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ORIGINAL RESEARCH

Assessing the Influence of Subsequent Immunotherapy on Overall Survival in Patients with Unresectable Stage III Non-Small Cell Lung Cancer from the PACIFIC Study

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ABSTRACT

Background: Historically, the standard of care for patients with unresectable, Stage III non-small cell lung cancer had been concurrent chemoradiotherapy. However, outcomes had been poor, with approximately 15% to 32% of patients alive at 5 years. In the placebo-controlled Phase III A PACIFIC trial, consolidation treatment with durvalumab after concurrent chemoradiotherapy significantly improved overall survival (OS) and progression-free survival in patients with unresectable, Stage III non-small cell lung cancer, establishing this regimen as a new standard of care in this setting. In the PACIFIC trial, crossover between treatment arms (durvalumab or placebo) was not permitted. However, after discontinuation from study treatment, patients from both arms of PACIFIC could switch to subsequent anticancer therapy, including durvalumab and other immunotherapies, which is known to influence standard intention-to-treat analysis of OS, potentially underestimating the effect of an experimental drug. Moreover, the introduction of immunotherapies has demonstrated marked improvements in the postprogression, metastatic non-small cell lung cancer setting.

Objective: To examine the influence of subsequent immunotherapy on OS in the PACIFIC trial.

Methods: Both a Rank Preserving Structural Failure Time Model (RPSFTM) and modified 2-stage method were used. RPSFTM assumes that a patient's survival time with no immunotherapy (counterfactual survival time) is equal to the observed time influenced by immunotherapy, multiplied by an acceleration factor, plus the time not influenced. The modified 2-stage method estimates the effect of immunotherapy by comparing postsubsequent-treatment-initiation survival times between patients with and without subsequent immunotherapy. In both models, OS was adjusted to reflect a hypothetical scenario in which no patients received subsequent immunotherapy. RPSFTM was also used for scenarios in which subsequent immunotherapy was received by increasing proportions of placebo patients but none of the durvalumab patients.

Results: In the intention-to-treat analysis (3-year follow-up), durvalumab improved OS versus placebo (stratified hazard ratio = 0.69; 95% CI, 0.55–0.86). Overall, 10% and 27% of durvalumab and placebo patients, respectively, received subsequent immunotherapy. With subsequent immunotherapy removed from both arms, estimated hazard ratio was 0.66 (95% CI, 0.53–0.84) with RPSFTM and 0.68 (95% CI, 0.54–0.85) with the modified 2-stage method. With subsequent immunotherapy removed from the durvalumab arm only (RPSFTM), estimated hazard ratio increased as the proportion of placebo patients receiving subsequent immunotherapy increased, up to 0.75 (95% CI, 0.60–0.94) maximum (assuming all placebo patients with subsequent treatment received immunotherapy).

Conclusions: Results were consistent with the intention-to-treat analysis, supporting the conclusion that durvalumab after chemoradiotherapy provides substantial OS benefit in patients with Stage III, unre-

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with an estimated 1.8 million deaths attributed to it in 2018.¹ Non-small cell lung cancer (NSCLC) accounts for the majority (80%–85%) of all cases² and approximately 25% of these patients present with Stage III, locally advanced disease, the majority of whom have unresectable tumors.³ Until recently, for such patients, treatment with curative intent was composed of platinum-based doublet chemotherapy, concurrent with radiotherapy (ie, chemoradiotherapy [CRT]).^{4,5} However, outcomes were poor: Most patients had disease progression after CRT, with approximately 15% to 32% of patients alive at 5 years.^{6,7} Additionally, for many years, no clinical studies of systemic therapy with curative intent in patients with disease control after CRT led to improved outcomes, until the Phase III PACIFIC trial of durvalumab.^{8–15}

Durvalumab is an immune checkpoint inhibitor that blocks programmed cell death-ligand 1 (PD-L1) binding to programmed cell death-1 and CD80, allowing T cells to recognize and kill tumor cells.^{16,17} In the Phase III PACIFIC trial of unresectable, Stage III NSCLC patients without disease progression after concurrent CRT, durvalumab was associated with significant improvements in the primary end points of progression-free survival and overall survival (OS) versus placebo.^{13–15} Based on these findings, durvalumab has been approved in the United States, Europe, and elsewhere for the treatment of patients with Stage III or locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based CRT (in Europe, patients must have tumors that express PD-L1 on $\geq 1\%$ of tumor cells).^{18–20} After progression, the disease is no longer in a potentially curative setting and, therefore, patients will receive palliative treatment or treatment to extend survival for metastatic NSCLC, which includes chemotherapy and other immune checkpoint inhibitors/anti-programmed cell death-1/PD-L1 antibodies (or, in the case of patients with sensitizing tumor *EGFR* or *ALK* mutations, appropriate targeted therapy).^{21–23} Historically, the 5-year survival rates for patients with metastatic NSCLC have been as low as 10%;²⁴ however, the introduction of immunotherapies has demonstrated marked improvements in this setting, increasing the rates by an estimated 10% or more.^{25,26}

Treatment switching refers to the situation in a randomized, controlled trial in which patients switch from their randomly assigned treatment to an alternative treatment. Treatment switching is common in oncology trials due to ethical and real-world clinical practice reasons. In PACIFIC, patients could receive the study drug (durvalumab or placebo) up to 12 months or until progression but, thereafter, study drug was discontinued; crossover between treatment arms was not permitted.¹³ However, patients from both arms could switch to subsequent anticancer therapy, including durvalumab and other immunotherapies, after discontinuation from study treatment (for any reason).

It is recognized that any subsequent treatments prescribed upon disease progression may influence the standard intention-to-treat (ITT) analysis of OS, in which data are analyzed according to randomized therapy, potentially underestimating the effect of the experimental drug.²⁷ Several statistical methods have been developed to adjust survival data for the potential influence of subse-

quent treatment. One such method is the Rank Preserving Structural Failure Time Model (RPSFTM), which, by adjusting survival time for patients with a subsequent treatment of interest, can estimate survival as if the patient had not received subsequent treatment, thereby specifically preserving randomization.^{27–29} RPSFTM is a well-recognized method for health technology assessment²⁸ and has been used to adjust for confounding effects of subsequent treatment in clinical trials of renal cell carcinoma; gastrointestinal stromal tumors; melanoma; ovarian cancer; neuroendocrine tumors; and, most recently, NSCLC.^{30–40} Other methods include a 2-stage approach, which is appropriate when treatment switching is permitted after a disease-related time point such as disease progression.²⁷ The 2-stage method has found favor for health technology assessment when the required assumption of a common treatment effect for RPSFTM is not met.²⁸ However, if used to analyze OS in the PACIFIC trial, this approach would need to be modified (ie, via use of a secondary baseline not defined by disease progression) because switching to a subsequent anticancer therapy (eg, immunotherapy) may not have occurred at progression in this study. Finally, the inverse probability of censoring weighting (IPCW) method,⁴¹ which predicts the stage at which the patients initiate subsequent immunotherapy based on predictive covariates for all patients, would not be suitable for analyzing OS in the PACIFIC study because there were not sufficient numbers of patients initiating immunotherapy during selected time periods within follow-up or sufficient information available.

Here we report results using the RPSFTM approach, and a new modified 2-stage method (M2SM), to examine the influence of subsequent immunotherapy on OS in the PACIFIC study.

Patients and Methods

Details of the PACIFIC study design have been previously published.^{13–15} This was an international, multicenter, Phase III, randomized, double-blind, placebo-controlled study of adult patients with unresectable, Stage III NSCLC without evidence of disease progression following ≥ 2 cycles of definitive platinum-based concurrent CRT. Patients were randomized 2:1 to receive durvalumab intravenously, at a dose of 10 mg/kg body weight, or matching placebo every 2 weeks up to 12 months or until confirmed disease progression, initiation of alternative cancer therapy, unacceptable toxicity, or consent withdrawal. Randomization was stratified according to age (<65 years vs ≥ 65 years), sex, and smoking history (current/former smoker vs never smoked). Analysis of the primary end point OS (defined as the time from randomization until death from any cause) included all patients who underwent randomization according to the ITT principle. Three methodological approaches were considered as potential candidates for OS adjustment modeling: an RPSFTM, a 2-stage method, and an IPCW method.

The RPSFTM approach uses a counterfactual framework to estimate the causal treatment effect.²⁷ The counterfactual survival times are those that would have been observed if no immunotherapy had been given. In the current analysis, the RPSFTM assumed that exposure to immunotherapy extends the lifetime of a patient by $\exp(-\psi)$ in which ψ is assumed to be the same regardless of the line of treatment (ie, subsequent immunotherapy immediately after randomized treatment has the same ψ as immunother-

apy initiated after other subsequent treatments). Based on ψ , the counterfactual survival times were computed for immunotherapy initiators (ie, their survival time if they had not had immunotherapy). After removing the immunotherapy effect, the underlying survival was assumed to be the same for the 2 randomized treatment arms. In the RPSFTM, each patient acts as his or her own reference and unmeasured confounding does not appear to have an influence.⁴²

In our evaluation, the RPSFTM used G-estimation, which is a grid search across a range of possible values, to select a value of ψ , so that the log-rank hazard ratio at counterfactual basis is equal to 1 (the counterfactual survival distribution for the durvalumab arm was assumed to be equal to the counterfactual survival distribution for the placebo arm). The model assumed that immunotherapy was effective from treatment start. Recensoring was performed based on all times after the counterfactual administration censoring time, but the decision was made to use the more conservative results derived without recensoring.

The RPSFTM was considered feasible and was, therefore, used to investigate 2 hypothetical scenarios of interest representing different treatment patterns:

- No subsequent immunotherapy was received by patients randomized to either study arm; and
- No subsequent immunotherapy was received by patients in the durvalumab arm, whereas in the placebo arm, a variable proportion (20%, 40%, 60%, 80%, and 100%) of the patients who had received any subsequent anticancer treatment were assumed to have received immunotherapy based on the same prescription pattern as observed in the clinical trial.

The latter scenario was explored to provide information for current and future medical practice in which the percentage of patients receiving immunotherapy will likely be different from the percentage in the clinical trial. To estimate the hazard ratios (HRs) for counterfactual survival, we simulated the trial outcomes for 1,000 sets of patients for each scenario. In addition, for both scenarios, both a log-rank test and adjusted stratified Cox model (the former designated the primary analysis) were used to calculate HRs and 95% CIs.

The standard 2-stage method, as defined in the UK National Institute for Health and Care Excellence Decision Support Unit Technical Support Document,^{16,27} is based on progression. In this model, it is assumed that progression is a secondary baseline at which time approximately all treatment switching occurs. An obstacle in applying the published 2-stage method²⁷ to PACIFIC was that the preceding assumption—treatment switching occurs at progression—was not met (patients started subsequent immunotherapy a median of ~6 months after progression). If this method had been used, an immortal time bias would have been introduced, based on the period of time between progression and treatment switching in which patients could not die.

We accordingly modified the 2-stage procedure to adjust for subsequent immunotherapy. In this M2SM approach, the start of subsequent treatment, rather than disease progression, is used as a secondary baseline, and the survival time of patients switching to the subsequent treatment of interest (in this case, immunotherapy) is substituted with a predicted survival time based on that of patients receiving alternative subsequent treatments (eg, traditional chemotherapy).

As shown in Figure 1, patients with subsequent anticancer treatment were subdivided into 3 groups: those who received immunotherapy as first subsequent treatment (Group A), those who received immunotherapy as second or later subsequent treatment (ie, not having received immunotherapy as first subsequent treat-

ment) (Group B), and those who never received immunotherapy (Group C). In Step 1, we compared the survival times of patients in Group B versus patients in Group C after initiation of second or later subsequent treatment and computed the acceleration factor, based on accelerated failure time models, to estimate the amount in which survival is extended by initiation of immunotherapy.⁴³ We then multiplied Group B survival time after initiation of immunotherapy by the acceleration factor to calculate the survival time if Group B patients had not received immunotherapy. In Step 2, we compared survival times of patients in Group A versus patients in Group C plus Updated Group B after initiation of first subsequent treatment and computed the acceleration factor based on accelerated failure time models. We then multiplied Group A survival time after initiation of first subsequent treatment by the acceleration factor to calculate the survival time if Group A patients had not received immunotherapy. In Step 3 (final step), with the subsequent treatment Groups A and B updated, their survival times were transformed to reflect what they would have been if no patients in either group had received subsequent immunotherapy. This allowed us to compare the survival times of patients in the durvalumab arm versus the placebo arm (based on Updated Groups A + B + Group C).

Because both Steps 1 and 2 in the M2SM were observational, we tested for potential confounding using a univariate analysis to compare covariates (including patient-reported outcomes and efficacy measurements from the date closest to, but before, treatment initiation; patient demographic characteristics; and time from randomization to initiation) between patients who had or had not received immunotherapy. (For patients in Group C, treatment initiation is defined as the start of either second subsequent treatment, when compared with Group B, or first subsequent treatment, when compared with Group A; patients without subsequent treatment, for whom the original times are used, are not included in Group C.) Covariates that differed significantly ($P < 0.05$, based on a χ^2 test or t test, depending on the covariate) were selected for prediction of immunotherapy initiation using logistic regression. Based on Bayesian information criterion, significant variables were subsequently selected and used to predict immunotherapy use in Groups B and A using 2 approaches—propensity weighting (described for observational studies elsewhere⁴⁴) and regression (described for treatment switching elsewhere²⁷). Both approaches were performed for Weibull, loglogistic, lognormal, generalized gamma, and exponential distributions. We adjusted survival times using an acceleration factor selected by the best Akaike information criterion. We then compared durvalumab versus placebo, calculating HR and the corresponding 95% CI using a log-rank test with stratification factors (age, sex, and smoking history).

However, because the covariate selection process was based on small datasets and modeling in different steps, M2SM was only used to support the RPSFTM findings; in addition, we decided not to build in bootstrapping for 95% CI, but to accept that the final 95% CI obtained did not take into account uncertainty in the updating process. (Recensoring results can be obtained upon request but only slightly differed.)

The IPCW method was also initially considered, but not used for the reasons described in the **Supplemental** in the online version at doi: 10.1016/j.curtheres.2021.100640. All analyses were conducted using R statistical software version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

ITT analysis of OS

At the 3-year ITT analysis of PACIFIC (data cutoff date: January 31, 2019), durvalumab was associated with a statistically signifi-

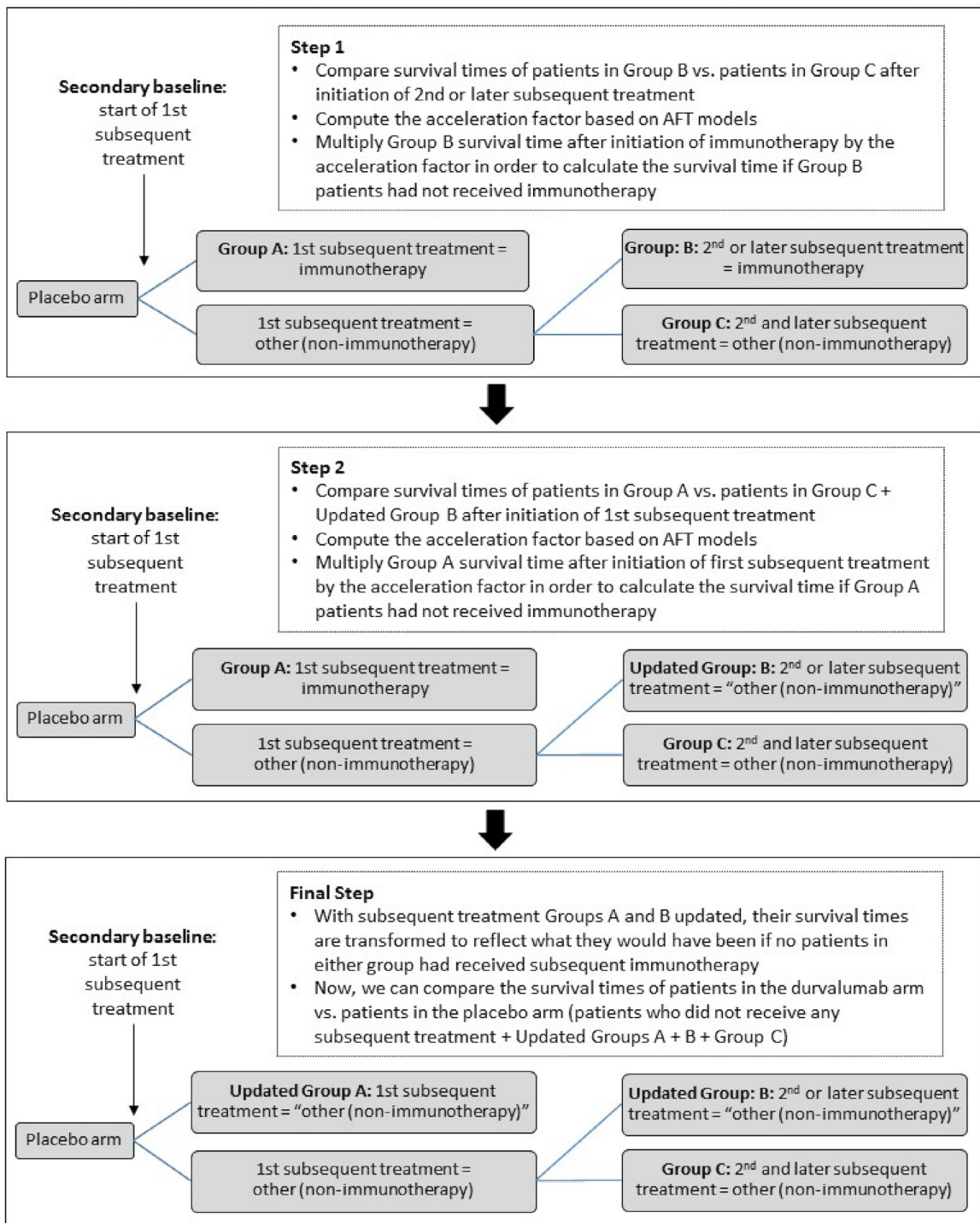


Figure 1. Modified 2-stage method (M2SM): Procedure for transforming the postsecondary-baseline survival times of patients in the placebo arm who received subsequent immunotherapy into what their survival times would have been if they had not received immunotherapy (this same procedure can be applied to patients in the durvalumab arm).
AFT = Accelerated failure time.

cant and clinically meaningful improvement in OS compared with placebo (stratified HR = 0.69; 95% CI, 0.55–0.86).¹⁵ Additionally, median OS was not reached (NR) (95% CI, 38.4–NR) for the durvalumab arm and 29.1 months (95% CI, 22.1–35.1) for the placebo arm. The results were consistent with previous reports of the primary ITT analysis of OS (HR = 0.68; 95% CI, 0.53–0.87).^{14,19}

Subsequent anticancer therapy after discontinuation of study treatment

At the January 31, 2019 data cutoff date, a total of 343 patients in PACIFIC had received subsequent anticancer treatment: 43.3% (206 out of 476) of patients randomized to durvalumab and

Table 1
Summary of subsequent anticancer therapies received by patients who progressed during the PACIFIC study (data cutoff date, January 31, 2019).

Therapy*	Durvalumab (n = 476)	Placebo (n = 237)	Total (N = 713)
Patients receiving postprogression disease-related anticancer therapy	206 (43.3)	137 (57.8)	343 (48.1)
Chemotherapy	138 (29.0)	81 (34.2)	219 (30.7)
Carboplatin	79 (16.6)	44 (18.6)	123 (17.3)
Pemetrexed	48 (10.1)	31 (13.1)	79 (11.1)
Gemcitabine	44 (9.2)	24 (10.1)	68 (9.5)
Paclitaxel	39 (8.2)	22 (9.3)	61 (8.6)
Docetaxel	42 (8.8)	15 (6.3)	57 (8.0)
Cisplatin	20 (4.2)	16 (6.8)	36 (5.0)
Vinorelbine	16 (3.4)	8 (3.4)	16 (2.2)
Gimeracil + oteracil potassium + tegafur	8 (1.7)	4 (1.7)	12 (1.7)
Amrubicin	2 (0.4)	1 (0.4)	3 (0.4)
Fluorouracil	0	1 (0.4)	1 (0.1)
Irinotecan	0	1 (0.4)	1 (0.1)
Nedaplatin	1 (0.2)	0	1 (0.1)
Oxaliplatin	0	1 (0.4)	1 (0.1)
Topotecan	0	1 (0.4)	1 (0.1)
Uncoded	1 (0.2)	1 (0.4)	2 (0.3)
Radiotherapy	89 (18.7)	60 (25.3)	149 (20.9)
Immunotherapy	46 (9.7)	63 (26.6)	109 (15.3)
Nivolumab	33 (6.9)	52 (21.9)	55 (11.9)
Pembrolizumab	10 (2.1)	8 (3.4)	18 (2.5)
Atezolizumab	2 (0.4)	1 (0.4)	3 (0.4)
Durvalumab	1 (0.2)	2 (0.8)	3 (0.4)
Ipilimumab	1 (0.2)	1 (0.4)	2 (0.3)
Tremelimumab	1 (0.2)	0	1 (0.1)
Avelumab	0	1 (0.4)	1 (0.1)
BMS-986205	1 (0.2)	0	1 (0.1)
Uncoded	3 (0.6)	1 (0.4)	4 (0.6)
Systemic targeted therapy	50 (10.5)	34 (14.3)	84 (11.8)
Erlotinib	10 (2.1)	13 (5.5)	23 (3.2)
Afatinib	11 (2.3)	4 (1.7)	15 (2.1)
Bevacizumab	7 (1.5)	3 (1.3)	10 (1.4)
Ramucirumab	9 (1.9)	2 (0.8)	11 (1.5)
Crizotinib	4 (0.8)	6 (2.5)	10 (1.4)
Gefitinib	4 (0.8)	3 (1.3)	7 (1.0)
Necitumumab	3 (0.6)	2 (0.8)	5 (0.7)
Osimertinib	3 (0.6)	2 (0.8)	5 (0.7)
Nintedanib	3 (0.6)	1 (0.4)	4 (0.6)
Alectinib	2 (0.4)	1 (0.4)	3 (0.4)
Dasatinib	1 (0.2)	0	1 (0.1)
Lenvatinib	0	1 (0.4)	1 (0.1)
Vemurafenib	1 (0.2)	0	1 (0.1)
Glesatinib	1 (0.2)	0	1 (0.1)
Itacitinib	1 (0.2)	0	1 (0.1)
Lorlatinib	0	1 (0.4)	1 (0.1)
Naquotinib	1 (0.2)	0	1 (0.1)
Sitratatinib	1 (0.2)	0	1 (0.1)
Vandetanib	1 (0.2)	0	1 (0.1)
Uncoded	2 (0.4)	0	2 (0.3)
Other	1 (0.2)	0	1 (0.1)
Uncoded	1 (0.2)	0	1 (0.1)

* Values are presented as n (%).

57.8% (137 out of 237) of patients randomized to placebo (Table 1). Specifically, 109 patients received subsequent immunotherapy: 9.7% (46 out of 476) of patients randomized to durvalumab and 26.6% (63 out of 237) of patients randomized to placebo. Of these patients, only 46% (21 out of 46 on durvalumab and 29 out of 63 on placebo) received immunotherapy as their first subsequent treatment. Patients in the durvalumab and placebo arms who received subsequent immunotherapy remained on immunotherapy for a median of 0.88 and 0.78 years, respectively (31% and 28% of their total 2.81 and 2.78 years of OS, respectively).

Baseline patient and disease characteristics of patients who received subsequent immunotherapy were generally similar to those who did not, regardless of treatment (see **Supplemental Table 1** in the online version at doi:10.1016/j.curtheres.2021.100640).

RPSFTM

The RPSFTM without recensoring produced an acceleration factor $\exp(\psi)$ of 0.59, which was used to shorten the survival time of patients after receiving on-trial immunotherapy. The counterfactual Kaplan-Meier OS curves, whereby any immunotherapy effect was excluded from the placebo and durvalumab treatment arms (ie, the durvalumab treatment effect was also taken out of the survival data) showed equivalence, indicating that application of the RPSFTM was successful.

When the effect of subsequent immunotherapy was removed from both arms, the estimated HR was 0.66 (95% CI, 0.53–0.84) by log-rank test (0.68; 95% CI, 0.55–0.85 by adjusted stratified Cox model) and the corresponding median OS estimates were

	Durvalumab	Placebo	HR (95% CI)
Median OS (95% CI), months			
RPSFTM	NR (37.0–NR)	26.9 (21.2–31.0)	0.66 (0.53–0.84)
Primary ITT analysis ^{9,13}	NR (34.7–NR)	28.7 (22.9–NR)	0.68 (0.53–0.87)

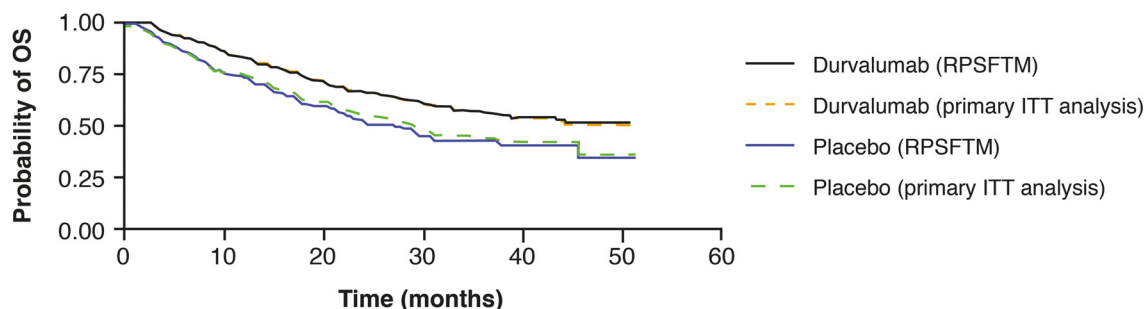


Figure 2. Rank Preserving Structural Failure Time Model (RPSFTM): Observed and adjusted Kaplan-Meier curves for overall survival (OS) when no subsequent immunotherapy is received in either treatment arm (based on the log-rank test). HR = hazard ratio; ITT = intention to treat; NR = not reached.

NR (95% CI, 37.0–NR) and 26.9 months (95% CI, 21.2–31.0) in the durvalumab and placebo arms, respectively. The Kaplan-Meier curves before and after removing the effect of subsequent immunotherapy, presented in Figure 2, suggested minimal change in survival relative to the primary ITT analysis.

Two alternative scenarios assumed that (1) patients in the placebo arm received subsequent immunotherapy, as prescribed in the trial (first versus second/later treatment), and (2) an increasing proportion of patients in the placebo arm received subsequent immunotherapy (based on the same prescription patterns in the trial), with the maximum number of placebo patients included in this scenario equalling those who had received any subsequent anticancer treatment (n = 137). In contrast, all patients in the durvalumab arm were assumed to have not received any subsequent immunotherapy in either scenario. In these cases, the inverse of the acceleration factor was used to lengthen the survival time for applicable patients in the placebo arm after starting immunotherapy. For durvalumab-treated patients, the acceleration factor was used to shorten the survival time after their first subsequent immunotherapy.

As shown in Figure 3, the first part of this analysis (receipt of subsequent immunotherapy as prescribed in the trial for patients from the placebo arm, with no subsequent immunotherapy for those in the durvalumab arm) showed minimal influence in the OS curves for either treatment arm. Consequently, the estimated HR changed little from the original ITT analysis to 0.70 (95% CI, 0.55–0.88) by log-rank test (0.71; 95% CI, 0.57–0.88 by adjusted stratified Cox model), with corresponding median OS estimates of NR (95% CI, 37.0–NR) in the durvalumab arm and 29.1 months (95% CI, 22.1–35.1) in the placebo arm. In this case, subsequent immunotherapy appeared to have minimal influence on OS of patients in the placebo arm when compared with the influence of durvalumab on patients in the durvalumab arm. As expected, increasing the proportion of additional patients in the placebo arm who received subsequent immunotherapy according to the same prescription pattern was associated with increases in the estimated HR (Table 2).

M2SM

The M2SM resulted in an adjusted acceleration factor of 1.43 using propensity weighting and 1.26 using regression for patients in the placebo arm receiving immunotherapy as second or later subsequent treatment. Identified adjustment variables were time to deterioration of dyspnea and time (from randomization) to start of subsequent treatment.

For patients in the placebo arm who received immunotherapy as first subsequent treatment, the adjusted acceleration factor was 1.27 using propensity weighting and 1.05 using regression. Adjustment variables included time to deterioration of dyspnea and region, specifically Asia (compared with Europe and North America).

In the durvalumab arm, the adjusted acceleration factor was 0.73 for patients who received immunotherapy as second line or later treatment using propensity weighting and 0.72 using regression; adjustment variables were time (from randomization) to start of subsequent treatment, EGFR mutation status, and time to deterioration of physical functioning. These data suggest that this population was in some way distinct. Finally, the adjusted acceleration factor for patients in the durvalumab arm who received immunotherapy as first subsequent treatment was 1.24 using both propensity weighting and regression; no variables were selected for this group.

Using these data, comparison of the adjusted durvalumab and adjusted placebo arms resulted in HR = 0.68 (95% CI, 0.54–0.85) (Figure 4), consistent with an HR = 0.69 when both arms were unadjusted (ie, the ITT analysis). Recensoring resulted in an HR = 0.65. Adjusting only the placebo arm or durvalumab arm data resulted in very similar HRs (0.68 and 0.69, respectively).

Discussion

We used 2 models, the RPSFTM and a M2SM, which uniquely utilized propensity weighting, to predict the influence of subsequent immunotherapy received after disease progression on OS of

	Durvalumab	Placebo	HR (95% CI)
Median OS (95% CI), months			
RPSFTM	NR (37.0–NR)	29.1 (22.1–35.1)	0.70 (0.55–0.88)
Primary ITT analysis ^{9,13}	NR (34.7–NR)	28.7 (22.9–NR)	0.68 (0.53–0.87)

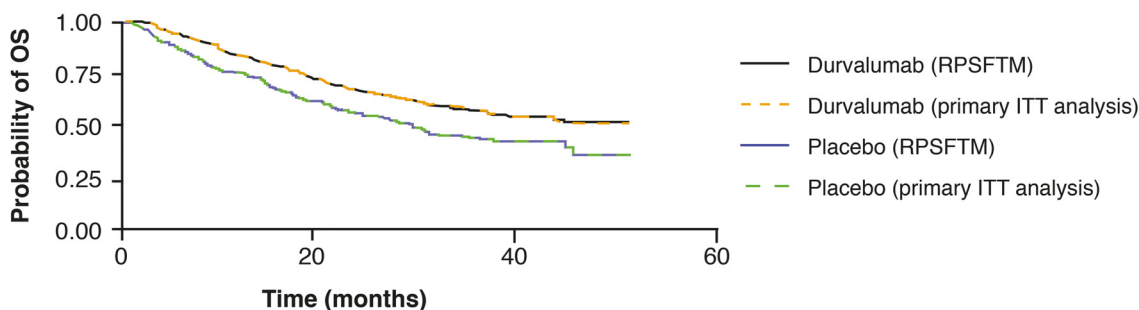


Figure 3. Rank Preserving Structural Failure Time Model (RPSFTM): Observed and adjusted Kaplan–Meier curves for overall survival (OS), assuming that patients in the placebo arm received subsequent immunotherapy as prescribed in the trial, and that patients in the durvalumab arm received no subsequent immunotherapy (based on the log-rank test). HR = hazard ratio; ITT = intention to treat; NR = not reached.

	Durvalumab	Placebo	HR (95% CI)
Median OS (95% CI), months			
Modified two-stage method	NR (38.4–NR)	27.9 (22.1–34.2)	0.68 (0.54–0.85)
Primary ITT analysis ^{9,13}	NR (34.7–NR)	28.7 (22.9–NR)	0.68 (0.53–0.87)

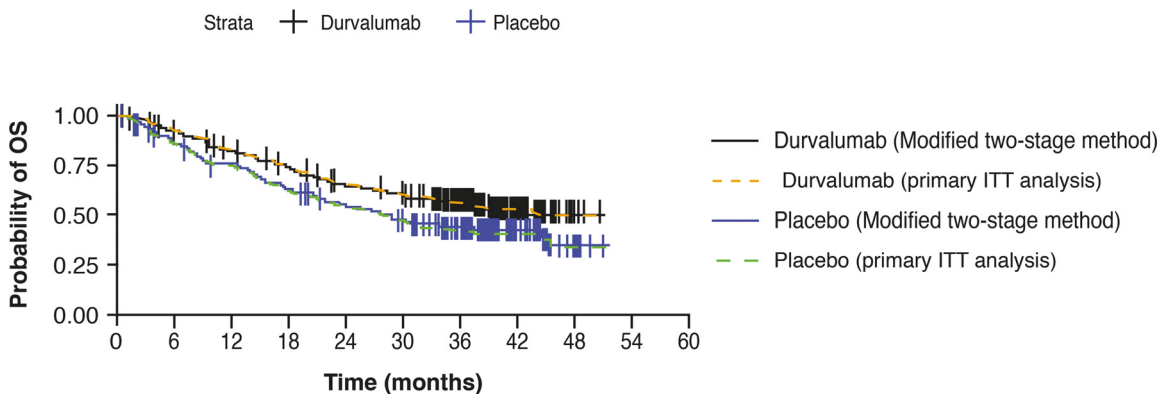


Figure 4. Modified 2-stage method: Observed and adjusted Kaplan–Meier curves for overall survival (OS) when no subsequent immunotherapy is received in either treatment arm. HR = hazard ratio; ITT = intention to treat; NR = not reached.

Table 2

RPSFTM: impact on overall survival of durvalumab versus placebo in an alternative scenario in which an increasing proportion of patients in the placebo arm received immunotherapy,* with no subsequent immunotherapy in the durvalumab arm (based on the log-rank test).†

Proportion of patients in the placebo arm receiving subsequent immunotherapy (of 137 placebo patients who received any subsequent anticancer treatment)	Hazard ratio (95% CI)
0% (base case adjustment)	0.66 (0.53–0.84)
20%	0.68 (0.54–0.85)
27% (patients who received subsequent immunotherapy in the trial)	0.70 (0.55–0.88)
40%	0.69 (0.55–0.87)
60%	0.71 (0.57–0.89)
80%	0.73 (0.58–0.91)
100%	0.75 (0.60–0.94)

* Only those patients in the placebo arm who received any subsequent anticancer treatment were eligible for inclusion in the model (n=137).

† See Supplemental Table S2 for similar results by the adjusted stratified Cox model.

patients with unresectable, Stage III NSCLC enrolled in the Phase III PACIFIC study. In a first scenario, investigated with each model, the effect of subsequent immunotherapy was removed from both treatment arms. The similarity between the estimated HRs for OS with each model (0.66 with RPSFTM and 0.68 with M2SM) and those observed in the primary and updated 3-year ITT analysis of the PACIFIC trial (HR = 0.68 and 0.69, respectively)^{14,15,19} suggests that subsequent immunotherapy, received after disease progression on either placebo or durvalumab, had minimal influence on OS compared with the benefit already conferred by earlier treatment with durvalumab.

These results may be explained, in part, by the relatively low percentage of patients who received subsequent immunotherapy, 9.7% and 26.6% in the durvalumab and placebo arms, respectively (22.3% and 46.0% of patients in each arm who received any subsequent anticancer treatment). Furthermore, more than half of subsequent immunotherapy was received as second or later subsequent treatment, and the median duration of this treatment was relatively short. This theory is supported by the findings of our second RPSFTM scenario, which tested the effect of variable proportions of placebo arm patients receiving subsequent immunotherapy, whereas those in the durvalumab arm were assumed to have had no subsequent immunotherapy. This scenario showed that, as the proportion of patients in the placebo arm receiving subsequent immunotherapy increased, so too did the HR, suggesting a growing positive influence of subsequent immunotherapy on OS among patients in the placebo arm.

Because PACIFIC involved 235 sites in 26 countries,^{13–15} the treatment patterns observed were not specific to clinical practice in any 1 country. Our findings suggest that the RPSFTM could be adapted to estimate OS benefit with durvalumab according to local treatment practices in patients with unresectable, Stage III NSCLC following CRT. The testing of different percentages of subsequent immunotherapy prescription enables evaluation using country- or time-specific prescription practices (ie, utilization of immunotherapy as subsequent treatment will differ by country such as in the United Kingdom, Japan, and Australia). However, our analyses require validation based on differing prescription percentages in line with local practice.

The RPSFTM and M2SM each have advantages and disadvantages that relate mainly to the required assumptions for each approach and how well these hold for the particular clinical trial for which the effect of treatment switching is being tested. An advantage of the RPSFTM over the 2-stage method is that the former approach does not require all variables predicting choice of treatment and patient outcomes to be captured, but uses only the randomization of the trial, the observed survival and treatment history to identify the treatment effect.²⁷ However, a fundamental assumption of the RPSFTM is a common treatment effect; that is, that all patients receive the same degree of benefit from their time on the experimental treatment (or, as reported here, from subsequent immunotherapy), regardless of when it is received. In PACIFIC, the 2 most common immunotherapies received as subsequent anticancer therapy were nivolumab and pembrolizumab for which comparative effectiveness has been demonstrated for recurrent or advanced NSCLC,⁴⁵ supporting this assumption. Although simulation studies have shown that the RPSFTM works well when the common treatment effect assumption holds,⁴⁶ relaxing this assumption in more complex versions of the model is less successful.⁴⁶ For the PACIFIC analysis, the assumed common treatment effect translates into an equal acceleration factor across different immunotherapies, regardless of when they were prescribed and of the disease stage. However, insufficient data are currently available to reliably estimate different acceleration factors for different immunotherapies. In addition, the RPSFTM evaluation is indicative and not conclu-

sive; for example, it is possible that the group of patients prescribed immunotherapy differed from the population of patients who received any subsequent anticancer treatment as well as the total population (eg, if there was a conscious choice to administer immunotherapy to a targeted population that was not representative of the total population), meaning that a simple weighted average may not have precisely represented actual clinical practice if effect modification plays a role. In addition, RPSFTM, as applied to PACIFIC, may erroneously assume that other subsequent anticancer therapies are less effective than subsequent immunotherapy, which may not necessarily be the case (eg, for targeted therapies); this requires further understanding. Unlike the RPSFTM, the 2-stage method does not need to assume a common treatment effect because the procedure involves estimating a treatment effect specifically for patients who receive subsequent immunotherapy²⁷; this aspect of the 2-stage method seems to be an advantage in the context of the PACIFIC analyses presented here. However, results for the M2SM should be interpreted with caution, due to the covariate selection process (which is based on small datasets) and modeling in different steps; bootstrapping was not built into calculating the 95% CI and, overall, the model may be associated with more uncertainty.

An essential requirement for the 2-stage method is the ability to define a specific disease-related time point (commonly disease progression) as a secondary baseline, soon after which treatment switching occurs (or, as here, subsequent immunotherapy treatment is started); if the interval between these 2 points is large, then bias is likely because patients will no longer necessarily be at a similar stage of disease and time-dependent confounding may occur.²⁷ The method makes no attempt to adjust for such time-dependent confounding, but instead relies on the assumption that none occurs between the disease-related time point and treatment switching. In applying the 2-stage method to the PACIFIC data, we were unable to use disease progression as a secondary baseline, as is standard, due to the unexpectedly long interval (a median of ~6 months) between progression and the start of subsequent immunotherapy. By choosing the start of subsequent treatment (separately, for first and second/later treatment) as a secondary baseline, we eliminated the possibility of time-dependent confounding after the secondary baseline. For patients who received subsequent immunotherapy as third or later subsequent treatment, only the time from initiation of immunotherapy was used. Patients having immunotherapy prescribed as a third or later treatment may be closer to death, resulting in a somewhat smaller adjustment of the placebo arm. In addition, we adjusted for covariates so that the influence on the acceleration factor was limited because the number of patients having immunotherapy as second or later subsequent treatment was too small to model the number of subsequent treatments, individually (ie, for patients with immunotherapy as second subsequent treatment, third subsequent treatment, and so on). However, the availability of prognostic covariate data at the defined secondary baseline is an essential component of the 2-stage method, to adjust for any differences between patients who did or did not switch treatment (or start immunotherapy, as here).

In addition to the limitations of the RPSFTM and M2SM analyses discussed above, neither method accounted for the differing availability of individual immunotherapies in each country or for variation in immunotherapy prescribing behaviors between countries, which may complicate interpretation of the results. In addition, not only did the placebo and durvalumab arms vary with respect to the proportion of patients receiving subsequent immunotherapy, but different chemotherapies, immunotherapies, and targeted therapies were also employed (Table 1). However, the proportion of patients who received subsequent targeted therapies was similar in the durvalumab and placebo arms (10.5% and 14.3%, respectively), as was the proportion who received chemotherapy

(29.0% and 34.2%, respectively). Furthermore, the 2 most commonly prescribed agents within each category of targeted therapy, chemotherapy, and immunotherapy were the same in each treatment arm.

Conclusions

Our findings predict that, after removing the effects of subsequent immunotherapy, the substantial OS benefit with durvalumab after CRT in patients with Stage III, unresectable NSCLC would be unchanged compared with the primary ITT analysis. Earlier treatment with durvalumab, after completion of CRT and before progression, appeared to be associated with improved OS compared with starting immunotherapy after disease progression, as evidenced by the data obtained from the placebo arm.

Declaration of Competing Interest

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Conceptualization, methodology, and analysis were undertaken by M. Ouwens and Y. Zhang. All authors participated in interpretation of the data as well as development and approval of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2021.100640.

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