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Brief report: Three-year overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC - Update from PACIFIC

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Abstract: 248 [Limit 250 words (structured)]

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Figures/tables: 2 figures and 1 table (plus 2 supplemental figures) [Limit 3 tables/figures in main text (no limit on supplemental tables/figures)]

References: 12 [Limit 15]

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Abstract (248/250 words maximum)

Background: In the phase 3 PACIFIC study of patients with unresectable, Stage III NSCLC without progression after chemoradiotherapy (CRT), durvalumab demonstrated significant improvements versus placebo in the primary endpoints of progression-free survival (HR, 0.52; 95% CI, 0.42–65; 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, up to 12 months. OS was analyzed using a stratified log-rank test in the ITT population. Medians and rates at 12, 24 and 36 months were estimated by 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). Median duration of follow-up was 33.3 months. Updated OS remained consistent with that previously reported (stratified HR 0.69, 95% CI, 0.55–0.86); median OS not reached with durvalumab versus 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 following CRT and further establish the PACIFIC regimen as the standard of care in this population.

Keywords (3–5): durvalumab; NSCLC; overall survival; PACIFIC; three-year update

Introduction

Non-small-cell lung cancer (NSCLC) is one of the leading causes of mortality worldwide and approximately 30% of patients are diagnosed with 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 15–30%.[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 IgG1 monoclonal antibody that blocks programmed cell death ligand 1 (PD-L1) from binding to programmed death 1 (PD-1) and CD-80, resulting in anti-tumor 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 on CRT, durvalumab demonstrated significant improvements in the primary endpoints of progression-free survival (PFS; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.42–0.65; P<0.001) and overall survival (OS; HR, 0.68; 95% CI, 0.53–0.87; P=0.00251).[7–9] With immune-mediated adverse events (imAEs) occurring in 24.2% and 8.1% of patients in the durvalumab and placebo groups, respectively, but with similar rates of grade 3/4 imAEs (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 on CRT,[9,11] 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 1–42 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 durvalumab 10 mg/kg intravenously or placebo every two 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 vs ≥65 years), sex, and smoking history (current or former vs never smoked).

Endpoints 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 endpoint OS (defined as the time from randomization until death from any cause); the OS rates at the landmarks 12, 24, and 36 months; the time to first subsequent therapy or death and time to second subsequent therapy or death; and types of post-discontinuation disease-related anticancer therapies administered. In addition, analyses of OS by PD-L1 expression levels on tumor cells (based on PD-L1 testing of pre-CRT archived tumor tissue using the Ventana SP263 immunohistochemistry assay) was performed using pre-specified (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 endpoints included all patients who underwent randomization, according to the intention-to-treat (ITT) principle. For OS, the effect of durvalumab as compared with placebo was estimated and the HR, along with corresponding 95% CI, were reported. Between-group comparisons were performed 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 pre-specified 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. Medians and the percentages of patients alive (OS rates) at 12-, 24-, and 36-months were estimated by Kaplan–Meier method.

Results

A total of 713 patients were randomized, of whom 709 received treatment (durvalumab, n=473; 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]

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 **Supplemental Figure S1** 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,[8] with a 31% reduction in the risk of death (HR: 0.69; 95% CI: 0.55–0.86; **Figure 1**). The Kaplan–Meier estimate of the median OS was 29.1 months in the placebo group, while it was still not reached in the durvalumab group (**Figure 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, (**Figure 2**) was consistent with that reported at the time of the primary OS analysis.[8]

Following study treatment discontinuation, 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 compared with placebo (HR, 0.58 [95% CI, 0.47–0.71]; **Supplemental Figure S2A**), as was time to second subsequent therapy or death (HR, 0.61 [95% CI, 0.49–0.75]; **Supplemental Figure S2B**).

Conclusions

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 histology, 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 observed broadly irrespective of PD-L1 expression, consistent with findings from pre-specified 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 over 20 months (versus placebo) at this update (data not shown; manuscript in preparation). An exception was the PD-L1 <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 <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 <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 evaluable[7,8]), and 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 anti-cancer treatment is likely underpinned by fewer progression events with durvalumab versus placebo. Notably, among patients who received subsequent anti-cancer 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 the use of a first subsequent anti-cancer treatment.[12]

Overall, the findings of this analysis underscore the long-term survival benefit with durvalumab following CRT and further establish the PACIFIC regimen as the standard of care in patients with unresectable, Stage III NSCLC who do not progress on CRT.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394–424.
2. Walters S, Maringe C, Coleman MP, et al, on behalf of the ICBP Module 1 Working Group. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004–2007. *Thorax.* 2013;68:551–564.
3. Quint LE. Lung cancer: assessing resectability. *Cancer Imaging.* 2003;4:15–18.
4. 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.
5. 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.
6. Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res.* 2015;3:1052–1062.
7. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med.* 2017;377:1919–1929.
8. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med.* 2018;379:2342–2350.
9. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2018. Available from: https://www.ema.europa.eu/en/documents/product-information/imfizi-epar-product-information_en.pdf (last accessed April 22, 2019).

10. Hui R, Özgüroğlu M, Villegas A, et al. Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, locally advanced, unresectable non-small cell lung cancer: results from the randomised phase 3 PACIFIC study. *Lancet.* 2019 (in press).
11. US Food and Drug Safety Administration. IMFINZI (Durvalumab) Label 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761069s002lbl.pdf (last accessed April 22, 2019).
12. Planchard D, Cho BC, Gray JE, et al. First subsequent treatment after discontinuation of durvalumab in unresectable, Stage III NSCLC patients from PACIFIC. Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA, May 31–June 4, 2019 (Abstract 9054).

Figures and tables.

Figure 1. Updated analysis of overall survival in the ITT population. Shown are Kaplan Meier curves for overall survival. The tick marks indicate censored data, and the dashed vertical lines indicate the times of landmark analyses of overall survival. The ITT population included all the patients who underwent randomization. NR denotes not reached.

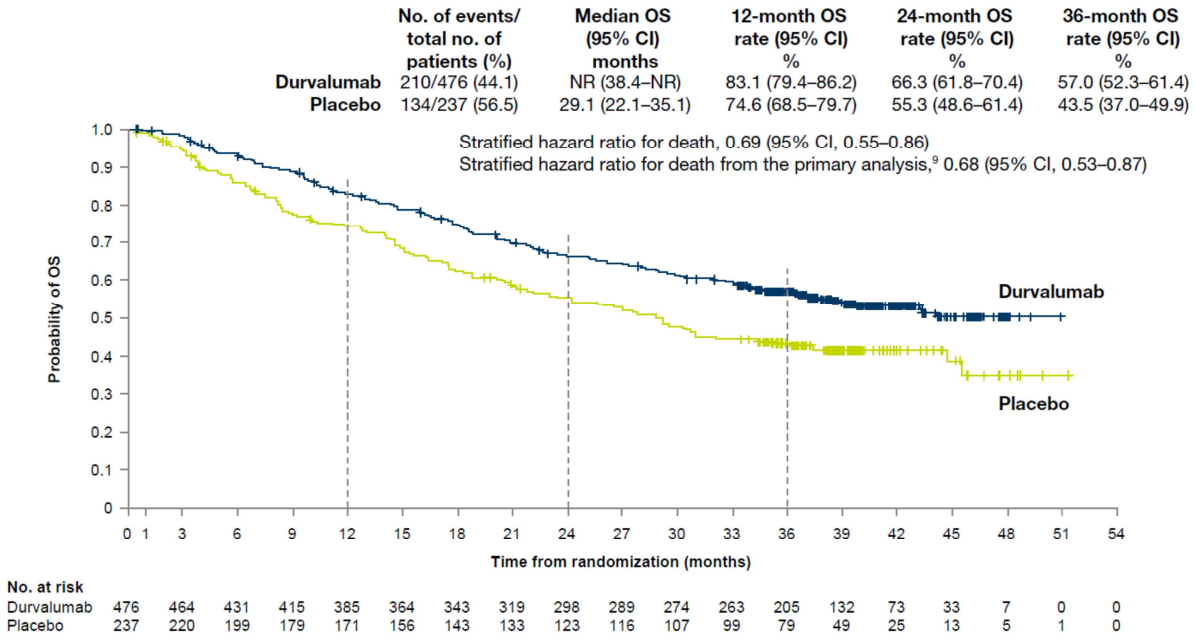
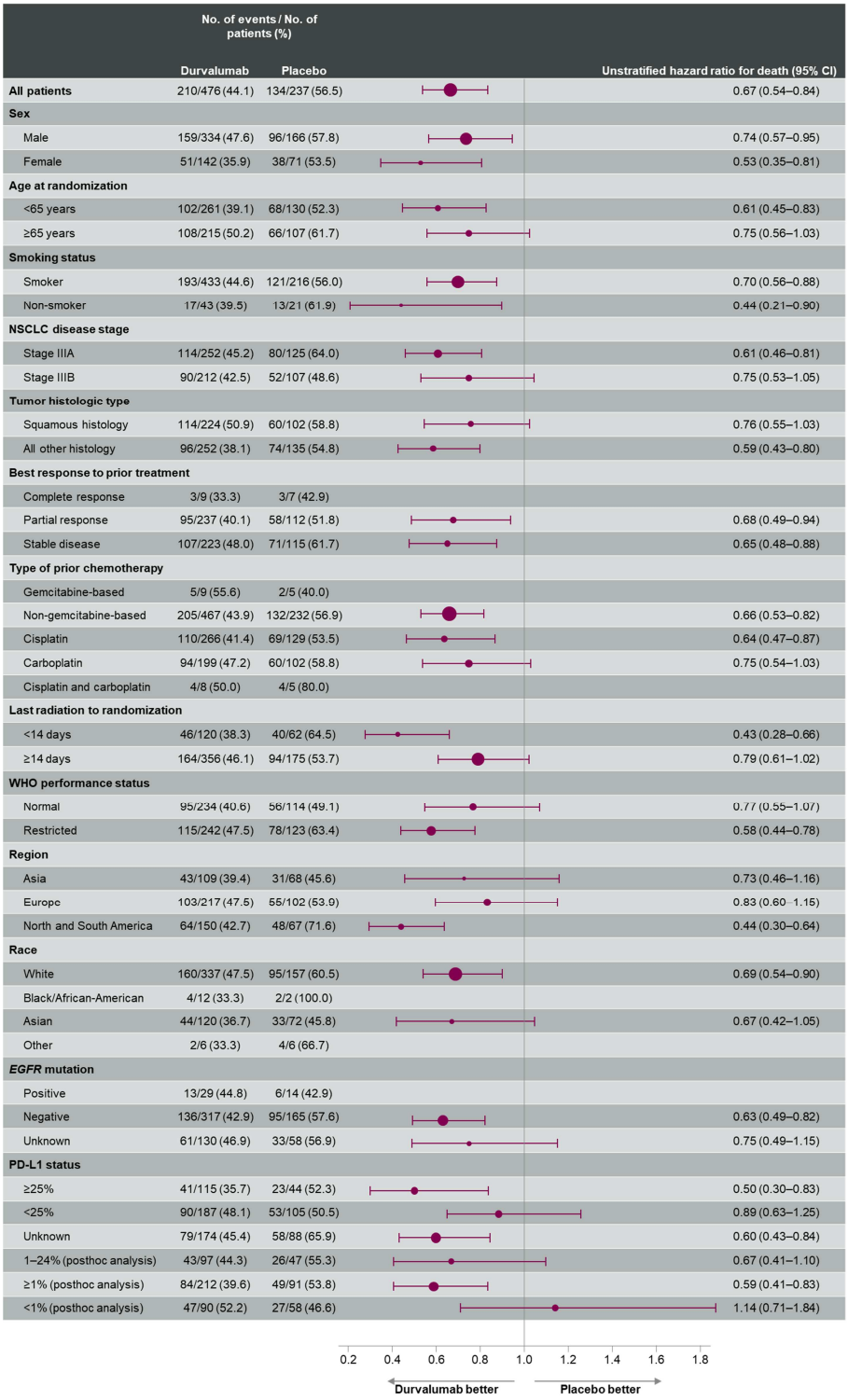


Figure 2. Updated overall survival by pre-specified and post-hoc exploratory subgroups in the ITT population.*



*Hazard ratio and 95% CI were not calculated if the subgroup had less than 20 events.

Table 1. Post-discontinuation disease-related anticancer therapy (ITT population).

	Number (%) of patients	
	Durvalumab (n=476)	**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 therapies†	50 (10.5)	34 (14.3)
Other	1 (0.2)	0

*Primarily, nivolumab (durvalumab, n=33; placebo, n=52) or pembrolizumab (durvalumab, n=10; placebo, n=8). †Including tyrosine kinase inhibitors, among other treatments.