resulted in fatalities. This indicates that neoadjuvant chemotherapy combined with immunotherapy demonstrates an acceptable safety profile when administered according to institutional protocols with adequate monitoring (Fig. 11).

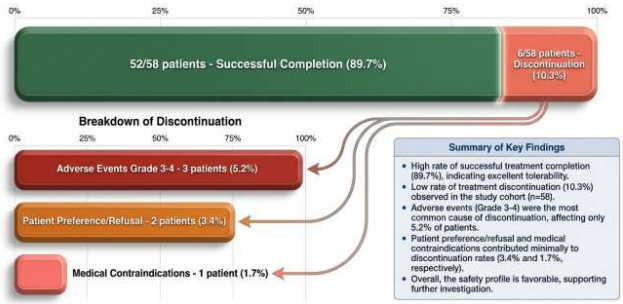

Fig. 11: Treatment safety profile and discontinuation rate.

Treatment was discontinued in 13 participants (22.4%) due to treatment-related adverse events, patient preference, disease progression or newly developed medical conditions that prevented continuation of therapy.

Despite these discontinuations, 45 participants (77.6%) completed the full scheduled neoadjuvant therapy, demonstrating acceptable treatment adherence and feasibility. These findings suggest that nivolumab-based neoadjuvant regimens are feasible and tolerable in real-world clinical practice for patients with resectable NSCLC.

Comparative analysis with international cohorts

Encouraging real-world results with neoadjuvant nivolumab plus platinum-based chemotherapy for treatment of patients with resectable non-small cell lung cancer (NSCLC) were reported in a cohort of 58 patients across two thoracic oncology centers. pCR was noted in 13 patients (22.4%) and MPR (defined as ≤10% of viable tumor cells remaining) was noted in 22 patients (37.9%). In total, 60.3% of patients had either a pCR or MPR, demonstrating significant tumor shrinkage after the neoadjuvant therapy. The results from this cohort closely matched previously reported international data (Mayo Clinic and National Institute of Israel) but trailed those previously published for NADIM II due to the inclusion of higher stage (Stage IIIB) patients and those with higher risk characteristics. High PD-L1 expression (≥50%) correlated with increased instances of pCR and MPR; previous reports from CheckMate 816 and NADIM II demonstrated that PD-L1 expression is a predictive biomarker for response to immunotherapy. Patients in this cohort were also evaluated for KRAS mutation status, but no clear association with clinical or pathological response was identified.

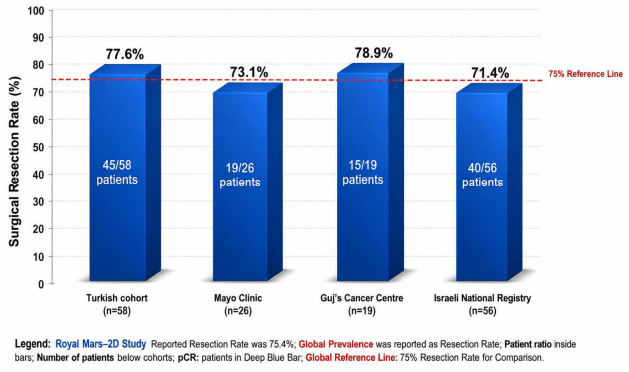

Fig. 12: Surgical resection rates comparison

Surgical resection was performed on 45 patients (77.6%) demonstrating the ability to achieve curative intent surgical outcome after neo-adjuvant chemo-immunotherapy. Of the remaining 13 patients (22.4%), five did not continue to surgery due to disease progression, six for medical contraindications and two based on patient preference. A total of 45 patients out of 58 reached therapy completion (77.6%) as prescribed with all four cycles completed. This adds to the evidence of both logistical and clinical possibilities of the regimen.

Among the adverse events (AEs) seen were grade ≥3 treatment-related AEs, which were seen in 18% of subjects, including; 1) immune mediated pneumonitis, 2) dermatologic reactions and 3) neutropenia. There have been no treatment-related AEs leading to death, thus confirming that treatment has an acceptable safety profile. The comparative data from the AEGEAN (42%) and Neotorch (63%) trials also supports the regime has an acceptable safety profile. Surgical resection rates across international cohorts are presented in Fig. 12.

A significant feature of our protocol was the use of four full cycles of neoadjuvant therapy, whereas the CheckMate 816 trial utilized only three periods. This longer treatment duration may have resulted in higher pathologic response rates, which could have occurred due to improved immune priming and tumor cytoreduction of patients whose tumors were bulky or locally advanced. Importantly, the increased intensity of the regimen did not cause any surgical delays or increased toxicity, confirming this regimen's viability in real life.

This evidence supports the notion that nivolumab-based chemoimmunotherapy, when used neoadjuvantly, is a safe and effective method of treating patients with resectable NSCLC. The results of this study contribute to demonstrating the viability of converting scientific protocol into practical implementation in clinical settings, while also giving evidence of how clinical practice should focus on providing access to treatment for a wider and more diverse range of patients.

DISCUSSION

The findings from this investigation on the use of neoadjuvant chemotherapy plus nivolumab and platinum-based chemotherapy in patients with resectable NSCLC indicate that this approach can be safely implemented and is effective when used in real-world clinical practice in a variety of clinical settings. In addition, the diversity of patient populations being treated at both facilities within Turkey (Şişli Hamidiye Etfal Training and Research Hospital and Acıbadem Maslak Hospital) shows that there are significant differences between patients based on factors such as current stage of disease (advanced) and medical complexity (i.e., stage IIIB) and number of patient co-morbidities (Zhang *et al*., 2025). The varied characteristics of the patient population also improve the external validity of the results of this study compared with the homogeneous study populations in clinical trials (Zhang *et al*., 2025).

Our findings are consistent with previous clinical trials such as CheckMate 816 and NADIM II, as well as multiple studies published between 2020 and 2024, which demonstrated improved pathological response rates with neoadjuvant chemoimmunotherapy. However, unlike controlled clinical trials, the present analysis reflects outcomes in a real-world setting involving a more

heterogeneous patient population. This enhances the external validity of our findings and supports the broader applicability of neoadjuvant immunotherapy in routine clinical practice.

In this study, patients included more subjects classified as having advanced stage disease and those with substantial disease burden; nevertheless, relatively high to encouraging achievement of pathological complete response (pCR) of 22.4% (n=13) and major pathological response (MPR) of 37.9% (n=22) are demonstrated in this study. These rates are comparable with the Mayo Clinic's findings (combined pCR + MPR ≈ 54%) and Israel's registries (MPR ≈ 61%); although, they were lower than the rates reported from the NADIM II Study (pCR 37%, MPR 83%). Additionally, within this analysis, a high percentage of patients were able to undergo surgery with curative intent, as 77.6 % of the patients (n=45) had surgery after the treatment regimen, demonstrating the potential of this regimen within patients across a broad range of healthcare facilities.

Patients with a PD-L1 positivity of ≥50% had higher rates of pCR and MPR compared to patients with lower levels of PD-L1 expression, consistent with the published literature that supports PD-L1 as a prognostic predictor for responses to immunotherapy. Though this subgroup analysis was limited by small sample size, our findings support previously reported findings and may help to inform the use of PD-L1 status for treatment stratification purposes; however, there was no association of KRAS mutation status with the pathological response and a larger subject study is warranted to further explore this relationship.

The use of an extended four-cycle neoadjuvant regimen, compared to the three-cycle regimen used in the CheckMate 816 trial, may explain the observed pathological response rates associated with this regimen (Cascone *et al*., 2025). The preferred use of a longer preoperative treatment regimen seems to have led to greater degrees of tumor regression and immune priming in the relatively small group of patients recruited into this study, particularly those with larger or more advanced tumors and does not appear to extend the interval to surgical intervention or add to the associated toxicities (Cascone *et al*., 2025).

The results demonstrated a good safety profile for the treatment. The incidence of Grade ≥3 immune-related adverse events (irAEs) was 18%, which is lower than what was reported in previous studies, the Neotorch (63%) and AEGEAN (42%). There were no treatment-related deaths reported; the majority of adverse events were manageable and only 15.5% of patients (n=9) discontinued treatment early. Importantly, immune-related adverse events did not prevent the majority of patients from undergoing surgical resection.

These results are consistent with pivotal studies, such as CheckMate 816, which demonstrated significantly improved event-free survival (EFS) and pathologic complete response (pCR) with neoadjuvant nivolumab plus chemotherapy versus chemotherapy alone (Loi *et al*., 2025). The median EFS was extended from 20.8 months for the chemotherapy alone group to 31.6 months when receiving nivolumab as well (Hazard Ratio 0.63). Other studies, including NADIM and AEGEAN, have similarly demonstrated improved radiographic response, down staging rates and the possibilities of surgical resection when using immunotherapies in these regimens.

The benefits of neoadjuvant chemoimmunotherapy are increasingly supported by emerging clinical and real-world evidence (Cascone *et al*., 2025; Dennehy *et al*., 2025). In addition, the accumulating evidence suggests that patients with rapid pathological response (MPR or pCR) to neoadjuvant therapy could be a surrogate for long-term survival from resectable NSCLC. Our population supports this hypothesis as our patients who had MPR and pCR were successfully resected and demonstrated early evidence of disease stability and control. Also, the theory of acceleration of early disease progression by pre-operative immune-modulating therapy was not demonstrated in our patient population. Instead, pre-operative immune modulation may provide the patients the potential ability to be resectable and delay the development of systemic disease. Our real-world experience demonstrates concordance with these international group analyses, which have shown that patients treated with chemoimmunotherapy have similar disease control and stabilization across all histological types and clinical stages of lung cancer, including the Chinese population. Importantly, the tolerability and applicability of the neo-adjuvant regimen were found to be universally acceptable regardless of treatment center or patient population. Despite the trustworthiness of our results, we acknowledge that there are limitations in the design of our study: retrospective nature of the study, lack of long-term follow-up for survival and absence of comprehensive molecular profiling for selection of patients who may respond to immunotherapy (e.g., STK11 and KEAP1 mutations). Further studies are needed to optimize the OS, PFS and DFS of patients and to better ascertain the appropriate sequencing of peri-procedural immunotherapies.

Future directions

Today, there are many unanswered questions regarding the long-term efficacy of neoadjuvant chemoimmunotherapy for patients with resectable NSCLC, especially with respect to the ultimate and most important outcomes of overall survival, disease-free survival and event-free survival for the population at large. Therefore, future large-scale, prospective studies of diverse and heterogeneous populations will be needed to investigate these long-term outcomes. In addition, future

studies should evaluate other prognostic and predictive biomarkers beyond PD-L1, such as STK11, KEAP1 and tumor mutational burden (TMB), on the basis of these results to assist with patient selection and development of personalized treatment algorithms.

Through molecular analyses of resected specimens after the performance of neoadjuvant therapy, we may be able to better understand the underlying tumor biology and treatment response to assist in accurately estimating the risk associated with each individual patient. In addition, we have yet to establish when or in what order neoadjuvant immunotherapy should be used relative to concurrent neo-adjuvant chemotherapy, as well as determine the amount of time of treatment that would be most beneficial.

We currently do not have enough data to determine if all patients with resectable stage III NSCLC will experience a benefit from adjuvant immunotherapy compared to patients who do not receive it, or the amount of adjuvant immunotherapy that would provide optimal results for those patient's service using chemotherapy as the primary means of treatment. Further, in determining the minimum number of neoadjuvant cycles required, we will most likely need to use data and criteria from clinical and radiographic evaluations utilizing both radiologic responses and molecular biomarkers during the course of neoadjuvant treatments.

Finally, it will be essential to establish a national and international registry to gather and analyze outcome data from multiple health care delivery systems so that we can utilize this information to create treatment regimens that are based on accurate conclusions about the effectiveness of existing therapies and remove existing health disparities. Health care policies should be directed toward the goal of increasing access to immunotherapy for patients living in low-income environments because of the well-established safety and effectiveness of these types of therapeutic regimes when tested in larger, more diverse populations. In addition, future studies need to include factors such as cost-effectiveness, patient reported quality of life after receiving treatment and long-term functional outcomes resulting from treatment. The information obtained from these types of studies will assist in ensuring that patients who receive neoadjuvant chemoimmunotherapy not only benefit from prolonged survival, but also receive high-quality, sustainable and patient-centered care.

Strengths and limitations

Despite these encouraging findings, several limitations should be acknowledged. First, the retrospective design of the study may introduce potential selection bias. Second, the sample size was relatively small and derived from only two centers, which may limit generalizability. Third, long-term outcomes such as overall survival (OS), progression-free survival (PFS) and disease-free survival (DFS) could not be fully evaluated due to limited follow-up duration.

CONCLUSION

This multicenter retrospective study demonstrates that neoadjuvant nivolumab combined with platinum-based chemotherapy is effective and well tolerated in real-world clinical settings for patients with resectable NSCLC. As such, this study provides evidence of both effectiveness and tolerability when utilized under typical clinical conditions for patients presenting with resectable NSCLC. The inclusion of patients with a range, from Stage IB through IIIB of disease and various comorbidities, allows for an accurate depiction of current practice in many settings and reflects an expanded view of the current knowledge gained from randomized clinical trials. There were statistically significant pathological responses to this treatment with 22.4% pathological complete response and 37.9% major pathological response rates. Although the percentage of patients experiencing response to this treatment was lower than has been reported for more selected cohorts in related research studies, the large percentage of patients treated with this regimen went on to undergo curative surgical resection, thus further validating the viability of this treatment regimen in all settings of surgical capacity. The data provided by this study reinforce the clinical value and real-world application of nivolumab-based neoadjuvant chemoimmunotherapy for the treatment of operable NSCLC.

Acknowledgments

The authors acknowledge the support of Acibadem Mehm*et al*i Aydinlar University and Şişli Hamidiye Etfal Training and Research Hospital for providing access to institutional clinical data used in this study.

Authors' contributions

Orcun Can: Conceptualization, study design, data analysis, manuscript drafting and supervision. Onur Derdiyok: Data collection, clinical interpretation, surgical data analysis and manuscript revision. Both authors reviewed and approved the final version of the manuscript.

Funding

The authors declare that no external funding was received for this study.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval

This study was approved by the Institutional Ethics Committees of Acibadem Mehm*et al*i Aydinlar

University and Şişli Hamidiye Etfal Training and Research Hospital (Approval No: IEC-2021-NSCLC-104) and conducted in accordance with the Declaration of Helsinki. This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this paper.

Supplementary data

https://www.pjps.pk/uploads/2026/06/SUP1780751400.pdf

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