Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC—Update from PACIFIC

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Trial Registration: A Global Study to Assess the Effects of MEDI4736 following Concurrent Chemoradiation in Patients with Stage III Unresectable Non-Small Cell Lung Cancer. NCT02125461

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ABSTRACT

Introduction: In the phase 3 PACIFIC study of patients with unresectable stage III NSCLC without progression after chemoradiotherapy, durvalumab demonstrated significant improvements versus placebo in the primary end points of progression-free survival (hazard ratio [HR] = 0.52, 95% confidence interval [CI]: 0.42–0.65, p < 0.0001) and overall survival (OS) (HR = 0.68, 95% CI: 0.53–0.87, p = 0.00251), with manageable safety and no detrimental effect on patient-reported outcomes. Here, we report 3-year OS rates for all patients randomized in the PACIFIC study.

Methods: Patients, stratified by age, sex, and smoking history, were randomized (2:1) to receive durvalumab, 10 mg/kg intravenously every 2 weeks, or placebo for up to 12 months. OS was analyzed by using a stratified log-rank test in the intention-to-treat population. Medians and rates at 12, 24, and 36 months were estimated by the Kaplan-Meier method.

Results: As of January 31, 2019, 48.2% of patients had died (44.1% and 56.5% in the durvalumab and placebo groups, respectively). The median duration of follow-up was 33.3 months. The updated OS remained consistent with that previously reported (stratified HR = 0.69 [95% CI: 0.55–0.86]); the median OS was not reached with durvalumab but was 29.1 months with placebo. The 12-, 24- and 36-month OS rates with durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3%, and 57.0% versus 43.5%, respectively. All secondary outcomes examined showed improvements consistent with previous analyses.

Conclusions: Updated OS data from PACIFIC, including 3-year survival rates, demonstrate the long-term clinical benefit with durvalumab after chemoradiotherapy and further establish the PACIFIC regimen as the standard of care in this population.

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Keywords: Durvalumab; NSCLC; Overall survival; PACIFIC; Three-year update

Introduction

NSCLC is one of the leading causes of mortality worldwide; in approximately 30% of patients, it is diagnosed when they already have stage III disease, which is often unresectable.1-3 The historical standard of care for patients with unresectable stage III NSCLC was platinum-based doublet chemotherapy concurrent with radiotherapy (chemoradiotherapy [CRT]) with curative intent; however, patient prognosis with this treatment was poor, with 5-year survival rates of approximately 15 to 30%.4,5 In 2017, management of stage III NSCLC changed with publication of results from the PACIFIC trial and subsequent worldwide health authority approvals of durvalumab in this setting.

Durvalumab is a selective, high-affinity, human immunoglobulin G1 monoclonal antibody that blocks programmed cell death ligand 1 (PD-L1) from binding to programmed death 1 and CD80, resulting in antitumor T-cell activity.6 In the phase III PACIFIC study (NCT02125461) of durvalumab versus placebo in patients with unresectable stage III NSCLC who did not progress while undergoing CRT, durvalumab demonstrated significant improvements in the primary end points of progression-free survival (PFS) (hazard ratio [HR] = 0.52, 95% confidence interval [CI]: 0.42–0.65, p < 0.0001) and overall survival (OS) (HR = 0.68, 95% CI: 0.53–0.87, p = 0.00251).7-9 With immune-mediated adverse events occurring in 24.2% and 8.1% of patients in the durvalumab and placebo groups, respectively, but with similar rates of grade 3 or 4 immune-mediated adverse events (3.4% and 2.6%), safety was manageable with durvalumab,7 and durvalumab had no detrimental effect on patient-reported outcomes.10 These results have led to the approval of durvalumab for patients with unresectable stage III NSCLC who have not progressed while undergoing CRT10-11 and use of the PACIFIC regimen (CRT followed by durvalumab) as the new standard of care in this setting.

Here, we report updated OS outcomes from PACIFIC, approximately 3 years after the last patient was randomized to this trial, to provide insight into the durability of the effect of durvalumab.

Methods

Study Design

The PACIFIC study design, eligibility criteria, and assessments have been fully described previously.7,8 Eligible patients had histologically and/or cytologically documented stage III unresectable NSCLC, with a WHO performance score of 0 or 1. Patients had to have received at least two cycles of platinum-based chemotherapy concurrently with definitive radiation therapy without progression, and the last radiation dose was
administered 1 to 42 days before randomization. Tumor tissue collection was not a prerequisite for inclusion in PACIFIC and enrollment was not restricted to any threshold levels for PD-L1 expression. Patients were randomized 2:1 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 consent withdrawal. Randomization was stratified by age of the patient (<65 years versus ≥65 years), sex, and smoking history (current or former smoker versus never smoked).

**End Points and Assessments**

In this post hoc, exploratory analysis, we report data from up to January 31, 2019, the data cutoff (approximately 3 years after the last patient was randomized), including an update of the primary end point OS (defined as the time from randomization until death from any cause); the OS rates at the landmarks of 12, 24, and 36 months; the time to first subsequent therapy or death and time to second subsequent therapy or death; and the types of postdiscontinuation disease-related anticancer therapies administered. In addition, analyses of OS by PD-L1 expression levels on tumor cells (TCs) (based on PD-L1 testing of pre-CRT archived tumor tissue by using the Ventana SP263 immunohistochemistry assay) was performed with use of prespecified (25%) and exploratory post hoc (1%) PD-L1 cutoffs. Safety data were not collected at this data cutoff.

**Statistical Analysis**

This post hoc analysis of efficacy end points included all patients who underwent randomization according to the intention-to-treat principle. For OS, the effect of durvalumab as compared with that of placebo was estimated and the HR and corresponding 95% CI were reported. Between-group comparisons were performed by using a stratified log-rank test, with the stratification factors consistent with those used for randomization (age, sex, and smoking history). For all planned analyses of OS in the prespecified and post hoc subgroups, an unstratified Cox regression model was used to calculate HR and 95% CI. No adjustment for multiple comparisons was performed for these subgroup analyses. The medians and percentages of patients alive (OS rates) at 12, 24, and 36 months were estimated by the Kaplan-Meier method.

**Results**

A total of 713 patients were randomized, of whom 709 received treatment (durvalumab [n = 473] or placebo [n = 236]); the last patient had completed the protocol-defined 12 months of study treatment in May 2017. Baseline characteristics were well balanced in the two treatment groups, as previously reported.7,8
**Figure 2.** Updated overall survival by prespecified and post hoc exploratory subgroups in the intention-to-treat population.*

*(Hazard ratio and 95% confidence interval [CI] were not calculated if the subgroup had <20 events.) PD-L1, programmed death ligand 1.

| Subgroup                                | No. of events/No. of patients (%) | Unstratified hazard ratio for death (95% CI) |
|-----------------------------------------|-----------------------------------|---------------------------------------------|
| All patients                            | Durvalumab 210/476 (44.1) | 134/237 (56.5) | 0.67 (0.54–0.84) |
| Sex                                      |                                    |                                            |                            |
| Male                                    |                                    |                                            |                            |
| 158/234 (47.6)                          | 60/106 (57.8)                       | 0.74 (0.57–0.95)                           |
| Female                                  |                                    |                                            |                            |
| 51/142 (35.9)                           | 36/71 (53.5)                        | 0.93 (0.35–2.81)                           |
| Age at randomization                     |                                    |                                            |                            |
| <65 years                                |                                    |                                            |                            |
| 102/261 (39.1)                          | 68/130 (52.3)                       | 0.81 (0.45–0.83)                           |
| ≥65 years                               |                                    |                                            |                            |
| 108/215 (50.2)                          | 66/107 (61.1)                       | 0.75 (0.56–1.03)                           |
| Smoking status                           |                                    |                                            |                            |
| Smoker                                  |                                    |                                            |                            |
| 193/433 (44.8)                          | 121/216 (56.0)                      | 0.70 (0.38–0.98)                           |
| Non-smoker                              |                                    |                                            |                            |
| 17/43 (39.5)                            | 13/21 (61.9)                        | 0.44 (0.21–0.95)                           |
| NSCLC disease stage                     |                                    |                                            |                            |
| Stage IIA                                |                                    |                                            |                            |
| 114/252 (45.2)                          | 80/125 (64.0)                       | 0.81 (0.48–0.81)                           |
| Stage IIIB                               |                                    |                                            |                            |
| 90/212 (42.5)                           | 52/107 (48.6)                       | 0.75 (0.53–0.95)                           |
| Tumor histologic type                   |                                    |                                            |                            |
| Squamous histology                      |                                    |                                            |                            |
| 114/224 (50.9)                          | 60/102 (58.8)                       | 0.76 (0.55–1.03)                           |
| All other histology                     |                                    |                                            |                            |
| 90/252 (36.1)                           | 74/135 (54.8)                       | 0.59 (0.43–0.80)                           |
| Best response to prior treatment        |                                    |                                            |                            |
| Complete response                        |                                    |                                            |                            |
| 3/9 (33.3)                              | 3/7 (42.9)                          |                                            |
| Partial response                        |                                    |                                            |                            |
| 95/237 (40.1)                           | 58/112 (51.8)                       | 0.69 (0.49–0.94)                           |
| Stable disease                          |                                    |                                            |                            |
| 107/223 (48.0)                          | 71/115 (61.7)                       | 0.83 (0.48–0.88)                           |
| Type of prior chemotherapy              |                                    |                                            |                            |
| Gemcitabine-based                       |                                    |                                            |                            |
| 5/9 (55.6)                              | 2/5 (40.0)                          |                                            |
| Non-gemcitabine-based                   |                                    |                                            |                            |
| 205/487 (43.9)                          | 130/232 (56.9)                      | 0.86 (0.53–0.82)                           |
| Cisplatin                               |                                    |                                            |                            |
| 110/200 (55.0)                          | 69/128 (53.5)                       | 0.84 (0.47–0.87)                           |
| Carboplatin                             |                                    |                                            |                            |
| 94/199 (47.2)                           | 69/102 (58.8)                       | 0.75 (0.54–1.03)                           |
| Cisplatin and carboplatin               |                                    |                                            |                            |
| 4/8 (50.0)                              | 4/5 (80.0)                          |                                            |
| Last radiation to randomization         |                                    |                                            |                            |
| <14 days                                |                                    |                                            |                            |
| 48/120 (36.3)                           | 40/62 (64.5)                        | 0.43 (0.29–0.68)                           |
| ≥14 days                                |                                    |                                            |                            |
| 164/355 (46.1)                          | 94/175 (53.7)                       | 0.79 (0.61–1.02)                           |
| WHO performance status                  |                                    |                                            |                            |
| Normal                                  |                                    |                                            |                            |
| 95/234 (40.6)                           | 58/114 (49.1)                       | 0.77 (0.55–1.07)                           |
| Restricted                              |                                    |                                            |                            |
| 115/242 (47.5)                          | 78/123 (63.4)                       | 0.79 (0.44–0.78)                           |
| Region                                  |                                    |                                            |                            |
| Asia                                    |                                    |                                            |                            |
| 43/106 (39.4)                           | 31/88 (45.6)                        | 0.73 (0.48–1.18)                           |
| Europe                                  |                                    |                                            |                            |
| 103/217 (47.5)                          | 55/102 (53.9)                       | 0.83 (0.60–1.15)                           |
| North and South America                 |                                    |                                            |                            |
| 64/150 (42.7)                           | 43/87 (71.6)                        | 0.44 (0.30–1.04)                           |
| Race                                     |                                    |                                            |                            |
| White                                   |                                    |                                            |                            |
| 160/337 (47.5)                          | 95/157 (60.5)                       | 0.89 (0.54–0.90)                           |
| Black/African-American                  |                                    |                                            |                            |
| 4/12 (33.3)                             | 2/2 (100.0)                         |                                            |
| Asian                                   |                                    |                                            |                            |
| 44/120 (36.7)                           | 33/72 (45.8)                        | 0.67 (0.42–1.05)                           |
| Other                                   |                                    |                                            |                            |
| 2/6 (33.3)                              | 4/6 (66.7)                          |                                            |
| EGFR mutation                           |                                    |                                            |                            |
| Positive                                |                                    |                                            |                            |
| 13/29 (44.8)                            | 6/14 (42.9)                         |                                            |
| Negative                                |                                    |                                            |                            |
| 116/217 (42.9)                          | 95/185 (57.6)                       | 0.83 (0.49–0.92)                           |
| Unknown                                 |                                    |                                            |                            |
| 81/130 (46.9)                           | 33/88 (50.0)                        | 0.75 (0.49–1.15)                           |
| PD-L1 status                            |                                    |                                            |                            |
| ≥25%                                    |                                    |                                            |                            |
| 41/115 (35.7)                           | 23/44 (52.3)                        | 0.50 (0.30–0.83)                           |
| <25%                                    |                                    |                                            |                            |
| 90/187 (48.1)                           | 53/106 (50.5)                       | 0.89 (0.63–1.25)                           |
| Unknown                                 |                                    |                                            |                            |
| 78/174 (45.4)                           | 58/86 (65.6)                        | 0.80 (0.43–0.94)                           |
| 1–24% post hoc analysis                 |                                    |                                            |                            |
| 43/97 (44.3)                            | 26/47 (55.3)                        | 0.67 (0.41–1.10)                           |
| ≥1% post hoc analysis                   |                                    |                                            |                            |
| 84/212 (39.3)                           | 49/91 (53.8)                        | 0.59 (0.41–0.83)                           |
| <1% post hoc analysis                   |                                    |                                            |                            |
| 47/90 (52.2)                            | 27/58 (46.6)                        | 1.14 (0.71–1.84)                           |

**Note:** PD-L1, programmed death ligand 1.
As of January 31, 2019 (data cutoff), 48.2% of patients had died (44.1% and 56.5% in the durvalumab and placebo groups, respectively [see Supplementary Fig. 1 for patient disposition]). The median duration of follow-up was 33.3 months (range 0.2–51.3). In total, 45 new OS events had been reported since the primary analysis of OS (data cutoff March 22, 2018). The updated OS benefit with durvalumab compared with placebo was consistent with the primary analysis result,8 with a 31% reduction in the risk of death (HR = 0.69 [95% CI: 0.55–0.86] [Fig. 1]). The Kaplan-Meier estimate of the median OS was 29.1 months in the placebo group, whereas it was still not reached in the durvalumab group (see Fig. 1). The 12-, 24-, and 36-month OS rates with durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3%, and 57.0% versus 43.5%, respectively. In addition, the updated subgroup analysis of OS, including by PD-L1 status (Fig. 2), was consistent with that reported at the time of the primary OS analysis.8

After discontinuation of the study treatment, 43.3% and 57.8% in the durvalumab and placebo groups, respectively, received subsequent anticancer therapy (Table 1); in total, 9.7% and 26.6%, respectively, subsequently received immunotherapy (primarily, nivolumab or pembrolizumab). Consistent with the results reported at the time of the primary OS analysis, time to first subsequent therapy or death was markedly longer with durvalumab than with placebo (HR = 0.58 [95% CI: 0.47–0.71] [Supplementary Fig. 2A]), as was time to second subsequent therapy or death (HR = 0.61 [95% CI: 0.49–0.75] [Supplementary Fig. 2B]).

### Discussion

The updated results from PACIFIC (approximately 3 years from randomization of the last patient) demonstrate that the clinical benefits of durvalumab, in terms of OS and time to first and second subsequent therapy or death, are maintained over the longer term. Importantly, more than 50% of patients receiving durvalumab were alive at 36 months (specifically, 57.0% versus 43.5% receiving placebo). Improvement in OS with durvalumab versus placebo was observed across most patient subgroups, including those based on disease stage, tumor histologic type, and smoking status, supporting the use of durvalumab in this patient setting. However, some subgroups were small and not powered to assess efficacy, nor were they necessarily balanced with respect to other baseline characteristics. Therefore, future investigation of potential biomarkers may be warranted.

Improved OS with durvalumab was broadly observed irrespective of PD-L1 expression, which is consistent with findings from prespecified and post hoc analyses carried out at the time of the primary OS analysis.8 This includes patients with unknown PD-L1 expression status, for whom median OS was improved by more than 20 months (versus placebo) at this update (data not shown, manuscript in preparation). An exception was the PD-L1 less than 1% subgroup (post hoc analysis), which numerically favored placebo at this update (HR = 1.14 [95% CI: 0.71–1.84]) and at the time of the primary OS analysis (HR = 1.36 [95% CI: 0.79–2.34]). Previous analysis of the placebo arm in the PD-L1 TC less than 1% subgroup that suggested overperformance was confirmed in this analysis (data not shown, manuscript in preparation). The relatively small size of the PD-L1 TC less than 1% subgroup (n = 148), the fact that not all patients in PACIFIC could provide a suitable tumor sample for assessment of PD-L1 expression (63% were PD-L1-evaluable7,8), and the fact that PD-L1 data were based on pre-CRT samples, which may not reflect changes in expression potentially incurred by CRT, should also be taken into consideration when drawing definitive conclusions. PACIFIC was not designed to evaluate the efficacy of durvalumab based on PD-L1 status.

The observation that proportionally fewer patients in the durvalumab arm received subsequent anticancer treatment is likely underpinned by fewer progression events with durvalumab than with placebo. Notably, among patients who received subsequent anticancer therapy, a greater proportion of patients in the placebo arm received subsequent immunotherapy. Otherwise, as reported elsewhere,12 first subsequent treatment type was generally similar between the treatment arms; platinum-doublet chemotherapy was the most common, in part because the study was conducted in the pre–immune checkpoint inhibitor era. Baseline patient and disease characteristics were broadly similar irrespective of treatment arm and use of a first subsequent anticancer treatment.12

### Table 1. Postdiscontinuation Disease-Related Anticancer Therapy (Intention-to-Treat Population)

| Therapy                        | Receiving Durvalumab (n = 476) | Receiving Placebo (n = 237) |
|--------------------------------|-------------------------------|----------------------------|
| Any therapy                    | 206 (43.3)                    | 137 (57.8)                  |
| Radiotherapy                   | 89 (18.7)                     | 60 (25.3)                   |
| Immunotherapy*                 | 46 (9.7)                      | 63 (26.6)                   |
| Cytotoxic chemotherapy         | 138 (29.0)                    | 81 (34.2)                   |
| Other systemic therapy†        | 50 (10.5)                     | 34 (14.3)                   |
| Other                          | 1 (0.2)                       | 0                           |

*Primarily, nivolumab (durvalumab [n = 33] and placebo [n = 52]) or pembrolizumab (durvalumab [n = 10] and placebo [n = 8]).
†Including tyrosine kinase inhibitors, among other treatments.
Overall, the findings of this analysis underscore the long-term survival benefit with durvalumab after CRT and further establish the PACIFIC regimen as the standard of care in patients with unresectable stage III NSCLC who do not progress while undergoing CRT.

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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.2019.10.002.

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