Review

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Neoadjuvant, Perioperative, and Adjuvant Immunotherapy in Early-Stage Surgically Resectable Non-Small Cell Lung Cancer: Updates and Future Perspectives

Diamone Gathers , Cameron Oswalt , Laura Alder , Kevin Chen , Jordyn Higgins , Jeffrey Clarke , Eziafa Oduah *

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Review

Neoadjuvant, Perioperative, and Adjuvant Immunotherapy in Early-Stage Surgically Resectable Non-Small Cell Lung Cancer: Updates and Future Perspectives

Diamone Gathers [1,2], Cameron Oswalt [1,2], Laura Alder [1,2], Kevin Chen [3], Jordyn Higgins, Jeffrey Clarke [1,2] and Eziafa I. Oduah [1,2,*]

[1] Duke University, School of Medicine, Duke University Health Systems, Durham, NC, United States
[2] Duke Cancer Institute, Durham, NC, United States
[3] University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC, United States
* Correspondence: eziafa.oduah@duke.edu

Simple Summary: Immunotherapy has changed the landscape of non-small cell lung cancer (NSCLC) treatment. Although initially studied in the advanced/metastatic setting, recent trials have demonstrated impressive benefit in early-stage disease. This review will focus on the various immune checkpoint inhibitor regimens studied and approved in surgically resectable NSCLC patients, outline unanswered questions in the field, and highlight the vital role of multi-disciplinary discussions in this patient population.

Abstract: Historically, systemic therapy for resectable non-small cell lung cancer (NSCLC) has been associated with modest impact in overall survival. Current treatment options for early-stage resectable NSCLC include use of neoadjuvant, adjuvant, and perioperative immunotherapy in combination with chemotherapy. In this review, we will explore current treatment paradigms and emerging opportunities for improved survival outcomes in using immunotherapeutic approaches in the treatment of early-stage resectable NSCLC.

Keywords: non-small cell lung cancer (NSCLC); immunotherapy; early-stage NSCLC; neoadjuvant; perioperative; adjuvant

1. Introduction

Lung cancer remains the leading cause of cancer mortality. In the United States there was an estimated 234,580 new cases and approximately 125,070 deaths annually for the year 2024 [1]. Approximately 30% of patients with non-small cell lung cancer (NSCLC) are diagnosed at an early stage, for which curative surgery is the treatment of choice [3–6]. Recent outcomes data from the SEER registry indicate that the 5-year survival for patients with localized NSCLC and for those with regional nodal metastasis is 60% and 37% respectively [7]. These statistics demonstrate that early-stage NSCLC is associated with a significant risk of local and distant recurrence and lung cancer related mortality after curative surgery, which necessitates the incorporation of advanced systemic therapies into the treatment paradigm of surgically resectable NSCLC.

Initial efforts to improve survival for surgically resectable NSCLC focused on the use of post-operative (adjuvant) or pre-operative (neoadjuvant) platinum-based chemotherapy regimens. Studies have shown that the use of adjuvant chemotherapy in patients with early stage surgically resected NSCLC was of overall modest clinical impact on survival [1]. The lung adjuvant cisplatin evaluation (LACE) meta-analysis showed that adjuvant cisplatin improved overall survival (OS) by 5.4%, showing benefit primarily in Stage II-IIIA patients [8]. Although some studies of neoadjuvant

chemotherapy were promising compared to available adjuvant data, statistically significant OS benefits were not demonstrated. Moreover, some trials were aborted early when survival data on the adjuvant approach emerged. With the advent of immunotherapy and targeted therapies, within the last decade, there has been robust efforts on incorporating these agents into the treatment landscape of surgically resectable NSCLC to improve survival.

Activation of the anti-tumor immune response by immune checkpoint inhibition was effective in metastatic lung cancer, paving the way for their inclusion into earlier stages of NSCLC [9–13]. The addition of immunotherapy into neoadjuvant (inductive or pre-operative) systemic therapy for early-stage NSCLC yielded improved outcomes in patients. However, the rate of pathologic complete responses, a surrogate for long-term survival, on the post-surgical regimes remains below 30% [14–16]. Adjuvant (postoperative) and perioperative approaches of immunotherapy combinations are now also standard of care for select early-stage NSCLC patients. Despite these significant advances in the treatment of early-stage NSCLC, unanswered questions remain, and debates continue over the utility of neoadjuvant, adjuvant versus perioperative immunotherapeutic approaches.

In this narrative review, the data on key clinical trials incorporating neoadjuvant, adjuvant and perioperative immunotherapy strategies that have shaped the current treatment landscape in early-stage NSCLC without actionable EGFR and ALK alterations are described and summarized in Table 1. Current challenges, ongoing studies and opportunities for future research that will shape the future of immunotherapy in early-stage NSCLC are also discussed.

Table 1. Summary of major reported neoadjuvant, perioperative and adjuvant trials incorporating checkpoint inhibition.

Study (Stage)	Study Arms	Efficacy endpoints	mEFS /DFS/PFS (months)	mOS (months)	mPR (%)	pCR (%)
NEOADJUVANT						
CheckMate 816 Stage IB* - IIIA+	Nivo+CT vs CT	1º: EFS and pCR 2º: OS	EFS: 43.8 vs 18.4 HR 0.66 (CI 0.49-0.90)	mOS not NR HR for mOS 0.71 (CI 0.47-1.07)	36.9 vs. 8.9 OR 5.70 (CI 3.16-10.26)	24 vs 2.2 OR 13.94 (CI 3.49 - 55.75)
NEOSTAR	Nivo+CT vs Ipi+Nivo+CT	1º: mPR 2º: pCR, OS, EFS	EFS: NR	NR	32.1 (80% CI 18.7-43.1) vs 50 (80% CI 34.6-61.1)	18.2 (CI 5.2-40.3) vs 18.2 (CI 5.2-40.3)
PERIOPERATIVE						
NADIM Stage IIIA+	single arm CT+Nivo → Nivo	1º: 24mo PFS 2º: 5 yr PFS and OS	PFS: 77.1 (CI 59.9-87.7) PFS: 65·0 (CI 49·4–76·9)	69.3 (CI 53·7–80·6)	83 (CI 68-93)	63.4 (CI 62-91)
NADIM II Stage IIIA-IIIB++	CT+Nivo →Nivo vs CT→ placebo	1º: pCR 2º: 24-month PFS and OS	PFS: 67.2 vs 40.9 HR 0.47 (CI 0.25-0.88)	85 vs 63.6 HR 0.43 (CI 0.19-0.98)	53 vs 14 RR, 3.82 (CI 1.49-9.79)	37 vs 7 RR, 5.34 (CI 1.34-21.23)
KEYNOTE 671 Stage II-IIIB# ++	Pembro+CT vs CT	1º: EFS and OS 2º: pCR and mPR	EFS: 62.4 vs 40.6 HR 0.58 (CI 0.46-0.72)	64 vs 71 HR 0·72 (CI 0·56–0·93)	30.2 vs 11 Difference, 19.2 (CI 13.9- 24.7)	18.1 vs 4.1 Difference, 14.2 (CI 10.1- 18.7)
CheckMate 77T Stage IIA-IIIB++	Nivo+CT→ Nivo vs CT→placebo	1º: EFS 2º: pCR, mPR, OS	EFS: 70.2 vs 50 HR 0.58 (CI 0.42 - 0.81)	NR	35.4 vs 12.1 OR, 4.01 (CI 2.48- 6.49)	25.3 vs 4.7 OR, 6.64 (CI 3.4 -12.97)

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AEGEAN (stage II-IIIB [N2 node])++	CT+Durv →Durv vs CT → placebo	1⁰: EFS and pCR 2⁰: mPR, DFS, OS	EFS: NR vs 30 HR, 0.69 (CI, 0.55-0.88)	NR	33 vs 12.3 Difference, 21 (CI 15.1-26.9)	17.2 vs 4.3 Difference, 13.0 (CI 8.7- 17.6)
NEOTORCH Stage II-IIIB++	CT+Tori → Tori vs CT + placebo→ placebo	1⁰: IA-EFS, mPR 2⁰: IRC-EFS, OS, pCR	EFS: NR vs15.1 HR, 0.40 (CI 0.28-0.57)	NE vs 30.4 HR 0.62 (CI 0.33-0.76)	48.5 vs 8.4 Difference, 40.2 (CI, 32.2-48.1)	24.8 vs 1 Difference, 23.1 (CI 17.6-29.8)
RATIONALE 315 Stage II-IIIA++	CT+TIS→ TIS vs CT+placebo → placebo`	1⁰: EFS, mPR 2⁰: IRC-EFS, OS, pCR	EFS: NR for both HR: 0.56 (CI 0.40 - 0.79)	NR for both HR 0.62 (CI, 0.39-0.98)	56 vs 15 Difference 41 (CI, 33-95)	41 vs 6 Difference 35 (CI, 28-42)
ADJUVANT						
PEARLS/ KEYNOTE 091 Stage IB* – IIIA+	Pembro vs placebo	1⁰: DFS in study population and PDL1 ≥ 50%	DFS ITT: 53.6 vs 43 HR 0·76 (CI 0·63–0·91) DFS PDL1 ≥50%: NR vs NR HR 0·82 (CI 0·57–1·18)	Not reported	NA	NA
IMpower 010 Stage IB* - IIIA+	Atezo vs BSC	1⁰: IA-DFS in: -Stage II-IIIA (PD-L1 ≥ 1%) Stage II-IIIA PDL1 ≥ 50% -Stage II-IIIA (all PD-L1) -Stage IB-IIIA (all PD-L1)	68.5 vs 37.3 0.7 (0.55, 0.91) NR vs 41.1 0.48 (0.32-0.72) 57.4 vs 40.8 0.83 (0.69-1.00) 65.6 vs 47.8 0.85 (0.71-1.01)	NR vs 87.1 0.77 (0.56-1.06) NR vs 87.1 0.47 (0.28, 0.77) NR vs NR 0.94 (0.75, 1.19) NR vs NR 0.97 (0.78, 1.22)	NA	NA

Abbreviations: EFS, event free survival; DFS, disease free survival; OS, overall survival; mPR, major pathologic response, pCR, complete pathologic response; HR, hazard ratio; CI, confidence interval (all CI were at least 95%, except where indicated); OR, odd's ratio; RR, relative ratio; IA-DFS: investigator assessed disease free survival, NR, not reached; NE, not estimable; CT, chemotherapy; Nivo, nivolumab; Ipi, ipilimumab; Pembro, pembrolizumab; Durv, durvalumab; Atezo, atezolizumab; TIS, tislelizumab; BSC, best supportive care; NA, not applicable * Stage IB (tumors ≥4 cm) , # with involvement of ≥1 ipsilateral mediastinal lymph node or subcarinal lymph node [N2 node stage], +AJCC 7th edition; ++ AJCC 8th edition.

2. Neoadjuvant Chemotherapy and Immunotherapy Approaches

Evaluation of neoadjuvant systemic therapy for the treatment of early stage surgically resectable NSCLC predates the era of immunotherapy. Initial studies of neoadjuvant systemic therapies investigated the addition of platinum-doublet chemotherapies prior to surgery. In the Spanish Phase III study, 624 patients with Stage IA to Stage IIIA NSCLC were randomized to neoadjuvant chemotherapy plus surgery, surgery alone versus surgery followed by adjuvant chemotherapy. There were no significant differences in 5-year disease-free survival (DFS) between the neoadjuvant and adjuvant chemotherapy arms. The 5-year DFS was 38.3% in the preoperative population vs 34.1% in the postoperative population with a hazard ratio [HR] for progression or death, 0.92; p= .176). The

5-year DFS rate in the adjuvant arm was 36.6% compared to 34.1% in the surgery arm (HR 0.96; p = .74). It was further noted that a higher proportion of patients completed three planned chemotherapy cycles in the preoperative arm (90.4%) compared to the postoperative arm (60.9%) [17].

Two additional phase III studies were performed to further assess the benefits of neoadjuvant chemotherapy. The CHEST trial and SWOG 9900 both compared neoadjuvant chemotherapy regimens followed by surgery alone versus surgery alone in patients with Stage IB to Stage IIIA NSCLC [18,19]. The reported results from both studies showed modest efficacy however both studies were terminated prematurely due to the emergence of data supporting a greater survival benefit with adjuvant chemotherapy. A meta-analysis of 13 randomized control trials was performed (data ranging from 1985-2005 and Stage IB-IIIA), evaluating the benefit of neoadjuvant chemotherapy versus surgery alone. The overall survival of NSCLC patients in the neoadjuvant chemotherapy arm were improved significantly, compared with those undergoing surgery-alone (combined HR = 0.84; 95% CI, 0.77–0.92; p = 0.0001). When only patients with stage III NSCLC were considered, the result was similar (combined HR = 0.84; 95% confidence interval, 0.75–0.95; p = 0.005) [20].

The emergence of immunotherapy onto the therapeutic landscape for metastatic NSCLC paved the way for consideration of new neoadjuvant treatment approach. Early data indicated that the use of neoadjuvant immunotherapy in resectable NSCLC was feasible and safe, with no significant compromise in surgical outcomes. In a Phase 2 study of Stage I to Stage IIIA resectable NSCLC, preoperative nivolumab 3mg/kg was administered every 2 weeks for 2 doses followed by surgery. Neoadjuvant nivolumab was found to have an acceptable side effect profile and resulted in a major pathologic response (mPR), defined as the presence of no more than 10% viable tumor cells, in 45% of resected tumors [21]. Another earlier study investigated the addition of immunotherapy to chemotherapy in a Phase II trial of Stage IB to Stage IIIA resectable NSCLC. Neoadjuvant carboplatin, nab-paclitaxel, and atezolizumab was administered every 3 weeks for 2 cycles, followed by interim evaluation. An additional 2 cycles were given if no progression was detected after the first 2 cycles, followed by surgery. Thirty total patients were enrolled (75% with Stage IIIA disease), and 17 of these patients (57%) had a mPR. The treatment was tolerable with manageable side effects, without significant compromise of surgical feasibility [22].

CheckMate (CM) 816 was the first phase III clinical trial to demonstrate the benefits of neoadjuvant immunotherapy in resectable NSCLC. Patients with Stage IB (tumors > 4cm) to Stage IIIA disease, without EGFR or ALK alterations were randomized to receive 3 cycles of neoadjuvant platinum doublet chemotherapy with nivolumab (360mg) every 3 weeks, 3 cycles of platinum doublet chemotherapy alone every 3 weeks, or dual immunotherapy with 3 cycles of q3 weekly nivolumab (3mg/kg) and ipilimumab (1mg/kg) every 2 weeks. Surgery occurred within 6 weeks of completion of neoadjuvant therapy. Of note, the dual immunotherapy arm was closed early after the results of the NADIM and NEOSTAR trials were reported [15,23].

The two primary endpoints of CheckMate 816 were event-free survival (EFS) and pathologic complete response (pCR), defined as 0% residual viable tumor cells in the primary tumor and sampled lymph nodes. In the initial report, the median EFS was 31.6 months (95% confidence interval [CI], 30.2 - not reached [NR]) in the chemotherapy-immunotherapy arm compared to 20.8 months in the chemotherapy alone arm (95% CI, 14.0 - 26.7). pCR was statistically significantly higher in the chemotherapy-immunotherapy arm compared to the chemotherapy arm at 24.0% (95% CI, 18.0 - 31.0) vs 2.2% (95% CI, 0.6 - 5.6), respectively (odds ratio, 13.94; 99% CI, 3.49 - 55.75; P<0.001). pCR rates were better in patients receiving chemotherapy-nivolumab across all subgroups except never smokers. At the first interim analysis, the HR for death was 0.57 (99.67% CI, 0.30 - 1.07) in the chemotherapy-immunotherapy arm compared to the chemotherapy alone arm, though median OS had not been reached in either group. When compared to the chemotherapy alone arm, neoadjuvant chemoimmunotherapy did not negatively impact the ability to perform surgical resection. Approximately 83.2% of patients in the chemotherapy-nivolumab arm underwent surgery, compared to 75.4% in the chemotherapy arm alone. Adverse events (AE) occurred at similar rates between the two groups with 92.6% of patients in the chemoimmunotherapy group experiencing any AE

compared to 97.2% in the chemotherapy alone group; grade 3-4 treatment-related adverse events occurred in 33.5% of patients receiving immunotherapy compared to 26.9% in the chemotherapy alone group. In conclusion, CheckMate 816 demonstrated that neoadjuvant chemotherapy plus nivolumab had a significant benefit over chemotherapy alone with respect to EFS and pCR without increased safety events or compromising surgical feasibility [24]. Nivolumab became the first immunotherapeutic to receive Food and Drug Administration approval in combination with platinum-doublet chemotherapy in the neoadjuvant setting for resectable NSCLC in March 2022 [25].

The 4-year survival update of Checkmate 816 demonstrated continued benefit with the addition of nivolumab. The median EFS in the nivolumab arm was 43.8 months compared to the 18.4 months in the chemotherapy alone arm (HR 0.66; 95% CI, 0.49 -0.90). The 4-year EFS rates of 49% versus 38%. There was a 13% improvement in OS in the nivolumab arm compared to the chemotherapy alone at 4-years (71% vs 58%). The median OS was not yet reached in either group. Importantly, patients in the immunotherapy arm who achieved a pCR demonstrated improved OS compared to those who did not. This 4-year analysis has now demonstrated a survival benefit with the addition of immunotherapy, sustained EFS benefit over time compared to chemotherapy alone while highlighting the long-term benefits of achieving a pCR [26].

In an exploratory analysis of the dual immunotherapy arm of CheckMate 816 (three cycles of nivolumab every 2 weeks and one cycle of ipilimumab) compared to chemotherapy, there was improved EFS (54.8 months versus 20.9 months), longer 3-year OS rates (73% versus 61%), and higher pCR rates (20.4% versus 4.6%) in the dual immunotherapy arm compared to chemotherapy. Moreover, there were lower rates of grade 3 or 4 treatment-related adverse events (14% versus 36%) in the dual immunotherapy group as well [27]. This data suggests that dual immunotherapy approaches could be a reasonable approach for patients for whom there is a need to avoid chemotherapy. Another dual neoadjuvant immunotherapy approach was demonstrated in the phase II NeoCOAST trial. The NeoCOAST trial compared durvalumab alone, durvalumab plus oleclumab, durvalumab plus monalizumab, and durvalumab plus danvatirsen followed by surgery. The trial demonstrated that combination neoadjuvant immunotherapy approaches resulted in higher mPR rates while maintaining similar safety profiles. The enhanced responses were attributed to enhanced immune infiltration, interferon responses, and functional immune cell activation seen on immune profiling analysis [28].

The benefit of neoadjuvant chemoimmunotherapy over neoadjuvant chemotherapy has been clearly demonstrated both in clinical trials and meta-analysis reports. A meta-analysis of neoadjuvant chemoimmunotherapy versus chemotherapy in resectable NSCLC demonstrated improved pooled OS (HR 0.65), EFS (HR 0.59), mPR (risk ratio 3.42), and pCR (risk ratio 5.52) favoring neoadjuvant chemoimmunotherapy over chemotherapy. This analysis also demonstrated that the EFS benefit was sustained even in the PD-L1 <1% population (HR 0.74) [29]. A similar systematic review and meta-analysis of neoadjuvant chemoimmunotherapy compared to chemotherapy alone demonstrated 2-year EFS and pCR benefits irrespective of PD-L1 status, platinum chemotherapy selection, number of neoadjuvant cycles, or the use of adjuvant immunotherapy. However, their results showed a higher risk of relapse in tumor cells negative for PD-L1 compared to low or high PD-L1 scores [30]. As the neoadjuvant treatment landscape continues to evolve, it will be paramount to continue similar analyses to determine the best treatment approaches across different patient and tumor characteristics and the most appropriate trial end points to assess neoadjuvant immunotherapy outcomes.

3. Perioperative Checkpoint Blockade in Early-Stage NSCLC

Given the success of including checkpoint inhibitors in the neoadjuvant and adjuvant settings (discussed below), multiple studies began to assess a sandwich approach, in which immunotherapy was layered on post-operatively in patients who received neoadjuvant chemo-immunotherapy strategies.

NADIM was the first trial to test the addition of perioperative checkpoint inhibition in patients with resectable NSCLC [31]. This was a single-arm phase II trial in Spain that enrolled 46 individuals with resectable stage IIIA NSCLC. Neoadjuvant platinum-doublet chemotherapy combined with nivolumab was given for up to three cycles followed by surgery and adjuvant nivolumab for up to 1 year. Among the 41 patients who underwent surgery, 83.0% (95% CI, 68-93) had a major pathological response, including 63.4% (95% CI, 62-91) with a complete pathological response (pCR) [31]. PD-L1 TPS was significantly higher in patients who had a pCR (p=0·042). Follow-up was concluded at 60 months in July 2023 and showed a 5-year progression-free survival in the intention-to-treat population of 65·0% (95% CI, 49·4–76·9), and overall survival of 69·3% (95% CI, 53·7–80·6). Disease progression occurred in 11 (24%) patients [32]. Neoadjuvant treatment did not significantly delay planned surgery. This initial trial was instrumental in demonstrating the safety and efficacy of perioperative immunotherapy treatment in a population at high risk of recurrence.

In follow up to the NADIM trial, the investigators evaluated the perioperative approach in resectable stage IIIA and IIIB NSCLC. In NADIM II, patients with resectable stage IIIA/B NSCLC were randomized 2:1 to receive neoadjuvant platinum doublet chemotherapy plus nivolumab vs SOC neoadjuvant chemotherapy followed by surgery. Adjuvant nivolumab was administered to patients in the experimental arm who achieved R0 resection. Similar to NADIM, the addition of nivolumab increased pCR (37% vs 7%) (RR, 5.34; 95% CI, 1.34-21.23; P=0.02) [33]

Perioperative pembrolizumab was reported in the KEYNOTE-671 clinical. Patients with either stage II, IIIA, or IIIB disease were assigned to receive neoadjuvant cisplatin-based chemotherapy in combination with pembrolizumab (200 mg) or placebo once every 3 weeks for 4 cycles, followed by surgery and adjuvant pembrolizumab (200 mg) or placebo once every 3 weeks for up to 13 cycles respectively [34]. At 24 months follow up, EFS in the pembrolizumab arm was 62.4%, as compared to 40.6% in the placebo group (HR for progression, recurrence, or death, 0.58; 95% CI, 0.46-0.72; p<0.001). Like other studies, the inclusion of neoadjuvant pembrolizumab resulted in a higher pCR rate, 18.1% versus 4.0% in chemotherapy alone (95% CI, 10.1-18.7; p<0.0001). Similarly, 30.2% of the pembrolizumab group achieved a mPR versus 11.0% of the placebo group (95% CI, 13.9 - 24.7; p<0.0001) [34]. At the second interim analysis, 36-month OS estimates were 71% (95% CI 66–76) in the pembrolizumab group and 64% (58–69) in the placebo group (HR 0·72 [95% CI 0·56–0·93]; p=0·0052). Median event free survival (EFS) was 47·2 months (95% CI, 32·9-not reached [NR]) in the pembrolizumab group and 18·3 months (95% CI, 14·8–22·1) in the placebo group (HR 0·59 [95% CI, 0·48–0·72]) [35]. Based on these results, pembrolizumab became the first immunotherapy to receive FDA approval for perioperative use in early-stage resectable NSCLC.

CheckMate 77T was another Phase III study investigating peri-operative immune checkpoint inhibition [36]. Patients with stage IIA to IIIB NSCLC received either neoadjuvant nivolumab plus platinum-doublet based chemotherapy or neoadjuvant chemotherapy plus placebo every 3 weeks for 4 cycles, followed by surgery and adjuvant nivolumab or placebo every 4 weeks for 1 year. At a median follow-up of 25.4 months, the 18-month EFS was 70.2% in the nivolumab group and 50.0% in the chemotherapy group (HR for disease progression or recurrence, abandoned surgery, or death, 0.58; 97.36% CI, 0.42 - 0.81; P<0.001) [24]. A higher percent of patients in the nivolumab group achieved a pCR at 25.3%, compared to 4.7% in the chemotherapy group (odds ratio, 6.64; 95% CI, 3.40 - 12.97), similar to the results seen in CheckMate 816 [24].Both CheckMate 77T and 816 showed that patients who achieved pCR had significantly better outcomes with improved EFS. A higher percentage of patients also reached a mPR with nivolumab, 35.4% vs 12.1% (odds ratio, 4.01; 95% CI, 2.48 - 6.49) [36]. In the landmark analysis of EFS per adjuvant treatment status, using the date of definitive surgery as the landmark timepoint, there was an observed EFS benefit in patients receiving nivolumab vs placebo. Although this was used to suggest the added benefit of nivolumab in the adjuvant phase of treatment, it remains unclear what the contribution of addition of adjuvant nivolumab over neoadjuvant nivolumab alone, since the data was in comparison to patients who received neoadjuvant chemotherapy alone. This remains an ongoing question and a debated topic

given that no trial has yet reported data powered to compare the benefit of perioperative immunotherapy over the inclusion of neoadjuvant immunotherapy with chemotherapy alone.

Lastly, the AEGEAN trial assessed the addition of durvalumab to a standard neoadjuvant chemotherapy regimen in patients with resectable NSCLC (stage II to IIIB [N2 node stage]. Patients were treated with either platinum-based chemotherapy plus durvalumab or placebo administered intravenously every 3 weeks for 4 cycles before surgery, followed by adjuvant durvalumab or placebo intravenously every 4 weeks for 12 cycles [37]. pCR occurred at a higher rate, 17.2% vs. 4.3% (95% CI, 8.7 to 17.6; P<0.001) in the durvalumab arm compared to placebo arm. The EFS at 12 months was also significantly higher in the durvalumab group, at 73.4% vs 64.5%. EFS and pCR benefit were observed regardless of stage and PD-L1 expression [30]. At the second planned interim analysis, the median EFS was not reached (95% CI, 42.3-NR) with the durvalumab regimen (n = 366) compared with 30.0 months (95% CI, 20.6-NR) with the placebo regimen (HR, 0.69; 95% CI, 0.55-0.88) at a median follow-up in censored patients of 25.9 months (range, 0.0-58.6). The 3-year EFS rates were 60.1% and 47.9%, respectively [38].

Other studies have also demonstrated the benefit of addition of perioperative PD-1 blockade to standard chemotherapy. The phase III NEOTORCH trial randomized resectable stage II-IIIB (AJCC 8th edition) patients 1:1 to receive toripalimab or placebo in combination with platinum-based chemotherapy for 3 cycles followed by surgery and an additional cycle adjuvantly [39]. Patients then continued toripalimab or placebo maintenance for 13 additional cycles to complete one year of total treatment. The interim analysis for stage III disease demonstrated a significant benefit with the addition of toripalimab. Major pathologic responses were achieved in 48.5% of patients in the toripalimab arm versus 8.4% in the placebo arm while the rate of pCR in the toripalimab treatment arm was 24.8% compared to 1.0% in the placebo arm. Investigator-assessed EFS was in favor of the toripalimab arm (median: NE vs 15.1mo, HR: 0.40 (95% CI 0.28-0.57). Safety profile is consistent with prior chemoimmunotherapy combination trials, with the majority of toxicities arising from the chemotherapy treatment. The toripalimab arm did have increased rates of transaminitis, hypothyroidism, and pneumonitis, consistent with the known toxicities of ICIs.

Similarly, the RATIONALE 315 trial also demonstrated improved outcomes in patients who received perioperative tislelizumab in addition to platinum-based chemotherapy [40]. This study was conducted in a similar population with slight differences in treatments. Patients were randomized to receive three to four cycles of neoadjuvant chemotherapy with tislelizumab or placebo, followed by eight 6-week cycles of adjuvant tislelizumab or placebo after surgical resection. More patients received three cycles of neoadjuvant treatment (55%) compared to 4 cycles (37%). The addition of tislelizumab to chemotherapy resulted in a significant increase in patients who achieved a mPR (56 % vs 15%) or pCR (41% vs 6%), as well as improvement in EFS (HR: 0.56 [95% CI, 0.40-0.79]). A trend towards improved overall survival was seen with tislelizumab but was not statistically significant. Treatment-related adverse events were similar across both groups with the tislelizumab experiencing more immune-related adverse events (40% vs 18%) such as skin reactions, pneumonitis, hepatitis, and endocrinopathies.

4. Adjuvant Immunotherapy in Early-Stage NSCLC

Adjuvant therapy alone following surgery remains an option for patients who did not receive neoadjuvant systemic therapy. The goal of adjuvant therapy is to eliminate micrometastases and to prevent recurrence. For patients with stage IB and IIA disease and negative margins, adjuvant chemotherapy is only recommended for those with high-risk features such as poorly differentiated tumors, vascular invasion, wedge resection, visceral pleural involvement, and unknown lymph node status. For patients with stage IIB to stage IIIB and negative margins, adjuvant chemotherapy is a category 1 recommendation per the NCCN Guidelines [41]. Current clinical trials are exploring chemotherapy with concurrent or subsequent immunotherapy in patients with resectable NSCLC [42]. In addition, use of immune checkpoint inhibition has been shown to reverse the surgically induced inflammatory response and enhance anti-tumor activity of T cells [43,44].

Adjuvant immunotherapy was investigated in the postoperative setting. PEARLS/Keynote-091 investigated use of pembrolizumab compared to placebo in early-stage resectable NSCLC after curative surgery with or without adjuvant chemotherapy. The primary endpoints were DFS in the overall population and in the PD-L1 TPS ≥ 50%. Adjuvant pembrolizumab improved DFS in the overall population compared to placebo. Median DFS was 58.7 months in the pembrolizumab arm vs 34.9 months in the placebo arm (HR, 0.73 [95% CI, 0.60–0.89]), with estimated 18-month DFS rates at 73.8% for pembrolizumab and 63.1% in the placebo group [45]. In the PDL1 ≥ 50% population, median DFS was not reached in both the pembrolizumab (95% CI 44·3 to not reached) and placebo groups (95% CI 35·8 to not reached). Interesting, there was no statistically significant improvement in median DFS in the pembrolizumab group over the placebo in PDL1 >50% patients. HR 0·82 [95% CI, 0·57–1·18]; p=0·14). In the updated analysis of patients who received chemotherapy at the median follow up of 51.7 months, the DFS benefit of pembrolizumab over placebo was maintained in the ITT population. The 4-year DFS rate was in the pembrolizumab vs control groups were 57.0% (95% CI, 47.9%–65.1%) vs 49.1% (95% CI, 39.8%–57.8%). There were no statistically significant differences in median DFS in both arms in the PD-L1 TPS ≥ 50% patient population [46].

In the Impower010 trial, patients with stage IB–IIIA NSCLC who had received adjuvant chemotherapy after surgical resection were randomized to receive atezolizumab or best supportive care. In patients with PD-L1 positive stage II–IIIA disease, at a median follow-up of 32 months, atezolizumab showed improved DFS compared to best supportive care (HR 0.66; 95% CI 0.50–0.88; p=0.0039). Moreover, atezolizumab showed improved DFS over placebo in all stage II-IIIA patients (0.79; 0.64–0.96; p=0.020) regardless of PDL1 status. In the ITT population, HR for DFS was 0.81 (0.67–0.99; p=0.040). Atezolizumab-related grade 3 and 4 adverse events occurred in 11% of 495 patients and grade 5 events occurred in 1% of patients [47]. In the updated overall survival analysis, an OS HR 0.43 (95% CI 0.24-0.78) was reported in favor of atezolizumab over placebo in and PDL1 >50% stage II-IIIA patients. In the ITT population, OS data also had a trend in favor of atezolizumab but is not statistically significant and remains immature [48].

Interestingly, the BR31 trial which examined the benefit of adjuvant durvalumab treatment following surgery and optional adjuvant chemotherapy found no additional benefit regardless of PD-L1 thresholds [49], which is contrary to the results of the existing adjuvant ICI trials IMPower010 and Keynote091. Although the administration of adjuvant chemotherapy prior to durvalumab was optional, most patients (84%) received adjuvant chemotherapy in this study. Additional ongoing studies of adjuvant immunotherapy approaches including the IMPower030, ANVIL, ALCHEMIST and MERMAID trials are ongoing and will add to the growing body of literature for use of immune checkpoint inhibitors in the adjuvant setting (described in Table 2).

Table 2. Ongoing Clinical Trials of Immunotherapy in Resectable NSCLC.

NCT Number	Study Phase	Disease Stage	Treatment Arms	Endpoints (primary and secondary)
			NEOADJUVANT	
NCT06385262	II	Stage 1B-IIIA	A: Neoadjuvant platinum doublet chemotherapy + cemiplimab q3 weeks x3 cycles with alirocumab q4 weeks B: Neoadjuvant platinum doublet chemotherapy + cemiplimab q3 weeks x3 cycles without alirocumab	pCR, ORR, DFS, OS, AE
NCT06718309	II	Stage II- IIIB	Single arm: Immunotherapy + cisplatin/carboplatin + pemetrexed OR paclitaxel x1 cycle -> SBRT -> repeat	pCR, mPR EFS R0 resection rate

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			chemoimmunotherapy -> resection -> maintenance immunotherapy x1 year	AE
NCT04506242	II	Stage II-IIIB	Single arm: Neoadjuvant camrelizumab + apatinib x3 cycles -> resection -> adjuvant camrelizumab	mPR, pCR EFS, DFS ORR AEs
NCT05800340	II	Stage IIB-IIIB	Single Arm:Toripalimab + nab-paclitaxel/carboplatin OR pemetrexed/carboplatin -> resection or radiation -> adjuvant investigator's choice	pCR, mPR EFS OS AE
NCT06743581	Ib/IIa	Early Stage	Single Arm: Neoadjuvant cemiplimab + dupilumab combination therapy	Safety mPR, pCR Tolerability EFS, OS
NCT04638582	II	Stage IA3 - IIA	A: Neoadjuvant pembrolizumab + adjuvant pembrolizumab +/- adjuvant chemotherapy B: Neoadjuvant pembrolizumab and chemotherapy + adjuvant pembrolizumab +/- adjuvant chemotherapy	ctDNA resolution Radiologic response pCR rate, mPR AE Perioperative complications
NCT05527808	II	Stage II-IIIA	Single Arm: Neoadjuvant Tislelizumab + pemetrexed + platinum Q3W x2-4 cycles	mPR, pCR ORR AE, Surgery delay Minimally invasive surgery rate
ADJUVANT				
NCT06732401	III		A: Durvalumab q28d x12 cycles B: Durvalumab and Ceralasertib q28d x12 cycles	DFS OS AE
NCT04267848	III		A: Active comparator – platinum doublet + observation B: Experimental: platinum doublet + sequential pembrolizumab C: Experimental: platinum doublet + combination pembrolizumab	DFS OS
NCT06528847	II	Stage IB, Grade 3	Single Arm:1200mg benmelstobart q3w x16 cycles	DFS OS AE
NCT04966663	II	Early Stage	Single Arm:Pemetrexed OR gemcitabine + cisplatin OR carboplatin, + nivolumab	RFS
NCT06498635	III	Stage II-IIIB	A: Durvalumab – q28d x12 cycles with CT and blood sample collection	DFS EFS OS

			B: Active Surveillance – 12mo with CT and blood sample collection	AE
PERIOPERATIVE				
NCT06572722	II	Early Stage	A: Atezolizumab B: Nivolumab C: Pembrolizumab (random assignment to 1:1:1 ratio)	DFS OS mPR
NCT05825625	II	Stage II, IIIA, IIIB (T3N2 only)	Single Arm: SOC platinum-based chemotherapy + atezolizumab + tigoralumab x2 cycles -> surgery -> SOC platinum- based chemo + atezolizumab + tiragolumab for up to 1 year	mPR, pCR Radiological response by RECIST v1.1 EFS, OS AE
NCT06109402	II	Stage II/IIIB (N2) NSCLC	A: Neoadjuvant Immunochemotherapy + adjuvant immunotherapy B: Adjuvant immunochemotherapy + immunotherapy	ORR pCR, mPR EFS, OS 5y EFS, 5y OFS AE, HRQol

Abbreviations: pCR, pathological complete response; mPR, major pathological response; OR, objective response; EFS, event free survival; DFS, disease free survival; OS, overall survival; ORR, overall response rate; RFS, relapse free survival; AE, adverse events; ctDNA, circulating tumor DNA; HRQol, health related quality of life; WT, wild type.

5. Ongoing Studies

Emerging studies incorporating combinations with immune checkpoint inhibitors are ongoing. The previously discussed phase II platform NeoCOAST trial in which patients were randomized to receive neoadjuvant durvalumab alone, durvalumab + oleclumab (anti-CD73), durvalumab + monalizumab (anti-NKG2A) or durvalumab + danvatirsen (anti-STAT3) showed promising results [28]. mPR was observed in 11.1% with durvalumab alone, 19.0% with durvalumab + oleclumab, 30.0% with durvalumab + monalizumab, and 31.3% with durvalumab + danvatirsen. Building upon this concept, the NeoCOAST-2 trial randomized patients to receive neoadjuvant platinum doublet chemotherapy combined with one of four investigational regimens: durvalumab + oleclumab, durvalumab + monalizumab, volrustomig (bi-specific PD-1/CTLA-4) or durvalumab + datopotamab deruxtecan (TROP2-directed antibody-drug conjugate) for 4 cycles, followed by up to 1 year of adjuvant investigational agent after surgery [50]. Interim analysis found pCR rates of 20.0%, 26.7%, and 34.1% and MPR rates of 45.0%, 53.3%, and 65.9% with the durvalumab + oleclumab, durvalumab + monalizumab, and durvalumab + datopotamab deruxtecan arms respectively. Grade 3 or higher treatment-related adverse events were seen in 31.1%, 29.6%, and 18.5% respectively for these combinations. These findings are likely to usher in the next generation of combination treatment regimens in the perioperative space. Ongoing trials continue to investigate novel combinations with immune checkpoint inhibitors including anti-LAG-3, anti-IgG1, and anti-BTLA monoclonal antibodies as well as mRNA cancer vaccines in advanced disease. A comprehensive list of ongoing clinical trials of immunotherapy in resectable NSCLC is provided in Table 2.

6. Discussion

The incorporation of immune checkpoint blockade into the treatment paradigm for ALK/EGFR negative surgically resectable early-stage NSCLC was a tremendous advance in therapy and patient outcomes. The addition of immunotherapy to neoadjuvant chemotherapy not only improved

efficacy but was well tolerated and did not impact surgical outcomes compared to neoadjuvant chemotherapy alone. The ability to attain pCR is inarguably one of the most important efficacy and survival indicators following neoadjuvant immunotherapy. However, pCR remain close to 20% on all established regimens of anti-PD1 and chemotherapy combinations, raising the impetus for ongoing and future studies to improve survival in early-stage NSCLC.

The perioperative approach, involving the layering-on of checkpoint inhibition post-operatively for a year in patients who received neoadjuvant chemo-immunotherapy, is an attempt to improve survival. While the OS read outs on KN671 and CM77T support the clear benefit of the addition of immune checkpoint inhibition to neoadjuvant chemotherapy, the individual benefit of continuation anti-PD1 postoperatively is difficult to discern due to the study design. It is likely that there are subsets of patients for whom postoperative immunotherapy would be of incremental benefit. However, prospectively designed studies that answer the questions regarding the molecular markers or clinical features that define specific subsets of patients most likely to obtain benefit from the sandwich approach are lacking. The ongoing ADOPT-lung and PROSPECT-lung trials may help elucidate an answer by comparing neoadjuvant vs perioperative durvalumab and perioperative vs investigator choice of pembrolizumab, nivolumab, and atezolizumab respectively [51,52]. These findings will hopefully help ensure patients are treated with the most appropriate agents for the optimal duration to avoid overtreatment and unnecessary toxicities, as well as potentially help identify the most appropriate backbone systemic therapy regimen for which to add novel therapies in future clinical trials.

Strategies incorporating neoadjuvant immunotherapies are frequently preferred over adjuvant only (or post-operative) regimens due to higher rates of completion of planned systemic treatments, earlier treatment of micrometastatic disease, and more robust anti-tumor immune response in the presence of the tumor [53]. Moreover, the ability to attain a pCR correlates with better survival in clinical trials. However, although uncommon, some patients experience disease progression while on neoadjuvant therapy and may no longer be candidates for definitive surgery. This forms the basis of arguments that favor an adjuvant only approach. More importantly, it raises the question of appropriate patient selection for neoadjuvant therapy versus upfront surgery for patients with surgically resectable early-stage disease. The exclusion of patients with driver alterations in EGFR and ALK from studies of neoadjuvant chemo-immunotherapy is an established practice, especially considering results from the ADAURA and ALINA studies showing benefit for adjuvant therapy for these patients [54,55]. Clinical trials investigating neoadjuvant and adjuvant strategies in resectable NSCLC with other actionable molecular alterations are currently underway and may yield data that will steer other patients onto targeted therapy approaches [56]. The role of other yet nonactionable molecular alterations such *as STK 11, KEAP1, TP53* mutations and other known markers of poorer responses to ICI, in determining appropriateness of neoadjuvant immunotherapies vs adjuvant and perioperative approaches is another area for investigation.

The role of neoadjuvant chemoimmunotherapy in borderline resectable patients for downstaging is controversial. The clinical trials for the currently approved regimens only included surgically resectable candidates at time of enrollment, however, there is data demonstrating the potential for downstaging after perioperative treatments [57]. For example, in the Checkmate 816 study, patients who received chemotherapy and nivolumab had higher rates of lobectomy and lower rates of pneumonectomy compared to chemotherapy alone [24]. The NADIM II trial recruited only stage IIIA or IIIB patients and found that nodal downstaging occurred in 72% of the patients who received neoadjuvant chemotherapy & nivolumab compared to 40% in patients who received chemotherapy alone.[43] These findings are particularly intriguing as 66% of patients in this study had N2 disease with 38% of them being multi-station N2 [33]. Importantly, all patients in this trial were deemed to be surgically resectable at time of enrollment, highlighting the role of a multidisciplinary approach in determining eligibility for one strategy or the other for borderline resectable disease. Of note, patient eligibility for resection and stage specific treatments will likely change with the recent updates to the TNM classification system [58].

One critical question remains – how can the field significantly push the boundary on pCR rates beyond 20-30%? The resistance to immune checkpoint inhibitors (ICI) poses a significant challenge to many NSCLC patients. The deep and durable responses to ICI evident in responders have inspired investigators to develop strategies that can overcome resistance and further harness the immune system against cancer. Applying such strategies earlier in the treatment course of surgically resectable NSCLC is likely to increase pCR and consequently lead to improved patient survival. Areas of recent investigation include focusing on other targets such as dendritic cells and natural killer cells, modulating the immune microenvironment by targeting inhibitory proteins such as proprotein convertase subtilisin/kexin type 9 (PCSK9) [59–62]. In a recent analysis of TOP1501, a single arm phase II study of perioperative pembrolizumab in 30 surgically resectable stage IB-IIIA NSCLC, the mean plasma PCSK9 was statistically significantly higher at the completion of neoadjuvant pembrolizumab and surgery. Compared to patients with mPR, PCSK9 levels were numerically higher in those without mPR. The mean difference in baseline versus post neoadjuvant pembrolizumab PCSK9 was 25.0 ng/mL ($p=0.0015$), whereas the mean difference in completion of neoadjuvant pembrolizumab versus the postsurgery time point was 40.2 ng/mL ($p\leq0.0001$) [63,64]. A phase II study evaluating the impact of neoadjuvant chemoimmunotherapy plus or minus PCSK9 inhibitor is currently ongoing (NCT06385262) and will provide additional knowledge regarding PCSK9's inhibitory immunomodulation. Other strategies include targeting the adenosine pathway; combination strategies including the addition antibody drug conjugates to neoadjuvant therapies. Approaches such as T cell expansion strategies, vaccine therapy and CAR-T therapy are being investigated in advanced stages of NSCLC but have yet to appear in the early stage.

7. Conclusions

In summary, as the therapeutic landscape of surgically resectable NSCLC continues to expand, the opportunity for ongoing investigation into the best treatment approach based on patient-specific characteristics, predictors of response and/or resistance, intensification of therapy in select patients to increase the pCR rates continue to grow. Such efforts need to be combined with multidisciplinary approaches and screening strategies that decrease the mortality burden from lung cancer. The incremental strides made in the past decade, along with promising emerging advances in medical, surgical, radiation oncology techniques in NSCLC position the field towards further success.

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Abbreviations

The following abbreviations are used in this manuscript:

pCR	pathological complete response
mPR	major pathologic response
AE	Adverse event
OR	Objective response
OS	Overall Survival
EFS	Event free survival
DFS	disease free survival
PFS	Progression free survival
ORR	overall response rate
RFS	relapse free survival
WT	wild type
HRQol	health related quality of life
NSCLC	Nonsmall cell lung cancer
SEER	Surveillance, Epidemiology and End Results Program
PD-L1	Programmed Death Ligand 1
TPS	Tumor Proportion Score
HR	Hazard ratio
CI	Confidence interval
RR	Relative risk
CT	Chemotherapy
TIS	Tislelizumab
BSC	Best supportive care
PCSK9	Proprotein convertase subtilisin/kexin type 9

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