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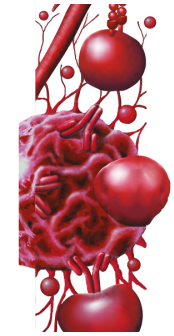

Durvalumab after chemoradiotherapy in patients with stage III non-small-cell lung cancer: real-world outcomes versus clinical trial results

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Aim: We investigated the effectiveness of durvalumab post-concurrent CRT (cCRT) and post-sequential CRT (sCRT) versus cCRT and sCRT alone and compared these outcomes with the PACIFIC trial. **Methods:** Four cohorts of stage III NSCLC patients who received CRT were included: cCRT with and without durvalumab, sCRT with and without durvalumab. PFS and OS were analyzed using Cox regression. **Results:** Durvalumab improved PFS (cCRT: aHR = 0.69, sCRT: aHR = 0.71) and OS (cCRT: aHR = 0.71, sCRT: aHR = 0.32), although not all results were significant. PFS was longer in the real-world than in the trial, while OS did not differ. **Conclusion:** Durvalumab after CRT improved the survival outcomes. The difference between PFS in our study and the trial may be due to differences in follow-up methods.

Plain language summary: We assessed a medicine called durvalumab on patients with non-small cell lung cancer who received chemoradiotherapy in a real-world setting. We compared their outcomes with those from a clinical trial. Patients who received two types of chemoradiotherapy with or without durvalumab were included, and their progression-free survival (PFS) and overall survival (OS) outcomes were analyzed. We found that patients treated with durvalumab had better PFS and OS than those treated without durvalumab. PFS was longer in the real-world than in the clinical trial, but OS was similar. The difference in PFS may be due to differences in measuring PFS.

Tweetable abstract: Real-world stage III NSCLC patients who received durvalumab after CRT had better outcomes than those who received CRT alone. Longer PFS in real-world versus trial may be due to follow-up differences.

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Keywords: concurrent chemoradiotherapy • durvalumab • effectiveness–efficacy gap • NSCLC • observational study • overall survival • progression-free survival • sequential chemoradiotherapy

Approximately 20–35% of patients with non-small-cell lung cancer (NSCLC) are diagnosed with locally advanced disease [1]. For decades, the standard treatment for these patients was concurrent or sequential chemoradiotherapy (cCRT or sCRT) [2]. However, this standard treatment regime changed with the results of the PACIFIC trial

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demonstrating a progression free survival (PFS) and overall survival (OS) benefit for durvalumab versus placebo after cCRT [3,4]. As a result, durvalumab after chemoradiotherapy (CRT) has become the first Immune checkpoint inhibitor approved for treating stage III NSCLC patients, and is currently considered the standard of care [5,6].

Nevertheless, treatment effects observed in randomized clinical trials (RCT) may not be observed in daily clinical practice [7,8], since these patients are usually older, have more comorbidities and worse performance states which could lead to worse baseline prognosis. Additionally, follow-up of patients treated in daily clinical practice is less standardized than in clinical trials. Furthermore, in clinical practice, durvalumab after sCRT is usually offered to less fit patients [5,6], which may further influence their survival outcomes given that sCRT is also less effective compared with cCRT [9]. Real-world studies have the potential to address these knowledge gaps.

To date, 21 real-world studies evaluated the effectiveness of durvalumab in stage III NSCLC patients [10–30]. A meta-analysis summarized 13 of these studies (n = 1885) and reported marginally better OS survival rates than reported in the PACIFIC trial (12-month OS: 90 vs 83.3%) [31]. Also the large single arm, observational PACIFIC-R study (n = 1399) suggested that the effectiveness of durvalumab in the real-world is at least comparable with the clinical trial [10]. However, recently another large study by Sanker *et al.* (2022) demonstrated that the OS of durvalumab in the real-world is shorter than in the trial (median OS: 34.7 vs 47.5 months), with an effectiveness-efficacy gap (EE gap) of 0.72 [26]. So far, this was the only study that quantified the difference between the real-world study and PACIFIC trial (expressed as EE gap) whereas other studies (n = 20) only provided a descriptive comparison. Moreover, most observational studies (n = 12) did not assess the relative effectiveness of durvalumab because they lack a control group [10,13–15,17–22,27,28]. Lastly, only five studies included patients treated with sCRT [10,11,13,22,27].

Here, we assess the real-world effectiveness of durvalumab in a Dutch cohort of stage III NSCLC patients who received durvalumab after cCRT or sCRT versus stage III NSCLC patients who received cCRT or sCRT alone. Additionally, we compare the real-world survival outcomes to the outcomes of the PACIFIC trial by reconstructing individual patient data of the trial.

Methods

Setting, design & study population

We conducted a multicenter, retrospective, cohort study in five hospitals spread out geographically over the Netherlands, including four large teaching hospitals (St Antonius Hospital Utrecht/Nieuwegein (SAZ), Canisius Wilhelmina Hospital Nijmegen (CWZ), Catharina Hospital Eindhoven (CZE), OLVG Amsterdam (OLVG)) and one academic centre (Maastricht University Medical Center+ (MUMC)). Patients diagnosed with stage III NSCLC and treated with CRT between January 2012 and December 2021 were identified in these hospitals. The following methods were used to select eligible patients; the OLVG used the Clinical Data Collector (CTcue®), the MUMC used their local developed and Gamp5 validated software application for data collection, and the SAZ, CWZ and CZE used the database of the Netherlands Cancer Registry.

Patients were excluded if they; received less than two cycles of platinum-based chemotherapy during CRT; had disease progression before the completion of CRT; or had lung resection during the time that CRT was applied. The population was divided into the following four cohorts; cCRT with durvalumab, cCRT without durvalumab, sCRT with durvalumab and sCRT without durvalumab. Durvalumab patients received at least one dose of adjuvant durvalumab. Patients treated without durvalumab were referred to as historical controls because they were treated with CRT alone in the pre-durvalumab era (before 1 April 2018). Patients treated with CRT alone in the durvalumab-era were excluded.

Baseline characteristics were extracted from the patients' Electronic Health Records between 30 days before and 30 days after the date of diagnosis. Follow-up information was collected until the end of this study on 1 July 2022. The study design is schematically depicted in Figure 1.

Study data were collected, anonymized, and managed using REDCap electronic data capture tools [32]. All methods were carried out in accordance with relevant guidelines and regulations. The ethics committees, the Santeon Institutional Review Board (SBD 2021-001) and the academic hospital Maastricht/University Maastricht (2021-2843), approved the study and waived the need for informed consent. The study was performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

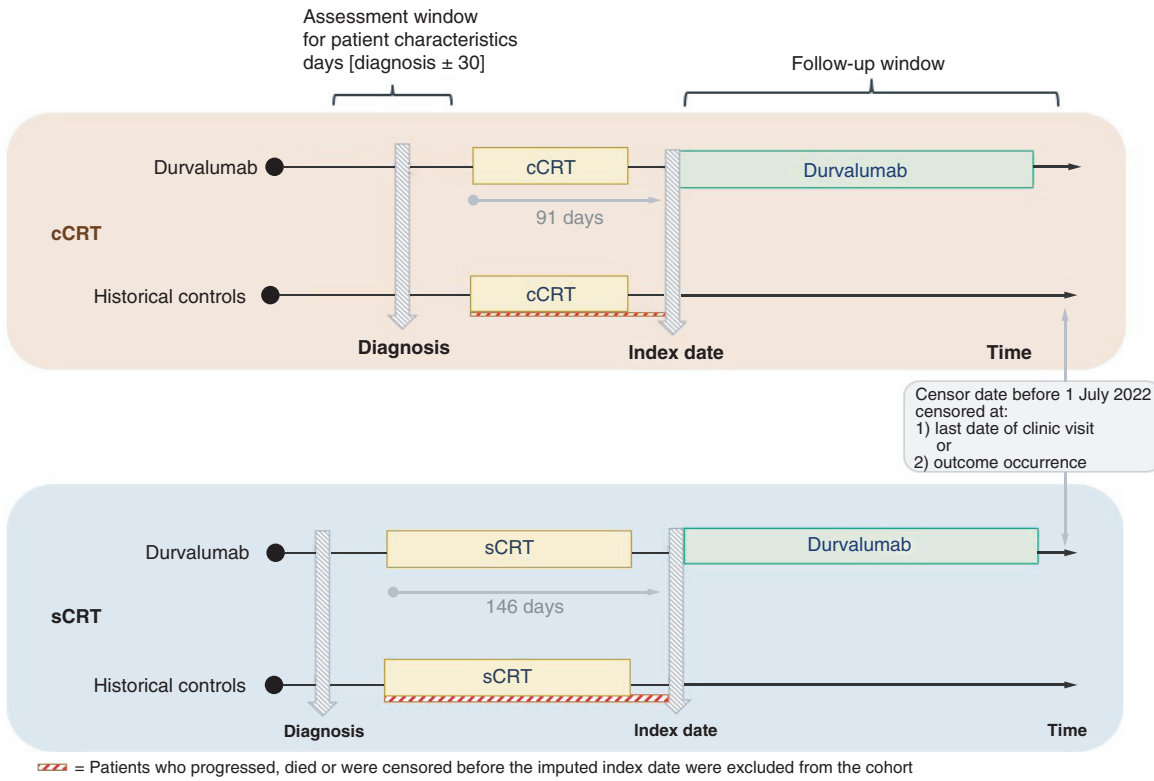

Figure 1. Study design overview. The orange rectangle displays the timeline for patients treated with cCRT with durvalumab or without durvalumab (historical controls). The blue rectangle displays a timeline for patients treated with sCRT with durvalumab or without durvalumab (historical controls).
cCRT: Concurrent chemoradiotherapy; sCRT: Sequential chemoradiotherapy.

Outcomes

The primary outcome PFS, expressed in months, was calculated from the index-date till the date of disease progression or death, or till the date of censoring, whichever occurred first. The date of disease progression was determined by the earliest medical note from the thoracic oncologist stating that the disease had progressed. The secondary outcome OS, expressed in months, was calculated from the index-date till the date of death or censoring. Patients without progression and/or those who were still alive at the end of follow-up were censored at the date of their last clinic visit.

The start date of durvalumab treatment was used as index date for patients treated with durvalumab. Because historical controls did not receive durvalumab, imputed index dates were used which were calculated in two steps. First, the median time between the start date of cCRT or sCRT and the start date of durvalumab was calculated. Second, for both the historical controls treated with cCRT and sCRT these median times were added on to the start date of CRT to generate an imputed index date. Patients within the historical control cohort who progressed, died or were censored before the imputed index date were excluded (n = 23) to avoid immortal time bias [33]. The median time between the start of sCRT and start of durvalumab was 146 days [range 97–188 days] and the median time between start of cCRT and durvalumab was 91 days [range 49–189 days] (Figure 1).

Potential confouders &/or effect modifiers

The following characteristics were included in the analyses: age, gender, body mass index (BMI), Eastern Cooperative Oncology Group-Performance status (ECOG-PS), histology subtype and disease stage. All patient characteristics were extracted within 30 days before or after diagnosis (Figure 1).

Data analysis

Statistical software (R version 4.1.2) was used to conduct the data analyses. Descriptive statistics for categorical variables were reported as the number of observations (proportions), while the mean [±standard deviation (SD)]

Table 1. Patient characteristics of stage III NSCLC patients treated with cCRT and sCRT with or without durvalumab (historical controls).

Characteristics	cCRT (n = 267)			sCRT (n = 116)		
	Durvalumab (n = 106)	Historical controls (n = 161)	p-value	Durvalumab (n = 21)	Historical controls (n = 95)	p-value
Age, years (mean, sd)	64.2 (9.5)	63.4 (9.3)	0.51	64.5 (9.7)	69.2 (8.2)	0.02
Sex (male, n (%))	54 (50.9)	86 (53.4)	0.84	8 (38.1)	54 (56.8)	0.19
BMI, kg/m^2 (mean, sd)	26.0 (4.5)	24.8 (4.5)	0.04	25.9 (3.1)	24.5 (3.9)	0.08
ECOG-PS (n (%))			0.05			0.12
0	62 (58.5)	90 (55.9)		9 (42.9)	39 (41.1)	
1	41 (38.7)	49 (30.4)		11 (52.4)	44 (46.3)	
≤2	1 (0.9)	6 (3.7)		1 (4.8)	7 (7.4)	
unknown	2 (1.9)	16 (9.9)		0	5 (5.3)	
Disease stage (n, (%))			0.03			<0.01
IIIa	44 (41.5)	83 (51.6)		7 (33.3)	35 (36.8)	
IIIb	46 (43.4)	70 (43.5)		8 (38.1)	53 (55.8)	
IIIc	6 (5.7)	3 (1.9)		4 (19.0)	7 (7.4)	
unknown	10 (9.4)	5 (3.1)		2 (9.5)	0	
Histology (n, (%))			0.39			1.0
Squamous	32 (30.2)	58 (36.0)		8 (38.1)	35 (36.8)	
Nonsquamous	74 (69.8)	103 (64.0)		13 (61.9)	60 (63.2)	
Days between end radiation and start durvalumab (median [range])	41 [6–124]	–		47 [8–93]	–	
Number of durvalumab administrations (median [range])	16 [1–27]	–		10 [1–27]	–	
Months of treatment duration durvalumab (median [range])	8 [1–40]	–		5 [1–13]	–	

BMI: Body mass index; cCRT: Concurrent chemoradiotherapy; ECOG-PS: Eastern Cooperative Group performance status; sCRT: Sequential chemoradiotherapy.

was provided for normally distributed continuous data and the median [range] was provided for non-normally distributed continuous data. Chi-square and t-tests were used to compare the baseline characteristics between patients treated with and without durvalumab.

The Kaplan-Meier (KM) method was used to visualize survival curves for PFS and OS for the four cohorts. For both the sCRT and cCRT regime, patients treated with durvalumab were compared with patients treated without durvalumab (historical controls). For this comparison simple and multiple Cox regression were used to calculate unadjusted and adjusted hazard ratios (HR) and their 95% confidence Intervals (CIs). The covariates mentioned above were tested with simple Cox regression analysis for both cohorts to identify variables associated with PFS or OS. All variables with a p-value ≤ 0.20 and three other variables; age, gender and the type of treatment (durvalumab or historical control), were used to construct multiple Cox regression models. Multiple imputation was used to impute the missing observations for ECOG PS under the assumption that data were missing at random.

Lastly, for both cCRT patients treated with durvalumab and without durvalumab we compared the effectiveness outcomes of our cohort (the 'real-world') to efficacy outcomes of the PACIFIC cohort by estimating HRs. Therefore, the algorithm developed by Guyot and colleagues was used to reconstruct individual patient data from the published OS and PFS curves from the PACIFIC trial [3,34,35].

Results

Baseline characteristics

We included 267 cCRT patients, of which 106 were treated with durvalumab and 161 were treated without durvalumab (controls), and 116 sCRT patients, of which 21 were treated with durvalumab and 95 without durvalumab (controls). For the cCRT group, patients treated with durvalumab had a higher BMI (26.0 vs 24.8 kg/m2), more often an ECOG PS 1 (38.7 vs 30.4%), and less often a disease stage IIIa (41.5 vs 51.6%) compared with the historical controls (Table 1). In the sCRT group, patients treated with durvalumab were younger (64.5 vs 69.2 year) and had less often disease stage IIIb (38.1 vs 55.8%) compared with the historical controls.

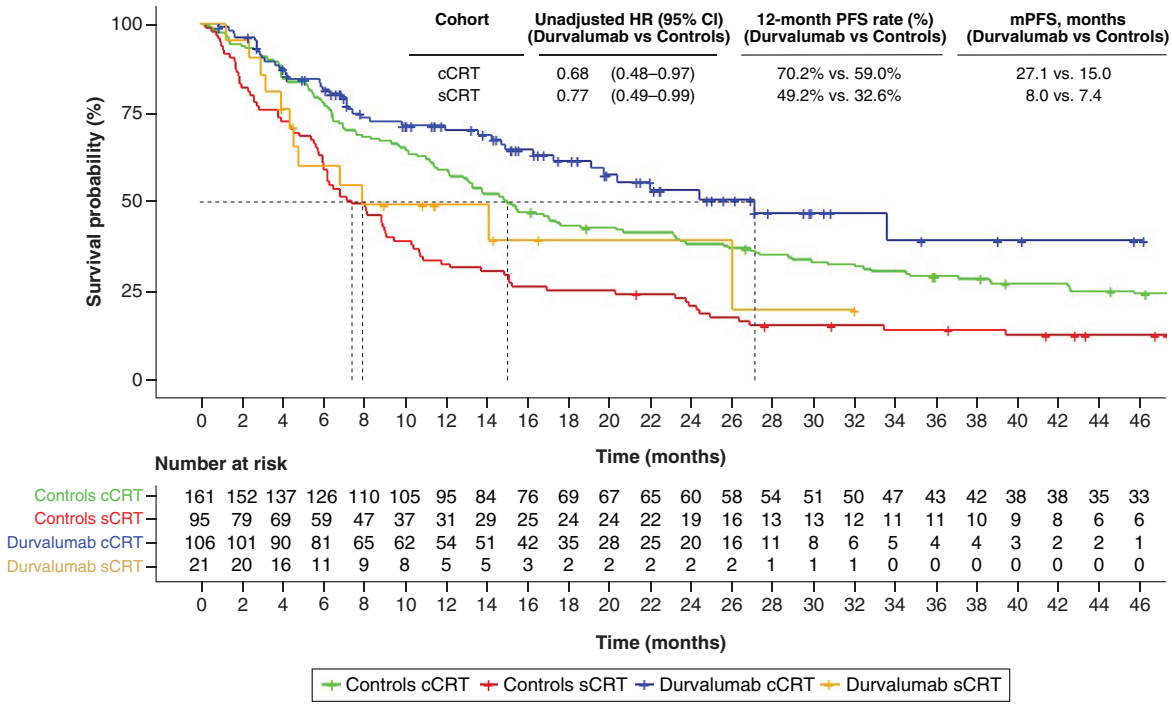

Figure 2. Kaplan-Meier curves for progression-free survival for patients who received concurrent chemoradiotherapy or sequential chemoradiotherapy with and without durvalumab.
cCRT: Concurrent chemoradiotherapy; sCRT: Sequential chemoradiotherapy.

Medians for the time between the end of CRT and the start of durvalumab, number of durvalumab administrations per patient and treatment duration can be found in Table 1. The median follow-up time was 15.4 (range: 1.0–46.1) months for patients treated with durvalumab and 25.3 (range: 0.5–92.5) months for patients treated without durvalumab.

Survival outcomes

Progression-free survival

In the cCRT cohorts, the observed median PFS (mPFS) for durvalumab patients was longer (27.1 months [95% CI: 19.2–not reached (NR)] versus 15.0 months [95% CI: 12.3–20.7]) and the 12-months PFS rate was higher (70.2% vs 59.0%) than for historical control patients (Figure 2). The unadjusted HR: 0.68 (95% CI: 0.48–0.97) and adjusted HR: 0.69 (95% CI: 0.49–0.99) for PFS were better for patients treated with durvalumab than for patients treated without durvalumab. None of the other variables were significantly associated with PFS in the multiple Cox regression model (Table 2).

In the sCRT cohorts, the observed mPFS for durvalumab patients was slightly longer (8.0 months [95% CI: 4.6–NR) versus 7.4 months [95% CI: 6.1–10.3]) and the 12-months PFS rate was higher (49.2 vs 32.6%) than for historical control patients. The unadjusted HR: 0.77 (95% CI: 0.42–1.42)) and adjusted HR: 0.71 (95% CI: 0.37–1.40) for PFS were better for patients treated with durvalumab than for patient treated without durvalumab, although these results were not significant. None of the other variables were significantly associated with PFS in the multiple Cox regression model (Table 2).

Overall survival

In the cCRT cohorts, the median OS (mOS) was not reached versus 39.5 months (95% CI: 30.1–52.1 months) in patients treated with durvalumab and without durvalumab (Figure 3). The 12-months OS rate for patients treated with durvalumab was higher than for patients treated without durvalumab (83.9% vs 77.5%). The unadjusted HR: 0.69 (95% CI: 0.43–1.10) and adjusted HR: 0.71 (95% CI: 0.44–1.13) for OS were better for patients treated with durvalumab than for patients treated without durvalumab, although these results were not significant. None of the other included variables were significantly associated with OS in the multiple Cox regression model (Table 3).

Table 2. Progression free survival. Simple- and multiple cox-regression model for the concurrent chemoradiotherapy and sequential chemoradiotherapy population.

	cCRT (n = 267)						sCRT (n = 116)					
	Simple model			Multiple model			Simple model			Multiple model		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Type of treatment												
Control	Ref.						Ref.					
Durvalumab	0.68	0.48–0.97	0.04	0.69	0.49–0.99	0.04	0.77	0.42–1.41	0.40	0.71	0.37–1.40	0.33
Age												
<75 years	Ref.						Ref.					
≥75 years	1.12	0.71–1.77	0.64	1.17	0.73–1.89	0.51	0.76	0.48–1.19	0.23	0.80	0.49–1.30	0.36
Gender												
Male	Ref.						Ref.					
Female	1.01	0.75–1.37	0.94	1.02	0.75–1.39	0.91	0.96	0.67–1.37	0.82	0.70	0.49–1.30	0.11
BMI												
<30	Ref.						Ref.					
≥30	0.82	0.53–1.27	0.39				1.16	0.55–2.44	0.70			
ECOG												
PS 0	Ref.						Ref.					
≥PS 1	0.98	0.71–1.36	0.91	0.93	0.67–1.28	0.64	1.00	0.66–1.53	0.99	0.93	0.60–1.44	0.75
Disease stage												
IIIa	Ref.						Ref.					
IIIb	1.12	0.82–1.54	0.46				1.60	1.03–2.48	0.04	1.56	0.99–2.47	0.06
Other (IIIc or unknown)	0.75	0.39–1.44	0.39				0.95	0.44–2.07	0.90	1.01	0.43–2.37	0.98
Histology												
Non-squamous	Ref.						Ref.					
Squamous	0.91	0.66–1.26	0.58				1.02	0.67–1.54	0.94			

BMI: Body mass index; cCRT: Concurrent chemoradiotherapy; ECOG PS: Eastern Cooperative Group performance status; sCRT: Sequential chemoradiotherapy.

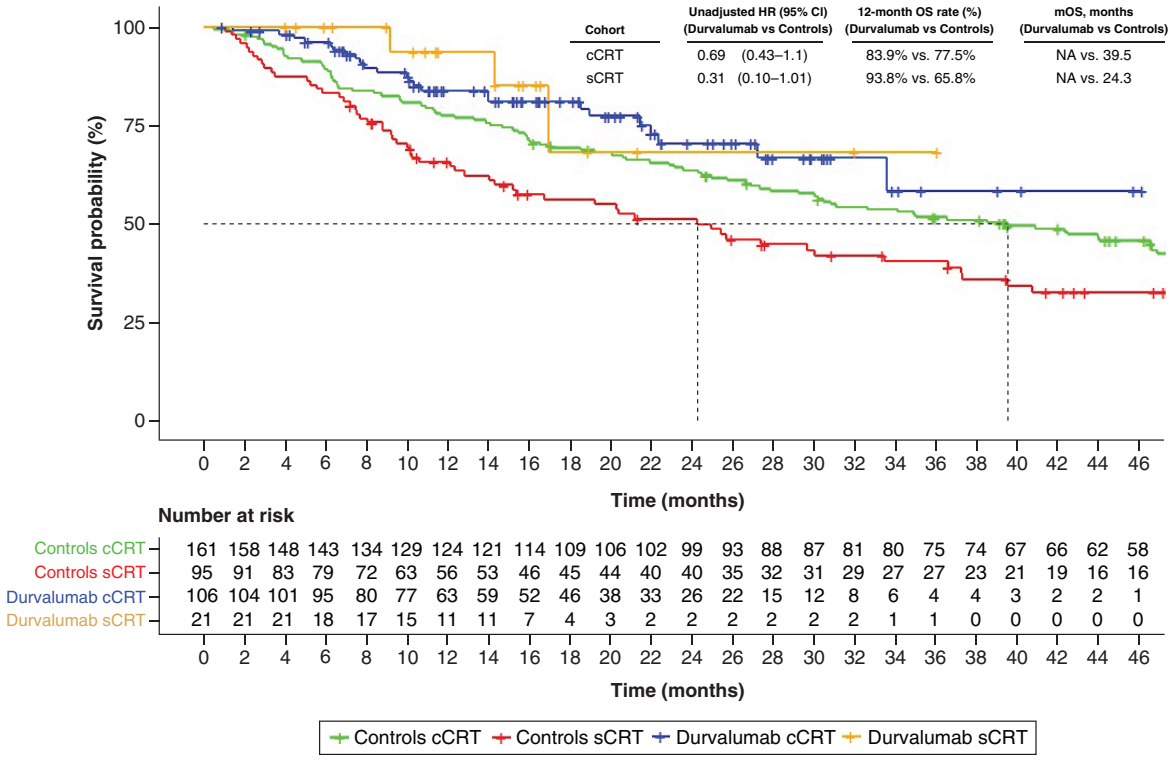

Figure 3. Kaplan-Meier curves for overall survival for patients who received concurrent chemoradiotherapy or sequential chemoradiotherapy with and without durvalumab.
cCRT: Concurrent chemoradiotherapy; sCRT: Sequential chemoradiotherapy.

Table 3. Overall survival; simple- and multiple cox-regression model for the concurrent chemoradiotherapy and sequential chemoradiotherapy population.

	cCRT (n = 267)						sCRT (n = 116)					
	Simple model			Multiple model			Simple model			Multiple model		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Type of treatment												
Control	Ref.						Ref.					
Durvalumab	0.69	0.43–1.10	0.12	0.71	0.44–1.13	0.15	0.31	0.1–1.01	0.05	0.32	0.09–1.03	0.06
Age												
<75 years	Ref.						Ref.					
≥75 years	1.29	0.77–2.16	0.33	1.19	0.67–2.11	0.55	0.87	0.50–1.49	0.60	0.85	0.45–1.61	0.61
Gender												
Male	Ref.						Ref.					
Female	0.95	0.67–1.36	0.80	0.91	0.62–1.33	0.62	1.37	0.84–2.24	0.21	1.44	0.82–2.51	0.20
BMI												
<30	Ref.						Ref.					
≥30	0.74	0.43–1.28	0.28				1.15	0.54–2.41	0.72			
ECOG												
PS 0	Ref.						Ref.					
≥PS 1	1.47	1.01–2.13	0.05	1.43	0.97–2.10	0.07	0.96	0.58–1.61	0.89	0.93	0.54–1.60	0.78
Disease stage												
IIIa	Ref.						Ref.					
IIIb	1.11	0.77–1.61	0.57				1.10	0.66–1.83	0.72	1.08	0.61–1.92	0.79
Other (IIIc or unkown)	0.89	0.42–1.86	0.75				0.30	0.07–1.25	0.10	0.41	0.09–1.83	0.24
Histology												
Non-squamous	Ref.						Ref.					
Squamous	0.86	0.48–1.57	0.62				0.95	0.72–1.26	0.74			

BMI: Body mass index; cCRT: Concurrent chemoradiotherapy; ECOG PS: Eastern Cooperative Group performance status; sCRT: Sequential chemoradiotherapy.

In the sCRT cohorts, the mOS for durvalumab patients was not reached and the mOS for the historical control patients was 24.3 months. The 12-months OS rate for patients treated with durvalumab was higher than for patients treated without durvalumab (93.8 vs 65.8%). The unadjusted HR: 0.31 (95% CI: 0.10–1.01) and adjusted 0.32 (95% CI: 0.09–1.03) for OS were better for patients treated with durvalumab than for patients treated without durvalumab, although these results were not significant. None of the other included variables were significantly associated with OS in the multiple Cox regression model (Table 3).

Real-world versus PACIFIC trial

Durvalumab arm comparison

A total of 476 patients in the PACIFIC study and 105 patients in our real-world cohort were treated with cCRT followed by durvalumab. In the real-world, the proportion of males was significantly lower (50.9 vs 70.2%) and there were fewer patients with an ECOG PS of 1 (38.7% vs 50.4%) than in the PACIFIC trial. The proportion of patients with disease stage IIIa (41.5 vs 52.9%) and with squamous histology (30.2 vs 47.1%) were significantly lower in the real-world than in the PACIFIC trial. Besides, all patients in the PACIFIC trial were treated with durvalumab 42 days after the end of CRT while only 56 patients (52.8%) in the real-world received durvalumab within this timeframe (Supplementary Table 1).

The mPFS observed in the real-world was significantly longer than the mPFS reported in the PACIFIC trial, respectively 27.1 months (95% CI: 19.2–NR) and 16.8 months (95% CI: 13.0–18.1) (HR: 0.64; 95% CI: 0.46–0.91). The 12-months PFS rate was also higher for patients treated in the real-world versus patients treated in the PACIFIC trial (70.2 vs 55.9%) (Figure 4). For both cohorts, the mOS was not reached and the 12-months survival rates were comparable, 83.8% for the real-world and 83.1% for the trial population. There was no significant difference observed in OS (HR: 0.83; 95% CI: 0.54–1.26) (Figure 5).

Control arm comparison

In the PACIFIC study a total of 273 patients were treated with cCRT followed by placebo (hereafter referred to as controls) and in our real-world cohort 161 patients were treated with cCRT alone (historical controls). In the real-world, the proportion of males was lower (53.4% vs 70.0%) and there were fewer patients with an ECOG PS

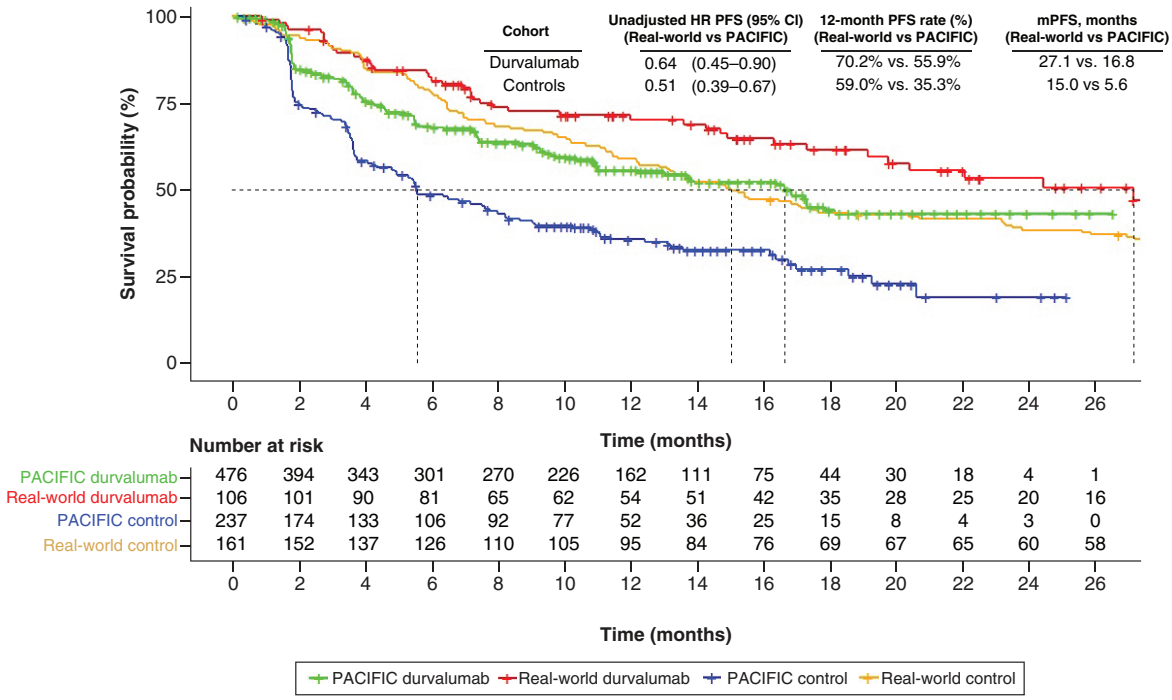

Figure 4. Kaplan-Meier curves for progression-free survival of patients who received concurrent chemoradiotherapy with durvalumab and without durvalumab (controls) in the real-world and in the PACIFIC trial.
PFS: Progression-free survival.

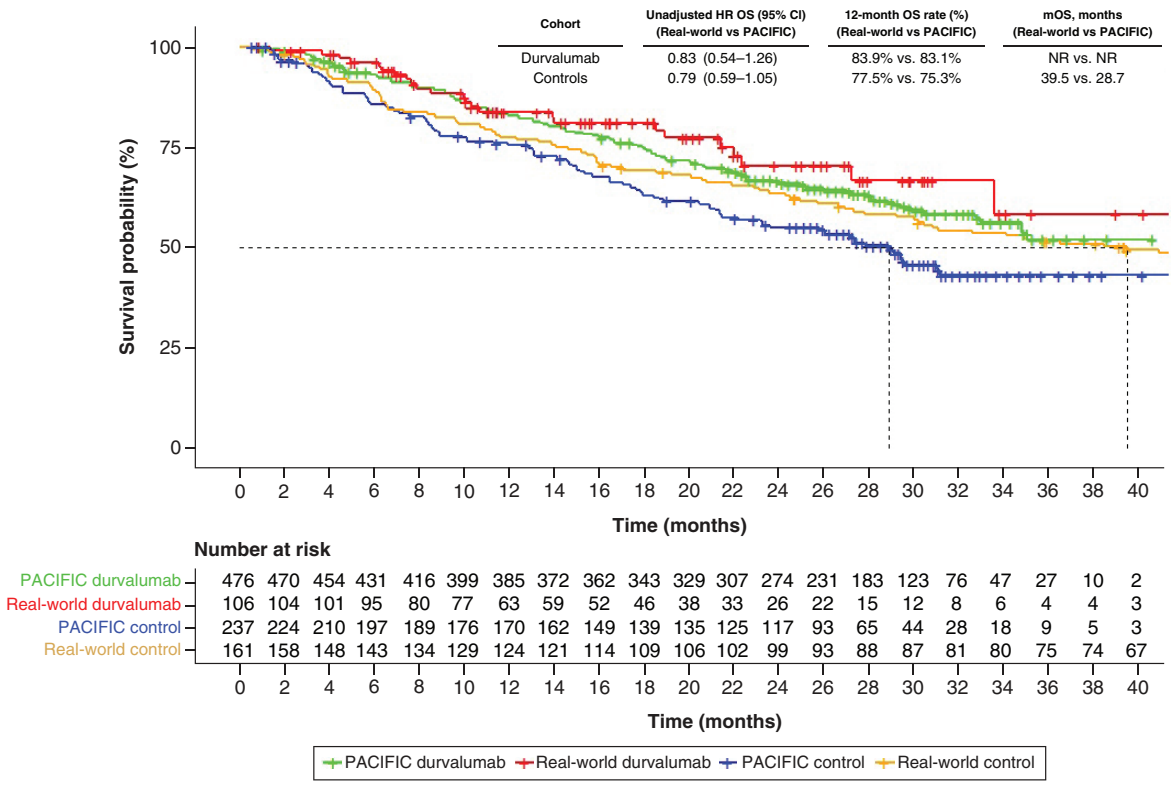

Figure 5. Kaplan-Meier curves for overall survival of patients who received concurrent chemoradiotherapy with durvalumab and without durvalumab (controls) in the real-world and in the PACIFIC trial.
OS: Overall survival.

of 1 (30.4 vs 51.5%) than in the PACIFIC trial. In addition, in the real-world 6 (3.7%) patients with an ECOG PS of 2 were included, while these patients were not included in the PACIFIC trial (Supplementary Table 1).

Furthermore, the mPFS observed in the real-world was significantly longer than the mPFS reported in the PACIFIC trial (15.0 months [95% CI: 12.3–20.7] verus 5.6 months [95% CI: 4.6–7.8]; HR: 0.51; 95% CI: 0.39–0.67)). The 12-months PFS rate was also higher for patients treated in the real-world versus patients treated in the PACIFIC trial (59.0 vs 35.3%), see Figure 4. The mOS observed in the real-world was longer than the mOS observed in the PACIFIC (39.5 [95% CI: vs 28.7 months [95% CI: 22.9–NR]) (HR: 0.79; 95% CI: 0.59–1.05)). The 12-months OS rates were comparable between the real-world and the PACIFIC trial (77.5 vs 75.3%) (Figure 5).

Discussion

In this retrospective follow-up study, we assessed the real-world effectiveness of durvalumab after cCRT or sCRT in patients with stage III NSCLC. Our findings illustrate administering durvalumab after CRT improves both PFS and OS compared with historical controls treated CRT alone, although statistical significance is lacking. Moreover, the mPFS for durvalumab treatment reported in our study (27.1 months) was significantly longer than the mPFS in the PACIFIC trial (16.8 months), while the OS results did not differ. The difference in mPFS could be the result of differences in follow-up methods between the real-world and clinical trial.

For patients treated with cCRT in our cohort, durvalumab improved the PFS (HR 0.74) and the OS (HR 0.71). Our HRs were in line with the HRs reported by Sanker *et al.* and Pichert *et al.* [25,26]. According to the large study of Sanker *et al.* (n = 1995), durvalumab after cCRT improved the PFS (HR: 0.62, 95% CI: 0.55–0.70) and OS (HR: 0.57, 95% CI: 0.50–0.66) compared with cCRT alone. According to the cancer registry study of Pichert *et al.*, durvalumab after CRT improved the OS compared to CRT alone (HR: 0.71, 95% CI: 0.67–0.82). However, this result was not stratified for cCRT or sCRT and PFS was not assessed.

For patient treated with sCRT in our study, durvalumab improved both the PFS (HR 0.71) and OS (HR 0.31), although few patients (n = 21) were treated with durvalumab. To our knowledge, no studies have evaluated the relative effectiveness of durvalumab after sCRT. Nevertheless, in a large single arm study (PACIFIC-R), patients treated with durvalumab after sCRT had shorter PFS than patients treated with durvalumab after cCRT (19.3 vs 23.7 months). Also the phase II PACIFIC 6 trial reported a short mPFS of 10.9 months [36]. However, in the study of Vranker *et al.*, the PFS of durvalumab was not influenced by the type of CRT (sequential or concurrent) in the univariable analysis [27]. Of note, sCRT is proposed for elderly and/or less fit patients with clinically relevant comorbidities, which might explain the inferior PFS outcomes of patients treated with sCRT versus patients treated with cCRT [5,37].

We also compared the PFS of cCRT patients treated with durvalumab in our cohort with the PFS of cCRT patients treated with durvalumab in the trial. We observed a significant HR of 0.64 (95% CI: 0.46–0.91) in favor of durvalumab in the real-world. This additional PFS benefit in the real-world population does not extend to OS outcomes because the OS benefit in our cohort was comparable to the OS reported in the PACIFIC trial. Our observation is in line with the results of the PACIFIC-R study, which showed a longer PFS (21.7 months) [10] than in the PACIFIC trial (16.8 months) [3]. Bruni *et al.* also found superior PFS outcomes (23.0 months) in real-world patients receiving durvalumab [22]. The OS observed in both studies did not reach the median and therefore could not be compared with the registration trial.

These findings give rise to the question whether the PFS observed in the real world is overestimated, especially in the context of a comparable OS. This observation may be explained by differences in establishing progressive disease. First, in the real-world, the frequency of radiological imaging is lower and less consistent than the strictly timed imaging scheme (every 8 weeks) used in the PACIFIC trial, which caused delayed or even missed progression events near the end of follow-up [38,39]. Second, the radiological evaluation of treatment response in the context of CRT is complex because it is difficult to distinguish true progression from radiation fibrosis [40]. In clinical practice, physicians may be extra careful to declare that patients have progressive disease and to prematurely discontinue immunotherapy. Third, contrary to the original RECIST criteria, the iRECIST criteria require confirmation of progressive disease within 4–8 weeks after the initial signs of progression of new disease [41–44]. So, the use of the iRECIST in the real world could delay the detection of progression events and probably fewer true progression events may occur [42]. These effects might be observed in the decline around two months in PFS KM curves of the PACIFC trial (Figure 4), whereas the first drop in the PFS curve of our cohort is later and smaller than the first drop in the PFS curve of the PACIFIC. Our observation of prolonged PFS but similar OS in the real-world versus

the trial appears unique to durvalumab post-CRT treatment, since we did not find comparable results for other immunotherapy treatments in the context of NSCLC.

The real world effectiveness of durvalumab appears to be a complex area of research for several reasons. In addition to the aforementioned challenge of defining progressive disease in the setting of CRT and immunotherapy, several studies [11,16,22,29] used the end of CRT rather than the start of durvalumab as the index date for the calculation of PFS which leads to an overestimated PFS. Also, the duration of sCRT is longer than cCRT, which may have affected the outcome measures of durvalumab in studies that did not include historical controls. Finally, including a historical cohort requires the imputation of an index date and exclusion of patients that progressed before that date. The strengths of our study are that we used a valid index date and minimized the risk for immortal time bias [45]. We also included historical controls to investigate the relative effectiveness of durvalumab and we are the first to include a sCRT cohort. Our study also has some limitations. First, our study lacks power to properly evaluate the effect of durvalumab in a cohort of sCRT pretreated patients. Second, the follow-up time for patients treated with durvalumab was relatively short which explains why the median OS was not reached. Another limitation is that we do not have information on the follow-up methods for disease progression to confirm our explanation for the differences seen in PFS between the real-world and the PACIFIC trial. Lastly, at baseline, the tumor PDL1 expression was not available in the majority of patients (n = 244, 64%).

Conclusion

In both the sCRT and cCRT cohort, we observed that durvalumab following CRT improves the survival outcomes compared with CRT alone. The observed PFS of durvalumab after cCRT in our cohort is significantly longer than the PFS reported in the PACIFIC trial which could be the result of differences in follow-up methods between the real-world and clinical trial.

Summary points

- The PACIFIC trial demonstrated survival benefit of durvalumab post concurrent chemoradiotherapy (CRT) in patients with stage III NSCLC. However, clinical trial results may not be generalizable to daily clinical practice. Therefore, real-world studies are needed to address this knowledge gap.
- The real-world effectiveness of durvalumab appears to be a complex area of research because the type of CRT (concurrent or sequential) could affect the outcomes. In addition, the pretreatment with CRT may introduce immortal time bias, as patients with progressive disease before the start of durvalumab were excluded.
- This Dutch multicenter, retrospective, cohort study investigated the real-world effectiveness of patients treated with durvalumab post concurrent CRT (cCRT) or sequential CRT (sCRT) versus historical controls treated with concurrent CRT (cCRT) or sequential CRT (sCRT) alone. These results were compared with the results of the PACIFIC trial.
- Patients diagnosed with stage III NSCLC and who received first line CRT were included. The population was divided into four cohorts; cCRT with durvalumab (n = 106), cCRT without durvalumab (n = 161), sCRT with durvalumab (n = 21) and sCRT without durvalumab (n = 95).
- Both cCRT and sCRT patients treated with durvalumab had better PFS (cCRT: aHR: 0.69, 95% CI: 0.49–0.99 and sCRT cohort: aHR: 0.71, 95% CI: 0.37–1.40) and OS (cCRT: aHR: 0.71, 95% CI: 0.44–1.13 and sCRT cohort: aHR: 0.32, 95% CI: 0.09–1.03) than the historical controls, although not all results were significant.
- The median progression-free survival (mPFS) for durvalumab treatment observed in our study was significantly longer than the mPFS observed in the PACIFIC trial (27.1 vs 16.8 months), while the OS results were not different.
- We hypothesized that this discrepancy in mPFS is due to differences in the methods and frequency of PFS assessment during follow-up in the real-world and in the trial.
- The strengths of our study are that we included historical controls to investigate the relative effectiveness of durvalumab post cCRT and post sCRT. We also minimized the risk for immortal time bias.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/imt-2023-0002

Author contributions

MV Verschueren, LT Bloem, ACG Egberts, VDEMW Garde and BJM Peters were involved in creating the research question and study design. BJM Peters contributed to study supervision. MV Verschueren, T Dijs, A.v.V, JL G, SC, LEL H and AAJ Smit were responsible for acquisition of data. MV Verschueren and BJM Peters performed the data analysis. All authors contributed to interpretation of data. MV Verschueren and B.J.M wrote the main manuscript text. All authors reviewed the manuscript.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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