Original Study

Durvalumab After Concurrent Chemoradiotherapy in Elderly Patients With Unresectable Stage III Non–Small–Cell Lung Cancer (PACIFIC)

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Abstract

Elderly patients experience high rates of NSCLC-related mortality. We assessed outcomes from PACIFIC with a post-hoc (70-year) age threshold. Consolidation durvalumab (post-chemoradiotherapy) improved PFS and OS in patients aged ≥70 and <70 with manageable safety and no detrimental impact on patient-reported outcomes versus placebo; grade 3/4 and serious AEs were more common with durvalumab vs. placebo among patients aged ≥70.

Background: The PACIFIC trial demonstrated that consolidation durvalumab significantly improved PFS and OS (the primary endpoints) vs. placebo in patients with unresectable, stage III NSCLC whose disease had not progressed after platinum-based, concurrent chemoradiotherapy (CRT). We report exploratory analyses of outcomes from PACIFIC by age. **Patients and Methods:** Patients were randomized 2:1 (1-42 days post-CRT) to receive 12-months' durvalumab (10 mg/kg intravenously every-2-weeks) or placebo. We analyzed PFS and OS (unstratified Cox-proportional-hazards models), safety and patient-reported outcomes (PROs: symptoms, functioning, and global-health-status/quality-of-life) in subgroups defined by a post-hoc 70-year age threshold. Data cut-off for PFS was February 13, 2017 and for OS, safety and PROs was March 22, 2018. **Results:** Overall, 158 of 713 (22.2%) and 555 of 713 (77.8%) randomized patients were aged ≥70 and <70 years, respectively. Durvalumab improved PFS and OS among patients aged ≥70 (PFS: hazard ratio [HR], 0.62 [95% CI, 0.41-0.95]; OS: HR, 0.78 [95% CI, 0.50-1.22]) and <70 (PFS: HR, 0.53 [95% CI, 0.42-0.67]; OS: HR, 0.66 [95% CI, 0.51-0.87]), although the estimated HR-95% CI for OS crossed one among patients aged ≥70. Durvalumab exhibited a manageable safety profile and did not detrimentally affect PROs vs. placebo, regardless of

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age; grade 3/4 (41.6% vs. 25.5%) and serious adverse events (42.6% vs. 25.5%) were more common with durvalumab vs. placebo among patients aged ≥70. **Conclusion:** Durvalumab was associated with treatment benefit, manageable safety, and no detrimental impact on PROs, irrespective of age, suggesting that elderly patients with unresectable, stage III NSCLC benefit from treatment with consolidation durvalumab after CRT. However, small subgroup sizes and imbalances in baseline factors prevent robust conclusions.

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Keywords: Exploratory analysis, Immune-checkpoint inhibitors, Patient-reported outcomes, Survival, Safety

Introduction

Approximately 85% of lung cancer patients are diagnosed with non-small-cell lung cancer (NSCLC),[1] with approximately a third of patients being diagnosed at stage III.[2,3] Historically, the standard of care (SoC) for patients with unresectable, stage III NSCLC was platinum-based, concurrent chemoradiotherapy (CRT) with curative intent. However, outcomes have been poor, with median progression-free survival (PFS) of approximately 8 months and about 15% to 32% of patients alive at 5 years.[4-6]

Durvalumab is a selective, high-affinity, human IgG1 monoclonal antibody that blocks programmed cell death-ligand 1 (PD-L1) binding to programmed cell death protein-1 (PD-1) and CD80, permitting T cells to recognize and kill tumor cells.[7] In PACIFIC, a placebo-controlled, Phase 3 trial of 12 months' durvalumab as consolidation therapy in patients with unresectable, stage III NSCLC whose disease had not progressed following platinum-based concurrent CRT, the primary endpoints of PFS and overall survival (OS) were met. Durvalumab improved PFS (stratified hazard ratio [HR], 0.52; 95% CI, 0.42-0.65; $P < 0.0001$; median, 16.8 vs. 5.6 months) and OS (stratified HR, 0.68; 95% CI, 0.53-0.87; $P = 0.00251$; median not reached [NR] vs. 28.7 months) vs. placebo with manageable safety, and did not detrimentally affect patient-reported outcomes (PROs; symptoms, physical functioning, and global health status/quality of life [QoL]).[8–11] A recent, pre-planned, exploratory update from PACIFIC also demonstrated durable PFS (stratified HR, 0.55; 95% CI, 0.44-0.67; median, 17.2 vs. 5.6 months) and sustained OS benefit (stratified HR, 0.71; 95% CI, 0.57-0.88; median, 47.5 vs. 29.1 months) with durvalumab at 4 years.[12] Durvalumab received global approvals and the 'PACIFIC regimen' (consolidation durvalumab after platinum-based CRT) has become the new SoC in this disease setting.[8,13,14]

The highest rates of NSCLC-related mortality are among elderly patients;[15] the median age of patients at the time of lung-cancer diagnosis is approximately 70 years.[16] Nevertheless, elderly patients remain systematically underrepresented in clinical trials, and much of the clinical data regarding their treatment is extrapolated from data sets comprised of predominantly younger patient cohorts.[17-20] This can be accounted for, at least partially, by the stringent inclusion/exclusion criteria often employed by clinical trials (eg, regarding performance status and the presence of comorbidities), which means that only highly selected elderly patients can be enrolled. Consequently, there is an unmet need to better understand the efficacy and safety of immunotherapy in elderly patients with NSCLC, including as part of curative-intent treatment sequences in the stage III NSCLC setting.[17,21]

The PACIFIC trial was designed to assess clinical outcomes with durvalumab in an unselected patient population, with enrolment stratified according to a 65-year age threshold. Nevertheless, in previous exploratory subgroup analyses from the trial, PFS and OS benefit with durvalumab was observed regardless of a prespecified 65-year age threshold: PFS (≥65 years: HR, 0.74 [95% CI, 0.54-1.01]; <65 years: HR, 0.43 [95% CI, 0.32-0.57]) and OS (≥65 years: HR, 0.76 [95% CI, 0.55-1.06]; <65 years: HR, 0.62 [95% CI, 0.44-0.86]) favored durvalumab vs. placebo, irrespective of age.[9,10] Here, we report exploratory analyses of clinical outcomes from PACIFIC according to a post-hoc age threshold of 70 years to better reflect the median age at which NSCLC is diagnosed.

Methods

Patients

PACIFIC (NCT02125461) was a Phase 3, double-blind, international, multicenter trial of adult patients (aged ≥18 years) with World Health Organization performance status (WHO PS) 0 or 1 and no evidence of disease progression following at least 2 cycles of platinum-based, concurrent CRT.[10] Eligible patients had documented unresectable, stage III NSCLC according to the *Staging Manual in Thoracic Oncology Version 7* of the International Association for the Study of Lung Cancer. Patients with unresolved grade >2 toxicities (assessed per Common Terminology Criteria for Adverse Events [CTCAE] version 4.03), or grade ≥2 pneumonitis/radiation pneumonitis, from prior CRT were excluded from the trial. All patients provided informed written consent for participation, which was approved by the relevant ethics committees and performed in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice and the Declaration of Helsinki.

Study Design

Patients were randomized 2:1 (1-42 days post-CRT) to receive durvalumab (10 mg/kg intravenously every-two-weeks) or placebo for 12 months or until confirmed progression, alternative anticancer therapy initiation, unacceptable toxicity, or consent withdrawal. Randomization was stratified by age (<65 years vs. ≥65 years), sex, and smoking history (current or former smoker vs. never smoked).

Patients were followed for survival and permitted retreatment with their assigned trial regimen after initial completion as long as all of the following criteria were met: firstly, disease control was

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achieved at the end of 12 months treatment; secondly, the disease progressed during follow-up; and thirdly, the patient had not subsequently received another systemic, anticancer therapy.

Endpoints and Assessments

The primary endpoints were PFS (per Response Evaluation Criteria in Solid Tumours version 1.1 [RECIST v1.1] by blinded independent central review [BICR]) and OS. Secondary endpoints included 12- and 18-month PFS rates, objective response rate (ORR), duration of response (DoR), and time to death or distant metastasis (TTDM) (all RECIST-assessed by BICR), as well as 12- and 24-month OS rates, safety (assessed per CTCAE version 4.03), and PROs (ie, symptoms, functioning, and global health status/QoL).

In the current exploratory analysis, between-treatment comparisons of PFS, OS, TTDM, ORR, the incidence of new lesions, post-discontinuation disease-related anticancer therapy, safety, and PROs were performed in subgroups of patients aged ≥70 and <70 years at study baseline (a post-hoc age threshold).

PROs were evaluated using two questionnaires developed by the European Organisation for Research and Treatment of Cancer (EORTC) Study Group on QoL: QoL questionnaire – Core 30 (QLQ-C30; version 3) and its lung cancer module, QoL Questionnaire – Lung Cancer (QLQ-LC13). PROs were assessed at randomization, week 4, week 8, every 8 weeks until week 48, and then every 12 weeks until disease progression. To capture clinically meaningful changes/differences in PROs, scores for symptoms, functioning, or global health status/QoL were calculated according to scoring manuals/guidelines and range from 0 to 100. Higher scores are indicative of greater severity for symptom scales/items and better health status/function for global health status/QoL and functioning scales. The last assessment for patients who discontinued treatment due to progression was day 30 after the final dose. Patients continuing treatment beyond RECIST-progression due to clinical benefit (at the investigator's discretion) continued completing questionnaires as long as they remained on treatment. Patients who discontinued treatment for reasons other than confirmed progression continued completing the questionnaires until confirmed progression. PROs were assessed as mean change in score at week 48 (from baseline), time to deterioration (TTD) from randomization, and improvement rate. The following changes in score were considered clinically meaningful: a ≥10-point increase (worsening) or decrease (improvement) for symptom scales/items, and a ≥10-point increase (improvement) or decrease (worsening) for functioning scales and global health status/QoL.[22] Therefore, EORTC QLQ-C30 global health status/QoL and functional scales were based on patients with baseline scores of ≥10, and EORTC QLQ-C30/LC13 symptom scales/items were based on patients with baseline scores of ≤90.

Statistical Analyses

Analysis of RECIST-assessed endpoints (PFS, TTDM, ORR, and the incidence of new lesions) was based on the data cut-off (DCO) for the primary analysis of PFS (February 13, 2017). OS, safety, and PROs were analyzed based on the DCO for the primary analysis of OS (March 22, 2018). All data were summarized based on the intent-to-treat (ITT) population except for adverse events (AEs), which were summarized based on the as-treated population.

Treatment effects (HRs and corresponding 95% CIs) for PFS, OS, and TTDM were estimated using unstratified Cox proportional-hazards models with treatment as the only covariate. Medians for these time-to-event endpoints were estimated with the Kaplan–Meier method. ORRs were summarized with descriptive statistics and corresponding 95% CIs were calculated using the Clopper–Pearson method. AEs were summarized with descriptive statistics.

Changes in PRO scores at week 48 (from baseline) for longitudinal endpoints of interest were summarized for the age-defined subgroups with descriptive statistics (expressed as mean and standard deviation [SD]). The longitudinal endpoints of interest were cough, dyspnea, and chest pain (per EORTC QLQ-LC13), and fatigue, appetite loss, physical functioning, and global health status/QoL (per EORTC QLQ-C30). All of these were prespecified longitudinal endpoints of interest for the full ITT population.[11]

For PROs, TTD was defined as time from randomization to the date of the first clinically relevant deterioration (≥10-point change in score from baseline) or death. For the age-defined subgroups, we analyzed lung cancer-related symptoms of cough, dyspnea, chest pain, and hemoptysis (per EORTC QLQ-LC13), and global health status/QoL (per EORTC QLQ-C30). These symptoms/scales were considered the primary PROs for the prespecified analysis of TTD in the full ITT population.[11] HRs (and associated 95% CIs) were estimated using unstratified Cox proportional-hazards models with treatment as the only covariate. Improvement rate for PROs was defined as the proportion of patients with improvement as the percentage of patients with two consecutive assessments, separated by ≥14 days, which showed clinically relevant improvement (≥10-point change in score from baseline). The symptoms/scales analyzed for the age-defined subgroups were the same as those analyzed for TTD. Odds ratios (ORs) and corresponding 95% CIs were calculated with logistic regression.

AstraZeneca's data sharing policy is described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Results

Patients

In total, 713 patients were randomized; 158 of 713 (22.2%) and 555 of 713 (77.8%) patients were aged ≥70 and <70 years, respectively. Overall, 476 of 713 (66.8%) patients were randomized to durvalumab (101 of 158 [63.9%] and 375 of 555 [67.6%] patients aged ≥70 and <70 years, respectively) and 237 of 713 (33.2%) were randomized to placebo (57 of 158 [36.1%] and 180 of 555 [32.4%] patients aged ≥70 and <70 years, respectively).

There was no clinically meaningful difference in the proportion of patients who completed protocol-defined 12-month treatment between the durvalumab and placebo arms among patients aged ≥70 years (durvalumab, 39.0%; placebo, 41.1%) (DCO March 22, 2018; median follow-up, 25.2 months [0.2-43.1 months]) (Supplemental Table 1). Meanwhile, the proportion of patients who completed protocol-defined 12-month treatment was higher in the durvalumab arm among patients aged <70 years (durvalumab, 51.7%; placebo, 32.8%), which is consistent with findings for the full ITT population.[9] Few patients received retreatment with durvalumab following completion of the protocol-

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defined, 12 months of study treatment in both age groups (≥70 years, 2.0%; <70 years, 4.3%).

Clinical Characteristics at Baseline

Among patients aged ≥70 years, 56 of 158 (35.4%) were aged ≥75 years, accounting for 36.6% and 33.3% of patients in the durvalumab and placebo arms of this group, respectively. Among patients aged <70 years, 164 of 555 (29.5%) were aged ≥65 to <70 years, accounting for 30.4% and 27.8% of patients in the durvalumab and placebo arms of this group, respectively.

Baseline patient and disease characteristics were generally well balanced (Supplemental Tables 2 and 3). However, irrespective of study arm, a higher proportion of patients aged ≥70 years, vs. <70 years, were male (≥70 years, 75.3%; <70 years, 68.6%) and received carboplatin-based chemotherapy during CRT (≥70 years, 61.4%; <70 years, 36.8%). Clinically meaningful imbalances in baseline factors were observed between the durvalumab and placebo arms among patients aged ≥70 years: a lower proportion of patients in the durvalumab arm were of Asian ethnicity (durvalumab, 21.8%; placebo, 38.6%) (consistently, a lower proportion of patients in the durvalumab arm were recruited in Asia [durvalumab, 20.8%; placebo, 36.8%]); a lower proportion of patients in the durvalumab arm received pre-CRT induction chemotherapy (durvalumab, 17.8%; placebo, 29.8%); and a higher proportion of patients in the durvalumab arm had PD-L1 expression on ≥25% of tumor cells (TCs) (durvalumab, 32.7%; placebo, 15.8%). PD-L1 expression was determined from retrospective testing of optionally provided, archived, pre-CRT tumor tissue samples; among patients aged ≥70 years, 35.6% and 42.1% had unknown PD-L1 expression status in the durvalumab and placebo arms, respectively.

In general, the presence of most comorbidities at study baseline was higher among patients aged ≥70 years compared with patients aged <70 years (Table 1). While the prevalence of most comorbidities was well balanced between the durvalumab and placebo arms within each age group, some imbalances were observed among patients aged ≥70 years. A higher proportion in the durvalumab arm had pre-existing cardiovascular (CV) disorders (durvalumab, 75.2%; placebo, 63.2%); hypertension (durvalumab, 64.4%; placebo, 61.4%), atrial fibrillation (durvalumab, 11.9%; placebo, 7.0%), and coronary artery disease (durvalumab, 11.9%; placebo, 5.3%) were the most common. A lower proportion in the durvalumab arm had pre-existing respiratory, thoracic, and mediastinal disorders (durvalumab, 58.4%; placebo, 68.4%); chronic obstructive pulmonary disease (COPD) (durvalumab, 38.6%; placebo, 28.1%), cough (durvalumab, 23.8%; placebo, 35.1%), and dyspnea (durvalumab, 11.9%; placebo, 15.8%) were the most common. A lower proportion in the durvalumab arm had pre-existing skin/subcutaneous tissue disorders (durvalumab, 8.9%; placebo, 28.1%). No clinically meaningful between-arm differences in the prevalence of baseline comorbidities were observed among patients aged <70 years.

Regardless of age, approximately three-quarters of patients were randomized to study treatment ≥14 days following completion of radiotherapy (RT) (≥70 years, 77.2%; <70 years, 73.7%). Among patients aged ≥70 years, a higher proportion were randomized ≥14 days following RT in the durvalumab arm (durvalumab, 81.2%; placebo, 70.2%); similar proportions of patients in each arm were randomized ≥14 days following RT among patients aged <70 years (durvalumab, 73.1%; placebo, 75.0%).

Efficacy

At the time of the primary analysis for PFS (DCO February 13, 2017), PFS was improved with durvalumab, vs. placebo, regardless of age (median follow-up, 14.5 months [0.2-29.9 months]) (Figure 1). Among patients aged ≥70 years, median PFS was 12.3 months (95% CI, 9.2 months-not estimable [NE]) with durvalumab vs. 6.1 months (95% CI, 3.6-10.9 months) with placebo (HR, 0.62; 95% CI, 0.41-0.95). Among patients aged <70 years, median PFS was 16.9 months (95% CI, 13.7 months-NE) with durvalumab vs. 5.6 months (95% CI, 4.2-8.0 months) with placebo (HR, 0.53; 95% CI, 0.42-0.67).

At the time of the primary analysis for OS (DCO March 22, 2018), OS benefit favored durvalumab, vs. placebo, regardless of age (median follow-up, 25.2 months [0.2-43.1 months]) (Figure 2). Among patients aged ≥70 years, median OS was 29.0 months (95% CI, 21.0 months NE) with durvalumab vs. 26.9 months (95% CI, 14.9-29.3 months) with placebo (HR, 0.78; 95% CI, 0.50-1.22). Among patients aged <70 years, median OS was not reached (NR) (95% CI, 34.7 months-NE) with durvalumab vs. 31.0 months (95% CI, 22.9 months-NE) with placebo (HR, 0.66; 95% CI, 0.51-0.87).

TTDM benefit (assessed at the time of the primary analysis for PFS) favored durvalumab, vs. placebo, regardless of age. Among patients aged ≥70 years, median TTDM was 17.8 months (95% CI, 13.6 months-NE) with durvalumab vs. 14.0 months (95% CI, 7.4 months-NE) with placebo (HR, 0.66; 95% CI, 0.39-1.13). Among patients aged <70 years, median TTDM was NR (95% CI, NE-NE) with durvalumab vs. 14.6 months (95% CI, 10.6-18.6 months) with placebo (HR, 0.53; 95% CI, 0.39-0.71).

ORR (assessed at the time of the primary analysis for PFS) was proportionally higher with durvalumab compared with placebo regardless of age (Table 2). Among patients aged ≥70 years, ORR was 31.9% (95% CI, 22.5-42.5) with durvalumab vs. 17.6% (95% CI, 8.4-30.9) with placebo. Among patients aged <70 years, ORR was 27.6% (95% CI, 23.0-32.5) with durvalumab vs. 15.4% (95% CI, 10.2-21.9) with placebo.

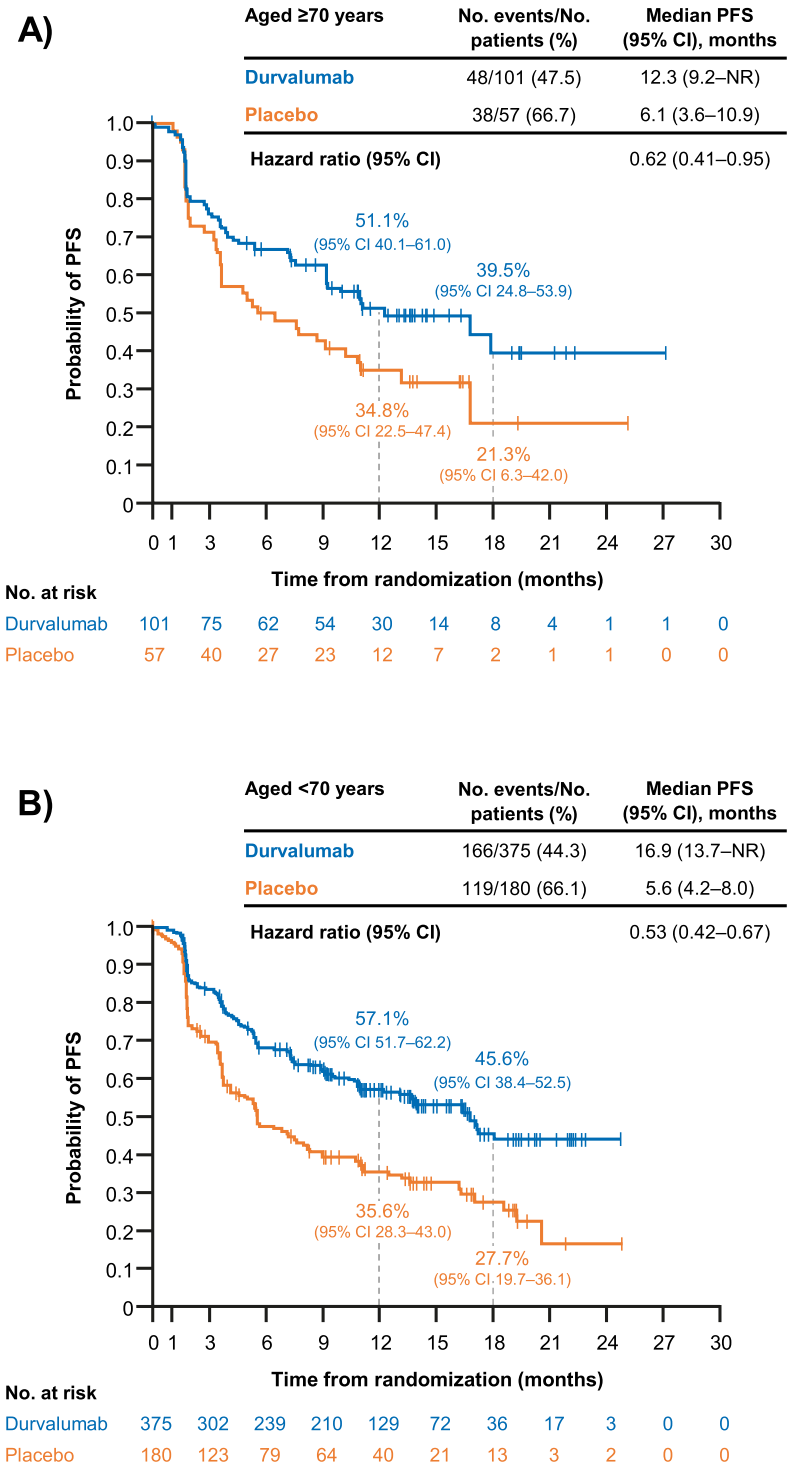
Overall, the frequency of new lesions (assessed at the time of the primary analysis for PFS) was similar in the durvalumab and placebo arms in patients aged ≥70 years (durvalumab, 14.9%; placebo, 19.3%) (Supplemental Table 4). Consistent with the full ITT population,[10] a lower proportion of patients had new lesions in the durvalumab arm compared with placebo among patients aged <70 years (durvalumab, 21.9%; placebo, 36.1%). The incidence of new brain lesions was low in the durvalumab arm among patients aged ≥70 years (durvalumab, 1.0%; placebo, 7.0%).

Postdiscontinuation Disease-Related Anticancer Therapy

Consistent with the full ITT population,[9] a lower proportion of patients received a subsequent anticancer therapy in the durvalumab arm compared with the placebo arm among patients aged ≥70 years (durvalumab, 36.6%; placebo, 50.9%) and <70 years

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Figure 1 PFS (BICR) in patients aged (A) ≥70 years and (B) <70 years. Based on the ITT population. Shown are Kaplan–Meier curves for PFS. The vertical tick marks indicate censored observations. The dashed vertical lines indicate the times of landmark analyses for PFS. HRs and 95% CIs were calculated using unstratified Cox-proportional-hazards models. Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; ITT=intent-to-treat; NE = not reached; PFS = progression-free survival.



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Table 1 Current Medical History at Baseline in Patients Aged ≥70 Years and <70 Years[a]

System Organ Class, n (%) Investigator's Preferred Term	Aged ≥70 Years		Aged <70 Years	
	Durvalumab (N = 101)	Placebo (N = 57)	Durvalumab (N = 375)	Placebo (N = 180)
Blood and lymphatic system disorders	25 (24.8)	12 (21.1)	57 (15.2)	24 (13.3)
Anemia	18 (17.8)	9 (15.8)	39 (10.4)	19 (10.6)
Cardiovascular disorders	76 (75.2)	36 (63.2)	177 (47.2)	82 (45.6)
Atrial fibrillation	12 (11.9)	4 (7.0)	10 (2.7)	2 (1.1)
Coronary artery disease	12 (11.9)	3 (5.3)	12 (3.2)	10 (5.6)
Hypertension	65 (64.4)	35 (61.4)	134 (35.7)	64 (35.6)
Eye disorders	14 (13.9)	4 (7.0)	15 (4.0)	9 (5.0)
Gastrointestinal disorders	53 (52.5)	34 (59.6)	165 (44.0)	81 (45.0)
Constipation	21 (20.8)	10 (17.5)	47 (12.5)	26 (14.4)
Esophagitis	4 (4.0)	7 (12.3)	40 (10.7)	17 (9.4)
Gastroesophageal reflux disease	21 (20.8)	8 (14.0)	51 (13.6)	20 (11.1)
Nausea	9 (8.9)	7 (12.3)	35 (9.3)	20 (11.1)
General disorders and administration site conditions	29 (28.7)	20 (35.1)	88 (23.5)	39 (21.7)
Fatigue	16 (15.8)	15 (26.3)	65 (17.3)	20 (11.1)
Immune system disorders	14 (13.9)	3 (5.3)	31 (8.3)	13 (7.2)
Injury, poisoning, and procedural complications	18 (17.8)	9 (15.8)	60 (16.0)	23 (12.8)
Investigations	17 (16.8)	4 (7.0)	35 (9.3)	11 (6.1)
Metabolism and nutrition disorders	59 (58.4)	35 (61.4)	142 (37.9)	75 (41.7)
Decreased appetite	10 (9.9)	9 (15.8)	19 (5.1)	12 (6.7)
Hypercholesterolemia	14 (13.9)	6 (10.5)	29 (7.7)	17 (9.4)
Hyperlipidemia	20 (19.8)	6 (10.5)	37 (9.9)	15 (8.3)
Type-2 diabetes	23 (22.8)	9 (15.8)	59 (15.7)	29 (16.1)
Musculoskeletal and connective tissue disorders	39 (38.6)	20 (35.1)	108 (28.8)	46 (25.6)
Arthritis	10 (9.9)	6 (10.5)	13 (3.5)	4 (2.2)
Back pain	12 (11.9)	6 (10.5)	26 (6.9)	15 (8.3)
Nervous system disorders	29 (28.7)	22 (38.6)	87 (23.2)	32 (17.8)
Psychiatric disorders	33 (32.7)	19 (33.3)	103 (27.5)	51 (28.3)
Anxiety	10 (9.9)	8 (14.0)	43 (11.5)	19 (10.6)
Depression	12 (11.9)	3 (5.3)	42 (11.2)	14 (7.8)
Insomnia	23 (22.8)	12 (21.1)	49 (13.1)	29 (16.1)
Renal and urinary disorders	16 (15.8)	6 (10.5)	19 (5.1)	15 (8.3)
Reproductive system and breast disorders	16 (15.8)	8 (14.0)	28 (7.5)	12 (6.7)
Benign prostatic hyperplasia	13 (12.9)	7 (12.3)	17 (4.5)	6 (3.3)
Respiratory, thoracic, and mediastinal disorders	59 (58.4)	39 (68.4)	184 (49.1)	96 (53.3)
Chronic obstructive pulmonary disease	39 (38.6)	16 (28.1)	80 (21.3)	42 (23.3)
Cough	24 (23.8)	20 (35.1)	94 (25.1)	45 (25.0)
Dyspnea	12 (11.9)	9 (15.8)	47 (12.5)	17 (9.4)
Skin and subcutaneous tissue disorders	9 (8.9)	16 (28.1)	55 (14.7)	16 (8.9)

Based on the ITT population.
Abbreviation: ITT = intent-to-treat.
* Only terms reported by ≥10% of patients in either treatment arm (for either age group) are summarized. 'Current' medical history refers to events with a start date prior to trial randomization, but which had not resolved at randomization.

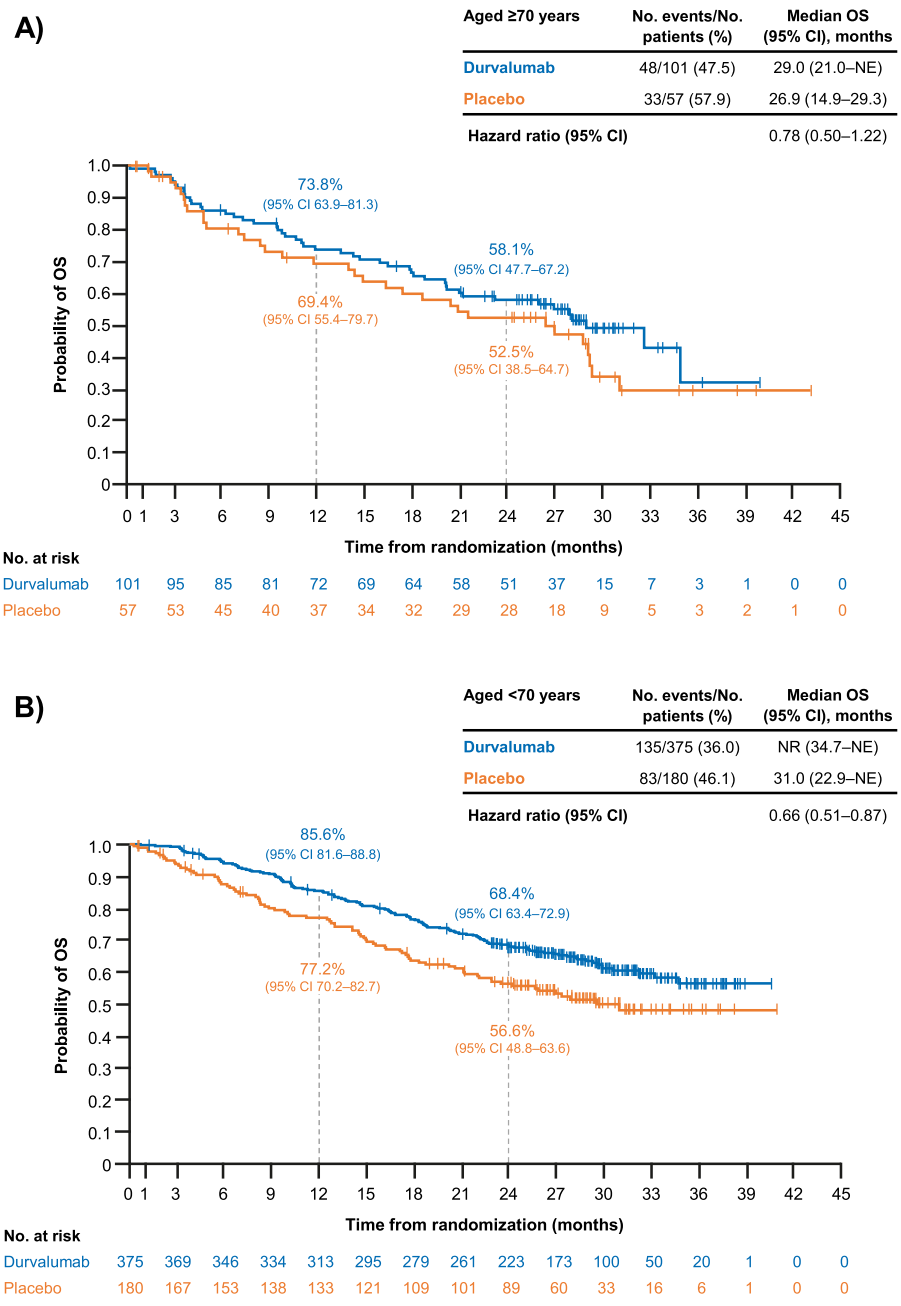
(durvalumab, 42.1%; placebo, 55.0%) (Supplemental Table 5). Likewise, subsequent immunotherapy (primarily nivolumab or pembrolizumab) was received by a lower proportion of patients in the durvalumab arm compared with the placebo arm among patients aged ≥70 years (durvalumab, 9.9%; placebo, 24.6%) and <70 years (durvalumab, 7.5%; placebo, 21.7%).

Safety

During the study, most patients (>94%) experienced any-grade, all-cause AEs irrespective of age or the study treatment received (Table 3). A higher proportion of patients aged ≥70 years experienced grade 3/4 (durvalumab, 41.6%; placebo, 25.5%) and serious AEs (durvalumab, 42.6%; placebo, 25.5%) with durvalumab compared with placebo. Meanwhile, the incidence of

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Figure 2 OS in patients aged (A) ≥70 years and (B) <70 years. Based on the ITT population. Shown are Kaplan–Meier curves for OS. The vertical tick marks indicate censored observations. The dashed vertical lines indicate the times of landmark analyses for OS. HRs and 95% CIs were calculated using unstratified Cox-proportional-hazards models. Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; NE = not estimable; NR = not reached; OS = overall survival.



grade 3/4 (durvalumab, 30.2%; placebo, 29.1%) and serious AEs (durvalumab, 25.4%; placebo, 22.3%) was similar with durvalumab and placebo among patients aged <70 years. The most common AEs of maximum grade 3/4 among patients aged ≥70 years were CV disorders (durvalumab, 12.9%; placebo, 1.8%), respiratory, thoracic, and mediastinal disorders (durvalumab, 11.9%; placebo, 9.1%), infections and infestations (durvalumab, 10.9%; placebo, 1.8%), metabolism and nutrition disorders (durvalumab, 7.9%; placebo, 9.1%), and blood and lymphatic system disorders (durvalumab, 6.9%; placebo, 1.8%) (Supplemental Table 6).

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Table 2 Antitumor Response (BICR) in Patients Aged ≥70 Years and <70 Years

	Aged ≥70 Years		Aged <70 Years	
	Durvalumab (N = 91)	Placebo (N = 51)	Durvalumab (N = 352)	Placebo (N = 162)
ORR*				
n (%)	29 (31.9)	9 (17.6)	97 (27.6)	25 (15.4)
[95% CI]	[22.5-42.5]	[8.4-30.9]	[23.0-32.5]	[10.2-21.9]
DoR[a]	n = 29	n = 9	n = 97	n = 25
Median duration (95% CI), months	NR (7.5-NE)	NR (1.1-NE)	NR (NE-NE)	13.8 (5.9-NE)
Percentage remaining in response at[a,b]				
6 months (%)	78.9	77.8	85.9	64.1
12 months (%)	72.8	66.7	73.6	52.2
18 months (%)	72.8	NR	73.6	39.2

Based on the ITT population.
Abbreviations: BICR = blinded independent central review; CI = confidence interval; DoR = duration of response; ITT = intent-to-treat; NE = not estimable; NR = not reached; ORR = objective response rate.
* ORR for N evaluable patients includes unconfirmed responses.
[a] Summary based on evaluable patients.
[b] Calculated using the Kaplan–Meier method.

Table 3 Adverse Events in Patients Aged ≥70 Years and <70 Years

	Aged ≥70 Years		Aged <70 Years	
AE Category*	Durvalumab (N = 101)	Placebo (N = 55)	Durvalumab (N = 374)	Placebo (N = 179)
Any-grade all-causality AEs, n (%)	100 (99.0)	53 (96.4)	360 (96.3)	169 (94.4)
Grade 3/4	42 (41.6)	14 (25.5)	113 (30.2)	52 (29.1)
Outcome of death	11 (10.9)	7 (12.7)	10 (2.7)	8 (4.5)
Leading to discontinuation	22 (21.8)	9 (16.4)	51 (13.6)	14 (7.8)
Serious AEs, n (%)	43 (42.6)	14 (25.5)	95 (25.4)	40 (22.3)
Immune-mediated AEs, n (%)[a]	20 (19.8)	8 (14.5)	96 (25.7)	11 (6.1)
AEs leading to dose delay, n (%)	51 (50.5)	16 (29.1)	152 (40.6)	56 (31.3)
Pneumonitis/radiation pneumonitis[b]				
Any grade[c]	33 (32.7)	18 (32.7)	128 (34.2)	40 (22.3)
Grade 1	10 (9.9)	6 (10.9)	57 (15.2)	19 (10.6)
Grade 2	13 (12.9)	5 (9.1)	59 (15.8)	17 (9.5)
Grade 3	8 (7.9)	3 (5.5)	9 (2.4)	3 (1.7)
Grade 5	2 (2.0)	4 (7.3)	3 (<1)	1 (<1)
Leading to discontinuation	9 (8.9)	5 (9.1)	21 (5.6)	5 (2.8)

Based on the as-treated population.
Abbreviation: AE = adverse event.
* Includes AEs with an onset date on or after the date of the first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication, or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
[a] An AE of special interest requiring the use of systemic steroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy, consistent with an immune-mediated mechanism of action, and where there is no clear alternate etiology.
[b] Pneumonitis is a composite term that includes events of acute interstitial pneumonitis, interstitial lung disease, pneumonitis, pulmonary fibrosis, and radiation pneumonitis (alveolitis and diffuse alveolar damage were also included, but no events were found).
[c] No grade 4 pneumonitis/radiation pneumonitis events were reported.

Among patients aged ≥70 years with pre-existing CV disorders at study baseline, 16.9% and 2.9% experienced on-study CV AEs of maximum grade 3/4 with durvalumab and placebo, respectively (Supplemental Table 7), accounting for all patients in this age group who experienced CV AEs of maximum grade 3/4 during the study (regardless of study treatment).

Irrespective of the study treatment received, a higher proportion of patients aged ≥70 years experienced fatal AEs during the study compared with patients aged <70 years (Table 3). The incidence of fatal AEs was similar with durvalumab and placebo among patients aged ≥70 years (durvalumab, 10.9%; placebo, 12.7%) and <70 years (durvalumab, 2.7%; placebo, 4.5%).

The incidence of any-grade pneumonitis/radiation pneumonitis among patients aged ≥70 years during the study was the same with durvalumab and placebo (32.7% for both) (Table 3). Meanwhile, consistent with the full as-treated population,[9,10] the incidence of any-grade pneumonitis/radiation pneumonitis was proportionally higher with durvalumab (34.2%) compared with placebo (22.3%) among patients aged <70 years. Irrespective of the study treatment received, the incidence of grade 3 pneumonitis/radiation

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pneumonitis was proportionally higher among patients aged ≥70 years (durvalumab, 7.9%; placebo, 5.5%) compared with patients aged <70 years (durvalumab, 2.4%; placebo, 1.7%) (no grade 4 pneumonitis/radiation pneumonitis events were reported).

The incidence of any-grade, immune-mediated AEs (imAEs) was similar with durvalumab (19.8%) and placebo (14.5%) among patients aged ≥70 years (Table 3). Meanwhile, among patients aged <70 years, the incidence of imAEs was proportionally higher with durvalumab (25.7%) compared with placebo (6.1%). Among patients aged ≥70 years, the most commonly reported imAEs were pneumonitis (durvalumab, 9.9%; placebo, 10.9%), hypothyroidism (durvalumab, 8.9%; placebo, 3.6%), hyperthyroidism (durvalumab 2.0%; placebo, 0%), and dermatitis (durvalumab, 1.0%; placebo, 0%) (Supplemental Table 8). Similarly, the most commonly reported imAEs among patients aged <70 years were pneumonitis (durvalumab, 11.0%; placebo, 5.6%), hypothyroidism (durvalumab, 9.6%; placebo, <1%), hyperthyroidism (durvalumab, 2.9%; placebo 0%), and rash (durvalumab, 1.3%; placebo, <1%). Apart from pneumonitis, no grade 3/4 imAEs were reported in ≥1% of patients irrespective of age or the study treatment received. Grade 3 immune-mediated pneumonitis was reported in 5.0% and 3.6% of patients with durvalumab and placebo, respectively, among patients aged ≥70 years (and 1.1% and 2.2% of patients, respectively, among patients aged <70 years) (no grade 4 pneumonitis events were reported).

Interruption of study treatment (ie, dose delay) due to AEs was more common with durvalumab, compared with placebo, among patients aged ≥70 (durvalumab, 50.5%; placebo, 29.1%) and <70 years (durvalumab, 40.6%; placebo, 31.3%) (Table 3). A higher proportion of patients aged ≥70 years, compared with patients aged <70 years, permanently discontinued durvalumab (≥70 years, 21.8%; <70 years, 13.6%) and placebo (≥70 years, 16.4%; <70 years, 7.8%) due to AEs; the difference between the proportions of patients aged ≥70 and <70 years who discontinued treatment due to AEs was similar for durvalumab (difference, +8.2%) and placebo (difference, +8.6%).

Patient-Reported Outcomes

Overall, more than three-quarters of patients completed both EORTC questionnaires (QLQ-C30 and QLQ-LC13) up to week 48 in both treatment arms, regardless of age group (Supplemental Table 9). At baseline, no clinically relevant between-arm differences in scores for global health status/QoL, physical functioning, or symptoms were observed in either of the age groups. PRO scores remained stable for most PROs at week 48 (relative to baseline) irrespective of age or treatment arm (Supplemental Table 10). Among patients aged ≥70 years, no clinically meaningful between-arm differences (≥10-point difference between changes in scores) were observed for most PROs, including in key lung cancer-related symptoms of dyspnea and chest pain (all assessed with QLQ-LC13), as well as fatigue, physical functioning, and global health status/QoL (assessed with QLQ-C30); however, a clinically meaningful difference favoring durvalumab was observed for cough symptom (assessed with QLQ-LC13) (mean change in score: durvalumab, −9.0 [SD, 26.8]; placebo, 3.5 [SD, 33.1]). No clinically meaningful between-arm differences were observed among patients aged <70 years.

TTD and the proportion of patients with clinically relevant improvements in global health status/QoL (assessed with QLQ-C30) and key lung cancer-related symptoms were generally consistent with the full ITT population regardless of age (Figures 3 and 4). Broadly, there were no clinically important between-arm differences in TTD of global health status/QoL (assessed with QLQ-C30), or in key lung cancer-related symptoms of cough, dyspnea, chest pain, and hemoptysis (all assessed with QLQ-LC13), among patients aged ≥70 or <70 years. The only exception was hemoptysis symptom, for which TTD was longer with durvalumab, vs. placebo, among patients aged <70 years (HR, 0.68; 95% CI, 0.49-0.96) (Figure 3). Similarly, no clinically important between-arm differences were observed in the proportion of patients with clinically relevant improvements in global health status/QoL, or in most of the key lung cancer-related symptoms, among patients aged ≥70 or <70 years. The only exception was cough symptom, which favored placebo, vs. durvalumab, among patients aged <70 years (OR, 0.61; 95% CI, 0.40-0.94) (Figure 4).

Discussion

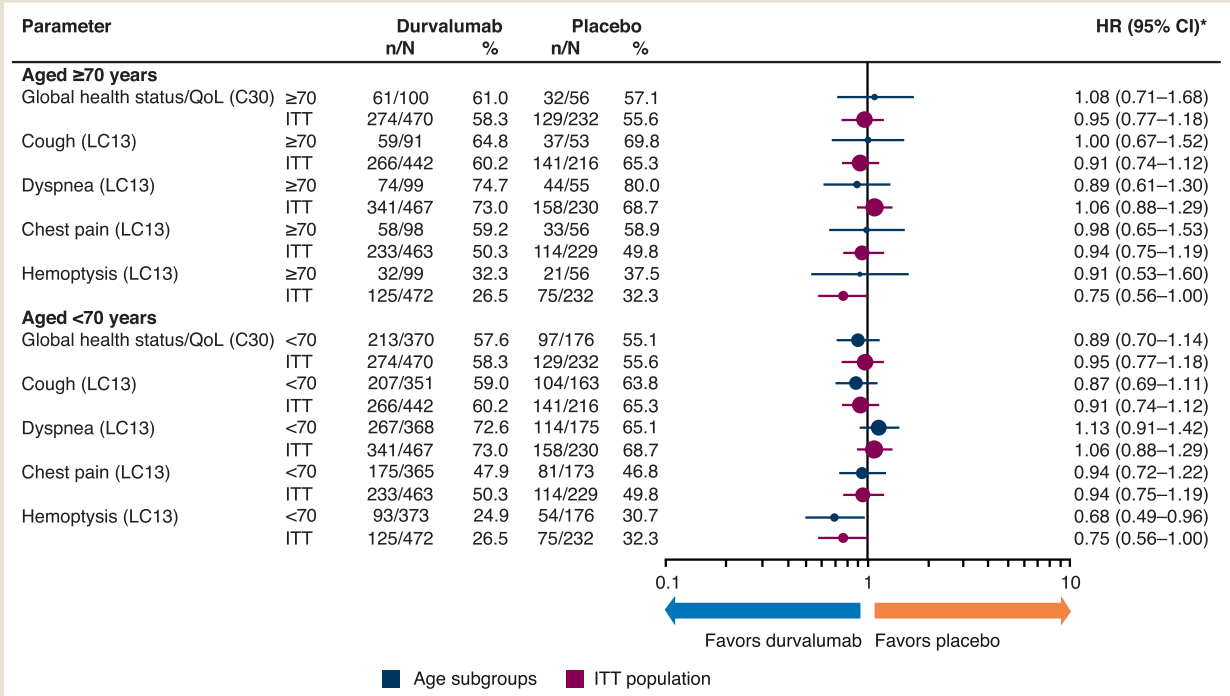
Although PACIFIC was not specifically designed to assess clinical outcomes with durvalumab in elderly patients, results from this exploratory, post-hoc analysis indicate that durvalumab was associated with treatment benefit, and a manageable safety profile, regardless of a post-hoc age threshold of 70 years. Moreover, the use of durvalumab did not compromise PROs (ie, symptoms, functioning, and global health status/QoL) compared with placebo among patients aged ≥70 years. These results suggest that eligible patients should not be excluded from receiving the PACIFIC regimen based on their age alone. It should be noted that performance status is considered a more clinically relevant patient factor than age when selecting cancer patients for curative-intent treatment, which was reflected by the restriction of PACIFIC trial enrolment to patients with good performance status (ie, WHO PS 0 or 1).

PFS, OS, and TTDM benefit favored durvalumab vs. placebo irrespective of age; treatment benefit among patients aged ≥70 years was therefore observed in spite of the potential impact of immunosenescence (the age-related decline of the immune system).[15] The findings of the current analysis are consistent with those of other studies that report treatment benefit with immune checkpoint inhibitors (ICIs) among elderly patients in the advanced/metastatic NSCLC setting and across other advanced-stage tumors.[23-26]

In the current study, OS and TTDM benefit with durvalumab appeared to be weaker among patients aged ≥70 years (OS: HR, 0.78 [95% CI, 0.50-1.22]; TTDM: HR, 0.66 [95% CI, 0.39-1.13]) compared with those aged <70 years (OS: HR, 0.66 [95% CI, 0.51-0.87]; TTDM: HR, 0.53 [95% CI, 0.39-0.71]); the HR 95% CIs for patients aged ≥70 years crossed one. However, the number of patients aged ≥70 years was small (N = 158) and inadequately sized for statistical comparison. The reasons for the less favorable HR estimates among patients aged ≥70 years are unclear but may be driven, at least partially, by imbalances in potentially prognostic baseline factors between the age groups. For example, male sex (75.3% vs. 68.6%), receipt of

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Figure 3 TTD of global health status/QoL and lung cancer-related symptoms in patients aged ≥70 years and <70 years. Based on the ITT population. Shown are forest plots of TTD for global health status/QoL and key lung cancer-related symptoms for the age subgroups. Data for the full ITT population is shown alongside the data for each age group. TTD was defined as time from randomization to the date of the first clinically relevant deterioration (≥10-point change in score from baseline) or death. Data were gathered from the EORTC QLQ-C30 and EORTC QLQ-LC13. C30 global health status or QoL was assessed in patients with baseline scores of ≥10. LC13 symptom scales and items were assessed in patients with baseline scores of ≤90. *HR <1 favors durvalumab. HRs and 95% CIs were calculated using Cox proportional-hazards models; an unstratified approach was used for analyses within the age groups. Analyses of the full ITT population were adjusted for the trial stratification factors, as reported elsewhere.[11] Abbreviations: CI = confidence interval; C30 = Core 30; EORTC QLQ = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HR = hazard ratio; ITT = intent-to-treat; LC13 = Lung Cancer 13; n = total number of events; N = total number of patients; TTD = time to deterioration; QoL = quality of life.

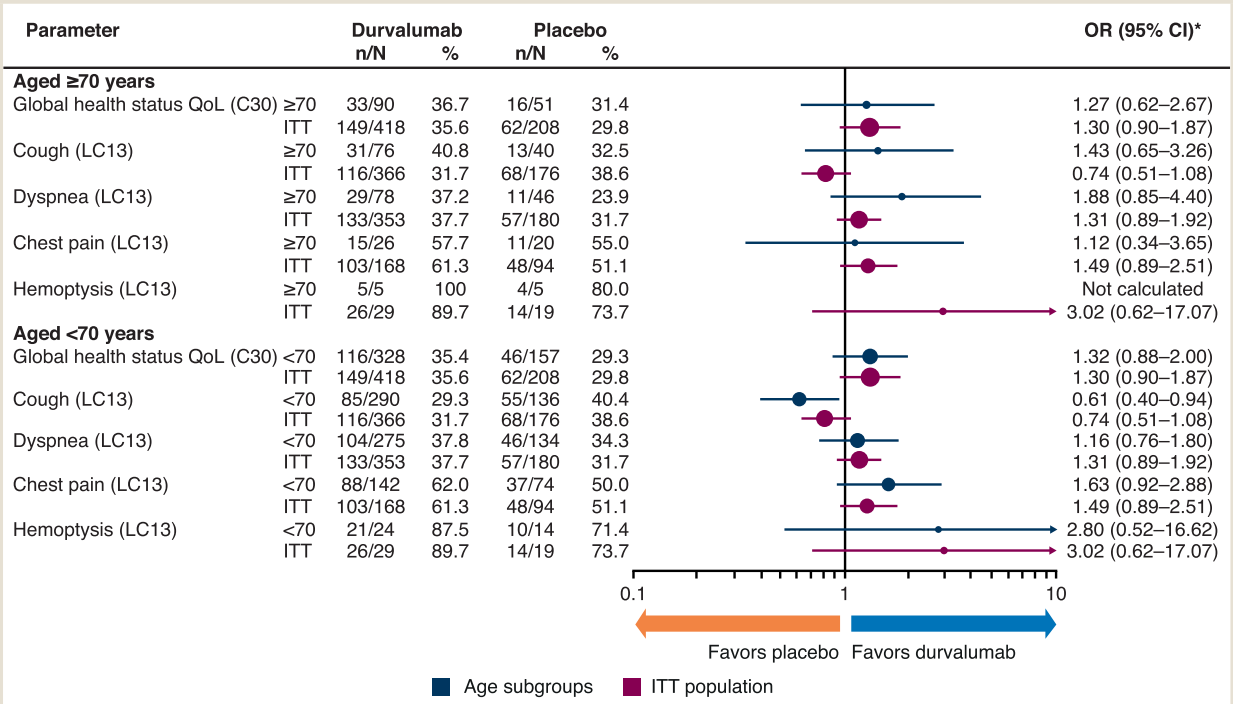


carboplatin-based chemotherapy during CRT (61.4% vs. 36.8%), and randomization to durvalumab ≥14 days following completion of RT (81.2% vs. 73.1%) were more common among patients aged ≥70 years compared with patients aged <70 years. Prespecified subgroup analyses from PACIFIC demonstrated that male sex, receipt of carboplatin-based chemotherapy, and randomization to durvalumab ≥14 days following RT correlated with weaker OS benefit;[9] male sex (vs. female) and carboplatin-based CRT regimens (vs. cisplatin-based regimens) have also been associated with worse survival in other studies of patients with NSCLC.[27,28] Imbalances in baseline factors between the durvalumab and placebo arms among patients aged ≥70 years may also account for the less favorable HR estimates compared with patients aged <70 years. Among patients aged ≥70 years, a higher proportion had pre-existing CV disorders (75.2% vs. 63.2%) and COPD (38.6% vs. 28.1%) in the durvalumab arm compared with the placebo arm, and a lower proportion were of Asian ethnicity (21.8% vs. 38.6%). In lung cancer patients, pre-existing CV disorders and COPD have been identified as prognostic factors for worse survival outcomes, and Asian ethnicity has been identified as a prognostic factor for better survival outcomes.[29-33]

Consistent with the full as-treated population,[9,10] durvalumab had a broadly manageable safety profile. However, on-study grade 3/4 (41.6% vs. 25.5%) and serious AEs (42.6% vs. 25.5%) were proportionally more common with durvalumab compared with placebo among patients aged ≥70 years. In contrast, the incidence of these events was similar with durvalumab and placebo among patients aged <70 years, suggesting that durvalumab treatment may be associated with relatively more severe AEs in older patients. However, as noted for efficacy outcomes above, these safety findings could be driven, at least in part, by imbalances in prognostic baseline factors between the durvalumab and placebo arms among patients aged ≥70 years. For instance, CV disorders were among the most common on-study AEs of maximum grade 3/4 reported with durvalumab among patients aged ≥70 years (12.9%) but were comparatively uncommon with placebo (1.8%), which may have been driven by the higher prevalence of pre-existing CV disorders at study baseline among patients aged

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Figure 4 Improvements in global health status/QoL and lung cancer-related symptoms in patients aged ≥70 years and <70 years. Based on the ITT population. Shown are forest plots of improvement in global health status/QoL and key lung cancer-related symptoms for the age subgroups. Data for the full ITT population is shown alongside the data for each age group. Improvement rate was defined as the proportion of patients with improvement as the percentage of patients with two consecutive assessments, separated by ≥14 days, which showed clinically relevant improvement (≥10-point change in score from baseline). Data were gathered from the EORTC QLQ-C30 and EORTC QLQ-LC13. C30 global health status or quality of life was assessed in patients with baseline scores of ≥10. LC13 symptom scales and items were assessed in patients with baseline scores of ≤90. *OR >1 favors durvalumab. ORs and 95% CIs were calculated using logistic regression; an unstratified approach was used for analyses within the age groups. Analyses of the full ITT population were adjusted for trial stratification factors, as reported elsewhere.[11] ORs and 95% CIs were not calculated in subgroups that had <20 events. Abbreviations: CI = confidence interval; C30 = Core 30; EORTC QLQ = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HR = hazard ratio; ITT = intent-to-treat; LC13 = Lung Cancer 13; n = total number of events; N = total number of patients; QoL = quality of life.



≥70 years in the durvalumab arm (75.2%) compared with the placebo arm (63.2%). Indeed, all patients aged ≥70 years who experienced CV AEs of maximum grade 3/4 during the study had pre-existing CV disorders at baseline (regardless of study treatment).

Irrespective of whether patients received durvalumab or placebo, fatal AEs, grade 3/4 pneumonitis/radiation pneumonitis, and AEs leading to study treatment discontinuation were more common among patients aged ≥70 years compared with patients aged <70 years. This is consistent with previous findings from a large, pooled analysis of data from patients who received concurrent CRT in the stage III NSCLC setting, which reported worse OS and higher rates of toxicity, treatment discontinuation due to AEs, and death among patients aged ≥70 compared with patients aged <70 years.[34] Moreover, a higher incidence of pneumonitis/radiation pneumonitis was also observed among patients aged ≥70 years in subgroup analyses from trials of CRT.[17,35,36] Thus, these safety findings possibly reflect age-related and/or CRT-related morbidity.

Consistent with the full ITT population,[11] the findings of this analysis do not indicate any detrimental effect of up to 12 months of durvalumab monotherapy, vs. placebo, on key PROs (in terms of change in score at week 48 [from baseline], TTD, or improvement rate) in patients aged ≥70 years. This provides additional context to the safety data reported here, indicating that irrespective of age, durvalumab can be administered safely following CRT, without compromising patient QoL.

The current analysis is limited by its unplanned, post-hoc nature and the sample sizes (especially for the placebo arm among patients aged ≥70 years; N = 57), which preclude robust conclusions; smaller sample size creates greater uncertainty in estimating treatment effects, as illustrated by the wide HR 95% CIs reported for OS and TTDM for patients aged ≥70 years. Moreover, as enrolment onto PACIFIC was not stratified according to a 70-year age thresh-

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old, there were several imbalances in potentially prognostic baseline factors between the durvalumab and placebo arms (eg, Asian ethnicity, pre-existing COPD, and pre-existing CV disorders) among patients aged ≥70 years, which may have biased clinical outcomes in this age group. Studies that enrich enrolment of elderly patients are needed to more accurately determine the efficacy and safety of ICI administered as part of curative-intent treatment sequences (eg, after CRT) in this patient population. Preliminary efforts have begun; the ongoing phase-2 NEJ039A study is assessing the efficacy and safety of ICI (with durvalumab) following platinum-based CRT in frail/elderly patients.[37] Moreover, the ongoing PACIFIC-R study (NCT03798535) will provide the opportunity to evaluate real-world outcomes with consolidation ICI after CRT in elderly patients.

Conclusion

In conclusion, durvalumab was associated with treatment benefit, vs. placebo, in patients with unresectable, stage III NSCLC whose disease did not progress after platinum-based, concurrent CRT, irrespective of a post-hoc age threshold of 70 years. Moreover, durvalumab had a broadly manageable safety profile, and did not detrimentally affect PROs compared with placebo, irrespective of age. Taken together, these results indicate that elderly patients derive benefit from treatment with the PACIFIC regimen, suggesting that eligible patients should not be excluded from receiving this regimen based on their age alone. However, as the analysis is post-hoc and exploratory by nature, it lacks adequate statistical power to establish treatment benefit definitively. As trial enrolment was not stratified according to a 70-year age threshold the subgroup analyses are subject to imbalances in potentially prognostic baseline factors and population sizes. Evaluating a real-world population of patients with unresectable, stage III NSCLC, as in the ongoing PACIFIC-R study (NCT03798535), will provide important insights into the efficacy and safety of administering ICIs following CRT in elderly patients.

Clinical Practice Points

- Platinum-based, concurrent chemoradiotherapy (CRT) with active follow-up was the standard of care (SoC) for patients with unresectable, stage III NSCLC.
- The PACIFIC trial demonstrated that durvalumab significantly improved PFS and OS vs. placebo in patients with unresectable, stage III NSCLC without disease progression following platinum-based, concurrent CRT. Subsequently, the 'PACIFIC regimen' (consolidation durvalumab after CRT) has become the new SoC in this disease setting.
- Elderly patients experience high rates of NSCLC-related mortality but are underrepresented in clinical trials. This exploratory analysis from PACIFIC, using a post-hoc age threshold of 70 years, demonstrates that durvalumab is associated with PFS and OS benefit irrespective of age.
- Durvalumab also exhibited a manageable safety profile and did not detrimentally affect patient-reported outcomes compared with placebo in patients aged ≥70 years; a higher proportion of patients aged ≥70 years experienced grade 3/4 and serious adverse events with durvalumab vs. placebo (while the incidence of these events was similar with durvalumab and placebo among patients aged <70 years).
- These results indicate that elderly patients with unresectable, stage III NSCLC benefit from treatment with the 'PACIFIC regimen', suggesting that eligible patients should not be excluded from receiving this regimen based on their age alone.
- Nevertheless, the exploratory, post-hoc nature of this subgroup analysis, and imbalances in potentially prognostic baseline factors and subgroup sizes, preclude robust conclusions.
- Prospective, adequately powered studies are required to provide definitive conclusions on the efficacy and safety of the PACIFIC regimen in elderly patients with unresectable, stage III NSCLC.

Author Contributions

Mark A. Socinski: *Conceptualization, Visualization, Writing - review & editing.* Mustafa Özgüroğlu: *Investigation, Writing - review & editing.* Augusto Villegas: *Investigation, Writing - review & editing.* Davey Daniel: *Investigation, Writing - review & editing.* David Vicente: *Investigation, Writing - review & editing.* Shuji Murakami: *Investigation, Writing - review & editing.* Rina Hui: *Investigation, Writing - review & editing.* Jhanelle E. Gray: *Writing - review & editing.* Keunchil Park: *Investigation, Writing - review & editing.* Mark Vincent: *Investigation, Writing - review & editing.* Helen Mann: *Formal Analysis, Writing - review & editing.* Michael Newton: *Conceptualization, Writing - review & editing.* Phillip A. Dennis: *Conceptualization, Writing - review & editing.* Scott J. Antonia*: Investigation, Writing - review & editing.*

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2021.05.009.

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