Simultaneous Durvalumab and Platinum-Based Chemoradiotherapy in Unresectable Stage III Non–Small Cell Lung Cancer: The Phase III PACIFIC-2 Study

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ABSTRACT

PURPOSE Immunotherapy targeting PD-L1 improves outcomes in patients with unresectable stage III non–small cell lung cancer (NSCLC) and no progression after definitive, concurrent chemoradiotherapy (cCRT). Earlier administration of immunotherapy, simultaneously with cCRT, may improve outcomes further.

METHODS Eligible patients were randomly assigned (2:1) to receive either durvalumab or placebo administered from the start of cCRT. Patients without progression after completing cCRT received consolidation durvalumab or placebo (per initial random assignment) until progression. The primary end point was progression-free survival (PFS) by blinded independent central review. Key secondary end points included objective response rate (ORR), overall survival (OS), the proportion of patients alive at 24 months (OS24), and safety.

RESULTS In total, 328 patients were randomly assigned to receive durvalumab (n = 219) or placebo (n = 109). There was no statistically significant difference with durvalumab versus placebo in PFS (hazard ratio [HR], 0.85 [95% CI, 0.65 to 1.12]; $P = .247$) or OS (HR, 1.03 [95% CI, 0.78 to 1.39]; $P = .823$); OS24 was 58.4% versus 59.5%, respectively. Confirmed ORR was 60.7% with durvalumab versus 60.6% with placebo (difference, 0.2% [95% CI, −15.2 to 16.3%]; $P = .976$). With durvalumab versus placebo, respectively, maximum grade 3 or 4 adverse events (AEs) occurred in 53.4% versus 59.3% of patients, pneumonitis or radiation pneumonitis (group term) in 28.8% (grade ≥3: 4.6%) versus 28.7% (grade ≥3: 5.6%), AEs leading to discontinuation of durvalumab or placebo in 25.6% versus 12.0%, and fatal AEs in 13.7% versus 10.2%.

CONCLUSION Among patients with unresectable stage III NSCLC, durvalumab administered from the start of cCRT failed to demonstrate additional benefit compared with cCRT plus placebo. Consolidation durvalumab following definitive cCRT remains the standard of care in this setting.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Data Supplement
- Protocol

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INTRODUCTION

In the phase III PACIFIC trial, 12 months of consolidation durvalumab had a favorable benefit-risk profile versus placebo among patients with unresectable stage III non–small cell lung cancer (NSCLC) and no progression following definitive, concurrent chemoradiotherapy (cCRT).[1-5] In PACIFIC, durvalumab significantly improved progression-free survival (PFS; stratified hazard ratio [HR], 0.52 [95% CI, 0.42 to 0.65]; $P < .0001$) and overall survival (OS; stratified HR, 0.68 [95% CI, 0.53 to 0.87]; $P = .0025$) versus placebo.[1-3] With a manageable safety profile, no negative impact on patient-reported outcomes, and sustained improvement at 5 years in PFS (5-year rate [95% CI], 33.1% [28.0 to 38.2] *v* 19.0% [13.6 to 25.2]) and OS (5-year rate [95% CI], 42.9% [38.2 to 47.4] *v* 33.4% [27.3 to 39.6]), the PACIFIC regimen remains the standard of care (SoC) in this setting.[1-3,6-9]

Despite the efficacy of the PACIFIC regimen, unmet need remains, as approximately 27%-50% of patients may be ineligible for consolidation durvalumab due to early disease progression, pneumonitis, or cCRT-related toxicities.[10-12] Preclinical evidence suggests synergy between CRT and immunotherapies like durvalumab that target PD-1 or its

CONTEXT

Key Objective

Does administration of immunotherapy simultaneously with concurrent chemoradiotherapy (cCRT) improve outcomes for patients with unresectable stage III non–small cell lung cancer (NSCLC)?

Knowledge Generated

Among 328 patients with unresectable stage III NSCLC randomly assigned to receive durvalumab (n = 219) or placebo (n = 109) simultaneously with cCRT, there was no statistically significant difference with durvalumab versus placebo in progression-free survival (hazard ratio [HR], 0.85 [95% CI, 0.65 to 1.12]; $P = .247$) or overall survival (HR, 1.03 [95% CI, 0.78 to 1.39]; $P = .823$). The safety profile of durvalumab in this study was generally consistent with durvalumab's known profile.

Relevance *(T.E. Stinchcombe)*

Consolidation durvalumab remains the standard, and concurrent immunotherapy and thoracic radiation should not be investigated in future clinical trials.*

*Relevance section written by JCO Associate Editor Thomas E. Stinchcombe, MD.

ligand PD-L1.[13] Chemotherapy enhances anticancer immune responses and induces tumor PD-L1 expression.[14-17] Radiotherapy has multiple immunomodulatory effects, including increased homing of immune cells to tumors, improved antigen presentation, and upregulation of tumor PD-L1 expression.[18,19] Such effects are nonredundant with those of PD-(L)1 blockade, and synergistic anticancer activity with radiotherapy and immunotherapy, with or without chemotherapy, has been observed in vivo.[20-22] Thus, it was hypothesized that earlier initiation of durvalumab, from the start of definitive cCRT, may reduce early progression, deepen responses to cCRT, and provide additional patients the opportunity to benefit from consolidation immunotherapy.

Here we report results from PACIFIC-2 (ClinicalTrials.gov identifier: NCT03519971), the first phase III study designed to assess the efficacy and safety of simultaneous immunotherapy plus cCRT followed by consolidation immunotherapy in this setting. PACIFIC-2 was designed and initiated after the initial PFS findings from PACIFIC,[1] before long-term outcomes established the PACIFIC regimen as the SoC in this setting,[3-5,7-9] and before readouts from early-phase trials investigating simultaneous immunotherapy plus cCRT in this setting, which subsequently showed encouraging safety and mixed efficacy.[23-29]

METHODS

Patients

Eligible patients were age ≥18 years with newly diagnosed, histologically or cytologically documented, unresectable stage III NSCLC (per version 8 of the International Association for the Study of Lung Cancer staging manual in thoracic oncology),[30] WHO or Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and measurable disease per RECIST v 1.1.[31] Resectability was determined per investigator's clinical judgment. Provision of an archived tumor tissue block or recent (≤3 months) tumor biopsy was mandatory. Epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase testing were not required, and PD-L1 testing was prioritized when necessary due to limited availability of tissue samples. Full eligibility criteria are provided in the Data Supplement (Table S1, online only).

Study Design and Treatment

In this double-blind, placebo-controlled, phase III trial, patients were randomly assigned 2:1, stratified by age (<65 *v* ≥65 years) and disease stage (stage IIIA *v* stage IIIB/IIIC), to receive durvalumab (1,500 mg) or placebo intravenously once every 4 weeks from the start of cCRT (Data Supplement, Fig S1). Patients without disease progression (investigator assessed) after completing cCRT received consolidation durvalumab (1,500 mg) or placebo once every 4 weeks (per initial random assignment) until progression, consent withdrawal, or other discontinuation criteria were met. Crossover within the study was not permitted; however, patients could receive immunotherapy after progression per investigator discretion. CRT details are provided in the Data Supplement.

PACIFIC-2 was run in accordance with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines. The protocol and all modifications were approved by relevant ethics committees and regulatory authorities. All patients provided written informed consent.

End Points and Assessments

The primary end point was PFS per RECIST 1.1 by blinded independent central review (BICR), defined as time from

random assignment until objective disease progression or death by any cause. Alpha-controlled secondary end points were objective response rate (ORR) per RECIST 1.1 by BICR, OS, and the 24-month OS rate (OS24). Other key secondary end points included complete response rate, duration of response (DoR), and disease control rate at 24 weeks (from random assignment), all by BICR per RECIST 1.1, and safety and tolerability. Tumor assessments are described in the Data Supplement. Safety was monitored continuously, with adverse events (AEs) graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Statistical Analysis

Statistical methods, including hypotheses, sample size, power calculations, planned interim analyses, the hierarchical testing procedure, and statistical tests used, are presented in the Data Supplement. Efficacy analyses used the intention-to-treat population comprising all randomized patients. Safety analyses included all patients who received ≥1 dose of study treatment.

RESULTS

Patients and Treatment

Between April 17, 2018, and July 22, 2019, 328 patients were randomly assigned at 87 sites across 14 countries in Central or Eastern Europe (n = 154), Asia (n = 104), and Central or South America (n = 70) to receive durvalumab (n = 219) or placebo (n = 109; Fig 1). Baseline characteristics were generally balanced between arms (Table 1). The median age was 63.0 years, and 25% of patients were female. Almost all patients had stage IIIA (34.5%) or IIIB/C (64.9%) disease at baseline; two (0.6%; one in each arm) had stage IV disease. A numerically higher proportion of patients in the durvalumab versus placebo arm had T4 tumors (57.5% *v* 48.6%) and squamous histology (55.3% *v* 47.7%). PD-L1 and *EGFR* testing was retrospective. PD-L1 tumor cell expression by Ventana SP263 assay was ≥1% in 173 (52.7%) patients, <1% in 122 (37.2%), and unknown in 33 (10.1%). *EGFR* mutations were detected in 13 (4.0%) patients; however, 143 (43.6%) had unknown *EGFR* status.

At data cutoff (September 7, 2023), the median follow-up among all (censored) patients was 30.5 (55.5) months. All but one patient in the durvalumab arm (99.5%) and all patients in the placebo arm received treatment (Fig 1). In both arms, carboplatin/paclitaxel was the most common chemotherapy regimen (Data Supplement, Table S2). The median (IQR) planning target volume (PTV) was 466.8 (325.7-661.5) cm^3 in the durvalumab arm and 429.6 (293.1-604.2) cm^3 in the placebo arm (Data Supplement, Table S3). Planned PTV was <450 cm^3 in 46.6% versus 53.2% and ≥450 cm^3 in 51.6% versus 45.0% of patients in the durvalumab versus placebo arm, respectively, and missing for 1.8% in each arm. Overall, 88.1% and 90.8% of patients in the durvalumab and placebo arms received a complete course of CRT per the investigator (Fig 1); the most common reason for CRT discontinuation was AEs in both arms. Similar proportions discontinued durvalumab (83.9%) and placebo (84.4%), most commonly due to disease progression (Fig 1); 26.6% discontinued durvalumab and 13.8% discontinued placebo due to AEs.

Chemotherapy exposure is presented in the Data Supplement (Table S2). In both arms, the median radiotherapy duration was 6.14 weeks and the median total radiation dose was 60.0 Gy; >90% of patients received ≥57 to ≤63 Gy (Data Supplement, Table S4). Patients received a median of 10.0 infusions of durvalumab or 10.5 infusions of placebo (Data Supplement, Table S4).

Overall, 46.6% of patients in the durvalumab arm and 52.3% in the placebo arm received subsequent anticancer therapy following progression, most commonly chemotherapy or radiotherapy (Data Supplement, Table S5); 4.1% versus 21.1%, respectively, received subsequent immunotherapy.

Efficacy

There was no statistically significant improvement in PFS with durvalumab versus placebo (HR, 0.85 [95% CI, 0.65 to 1.12]; P = .247; Fig 2A). The median PFS was 13.8 versus 9.4 months with durvalumab versus placebo. Kaplan-Meier curves for PFS overlapped during the first 6 months of treatment, with sustained and stable separation favoring durvalumab beyond 9 months. PFS HRs for most prespecified subgroups were consistent with the overall analysis (Fig 3A); numerical differences were observed for subgroups based on sex, age, region, and PTV, although these comparisons were not formally tested.

For OS, there was no statistically significant difference between study arms (HR, 1.03 [95% CI, 0.78 to 1.39]; P = .823; Fig 2B). The median OS was 36.4 versus 29.5 months with durvalumab versus placebo. Kaplan-Meier curves for OS crossed at approximately 24 months, favoring placebo before crossing and durvalumab after approximately 27 months, with overlap beyond 54 months. OS24 was 58.4% (95% CI, 51.6 to 64.7) with durvalumab versus 59.5% (95% CI, 49.6 to 68.2) with placebo (HR, 1.04 [95% CI, 0.72 to 1.50]; P = .847). OS subgroup analyses were largely consistent with the overall OS analysis (Fig 3B).

Confirmed ORR was 60.7% with durvalumab versus 60.6% with placebo (difference, 0.2% [95% CI, −15.2 to 16.3%]; P = .976). The median DoR was 30.7 versus 18.6 months with durvalumab versus placebo. Best tumor response and associated outcomes are summarized in the Data Supplement (Table S6).

Safety

Treatment-emergent AEs of any cause occurred in 98.6% versus 100% of patients with durvalumab versus placebo

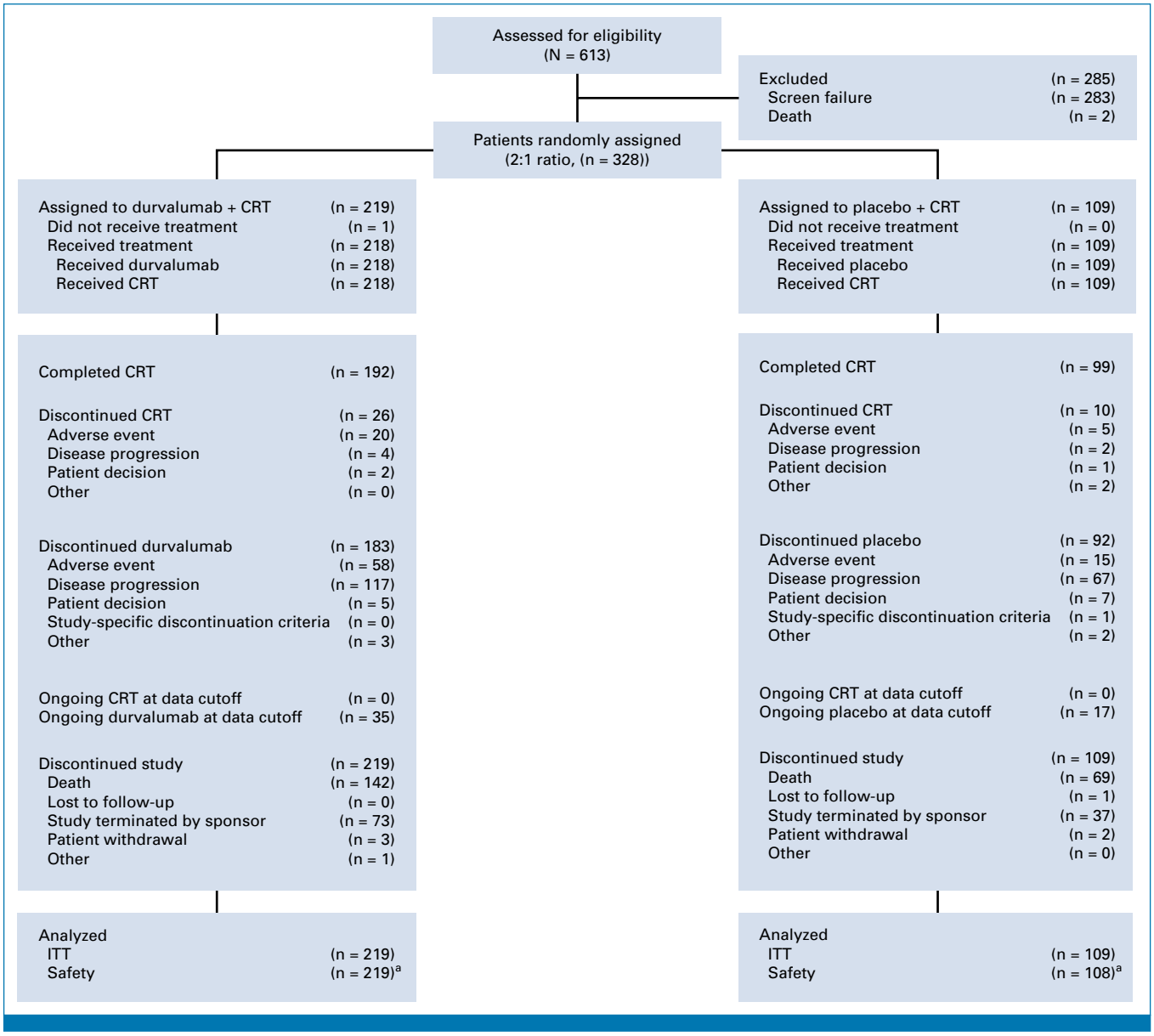

FIG 1. Patient disposition. [a]The safety analysis set includes all patients who underwent random assignment and received at least one dose of trial treatment or placebo; one patient assigned to the placebo group erroneously received a single cycle of durvalumab and was included in the durvalumab group for the safety analysis set. CRT, chemoradiotherapy; ITT, intention-to-treat.

(Table 2). Anemia, pneumonitis or radiation pneumonitis (group term), neutropenia, nausea, and leukopenia were among the most common AEs, with few differences in incidence or severity between arms. Maximum grade 3 or 4 AEs occurred in 53.4% versus 59.3% of patients with durvalumab versus placebo, serious AEs in 47.0% versus 51.9%, AEs leading to discontinuation of durvalumab/placebo in 25.6% versus 12.0% (Data Supplement, Table S7), and fatal AEs in 13.7% versus 10.2%.

Combined rates of pneumonitis or radiation pneumonitis (group term) were 28.8% (grade ≥3: 4.6%) versus 28.7% (grade ≥3: 5.6%) with durvalumab versus placebo. One patient in the durvalumab arm and two in the placebo arm had grade 5 pneumonitis or radiation pneumonitis (group term) considered causally related to durvalumab/placebo. Immune-mediated AEs (imAEs) of any grade (grade ≥3) occurred in 34.7% (8.7%) versus 15.7% (2.8%) of patients with durvalumab versus placebo, and imAEs of pneumonitis occurred in 12.7% (3.7%) versus 8.3% (1.9%; Data Supplement, Table S8).

Post hoc analyses were performed to assess AE frequency by time to onset (0 to ≤4, >4 to ≤16, and >16 months; Data Supplement, Table S9). Although rates of any-grade AEs were similar between study arms across all three time points,

TABLE 1. Baseline Patient Demographics and Disease Characteristics (ITT population)

Characteristic	Durvalumab + CRT (n = 219)	Placebo + CRT (n = 109)
Age, years, median (range)	63 (36-84)	63 (38-84)
Age category, years, No. (%)		
<65	125 (57.1)	62 (56.9)
≥65	94 (42.9)	47 (43.1)
Sex, No. (%)		
Male	166 (75.8)	80 (73.4)
Female	53 (24.2)	29 (26.6)
Region, No. (%)		
Asia	65 (29.7)	39 (35.8)
Europe	108 (49.3)	46 (42.2)
Central or South America	46 (21.0)	24 (22.0)
Race, No. (%)		
White	141 (64.4)	62 (56.9)
Asian	65 (29.7)	39 (35.8)
Black or African American	2 (0.9)	0
Other	11 (5.0)	8 (7.3)
Smoking status, No. (%)		
Smoker	187 (85.4)	89 (81.7)
Nonsmoker	32 (14.6)	20 (18.3)
WHO/ECOG performance status, No. (%)		
0 (normal activity)	98 (44.7)	53 (48.6)
1 (restricted activity)	121 (55.3)	56 (51.4)
Histology, No. (%)[a]		
Squamous	121 (55.3)	52 (47.7)
Nonsquamous	98 (44.7)	57 (52.3)
PD-L1 status, No. (%)		
<1% (negative)	86 (39.3)	36 (33.0)
≥1% (positive)	113 (51.6)	60 (55.0)
Unknown	20 (9.1)	13 (11.9)
EGFR mutation, No. (%)		
Positive	7 (3.2)	6 (5.5)
Negative	112 (51.1)	60 (55.0)
Unknown[b]	100 (45.7)	43 (39.4)
Disease stage, No. (%)[c,d]		
IIIA	76 (34.7)	37 (33.9)
IIIB	109 (49.8)	51 (46.8)
IIIC	33 (15.1)	20 (18.3)
IV	1 (0.5)	1 (0.9)
TNM class at screening, No. (%)		
Primary tumor, No. (%)		
TX	2 (0.9)	1 (0.9)
T1	15 (6.8)	10 (9.2)
T2	37 (16.9)	13 (11.9)
T3	39 (17.8)	32 (29.4)
T4	126 (57.5)	53 (48.6)
Regional lymph nodes, No. (%)		
N0	25 (11.4)	7 (6.4)
N1	16 (7.3)	14 (12.8)
N2	124 (56.6)	60 (55.0)

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TABLE 1. Baseline Patient Demographics and Disease Characteristics (ITT population) (continued)

Characteristic	Durvalumab + CRT (n = 219)	Placebo + CRT (n = 109)
N3	54 (24.7)	28 (25.7)
Distant metastases, No. (%)		
M0	218 (99.5)	108 (99.1)
M1b	1 (0.5)	1 (0.9)

NOTE. Data cutoff date, September 7, 2023.
Abbreviations: CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; IASLC, International Association for the Study of Lung Cancer; ITT, intention-to-treat.
[a]At diagnosis.
[b]In the durvalumab and placebo arms, respectively, *EGFR* status was unknown in 32 (49.2%) of 65 and 13 (33.3%) of 39 patients enrolled in Asia; 45 (41.7%) of 108 and 22 (47.8%) of 46 patients enrolled in Europe; and 23 (50.0%) of 46 and eight (33.3%) of 24 patients enrolled in Central or South America.
[c]Per eCRF.
[d]According to version 8 of the IASLC Staging Manual in Thoracic Oncology.[30]

grade 3 and 4 AEs (57.1% *v* 52.8%), AEs leading to discontinuation of durvalumab/placebo (14.2% *v* 5.6%), and fatal AEs (6.8% *v* 4.6%) were more common with durvalumab than placebo from 0 to ≤4 months. Fatal AEs in the durvalumab arm from 0 to ≤4 months were largely driven by fatal infections/infestations (n = 6) and respiratory, thoracic, and mediastinal disorders (mainly hemoptysis [n = 2] and pulmonary hemorrhage [n = 2]; Data Supplement, Table S10); none of these events occurred in the placebo arm during this time.

DISCUSSION

In PACIFIC-2, simultaneous durvalumab plus definitive cCRT followed by consolidation durvalumab did not significantly improve PFS versus cCRT plus placebo in patients with unresectable stage III NSCLC. Although 2- and 3-year PFS rates were numerically higher with durvalumab versus placebo, Kaplan-Meier curves did not separate in the first 6 months. Key secondary end points were consistent with the primary end point, with no significant difference in ORR or OS observed between arms. Subgroup analyses were largely consistent with the overall analyses; although numerical HR differences were observed for some subgroups, results should be interpreted with caution given the small number of patients and events.

The safety profile of durvalumab in PACIFIC-2 was generally consistent with durvalumab's known profile,[1,2] which is notable given that patients received durvalumab both in combination with cCRT and until progression. However, important between-arm differences were observed in fatal AEs and AEs leading to treatment discontinuation, which were more prevalent with durvalumab and affected the proportion of patients receiving consolidation treatment. These differences were most pronounced within the first 4 months of treatment, which approximates the duration of SoC cCRT and post-CRT convalescence. The difference in fatal AEs occurring from 0 to ≤4 months after random assignment was driven largely by hemoptyses/pulmonary hemorrhages and infections/infestations.

Of the eight fatal bleeding events reported in PACIFIC-2, six occurred in the durvalumab arm, with four occurring in the first 4 months of treatment. The frequency and timing of these events in the durvalumab arm may be explained by differences in baseline disease characteristics, as most events occurred in patients with risk factors for pulmonary hemorrhage from thoracic irradiation (eg, squamous histology, stage T4 tumors, and invasion of major thoracic vessels), which were more common in the durvalumab arm.[32] Among 43 (13.1%) patients with T4 tumors invading the heart or major thoracic vessels at baseline, 31 (9.5%) had squamous histology, 25 of whom were randomly assigned to durvalumab (Data Supplement, Table S11).

Fatal infections were also more prevalent with durvalumab versus placebo (6.8% *v* 1.9%), primarily during the first 4 months (2.7% *v* 0%) or beyond 16 months (2.7% *v* 0%) of treatment (Data Supplement, Table S10). Beyond 16 months, this may have been influenced by long treatment duration (up to 63 months) and the COVID-19 pandemic (two deaths due to documented COVID-19 in the durvalumab arm). However, the difference during the first 4 months of treatment, when CRT was administered and steroids were more likely to be administered, is notable. Six fatal infections occurred in the durvalumab arm during this period (pneumonia, n = 4; septic shock, n = 1 [K. pneumoniae]; sepsis, n = 1 [C. difficile per blood culture]), versus 0 in the placebo arm. This difference may have been influenced by higher rates of grade ≥3 neutropenia in the durvalumab arm (13.7% *v* 7.4%; Table 2) and is consistent with a recent analysis indicating that risk of severe infection is increased when combining chemotherapy with immunotherapy.[33]

The overall rate of fatal AEs (13.7%) in the durvalumab arm was consistent with rates observed in phase II studies of simultaneous treatment with PD-(L)1 inhibitors and

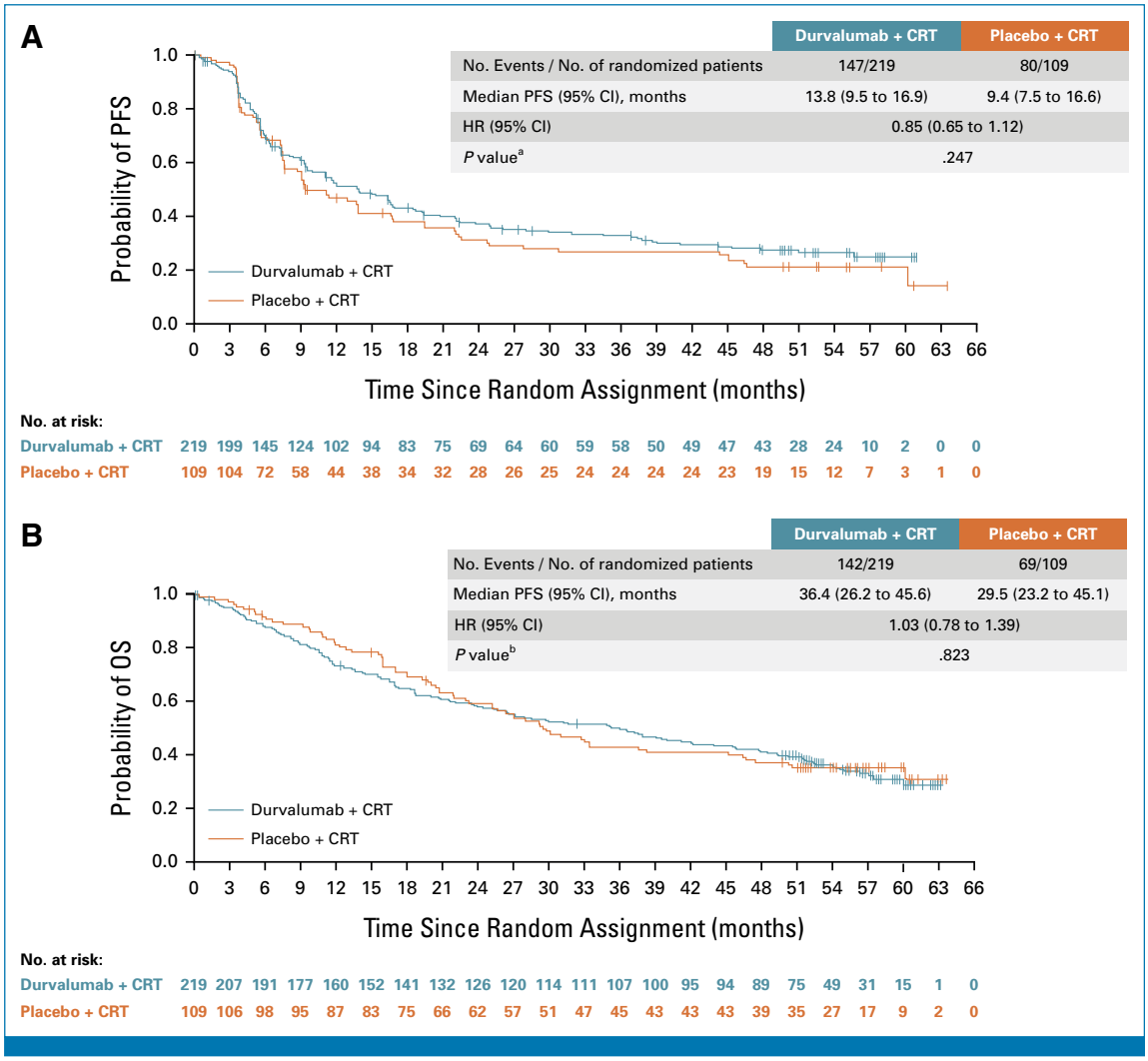

FIG 2. Kaplan-Meier analysis of (A) PFS by BICR and (B) OS (ITT population). Tick marks on the curves indicate censored observations. PFS per RECIST v1.1. PFS and OS were analyzed using a stratified log-rank test adjusting for age and disease stage, with HRs and 95% CIs estimated using a Cox proportional hazards model. Kaplan-Meier methodology was used to calculate medians for time-to-event end points. Data cutoff date, September 7, 2023. [a]Based on the Lan and DeMets approach that approximates the O'Brien Fleming spending functions[42]; the two-sided *P* value boundary for declaring statistical significance for PFS is .0416 for an overall 5% alpha. [b]The two-sided *P* value boundary for declaring statistical significance for OS is .045 or .05 depending on the previous levels of the multiple testing procedure. BICR, blinded independent central review; CRT, chemoradiotherapy; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

cCRT.[24,25,29] In addition, the overall rate of fatal pulmonary hemorrhage in PACIFIC-2 was consistent with that previously reported for patients with stage III NSCLC treated with CRT.[23,24,32]

Consistent with durvalumab's mechanism of action, imAEs were more common with durvalumab (34.7%) versus placebo (15.7%); however, the nature and incidence of imAEs with durvalumab were consistent with durvalumab's established safety profile.[1,2] The addition of durvalumab to CRT did not appear to increase the frequency or severity of pneumonitis compared with durvalumab's established safety profile.[1,2]

The rationale for simultaneous administration of immunotherapy and CRT in PACIFIC-2 was to maximize potential synergy with the immunomodulatory effects of CRT, thereby increasing the likelihood, depth, and DoR from the start of definitive therapy. This strategy inherently included many patients who otherwise would not have the opportunity to benefit from a consolidation-only approach due to early progression, radiation pneumonitis, or other toxicity potentially disqualifying them from receiving consolidation durvalumab. However, in PACIFIC-2 this approach failed to provide additional benefit and increased toxicity during CRT compared with CRT alone, with a relatively high rate of durvalumab discontinuations during or shortly after CRT.

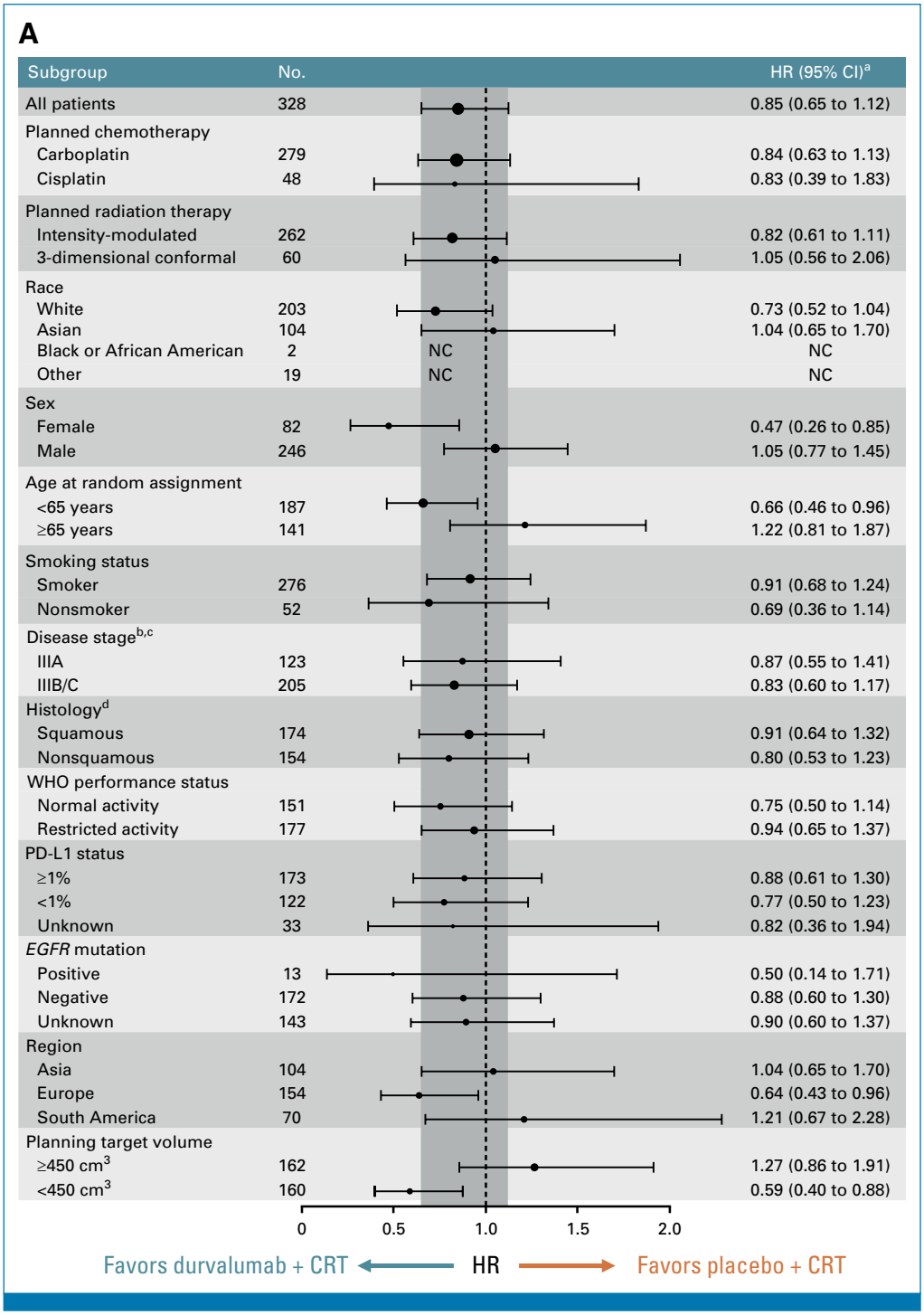

FIG 3. Forest plots of (A) PFS by BICR and (B) OS in prespecified patient subgroups (ITT population). PFS per RECIST v1.1. An HR of <1 favors durvalumab and is associated with a longer PFS/OS than placebo. The size of circle is proportional to the number of events. The gray band represents the 95% CI for the main PFS/OS HR. For all patients, the analysis is based on the main stratified analysis, whereas for the subgroups, the HR and CI were calculated using an unstratified Cox proportional hazards model, with treatment as the only covariate and ties handled by Efron approach. Data cutoff date, September 7, 2023. [a]HRs and 95% CIs were not calculated if a subgroup had fewer than five events in either treatment arm. [b]At screening. [c]According to version 8 of the IASLC Staging Manual in Thoracic Oncology.[30] [d]Per IVRS. BICR, blinded independent central review; EGFR, epidermal growth factor receptor; HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; ITT, intention-to-treat; IVRS, interactive voice response system; NC, not calculable; OS, overall survival; PFS, progression-free survival. (continued on following page)

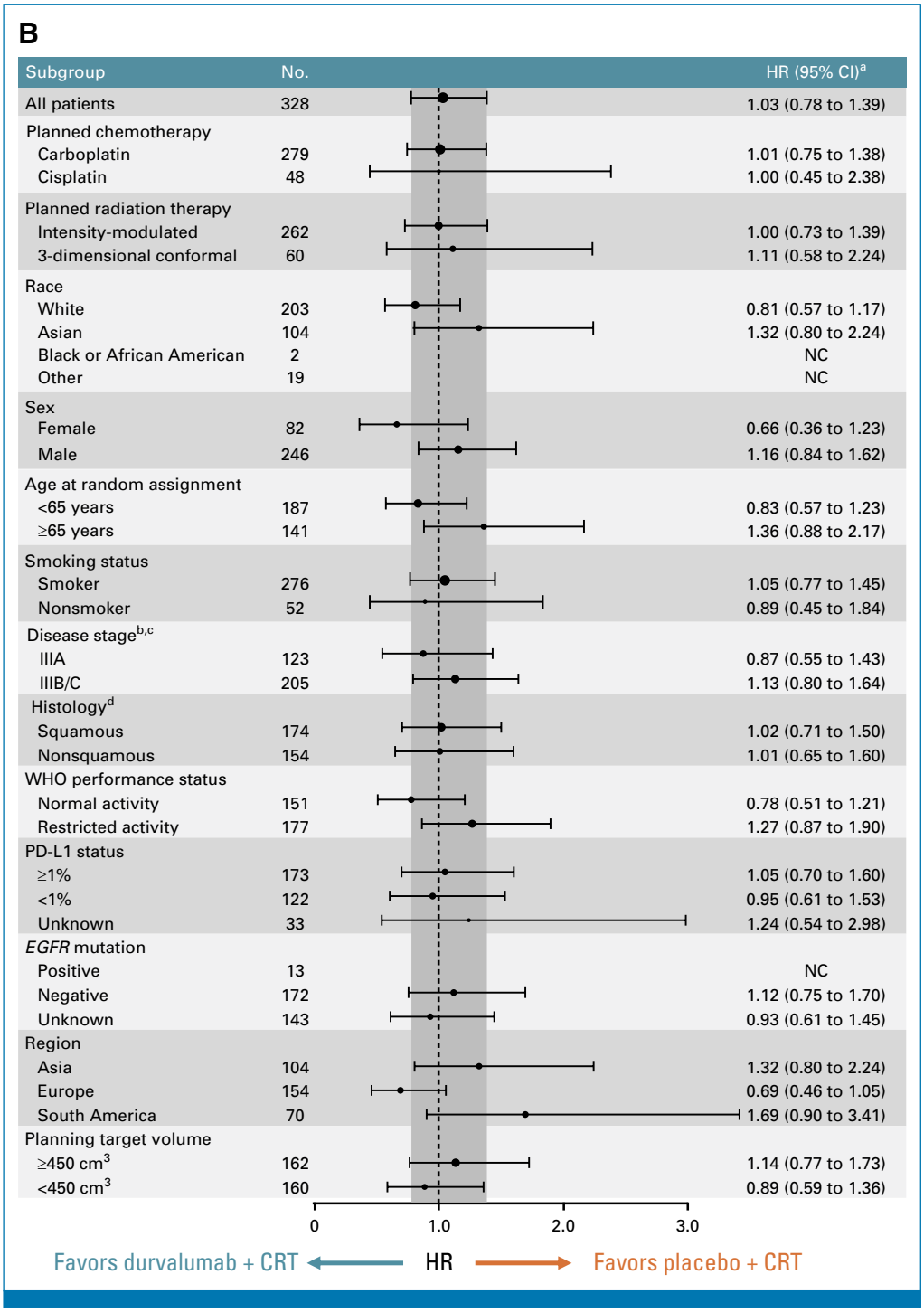

FIG 3. (Continued).

This observation is consistent with recently reported results from CheckMate-73L, a phase III trial that found simultaneous immunotherapy (nivolumab) plus CRT followed by consolidation immunotherapy (nivolumab plus ipilimumab) did not improve PFS versus the PACIFIC regimen in this setting.[34] Although immunotherapy at other points in the treatment journey (eg, induction therapy) may yet provide benefit to patients,[35] the results of PACIFIC-2 suggest that the current strategy of consolidation immunotherapy after cCRT, as in PACIFIC,[1-3] may be the most appropriate application of these treatments.

The median OS with durvalumab in PACIFIC-2 was lower than in PACIFIC (36.4 *v* 47.5 months), whereas the placebo arms performed similarly (29.5 *v* 29.1 months).[3] However, it is important to note differences between the study populations driven by study design. In PACIFIC, patients must have completed a full course of cCRT, had no evidence of

TABLE 2. Treatment-Emergent AEs (Safety Analysis Set)

AE	Durvalumab + CRT (n = 219), No. (%)		Placebo + CRT (n = 108), No. (%)	
Any grade	216 (98.6)		108 (100)	
Treatment-related	206 (94.1)		99 (91.7)	
Related to durvalumab/placebo[a]	130 (59.4)		48 (44.4)	
Maximum grade 3 or 4[b]	117 (53.4)		64 (59.3)	
Treatment-related	91 (41.6)		51 (47.2)	
Related to durvalumab/placebo[a]	32 (14.6)		15 (13.9)	
Grade 5 (outcome of death)	30 (13.7)		11 (10.2)	
Treatment-related	2 (0.9)		2 (1.9)	
Related to durvalumab/placebo[a]	1 (0.5)		2 (1.9)	
Serious AE	103 (47.0)		56 (51.9)	
Treatment-related	52 (23.7)		33 (30.6)	
Related to durvalumab/placebo[a]	28 (12.8)		14 (13.0)	
Any TEAE leading to discontinuation of durvalumab/placebo	56 (25.6)		13 (12.0)	
Most common TEAE (≥15% in any arm)[c]	Any grade	Grade ≥3	Any grade	Grade ≥3
Anemia	92 (42.0)	16 (7.3)	41 (38.0)	11 (10.2)
Pneumonitis or radiation pneumonitis (group term)	63 (28.8)	10 (4.6)	31 (28.7)	6 (5.6)
Neutropenia	60 (27.4)	30 (13.7)	28 (25.9)	8 (7.4)
Nausea	56 (25.6)	2 (0.9)	26 (24.1)	0
Leukopenia	49 (22.4)	20 (9.1)	19 (17.6)	8 (7.4)
Decreased appetite	46 (21.0)	1 (0.5)	21 (19.4)	0
Cough	46 (21.0)	0	18 (16.7)	2 (1.9)
Thrombocytopenia	44 (20.1)	10 (4.6)	20 (18.5)	3 (2.8)
Pneumonia	43 (19.6)	24 (11.0)	23 (21.3)	13 (12.0)
Radiation esophagitis	42 (19.2)	6 (2.7)	23 (21.3)	4 (3.7)
Fatigue	38 (17.4)	4 (1.8)	16 (14.8)	1 (0.9)
Hypothyroidism	37 (16.9)	1 (0.5)	9 (8.3)	0
Constipation	35 (16.0)	2 (0.9)	31 (28.7)	0
Lymphopenia	29 (13.2)	21 (9.6)	18 (16.7)	15 (13.9)

NOTE. Per NCI-CTCAE v4.03. Data cutoff date, September 7, 2023. The safety analysis set includes all patients who underwent random assignment and received at least one dose of trial treatment or placebo; one patient assigned to the placebo group erroneously received a single cycle of durvalumab and was included in the durvalumab group for the safety analysis set.

Abbreviations: AE, adverse event; CRT, chemoradiotherapy; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent AE.

[a]Any AE causally related to durvalumab/placebo, regardless of causality to standard-of-care CRT.

[b]Excludes any patients who experienced any AE of maximum CTCAE grade 5.

[c]In descending order of frequency of any-grade AEs based on the durvalumab + CRT arm.

progression during or shortly after completion of cCRT, had recovered from any cCRT-related toxicities to grade ≤2, and had an ECOG PS of 0 or 1 after cCRT.[1] By comparison, patients in PACIFIC-2 were randomly assigned before cCRT, before it was known which patients would tolerate and/or respond to cCRT; thus, PACIFIC-2 inherently included patients who otherwise would have been among the approximately 27%-50% of CRT patients ineligible for consolidation durvalumab due to early progression or CRT-related toxicity.[10-12]

PACIFIC-2 has several limitations. First, at the time the PACIFIC-2 study was initiated, long-term outcomes, including OS, from PACIFIC were still unknown and the PACIFIC regimen had yet to be established as a global SoC in this population; thus, the control arm for PACIFIC-2 does not reflect the current SoC (ie, the PACIFIC regimen). Second, although *EGFR* testing has become more prevalent in this setting over time, *EGFR* testing was not globally routine clinical practice before initiation of PACIFIC-2, with testing rates varying widely by region, and was not required for study enrollment.[36-39] Since the initiation of PACIFIC-2, evidence has emerged that patients with *EGFR* mutations derive limited benefit from anti–PD-(L)1 therapies.[40] Moreover, the treatment landscape for *EGFR*-mutated NSCLC has changed since the

initiation of PACIFIC-2. For example, the phase III LAURA trial (ClinicalTrials.gov identifier: NCT03521154) established the benefit of osimertinib in this population as recently as 2024.[41] Thus, lack of mandated *EGFR* testing in PACIFIC-2 is an important limitation. On the basis of durvalumab's mechanism of action, PD-L1 testing was prioritized over *EGFR* testing in PACIFIC-2, and 43.6% of patients had unknown *EGFR* status; however, most (172 of 185) patients with known *EGFR* status did not have a mutation, and regional differences in the proportion of patients with unknown *EGFR* status were modest. Finally, although most patients in PACIFIC-2 reached consolidation treatment before the COVID-19 pandemic, the pandemic may have affected accessibility of postdiscontinuation therapy.

In PACIFIC-2, simultaneous durvalumab plus definitive cCRT followed by consolidation durvalumab did not significantly improve PFS or OS versus cCRT plus placebo for patients with unresectable stage III NSCLC. The PACIFIC regimen, comprising 12 months of consolidation durvalumab after definitive cCRT among patients without progression after cCRT, has demonstrated robust efficacy with 5 years of follow-up, with replicable safety and efficacy, and remains the SoC in this setting.[2,3,6-9]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Simultaneous Durvalumab and Platinum-Based Chemoradiotherapy in Unresectable Stage III Non–Small Cell Lung Cancer: The Phase III PACIFIC-2 Study

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