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Comparative Effectiveness of Durvalumab Maintenance in Veterans with Stage III Non-Small Cell Lung Cancer: Real-World Outcomes Versus PACIFIC Trial Results

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ABSTRACT

Durvalumab has proven effective as a maintenance therapy following chemoradiotherapy in clinical trials for stage III non-small cell lung cancer (NSCLC), yet its impact in everyday clinical practice remains unclear. We conducted a multi-center observational study of veterans with stage III NSCLC to assess survival outcomes in those receiving durvalumab after chemoradiotherapy compared with patients treated with chemoradiotherapy alone. Survival analyses were performed using Kaplan–Meier estimates and Cox regression models, and outcomes were compared to PACIFIC trial results using an efficacy-effectiveness metric. The study included 1006 patients treated with durvalumab from 2017 to 2021 and 989 patients treated with chemoradiotherapy alone from 2015 to 2016. Durvalumab therapy was linked to improved progression-free survival (HR 0.62, 95% CI 0.55–0.70) and overall survival (HR 0.57, 95% CI 0.50–0.66). Despite these gains, overall survival in the veteran cohort was lower than in the PACIFIC trial population (HR 1.24, 95% CI 1.03–1.48; EE gap 0.73). These findings demonstrate that durvalumab provides meaningful survival benefits in real-world practice, though outcomes fall short of those reported in controlled clinical trials.

Keywords: Stage III non-small cell lung cancer, Durvalumab, Veteran population, Real-world effectiveness, survival outcomes

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Introduction

Durvalumab administered for a year following definitive concurrent chemoradiotherapy (cCRT) has become the recommended treatment for stage III non-small cell lung cancer (NSCLC), based on findings from the PACIFIC trial [1]. Long-term follow-up, with a median duration of 34 months, showed that maintenance durvalumab provides a 9.5% absolute increase in 5-year overall survival [2]. This benefit occurs alongside an acceptable safety profile and does not negatively impact patient-reported quality of life [3].

However, evidence from routine clinical practice regarding the real-world impact of adjuvant durvalumab remains limited. The effectiveness observed in everyday clinical settings may not match the efficacy demonstrated in controlled trials. Notably, veterans treated within the Veterans Health Administration (VHA) were excluded from PACIFIC, yet they now receive 12 months of durvalumab as standard care. This population often carries a higher burden of comorbidities and tobacco-related health issues, factors that could influence both therapy tolerance and treatment outcomes.

The present study aims to evaluate adherence to therapy, incidence of toxicities, and oncologic outcomes in veterans with stage III NSCLC treated with cCRT, with or without durvalumab consolidation. Furthermore, we compare outcomes in this veteran population to the results reported in PACIFIC, providing insight into the effectiveness of durvalumab in a large integrated healthcare system in the United States.

Materials and Methods

Data source

We leveraged the VA Informatics and Computing Infrastructure (VINCI) to identify eligible lung cancer patients. VINCI integrates electronic health record data and administrative information across all VA facilities, including tumor registry entries collected according to standardized procedures by trained registrars. The study protocol received approval from the local institutional review board.

Patient selection

Cohort 1 included patients with histologically confirmed stage III NSCLC (AJCC 8th edition) who underwent cCRT and received at least one durvalumab infusion between November 2017 and April 2021. First and last infusion dates were extracted from outpatient records and verified through detailed chart review. Staging and treatment information was supplemented by the Veterans Affairs Cancer Registry System (VACRS) when available.

For a historical comparison, Cohort 2 comprised patients treated consecutively with cCRT alone from January 2015 to December 2016, identified using VACRS data.

Outcomes and covariates

The primary outcomes were progression-free survival (PFS) and overall survival (OS). Radiographic progression was determined by physician review of imaging reports, and death dates were obtained primarily from the VA Vital Status File, supplemented by the VA Master Patient Index for recent deaths.

Demographic data including age, sex, and race were retrieved from the Master Patient Index. Comorbidities were quantified using the Charlson Comorbidity Index (CCI) [4, 5], based on ICD-10 codes recorded in the year preceding durvalumab initiation for Cohort 1, or the corresponding reference date for Cohort 2. Smoking status was obtained through Health Factors data [6, 7]. Concurrent chemotherapy regimens were recorded from infusion logs and supplemented by VACRS when available.

Durvalumab treatment duration was defined as the interval between the first and last infusions; patients with a single infusion were recorded as having a 1-day duration. The total number of infusions and reasons for discontinuation—including disease progression, immune-related adverse events (irAEs), other toxicities, declining performance, patient choice, loss to follow-up, death, or unknown causes—were determined via manual review of clinical documentation. Toxicities were classified as related to durvalumab if the treating physician judged them as possibly, probably, or definitely associated with the therapy.

Statistical approach

To explore differences in baseline characteristics between veterans who received durvalumab (Cohort 1) and those who underwent chemoradiotherapy alone (Cohort 2), categorical variables were evaluated using chi-square analyses, while continuous variables were examined with t-tests. Survival outcomes, specifically overall survival (OS) and progression-free survival (PFS), were initially estimated using the Kaplan–Meier method, with unadjusted comparisons between cohorts assessed through log-rank testing. To address potential confounders, multivariable Cox proportional hazards models were applied. Adjustments included age (modeled per 10-year increment), sex, race (African American, Caucasian, or other/unknown), smoking status (current, former, never, or unknown), Charlson Comorbidity Index (CCI: 0–2, 3–5, 6–8, ≥9), AJCC stage (IIIA, IIIB, IIIC, or unspecified stage III), concurrent chemotherapy regimen (carboplatin-paclitaxel versus alternative regimens), and tumor histology (adenocarcinoma, squamous cell carcinoma, or other).

For Cohort 1, survival intervals were counted from the date of the first durvalumab infusion to death (for OS) or to progression/death (for PFS). Cohort 2 lacked durvalumab initiation dates, so a proxy “start” was defined as the beginning of radiation plus 86 days, reflecting the median interval to durvalumab in Cohort 1. Patients in Cohort 2 who experienced progression before this surrogate start date were excluded (n = 48) to minimize bias. Follow-up was censored at the last VA encounter, with administrative censoring applied to those still under observation beyond April 15, 2021.

The gap between clinical trial efficacy and real-world effectiveness was assessed using two complementary methods. First, an efficacy-effectiveness (EE) factor was calculated by dividing each cohort’s median OS by the corresponding reference OS reported in PACIFIC [1, 8, 9]; values below 1 indicate reduced survival in practice

relative to trial results (e.g., 0.60 reflects a 40% shorter median survival). Second, hazard ratios for PFS and OS were derived by combining VA cohort data with reconstructed individual patient data from PACIFIC Kaplan–Meier curves using an online reconstruction tool and proportional hazards regression models [10]. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA) and R version 4.0.2 (R Core Team, Vienna, Austria).

Results and Discussion

Baseline patient characteristics

In total, 1006 veterans who received cCRT followed by at least one durvalumab infusion comprised Cohort 1, while 989 patients treated with cCRT alone before durvalumab availability formed Cohort 2. Across the combined population, the median age was 68 years (IQR: 64–72), with a predominance of males (96.3%) and Caucasians (75.8%). Regarding smoking status, 43.5% were current smokers and 36.9% were former smokers. Histologic analysis revealed adenocarcinoma in 41.6% and squamous cell carcinoma in 50.5% of patients.

Compared with Cohort 1, Cohort 2 had fewer patients with severe comorbidities (26.1% with CCI ≥9 versus 37.7%) and a higher proportion of stage IIIA disease (67.4% versus 55.6%). Otherwise, demographic and clinical characteristics were broadly similar between the groups. **Table 1** provides a comparative summary of these VA cohorts alongside the PACIFIC trial population.

Table 1. Characteristics of patients who received cCRT plus durvalumab versus cCRT alone in the real-world setting and in the PACIFIC trial.

Variable		Cohort 1 (cCRT Plus Durvalumab)	Cohort 2 (cCRT Alone)	p-Value *	Durvalumab Group (PACIFIC) [1]	Placebo Group (PACIFIC) [1]
N		1006	989		476	237
Age, median in years (IQR)		69 (64–72)	68 (64–71)	0.009	64	64
Race, n (%)	African American	221 (22.0)	161 (16.3)	0.001	120 (25.2)	72 (30.4)
	Caucasian	745 (74.1)	767 (77.6)		337 (70.8)	157 (66.2)
	Other/unknown	40 (3.98)	61 (6.17)		120 (25.2)	72 (30.4)
Sex, n (%)	Female	47 (4.67)	26 (2.63)	0.015	142 (29.8)	71 (30.0)
	Male	959 (95.3)	963 (97.4)		334 (70.2)	166 (70.0)
CCI, n (%)	0–2	148 (14.7)	241 (24.4)	<0.001		
	3–5	342 (34.0)	363 (36.7)			
	6–8	137 (13.6)	127 (12.8)			
	9+	379 (37.7)	258 (26.1)			
Smoking, n (%)	Current	435 (43.2)	432 (43.7)	0.001	79 (16.6)	38 (16.0)
	Former	402 (40.0)	334 (33.8)		354 (74.4)	178 (75.1)
	Never	87 (8.65)	98 (9.91)		43 (9.0)	21 (8.9)
	Unknown	82 (8.15)	125 (12.6)		-	-
Stage, n (%)	IIIA	559 (55.6)	667 (67.4)	<0.001	252 (52.9)	125 (52.7)
	IIIB	352 (35.0)	322 (32.6)		212 (44.5)	107 (45.1)
	IIIC	66 (6.56)	--		-	-
	III NOS	29 (2.88)	--		12 (2.5)	5 (2.1)
Concurrent chemotherapy, n (%)	Carboplatin/ paclitaxel	711 (70.7)	700 (70.8)	<0.001		
	Cisplatin/etoposide	62 (6.16)	92 (9.30)			
	Platinum/pemetrexed	106 (10.5)	6 (0.61)			
	Other/unknown	127 (12.6)	191 (19.3)			
Histology	Adenocarcinoma	490 (48.7)	340 (34.4)	<0.001	252 (52.9)	135 (57.0)
	Squamous cell carcinoma	485 (48.2)	522 (52.8)		224 (47.1)	102 (43.0)
	Other	31 (3.08)	127 (12.8)		-	-
Time from RT end to durvalumab		42 (29–63)	--			

start, median in days (IQR)	

* p-Value represents a comparison in baseline characteristics between Cohorts 1 and 2.

Progression-free and overall survival

Survival outcomes

Analysis of survival revealed that veterans receiving durvalumab after cCRT (Cohort 1) experienced substantially improved outcomes compared with those treated with cCRT alone (Cohort 2). Across all observed time points, both progression-free survival (PFS) and overall survival (OS) were higher in the durvalumab group, with differences reaching statistical significance (log-rank $p < 0.001$ for both endpoints) **(Figure 1)**.

Among patients who were censored, the median follow-up was 19.9 months in Cohort 1 and 58.4 months in Cohort 2. In terms of PFS, Cohort 1 showed 12-month and 24-month rates of 57.2% (95% CI: 54.0–59.7) and 42.7% (95% CI: 39.2–46.3), respectively. By comparison, patients in Cohort 2 had 12-month and 24-month PFS rates of 44.9% (95% CI: 41.6–48.2) and 26.3% (95% CI: 23.4–29.2). The median PFS was also longer in the durvalumab-treated patients, at 16.9 months (95% CI: 17.1–20.3) versus 9.6 months (95% CI: 9.0–11.1) in the non-durvalumab cohort.

Overall survival followed a similar pattern. The median OS for Cohort 1 reached 34.7 months (95% CI: 31.5–not reached), substantially higher than the 19.2 months (95% CI: 17.6–21.6) observed in Cohort 2. At 12 and 24 months, OS in the durvalumab group was 77.0% (95% CI: 74.4–79.7) and 61.9% (95% CI: 58.4–65.3), compared with 63.9% (95% CI: 60.9–66.9) and 43.8% (95% CI: 40.7–46.9) in patients who did not receive durvalumab.

Collectively, these results indicate a clear survival advantage for veterans treated with adjuvant durvalumab following cCRT, with both short-term and longer-term benefits in PFS and OS relative to the historical cCRT-only cohort.

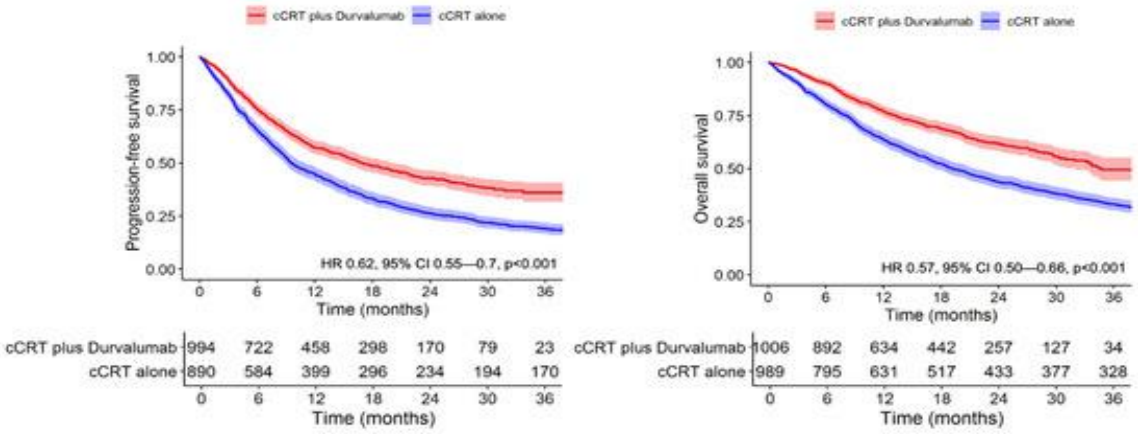

Figure 1. Adjuvant durvalumab significantly extends progression-free and overall survival in Veterans with stage III NSCLC.

Multivariable analysis of survival

After controlling for potential confounding factors, patients in Cohort 1 who received durvalumab demonstrated significantly better outcomes than those in Cohort 2. Specifically, the adjusted hazard ratio (HR) for progression-free survival (PFS) was 0.62 (95% CI: 0.55–0.70, $p < 0.001$), while overall survival (OS) was improved with an adjusted HR of 0.57 (95% CI: 0.50–0.66, $p < 0.001$) **(Table 2)**.

Within the OS model, advancing age and higher comorbidity burden were the strongest predictors of mortality. Each 10-year increase in age was associated with a 20% higher risk of death (HR 1.20; 95% CI: 1.10–1.32; $p < 0.001$), and patients with a Charlson Comorbidity Index of 9 or greater had a 26% higher risk compared with those with a CCI of 0–2 (HR 1.26; 95% CI: 1.06–1.50; $p = 0.008$).

For PFS, several factors predicted shorter survival. Male sex showed a trend toward increased risk (HR 1.36; 95% CI: 0.95–1.94; $p = 0.09$), older age was associated with worse outcomes (HR 1.12 per 10 years; 95% CI: 1.03–1.22; $p = 0.009$), and stage IIIC disease conferred a significantly higher risk of progression compared with stage IIIA/IIIB (HR 1.49; 95% CI: 1.07–2.07; $p = 0.019$). Interestingly, patients with squamous cell

histology experienced improved PFS relative to other histologic subtypes (HR 0.86; 95% CI: 0.77–0.97; p = 0.01).

Overall, these findings confirm that durvalumab consolidation provides a substantial survival advantage in this veteran population, even after adjusting for key clinical and demographic risk factors.

Table 2. Multivariable Cox regression analysis of progression-free survival and overall survival in veterans with stage III NSCLC.

		PFS		OS	
Variable		**HR (95% CI)**	**p-Value**	**HR (95% CI)**	**p-Value**
Cohort	Cohort 2 (pre-durvalumab)	Ref	Ref	Ref	Ref
	Cohort 1 (durvalumab)	0.62 (0.55–0.70)	<0.001	0.57 (0.50–0.66)	<0.001
Age (per 10 years)		1.12 (1.03–1.22)	0.009	1.20 (1.10–1.32)	<0.001
Male		1.36 (0.95–1.94)	0.09	1.33 (0.92–1.93)	0.13
Race	African American	Ref	Ref	Ref	Ref
	Caucasian	1.03 (0.89–1.19)	0.69	1.16 (0.98–1.36)	0.08
	Other/unknown	1.05 (0.81–1.37)	0.71	1.05 (0.78–1.41)	0.74
Smoking	Current	Ref	Ref	Ref	Ref
	Former	1.01 (0.89–1.15)	0.85	1.04 (0.91–1.19)	0.58
	Never	1.03 (0.85–1.25)	0.79	1.01 (0.82–1.24)	0.94
	Unknown	1.07 (0.89–1.30)	0.47	1.10 (0.90–1.34)	0.34
Stage	IIIA	Ref	Ref	Ref	Ref
	IIIB	1.23 (1.09–1.38)	<0.001	1.21 (1.07–1.37)	0.003
	IIIC	1.49 (1.07–2.07)	0.019	1.23 (0.81–1.86)	0.32
	III NOS	0.89 (0.51–1.57)	0.69	0.95 (0.48–1.85)	0.87
Chemotherapy	Other/unknown	Ref	Ref	Ref	Ref
	Carboplatin/paclitaxel	1.01 (0.89–1.14)	0.93	0.96 (0.85–1.10)	0.58
Histology	Adenocarcinoma	Ref	Ref	Ref	Ref
	Squamous cell carcinoma	0.86 (0.77–0.97)	0.01	0.97 (0.85–1.10)	0.59
	Other	1.02 (0.83–1.25)	0.87	1.07 (0.86–1.32)	0.55
CCI	0–2	Ref	Ref	Ref	Ref
	3–5	1.18 (1.01–1.38)	0.04	1.22 (1.03–1.43)	0.02
	6–8	1.30 (1.07–1.58)	0.008	1.12 (0.91–1.38)	0.30
	9+	1.20 (1.02–1.41)	0.03	1.26 (1.06–1.50)	0.008

Efficacy-effectiveness factor analysis

To evaluate how real-world outcomes aligned with those observed in the PACIFIC trial, we compared overall survival (OS) and progression-free survival (PFS) between veterans receiving cCRT plus durvalumab (Cohort 1) and the durvalumab-treated cohort in PACIFIC. The efficacy-effectiveness (EE) factor for OS in Cohort 1 was 0.73, indicating that median survival in routine clinical practice was approximately 27% shorter than that reported in the clinical trial. Correspondingly, the hazard ratio for OS was 1.24 (95% CI: 1.03–1.48; p = 0.02), suggesting a modest but statistically significant reduction in survival in the real-world setting **(Figure 2)**.

In contrast, progression-free survival did not differ meaningfully between the two populations. The hazard ratio for PFS was 0.98 (95% CI: 0.84–1.13; p = 0.82), indicating comparable disease control in veterans treated outside of the clinical trial environment **(Figure 2)**.

These results highlight a modest efficacy-effectiveness gap for overall survival, while PFS outcomes appear largely consistent between real-world practice and the PACIFIC trial.

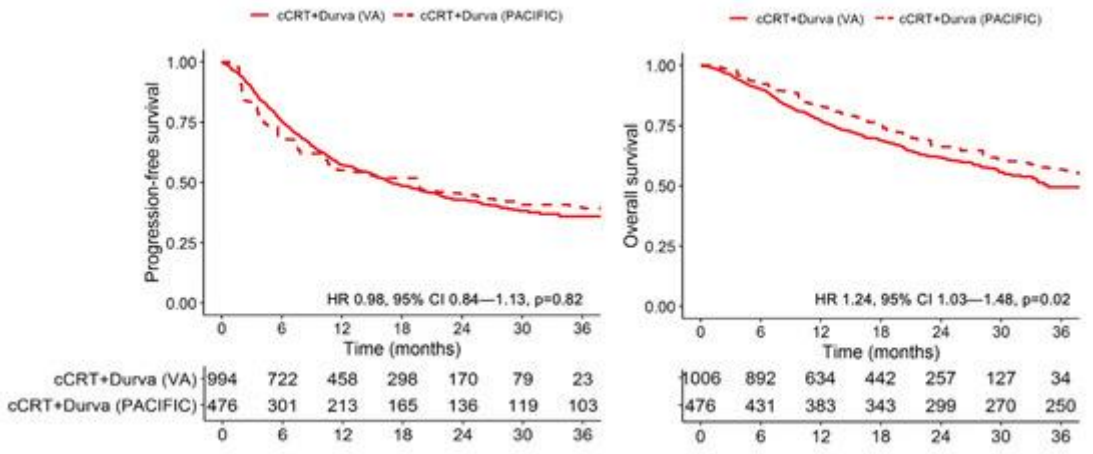

Figure 2. Kaplan–Meier curves illustrate progression-free survival (PFS) and overall survival (OS) among veterans in the real-world cohort compared with patients from the PACIFIC trial, all receiving concurrent chemoradiotherapy and durvalumab for stage III NSCLC.

To understand the reduced OS in veterans, we examined treatment patterns and found that Cohort 1 patients underwent shorter durvalumab therapy and had higher rates of discontinuation due to toxicity than PACIFIC participants. In Cohort 1, the median number of infusions was 12 (IQR: 5–23), and the median therapy duration was 215 days (IQR: 84–350). By comparison, PACIFIC patients received a median of 20 infusions (range: 1–27) over a median period of 310 days.

Discontinuation in Cohort 1 occurred for several reasons: completion of planned therapy (n = 314, 31.2%), disease progression (n = 221, 21.9%), irAE (n = 152, 15.1%), and non-irAE toxicity attributed to durvalumab (n = 60, 5.9%). Among the 152 patients stopping therapy due to irAEs, the most common grade ≥3 event was pneumonitis (n = 109, 10.8%). At the last follow-up, 136 patients (13.5%) were still receiving durvalumab. In PACIFIC, reasons for stopping among 713 patients included completion of therapy (n = 202, 28.3%), disease progression (n = 148, 20.8%), and adverse events prompting discontinuation (n = 73, 10.2%), with grade 3–4 pneumonitis occurring in 3.4% [1].

Discussion

This report describes the largest cohort of veterans with stage III NSCLC treated with cCRT followed by adjuvant durvalumab, including over 1000 patients from VHA centers [1]. Durvalumab consolidation was linked to substantial gains in PFS and OS compared with historical controls, although OS in this veteran population remained lower than PACIFIC trial results, yielding an EE gap of 0.73 [1, 8, 9]. To our knowledge, this is the first study to directly contrast real-world and clinical trial outcomes in a population excluded from PACIFIC.

An ongoing international observational study (PACIFIC-R, NCT03798535) aims to assess real-world efficacy of cCRT and adjuvant durvalumab, but findings are not yet available [1]. Veterans constitute a diverse patient population, including older individuals, those with multiple comorbidities, and residents of rural areas—groups often excluded from clinical trials. These real-world data provide an important perspective on the therapy's effectiveness [1].

In veterans, durvalumab consolidation after cCRT was associated with clear improvements in OS and PFS compared to a contemporary cohort without durvalumab. Cohort 2's outcomes align with prior reports of veterans treated with cCRT alone [11]. Notably, median PFS was similar between real-world veterans and PACIFIC participants (16.9 vs. 16.8 months), whereas median OS was shorter (34.7 vs. 47.5 months, EE gap 0.73), potentially reflecting higher competing mortality or lower treatment tolerance in the veteran population [1]. Veterans also had shorter median durvalumab exposure than PACIFIC participants (7.1 vs. 10.0 months) and higher discontinuation rates due to toxicity (21% vs. 15%), particularly pneumonitis (10.8% vs. 3.4% grade 3–4) [1]. These observations support further investigation of optimal treatment duration to balance effectiveness and safety.

As in other real-world analyses of immune checkpoint inhibitors [12-17], OS was generally shorter than in clinical trials. Contributing factors may include veteran-specific characteristics—older age, male predominance, higher comorbidity burden—and potential biases inherent to retrospective CDW data analysis [1]. Moreover, treatment

discontinuation due to toxicity was more frequent. While irAEs have been associated with improved PFS in some studies, grade 3–4 irAEs can lead to worse OS due to treatment-related mortality [18]. Pneumonitis, the most clinically concerning irAE, is further complicated by prior radiotherapy and preexisting pulmonary disease. Our cohort experienced higher rates of severe pneumonitis leading to durvalumab discontinuation than PACIFIC [1]. Veterans also exhibit higher prevalence of smoking [19, 20] and chronic obstructive pulmonary disease [21, 22], both established risk factors for immune-mediated pneumonitis [23]. Ongoing cigarette exposure in combination with thoracic radiotherapy may amplify lung toxicity risk [24]. In Cohort 1, 43.2% were current smokers compared with 16.6% in PACIFIC. Furthermore, smoking and baseline lung disease have been linked to more severe pneumonitis resistant to steroid therapy [25-27].

The strengths of this study include a large sample size, a contemporary study period, the inclusion of a modern comparator cohort, and access to patient charts that allowed for manual verification of treatment dates and reasons for durvalumab discontinuation within an integrated healthcare system. Staging assessment in both cohorts was conducted using similar methods, including manual chart review supplemented with Veterans Affairs Cancer Registry System (VACRS) data when available. Widespread adoption of fluorodeoxyglucose–positron emission tomography (FDG-PET) has not led to meaningful stage migration in NSCLC patients after 2002 [28-30], ensuring that stage comparisons between patients treated from 2015 to 2016 remain valid.

Limitations of the analysis include differences in how durvalumab recipients (Cohort 1) and patients potentially eligible for durvalumab (Cohort 2) were identified, which could introduce optimistic selection bias favoring Cohort 1. To address this, patients in Cohort 2 who experienced disease progression before the estimated durvalumab start date were excluded. Encouragingly, there were no major differences in measured baseline characteristics between groups; in fact, Cohort 1 had slightly higher rates of severe comorbidities compared with Cohort 2, which contrasts with what would be expected if healthy-user bias were present. Comparisons between durvalumab-treated veterans and historical controls remain subject to the inherent limitations of retrospective analyses, including unmeasured confounders and potential selection bias.

Conclusion

Veterans with stage III NSCLC treated with curative-intent cCRT followed by adjuvant durvalumab experienced significant improvements in both progression-free survival (PFS) and overall survival (OS) compared with a contemporary veteran cohort receiving cCRT alone, as well as historical data. Although PFS outcomes were comparable, OS was lower in the veteran population relative to PACIFIC trial participants. Further research is needed to determine the factors contributing to higher durvalumab discontinuation rates, increased pneumonitis incidence, and reduced OS among veterans with stage III NSCLC receiving cCRT and adjuvant durvalumab.

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Conflict of Interest: A.K.B. serves as a consultant for Boston Consulting Group. G.W.S. serves an uncompensated position on the Board of Directors for the Optimal Cancer Alliance. D.M. participated in a steering committee for AstraZeneca in June 2020. M.J.K. has received research funding from Novartis, AstraZeneca, Bristol-Myers Squibb, Regeneron, and Genentech. K.S., L.Z., D.E., M.D.G. and N.R. do not have any conflict of interest.

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Ethics Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Veterans Affairs Ann Arbor Healthcare System (protocol name “Impact of immunotherapy on patterns of care and outcomes of Veterans”, date approved 6 February 2020).

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