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ORIGINAL ARTICLE

Durvalumab After Sequential Chemoradiotherapy in Stage III, Unresectable NSCLC: The Phase 2 PACIFIC-6 Trial

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Disclosure: Dr. Garassino reports receiving grants from AstraZeneca and Merck and personal fees from AstraZeneca, Merck, Roche, Bristol-Myers Squibb, Celgene, Boehringer Ingelheim, Novartis, GlaxoSmithKline, Pfizer, Eli Lilly, and Takeda. Mazieres reports receiving grants or contracts paid to the institution from AstraZeneca, Roche, and Pierre Fabre and payment or honoraria from Merck, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, Daiichi, and Pfizer. Reck reports receiving consulting fees from Amgen, Bristol-Myers Squibb, Beigene, Merck Sharp & Dohme, Novartis, Janssen, Roche, GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Mirati, Merck, Pfizer, and Sanofi; receiving payment or honoraria from Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Beigene, Eli Lilly, Merck Sharp & Dohme, Mirati, Merck, Novartis, Janssen, Pfizer, Roche, Sanofi, and GlaxoSmithKline; and having participation on a data safety monitoring board/advisory board for Daiichi and Sanofi. Chouaid reports receiving grants paid to the institution, consulting fees, and support for attending meetings and/or travel from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Roche, Sanofi Aventis, Bristol-Myers Squibb, Merck Sharp & Dohme, Eli Lilly, Novartis, Pfizer, Takeda, Bayer, and Amgen. Reinmuth reports receiving consulting fees from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Takeda, AstraZeneca, Merck, and Pfizer; receiving payment or honoraria from Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Merck Sharp & Dohme, Pfizer, Novartis, Merck, Janssen, Roche, and Takeda; and having participation on a data safety monitoring board/advisory board for Symphogen. Cove-Smith reports having a chief investigator contract with AstraZeneca. Mansy reports receiving payment or honoraria from AstraZeneca and having participation on a data safety monitoring board/advisory board for Merck Sharp & Dohme, Amgen, and Pfizer. Cortinovis reports receiving payment or honoraria from Bristol-Myers Squibb and having participation on a data safety monitoring board/advisory board for Bristol-Myers Squibb, Roche, Novartis, Amgen, AstraZeneca, Merck Sharp & Dohme, and Boehringer Ingelheim. Migliorino reports receiving payment or honoraria from Eli Lilly, Bristol-Myers Squibb, Roche, Boehringer Ingelheim, Novartis, Takeda, AstraZeneca, and Pfizer; receiving support for attending meetings and/or travel from Bristol-Myers Squibb, Boehringer Ingelheim, Roche, Takeda, and AstraZeneca; and having participation on a data safety monitoring board/advisory board for Roche, Takeda, AstraZeneca, Pfizer, and Novartis. Delmonte reports receiving payment or honoraria from Bristol-Myers Squibb; receiving support for attending meetings and/or travel from Roche and Merck Sharp & Dohme; and having participation on a data safety monitoring board/advisory board for Novartis. Sánchez reports receiving consulting fees and payment or honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, and Roche. Velarde reports receiving payment or honoraria and support for attending meetings and/or travel from AstraZeneca, Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, Pfizer, and Boehringer Ingelheim. Bernabe reports receiving an investigational grant from Roche; receiving payment or honoraria from Roche, Bristol-Myers Squibb, Pfizer, Merck Sharp & Dohme, Amgen, Takeda, and AstraZeneca; having participation on a data safety monitoring board/advisory board for Takeda, Roche, Bristol-Myers Squibb, and AstraZeneca. Paz-Ares reports receiving grants paid to the institution from Merck Sharp & Dohme, AstraZeneca, Pfizer, and Bristol-Myers Squibb; consulting fees from Eli Lilly, Merck Sharp & Dohme, Roche, Pharmamar, Merck, AstraZeneca, Novartis, Servier, Amgen, Pfizer, Sanofi, Bayer, Bristol-Myers Squibb, Mirati, GlaxoSmithKline, Janssen, and Takeda; and payment or honoraria from AstraZeneca, Janssen, Merck, and Mirati. Perez reports having employment and stock options with AstraZeneca. Trunova reports having employment and stock options with AstraZeneca. Foroutanpour reports having employment with AstraZeneca (contractor). Faivre-Finn reports receiving research grants and related add-on activities, consulting fees, and payment or honoraria paid to the institution from AstraZeneca; receiving support for attending meetings and/or travel; and having participation on a data safety monitoring board/advisory board from AstraZeneca. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2022.07.1148

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Received 26 May 2022; revised 15 July 2022; accepted 20 July 2022
Available online - 9 August 2022

ABSTRACT

Introduction: On the basis of the findings of the phase 3 PACIFIC trial (NCT02125461), durvalumab is standard of care for patients with stage III, unresectable NSCLC and no disease progression after concurrent chemoradiotherapy (cCRT). Many patients are considered unsuitable for cCRT owing to concerns with tolerability. The phase 2 PACIFIC-6 trial (NCT03693300) evaluates the safety and tolerability of durvalumab after sequential CRT (sCRT).

Methods: Patients with stage III, unresectable NSCLC and no progression after platinum-based sCRT were enrolled to receive durvalumab (1500 mg intravenously) every 4 weeks for up to 24 months. The primary end point was the incidence of grade 3 or 4 adverse events possibly related to treatment occurring within 6 months. Secondary end points included investigator-assessed progression-free survival (PFS; Response Evaluation Criteria in Solid Tumors version 1.1) and overall survival.

Results: Overall, 117 patients were enrolled (59.8% with performance status >0, 65.8% aged ≥65 y, and 37.6% with stage IIIA disease). Median treatment duration was 32.0 weeks; 37.6% of patients remained on treatment at data cutoff (July 15, 2021). Grade 3 or 4 AEs occurred in 18.8% of patients. Five patients had grade 3 or 4 possibly related adverse events within 6 months (incidence: 4.3%; 95% confidence interval: 1.4–9.7), including two pneumonitis cases. Two patients (1.7%) had grade 5 AEs of any cause. Survival data maturity was limited. Median PFS was 10.9 months (95% confidence interval: 7.3–15.6), and 12-month PFS and overall survival rates were 49.6% and 84.1%, respectively.

Conclusions: Durvalumab after sCRT had a comparable safety profile with that observed with durvalumab after cCRT in PACIFIC and had encouraging preliminary efficacy in a frailer population.

Keywords: Durvalumab; Immunotherapy; Sequential chemoradiotherapy; Non–small-cell lung cancer; Locally advanced

Introduction

The findings of the phase 3 PACIFIC trial (NCT02125461) established up to 12 months of consolidation therapy with the programmed cell death-ligand 1 (PD-L1) inhibitor, durvalumab, as the global standard of care (SoC) for patients with stage III, unresectable NSCLC whose disease has not progressed after platinum-based chemoradiotherapy (CRT).[1–5] In PACIFIC, durvalumab after platinum-based, concurrent CRT (cCRT) significantly improved the primary end points of progression-free survival (PFS; assessed by blinded independent central review using Response Evaluation Criteria in Solid Tumors [RECIST]) ($p < 0.001$) and overall survival (OS) ($p = 0.0025$) versus placebo.[1,2] At the most recent update from PACIFIC (with approximately 5 y of follow-up), median PFS was 16.9 months (95% confidence interval [CI]: 13.0–23.9) versus 5.6 months (95% CI: 4.8–7.7) with durvalumab versus placebo (hazard ratio = 0.55; 95% CI: 0.45–0.68), and median OS was 47.5 months (95% CI: 38.1–52.9) versus 29.1 months (95% CI: 22.1–35.1) (hazard ratio = 0.72; 95% CI: 0.59–0.89)[6]; the estimated 5-year PFS and OS rates 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. Importantly, given that the historical SoC after CRT was observation alone, durvalumab had a manageable safety profile and did not detrimentally affect patient-reported outcomes compared with placebo.[2,7]

cCRT is associated with improved survival and better locoregional control versus sequential CRT (sCRT) and is recognized as the preferred treatment strategy for stage III, unresectable NSCLC.[3,5,8–12] Nevertheless, many patients receive sCRT in real-world clinical practice, with rates of sCRT use being higher across Europe than other regions.[13–20] Patients can receive sCRT instead of cCRT for several reasons, including concerns about the tolerability of cCRT, advanced age or frailty, comorbidities, volume and location of disease, and access to radiation facilities in a timely fashion.[13,14,19,21]

Given the frequent use of sCRT in real-world clinical practice, the question of whether durvalumab can be

administered safely after sCRT, with the ultimate goal of improving outcomes for patients who receive CRT in this manner, is of considerable interest. PACIFIC-6 (NCT03693300) was designed to evaluate the safety and tolerability of durvalumab after sCRT. Here, we report the primary safety analysis and preliminary efficacy data from PACIFIC-6.

Materials and Methods

Trial Design and Patients

PACIFIC-6 is an ongoing, multicenter, open-label, single-assignment, practice-informing, phase 2 trial. Patients were enrolled in the following two cohorts: (1) patients with Eastern Cooperative Oncology Group performance status (PS) 0 or 1 and (2) patients with PS 2. Eligible patients were at least 18 years of age and had histologically or cytologically documented NSCLC with stage III, unresectable NSCLC according to the International Association for the Study of Lung Cancer staging manual (eighth edition).[22] Positron emission tomography or computed tomography, magnetic resonance imaging of the brain, and endobronchial ultrasound with biopsy at diagnosis were highly encouraged (but not mandatory).

Patients must have completed sCRT consisting of at least two cycles of platinum-based chemotherapy (containing etoposide, vinblastine, vinorelbine, a taxane, pemetrexed, or gemcitabine, per local SoC) followed by radiotherapy (RT) (total dose: 60 Gy ±10%), with no more than a 6-week interval between the last dose of chemotherapy and the start of RT; a one-cycle overlap between chemotherapy and RT was permitted provided the chemotherapy regimen did not contain gemcitabine. For RT, study sites were encouraged to adhere to the following organs at risk dose limits: mean lung dose less than 20 Gy or V20 less than 35% (or both), mean esophagus dose less than 34 Gy, and heart dose V45 less than 35% or V30 less than 30%. Previous thoracic RT must have been completed less than or equal to 42 days before the first durvalumab infusion, and patients were required to have no evidence of progression after sCRT (per RECIST version 1.1) and adequate bone marrow and organ function. Exclusion criteria included mixed small cell and NSCLC tumor histologic type; receipt of cCRT for stage III NSCLC, or sCRT with more than or equal to two concomitant cycles; unresolved toxicity of grade greater than or equal to 2 from previous sCRT (per Common Terminology Criteria for Adverse Events); previous exposure to immune-mediated therapy; use of immunosuppressive medication less than or equal to 14 days before starting durvalumab; a history of allogenic organ transplantation, active or previous documented autoimmune or inflammatory disorders, leptomeningeal carcinomatosis, active primary immunodeficiency, or another primary malignancy; and active infection or uncontrolled intercurrent illness. Comprehensive eligibility criteria are listed in Supplementary Table 1.

All patients provided written informed consent to participate in the study, which was approved by relevant ethics committees or institutional review boards and was run in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice and the Declaration of Helsinki.

Treatment

All patients received durvalumab (1500 mg) intravenously every 4 weeks for up to 24 months (i.e., 26 doses) or until disease progression, unacceptable toxicity, initiation of alternative anticancer therapy, or consent withdrawal. Patients could be treated beyond progression if the investigator considered that they were still deriving benefit.

End Points and Assessments

The primary end point was the incidence of grade 3 or 4 treatment-related adverse events (TRAEs) observed within 6 months of starting durvalumab. In the study case report forms, investigators were asked to give a yes or no response to whether there was a "reasonable possibility that the adverse event (AE) was caused by the investigational product" (i.e., durvalumab), and the TRAE-equivalent term "possibly related adverse event" (PRAE) was adopted. For this reason, we use PRAE rather than TRAE in this report. Secondary end points were PFS, objective response rate (ORR), and duration of response, all investigator assessed per RECIST version 1.1, as well as OS, lung cancer mortality (i.e., NSCLC-related death), and safety. Exploratory end points included, but were not limited to, the association between tumoral expression of PD-L1 and efficacy outcomes.

AEs were graded using Common Terminology Criteria for Adverse Events version 4.03; safety follow-up continued for 90 days after discontinuation of study treatment. Tumors were assessed by CT scan (preferred) or magnetic resonance imaging at study baseline (per local practice) and subsequently every 8 weeks up to week 52 and then every 12 weeks until confirmed radiological progression. After discontinuing study treatment, patients were followed for confirmed radiological progression (if they had not already progressed) and survival.

The provision of archival tumor tissue was mandatory for the evaluation of tumor-based biomarkers. PD-L1 tumor cell (TC) expression was determined centrally using the fully validated VENTANA PD-L1

(SP263) immunohistochemistry assay; samples were scored using a 1% expression threshold.

Statistical Analyses

PACIFIC-6 is a safety study, and no formal sample size calculation was performed. The protocol permitted enrollment of up to 150 patients across two cohorts: 100 to 120 patients could be enrolled into the PS 0 or 1 cohort and up to 30 patients could be enrolled into the PS 2 cohort. The primary analysis was performed when the last patient dosed had the opportunity to receive durvalumab for 6 months. The safety analysis set (used for analyses of both safety and efficacy) included all patients who received at least one durvalumab infusion.

Baseline patient and disease characteristics, as well as details regarding previous sCRT and exposure to durvalumab, were summarized descriptively. Treatment exposure was assessed in terms of duration, number of cycles received, and relative dose intensity (i.e., the percentage of actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation, progression, or data cutoff [whichever occurred earlier]). Safety and investigator-assessed tumor response data were also summarized descriptively, with associated 95% CIs calculated (where applicable) using the Clopper–Pearson method. Time-to-event end points were analyzed using the Kaplan–Meier method to estimate medians and landmark rates (e.g., 12-mo PFS); 95% CIs for the medians and landmark rates were derived using the Brookmeyer–Crowley and Greenwood methods, respectively. Efficacy analyses were repeated for patients with known PD-L1 status, with patients grouped according to PD-L1 expression ($<$1% and $\geq$1%). SAS version 9.3 or higher was used for all analyses.

Results

Patients and Treatment

Between April 16, 2019, and December 30, 2020, 117 patients were enrolled across 25 centers in six countries, including Italy (39 patients), Spain (30), Germany (18), France (16), the United Kingdom (12), and the United States (2). Median age was 68.0 (range: 39–85) years; 65.8% and 17.9% of patients were aged at least 65 years and at least 75 years, respectively (Table 1). Most were of male sex (62.4%) and had stage IIIB or IIIC disease (61.5%), adenocarcinoma tumor histologic type (53.8%), and PS 0 (40.2%) or 1 (57.3%). Only three patients (2.6%) with PS 2 were enrolled.

Nearly all patients (98.3%) had a past or present medical conditions at baseline. Overall, 59.0% had a history of vascular disorders (mostly hypertension, which was reported in 50.4% of all enrolled patients) and 23.1% had a history of cardiac disorders. A total of 53.8% had a history of respiratory disorders, most often chronic obstructive pulmonary disease (reported in 28.2% of all enrolled patients); respiratory symptoms reported at baseline included cough (14.5%), dyspnea (9.4%), and exertional dyspnea (7.7%). Approximately half of all patients (51.3%) had a history of metabolic disorders, most often dyslipidemia (reported in 14.5% of all enrolled patients), hypercholesterolemia (13.7%), diabetes mellitus—unspecified type (12.0%), and type 2 diabetes mellitus (9.4%).

As mandated by the protocol, all patients started RT within 6 weeks of their last chemotherapy dose during previous sCRT. Furthermore, 19 patients (16.2%) had overlapping cycles of chemotherapy and RT, noting that a one-cycle overlap was permitted by the protocol; one patient had more than one overlapping cycle and was reported as a protocol deviation (Table 2). Patients received a median of 4.0 chemotherapy cycles (range: 1–9), with the most used regimens being carboplatin–vinorelbine (26.5%) and carboplatin–paclitaxel (19.7%). Median time to the start of durvalumab from completion of RT was 26.0 (range: 8–67) days. Most patients (95.7%) started durvalumab more than or equal to 14 days after RT; 18 patients (15.4%) did not start durvalumab within the protocol-specified period of less than or equal to 42 days after RT and were reported as protocol deviations.

As of July 15, 2021, the median follow-up duration was 12.9 (range: 1.4–25.5) months. All patients received at least one durvalumab infusion and had the opportunity to receive treatment for at least 6 months. Overall, three patients (2.6%) had completed the protocol-defined 24 months of study treatment, whereas 44 (37.6%) had ongoing treatment and 73 (62.4%) had discontinued treatment; disease progression (n = 35; 29.9%) and AEs (n = 25; 21.4%) were the most common reasons for discontinuing treatment. The median total duration of treatment was 32.0 (range: 4–105) weeks. Patients received a median of 8.0 durvalumab infusions (range: 1–26), and the median relative dose intensity was 100.0% (range: 63.6%–100.0%).

Safety

Almost all patients (94.9%) had at least one AE of any cause and grade; grade 3 or 4 AEs and AEs leading to treatment discontinuation occurred in 22 (18.8%) and 25 patients (21.4%), respectively (Table 3). The most frequently reported AEs of any cause and grade were cough (31.6%), asthenia (23.9%), dyspnea (23.1%), and fatigue (20.5%) (Table 4). No individual grade 3 or 4 AEs occurred in more than two patients (1.7%); those

Table 1. Baseline Patient and Disease Characteristics

Characteristic	ECOG PS 0 or 1 (n = 114)	ECOG PS 2 (n = 3)	All Patients (N = 117)
Median age (range), y	68.0 (39-85)	65.0 (53-77)	68.0 (39-85)
Age group, n (%)			
<65 y	39 (34.2)	1 (33.3)	40 (34.2)
≥65 y	75 (65.8)	2 (66.7)	77 (65.8)
≥75 y	20 (17.5)	1 (33.3)	21 (17.9)
Sex, n (%)			
Men	71 (62.3)	2 (66.7)	73 (62.4)
Women	43 (37.7)	1 (33.3)	44 (37.6)
Race, n (%)			
White	101 (88.6)	3 (100.0)	104 (88.9)
Unknown	13 (11.4)	0	13 (11.1)
Smoking history, n (%)			
Never smoker	9 (7.9)	0	9 (7.7)
Former smoker	73 (64.0)	2 (66.7)	75 (64.1)
Current smoker	32 (28.1)	1 (33.3)	33 (28.2)
ECOG PS, n (%)			
0	47 (41.2)	0	47 (40.2)
1	67 (58.8)	0	67 (57.3)
2	0	3 (100.0)	3 (2.6)
Histologic type, n (%)			
Adenocarcinoma	63 (55.3)	0	63 (53.8)
Squamous cell	42 (36.8)	3 (100.0)	45 (38.5)
Other	9 (7.9)	0	9 (7.7)
Disease stage at baseline, n (%)			
IA	1 (0.9)	0	1 (0.9)
IIIA	44 (38.6)	0	44 (37.6)
IIIB	58 (50.9)	1 (33.3)	59 (50.4)
IIIC	11 (9.6)	2 (66.7)	13 (11.1)
PD-L1 expression on TCs, n (%)			
<1%	34 (29.8)	0	34 (29.1)
≥1%	33 (28.9)	3 (100.0)	36 (30.8)
Missing	47 (41.2)	0	47 (40.2)

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1; PS, performance status; TC, tumor cell.

reported in two patients each were hypertension, pneumonia, pneumonitis, pulmonary embolism, and radiation pneumonitis. The most frequent AEs leading to treatment interruption were pneumonitis (6.8%), pyrexia (6.8%), pneumonia (5.1%), and dyspnea (5.1%). Meanwhile, pneumonitis (n = 12; 10.3%), interstitial lung disease (ILD) (n = 3; 2.6%), radiation pneumonitis (n = 3; 2.6%), and lung disorder (n = 2; 1.7%) were the most frequent AEs leading to treatment discontinuation (Supplementary Table 2). A breakdown of pneumonitis, ILD, and radiation pneumonitis by severity is provided in Table 5. Serious AEs occurred in 23 patients (19.7%) (Supplementary Table 3), and two patients (1.7%) had grade 5 AEs (pneumonitis and pulmonary sepsis).

Overall, any-grade PRAEs were reported in 76.9% of patients (Table 3). The most frequently reported PRAEs were pneumonitis (17.1%), asthenia (15.4%), and pruritus (14.5%) (Supplementary Table 4). Regarding the primary end point, five of 117 patients had grade 3 or 4 PRAEs (incidence: 4.3%; 95% CI: 1.4–9.7), all of whom experienced these events within 6 months of starting durvalumab; the events included pneumonitis (n = 2), adrenal insufficiency (n = 1), hypothyroidism (n = 1), and leukopenia (n = 1). Serious PRAEs were reported in six patients (5.1%); five had pneumonitis and one had ILD. One patient (0.9%) had a grade 5 PRAE (the same grade 5 pneumonitis AE mentioned previously).

In total, 86 patients (73.5%) had AEs of special or potential interest (referred to as AESIs and AEPIs, respectively). These included dermatitis or rash (31.6%), pneumonitis or ILD (21.4%), arthralgia (17.9%), diarrhea or colitis (17.1%), hypothyroid events (14.5%), and hyperthyroid events (11.1%) (Supplementary Table 5). AESIs and AEPIs were mostly of grade 1 or 2. Overall, 16.2%, 1.7%, and 0.9% of patients had pneumonitis or ILD events of maximum grades 2, 3 or 4, and 5,

Table 2. Previous Sequential CRT

Variable	ECOG PS 0 or 1 (n = 114)	ECOG PS 2 (n = 3)	All Patients (N = 117)
Type of previous CRT, n (%)			
No overlap of CT and RT	96 (84.2)	2 (66.7)	98 (83.8)
≥1 cycle overlap of CT and RT[a]	18 (15.8)	1 (33.3)	19 (16.2)
Previous CT cycles, median (range)	4.0 (1-9)	4.0 (3-4)	4.0 (1-9)
CT regimen used, n (%)[b,c]			
Carboplatin-vinorelbine	30 (26.3)	1 (33.3)	31 (26.5)
Carboplatin-paclitaxel	21 (18.4)	2 (66.7)	23 (19.7)
Carboplatin-pemetrexed	18 (15.8)	0	18 (15.4)
Cisplatin-pemetrexed	13 (11.4)	0	13 (11.1)
Cisplatin-vinorelbine	12 (10.5)	0	12 (10.3)
Carboplatin-gemcitabine	7 (6.1)	0	7 (6.0)
Cisplatin-gemcitabine	7 (6.1)	0	7 (6.0)
Total previous RT dose, n (%)[d]			
≥54 to ≤60 Gy	75 (65.8)	3 (100.0)	78 (66.7)
>60 to ≤66 Gy	37 (32.5)	0	37 (31.6)
Median time (range) from completion of RT to initiation of durvalumab, d[e]	26.0 (8-67)	27.0 (17-40)	26.0 (8-67)
Time from completion of RT to initiation of durvalumab, n (%)			
<14 d	5 (4.4)	0	5 (4.3)
≥14 d	109 (95.6)	3 (100.0)	112 (95.7)
Best response to previous CRT, n (%)[f]			
Complete response	1 (0.9)	0	1 (0.9)
Partial response	73 (64.0)	2 (66.7)	75 (64.1)
Stable disease	31 (27.2)	1 (33.3)	32 (27.4)
Progressive disease	0	0	0
Non-evaluable or not applicable	9 (7.9)	0	9 (7.7)

[a]One patient (0.9%) in the PS 0 or 1 cohort received more than one overlapping cycle of CT and RT (i.e., concurrent CRT) and was reported as a protocol deviation.
[b]Only CT regimens used in more than or equal to 5% of all patients are tabulated.
[c]One patient (0.9%) in the PS 0 or 1 cohort received single-agent carboplatin and was reported as a protocol deviation.
[d]One patient received a total previous RT dose of less than 54 Gy, and one patient received a total dose of more than 66 Gy; both patients were in the PS 0 or 1 cohort.
[e]Per the protocol, RT should have been completed within 42 days of starting durvalumab; 18 of 117 patients (15.4%) did not start durvalumab within this time frame and were reported as protocol deviations.
[f]Per protocol, patients must not have progressed on previous sequential CRT, per investigator assessment (RECIST version 1.1). Patients with non-measurable disease or no evidence of disease at baseline by computed tomography or MRI were eligible.
CRT, chemoradiotherapy; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; Gy, Gray; MRI, magnetic resonance imaging; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy.

respectively. There were 34 patients (29.1%) who had AESIs or AEPIs requiring systemic steroids, which were high dose (≥40 mg prednisone or equivalent) in 17 patients (14.5%); no other immunosuppressants were used to manage AESIs or AEPIs. In addition, 17 (14.5%) patients had AESIs or AEPIs necessitating endocrine replacement therapy. AESIs or AEPIs leading to temporary interruption or permanent discontinuation of durvalumab were reported in 17.1% and 14.5% of patients, respectively. Pneumonitis or ILD led to temporary interruption and permanent discontinuation of durvalumab in 6.8% and 12.8% of patients, respectively, and was the most common AESI or AEPI leading to discontinuation. In addition, 13 of 25 patients (52.0%) with pneumonitis or ILD had their event resolve by the data cutoff.

Efficacy

At the data cutoff, 61 patients (52.1%) had experienced a progression event and the median follow-up duration among patients censored for PFS was 11.0 (range: <0.1 to 22.3) months. Median PFS was 10.9 (95% CI: 7.3–15.6) months, and the 12-month PFS rate was 49.6% (95% CI: 39.5–58.9) (Fig. 1*A*). Overall, 25 (21.4%) patients had died, with 90 (76.9%) patients remaining in survival follow-up (two patients [1.7%] withdrew consent). The median follow-up duration among patients censored for OS was 13.3 (range: 4.4–25.6) months. The 12-month and 24-month OS rates were 84.1% (95% CI: 75.6–89.9) and 69.8% (95% CI: 55.8–80.2), respectively (Fig. 1*B*). Furthermore, 17 patients (14.5%) had NSCLC-related deaths; the 12-month and 24-month NSCLC-related survival rates were 88.7%

Table 3. Safety Summary

AE Category, n (%)	ECOG PS 0 or 1 (n = 114)		ECOG PS 2 (n = 3)		All Patients (N = 117)	
	Any Cause	PRAE[a]	Any Cause	PRAE[a]	Any Cause	PRAE[a]
Any	108 (94.7)	87 (76.3)	3 (100)	3 (100)	111 (94.9)	90 (76.9)
Grade 3 or 4	22 (19.3)	5 (4.4)	0	0	22 (18.8)	5 (4.3)
Serious	23 (20.2)	6 (5.3)	0	0	23 (19.7)	6 (5.1)
Fatal	2 (1.8)	1 (0.9)	0	0	2 (1.7)	1 (0.9)
Leading to discontinuation of durvalumab	25 (21.9)	19 (16.7)	0	0	25 (21.4)	19 (16.2)
Immune mediated	46 (40.4)	42 (36.8)	2 (66.7)	2 (66.7)	48 (41.0)	44 (37.6)

[a]Causal attribution of adverse events was assessed by the investigators. "PRAE" is used here to align with wording on the case report form, which asked investigators to give a yes or no response to whether there was a "reasonable possibility that the adverse event was caused by the investigational product" (i.e., durvalumab); thus, PRAE is an alternative nomenclature for the term "treatment-related adverse event."
AE, adverse event; ECOG, Eastern Cooperative Oncology Group; PRAE, possibly related adverse event; PS, performance status.

Table 4. AEs of Any Cause

AE Preferred Term, n (%)	ECOG PS 0 or 1 (n = 114)		ECOG PS 2 (n = 3)		All Patients (N = 117)	
	Any Grade[a]	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade[a]	Grade 3 or 4
Any	108 (94.7)	22 (19.3)	3 (100)	0	111 (94.9)	22 (18.8)
Cough	35 (30.7)	0	2 (66.7)	0	37 (31.6)	0
Asthenia	26 (22.8)	0	2 (66.7)	0	28 (23.9)	0
Dyspnea	25 (21.9)	1 (0.9)	2 (66.7)	0	27 (23.1)	1 (0.9)
Fatigue	24 (21.1)	0	0	0	24 (20.5)	0
Pneumonitis	21 (18.4)	2 (1.8)	1 (33.3)	0	22 (18.8)	2 (1.7)
Pyrexia	22 (19.3)	1 (0.9)	0	0	22 (18.8)	1 (0.9)
Arthralgia	21 (18.4)	0	0	0	21 (17.9)	0
Pruritus	19 (16.7)	0	2 (66.7)	0	21 (17.9)	0
Constipation	20 (17.5)	0	0	0	20 (17.1)	0
Diarrhea	19 (16.7)	0	0	0	19 (16.2)	0
Back pain	16 (14.0)	0	0	0	16 (13.7)	0
Nausea	16 (14.0)	0	0	0	16 (13.7)	0
Non-cardiac chest pain	14 (12.3)	0	1 (33.3)	0	15 (12.8)	0
Hypothyroidism	13 (11.4)	1 (0.9)	1 (33.3)	0	14 (12.0)	1 (0.9)
Rash	12 (10.5)	0	1 (33.3)	0	13 (11.1)	0
Decreased appetite	11 (9.6)	0	1 (33.3)	0	12 (10.3)	0
Headache	11 (9.6)	1 (0.9)	1 (33.3)	0	12 (10.3)	1 (0.9)
Hyperthyroidism	12 (10.5)	0	0	0	12 (10.3)	0
Pneumonia	10 (8.8)	2 (1.8)	0	0	10 (8.5)	2 (1.7)
Nasopharyngitis	9 (7.9)	0	0	0	9 (7.7)	0
Peripheral edema	9 (7.9)	0	0	0	9 (7.7)	0
Paresthesia	9 (7.9)	0	0	0	9 (7.7)	0
Productive cough	9 (7.9)	0	0	0	9 (7.7)	0
Vomiting	8 (7.0)	0	0	0	8 (6.8)	0
Blood creatinine increased	7 (6.1)	0	0	0	7 (6.0)	0
GGT increased	7 (6.1)	0	0	0	7 (6.0)	0
Hyperglycemia	6 (5.3)	0	1 (33.3)	0	7 (6.0)	0
ALT increased	6 (5.3)	0	0	0	6 (5.1)	0
Dizziness	6 (5.3)	0	0	0	6 (5.1)	0
Dry mouth	6 (5.3)	0	0	0	6 (5.1)	0
Hypertension	6 (5.3)	2 (1.8)	0	0	6 (5.1)	2 (1.7)
Hypomagnesemia	6 (5.3)	0	0	0	6 (5.1)	0
Insomnia	6 (5.3)	0	0	0	6 (5.1)	0
Weight decreased	6 (5.3)	0	0	0	6 (5.1)	0
Radiation pneumonitis	4 (3.5)	2 (1.8)	0	0	4 (3.4)	2 (1.7)
Pulmonary embolism	3 (2.6)	2 (1.8)	0	0	3 (2.6)	2 (1.7)

Note: Tabulated AE terms are limited to any-grade AEs reported in more than or equal to 5% of patients or grade 3 or 4 AEs reported in at least two patients.
[a]Two patients (both with PS 0 or 1) had grade 5 AEs, including one patient with pulmonary sepsis and one patient with pneumonitis.
AE, adverse event; ALT, alanine aminotransferase; ECOG, Eastern Cooperative Oncology Group; GGT, gamma-glutamyl transferase; PS, performance status.

Table 5. Summary of Pneumonitis, Interstitial Lung Disease, and Radiation Pneumonitis Events by Severity

	Max. CTCAE Grade (N = 117)					Action Taken With Durvalumab (N = 117)	
AE Preferred Term, n (%)	Any AE	Grade 1	Grade 2	Grade 3 or 4	Grade 5	Interrupted	Discontinued
Pneumonitis	22 (18.8)	2 (1.7)	17 (14.5)	2 (1.7)	1 (0.9)	8 (6.8)	12 (10.3)
Interstitial lung disease	3 (2.6)	1 (0.9)	2 (1.7)	0	0	0	3 (2.6)
Radiation pneumonitis	4 (3.4)	1 (0.9)	1 (0.9)	2 (1.7)	0	0	3 (2.6)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Max., maximum.

(95% CI: 80.9–93.5) and 78.7% (95% CI: 64.0–88.0), respectively. Outcomes for the PS 0 or 1 cohort were broadly consistent with the overall population (Supplementary Table 6): median PFS was 13.1 (95% CI: 7.4–16.7) months, the 12-month PFS rate was 50.1% (95% CI: 39.9–59.5), and the 12-month and 24-month OS rates were 84.6% (95% CI: 76.0–90.3) and 71.4% (95% CI: 57.1–81.6), respectively. Two of the three patients in the PS 2 cohort had died at the data cutoff, and one remained in survival follow-up.

In the overall population, one patient had a confirmed complete response and 19 had a confirmed partial response during durvalumab therapy, giving a confirmed ORR of 17.1% (95% CI: 11.1–25.8). An additional six patients (5.1%) had unconfirmed responses. The median duration of response was not reached; 15 of 20 patients (75.0%) with confirmed responses had an ongoing response at data cutoff. All tumor responses occurred among patients in the PS 0 or 1 cohort.

Exploratory Analyses of Efficacy Based on PD-L1 Expression

The PD-L1 biomarker-evaluable population included 70 patients (59.8%). Among these patients, 34 (48.6%) had PD-L1 expression on less than 1% of TCs and 36 (51.4%) had PD-L1 expression on more than or equal to 1% of TCs. Efficacy outcomes according to PD-L1 expression are summarized in Supplementary Table 7. In general, we observed numerical trends suggesting the more than or equal to 1% subgroup gained more clinical benefit than the less than 1% subgroup: median PFS was 13.6 months (95% CI: 7.4–not estimable) versus 10.9 months (95% CI: 5.3–22.0); the 12-month PFS rate was 54.8% (95% CI: 35.5–70.6) versus 49.4% (95% CI: 30.5–65.8); the 12-month OS rate was 91.5% (95% CI: 75.9–97.2) versus 77.4% (95% CI: 57.9–88.6); the 24-month OS rate was 60.2% (95% CI: 18.9–85.7) versus 70.3% (95% CI: 46.9–84.9); and confirmed ORR was 19.4% (95% CI: 8.2–36.0) versus 11.8% (95% CI: 3.4–28.2).

Discussion

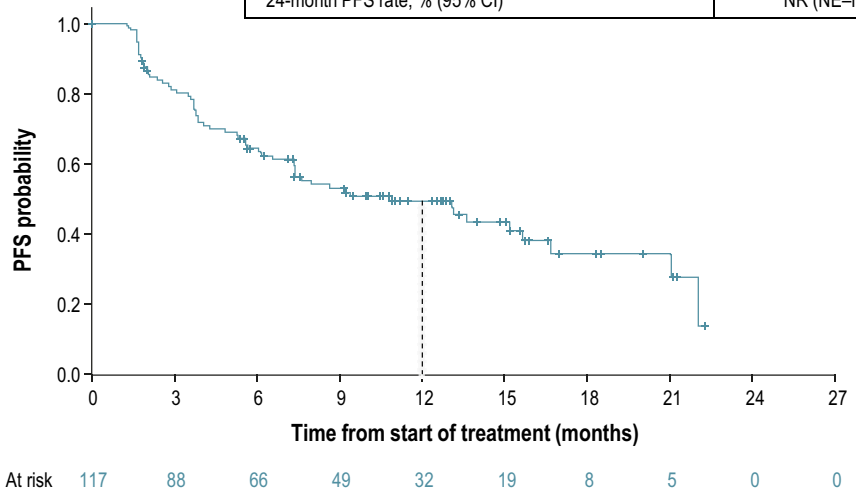
PACIFIC-6 evaluates the safety and tolerability of durvalumab in patients with stage III, unresectable NSCLC whose disease had not progressed after platinum-based sCRT. In this setting, the safety profile of durvalumab was consistent with the profile observed in the PACIFIC trial, in which durvalumab was administered after platinum-based cCRT.[1,2] Only five of 117 patients (4.3%) had grade 3 or 4 PRAEs within 6 months of starting treatment, demonstarting that durvalumab was generally well tolerated after sCRT.

On the basis of the findings of the PACIFIC trial, durvalumab is the global SoC for patients with stage III, unresectable NSCLC that has not progressed after platinum-based CRT.[3–5,23,24] International treatment guidelines recognize cCRT as SoC for stage III, unresectable NSCLC because concurrent treatment has been found to be more efficacious than sCRT.[3,5,8–12] Nevertheless, patients often receive sCRT in real-world clinical practice,[13–21] with guidelines recognizing sCRT as an acceptable approach for patients who are considered unsuitable for cCRT (i.e., elderly or less fit patients with clinically relevant comorbidities).[3,12,25] In the United States, the Food and Drug Administration-approved indication for durvalumab is limited to patients who received cCRT.[24] Meanwhile, the European Medicines Agency-approved indication encompasses patients who received cCRT or sCRT, although it also restricts use of durvalumab to patients with PD-L1 TC more than or equal to 1%.[23] As PACIFIC trial enrollment was restricted to patients who received cCRT,[1] there are limited data regarding the tolerability of durvalumab after sCRT. Thus, PACIFIC-6 was initiated to evaluate the safety and tolerability of durvalumab in this setting.

Reflecting the factors often considered when determining if a patient is eligible for cCRT, the population of PACIFIC-6 was relatively more frail compared with the population of PACIFIC[1]: a higher proportion of patients were aged more than or equal to 65 years (65.8% versus 45.2%; median age: 68.0 [range: 39–85] versus 64.0 [range: 23–90] y) and had PS more than 0 (59.8% versus 50.8%), and a lower proportion had stage IIIA disease (37.6% versus 52.9%) compared with PACIFIC. Despite comprising a less fit population, we did not observe a higher incidence of grade 3 or 4 AEs and serious AEs in PACIFIC-6 compared with either the durvalumab or placebo arms of PACIFIC, although more patients

A

	All patients (N = 117)
Total progression events, n (%)	61 (52.1)
Median PFS, months (95% CI)	10.9 (7.3–15.6)
12-month PFS rate, % (95% CI)	49.6 (39.5–58.9)
24-month PFS rate, % (95% CI)	NR (NE–NE)



B

	All patients (N = 117)
Deaths, n (%)	25 (21.4)
Median OS, months (95% CI)	25.0 (25.0–NE)
12-month OS rate, % (95% CI)	84.1 (75.6–89.9)
24-month OS rate, % (95% CI)	69.8 (55.8–80.2)

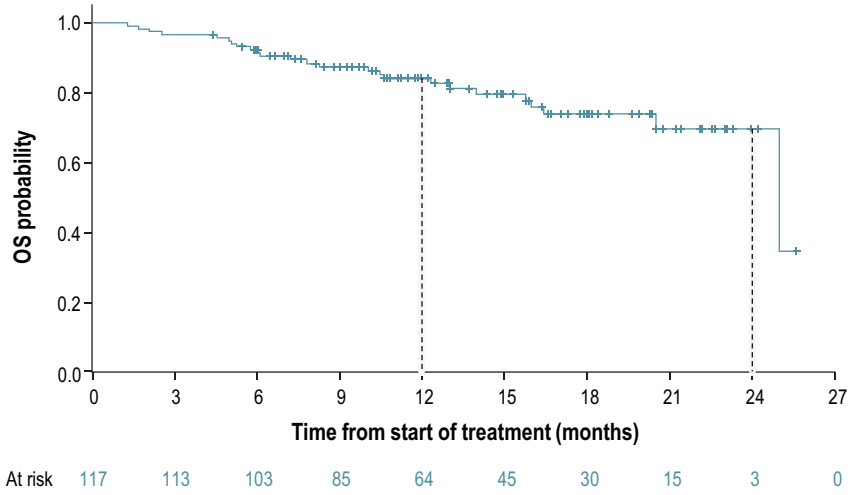


Figure 1. Kaplan–Meier distributions for (*A*) PFS and (*B*) OS. PFS is defined as the time from the date of the first dose of durvalumab to the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient discontinues durvalumab or receives another anticancer therapy before progression. OS is defined as the time from the date of the first dose of durvalumab to death from any cause. The median follow-up duration was 11.0 (range: <0.1 to 22.3) months and 13.3 (range: 4.4–25.6) months among patients censored for PFS and OS, respectively. CI, confidence interval; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

discontinued study treatment owing to AEs in PACIFIC-6 (21.4%) compared with PACIFIC (durvalumab: 15.4%; placebo: 9.8%).[2]

The PACIFIC-6 protocol allows durvalumab to be administered for up to 2 years (whereas treatment was limited to 1 y in PACIFIC[1]); this guidance was based on data from CheckMate-153 that indicated continuing immunotherapy beyond a 1-year fixed duration improved outcomes in patients with advanced NSCLC.[26,27] Exposure data indicate that this difference in the permitted duration of therapy does not account for the higher rate of treatment discontinuation owing to AEs observed in the current study: the median duration of treatment in PACIFIC-6 (32.0 wk) was lower than PACIFIC (40.1 wk),[2] and patients received a median of eight durvalumab infusions in PACIFIC-6 (administered in 4-wk cycles; equivalent to 16 infusions when administered in 2-wk cycles) compared with 20 infusions in PACIFIC (administered in 2-wk cycles).[2] Overall, few patients (2.6%) were able to complete 2 years of durvalumab therapy in PACIFIC-6 (acknowledging that 37.8% of patients were still receiving durvalumab at data cutoff).

Consistent with PACIFIC, pneumonitis was the AE most frequently leading to treatment discontinuation in PACIFIC-6 (reported in 10.3% of patients). Despite a lower overall incidence of pneumonitis in PACIFIC-6, the rate of discontinuation owing to pneumonitis was slightly higher than the rate observed with durvalumab in PACIFIC (4.8%).[2,28,29] We are uncertain of the factors that underpin this observation, but it could be driven (at least partially) by differences in the underlying study populations. Speculatively, physicians may have been more inclined to stop durvalumab in response to pneumonitis in PACIFIC-6 because of relatively less fit nature of the study population. Indeed, the incidence of pneumonitis of grade 3 or greater was comparable between the studies,[2,28,29] suggesting the higher rate of discontinuation in PACIFIC-6 was not because pneumonitis occurred with greater severity. Overall, these safety findings are consistent with previous observations that, although cCRT is associated with greater toxicity than sCRT, rates of both acute and late pulmonary toxicities seem comparable on the basis of available data,[9,11] and with findings from PACIFIC that revealed pulmonary toxicity was not substantially exacerbated by subsequent use of durvalumab.[1]

The current analysis from PACIFIC-6 was timed for maturity of the primary safety end point, and not the secondary efficacy end points. With a median follow-up duration of only 12.9 months, and most patients (>75%) remaining in follow-up, the maturity of the survival data is limited at the current data cutoff. A final analysis from PACIFIC-6 is planned and will allow for more robust analyses on the basis of sufficiently matured survival data. In the current analysis, an estimated 49.6% (12-mo PFS) of all patients were alive and progression free, and 84.1% (12-mo OS) were alive overall, 12 months after starting durvalumab. Although caution is advised when comparing outcomes between studies, it is notable that the survival rates are comparable with those observed for the durvalumab arm of PACIFIC (12-mo PFS: 55.7%; 12-mo OS: 83.1%) and higher than those observed for the placebo arm (12-mo PFS: 34.5%; 12-mo OS: 74.6%).[6] The efficacy outcomes from PACIFIC-6 are encouraging considering that the patients enrolled were typically older, had poorer PS, had more advanced disease (i.e., stage IIIB or IIIC), and had received a less efficacious CRT regimen than patients in PACIFIC. Indeed, multivariable analyses from PACIFIC revealed that younger age, PS 0, and stage IIIA disease are prognostic for better survival outcomes.[6]

The encouraging outcomes observed with durvalumab after sCRT in PACIFIC-6 are reinforced by the findings of real-world studies.[18,30] These include PACIFIC-R (NCT03798535), an international, observational study of patients who received durvalumab through an early access program. Approximately 14% of patients received sCRT before starting durvalumab in PACIFIC-R, and median real-world PFS was more than 19 months in this subpopulation (measured from the start of durvalumab therapy)[30]; it should be noted that PFS is typically overestimated in real-world studies owing to less frequent and consistent use of radiological assessment. Together with the findings from PACIFIC-R, the results of PACIFIC-6 indicate that survival outcomes for patients who receive sCRT may be improved with subsequent use of durvalumab, supporting efforts to confirm the benefit of this strategy in a phase 3 trial.[31]

Numerical trends in efficacy outcomes from PACIFIC-6 suggest that patients with PD-L1 expression on more than or equal to 1% of TCs gained relatively more clinical benefit from durvalumab therapy than patients with PD-L1 expression on less than 1% of TCs, although PD-L1 expression level was unknown for 40.2% of patients and was determined from tumor samples collected before sCRT. Findings from preclinical studies suggest that radiation induces immunogenic changes that may prime tumors to respond to PD-L1 inhibition (e.g., upregulation of cell-surface PD-L1 expression).[32–35] PD-L1 expression has been an imperfect clinical biomarker for predicting response to immune checkpoint inhibitors and, in this setting, CRT is expected to induce changes in PD-L1 expression such that expression levels determined from tumor samples collected before CRT likely do not reflect the expression levels at the time immune checkpoint inhibitor therapy is given.[36] Preclinical evidence also suggests that giving PD-L1 inhibitors as close

as possible to RT may increase their effectiveness.[33] Consistent with this hypothesis, better survival outcomes were observed among patients who received durvalumab within 14 days of completing RT in PACIFIC[6,37]; it is important to note that the timing of durvalumab initiation after CRT may associate with other clinical factors that are prognostic for survival, which may bias this analysis. Although a similar analysis using the PACIFIC-6 cohort would be an interesting avenue for future research, interpretation would be limited as very few patients started durvalumab within 14 days of completing RT (n = 5).

As a single-arm study, PACIFIC-6 is limited by the lack of a comparator arm. Thus, we cannot draw definitive conclusions regarding the benefit of durvalumab after sCRT. Moreover, only three patients were enrolled into the PS 2 cohort in this practice-informing study, reflecting the challenges associated with treating patients with poor PS in real-world clinical practice.[38,39] Stringent eligibility criteria for the study (e.g., regarding the absence of certain comorbidities) would have presented a substantial barrier to the enrollment of these patients. Another limitation is that reasons for use of sCRT (i.e., instead of cCRT) were not collected; therefore, we are uncertain of the impact of frailty on patient selection (i.e., whether the enrolled patients mostly received sCRT because of frailty concerns versus other possible reasons [e.g., logistical constraints]). PACIFIC-6 is also limited by the fact that RT planning parameters were not collected within the study case report form. These data are of interest as disease volume is a known prognostic factor for survival and several other RT planning parameters (e.g., RT modality and RT dose delivered to organs at risk) correlate with the occurrence and severity of pneumonitis.[40–44] Future studies investigating the correlation of these parameters with survival and high-grade AEs in patients who subsequently receive durvalumab are warranted.

In conclusion, durvalumab after sCRT had a comparable safety profile with that observed with durvalumab after cCRT in PACIFIC and had encouraging preliminary efficacy in a frailer patient population. This suggests that durvalumab after sCRT may be a reasonable alternative treatment strategy for patients who are considered unsuitable for cCRT. The ongoing, phase 3 PACIFIC-5 trial (NCT03706690) is assessing the efficacy and safety of durvalumab after either sCRT or cCRT in patients with stage III, unresectable NSCLC.

CRediT Authorship Contribution Statement

Marina C. Garassino: Resources, Conceptualization, Investigation, Visualization, Writing - review & editing.

Julien Mazieres, Martin Reck, Corinne Faivre-Finn: Resources, Conceptualization, Investigation, Writing - review & editing.

Christos Chouaid, Helge Bischoff, Niels Reinmuth, Laura Cove-Smith, Talal Mansy, Diego Cortinovis, Marina R. Migliorino, Angelo Delmonte, José Garcia Sánchez, Luis Enrique Chara Velarde, Reyes Bernabe, Luis Paz-Ares: Resources, Investigation, Writing - review & editing.

Ignacio Diaz Perez, Nataliya Trunova: Project administration, Conceptualization, Writing – review & editing.

Kayhan Foroutanpour: Data curation, Formal Analysis, Writing – review & editing.

Acknowledgments

This study (NCT03693300) was funded by AstraZeneca. The authors thank the patients, their families and caregivers, and all investigators involved in this study. Medical writing support, under the direction of the authors, was provided by Aaron Korpal, PhD, and Catherine Crookes, BSc., of Ashfield MedComms (Manchester, United Kingdom), an Inizio company, and was funded by AstraZeneca. Prof. Faivre-Finn is supported by a grant from the National Institute for Health Research Manchester Biomedical Research Centre.

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.2022.07.1148.

References

1. 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.
2. 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.
3. 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.
4. Remon J, Soria JC, Peters S, ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. 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.
5. Park K, Vansteenkiste J, Lee KH, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with locally advanced unresectable non-small-cell lung cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS. *Ann Oncol*. 2020;31:191–201.

6. 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.
7. Hui R, Ozguroglu 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.
8. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol*. 1999;17:2692–2699.
9. Auperin A, Le Pechoux 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.
10. Liang HY, Zhou H, Li XL, Yin ZH, Guan P, Zhou BS. Chemoradiotherapy for advanced non-small cell lung cancer: concurrent or sequential? It's no longer the question: a systematic review. *Int J Cancer*. 2010;127:718–728.
11. 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.
12. 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:iv1–iv21.
13. Driessen EJ, Bootsma GP, Hendriks LE, et al. Stage III non-small cell lung cancer in the elderly: patient characteristics predictive for tolerance and survival of chemoradiation in daily clinical practice. *Radiother Oncol*. 2016;121:26–31.
14. Walraven I, Damhuis RA, Ten Berge MG, et al. Treatment variation of sequential versus concurrent chemoradiotherapy in stage III non-small cell lung cancer patients in the Netherlands and Belgium. *Clin Oncol (R Coll Radiol)*. 2017;29:e177–e185.
15. Harden S, Khakwani A, Beckett P, Adizie JB. P1.17-04 curative intent treatment for stage III NSCLC in England. *J Thorac Oncol*. 2018;13:S656.
16. Agulnik J, Kasymjanova G, Pepe C, et al. Understanding clinical practice and survival outcomes in patients with unresectable stage III non-small-cell lung cancer in a single centre in Quebec. *Curr Oncol*. 2020;27:e459–e466.
17. Seung SJ, Hurry M, Walton RN, Evans WK. Retrospective cohort study of unresectable stage III non-small-cell lung cancer in Canada. *Curr Oncol*. 2020;27:e354–e360.
18. 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.
19. Hung A, Lee KM, Lynch JA, et al. Chemoradiation treatment patterns among United States Veteran Health Administration patients with unresectable stage III non-small cell lung cancer. *BMC Cancer*. 2021;21:824.
20. 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.
21. De Ruysscher D, Botterweck A, Dirx M, et al. Eligibility for concurrent chemotherapy and radiotherapy of locally advanced lung cancer patients: a prospective, population-based study. *Ann Oncol*. 2009;20:98–102.
22. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth edition lung cancer stage classification. *Chest*. 2017;151:193–203.
23. European Medicines Agency. Imfinzi (durvalumab) product information. https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf. Accessed May 16, 2022.
24. Food and Drug Administration. Durvalumab prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761069s029lbl.pdf. Accessed May 16, 2022.
25. Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J*. 2009;34:17–41.
26. Spigel DR, McLeod M, Hussein MA, et al. Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC). *Ann Oncol*. 2017;28:v461.
27. Waterhouse DM, Garon EB, Chandler J, et al. Continuous versus 1-year fixed-duration nivolumab in previously treated advanced non-small-cell lung cancer: CheckMate 153. *J Clin Oncol*. 2020;38:3863–3873.
28. Vansteenkiste J, Naidoo J, Faivre-Finn C, et al. MA05.02 PACIFIC subgroup analysis: pneumonitis in stage III, unresectable NSCLC patients treated with durvalumab vs. placebo after CRT. *J Thorac Oncol*. 2018;13(suppl):S370–S371.
29. Vansteenkiste JF, Naidoo J, Faivre-Finn C, et al. Efficacy of durvalumab in patients with stage III NSCLC who experience pneumonitis (PACIFIC). *Ann Oncol*. 2019;30:v592–v593.
30. Girard N, Smit HJM, Sibille A, et al. 1171MO PACIFIC-R real-world study: treatment duration and interim analysis of progression-free survival in unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. *Ann Oncol*. 2021;32(suppl 5):S939–S940.
31. 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:ix113–ix114.
32. 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.
33. 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.
34. 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.
35. 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.

36. 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.
37. 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.
38. Gajra A, Marr AS, Ganti AK. Management of patients with lung cancer and poor performance status. *J Natl Compr Canc Netw*. 2014;12:1015–1025.
39. Khaki AR, Glisch C, Petrillo LA. Immunotherapy in patients with poor performance status: the jury is still out on this special population. *JCO Oncol Pract*. 2021;17:583–586.
40. Morgensztern D, Waqar S, Subramanian J, Gao F, Trinkaus K, Govindan R. Prognostic significance of tumor size in patients with stage III non-small-cell lung cancer: a surveillance, epidemiology, and end results (SEER) survey from 1998 to 2003. *J Thorac Oncol*. 2012;7:1479–1484.
41. Kim YH, Ahn SJ, Kim YC, et al. Predictive factors for survival and correlation to toxicity in advanced Stage III non-small cell lung cancer patients with concurrent chemoradiation. *Jpn J Clin Oncol*. 2016;46:144–151.
42. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. *J Clin Oncol*. 2017;35:56–62.
43. Jain V, Berman AT. Radiation pneumonitis: old problem, new tricks. *Cancers (Basel)*. 2018;10:222.
44. Katsui K, Ogata T, Watanabe K, et al. Radiation pneumonitis after definitive concurrent chemoradiotherapy with cisplatin/docetaxel for non-small cell lung cancer: analysis of dose-volume parameters. *Cancer Med*. 2020;9:4540–4549.