



Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC—an Update From the PACIFIC Trial

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ABSTRACT

Introduction: In the Phase 3, placebo-controlled PACIFIC trial of patients with unresectable, stage III NSCLC without disease progression after concurrent chemoradiotherapy, consolidative durvalumab was associated with significant improvements in the primary end points of overall survival (OS) (hazard ratio [HR] = 0.68; 95% confidence interval [CI]: 0.53–0.87; $p = 0.00251$; data cutoff, March 22, 2018) and progression-free survival (PFS) (blinded independent central review; Response Evaluation Criteria in Solid Tumors version 1.1) (HR = 0.52; 95% CI: 0.42–65; $p < 0.0001$; February 13, 2017) with manageable safety. Here, we report updated analyses of OS and PFS, approximately 4 years after the last patient was randomized.

Methods: Patients with WHO performance status of 0 or 1 (and any tumor programmed death-ligand 1 status) were randomized (2:1) to intravenous durvalumab (10 mg/kg) or placebo, administered every 2 weeks (≤ 12 months), stratified by age, sex, and smoking history. OS and PFS were analyzed using a stratified log-rank test in the intent-to-treat population. Medians and 4-year OS and PFS rates were estimated by the Kaplan–Meier method.

Results: Overall, 709 of 713 randomized patients received durvalumab (n/N=473/476) or placebo (n/N=236/237). As of March 20, 2020 (median follow-up = 34.2 months; range: 0.2–64.9), updated OS (HR = 0.71; 95% CI: 0.57–

0.88) and PFS (HR = 0.55; 95% CI: 0.44–0.67) remained consistent with the primary analyses. The median OS for durvalumab was reached (47.5 mo; placebo, 29.1 months). Estimated 4-year OS rates were 49.6% versus 36.3% for durvalumab versus placebo, and 4-year PFS rates were 35.3% versus 19.5% respectively.

Conclusion: These updated exploratory analyses demonstrate durable PFS and sustained OS benefit with durvalumab after chemoradiotherapy. An estimated 49.6% of patients randomized to durvalumab remain alive at 4 years (placebo, 36.3%), and 35.3% remain alive and progression-free (placebo, 19.5%).

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Keywords: Durvalumab; Locally advanced NSCLC; PACIFIC; Overall survival; Progression-free survival

Introduction

Until recently, platinum-based, concurrent chemoradiotherapy (CRT) followed by observation was the standard of care for patients with unresectable, stage III NSCLC and good performance status. However, patient

prognosis was poor, with a 5-year survival rate of approximately 15% to 32%.^{1,2} Moreover, there was no evidence that continuing chemotherapy, utilizing other systemic anticancer agents after CRT, or escalating the radiation dose could improve survival.²⁻⁴

Durvalumab is a selective, high-affinity, human immunoglobulin G1 monoclonal antibody that blocks the interaction of programmed death-ligand 1 (PD-L1) with programmed cell death protein 1 and CD80, allowing T-cells to recognize and kill tumor cells (TCs).⁵ In the placebo-controlled, phase-3 PACIFIC trial of patients with unresectable, stage III NSCLC whose disease did not progress after concurrent CRT, consolidative durvalumab (≤ 12 months) significantly prolonged overall survival (OS) (stratified hazard ratio [HR] = 0.68; 95% confidence interval [CI]: 0.53–0.87; $p = 0.00251$; median, not reached versus 28.7 months; data cutoff March 22, 2018) and progression-free survival (PFS) (stratified HR = 0.52; 95% CI: 0.42–0.65; $p < 0.0001$; median, 16.8 versus 5.6 months; data cutoff February 13, 2017).⁶⁻⁸ Durvalumab exhibited a manageable safety profile and did not detrimentally impact patient-reported quality of life.^{6,7,9} On the basis of these results, durvalumab received global approvals and the “PACIFIC regimen” (12 mo durvalumab after CRT) became the new standard of care in this setting.^{8,10,11}

The OS benefit with durvalumab was sustained at an updated analysis that took place approximately 3 years after the last patient was randomized to PACIFIC (stratified HR = 0.69; 95% CI: 0.55–0.86; data cutoff January 31, 2019).¹² Here, we report updated OS, and PFS, from a preplanned, exploratory analysis of PACIFIC, approximately 4 years after the last patient was randomized, including the first estimate of median OS for the durvalumab arm.

Materials and Methods

Study Design

The design of the PACIFIC trial has been described elsewhere.^{6,7} Briefly, patients with a WHO performance score of 0 or 1 and documented stage III, unresectable NSCLC who had received at least two cycles of platinum-based, concurrent CRT without disease progression were enrolled and randomized 1 to 42 days post-CRT (total prescription radiotherapy dose typically 60–66 Gy in 30–33 fractions). Patients with unresolved toxicities of grade greater than 2 (or grade greater than or equal to 2 pneumonitis/radiation-pneumonitis) from prior CRT were excluded (assessed per Common Terminology Criteria for Adverse Events version 4.03). Tumor tissue collection was not required, and trial enrollment was not restricted by PD-L1 expression level or oncogenic

driver gene mutation status. Patients were randomized in a two-to-one ratio, stratified by age (< 65 versus ≥ 65 years), sex, and smoking history (current or former smoker versus never smoked) to receive durvalumab (10 mg/kg intravenously) or placebo every 2 weeks for up to 12 months or until confirmed disease progression, initiation of alternative cancer therapy, unacceptable toxicity, or withdrawal of consent.

End Points and Assessments

In this exploratory analysis, we report the data up to March 20, 2020, including updates of the following: (1) OS and PFS (blinded independent central review; Response Evaluation Criteria in Solid Tumors version 1.1) for the intent-to-treat (ITT) population; (2) OS and PFS rates at 12, 24, 36, and 48 months; (3) the types of postdiscontinuation disease-related anticancer therapies administered; and (4) time to first and time to second subsequent therapy or death. Furthermore, we updated the analyses of OS and PFS in patient subgroups defined by prespecified and post hoc baseline factors. This included PD-L1 status, which was determined on the basis of testing of archived, pre-CRT tumor tissue and analyzed at prespecified (25%) and exploratory post hoc (1%) PD-L1 TC expression thresholds (using the Ventana SP263 immunohistochemistry assay [Ventana Medical Systems, Tuscon, AZ]). Safety data were not collected at this data cutoff.

Statistical Analysis

For time-to-event end points, treatment effects for durvalumab versus placebo were estimated from HRs calculated using a stratified log-rank test in the ITT population (with the same stratification factors used for randomization). Unstratified Cox proportional hazards models were used to calculate treatment effects in patient subgroups; no adjustment for multiple comparisons was performed. Medians and landmark rates (e.g., 48-month OS and PFS rates) were estimated using the Kaplan–Meier method.

Results

Patients

In total, 709 of 713 randomized patients received treatment in the durvalumab ($n/N = 473/476$) and placebo arms ($n/N = 236/237$); the last patient completed protocol-defined 12-month study treatment in May 2017. The baseline characteristics were well balanced between the durvalumab and placebo arms, as reported previously.^{6,7} As of March 20, 2020, 51.9% and 62.9% of patients randomized to durvalumab and placebo, respectively, had died ([Supplementary Fig. 1](#)). The median duration of follow-up was 34.2 months (range: 0.2–64.9).

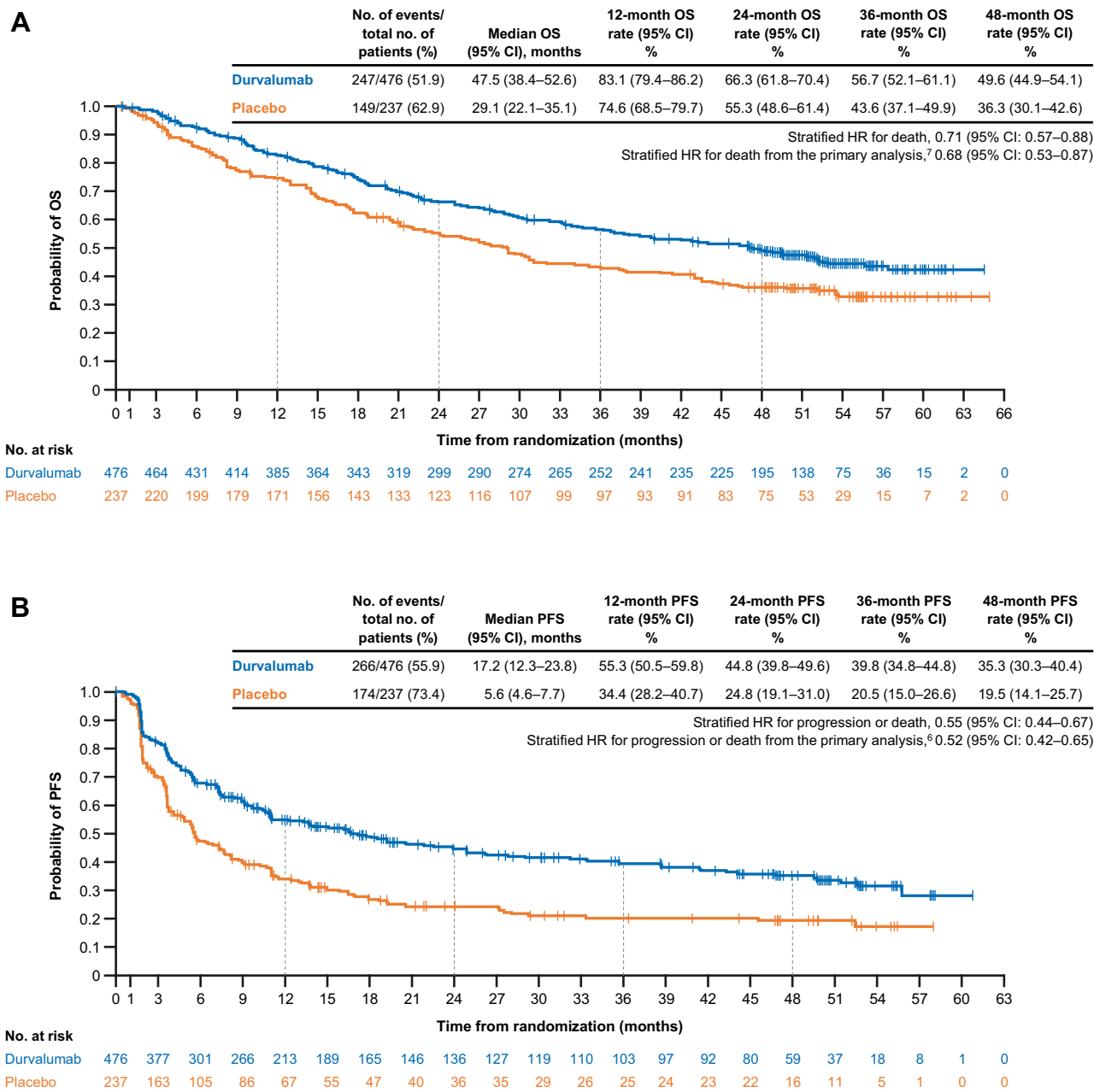


Figure 1. Updated (A) OS and (B) PFS in the ITT population. PFS was assessed by BICR. Vertical tick marks indicate censored observations. OS is defined as the time from randomization until death from any cause. PFS is defined as the time from randomization to the date of the first documented event of tumor progression or death in the absence of disease progression. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival.

Overall Survival

In total, 97 additional deaths were reported since the primary analysis of OS (March 22, 2018), and 52 new deaths were reported since the last update of the OS analysis (January 31, 2019). Updated OS was consistent with the primary analysis; there was a 29% reduction in the risk of death with durvalumab (stratified HR = 0.71; 95% CI: 0.57–0.88) (Fig. 1A). The Kaplan–Meier estimate

of median OS was reached for durvalumab (47.5 months; placebo, 29.1 months). The 48-month OS rate was estimated as 49.6% for durvalumab versus 36.3% for placebo. Updated analyses of OS by subgroup were consistent with the previous reports (Fig. 2)^{7,12,13}; OS benefit favored durvalumab across all PD-L1 subgroups except patients with PD-L1 expression on less than 1% of TCs (HR = 1.05; 95% CI: 0.69–1.62) (Supplementary Fig. 2).

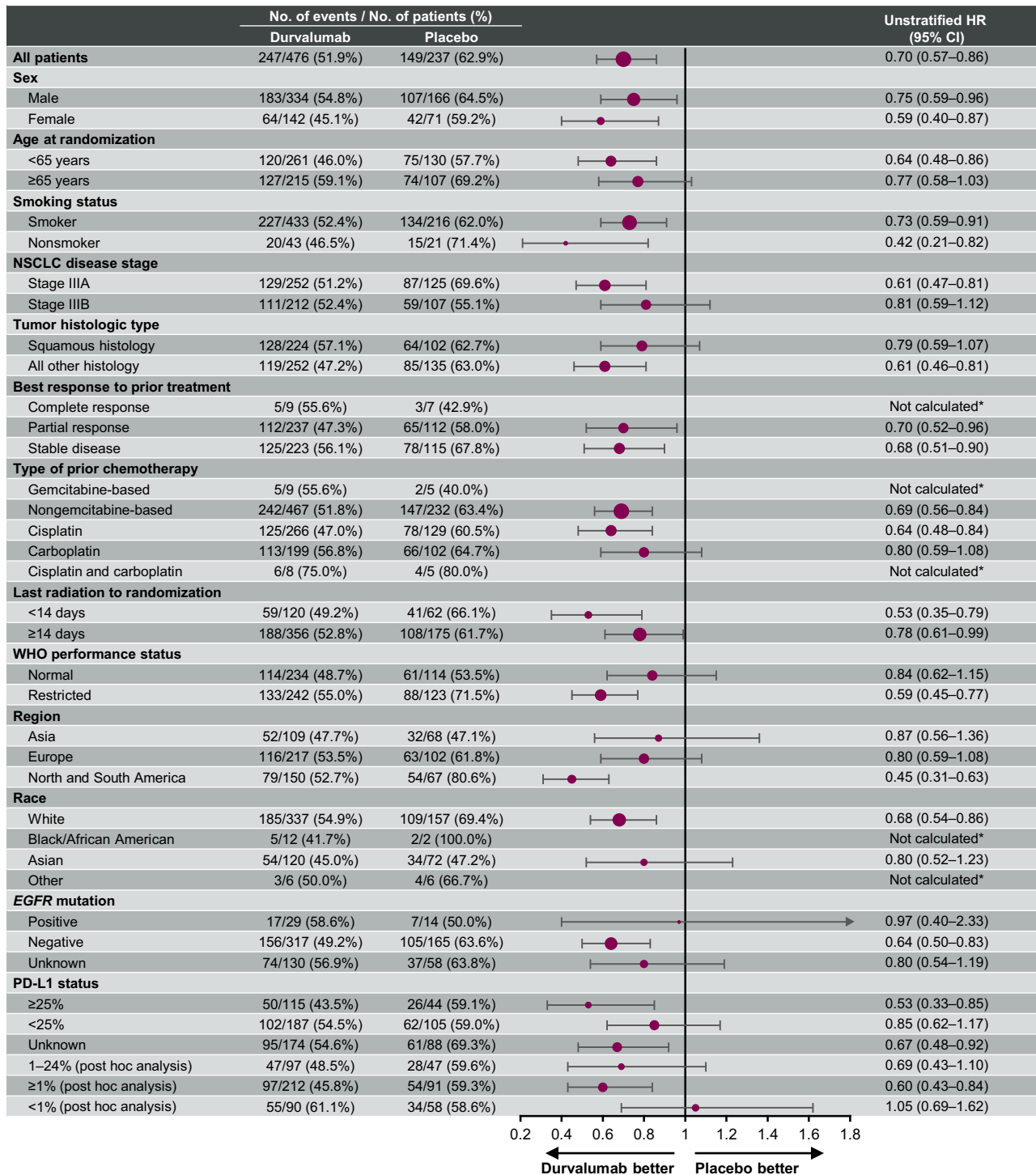


Figure 2. Updated OS by prespecified and post hoc exploratory subgroups. *HRs and 95% CIs were not calculated if the subgroup had less than 20 events. CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; WHO, World Health Organization.

Progression-Free Survival

In total, 69 additional PFS events were reported since the primary analysis of PFS (February 13, 2017), and 24 new PFS events were reported since the primary

analysis of OS (March 22, 2018). Updated PFS was consistent with the primary analysis; there was a 45% reduction in the risk of disease progression or death with durvalumab (stratified HR = 0.55; 95% CI:

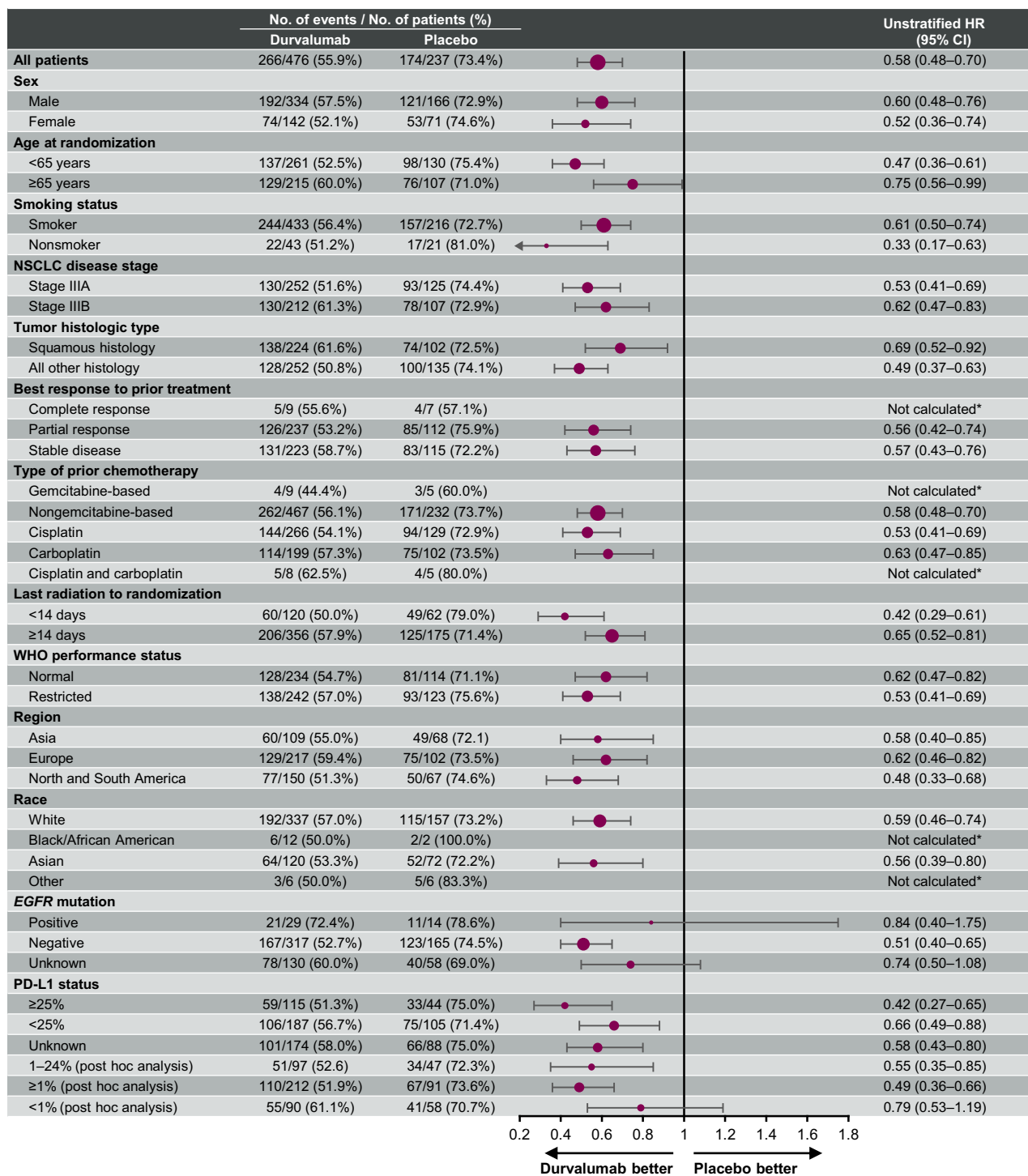


Figure 3. Updated PFS by prespecified and exploratory post hoc subgroups. PFS was assessed by BICR. *HRs and 95% CIs were not calculated if the subgroup had less than 20 events. BICR, blinded independent central review; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival; WHO, World Health Organization.

0.44–0.67) (Fig. 1B). The Kaplan–Meier estimate of median PFS was 17.2 months and 5.6 months for durvalumab and placebo, respectively. The 48-month PFS rate was estimated as 35.3% for durvalumab versus 19.5%

for placebo. Updated analyses of PFS by subgroup were consistent with the previous reports (Fig. 3)^{6,13}; PFS benefit favored durvalumab across all PD-L1 subgroups (Supplementary Fig. 3).

Postdiscontinuation Anticancer Therapy

After discontinuing the study treatment, 47.3% and 58.2% of patients received subsequent disease-related anticancer therapy in the durvalumab and placebo arms, respectively (Supplementary Table 1); 11.6% and 28.3% received subsequent immunotherapy, respectively. Consistent with the results reported at the time of the primary analysis of OS, the time to first subsequent therapy or death (stratified HR = 0.62; 95% CI: 0.51–0.76) and the time to second subsequent therapy or death (stratified HR = 0.62; 95% CI: 0.51–0.77) were longer with durvalumab versus placebo (Supplementary Fig. 4).

Discussion

These updated results demonstrate that durvalumab provides sustained survival benefit over the longer term. At 4 years, an estimated 49.6% of patients randomized to durvalumab were alive (placebo, 36.3%), and 35.3% were alive and free of disease progression (placebo, 19.5%). Notably, the median OS for the durvalumab arm was reached at this update (47.5 months; placebo, 29.1 months). OS and PFS favored durvalumab versus placebo across almost all prespecified patient subgroups, including subgroups defined by age, sex, race, disease stage, tumor histologic type, smoking status, and CRT-related variables, supporting the use of the PACIFIC regimen as the standard of care in a broad population. Nevertheless, the subgroup analyses are limited by small sample sizes and none were statistically powered to assess efficacy, nor were they necessarily balanced with respect to other baseline factors.

The PACIFIC trial was designed as an all-comers study and not to evaluate clinical outcomes according to any tumor biomarker status. Consistent OS and PFS benefit with durvalumab was observed across all prespecified subgroups with the exception of the *EGFR*-positive subgroup, for which survival benefit was uncertain. However, the small size of this subgroup (N = 43) and the exploratory nature of the analysis preclude definitive conclusions.

Consistent with previous analyses from the PACIFIC study,¹³ OS and PFS benefit favored durvalumab versus placebo across all PD-L1 subgroups with the exception of OS in patients with PD-L1 expression on less than 1% of TCs (HR = 1.05; 95% CI: 0.69–1.62), despite PFS favoring durvalumab in this post hoc subgroup. However, as reported previously, the PD-L1 subgroup analyses are limited by the relatively small number of patients with PD-L1 expression on less than 1% of TCs, the use of pre-CRT tumor samples to assess PD-L1 expression, and the incomplete provision of tumor tissue; PD-L1–assessable samples were available for only 63% of all randomized patients.^{13,14} Moreover, with respect to OS, the placebo

arm overperformed in the PD-L1 TC less than 1% subgroup compared with the ITT population; this may be accounted for by imbalances in potentially prognostic baseline factors, as described previously.¹³ Therefore, robust conclusions regarding the impact of PD-L1 expression on efficacy cannot be drawn.

Fewer patients in the durvalumab arm received subsequent anticancer treatment compared with the placebo arm. This was likely driven by improved PFS and fewer progression events observed with durvalumab. Notably, fewer patients received subsequent immunotherapy in the durvalumab arm (11.6%) compared with the placebo arm (28.3%), but this did not negate the OS benefit with the PACIFIC regimen. Otherwise, the proportions of patients who received subsequent treatment with each type of anticancer therapy were similar between the durvalumab and placebo arms. Likely owing to the time of initiation of the trial and the standards of care in systemic therapy at that time, chemotherapy was the most common subsequent therapy across both arms.

In conclusion, these updated, exploratory analyses from PACIFIC demonstrate durable PFS and sustained OS benefit with the standard-of-care PACIFIC regimen (durvalumab after CRT). An estimated 49.6% of patients randomized to durvalumab remain alive at 4 years (placebo, 36.3%), and an estimated 35.3% remain alive and progression-free (placebo, 19.5%).

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at <https://doi.org/10.1016/j.jtho.2020.12.015>.

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