

## ORIGINAL ARTICLE

# Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Kurata, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Faivre-Finn, M. Reck, J. Vansteenkiste, D.R. Spigel, C. Wadsworth, G. Melillo, M. Taboada, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators\*

## ABSTRACT

**BACKGROUND**

An earlier analysis in this phase 3 trial showed that durvalumab significantly prolonged progression-free survival, as compared with placebo, among patients with stage III, unresectable non-small-cell lung cancer (NSCLC) who did not have disease progression after concurrent chemoradiotherapy. Here we report the results for the second primary end point of overall survival.

**METHODS**

We randomly assigned patients, in a 2:1 ratio, to receive durvalumab intravenously, at a dose of 10 mg per kilogram of body weight, or matching placebo every 2 weeks for up to 12 months. Randomization occurred 1 to 42 days after the patients had received chemoradiotherapy and was stratified according to age, sex, and smoking history. The primary end points were progression-free survival (as assessed by blinded independent central review) and overall survival. Secondary end points included the time to death or distant metastasis, the time to second progression, and safety.

**RESULTS**

Of the 713 patients who underwent randomization, 709 received the assigned intervention (473 patients received durvalumab and 236 received placebo). As of March 22, 2018, the median follow-up was 25.2 months. The 24-month overall survival rate was 66.3% (95% confidence interval [CI], 61.7 to 70.4) in the durvalumab group, as compared with 55.6% (95% CI, 48.9 to 61.8) in the placebo group (two-sided  $P=0.005$ ). Durvalumab significantly prolonged overall survival, as compared with placebo (stratified hazard ratio for death, 0.68; 99.73% CI, 0.47 to 0.997;  $P=0.0025$ ). Updated analyses regarding progression-free survival were similar to those previously reported, with a median duration of 17.2 months in the durvalumab group and 5.6 months in the placebo group (stratified hazard ratio for disease progression or death, 0.51; 95% CI, 0.41 to 0.63). The median time to death or distant metastasis was 28.3 months in the durvalumab group and 16.2 months in the placebo group (stratified hazard ratio, 0.53; 95% CI, 0.41 to 0.68). A total of 30.5% of the patients in the durvalumab group and 26.1% of those in the placebo group had grade 3 or 4 adverse events of any cause; 15.4% and 9.8% of the patients, respectively, discontinued the trial regimen because of adverse events.

**CONCLUSIONS**

Durvalumab therapy resulted in significantly longer overall survival than placebo. No new safety signals were identified. (Funded by AstraZeneca; PACIFIC ClinicalTrials.gov number, NCT02125461.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Antonia at the H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Dr., MRC 3-E, Tampa, FL 33612, or at [scott.antonio@moffitt.org](mailto:scott.antonio@moffitt.org).

\*A complete list of the investigators in the PACIFIC trial is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

This article was published on September 25, 2018, at [NEJM.org](http://NEJM.org).

DOI: 10.1056/NEJMoa1809697

Copyright © 2018 Massachusetts Medical Society.

**H**ISTORICALLY, PATIENTS WITH A GOOD performance status and stage III (locally advanced), unresectable non–small-cell lung cancer (NSCLC) have been treated with platinum-based, doublet chemotherapy administered with definitive-dose radiotherapy (concurrent chemoradiotherapy).<sup>1</sup> However, outcomes have been poor because most patients have disease progression after chemoradiotherapy, with approximately 15 to 30% of patients remaining alive at 5 years, which corresponds to a median survival of no more than 28 months.<sup>1,2</sup> Several studies have tested the administration of systemic therapy with curative intent after patients had disease control with chemoradiotherapy. However, to date, these therapies have proved ineffective, with a median survival after consolidation treatment ranging from 18 to 23 months.<sup>3–7</sup>

Immune checkpoint inhibitors targeting programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) have shown activity in the treatment of numerous cancers, including advanced NSCLC.<sup>8,9</sup> Durvalumab is a selective, high-affinity, engineered, human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80, allowing T cells to recognize and kill tumor cells.<sup>10,11</sup> Preclinical evidence suggests that chemoradiotherapy may up-regulate PD-L1 expression in tumor cells,<sup>11–17</sup> and it is hypothesized that PD-L1 blockade may help restore systemic and long-term immune response after chemoradiotherapy.

PACIFIC was a randomized, placebo-controlled, phase 3 trial evaluating the immune checkpoint inhibitor durvalumab in patients with stage III, unresectable NSCLC who did not have disease progression after concurrent chemoradiotherapy.<sup>18</sup> At the first planned interim analysis, the trial showed that durvalumab significantly prolonged progression-free survival (one of the two primary end points), as compared with placebo, with median durations of 16.8 months (95% confidence interval [CI], 13.0 to 18.1) and 5.6 months (95% CI, 4.6 to 7.8), respectively (stratified hazard ratio for disease progression or death, 0.52; 95% CI, 0.42 to 0.65;  $P < 0.001$ ).<sup>18</sup> On the basis of these results, durvalumab was approved for the treatment of unresectable, stage III NSCLC in patients whose disease had not progressed after platinum-based chemoradiotherapy.<sup>19,20</sup>

Here, we report the results for the second primary end point of overall survival in the PACIFIC trial. Updated results for progression-free survival

and for secondary efficacy and safety end points are also reported.

## METHODS

### PATIENTS

Eligibility criteria, as reported previously,<sup>18</sup> included histologically or cytologically documented stage III, unresectable NSCLC according to the *Staging Manual in Thoracic Oncology*, version 7, of the International Association for the Study of Lung Cancer.<sup>21</sup> Patients also had to have received at least two cycles of platinum-based chemotherapy (containing etoposide, vinblastine, vinorelbine, a taxane [paclitaxel or docetaxel], or pemetrexed) concurrently with definitive radiation therapy.<sup>18</sup> Eligible patients must not have had progression after chemoradiotherapy and had to have received their last radiation dose within 1 to 42 days before randomization. (Details are provided in the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

### TRIAL DESIGN AND INTERVENTIONS

This multicenter, randomized, double-blind, placebo-controlled, phase 3 trial was conducted at 235 investigative sites in 26 countries, including centers in Asia, Australia, Europe, North America, South America, and South Africa. Patients were randomly assigned in a 2:1 ratio to receive durvalumab intravenously, at a dose of 10 mg per kilogram of body weight, or matching placebo every 2 weeks up to 12 months or until confirmed disease progression, the initiation of alternative cancer therapy, unacceptable toxic events, or withdrawal of consent. Randomization was stratified according to age of the patient (<65 years vs. ≥65 years), sex, and smoking history (current or former smoker vs. never smoked). After the discontinuation or completion of the trial regimen, patients were followed for survival. Patients could receive their assigned trial regimen again if disease control had occurred at the end of 12 months and if progression occurred during follow-up.

### END POINTS AND ASSESSMENTS

The primary end points were overall survival and progression-free survival, assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and evaluated by means of blinded independent central review. Overall sur-

vival was defined as the time from randomization until death from any cause. Progression-free survival was defined as the time from randomization until the date of objective disease progression or death from any cause in the absence of progression.

Secondary efficacy end points included the rate of overall survival at 24 months after randomization, the objective response rate, duration of response, the rates of progression-free survival at 12 and 18 months, the time to death or distant metastasis (defined as any new lesion outside the radiation field, according to RECIST, version 1.1, or proven by biopsy) (see the Supplementary Methods section in the Supplementary Appendix), and the time to second progression (defined as the time from randomization to the earliest of the progression events subsequent to that used for the analysis of progression-free survival). The time to second progression was defined according to local standard practice and assessed by investigators and could include any of the following: objective assessment of progression as assessed radiologically, symptomatic progression, or death. The time to the first subsequent therapy or death and the time to the second subsequent therapy or death were supportive assessments for progression-free survival and the time to second progression, respectively.

In addition to the estimates for progression-free survival, the objective response rate, duration of response, and the time to death or distant metastasis were based on RECIST, version 1.1, according to blinded independent central review assessments. RECIST assessments were not collected for the analysis of time to second progression. Efficacy was assessed every 8 weeks for the first 12 months and every 12 weeks thereafter. All reported efficacy end points are for durvalumab or placebo only and were derived from the time of randomization (i.e., did not include the previous chemoradiotherapy period).

Safety assessments included adverse events, serious adverse events, vital signs, and physical and laboratory examinations. Also assessed were adverse events of special interest and immune-mediated adverse events, which were defined as adverse events of special interest that led to the use of systemic glucocorticoids, endocrine therapy, or other immunosuppressants, that were consistent with an immune-mediated mechanism, and that had no clear alternative cause. Adverse events and serious adverse events were classified according

to system organ class and preferred term in the *Medical Dictionary for Regulatory Activities*, version 19.1, and were graded according to the Common Terminology Criteria for Adverse Events, version 4.03.

Patients provided archived tumor tissue samples (if available), which had been obtained before chemoradiotherapy, for PD-L1 testing with the use of the Ventana SP263 immunohistochemical assay. However, patients were enrolled regardless of PD-L1 expression status. Prespecified analyses of outcomes as a function of PD-L1 expression levels on tumor cells with the use of a 25% cutoff were conducted. In addition, at the request of health regulatory authorities, an exploratory post hoc analysis was conducted that used a PD-L1 expression-level cutoff of 1%. (An additional PD-L1 subgroup with a cutoff of 1 to 24% was also analyzed; see the Supplementary Appendix.)

#### TRIAL OVERSIGHT

As reported previously,<sup>18</sup> the trial was designed by representatives of the sponsor (AstraZeneca) and academic advisors. The trial was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council on Harmonisation guidelines for Good Clinical Practice, with any applicable laws and requirements, and with any conditions that were required by a regulatory authority, institutional review board, or independent ethics committee that had approved this trial to be conducted in its territory. (For details, see the Supplementary Methods section in the Supplementary Appendix.)

The data were collected and analyzed by the sponsor after review and a recommendation by the independent data and safety monitoring committee to unblind the data. The manuscript was written by the authors, with editorial assistance funded by the sponsor and conducted in accordance with Good Publication Practice guidelines. The authors had access to the data and vouch for the accuracy and completeness of the data and analyses and for the adherence of the trial to the protocol, available at NEJM.org.

#### STATISTICAL ANALYSIS

The sample size that was required for the analysis of the primary end points and the statistical methods have been described previously.<sup>18</sup> For overall survival, the final analysis was planned to be conducted when approximately 491 deaths had oc-

curred among 713 patients who had undergone randomization (69% maturity). If the true hazard ratio for death in the analysis of overall survival was 0.73, this number of deaths would provide the trial with at least 85% power to show a significant difference, assuming a 2.5% two-sided significance level in the intention-to-treat population; this translates to an 8-month benefit in the median overall survival in the durvalumab group over 22 months in the placebo group (i.e., 30 months in the durvalumab group) if overall survival is exponentially distributed. In addition, two interim analyses for overall survival were planned to be conducted when approximately 285 and 393 deaths had occurred. The Lan–DeMets spending function that approximates an O’Brien–Fleming approach was used to account for multiple comparisons, which were introduced by including interim analyses for superiority.<sup>22</sup>

The data cutoff for the first interim analysis of overall survival occurred on March 22, 2018, after 299 deaths had occurred (61% of the expected 491 events). The results of this interim analysis were reviewed by an independent data and safety monitoring committee that concluded that the prespecified criteria for unblinding of the data had been fulfilled (i.e., that the P value had crossed the efficacy boundary of 0.00274) and recommended unblinding of the data. Since the trial reached statistical significance on the basis of this interim analysis, the results presented herein are to be considered final for overall survival.

Analyses of the efficacy end points included all the patients who underwent randomization, according to the intention-to-treat principle. For time-to-event end points, such as progression-free survival and overall survival, the effect of durvalumab as compared with placebo was estimated by the hazard ratio (together with its corresponding confidence interval of 100[1– $\alpha$ ]%, with adjustment for the interim analysis, or with a 95% confidence interval and P value) in the intention-to-treat population. Between-group comparisons were performed by a stratified log-rank test; the stratification factors were those that had been used for randomization (age, sex, and smoking history). The Kaplan–Meier method was used to calculate medians and their associated 95% confidence intervals. Sensitivity analyses for overall survival included the assessment of attrition bias.

For all the planned analyses of overall survival in prespecified subgroups, an unstratified Cox re-

gression model was used to calculate hazard ratios and 95% confidence intervals. No adjustment for multiple comparisons was planned for these subgroup analyses. Response rates were estimated with the use of the Clopper–Pearson method and compared with the use of Fisher’s exact test. The type I error was controlled for the primary end points, the overall survival rate at 24 months, and the objective response rate, as described previously,<sup>18</sup> but not for other secondary end points; therefore, P values are not reported. Safety data were summarized for the as-treated population. Details are provided in the statistical analysis plan, which is available with the protocol.

## RESULTS

### PATIENTS AND TRIAL INTERVENTIONS

From May 2014 through April 2016, a total of 713 patients underwent randomization, of whom 709 (99.4%) received at least one dose of durvalumab or placebo after chemoradiotherapy (473 patients received durvalumab and 236 received placebo) (Fig. 1). A summary of the demographic and clinical characteristics of the patients at baseline is provided in Table S1 in the Supplementary Appendix. As previously reported,<sup>18</sup> the baseline characteristics were well balanced between the trial groups.

As of March 22, 2018, which was the data-cutoff date for this analysis, 299 patients (183 in the durvalumab group and 116 in the placebo group) had died. The overall median duration of follow-up for overall survival was 25.2 months (range, 0.2 to 43.1). The median number of infusions received was 20 (range, 1 to 27) in the durvalumab group and 14 (range, 1 to 26) in the placebo group. The median duration of receipt of the trial intervention was 40.1 weeks (range, 1 to 54) in the durvalumab group and 28.0 weeks (range, 1 to 53) in the placebo group.

After discontinuation of the intervention, 195 patients (41.0%) in the durvalumab group and 128 (54.0%) in the placebo group received subsequent disease-related anticancer therapy (Table S2 in the Supplementary Appendix). A total of 128 patients in the durvalumab group (26.9%) and 71 in the placebo group (30.0%) received subsequent cytotoxic chemotherapy; 38 patients (8.0%) and 53 (22.4%), respectively, received additional immunotherapy, and 47 (9.9%) and 31 (13.1%) received subsequent (non-immunotherapy-based) targeted



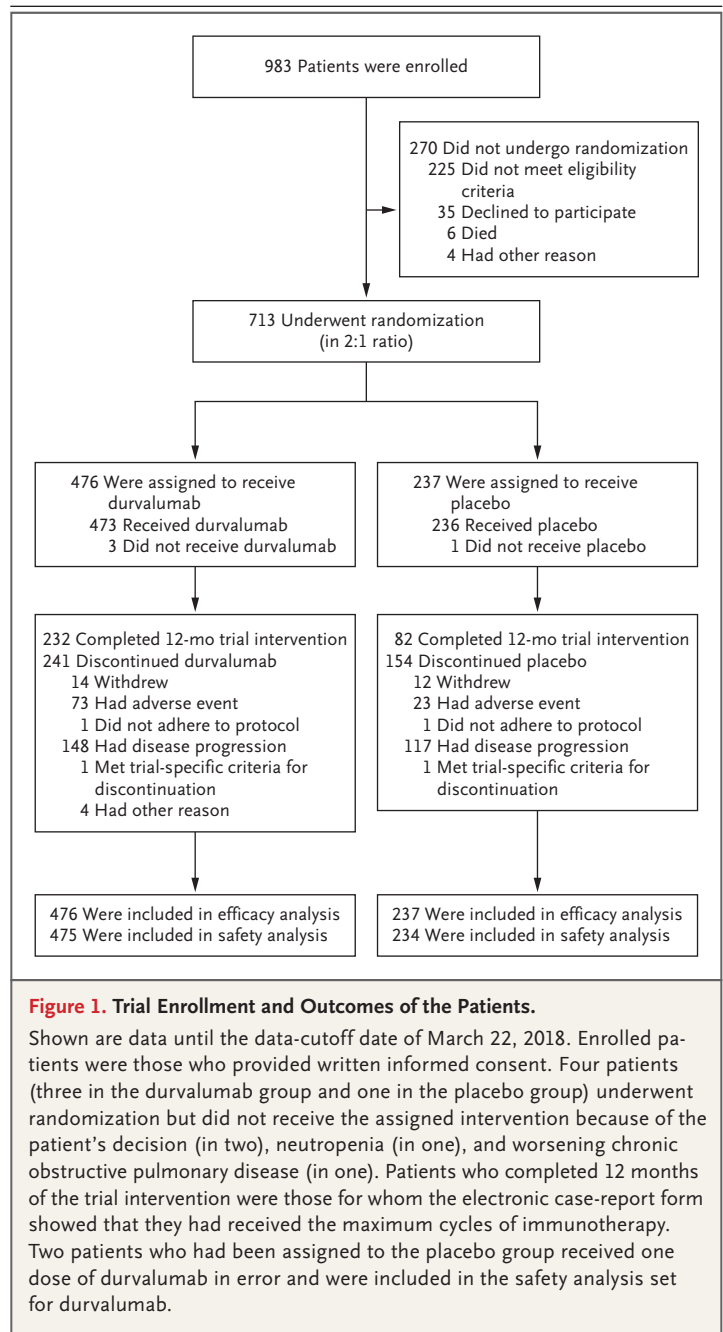
therapy. In addition, 82 patients (17.2%) in the durvalumab group and 56 (23.6%) in the placebo group received subsequent radiotherapy.

#### EFFICACY

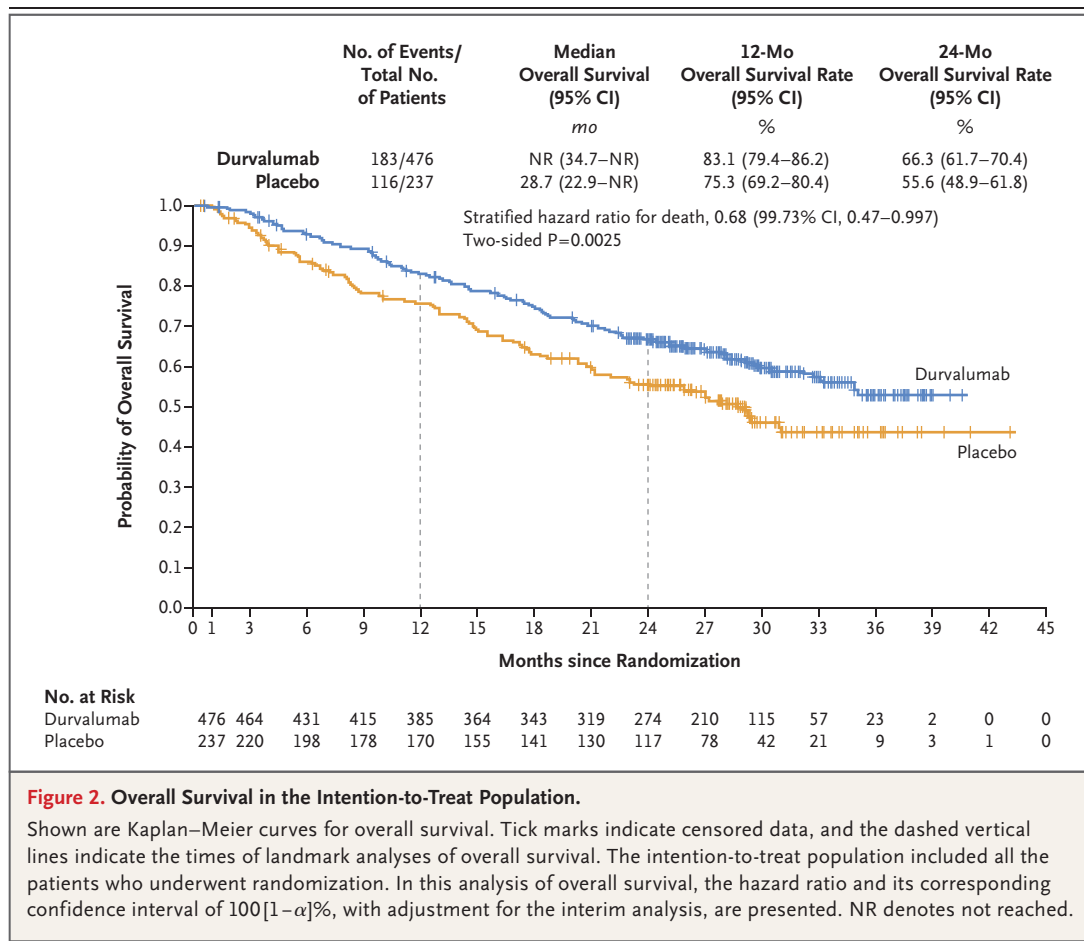
The 12-month overall survival rate was 83.1% (95% CI, 79.4 to 86.2) in the durvalumab group, as compared with 75.3% (95% CI, 69.2 to 80.4) in the placebo group. The 24-month overall survival rate was 66.3% (95% CI, 61.7 to 70.4) in the durvalumab group, as compared with 55.6% (95% CI, 48.9 to 61.8) in the placebo group (two-sided  $P=0.005$ ). Durvalumab significantly prolonged overall survival, as compared with placebo (stratified hazard ratio for death, 0.68; 99.73% CI, 0.47 to 0.997;  $P=0.0025$ ) (Fig. 2). The overall survival benefit with durvalumab was observed across all the prespecified subgroups, as defined according to the demographic characteristics of the patients, baseline clinicopathologic features, and response to previous treatment (Fig. S1 in the Supplementary Appendix).

At the time of data cutoff, the median progression-free survival from randomization, according to blinded independent central review, was 17.2 months (95% CI, 13.1 to 23.9) in the durvalumab group, as compared with 5.6 months (95% CI, 4.6 to 7.7) in the placebo group (stratified hazard ratio for disease progression or death, 0.51; 95% CI, 0.41 to 0.63) (Fig. S2 in the Supplementary Appendix). The results of exploratory post hoc analyses of progression-free survival and overall survival among patients with different PD-L1 expression levels (on the basis of archived tumor samples obtained before chemoradiotherapy [if available]) are shown in Figure S3 in the Supplementary Appendix. (Further information is provided in the Supplementary Discussion section in the Supplementary Appendix.)

In the updated analysis, the time to death or distant metastasis was longer in the durvalumab group than in the placebo group (median, 28.3 months [95% CI, 24.0 to 34.9] vs. 16.2 months [95% CI, 12.5 to 21.1]; stratified hazard ratio, 0.53; 95% CI, 0.41 to 0.68) (Fig. 3). In addition, the updated frequency of new lesions, as assessed by blinded independent central review, was 22.5% in the durvalumab group and 33.8% in the placebo group, with a lower incidence of new brain metastases in the durvalumab group than in the placebo group (6.3% vs. 11.8%) (Table 1). As of the data-cutoff date, a second progression event or death



occurred in 361 patients (217 in the durvalumab group and 144 in the placebo group). The time to second progression or death as assessed by the investigators according to local standard practice was longer in the durvalumab group than in the placebo group (median, 28.3 months [95% CI, 25.1 to 34.7] vs. 17.1 months [95% CI, 14.5 to 20.7]; stratified hazard ratio, 0.58; 95% CI, 0.46 to 0.73) (Fig. S4 in the Supplementary Appendix). The time



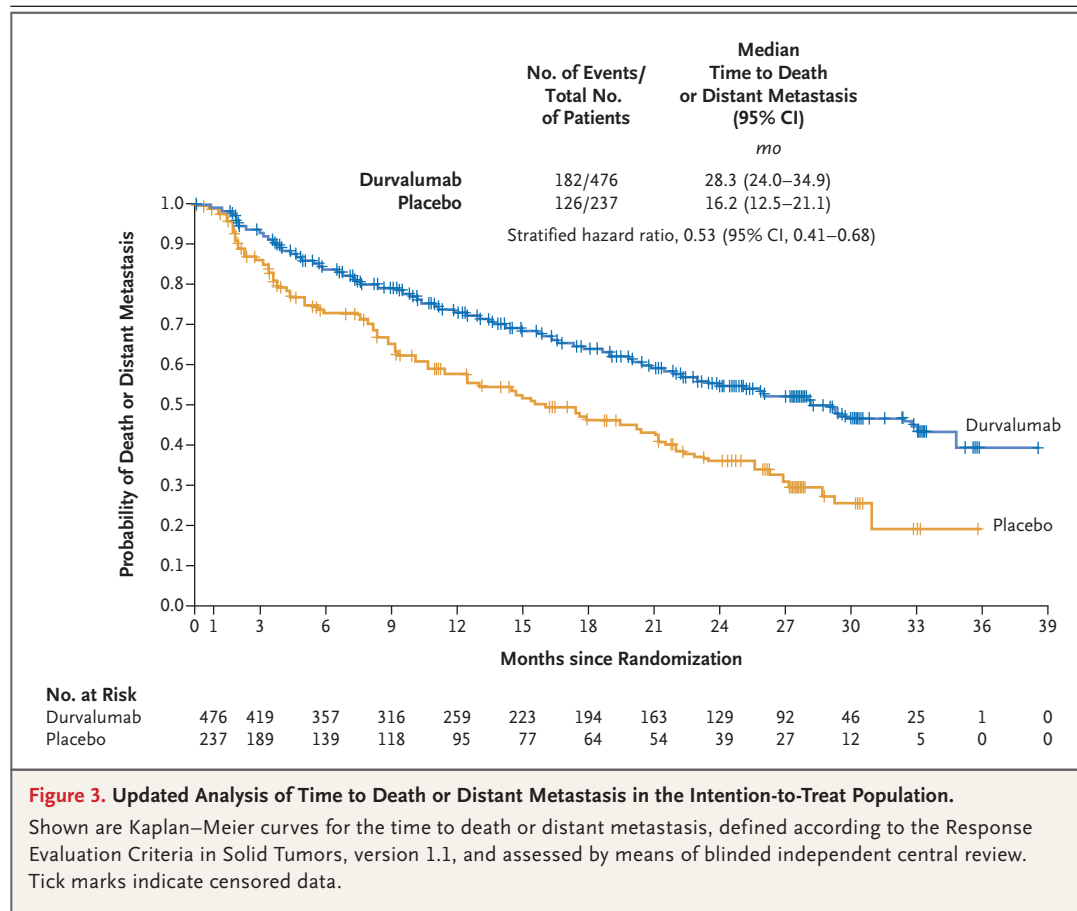
to the first subsequent therapy or death as well as the time to the second subsequent therapy or death were also longer in the durvalumab group than in the placebo group (Figs. S5 and S6 in the Supplementary Appendix).

In the updated analyses, the overall response rate was 30.0% (95% CI, 25.8 to 34.5) in the durvalumab group, as compared with 17.8% (95% CI, 13.0 to 23.6) in the placebo group ( $P<0.001$ ) (Table S3 in the Supplementary Appendix). The median duration of response was not reached (95% CI, 27.4 months to not reached) in the durvalumab group and was 18.4 months (95% CI, 6.7 to 24.5) in the placebo group (Table S3 in the Supplementary Appendix). Among patients who had a response, 73.5% of those in the durvalumab group had an ongoing response at 18 months, as compared with 52.2% in the placebo group (Table S3 in the Supplementary Appendix).

#### SAFETY

As of the new data-cutoff date, the safety profiles of durvalumab and placebo were consistent with those previously reported (Table S4 in the Supplementary Appendix).<sup>18</sup> Maximum-grade 3 or 4 adverse events of any cause occurred in 30.5% of the patients in the durvalumab group and in 26.1% of those in the placebo group. Discontinuation of the trial regimen because of adverse events occurred in 15.4% of the patients in the durvalumab group and in 9.8% of those in the placebo group. The most frequent adverse events leading to the discontinuation of the trial regimen were pneumonitis (in 4.8% of the patients in the durvalumab group and in 2.6% of those in the placebo group), radiation pneumonitis (in 1.3% and 1.3%, respectively), and pneumonia (in 1.1% and 1.3%).

Serious adverse events occurred in 29.1% of the patients in the durvalumab group and in 23.1%



of those in the placebo group, and death due to adverse events occurred in 4.4% and 6.4%, respectively. Adverse events of special interest that were of any grade or cause were reported in 66.7% of the patients in the durvalumab group and in 49.1% of those in the placebo group, with 56.8% and 43.6% of patients, respectively, reporting grade 1 or 2 events.

## DISCUSSION

In this updated analysis of the PACIFIC trial, the primary end point of overall survival was significantly longer with durvalumab than with placebo among patients with unresectable, stage III NSCLC. With the between-group difference in median progression-free survival remaining more than 11 months, the results of the analysis of overall survival indicate that the progression-free survival benefit has translated to a significant prolongation in overall survival. This result is consistent with previously reported associations between pro-

gression-free survival and overall survival among patients with stage III NSCLC.<sup>23</sup> Moreover, the prolongation of overall survival with durvalumab was observed in all the prespecified subgroups.

The updated results for secondary end points, including the time to death or distant metastasis, the incidence of new lesions, and the objective response rate, remain consistent with those that were previously reported<sup>18</sup> and continue to show the substantial anticancer activity of durvalumab treatment in patients after induction therapy and its favorable effect on preventing metastatic spread, which may help to explain the observed survival benefit. In addition, durvalumab therapy resulted in a longer time to second progression or death than placebo, as well as longer times to the first subsequent therapy or death and to the second subsequent therapy or death — results that show the long-term benefit of durvalumab treatment.

No new safety signals were identified after further follow-up. These findings help to define the safety profile of durvalumab use after chemo-

**Table 1.** Updated Incidence of New Lesions, as Assessed by Blinded Independent Central Review, in the Intention-to-treat Population.\*

New Lesion Site	Durvalumab Group (N = 476)	Placebo Group (N = 237)
	<i>no. of patients (%)</i>	
Any site	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal gland	3 (0.6)	5 (2.1)
Other	10 (2.1)	5 (2.1)

\* Lesions were assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1. A patient may have had more than one new lesion site.

radiotherapy, despite the trial being limited in its ability to distinguish or assign causality for some adverse events or to identify risk factors for their occurrence, owing to incomplete data regarding previous treatment.

In conclusion, this trial showed a survival advantage with durvalumab therapy after concurrent chemoradiation therapy in patients with stage III, unresectable NSCLC.

Supported by AstraZeneca.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families and caregivers; all the investigators who were involved in this trial; Anne-Marie Boothman, Ph.D., of AstraZeneca, and Louis Viviers, M.D., of Quintiles IMS, for contributions to the trial; and Andrew Gannon, M.S., M.A., of Cirrus Communications (an Ashfield company) for medical writing assistance with an earlier version of the manuscript.

#### APPENDIX

The authors' full names and academic degrees are as follows: Scott J. Antonia, M.D., Ph.D., Augusto Villegas, M.D., Davey Daniel, M.D., David Vicente, M.D., Shuji Murakami, M.D., Rina Hui, Ph.D., Takayasu Kurata, M.D., Ph.D., Alberto Chiappori, M.D., Ki H. Lee, M.D., Ph.D., Maïke de Wit, M.D., Ph.D., Byoung C. Cho, M.D., Ph.D., Maryam Bourhaba, M.D., Xavier Quantin, M.D., Ph.D., Takaaki Tokito, M.D., Ph.D., Tarek Mekhal, M.D., David Planchard, M.D., Ph.D., Young-Chul Kim, M.D., Ph.D., Christos S. Karapetis, M.D., Sandrine Hiret, M.D., Gyula Ostoros, M.D., Kaoru Kubota, M.D., Ph.D., Jhanelle E. Gray, M.D., Luis Paz-Ares, M.D., Ph.D., Javier de Castro Carpeño, M.D., Ph.D., Corinne Faivre-Finn, M.D., Ph.D., Martin Reck, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., David R. Spigel, M.D., Catherine Wadsworth, B.A., B.V.Sc., Giovanni Melillo, M.D., Maria Taboada, M.Sc., Phillip A. Dennis, M.D., Ph.D., and Mustafa Özgüroğlu, M.D.

The authors' affiliations are as follows: the H. Lee Moffitt Cancer Center and Research Institute, Tampa (S.J.A., A.C., J.E.G.), Cancer Specialists of North Florida, Jacksonville (A.V.), Florida Cancer Specialists, Fleming Island (A.V.), and Florida Hospital Cancer Institute, Orlando (T.M.) — all in Florida; Tennessee Oncology, Chattanooga (D.D.), and Sarah Cannon Research Institute, Nashville (D.D., D.R.S.) — both in Tennessee; Hospital Universitario Virgen Macarena, Seville (D.V.), and Hospital Universitario 12 de Octubre, CiberOnc, Universidad Complutense and Spanish National Cancer Research Center (L.P.-A.), and Hospital Universitario La Paz (J.C.C.), Madrid — all in Spain; Kanagawa Cancer Center, Yokohama (S.M.), Kansai Medical University Hospital, Hirakata (T.K.), Kurume University Hospital, Kurume (T.T.), and Nippon Medical School Hospital, Tokyo (K.K.) — all in Japan; Westmead Hospital and the University of Sydney, Sydney (R.H.), and Flinders University and Flinders Medical Centre, Adelaide, SA (C.S.K.) — all in Australia; Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju (K.H.L.), Yonsei Cancer Center, Yonsei University College of Medicine, Seoul (B.C.C.), and Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Gwangju (Y.-C.K.) — all in South Korea; Vivantes Klinikum Neukoelln, Berlin (M.W.), and the Lung Clinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf (M.R.) — both in Germany; Centre Hospitalier Universitaire de Liège, Liège (M.B.), and University Hospitals KU Leuven, Leuven (J.V.) — both in Belgium; Centre Hospitalier Universitaire de Montpellier and Institut du Cancer de Montpellier Val d'Aurelle, Montpellier (X.Q.), Institut Gustave Roussy, Villejuif (D.P.), and Institut de Cancérologie de l'Ouest—site René Gauducheau, Saint Herblain (S.H.) — all in France; National Koranyi Institute of Pulmonology, Budapest, Hungary (G.O.); the University of Manchester and the Christie NHS Foundation Trust, Manchester (C.F.-F.), AstraZeneca, Alderley Park (C.W.), and AstraZeneca, Cambridge (M.T.) — all in the United Kingdom; AstraZeneca, Gaithersburg, MD (G.M., P.A.D.); and Istanbul University—Cerrahpasa, Cerrahpasa School of Medicine, Istanbul, Turkey (M.Ö.).

#### REFERENCES

1. Yoon SM, Shaikh T, Hallman M. Therapeutic management options for stage III non-small cell lung cancer. *World J Clin Oncol* 2017;8:1-20.
2. Bradley JD, Hu C, Komaki RU, et al. Long-term results of RTOG 0617: a randomized phase 3 comparison of standard dose versus high dose conformal chemoradiation therapy +/- cetuximab for stage III NSCLC. *Int J Radiat Oncol Biol Phys* 2017;99:Suppl:S105. abstract.
3. Ahn JS, Ahn YC, Kim JH, et al. Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small-cell lung cancer: KCSG-LU05-04. *J Clin Oncol* 2015;33:2660-6.
4. Skrzypski M, Jassem J. Consolidation systemic treatment after radiochemotherapy for unresectable stage III non-small cell lung cancer. *Cancer Treat Rev* 2018; 66:114-21.
5. Tsujino K, Kurata T, Yamamoto S, et al. Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer? A pooled analysis of the literature. *J Thorac Oncol* 2013;8:1181-9.
6. Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol* 2008;26:2450-6.



7. Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol* 2008;26:5755-60.
8. Moya-Horno I, Viteri S, Karachaliou N, Rosell R. Combination of immunotherapy with targeted therapies in advanced non-small cell lung cancer (NSCLC). *Ther Adv Med Oncol* 2018;10:1758834017745012.
9. O'Kane GM, Labbé C, Doherty MK, Young K, Albaba H, Leighl NB. Monitoring and management of immune-related adverse events associated with programmed cell death protein-1 axis inhibitors in lung cancer. *Oncologist* 2017;22:70-80.
10. Ibrahim R, Stewart R, Shalabi A. PD-L1 blockade for cancer treatment: MEDI4736. *Semin Oncol* 2015;42:474-83.
11. Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res* 2015;3:1052-62.
12. Chakraborty M, Abrams SI, Coleman CN, Camphausen K, Schlom J, Hodge JW. External beam radiation of tumors alters phenotype of tumor cells to render them susceptible to vaccine-mediated T-cell killing. *Cancer Res* 2004;64:4328-37.
13. Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* 2014;124:687-95.
14. Dovedi SJ, Adlard AL, Lipowska-Bhal-la G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res* 2014;74:5458-68.
15. Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J Immunol* 2005;174:7516-23.
16. Reits EA, Hodge JW, Herberts CA, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med* 2006;203:1259-71.
17. Zhang P, Su DM, Liang M, Fu J. Chemopreventive agents induce programmed death-1-ligand 1 (PD-L1) surface expression in breast cancer cells and promote PD-L1-mediated T cell apoptosis. *Mol Immunol* 2008;45:1470-6.
18. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017;377:1919-29.
19. AstraZeneca. Imfinzi (durvalumab): U.S. prescribing information. February 2018 (<https://www.imfinzi.com/>).
20. AstraZeneca Imfinzi (durvalumab) press releases (<https://www.astrazeneca.com/media-centre/press-releases.html>).
21. Goldstraw P, ed. Staging manual in thoracic oncology. 7th ed. Aurora, CO: International Association for the Study of Lung Cancer, 2010.
22. Lan K-KG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659-63.
23. Mauguén A, Pignon JP, Burdett S, et al. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: a re-analysis of meta-analyses of individual patients' data. *Lancet Oncol* 2013;14:619-26.

Copyright © 2018 Massachusetts Medical Society.