



HAL
open science

Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study

Nicolas Girard, Jair Bar, Pilar Garrido, Marina Chiara Garassino, Fiona M.A. McDonald, Françoise Mornex, Andrea Riccardo Filippi, Hans J.M. Smit, Solange Peters, John K. Field, et al.

► To cite this version:

Nicolas Girard, Jair Bar, Pilar Garrido, Marina Chiara Garassino, Fiona M.A. McDonald, et al.. Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study. *Journal of Thoracic Oncology*, 2023, 18 (2), pp.181-193. 10.1016/j.jtho.2022.10.003 . hal-04122372

HAL Id: hal-04122372

<https://hal.science/hal-04122372>

Submitted on 22 Jun 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License



Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study

*Corresponding author.

Disclosure: Dr. Girard reports receiving research grants/support from AstraZeneca, Amgen, Boehringer Ingelheim, Eli Lilly, Hoffmann-La Roche, Janssen, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Sivan, and Trizell; having consultative services for Bristol Myers Squibb, AstraZeneca, AbbVie, Amgen, Boehringer Ingelheim, Eli Lilly, Hoffmann-La Roche, Janssen, Merck, Merck Sharp & Dohme, Mirati, Novartis, Pfizer, Roche, Sanofi, and Sivan; receiving payment for expert testimony from AstraZeneca; having participation on a data safety monitoring board for Roche; having leadership role in the International Thymic Malignancy Interest Group; and having employment of a family member with AstraZeneca. Dr. Bar reports receiving support from Sheba Medical Center and Institute of Oncology during the conduct of the study; receiving research grants paid to the institution from AstraZeneca, Takeda, OncoHost, ImmuneAI, Merck Sharp & Dohme, Roche, and Eli Lilly; receiving research grants from the Israel Cancer Research Fund, Tel Aviv University; receiving consulting fees from Merck Sharp & Dohme, Bristol Myers Squibb, Roche, AstraZeneca, Novartis, Pfizer, Causalis, Bayer, and Takeda; receiving advisory fees from Roche, AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, AbbVie, Roche, Causalis, and Novartis; having leadership role in the Lung Ambition Alliance—Israel; and having stock ownership in Causalis. Dr. Garrido reports receiving personal fees from AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, IO Biotech, Janssen, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Takeda; receiving support for attending meetings and/or travel support from AstraZeneca and Roche. Dr. Garassino reports receiving grants from AstraZeneca and Merck; personal fees from AstraZeneca, Merck, Roche, Bristol Myers Squibb, Celgene, Boehringer Ingelheim, Novartis, GlaxoSmithKline, Pfizer, Eli Lilly, and Takeda. Dr. McDonald reports receiving support from AstraZeneca during the conduct of the study; consulting fees and payment or honoraria from AstraZeneca. Dr. Filippi reports receiving personal fees and nonfinancial support from AstraZeneca, Roche, Merck Sharp & Dohme, Ipsen, and Reflexion Medical Inc.; research grants paid to the institution and travel support from AstraZeneca. Dr. Smit reports receiving personal fees for participation on advisory boards for Merck Sharp & Dohme, Bristol Myers Squibb, and AstraZeneca. Dr. Peters reports having participation as a subinvestigator in trials (institutional financial support for clinical trials) sponsored by Amgen, AstraZeneca, Biodesix, Boehringer Ingelheim, Bristol Myers Squibb, Clovis, GlaxoSmithKline, Illumina, Eli Lilly, Merck Sharp & Dohme, Merck Serono, Mirati, Novartis, Pfizer, Phosphatidyl Therapeutics, and Roche/Genentech; having participation on an advisory board for, and consulting fees paid to the institution from, AbbVie, Amgen, AstraZeneca, Bayer, Beigene, Biocartis, Boehringer Ingelheim, Bristol Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, ecancer, Eli Lilly, Elsevier, Fishawack, Foundation Medicine, Illumina, Imedex, IQVIA, Incyte, Janssen, Medscape, Merck Sharp & Dohme, Merck Serono, Merrimack, Novartis, OncologyEducation, Pfizer, PharmaMar, Phosphatidyl Therapeutics, PER, PRIME, Regeneron, RMEI, Roche/Genentech, RTP, Sanofi, Seattle Genetics, and Takeda; receiving payment or honoraria paid to the institution from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, ecancer, Eli Lilly, Illumina, Imedex, Medscape, Merck Sharp & Dohme, Novartis, PER, Pfizer, Prime, Roche/Genentech, RTP, Sanofi, and Takeda; and receiving support for attending meetings and/or travel paid to the institution from AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche/Genentech, and Takeda. Dr. Christoph reports receiving payment and travel support from AstraZeneca for attending scientific boards during the conduct of this study; grants or

contracts, consulting fees, payment or honoraria, payment for expert testimony, support for attending meetings and/or travel, participation on a data safety monitoring board/advisory board, and other payments made to the institution from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sanofi, and Takeda. Dr. Sibille reports having membership on advisory boards for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Takeda. Dr. Fietkau reports having membership on advisory boards for, or receiving honoraria for lectures or grants from, AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, Novocure, Sennewald, Siemens, Fresenius, and Merck Darmstadt; receiving support for attending meetings and/or travel from Promedica, Merck Sharp & Dohme, Medupdate, AstraZeneca, Streamedup!, Sennewald, Uni Hamburg Eppendorf, DEGRO, Novocure, Uni Freiburg, DKG, and Bristol Myers Squibb. Dr. Haakensen reports receiving payment or honoraria from Takeda, Bristol Myers Squibb, and AstraZeneca; receiving payment for expert testimony from AstraZeneca; having participation on advisory boards for Pfizer and AstraZeneca; and receipt of materials or drugs from AstraZeneca, Ultimovacs, and Bristol Myers Squibb. Dr. Chouaid reports receiving consulting fees from Roche, AstraZeneca, GlaxoSmithKline, Bristol Myers Squibb, and Merck Sharp & Dohme; payment or honoraria from Roche, AstraZeneca, GlaxoSmithKline, Bristol Myers Squibb, Merck Sharp & Dohme, Amgen, and Sanofi; personal fees and nonfinancial support from AstraZeneca, AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Hoffman-La Roche, Janssen, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Takeda, Eli Lilly, and Sandoz; and support for attending meetings and/or travel from Roche, AstraZeneca, GlaxoSmithKline, Bristol Myers Squibb, and Merck Sharp & Dohme. Dr. Markman reports receiving grants paid to the institution from Bristol Myers Squibb, Amgen, and Pierre Fabre and having participation on advisory boards for Bristol Myers Squibb, Amgen, and Merck. Dr. Hiltermann reports receiving fees and nonfinancial support to institution from AstraZeneca, Bristol Myers Squibb, Hoffman-La Roche, Merck Sharp & Dohme, Novartis, Roche, and Pfizer. Dr. Taus reports receiving personal fees and nonfinancial support from Roche, Lilly, GlaxoSmithKline, Bristol Myers Squibb, Merck Sharp & Dohme, Pfizer, and AstraZeneca, outside of the current work. Dr. Sawyer, Ms. Chander, and Ms. Licour report having employment and stock ownership with AstraZeneca. Dr. Allen reports having stock ownership with AstraZeneca, former employment by AstraZeneca (during the conduct of the study), and current employment by AbbVie. Dr. Solomon reports receiving financial support paid to the institution from AstraZeneca; having participation on advisory boards for AstraZeneca, Pfizer, Novartis, Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Lilly, Amgen, Takeda, Janssen, and BeiGene; receiving payment or honoraria for lectures or presentations from AstraZeneca, Pfizer, Roche, Bristol Myers Squibb, Amgen, and Takeda; and having leadership in the Thoracic Oncology Group of Australia and the Cancer Council of Victoria. The remaining authors declare no conflict of interest.

Address for correspondence: Nicolas Girard, MD, Institut du Thorax, Institut Curie 26 rue d'Ulm, Paris F-75005, France. E-mail: nicolas.girard2@curie.fr

© 2022 International Association for the Study of Lung Cancer. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

ISSN: 1556-0864

<https://doi.org/10.1016/j.jtho.2022.10.003>

Nicolas Girard, MD, PhD,^{a,*} Jair Bar, MD, PhD,^{b,c} Pilar Garrido, MD, PhD,^d Marina C. Garassino, MD,^e Fiona McDonald, MD, FRCR,^f Françoise Mornex, MD, PhD,^g Andrea R. Filippi, MD,^h Hans J. M. Smit, MD, PhD,ⁱ Solange Peters, MD, PhD,^j John K. Field, PhD, FRCPath,^k Daniel C. Christoph, MD, PhD,^l Anne Sibille, MD,^m Rainer Fietkau, MD, PhD,ⁿ Vilde D. Haakensen, MD, PhD,^o Christos Chouaid, MD, PhD,^p Ben Markman, MBBS, FRACP,^q T. Jeroen N. Hiltermann, MD, PhD,^r Alvaro Taus, MD,^s William Sawyer, PhD,^t Allison Allen, PhD,^u Pratibha Chander, MPH,^u Muriel Licour, MSc,^v Benjamin Solomon, MBBS, PhD, FRACP^w

^aInstitut du Thorax Curie Montsouris, Institut Curie, Paris, France and UVSQ, Paris Saclay, Versailles, France

^bInstitute of Oncology, Sheba Medical Centre, Ramat Gan, Israel

^cFaculty of Medicine, Tel Aviv University, Tel Aviv, Israel

^dMedical Oncology Department, Hospital Ramón y Cajal, Universidad de Alcalá, Madrid, Spain

^eDepartment of Hematology/Oncology, The University of Chicago, Chicago, Illinois

^fLung Unit, The Royal Marsden NHS Foundation Trust, London, United Kingdom

^gDepartment of Radiation Oncology, Centre Hospitalier Universitaire de Lyon, Lyon, France

^hRadiation Oncology Department, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo and University of Pavia, Pavia, Italy

ⁱDepartment of Pulmonary Diseases, Rijnstate Hospital, Arnhem, The Netherlands

^jDepartment of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

^kRoy Castle Lung Cancer Research Programme, Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, United Kingdom

^lDepartment of Medical Oncology/Hematology, Evang. Kliniken Essen-Mitte, Evang. Huysens-Stiftung Essen-Huttrop, Essen, Germany

^mDepartment of Pneumology and Allergology, Centre Hospitalier Universitaire de Liège, Liège, Belgium

ⁿDepartment of Radiation Oncology, Universitätsklinikums Erlangen, Erlangen, Germany

^oDepartment of Oncology and Institute for Cancer Research, Oslo University Hospital, Oslo, Norway

^pService de Pneumologie, Centre Hospitalier Intercommunal de Créteil, Créteil, France

^qCabrini Hospital and Monash University, Melbourne, Victoria, Australia

^rUniversity of Groningen, Department of Pulmonary Diseases, University Medical Center Groningen, Groningen, The Netherlands

^sDepartment of Medical Oncology, Hospital del Mar-CIBERONC, Barcelona, Spain

^tAstraZeneca, Cambridge, United Kingdom

^uAstraZeneca, Gaithersburg, Maryland

^vAstraZeneca, Courbevoie, France

^wDepartment of Medical Oncology, Peter MacCallum Cancer Centre and University of Melbourne, Victoria, Australia

Received 10 May 2022; revised 16 September 2022; accepted 2 October 2022

Available online - 25 October 2022

ABSTRACT

Introduction: The phase 3 PACIFIC trial established consolidation therapy with durvalumab as standard of care for patients with unresectable, stage III NSCLC and no disease progression after definitive chemoradiotherapy (CRT). The observational PACIFIC-R study assesses the real-world effectiveness of durvalumab in patients from an early access program. Here, we report treatment characteristics and a preplanned analysis of real-world progression-free survival (rwPFS).

Methods: PACIFIC-R (NCT03798535) is an ongoing, international, retrospective study of patients who started durvalumab (intravenously; 10 mg/kg every 2 wk) within an early access program between September 2017 and December 2018. The primary end points are investigator-assessed rwPFS and overall survival (analyzed by Kaplan-Meier method).

Results: As of November 30, 2020, the full analysis set comprised 1399 patients from 11 countries (median follow-up duration, 23.5 mo). Patients received durvalumab for a median of 11.0 months. Median rwPFS was 21.7 months (95% confidence interval: 19.1–24.5). RwPFS was numerically longer among patients who received concurrent versus sequential CRT (median, 23.7 versus 19.3 mo) and among patients with programmed cell death-ligand 1 expression greater than or equal to 1% versus less than 1% (22.4 versus 15.6 mo). Overall, 16.5% of the patients had adverse events leading to treatment discontinuation; 9.5% of all patients discontinued because of pneumonitis or interstitial lung disease.

Conclusions: Consolidation durvalumab after definitive CRT was well tolerated and effective in this large, real-world cohort study of patients with unresectable, stage III NSCLC. As expected, rwPFS was longer among patients who

received concurrent versus sequential CRT and patients with higher programmed cell death-ligand 1 expression. Nevertheless, favorable rwPFS outcomes were observed regardless of these factors.

© 2022 International Association for the Study of Lung Cancer. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Consolidation therapy; Immunotherapy; Locally advanced NSCLC; PD-L1 inhibition; Real-world data

Introduction

Approximately 20% to 30% of patients with NSCLC are diagnosed with stage III disease.¹⁻³ The historic standard of care (SoC) for patients with unresectable, stage III NSCLC was platinum-based chemotherapy administered concurrently with radiotherapy (cCRT), followed by active surveillance. This strategy was associated with 5-year overall survival (OS) rates ranging from 15% to 32%,⁴⁻⁷ and there was no evidence that survival could be improved further with induction or consolidation therapy, either with chemotherapeutics or with other systemic anticancer agents.⁸⁻¹³ This changed after the primary data readouts from the phase 3 PACIFIC trial (NCT02125461).^{14,15}

In PACIFIC, up to 12 months of consolidation therapy with durvalumab (an inhibitor of programmed cell death-ligand 1 [PD-L1]¹⁶) significantly improved progression-free survival (PFS) and OS versus placebo in patients with unresectable, stage III NSCLC and no disease progression after definitive cCRT.^{14,15} Consolidation durvalumab also exhibited a manageable safety profile, and patient-reported outcomes were comparable with placebo.^{14,15,17}

Updates from PACIFIC revealed that the robust survival benefit associated with durvalumab is sustained over time.¹⁸⁻²⁰ At the most recent update, median PFS (measured from random assignment) with durvalumab versus placebo was 16.9 months (95% confidence interval [CI]: 13.0-23.9) versus 5.6 months (95% CI: 4.8-7.7) (stratified hazard ratio [HR]: 0.55; 95% CI: 0.45-0.68), and median OS with durvalumab versus placebo was 47.5 months (95% CI: 38.1-52.9) versus 29.1 months (95% CI: 22.1-35.1) (stratified HR = 0.72; 95% CI: 0.59-0.89) (Kaplan-Meier estimates).²⁰ The 5-year PFS and OS rates for durvalumab versus placebo were 33.1% (95% CI: 28.0-38.2) versus 19.0% (95% CI: 13.6-25.2) and 42.9% (95% CI: 38.2-47.4) versus 33.4% (95% CI: 27.3-39.6), respectively.²⁰

On the basis of the findings of PACIFIC, durvalumab became the first anticancer medicine to be approved as a consolidation therapy for patients with unresectable,

stage III NSCLC and no disease progression after CRT and has subsequently been established as the global SoC in this setting.²¹⁻²⁴ Owing to the poor prognosis associated with unresectable, stage III NSCLC, the heterogeneity of this patient population, and the variability in real-world multidisciplinary treatment approaches,^{25,26} there is a need for real-world data on the use, effectiveness, and tolerability of the PACIFIC regimen (i.e., consolidation durvalumab following CRT). Once the primary results from PACIFIC were available, an early access program (EAP) was started to provide ethical access to durvalumab. PACIFIC-R (NCT03798535) subsequently enrolled patients who received durvalumab through the EAP with the aim of providing the first real-world data on the use and effectiveness of the PACIFIC regimen. This includes data for patients who received sequential CRT (sCRT) and patients with PD-L1 expression less than 1%. A preliminary safety analysis from PACIFIC-R, based on the first 3 months of treatment using data from the first of several preplanned, retrospective chart extractions (spaced in a 5-y period), provided early evidence of the real-world tolerability of the PACIFIC regimen.²⁷ Here, we report more comprehensive analyses from PACIFIC-R, based on the second planned chart extraction (with approximately 2 y of follow-up), including treatment characteristics and a preplanned analysis of real-world PFS (rwPFS), as well as a preliminary OS analysis.

Methods and Materials

Study Design

PACIFIC-R is an ongoing, international, retrospective study of a cohort of patients who received at least one dose of durvalumab through an EAP. The study consists of a retrospective review of established medical records for a subset of adult patients with unresectable, stage III NSCLC. Chart extractions are planned at prespecified intervals over a 5-year period starting from the index date (i.e., the date of the first durvalumab infusion received within the EAP); a target of four (and a maximum of five) extractions are planned for each participant (Fig. 1). Details regarding the design of the EAP are available in the [Supplementary Methods](#). In contrast with the design of the PACIFIC trial,¹⁴ the EAP initially permitted durvalumab treatment to continue until disease progression (a 12-mo limit was applied in PACIFIC); did not exclude patients with poor performance status (PS) (PACIFIC enrollment was restricted to patients with PS 0 or 1); and allowed enrollment of patients who received either cCRT or sCRT (only cCRT was allowed in PACIFIC) in most participating countries (France being the exception).

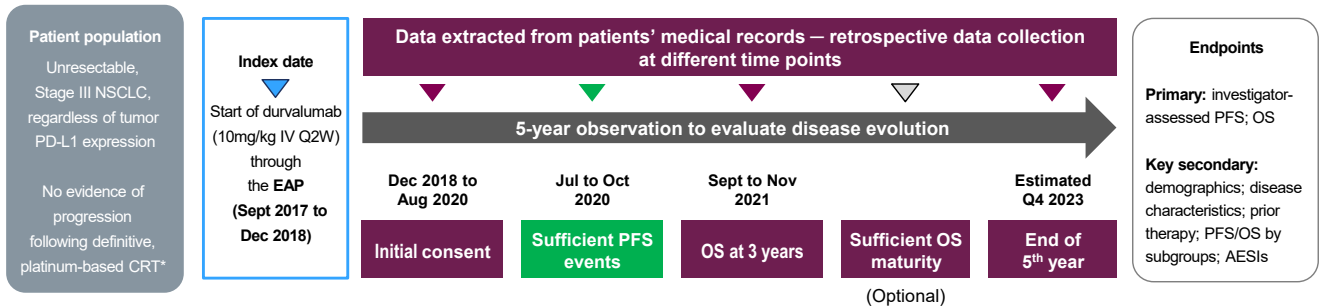


Figure 1. PACIFIC-R study design. The current analysis is based on the second data extraction of PACIFIC-R (highlighted in green), which was timed to allow sufficient PFS maturity. *Patients had completed platinum-based chemotherapy concurrent or sequential to radiotherapy within the previous 12 weeks without evidence of disease progression. AESIs, adverse events of special interest; CRT, chemoradiotherapy; EAP, early access program; IV, intravenously; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q, quarter; Q2W, every 2 weeks.

In accordance with regulatory requirements, a country was eligible to enter PACIFIC-R once the EAP had closed in that country. To be enrolled, patients must have started durvalumab within the EAP between September 2017 and December 2018 and have provided informed consent for data to be retrieved from their medical records. Patients who died during or after the EAP and before PACIFIC-R enrollment were eligible where local laws allowed for a consent waiver, or next-of-kin consent, provided all other entry criteria were met. Patients who received durvalumab in clinical studies were excluded.

Assessments

The primary end points are (1) rwPFS (measured from the index date to the date of investigator-determined disease progression or death [if no progression], or the end of follow-up) and (2) OS (measured from the index date to death, or the end of follow-up). Given the real-world nature of PACIFIC-R, progression could be determined by either investigator's assessment or according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, depending on local practice.

Key secondary end points include the following: (1) rwPFS and OS for subgroups of interest; (2) durvalumab treatment characteristics (e.g., treatment duration and time to start of durvalumab from completion of CRT); (3) demographics, disease characteristics, and details of prior therapy; and (4) adverse events (AEs) of special interest (AESIs).

The AESIs, defined as AEs potentially attributable to an immune-mediated cause (and reported in association with durvalumab), were collected when they required at least one of the following actions: concomitant use of systemic corticosteroids, use of immunosuppressants or endocrine therapies; and temporary interruption or permanent discontinuation

of durvalumab. Predefined AESIs considered in the study were as follows: diarrhea or colitis and intestinal perforation; pneumonitis or interstitial lung disease (ILD); hepatitis or transaminase increases; endocrinopathies (hypophysitis or hypopituitarism, adrenal insufficiency, hyperthyroidism or hypothyroidism, and type 1 diabetes mellitus); rash or dermatitis; nephritis or blood creatinine increase; pancreatitis or serum lipase and amylase increase; myocarditis; myositis or polymyositis; neuropathy or neuromuscular toxicity (Guillain-Barré syndrome and myasthenia gravis); and other less frequent events with a potential immune-mediated cause (e.g., rheumatological events).

Statistical Analyses

Analyses were based on the full analysis set (all eligible, enrolled patients), or subgroups thereof, and were descriptive in nature with summary statistics for continuous variables or numbers and frequency for calculation of categorical variables. Missing values were not imputed. All analyses in this report were based on the second planned chart extraction from PACIFIC-R (extraction end date: November 30, 2020). The timing of this extraction was based on an estimate of when there would be enough observed progression events to determine median rwPFS (and corresponding 95% CI) for the full analysis set.

The rwPFS and OS data were censored for patients lost to follow-up (i.e., still alive as of their last visit or contact before the database cutoff). Medians and landmark rates were calculated by Kaplan-Meier method and corresponding 95% CIs were calculated by Greenwood's method.

Although Spain did not participate in PACIFIC-R, Spanish data were sourced from an externally sponsored, locally initiated study with the same design & study materials (NCT04285866). As regulatory restrictions in

Spain allowed only one data extraction, it was decided that data collection should be timed to allow for sufficient PFS maturity. Ultimately, the timing of data collection for the Spanish study was in line with the second planned chart extraction from PACIFIC-R (also timed for sufficient PFS maturity). Therefore, the Spanish data set was integrated for the analyses reported in this article (after internal quality review by AstraZeneca) but will not be integrated for analyses based on future PACIFIC-R chart extractions. November 30, 2020, was the last date of data entry for the analyses reported in this article; data cleaning was performed up to a database cutoff date of April 8, 2021, for the main PACIFIC-R cohort and July 2, 2021, for the Spanish data set.

Results

Patients and Hospital Site Characteristics

As of November 30, 2020 (end date of the second chart extraction), the full analysis set included 1399 eligible patients. Patients were enrolled across 290 hospital sites in 11 participating countries, including France (n = 342), Spain (244), Australia (165), The Netherlands (155), Belgium (118), Italy (116), Israel (92), Germany (62), the United Kingdom (54), Norway (36), and Switzerland (15). Most hospital sites (67.2%) had a primary medical specialty of medical or clinical oncology (Supplementary Table 1). The median follow-up duration in the full analysis set was 23.5 months (range: <0.1 to 35.3 mo); three patients (0.2%) were lost to follow-up.

An additional 347 patients who were potentially eligible for PACIFIC-R, but who were not enrolled, were identified by the participating hospital sites (as described in the Supplementary Methods).

Demographics, Disease Characteristics, and Medical History

The median age of the patients in the full analysis set was 66.0 years at EAP entry; 21.2% and 10.4% were aged 70 to 75 years and above 75 years, respectively (Table 1). Most patients were male (67.5%), current or former smokers (92.1%), and had a PS of 0 or 1 (98.0%) at EAP entry. The majority of patients (94.7%) had stage III disease at the time of initial NSCLC diagnosis, with the remainder relapsing to stage III from earlier disease stages. Overall, 5.3%, 43.4%, and 51.3% of the patients had stages IA to IIB, IIIA, and IIIB or IIIC disease, respectively, at the time of initial NSCLC diagnosis; 55.0% had N2 disease (Supplementary Table 2). Most patients (64.0%) had nonsquamous tumor histologic type. Comorbidities were reported in 71.5% of all patients (Supplementary Fig. 1). Hypertension was the most prevalent comorbidity (32.3%), followed by

Table 1. Patient Demographics and Disease Characteristics

Characteristics	Full Analysis Set (N = 1399)
Median age at EAP inclusion, y (range)	66.0 (26-88)
Age category at EAP inclusion, n (%)	
<70 y	958 (68.5)
70-75 y	296 (21.2)
>75 y	145 (10.4)
Sex, n (%)	
Male	944 (67.5)
Female	455 (32.5)
Smoking status at EAP inclusion, n (%)	
Never	111 (7.9)
Current	456 (32.6)
Former	832 (59.5)
ECOG or WHO PS at EAP inclusion, n (%)	n = 951 ^a
0	489 (51.4)
1	443 (46.6)
2 or 3	19 (2.0)
Disease stage at initial NSCLC diagnosis, n (%)	n = 1392 ^b
IA to IIB	74 (5.3)
IIIA	604 (43.4)
IIIB or IIIC	714 (51.3)
Histologic subtype at stage III diagnosis, n (%)	n = 1378 ^c
Squamous	496 (36.0)
Nonsquamous	882 (64.0)
PD-L1 status, n (%)	n = 967 ^d
≥1%	700 (72.4)
<1%	174 (18.0)
Inconsistent	93 (9.6)
EGFR status, n (%)	n = 582 ^e
Mutated	46 (7.9)
Wild type	517 (88.8)
Inconclusive or unknown	19 (3.3)

Note: Percentages reported in the table are calculated using the number of patients with available data (for each variable).

^aECOG or WHO PS at EAP inclusion data was missing for 448 patients.

^bDisease stage at initial diagnosis was determined according to the seventh or eighth editions of the American Joint Committee on Cancer staging manual; data were missing for seven patients.

^cHistologic subtype at stage III diagnosis data was missing or unknown for 21 patients.

^dPD-L1 was not tested for in 431 patients, and data were missing for one patient. The PD-L1 inconsistent subgroup represents patients who were tested for PD-L1 but whose test results were not clearly reported owing to misalignment of three different variables in their case report forms (that precluded classification of the PD-L1 expression level as ≥1% or <1%); the variables were tumor cell %, PD-L1 status (positive or negative), and the threshold level used for classifying PD-L1 status.

^eEGFR mutation status was not tested for in 817 patients.

EAP, early access program; ECOG or WHO PS, Eastern Cooperative Oncology Group or WHO performance status; PD-L1, programmed cell death-ligand 1.

chronic obstructive pulmonary disease (25.2%), and diabetes (13.4%).

Overall, 967 of 1399 patients (69.1%) were tested for PD-L1. Among those tested, 72.4% and 18.0% had expression on greater than or equal to 1% and less than 1% of tumor cells (TCs), respectively; test results were reported inconsistently for 9.6% of patients, precluding PD-L1 classification. Clinical characteristics were generally well balanced across the PD-L1 subgroups ([Supplementary Table 3](#)).

In total, 582 of 1399 patients (41.6%) were tested for *EGFR* mutations. Among those tested, 7.9% and 88.8% had *EGFR*-mutated and *EGFR* wild-type tumors, respectively; results were unknown or inconclusive for the remainder. Test results for this and other oncogenic aberrations are summarized in [Supplementary Table 4](#).

Characteristics of Prior CRT

Patients typically received cCRT (76.6%); 14.4% received sCRT ([Supplementary Table 5](#)). cCRT was more common across all participating countries except Italy, where cCRT (44.8%) and sCRT (42.2%) were used in similar proportions. Compared with patients who received cCRT, a higher proportion of patients who received sCRT were greater than or equal to 70 years of age (40.8% versus 29.0%) and had stage IIIB or IIC disease (61.7% versus 50.7%) ([Supplementary Table 6](#)). Other clinical characteristics were well balanced across the patient subgroups receiving the two types of CRT.

The median total radiotherapy (RT) dose in the full analysis set was 66.0 Gy (range: 8.0–92.0 Gy; n = 1344 with available data). Most patients received a total RT dose greater than 60 Gy to less than or equal to 66 Gy (52.4%), whereas 41.4% received less than or equal to 60 Gy. Among the patients who received cCRT, 51.2% and 37.3% had cisplatin-based and carboplatin-based chemotherapy, respectively; a further 11.6% switched between cisplatin-based and carboplatin-based regimens ([Supplementary Table 7](#)). Vinorelbine and paclitaxel were the most used nonplatinum chemotherapies during cCRT; 33.1% and 27.6% of patients who received cCRT had vinorelbine-containing and paclitaxel-containing regimens, respectively. Induction and consolidation chemotherapy were used in 48.4% and 6.4% of patients who received cCRT, respectively ([Supplementary Table 5](#)).

The RECIST-defined best response to CRT (based on 1072 patients with available data) included complete response (3.8%), partial response (61.0%), stable disease (24.4%), and progressive disease (1.2%) and was either not assessable or unknown for 9.5% of the patients.

Characteristics of Durvalumab Treatment

The median time to start of durvalumab from the end of RT was 56.0 days (1.8 months) (range: –35 to 981

d [–1.1 to 32.2 mo]; n = 1365) in the full analysis set; one patient started durvalumab before finishing RT. Overall, 30.1% of the patients started durvalumab within 42 days (and 1.2% within 14 d) of finishing RT; meanwhile, 14.4% and 1.0% started more than 3 months and more than 6 months after finishing RT, respectively.

At the time of database cutoff, the median total treatment duration (including the duration of dose interruptions) was 334.5 days (11.0 months) (range: 1–1029 d [<0.1 to 33.8 mo]; n = 1388). Overall, 19.8% and 4.2% of the patients received durvalumab for a total duration of more than 12 months and more than 14 months, respectively. Patients received a median of 22.0 durvalumab infusions (range: 1–65 infusions; n = 1339), with 7.1% receiving more than 26 infusions; 26 infusions represent a 12-month treatment duration when administered every 2 weeks without interruption. Overall, 11.2% of patients interrupted durvalumab treatment temporarily. The median duration of these interruptions was 29.0 days (1.0 months) (range: 3–295 d [0.1–9.7 mo]; n = 150).

Reasons for Discontinuing Durvalumab

Overall, 47.1% of the patients in the full analysis set completed durvalumab treatment; determination of whether a patient had completed treatment was based on the investigator's decision per their country-specific protocol. The median time to treatment discontinuation among patients considered to have completed treatment was 11.9 months ([Table 2](#)). The most common reasons for not completing treatment were disease progression (occurring in 26.9% of the patients in the full analysis set; median time to discontinuation, 4.9 mo) and AEs (occurring in 16.7% of the patients in the full analysis set; median time to discontinuation, 2.8 mo).

Preplanned Analysis of rwPFS

At the time of the database cutoff, 737 of 1399 patients (52.7%) had either experienced disease progression (n = 659) or had died without documentation of progression (n = 78); progression was determined per RECIST in 458 of 659 patients (69.5%), per investigator's assessment in 171 of 659 patients (25.9%), and by unknown means in 30 of 659 patients (4.6%). Median rwPFS was 21.7 months (95% CI: 19.1–24.5) in the full analysis set ([Fig. 2](#)); 62.2% (95% CI: 59.6–64.6) and 48.2% (95% CI: 45.4–50.9) of the patients were estimated to be alive and free of progression at 12 and 24 months, respectively.

Subgroup analyses were performed to evaluate possible associations between rwPFS and prognostic factors of interest. As found in [Figure 3A to D](#), rwPFS was numerically longer among patients with PD-L1

Table 2. Reasons for and Timing of Durvalumab Treatment Discontinuation

Full Analysis Set (N = 1399)		
Reason ^a	n (%)	Median Time to Discontinuation, mo (Range) ^b
Completed treatment ^c	659 (47.1)	11.9 (5.5-28.5) ^d
Disease progression	377 (26.9)	4.9 (0.0-30.2) ^d
Adverse event	233 (16.7)	2.8 (0.0-19.6)
Death	21 (1.5)	1.9 (0.0-13.6)
Patient decision	20 (1.4)	6.0 (0.0-19.5)
Other	68 (4.9)	5.9 (0.0-28.2) ^d

^aThree patients (0.2%) in the full analysis set were lost to follow-up, and 18 (1.3%) were still receiving durvalumab treatment at the time of data cutoff.

^bMeasured from the index date (i.e., the date if the first durvalumab infusion received within the EAP); 1 month equates to 30.44 days.

^cBased on the investigator’s decision per their country-specific protocol and, where applicable, was beyond 12 months of treatment.

^dDuration of exposure data was missing for four patients who completed treatment, three patients who discontinued owing to disease progression, and two patients who discontinued for other reasons.

EAP, early access program.

expression greater than or equal to 1% versus less than 1% (median, 22.4 versus 15.6 mo, respectively), stage IIIA versus IIIB or IIIC disease (median, 23.7 versus 19.2 mo, respectively), and nonsquamous versus squamous tumor histologic type (median, 25.3 versus 14.6 mo, respectively). RwpPFS was also numerically longer among patients who received cCRT versus sCRT (median, 23.7 versus 19.3 mo, respectively), those who received cisplatin versus carboplatin during CRT (median, 24.4 versus 18.8 mo), and those who received durvalumab

less than or equal to 42 days versus more than 42 days after finishing RT (median, 25.7 versus 20.8 mo, respectively) (Supplementary Table 8). Meanwhile, rwPFS was numerically similar among patients aged less than 70 years and 70 to 75 years (median, 22.8 versus 22.4 mo, respectively) and was comparatively shorter among patients aged greater than 75 years (median, 19.2 mo). Compared with the full analysis set, rwPFS was numerically longer among patients with known *KRAS* mutations (median, 24.2 mo) and numerically shorter

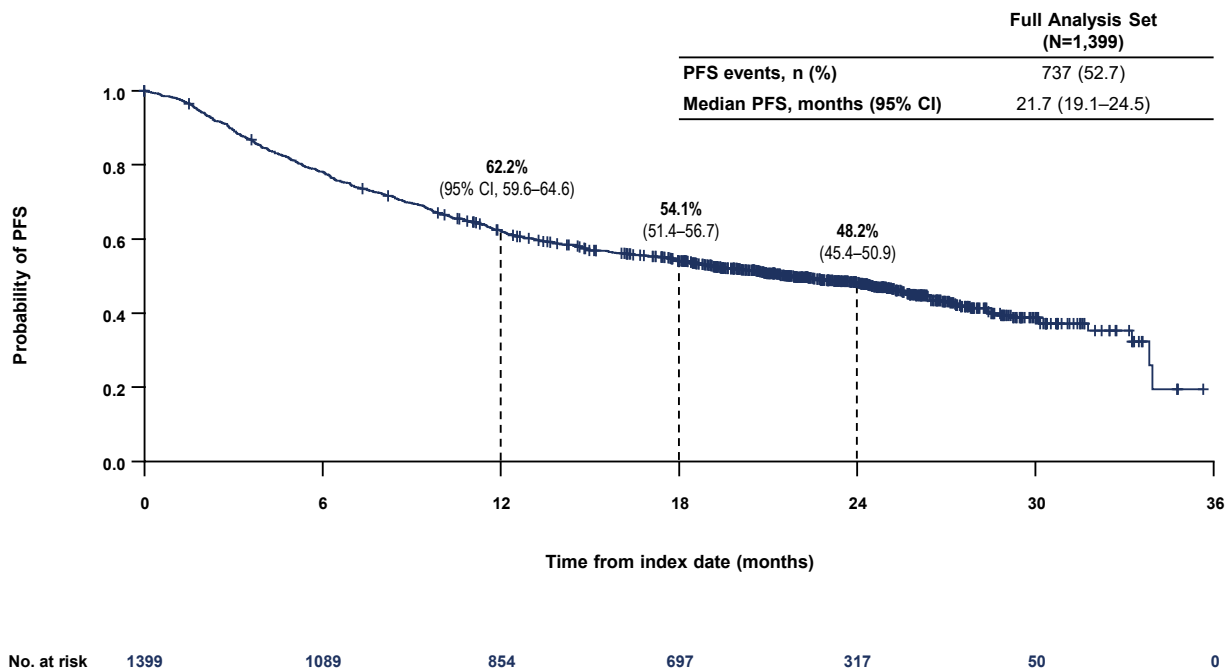


Figure 2. Real-world PFS in the full analysis set. Shown is a Kaplan-Meier distribution of real-world PFS in the full analysis set. The tick marks represent censored observations, and the dashed lines represent 12-, 18-, and 24-month landmark analyses. At the time of the database cutoff, the median duration of follow-up for patients who remained censored for PFS was 23.0 months (range: 0.0-35.6 mo); 10 patients (0.7%) were lost to follow-up. CI, confidence interval; PFS, progression-free survival.

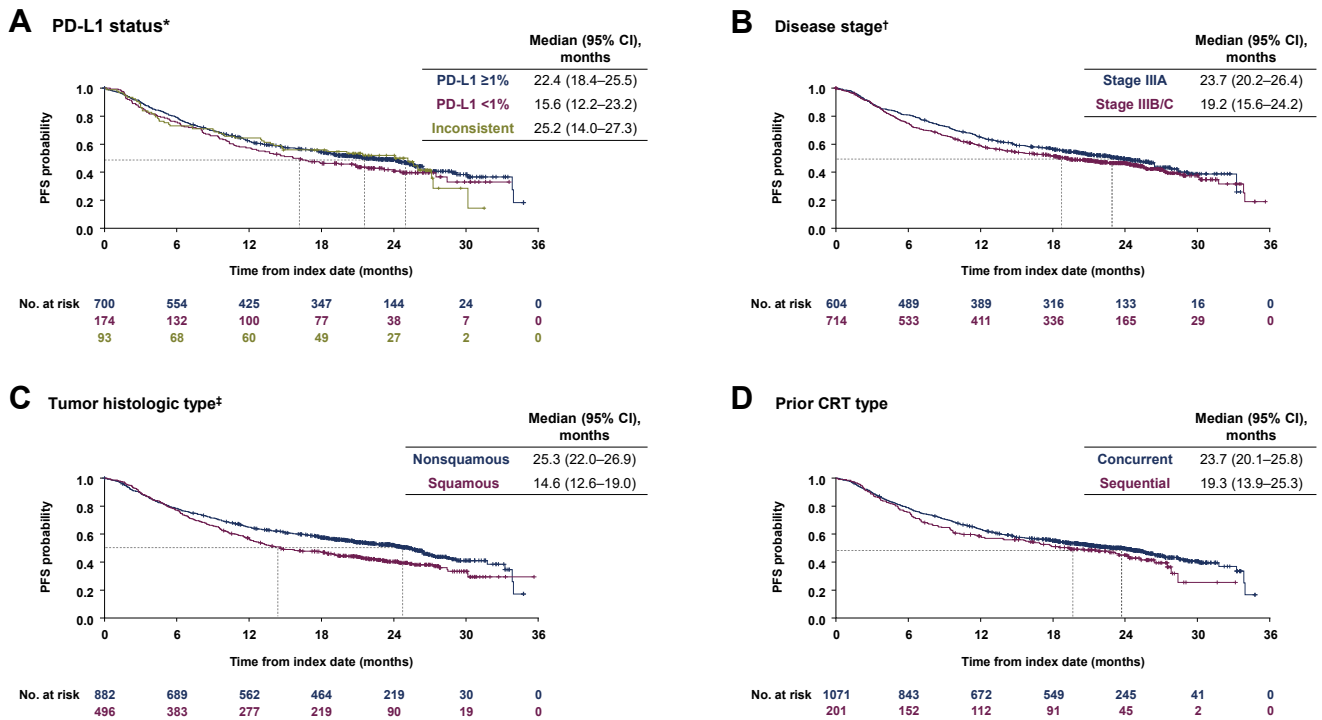


Figure 3. Real-world PFS in subgroups of interest. Shown are Kaplan-Meier distributions of real-world PFS for subgroups defined by (A) PD-L1 status, (B) disease stage, (C) tumor histologic type, and (D) prior CRT type. The tick marks represent censored observations, and the dashed lines illustrate the extrapolation of median PFS. *The PD-L1 inconsistent subgroup represents patients who were tested for PD-L1 but whose test results were not clearly reported owing to misalignment of three different variables in their case report forms (that precluded classification of the PD-L1 expression level as ≥1% or <1%); the variables were tumor cell %, PD-L1 status (positive or negative), and the threshold level used for classifying PD-L1 status. †As reported at the time of initial NSCLC diagnosis. ‡As reported at the time of stage III diagnosis. CI, confidence interval; CRT, chemoradiotherapy; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.

among patients with known *EGFR* mutations (median, 11.1 mo) (Supplementary Table 8).

Preliminary Analysis of OS

At the time of the database cutoff, 430 of 1399 patients (30.7%) had died. Median OS was not reached in the full analysis set; 71.2% (95% CI: 68.8–73.6) of the patients were estimated to be alive at 24 months.

AESIs

In total, 654 of 1399 patients (46.7%) in the full analysis set experienced AESIs; 11.2% (n = 156) and 16.5% (n = 231) of the patients had AESIs leading to temporary interruption and permanent discontinuation of durvalumab, respectively. Pneumonitis or ILD was the most common AESI leading to interruption (5.2% of the full analysis set) and permanent

Table 3. AESIs Leading to Interruption and Permanent Discontinuation of Durvalumab

AESI Category	Full Analysis Set (N = 1399)	
	Temporary Interruption, n (%)	Permanent Discontinuation, n (%)
Any	156 (11.2)	231 (16.5)
Pneumonitis or ILD	73 (5.2)	133 (9.5)
Diarrhea or colitis and intestinal perforation	16 (1.1)	15 (1.1)
Hepatitis or transaminase increases	10 (0.7)	17 (1.2)
Endocrinopathies	18 (1.3)	10 (0.7)
Other ^a	33 (2.4)	51 (3.6)

Note: AESI categories leading to temporary interruption and permanent discontinuation of durvalumab in less than 1% of the full analysis set are not tabulated. ^aFree term written events (which may include the other terms listed in the table). AESI, adverse event of special interest; ILD, interstitial lung disease.

discontinuation (9.5% of the full analysis set) (Table 3), noting that it is difficult to differentiate between immunotherapy-induced and RT-induced pneumonitis. Other AEs leading to interruption or permanent discontinuation of treatment included diarrhea or colitis and intestinal perforation, hepatitis or transaminase increases, and endocrinopathies (Table 3). RwpPFS among patients who had AEs leading to interruption or permanent discontinuation of treatment was consistent with the full analysis set (median, 20.7 mo, 95% CI: 16.0–24.1, n = 367).

Pneumonitis or ILD

Overall, 250 patients in the full analysis set experienced pneumonitis or ILD (250 of 1399; 17.9%). Among patients who experienced pneumonitis or ILD, 23 (9.2%) had more than one event and four (1.6%) had more than two events. Median time to onset of the first event, measured from the start of durvalumab, was 68.5 days (2.3 months) (range: –41 to 444 d [–1.3 to 14.6 mo]; n = 250). In all, 4.0% (n = 56), 8.4% (n = 118), 2.9% (n = 41), and 0.4% (n = 5) of the patients in the full analysis set had pneumonitis or ILD events classified as mild, moderate, severe, and life threatening or fatal, respectively (assessed by the investigator), whereas 2.6% (n = 37) had events of unknown severity (noting that a single patient could have multiple events of different severity). Use of corticosteroids to manage pneumonitis or ILD was required in 199 patients with the event (199 of 250; 79.6%). Two patients (0.1%) had fatal pneumonitis or ILD events in the full analysis set. Both fatal events were recurrences of pneumonitis or ILD; one patient had been rechallenged with durvalumab, and the other had discontinued durvalumab permanently, following their original pneumonitis or ILD event.

Discussion

PACIFIC-R provides valuable insights into the treatment patterns and outcomes with the PACIFIC regimen in the real-world setting, on the basis of a population of more than 1000 patients enrolled across 11 countries. Median rwpPFS was 21.7 months and nearly half of all patients were alive and free of disease progression 2 years after starting durvalumab. Furthermore, more than 70% of the patients were alive at 2 years regardless of their progression status. These findings confirm the effectiveness of durvalumab after definitive CRT in a large, predominantly European population with unresectable, stage III NSCLC. Durvalumab treatment, which lasted for a median duration of 11 months, was also well tolerated in the real-world setting, with safety observations being aligned with the known profile of

durvalumab administered after CRT in the unresectable, stage III NSCLC setting.^{14,15,28}

The outcomes from PACIFIC-R align with other real-world studies of the PACIFIC regimen.^{29–33} For instance, Taugner et al.³⁰ reported a rwpPFS rate of 62% at 12 months with durvalumab in their prospective study, which is consistent with the corresponding rate from PACIFIC-R. Moreover, outcomes for most of the analyzed subgroups from PACIFIC-R compare favorably with patients who received CRT alone in the pre-immunotherapy era^{25,34}; in the international KINDLE study, median rwpPFS was 12.1 and 10.4 months with cCRT and sCRT (without consolidation immunotherapy), respectively, among patients with unresectable, stage III NSCLC (acknowledging that the index date was the date of initial diagnosis for KINDLE, whereas it was the date that durvalumab was started within the EAP [i.e., post-CRT] in PACIFIC-R).²⁵

Favorable rwpPFS outcomes were observed across subgroups of interest in PACIFIC-R, and the results were broadly aligned with the findings of the PACIFIC trial^{20,35,36}; better survival outcomes were observed for younger patients, patients with stage IIIA disease, patients with nonsquamous tumor histologic type, and patients who received cisplatin (during CRT) in both studies.^{20,36}

As expected, better rwpPFS outcomes were observed among patients who received cCRT compared with sCRT; this aligns with other studies that revealed the superiority of cCRT in the unresectable, stage III NSCLC setting.^{5,37–39} Although cCRT is recognized as the SoC,^{23,40,41} patients often receive sCRT in real-world clinical practice owing to concerns with the tolerability of concurrent treatment (among other reasons). Reassuringly, favorable rwpPFS outcomes were still observed among patients who received sCRT in PACIFIC-R (median, 19.3 mo). The PACIFIC trial did not enroll patients who received prior sCRT; therefore, the benefit of consolidation therapy with durvalumab in these patients has not yet been established definitively. Use of durvalumab after sCRT falls outside of the approved label for durvalumab in the United States²²; meanwhile, the label approved by the European Medicines Agency allows use of either cCRT or sCRT.²¹ The favorable real-world outcomes found in the sCRT subset of PACIFIC-R complement recently published findings from the phase 2, single-arm, PACIFIC-6 trial, which revealed encouraging outcomes with durvalumab after sCRT.²⁸ Together, the findings of these studies suggest that durvalumab after sCRT could be a reasonable treatment strategy for patients who are considered unsuitable for cCRT; the benefit of this strategy is currently being investigated in the phase 3 PACIFIC-5 trial (NCT03706690).

Better outcomes were also observed among patients with PD-L1 expression greater than or equal to 1% compared with less than 1%, consistent with observations from PACIFIC.^{20,35} Nevertheless, favorable rwPFS outcomes were still observed among patients with PD-L1 expression less than 1% (median, 15.6 mo). Patients with PD-L1 expression on less than 1% of TCs are excluded from the European Medicines Agency label based on an exploratory, post hoc analysis^{21,24}; no restrictions regarding PD-L1 status are applied in other regions, including the United States.²²

The analyses of outcomes for subgroups should be interpreted with caution. Because of the variance in clinical practice patterns across the world, many of the subgroup variables are inevitably associated with other clinical factors that may bias outcomes. For example, patterns of cCRT versus sCRT use in PACIFIC-R varied between countries, by age, and by disease stage; use of sCRT was more common among patients enrolled in Italy, patients aged greater than or equal to 70 years, and patients diagnosed with more advanced disease (i.e., stage IIIB or IIIC).

Preclinical evidence suggests that radiotherapy induces immunomodulatory changes, including up-regulation of PD-L1, which potentially prime tumors to respond to immunotherapy.⁴²⁻⁴⁵ PD-L1 has been an imperfect biomarker of response to immunotherapy, and dynamic changes induced by CRT may affect the reliability of PD-L1 expression measured before CRT.⁴⁶ Interestingly, rwPFS was better among patients who received durvalumab closer to the end of RT, consistent with findings from PACIFIC.⁴⁷ We are uncertain of the factors underpinning this observation, but preclinical evidence suggests that administering PD-L1 inhibitors as close as possible to CRT may increase effectiveness.⁴³ Nevertheless, it should be acknowledged that the timing of durvalumab initiation after CRT may correlate with other clinical factors that influence survival outcomes. The ongoing phase 3 PACIFIC-2 trial (NCT03519971) is investigating concurrent administration of durvalumab with cCRT.

The median rwPFS reported in PACIFIC-R is longer than the median PFS reported with durvalumab in PACIFIC (16.8 mo).¹⁴ This may seem unexpected as, owing to strict enrollment criteria, clinical trial cohorts are typically healthier than real-world populations. Several factors can contribute to overestimation of PFS in the real-world setting. For instance, as local laws did not allow for a consent waiver, study sites in the United Kingdom and Germany were unable to collect information on patients who received durvalumab within the EAP but died before PACIFIC-R enrollment (50 early deaths were not counted). Moreover, assessments for disease progression typically occur less frequently in the

real-world setting, causing delays in detection; therefore, PFS is generally overestimated in real-world studies. This issue may have been exacerbated by the coronavirus disease 2019 pandemic, which could have resulted in fewer hospital visits.⁴⁸ Lastly, the use of RECIST criteria for tumor assessments is heterogeneous across countries. Although progression had to be determined radiologically in PACIFIC, and was subject to blinded independent central review, patients in PACIFIC-R could have progression determined based on either radiological or clinical evidence.²² Future analyses to investigate the impact of the abovementioned limitations on rwPFS would be of interest.

The 2-year OS rate was also higher in PACIFIC-R (71.2%) compared with PACIFIC (66.3%).¹⁵ As mentioned for rwPFS, overestimation of OS can be attributed to the fact that study sites in the United Kingdom and Germany could not collect information on patients who died before PACIFIC-R enrollment. Further analyses are planned on the basis of future chart extractions from PACIFIC-R, which will allow for more robust analyses of OS outcomes using sufficiently matured survival data. These analyses will provide valuable insights into the real-world effectiveness of the PACIFIC regimen.

Almost half of all patients completed durvalumab treatment in PACIFIC-R (47.1%), which is consistent with the corresponding rate in PACIFIC.¹⁵ This suggests that patients are as likely to complete durvalumab treatment in the real-world setting as in a clinical trial. Aligned with PACIFIC,¹⁵ the most common reasons for prematurely discontinuing durvalumab were disease progression and AEs, with pneumonitis or ILD being the most common AE leading to discontinuation.

The parameters for durvalumab use in the EAP (from which patients were enrolled onto PACIFIC-R) were wider in scope than those recommended in current approvals and guidelines.²¹⁻²³ Therefore, treatment patterns in PACIFIC-R may not align exactly with the way in which durvalumab is used in real-world practice currently. For example, the EAP initially allowed patients to continue durvalumab treatment in this curative-intent setting until they experienced disease progression (except in France), whereas current approvals include a 12-month treatment cap.^{21,22} Nevertheless, only 19.8% and 4.2% of patients received durvalumab for a total duration of more than 12 and more than 14 months, respectively, and only 7.1% received more than 26 durvalumab infusions, so the impact of this on clinical outcomes is likely to be small. The optimal duration of consolidation immunotherapy in the unresectable, stage III NSCLC setting remains a matter of debate, and some ongoing trials permit treatment durations of more than 12 months.^{49,50}

Although the EAP did not exclude patients on the basis of ECOG PS in most countries, the PACIFIC-R cohort includes very few patients with PS greater than 1 (2.0%); this is lower than may have been expected for a real-world patient population (although it should be acknowledged that PS data were missing for 448 patients). Limited recruitment of patients with PS greater than 1 may be because the EAP was the first time the PACIFIC regimen was used outside of clinical trials: given the relative novelty of the regimen at the time, clinicians may have initially been cautious about administering durvalumab to patients whose clinical characteristics did not align closely with the population of PACIFIC (which restricted enrollment to patients with PS 0 or 1¹⁴).

In conclusion, the findings from PACIFIC-R reveal that consolidation therapy with durvalumab after definitive CRT is well tolerated and effective in this curative-intent setting on the basis of a large, international, real-world population. As expected, rwPFS outcomes were better among patients who received cCRT versus sCRT and among patients with PD-L1 expression greater than or equal to 1% versus less than 1%. Nevertheless, favorable rwPFS outcomes were observed regardless of prior CRT type and PD-L1 status. Outcomes were broadly consistent with the PACIFIC trial, although the median rwPFS reported for PACIFIC-R was longer than the median PFS reported with durvalumab in PACIFIC; limitations associated with assessing disease progression in the real-world setting likely caused an overestimation of rwPFS. Although durvalumab was generally well tolerated, pneumonitis or ILD led to treatment discontinuation in 9.5% of patients; clinical vigilance is required to ensure effective diagnosis and management of this important and potentially serious toxicity. Overall, the findings of PACIFIC-R suggest that the potential of the PACIFIC regimen found in its pivotal phase 3 trial is being translated to real-world clinical practice as the global SoC for patients with unresectable, stage III NSCLC.

CRedit Authorship Contribution Statement

Nicolas Girard: Resources, Conceptualization, Visualization, Writing—review and editing.

Jair Bar: Resources, Conceptualization, Writing—review and editing.

Pilar Garrido: Resources, Conceptualization, Writing—review and editing.

Marina C. Garassino: Resources, Conceptualization, Writing—review and editing.

Fiona McDonald: Resources, Conceptualization, Visualization, Writing—review and editing.

Françoise Mornex: Resources, Conceptualization, Writing—review and editing.

Andrea R. Filippi: Resources, Conceptualization, Writing—review and editing.

Hans J. M. Smit: Resources, Conceptualization, Writing—review and editing.

Solange Peters: Resources, Conceptualization, Writing—review and editing.

John K. Field: Resources, Conceptualization, Writing—review and editing.

Daniel C. Christoph: Resources, Conceptualization, Writing—review and editing.

Anne Sibille: Resources, Conceptualization, Writing—review and editing.

Rainer Fietkau: Resources, Conceptualization, Writing—review and editing.

Vilde D. Haakensen: Resources, Conceptualization, Writing—review and editing.

Christos Chouaid: Resources, Conceptualization, Writing—review and editing.

Ben Markman: Resources, Conceptualization, Writing—review and editing.

T. Jeroen N. Hiltermann: Resources, Conceptualization, Writing—review and editing.

Alvaro Taus: Resources, Conceptualization, Writing—review and editing.

William Sawyer: Investigation, Data curation, Formal analysis, Writing—review and editing.

Allison Allen: Project administration, Writing—review and editing.

Pratibha Chander: Project administration, Data curation, Writing—review and editing.

Muriel Licour: Project administration, Supervision, Investigation, Conceptualization, Data curation, Writing—review and editing.

Benjamin Solomon: Resources, Conceptualization, Writing—review and editing.

Acknowledgments

Medical writing support, under the direction of the authors, was provided by Aaron Korpall, PhD, of Ashfield MedComms (Manchester, UK), an Inizio company, and was funded by AstraZeneca. The PACIFIC-R study (NCT03798535) was sponsored by AstraZeneca.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at <https://doi.org/10.1016/j.jtho.2022.10.003>.

References

1. Royal College of Physicians. NLCA annual report (for the 2018 audit period), version 2. <https://www.rcplondon.ac.uk/projects/outputs/annual-report-version-2-published-march-2021>. Accessed January 28, 2022.

2. Chen VW, Ruiz BA, Hsieh MC, Wu XC, Ries LAG, Lewis DR. Analysis of stage and clinical/prognostic factors for lung cancer from SEER registries: AJCC staging and collaborative stage data collection system. *Cancer*. 2014;120(suppl 23):3781-3792.
3. Walters S, Maringe C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. *Thorax*. 2013;68:551-564.
4. Yoon SM, Shaikh T, Hallman M. Therapeutic management options for stage III non-small cell lung cancer. *World J Clin Oncol*. 2017;8:1-20.
5. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28:2181-2190.
6. Hansen RN, Zhang Y, Seal B, et al. Long-term survival trends in patients with unresectable stage III non-small cell lung cancer receiving chemotherapy and radiation therapy: a SEER cancer registry analysis. *BMC Cancer*. 2020;20:276.
7. Bradley JD, Hu C, Komaki RR, et al. Long-term results of NRG oncology RTOG 0617: standard- versus high-dose chemoradiotherapy with or without cetuximab for unresectable Stage III non-small-cell lung cancer. *J Clin Oncol*. 2020;38:706-714.
8. Vokes EE, Herndon JE 2nd, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol*. 2007;25:1698-1704.
9. Senan S, Brade A, Wang LH, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced non-squamous non-small-cell lung cancer. *J Clin Oncol*. 2016;34:953-962.
10. Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol*. 2008;26:5755-5760.
11. Ahn JS, Ahn YC, Kim JH, et al. Multinational randomized Phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable Stage III non-small-cell lung cancer: KCSG-LU05-04. *J Clin Oncol*. 2015;33:2660-2666.
12. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16:187-199.
13. Flentje M, Huber RM, Engel-Riedel W, et al. GILT-A randomised phase III study of oral vinorelbine and cisplatin with concomitant radiotherapy followed by either consolidation therapy with oral vinorelbine and cisplatin or best supportive care alone in stage III non-small cell lung cancer. *Strahlenther Onkol*. 2016;192:216-222.
14. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in Stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919-1929.
15. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379:2342-2350.
16. Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res*. 2015;3:1052-1062.
17. Hui R, Özgüroğlu M, Villegas A, et al. Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study. *Lancet Oncol*. 2019;20:1670-1680.
18. Gray JE, Villegas A, Daniel D, et al. Three-year overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC-update from PACIFIC. *J Thorac Oncol*. 2020;15:288-293.
19. Faivre-Finn C, Vicente D, Kurata T, et al. Four-year survival with durvalumab after chemoradiotherapy in Stage III NSCLC-an update from the PACIFIC trial. *J Thorac Oncol*. 2021;16:860-867.
20. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in Stage III non-small-cell lung cancer. *J Clin Oncol*. 2022;40:1301-1311.
21. European Medicines Agency. Imfinzi (durvalumab) Product Information; 2022. https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf. Accessed January 28, 2022.
22. Food and Drug Administration. Durvalumab prescribing information; 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761069s029lbl.pdf. Accessed January 28, 2022.
23. Daly ME, Singh N, Ismaila N, et al. Management of Stage III non-small-cell lung cancer: ASCO Guideline. *J Clin Oncol*. 2022;40:1356-1384.
24. Remon J, Soria JC, Peters S. ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy. *Ann Oncol*. 2021;32:1637-1642.
25. Jazieh AR, Onal HC, Tan DSW, et al. Real-world treatment patterns and clinical outcomes in patients with Stage III NSCLC: results of KINDLE, a multicountry observational study. *J Thorac Oncol*. 2021;16:1733-1744.
26. Huber RM, De Ruyscher D, Hoffmann H, Reu S, Tufman A. Interdisciplinary multimodality management of stage III nonsmall cell lung cancer. *Eur Respir Rev*. 2019;28:190024.
27. McDonald F, Mornex F, Garassino MC, et al. 79MO PACIFIC-R: real-world characteristics of unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. *J Thorac Oncol*. 2021;16:S738-S739.
28. Garassino MC, Mazieres J, Reck M, et al. Durvalumab After Sequential Chemoradiotherapy in Stage III, Unresectable NSCLC: The Phase 2 PACIFIC-6 Trial. *J Thorac*

- Oncol.* 2022;17(12):1415-1427. doi:10.1016/j.jtho.2022.07.1148
29. Faehling M, Schumann C, Christopoulos P, et al. Durvalumab after definitive chemoradiotherapy in locally advanced unresectable non-small cell lung cancer (NSCLC): real-world data on survival and safety from the German expanded-access program (EAP). *Lung Cancer.* 2020;150:114-122.
 30. Taugner J, Käsmann L, Eze C, et al. Real-world prospective analysis of treatment patterns in durvalumab maintenance after chemoradiotherapy in unresectable, locally advanced NSCLC patients. *Invest New Drugs.* 2021;39:1189-1196.
 31. Jung HA, Noh JM, Sun JM, et al. Real world data of durvalumab consolidation after chemoradiotherapy in stage III non-small-cell lung cancer. *Lung Cancer.* 2020;146:23-29.
 32. Bruni A, Scotti V, Borghetti P, et al. A real-world, multicenter, observational retrospective study of durvalumab after concomitant or sequential chemoradiation for unresectable stage III non-small cell lung cancer. *Front Oncol.* 2021;11:744956.
 33. Hu HP, Walker C, Swaminath A. Real-world outcomes of chemoradiation and consolidative durvalumab in unresectable stage III non-small-cell lung cancer – a systematic review. *Int J Radiat Oncol Biol Phys.* 2021;111:e438.
 34. Horinouchi H, Atagi S, Oizumi S, et al. Real-world outcomes of chemoradiotherapy for unresectable Stage III non-small cell lung cancer: the SOLUTION study. *Cancer Med.* 2020;9:6597-6608.
 35. Paz-Ares L, Spira A, Raben D, et al. Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. *Ann Oncol.* 2020;31:798-806.
 36. Socinski MA, Özgüroğlu M, Villegas A, et al. Durvalumab after concurrent chemoradiotherapy in elderly patients with unresectable Stage III non-small-cell lung cancer (PACIFIC). *Clin Lung Cancer.* 2021;22:549-561.
 37. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst.* 2011;103:1452-1460.
 38. O'Rourke N, Roqué I, Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev.* 2010;(6):CD002140.
 39. El-Sharouni SY, Kal HB, Battermann JJ, Schramel FM. Sequential versus concurrent chemo-radiotherapy in inoperable stage III non-small cell lung cancer. *Anti-cancer Res.* 2006;26:495-505.
 40. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017;28(suppl 4):iv1-iv21.
 41. Bezjak A, Temin S, Franklin G, et al. Definitive and adjuvant radiotherapy in locally advanced non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline endorsement of the American Society for Radiation Oncology evidence-based clinical practice guideline. *J Clin Oncol.* 2015;33:2100-2105.
 42. Sato H, Okonogi N, Nakano T. Rationale of combination of anti-PD-1/PD-L1 antibody therapy and radiotherapy for cancer treatment. *Int J Clin Oncol.* 2020;25:801-809.
 43. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res.* 2014;74:5458-5468.
 44. Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest.* 2014;124:687-695.
 45. Dovedi SJ, Cheadle EJ, Popple AL, et al. Fractionated radiation therapy stimulates antitumor immunity mediated by both resident and infiltrating polyclonal T-cell populations when combined with PD-1 blockade. *Clin Cancer Res.* 2017;23:5514-5526.
 46. Kordbacheh T, Honeychurch J, Blackhall F, Faivre-Finn C, Illidge T. Radiotherapy and anti-PD-1/PD-L1 combinations in lung cancer: building better translational research platforms. *Ann Oncol.* 2018;29:301-310.
 47. Faivre-Finn C, Spigel DR, Senan S, et al. Impact of prior chemoradiotherapy-related variables on outcomes with durvalumab in unresectable stage III NSCLC (PACIFIC). *Lung Cancer.* 2021;151:30-38.
 48. Richards M, Anderson M, Carter P, Ebert BL, Mossialos E. The impact of the COVID-19 pandemic on cancer care. *Nat Cancer.* 2020;1:565-567.
 49. Wu YL, Wang L, Sendur MAN, et al. PACIFIC-5: Phase III study of durvalumab after either concurrent or sequential chemoradiotherapy (CRT) in patients with stage III NSCLC. *Ann Oncol.* 2019;30(suppl 9):ix113-ix114.
 50. Zhou Q, Chen M, Wu G, et al. GEMSTONE-301: a phase III clinical trial of CS1001 as consolidation therapy in patients with locally advanced/unresectable (stage III) non-small cell lung cancer (NSCLC) who did not have disease progression after prior concurrent/sequential chemoradiotherapy. *Transl Lung Cancer Res.* 2020;9:2008-2015.