ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL ARTICLE

Durvalumab after sequential chemoradiotherapy in unresectable stage III non-small-cell lung cancer—final analysis from the phase II PACIFIC-6 trial

M. C. Garassino[1,2*], J. Khalifa[3], M. Reck[4], C. Chouaid[5], H. Bischoff[6], N. Reinmuth[7], L. Cove-Smith[8], T. Mansy[9], D. L. Cortinovis[10], M. R. Migliorino[11], A. Delmonte[12], J. Garcia Sánchez[13], L. E. Chara Velarde[14], R. Bernabe[15], L. Paz-Ares[16], P. Chander[17], I. Diaz Perez[17], K. Foroutanpour[17], U. Emeribe[17] & C. Faivre-Finn[18]

[1]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2]Department of Medicine, The University of Chicago, Chicago, USA; [3]Oncopole Claudius Regaud, Toulouse, France; [4]Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [5]Service de Pneumologie, Centre Hospitalier Intercommunal de Créteil, Créteil, France; [6]Thoraxklinik Heidelberg, Heidelberg, Germany; [7]Thoracic Oncology, Asklepios Fachkliniken München-Gauting, Member of the German Center for Lung Research (DZL), Gauting, Germany; [8]The Christie NHS Foundation Trust and Manchester University Hospitals Foundation Trust, Manchester, UK; [9]South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK; [10]Oncology Unit, Fondazione IRCCS San Gerardo dei Tintori Monza/Università degli Studi Milano-Bicocca, Monza-Brianza, Italy; [11]San Camillo-Forlanini Hospital, Rome, Italy; [12]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; [13]Medical Oncology Department, Hospital Arnau de Vilanova, Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (FISABIO), Valencia, Spain; [14]Hospital Universitario de Guadalajara, Guadalajara, Spain; [15]Hospital Universitario Virgen del Rocio, Seville, Spain; [16]Universidad Complutense, CiberOnc, CNIO and Hospital Universitario 12 de Octubre, Madrid, Spain; [17]AstraZeneca, Gaithersburg, USA; [18]The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK

Available online xxx

Background: Durvalumab after concurrent chemoradiotherapy (cCRT) is the standard of care for patients with unresectable, stage III non-small-cell lung cancer (NSCLC). However, patients often receive sequential chemoradiotherapy (sCRT) due to factors including advanced age or frailty, comorbidities, or disease- or access-related concerns. The phase II PACIFIC-6 trial (NCT03693300) evaluated the safety of durvalumab after sCRT in this setting. Interim results indicated a similar safety profile to that observed with durvalumab after cCRT, with encouraging preliminary efficacy. We report outcomes from the final analysis.

Patients and methods: Adults with unresectable, stage III NSCLC, Eastern Cooperative Oncology Group performance status $\leq$2, and no disease progression following platinum-based sCRT were enrolled to receive durvalumab 1500 mg intravenously once every 4 weeks for up to 24 months. The primary endpoint was the incidence of grade 3/4 adverse events (AEs) possibly related to treatment (PRAEs) occurring within 6 months. Secondary endpoints included overall survival (OS) and progression-free survival (PFS; investigator assessed as per RECIST v1.1).

Results: As of 20 March 2023, 117 patients (65.8% aged $\geq$65 years; 98.3% with past or present comorbidities) were enrolled. Overall, 27.4% of patients had grade 3/4 AEs and 6.0% had grade 3/4 PRAEs, including two patients (1.7%) with pneumonitis. Three patients (2.6%) had fatal AEs, with one (0.9%) having a fatal PRAE (pneumonitis). Overall, 27.4% discontinued durvalumab due to AEs. Median follow-up was 32.6 and 30.2 months among patients censored for OS and PFS, respectively. Median OS was 39.0 months [95% confidence interval (CI) 30.6 months-not calculable]; 3-year OS rate was 56.5% (95% CI 46.4% to 65.5%). Median PFS was 13.1 months (95% CI 7.4-19.9 months); 2-year PFS rate was 35.3% (95% CI 26.5% to 44.3%).

Conclusions: Durvalumab after sCRT was well tolerated and could be an alternative treatment strategy when cCRT is not feasible. Confirmatory randomized phase III data are awaited.

Key words: durvalumab, immunotherapy, PD-L1, locally advanced NSCLC, sequential chemoradiotherapy

INTRODUCTION

Consolidation therapy with durvalumab (for up to 12 months) is the standard of care for patients with unresectable, stage III non-small-cell lung cancer (NSCLC) who do not have disease progression following platinum-based concurrent chemoradiotherapy (cCRT).[1-3] This regimen received global approvals based on the results of the phase III PACIFIC trial (NCT02125461), with approval by the European Medicines Agency in patients with programmed

*Correspondence to: Prof. Marina C. Garassino, Department of Medicine, Section of Hematology/Oncology, The University of Chicago, 5841 S Maryland Ave, MC 2115, Chicago IL 60637, USA. Tel: +1 718-675-2060
E-mail: mgarassino@bsd.uchicago.edu (M. C. Garassino).

death-ligand 1 (PD-L1) expression on ≥1% of tumor cells (TCs).[2,4,5] In PACIFIC, durvalumab following cCRT was associated with significant improvements in the primary endpoints of progression-free survival (PFS) and overall survival (OS) versus placebo following cCRT.[6,7] In addition, durvalumab was associated with a manageable safety profile and no detrimental impact on quality of life compared with placebo.[6-8] Moreover, the 5-year survival data from PACIFIC demonstrated that the benefit with durvalumab was sustained over time.[9]

cCRT is the preferred approach in unresectable, stage III NSCLC and is associated with improved survival versus sequential chemoradiotherapy (sCRT).[1,3,10,11] Nevertheless, many patients do receive sCRT in routine clinical practice due to the increased risk of adverse events (AEs) with cCRT, concerns about tolerability in patients with advanced age or frailty and patients with comorbidities, issues with volume and location of disease, and potential difficulties in accessing radiation facilities.[12-16] For example, in PACIFIC-R (NCT03798535), an observational study of patients who received durvalumab through an early access program, 201 of the 1399 participants (14.4%) received sCRT.[12]

Given that patients not eligible for cCRT often receive sCRT, and that some patients may receive sCRT instead of cCRT for other than medical reasons, the phase II PACIFIC-6 study (NCT03693300; https://clinicaltrials.gov/study/NCT03693300) was initiated to assess the safety and tolerability of durvalumab following sCRT. Interim results from PACIFIC-6 (data cut-off: 15 July 2021) demonstrated that durvalumab was generally well tolerated after sCRT and the safety profile appeared broadly consistent with that observed with durvalumab after cCRT in PACIFIC.[17] The interim analysis was timed for maturity of the primary safety endpoint, which was the incidence of grade 3/4 AEs possibly related to treatment (PRAEs) occurring within 6 months. Thus, survival data at that time were of insufficient maturity owing to the limited follow-up duration. Here, we report updated safety and efficacy outcomes from the final analysis of PACIFIC-6, including updated analysis of OS.

PATIENTS AND METHODS

Study design and patients

PACIFIC-6 was a multicenter, open-label, single-arm, practice-informing, phase II trial.[17] Patients aged ≥18 years with histologically or cytologically documented unresectable, stage III NSCLC according to the eighth edition of the AJCC Cancer Staging Manual,[18] who had no evidence of progression following platinum-based sCRT (as assessed by the investigator as per RECIST v1.1), and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2 were enrolled. Positron emission tomography or computed tomography, magnetic resonance imaging of the brain, and endobronchial ultrasound with biopsy at diagnosis were encouraged, but not mandatory. Resectability was determined by investigator assessment, and patients who had disease considered for surgical treatment as part of their care plan were excluded. Decisions to treat with sCRT versus cCRT were made by the investigator, and reasons for the selection of sCRT were not captured in the study database. Patients were divided into two cohorts: one for those with an ECOG PS of 0 or 1 and one for those with an ECOG PS of 2. sCRT consisted of two or more cycles of platinum-based, histology-driven chemotherapy (containing etoposide, gemcitabine, pemetrexed, a taxane, vinblastine, or vinorelbine as per local protocol) followed by radiotherapy (total dose 60 Gy ± 10%) within 6 weeks of completing chemotherapy. If the chemotherapy regimen did not include gemcitabine, a one-cycle overlap between chemotherapy and radiotherapy was permitted. The reasons for patients receiving sCRT rather than cCRT were not captured as these decisions occurred before study enrollment as per investigator decision and based on local regulations. Key exclusion criteria included mixed small-cell and NSCLC histology, receipt of cCRT for locally advanced NSCLC, receipt of sCRT with two or more concomitant cycles of chemotherapy and radiotherapy, and unresolved grade ≥2 toxicity from previous sCRT.

Following sCRT, all patients received durvalumab 1500 mg intravenously every 4 weeks for up to 24 months or until disease progression, initiation of alternative cancer therapy, unacceptable toxicity, or withdrawal of consent. Durvalumab could be given beyond disease progression at the investigator's discretion for patients who were determined to be still deriving benefit.

Objectives and endpoints

The primary objective was to investigate the safety and tolerability of durvalumab in terms of the incidence of grade 3/4 PRAEs occurring within 6 months of starting durvalumab. AEs were categorized as PRAEs or not based on 'yes' or 'no' responses by the investigators to the question in the study case report forms as to whether there was a reasonable possibility that the AE was caused by the investigational product (i.e. durvalumab). Patients were followed up for safety throughout treatment and for 90 days following durvalumab discontinuation. AEs were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03.

Secondary objectives included the assessment of efficacy in terms of PFS, objective response rate (ORR), and duration of response (DoR), all based on investigator assessment as per RECIST v1.1, as well as OS and lung cancer mortality. PFS was defined as the time from the first date of treatment until the date of objective disease progression or death (by any cause in the absence of progression). OS was defined as the time from the first date of treatment until death due to any cause. Tumors were assessed by computerized tomography or magnetic resonance imaging at baseline, then every 8 weeks until week 52, and every 12 weeks thereafter for a maximum of 24 months or until confirmed radiological progression, whichever occurred first. Radiological progression and survival were also assessed beyond study treatment discontinuation.

The association between PD-L1 tumor expression and efficacy was an exploratory objective. PD-L1 TC expression was determined centrally from archival tumor samples using the VENTANA PD-L1 (SP263) immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ) and categorized using a 1% TC expression threshold for positivity.

Statistical analysis

PACIFIC-6 was designed as a safety study, and no formal sample size calculation was carried out. Up to 150 patients could be enrolled, based on an enrollment target of 100-120 in the ECOG PS 0 or 1 cohort and allowing up to 30 in the ECOG PS 2 cohort. The primary safety analysis, based on an interim analysis planned for when the last patient dosed had had the opportunity to receive durvalumab for 6 months, was reported previously.[17] The final analysis (reported here) was planned for when the last patient dosed had had the opportunity to receive durvalumab for a maximum of 24 months, followed by a 90-day safety follow-up period. The safety analysis set, comprising all patients who received at least one dose of study drug, was used for both safety and efficacy analyses. Baseline characteristics, exposure to durvalumab, tumor response, and AE data were summarized descriptively. Where applicable, 95% confidence intervals (CIs) were calculated using the Clopper—Pearson method for tumor response and AE data. Time-to-event endpoints were analyzed using the Kaplan—Meier method; 95% CIs were calculated using the Brookmeyer—Crowley method for medians and the Greenwood method for landmark survival rates. All analyses were conducted using SAS version 9.3 or higher (SAS institute, Cary, NC).

Study ethics

The trial was run in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice, the Declaration of Helsinki, and applicable regulatory requirements. The study protocol and amendments were approved by the relevant institutional review boards or independent ethics committees in France [Comite de protection des personnes (CPP) SUD-OUEST et OUTRE-MER 4], Germany (Ethikkommission der ärztekammer Schleswig-Holstein), Italy (Comitato etico Brianza; Comitato etico dell'area vasta Emilia Nord; Comitato etico campania nord Azienda ospedaliera san giuseppe Moscati di Avellino; Comitato Etico Degli irccs istituto Europeo di oncologia E centro cardiologico Monzino; Comitato etico Lazio 1; Comitato etico della fondazione IRCCS "Istituto nazionale dei tumori"—Milano; Comitato etico della romagna—Cerom), Spain (Comité de Ética de la Investigación con Medicamentos del Hospital Universitari de Bellvitge), the UK (East of England—Essex Research Ethics Committee), and the United States (Advarra IRB). All patients provided written informed consent to participate in the study.

Table 1. Baseline patient and disease characteristics

Characteristic	Patients, *n* (%) All (*n* = 117)
Median age (range), years	68.0 (39.0-85.0)
Age ≥65 years	77 (65.8)
Sex	
Male	73 (62.4)
Female	44 (37.6)
Race	
White	104 (88.9)
Unknown	13 (11.1)
Smoking history[a]	
Never smoker	9 (7.7)
Former smoker	75 (64.1)
Current smoker	33 (28.2)
ECOG PS	
0	47 (40.2)
1	67 (57.3)
2	3 (2.6)
Histological type	
Adenocarcinoma	63 (53.8)
Squamous cell	45 (38.5)
Other	9 (7.7)
Disease stage at baseline	
IA	1 (0.9)
IIIA	42 (35.9)
IIIB	61 (52.1)
IIIC	13 (11.1)
PD-L1 TC expression	
<1%	34 (29.1)
≥1%	36 (30.8)
Missing	47 (40.2)

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; TC, tumor cell.
[a]History of nicotine use per the investigator.

RESULTS

Patients and treatment

Between 16 April 2019 and 30 December 2020, 117 patients who had received prior sCRT as per investigator decision and based on local regulations were enrolled across 25 centers in six countries, including Italy (*n* = 39), Spain (*n* = 30), Germany (*n* = 18), France (*n* = 16), the UK (*n* = 12), and the United States (*n* = 2).[17] The median patient age was 68.0 years (range 39-85 years), and the majority of patients were aged ≥65 years [77 patients (65.8%)], white [104 patients (88.9%)], male [73 patients (62.4%)], current/former smokers [108 patients (92.3%)], and had an ECOG PS of 0 [47 patients (40.2%)] or 1 [67 patients (57.3%)] (Table 1); 3 patients (2.6%) had an ECOG PS of 2. Disease stage at baseline was IIIA, IIIB, and IIIC in 42 (35.9%), 61 (52.1%), and 13 (11.1%) patients, respectively; 1 patient (0.9%) with stage IA disease was enrolled and included in the safety analysis set. Over half of the patients had adenocarcinoma [63 patients (53.8%)], while 45 (38.5%) had squamous-cell carcinoma. The majority of patients [*n* = 115 (98.3%)] had prior or current comorbidities, which were most commonly vascular [69 patients (59.0%)], respiratory [62 patients (53.0%)], and metabolic [60 patients (51.3%)] disorders. In total, 79 patients (67.5%) received carboplatin-based chemotherapy as part of sCRT. Most [98 (83.8%)] patients received sCRT without any chemotherapy overlapping with

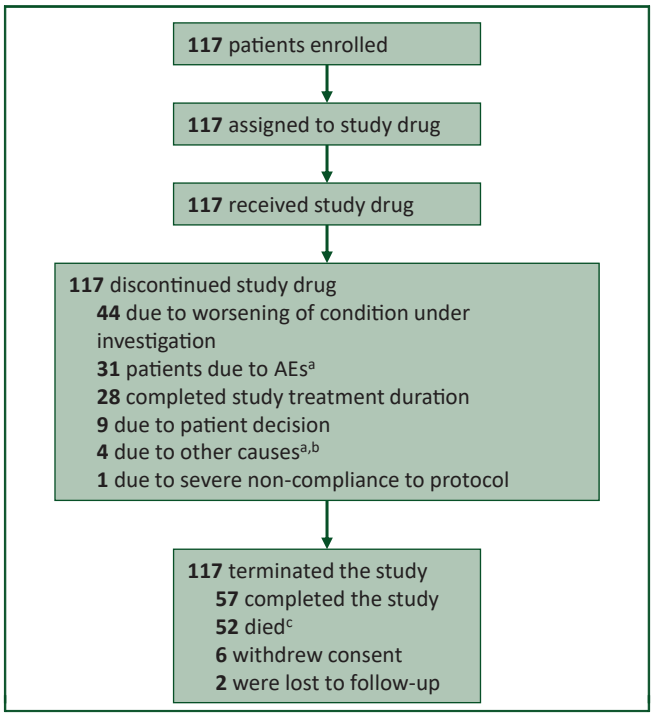

Figure 1. Flow diagram of enrollment and disposition.
[a]For one patient for whom treatment with study drug was delayed due to an AE, the investigator decided to permanently discontinue the study drug because of the length of time that had passed since the last treatment administration. In this figure, this patient was counted in the 'other' category (clinical decision) for the reason of study drug discontinuation, whereas in Table 2, this patient was counted as having been reported with AEs leading to the discontinuation of study drug.
[b]Other causes for discontinuation were clinical decision ($n = 2$), exclusion criteria met ($n = 1$), and maximal benefit received as patient underwent curative surgical resection ($n = 1$).
[c]One patient was alive at the data cut-off date but reported as a death on the end of the study form because this patient died 1 day after the data cut-off date. Therefore, this patient is counted in the death category in this figure; however, for all other statistical analyses considering the data entered at the data cut-off date, the patient is considered alive. AE, adverse event.

radiotherapy, and 19 (16.2%) had at least one cycle of overlap based on a 21-day cycle for chemotherapy (study protocol permitted one cycle of overlap). One patient (0.9%) received cCRT; this was assessed as an important protocol deviation.

All 117 patients received durvalumab; none remained on study treatment at the data cut-off of 20 March 2023 (Figure 1). The median total treatment duration was 41.0 weeks (range 4-108 weeks) and patients received a median of 9 (range 1-26) durvalumab infusions; 28 (23.9%) patients completed 24 months of durvalumab treatment. The main reasons for early discontinuation of durvalumab were disease progression [44 patients (37.6%)], AEs [31 patients (26.5%)], and patient decision [9 patients (7.7%)]. In total, 46 patients (39.3%) received subsequent anticancer therapy, most commonly cytotoxic chemotherapy [37 patients (31.6%)] and radiotherapy [10 patients (8.5%)] (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105071).

Safety

Overall, 32 patients (27.4%) had grade 3/4 AEs and 7 (6.0%) had grade 3/4 PRAEs (Table 2); 5 patients (4.3%; 95% CI 1.4% to 9.7%) had grade 3/4 PRAEs within 6 months (primary endpoint; reported previously).[17] Cough was the most frequent any-grade AE [45 patients (38.5%)]; pneumonia was the most frequent grade 3/4 AE [5 patients (4.3%)] (Table 3). Pneumonitis was the most frequent any-grade PRAE [20 patients (17.1%)] and grade 3/4 PRAE [2 patients (1.7%)] (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105071). Serious AEs and serious PRAEs were reported in 32 (27.4%) and 7 (6.0%) patients, respectively (Table 2). Fatal AEs were reported in three patients (2.6%); one (0.9%) patient had a fatal PRAE of pneumonitis, while the other two cases were not treatment-related (cardiac arrest and pulmonary sepsis). In total, 32 patients (27.4%) discontinued durvalumab due to AEs, most commonly due to pneumonitis [12 patients (10.3%)], interstitial lung disease [3 patients (2.6%)], and radiation pneumonitis [3 patients (2.6%); Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105071].

Efficacy

At data cut-off, 51 patients (43.6%) had died. Median follow-up was 32.6 months (range 4.4-45.7 months) among patients censored for OS. Median OS was 39.0 months [95% CI 30.6 months-not calculable (NC)], and the 3-year OS rate was 56.5% (95% CI 46.4% to 65.5%) (Figure 2A and Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105071). A total of 41 patient (35.0%) deaths were related to NSCLC. Median NSCLC-related survival was 41.8 months (95% CI 36.5 months-NC), and the 3-year NSCLC-related survival rate was 63.1% (95% CI 52.5% to 71.9%) (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105071). Ten patients (8.5%) died due to causes not related to NSCLC, including coronavirus disease 2019 (COVID-19) pneumonia, degradation of general status, pulmonary sepsis, acute respiratory failure, viral pneumonia, influenza A pneumonia, cardiac arrest, and septic shock [one patient (0.9%) for each condition], and two (1.7%) due to unknown causes.

A total of 75 patients (64.1%) had experienced PFS events. Median follow-up was 30.2 months (range 0.0-43.3 months) among patients censored for PFS. Median PFS was 13.1 months (95% CI 7.4-19.9 months), and the 2-year PFS rate was 35.3% (95% CI 26.5% to 44.3%) (Figure 2B and Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105071).

Overall, 24 patients had a confirmed objective response [confirmed ORR 20.5% (95% CI 13.6% to 29.0%)] (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105071); 3 patients (2.6%) had a complete response and 21 (17.9%) had a partial response. Median DoR was not reached, with 17 patients (14.5%) having ongoing responses at data cut-off.

PD-L1 expression level was known for 70 patients (59.8%). There were numerical trends for increased benefit in patients with PD-L1 expression on $\geq$1% of TCs than those with expression on $<$1% of TCs (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2025.105071);

Table 2. Safety summary

AE category, *n* (%)	ECOG PS 0/1 (*n* = 114)		ECOG PS 2 (*n* = 3)		All patients (*n* = 117)	
	Any cause	PRAE[a]	Any cause	PRAE[a]	Any cause	PRAE[a]
Any AE	108 (94.7)	87 (76.3)	3 (100)	3 (100)	111 (94.9)	90 (76.9)
Maximum grade 3 or 4[b]	32 (28.1)	7 (6.1)	0	0	32 (27.4)	7 (6.0)
Serious	32 (28.1)	7 (6.1)	0	0	32 (27.4)	7 (6.0)
Fatal	3 (2.6)[c]	1 (0.9)[d]	0	0	3 (2.6)[c]	1 (0.9)[d]
Leading to discontinuation of durvalumab	32 (28.1)	19 (16.7)	0	0	32 (27.4)	19 (16.2)
Immune-mediated	48 (42.1)	43 (37.7)	2 (66.7)	2 (66.7)	50 (42.7)	45 (38.5)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; PRAE, AE possibly related to treatment.
[a]Causal attribution of AEs was assessed by the investigator. 'PRAE' is used here to align with the 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 AE'.
[b]AEs were graded as per CTCAE version 4.03.
[c]AEs leading to death were pneumonitis, cardiac arrest, and pulmonary sepsis (*n* = 1 each).
[d]The single case of a PRAE leading to death was pneumonitis.

for patients with PD-L1 TC ≥1% versus <1%, respectively, 3-year OS rates were 61.9% (95% CI 41.3% to 77.0%) versus 47.8% (95% CI 29.6% to 63.9%), 2-year PFS rates were 41.1% (24.6% to 56.9%) versus 29.2% (14.8% to 45.2%), and confirmed ORR was 22.2% (10.1% to 39.2%) versus 14.7% (5.0% to 31.1%).

DISCUSSION

Based on the findings of the phase III PACIFIC trial, durvalumab after cCRT is the global standard of care for patients with unresectable, stage III NSCLC.[1-3,6,7] However, many patients receive sCRT in routine clinical practice due to concerns about cCRT tolerability, especially in patients of advanced age or those who are frail, comorbidities increasing the risk of AEs, volume and location of disease, and difficulties gaining access to radiotherapy.[12-16] In PACIFIC-6, durvalumab administered after sCRT showed encouraging efficacy and was generally well tolerated. The safety profile in PACIFIC-6 was broadly similar to that observed in PACIFIC, though cross-trial comparisons should be interpreted with caution given the differences in study design (e.g. consolidation durvalumab could be given for up to 2 years in PACIFIC-6 versus 1 year in PACIFIC[6,7]), potential differences in treatment received before study enrollment, and potential differences in fitness/frailty between the study populations as suggested by the receipt of sCRT by all patients in PACIFIC-6. The incidence of maximum grade 3/4 AEs in PACIFIC-6 was 27.4% and the incidence of fatal AEs was low at 2.6%, consistent with the rates reported in PACIFIC (30.5% and 4.4%, respectively).[7] The proportion of patients who discontinued durvalumab due to AEs was 27.4% in PACIFIC-6, whereas the rate was 15.4% in PACIFIC, though a direct comparison is

Table 3. Adverse events of any cause

Adverse event, *n* (%)	ECOG PS 0/1 (*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
Cough	43 (37.7)	0	2 (66.7)	0	45 (38.5)	0
Asthenia	29 (25.4)	0	2 (66.7)	0	31 (26.5)	0
Dyspnea	27 (23.7)	1 (0.9)	2 (66.7)	0	29 (24.8)	1 (0.9)
Arthralgia	23 (20.2)	1 (0.9)	1 (3.3)	0	24 (20.5)	1 (0.9)
Diarrhea	24 (21.2)	0	0	0	24 (20.5)	0
Fatigue	24 (21.1)	0	0	0	24 (20.5)	0
Constipation	23 (20.2)	0	0	0	23 (19.7)	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)
Pruritus	19 (16.7)	0	2 (66.7)	0	21 (17.9)	0
Headache	17 (14.9)	1 (0.9)	1 (33.3)	0	18 (15.4)	1 (0.9)
Back pain	17 (14.9)	0	0	0	17 (14.5)	0
Nausea	17 (14.9)	0	0	0	17 (14.5)	0
Hypothyroidism	15 (13.2)	1 (0.9)	1 (33.3)	0	16 (13.7)	1 (0.9)
Non-cardiac chest pain	15 (13.2)	0	1 (33.3)	0	16 (13.7)	0
Decreased appetite	14 (12.3)	0	1 (33.3)	0	15 (12.8)	0
Rash	13 (11.4)	0	1 (33.3)	0	14 (12.0)	0
Pneumonia	13 (11.4)	5 (4.4)	0	0	13 (11.1)	5 (4.3)
Hyperthyroidism	12 (10.5)	0	0	0	12 (10.3)	0
Hypertension	7 (6.1)	3 (2.6)	1 (33.3)	0	8 (6.8)	3 (2.6)
Pulmonary embolism	4 (3.5)	3 (2.6)	0	0	4 (3.4)	3 (2.6)

Tabulated AE terms are limited to those reported in at least 10% of all patients at any grade or at least 2% of all patients at a maximum grade of 3 or 4 (as graded as per CTCAE version 4.03).
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]Three patients had grade 5 AEs (all were in the ECOG PS 0/1 cohort); the events were pulmonary sepsis, cardiac arrest, and pneumonitis (*n* = 1 each).

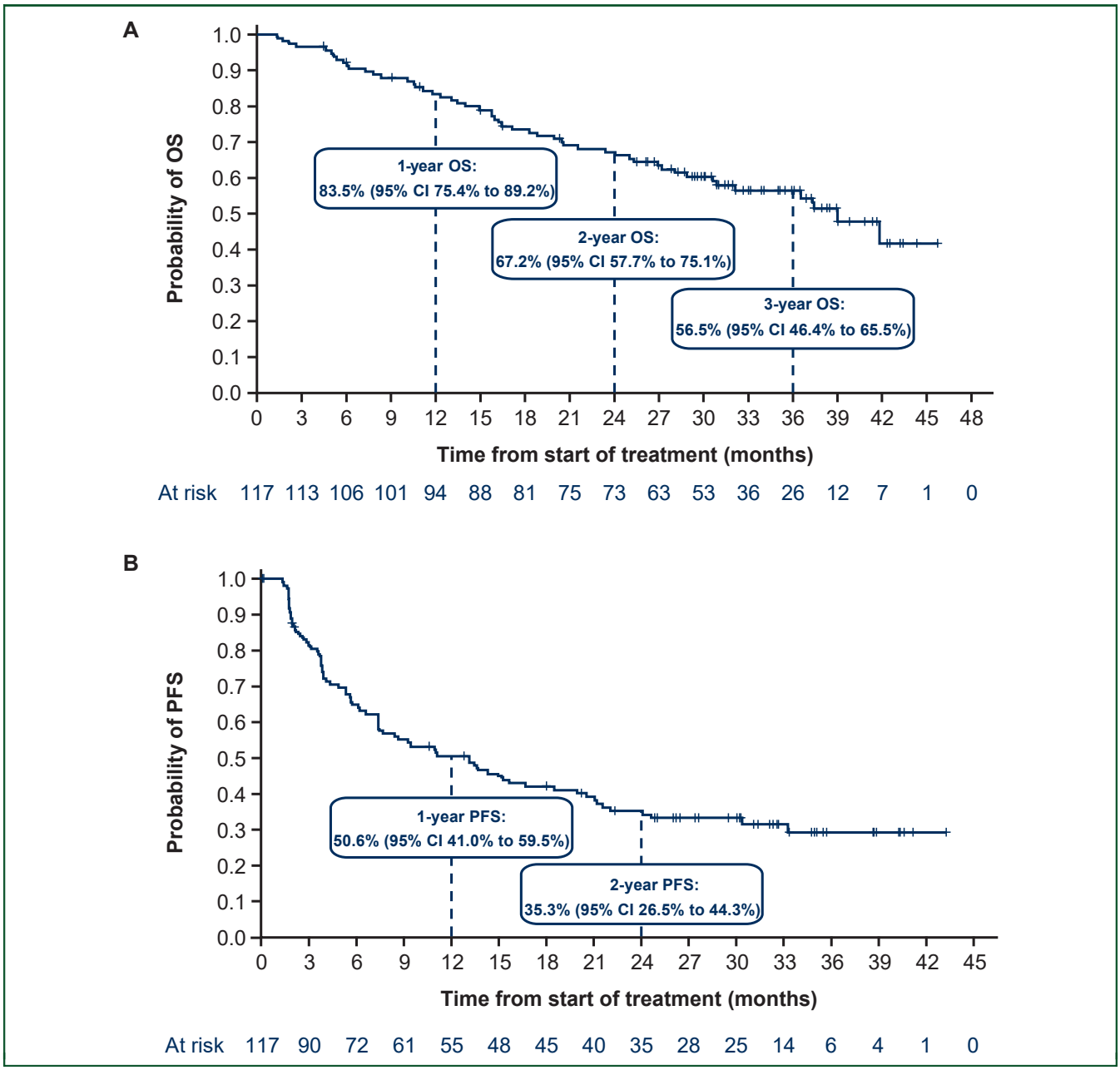

Figure 2. Overall and progression-free survival. Kaplan—Meier plots of (A) OS and (B) PFS. The dashed lines represent the time points for yearly landmark data. PFS was assessed by the investigator using RECIST version 1.1. As per the protocol, RECIST assessments were only collected for the first 2 years, as PFS was a secondary endpoint; because of this, the 3-year PFS landmark rate is not displayed.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

confounded by differences in study population and design, namely that the up to 2-year treatment duration in PACIFIC-6 gave more time in which to discontinue treatment than in PACIFIC.[7] Encouraging efficacy was also observed with durvalumab following sCRT after a median follow-up for OS and PFS of ≥2.5 years; median OS and PFS were 39.0 months and 13.1 months, respectively, with a 3-year OS rate of 56.5% and a 2-year PFS rate of 35.3%.

The safety and long-term efficacy findings from PACIFIC-6 are encouraging given that sCRT is associated with worse outcomes than cCRT[11] and that the study population may have been less fit/more frail than patients in PACIFIC.[6] As cCRT is associated with an absolute survival benefit versus sCRT, the similarity between 3-year landmark OS rates in PACIFIC (56.7%) and PACIFIC-6 (56.5%) is noteworthy.[9,11] Moreover, while clinical trial populations tend to be younger and/or fitter than corresponding real-world populations[19-21] and all patients in PACIFIC-6 were considered fit enough to receive durvalumab, the fact that all patients in PACIFIC-6 received sCRT suggests that the PACIFIC-6 population may have been less fit/more frail than study populations in which most or all patients received cCRT. However, it should be noted that the choice of sCRT was made by the investigators before the patients being considered for inclusion in PACIFIC-6, and the reasons for choosing sCRT rather than cCRT were not captured in the

study database. Thus, some patients suitable for cCRT may have received sCRT for other than medical reasons. Unfortunately, the absence of this information limits insights into the fitness/frailty/comorbidities of patients in PACIFIC-6. For example, the median age and ECOG PS in PACIFIC-6 and PACIFIC[9] were comparable (age: 68 and 64 years, respectively; ECOG PS of 0-1: 97.4% and 99.6%, respectively), and on their own, these data do not suggest a substantially less fit population in PACIFIC-6. Another limitation of the available dataset is that no data were collected for the Charlson Comorbidity Index, activities of daily living, or similar frailty parameters, which would provide further insight given that age and PS are imperfect surrogates for frailty.[22-25] In summary, the absence of these data illustrates the need for standardized frailty measures to be utilized across clinical studies in order to capture treatment patterns and outcomes.

With the caveat of cross-trial comparisons, the OS and PFS findings from PACIFIC-6 appear promising in the context of outcomes from the placebo arm of PACIFIC (median OS and PFS of 29.1 and 5.6 months, respectively)[9] and for other historical cohorts of patients who did not receive immunotherapy after sCRT.[10,26] The data from this study also appear consistent with the efficacy outcomes observed among patients who received durvalumab after sCRT in the real-world PACIFIC-R study.[12] It should be highlighted that the median OS of 39 months and 3-year OS rate in PACIFIC-6 are not yet fully mature given the number of patients censored before these landmarks, as evidenced by the median follow-up in censored patients of 32.6 months, which contrasts with the longer follow-up (60.1 months for censored patients) and more mature data reported from PACIFIC.[9] It is also important to note that PACIFIC-6 was designed as a safety study, and it is not possible to draw robust conclusions regarding the benefit of durvalumab after sCRT due to the single-arm design.

Conclusions

Durvalumab after sCRT was well tolerated and could represent an alternative treatment strategy for patients who do not receive cCRT. The phase III PACIFIC-5 trial (NCT03706690), which is assessing the efficacy and safety of durvalumab after either cCRT or sCRT, is ongoing and will provide further insight.[27]

FUNDING

This work was supported by AstraZeneca (no grant number).

ROLE OF THE FUNDER

In cooperation with the investigators, AstraZeneca participated in study design and conduct; data collection, management, analysis, and interpretation; preparation, review, and approval of the manuscript; and the decision to submit the manuscript for publication.

ACKNOWLEDGEMENTS

CFF is supported by a grant from the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre. Medical writing support, under the direction of the authors, was provided by Werner Gerber, PhD (Fourways, South Africa) and Aaron Korpal, PhD (Manchester, UK), of Ashfield MedComms, an Inizio Company, and was funded by AstraZeneca.

DISCLOSURE

MCG reports honoraria received from MSD Oncology, AstraZeneca/MedImmune, GlaxoSmithKline, Takeda, Roche, Bristol Myers Squibb, Daiichi-Sankyo/AstraZeneca, Regeneron, Pfizer, Blueprint Medicines, Novartis, and Sanofi/Aventis; consulting or advisory roles for Bristol Myers Squibb, MSD, AstraZeneca, Novartis, Takeda, Roche, Sanofi/Aventis, Celgene, Daiichi-Sankyo, Pfizer, Seattle Genetics, Eli Lilly, GlaxoSmithKline, Bayer Healthcare Pharmaceuticals, Blueprint Medicines, Janssen, Regeneron, AbbVie, Mirati, Merck, and Boehringer Ingelheim; participating in speaker's bureau for AstraZeneca, MSD Oncology, Merck, Mirati, and Daiichi-Sankyo/AstraZeneca; research funding received from Bristol Myers Squibb, MSD, Roche/Genentech, AstraZeneca/MedImmune, Pfizer, GlaxoSmithKline, Novartis, Merck, Incyte, Takeda, Spectrum Pharmaceuticals, Blueprint Medicines, Eli Lilly, Ipsen, Janssen, Exelixis, Sanofi, Pfizer, and Amgen; and travel/accommodation support from Pfizer, Roche, and AstraZeneca. JK reports receiving payments or honoraria from AstraZeneca, MSD, and Bristol Myers Squibb. MR reports acting as an invited speaker for Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, GlaxoSmithKline, Lilly, MSD, Merck, Mirati, Novartis, Pfizer, Roche, Regeneron, and Sanofi; participating in speaker's bureau for Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, GlaxoSmithKline, Lilly, MSD, Merck, Mirati, Novartis, Pfizer, Roche, Regeneron, and Sanofi; serving on advisory boards for Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, GlaxoSmithKline, Lilly, MSD, Merck, Mirati, Novartis, Pfizer, Roche, Regeneron, and Sanofi; serving as an officer for ESMO; receiving research grants from Bristol Myers Squibb and Boehringer Ingelheim; and serving as principal investigator for Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, BeiGene, GlaxoSmithKline, Lilly, MSD, Merck, Mirati, Novartis, and Roche. CC reports acting as an invited speaker for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Roche, Lilly, Pfizer, MSD, Bristol Myers Squibb, Takeda, Sanofi, Daiichi-Sankyo, Gilead, and Amgen; serving on advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Roche, Lilly, Pfizer, MSD, Bristol Myers Squibb, Takeda, Sanofi, Daiichi-Sankyo, Gilead, and Amgen; and receiving research grants and funding from AstraZeneca, Roche, Pfizer, Bristol Myers Squibb, and Takeda. NR reports acting as an invited speaker for Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, GlaxoSmithKline, Hoffmann-La Roche, Janssen,

Lilly, MSD, Merck, Pfizer, and Takeda; and serving on advisory boards for AstraZeneca, Bristol Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Janssen, MSD, Merck, Pfizer, Symphogen, and Takeda. LCS reports acting as an invited speaker for Lilly. DLC reports participating in speaker's bureau for MSD and Bristol Myers Squibb; and serving on advisory boards for Roche, Seagen, Amgen, Sanofi Genzyme, AstraZeneca, and Janssen. MRM reports acting as an invited speaker for AstraZeneca, Roche, Novartis, and Takeda. AD reports serving on advisory boards for Novartis, Takeda, and Sanofi. JGS reports acting as an invited speaker for Bristol Myers Squibb, MSD, and Takeda; serving on advisory boards for Pfizer and Sanofi; serving as an officer for ESMO; and serving as principal investigator for Pfizer. LECV reports acting as an invited speaker for AstraZeneca, Roche, MSD, Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, and Amgen. LPA reports acting as an invited speaker for Altum Sequencing and STAb Therapeutics; serving on the board of directors for Altum Sequencing and STAb Therapeutics; receiving consulting fees from Lilly, MSD, Roche, PharmaMar, Merck, AstraZeneca, Novartis, Amgen, Pfizer, Sanofi, Bayer, Bristol Myers Squibb, Mirati, GlaxoSmithKline, Janssen, Takeda, Regeneron, and Sanofi; and receiving grant or funds from MSD, AstraZeneca, Bristol Myers Squibb, Pfizer, and PharmaMar. PC reports employment and stock ownership at AstraZeneca. IDP reports employment and stock ownership at AstraZeneca. KF reports employment at AstraZeneca. UE reports employment and stock ownership at AstraZeneca. CFF reports receiving research grants from AstraZeneca/MedImmune, Elekta, and MSD; and serving in an advisory role for AstraZeneca/MedImmune and MSD. All other authors have declared no conflicts of interest.

DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at: https://www.astrazenecaclinicaltrials.com/our-transparency-commitments/. Data for studies directly listed on Vivli can be requested through Vivli at: www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at: https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

REFERENCES

1. Daly ME, Singh N, Ismaila N, et al. Management of stage III non-small-cell lung cancer: ASCO guideline. *J Clin Oncol*. 2022;40(12):1356-1384.
2. Remon J, Soria JC, Peters S. ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy. *Ann Oncol*. 2021;32(12):1637-1642.
3. 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(2):191-201.
4. US Food and Drug Administration. Imfinzi prescribing information. 2023. Available at https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/9496217c-08b3-432b-ab4f-538d795820bd/9496217c-08b3-432b-ab4f-538d795820bd_viewable_rendition__v.pdf. Accessed December 7, 2023.
5. European Medicines Agency. Imfinzi summary of product characteristics. 2023. Available at https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf. Accessed December 7, 2023.
6. 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(20):1919-1929.
7. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350.
8. 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(12):1670-1680.
9. 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(12):1301-1311.
10. 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(13):2181-2190.
11. O'Rourke N, Roqué i, Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev*. 2010;(6):CD002140.
12. Girard N, Bar J, Garrido P, et al. Treatment characteristics and real-world progression-free survival in patients with unresectable stage III NSCLC who received durvalumab after chemoradiotherapy: findings from the PACIFIC-R study. *J Thorac Oncol*. 2023;18(2):181-193.
13. 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(11):e177-e185.
14. 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(1):26-31.
15. 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(1):824.
16. 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(1):98-102.
17. Garassino MC, Mazieres J, Reck M, et al. Durvalumab after sequential chemoradiotherapy in stage III, unresectable NSCLC: the phase 2 PACIFIC-6 trial. *J Thorac Oncol*. 2022;17(12):1415-1427.
18. Amin MB, editor. *AJCC Cancer Staging Manual*.. 8th ed. Chicago, Illinois: American College of Surgeons; 2018.
19. Jin S, Pazdur R, Sridhara R. Re-evaluating eligibility criteria for oncology clinical trials: analysis of investigational new drug applications in 2015. *J Clin Oncol*. 2017;35(33):3745-3752.
20. Rashdan S, Gerber DE. Immunotherapy for non-small cell lung cancer: from clinical trials to real-world practice. *Transl Lung Cancer Res*. 2019;8(3):202-207.
21. Ludmir EB, Mainwaring W, Lin TA, et al. Factors associated with age disparities among cancer clinical trial participants. *JAMA Oncol*. 2019;5(12):1769-1773.
22. Fletcher J, Reid N, Hubbard RE, et al. Frailty index, not age, predicts treatment outcomes and adverse events for older adults with cancer. *J Frailty Aging*. 2024;13(4):487-494.
23. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol*. 2011;29(25):3457-3465.

24. Jolly TA, Deal AM, Nyrop KA, et al. Geriatric assessment-identified deficits in older cancer patients with normal performance status. *Oncologist*. 2015;20(4):379-385.
25. Fletcher J, Reid N, Hubbard RE, et al. EP04.01-013 Frailty index predicts treatment outcomes in older adults with lung cancer. *J Thorac Oncol*. 2022;17(9):S251.
26. 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(10):1733-1744.
27. 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.