Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2025, Volume 5, Issue 1, Page No: 59-67

Available online at: www.galaxypub.co/page/journals

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Nivolumab plus Ipilimumab in Relapsed Locally Advanced NSCLC Post-Durvalumab Consolidation: A Retrospective Efficacy and Safety Analysis

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Received: 12 October 2024; **Revised:** 28 January 2025; **Accepted:** 29 January 2025

ABSTRACT

The combination of nivolumab and ipilimumab has shown encouraging outcomes in treating metastatic non-small-cell lung cancer (NSCLC). However, its effectiveness in NSCLC patients who relapse after durvalumab consolidation following concurrent chemoradiotherapy (CCRT) remains unclear. This retrospective study analyzed clinical records of NSCLC patients treated with nivolumab plus ipilimumab between January 2021 and June 2022 after prior CCRT and durvalumab. A cohort of 30 individuals was included. Patients received a median of 11 durvalumab cycles. The median progression-free survival (PFS) and overall survival (OS) with the combination therapy were 4.2 months (95% CI: 0.7–7.7) and 18.5 months (95% CI: 3.5–33.5), respectively. PFS at 6 and 12 months was 46.7% (95% CI: 28.8–64.5) and 36.4% (95% CI: 19.0–53.7). Multivariate analysis revealed that receiving durvalumab for at least 6 months was significantly associated with improved PFS ($p = 0.04$) and OS ($p = 0.001$). Grade 3 toxicities, including pneumonitis, skin inflammation, and colitis, occurred in 10% of the cases. These findings suggest the nivolumab–ipilimumab regimen may be a viable and tolerable option, particularly for patients who completed at least 6 months of durvalumab prior to relapse.

Keywords: Nivolumab, Ipilimumab, Durvalumab, Concurrent chemoradiotherapy, NSCLC

How to Cite This Article: Flores M, Quispe L, Torres E. Nivolumab plus Ipilimumab in Relapsed Locally Advanced NSCLC Post-Durvalumab Consolidation: A Retrospective Efficacy and Safety Analysis. 2025;5(1):59-67. https://doi.org/10.51847/hSBHy4Z8cq

Introduction

Immune checkpoint inhibitors (ICIs) are now widely applied as standard-of-care treatments across several tumor types [1, 2]. In non-small-cell lung cancer (NSCLC), ICIs demonstrate therapeutic benefits as initial therapy, perioperative adjuvant or neoadjuvant treatment, or maintenance following concurrent chemoradiotherapy (CCRT) [3-8]. Durvalumab, a PD-L1-blocking agent used post-CCRT, has become a standard for unresectable locally advanced NSCLC (LA-NSCLC), offering a notable 5-year overall survival (OS) rate of 42.9% [9]. Still, nearly 66% of patients relapse and require alternative strategies.

ICIs targeting PD-(L)1 and CTLA-4 work via distinct but complementary mechanisms to amplify anti-tumor immunity [10]. PD-1 interaction with PD-L1 and PD-L2 suppresses T-cell activity and cytokine production [11], leading to what's termed "exhausted" T cells in chronic stimulation scenarios [12]. CTLA-4, a CD28 mimic, binds B7-1/2 with high affinity but fails to transmit co-stimulatory signals, thereby blocking CD28-dependent activation [13]. While various checkpoint molecules are under investigation, only PD-1/PD-L1 and CTLA-4 blockers have received approval for widespread clinical use.

Notably, nivolumab plus ipilimumab has delivered enhanced 5-year survival outcomes, even among patients with tumor PD-L1 levels under 1% [14]. Furthermore, this combination has shown benefit in metastatic melanoma cases that progressed on prior PD-(L)1 monotherapy [15]. In patients relapsing post-durvalumab consolidation, the impaired PD-L1 response suggests a potential advantage for dual checkpoint inhibition. Yet, the impact of nivolumab plus ipilimumab in this setting has not been determined.

Thus, this study evaluated the therapeutic value of nivolumab plus ipilimumab in patients with LA-NSCLC who experienced recurrence after treatment with CCRT followed by durvalumab.

Materials and Methods

Patients

This retrospective, multicenter study included individuals with locally advanced NSCLC who experienced progression following treatment with CCRT and subsequent durvalumab, and who were later managed using the nivolumab plus ipilimumab regimen. The patients were treated at four institutions in Japan between January 2021 and June 2022, regardless of whether chemotherapy was administered concurrently.

Eligibility criteria included: (i) confirmed pathologic diagnosis of NSCLC, and (ii) recurrence after definitive CCRT followed by durvalumab consolidation. Recurrence was identified on CT imaging, with or without biopsy confirmation. Local recurrence included progression of the primary lung lesion or involvement of a single ipsilateral mediastinal, hilar, or supraclavicular lymph node. Clinical staging adhered to the eighth edition of the TNM classification system [16]. Tumor PD-L1 expression levels were assessed using the tumor proportion score (TPS), based on the Pharm Dx 22C3 assay (Agilent, Santa Clara, CA, USA).

This study was approved by the Clinical Research Review Board of Saitama Medical University (approval number: 2022-018) and conducted in accordance with the Declaration of Helsinki. Due to the retrospective design, informed consent was waived.

Treatment and monitoring protocol

Following CCRT, durvalumab was given biweekly at 10 mg/kg for up to 12 months or until progression, toxicity, or at the physician's discretion. Nivolumab was infused at either 240 mg every 2 weeks or 360 mg every 3 weeks. Ipilimumab was administered at 1 mg/kg every 6 weeks intravenously, with discontinuation upon progression or unacceptable side effects. When chemotherapy was part of the regimen, patients received carboplatin (AUC 5) paired with either pemetrexed (500 mg/m² for non-squamous cases) or paclitaxel (200 mg/m² for squamous cases). Adverse events were graded using CTCAE v5.0. Imaging and clinical evaluations were conducted based on RECIST v1.1 guidelines [17]. Investigators documented anonymized data into secure electronic records. The primary objective focused on progression-free survival (PFS) and 6-month PFS from the start of nivolumab–ipilimumab therapy. Secondary measures included overall survival (OS), objective response rate (ORR), and safety, aligned with the PFS data cutoff.

Statistical methods

PFS and OS were calculated through Kaplan–Meier survival analysis. Cox models were applied for univariate and multivariate evaluations of patient subgroups. Significance was defined as $p < 0.05$. Data processing was conducted with Microsoft Excel 2019 and JMP 14.0.

Results and Discussion

Patient profile and treatment summary

A total of 30 participants were evaluated in this study. As of the cutoff on 31 December 2022, median follow-up was 10.3 months, ranging from 1.4 to 23.3 months. Key clinical data are listed in **Table 1**. The cohort's median age was 72 years (span: 50–80), and 29 individuals (96.7%) were male. Lung squamous cell carcinoma was seen in 15 cases (50%), adenocarcinoma in 14 (46.7%), and one patient (3.3%) had a tumor categorized as unspecified. Most patients (96.7%) had an ECOG performance status score of 0 or 1.

Tumor PD-L1 status by TPS showed <1% in 9 patients (30%), 1–49% in 14 (46.7%), and at least 50% in 5 (16.7%). Among the total, 25 patients were negative for EGFR, ALK, and ROS1 alterations, and 5 were not tested for driver mutations.

Patients received a median of 10.5 doses of durvalumab (range: 1–26), with treatment lasting a median of 5.8 months (range: 0.03–11.9). Disease recurrence occurred at a median of 6.8 months post-radiation (range: 1.7–30.7). The majority (26 patients) underwent nivolumab plus ipilimumab alone, reflecting the CheckMate 227 protocol; 4 received the combination alongside platinum-doublet chemotherapy as per CheckMate 9LA.

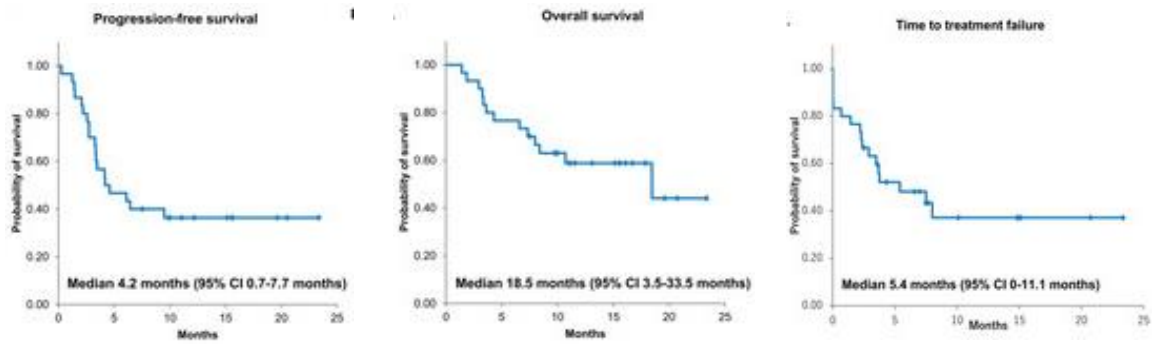
Table 1. Patient Profiles

Patient Characteristics	Total n = 30 (%) (Range)
Age Median (range) years	72 (50–80)
Sex Male/Female	29/1 (96.7/3.3)
Smoking History Former/Never	29/1 (96.7/3.3)
Histology Squamous/Adenocarcinoma/NOS	15/14/1 (50/46.7/3.3)
ECOG Performance Status 0/1/2	10/19/1 (33.3/63.3/3.3)
PD-L1 Expression <1% / 1–49% / ≥50% / Unknown	9/14/5/2 (30/46.7/16.7/6.7)
Pattern of Recurrence Local / Distant / Local + Distant	9/13/8 (30/43.3/26.7)
Sites of Distant Metastasis Brain / Bone / Lung / Liver / Others	9/5/2/2/6 (30/16.7/6.7/6.7/20)
Time from End of Radiotherapy to Recurrence Median (range) months	6.8 (1.7–30.7)
Number of Durvalumab Cycles Median (range)	10.5 (1–26)
Duration of Durvalumab Therapy Median (range) months	5.8 (0.03–11.9)
Subsequent Treatment Regimen	
Nivolumab + Ipilimumab alone	26 (86.7)
Nivolumab + Ipilimumab + Carboplatin + Paclitaxel	3 (10)
Nivolumab + Ipilimumab + Carboplatin + Pemetrexed	1 (3.3)

AD: adenocarcinoma; SQ: squamous carcinoma; NOS: not otherwise specified; ECOG-PS: Eastern Cooperative Oncology Group performance status; PD-L1: programmed death-ligand 1; dur: durvalumab; nivo: nivolumab; ipi: ipilimumab; CBDCA: carboplatin; PEM: pemetrexed; PTX: paclitaxel.

Clinical outcomes

Median PFS was 4.2 months (95% CI: 0.7–7.7), and median OS reached 18.5 months (95% CI: 3.5–33.5). Time to treatment failure (TTF) averaged 5.4 months (95% CI: 0–11.1) **(Figure 1)**. PFS at 6 months stood at 46.7% (95% CI: 28.8–64.5), and at 12 months was 36.4% (95% CI: 19.0–53.7). Seven patients showed partial responses, 14 had stable disease, and 9 progressed. ORR was 23.3% (95% CI: 12–41), while disease control rate was 70% (95% CI: 52–83) **(Table 2)**.



a) b) c)

Figure 1. Kaplan–Meier plots for PFS, OS, and TTF.

Table 2. Best tumor responses.

	Total n, 30	95% CI
PR	7	
SD	14	
PD	9	
ORR	23.3%	12–41
DCR	70%	52–83

Univariate analysis linked improved PFS to durvalumab cycle number (p = 0.005), duration ≥6 months (p = 0.005), and recurrence interval post-CCRT (p = 0.04). OS correlated with durvalumab cycles (p = 0.005),

treatment completion (p = 0.02), and treatment duration ≥6 months (p = 0.005). Multivariate modeling identified durvalumab duration ≥6 months as an independent predictor of PFS (HR 0.3 [CI: 0.1–1], p = 0.04) and OS (HR 0.1 [CI: 0.02–0.4], p = 0.0007).

Table 3. Univariate and multivariate analyses of factors predicting PFS and OS.

Progression-Free Survival (PFS)

Variable	Category	Median PFS (months)	HR	95% CI	p-value	HR (Adj)	95% CI (Adj)	p-value (Adj)
Age	<75 / ≥75	4.6 / 3.5	1.0	0.4–3.0	0.99	–	–	–
Gender	Male / Female	4.2 / 4.6	0.7	0.1–13.1	0.77	–	–	–
ECOG-PS	0 / 1	NR / 5.2	0.7	0.2–2.0	0.53	–	–	–
Histology	Sq / Non-Sq	6.1 / 4.1	1.0	0.4–2.6	0.99	–	–	–
PD-L1 (%)	<1 / ≥1	NR / 3.5	0.4	0.1–1.1	0.06	0.6	0.2–1.8	0.38
	<50 / ≥50	6.1 / 3.3	0.6	0.2–2.1	0.39	–	–	–
Brain metastasis	No / Yes	4.6 / 4.1	1.0	0.4–2.8	0.97	–	–	–
Low-dose CBDCA	No / Yes	6.1 / 3.5	0.8	0.3–2.5	0.67	–	–	–
Durvalumab start <14 days after RT	Yes / No	6.4 / 4.1	1.0	0.4–2.7	0.99	–	–	–
Durvalumab cycles	≥11 / <11	NR / 3.3	0.3	0.1–0.7	0.005	–	–	–
Durvalumab completed	Yes / No	NR / 3.5	0.5	0.2–1.2	0.12	–	–	–
Durvalumab duration (months)	≥6 / <6	NR / 3.3	0.3	0.1–0.7	0.005	0.3	0.1–1.0	0.04
Recurrence type	Local / Distant	NR / 4.1	0.5	0.1–1.4	0.20	1.0	0.3–3.4	0.97
Time to relapse from CCRT (months)	≥6 / <6	NR / 3.5	0.4	0.1–0.9	0.04	–	–	–

Overall Survival (OS)

Variable	Category	Median OS (months)	HR	95% CI	p-value	HR (Adj)	95% CI (Adj)	p-value (Adj)
Age	<75 / ≥75	18.5 / 8.4	0.6	0.2–2.5	0.40	0.6	0.2–2.5	–
Gender	Male / Female	18.5 / 8.0	0.4	0.1–6.9	0.41	0.4	0.1–6.9	–
ECOG-PS	0 / 1	18.5 / NR	1.7	0.5–5.2	0.40	1.7	0.5–5.2	0.24
Histology	Sq / Non-Sq	NR / 18.5	1.8	0.6–6.1	0.33	1.8	0.6–6.1	–
PD-L1 (%)	<1 / ≥1	NR / 18.5	0.5	0.1–1.7	0.28	0.5	0.1–1.7	–
	<50 / ≥50	18.5 / NR	2.8	0.5–50.4	0.26	2.8	0.5–50.4	0.08
Brain metastasis	No / Yes	18.5 / NR	0.9	0.2–2.7	0.82	0.9	0.2–2.7	–
Low-dose CBDCA	No / Yes	NR / 18.5	0.7	0.2–2.7	0.60	0.7	0.2–2.7	–
Durvalumab start <14 days after RT	Yes / No	18.5 / NR	1.5	0.5–5.5	0.50	1.5	0.5–5.5	–
Durvalumab cycles	≥11 / <11	NR / 7.3	0.2	0.04–0.6	0.005	0.2	0.04–0.6	–
Durvalumab completed	Yes / No	18.5 / 8.4	0.2	0.03–0.8	0.02	0.2	0.03–0.8	–
Durvalumab duration (months)	≥6 / <6	NR / 7.3	0.2	0.04–0.6	0.005	0.2	0.04–0.6	0.0007
Recurrence type	Local / Distant	18.5 / NR	0.6	0.1–1.8	0.35	0.6	0.1–1.8	–

Time to relapse from CCRT (months)	≥6 / <6	18.5 / 8.2	0.4	0.1–1.3	0.13	0.4	0.1–1.3

HR, hazard ratio; CI, confidence interval; NR, not reached; ECOG-PS, Eastern Cooperative Oncology Group performance status; Sq, squamous cell carcinoma; PD-L1, programmed death-ligand 1; CBDCA, carboplatin; dur, durvalumab; CCRT, concurrent chemoradiotherapy.

To explore outcomes further, patients were categorized into three groups based on the timing of disease progression following durvalumab: progression within 6 months, between 6 and 12 months, and beyond 12 months after treatment completion. Individuals who relapsed within 6 months had a median PFS of 3.5 months (95% CI: 1.5–6.4). In contrast, the median PFS was unreached for patients relapsing between 6–12 months (95% CI: 0.3–unreached, p = 0.10), as well as for those completing 12 months of durvalumab treatment (95% CI: 2.1–unreached, p = 0.09). Median OS for the <6-month relapse group was 8.2 months (95% CI: 3.3–unreached), while those relapsing between 6–12 months had a median OS of 10.7 months (95% CI: 3–unreached, p = 0.61). For patients who completed one year of durvalumab, the median OS was 18.5 months (95% CI: 3.6–unreached, p = 0.08).

Safety

Immune-related adverse events (irAEs) graded using standard terminology are summarized in **Table 4**. The most frequent irAEs included hepatic impairment (20%), dermatologic reactions (20%), thyroid dysfunction (16.7%), pneumonitis (10%), arthralgia (10%), and diarrhea (6.7%). Grade 3 events observed were pneumonitis (3.3%), cutaneous reactions (3.3%), and diarrhea (3.3%). No treatment-associated fatalities were noted, and no unexpected immune toxicities were reported.

Table 4. Immune-related adverse events from nivolumab combined with ipilimumab.

Variable	All Grades n (%)	≥ Grade 3 n (%)
Hyper- or hypothyroidism	5 (16.7)	0
Adrenal insufficiency	1 (3.3)	0
Pneumonitis	3 (10)	1 (3.3)
Liver dysfunction	6 (20)	0
Diarrhea	2 (6.7)	1 (3.3)
Skin disorder	6 (20)	1 (3.3)
Arthralgia	3 (10)	0
Stomatitis	1 (3.3)	0
Shingles	1 (3.3)	0
Eosinophilia	1 (3.3)	0
γ-GTP increased	1 (3.3)	0
ALP increased	1 (3.3)	0

irAE, immune-related adverse events; γ-GTP, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase.

A total of 26.7% (8/30) of patients experienced overlapping AEs, with 2 showing an exacerbation of severity during nivolumab plus ipilimumab **(Figure 2)**.

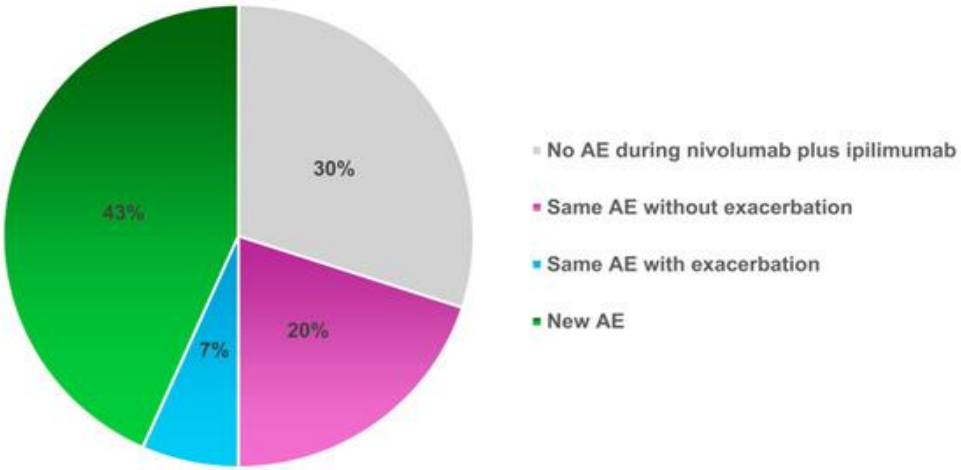


Figure 2. Adverse event comparison between durvalumab and nivolumab plus ipilimumab treatments. The proportion of patients receiving nivolumab plus ipilimumab was stratified by those with no prior AEs on durvalumab, those with matching AEs, and those with newly observed AEs. AE, adverse events.

This study identifies a moderate clinical benefit of combining nivolumab with ipilimumab in locally advanced NSCLC patients who experienced recurrence following initial CCRT and durvalumab. The design references prior findings indicating that disease progression within 24 weeks is a strong predictor of survival for NSCLC patients receiving immune checkpoint inhibitors [18]. In the CheckMate 227 study involving metastatic NSCLC, a 6-month PFS of 40–50% was reported [14]. Our findings demonstrate a 6-month PFS rate of 46.7%, supporting the utility of nivolumab plus ipilimumab even after prior CCRT–durvalumab exposure. Moreover, the 12-month PFS rate was 36.4%. Patients who remained on durvalumab for at least 6 months showed significantly superior PFS and OS outcomes. To date, this is the first report indicating survival advantages of this combination therapy in post-CCRT–durvalumab relapse.

Significant clinical interest remains in identifying optimal strategies for patients relapsing after CCRT and durvalumab. Alternatives include traditional cytotoxic regimens, platinum-based treatments, or combinations with PD-(L)1 inhibitors [19]. Previous studies by Imai *et al*. reported a 16.7% response and a median PFS of 4.2 months for platinum regimens in post-CRT settings without prior durvalumab [20]. Miyawaki *et al.* also evaluated platinum therapy in similar populations [21]. Despite prior durvalumab, our findings suggest nivolumab plus ipilimumab performs comparably or better than these studies. Meanwhile, Amino *et al.* documented a 45% response in patients using anti-PD-1 monotherapy after CRT in stage III NSCLC [22]. Nonetheless, current evidence implies that rechallenging with PD-(L)1 inhibitors may yield limited effects [23]. By contrast, concurrent targeting of PD-(L)1 and CTLA-4 may rejuvenate anti-tumor responses in patients previously treated with either inhibitor alone. In melanoma, adding CTLA-4 blockade after PD-1 therapy has shown improved PFS [15, 24]. Long-term analyses have consistently found nivolumab plus ipilimumab to outperform nivolumab monotherapy, both with and without chemotherapy, in multiple malignancies, including melanoma and lung cancer [14, 25, 26]. Potential contributors to the positive outcomes here include post-radiation immune activation [22], as well as potential selection bias favoring patients likely to benefit from combination therapy.

Relapse occurring post-durvalumab cessation seemed more responsive to immune combination therapy, suggesting tumor re-emergence linked to stopping treatment. However, this study was unable to determine whether dual or single-agent checkpoint inhibition is ideal for re-establishing tumor control in such patients. Furthermore, this cohort did not reveal substantial survival differences based on PD-L1 levels, recurrence sites, or relapse timing following durvalumab. Similar to prior literature, distant metastasis was the most common relapse pattern [27]. Local relapse could reflect partially active immune control against wider progression, yet this was not associated with improved outcomes in the present study.

Combination therapy with nivolumab and ipilimumab in patients previously treated with radiation did not show a marked increase in toxicity compared to that observed in the CheckMate 227 trial [7, 8]. Notably, eight participants in this study experienced adverse events similar to those seen during durvalumab therapy, while two exhibited a worsening in grade, specifically skin toxicity and grade 2 pneumonitis. Although severe irAEs such as grade 3–4 pneumonitis, dermatitis, and colitis were documented, the limited follow-up period may have

underestimated these events. It is well known that combined immunotherapy generally results in higher rates of grade 3–4 AEs compared to single-agent PD-1 inhibitors [28, 29]. Thus, careful monitoring is needed when prescribing nivolumab plus ipilimumab.

This study has several limitations worth emphasizing. Firstly, the retrospective nature and small sample size may have led to inaccuracies in reported outcomes. Larger studies are needed to validate whether factors like PD-L1 < 1% or local recurrence pattern can predict treatment response. Four patients receiving the CheckMate 9LA protocol were also included, and their outcomes—both PFS and OS—were comparable to those treated with the CheckMate 227 regimen (data not displayed). The CheckMate 9LA approach could be favored for patients with rapid progression or significant tumor burden and may represent a suitable option for relapse after CCRT–durvalumab. While this study suggests that nivolumab plus ipilimumab may benefit NSCLC patients with recurrence post-durvalumab consolidation, treatment decisions must align with established guidelines and regulatory approvals.

Secondly, the long-term benefits of ICIs were not assessed. However the PACIFIC trial showed enhanced survival with durvalumab; nearly 45% of patients experienced disease recurrence within a year of CCRT–durvalumab [9]. We believe that prompt data generation on the efficacy of nivolumab plus ipilimumab in such patients is critical. Even with limited observation, a survival plateau effect was noted, warranting early study dissemination.

Thirdly, this evaluation did not include additional tumor biomarkers beyond PD-L1, such as tumor mutational burden or microenvironment characteristics. These biomarkers could help determine whether dual checkpoint blockade or monotherapy is more suitable after durvalumab failure [30]. Also, improved predictive markers are needed to avoid overtreatment and unnecessary toxicity in potential non-responders. In this research, PD-L1 was assessed using 22C3 at diagnosis, while previous durvalumab trials employed SP263; however, results from both assays are known to correlate well [31]. Due to widespread usage, 22C3 remains the preferred assay for PD-L1 evaluation in clinical practice in Japan.

Conclusion

The combination of nivolumab and ipilimumab appears to be a viable and effective treatment approach for LA-NSCLC patients experiencing relapse following CCRT–durvalumab. This treatment may yield greater benefits in those who have received durvalumab for at least 6 months. Future prospective trials comparing this regimen to cytotoxic treatments, with or without PD-(L)1 blockade, are encouraged.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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