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Real-world experience of consolidation durvalumab after concurrent chemoradiotherapy in stage III non-small cell lung cancer

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Abstract

Background: Durvalumab consolidation is associated with improved survival following concurrent chemoradiotherapy (CCRT) in patients with stage III non-small cell lung cancer (NSCLC). Given the heterogeneity of stage III NSCLC patients, in this study we evaluated the efficacy and safety of durvalumab in the real-world setting.

Method: Unresectable stage III NSCLC patients were retrospectively studied: one cohort received CCRT, another had CCRT-durvalumab. Primary endpoints were progression-free survival (PFS) and overall survival (OS), secondary endpoints were relapse rate and safety. In CCRT-durvalumab cohort, association between blood markers with survival and pneumonitis risk were analyzed.

Results: A total of 84 patients were enrolled: 45 received CCRT, and 39 received CCRT-durvalumab.

Median PFS was 17.5 months for CCRT-durvalumab and 8.9 months for CCRT-alone (HR 0.47, $p = 0.038$). Median OS was not-reached for CCRT-durvalumab and 22.3 months for CCRT-alone (HR 0.35, $p = 0.024$). Both *EGFR*-positive and wild-type (WT) patients had numerically improved PFS with durvalumab consolidation compared to CCRT-alone, 17.5 versus 10.9 months and 11.8 versus 6.63 months, respectively (interaction p-value = 0.608). Grade 2+ pneumonitis was detected in 25% of patients in the durvalumab cohort. Most pneumonitis occurred at 3.5 weeks after durvalumab initiation. Baseline neutrophil-to-lymphocyte ratio (NLR) ≥ 3 and ≥5 were associated with shorter PFS with durvalumab. Week 6 platelet-lymphocyte-ratio ≥ 180 was associated with a lower risk of pneumonitis.

Conclusion: In this real-world study, durvalumab consolidation post CCRT was associated with a statistically significant improvement in PFS and OS. Effect of durvalumab on PFS was not modified by EGFR status. Active surveillance for pneumonitis is crucial. Baseline NLR may help to predict the benefit of treatment with durvalumab.

KEYWORDS
consolidation, Durvalumab, non-small cell lung cancer, real-world, stage III

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INTRODUCTION

Despite multiple earlier efforts,[1–4] very little progress has been made in the treatment of unresectable stage III non-small cell lung cancer (NSCLC) and prognosis remains poor with 5-year overall survival (OS) of 15%[5]. More recently, results from the PACIFIC study, a randomized phase III study, showed the addition of consolidation durvalumab following concurrent platinum based chemoradiotherapy was associated with an improvement in progression-free survival (PFS) (16.9 vs. 5.6 months, HR 0.55) and overall survival (OS) (5-year OS 42.9% vs. 33.4%, HR 0.72) compared to placebo at 5 years.[6,7] Based on results from the PACIFIC study, durvalumab is now approved for stage III NSCLC in many countries including Singapore.

Given the heterogeneity of stage III NSCLC patients,[8,9] it is crucial to evaluate the efficacy and safety of durvalumab when used in the real-world setting. The benefit of consolidation durvalumab is uncertain in epidermal growth factor receptor (EGFR) mutation positive patients as they constituted only 6% in the PACIFIC study. Presently, real-world data is scarce on the efficacy of consolidation durvalumab in NSCLC with *EGFR* mutations.

Systemic inflammation plays a critical role in tumor development and it is associated with prognosis in solid tumors due to its effect on the immune response to the disease.[10,11] The neutrophil-to-lymphocyte ratio (NLR) is a marker for the general immune response to stress stimuli.[12,13] Recent studies have reported that elevated neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are associated with poorer outcomes in NSCLC patients treated with immune-checkpoint inhibitors (ICIs).[14–19] Low PLR at baseline has also been reported to be associated with the development of immune-related adverse events (IrAEs).[17]

On this background, we sought to determine the efficacy and safety of durvalumab consolidation in unresectable stage III NSCLC patients in a tertiary institution in Singapore. Outcomes of *EGFR* positive and wild-type patients were also evaluated. In addition, for patients who received durvalumab consolidation, the association between clinical outcomes (PFS, OS and the risk of pneumonitis) and NLR and PLR at baseline and at 6 weeks[20] after durvalumab initiation were analyzed.

METHOD

Study design

This was an institutional review board approved retrospective cohort study (DSRB 2021/00221).

Study population

We describe the outcomes of two cohorts of unresectable stage III NSCLC patients treated at the National University Cancer Institute Singapore: one cohort received definitive concurrent platinum-based chemoradiation (CCRT) alone between January 2013 to December 2017 before the availability of durvalumab; another cohort were treated with consolidation durvalumab at 10 mg/kg IV every 2 weeks for up to 12 months following CCRT between January 2018 to August 2020, following the approval of durvalumab in stage III NSCLC. Patients in the earlier cohort were staged according to the AJCC seventh edition of staging, while in the latter cohort, they were staged according to the eighth edition. All patients in the CCRT-durvalumab cohort received positron emission tomography-computed tomography (PET-CT) and magnetic resonance imaging (MRI) brain as part of pretreatment work-up. In the CCRT-alone cohort, more than half (57.7%, 26 out of 45 patients) underwent PET-CT and MRI brain as pretreatment work-up. The remaining 19 patients had CT thorax/abdomen, bone scan and contrasted brain imaging as routine staging. Patients who received sequential chemoradiotherapy and those who progressed within 42 days after CCRT were excluded.

Thoracic irradiation therapy

Radiation technique was similar between the two cohorts. Radiation therapy was delivered at 2 Gy per fraction daily, five fractions per week. The total prescribed dose ranged from 60 to 66 Gy. All patients underwent CT simulation-based planning. 4D-CT simulation was utilized based on physicians' discretion, typically for lower lobe tumors. Tumor volumes were delineated using PET-CT diagnostic imaging. The quantitative analyses of normal tissue effects in the clinic (QUANTEC) dose constraints were adopted for treatment planning. Radiation therapy was delivered via either intensity modulated radiation therapy or Arc therapy. Image-guided radiation therapy using cone beam CT was used for all cases.

Covariates

Clinical data were collected from the institutional electronic medical records. These data included age at diagnosis, gender, race, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histology, EGFR status and programmed death-ligand 1 (PD-L1) tumor proportion score (TPS). In the durvalumab cohort, full blood count at baseline and at 6 weeks after treatment initiation were used to calculate baseline neutrophil-to-lymphocyte ratio (NLR) (absolute neutrophil count/absolute lymphocyte count) and platelet-to-lymphocyte ratio (PLR) (platelet count/lymphocyte count).

Outcomes

The primary outcomes were progression-free survival (PFS) and overall survival (OS). Progression-free survival was

defined from the end of CCRT to the date of the first documented event of tumor progression or death. Overall survival was defined from the end of CCRT until death from any cause. In the CCRT-alone cohort, for patients who received consolidation chemotherapy post CCRT, PFS was defined from the end of consolidation chemotherapy until tumor progression or death, and OS defined from end of consolidation chemotherapy until death from any cause. The secondary outcomes were locoregional relapse rate at 1 year, distant relapse rate at 1 year, pattern of relapse, objective response rate to CCRT and adverse events. Locoregional relapse was defined from end of CCRT until progression of disease in the primary tumor and mediastinal, supraclavicular lymph nodes. Distant relapse was defined from the end of CCRT to development of disease in the contralateral lung, pleural, pericardium, brain, bones, or other organs. Objective response rate was assessed by independent radiological review according to RECIST 1.1. Adverse events were graded using the Common Terminology Criteria for Adverse Events version 4.0 and 5.0 for events before and after November 2017, respectively. In the definitive CCRT cohort, CT scan was done at the end of CCRT and 3–6 monthly thereafter in the next 5 years. Response was assessed 3 months after the end of CCRT. For the cohort that received consolidation durvalumab, CT scan was done at the end of CCRT, every 3-monthly during 1 year of consolidation durvalumab, and 3–6 monthly thereafter for the next 5 years. In this cohort, response was assessed at the end of CCRT, as patients were initiated on durvalumab consolidation within 42 days from the end of CCRT as per the PACIFIC trial.

Statistical analysis

Frequency with percentage and median with interquartile range were used to describe the baseline characteristics, patterns of relapse and adverse events of the two cohorts in this study. The differences in the proportions for baseline characteristics, patterns of relapse and adverse events between the two cohorts were analyzed using the Chi-square test or Mann–Whitney U test where appropriate. The Kaplan Meier curves was used to describe the time to event data. The log rank test was used to compare the time to event intervals between the two cohorts. The Cox proportional hazards regression model was used for the analysis of the progression-free and overall survival outcomes. The Fine and Gray proportional subhazards model was used for the analysis of the time to locoregional relapse and distant relapse outcomes with death as a competing risk. The logistic regression model was used for the analysis of pneumonitis (any grade) as a dichotomous outcome. Time to pneumonitis (any grade) was modeled within a Royston Parmar spline model, where changes in hazard rates were described by time-varying hazards.

NLR data were analyzed as a continuous variable dichotomized into prespecified cutoffs for ≥3 versus <3 and ≥5 versus <5.[17] PLR data were analyzed as a continuous variable or dichotomized into prespecified cutoffs for ≥180 versus <180.[17] A univariable logistic regression model was used to analyze the effect of NLR on the odds of pneumonitis while a univariable was used to analyze the effect of NLR on PFS.

For all analyses, two-sided p-values of less than 0.05 were considered statistically significant. All analyses were performed using R-4.0.0 (with packages "survival", "survRM2", "rstpm2", and "ggplot2").

RESULTS

Between January 2013 to August 2020, 84 patients were enrolled: 45 received CCRT alone and 39 received durvalumab consolidation following CCRT. The median age was 64.8 years. The majority were male (82.1%), Chinese (75.0%), and of Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 (95.3%). A total of 36% were current smokers, 44.0% had stage IIIA disease and about half (56%) had adenocarcinoma histology. About a fifth of patients (21.4%) harbored *EGFR* mutations. For those with known PD-L1 TPS, 65.5% had PD-L1 TPS of ≥1%. Baseline characteristics were generally well balanced between the two cohorts, except for higher proportion of stage IIIA disease in CCRT-alone cohort compared to the durvalumab cohort (Table 1). Cisplatin and etoposide was the most common chemotherapy regimen administered, and median number of chemotherapy cycles was 2 (Table 1). In the durvalumab cohort, the median time to starting durvalumab after CCRT was 38 days, and the median number of cycles of durvalumab was 13. The median duration of follow-up was 21.6 months for CCRT-alone cohort and 15.06 months for the durvalumab cohort, respectively.

The median PFS was 17.5 months (95% CI: 11.3 to NR) for the durvalumab cohort, and 8.9 months (95% CI: 5.8 to 16.3) for the CCRT-alone cohort (HR 0.47, 95% CI: 0.23–0.96, $p = 0.038$) (Figure 1). The median OS was not reached at time of analysis for the durvalumab cohort and 22.3 months (95% CI: 15.2-NR) for the CCRT-alone cohort (HR 0.35, 95% CI: 0.14–0.87, $p = 0.024$). The two-year overall survival rate was 75.2% versus 42.8%, respectively (Figure 2).

In the durvalumab cohort, 74.4% had a partial response after CCRT, and none had progressive disease. In the CCRT-alone cohort, the response rate was lower at 57.8%, and 4.4% of patients had disease progression. Distant relapse was the most common pattern of relapse in both cohorts (Table S1). Locoregional relapse rate at 1 year was 44.6% versus 16% (HR 0.40, $p = 0.020$), and distant relapse rate at 1 year was 46.9% versus 26.2% (HR 0.54, $p = 0.059$) in the CCRT-alone cohort and durvalumab cohort, respectively (Figures S1 and S2). Eight out of 39 (20.5%) patients in the durvalumab cohort had distant-only failure and amongst them, five patients (62.5%) had solitary sites of distant metastases. The central nervous system (CNS) was the most common site of distant relapse ($n = 2$), for which both

TABLE 1 Patient demographics

		Overall	CCRT-only	CCRT with durvalumab	*p*-value
N		84	45	39	
Age at diagnosis (median [IQR])		64.76 [58.52, 70.00]	65.50 [59.50, 71.54]	64.00 [58.00, 69.00]	0.326
Gender (%)	Female	15 (17.9)	7 (15.6)	8 (20.5)	0.554
	Male	69 (82.1)	38 (84.4)	31 (79.5)	
Race (%)	Chinese	63 (75.0)	32 (71.1)	31 (79.5)	0.412
	Malay	5 (6.0)	2 (4.4)	3 (7.7)	
	Indian	10 (11.9)	6 (13.3)	4 (10.3)	
	Others	6 (7.1)	5 (11.1)	1 (2.6)	
Smoking history (%)	Current smoker	30 (35.7)	18 (40.0)	12 (30.8)	0.574
	Ex-smoker	36 (42.9)	17 (37.8)	19 (48.7)	
	Never-smoker	18 (21.4)	10 (22.2)	8 (20.5)	
ECOG (%)	0	35 (41.7)	15 (33.3)	20 (51.3)	0.224
	1	45 (53.6)	28 (62.2)	17 (43.6)	
	2	4 (4.8)	2 (4.4)	2 (5.1)	
Clinical stage (%)	IIIA	37 (44.0)	24 (53.3)	13 (33.3)	**<0.001**
	IIIB	36 (42.9)	21 (46.7)	15 (38.5)	
	IIIC	11 (13.1)	0 (0.0)	11 (28.2)	
Histological subtype (%)	Adenocarcinoma	47 (56.0)	22 (48.9)	25 (64.1)	0.208
	Squamous cell carcinoma	25 (29.8)	14 (31.1)	11 (28.2)	
	Others	12 (14.3)	9 (20.0)	3 (7.7)	
EGFR mutation status (%)	Yes	18 (21.4)	13 (28.9)	5 (12.8)	0.181
	No	29 (34.5)	15 (33.3)	14 (35.9)	
	Unknown	37 (44.0)	17 (37.8)	20 (51.3)	
PDL-1 TPS (%)	<1	9 (10.7)	1 (2.2)	8 (20.5)	**<0.001**
	≥1	18 (21.4)	1 (2.2)	17 (43.6)	
	Unknown	57 (67.9)	43 (95.6)	14 (35.9)	
Chemotherapy regimen (%)	Cisplatin and etoposide	32 (38.1)	19 (42.2)	13 (33.3)	**0.006**
	Carboplatin and paclitaxel	22 (26.2)	16 (35.6)	6 (15.4)	
	Cisplatin and pemetrexed	21 (25.0)	5 (11.1)	16 (41.0)	
	Carboplatin and pemetrexed	2 (2.4)	0 (0.0)	2 (5.1)	
	Others	7 (8.3)	5 (11.1)	2 (5.1)	
Chemotherapy cycles (median [IQR])		2.00 [2.00, 3.75]	2.00 [2.00, 4.00]	2.00 [2.00, 3.00]	0.901

Abbreviations: CCRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

patients underwent surgical resection. Other sites included bone, adrenal and lymph node, for which one patient each developed recurrence in these sites and received high dose radiotherapy.

On subset analysis, both *EGFR* mutation positive and *EGFR* wild-type (WT) patients had longer PFS with durvalumab consolidation compared to CCRT alone, 17.5 versus 10.9 months (log-rank $p = 0.907$) and 11.8 versus 6.63 months (log-rank $p = 0.419$), respectively (Table S2). There was a statistically significant improvement in OS and locoregional relapse with consolidation durvalumab for patients with EGFR WT NSCLC but not for *EGFR*-mutated NSCLC (Table S2). However, subgroup analysis showed that there was no significant effect modification on PFS, OS, local relapse and distant relapse by *EGFR* mutation status (interaction *p*-value >0.05) (Table S2).

Safety

Adverse event of any cause and grade occurred in 88.9% of the CCRT alone cohort and 87.2% of the durvalumab cohort, grade 3 or more adverse events occurred in 20.0 and 12.8%, respectively (Table 2). Odynophagia, fatigue,

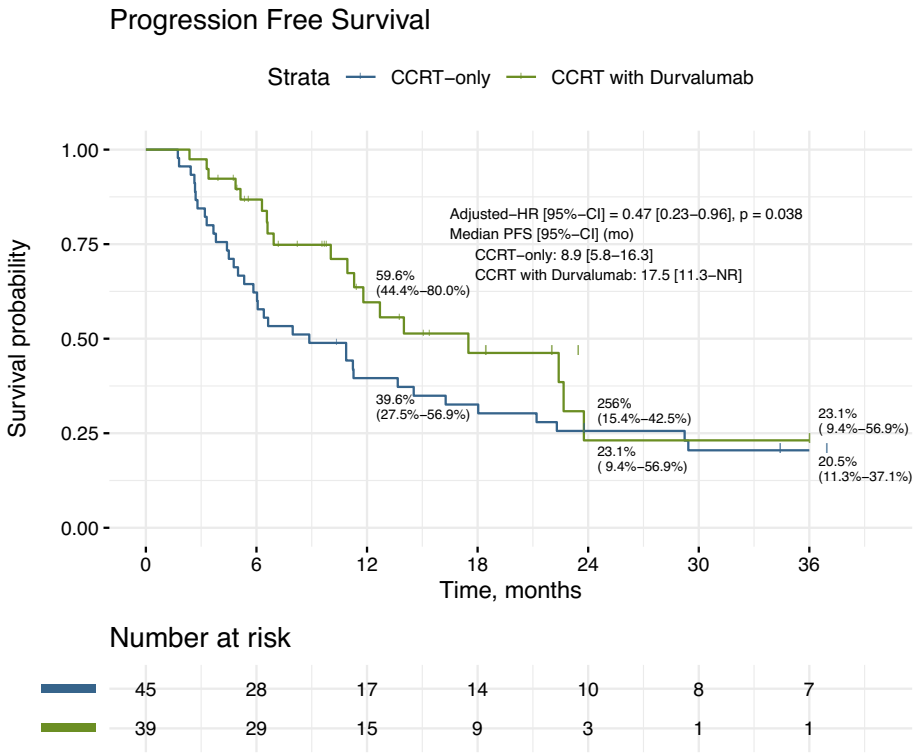

FIGURE 1 Progression-free survival (PFS) of CCRT-durvalumab versus CCRT-alone. The median PFS was 17.5 months (95% CI: 11.3 to NR) for CCRT-durvalumab cohort, and 8.9 months (95% CI: 5.8 to 16.3) for CCRT-alone cohort (HR 0.47, 95% CI: 0.23 to 0.96, $p = 0.038$)

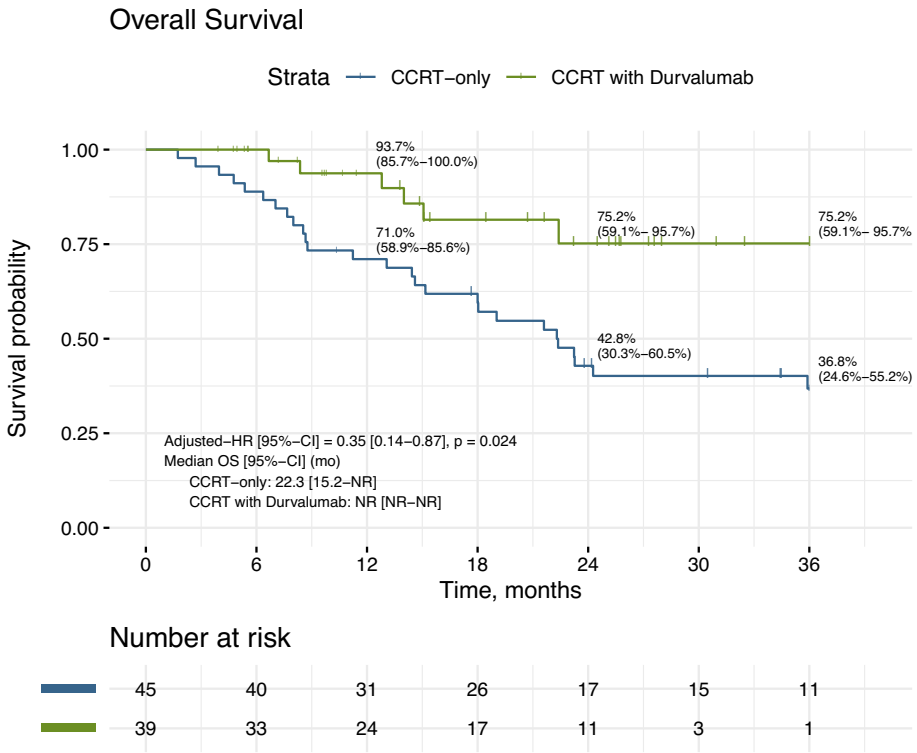

FIGURE 2 Overall survival of CCRT-durvalumab versus CCRT-alone. Median OS was not reached (NR) at time of analysis for durvalumab cohort and 22.3 months (95% CI: 15.2 to NR) for CCRT-alone cohort (HR 0.35, 95% CI: 0.14 to 0.87, $p = 0.024$). The two-year overall survival rate was 75.2% versus 42.8%, respectively

dermatitis, esophagitis and pneumonitis were the most common any-grade AE, while pneumonitis was the most common high grade (grade 3 or more) AE (7.7% in the durvalumab cohort, and 4.4% in the CCRT-alone cohort). Overall, there was a higher incidence of dermatitis (33.3% vs. 11.1%, $p = 0.017$) and pneumonitis (28.2% vs. 4.4%,

TABLE 2 Adverse events of any cause

	All grades			Grade 3/4 only		
	CCRT-only	CCRT with durvalumab	*p*-value	CCRT-only	CCRT with durvalumab	*p*-value
N	45	39		45	39	
Any AE	40 (88.9)	34 (87.2)	0.809	9 (20.0)	5 (12.8)	0.558
Skin						
Dermatitis (%)	5 (11.1)	13 (33.3)	**0.017**	-	-	-
Rash (%)	7 (15.6)	5 (12.8)	0.765	-	-	-
Dry skin (%)	0 (0.0)	2 (5.1)	0.213	-	-	-
Eczema (%)	0 (0.0)	2 (5.1)	0.213	-	-	-
Gastrointestinal						
Odynophagia (%)	24 (53.3)	15 (38.5)	0.194	0 (0.0)	2 (5.1)	0.213
Esophagitis (%)	10 (22.2)	6 (15.4)	0.579	3 (6.7)	0 (0.0)	0.245
Dysphagia (%)	4 (8.9)	2 (5.1)	0.681	-	-	-
Mucositis (%)	1 (2.2)	2 (5.1)	0.595	0 (0.0)	1 (2.6)	0.464
Nausea (%)	7 (15.6)	5 (12.8)	0.765	-	-	-
Diarrhea (%)	3 (6.7)	1 (2.6)	0.620	1 (2.2)	0 (0.0)	1.000
Constipation (%)	2 (4.4)	1 (2.6)	1.000	-	-	-
Dysgeusia (%)	1 (2.2)	1 (2.6)	1.000	-	-	-
Gastritis (%)	1 (2.2)	0 (0.0)	1.000	-	-	-
Colitis (%)	1 (2.2)	0 (0.0)	1.000	1 (2.2)	0 (0.0)	1.000
Vomiting (%)	2 (4.4)	1 (2.6)	1.000	1 (2.2)	0 (0.0)	1.000
Pulmonological						
Pneumonitis (%)	2 (4.4)	11 (28.2)	**0.005**	2 (4.4)	3 (7.7)	0.660
Cough (%)	10 (22.2)	3 (7.7)	0.078	-	-	-
Pneumonia (%)	3 (6.7)	1 (2.6)	0.620	3 (6.7)	0 (0.0)	0.245
Hematological						
Bicytopenia (%)	1 (2.2)	1 (2.6)	1.000	-	-	-
Neutropenia (%)	1 (2.2)	1 (2.6)	1.000	-	-	-
Others						
Fatigue (%)	12 (26.7)	10 (25.6)	1.000	-	-	-
Lethargy (%)	4 (8.9)	1 (2.6)	0.366	-	-	-
Myositis (%)	0 (0.0)	2 (5.1)	0.213	0 (0.0)	1 (2.6)	0.464
Myalgia (%)	0 (0.0)	2 (5.1)	0.213	-	-	-
Rheumatological						
Arthralgia (%)	0 (0.0)	1 (2.6)	0.464	-	-	-
Spondyloarthritis (%)	0 (0.0)	1 (2.6)	0.464	-	-	-
Neurological						
Neuropathy (%)	2 (4.4)	1 (2.6)	1.000	-	-	-
Electrolytes						
Hyponatremia (%)	-	-	-	-	-	-
Endocrine						
Thyroiditis (%)	0 (0.0)	3 (7.7)	0.096	-	-	-

Abbreviations: AE, adverse events; CCRT, concurrent chemoradiotherapy.

$p = 0.005$) in the durvalumab cohort compared to the CCRT-alone cohort (Table 2).

In the durvalumab cohort, 59% of patients experienced immune-related adverse events (IrAEs) of any grade. Dermatitis (33.3%) and pneumonitis (28.2%) were the most common organ-specific IrAEs reported. A total of 25% of patients (10 out of 39) experienced grade 2 or higher pneumonitis. These patients all received a course of immunosuppressants and all recovered except one patient who died from complications. One patient developed grade

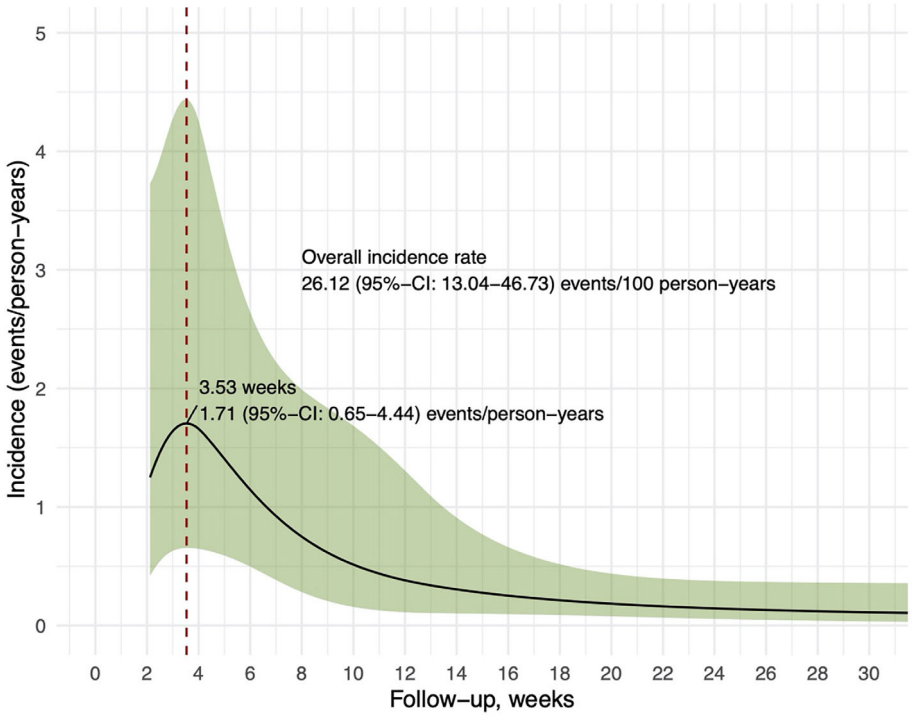

FIGURE 3 Time-varying incidence of pneumonitis. The overall incidence rate of pneumonitis was 26 events per 100 person-years. Most pneumonitis events develop early at 3.5 weeks post durvalumab initiation

4 pneumonitis at the end of one-year durvalumab consolidation. He required a course of steroids and prolonged used of adjunct with mycofenolate mofetil but eventually recovered. Five patients were subsequently rechallenged with durvalumab with no recurrence of pneumonitis. The overall incidence rate of pneumonitis was 26 events per 100 person-years. Most pneumonitis events develop early at 3.5 weeks post durvalumab initiation (Figure 3).

NLR and PLR as predictors for progression-free survival and pneumonitis

In the durvalumab cohort, patients with baseline NLR ≥3 and ≥5 were predictive of shorter PFS (HR 6.775, 95% CI: 0.88–52.12, $p = 0.018$; HR 2.845, 95% CI: 1.071–7.558, $p = 0.041$). Week 6 PLR ≥180 was predictive of lower odds of developing pneumonitis (OR = 0.135, 95% CI: 0.016–0.832, $p = 0.038$) (Table S3).

DISCUSSION

In this real-world experience (RWE), durvalumab consolidation post CCRT was associated with a statistically significant improvement in PFS and OS, a finding similar to the PACIFIC trial. Our reported PFS of 17.5 months was consistent with that reported in the PACIFIC trial and other RWEs.[6,7,21] To date, there have been a few published data on the efficacy of durvalumab in Korea, Japan, Germany and United States, demonstrating improved PFS and local control.[21–24] A German study reported a median PFS of 20.1 months, and 2-year OS of 66% with consolidation durvalumab, while a Japanese study reported a 1-year local control rate of 86% and 1-year PFS of 58%.[21,23] Similarly, experience from the US showed a 1-year PFS and OS of 65 and 85%, respectively.[24]

The impact of consolidation durvalumab post CCRT on locoregional control is unknown. In our study, the locoregional relapse at 1 year was 44.6% versus 16% (HR 0.40, $p = 0.020$), in the durvalumab and CCRT alone cohort, respectively. This finding is similar to that reported from two retrospective studies.[23,24] Abe and colleagues reported a 1-year local control rate of 86% versus 62% ($p = 0.005$) in the durvalumab cohort, compared to the CCRT cohort.[23] Similarly, Offin et al. reported that local control was improved in stage III NSCLC patients treated with durvalumab and chemoradiation compared with historical records with CCRT alone.[24]

A follow-up exploratory analysis of the PACIFIC study reported that most patients with progression had limited sites of extrathoracic disease, suggesting the potential role for ablative, oligometastasis-directed therapies.[25] Similarly, a US study of 62 locally advanced NSCLC patients treated with CCRT and durvalumab also reported that nearly half of the patients with distant relapse were potential candidates for metastasis-directed therapy at first progression.[24] A previous study has shown that stereotactic ablative radiotherapy can significantly improve disease outcome in oligometastatic NSCLC patients with primary local control.[26] In our study, five out of eight patients (62.5%) in the durvalumab cohort with distant relapse had oligometastasis, for which they received surgery or high dose radiotherapy. Findings from our study are consistent with results from the PACIFIC trial

and a US study,[24,25] suggesting that in patients with distant relapse following durvalumab consolidation, the majority had limited extra-thoracic disease amenable to local directed therapies.

The toxicities of durvalumab in our study was consistent with that of the PACIFIC trial, with pneumonitis and skin toxicity being two of the most common IrAEs reported. Most adverse events were low grade. In the PACIFIC trial, pneumonitis was the most frequent adverse event leading to treatment discontinuation, occurring in 33.9% and 24.8% of patients administered with durvalumab and placebo, respectively.[6] Grade 3 or 4 pneumonitis was seen in 3.4% of the durvalumab cohort, compared to 2.6% in the placebo arm. In our study, 28% (11 out of 39) in the durvalumab cohort developed pneumonitis, and the majority (10 out of 11 cases) were grade 2 or higher in severity. These patients were all symptomatic, required bronchoscopic assessment and received prolonged duration of steroids. These findings highlight that whilst consolidation durvalumab can improve survival in stage III NSCLC, complications of pneumonitis can be debilitating in a significant proportion of patients, underscoring the need for close surveillance and early multidisciplinary management of pneumonitis. In addition, pneumonitis occurred early in our study, with its peak of onset occurring at 3.5 weeks following durvalumab initiation. The PACIFIC trial also reported a median time to onset of pneumonitis at about 8 weeks after the first durvalumab dose.[27] Similarly, a Korean study reported a median radiation pneumonitis-free survival of 3.1 months following durvalumab initiation.[22] Taken together, pneumonitis most frequently develops within the first 3 months of durvalumab initiation. Our study is one of the few studies that evaluated the overall incidence rate and time-varying incidence of pneumonitis from durvalumab.

The benefit of durvalumab consolidation in *EGFR* mutation positive patients remains unclear. A recent post hoc exploratory analysis of 35 *EGFR* mutation positive patients from the PACIFIC trial revealed a similar survival benefit of durvalumab treatment versus placebo.[28] In addition, a retrospective study of 37 patients with *EGFR* mutated NSCLC reported that these patients did not benefit from consolidation durvalumab and experienced a high frequency of IrAEs.[29] Several retrospective studies have also demonstrated smaller benefits of durvalumab consolidation in *EGFR* positive NSCLC compared to wild-type patients following chemoradiation.[30,31] Recently, a multicenter retrospective analysis involving 323 stage III NSCLC patients across Europe and America reported limited activity of consolidation durvalumab in those harboring *EGFR* mutation, *BRAF* mutation and *ALK* rearrangement, but not for those harboring *KRAS* mutation.[32] In our study, both *EGFR*-mutation positive and WT patients had longer PFS and OS with durvalumab consolidation compared to CCRT alone. The magnitude of benefit appeared greater in the WT patients. As our sample size was relatively small, we were unable to draw definitive conclusion in this group of patients. Future larger studies are needed to clarify the role of consolidation durvalumab in this patient group.

In recent years, there has been emerging data on the prognostic value of inflammation-related peripheral blood markers such as NLR, PLR in NSCLC patients receiving immunotherapy.[14–16,18,19] In a multicenter retrospective study of 466 NSCLC patients across Europe, Mezquita and colleagues reported that derived NLR >3 correlated with worse outcome for ICIs, but not for chemotherapy.[18] A recent meta-analysis of 21 studies involving 1845 NSCLC patients showed that high pretreatment NLR and PLR were associated with poorer outcomes in patients treated with ICIs.[19] In our study, we showed that baseline NLR ≥3 and ≥5 were predictive of shorter PFS with durvalumab, a finding similar to previous reports. In a recent Taiwan study of 31 patients, Chu and colleagues also reported that patients with low baseline NLR (<3.8) had significantly longer post-CCRT PFS and time to distant metastasis or death compared to patients with high NLR on durvalumab.[33] Taken together, baseline NLR may help predict benefit with durvalumab in stage III NSCLC.

On a parallel note, several retrospective studies have reported NLR and PLR as predictive factors for irAEs in patients with advanced NSCLC treated with ICIs.[16,17] The exact mechanisms of irAEs have remained unclear. Postulated mechanisms include the production of autoantibodies and that ICIs may unmask low level self-reacting T cells.[34] An earlier study in pancreatic cancer revealed that an elevated NLR level was associated with an elevated level of peripheral blood regulatory T cells.[35] These observations lay the basis for studying the predictive role of NLR and PLR in IrAEs. Pavan and colleagues reported that low baseline NLR and PLR were associated with the development of IrAEs in advanced NSCLC treated with ICIs.[17] Similarly, Lee and colleagues also reported that low NLR <3 at baseline was associated with higher occurrence of IrAEs in a case–control study.[16] While our study did not demonstrate an association between baseline PLR or NLR and toxicity, we found that an elevated PLR of ≥180 at week 6 was associated with a lower risk of pneumonitis. This finding is novel and warrants further larger studies in the future. NLR and PLR are readily available, inexpensive biomarkers for outcomes of patients receiving ICIs, and future studies involving larger cohort of patients are needed to validate their application.

Several limitations are acknowledged. First, this was a retrospective single institution study. Second, the sample size was relatively small. Third, there was a significant proportion of patients with unknown or untested *EGFR* mutation status. This was largely attributed to the patients with squamous histology (29.8%) for whom *EGFR* mutation was not tested. The percentage of *EGFR* mutation was also higher in the CCRT-alone cohort compared to the CCRT-durvalumab cohort, representing a potential selection bias whereby, following durvalumab approval, patients with known *EGFR* mutations could not have been offered durvalumab consolidation. If so, this may compromise the analysis and impact the results of durvalumab treatment in this group of patients. Lastly, there was a significant proportion of patients with unknown PD-L1 status, and an imbalance

in PD-L1 status between the two arms. This was largely driven by the CCRT-alone cohort which were recruited between January 2013 to December 2017, during which PD-L1 testing was not readily available in the earlier years between 2013 to 2015, and not routinely tested in stage III NSCLC. Nonetheless, this is one of the few RWEs of consolidation durvalumab that has been reported and all patients who received durvalumab in our study fulfilled the criteria as per the PACIFIC study. Although the sample size of patients with *EGFR* mutations was small, our study highlighted that durvalumab may be beneficial in this group of patients.

Despite the survival benefit with consolidation durvalumab post CCRT, efforts are required to improve outcomes in patients with locally advanced unresectable NSCLC. A phase II trial of concurrent pembrolizumab with chemoradiation in stage III NSCLC have reported promising results.[36] A recent phase II trial of durvalumab in combination with oleclumab or monalizumab after CCRT has shown improved response rates and PFS compared to durvalumab alone.[37] Ongoing studies include concurrent durvalumab with chemoradiation,[38] consolidation durvalumab following stereotactic radiotherapy in early stage unresected NSCLC,[39] consolidation durvalumab following sequential chemoradiation[40] and M7824 with CCRT (NCT03840902). In patients with stage III NSCLC with *EGFR* mutations, a phase II study reported concurrent gefitinib with chemoradiation was tolerable,[41] and a phase III study of maintenance osimertinib following chemoradiation is ongoing.[42]

In conclusion, in this RWE, durvalumab consolidation post CCRT was associated with a statistically significant improvement in PFS and OS. Pneumonitis, a common and debilitating complication, occurred early following durvalumab initiation. This finding highlights to oncologists the need for close surveillance especially in the early phase of treatment. Further studies are needed to validate the role of NLR and PLR in unresectable stage III NSCLC.

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CONFLICT OF INTEREST

All authors have no conflict of interest to declare except BC Goh and Ross Soo. Ross Soo received research funding from AstraZeneca and Boehringer Ingelheim, and received honorarium from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Merck, Roche, Takeda, Yuhan, Novartis, Lilly, Amgen and Puma. BC Goh received honorarium from Novartis, MSD, Bayer Healthcare and provided consultancy for Bayer Healthcare, MSD and Adagene. He also has stock ownership in Gilead Sciences, Merus Therapeutics.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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