ORIGINAL ARTICLE

Symptomatic Pneumonitis With Durvalumab After Concurrent Chemoradiotherapy in Unresectable Stage III NSCLC

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ABSTRACT

Introduction: In the placebo-controlled, phase 3 PACIFIC trial, durvalumab significantly prolonged progression-free survival (PFS) ($p < 0.0001$) and overall survival (OS) ($p = 0.00251$) in patients with unresectable stage III NSCLC and no progression after platinum-based concurrent chemoradiotherapy (cCRT). Pneumonitis or radiation pneumonitis (PRP) was common in both arms. We report exploratory analyses evaluating the association of symptomatic (grade ≥2) PRP (G2+PRP) with baseline factors and clinical outcomes.

Methods: Patients with WHO performance status of 0 or 1 were randomized (2:1) to 12 months of durvalumab or

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placebo, 1 to 42 days after cCRT. Associations between baseline factors and on-study G2+PRP in durvalumab-treated patients were investigated using univariate and multivariate logistic regression. PFS and OS were analyzed using Cox proportional hazards models adjusted for time-dependent G2+PRP plus covariates for randomization stratification factors without and with additional baseline factors.

Results: On-study G2+PRP occurred in 94 of 475 (19.8%) and 33 of 234 patients (14.1%) on durvalumab and placebo, respectively (median follow-up, 25.2 mo); grade greater than or equal to 3 PRP was uncommon (4.6% and 4.7%, respectively). Time to onset and resolution of G2+PRP was similar with durvalumab and placebo. Univariate and multivariate analyses identified patients treated in Asia, those with stage IIIA disease, those with performance status of 1, and those who had not received induction chemotherapy as having a higher risk of G2+PRP. PFS and OS benefit favoring durvalumab versus placebo was maintained regardless of time-dependent G2+PRP.

Conclusions: Factors associated with higher risk of G2+PRP with durvalumab after cCRT were identified. Clinical benefit was maintained regardless of on-study G2+PRP, suggesting the risk of this event should not deter the use of durvalumab in eligible patients with unresectable stage III NSCLC.

Keywords: Immunotherapy; Radiotherapy; Durvalumab; Pulmonary toxicity; Locally advanced NSCLC

Introduction

Historically, the standard of care for patients with unresectable stage III NSCLC and adequate performance status (PS) was platinum-based chemotherapy and radiotherapy (RT) administered concurrently (or sequentially in patients considered unsuitable for concurrent treatment), leading to 2-year overall survival (OS) rates between 50% and 60%.[1–3]

Immune checkpoint inhibition (ICI) of the programmed cell death-(ligand) 1 (PD-[L]1) pathway has revolutionized the management of advanced NSCLC. PACIFIC (NCT02125461) was the first phase 3 trial to reveal the benefits of ICI in nonmetastatic NSCLC; patients with unresectable stage III NSCLC and no tumor progression after platinum-based, concurrent chemoradiotherapy (cCRT) were randomized to receive durvalumab or placebo for up to 12 months. Durvalumab significantly prolonged progression-free survival (PFS) (stratified hazard ratio [HR] = 0.52, 95% confidence interval [CI]: 0.42–0.65, $p < 0.0001$) and OS (stratified HR = 0.68, 95% CI: 0.53–0.87, $p = 0.00251$), with manageable safety and no detrimental impact on quality of life versus placebo.[4–7] Moreover, a 5-year update revealed sustained OS and durable PFS benefit with durvalumab.[8] The PACIFIC regimen (consolidation durvalumab after platinum-based CRT) received approvals in the United States of America, Japan, Europe, and elsewhere[6,9,10] and has become a standard of care in this setting.

Although ICI is generally well tolerated compared with chemotherapy, ICI-related toxicities may occur.[11,12] Of these, pneumonitis can be the most serious[13] and is of particular concern in the post-CRT setting, as it is also a common complication of radiation (RT-pneumonitis). When ICI-related pneumonitis is suspected, clinical vigilance is required to effectively diagnose and manage this adverse event (AE).[14] Interventions range from observation (for grade 1 [asymptomatic] pneumonitis; graded per Common Terminology Criteria for Adverse Events [CTCAE] and typically diagnosed based on radiological findings) to temporary or permanent ICI cessation and immunosuppressive therapy (for grade ≥2 [symptomatic] pneumonitis).[12,15]

Challenges associated with the differential diagnosis of pneumonitis with ICI delivered soon after CRT, and differences in diagnostic procedures across centers (as allowed by the PACIFIC protocol, which did not mandate specific tests), meant the attribution of pneumonitis to ICI could not be established reliably in PACIFIC. Therefore, all-cause pneumonitis (pneumonitis or RT-pneumonitis) was reported. Any-grade pneumonitis or RT-pneumonitis occurred in 33.9% and 24.8% of patients with durvalumab and placebo, respectively; grade 3 or 4 events were reported in 3.4% and 3.0% of patients, respectively.[6] With broad application of the PACIFIC regimen, the diagnosis and management of pneumonitis or RT-pneumonitis in this setting, particularly clinically relevant grade greater than or equal to 2 events, has become a subject of considerable interest. To give further insight to clinicians, we report detailed, post hoc analyses from PACIFIC that characterize grade greater than or equal to 2 pneumonitis or RT-pneumonitis and evaluate its potential association with baseline factors and clinical outcomes.

Materials and Methods

Patients, Study Design, and Treatment

PACIFIC is a phase 3, randomized, double-blind trial of adult patients with unresectable stage III NSCLC, WHO PS 0 or 1, any tumor PD-L1 status, and no tumor progression after platinum-based cCRT (≥2 cycles). Patients

with unresolved grade greater than 2 toxicities (CTCAE version 4.03), or grade greater than or equal to 2 pneumonitis or RT-pneumonitis, from prior cCRT were excluded. Participants were randomized (2:1), 1 to 42 days after completing cCRT, to durvalumab (10 mg/kg intravenously) or placebo, administered every 2 weeks for 12 months or until confirmed progression, initiation of alternative anticancer therapy, unacceptable toxicity, or consent withdrawal. Randomization was stratified by age, sex, and smoking history. All patients provided written informed consent for participation in the trial. Further details of the trial design are published elsewhere.[4]

The primary end points were PFS (according to Response Evaluation Criteria in Solid Tumors version 1.1; assessed by blinded independent central review) and OS. Secondary end points included time to death or distant metastasis (TTDM; blinded independent central review) and safety.

Assessment of Pneumonitis or RT-Pneumonitis

Pneumonitis or RT-pneumonitis was investigator assessed (CTCAE version 4.03) and defined as a focal or diffuse inflammation of the lung parenchyma; this included diagnoses of acute interstitial pneumonitis, interstitial lung disease, pneumonitis, pulmonary fibrosis, alveolitis, diffuse alveolar damage, and RT-pneumonitis. In all cases, institutional standards in serologic, immunologic, and histologic testing were recommended in the protocol to rule out neoplastic, infectious, or other possible causes. On-study pneumonitis or RT-pneumonitis was defined as a de novo event that occurred during study treatment or a preexisting grade 1 event that worsened during the study and within 90 days of last dose of study medication or before the initiation of subsequent anticancer therapy (whichever occurred earlier). We characterized time to onset and resolution of grade greater than or equal to 2 pneumonitis or RT-pneumonitis and investigated the association of grade greater than or equal to 2 pneumonitis or RT-pneumonitis with (1) baseline characteristics and (2) study treatment exposure. Moreover, we investigated the association of grade greater than or equal to 2 pneumonitis or RT-pneumonitis with efficacy and safety outcomes and summarized the clinical management and outcomes of grade greater than or equal to 2 pneumonitis or RT-pneumonitis cases. Guidelines for managing ICI-related toxicities, including pneumonitis (see the Supplementary Methods), were provided to the investigators; these were considered recommendations, and, ultimately, management decisions were left to the investigator's clinical judgment.

Statistical Analyses

All analyses were based on the data cutoff for the primary OS analysis (March 22, 2018).[5] The following were summarized with descriptive statistics using the as-treated population: times to onset and resolution of grade greater than or equal to 2 pneumonitis or RT-pneumonitis; study treatment exposure by the presence or absence of grade greater than or equal to 2 pneumonitis or RT-pneumonitis; treatment-emergent, all-causality AEs by the presence or absence of grade greater than or equal to 2 pneumonitis or RT-pneumonitis; and clinical management and outcomes of grade greater than or equal to 2 pneumonitis or RT-pneumonitis cases.

We investigated associations between baseline clinical characteristics and grade greater than or equal to 2 pneumonitis or RT-pneumonitis with descriptive statistics and regression analyses using the intent-to-treat population. Univariate logistic regression models were used to assess the relative risk by odds ratios (ORs) and 95% CIs for occurrence of grade greater than or equal to 2 pneumonitis or RT-pneumonitis for individual baseline characteristics. Multivariate logistic regression models were used to investigate the relative importance of these characteristics and interactions between them, through backward selection. Regression analyses were performed in the durvalumab arm using the as-treated population; similar analyses were not performed for placebo because the sample size was insufficient.

To investigate the possible impact of on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis on clinical benefit with durvalumab versus placebo, we performed analyses to assess whether there was any change in observed treatment effects (HRs) for PFS, OS, and TTDM when adjusting for the occurrence of this event. Aligned with the methodology used for prespecified time-to-event analyses from PACIFIC, Cox proportional hazards models were used to estimate HRs and 95% CIs (based on the intent-to-treat population) for durvalumab versus placebo stratified by age, sex, and smoking history (the randomization stratification factors). Two models were fitted to the efficacy data to assess the impact of grade greater than or equal to 2 pneumonitis or RT-pneumonitis. Occurrence of on-study pneumonitis is a post-baseline event and as such has an implicit association with duration of therapy and thus the efficacy measures; therefore, model 1 added a covariate for time-dependent grade greater than or equal to 2 pneumonitis or RT-pneumonitis. Acknowledging the risk of (time-dependent) pneumonitis is also affected by baseline characteristics; model 2 incorporated further covariates for additional baseline characteristics (disease stage, histology [squamous vs nonsquamous], best response to prior therapy, WHO PS, region, and race).

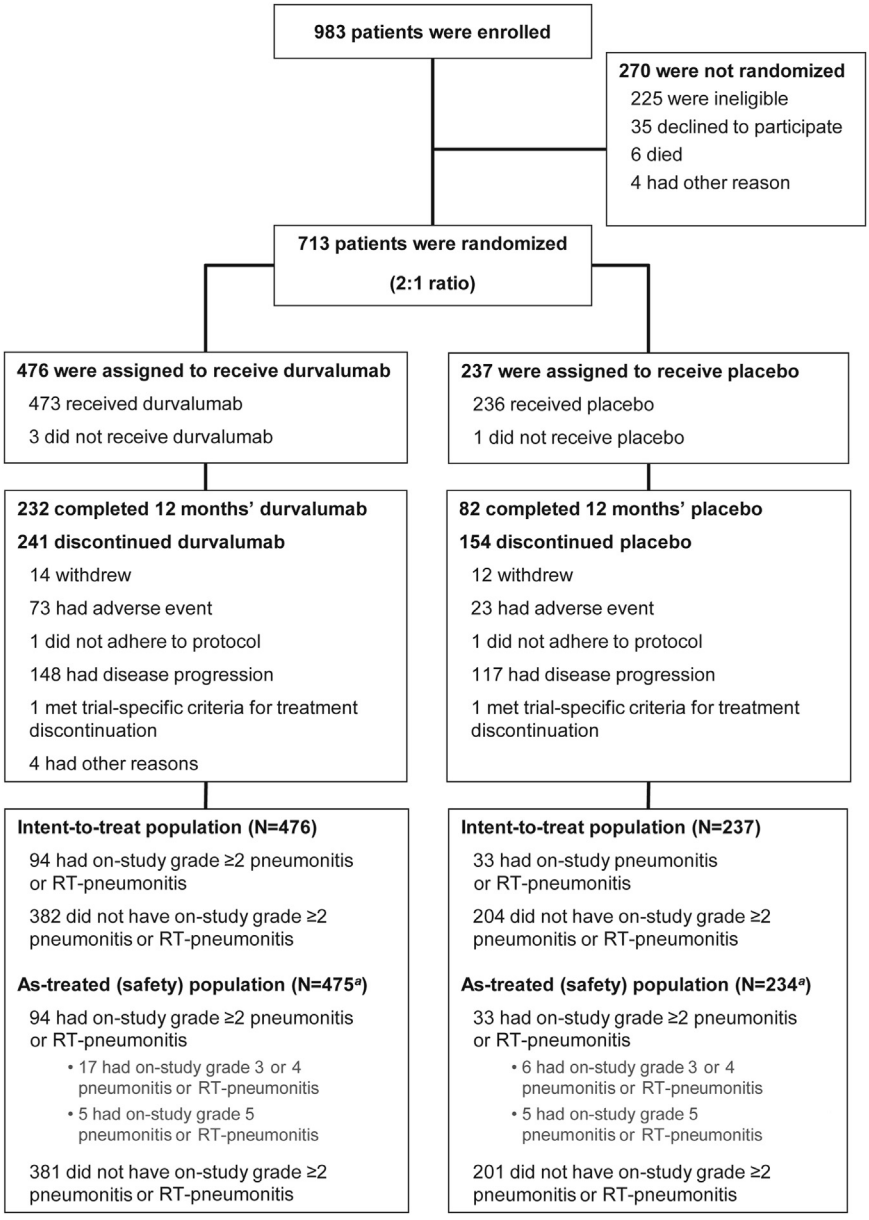

Figure 1. CONSORT Diagram. Shown are data collected up to March 22, 2018, the last data cutoff for which safety data (including pneumonitis or RT-pneumonitis) was analyzed. Patients who completed (protocol-defined) 12 months' durvalumab or placebo are those for whom the electronic case report form revealed that they had received the maximum number of cycles of study treatment. [a]Two patients who were randomized to placebo erroneously received one dose of durvalumab and were included in the durvalumab as-treated population. RT, radiotherapy.

Results

Patients and Grade Greater Than or Equal to 2 Pneumonitis or RT-Pneumonitis

In the PACIFIC trial, 709 of 713 patients who were randomized to durvalumab (n/N = 473 of 476) or placebo (n/N = 236 of 237) received a study treatment (Fig. 1); two patients assigned to placebo erroneously received one dose of durvalumab and were included in the durvalumab as-treated population. As of March 22, 2018 (median follow-up, 25.2 mo [range, 0.2–43.1]), on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis had occurred in 94 of 475 (19.8%) and 33 of 234 patients (14.1%) who received durvalumab and placebo, respectively (as-treated population); 22 of 475 (4.6%) and 11 of 234 patients (4.7%) experienced grade greater than or equal to 3 events and five of 475 (1.1%) and five of 234 (2.1%) experienced grade 5 (fatal) events, respectively. One patient (durvalumab) with preexisting grade 1 pneumonitis or RT-pneumonitis at baseline experienced on-study worsening of their event (to grade 2). Recurrence of on-study, grade greater than or equal to 2 pneumonitis

or RT-pneumonitis was uncommon (durvalumab, three of 475 [0.6%]; placebo, two of 234 [0.9%]), and no patients experienced more than 2 events. A breakdown of on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis events by the investigators' preferred attribution term is provided (Supplementary Table 1).

Although the PACIFIC protocol originally mandated randomization to study treatment within 14 days of completing CRT, this criterion was amended to 42 days to allow enrollment of patients recovering from CRT-related toxicities.[4] Among patients who received durvalumab and were randomized less than 14 days post-CRT, 20 of 120 (16.7%) experienced grade greater than or equal to 2 pneumonitis or RT-pneumonitis (five of 120 [4.2%] had grade greater than or equal to 3 events; none were fatal); meanwhile, 74 of 355 (20.8%) who were randomized more than or equal to 14 days post-CRT experienced grade greater than or equal to 2 pneumonitis or RT-pneumonitis (17 of 355 [4.8%] had grade greater than or equal to 3 events; five of 355 had fatal events [1.4%]). Among patients who received placebo and were randomized less than 14 days post-CRT, five of 60 (8.3%) experienced grade greater than or equal to 2 pneumonitis or RT-pneumonitis (three of 60 [5.0%] had grade greater than or equal to 3 events; two of 60 had fatal events [3.3%]); meanwhile, 28 of 174 (16.1%) patients who were randomized more than or equal to 14 days post-CRT experienced grade greater than or equal to 2 pneumonitis or RT-pneumonitis (eight of 174 [4.6%] had grade greater than or equal to 3 events; three of 174 had fatal events [1.7%]).

Times to Onset and Resolution of Grade Greater Than or Equal to 2 Pneumonitis or RT-Pneumonitis

Median time to onset of grade greater than or equal to 2 pneumonitis or RT-pneumonitis from initiation of durvalumab (53.5 d [range: 2–406]; n = 94) and placebo (55.0 d [14–253]; n = 33) was similar; onset occurred more than 90 days after the first dose in 18 of 94 (19.1%) and seven of 33 patients (21.2%) with durvalumab and placebo, respectively. Median time to onset from the completion of RT was also similar with durvalumab (70.0 d [range: 21–433]; n = 94) and placebo (79.0 d [34–271]; n = 33). Excluding events ongoing at the data cutoff, median time to resolution of grade greater than or equal to 2 pneumonitis or RT-pneumonitis (or death) was similar with durvalumab (57.5 d [2–588]; n = 64) and placebo (52.0 d [4–186]; n = 19). Times to onset and resolution of grade greater than or equal to 2 pneumonitis or RT-pneumonitis according to the time elapsed between RT completion and randomization to durvalumab or placebo are provided (Supplementary Table 2).

Association Between Grade Greater Than or Equal to 2 Pneumonitis or RT-Pneumonitis and Baseline Characteristics

Baseline characteristics were generally well balanced irrespective of the occurrence of on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis (Supplementary Tables 3–5). Nevertheless, in both the durvalumab and placebo arms, a higher proportion of patients with grade greater than or equal to 2 pneumonitis or RT-pneumonitis were of Asian ethnicity (durvalumab, 35 of 94 [37.2%]; placebo, 16 of 33 [48.5%]) versus those without grade greater than or equal to 2 pneumonitis or RT-pneumonitis (durvalumab, 85 of 382 [22.3%]; placebo, 56 of 204 [27.5%]); a higher proportion of patients with grade greater than or equal to 2 pneumonitis or RT-pneumonitis were treated in Asia (durvalumab, 31 of 94 [33.0%]; placebo, 15 of 33 [45.5%]) versus those without grade greater than or equal to 2 pneumonitis or RT-pneumonitis (durvalumab, 78 of 382 [20.4%]; placebo, 53 of 204 [26.0%]); a higher proportion of patients with grade greater than or equal to 2 pneumonitis or RT-pneumonitis were nonsmokers (durvalumab, 18 of 94 [19.1%]; placebo, six of 33 [18.2%]) versus those without grade greater than or equal to 2 pneumonitis or RT-pneumonitis (durvalumab, 25 of 382 [6.5%]; placebo, 15 of 204 [7.4%]); and a lower proportion of patients with grade greater than or equal to 2 pneumonitis or RT-pneumonitis had prior chronic obstructive pulmonary disease (COPD) (durvalumab, 18 of 94 [19.1%]; placebo, four of 33 [12.1%]) versus those without grade greater than or equal to 2 pneumonitis or RT-pneumonitis (durvalumab, 101 of 382 [26.4%]; placebo, 54 of 204 [26.5%]). Moreover, in the durvalumab arm only, a higher proportion of patients with grade greater than or equal to 2 pneumonitis or RT-pneumonitis had PS 1 (60 of 94 [63.8%]) versus those without grade greater than or equal to 2 pneumonitis or RT-pneumonitis (180 of 382 [47.1%]), and a higher proportion of patients with grade greater than or equal to 2 pneumonitis or RT-pneumonitis had stage IIIA disease (61 of 94 [64.9%]) versus those without grade greater than or equal to 2 pneumonitis or RT-pneumonitis (191 of 382 [50.0%]).

Most patients received a RT dose between 54 and 66 gray (Gy) (Supplementary Table 6). The median total RT dose among patients with on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis (durvalumab, 60.0 Gy [range: 55.0–70.2]; placebo, 60.6 Gy [60.0–70.2]) was numerically lower versus those without grade greater than or equal to 2 pneumonitis or

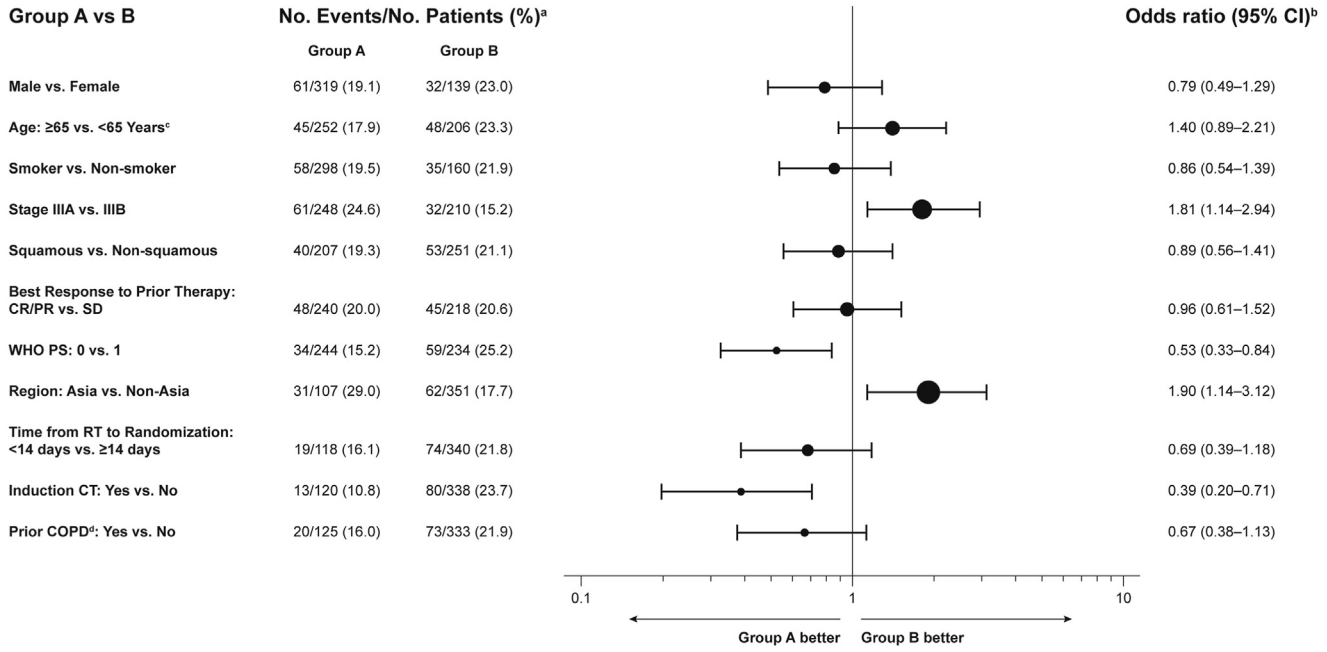

Figure 2. Univariate analyses of baseline factors potentially associated with grade greater than or equal to 2 pneumonitis or RT-pneumonitis in durvalumab-treated patients. [a]Seventeen patients were excluded from the analyses due to missing data for stage and/or best response to prior therapy. [b]The OR of grade ≥2 pneumonitis or RT-pneumonitis occurrence was derived using logistic regression; an OR for group A versus group B of <1 implies lower risk of grade ≥2 pneumonitis or RT-pneumonitis for group A relative to group B. [c]Age at randomization. [d]COPD was analyzed as a grouped term comprising diagnoses of COPD, bronchitis chronic, emphysema, and obstructive airways disorder. CI, confidence interval; COPD, chronic obstructive pulmonary disease; CR, complete response; CT, chemotherapy; OR, odds ratio; PR, partial response; RT, radiotherapy; SD, stable disease; PS, performance status.

RT-pneumonitis (durvalumab, 61.5 Gy [45.0–70.2]; placebo, 63.0 Gy [54.0–70.2]), regardless of treatment arm. Carboplatin–paclitaxel was the most used chemotherapy regimen during platinum-based CRT, followed by cisplatin–etoposide; similar proportions of patients received these regimens regardless of the occurrence of grade greater than or equal to 2 pneumonitis or RT-pneumonitis in both the durvalumab and placebo arms (Supplementary Table 6). A small proportion of patients received induction chemotherapy before CRT[4]; in the durvalumab arm only, a lower proportion of patients with grade greater than or equal to 2 pneumonitis or RT-pneumonitis (13 of 94 [13.8%]) received induction chemotherapy versus those without grade greater than or equal to 2 pneumonitis or RT-pneumonitis (110 of 382 [28.8%]) (Supplementary Table 6).

Univariate analyses in durvalumab-treated patients identified a higher risk of on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis among patients treated in Asia (OR, 1.90; 95% CI: 1.14–3.12), patients with stage IIIA disease (OR, 1.81; 95% CI: 1.14–2.94), patients with PS 1 (OR, 0.53; 95% CI: 0.33–0.84), and patients who had not received induction chemotherapy (OR, 0.39; 95% CI: 0.20–0.71) (Fig. 2). These factors were also associated with significantly higher risk in multivariate backward-selection analyses (nominal $p < 0.05$) (Supplementary Table 7). The multivariate analyses also identified patients without prior COPD as having a higher risk of grade greater than or equal to 2 pneumonitis or RT-pneumonitis, and multivariate interaction models further identified significant interactions (nominal $p < 0.1$) between (1) PS and prior COPD and (2) geographic region and induction chemotherapy (Supplementary Table 7).

Grade Greater Than or Equal to 2 Pneumonitis or RT-Pneumonitis and Efficacy Outcomes

In the Cox analyses adjusting for time-dependent occurrence of on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis, OS, PFS, and TTDM benefit of durvalumab versus placebo was maintained in both model 1 (which used the trial stratification factors and time-dependent grade ≥2 pneumonitis or RT-pneumonitis as covariates) and model 2 (which further incorporated additional baseline factors); results from both models were consistent with the intent-to-treat analyses (Table 1). The time-dependent covariate for grade greater than or equal to 2 pneumonitis or RT-pneumonitis was not a significant factor for PFS and TTDM in either model (nominal $p > 0.1$) but was nominally significant for OS in both models (patients

Table 1. OS, PFS, and TTDM Adjusted for the Time-Dependent Occurrence of Grade Greater Than or Equal to 2 Pneumonitis or RT-Pneumonitis and for the Intent-to-Treat Population

	No. of Events/No. of Patients (%)		HR (95% CI) for Durvalumab vs. Placebo	
Outcome	Durvalumab	Placebo	Adjusted for Time-Dependent Grade ≥2 Pneumonitis or RT-Pneumonitis	ITT Analysis[a]
OS	183/476 (38.4)	116/237 (48.9)		
Model 1[b]			0.67 (0.53-0.85)	0.68 (0.53-0.87)[5,6]
Model 2[c]			0.63 (0.50-0.80)	–
PFS (BICR)	243/476 (51.1)	173/237 (73.0)		
Model 1[b]			0.54 (0.44-0.66)	0.51 (0.41-0.63)[5]
Model 2[c]			0.52 (0.42-0.64)	–
TTDM (BICR)	182/476 (38.2)	126/237 (53.2)		
Model 1[b]			0.55 (0.44-0.70)	0.53 (0.41-0.68)[5]
Model 2[c]			0.51 (0.41-0.65)	–

[a]For the ITT analyses, PFS, OS, and TTDM were assessed using a stratified Cox proportional hazards model (to estimate HRs and 95% CIs), adjusted for trial stratification factors: age at randomization (<65 vs. ≥65 y), sex (male vs. female), and smoking history (smoker vs. never smoked).[4-6] HR less than 1 favors durvalumab over placebo.
[b]Model 1 (the base model) accounts for stratification factors at randomization (aligned with the ITT analyses) and the time-dependent occurrence of grade greater than or equal to 2 pneumonitis or RT-pneumonitis.
[c]Model 2 is the base model plus additional baseline factors: stage of disease (IIIA vs. IIIB), histology (squamous vs. nonsquamous), best response to prior anticancer therapy (complete response vs. partial response vs. stable disease), WHO performance status (0 vs. 1), region (Asia vs. Europe vs. North America and South America), and race (White vs. Black or African American vs. Asian vs. Other).
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; TTDM, time to death or distant metastasis.

with grade ≥2 pneumonitis or RT-pneumonitis had an increased risk of death at any given time versus those without the event); however, the benefit of durvalumab versus placebo was unchanged when the time-dependent covariate was incorporated into the OS models. Results from Cox models for OS, PFS, and TTDM in subsets of patients with and without on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis (with treatment as the only covariate) are provided (Supplementary Table 8); these subset analyses were limited to patients who received more than or equal to 24 weeks of treatment to address potential bias from misclassification of patients who were not on study treatment long enough to experience pneumonitis.

Grade Greater Than or Equal to 2 Pneumonitis or RT-Pneumonitis and Safety Outcomes

Among patients who experienced on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis, the incidence of serious AEs was proportionally higher with durvalumab (53.2%) versus placebo (36.4%); meanwhile, the incidence of grade 3 or 4 AEs and AEs leading to treatment discontinuation was similar between the treatment arms (Table 2).

When comparing patients with on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis and patients without this event, the incidence of grade 3 or 4 AEs was similar, both for durvalumab and placebo (Table 2). With durvalumab, the incidence of AEs leading to treatment discontinuation (36.2% versus 10.2%), serious AEs (53.2% versus 23.1%), and fatal AEs (7.4% versus 3.7%) was higher among patients with grade greater than or equal to 2 pneumonitis or RT-pneumonitis. Likewise, with placebo, the incidence of AEs leading to treatment discontinuation (33.3% versus 6.0%), serious AEs (36.4% versus 20.9%), and fatal AEs (18.2% versus 4.5%) was higher among patients with grade greater than or equal to 2 pneumonitis or RT-pneumonitis.

Grade Greater Than or Equal to 2 Pneumonitis or RT-Pneumonitis and Study Treatment Exposure

Cumulative exposure to durvalumab (Fig. 3*A*) and placebo (Fig. 3*B*) was proportionally lower among patients with on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis versus those who did not experience this event. Correspondingly, a lower proportion of patients who experienced grade greater than or equal to 2 pneumonitis or RT-pneumonitis completed the (protocol-defined) 12 months of durvalumab therapy (37 of 94 [39.4%] with and 195 of 382 [51.5%] without the event); the trend was similar for placebo (nine of 33 [27.3%] and 73 of 204 [36.0%], respectively) (Supplementary Table 9). With durvalumab, 76 of 94 (80.9%) patients who experienced grade greater than or equal to 2 pneumonitis or RT-pneumonitis stopped treatment to manage this AE; 54 of 76 (71.1%) of these patients were rechallenged with durvalumab, and five of 54 (9.3%) of the

Table 2. Treatment-Emergent, All-Causality Adverse Events by Presence or Absence of Grade Greater Than or Equal to 2 Pneumonitis or RT-Pneumonitis

	Present		Absent	
AE Category	Durvalumab (n = 94)	Placebo (n = 33)	Durvalumab (n = 381)	Placebo (n = 201)
Any-grade, n (%)	94 (100)	33 (100)	366 (96.1)	189 (94.0)
Grade 3 or 4, n (%)	32 (34.0)	9 (27.3)	123 (32.3)	57 (28.4)
Grade 5 (fatal), n (%)	7 (7.4)	6 (18.2)	14 (3.7)	9 (4.5)
Leading to discontinuation, n (%)	34 (36.2)	11 (33.3)	39 (10.2)	12 (6.0)
Serious, n (%)	50 (53.2)	12 (36.4)	88 (23.1)	42 (20.9)

AE, adverse event; RT, radiotherapy.

rechallenged patients went on to permanently discontinue treatment due to worsening or recurrence of pneumonitis or RT-pneumonitis.

Clinical Management and Outcomes of Grade Greater Than or Equal to 2 Pneumonitis or RT-Pneumonitis

With durvalumab, the most common interventions for grade greater than or equal to 2 pneumonitis or RT-pneumonitis were administration of any-dose (84 of 94 [89.4%]) and high-dose systemic corticosteroids (53 of 94 [56.4%]; defined as a dose equating to ≥40 mg prednisone daily) and temporary interruption of treatment (49 of 94 [52.1%]) (Table 3); intervention rates were generally similar with placebo. Corticosteroid administration for a continuous period of more than or equal to 12 weeks to manage grade greater than or equal to 2 pneumonitis or RT-pneumonitis was required by 25 of 94 (26.6%) and five of 33 (15.2%) patients who experienced this event with durvalumab and placebo, respectively. Additional immunosuppression (beyond

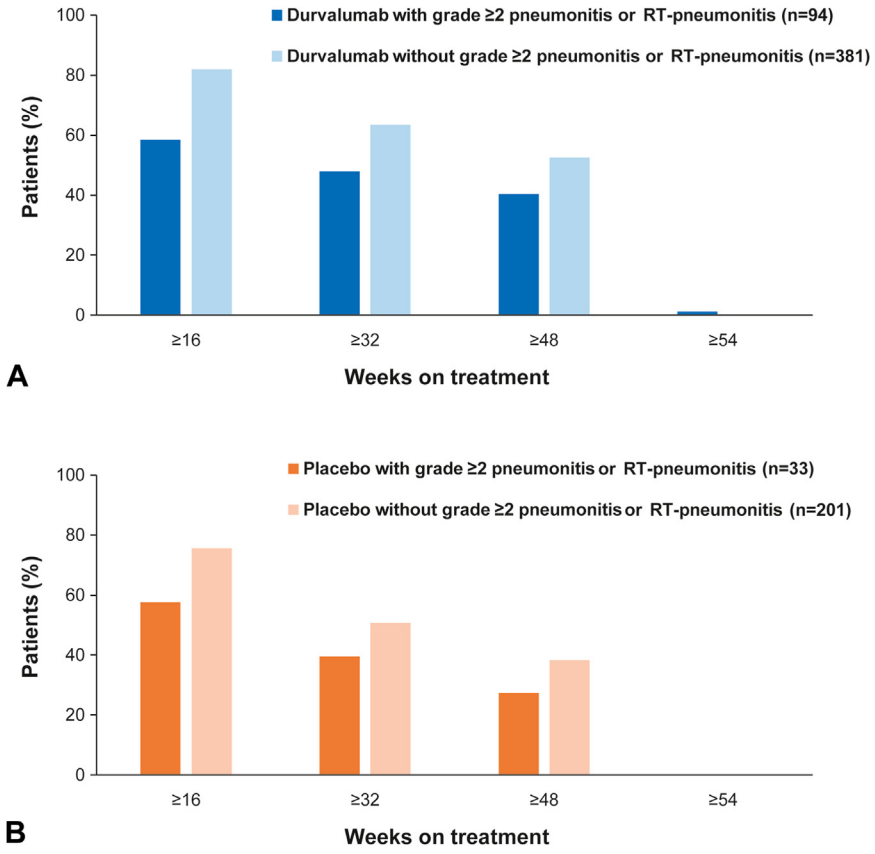

Figure 3. Study treatment exposure by presence or absence of grade greater than or equal to 2 pneumonitis or RT-pneumonitis in patients who received (*A*) durvalumab and (*B*) placebo. RT, radiotherapy.

Table 3. Management and Outcomes of Grade Greater Than or Equal to 2 Pneumonitis or RT-Pneumonitis

No. of Patients (Durvalumab – n = 94)

Grade ≥2 Pneumonitis or RT-Pneumonitis		Management or Intervention					Clinical Outcome		
Highest CTCAE Grade	Any AE	Temporary Treatment Interruption	Permanent Treatment Discontinuation	Any-Dose Corticosteroid	High-Dose Corticosteroid[a]	Other Treatment[b]	Resolved[c]	Not Resolved	Fatal
2	72	45[d]	12[d]	63	37	0	47	25	-
3	17	4	11[e]	16	11	0	12	5	-
4	0	0	0	0	0	0	0	0	-
5	5	0	5	5	5	2	0	0	5
Total, n (%)	94 (100)	49 (52.1)	28 (29.8)	84 (89.4)	53 (56.4)	2 (2.1)	59 (62.8)	30 (31.9)	5 (5.3)

No. of Patients (Placebo – n = 33)

Grade ≥2 Pneumonitis or RT-Pneumonitis		Management or Intervention					Clinical Outcome		
Highest CTCAE Grade	Any AE	Temporary Treatment Interruption	Permanent Treatment Discontinuation	Any-Dose Corticosteroid	High-Dose Corticosteroid[a]	Other Treatment[b]	Resolved[c]	Not resolved	Fatal
2	22	15[d]	3[d]	19	14	0	15	7	-
3	6	3	4[e]	6	6	0	2	4	-
4	0	0	0	0	0	0	0	0	-
5	5	0	3[f]	5	4	1	0	0	5
Total, n (%)	33 (100)	18 (54.5)	10 (30.3)	30 (90.9)	24 (72.7)	1 (3.0)	17 (51.5)	11 (33.3)	5 (15.2)

Note: Data are tabulated according to responses in the AE eCRF. In the course of the study, patients could receive several interventions for pneumonitis or RT-pneumonitis (e.g., a patient could have both "interrupted" and "discontinued" study treatment).

[a]A dose that equates to at least 40 mg prednisone daily.

[b]Two durvalumab-treated patients received infliximab and one placebo-treated patient received cyclophosphamide and tacrolimus.

[c]Resolution of pneumonitis or RT-pneumonitis was determined by the investigator in accordance with local practice.

[d]Among patients with an event of maximum (max.) grade 2, 21 (durvalumab, 17; placebo, 4) had grade 2 events for which a treatment dose action of interruption or discontinuation was not recorded on the AE eCRF: six (durvalumab, 3; placebo, 3) had an exposure record indicating "treatment cycle delay" for reason of AE during the event; three (durvalumab, 2; placebo, 1) had a record indicating "treatment cycle delay" for reason of AE at one of the next two doses after the event ended; four (all durvalumab) had an event occur after completing the max. number of cycles of study treatment, so no dose action could be taken; three (all durvalumab) had treatment end shortly after the start of the event; and five (all durvalumab) had no dose action taken either during or soon after the event.

[e]Among patients with an event of max. grade 3, nine (durvalumab, 6; placebo, 3) had grade 3 events for which treatment discontinuation was not recorded on the AE eCRF: four (durvalumab, 2; placebo, 2) had an event occur after completing the max. number of cycles of study treatment, so no dose action could be taken (one additional patient discontinued placebo for grade 3 pneumonitis or RT-pneumonitis [and is tabulated as discontinuing at this toxicity grade] but subsequently experienced a separate on-study grade 5 event, for which no dose action could be taken); and five (durvalumab, 4; placebo, 1) interrupted, but did not permanently discontinue, study treatment.

[f]Among patients with an event of max. grade 5, two (both placebo) had grade 5 events for which a treatment discontinuation was not recorded on the AE eCRF: one had already discontinued treatment due to a previous separate grade 3 pneumonitis or RT-pneumonitis event (as mentioned previously) and one had an event occur after completing the max. number of cycles of study treatment, so no dose action could be taken in either case.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; eCRF, electronic case report form; RT, radiotherapy.

corticosteroids) to manage grade greater than or equal to 2 pneumonitis or RT-pneumonitis was uncommon with durvalumab (two of 94 [2.1%]; both patients received infliximab) and placebo (one of 33 [3.0%]; the patient received cyclophosphamide and tacrolimus); all three patients who received additional immunosuppression subsequently had fatal pneumonitis or RT-pneumonitis events. Overall, 28 of 94 (29.8%) and 10 of 33 patients (30.3%) permanently discontinued durvalumab and placebo, respectively, to manage grade greater than or equal to 2 pneumonitis or RT-pneumonitis. For durvalumab, this included 12 of 72 (16.7%) and 11 of 17 patients (64.7%) with events of maximum grade 2 and 3, respectively (no grade 4 events were reported); similar proportions of patients discontinued placebo at each toxicity grade.

In PACIFIC, resolution of pneumonitis or RT-pneumonitis was determined by the investigator in accordance with local practice. At the data cutoff, 59 of 94 (62.8%) and 17 of 33 patients (51.5%) who experienced grade greater than or equal to 2 pneumonitis or RT-pneumonitis with durvalumab and placebo, respectively, had an event resolve. Among patients with events of maximum grade 2, 47 of 72 (65.3%) and 15 of 22 (68.2%) who received durvalumab and placebo, respectively, achieved resolution. Among patients who experienced events of maximum grade 3, 12 of 17 (70.6%) and two of six (33.3%) who received durvalumab and placebo, respectively, achieved resolution. Overall, pneumonitis or RT-pneumonitis events had a fatal outcome in five of 94 (5.3%) and five of 33 patients (15.2%) with durvalumab and placebo, respectively.

Discussion

In the PACIFIC trial, on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis occurred in 19.8% and 14.1% of patients who received durvalumab and placebo, respectively; grade greater than or equal to 3 pneumonitis or RT-pneumonitis was uncommon (<5%). Median time to onset of grade greater than or equal to 2 pneumonitis or RT-pneumonitis from initiation of durvalumab and placebo was similar, and most cases occurred within 3 months (approximately 80%). In patients who received the PACIFIC regimen, univariate and multivariate analyses identified patients treated in Asia (versus non-Asia), those with stage IIIA disease (versus IIIB), those with PS 1 (versus 0), and those who had not received induction chemotherapy (versus those who had) as having a higher risk of experiencing grade greater than or equal to 2 pneumonitis or RT-pneumonitis. Clinical benefit with durvalumab was maintained regardless of on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis. Moreover, durvalumab exhibited a manageable safety profile broadly irrespective of this event. Reassuringly, fatal pneumonitis or RT-pneumonitis events were uncommon, and the incidence was comparable with durvalumab (1.1%) and placebo (2.1%). These findings are generally consistent with previously reported analyses of on-study, any-grade pneumonitis or RT-pneumonitis from PACIFIC.[16,17]

Pneumonitis is of concern to patients with NSCLC as pulmonary function can already be compromised by local tumor burden and co-existent pulmonary and cardiac comorbidities. Moreover, pneumonitis is a common complication of RT, and prior chest RT correlates with pneumonitis occurrence on ICI therapy, suggesting possible synergy between these treatments with regard to the development of pneumonitis.[18–21] Therefore, exploring the association of pneumonitis occurring on ICI therapy with clinically relevant factors, and assessing its impact on the efficacy of ICI (as reported here), is vital to informing patient management and potential risk assessment for the development of pneumonitis.

Patients who experienced on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis in PACIFIC had a worse OS prognosis compared with patients who did not experience this event. This is consistent with findings from other studies of patients who received ICI, which suggest that (unlike other ICI-related AEs), pneumonitis correlates with poorer survival.[22–24] Nevertheless, it is not possible to conclude specifically on the prognostic impact of ICI-related pneumonitis based on data from PACIFIC as RT-pneumonitis is also associated with poorer OS,[25] and the causes of pneumonitis could not be established reliably in the post-CRT treatment setting.

The incidence of any-grade and grade greater than or equal to 2 pneumonitis or RT-pneumonitis in PACIFIC was higher compared with trials of PD-1 and PD-L1 ICI in stage IIIB or IV NSCLC.[4,6,26–31] This is likely owing to curative-intent RT received before enrollment, a hypothesis supported by the higher incidence of pneumonitis or RT-pneumonitis in the placebo arm of PACIFIC relative to the control arms of the aforementioned studies (where, unlike PACIFIC, the treatment paradigm did not mandate receipt of RT 1–42 d before starting ICI).[4,6,26–31] Although pneumonitis or RT-pneumonitis was common in PACIFIC, most events were grade 1 or 2 (asymptomatic or presenting with mild symptoms not requiring oxygen supplementation), consistent with other studies of ICI administered after CRT.[4,6,32–35]

There did not seem to be a clinically meaningful association between the incidence or severity of grade greater than or equal to 2 pneumonitis or RT-pneumonitis and whether patients were randomized within or beyond 14 days of completing CRT, suggesting that durvalumab

initiation should not be delayed for the sole purpose of reducing the risk of pneumonitis. Nevertheless, the timing of durvalumab initiation after CRT in PACIFIC was not random and may have been biased by associations with potentially prognostic baseline characteristics; for example, patients with smaller disease volumes and a lower lung RT dose may have recovered from CRT more rapidly, possibly allowing them to start durvalumab earlier.

The finding that patients treated in Asia were at higher risk of grade greater than or equal to 2 pneumonitis or RT-pneumonitis with the PACIFIC regimen (found in both univariate and multivariate analyses) aligns with the high incidence of this event observed in real-world Asian cohorts.[33–36] Grade greater than or equal to 2 pneumonitis or RT-pneumonitis incidence was also higher among patients from Asia in the placebo arm of PACIFIC. These results align with the finding that pneumonitis events were more common among Asian patients who receive other anticancer agents (e.g., EGFR tyrosine kinase inhibitors[37]). Thus, Asian patients may have a higher risk of being diagnosed with having pneumonitis related to anticancer therapy in general.

The higher risk of grade greater than or equal to 2 pneumonitis or RT-pneumonitis among patients with stage IIIA (versus IIIB) NSCLC (found in both univariate and multivariate analyses) was unexpected as, typically, larger lung volumes are irradiated (a known risk factor for RT-pneumonitis[18]) in patients with stage IIIB disease. We are uncertain of the factors underpinning this finding; however, the risk factor analyses are limited by small patient numbers and their post hoc nature and may be biased by unobserved imbalances in baseline factors that correlate with the incidence or severity of pneumonitis or RT-pneumonitis. For instance, RT-planning parameters were not collected in PACIFIC, and several correlate with the severity of pneumonitis (e.g., intensity-modulated RT is associated with lower rates of grade $\geq$3 pneumonitis versus three-dimensional conformal RT,[38] and larger tumor volume is associated with a larger area of normal lung being irradiated, leading to a higher risk of RT-pneumonitis).[39]

The higher risk of grade greater than or equal to 2 pneumonitis or RT-pneumonitis among patients who did not receive (pre-CRT) induction chemotherapy (found in both univariate and multivariate analyses) was also unexpected. Theoretically, induction chemotherapy may have reduced the patients' tumor volume, leading to reduced RT treatment volumes and less pulmonary toxicity during and after CRT; there is some evidence to support this.[18,40] Nevertheless, this finding should be interpreted cautiously given the aforementioned limitations of the risk factor analyses and because information on disease volume is not available. Moreover, this particular analysis is likely biased as few Asian patients (who are more susceptible to developing pneumonitis) received induction chemotherapy in PACIFIC[41]; indeed, a nominally significant ($p < 0.1$) interaction between geographic region and the use of induction chemotherapy was identified.

Grade greater than or equal to 2 pneumonitis or RT-pneumonitis did not affect clinical benefit with durvalumab in the adjusted Cox analyses: the treatment effect estimates were consistent with the intent-to-treat results. Therefore, benefit was observed even though patients who experienced grade greater than or equal to 2 pneumonitis or RT-pneumonitis were less likely to complete the 12-month treatment course. Our finding that pneumonitis or RT-pneumonitis did not affect benefit with durvalumab aligns with findings from a small, real-world cohort of patients who received durvalumab after CRT.[42] Nevertheless, as on-study pneumonitis or RT-pneumonitis may occur as a late side effect of prior CRT or because of study treatment, interpretation of the exploratory models we report (which adjusted for grade $\geq$2 pneumonitis or RT-pneumonitis as a time-dependent factor) is subject to potential bias. In addition, the exploratory models used did not account for the time elapsed from CRT to randomization to study treatment as a potentially prognostic baseline factor; future studies should seek to address this.

Aligned with management guidelines,[12,15] interruption of durvalumab and administration of corticosteroids were common interventions for grade greater than or equal to 2 pneumonitis or RT-pneumonitis. Most patients with events of maximum grade 2 did not permanently discontinue durvalumab; treatment rechallenge in this scenario may be appropriate as most had their events resolve. Grade greater than or equal to 2 pneumonitis or RT-pneumonitis lasted approximately 8 weeks (median), indicating that standard steroid tapers of 4 to 6 weeks may be insufficient. Moreover, the wide range of time to resolution for grade greater than or equal to 2 pneumonitis or RT-pneumonitis indicates that some patients require longer management. Indeed, some patients required corticosteroids for a continuous period of greater than or equal to 12 weeks (as observed in other studies[43]), and a higher proportion required this to manage grade greater than or equal to 2 pneumonitis or RT-pneumonitis in the durvalumab arm versus the placebo arm. As expected, permanent discontinuation of durvalumab was common among patients with grade greater than or equal to 3 pneumonitis or RT-pneumonitis.

In PACIFIC, attribution of pneumonitis to ICI or RT was determined according to local practice[44]; lack of central review meant that attribution could not be established

reliably, so analyses of pneumonitis were performed regardless of attribution for the purposes of the current report. Although clinical presentation and radiographic evaluation do not always allow for discrimination between RT- and ICI-related pneumonitis, future studies may benefit from the use of radiomics to distinguish between these causes.[45] Further research is also required to determine whether the features and outcomes of pneumonitis occurring post-CRT differ in their natural history when occurring on, or in the absence of, ICI. Moreover, there is evidence that RT dose-volume factors, including RT techniques, correlate with the occurrence or severity of pneumonitis in patients with stage III NSCLC who undergo CRT.[38,46,47] The association of these parameters with pneumonitis should be investigated in the context of the PACIFIC regimen. Initial efforts have begun with retrospective, real-world analyses identifying elevated lung V20 (the percentage of lung volume receiving a RT dose >20 Gy) as a risk factor for grade greater than or equal to 2 pneumonitis or RT-pneumonitis.[35,48–50] RT dose-volume parameters are being collected in the observational PACIFIC-R study (NCT02125461), presenting a possible avenue for further investigation of their relationship with pneumonitis.

In conclusion, factors associated with higher risk of grade greater than or equal to 2 pneumonitis or RT-pneumonitis with the PACIFIC regimen were identified; however, the post hoc analyses of risk factors are limited in scope and other factors, including RT parameters, which were not collected in PACIFIC, could have contributed to these findings. These results therefore warrant further study and validation in other populations. Nevertheless, clinical benefit with durvalumab was maintained in patients who experienced on-study, grade greater than or equal to 2 pneumonitis or RT-pneumonitis, and most achieved resolution of this event, suggesting the risk of grade greater than or equal to 2 pneumonitis or RT-pneumonitis should not deter use of the PACIFIC regimen in eligible patients with unresectable stage III NSCLC.

CRediT Authorship Contribution Statement

Johan F. Vansteenkiste: Resources, Investigation, Conceptualization, Writing—review and editing.

Jarushka Naidoo: Resources, Investigation, Conceptualization, Writing—review and editing.

Corinne Faivre-Finn: Resources, Investigation, Conceptualization, Writing—review and editing.

Mustafa Özgüroğlu: Resources, Investigation, Conceptualization, Writing—review and editing.

Augusto Villegas: Resources, Investigation, Writing—review and editing.

Davey Daniel: Resources, Investigation, Writing—review and editing.

Shuji Murakami: Resources, Investigation, Writing—review and editing.

Rina Hui: Resources, Conceptualization, Investigation, Writing—review and editing.

Ki Hyeong Lee: Resources, Investigation, Writing—review and editing.

Byoung Chul Cho: Resources, Investigation, Writing—review and editing.

Kaoru Kubota: Resources, Investigation, Writing—review and editing.

Helen Broadhurst: Formal Analysis, Methodology, Writing—review and editing.

Catherine Wadsworth: Conceptualization, Writing—review and editing.

Michael Newton: Conceptualization, Writing—review and editing.

Piruntha Thiyagarajah: Conceptualization, Writing—review and editing.

Scott J. Antonia: Resources, Investigation, Writing—review and editing.

Disclosure

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Data Sharing

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's

data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Data for studies directly listed on Vivli can be requested through Vivli at: www.vivli.org.

Data for studies not listed on Vivli could be requested through Vivli at: https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/.

The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100638.

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