

# Association Between the Early Discontinuation of Durvalumab and Poor Survival in Patients With Stage III NSCLC



Narek Shaverdian, MD,<sup>a,\*</sup> Michael Offin, MD,<sup>b</sup> Annemarie F. Shepherd, MD,<sup>a</sup> Matthew D. Hellmann, MD,<sup>b</sup> Daniel R. Gomez, MD,<sup>a</sup> Jamie E. Chaft, MD,<sup>b</sup> Andreas Rimmer, MD<sup>a</sup>

<sup>a</sup>Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

<sup>b</sup>Thoracic Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York

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## ABSTRACT

**Introduction:** Durvalumab after concurrent chemoradiation (cCRT) has been found to improve outcomes of patients with unresected stage III NSCLC. However, the survival impact of discontinuing durvalumab early owing to adverse events (AEs) remains unknown.

**Methods:** Patients with stage III NSLCC treated with cCRT and greater than or equal to one dose of durvalumab across a multisite cancer center were evaluated. The median durvalumab treatment duration among patients who discontinued owing to AEs (2.1 mo) defined two patient cohorts: early discontinuation (<2.1 mo) and late discontinuation. Progression-free survival (PFS) and overall survival were assessed.

**Results:** In total, 113 patients treated with cCRT and a median of 8.5 months of durvalumab were assessed, of which 30 (26%) discontinued durvalumab owing to AEs after a median of 2.1 months of treatment. Patients in the early- and late-discontinuation cohorts were treated with a median of 0.9 and 4.3 months of durvalumab, respectively. The median PFS among patients who did not discontinue durvalumab owing to AEs was 29.5 months. Among patients that discontinued durvalumab owing to AEs, overall survival and PFS were inferior in the early- versus late-discontinuation cohort (median PFS = 10.7 versus 32.9 mo,  $p < 0.001$ ) and durvalumab treatment duration associated with PFS on multivariate analysis (hazard ratio = 0.52 [95% confidence interval: 0.31–0.88],  $p = 0.014$ ).

**Conclusions:** We found that the duration of durvalumab treatment among patients who discontinued therapy owing to AEs impacts survival. However, patients treated with approximately 4 months of durvalumab maintained

outcomes as compared with patients who did not discontinue therapy owing to AEs. Durvalumab rechallenge should be considered in patients with less than 2 months of therapy.

\*Corresponding author.

Drs. Shaverdian and Offin contributed equally to this work.

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Address for correspondence: Narek Shaverdian, MD, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, New York. E-mail: [shaverdn@mskcc.org](mailto:shaverdn@mskcc.org)

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**Keywords:** Durvalumab; Stage III NSCLC; Chemoradiation; Pneumonitis; Toxicity

## Introduction

Durvalumab after concurrent chemoradiation (cCRT) has been found to significantly improve overall survival (OS) and progression-free survival (PFS) versus cCRT alone in patients with unresected stage III NSCLC.<sup>1,2</sup> However, the impact of discontinuing durvalumab early owing to adverse events (AEs) remains unknown. In the PACIFIC trial, 15% of patients discontinued durvalumab because of AEs, but real-world data found approximately 25% of patients discontinue durvalumab before the planned 12 months owing to AEs.<sup>3</sup> To guide treatment decision-making, we evaluated the impact of durvalumab discontinuation on survival outcomes.

## Methods

Patients with stage III NSCLC treated and followed up at our multistate comprehensive cancer center between November 2017 and February 2020 with platinum-based cCRT, and greater than or equal to one dose of durvalumab (as previously described<sup>3</sup>) were retrospectively analyzed. Medical records were retrospectively reviewed for any AEs, defined by Common Terminology Criteria for Adverse Events version 5.0, leading to permanent durvalumab discontinuation. Radiation pneumonitis was defined as previously discussed<sup>4</sup> and included patients with pulmonary symptoms including new or progressive dyspnea or cough with computed tomography-based imaging changes predominantly involving the radiated field and with symptom occurring within 12 months of cCRT. Pneumonitis that did not meet the criteria for radiation pneumonitis was defined as immune checkpoint inhibitor pneumonitis. The median durvalumab treatment duration among patients who discontinued owing to AEs (2.1 mo) was used to define two patient cohorts: early discontinuation (<2.1 mo of durvalumab) and late discontinuation (≥2.1 mo).

The PFS and OS outcomes were defined from the start of cCRT and were determined and compared using Kaplan-Meier and log-rank analyses. Univariate and multivariate Cox proportional hazard models were used to determine associations between patient characteristics and durvalumab treatment duration assessed continuously with survival outcomes. A *p* value of less

than 0.05 was considered significant and statistics were performed using IBM Statistical Package for the Social Sciences version 27 (IBM, Armonk, NY). This study was institutional review board-approved, and as a retrospective study, no informed consent is required.

## Results

We identified 113 consecutive patients treated with cCRT with a median of 8.5 (interquartile range [IQR]: 2.3–11.8) months of durvalumab use. The median follow-up was 23.3 (IQR: 16.5–31.7) months. In total, 30 patients (26%) discontinued durvalumab owing to grade 2 and grade 3 AEs (grade 2, *n* = 26; grade 3, *n* = 4), there were no grade 4 or higher AEs. Pneumonitis (*n* = 23) led to most of the discontinuations and most cases were consistent with radiation pneumonitis (*n* = 20). Patients who discontinued durvalumab owing to AEs have treated a median of 2.1 (IQR: 0.9–4.4) months. Patients in the early- and late-discontinuation cohorts were treated with a median of 0.9 (IQR: 0.5–1.8) and 4.3 (IQR: 2.7–7.1) months of durvalumab, respectively. Pneumonitis led to most discontinuations in both cohorts (Table 1).

Among all patients (*n* = 113), the median PFS was 30.1 (95% confidence interval: 25.3–34.8) months; the median OS was not reached, but the 24-month OS was 77% (69%–85%). There was no significant difference in PFS between patients who did and did not discontinue durvalumab owing to AEs, with median PFS equal to 32.9 (24.1–41.8) versus 29.5 (20.3–38.7) months, respectively (*p* = 0.449). In addition, OS was similar between patients who did and did not discontinue durvalumab owing to AEs (*p* = 0.995).

Among patients that discontinued durvalumab owing to AEs (*n* = 30), PFS was inferior in the early-discontinuation versus late-discontinuation cohort, with median PFS equal to 10.7 (2.9–18.5) versus 32.9 (24.1–41.8) months, respectively (*p* < 0.001) (Fig. 1). On multivariate analysis, durvalumab treatment duration was found to be independently associated with PFS (hazard ratio = 0.52 [0.31–0.88], *p* = 0.014) (Table 2). In addition, OS was inferior in the early-discontinuation versus the late-discontinuation cohort (*p* = 0.007) (Fig. 1). Durvalumab treatment duration, when assessed as a continuous variable, did not reach statistical significance in association with OS (hazard ratio = 0.49, [0.24–1.03], *p* = 0.058) (Table 3).

## Discussion

To our knowledge, this study provides the first data to suggest that the duration of durvalumab treatment impacts survival among patients who discontinued owing to AEs, and suggests that there is

Table 1. Patient and Treatment Characteristics

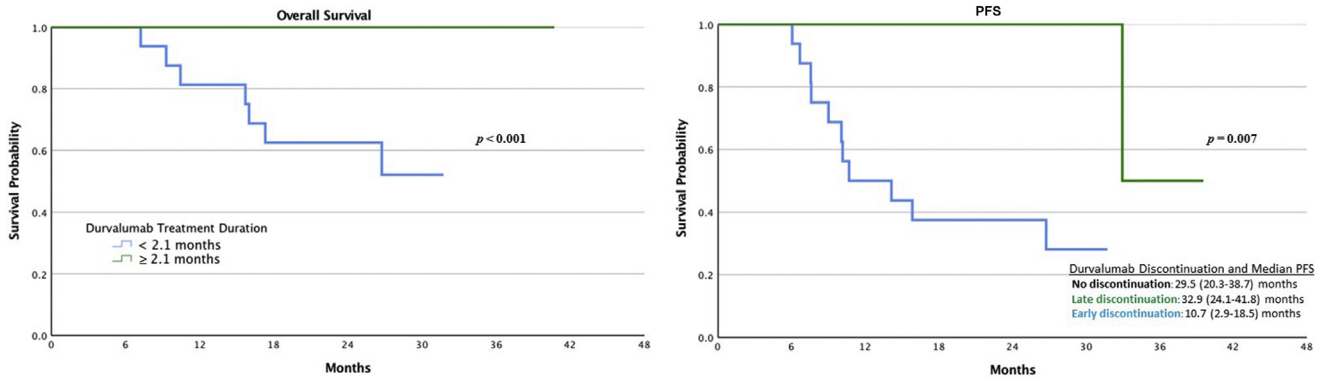
No. of Patients (%)				
Characteristics	All Patients (N = 113)	All Discontinued (n = 30)	Early Discontinuation (n = 16)	Late Discontinuation (n = 14)
Median age, range (y)	67 (49-86)	69 (54-86)	68 (54-86)	69 (56-74)
Sex				
Female	46 (41)	15 (50)	10 (62)	5 (36)
Male	67 (59)	15 (50)	6 (38)	9 (64)
Smoking history				
Ever	107 (95)	27 (90)	14 (88)	13 (92)
Never	6 (5)	3 (10)	2 (12)	1 (7)
Performance status				
ECOG 0	61 (54)	14 (47)	7 (44)	7 (50)
ECOG 1	52 (46)	16 (53)	9 (56)	7 (50)
Tumor Histology				
Adenocarcinoma	69 (61)	21 (70)	12 (75)	9 (64)
Squamous cell	34 (30)	6 (10)	1 (6)	5 (36)
Other	10 (9)	3 (20)	3 (19)	—
PD-L1 expression				
<1%	29 (26)	9 (30)	6 (37)	3 (21)
≥1%	55 (48)	15 (50)	8 (50)	7 (50)
Unknown	29 (26)	6 (20)	2 (13)	4 (29)
AJCC eighth overall stage				
IIIA	36 (32)	11 (37)	6 (38)	5 (36)
IIIB	59 (52)	12 (40)	7 (44)	5 (36)
IIIC	18 (16)	7 (23)	3 (19)	4 (28)
T stage				
T0 or T1	31 (27)	9 (29)	7 (44)	2 (14)
T2	22 (20)	5 (17)	4 (25)	1 (7)
T3	29 (26)	11 (37)	5 (31)	6 (43)
T4	31 (27)	5 (17)	—	5 (36)
N stage				
N0/N1	9 (7)	2 (7)	—	2 (14)
N2	62 (55)	17 (57)	9 (56)	8 (57)
N3	42 (38)	11 (37)	7 (44)	4 (29)
Median radiation dose, range (Gy)	60 (54-70)	60 (60-70)	60 (60-60)	60 (60-70)
Chemotherapy				
Carboplatin/paclitaxel	48 (42)	13 (43)	7 (44)	6 (43)
Carboplatin/pemetrexed	31 (27)	8 (27)	6 (37)	2 (15)
Cisplatin/pemetrexed	22 (20)	5 (17)	2 (13)	3 (21)
Cisplatin/etoposide	12 (11)	4 (13)	1 (6)	3 (21)
Time to durvalumab start <sup>a</sup>				
Median, IQR (mo)	1.5 (1.1-2)	1.5 (0.8-1.8)	1.5 (0.8-1.8)	1.5 (0.8-2.1)
Durvalumab treatment duration				
Median, IQR (mo)	8.5 (2.3-11.8)	2.1 (0.9- 4.4)	0.9 (0.5-1.8)	4.3 (2.7-7.1)
Durvalumab discontinuation reason				
Radiation pneumonitis	20 (66)	9 (56)	11 (79)	—
ICI pneumonitis	3 (10)	2 (13)	1 (7)	—
Colitis	2 (7)	1 (6)	1 (7)	—
Dermatitis	2 (7)	2 (13)	—	—
Myositis 3 (10)	2 (13)	1 (7)	—	—

<sup>a</sup>Defined from completion of cCRT.

AJCC, American Joint Committee on Cancer; cCRT, concurrent chemoradiation; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; IQR, interquartile range; PD-L1, programmed death-ligand 1.

a threshold treatment duration at which survival outcomes remain favorable. We found patients treated with less than approximately 2 months of durvalumab to have inferior PFS and OS. However,

patients who discontinued durvalumab after a median of approximately 4 months had outcomes similar to patients who never discontinued treatment owing to AEs.



**Figure 1.** Overall survival and PFS among patients who discontinued durvalumab early owing to AEs. Comparison of survival outcomes between the early-discontinuation (<2.1 mo of durvalumab, shown in blue) and late-discontinuation (≥2.1 mo of durvalumab, shown in green) patient cohorts. AE, adverse event; PFS, progression-free survival.

Similar to the findings of the PACIFIC trial, pneumonitis was the primary cause of durvalumab discontinuation among our patients.<sup>1</sup> Recent data suggest that durvalumab rechallenge may be feasible in patients who develop pneumonitis.<sup>5</sup> Therefore, strong consideration of durvalumab rechallenge may be warranted in patients who develop pneumonitis who received less than 4 months of therapy. In addition, anti-programmed death-ligand 1 rechallenge has been found feasible across a range of immune-related AEs<sup>6,7</sup>; therefore, given the substantial survival benefit of durvalumab, consideration should be given to rechallenge in patients who receive minimal therapy regardless of the specific AE.

Although we assessed over 100 patients treated with cCRT and durvalumab with a median follow-up of nearly 2 years, this study is single-institution and is limited by its retrospective nature. These findings are hypothesis-generating and require confirmation. In addition, as early radiation pneumonitis led to most discontinuations, further research on this toxicity is needed to develop specific strategies mitigating this risk.

### CRediT Authorship Contribution Statement

**Narek Shaverdian:** Conceptualization, Formal analysis, Writing - original draft.

**Michael Offin:** Conceptualization, Methodology, Writing - original draft.

**Annemarie F. Shepherd:** Methodology, Writing review and editing.

**Matthew D. Hellmann:** Data curation, Writing review and editing, Methodology.

**Daniel R. Gomez:** Conceptualization, Investigation, Methodology.

**Jamie E. Chaff:** Conceptualization, Investigation, Writing review and editing.

**Andreas Rimner:** Conceptualization, Investigation, Methodology.

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**Table 2.** Association Between Durvalumab Treatment Duration and Progression-Free Survival

Variable	Univariate		Multivariate <sup>a</sup>	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	1.01 (0.94-1.08)	0.763	—	—
Sex	2.12 (0.62-7.27)	0.231	—	—
Histology <sup>b</sup>	1.37 (0.36-5.18)	0.64	—	—
Stage IIIA vs. IIIB/IIIC	0.27 (0.06-1.26)	0.094	0.14 (0.03-0.78)	0.025
Carboplatin vs. cisplatin <sup>c</sup>	0.35 (0.08-1.61)	0.18	—	—
PD-L1 <1% vs. ≥1%	2.87 (0.79-10.4)	0.108	—	—
Durvalumab Tx time	0.63 (0.42-0.95)	0.028	0.52 (0.31-0.88)	0.014

<sup>a</sup>Variables with p < 0.1 on univariate analysis were selected for inclusion in multivariate analysis.

<sup>b</sup>Adenocarcinoma versus squamous/other.

<sup>c</sup>Carboplatin-based versus cisplatin-based chemotherapy regimens.

CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; Tx, treatment.

**Table 3.** Association Between Durvalumab Treatment Duration and Overall Survival

Variable	Univariate	
	HR (95% CI)	p Value
Age	1.04 (0.95-1.14)	0.392
Sex	1.39 (0.31-6.23)	0.665
Histology <sup>a</sup>	1.15 (0.22-5.96)	0.864
Stage IIIA vs. IIIB/IIIC	0.19 (0.02-1.66)	0.134
Carboplatin vs. cisplatin <sup>b</sup>	0.36 (0.04-2.99)	0.345
PD-L1 <1% vs. ≥1%	2.59 (0.43-15.57)	0.297
Durvalumab Tx time	0.49 (0.24-1.03)	0.058

<sup>a</sup>Adenocarcinoma versus squamous/other.

<sup>b</sup>Carboplatin-based versus cisplatin-based chemotherapy regimens.

CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; Tx, treatment.

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