1459PD Efficacy of durvalumab in patients with stage III NSCLC who experience pneumonitis (PACIFIC)

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Background: In the Phase III PACIFIC trial of patients with unresectable, Stage III non-small cell lung cancer (NSCLC) without progression after chemoradiotherapy (CRT), durvalumab significantly improved the primary endpoints progression-free survival (PFS) and overall survival (OS) versus placebo and was well-tolerated. Any-grade pneumonitis or radiation pneumonitis ('pneumonitis') occurred in 161 (33.9%) and 58 (24.8%) patients treated with durvalumab and placebo, respectively, with similar grade 3/4 rates (3.6% and 3.0%). Exploratory analyses were performed to investigate the efficacy of durvalumab in patients who developed pneumonitis.

Methods: Patients with WHO PS 0/1 (irrespective of tumor PD-L1 status) with $\geq$2 cycles of platinum-based CRT were randomized (2:1), 1–42 days following CRT, to durvalumab 10 mg/kg intravenously every 2 weeks or placebo for up to 12 months, stratified by age, sex, and smoking history. PFS and time to death or distant metastasis (TTDM) were assessed by blinded independent central review using RECIST v1.1. The impact of pneumonitis on efficacy was assessed via Cox proportional hazards models. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented.

Results: As of 22 March 2018, 713 patients were randomized of whom 709 received treatment. Using a step-wise approach, pneumonitis was assessed via univariate analyses and, when adjusted for the occurrence of (time-dependent) pneumonitis in the models, OS, PFS, and TTDM were consistent with results for the ITT population (Table). The pneumonitis time-dependent covariate was not significant ($P > 0.1$) in all models.

Conclusions: Treatment benefit with durvalumab versus placebo was maintained regardless of the occurrence of pneumonitis, which predominantly occurred with low-grade severity as previously reported. These findings suggest that low-grade pneumonitis should not deter use of durvalumab.

Clinical trial identification: NCT02125461 (release date: 29 April 2014).

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Table: 1459PD OS, PFS, and TTDM, adjusted for the time-dependent occurrence of pneumonitis* and for the ITT population

	No. of events/no. of patients (%)		HR (95% CI) for durvalumab vs. placebo	
	Durvalumab	Placebo	Adjusted for the time-dependent occurrence of pneumonitis**	ITT population***
OS	183/476 (38.4)	116/237 (48.9)		
Model 1 (base model)			0.70 (0.55–0.88)	0.68 (0.53–0.87)
Model 2			0.65 (0.51–0.83)	–
PFS	243/476 (51.1)	173/237 (73.0)		
Model 1 (base model)			0.54 (0.45–0.66)	0.51 (0.41–0.63)
Model 2			0.52 (0.42–0.64)	–
TTDM	182/476 (38.2)	126/237 (53.2)		
Model 1 (base model)			0.57 (0.45–0.71)	0.53 (0.41–0.68)
Model 2			0.53 (0.41–0.67)	–

Data cutoff: 22 March 2018.

*Pneumonitis occurred on Tx and within 90 days of last dose or prior to subsequent anticancer therapy (whichever occurred earlier).

**A Cox proportional hazards model adjusted for the time-dependent occurrence of pneumonitis using two sets of covariate models was used (with the Breslow method to control for ties): (1) accounting for stratification factors at randomization: age at randomization (<65 vs ≥ 65), sex (male vs female) and smoking history (smoker vs non-smoker), as used for the ITT population (base model); and (2) the base model plus additional baseline prognostic factors: stage of disease at study entry (IIIA vs IIIB), histology (squamous vs all other), best response to prior anticancer therapy (CR vs PR vs SD), WHO performance status (normal vs restricted activity), region (Asia vs Europe vs North America and South America) and race (White vs Black/African-American vs Asian vs Other).

***The analysis was performed using a stratified Log rank test, adjusted for age at randomization (<65 vs ≥ 65), sex (male vs female) and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach. CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTDM, time to death or distant metastasis.

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