Scientific Research Publishing

Advances in Lung Cancer, 2022, 11, 31-44
https://www.scirp.org/journal/alc
ISSN Online: 2169-2726
ISSN Print: 2169-2718

Immunotherapy in Early Stage Non-Small Cell Lung Cancer

Jeyanthi Ramanarayanan[1,2], Ganapathy Krishnan[3]

[1]Nancy N. and J. C. Lewis Cancer and Research Pavilion at St. Joseph's Candler Hospital, Jesup, USA
[2]Wayne County Cancer Care, Jesup, USA
[3]Adena Cancer Center, Adena Health System, Chillicothe, USA
Email: jeyanthiram88@hotmail.com

How to cite this paper: Ramanarayanan, J. and Krishnan, G. (2022) Immunotherapy in Early Stage Non-Small Cell Lung Cancer. *Advances in Lung Cancer*, **11**, 31-44.
https://doi.org/10.4236/alc.2022.113003

Received: June 16, 2022
Accepted: August 29, 2022
Published: September 1, 2022

Abstract

Immune-checkpoint inhibitors are extensively used in cancer treatment and have transformed the therapeutic landscape by inducing durable responses. Immunotherapy with checkpoint inhibitors targeting programmed death 1 (PD-1) receptor and programmed death ligand-1 (PDL-1) are used alone or with chemotherapy for treatment of metastatic non-small cell lung cancer (NSCLC). There is a great need for improving outcomes of patients with early stage NSCLC after surgical resection and with recent F. D. A. approval, immune checkpoint inhibitors are used as neoadjuvant or adjuvant therapy to enable curative resection and prevent or delay disease progression. In this article, we review the clinical studies evaluating the role of adjuvant and neoadjuvant immune checkpoint inhibitors in NSCLC and discuss the role of immunotherapy with radiation therapy in locally advanced non-metastatic NSCLC.

Keywords

Non-Small Cell Lung Cancer, Immunotherapy, Immune Checkpoint Inhibitors, Adjuvant, Neoadjuvant, Early Stage

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality and contributes to one-quarter of all cancer deaths in the United States [1]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer accounting for 85% of lung cancers diagnosed [2] [3]. About a third of NSCLC patients present with localized disease at diagnosis [4]. Surgically fit patients with localized disease are best managed with resection and five-year survival for stage IA is 50% and for IIIA disease is around 20% with most experiencing disease progression

[5]. Adjuvant cisplatin-based chemotherapy improves overall survival and has become the standard of care for patients with resected stage II and IIIA NSCLC [6]. A meta-analysis of studies evaluating the role of adjuvant cisplatin based chemotherapy showed 11% reduction in the risk of death and an absolute survival benefit of 5.4% at 5 years among patients who underwent chemotherapy [6] [7]. To improve outcomes for resectable stage IIIA tumors, pre-operative chemotherapy with or without radiation is recommended [8].

Widely used in clinical practice, programmed death-receptor 1 (PD-1) and its ligand (PD-L1) inhibitors have revolutionized the treatment of highly immunogenic cancers like melanoma and renal cell carcinoma [9] [10] [11] [12]. Immune checkpoint inhibitors, such as PD-1/PD-L1 monoclonal antibodies have also been successfully used in advanced lung cancer patients [13] [14] [15]. Anti-PD-1 and PD-L1 antibodies alone or combined with chemotherapy resulted in significant overall survival (OS) advantage in stage IV lung cancer [14] [16]. In 2015, pembrolizumab and nivolumab were approved for the treatment of PD-L1 expressing advanced NSCLC that progressed after treatment with platinum based chemotherapy [14] [17]. Improved outcome was also noted with locally advanced stage IIIB lung cancers when immunotherapy was administered after chemo-radiation therapy [18] [19]. Since approval, due to manageable toxicities and good safety profile observed in clinical practice, PD-1 and PD-L1 antibodies have moved up in the treatment of early stage NSCLC for use in both adjuvant and neoadjuvant settings [20] [21]. Though surgical resection is considered a curative modality in some patients with early stage NSCLC and adjuvant chemotherapy provides a survival benefit [22], to further improve on survival and prognosis, adjuvant and neoadjuvant immunotherapy are studied in clinical trials [23]-[42]. In this review, we summarize the progress made in the treatment of NSCLC patients with immunotherapy focusing on the non-metastatic setting.

2. Methods

We performed a literature search for published clinical trials using Pubmed, Ovid, Medline, clinical trials databases with keywords "early stage, non-small cell lung cancer, immunotherapy, immune checkpoint inhibitors, adjuvant, neoadjuvant," from January 2015 to current. Abstracts presented to ASCO annual meeting and ESMO meetings for a similar period were collected. We carefully selected and reviewed information on major clinical trials that led to drug approval. Abstracts, meeting reports were reviewed for updated information on completed trials when available using the same keywords. We have also listed a few of the many ongoing trials from the Clinical trials.gov website.

3. Results and Discussion

Adjuvant Immunotherapy in Early Stage NSCLC

The benefits of adjuvant immunotherapy are currently being evaluated in ongoing multicentered trials with the publication of some preliminary results [20]

[23]-[29]. Pembrolizumab (PD-1 inhibitor) has shown improvement in disease free survival (DFS) regardless of PDL-1 expression when used in patients who had undergone surgical resection for stage IB-IIIA NSCLC (NCT02504372; KEYNOTE 091) [23]. Among 1177 patients randomized to 200 mg pembrolizumab administered every 3 weeks for 6 cycles or placebo, pembrolizumab treated patients had a 24% reduction in risk of disease recurrence or death compared with placebo group (median, 53.6 months vs. 42 months; HR = 0.76; 95% CI, 0.63 - 0.91). A favorable trend in OS regardless of PD-L1 expression was seen and statistical significance was not reached yet due to few events reported. At two years of follow-up, 81.2% of patients receiving Keytruda were recurrence-free compared to 72.8% of patients on placebo. Updated second interim analysis of disease free survival in various subgroups was presented at the American Society of Clinical Oncology (ASCO, 2022) meeting [24].

IMpower010 is a multicentered phase III randomized trial that assessed the role of atezolizumab immunotherapy after chemotherapy among patients with early stage lung cancer (stage IB-IIIA) following surgery. [25] Among 1280 patients enrolled about 1269 patients completed 4 cycles of platinum-based chemotherapy and subsequently, 1005 patients underwent 16 cycles of atezolizumab 1200 mg given every week. Atezolizumab showed statistically significant disease free survival benefit vs. best supportive care (BSC); median disease free survival was 42.3 months in the atezolizumab group vs. 35.3 months in the BSC group ($p = 0.0205$, 2 sided) with a 21% improvement among patients with stages II-IIIA disease. In the PD-L1 > 1% population, disease free survival was not reached in atezolizumab group vs. 35.3 months in the BSC group ($p = 0.0039$, 2 sided). Adverse events of any grade were reported in 92.7% and 70.7% of atezolizumab and best supportive care group patients. A higher rate of discontinuation (18.2%) occurred in 18.2% of atezolizumab-treated patients. Based on the positive results, atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year is recommended per National Comprehensive Cancer Network (NCCN) guidelines in completely resected stage IIB-IIIA or high risk stage IIA PD-L1 ≥ 1% NSCLC after adjuvant chemotherapy [26].

Phase III ALCHEMIST trial (NCT02595944) evaluates the role of adjuvant therapy with nivolumab administered every 4 weeks for 1 year in improving overall survival (OS) and/or disease-free survival (DFS) over standard observation in patients with stage IB, II and IIIA NSCLC after surgical resection and standard adjuvant therapy [27]. The study has completed accrual and efficacy data is awaited.

In order to improve clinical outcomes among patients with a higher risk for relapse and avoid toxicity in patients who may not need any adjuvant therapy, minimal residual disease directed therapy after surgery is being explored in resected lung cancer. A phase III randomized, placebo controlled study (NCT02273375) is evaluating the efficacy and safety of durvalumab versus placebo following surgery and chemotherapy in patients with completely resected stage IB-IIIA NSCLC who have positive minimal residual disease (MRD+) post-surgery [28].

The study plans to enroll approximately 1360 patients to be randomized to either durvalumab or placebo, after adjuvant chemotherapy when administered and assess disease free survival (DFS) on all patients and based on PD-L1 expression.

In MERMAID-1 study, circulating tumor DNA (ctDNA) is assayed in plasma samples and, patients are randomized following successful surgery to standard-of-care adjuvant chemotherapy plus either durvalumab or placebo [29] [30]. The primary end point is to assess DFS in patients who have detectable MRD following surgery. In MERMAID-2, patients undergo surveillance for 96-week period when they are monitored for MRD status after surgery and adjuvant therapy then randomized to treatment once MRD is positive [31]. The primary end point in MERMAID-2 is DFS among patients who are PD-L1 TC ≥ 1%.

MRD assessment in lung cancer is investigational but if validated may be a convenient approach due to the availability of liquid biopsies and ctDNA. The ability to predict the risk of relapse after surgical resection in lung cancer may identify patients who would benefit from adjuvant therapy and serial ctDNA evaluation may also help us limit the duration of immunotherapy treatment among such patients.

Neoadjuvant Immunotherapy in Early stage NSCLC

Using immunotherapy in the upfront neoadjuvant setting was explored in numerous studies either alone or in combination with chemotherapy. Neoadjuvant therapy can enable patients undergo complete surgical resection by shrinking the tumor and eliminating distant micrometastatic disease thereby improving the surgical outcome [32]. There is also some pre-clinical evidence showing improved efficacy for neoadjuvant immunotherapy compared to adjuvant immunotherapy [33], and it is believed that neoadjuvant therapy may work better than adjuvant therapy due to intact tumor, immune system and anatomy of the lymphatic system that gets disrupted after surgery and wound healing [33] [34].

Single Agent Immunotherapy Neoadjuvant Studies

Single-agent PD-1 checkpoint therapy in early-stage NSCLC with nivolumab, pembrolizumab, or atezolizumab has shown that neoadjuvant immunotherapy is safe and feasible, producing a significant number of major pathologic responses after just two cycles of therapy [35] [36] [37]. In a pilot study reported by Forde *et al*., two preoperative doses of PD-1 inhibitor nivolumab 3 mg/kg every 2 weeks in surgically resectable stage IB-IIIA patients with NSCLC showed improved outcomes [34]. In this study, nivolumab was associated with few side effects and induced a major pathological response in 45% of patients who underwent resection. Additionally, a high tumor mutational burden was predictive of increased pathological responses to PD-1 blockade.

Research exploring sintilimab, a PD-1 inhibitor as a neoadjuvant therapy has also been conducted in a small study of 40 patients with stage IA-IIIB NSCLC [37]. All patients received two cycles of sintilimab and all but 3 patients underwent surgery. Major pathological response (MPR) was achieved in 15 patients (40.5%) and pathologic complete response (pCR) was achieved in six patients

(16.2%). Similar to previous studies, the PD-L1 expression in stromal cells correlated with the percentage of pathologic response of the primary tumor. In addition, patients with squamous cell cancers seemed to benefit more from treatment than other histologies.

Neoadjuvant durvalumab every 2 weeks for 2 doses following chemotherapy in the neoadjuvant setting was evaluated among 60 patients with stage IIIA, (N2) NSCLC [38]. Durvalumab has also continued adjuvantly for 1 year after surgery. Major pathological responses were observed in 34 (62%) patients and 1-year EFS rate was 73% (two-sided 90% CI, 63 to 82). It was concluded that durvalumab following chemotherapy neoadjuvantly and for 1 year after surgery was safe and resulted in better pathological responses than chemotherapy alone.

The NEOMUN trial (NCT03197467) evaluated neoadjuvant immunotherapy using pembrolizumab in early stage lung cancer followed by surgery in a phase II single arm study [35]. Two cycles of pembrolizumab were administered prior to surgery and of the 15 patients enrolled with stage IIA-IIIA NSCLC and Eichhorn *et al.* reported 4 patients (27%) who had a major pathologic response.

While results are awaited from immunotherapy adjuvant trials listed in **Table 1**, preliminary data on disease survival benefits are promising and likely to further improve overall survival among early stage NSCLC.

Table 1. Adjuvant immunotherapy trials in early stage NSCLC.

Trial NCT Number	Trial Name	Phase	Stage	Treatment	Primary Endpoint	Median DFS (Months)	Trial Status
{“type”: “clinical-trial”, “attrs”: {“text”: “NCT02486718”, “term_id”: “NCT02486718”}}NCT02486718	IMpower010	Phase 3	IB-IIIA	Atezolizumab	DFS	42.3	Completed accrual
{“type”: “clinical-trial”, “attrs”: {“text”: “NCT02595944”, “term_id”: “NCT02595944”}}NCT02595944	ANVIL	Phase 3	IB-IIIA	Nivolumab	DFS and OS	Not reported	Completed Accrual
{“type”: “clinical-trial”, “attrs”: {“text”: “NCT04317534”, “term_id”: “NCT04317534”}}NCT04317534	BTCRC LUN18-153	Phase 2	I	Pembrolizumab	DFS	Not reported	Ongoing
{“type”: “clinical-trial”, “attrs”: {“text”: “NCT04585477”, “term_id”: “NCT04585477”}}NCT04585477	Not available	Phase 2	I-III	Durvalumab	Decrease in ctDNA level	Not reported	Ongoing
{“type”: “clinical-trial”, “attrs”: {“text”: “NCT02273375”, “term_id”: “NCT02273375”}}NCT02273375	Not availabe	Phase 3	IB-IIIA	Durvalumab	DFS	Not reported	Ongoing
{“type”: “clinical-trial”, “attrs”: {“text”: “NCT02504372”, “term_id”: “NCT02504372”}}NCT02504372	PEARLS	Phase 3	IB-IIIA	Pembrolizumab	DFS	Not reported	Ongoing

Neoadjuvant Immunotherapy Combination Studies

In early stage NSCLC, combining immunotherapy in the adjuvant or neoadjuvant setting with surgery has become the new standard of care due to improved clinical outcomes. Results of the phase III CheckMate816 study that enrolled 358 patients with stage IB-IIIA NSCLC to receive three cycles of neoadjuvant nivolumab with platinum-based chemotherapy showed improved event free survival and response rates [39]. Patients were randomized to 4 cycles of neoadjuvant chemotherapy (n = 179) or nivolumab with chemotherapy (n = 179). The study reported a median event-free survival of 31.6 months for patients who received the combination of nivolumab and platinum-based chemotherapy, compared with 20.8 months for patients who received platinum-based chemotherapy alone (HR = 0.63; p = 0.005). The EFS difference among those with PD-L1 expression < 1% was 25.1 vs. 18.4 months (chemotherapy with immunotherapy vs. chemotherapy alone) and among patients with PD-L1 > 1% median EFS was not reached among patients who received chemotherapy with immunotherapy vs. 21.1 months for patients who received chemotherapy alone. Pathologic response rates were higher at 24% with neoadjuvant chemoimmunotherapy and was noted across all subgroups stratified by histology, PDL-1 and TMB status, compared to chemotherapy alone. While this is yet to be published, an interim analysis report updated a 2-year median OS rate of 83% for patients treated with nivolumab plus chemotherapy, compared with 71% for patients treated with chemotherapy alone (asco post) with an absolute benefit of 12%. Based on the study results, neoadjuvant nivolumab 360 mg dose with platinum-doublet chemotherapy every 3 weeks for up to 3 cycles is incorporated into NCCN treatment recommendation guidelines for treatment of resectable NSCLC with a tumor size greater than or equal to 4 cm or with positive lymph nodes (Table 2).

Table 2. SBRT and immunotherapy: Ongoing trials in early stage lung cancer.

Clinical Trial	Phase	Target	Study Group	Control Group	Stage	Primary Outcome
S1914/NRG	III	480	Atezolizumab + SBRT	SBRT	I-IIA and limited T3	OS
NRG-LU004 (ARCHON-1)	I	24	Accelerated/Conventional RT + Durvalumab	none	II-III	Safety
NCT03833154 (PACIFIC-4)	III	733	Durvalumab + SBRT	SBRT/Placebo	II-III	PFS
NCT03924869	III	530	Pembrolizumab + SBRT	SBRT/Placebo	I-II	EFS/OS
NCT03383302	I/II	31	Nivolumab + SBRT	SBRT/Placebo	I-II	Safety
NCT03217071	I-II	12	Pembrolizumab + SBRT (single dose)-surgery	Pembrolizumab-surgery	I-IIIA	change in tumor infiltrating CD3 + T cells
NCT03237377	II	9	Durvalumab + tremelimumab/RT	Durvalumab/RT	IIIA	Safety

The phase 3 AEGEAN trial is evaluating the benefit of combining durvalumab with chemotherapy in the neoadjuvant setting among 800 patients with resectable stage IIA to select IIIB NSCLC; The primary end points are pathologic complete response and EFS [40]. Patients receive durvalumab or placebo every 3 weeks with platinum-based chemotherapy for 4 cycles then go for surgery, followed by either durvalumab or placebo alone for an additional 12 cycles post-surgery. A combination of neoadjuvant nivolumab and ipilimumab has been studied in the NEOSTAR study that enrolled 40 patients with resectable lung cancer [41] [42]. Major pathologic responses were noted in 24% in nivolumab arm vs. 50% in the nivolumab plus ipilumab arm among 37 patients who underwent surgical resection. Nivolumab plus ipilimumab was associated with in higher pathologic complete response rates (10% vs. 38%).

Shu *et al.* evaluated the role of neoadjuvant nab-paclitaxel and carboplatin with atezolizumab in phase II study with patients with mostly 77% stage IIIA disease [36]. Successful surgical resection was achieved in 87% (R0 resection) of patients. From this small study it was concluded that atezolizumab plus carboplatin and nab-paclitaxel results in high major pathological response rates and could be a potential neoadjuvant regimen for resectable non-small-cell lung cancer. Table 3 lists the summary of a few of the neoadjuvant completed and ongoing trials in early stage NSCLC.

Immunotherapy in unresectable stage III NSCLC

The role of immunotherapy after definitive chemotherapy and radiation therapy was demonstrated in the PACIFIC trial among patients with locally advanced unresectable stage III NSCLC [17]. In this study of 713 patients randomized to durvalumab after chemoradiotherapy or placebo every 2 weeks for

Table 3. Neoadjuvant immunotherapy: Ongoing and completed trials in early stage lung cancer.

Trial	Registry Number	Phase	Stage	Treatment	Primary Endpoint	Trial Status
Checkmate 816	NCT02998528	III	IB-IIIA	Chemotherapy + Nivolumab vs. Chemotherapy	pCR and EFS improvement with nivolumab	Completed
KEYNOTE-617	NCT03425643	III	IIB-IIIA	Chemotherapy + pembrolizumab	EFS and OS	Active, not recruiting
IMpower 030	NCT03456063	III	II-IIIB	Chemotherapy + atezolizumab	EFS	Active, not recriting
NEOSTAR	NCT03158129	II	I–IIIA	Nivolumab or Nivolumab + Ipilimumab	MPR	Active, recriting
	NCT04326153	II	IIIA	Sintilimab + chemotherapy vs. chemotherapy	DFS	Active, recruiting
	NCT04989283	II	IIB-IIIA (superior sulcus tumors)	Atezolizumab + chemoradiation vs. chemoradiation	pCR	Active recruiting

12 months, progression free survival was significantly prolonged with durvalumab 16.8 months vs. 5.6 months with placebo (HR 0.52; $p < 0.001$). The 24-month overall survival rate was 66.3% (95% CI 61.7 to 70.4) in the durvalumab group, vs. 55.6% (95% CI, 48.9 to 61.8) in the placebo group (two-sided $p = 0.005$). Based on this study, regardless of the PDL-1 status, durvalumab was approved for use after definitive chemoradiotherapy for stage III unresectable lung cancer. Approximately a third of patients were alive and free of disease at 5 years and updated results as of January, 2021 showed a median OS of 47.5 months vs. 29.1 months (HR 0.72, 95% CI 0.59 - 0.89) and PFS of 16.9 months vs. 5.6 months (HR 0.55, 95% CI 0.45 - 0.68) in durvalumab and placebo groups respectively. Durvalumab has a category 1 by NCCN for patients with stage III NSCLC who have completed definitive chemoradiation and category 2A for stage II disease [26]. Immune mediated side effects are the limitations for use of immunotherapy in general. In the PACIFIC study, adverse events of any cause and grade was documented in 96.8% of the patients in the durvalumab group and 94.9% of the patients in the placebo group and discontinuation of durvalumab occurred in 15.4% of patients in the durvalumab group vs. 9.8% in the placebo group. Common adverse events that led to discontinuation of durvalumab and placebo were pneumonitis or radiation pneumonitis (in 6.3% and 4.3%, respectively) and pneumonia (in 1.1% and 1.3%). Immune-mediated adverse events of any grade were reported in 24.2% of patients in the durvalumab group and 8.1% of patients in the placebo group and common side effects included fatigue, lung inflammation (pneumonia/radiation pneumonitis), upper respiratory tract infection, dyspnea, cough, rash, diarrhea and arthralgia. In addition, it is potentially fatal side effects on the fetus, and patients are advised to avoid using the drug during pregnancy and breastfeeding.

Another phase III multicenter clinical trial (NCT05221840) compared the efficacy of durvalumab in combination with oleclumab (anti-CD73) or durvalumab with monalizumab (anti-NKG2A) against durvalumab alone in adults with locally advanced, stage III unresectable NSCLC, who have not progressed following platinum-based CRT [43]. In the earlier phase II COAST trial, after a median follow-up of 11.5 months, durvalumab combination with oleclumab reduced the risk of disease progression or death by 56% (hazard ratio [HR] of 0.44; 95% confidence interval [CI] 0.26 - 0.75), and monalizumab, durvalumab combination by 35% (HR of 0.65; 95% CI 0.49 - 0.85), when compared with durvalumab after definitive chemoradiation therapy in stage IIIB NSCLC. The results recently presented at the ESMO Congress also showed a 10-month PFS rate of 64.8% for the durvalumab plus oleclumab combination and 72.7% for durvalumab plus monalizumab, versus 39.2% with durvalumab alone, proving improved efficacy when immunotherapy is combined with specific targeted agents. The benefit was observed in both combinations across all subgroups stratified by histology, performance status, prior chemotherapy regimen.

The benefit of durvalumab when added concurrently with chemo-radiation therapy among patients with unresectable stage III NSCLC is being explored in

EA5181 study [44]. NRG LU004, is randomizing patients with unresectable locally advanced lung cancer patients who have high PD-L1 expression (≥50%) to either accelerated hypofractionated or conventionally fractionated radiation with durvalumab alone [45]. The results of these studies will help us understand the optimal administration schedule for immunotherapy with chemo-radiation to achieve maximum efficacy and tolerability.

Immunotherapy Combination with Stereotactic body radiotherapy (SBRT) in Early Sage and Locally Advanced NSCLC

Radiation therapy can modulate cytokines, tumor phenotypes and enhances antigen presentation thereby promoting tumor immunogenicity [45]. PD-1/PD-L1 inhibitors could activate resting T cells and enhance action of SBRT. Consistent with this hypothesis, in a small study by Luke *et al.*, SBRT followed by pembrolizumab patients with metastatic solid tumors [46] achieved high responses and disease control. In phase II randomized trial of SBRT followed by systemic immunotherapy with pembrolizumab, antitumor immune responses were significant among patients with metastatic NSCLC [47]. The results showed that patients treated with SBRT combined with pembrolizumab had improved median PFS (6.6 months vs. 1.9 months, $p = 0.19$) and overall survival rates (15.9 months vs. 7.6 months, $p = 0.16$). Campbell *et al.* reported in metastatic NSCLC that the addition of SBRT after progression on the PD-1 inhibitor led to increased responses and PFS associated with T cell activation status [48].

Additional studies showed that the combination of SBRT with immunotherapy treatment was safe [48] [49] [50] and since then multiple studies have recruited patients and are evaluating the efficacy of immune checkpoint inhibitors with radiation therapy for early stage NSCLC [51] [52] [53] (**Table 2**). Chang *et al.* postulated that combined immunotherapy and SBRT might reduce these recurrences by stimulating stronger cancer specific immune responses [54]. In an ongoing phase II study of 92 patients with early stage, T1 - T3 lung cancers were treated with SBRT (47) or SBRT with nivolumab every 4 weeks for 4 doses [55]. The efficacy of durvalumab, compared with placebo, given concurrently with definitive SBRT to patients who have refused surgery or with medically inoperable stage I/II, lymph node-negative NSCLC, is being evaluated in phase 3 PACIFIC-4 trial [56].

4. Conclusion

Cancer immunotherapy has induced long-term responses and improved survival in a proportion of patients with locally advanced and metastatic lung cancer. PD-1 and PDL-1 pathway inhibitors have expanded their role in the treatment of patients with early-stage lung cancer where they are likely to have improved efficacy due to the priming of intact host immune cells against tumor cells [33] [34]. Nevertheless, responses to immunotherapy in early stage lung cancer appear to be limited. Optimal dosing and combination schedule needs to be determined with reliable predictive biomarkers to identify subgroups that would

benefit from immunotherapy. Smaller trials have shown that tumor mutational burden and expansion of T cell clones specific for associated antigens in blood after neoadjuvant therapy correlates with a major pathological response [32] [34]. Larger randomized studies incorporating minimal residual disease, circulating tumor DNA measurement and biomarker assessment are needed to personalize the immunotherapy approach in early stage lung cancer.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Siegel, R.L., Miller, K.D., Fuchs, H.E., *et al.* (2021) Cancer Statistics, 2021. *CA*: *A Cancer Journal for Clinicians*, **71**, 7-33. https://doi.org/10.3322/caac.21654

[2] Herbst, R.S., Heymach, J.V. and Lippman, S.M. (2008) Lung Cancer. *New England Journal of Medicine*, **359**, 1367-1380. https://doi.org/10.1056/NEJMra0802714

[3] Simeone, J.C., Nordstrom, B.L., Patel, K., *et al.* (2019) Treatment Patterns and Overall Survival in Metastatic Non-Small-Cell Lung Cancer in a Real-World, US setting. *Future Oncology*, **15**, 3491-3502. https://doi.org/10.2217/fon-2019-0348

[4] SEER [Surveillance, Epidemiology, and End Results] (2015) Cancer Statistics Factsheets: Lung and Bronchus Cancer. http://seer.cancer.gov/statfacts/html/lungb.html

[5] Goldstraw, P., Crowley, J., Chansky, K., *et al.* (2007) The IASLC Lung Cancer Staging Project: Proposals for the Revision of the TNM Stage Groupings in the Forthcoming (Seventh) Edition of the TNM Classification of Malignant Tumours. *Journal of Thoracic Oncology*, **2**, 706-714. https://doi.org/10.1097/JTO.0b013e31812f3c1a

[6] Pignon, J.P., Tribodet, H., Scagliotti, G.V., *et al.* (2008) Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group. *Journal of Clinical Oncology*, **26**, 3552-3559. https://doi.org/10.1200/JCO.2007.13.9030

[7] Thomas, M., Rübe, C., Hoffknecht, P., *et al.* (2008) German Lung Cancer Cooperative Group. Effect of Preoperative Chemoradiation in Addition to Preoperative Chemotherapy: A Randomized Trial in Stage III Non-Small-Cell Lung Cancer. *The Lancet Oncology*, **9**, 636-648. https://doi.org/10.1016/S1470-2045(08)70156-6

[8] Brahmer, J.R., Tykodi, S.S., Chow, L.Q., *et al.* (2012) Safety and Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer. *New England Journal of Medicine*, **366**, 2455-2465. https://doi.org/10.1056/NEJMoa1200694

[9] Motzer, R.J., Tannir, N.M., McDermott, D.F., *et al.* (2018) Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *New England Journal of Medicine*, **378**, 1277-1290. https://doi.org/10.1056/NEJMoa1712126

[10] Robert, C., Long, G.V., Brady, B., *et al.* (2015) Nivolumab in Previously Untreated Melanoma without BRAF Mutation. *New England Journal of Medicine*, **372**, 320-330. https://doi.org/10.1056/NEJMoa1412082

[11] Larkin, J., Chiarion-Sileni, V., Gonzalez, R., *et al.* (2019) Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *New England Journal of Medicine*, **381**, 1535-1546. https://doi.org/10.1056/NEJMoa1910836

[12] Reck, M., Remon, J. and Hellmann, M.D. (2022) First-Line Immunotherapy for Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, **40**, 586-597.

https://doi.org/10.1200/JCO.21.01497

[13] Reck, M., Rodriguez-Abreu, D., Robinson, A.G., *et al.* (2016) Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, **375**, 1823-1833. https://doi.org/10.1056/NEJMoa1606774

[14] Hellmann, M.D., Paz-Ares, L., Bernabe Caro, R., *et al.* (2019) Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. New England Journal of Medicine, **381**, 2020-2031. https://doi.org/10.1056/NEJMoa1910231

[15] Gandhi, L., Rodriguez-Abreu, D., Gadgeel, S., *et al.* (2018) Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, **378**, 2078-2092. https://doi.org/10.1056/NEJMoa1801005

[16] Herbst, R.S., Baas, P., Kim, D.W., *et al.* (2016) Pembrolizumab versus Docetaxel for Previously Treated, PD-L1-Positive, Advanced Non-Small-Cell Lung Cancer (KEYNOTE-010): A Randomized Controlled Trial. *Lancet*, **387**, 1540-1550. https://doi.org/10.1016/S0140-6736(15)01281-7

[17] Antonia, S.J., Villegas, A., Daniel, D., *et al.* (2018) PACIFIC Investigators. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *New England Journal of Medicine*, **379**, 2342-2350. https://doi.org/10.1056/NEJMoa1809697

[18] Spigel, D.R., Faivre-Finn, C., Gray, J.E., *et al.* (2022) Five-Year Survival Outcomes from the PACIFIC Trial: Durvalumab after Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer. *Journal of Clinical Oncology*, **40**, 1301-1311. https://doi.org/10.1200/JCO.21.01308

[19] Steuer, C.E. and Ramalingam, S.S. (2021) Advances in Immunotherapy and Implications for Current Practice in Non–Small-Cell Lung Cancer. *JCO Oncology Practice*, **17**, 662-668. https://doi.org/10.1200/OP.21.00305

[20] Zhu, J., Li, R., Tiselius, E., *et al.* (2017) Immunotherapy (Excluding Checkpoint Inhibitors) for Stage I to III Non-Small Cell Lung Cancer Treated with Surgery or Radiotherapy with Curative Intent. *Cochrane Database of Systematic Reviews*, No. 12, Article No. CD011300. https://doi.org/10.1002/14651858.CD011300.pub2

[21] Chaft, J.E., Rimner, A., Weder, W., *et al.* (2021) Evolution of Systemic Therapy for Stages I-III Non-Metastatic Non-Small-Cell Lung Cancer. *Nature Reviews Clinical Oncology*, **18**, 547-557. https://doi.org/10.1038/s41571-021-00501-4

[22] Paz-Ares, L., O'Brien, M.E.R., Mauer, M., *et al.* (2022) VP3-2022: Pembrolizumab (Pembro) versus Placebo for Early-Stage Non-Small Cell Lung Cancer (NSCLC) Following Complete Resection and Adjuvant Chemotherapy (Chemo) When Indicated: Randomized, Triple-Blind, Phase III EORTC-1416-LCG/ETOP 8-15—PEARLS/KEYNOTE-091 Study. *Annals of Oncology*, **33**, 451-453. https://doi.org/10.1016/j.annonc.2022.02.224

[23] Felip, E., Altorki, N., Zhou, C., *et al.* (2021) Adjuvant Atezolizumab after Adjuvant Chemotherapy in Resected Stage IB-IIIA Non-Small-Cell Lung Cancer (IMpower010): A Randomised, Multicentre, Open-Label, Phase 3 Trial. *Lancet*, **398**, 1344-1357. https://doi.org/10.1016/S0140-6736(21)02098-5

[24] O'Brien, M.E.R., Paz-Ares, L., Jha, N., *et al.* (2022) EORTC-1416-LCG/ETOP 8-15—PEARLS/KEYNOTE-091 Study of Pembrolizumab versus Placebo for Completely Resected Early-Stage Non-Small Cell Lung Cancer (NSCLC): Outcomes in Subgroups Related to Surgery, Disease Burden, and Adjuvant Chemotherapy Use. *Journal of Clinical Oncology*, **40**, 8512. https://doi.org/10.1200/JCO.2022.40.16_suppl.8512

[25] Wakelee, H.A., Altorki, N.K., Zhou, C., *et al.* (2021) IMpower010: Primary Results of a Phase III Global Study of Atezolizumab versus Best Supportive Care after Ad-

juvant Chemotherapy in Resected Stage IB-IIIA Non-Small Cell Lung Cancer (NSCLC). *Journal of Clinical Oncology*, **39**, 8500. https://doi.org/10.1200/JCO.2021.39.15_suppl.8500

[26] Ettinger, D.S., Wood, D.E., Aisner, D.L., Akerley, W., Bauman, J.R., Bharat, A., *et al.* (2022) Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*, **20**, 497-530. https://www.nccn.org

[27] NCT02273375. Double Blind Placebo Controlled Study of Adjuvant MEDI14736 in Completely Resected NSCLC. https://www.clinicaltrials.gov

[28] NCT04385368. Phase III Study to Determine the Efficacy of Durvalumab in Combination with Chemotherapy in Completely Resected Stage II-III Non-Small Cell Lung Cancer (NSCLC) (MERMAID-1). https://www.clinicaltrials.gov

[29] Peters, S, Spigel, D., Ahn, M., Tsuboi, M., Chaft, J., Harpole, D., Goss, G., Arlesi, F.B., Abbosh, C., Polle, L., May, R., Dennis, P.A. and Swanton, C. (2021) P03.03 MERMAID-1: A Phase III Study of Adjuvant Durvalumab plus Chemotherapy in Resected NSCLC Patients with MRD+ Post-Surgery. *Journal of Thoracic Oncology*, **16**, S258-S259. https://doi.org/10.1016/j.jtho.2021.01.376

[30] NCT04642469. Phase III Study to Determine Efficacy of Durvalumab in Stage II-III Non-Small Cell Lung Cancer (NSCLC) after Curative Intent Therapy. (MERMAID-2). https://www.clinicaltrials.gov

[31] Felip, E., Rosell, R., Maestre, J.A., *et al.* (2012) Preoperative Chemotherapy plus Surgery versus Surgery plus Adjuvant Chemotherapy versus Surgery Alone in Early-Stage Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, **28**, 3138-3145. https://doi.org/10.1200/JCO.2009.27.6204

[32] Liu, J., Blake, S.J., Yong, M.C., Harjunpää, H., Ngiow, S.F., Takeda, K., Young, A., O'Donnell, J.S., Allen, S., Smyth, M.J. and Teng, M.W. (2016) Improved Efficacy of Neoadjuvant Compared to Adjuvant Immunotherapy to Eradicate Metastatic Disease. *Cancer Discovery*, **6**, 1382-1399. https://doi.org/10.1158/2159-8290.CD-16-0577

[33] Shu, C.A. and Cascone, T. (2021) What Is Neo? Chemoimmunotherapy in the Neoadjuvant Setting for Resectable Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, **39**, 2855-2858. https://doi.org/10.1200/JCO.21.01446

[34] Forde, P.M., Chaft, J.E., Smith, K.N., *et al.* (2018) Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. *New England Journal of Medicine*, **378**, 1976-1986. https://doi.org/10.1056/NEJMoa1716078

[35] Eichhorn, F., Klotz, L.V., Bischoff, H., *et al.* (2019) Neoadjuvant Anti-Programmed Death-1 Immunotherapy by Pembrolizumab in Resectable Nodal Positive Stage II/IIIa Non-Small-Cell Lung Cancer (NSCLC): The NEOMUN Trial. *BMC Cancer*, **19**, Article No. 413. https://doi.org/10.1186/s12885-019-5624-2

[36] Shu, C.A., Gainor, J.F., Awad, M.M., *et al.* (2020) Neoadjuvant Atezolizumab and Chemotherapy in Patients with Resectable Non-Small-Cell Lung Cancer: An Open-Label, Multicentre, Single-Arm, Phase II Trial. *The Lancet Oncology*, **21**, 786-795. https://doi.org/10.1016/S1470-2045(20)30140-6

[37] Gao, S., Li, N., Gao, S., *et al.* (2020) Neoadjuvant PD-1 Inhibitor (Sintilimab) in NSCLC. *Journal of Thoracic Oncology*, **15**, 816-826. https://doi.org/10.1016/j.jtho.2020.01.017

[38] Rothschild, S.I., Zippelius, A., Eboulet, E.I., *et al.* (2021) SAKK 16/14: Durvalumab in Addition to Neoadjuvant Chemotherapy in Patients with Stage IIIA (N2) Non-Small-Cell Lung Cancer—A Multicenter Single-Arm Phase II Trial. *Journal of*

Clinical Oncology, **39**, 2872-2880. https://doi.org/10.1200/JCO.21.00276

[39] Spicer, J.W.C. and Tanaka, F. (2021) Surgical Outcomes from the Phase 3 Check-Mate 816 Trial: Nivolumab (NIVO) + Platinum-Doublet Chemotherapy (Chemo) vs. Chemo alone as Neoadjuvant Treatment for Patients with Resectable Non-Small Cell Lung Cancer (NSCLC). *Journal of Clinical Oncology*, **39**, 8503. https://doi.org/10.1200/JCO.2021.39.15_suppl.8503

[40] Heymach, J.V., Taube, J.M., Mitusdomi, T., *et al.* (2019) P1.18-02 The AEGEAN Phase 3 Trial of Neoadjuvant/Adjuvant Durvalumab in Patients with Resectable Stage II/III NSCLC. *Journal of Thoracic Oncology*, **14**, S625-S626. https://doi.org/10.1016/j.jtho.2019.08.1318

[41] Sepesi, B., Cascone, T., William, W., *et al.* (2019) OA13.06 Surgical Outcomes Following Neoadjuvant Nivolumab or Nivolumab plus Ipilimumab in Non-Small Cell Lung Cancer—NEOSTAR Study. *Journal of Thoracic Oncology*, **14**, S241-S242. https://doi.org/10.1016/j.jtho.2019.08.481

[42] Cascone, T., William Jr., W.N., Weissferdt, A., *et al.* (2021) Neoadjuvant Nivolumab or Nivolumab plus Ipilimumab in Operable Non-Small Cell Lung Cancer: The Phase 2 Randomized NEOSTAR Trial. *Nature Medicine*, **27**, 504-514. https://doi.org/10.1038/s41591-020-01224-2

[43] Herbst, R.S., Majem, M., Barlesi, F., *et al.* (2022) COAST: An Open-Label, Phase, I.I., Multidrug Platform Study of Durvalumab Alone or in Combination with Oleclumab or Monalizumab in Patients with Unresectable, Stage III Non–Small-Cell Lung Cancer. *Journal of Clinical Oncology*, Article ID: JCO2200227. Epub Ahead of Print. https://doi.org/10.1200/JCO.22.00227

[44] NCT04092283. Testing the Addition of an Antibody to Standard Chemoradiation Followed by the Antibody for One Year to Standard Chemoradiation Followed by One Year of the Antibody in Patients with Unresectable Stage III NSCLC. http://www.clinicaltrials.gov

[45] NCT03801902. Accelerated Hypofractionated or Conventionally Fractionated Radiotherapy and Durvalumab in Treating Patients with Stage II-III Non-Small Cell Lung Cancer. http://www.clinicaltrials.gov

[46] Bernstein, M.B., Krishnan, S., Hodge, J.W., *et al.* (2016) Immunotherapy and Stereotactic Ablative Radiotherapy (ISABR): A Curative Approach? *Nature Reviews Clinical Oncology*, **13**, 516-524. https://doi.org/10.1038/nrclinonc.2016.30

[47] Luke, J.J., Lemons, J.M., Karrison, T.G., *et al.* (2018) Safety and Clinical Activity of Pembrolizumab and Multisite Stereotactic Body Radiotherapy in Patients with Advanced Solid Tumors. *Journal of Clinical Oncology*, **36**, 1611-1618. https://doi.org/10.1200/JCO.2017.76.2229

[48] Theelen, W.S.M.E., Peulen, H.M.U., Lalezari, F., *et al.* (2019) Effect of Pembrolizumab after Stereotactic Body Radiotherapy vs. Pembrolizumab alone on Tumor Response in Patients with Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. *JAMA Oncology*, **5**, 1276-1282. https://doi.org/10.1001/jamaoncol.2019.1478

[49] Campbell, A.M, Cai, W.L, Burkhardt, D., *et al.* (2019) Final Results of a Phase II Prospective Trial Evaluating the Combination of Stereotactic Body Radiotherapy (SBRT) with Concurrent Pembrolizumab in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC). *International Journal of Radiation Oncology, Biology, Physics*, **105**, S36-S37. https://doi.org/10.1016/j.ijrobp.2019.06.453

[50] Altorki, N.K., McGraw, T.E., Borczuk, A.C., *et al.* (2021) Neoadjuvant Durvalumab with or without Stereotactic Body Radiotherapy in Patients with Early-Stage Non-Small-Cell

Lung Cancer: A Single-Centre, Randomised Phase 2 Trial. *The Lancet Oncology*, **22**, 824-835. https://doi.org/10.1016/S1470-2045(21)00149-2

[51] NCT03217071. Pembrolizumab with and without Radiotherapy for Non-Small Cell Lung Cancer. http://www.clinicaltrials.gov

[52] NCT03446911. Combining SBRT and Immunotherapy in Early Stage NSCLC Patients Planned for Planned for Surgery. http://www.clinicaltrials.gov

[53] NCT03833154. Durvalumab vs Placebo with Stereotactic Body Radiation Therapy in Early Stage Unresected Non-small Cell Lung Cancer (NSCLC) Patients/Osimertinib Following SBRT in Patients With Early Stage Unresected NSCLC Harboring an EGFR Mutation. http://www.clinicaltrials.gov

[54] Chang, J.Y., Lin, S.H., Yao, L., *et al.* (2020) I-SABR Phase II Randomized Study of Nivolumab Immunotherapy and Stereotactic Ablative Radiotherapy in Early Stage NSCLC: Interim Analysis Adverse Effects. *Journal of Clinical Oncology*, **38**, 9035. https://doi.org/10.1200/JCO.2020.38.15_suppl.9035

[55] NCT03383302. SBRT with Immunotherapy in Early Stage Non-Small Cell Lung Cancer: Tolerability and Lung Effects. http://www.clinicaltrials.gov

[56] Melillo, G., Chand, V., Yovine, A., *et al.* (2021) Curative-Intent Treatment with Durvalumab in Early-Stage Cancers. *Advances in Therapy*, **38**, 2759-2778. https://doi.org/10.1007/s12325-021-01675-0