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Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

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abstract

PURPOSE The phase III PACIFIC trial compared durvalumab with placebo in patients with unresectable, stage III non–small-cell lung cancer and no disease progression after concurrent chemoradiotherapy. Consolidation durvalumab was associated with significant improvements in the primary end points of overall survival (OS; stratified hazard ratio [HR], 0.68; 95% CI, 0.53 to 0.87; $P = .00251$) and progression-free survival (PFS [blinded independent central review; RECIST v1.1]; stratified HR, 0.52; 95% CI, 0.42 to 0.65; $P < .0001$), with manageable safety. We report updated, exploratory analyses of survival, approximately 5 years after the last patient was randomly assigned.

METHODS Patients with WHO performance status 0 or 1 (any tumor programmed cell death-ligand 1 status) were randomly assigned (2:1) to durvalumab (10 mg/kg intravenously; administered once every 2 weeks for 12 months) or placebo, stratified by age, sex, and smoking history. Time-to-event end point analyses were performed using stratified log-rank tests. Medians and landmark survival rates were estimated using the Kaplan-Meier method.

RESULTS Seven hundred and nine of 713 randomly assigned patients received durvalumab (473 of 476) or placebo (236 of 237). As of January 11, 2021 (median follow-up, 34.2 months [all patients]; 61.6 months [censored patients]), updated OS (stratified HR, 0.72; 95% CI, 0.59 to 0.89; median, 47.5 *v* 29.1 months) and PFS (stratified HR, 0.55; 95% CI, 0.45 to 0.68; median, 16.9 *v* 5.6 months) remained consistent with the primary analyses. Estimated 5-year rates (95% CI) for durvalumab and placebo were 42.9% (38.2 to 47.4) versus 33.4% (27.3 to 39.6) for OS and 33.1% (28.0 to 38.2) versus 19.0% (13.6 to 25.2) for PFS.

CONCLUSION These updated analyses demonstrate robust and sustained OS and durable PFS benefit with durvalumab after chemoradiotherapy. An estimated 42.9% of patients randomly assigned to durvalumab remain alive at 5 years and 33.1% of patients randomly assigned to durvalumab remain alive and free of disease progression, establishing a new benchmark for standard of care in this setting.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

In the phase III, placebo-controlled PACIFIC trial of patients with unresectable, stage III non–small-cell lung cancer (NSCLC) whose disease had not progressed after platinum-based concurrent chemoradiotherapy (CRT), administration of durvalumab (a programmed cell death-ligand 1 [PD-L1] inhibitor) for up to 12 months improved overall survival (OS; stratified hazard ratio [HR], 0.68; 95% CI, 0.53 to 0.87; $P = .00251$; March 22, 2018 data cutoff [DCO]) and progression-free survival (PFS; stratified HR, 0.52; 95% CI, 0.42 to 0.65; $P < .0001$; February 13, 2017 DCO).[1-3] This degree of benefit with durvalumab versus placebo remained consistent at subsequent updates.[4,5] Furthermore, durvalumab exhibited a manageable safety profile and did not detrimentally affect patient-reported outcomes compared with placebo.[1,2,6] Durvalumab received global approvals on the basis of these findings,[3,7,8] establishing consolidation durvalumab after CRT (the PACIFIC regimen) as standard of care (SoC) for patients with unresectable, stage III NSCLC.

Historically, SoC was CRT followed by observation alone; however, this was associated with poor long-term survival.[9-12] There was no evidence that survival could be improved with induction or consolidation chemotherapy, consolidation therapy with other systemic

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CONTEXT

Key Objective

The phase III PACIFIC trial of patients with unresectable, stage III non–small-cell lung cancer whose disease had not progressed after chemoradiotherapy was, to our knowledge, the first study to demonstrate a survival advantage with immunotherapy in a curative-intent setting. Both primary end points of overall survival (OS) and progression-free survival (PFS) were improved with the programmed cell death-ligand 1 inhibitor durvalumab versus placebo. To provide insights into long-term outcomes, we report updated survival analyses, approximately 5 years after the last patient was randomly assigned.

Knowledge Generated

Updated OS and PFS remained consistent with the primary analyses; of patients randomly assigned to durvalumab, an estimated 42.9% remain alive at 5 years and 33.1% remain alive and progression-free. Consistent with prior reports, OS and PFS benefit continued to favor durvalumab over placebo in all prespecified patient subgroups.

Relevance

The findings support the continued use of consolidation durvalumab after chemoradiotherapy as the standard of care for patients with unresectable, stage III non–small-cell lung cancer.

anticancer agents, or by escalating the radiation dose.[11,13-17] As the first study to demonstrate a survival advantage with immunotherapy in a curative-intent setting, PACIFIC represents a landmark advancement in the treatment of this population.

To provide insights into long-term outcomes from PACIFIC, we report updated, exploratory analyses on the basis of the January 11, 2021 DCO (approximately 5 years after the last patient was randomly assigned), including updates to the primary analyses of OS and PFS with durvalumab versus placebo as well as updates to key secondary end points. Furthermore, we report new exploratory analyses that examine the prognostic association of baseline factors (other than assigned study treatment) with OS and PFS.

METHODS

Study Design

The design of PACIFIC is published elsewhere.[1,2] Patients with a WHO performance status (PS) of 0 or 1 and histologically or cytologically documented stage III (7th edition of the American Joint Committee on Cancer staging manual), unresectable NSCLC who had received concurrent CRT ($\geq$ 2 cycles; total prescription radiation dose typically 60 to 66 Gy in 30 to 33 fractions)[18] without disease progression were randomly assigned 1-42 days after CRT. Patients with unresolved grade $>$ 2 toxicities (Common Terminology Criteria for Adverse Events [AEs] v4.03) or grade $\geq$ 2 pneumonitis and/or radiation pneumonitis from prior CRT were excluded. Tumor tissue collection was not required nor was enrollment restricted by PD-L1 expression level or oncogenic driver gene aberration status. Additional details of the work-up required to confirm diagnosis are provided in Appendix 1 (online only; also see the Data Supplement [online only]).

Patients were randomly assigned (2:1), stratified by age ($<$ 65 *v* $\geq$ 65 years), sex, and smoking history (current or former smoker *v* never smoked), to durvalumab (10 mg/kg intravenously) or placebo, administered once every 2 weeks for up to 12 months; study treatment was discontinued if there was confirmed disease progression, initiation of alternative anticancer therapy, or the patient experienced unacceptable toxicity or withdrew consent. Patients were followed for survival after discontinuing study treatment. The study Protocol and amendments were approved by the relevant ethics committees. The study was performed in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice and the Declaration of Helsinki.

End Points and Assessments

We updated the primary analyses of OS and PFS (RECIST v1.1; assessed by blinded independent central review [BICR]) with durvalumab versus placebo in the intent-to-treat (ITT) population. Updated analyses of OS and PFS in exploratory subgroups defined by prespecified baseline factors (demographics, clinicopathologic features, and prior CRT-related variables), including PD-L1 expression on tumor cells (TCs) on the basis of testing of archived (pre-CRT) tumor tissue scored at a prespecified (25%) threshold (Ventana SP263 Immunohistochemistry Assay), were also performed.[1,2] We also updated analyses of additional PD-L1 subgroups defined by a post hoc (1%) threshold.[3,19]

Other updated end points include time to death or distant metastasis (TTDM; BICR), objective response rate (ORR; BICR), duration of response (BICR), incidence of new lesions (BICR), times to first (TFST) and second (TSST) subsequent therapy or death, and types of postdiscontinuation disease-related anticancer therapies administered.

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In addition, we performed a new exploratory, post hoc analysis of time to second progression (ie, time from random assignment to the earliest of the progression events subsequent to that used for PFS analysis) in patients who received durvalumab retreatment. Time to second progression was investigator-assessed per local standard practice and could include objective progression (assessed radiologically), symptomatic progression, or death.

Finally, we performed new exploratory, post hoc analyses to examine the prognostic association of baseline factors (other than assigned study treatment) with OS and PFS (BICR) in the ITT population; this was to identify factors other than study treatment that may associate with better or worse survival in the PACIFIC trial cohort.

Statistical Analysis

For time-to-event end points, analyses comparing durvalumab with placebo (ITT population) were performed using log-rank tests stratified using the same factors used to stratify patients at random assignment; this was for consistency with the original analyses.[1,2] Unstratified Cox regression models (with no adjustment for multiple comparisons) were used for subgroup analyses. Medians and landmark rates (eg, 5-year OS) were estimated by Kaplan-Meier method.

The prognostic association of baseline factors (other than assigned study treatment) with OS and PFS was analyzed using univariate and multivariable Cox regression models, as described in Appendix 1.

RESULTS

Patients

A total of 709 of 713 randomly assigned patients received study treatment in the durvalumab (473 of 476) and placebo arms (236 of 237). The last patient had completed protocol-defined study treatment in May 2017. Baseline characteristics were well balanced, as reported previously.[1,2]

As of January 11, 2021, 419 of 713 (58.8%) patients had died, including 264 of 476 (55.5%) and 155 of 237 (65.4%) patients who were randomly assigned to durvalumab and placebo, respectively (Fig 1); a breakdown of the attribution of deaths to disease progression and/or AEs is provided (Appendix Table A1, online only). Median duration of follow-up was 34.2 months (range, 0.2-74.7 months) for all randomly assigned patients and 61.6 months (0.4-74.7 months) for censored patients (ie, patients last known to be alive). Overall, 49.0% and 34.7% of patients randomly assigned to durvalumab and placebo completed 12 months of study treatment, respectively; 31.3% versus 49.6% discontinued because of disease progression and 15.4% versus 9.7% discontinued because of AEs.

OS and PFS With Durvalumab Versus Placebo

In total, 120 additional deaths were reported since the primary OS analysis (March 22, 2018 DCO); 23 were reported since the last update of OS (March 20, 2020 DCO). Updated OS was consistent with the primary analysis, with a 28% reduction in the risk of death with durvalumab versus placebo (stratified HR, 0.72; 95% CI, 0.59 to 0.89; Fig 2A).[2,3] Median OS was 47.5 months with durvalumab versus 29.1 months with placebo. The estimated 5-year OS rate was 42.9% with durvalumab versus 33.4% with placebo.

In total, 72 additional PFS events (BICR) were reported since the primary PFS analysis (February 13, 2017 DCO); three were reported since the last update of PFS (March 20, 2020 DCO). Updated PFS was consistent with the primary analysis, with a 45% reduction in the risk of disease progression or death with durvalumab versus placebo (stratified HR, 0.55; 95% CI, 0.45 to 0.68; Fig 2B).[1] Median PFS was 16.9 months with durvalumab versus 5.6 months with placebo. The estimated 5-year PFS rate was 33.1% with durvalumab versus 19.0% with placebo.

Updated OS and PFS (BICR) for patient subgroups were consistent with previous reports (Fig 3 and Appendix Fig A1, online only).[1,2,5,19] OS and PFS benefit favored durvalumab versus placebo across all PD-L1 subgroups, with the exception of OS in patients with PD-L1 TC expression $< 1\%$ (HR, 1.15; 95% CI, 0.75 to 1.75). Kaplan-Meier curves for durvalumab versus placebo in PD-L1 subgroups are provided (Appendix Figs A2 and A3, online only).

TTDM and the Incidence of New Lesions

Updated TTDM (BICR) was consistent with previous analyses of this end point (on the basis of the February 13, 2017 and March 20, 2020 DCOs), with a 41% reduction in the risk of death or distant metastasis with durvalumab versus placebo (stratified HR, 0.59; 95% CI, 0.47 to 0.74; Fig 4).[1,2] The incidence of new lesions (BICR) was proportionally lower with durvalumab (24.2%) versus placebo (33.3%); brain metastases were detected in 6.5% versus 11.8% of patients, respectively (imaging assessments of the CNS were performed at the investigator's discretion; Table 1).

Antitumor Response

ORR (BICR) was proportionally higher with durvalumab (29.8%) versus placebo (18.3%); median duration of response was not reached with durvalumab versus 18.4 months with placebo (Appendix Table A2, online only). Among patients with an objective response, 81.1%, 58.7%, and 51.1% were estimated to have an ongoing response at 1, 3, and 5 years, respectively, with durvalumab, versus 60.5% and 34.5% at 1 and 3 years, respectively, with placebo (Appendix Table A2); the 5-year rate for placebo was not estimable as no patients with

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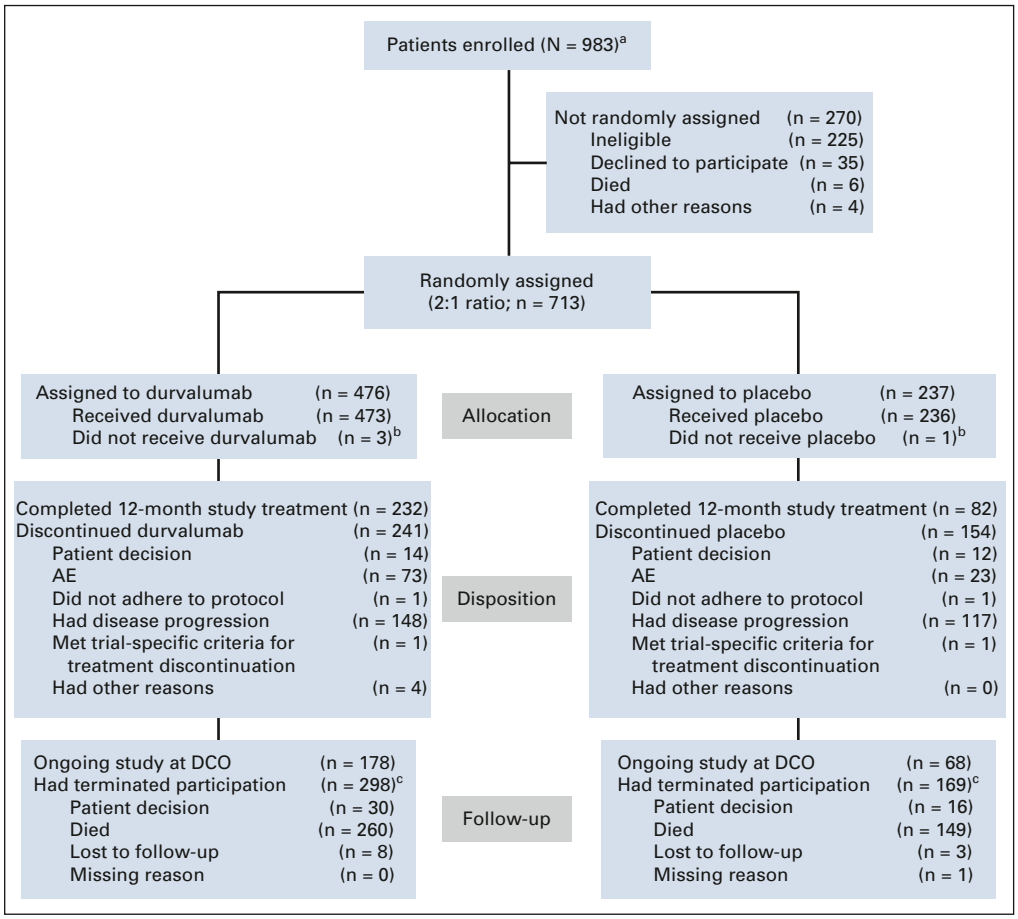


FIG 1. CONSORT diagram. Study data collected up to the DCO date of January 11, 2021. Patients who completed 12 months of study treatment are those for whom the electronic case report form showed that they had received the maximum number of cycles of study treatment. [a]Informed consent received. [b]Four patients did not receive their assigned study treatment because of neutropenia (n = 1), worsening chronic obstructive pulmonary disease (n = 1), and patient decision (n = 2). [c]Nine patients (durvalumab, n = 4; placebo, n = 5) who terminated the study because of patient decision have subsequently died; one additional patient (placebo arm) with missing termination reason has subsequently died. AE, adverse event; DCO, data cutoff.

ongoing responses in the placebo arm had reached this landmark.

Durvalumab Retreatment

Durvalumab retreatment (at the investigator's discretion) was permitted for patients who completed the initial 12 months of treatment and had disease control at the end of the 12 months, provided their disease progressed during follow-up and they had not received another systemic anticancer therapy. Overall, 34 of 476 (7.1%) patients in the durvalumab arm received retreatment; 4 of 34 (11.8%) completed 12 months of retreatment and 23 of 34 (67.6%) discontinued (7 of 34 [20.6%] were ongoing retreatment at DCO). Median time to second progression (measured from random assignment) among retreated patients was 48.0 months (95% CI, 38.9 to 64.6); 100% (95% CI, 100 to 100), 50.9% (95% CI, 32.8 to 66.5), and 34.0% (95% CI, 18.0 to 50.6) of patients were estimated to be alive and without a second progression at 2, 4, and 5 years, respectively. Nevertheless, this post hoc analysis is difficult to interpret in the absence of a complementary subgroup against which to draw comparisons. Moreover, second progression was investigator-assessed per local practice and only a small number of patients received retreatment, further limiting interpretation.

Subsequent Anticancer Therapy

Overall, 48.5% and 58.6% of patients randomly assigned to durvalumab and placebo, respectively, received ≥ 1 subsequent, disease-related, anticancer therapy (after discontinuing study treatment), most commonly chemotherapy (durvalumab, 33.0%; placebo, 35.9%; Table 2). Subsequent immunotherapy was less commonly used among patients randomly assigned to durvalumab (12.6%) versus placebo (29.1%). TFST (stratified HR, 0.65; 95% CI, 0.53 to 0.79) and TSST (stratified HR, 0.65; 95% CI, 0.53

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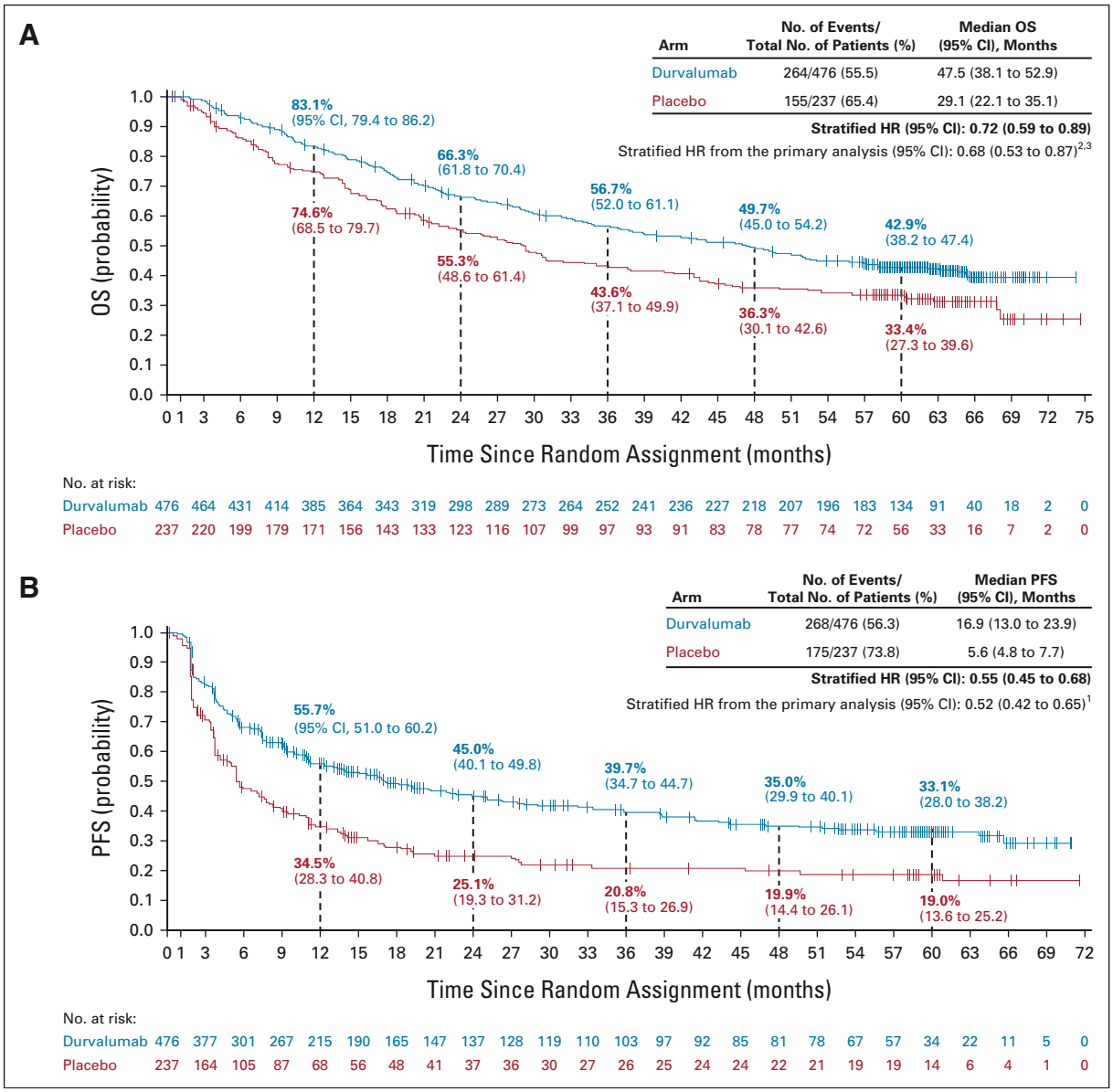


FIG 2. Updated (A) OS and (B) PFS (blinded independent central review) in the intent-to-treat population. The vertical dashed lines indicate yearly landmarks; the associated numerical values represent the OS and PFS rates at the landmark. OS was defined as time from random assignment until death from any cause. PFS was defined as time from random assignment to the date of the first documented event of tumor progression or death in the absence of disease progression. For PFS, patients who had not progressed or died at the time of the data cutoff were censored at the time of their last evaluable RECIST assessment; however, if the patient progressed or died after ≥ 2 missed visits, they were censored at the time of the latest evaluable RECIST assessment before the two missed visits. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

to 0.80) were improved with durvalumab versus placebo (Appendix Fig A4, online only), consistent with the previous analyses of these end points.[2,4,5]

Prognostic Baseline Factors for OS and PFS

Univariate analyses identified younger age (*v* ≥ 65 years), objective tumor response during prior CRT (*v* stable disease), nonsquamous tumor histologic type (*v* squamous), WHO PS 0 (*v* 1), cisplatin use during prior CRT (*v* carboplatin), and Asian race (*v* White) as favorable prognostic factors for OS (Appendix Table A3, online only). Nonsquamous tumor histologic type and Asian race were also prognostic for better PFS in the univariate analyses (Appendix Table A4, online only).

Multivariable analyses demonstrated that younger age, nonsquamous tumor histologic type, WHO PS 0, and Asian race remained favorable prognostic factors for OS (with female sex identified as an additional factor; Table 3),

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Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
All patients	264/476 (55.5)	155/237 (65.4)	0.72 (0.59 to 0.87)
Sex			
Male	192/334 (57.5)	112/166 (67.5)	0.75 (0.59 to 0.95)
Female	72/142 (50.7)	43/71 (60.6)	0.64 (0.44 to 0.94)
Age at random assignment			
< 65 years	130/261 (49.8)	79/130 (60.8)	0.66 (0.50 to 0.87)
≥ 65 years	134/215 (62.3)	76/107 (71.0)	0.79 (0.60 to 1.05)
Smoking status			
Smoker	244/433 (56.4)	140/216 (64.8)	0.75 (0.61 to 0.93)
Nonsmoker	20/43 (46.5)	15/21 (71.4)	0.42 (0.21 to 0.82)
NSCLC disease stage			
IIIA	136/252 (54.0)	91/125 (72.8)	0.61 (0.47 to 0.80)
IIIB	121/212 (57.1)	61/107 (57.0)	0.86 (0.63 to 1.17)
Tumor histologic type			
Squamous	138/224 (61.6)	67/102 (65.7)	0.82 (0.61 to 1.09)
All other	126/252 (50.0)	88/135 (65.2)	0.62 (0.47 to 0.81)
Best response to prior treatment			
Complete response	6/9 (66.7)	3/7 (42.9)	Not calculated[a]
Partial response	118/237 (49.8)	68/112 (60.7)	0.71 (0.52 to 0.95)
Stable disease	135/223 (60.5)	81/115 (70.4)	0.70 (0.53 to 0.92)
Prior chemotherapy type			
Gemcitabine-based	5/9 (55.6)	2/5 (40.0)	Not calculated[a]
Non–gemcitabine-based	259/467 (55.5)	153/232 (65.9)	0.70 (0.58 to 0.86)
Cisplatin	134/266 (50.4)	81/129 (62.8)	0.65 (0.50 to 0.86)
Carboplatin	121/199 (60.8)	69/102 (67.6)	0.81 (0.60 to 1.09)
Cisplatin and carboplatin	6/8 (75.0)	4/5 (80.0)	Not calculated[a]
Last radiation to random assignment			
< 14 days	64/120 (53.3)	43/62 (69.4)	0.54 (0.37 to 0.80)
≥ 14 days	200/356 (56.2)	112/175 (64.0)	0.79 (0.63 to 1.00)
WHO PS			
0 – Normal	121/234 (51.7)	65/114 (57.0)	0.84 (0.62 to 1.14)
1 – Restricted[b]	143/242 (59.1)	90/123 (73.2)	0.62 (0.47 to 0.80)
Region			
Asia	54/109 (49.5)	37/68 (54.4)	0.79 (0.52 to 1.20)
Europe	125/217 (57.6)	64/102 (62.7)	0.84 (0.62 to 1.14)
North and South America	85/150 (56.7)	54/67 (80.6)	0.47 (0.34 to 0.67)
Race			
White	200/337 (59.3)	110/157 (70.1)	0.72 (0.57 to 0.91)
Black or African American	5/12 (41.7)	2/2 (100)	Not calculated[a]
Asian	56/120 (46.7)	39/72 (54.2)	0.73 (0.48 to 1.09)
Other[c]	3/6 (50.0)	4/6 (66.7)	Not calculated[a]
EGFR or *ALK* aberration status			
Positive[d]	17/29 (58.6)	8/14 (57.1)	0.85 (0.37 to 1.97)
Negative	166/317 (52.4)	109/165 (66.1)	0.66 (0.52 to 0.84)
Unknown	81/130 (62.3)	38/58 (65.5)	0.85 (0.57 to 1.24)
PD-L1 expression level			
≥ 25%	51/115 (44.3)	27/44 (61.4)	0.52 (0.32 to 0.82)
< 25%	111/187 (59.4)	64/105 (61.0)	0.90 (0.67 to 1.23)
Unknown	102/174 (58.6)	64/88 (72.7)	0.68 (0.50 to 0.93)
1%-24% (post hoc analysis)	52/97 (53.6)	29/47 (61.7)	0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis)	103/212 (48.6)	56/91 (61.5)	0.61 (0.44 to 0.85)
< 1% (post hoc analysis)	59/90 (65.6)	35/58 (60.3)	1.15 (0.75 to 1.75)

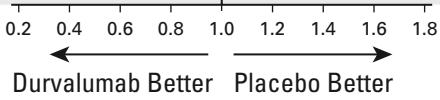


FIG 3. Updated OS by prespecified and exploratory, post hoc subgroups. [a]HRs and 95% CIs were not calculated if the subgroup had < 20 events. [b]Three patients with missing WHO PS were included in the PS 1 subgroup. [c]The other race category includes American Indian or Alaskan Native (n = 9), Native Hawaiian or Other Pacific Islander (n = 2), and Other (n = 1). [d]The subgroup includes 35 patients with tumors harboring *EGFR* mutations and, on the basis of local testing, eight patients with tumors harboring *ALK* alterations. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; PS, performance status.

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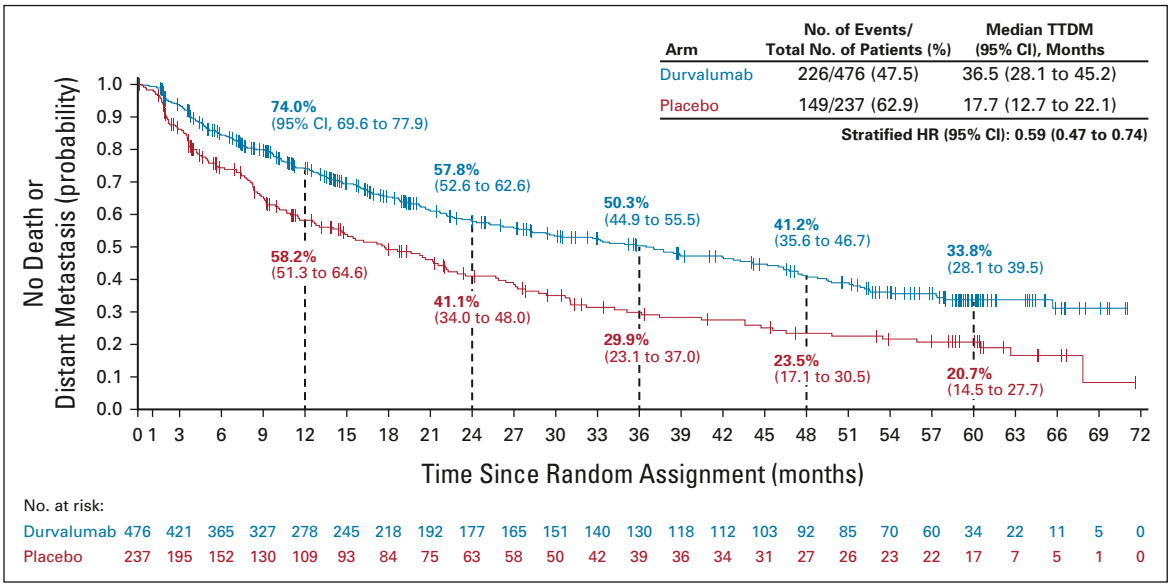


FIG 4. Updated TTDM (blinded independent central review) in the intent-to-treat population. The vertical dashed lines indicate yearly landmarks; the associated numerical values represent the TTDM rates at the landmark. TTDM was defined as time from random assignment until the first date of distant metastasis or death in the absence of distant metastasis. HR, hazard ratio; TTDM, time to death or distant metastasis.

indicating that they are independent of one another and of the assigned study treatment. Nonsquamous tumor histologic type and Asian race also remained prognostic factors for improved PFS (with stage IIIA [*v* IIIB] disease identified as an additional factor; Appendix Table A5, online only).

There was no change in the OS and PFS benefit observed with durvalumab versus placebo when accounting for differences in other baseline factors between treatment arms (Table 3 and Appendix Table A5): the treatment effects for OS (HR, 0.71; 95% CI, 0.58 to 0.87) and PFS (HR, 0.56; 95% CI, 0.46 to 0.68) were consistent with the main analyses of these end points (Fig 2).

TABLE 1. Incidence of New Lesions (blinded independent central review) in the Intent-to-Treat Population

New Lesion Site[a]	Durvalumab (n = 476)	Placebo (n = 237)
Any, No. (%)	115 (24.2)	79 (33.3)
Lung	64 (13.4)	43 (18.1)
Lymph nodes	35 (7.4)	28 (11.8)
Brain	31 (6.5)	28 (11.8)
Liver	11 (2.3)	8 (3.4)
Bone	9 (1.9)	8 (3.4)
Adrenal	3 (0.6)	5 (2.1)
Others[b]	10 (2.1)	4 (1.7)

[a]A patient could have more than one new lesion site.
[b]Includes lesions in the biliary tract, chest wall, heart, ovary, pancreas, pericardium, retroperitoneum, skin, spleen, uterus, and other (unspecified).

DISCUSSION

The estimated 5-year OS and PFS rates were 42.9% and 33.1% for durvalumab and 33.4% and 19.0% for placebo, respectively. Together with the primary analyses,[1,2] these updated results demonstrate robust and sustained survival benefit with durvalumab following CRT. Moreover, updates to secondary end points continue to demonstrate durable antitumor response and a reduced frequency of metastases with durvalumab. These findings support the continued use of the PACIFIC regimen as SoC for patients with unresectable, stage III NSCLC and are corroborated by the results of real-world studies.[20-22]

In PACIFIC, random assignment occurred after the completion of CRT and patients must have been free of disease progression, and have recovered from early CRT-related toxicities, as a condition of enrollment. Thus, the results reported here cannot be directly compared with the results of historic studies reporting long-term outcomes with CRT.

ORR (BICR) was approximately 10% higher with durvalumab versus placebo, and approximately half of the patients who responded to durvalumab had ongoing responses at 5 years. This biologically important and clinically relevant finding provides long-term evidence for a sustained improvement in local disease control with durvalumab. Furthermore, it supports a role for durvalumab in the treatment of patients with earlier-stage cancer.

Consistent with previous reports,[1,2,4,5] OS and PFS benefit continued to favor durvalumab over placebo in all

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TABLE 2. Postdiscontinuation Disease-Related Anticancer Therapy in the Intent-to-Treat Population

Type of Therapy	Durvalumab (n = 476)	Placebo (n = 237)
Any therapy, No. (%)	231 (48.5)	139 (58.6)
Radiotherapy	97 (20.4)	61 (25.7)
Immunotherapy[a]	60 (12.6)	69 (29.1)
Cytotoxic chemotherapy	157 (33.0)	85 (35.9)
Other systemic therapies[b]	53 (11.1)	35 (14.8)
Other	2 (0.4)[c]	0

[a]Primarily nivolumab (durvalumab, n = 37; placebo, n = 53) or pembrolizumab (durvalumab, n = 16; placebo, n = 10).
[b]Including tyrosine kinase inhibitors, among other treatments.
[c]Uncoded.

prespecified patient subgroups in the updated analyses, supporting the use of the PACIFIC regimen in a broad population. Previous exploratory analyses from PACIFIC also demonstrated consistent benefit with durvalumab across subgroups defined by additional (post hoc) CRT-related variables, including the nonplatinum chemotherapy agents used, the total radiation dose, and the use of induction chemotherapy before CRT.[18] PACIFIC was designed to assess clinical outcomes with durvalumab in an all-comers population, preventing definitive conclusions for subgroups. These subgroup analyses are limited by small sample sizes and a resulting lack of statistical power; for example, survival benefit with durvalumab among patients with epidermal growth factor receptor (*EGFR*) or

TABLE 3. Multivariable Cox Regression Analysis of Prognostic Baseline Factors for Overall Survival in the Intent-to-Treat Population

	Comparator		Reference		
Baseline Variable	Group	No. of Events/Total No. of Patients (%)	Group	No. of Events/Total No. of Patients (%)	HR (95% CI)
Treatment arm	Durvalumab	264/476 (55.5)	Placebo	155/237 (65.4)	0.71 (0.58 to 0.87)[a]
Age, years	≥ 65	210/322 (65.2)	< 65	209/391 (53.5)	1.30 (1.06 to 1.59)[a]
Disease stage[b]	IIIB	182/319 (57.1)	IIIA	227/377 (60.2)	1.03 (0.84 to 1.26)
Best response to prior treatment[c]	CR/PR	195/365 (53.4)	SD	216/338 (63.9)	0.88 (0.72 to 1.08)
Tumor histologic type	Squamous	205/326 (62.9)	Nonsquamous	214/387 (55.3)	1.28 (1.04 to 1.58)[a]
WHO PS	1[d]	233/365 (63.8)	0	186/348 (53.4)	1.23 (1.01 to 1.50)[a]
Prior platinum CT agent[e]	Cisplatin	215/395 (54.4)	Carboplatin	190/301 (63.1)	0.84 (0.69 to 1.03)
Race	Asian	95/192 (49.5)	White	310/494 (62.8)	0.63 (0.49 to 0.81)[a]
	Black or African American	7/14 (50.0)			0.81 (0.38 to 1.73)
	Other[f]	7/13 (53.8)			0.91 (0.41 to 1.99)
Sex	Male	304/500 (60.8)	Female	115/213 (54.0)	1.27 (1.01 to 1.61)[a]
Smoking status	Smoker	384/649 (59.2)	Nonsmoker	35/64 (54.7)	0.83 (0.56 to 1.22)
Time from CRT to random assignment, days	≥ 14	312/531 (58.8)	< 14	107/182 (58.8)	0.97 (0.77 to 1.22)
EGFR or *ALK* aberration status	Positive[g]	25/43 (58.1)	Negative	275/482 (57.1)	1.06 (0.69 to 1.64)
	Unknown	119/188 (63.3)			0.95 (0.73 to 1.23)
PD-L1 expression level	TC ≥ 25%	78/159 (49.1)	TC < 25%	175/292 (59.9)	0.82 (0.62 to 1.07)
	Unknown	166/262 (63.4)			1.19 (0.92 to 1.54)

NOTE. Except where stated otherwise, missing values were categorized as unknown for modeling purposes (no patients were omitted).
Abbreviations: ALK, anaplastic lymphoma kinase; CR, complete response; CRT, chemoradiotherapy; CT, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; PD-L1, programmed cell death-ligand 1; PR, partial response; PS, performance status; SD, stable disease; TC, tumor cell.
[a]HR < 1 favors the comparator group over the reference group; the identified prognostic factors are those for which the HR 95% CI does not cross one.
[b]Seventeen patients with stage IV (n = 4) or stage I/II (n = 13) disease were categorized as other (data not shown).
[c]Best response was categorized as other for 10 patients (data not shown); this category includes progression (n = 2), nonevaluable (n = 7), and not applicable (n = 1).
[d]WHO PS 1 group includes three patients with missing WHO PS data.
[e]Platinum chemotherapy agent was unknown for four patients, and 13 patients received both carboplatin and cisplatin (data not shown).
[f]Category includes American Indian or Alaskan Native (n = 9), Native Hawaiian or Other Pacific Islander (n = 2), Other (n = 1), and Missing (n = 1).
[g]The subgroup includes 35 patients with tumors harboring *EGFR* mutations and, on the basis of local testing, eight patients with tumors harboring *ALK* alterations.

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anaplastic lymphoma kinase (*ALK*) aberration–positive tumors is uncertain, considering that the subgroup contained only 43 patients and *EGFR* and *ALK* status was unknown for 26.4% of all randomly assigned patients. Moreover, as random assignment was not stratified for most of the subgroup factors, the results may be affected by intersubgroup and intrasubgroup imbalances in other baseline factors. Indeed, the new multivariable analyses reported with this update identified several baseline factors that were prognostic for OS and/or PFS outcomes regardless of whether patients were assigned to receive durvalumab or placebo (including age, tumor histologic type, WHO PS, race, sex, and disease stage). The independent association of these factors with survival outcomes was not unexpected, and the factors that were identified are broadly aligned with the factors reported by other studies in the stage III NSCLC setting.[23]

Survival benefit favored durvalumab versus placebo across PD-L1 subgroups; the only exception was OS in the post hoc subgroup with PD-L1 TC expression < 1% (HR, 1.15; 95% CI, 0.75 to 1.75), although PFS still favored durvalumab in this subgroup (HR, 0.80; 95% CI, 0.53 to 1.20). Numerous limitations preclude definitive conclusions regarding the impact of tumoral PD-L1 expression on outcomes with the PACIFIC regimen (as described elsewhere).[19,24] These include the use of tumor samples collected before CRT to determine PD-L1 expression (as CRT may upregulate PD-L1 expression), incomplete provision of tumor tissue (PD-L1–assessable samples were not available for 37% of randomly assigned patients), and the relatively small number of patients with PD-L1 TC expression < 1% (n = 148). Furthermore, the placebo arm appeared to overperform with respect to OS among patients with PD-L1 TC expression < 1% compared with the full PACIFIC ITT population (and with other trials of CRT for unresectable, stage III NSCLC),[2,11,14,15] which may have been driven by imbalances in potentially prognostic baseline factors.[24]

Consistent with the considerable PFS benefit and fewer progression events observed with durvalumab, TFST was improved with durvalumab versus placebo, and fewer patients received subsequent anticancer treatment in the durvalumab arm. Durvalumab also improved TSST, and the treatment effect sizes for TFST and TSST were the same (HR, 0.65), suggesting that long-term survival benefit with durvalumab is largely driven by improvements in PFS and that between-arm differences in the use of salvage therapies did not meaningfully affect long-term survival benefit with durvalumab. Importantly, survival benefit was observed with durvalumab after CRT despite more patients receiving subsequent immunotherapy in the placebo arm.

Safety outcomes from PACIFIC were reported with the primary analyses and were not updated for this 5-year follow-up analysis as no patients remained on the 12-month study treatment beyond the time of the primary OS analysis (March 22, 2018 DCO).[2] At the time of the primary OS analysis, all-causality AEs of maximum toxicity grade 3/4 occurred in 30.5% and 26.1% (and fatal AEs in 4.4% and 6.4%) of patients receiving durvalumab and placebo, respectively; 15.4% and 9.8% discontinued durvalumab and placebo because of AEs, mostly pneumonitis, radiation pneumonitis, and pneumonia.[2] Analyses of patient-reported outcomes from PACIFIC found no evidence for a detrimental effect of up to 12 months of durvalumab treatment on symptoms, functioning, or global health status and quality of life, with the results being comparable to placebo.[6] Taken together, these data suggest that clinical benefit with the PACIFIC regimen can be achieved without compromising safety or patient-reported outcomes. Subsequent, exploratory analyses from PACIFIC demonstrated broadly consistent results for safety and patient-reported outcomes irrespective of PD-L1 expression level and CRT-related variables, suggesting that durvalumab treatment is well managed regardless of these baseline factors.[18,19,25]

Further research is required to determine the optimum duration of durvalumab treatment following CRT. Use of a 12-month treatment duration in PACIFIC was an empiric decision made on the basis of the regimen used in a phase I/II first-in-human study of durvalumab (NCT01693562; the source of most of the available safety data for durvalumab at the time PACIFIC was designed and the results of which supported further development of the dose and duration).[26]

Given the unprecedented nature of the findings with the PACIFIC regimen, studies have been initiated to investigate the use of durvalumab after sequential CRT or radiotherapy alone (for patients who are chemotherapy-ineligible), and durvalumab in combination with novel anticancer agents post-CRT, with the aim of further extending clinical benefit to more patients in this setting.[27] In addition, a placebo-controlled, phase III study is investigating durvalumab administered concurrently with CRT (followed by consolidative durvalumab).[27] Finally, because PACIFIC was the first trial to show a survival advantage with an immunotherapy in a curative-intent setting, it established the rationale for further investigation of durvalumab in other curative-intent settings across other cancers.[27]

In conclusion, these updated survival analyses demonstrate robust and sustained survival benefit with durvalumab after CRT. An estimated 42.9% of patients randomly assigned to durvalumab remain alive at 5 years and 33.1% of patients randomly assigned to durvalumab remain alive and free of disease progression, establishing a new benchmark for SoC in this setting.

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A complete list of the investigators in the PACIFIC trial is provided in Appendix 2 (online only).

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Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

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No other potential conflicts of interest were reported.

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APPENDIX 1. SUPPLEMENTARY METHODS

Confirmation of Stage III Non–Small-Cell Lung Cancer Diagnosis

Imaging of the chest and abdomen was required at baseline (following chemoradiotherapy [CRT] and before random assignment) for assessing tumor burden at baseline and follow-up visits. Computed tomography examination of the chest and abdomen (including the liver and adrenal glands) with contrast media administration was the preferred method but was not compulsory. Use of magnetic resonance imaging (MRI) was recommended only where computed tomography was not feasible, or it was medically contraindicated. Imaging of the CNS was optional (ie, performed at the investigator's discretion), and MRI was the preferred method. 18-fluorodeoxyglucose positron emission tomography (PET) was also optional, but was not recommended as the sole method for identifying lesions because of CRT-related inflammatory changes resulting in increased fluorodeoxyglucose uptake on a baseline scan performed within the screening period for the study (ie, within 1-42 days after CRT completion). Such scans would not have been very interpretable so closely following completion of CRT and, therefore, would not have typically met the image acquisition requirements for use of RECIST. However, use of baseline (post-CRT) PET imaging was distinct from, and should not be confused with, the standard diagnostic use of PET scans (and brain/CNS MRI) by investigators, before CRT, for purposes of disease staging (which was not collected in case report forms as part of the trial).

Analysis of the Prognostic Association of Baseline Factors With Overall Survival and Progression-Free Survival

The prognostic association of baseline factors (other than assigned study treatment) with overall survival and progression-free survival was analyzed using univariate and multivariable Cox regression models, with input variables aligned with the factors that were prespecified for comparing survival outcomes with durvalumab versus placebo in subgroups. Variable selection was not performed, and all variables were retained in the final models as there was no strong a priori rationale to exclude any specific prespecified variable (apart from region); moreover, data-driven variable selection may produce biased regression coefficients. An additional benefit of including all prespecified variables in the models is that the impact of each variable on the outcome is adjusted for the effect of all other prespecified variables.

The prespecified variables were checked for the proportional hazards assumption using the Grambsch-Therneau statistical test (Grambsch PA, Therneau TM: Biometrika 81:515-526, 1994). In both multivariable and univariate analyses, most tests indicated proportional hazards with the only exceptions being for a few subgroups with small numbers of patients (eg, patients with epidermal growth factor receptor or anaplastic lymphoma kinase aberrations and patients in the other race category), which makes the results for these subgroups difficult to interpret. Thus, there was no clear evidence of nonproportional hazards.

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Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
All patients	268/476 (56.3)	175/237 (73.8)	0.58 (0.48 to 0.70)
Sex			
Male	192/334 (57.5)	122/166 (73.5)	0.61 (0.48 to 0.76)
Female	76/142 (53.5)	53/71 (74.6)	0.52 (0.36 to 0.74)
Age at random assignment			
< 65 years	140/261 (53.6)	100/130 (76.9)	0.46 (0.36 to 0.60)
≥ 65 years	128/215 (59.5)	75/107 (70.1)	0.76 (0.57 to 1.01)
Smoking status			
Smoker	246/433 (56.8)	158/216 (73.1)	0.61 (0.50 to 0.75)
Nonsmoker	22/43 (51.2)	17/21 (81.0)	0.33 (0.17 to 0.63)
NSCLC disease stage			
IIIA	132/252 (52.4)	95/125 (76.0)	0.53 (0.40 to 0.69)
IIIB	130/212 (61.3)	77/107 (72.0)	0.64 (0.48 to 0.85)
Tumor histologic type			
Squamous	138/224 (61.6)	74/102 (72.5)	0.71 (0.54 to 0.94)
All other	130/252 (51.6)	101/135 (74.8)	0.48 (0.37 to 0.63)
Best response to prior treatment			
Complete response	5/9 (55.6)	4/7 (57.1)	Not calculated[a]
Partial response	126/237 (53.2)	85/112 (75.9)	0.56 (0.43 to 0.74)
Stable disease	133/223 (59.6)	84/115 (73.0)	0.57 (0.44 to 0.76)
Prior chemotherapy type			
Gemcitabine-based	4/9 (44.4)	3/5 (60.0)	Not calculated[a]
Non–gemcitabine-based	264/467 (56.5)	172/232 (74.1)	0.58 (0.48 to 0.70)
Cisplatin	(54.9) 94/129	94/129 (72.9)	0.55 (0.42 to 0.71)
Carboplatin	114/199 (57.3)	76/102 (74.5)	0.62 (0.47 to 0.83)
Cisplatin and carboplatin	5/8 (62.5)	4/5 (80.0)	Not calculated[a]
Last radiation to random assignment			
< 14 days	62/120 (51.7)	49/62 (79.0)	0.45 (0.31 to 0.66)
≥ 14 days	206/356 (57.9)	126/175 (72.0)	0.64 (0.51 to 0.80)
WHO PS			
0 – Normal	127/234 (54.3)	82/114 (71.9)	0.62 (0.47 to 0.82)
1 – Restricted[b]	141/242 (58.3)	93/123 (75.6)	0.54 (0.41 to 0.70)
Region			
Asia	58/109 (53.2)	48/68 (70.6)	0.60 (0.41 to 0.88)
Europe	131/217 (60.4)	76/102 (74.5)	0.61 (0.46 to 0.82)
North and South America	79/150 (52.7)	51/67 (76.1)	0.47 (0.33 to 0.67)
Race			
White	195/337 (57.9)	117/157 (74.5)	0.58 (0.46 to 0.73)
Black or African American	7/12 (58.3)	2/2 (100.0)	Not calculated[a]
Asian	62/120 (51.7)	51/72 (70.8)	0.57 (0.39 to 0.83)
Other[c]	3/6 (50.0)	5/6 (83.3)	Not calculated[a]
***EGFR* or *ALK* aberration status**			
Positive[d]	21/29 (72.4)	11/14 (78.6)	0.82 (0.39 to 1.71)
Negative	169/317 (53.3)	124/165 (75.2)	0.52 (0.41 to 0.65)
Unknown	78/130 (60.0)	40/58 (69.0)	0.74 (0.51 to 1.09)
PD-L1 expression level			
≥ 25%	61/115 (53.0)	33/44 (75.0)	0.44 (0.29 to 0.67)
< 25%	105/187 (56.1)	77/105 (73.3)	0.64 (0.48 to 0.86)
Unknown	102/174 (58.6)	65/88 (73.9)	0.60 (0.44 to 0.82)
1%-24% (post hoc analysis)	50/97 (51.5)	36/47 (76.6)	0.51 (0.33 to 0.78)
≥ 1% (post hoc analysis)	111/212 (52.4)	69/91 (75.8)	0.47 (0.35 to 0.64)
< 1% (post hoc analysis)	55/90 (61.1)	41/58 (70.7)	0.80 (0.53 to 1.20)

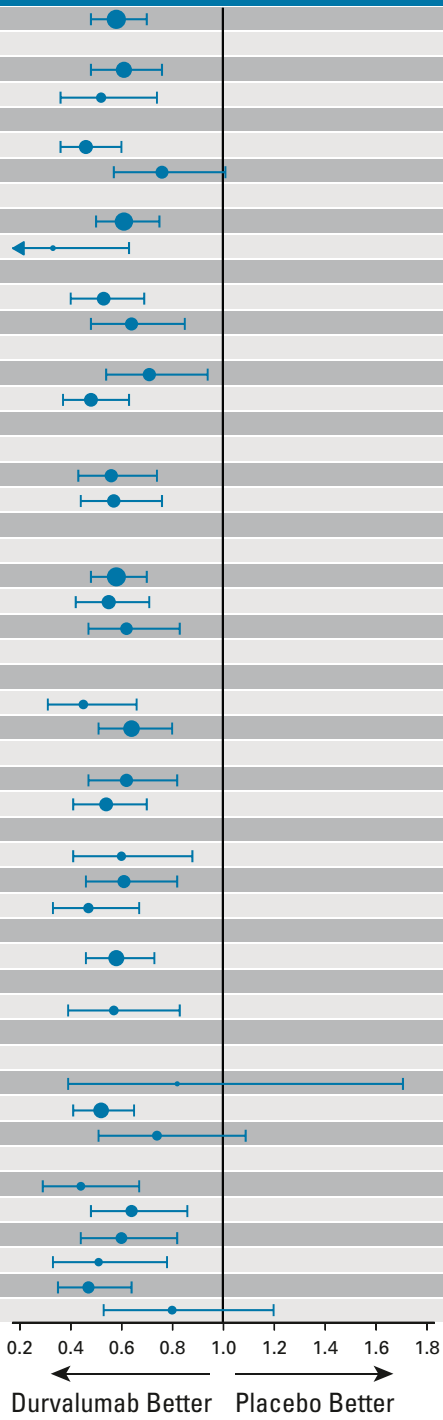


FIG A1. Updated PFS (blinded independent central review) by prespecified and exploratory, post hoc subgroups. [a]HRs and 95% CIs were not calculated if the subgroup had < 20 events. [b]Three patients with missing WHO PS were included in the PS 1 subgroup. [c]The other race category includes American Indian or Alaskan Native (n = 9), Native Hawaiian or Other Pacific Islander (n = 2), and Other (n = 1). [d]The subgroup includes 35 patients with tumors harboring *EGFR* mutations and, on the basis of local testing, eight patients with tumors harboring *ALK* alterations. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non–small-cell lung cancer; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PS, performance status.

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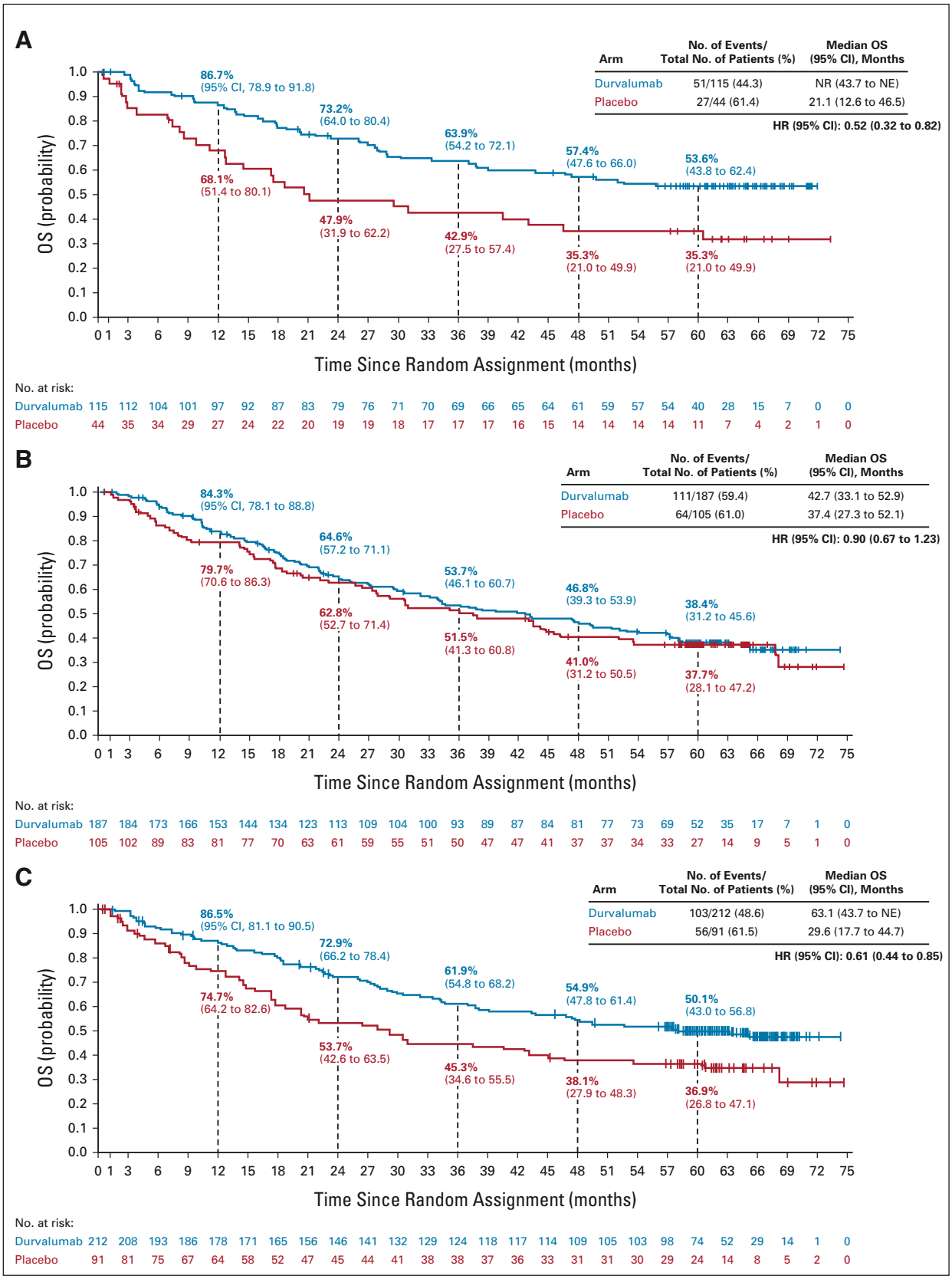


FIG A2. Updated OS by tumor PD-L1 expression level: (A) PD-L1 TC ≥ 25%, (B) PD-L1 TC < 25%, (C) PD-L1 TC ≥ 1%, (D) PD-L1 TC < 1%, (E) unknown PD-L1 status, and (F) PD-L1 TC 1%-24%. The vertical dashed lines indicate yearly landmarks; the associated numerical values represent the OS rates at the landmark. HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival; PD-L1, programmed cell death-ligand 1; TC, tumor cell. (continued on following page)

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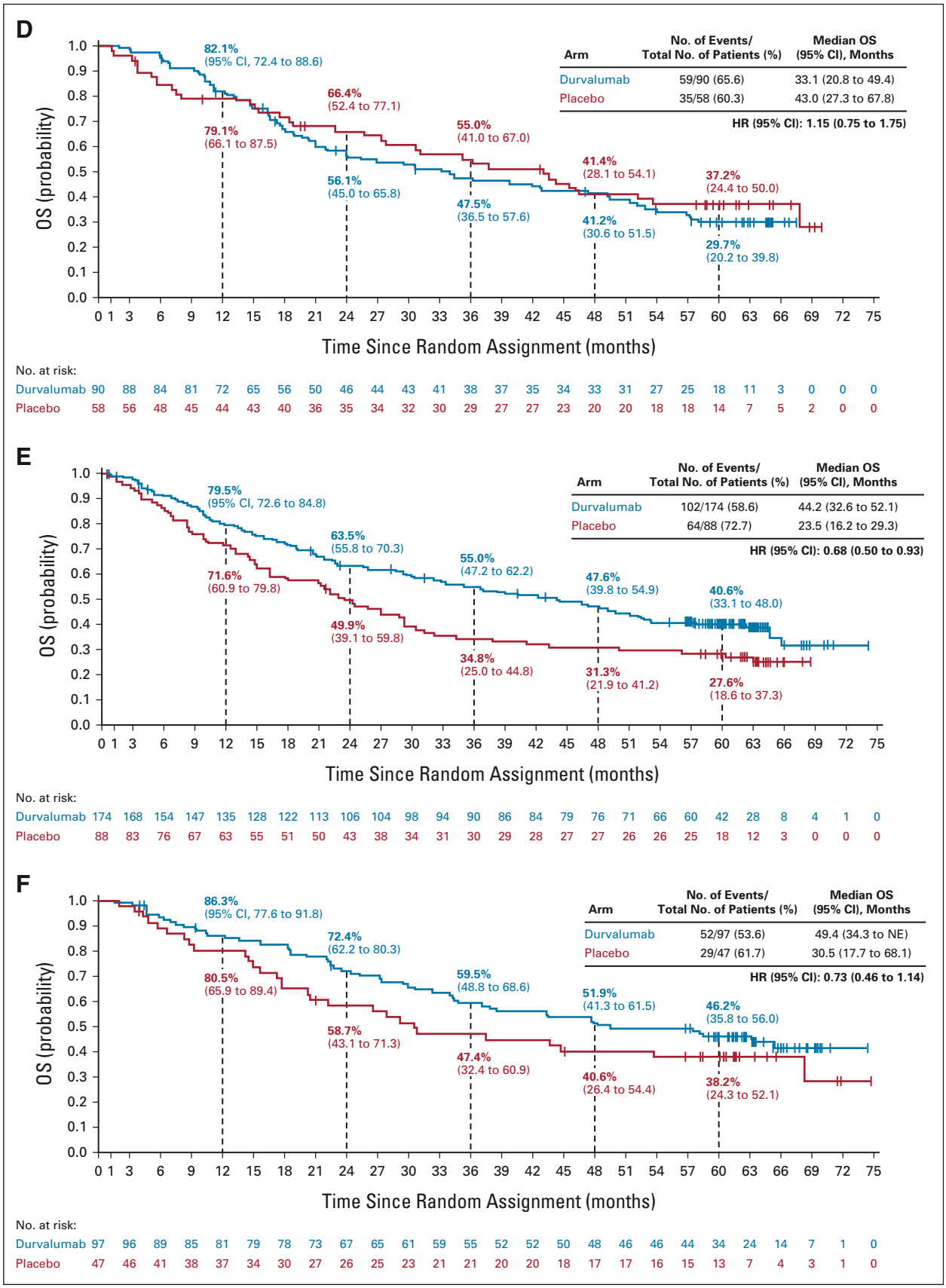


FIG A2. (Continued).

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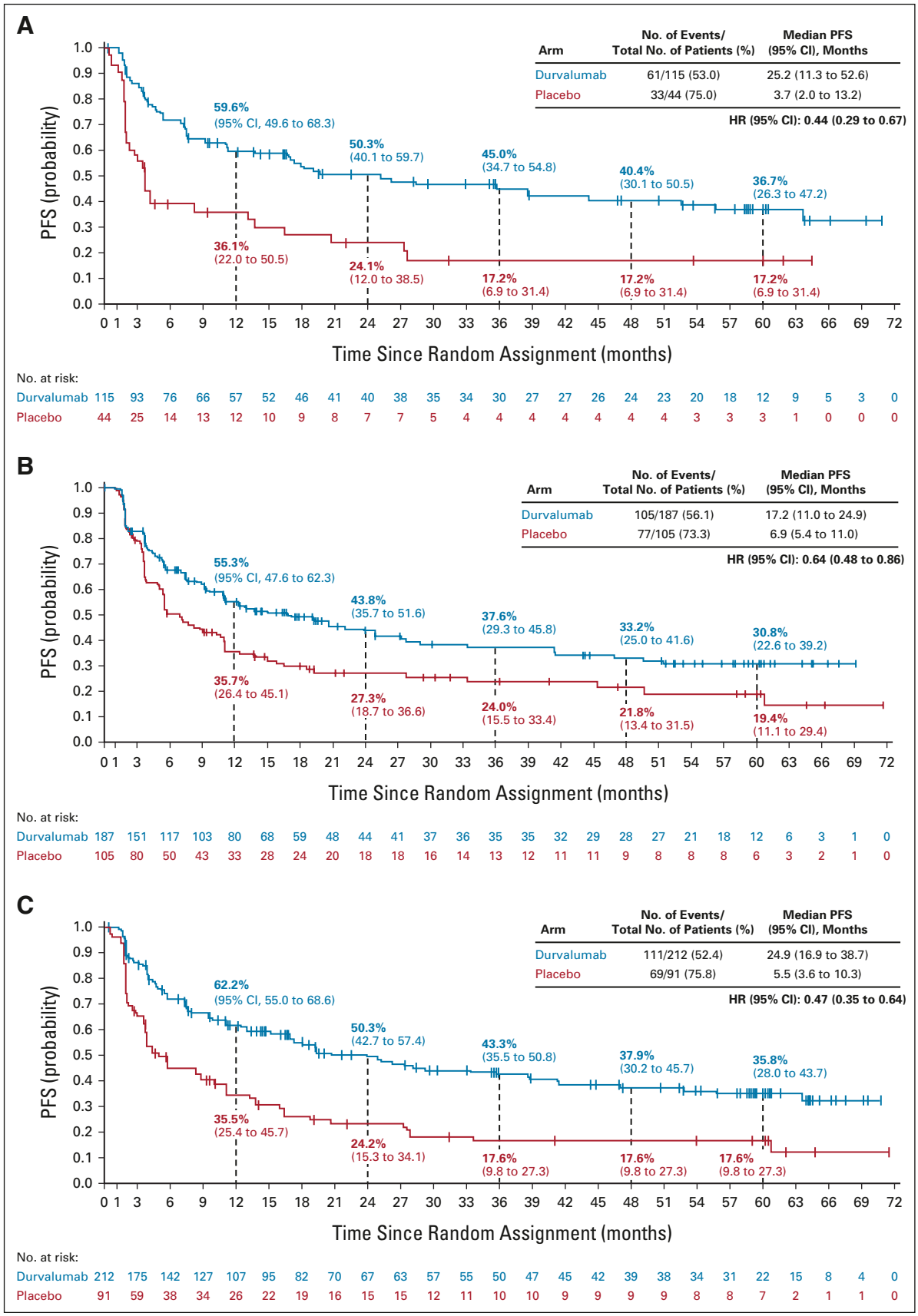


FIG A3. Updated PFS (blinded independent central review) by tumor PD-L1 expression level: (A) PD-L1 TC ≥ 25%, (B) PD-L1 TC < 25%, (C) PD-L1 TC ≥ 1%, (D) PD-L1 TC < 1%, (E) unknown PD-L1 status, and (F) PD-L1 TC 1%-24%. The vertical dashed lines indicate yearly landmarks; the associated numerical values represent the PFS rates at the landmark. (continued on following page)

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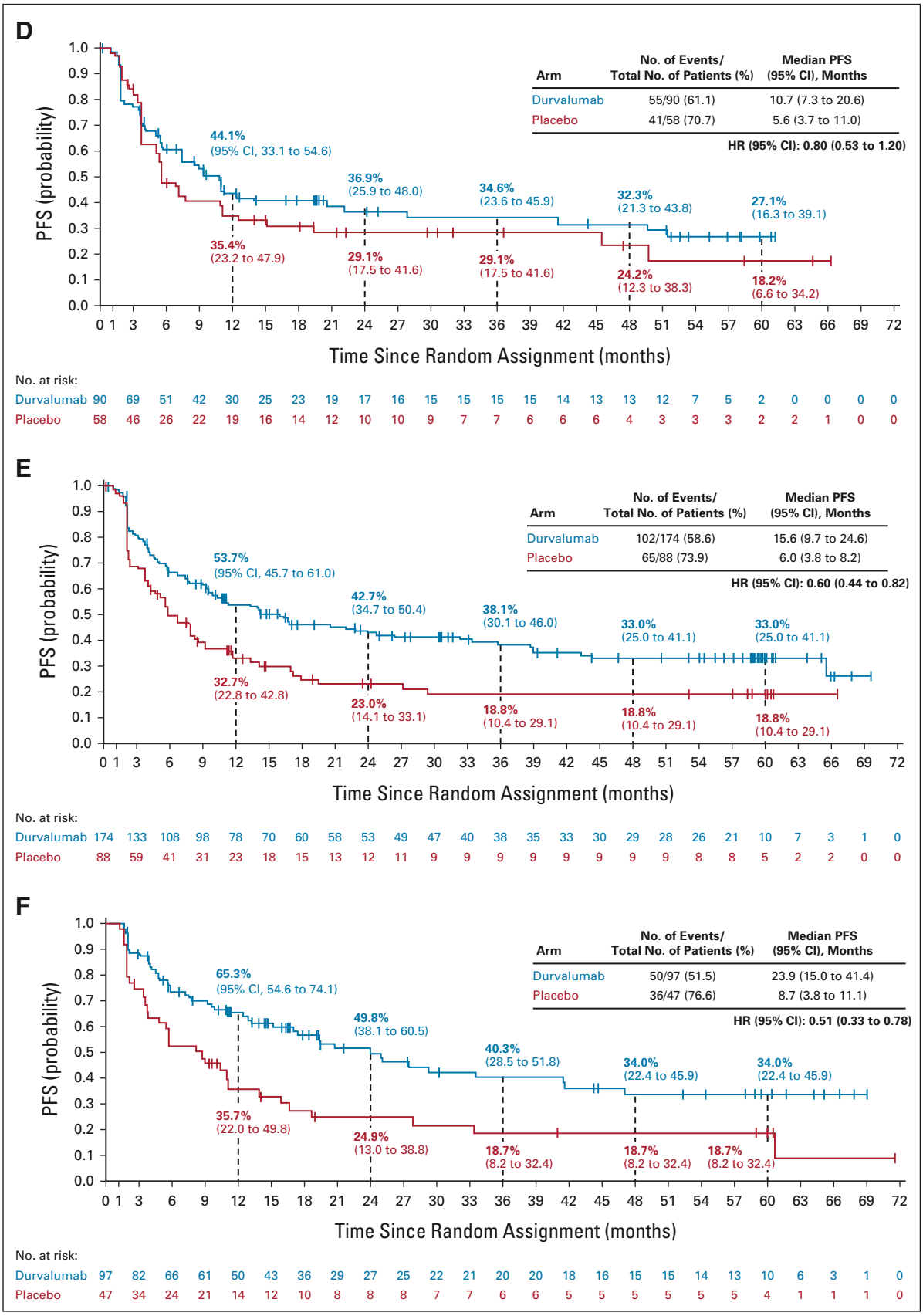


FIG A3. (Continued). HR, hazard ratio; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; TC, tumor cell.

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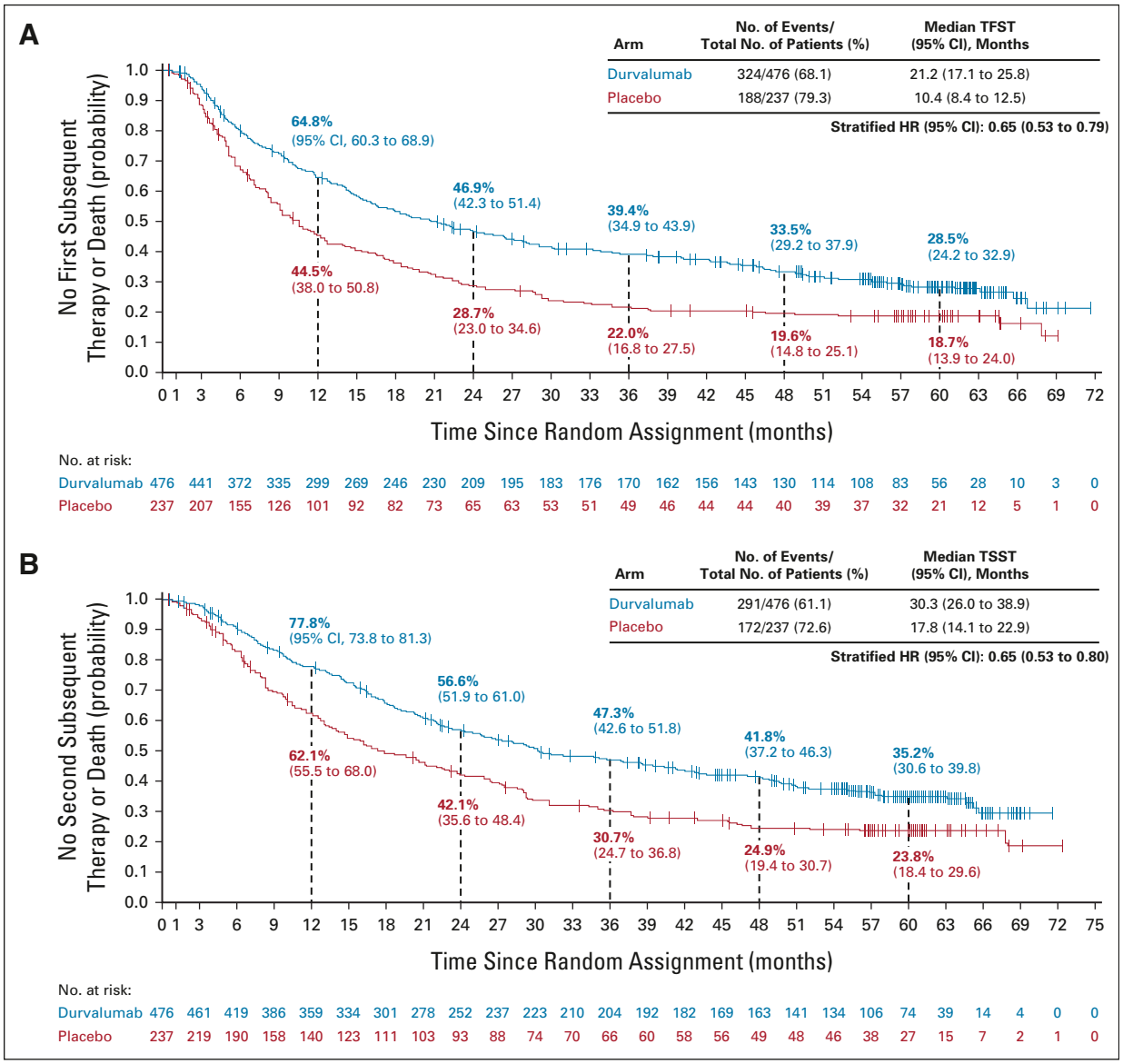


FIG A4. Updated times to (A) first and (B) second subsequent therapy or death in the intent-to-treat population. The vertical dashed lines indicate yearly landmarks; the associated numerical values represent the TFST and TSST rates at the landmark. TFST was defined as time from random assignment to the start of the first subsequent anticancer therapy after discontinuation of study treatment, or death, whichever occurred earlier. TSST was defined as the time from random assignment to the start of the second subsequent anticancer therapy after discontinuation of study treatment, or death, whichever occurred earlier. HR, hazard ratio; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

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TABLE A1. Causes of Death in the Intent-to-Treat Population

Category	Durvalumab (n = 476), No. (%)	Placebo (n = 237), No. (%)
Total deaths	264 (55.5)	155 (65.4)
Death related to disease under investigation only[a]	208 (43.7)	118 (49.8)
Death related to disease under investigation[a] and an AE with outcome of death	10 (2.1)	7 (3.0)
AE onset before subsequent therapy[b]	10 (2.1)	6 (2.5)
AE onset after start of subsequent therapy[c]	0	1 (0.4)
AE with outcome of death only	11 (2.3)	10 (4.2)
AE onset before subsequent therapy[b]	11 (2.3)	9 (3.8)
AE onset after start of subsequent therapy[c]	0	1 (0.4)
Death not because of either disease progression or an AE with a start date while on treatment or within the safety follow-up period	18 (3.8)	10 (4.2)
Unknown reason for death	14 (2.9)	9 (3.8)
Other deaths[d]	3 (0.6)	1 (0.4)

Abbreviation: AE, adverse event.

[a]Deaths related to disease under investigation as determined by the investigator.

[b]Includes AEs with an onset date (or pretreatment AEs that increase in severity) on or after the date of the first dose and ≤ 90 days following the last dose of study medication, or AEs with a start date ≤ the date of initiation of the first subsequent therapy (whichever occurs first).

[c]Includes AEs with a start date > 90 days following the last dose of study medication and AEs with a start date > the date of initiation of the first subsequent therapy (whichever occurs first).

[d]Includes patients who died and are not captured in the earlier categories and patients who died because of AEs with an onset date in the retreatment phase and ≤ 90 days following the last dose of study medication in the retreatment phase.

TABLE A2. Antitumor Response in the Intent-to-Treat Population (blinded independent central review)

End Point	Durvalumab (n = 443)[a]	Placebo (n = 213)[a]
Objective response		
No. (%)	132 (29.8)	39 (18.3)
95% CI[b]	25.6 to 34.3	13.4 to 24.2
DoR[c]		
Median (95% CI), months	NR (34.1 to NE)	18.4 (6.7 to 57.1)
Percentage remaining in response at[c]:		
12 months	81.1	60.5
24 months	70.0	42.2
36 months	58.7	34.5
48 months	53.0	34.5
60 months	51.1	NE

Abbreviations: DoR, duration of response; NE, not estimable; NR, not reached.

[a]Summary on the basis of patients with measurable disease at baseline (as determined by either of the two independent central reviewers) and responses include unconfirmed responses.

[b]Calculated using the Clopper-Pearson method.

[c]Calculated using the Kaplan-Meier method.

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TABLE A3. Univariate Cox Regression Analyses of Prognostic Baseline Factors for Overall Survival

	Comparator		Reference		
Baseline Variable	**Group**	**No. of Events/Total No. of Patients (%)**	**Group**	**No. of Events/Total No. of Patients (%)**	**HR (95% CI)**
Treatment arm	Durvalumab	264/476 (55.5)	Placebo	155/237 (65.4)	0.72 (0.59 to 0.87)[a]
Age, years	≥ 65	210/322 (65.2)	< 65	209/391 (53.5)	1.39 (1.15 to 1.69)[a]
Disease stage[b]	IIIB	182/319 (57.1)	IIIA	227/377 (60.2)	0.95 (0.78 to 1.16)
Best response to prior treatment[c]	CR/PR	195/365 (53.4)	SD	216/338 (63.9)	0.78 (0.64 to 0.94)[a]
Tumor histologic type	Squamous	205/326 (62.9)	Nonsquamous	214/387 (55.3)	1.30 (1.07 to 1.58)[a]
WHO PS	1[d]	233/365 (63.8)	0	186/348 (53.4)	1.30 (1.07 to 1.57)[a]
Prior platinum CT agent[e]	Cisplatin	215/395 (54.4)	Carboplatin	190/301 (63.1)	0.79 (0.65 to 0.96)[a]
Race	Asian	95/192 (49.5)	White	310/494 (62.8)	0.63 (0.50 to 0.80)[a]
	Black or African American	7/14 (50.0)			0.68 (0.32 to 1.44)
	Other[f]	7/13 (53.8)			0.82 (0.39 to 1.73)
Sex	Male	304/500 (60.8)	Female	115/213 (54.0)	1.20 (0.96 to 1.48)
Smoking status	Smoker	384/649 (59.2)	Nonsmoker	35/64 (54.7)	1.08 (0.76 to 1.52)
Time from CRT to random assignment, days	≥ 14	312/531 (58.8)	< 14	107/182 (58.8)	1.07 (0.86 to 1.33)
EGFR or *ALK* aberration status	Positive[g]	25/43 (58.1)	Negative	275/482 (57.1)	0.90 (0.60 to 1.36)
	Unknown	119/188 (63.3)			1.17 (0.94 to 1.45)
PD-L1 expression level	TC ≥ 25%	78/159 (49.1)	TC < 25%	175/292 (59.9)	0.80 (0.61 to 1.04)
	Unknown	166/262 (63.4)			1.12 (0.90 to 1.38)

NOTE. Except where stated otherwise, missing values were categorized as unknown for modeling purposes (no patients were omitted).

Abbreviations: ALK, anaplastic lymphoma kinase; CR, complete response; CRT, chemoradiotherapy; CT, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; PD-L1, programmed cell death-ligand 1; PR, partial response; PS, performance status; SD, stable disease; TC, tumor cell.

[a]HR < 1 favors the comparator group over the reference group; the identified prognostic factors are those for which the HR 95% CI does not cross one.

[b]Seventeen patients with stage IV (n = 4) or stage I/II (n = 13) disease were categorized as other (data not shown).

[c]Best response was categorized as other for 10 patients (data not shown); this category includes progression (n = 2), nonevaluable (n = 7), and not applicable (n = 1).

[d]WHO PS 1 group includes three patients with missing PS data.

[e]Platinum chemotherapy agent was unknown for four patients, and 13 patients received both carboplatin and cisplatin (data not shown).

[f]Category includes American Indian or Alaskan Native (n = 9), Native Hawaiian or Other Pacific Islander (n = 2), Other (n = 1), and Missing (n = 1).

[g]The subgroup includes 35 patients with tumors harboring *EGFR* mutations and, on the basis of local testing, eight patients with tumors harboring *ALK* alterations.

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TABLE A4. Univariate Cox Regression Analyses of Prognostic Baseline Factors for Progression-Free Survival (blinded independent central review)

	Comparator		Reference		
Baseline Variable	**Group**	**No. of Events/Total No. of Patients (%)**	**Group**	**No. of Events/Total No. of Patients (%)**	**HR (95% CI)**
Treatment arm	Durvalumab	268/476 (56.3)	Placebo	175/237 (73.8)	0.58 (0.48 to 0.70)[a]
Age, years	≥ 65	203/322 (63.0)	< 65	240/391 (61.4)	1.11 (0.92 to 1.34)
Disease stage[b]	IIIB	207/319 (64.9)	IIIA	227/377 (60.2)	1.20 (0.99 to 1.45)
Best response to prior treatment[c]	CR/PR	220/365 (60.3)	SD	217/338 (64.2)	0.85 (0.71 to 1.03)
Tumor histologic type	Squamous	212/326 (65.0)	Nonsquamous	231/387 (59.7)	1.25 (1.04 to 1.51)[a]
WHO PS	1[d]	234/365 (64.1)	0	209/348 (60.1)	1.16 (0.96 to 1.40)
Prior platinum CT agent[e]	Cisplatin	240/395 (60.8)	Carboplatin	190/301 (63.1)	0.92 (0.76 to 1.11)
Race	Asian	113/192 (58.9)	White	312/494 (63.2)	0.78 (0.63 to 0.96)[a]
	Black or African American	9/14 (64.3)			0.91 (0.47 to 1.77)
	Other[f]	9/13 (69.2)			1.04 (0.54 to 2.02)
Sex	Male	314/500 (62.8)	Female	129/213 (60.6)	1.05 (0.86 to 1.29)
Smoking status	Smoker	404/649 (62.2)	Nonsmoker	39/64 (60.9)	0.89 (0.64 to 1.24)
Time from CRT to random assignment, days	≥ 14	332/531 (62.5)	< 14	111/182 (61.0)	1.13 (0.91 to 1.40)
EGFR or *ALK* aberration status	Positive[g]	32/43 (74.4)	Negative	293/482 (60.8)	1.23 (0.85 to 1.77)
	Unknown	118/188 (62.8)			1.03 (0.83 to 1.28)
PD-L1 expression level	TC ≥ 25%	94/159 (59.1)	TC < 25%	182/292 (62.3)	0.93 (0.72 to 1.19)
	Unknown	167/262 (63.7)			1.04 (0.84 to 1.29)

NOTE. Except where stated otherwise, missing values were categorized as unknown for modeling purposes (no patients were omitted).

Abbreviations: ALK, anaplastic lymphoma kinase; CR, complete response; CRT, chemoradiotherapy; CT, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; PD-L1, programmed cell death-ligand 1; PR, partial response; PS, performance status; SD, stable disease; TC, tumor cell.

[a]HR < 1 favors the comparator group over the reference group; the identified prognostic factors are those for which the HR 95% CI does not cross one.

[b]Seventeen patients with stage IV (n = 4) or stage I/II (n = 13) disease were categorized as other (data not shown).

[c]Best response was categorized as other for 10 patients (data not shown); this category includes progression (n = 2), nonevaluable (n = 7), and not applicable (n = 1).

[d]WHO PS 1 group includes three patients with missing PS data.

[e]Platinum chemotherapy agent was unknown for four patients and 13 patients received both carboplatin and cisplatin (data not shown).

[f]Category includes American Indian or Alaskan Native (n = 9), Native Hawaiian or Other Pacific Islander (n = 2), Other (n = 1), and Missing (n = 1).

[g]The subgroup includes 35 patients with tumors harboring *EGFR* mutations and, on the basis of local testing, eight patients with tumors harboring *ALK* alterations.

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TABLE A5. Multivariable Cox Regression Analysis of Prognostic Baseline Factors for Progression-Free Survival (blinded independent central review) in the Intent-to-Treat Population

	Comparator		Reference		
Baseline Variable	**Group**	**No. of Events/Total No. of Patients (%)**	**Group**	**No. of Events/Total No. of Patients (%)**	**HR (95% CI)**
Treatment arm	Durvalumab	268/476 (56.3)	Placebo	175/237 (73.8)	0.56 (0.46 to 0.68)[a]
Age, years	≥ 65	203/322 (63.0)	< 65	240/391 (61.4)	1.03 (0.85 to 1.25)
Disease stage[b]	IIIB	207/319 (64.9)	IIIA	227/377 (60.2)	1.30 (1.07 to 1.58)[a]
Best response to prior treatment[c]	CR/PR	220/365 (60.3)	SD	217/338 (64.2)	0.91 (0.74 to 1.11)
Tumor histologic type	Squamous	212/326 (65.0)	Nonsquamous	231/387 (59.7)	1.35 (1.10 to 1.65)[a]
WHO PS	1[d]	234/365 (64.1)	0	209/348 (60.1)	1.12 (0.93 to 1.36)
Prior platinum CT agent[e]	Cisplatin	240/395 (60.8)	Carboplatin	190/301 (63.1)	0.94 (0.77 to 1.14)
Race	Asian	113/192 (58.9)	White	312/494 (63.2)	0.73 (0.58 to 0.93)[a]
	Black or African American	9/14 (64.3)			1.08 (0.55 to 2.10)
	Other[f]	9/13 (69.2)			0.95 (0.47 to 1.93)
Sex	Male	314/500 (62.8)	Female	129/213 (60.6)	1.15 (0.92 to 1.45)
Smoking status	Smoker	404/649 (62.2)	Nonsmoker	39/64 (60.9)	0.74 (0.51 to 1.07)
Time from CRT to random assignment, days	≥ 14	332/531 (62.5)	< 14	111/182 (61.0)	1.12 (0.90 to 1.40)
EGFR or *ALK* aberration status	Positive[g]	32/43 (74.4)	Negative	293/482 (60.8)	1.28 (0.86 to 1.89)
	Unknown	118/188 (62.8)			0.90 (0.69 to 1.17)
PD-L1 expression level	TC ≥ 25%	94/159 (59.1)	TC < 25%	182/292 (62.3)	1.05 (0.81 to 1.35)
	Unknown	167/262 (63.7)			1.20 (0.93 to 1.55)

NOTE. Except where stated otherwise, missing values were categorized as unknown for modeling purposes (no patients were omitted).

Abbreviations: ALK, anaplastic lymphoma kinase; CR, complete response; CRT, chemoradiotherapy; CT, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; PD-L1, programmed cell death-ligand 1; PR, partial response; PS, performance status; SD, stable disease; TC, tumor cell.

[a]HR < 1 favors the comparator group over the reference group; the identified prognostic factors are those for which the HR 95% CI does not cross one.

[b]Seventeen patients with stage IV (n = 4) or stage I/II (n = 13) disease were categorized as other (data not shown).

[c]Best response was categorized as other for 10 patients (data not shown); this category includes progression (n = 2), nonevaluable (n = 7), and not applicable (n = 1).

[d]WHO PS 1 group includes three patients with missing PS data.

[e]Platinum chemotherapy agent was unknown for four patients, and 13 patients received both carboplatin and cisplatin (data not shown).

[f]Category includes American Indian or Alaskan Native (n = 9), Native Hawaiian or Other Pacific Islander (n = 2), Other (n = 1), and Missing (n = 1).

[g]The subgroup includes 35 patients with tumors harboring *EGFR* mutations and, on the basis of local testing, eight patients with tumors harboring *ALK* alterations.

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