ORIGINAL ARTICLE

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

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Short title: Real-world PFS with Durvalumab

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ABSTRACT (250/250 words)

Introduction: The Phase 3 PACIFIC trial established consolidation therapy with durvalumab as standard of care for patients with unresectable, stage III non-small-cell lung cancer (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 (EAP). Here, we report treatment characteristics and a pre-planned 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-weeks) within an EAP between September-2017 and December-2018. The primary endpoints are investigator-assessed rwPFS and overall survival (analyzed by Kaplan-Meier method).

Results: As of November 30, 2020, the full analysis set comprised 1,399 patients from 11 countries (median follow-up duration, 23.5 months). Patients received durvalumab for a median of 11.0 months. Median rwPFS was 21.7 months (95% CI: 19.1–24.5). RwPFS was numerically longer among patients who received concurrent versus sequential CRT (median, 23.7 vs. 19.3 months) and among patients with programmed cell death-ligand 1 (PD-L1) expression ≥1% versus <1% (22.4 vs. 15.6 months). Overall, 16.5% of patients had adverse events leading to treatment discontinuation; 9.5% of all patients discontinued because of pneumonitis/interstitial lung disease.

Conclusions: Consolidation durvalumab following 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 higher among patients who received concurrent versus sequential CRT and patients with higher PD-L1 expression. Nevertheless, favorable rwPFS outcomes were observed regardless of these factors.

Keywords (max. 5): Consolidation therapy, immunotherapy, locally advanced NSCLC, PD-L1 inhibition, real-world data

Introduction

Approximately 20–30% of patients with non-small-cell lung cancer (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 anti-cancer agents.[8-13] This changed following 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 following 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 demonstrated 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]

Based on the findings of PACIFIC, durvalumab became the first anti-cancer medicine to be approved as consolidation therapy for patients with unresectable, stage III NSCLC and no disease progression following CRT, and has subsequently been established as the global SoC in this setting.[21-24] Due to the poor prognosis associated

with unresectable, stage III NSCLC, the heterogeneity of this patient population, and the variability in real-world multi-disciplinary treatment approaches,[25, 26] there is a need for real-world data on the use, effectiveness, and tolerability of this regimen. 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 <1%. A preliminary safety analysis from PACIFIC-R, based on the first 3 months of treatment using data from the first of several pre-planned, retrospective chart extractions (spaced over a 5-year 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 years of follow-up), including treatment characteristics and a pre-planned 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 ≥1 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 pre-specified 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-month limit was applied in PACIFIC); did not exclude patients with

poor performance status (PS) (PACIFIC enrollment was restricted to patients with PS 0/1); 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).

Per 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/after the EAP and prior to 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 endpoints 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) v1.1, depending on local practice.

Key secondary endpoints include: (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 of special interest (AESIs).

AESIs, defined as adverse events (AEs) potentially attributable to an immune-mediated etiology (and reported in association with durvalumab), were collected when they required ≥1 of the following actions: concomitant use of systemic corticosteroids, use of immunosuppressants and/or endocrine therapies; and temporary interruption/permanent discontinuation of durvalumab. Pre-defined AESIs considered in the study were: diarrhea/colitis and intestinal perforation; pneumonitis/interstitial lung disease (ILD); hepatitis/transaminase increase; endocrinopathies (hypophysitis/hypopituitarism, adrenal insufficiency, hyperthyroidism/hypothyroidism,

and type-1 diabetes mellitus); rash/dermatitis; nephritis/blood creatinine increase; pancreatitis/serum lipase and amylase increase; myocarditis; myositis/polymyositis; neuropathy/neuromuscular toxicity (Guillain–Barré syndrome and myasthenia gravis); and other less frequent events with a potential immune-mediated etiology (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 the median rwPFS (and corresponding 95% CI) for the full analysis set.

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 the AstraZeneca-initiated EAP, Spanish data were sourced from an externally sponsored, locally initiated study with the same enrollment criteria as PACIFIC-R. 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 dataset was integrated for the analyses reported in this article (following 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 dataset.

Results

Patients and Hospital Site Characteristics

As of November 30, 2020 (end date of the second chart extraction), the full analysis set included 1,399 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 (UK; 54), Norway (36), and Switzerland (15). Most hospital sites (67.2%) had a primary medical specialty of medical/clinical oncology (Supplementary Table 1). The median follow-up duration in the full analysis set was 23.5 months (range, <0.1–35.3 months); 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 patients in the full analysis set was 66.0 years at EAP entry; 21.2% and 10.4% were aged 70–75 years and >75 years, respectively (Table 1). Most patients were male (67.5%), current/former smokers (92.1%), and had a performance status of 0/1 (98.0%) at EAP entry. The majority (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 patients had stages IA–IIB, IIIA, and IIIB/C disease, respectively, at the time of initial NSCLC diagnosis; 55.0% had N2 disease (Supplementary Table 2). Most patients (64.0%) had non-squamous tumor histology. Comorbidities were reported in 71.5% of all patients (Supplementary Fig. 1). Hypertension was the most prevalent comorbidity (32.3%), followed by chronic obstructive pulmonary disease (25.2%), and diabetes (13.4%).

Overall, 967/1,399 patients (69.1%) were tested for PD-L1. Among those tested, 72.4% and 18.0% had expression on ≥1% and <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 patient subgroups based on PD-L1 expression (Supplementary Table 3).

In total, 582/1,399 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 aged ≥70 years (40.8% vs. 29.0%) and had stage IIIB/C disease (61.7% vs. 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 = 1,344 with available data). Most patients received a total RT dose >60 to ≤66 Gy (52.4%), while 41.4% received ≤60 Gy. Among 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 non-platinum 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).

RECIST-defined best response to CRT (based on 1,072 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 evaluable or unknown for 9.5% of 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, -35–981 days/-1.1–32.2 months; n = 1,365) in the full analysis set; one patient started durvalumab before finishing RT. Overall, 30.1% of patients started durvalumab within 42 days (and 1.2% within 14 days) of finishing RT; meanwhile, 14.4% and 1.0% started >3 months and >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 days/<0.1–33.8 months; n = 1,388). Overall, 19.8% and 4.2% of patients received durvalumab for a total duration of >12 and >14 months, respectively. Patients received a median of 22.0 durvalumab infusions (range, 1–65 infusions; n = 1,339), with 7.1% receiving >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 month (range, 3–295 days/0.1–9.7 months; n = 150).

Reasons for Discontinuing Durvalumab

Overall, 47.1% of 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 patients in the full analysis set; median time to discontinuation, 4.9 months) and AEs (occurring in 16.7% of patients in the full analysis set; median time to discontinuation, 2.8 months).

Pre-planned Analysis of RwPFS

At the time of the database cutoff, 737/1,399 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 458/659 patients (69.5%), per investigator's assessment in 171/659 patients (25.9%), and by unknown means in 30/659 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 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 shown in Fig. 3*A*–*D*, rwPFS was numerically longer among patients with PD-L1 expression ≥1% versus <1% (median, 22.4 vs.15.6 months, respectively), stage IIIA versus IIIB/C disease (median, 23.7 vs. 19.2 months, respectively), and non-squamous versus squamous histology (median, 25.3 vs. 14.6 months, respectively). RwPFS was also numerically longer among patients who received cCRT versus sCRT (median, 23.7 vs. 19.3 months, respectively), those who received cisplatin versus carboplatin during CRT (median, 24.4 vs. 18.8 months), and those who received durvalumab ≤42 days versus >42 days after finishing RT (median, 25.7 vs. 20.8 months, respectively) (Supplementary Table 8). Meanwhile, rwPFS was numerically similar among patients aged <70 years and 70–75 years (median, 22.8 vs. 22.4 months, respectively), and was comparatively shorter among patients aged >75 years (median, 19.2 months). Compared with the full analysis set, rwPFS was numerically longer among patients with known *KRAS* mutations (median, 24.2 months) and numerically shorter among patients with known *EGFR* mutations (median, 11.1 months) (Supplementary Table 8).

Preliminary Analysis of OS

At the time of the database cutoff, 430/1,399 patients (30.7%) had died. Median OS was not reached in the full analysis set; 71.2% (95% CI: 68.8–73.6) of patients were estimated to be alive at 24 months.

AESIs

In total, 654/1,399 patients (46.7%) in the full analysis set experienced AESIs; 11.2% (n = 156) and 16.5% (n = 231) of patients had AESIs leading to temporary interruption and permanent discontinuation of durvalumab, respectively. Pneumonitis/ILD was the most common AESI leading to interruption (5.2% of the full analysis set) and permanent discontinuation (9.5% of the full analysis set) (Table 3), noting that it is difficult to differentiate between immunotherapy-induced and radiotherapy-induced pneumonitis. Other AESIs leading to interruption or permanent discontinuation of treatment included diarrhea/colitis and/or intestinal perforation, hepatitis/transaminase increases, and endocrinopathies (Table 3). RwPFS among patients who had AESIs leading to interruption or permanent discontinuation of treatment was consistent with the full analysis set (median, 20.7 months; 95% CI: 16.0–24.1; n = 367).

Pneumonitis/ILD

Overall, 250 patients in the full analysis set experienced pneumonitis/ILD (250/1,399; 17.9%). Among patients who experienced pneumonitis/ILD, 23 (9.2%) had >1 event and four (1.6%) had >2 events. Median time to onset of the first event, measured from the start of durvalumab, was 68.5 days/2.3 months (range, -41–444 days/-1.3–14.6 months; n = 250). In all, 4.0% (n = 56), 8.4% (n = 118), 2.9% (n = 41) and 0.4% (n = 5) of patients in the full analysis set had pneumonitis/ILD events classified as mild, moderate, severe, and life threatening/fatal, respectively (assessed by the investigator), while 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/ILD was required in 199 patients with the event (199/250; 79.6%). Two patients (0.1%) had fatal pneumonitis/ILD events in the full analysis set. Both fatal

events were recurrences of pneumonitis/ILD; one patient had been rechallenged with durvalumab, and the other had discontinued durvalumab permanently, following their original pneumonitis/ILD event.

Discussion

PACIFIC-R provides valuable insights into treatment patterns and outcomes with the PACIFIC regimen in the real-world setting, based on a population of >1,000 patients enrolled across 11 countries. Median rwPFS was 21.7 months and nearly half of all patients were alive and free of disease progression 2 years after starting durvalumab. Furthermore, >70% of patients were alive at 2 years regardless of their progression status. These findings confirm the effectiveness of durvalumab following 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 following 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. reported a rwPFS rate of 62% at 12 months with durvalumab in their prospective study,[30] 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 rwPFS 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, while it was the date that durvalumab was started within the EAP [i.e., post-CRT] in PACIFIC-R).[25]

Favorable rwPFS 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 non-squamous histology, and patients who received cisplatin (during CRT) in both studies.[20, 36]

As expected, better rwPFS outcomes were observed among patients who received cCRT compared with sCRT; this aligns with other studies that demonstrated 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 due to concerns with the tolerability of concurrent treatment (among other reasons). Reassuringly, favorable rwPFS outcomes were still observed among patients who received sCRT in PACIFIC-R (median, 19.3 months). 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 following sCRT falls outside of the approved label for durvalumab in the US;[22] meanwhile, the label approved by the European Medicines Agency allows use of either cCRT or sCRT.[21] The favorable real-world outcomes seen in the sCRT subset of PACIFIC-R complement recently published findings from the phase 2, single-arm, PACIFIC-6 trial, which demonstrated encouraging outcomes with durvalumab following 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 ≥1% compared with <1%, consistent with observations from PACIFIC.[20, 35] Nevertheless, favorable rwPFS outcomes were still observed among patients with PD-L1 expression <1% (median, 15.6 months). Patients with PD-L1 expression on <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 US.[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, as well as by age and disease stage; use of sCRT was more common among patients enrolled in Italy, patients aged ≥70 years, and patients diagnosed with more advanced disease (i.e., stage IIIB/C).

Pre-clinical evidence suggests that radiotherapy induces immunomodulatory changes, including up-regulation of PD-L1, that 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 prior to CRT.[46] Interestingly, rwPFS was better among patients who received durvalumab closer to the end of radiotherapy, consistent with findings from PACIFIC.[47] We are uncertain of the factors underpinning this observation, but pre-clinical evidence suggests that administering PD-L1 inhibitors as close as possible to CRT may increase effectiveness.[43] However, it should be acknowledged that the timing of durvalumab initiation following 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 months).[14] This may seem unexpected as, due 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 UK and Germany were unable to collect information on patients who received durvalumab within the EAP but died prior to 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 COVID-19 pandemic, which could have resulted in fewer hospital visits.[48] Lastly, the use of RECIST criteria for tumor assessments is heterogeneous across countries. While 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. 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 to PACIFIC (66.3%).[15] As mentioned for rwPFS, overestimation of OS can be attributed to the fact that UK and German sites could not collect information on patients who died prior to PACIFIC-R enrollment. Further analyses are planned based on future chart extractions from PACIFIC-R, which will allow for more robust analyses of OS outcomes based on 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/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), while 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 >12 and >14 months, respectively, and only 7.1% received >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 >12 months.[49, 50]

Although the EAP did not exclude patients based on ECOG PS in most countries, the PACIFIC-R cohort includes very few patients with PS >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 was missing for 448 patients). Limited recruitment of patients with PS >1 may be because the EAP was the first time 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 0/1[14]).

Conclusions

The findings from PACIFIC-R demonstrate that consolidation therapy with durvalumab following definitive CRT is well tolerated and effective in this curative-intent setting based on 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 ≥1% versus <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. While durvalumab was generally well tolerated, pneumonitis/ILD led to treatment discontinuation in 9.5% of patients; clinical vigilance is required to ensure effective diagnosis and management this important and potentially serious toxicity. Overall, the findings of PACIFIC-R suggest the potential of the PACIFIC regimen seen 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.

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Tables and Figures

Table 1. Patient Demographics and Disease Characteristics

Characteristic	Full Analysis Set (N = 1,399)
Median age at EAP inclusion, years (range)	66.0 (26–88)
Age category at EAP inclusion, n (%)	
<70 years	958 (68.5)
70–75 years	296 (21.2)
>75 years	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/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 = 1,392[b]
IA to IIB	74 (5.3)
IIIA	604 (43.4)
IIIB/C	714 (51.3)
Histological subtype at stage III diagnosis, n (%)	n = 1,378[c]
Squamous	496 (36.0)
Non-squamous	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/unknown	19 (3.3)

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

[a]ECOG/WHO PS at EAP inclusion data was missing for 448 patients.
[b]Disease stage at initial diagnosis was determined according to the 7th or 8th editions of the American Joint Committee on Cancer staging manual; data were missing for seven patients.
[c]Histological subtype at stage III diagnosis data was missing/unknown for 21 patients.
[d]PD-L1 was not tested for in 431 patients, and data was 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 due 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.
[e]*EGFR* mutation status was not tested for 817 patients.

EAP, early access program; ECOG/WHO PS, Eastern Cooperative Oncology Group/World Health Organization performance status; NSCLC, non-small-cell lung cancer; PD-L1 programmed cell death-ligand 1.

Table 2. Reasons for and Timing of Durvalumab Treatment Discontinuation

	Full Analysis Set (N = 1,399)	
Reason[a]	**n (%)**	**Median Time to Discontinuation, Months (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]

[a]Three 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.

[b]Measured from the index date (i.e., date durvalumab infusion received within the EAP); 1 month equates to 30.44 days.

[c]Based on the investigator's decision per their country-specific protocol and, where applicable, was beyond 12 months of treatment.

[d]Duration of exposure data was missing for four patients who completed treatment, three patients who discontinued due to disease progression, and two patients who discontinued for other reasons.

EAP, early access program.

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

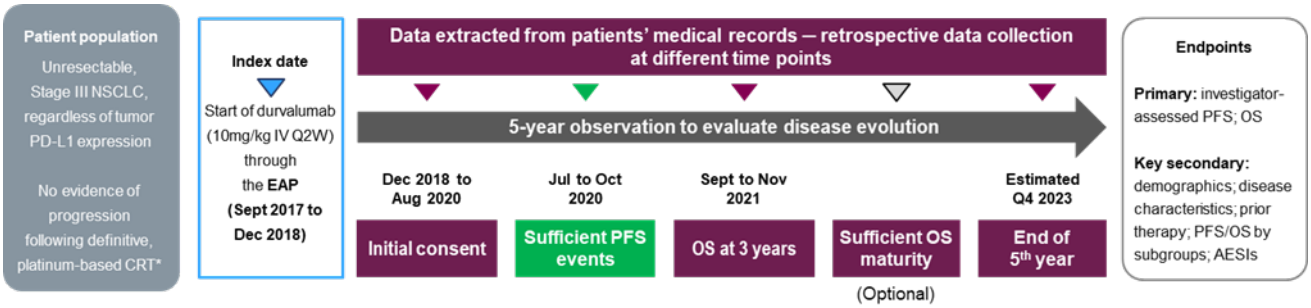
AESI Category	Full Analysis Set (N = 1,399)	
	Temporary Interruption, n (%)	**Permanent Discontinuation, n (%)**
Any	156 (11.2)	231 (16.5)
Pneumonitis/ILD	73 (5.2)	133 (9.5)
Diarrhea/colitis and/or intestinal perforation	16 (1.1)	15 (1.1)
Hepatitis/transaminase increases	10 (0.7)	17 (1.2)
Endocrinopathies	18 (1.3)	10 (0.7)
Other[a]	33 (2.4)	51 (3.6)

AESI categories leading to temporary interruption and permanent discontinuation of durvalumab in less than 1% of the full analysis set are not tabulated.

[a]Free term written events (which may include the other terms listed in the table).

AESI, adverse event of special interest; ILD, interstitial lung disease.

Figure 1. PACIFIC-R study design.

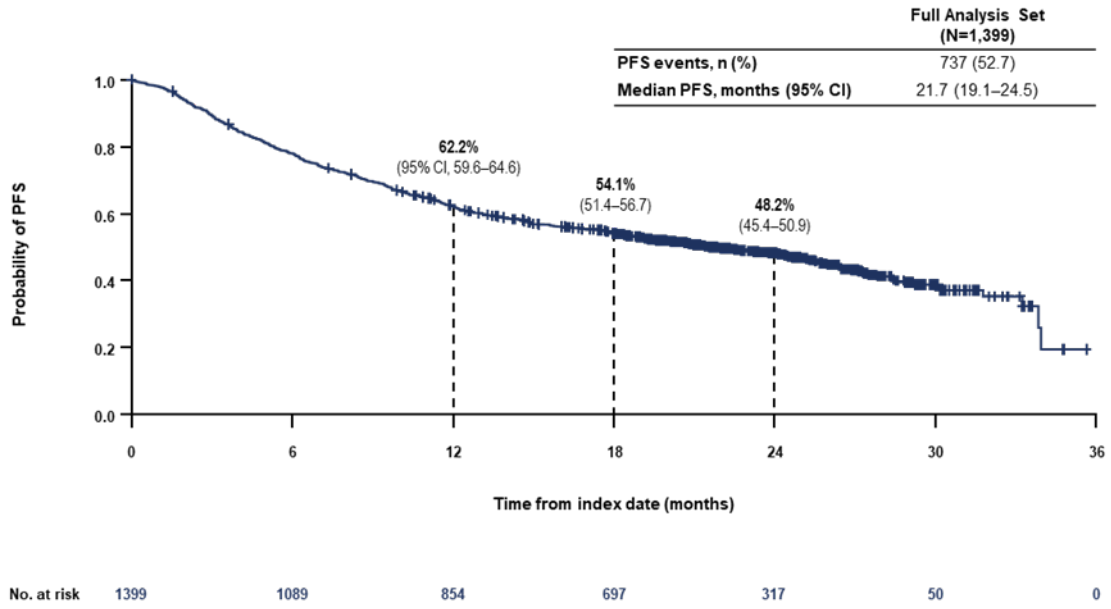


The current analysis is based on the second data extraction of PACIFIC-R (highlighted in green), which was timed to allow sufficient PFS maturity.

*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; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q, quarter; Q2W, every 2 weeks.

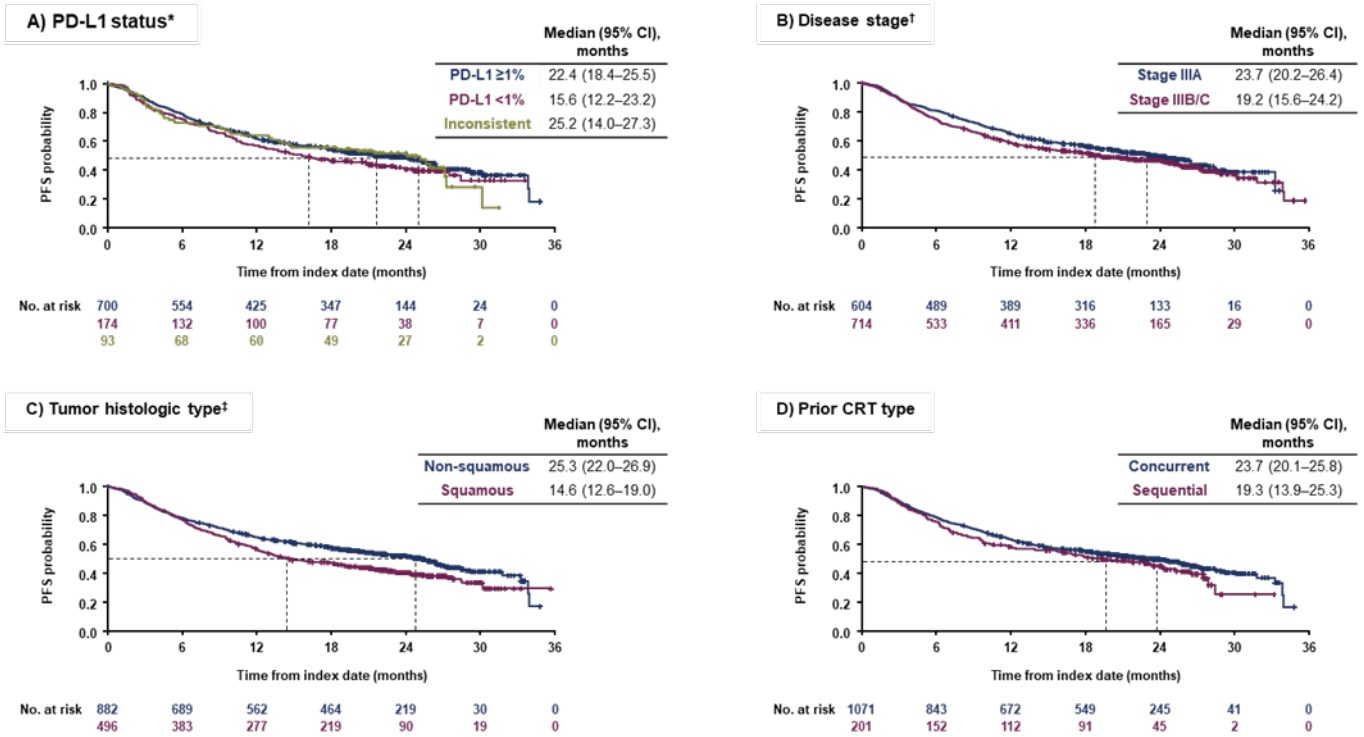
Figure 2. Real-world PFS in the full analysis set.



Kaplan-Meier Analysis 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 months) for the full analysis set; 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.



Kaplan-Meier analyses of real-world PFS in subgroups of interest. The tick marks represent censored observations, and the dashed lines illustrate the extrapolation of median rwPFS. *The PD-L1 inconsistent subgroup represents patients who were tested for PD-L1 but whose test results were not clearly reported due 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.

Supplementary Data

1. Supplementary Methods (PDF file)
    - Details of (1) the early access program and (2) non-enrolled patients identified by the PACIFIC-R study sites

2. Supplementary Tables and Figures (PDF file)
    - Supplementary tables 1–8 and supplementary figure 1