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RESEARCH ARTICLE

The S-REAL study: Spanish real-world data on unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy

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Abstract

Objectives The S-REAL study aimed to assess the effectiveness of durvalumab as consolidation therapy after definitive chemoradiotherapy (CRT) in a real-world cohort of patients with locally advanced, unresectable stage III non-small cell lung cancer (LA-NSCLC) included in a Spanish early access program (EAP).

Methods In this multicentre, observational, retrospective study we analysed data from patients treated in 39 Spanish hospitals, who started intravenous durvalumab (10 mg/kg every 2 weeks) between September 2017 and December 2018. The primary endpoint was progression-free survival (PFS). Secondary endpoints included patient characterization and adverse events of special interest (AESI).

Results A total of 244 patients were followed up for a median of 21.9 months [range 1.2–34.7]. Median duration of durvalumab was 45.5 weeks (11.4 months) [0–145]. Median PFS was 16.7 months (95% CI 12.2–25). No remarkable differences in PFS were observed between patients with programmed cell death-ligand 1 (PD-L1) expression $\geq 1\%$ or $< 1\%$ (16.7 versus 15.6 months, respectively). However, PFS was higher in patients who had received prior concurrent CRT (cCRT) versus sequential CRT (sCRT) (20.6 versus 9.4 months). AESIs leading to durvalumab discontinuation were registered in 11.1% of patients.

Conclusions These results are in line with prior published evidence and confirm the benefits of durvalumab in the treatment of LA-NSCLC patients in a real-world setting. We also observed a lower incidence of important treatment-associated toxicities, such as pneumonitis, compared with the pivotal phase III PACIFIC clinical study.

Keywords NSCLC · Durvalumab · Chemoradiotherapy · PD-L1 · PFS · Real-world

Abbreviations

AE	Adverse events
AESI	Adverse events of special interest
cCRT	Concurrent chemoradiotherapy
CT	Chemotherapy
EAP	Expanded access program
IQR	Interquartile range
LA-NSCLC	Locally advanced non-small cell lung cancer
OS	Overall survival
PD-L1	Programmed cell death ligand-1
PFS	Progression-free survival
Q1	Quartile 1 (25%)
Q3	Quartile 3 (75%)
sCRT	Sequential chemoradiotherapy
SD	Standard deviation
SOC	Standard of care

Extended author information available on the last page of the article

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Introduction

Lung cancer represents nearly 12% of total cancer diagnoses worldwide and continues to be the leading cause of cancer deaths. More than 2 million new cases were diagnosed in 2020, accounting for 18% of total cancer deaths worldwide [1]. In Spain, 29,188 new cases and 22,930 deaths were estimated in 2020 [2]. Non-Small Cell Lung Cancer (NSCLC) is the most common lung cancer (accounting for 80–85% of all cases), and 30% of these patients present with locally advanced disease at diagnosis [3]. NSCLC tumours encompasses squamous cell carcinoma, adenocarcinoma, and large cell carcinoma of the lung.

The standard of care (SOC) for inoperable stage III NSCLC has been until now a regimen of platinum-based doublet chemotherapy (CT) delivered concurrently or sequentially with radiotherapy (RT) followed by active surveillance [4, 5]. However, the 5-year overall survival (OS) rate achieved was only around 15–\30% after treatment completion [6, 7]. This changed after the publication of the first results of the landmark PACIFIC clinical trial, a randomised, double-blind, placebo-controlled, multi-centre phase 3 study confirming that 1 year of consolidation treatment with the anti-programmed cell death-ligand-1 (anti-PD-L1) durvalumab after completion of cCRT increased progression-free survival (PFS) and OS compared to placebo [7–9], and presented an acceptable safety profile with no negative impact on patient-reported quality of life [10]. Based on post-hoc analyses that showed improved outcomes in patients with PD-L1 expression levels ≥ 1%, in 2018 the European Medicines Agency (EMA) approved the use of durvalumab as consolidation therapy restricted to adult patients with PD-L1 ≥ 1% on tumour cells [11]. One year of durvalumab after cCRT became the new SOC for locally advanced unresectable stage III NSCLC patients with PD-L1 ≥ 1% and no disease progression after cCRT [12, 13].

Updated data from the PACIFIC study showed that the survival benefits associated with durvalumab were durable [14, 15] with a median OS of 47.5 versus 29.1 months (placebo) and a median PFS of 16.9 versus 5.6 months [14, 15]. The estimated 5-year rates for durvalumab and placebo were 42.9% versus 33.4% for OS and 33.1% versus 19.0% for PFS [16].

The safety and efficacy of durvalumab in subgroups of patients not previously included in the PACIFIC trial were barely known at the moment of this proposal [17–20]. The retrospective international PACIFIC-R study (NCT03798535) confirmed the efficacy of consolidative durvalumab after CRT in patients with unresectable stage III NSCLC who were included in an expanded access program (EAP) in Europe. Median PFS was 21.7 months (95% CI 19.2–24.5) after a median follow-up of 23 months [21], and the safety profile remained unchanged.

The heterogeneity of unresectable stage III NSCLC and the diversity of multidisciplinary treatment approaches used in the real-world setting justify the need to collect data from independent cohorts of patients to obtain a more detailed characterization. To achieve this goal, we performed this study to assess the real-world effectiveness and tolerability of durvalumab in a cohort of 244 patients with unresectable stage III NSCLC enrolled in a Spanish EAP. The aim of this study was to provide the first real-world data in Spain on the effectiveness of durvalumab in a broad cohort of patients receiving durvalumab outside the controlled criteria and context of clinical trials. We also addressed a detailed sociodemographic and clinical characterization of this patient population, including a description of the most common treatment patterns used in routine clinical practice in Spain.

Methods

Study design and patient population

The S-REAL study (ClinicalTrials.gov NCT04285866) was a Spanish multicentre, observational, retrospective study on patients with unresectable stage III LA-NSCLC treated in 39 participating centres who were enrolled in an EAP for durvalumab between 1 September 2017 and 21 December 2018. A total of 251 patients were screened; 244 met the study criteria and were included in data analyses. In April 2021, data collected in this study were integrated into the global analyses performed in the international real-world PACIFIC-R study (ClinicalTrials.gov NCT03798535) [21].

The aim of the study was to determine the effectiveness of at least 1 dose of durvalumab in unresectable stage III LA-NSCLC patients after completion of CRT. In addition, we also aimed to characterize this patient population and the routine management and regimen patterns used to treat their disease. Data were obtained retrospectively and during one routine clinical visit from the electronic medical records of the 39 participating hospitals. The index date was defined as the date on which patients in the EAP received the first dose of durvalumab. Patients were followed from the index date to the end of follow-up (date of death, withdrawal from study drug, loss to follow-up, or end of study [data cut off: April 8, 2021]).

Inclusion criteria:

- Patients ≥ 18 years at the time of enrolment, with a histologically or cytologically documented diagnosis of locally advanced or locally recurrent unresectable

NSCLC (stage III) (according to American Joint Committee on Cancer [AJCC] lung cancer edition 7 or 8).
- Patients treated with concurrent or sequential CRT (cCRT or sCRT) and showing no disease progression following CRT.
- Patients treated with at least one dose of durvalumab within the EAP.

Patients accepted in the EAP but not receiving treatment and patients treated with durvalumab in clinical studies prior to the index date (first dose of durvalumab received within the EAP) were excluded.

Study endpoints

The primary objective of the study was to determine the effectiveness of durvalumab in patients treated in real-life settings on the basis of PFS, which was defined as the time from the index date (date of the first dose of durvalumab) to the date of investigator-determined disease progression or death (if no progression) or the end of follow-up for censored patients.

Secondary objectives included:

- Determination of the effectiveness of durvalumab by means of the evaluation of 1-year PFS rate.
- Sociodemographic and clinical characteristics of patients with unresectable stage III LA-NSCLC treated with durvalumab, including age, sex, race, smoking habit, comorbidities (including previous malignancies), ECOG performance status (PS), NSCLC stage IIIA, IIIB or IIIC, PD-L1 status, oncogenic aberrations, tumour characteristics (including histology, size of the primary tumour, location of metastases at progression, date of progression, etc.), prior medication and lines of treatment, including RT (dose, dates, number of cycles, type, and fractions used), CT and CRT strategy (concurrent, sequential, concurrent plus induction, concurrent with no induction).
- Safety of durvalumab by means of description of adverse events (AE) of special interest (AESI) leading to temporary interruption or permanent discontinuation, or that required concomitant corticosteroids, immunosuppressants and/or endocrine therapies (AE were rated according to the National Cancer Institute´s Common Terminology Criteria for AE or CTCAE version 5.0).
- PFS assessment in subgroups of interest.

Further description of secondary objectives is included in the Supplementary Information.

Statistical analysis

A descriptive statistical analysis was performed. General descriptive statistics for continuous numerical variables included the number of observations, mean, standard deviation (SD), and median and interquartile ranges (IQR, Q1–Q3), when appropriate. For categorical variables, the frequency distribution and percentage of subjects with a certain event/characteristic were presented. Where relevant, two-sided 95% confidence interval (95% CI) limits of the mean for numerical variables and 95% CI limits for proportions was provided. PFS was estimated and plotted using the Kaplan–Meier method.

Missing values were not considered when calculating percentages or any other descriptive estimator, meaning that only valid values are presented. No methods for handling missing data were used. The analysis was performed using IBM SPSS Statistics software, Version 26.0 (IBM Corp. Armonk, NY).

Results

Baseline sociodemographic and clinical characterization of patients

A total of 244 patients with unresectable stage III NSCLC enrolled in the EAP that received at least one dose of durvalumab after definitive CRT were included for analysis.

The median follow-up from the start of durvalumab was 21.9 months [range 1.2–34.7] and only 2 patients (0.8%) were lost to follow-up. Baseline characteristics of patients at the time of EAP inclusion are summarised in Table 1. Overall, the median age of patients was 67.0 years at the time of EAP inclusion, and 18% were over 75 years. Most patients were men (79.9%), and the majority (97%) were current or former smokers. At the time of initial NSCLC diagnosis, 47.3% of patients presented nonsquamous histology and 92.7% had stage III disease. The most prevalent comorbidity was hypertension (39.3%), followed by chronic obstructive pulmonary disease (23.8%). From the total of patients tested for EGFR mutational status ($n = 98$), 2% had an EGFR-sensitizing mutation.

From a total of 176 patients (72.1%) tested for PD-L1-expression, 72.2% presented PD-L1 $\geq 1\%$ (PD-L1 positive patients), 19.9% had PD-L1 $< 1\%$, and 8.0% had unknown PD-L1 levels (Table 1). In general, baseline characteristics were similar across both PD-L1 subgroups (Supplementary Table 1).

Table 1 Baseline sociodemographic and clinical characteristics of the study population at inclusion in the early access program (EAP)

Parameters	N = 244
Age (years), median [range]	67.0 [42–86]
< 70 years, *n* (%)	151 (61.9%)
70–75 years, *n* (%)	50 (20.5%)
> 75 years, *n* (%)	43 (17.6%)
Men, *n* (%)	195 (79.9%)
Women, *n* (%)	49 (20.1%)
Smoking status, *n* (%)	
Non-smoker	8 (3.3%)
Former smoker	81 (33.2%)
Current Smoker	155 (63.5%)
Comorbidities, *n* (%)	
COPD	58 (23.8%)
Other CPD	12 (4.9%)
Diabetes	40 (16.4%)
Hypertension	96 (39.3%)
Cardiovascular disease	30 (12.3%)
Cerebrovascular disease	6 (2.5%)
Peripheral arterial disease	19 (7.8%)
Kidney disease	8 (3.3%)
Liver disease	4 (1.6%)
Endocrine disease	13 (5.3%)
Gastrointestinal disease	7 (2.9%)
Autoimmune diseases	6 (2.4%)
History of other cancers	57 (23.4%)
ECOG/WHO PS at index date, *n* (%)[a]	
0	105 (54.1%)
1	82 (42.3%)
2	7 (3.6%)
Histology type at NSCLC diagnosis, *n* (%)[b]	
Squamous carcinoma	110 (45.3%)
Adenocarcinoma	110 (45.3%)
Adenosquamous carcinoma	4 (1.6%)
Large cell carcinoma	5 (2.1%)
Other	10 (4.1%)
Unknown	4 (1.6%)
PD-L1 status at stage III NSCLC diagnosis, *n* (%)[c]	
< 1%	35 (19.9%)
≥ 1%	127 (72.2%)
Unknown	14 (8.0%)
Patients who received CRT, *n* (%)[d]	
Concomitant	170 (69.7%)
With induction CT	100 (41.0%)
With consolidation CT	10 (4.1%)
Sequential	38 (15.6%)
Time from end of CRT to start of durvalumab, *n* (%)	
< 14 days	1 (0.4%)
≥ 14 days	233 (95.5%)
≤ 42 days	13 (5.6%)
> 42 days	221 (94.4%)

Table 1 (continued)

Disease stage at initial diagnosis was determined according to the 7th or 8th editions of the American Joint Committee on Cancer (AJCC) staging manual. The "unknown" category includes patients whose PD-L1 test results were not clearly reported

COPD chronic obstructive pulmonary disease, *CPD* chronic pulmonary diseases, *CRT* chemoradiotherapy, *CT* chemotherapy, ECOG or WHO PS Eastern Cooperative Oncology Group or WHO performance status, *IASCL* International Association for Study of Lung Cancer, *NSCLC* non-small cell lung cancer, *PD-L1* programmed cell death-ligand 1, *RT* radiotherapy, *SD* standard deviation

[a]Missing data from 50 patients

[b]Missing data from 1 patient

[c]A total of 176 patients were tested for PD-L1 status using the 1% threshold

[d]A total of 36 patients had received other prior therapies

Induction CT was defined as any platinum-based CT administered at least 10 days prior to the start of RT. Consolidation CT was defined as any dose of platinum-based CT administered more than 10 days after the last dose of RT

Characterization of prior CRT regimens

One hundred seventy patients (69.7%) had received concurrent CRT (cCRT) and 38 patients (15.6%), sequential CRT (sCRT) (Table 1). The median dose of RT received was 66 Gray (Gy) delivered in a median of 33 fractions. After CRT, most patients achieved a partial response (76.8%) and 18.6% presented stable disease (Supplementary Table 2). Overall, 97.6% of patients with available data had not progressed. All patients had received platinum-based regimens of CT (Supplementary Table 3).

There was a higher proportion of older patients (≥ 70 years), and a higher percentage of patients who had been treated with sCRT presented large tumours (56.6% versus 47.1% of patients in the cCRT group) (Supplementary Table 4).

Durvalumab treatment

Median time to start of durvalumab after CRT was 72 days. Only 5.6% of patients started treatment within 42 days of CRT completion, and 94.4% were treated outside the 42-day window (Table 1). Median duration of durvalumab treatment was 10.5 months. Overall, 44.7% of patients completed 12 months of planned durvalumab regimen and received a median of 19.0 infusions. Temporary interruption of durvalumab was required in 11.1% of patients for a median of 23 days.

The main reason for permanent discontinuation of durvalumab was completion of the 12-month treatment regimen (44.7% of patients), followed by disease progression (32.4%), and AE (13.2%).

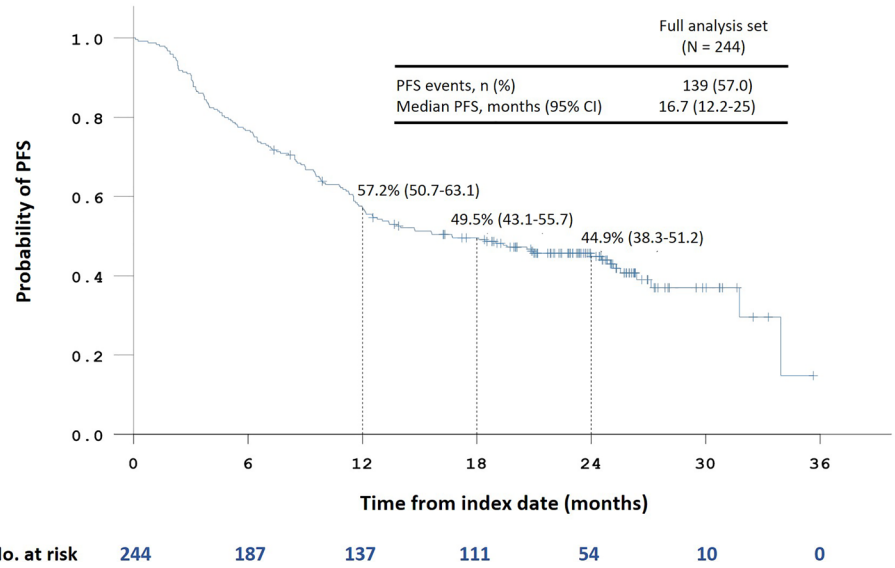

Fig. 1 Kaplan–Meier PFS curve for the full analysis set. "+" signifies censored observations. Dotted lines represent 12-, 18- and 24-months analyses. CI, confidence interval; PFS, progression-free survival

Analysis of survival outcomes in specific patient subgroups

Overall median PFS was 16.7 months (95% CI 12.2–25), with 57.2%, 49.5% and 44.9% of patients being progression-free at 12, 18 and 24 months, respectively (Fig. 1). The analyses performed on subgroups of interest showed that median PFS was similar among patients with PD-L1 ≥ 1% ($n = 127$) and patients with PD-L1 < 1% ($n = 35$) (16.7 versus 15.6 months, respectively)

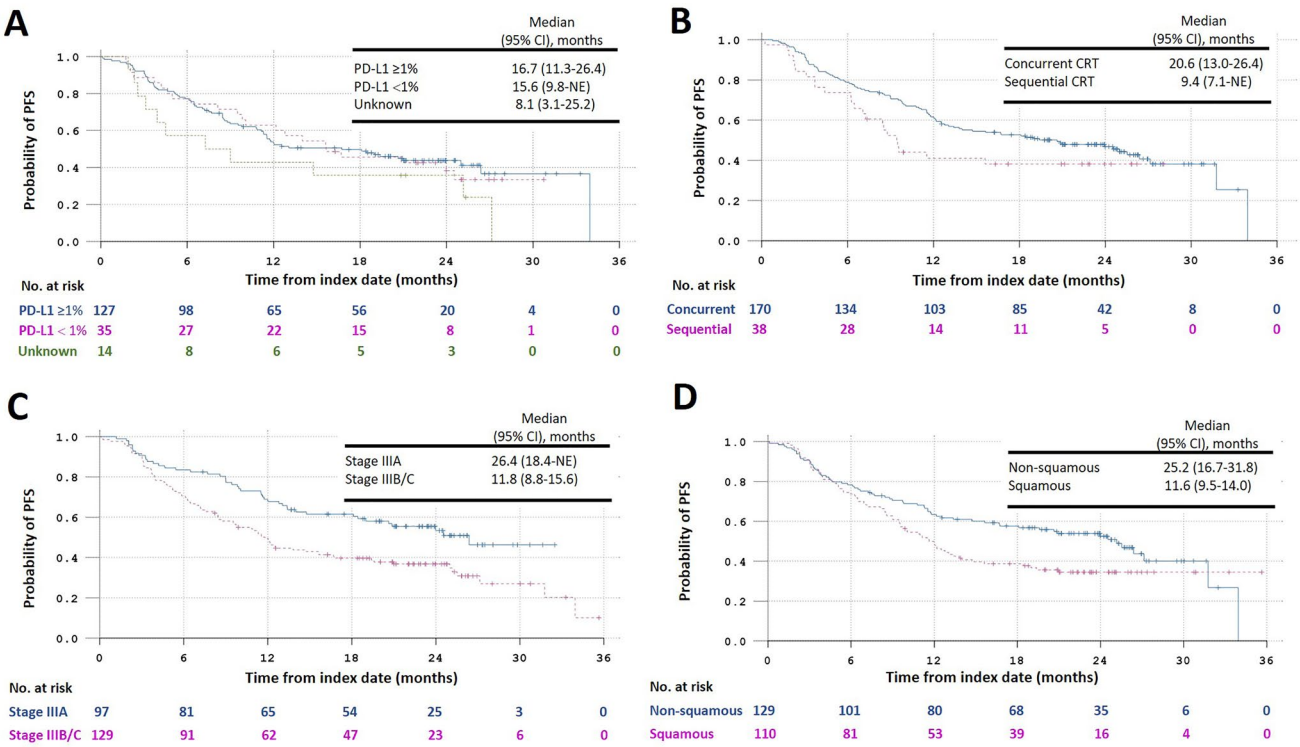

Fig. 2 Kaplan–Meier PFS curves for subgroups of interest defined by (A) PD-L1 status, (B) type of prior CRT, (C) disease stage, and (D) histologic subtype. "+" signifies censored observations. The "unknown" PD-L1 subgroup includes patients whose PD-L1 test results were not clearly reported in the case report forms and could not therefore be classified as PD-L1 expression level ≥ 1% or < 1%. *CI* confidence interval, *CRT* chemoradiotherapy, *PD-L1* programmed cell death ligand 1, *PFS* progression free-survival

(Fig. 2A). Longer PFS was observed in patients who had received cCRT ($n = 170$) versus those treated with sCRT ($n = 38$) during the first and second year of treatment (Table 3), which gave a superior overall median PFS of 20.6 months versus 9.4 months in each subgroup, respectively) (Fig. 2B). Overall PFS in patients > 75 years was higher than that of patients ≤ 75 (18.4 months versus 16.7 months). PFS was also consistently higher in patients at disease stage IIIA versus IIIB and IIIC (Table 2), with a median PFS of 26.4 versus 11.8 months, respectively (Fig. 2C), and the same was observed in patients with non-squamous versus squamous tumour histologic type (Table 2), with a median PFS of 25.2 versus 11.6 months, respectively (Fig. 2D). As expected, PFS was lower in patients with an ECOG PS 2 (19.0 versus 13.4 months). Median PFS was 20.9 months in 13 patients who started durvalumab < 42 days after the end of CRT versus 18.1 months in the 221 patients who started treatment > 42 days after CRT completion (Table 2).

Patterns of disease progression and recurrence

A total of 123 patients (51.3%) experienced progression (excluding 4 patients for whom this information was not available, and 2 patients with unknown types of recurrence according to available data). Local progression was reported in 63 patients (25.8%). Distant metastases were confirmed in 66 patients (27%).

Safety

In total, 94 patients (38.5%) presented AESIs, and durvalumab was temporarily interrupted in 26 of these cases (10.7%) and permanently discontinued in 27 (11.1%) The most frequent AESI was pneumonitis (13.9%), followed by endocrinopathies in 11.1% and dermatitis in 7% of patients (Table 3). Pneumonitis or interstitial lung disease (ILD) affected 14.8% of patients (36 out of 244 patients). Pneumonitis or ILD led to interruption of durvalumab in 4.1% of patients and permanent discontinuation in 7.8%. No fatal events were reported. Median time from the start

Table 2 Real-world PFS outcomes in the overall study population and in subgroups of interest at data collection

	N	Progression-free, *n* (%)	Overall median PFS (months) (95% CI)	PFS rate (%) 1 year (95% CI)	PFS rate (%) 2 years (95% CI)
Overall study population	244	104 (42.6%)	16.7 (12.2–25)	57.2 (50.7–63.1)	44.9 (38.3–51.2)
PD-L1 status at stage III diagnosis, *n* (%)[f]					
< 1%	127	13 (37.1%)	15.6 (9.8–NE)	62.9 (44.8–76.5)	38.3 (21.9–54.4)
≥ 1%	35	54 (42.3%)	16.7 (11.3–26.4)	53.0 (43.9–61.3)	43.8 (34.7–52.4)
Unknown	14	3 (21.4%)	8.1 (3.1–25.2)	42.9 (17.7–66.0)	35.7 (13.0–59.49)
Prior CRT					
Concurrent	170	74 (43.5%)	20.6 (13.0–26.4)	61.1 (53.3–67.9)	46.8 (38.9–54.3)
Sequential	38	15 (39.5%)	9.4 (7.1–NE)	41.1 (25.3–56.2)	38.1 (22.8–53.4)
Age at inclusion in the EAP					
≤ 75 years	201	88 (43.8%)	16.7 (12.1–26.4)	57.5 (50.3–64.0)	46.2 (39.1–53.1)
> 75 years	43	16 (37.2%)	18.4 (10.8–25.0)	55.8 (39.8–69.1)	39.7 (24.5–54.5)
ECOG or WHO PS score					
0–1	187	81 (43.3%)	19.0 (12.0–25.5)	57.5 (50.0–64.2)	45.2 (37.6–52.4)
2	7	3 (42.9%)	13.4 (4.0–NE)	57.1 (17.2–83.7)	42.9 (9.8–73.4)
Disease stage at stage III NSCLC diagnosis					
Stage IIIA	97	52 (53.6%)	26.4 (18.4–NE)	67.9 (57.5–76.2)	53.3 (42.3–63.2)
Stage IIIB/C	129	42 (32.6%)	11.8 (8.8–15.6)	49.4 (40.5–57.7)	36.8 (28.3–45.2)
Histology					
Squamous	110	39 (35.5%)	11.6 (9.5–14)	49 (39.3–57.9)	34.5 (25.6–43.5)
Non squamous	129	62 (48.1%)	25.2 (16.7–31.8)	63.3 (54.4–71.0)	52.5 (43.1–61.0)
Time from end of RT to start of durvalumab					
≤ 42 days	13	6 (46.2%)	20.9 (4.0–NE)	61.5 (30.8–81.8)	44.9 (17.7–69.0)
> 42 days	221	96 (43.4%)	18.1 (12.1–25.5)	76.5 (70.3–81.5)	45.7 (38.8–52.3)

The "unknown" category in the PD-L1 subgroup analysis includes patients whose PD-L1 test results were not clearly reported

CI confidence interval; *CRT* chemoradiotherapy; *EAP* expanded access program; *ECOG or WHO PS* Eastern Cooperative Oncology Group or WHO performance status; *NE* not estimable; *NSCLC* non-small cell lung cancer; *PD-L1* programmed cell death-ligand; *RT* radiotherapy

Table 3 Adverse events of interest (AESI)

	Total	Temporary interruption	Permanent discontinuation
Time to AESI occurrence (days), median [range]	99 [1–436][a]	82.5 [1–326][b]	101 [1–298][c]
Patients with any type of AESI, *n* (%)	94 (38.5%)	26 (10.7%)	27 (11.1%)
Types of AESI, *n* (%)			
Pneumonitis	34 (13.9%)	10 (4.1%)	16 (6.6%)
ILD	3 (1.2%)	0 (0%)	3 (1.2%)
Endocrinopathies	27 (11.1%)	3 (1.2%)	0 (0%)
Rash / dermatitis	17 (7.0%)	1 (0.4%)	1 (0.4%)
Diarrhoea / colitis / intestinal perforation	7 (2.9%)	3 (1.2%)	1 (0.4%)
Nephritis / blood creatinine increases	6 (2.5%)	4 (1.6%)	1 (0.4%)
Hepatitis or transaminase increases	4 (1.6%)	2 (0.8%)	2 (0.8%)
Neuropathy / neuromuscular toxicity	2 (0.8%)	0 (0%)	0 (0%)
Other	17 (7.0%)	5 (2%)	7 (2.9%)

AESI adverse event of special interest, *ILD* interstitial lung disease, *SD* standard deviation

[a]$n=117$ patients; [b]$n=28$ patients; [c]$n=31$ patients. Percentages were calculated over the total included patients ($N=244$)

of durvalumab to onset of the first pneumonitis/ILD event was 2.4 months. These events were mostly mild to moderate in intensity (83.3%): 38.9% of events were grade 1 (affecting 14 patients, 5.7%); 44.4% were grade 2 (16 patients, 6.6%); 11.1% were grade 3 (4 patients, 1.6%), and 2.78% were grade 4 (1 patient, 0.4%). The treatment of choice for 83.3% of events was corticosteroids.

Discussion

This S-REAL study provides valuable information on the characterization of a population of 244 patients with unresectable stage III NSCLC who received consolidative durvalumab treatment after definitive CRT in a real-world setting in Spain. Our PFS results were similar to the PACIFIC landmark study and the favourable results in selected subgroups of patients who were not included in the clinical trial [8, 9]

Several retrospective real-world studies have explored the use of durvalumab in other countries in more heterogeneous cohorts of patients. Median PFS with durvalumab after cCRT ranged from 16 to 23 months and 1-year PFS rates ranged from 56 to 66% [21–27]. In their retrospective study performed in Singapore, Huang et al. (2022) reported a median PFS of 17.5 months and a 1-year PFS rate of 62.2% in 39 patients [26]. Another study performed in Germany reported a median PFS of 20.1 months and a 1-year PFS of 56% in a population of 126 patients, including subjects with poor performance status and with autoimmune diseases [22]. Similar data were reported in real-life studies performed in the US (overall median PFS of 16.9 months and 1-year PFS of 57.2%) [27] and Japan (1-year PFS rate of 58%) [25]. Interestingly, the updated results of the large international PACIFIC-R (NCT03798535) study show a higher median PFS of 21.7 months (95% CI: .1–24.5), with a 1-year PFS rate of 62.2%. According to the authors, these favourable results could be due to the lower frequency of progression assessments or the heterogeneity of criteria used for tumour evaluations [21].

Viewing any comparison with caution, we found that the durvalumab survival outcomes and safety profile confirmed in the S-REAL cohort were similar or even higher than those reported in the PACIFIC clinical trial. Moreover, we observed that almost 45% of all patients were alive and free of disease progression 2 years after starting durvalumab.

Durvalumab can be administered within an EAP with more freedom than it would be in clinical trials or under currently approved indications and clinical guidelines [11, 13, 28]. For example, the S-REAL cohort enrolled in the EAP included patients with prior autoimmune disease, ECOG PS 2, patients treated with sequential CRT, or elderly patients in whom durvalumab showed similar effectiveness when compared with younger patients [11]. In our study, all subgroups analysed obtained a similar benefit with durvalumab, suggesting that this drug is safe in special, more frail subgroups of patients.

The results of the PACIFIC trial suggest that the timing and duration of durvalumab could have an impact on survival. Better outcomes were observed in patients who started durvalumab shortly after CRT completion (< 14 days) versus those who started after 14 days (hazard ratio, [HR] 0.39; 95% CI 0.26–0.58 versus HR 0.63, 95% CI 0.49–0.80, respectively). According to published post-hoc analyses, median PFS was not reached in patients who started durvalumab < 14 days after completing CRT, while

median PFS for durvalumab was 14.0 months in patients treated ≥ 14 days after CRT [29]. In our cohort, only 0.4% of patients started durvalumab < 14 days after the end of CRT, and 5.6% started within the 42 days time window, so there is no enough evidence to draw any conclusion in this regard. However, no notable differences in PFS were observed between patients initiating durvalumab ≤ 42 days or > 42 days after CRT. Our data confirm that in current clinical practice the goal of starting early treatment with durvalumab, as reported in the PACIFIC trial, has not yet been achieved. The median delay of 72 days before starting durvalumab observed in our study could be due to several reasons, such as the need to recover from toxicities associated with prior CRT treatment or bureaucratic red tape, among others. However, it is interesting to note that the overall effectiveness of durvalumab did not appear to be negatively affected by this delay.

Although cCRT is the SOC for unresectable stage III NSCLC in clinical guidelines [13, 28], in real clinical practice sCRT is used instead for several reasons, such as concerns regarding tolerance of cCRT or the patient's clinical status (advanced age or frailty). In our S-REAL cohort, 15.6% of patients had received sCRT, a similar rate as that reported in the PACIFIC-R cohort (14%). In both cohorts, patients who had received sCRT were older than those in the cCRT subset (median 70 years versus 66 years, respectively); specifically, 55.3% of patients in the sCRT group were aged ≥ 70 years versus 33.5% in the cCRT group. Our data suggest that durvalumab after sCRT also provided a benefit to these patients, with a median PFS of 9.4 months. Ongoing prospective clinical trials such as phase II PACIFIC-6 (NCT0369330) and phase III PACIFIC 5 (NCT03706690) [30, 31] will provide further evidence on the safety and efficacy of durvalumab after sCRT. Indeed, preliminary data from the PACIFIC-6 trial already point to a beneficial effect of durvalumab in this setting [30].

Our cohort of durvalumab patients also achieved longer PFS after cCRT versus sCRT, a finding that is in line with data from other real-world cohorts. Bruni et al. (2021) also observed longer median PFS in patients after cCRT (23 months versus 13.5 months after sCRT), although the difference was not significant [24]. This is similar to the PFS difference observed by Huang et al. (2022) (median PFS of 17.5 versus 8.9 months, after cCRT or sCRT, respectively; HR 0.47, $p = 0.038$) [26]. The same favourable trend was confirmed in the PACIFIC-R (median PFS of 23.7 months after cCRT versus 19.3 months after sCRT) [21]. Moreover, we observed that the magnitude of PFS benefit after cCRT versus sCRT was even numerically higher than previous reports (20.6 months versus 9.4 months, respectively). We also found that the partial response rate was higher than that reported in the PACIFIC trial and even in the PACIFIC-R study (76.8% versus 48.7% and 61%, respectively) [8, 21]. However, as CT scan results were not centrally reviewed in this real-practice context, no further conclusions can be drawn.

It is also important to highlight that overall toxicity observed in this S-REAL cohort was even lower than that reported in the pivotal PACIFIC trial. In fact, only 11.1% of patients in our cohort discontinued durvalumab due to AESI of any grade (versus 15.4% withdrawal reported in the PACIFIC study). In line with reports from other real-life cohorts [22, 23], we found that pneumonitis or ILD was the most common AESI, although its incidence was lower than that reported in the PACIFIC trial (14.8% versus 34%) and also in other real-world studies, including the PACIFIC-R study, which ranged between 17 and 28%, [21, 24, 26].

This study has some limitations, mainly due to its retrospective design. Comparative subgroup analyses should be interpreted with caution, as variability in real clinical practice may bias outcomes, for example, by excluding the consideration of other potential associated clinical factors. Data collection was limited to the availability of existing health records, so some data were incomplete or missing. This EAP did not observe the PD-L1 status in tumours to facilitate patient enrolment, so we had no data on PD-L1 status in 28% of patients. Also, variability in the follow-up patterns and radiological assessments among hospital centres must be considered.

Conclusions

This S-REAL study showed that durvalumab after CRT gave LA-NSCLC patients a PFS benefit generally in line with the results confirmed by the pivotal PACIFIC study, and that the safety profile was manageable. More importantly, the S-REAL patients represent a true-to-life population in terms of the CRT regimens received in routine clinical practice and the time from CRT completion to the start of durvalumab. Altogether, this study provides important real-world evidence on the efficacy, tolerability, and safety of durvalumab as consolidative therapy after definitive CRT.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest AGR has received speaker and consultant honoraria from AstraZeneca, Amgen and Takeda, and travel support from AstraZeneca, Takeda and MSD; AT has received personal fees and non-financial support from Pfizer, Roche, BMS, MSD, and AstraZeneca; RAA has received consultant and speaker honoraria from Boehringer, Novartis, Pharmamar and Roche, conference registration support from MSD Oncology, and has participated as PI coordinator in projects sponsored by Boehringer, Cebiotex, Janssen Oncology, Novartis, Rain Therapeutics and Roche; RBC has received speaker and/or consultant honoraria from Pfizer, Janssen, Sanofi, AstraZeneca, Bristol Myers, Roche, Takeda and Jannsen, and research funding from Roche; LV has received consultant honorarium from Boehringer Ingelheim, AstraZeneca and Sanofi and speaker honoraria from AstraZeneca, Sanofi, MSD, Pfizer and Roche. MASG has received speaker and lecturer honoraria from Takeda and Roche, and travel/meeting attendance support from Roche and PharmaMar; MD has received grants from Roche and travel/meeting attendance support from Lilly; SF has received speaker honorarium from Pfizer and Sanofi, and travel support from AstraZeneca and MSD; CA has received consultant honorarium from AstraZeneca, BMS, MSD and Novartis, research funding from MSD, Mirati and AstraZeneca, and travel support from Roche, Novartis, Takeda and Pierre Fabre; AB has received speaker and consultant honoraria from BMS, Roche, MSD, Sanofi and Takeda, and travel support from MSD, Roche and BMS; DI has received speaker/consultant honoraria from Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Hoffmann-La Roche, Janssen, Lilly, Merck, MSD, Novartis, Pfizer, Sanofi and Takeda, has participated in clinical trials sponsored by Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Hoffmann-La Roche, GSK, Janssen, Lilly, Merck, Mirati Therapeutics, MSD, Novartis, Pfizer and Sanofi, and has received research grants from AstraZeneca, BMS, Hoffmann-La Roche and GSK; LBH has received speaker honorarium from Roche, BMS and AstraZeneca, consultant honorarium from Boehringer and Sanofi, and meeting attendance support from MSD, Novartis, Sanofi and AstraZeneca; JLFP has received consultant and speaker honoraria from AstraZeneca; BM has received personal fees from Roche, BMS, MSD, Boehringer Ingelheim and Pfizer; XMR has received speaker and/or consultant honoraria from Novartis, Roche, Pfizer, Astra Zeneca and MSD, grants from BMS, travel/meeting attendance support from Roche, Lilly and MSD, and declares his membership of the boards of the Spanish Group for Transversal Oncology and Research in Orphan and Infrequent Tumors (GETTHI) and the Spanish Group for Cancer Immuno-Biotherapy (GETICA); MD has received consultant and/or speaker honoraria from AstraZeneca, Boehringer Ingelheim, Janssen Cilag, BMS MSD, Pfizer, Roche, Sanofi and Takeda; IGB has received consultant and/or speaker honoraria from MSD Oncology, Lilly, AstraZeneca and BMS/Celgene, Roche and Amgen, and travel support from MSD Oncology, Lilly and Daiichi Sankyo; DR-A has received consultant and speaker honoraria from Roche/Genentech, AstraZeneca, BMS, Boehringer Ingelheim, MSD, Merck Serono, Eli Lilly, Gilead, Sanofi, Regeneron, Incyte, Pfizer, Takeda and Novartis, and travel support from Roche, BMS, MSD, Sanofi, Regeneron and Novartis; GAJC has received speaker/consultant honoraria from AstraZeneca and Roche; LLM has received consultant/speaker honoraria from AstraZeneca; JMST has received speaker/consultant honoraria from AstraZeneca; PG has received consultant honorarium from Abbvie, Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi and Takeda, and direct funding from Medscape and Touch Medical. All other authors have no conflict of interest to declare.

Ethical approval (Research involving human participants and/or animals) and Informed consent This study followed the Helsinki Declaration, Good Clinical Practices and the Spanish Organic Law 3/2018 of 5 December on the Protection of Personal Data and digital rights guarantee. The study was approved by the Ethics Committee of Hospital Puerta de Hierro de Majadahonda (Madrid). Written informed consent was obtained from all enrolled patients. Patient medical information obtained for this study was confidential and was only disclosed to the researchers and third parties involved, as detailed in the informed consent form signed by the patients. Confidentiality standards were maintained by assigning each patient a unique subject identification number.

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