



# Exploring causes and consequences of early discontinuation of durvalumab after chemoradiotherapy for non-small cell lung cancer

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## ARTICLE INFO

### Keywords:

Lung cancer  
Immunotherapy  
Radiotherapy  
Durvalumab  
Toxicity  
Prognosis

## ABSTRACT

**Introduction:** For most locally advanced non-small cell lung cancer (LA-NSCLC) patients who complete definitive chemoradiotherapy (CRT) and do not experience disease progression, one year of adjuvant durvalumab is recommended. Here, we explore causes and consequences of early durvalumab discontinuation.

**Materials and Methods:** We reviewed patients treated for LA-NSCLC with definitive CRT who began adjuvant durvalumab between 2017 and 2021. Duration of durvalumab receipt and causes for early discontinuation were tabulated. Logistic regression models were utilized to evaluate predictors of early durvalumab discontinuation. Landmark analyses were performed to explore associations between early durvalumab discontinuation and clinical outcomes (progression-free survival (PFS), overall survival (OS)).

**Results:** Fifty-nine patients were included. Forty-one patients (69%) discontinued durvalumab early, most commonly for disease progression (n = 14) or lung toxicity (n = 10). Multivariable analysis revealed mean heart radiotherapy dose (MHD) was associated with risk of durvalumab discontinuation from progression (HR = 2.34 per 10 Gy, p = 0.052), and there was a trend suggesting an association between MHD and risk of durvalumab discontinuation from lung toxicity (HR = 2.16 per 10 Gy, p = 0.126). Median PFS duration following durvalumab initiation was 14 months, and median OS duration was 32 months. Landmark analyses that excluded patients with progression or death within one year of durvalumab initiation demonstrated improved outcomes for patients who completed one year of durvalumab (2-year PFS 100% v. 40%, p < 0.001; 2-year OS 100% v. 67%, p = 0.862). Improved outcomes were observed for patients who received MHD below the cohort median (9.3 Gy) compared to patients with higher MHD (median PFS 32 months v. 8 months, p < 0.001; 2-year OS 69% v. 44%, p = 0.088).

**Conclusion:** For LA-NSCLC patients treated with CRT followed by immunotherapy, extent of cardiac irradiation may be a risk factor for immunotherapy discontinuation, disease recurrence, and death.

## Introduction

Despite recent advances, lung cancer remains the leading cause of cancer mortality in the United States[1]. One key advancement in treating advanced non-small cell lung cancer (NSCLC) has been immune-checkpoint inhibitors targeting the programmed-death-1/programmed-death-ligand-1 (PD-1/PD-L1) axis. Based on the PACIFIC trial, adjuvant immunotherapy is recommended in the United States for most patients with locally advanced (LA-)NSCLC who complete curative-intent concurrent chemoradiotherapy (CRT) and lack evidence

of disease progression on post-treatment imaging[2].

The PACIFIC trial showed that adjuvant durvalumab following definitive CRT for NSCLC improves rates of progression-free survival (PFS) and overall survival (OS)[2]. Updated analyses demonstrate sizeable improvements in 5-year PFS (33% v. 19%) and OS (43% v. 33%) [3] that seem to be driven by improvements in intrathoracic and distant disease control[3–5].

Interestingly, approximately half of PACIFIC subjects who were randomized to receive adjuvant durvalumab did not complete the planned 12-month treatment course. In the durvalumab arm, 31% of

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<https://doi.org/10.1016/j.ctro.2023.100643>

Received 5 December 2022; Received in revised form 22 May 2023; Accepted 29 May 2023

Available online 1 June 2023

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patients discontinued treatment because of progression, 31% experienced Grade 3+ toxicity, 4.4% experienced death, and 15% discontinued treatment because of adverse events, where the most frequent adverse events leading to discontinuation were pulmonary toxicities such as pneumonitis[2,3,6]. Interestingly, 10% of subjects receiving placebo discontinued infusions due to adverse events, demonstrating that delayed toxicities from CRT can interfere with the receipt of adjuvant immunotherapy.

It remains unclear how radiotherapy parameters influence the course and effects of subsequent durvalumab, if radiation oncologists should adjust planning for patients who will receive durvalumab after CRT, and how unique immunotherapy-mediated adverse events manifest in the setting of cancer and CRT[7–9]. Understanding risk factors for early durvalumab discontinuation could further improve outcomes for LA-NSCLC patients treated with definitive CRT, prevention and management of toxicity, and monitoring tolerance. Here, we review our institution's experience with adjuvant durvalumab following CRT for NSCLC to describe causes, predictors, and consequences of early immunotherapy discontinuation.

## Materials and methods

### *Patients, treatment, follow-up*

This is a retrospective review and analysis of consecutive patients treated with concurrent CRT with curative intent at our institution and were started on adjuvant durvalumab between November 2017 and April 2021. Our IRB approved this retrospective analysis. Based on institutional practice patterns, patients with American Joint Committee on Cancer (AJCC) version 8.0 stage III NSCLC, unresectable stage II NSCLC, or oligometastatic stage IV NSCLC with radical treatment of all distant metastases were considered eligible for concurrent CRT and adjuvant durvalumab. All patients underwent staging positron-emission tomography/computed tomography (PET/CT), brain MRI or head CT, and 4-dimensional CT simulation. We utilized standard techniques for GTV, CTV, and PTV delineation, and standard previously-described normal-tissue constraints[10]. The standard radiotherapy regimen was 60 Gy in 30 fractions. Some patients were enrolled on prospective trials testing dose-painted radiotherapy and received doses of 48–60 Gy in 20 or 25 fractions (2-Gy equivalent doses of 49.6–62.0 Gy,  $\alpha/\beta = 10$  Gy). Weekly or daily cone-beam CT image-guidance was utilized. All patients received weekly carboplatin (area under the curve 2) and paclitaxel (45–50 mg/m<sup>2</sup>) during radiotherapy.

Patients underwent chest CT two to four weeks after CRT completion and before initiating adjuvant durvalumab to rule out progression. Durvalumab was generally given at a dose of 10 mg/kg every 2 weeks. Some patients received durvalumab doses of 1500 mg every four weeks due to logistical considerations (e.g., minimizing visits during COVID). Durvalumab was continued until disease progression in any location, or unacceptable toxicity, for a maximum of one year.

### *Data collection*

Clinical characteristics (gender, age, performance status), disease characteristics (stage, histology, PD-L1 tumor proportion score (TPS), mutational status), and treatment characteristics were tabulated. Mean radiotherapy dose received by the heart (MHD), lungs (excluding clinical target volumes), and esophagus was tabulated for each patient, as was lung volume receiving  $\geq 20$  Gy (V20) and  $\geq 5$  Gy (V5). As a measure of disease burden and gross tumor volume, pre-treatment total metabolic tumor volume (MTV) was calculated from each patient's staging PET/CT using a semiautomatic gradient-based contouring algorithm (MIMvista Corp, Cleveland, OH, U.S.A.), as in prior studies[11].

Duration of immunotherapy receipt was calculated in two ways: (1) number of infusions received, with each 10 mg/kg durvalumab dose counted as two weeks of immunotherapy and each 1500 mg durvalumab

dose counted as four weeks of immunotherapy, and (2) time interval between first and last durvalumab infusion. Patients who received at least 48 weeks of immunotherapy using either definition were deemed to have completed the immunotherapy course. Reasons for early immunotherapy discontinuation were abstracted from patients' medical records and categorized as disease progression, death without progression, pulmonary toxicity, or other toxicity.

### *Statistical analyses*

Descriptive statistics were used to report patient and treatment characteristics, durations of immunotherapy receipt, and causes for immunotherapy discontinuation. The most common reasons for immunotherapy discontinuation were identified, and treatment-related predictors of immunotherapy discontinuation for those reasons were tested using univariate logistic regression models. Variables with p-values below 0.20 in univariate models were included in a multivariable model.

Median follow-up duration was estimated using the Schemper method[11]. Kaplan-Meier curves and logrank testing were used to compare progression-free survival (PFS), which was not stratified into local or distant progression, and overall survival (OS) rates between patients who completed a course of adjuvant durvalumab and patients who discontinued durvalumab.

Cox proportional hazards models were utilized to test the prognostic value of durvalumab completion with respect to PFS and OS. To address immortal time bias, we utilized a landmark analysis technique, where patients with disease progression or death within one year after durvalumab initiation were excluded.

ANOVA analyses were used to assess differences in MHD between patients who discontinued durvalumab due to progression, lung toxicity, and other reasons. As MHD was implicated with early durvalumab discontinuation due to disease progression or lung toxicity, we generated violin plots to compare the distribution of MHDs in patients who discontinued durvalumab for those two reasons versus other patients. We tested MHD as a predictor of PFS and OS after durvalumab initiation among all patients using Kaplan-Meier curves and logrank testing.

Analyses were performed using Matlab (The Mathworks, Natick, MA, U.S.A.) and Stata (StataCorp, College Station, TX, U.S.A.).

## Results

### *Patient characteristics and immunotherapy receipt*

Fifty-nine patients were included. Patient characteristics are summarized in Table 1. Thirty-five patients (59%) could have been eligible for PACIFIC. Reasons for theoretical PACIFIC ineligibility were stage II or IV disease (n = 5), total radiation dose under 54 Gy (n = 7), or performance status 2–3 after radiotherapy completion (n = 15). The median time interval from completing CRT to beginning durvalumab was 35 days (IQR: 26 to 52 days). The median follow-up duration after durvalumab initiation was 29 months (IQR: 21 to 33 months).

The median number of durvalumab infusions received was 12 (IQR: 5 to 21). Twenty patients received at least one infusion of durvalumab using a fixed dose of 1500 mg every four weeks. Based on the number and doses of infusions received, the median duration of durvalumab therapy was 32 weeks (IQR: 12 to 48). Based on the interval from the first to last durvalumab infusion, the median duration of durvalumab therapy was 33 weeks (IQR: 15 to 49). Eighteen patients (31%) completed adjuvant durvalumab therapy. 41 patients (69%) discontinued durvalumab. The most common reasons for early durvalumab discontinuation were disease progression (n = 14), lung toxicity (n = 10), other toxicity (n = 7), or death without established disease progression (n = 4). Discontinuation for lung toxicity occurred after a median of 2 months from starting durvalumab therapy (range: 0 to 10 months), and durvalumab discontinuation for other toxicities occurred after a median of 5 months from starting durvalumab (range: 1 to 9

**Table 1**  
Patient and treatment characteristics.

|                                                 |                       |
|-------------------------------------------------|-----------------------|
| Gender, n (%)                                   |                       |
| Female                                          | 30 (51%)              |
| Male                                            | 29 (49%)              |
| Age, mean (range)                               | 68 (49 to 83)         |
| T stage (AJCC 8th edition), n (%)               |                       |
| T0/X                                            | 8 (14%)               |
| T1                                              | 13 (22%)              |
| T2                                              | 6 (10%)               |
| T3                                              | 8 (14%)               |
| T4                                              | 24 (41%)              |
| N Stage (AJCC 8th edition), n (%)               |                       |
| N0                                              | 9 (15%)               |
| N1                                              | 45 (76%)              |
| N2                                              | 3 (5%)                |
| N3                                              | 2 (3%)                |
| Clinical stage (AJCC 8th edition), n (%)        |                       |
| II                                              | 3 (5%)                |
| IIIA                                            | 30 (51%)              |
| IIIB                                            | 15 (25%)              |
| IIIC                                            | 8 (14%)               |
| IV                                              | 3 (5%)                |
| PS before RT, n (%)                             |                       |
| 0                                               | 10 (17%)              |
| 1                                               | 33 (56%)              |
| 2                                               | 15 (25%)              |
| 3                                               | 1 (2%)                |
| PS after RT, n (%)                              |                       |
| 0                                               | 7 (12%)               |
| 1                                               | 37 (63%)              |
| 2                                               | 13 (22%)              |
| 3                                               | 2 (3%)                |
| Histology, n (%)                                |                       |
| Adenocarcinoma                                  | 27 (46%)              |
| Squamous cell carcinoma                         | 25 (42%)              |
| Other/not specified                             | 7 (12%)               |
| PD-L1 tumor proportion score, n (%)             |                       |
| <1%                                             | 13 (22%)              |
| 1 to 49%                                        | 20 (34%)              |
| 50 to 100%                                      | 11 (19%)              |
| Unknown                                         | 15 (25%)              |
| Known EGFR mutation or ALK rearrangement, n (%) |                       |
| No                                              | 61 (98%)              |
| Yes                                             | 1 (2%)                |
| Metabolic tumor volume, median (range)          | 45 cc (2 to 261)      |
| RT course length, n (%)                         |                       |
| 30 fractions                                    | 40 (68%)              |
| 20-25 fractions                                 | 19 (32%)              |
| Mean esophagus RT dose, median (range)          | 15.4 Gy (2.9 to 34.3) |
| Mean heart RT dose, median (range)              | 9.3 Gy (0.2 to 29.2)  |
| Mean lung RT dose, median (range)               | 11.6 (2.1 to 20.2)    |
| Lung V20, median (range)                        | 22.3% (1.0% to 36%)   |
| Lung V5, median (range)                         | 40.6 (11.7% to 65.4%) |

AJCC, American Joint Committee on Cancer; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PS, performance status; PD-L1, programmed death-ligand 1; RT, radiation therapy; Lung V20, volume of lung receiving  $\geq 20$  Gy; Lung V5, volume of lung receiving  $\geq 5$  Gy.

months).

*Predictors and consequences of immunotherapy discontinuation*

Univariate and multivariable logistic regression models examining predictors of early durvalumab discontinuation due to disease progression are displayed in Table 2. In a multivariable model, MHD was associated with increased risk of durvalumab discontinuation due to disease progression (HR = 2.34 per 10 Gy,  $p = 0.052$ ). Logistic regression models did not reveal any statistically significant predictors of early durvalumab discontinuation due to lung toxicity, shown in Table 3. There was a trend suggesting an association between MHD and risk of durvalumab discontinuation due to lung toxicity (adjusted HR = 2.16 per 10 Gy,  $p = 0.126$ ). Violin plots depicting MHD distributions for patients who discontinued durvalumab due to progression, patients who discontinued durvalumab due to lung toxicity, and other patients are shown in Fig. 1. One-way ANOVA testing revealed a significant between-group difference in MHD ( $p = 0.034$ ).

Among the entire patient cohort, 27 patients (46%) developed disease progression, and 25 patients (42%) died. The median PFS duration following durvalumab initiation among all patients is 14 months, and the median OS duration following durvalumab initiation is 32 months.

**Table 2**  
**Predictors of durvalumab discontinuation due to disease progression.** Univariate logistic regression models were utilized to identify potential predictors of durvalumab discontinuation due to disease progression. Variables with p-values below 0.200 in univariate models were included in a multivariable logistic regression model. Bold font denotes statistical significance using a p-value cutoff of 0.05.

| Characteristic                    | Univariate Models          |              | Multivariable Model          |         |
|-----------------------------------|----------------------------|--------------|------------------------------|---------|
|                                   | Odds Ratio (95% CI)        | p-value      | Adjusted Odds Ratio (95% CI) | p-value |
| Metabolic tumor volume, per 10 cc | 1.06 (0.98 to 1.16)        | 0.156        | 1.08 (0.98 to 1.18)          | 0.158   |
| Stage Group                       |                            |              |                              |         |
| II-IIIA                           | [reference]                | –            |                              |         |
| IIIB-IV                           | 1.37 (0.41 to 4.56)        | 0.609        |                              |         |
| ECOG PS after RT completion       |                            |              |                              |         |
| 0-1                               | [reference]                | –            |                              |         |
| 2-3                               | 1.94 (0.53 to 7.13)        | 0.316        |                              |         |
| PD-L1 TPS                         |                            |              |                              |         |
| <1%                               | 2.57 (0.68 to 9.75)        | 0.166        | 2.74 (0.64 to 11.74)         | 0.175   |
| $\geq 1\%$ or unknown             | [reference]                | –            |                              |         |
| RT Dose (EQD2)                    |                            |              |                              |         |
| $\geq 60$ Gy                      | [reference]                | –            |                              |         |
| <60 Gy                            | 0.89 (0.24 to 3.32)        | 0.857        |                              |         |
| RT course length                  |                            |              |                              |         |
| 30 fractions                      | [reference]                | –            |                              |         |
| 20–25 fractions                   | 0.80 (0.21 to 2.98)        | 0.739        |                              |         |
| Mean heart RT dose, per 10 Gy     | <b>2.34 (1.03 to 5.31)</b> | <b>0.042</b> | 2.34 (0.99 to 5.53)          | 0.052   |
| Mean esophagus RT dose, per 10 Gy | 1.36 (0.69 to 2.67)        | 0.378        |                              |         |
| Mean lung RT dose, per 10 Gy      | 2.13 (0.42 to 10.84)       | 0.358        |                              |         |
| RT, radiation therapy             |                            |              |                              |         |

**Table 3**

**Predictors of durvalumab discontinuation due to lung toxicity.** Univariate logistic regression models were utilized to identify potential predictors of durvalumab discontinuation due to lung toxicity. Variables with p-values below 0.200 in univariate models were included in a multivariable logistic regression model.

| Characteristic                    | Univariate Models    |         | Multivariable Model          |         |
|-----------------------------------|----------------------|---------|------------------------------|---------|
|                                   | Odds Ratio (95% CI)  | p value | Adjusted Odds Ratio (95% CI) | p value |
| Metabolic tumor volume, per 10 cc | 0.90 (0.78 to 1.03)  | 0.135   | 0.89 (0.76 to 1.03)          | 0.105   |
| Stage Group                       |                      |         |                              |         |
| II-III A                          | [reference]          | –       |                              |         |
| IIIB-IV                           | 0.82 (0.20 to 3.27)  | 0.776   |                              |         |
| ECOG PS after RT completion       |                      |         |                              |         |
| 0-1                               | [reference]          | –       |                              |         |
| 2-3                               | 1.32 (0.72 to 5.93)  | 0.716   |                              |         |
| RT course length                  |                      |         |                              |         |
| 30 fractions                      | [reference]          | –       | [reference]                  | –       |
| 20-25 fractions                   | 2.50 (0.63 to 10.00) | 0.195   | 2.99 (0.68 to 13.22)         | 0.149   |
| Mean heart RT dose, per 10 Gy     | 1.95 (0.80 to 4.75)  | 0.141   | 2.16 (0.81 to 5.79)          | 0.126   |
| Mean esophagus RT dose, per 10 Gy | 0.97 (0.44 to 2.11)  | 0.934   |                              |         |
| Mean lung RT dose, per 10 Gy      | 1.56 (0.26 to 9.43)  | 0.629   |                              |         |
| Lung V20                          | 1.04 (0.95 to 1.13)  | 0.446   |                              |         |
| Lung V5                           | 1.03 (0.98 to 1.09)  | 0.257   |                              |         |

RT, radiation therapy

Landmark analyses demonstrated that completing the adjuvant durvalumab course was associated with favorable PFS (2-year PFS 100% v. 40%, logrank  $p < 0.001$ , Fig. 2). Completing the adjuvant durvalumab course was also associated with numerically higher OS (2-year OS 100% v. 67%, logrank  $p = 0.862$ , Fig. 3).

#### Association between MHD and clinical outcomes

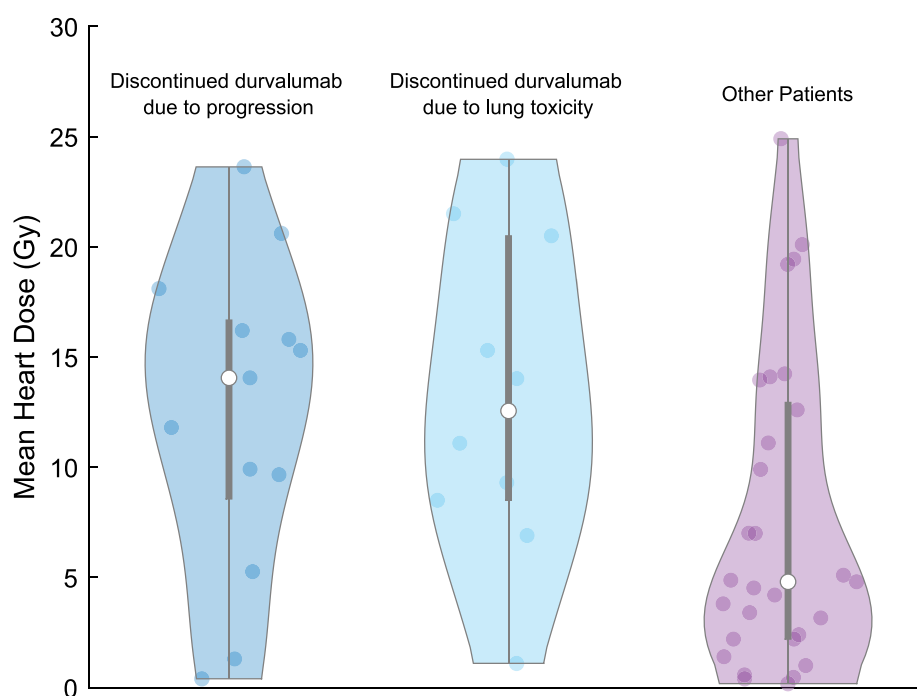
Kaplan Meier curves depicting PFS rate and OS rate, measured from initiation of durvalumab and evaluated after grouping patients by MHD, are shown in Fig. 4 and Fig. 5. The median PFS duration for patients who received MHDs below the cohort median (9.3 Gy) was 32 months, compared to 8 months for patients with higher MHDs (logrank  $p < 0.001$ , Fig. 4). Kaplan Meier analysis also revealed the 2-year OS rate for patients with MHD below the cohort median (9.3 Gy) was 69%, compared to 44% for patients with higher MHDs (logrank  $p = 0.088$ , Fig. 5).

#### Discussion

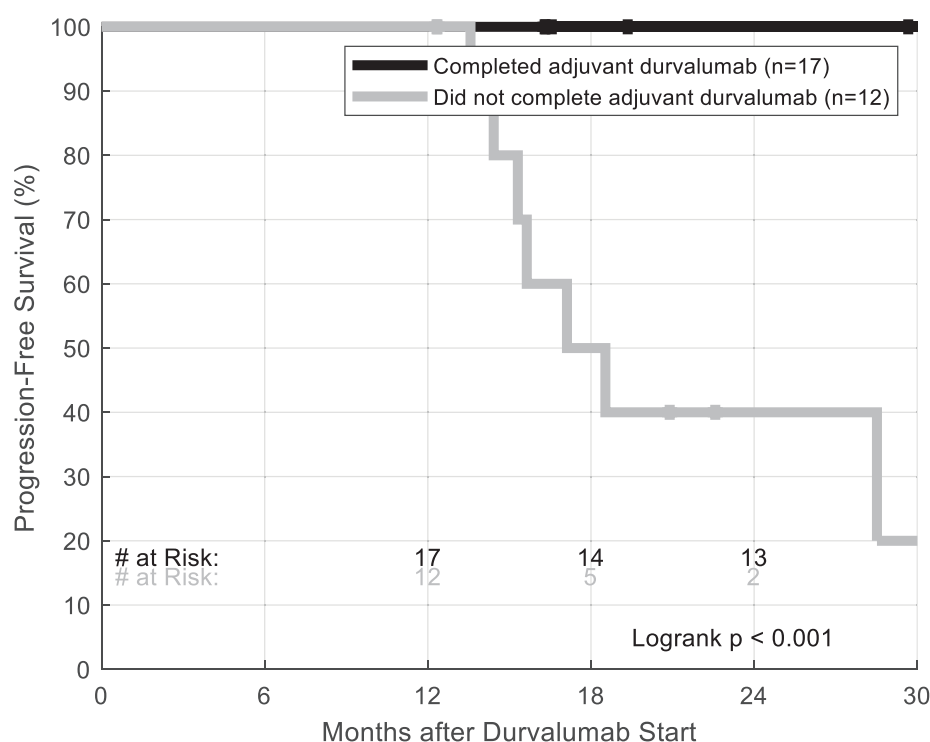
To our knowledge, this is the first study examining predictors and consequences of early durvalumab discontinuation following CRT for LA-NSCLC. As in the PACIFIC trial[2,4,5], we found that a minority of patients completed the planned one-year course of durvalumab, and the most common causes for durvalumab discontinuation were disease progression and toxicity. We found that early durvalumab discontinuation was associated with increased risk of disease relapse and death. In our cohort, extent of cardiac irradiation was significantly associated with early durvalumab discontinuation, disease progression, and death after durvalumab initiation. These findings, if validated in larger datasets, would add to a growing list of reasons why cardiac avoidance should be prioritized when planning CRT for LA-NSCLC.

#### Cardiac irradiation causes direct cardiac toxicity

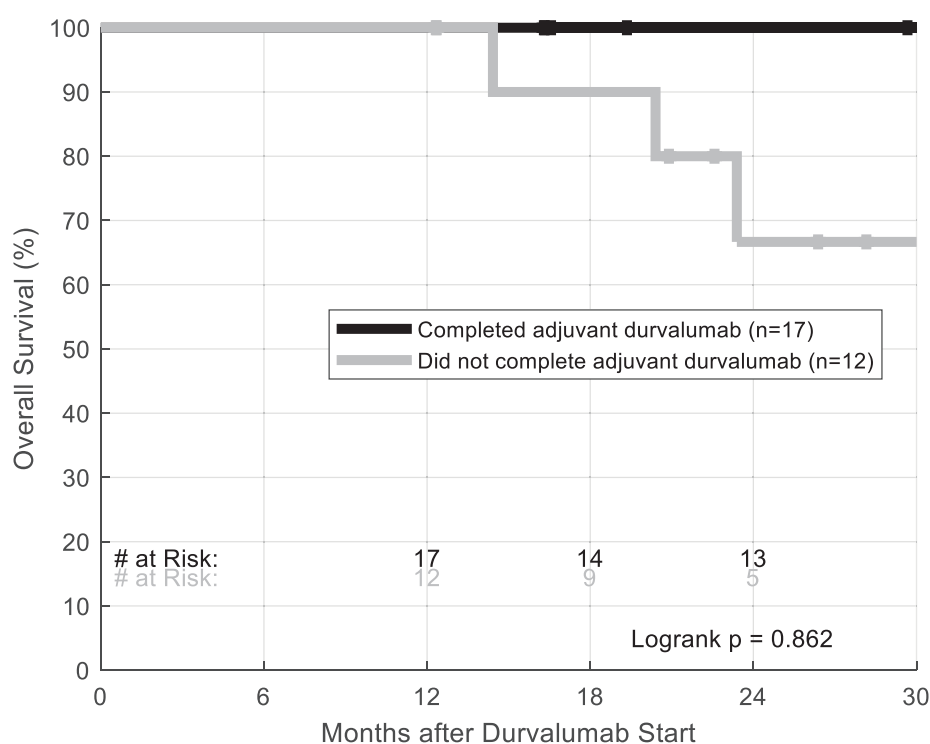
Radiation-induced acute inflammation can cause a pathogenic



**Fig. 1.** Violin plots and one-way ANOVA analysis. Mean heart radiotherapy doses for patients who discontinued durvalumab due to disease progression (n = 14), patients who discontinued durvalumab due to lung toxicity (n = 10), and other patients (n = 35) were compared. One-way ANOVA testing was used to compare the depicted groups and their mean heart radiotherapy doses.



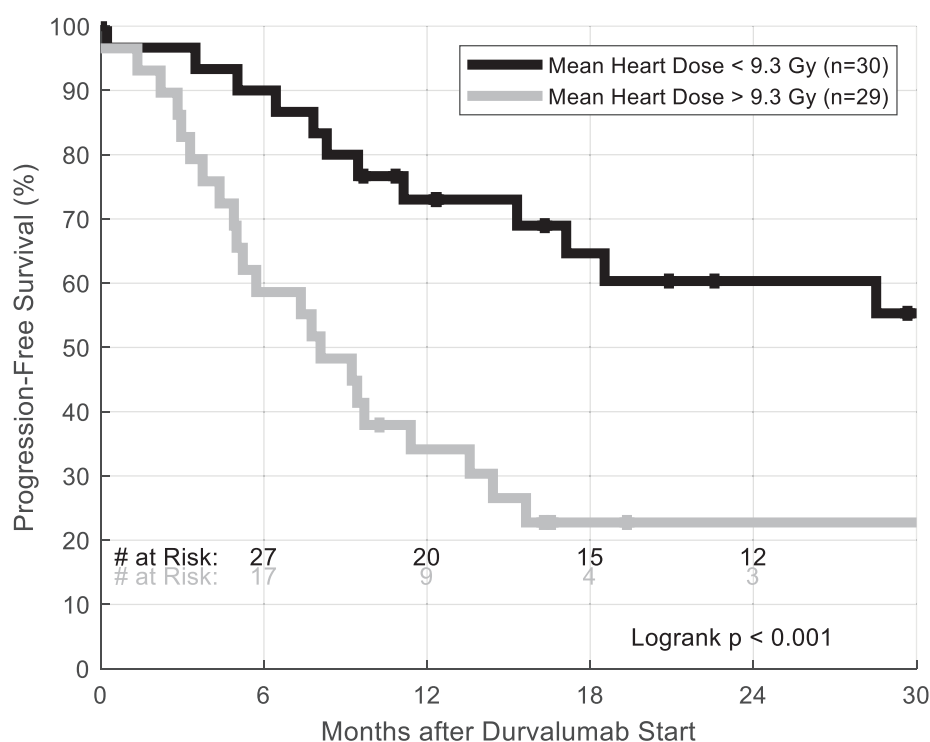
**Fig. 2.** Landmark analysis, with Kaplan-Meier curves depicting progression-free survival rates after durvalumab initiation for patients who completed a one-year course of durvalumab, compared to patients who did not complete one year of adjuvant durvalumab. Patients who developed disease progression or death within one year after durvalumab initiation were excluded from this analysis. Patients with follow-up duration of less than one year after durvalumab initiation were also excluded.



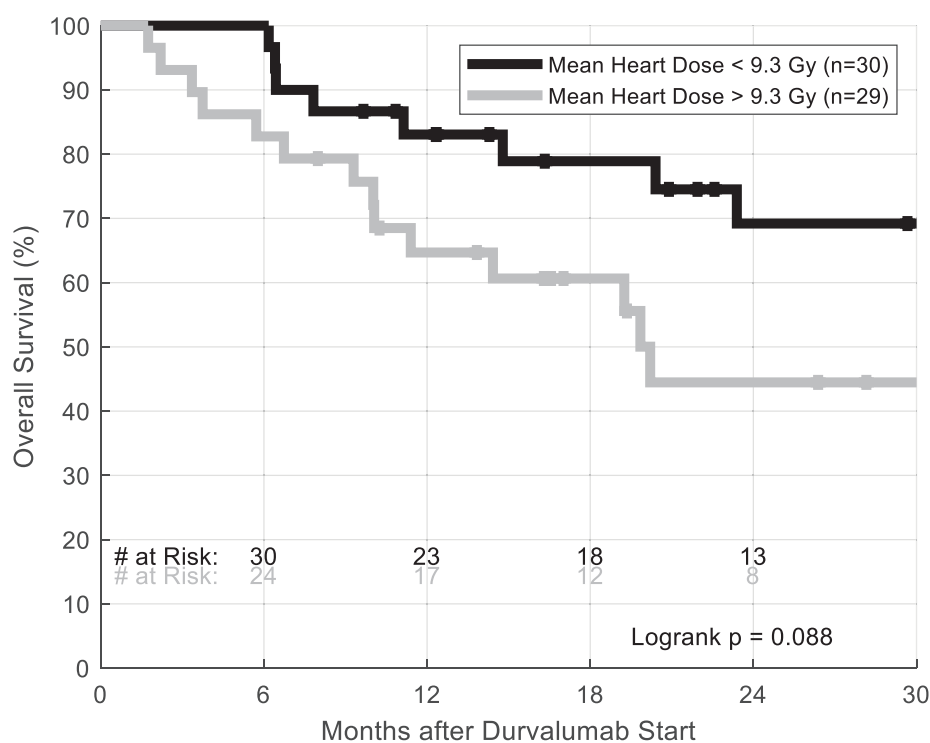
**Fig. 3.** Landmark analysis, with Kaplan-Meier curves depicting overall survival rates after durvalumab initiation for patients who completed a one-year course of durvalumab, compared to patients who did not complete one year of adjuvant durvalumab. Patients who developed disease progression or death within one year after durvalumab initiation were excluded from this analysis. Patients with follow-up duration of less than one year after durvalumab initiation were also excluded.

cascade leading to cardiac disease, coronary artery stenosis, myocardial atrophy, and pericardial constriction[12,13]. Using large datasets, several groups have identified extent of cardiac irradiation as predictive of subsequent cardiac events[14–18] and impaired OS[17,19,20], with recent data suggesting pericardial dose is a significant predictor of OS, rather than cardiac substructure dose[17,18]. A range of increasing

cardiac volumetric doses (V5 to  $\geq$  V50) have been shown to predict survival[17,19]. Recent retrospective studies have shown cardiac-event incidence was related to cardiac substructure dose in cancer[21–24]. There is a lack of randomized, prospective evidence that sparing cardiac substructures has a survival advantage over sparing the entire heart or is different from sparing portions of the heart as a single structure. Newer



**Fig. 4.** Kaplan Meier curves depicting rates of progression-free survival after durvalumab initiation for patients who received mean heart radiotherapy doses above or below the cohort median of 9.3 Gy.



**Fig. 5.** Kaplan Meier curves depicting rates of overall survival after durvalumab initiation for patients who received mean heart radiotherapy doses above or below the cohort median of 9.3 Gy.

data suggest radiation-induced cardiotoxicity may be modulated by the PD-1/PD-L1 axis[25,26]. Therefore, we chose MHD as an established predictor[14–20] of clinical outcomes and representation of heart dose. We acknowledge incoming evidence for the predictive value of cardiac substructures is compelling[21–24], and substructures can be analyzed

in future studies once their predictive value is established in large, prospective, randomized trials.



### Cardiac irradiation may detract from immunotherapy efficacy

Numerous studies have demonstrated associations between extent of cardiac irradiation and lymphopenia[27–30]. Lymphopenia and the related observation of elevated neutrophil-to-lymphocyte ratio (NLR) have been identified as poor prognostic factors for survival and progression in many cancer settings[31], including in patients recently treated with CRT for NSCLC[27,32,33] and patients treated with immune-checkpoint inhibitors for advanced NSCLC[34,35]. Radiotherapy-induced lymphopenia (RIL) has recently been implicated in reducing efficacy of adjuvant durvalumab and increasing risk of progression and death, adding further importance to reducing cardiac irradiation[36]. Our findings suggest that MHD as an estimate of cardiac irradiation may estimate blood-volume radiation exposure and subsequent NLR destabilization, and this may be why it is predictive of progression. The relationship between NLR and cardiac subsites remains unexplored.

### Cardiac irradiation may lead to lung toxicity and immunotherapy discontinuation

Pulmonary complications typically occur several months after completing thoracic radiotherapy and can affect quality-of-life and functional status. Pulmonary toxicity is now a common reason for withholding or discontinuing durvalumab after CRT for LA-NSCLC, and discontinuation worsens outcomes[37,38], as seen in our landmark results. The most recent PACIFIC safety data showed 1.9% of patients receiving durvalumab experienced pneumonitis, the most frequent adverse event prompting discontinuation, and pulmonary toxicity contributed to mortality[2].

Before durvalumab was added to the treatment paradigm for LA-NSCLC, numerous analyses established associations between extent of lung irradiation and risk of radiation pneumonitis[39,40]. Several studies also suggest that lung toxicity following radiotherapy can be a consequence of cardiac irradiation[41–44]. Murine studies have demonstrated that cardiac irradiation can cause diastolic dysfunction, pulmonary congestion, and pulmonary fibrosis[45]. The current study detected a potential trend for MHD to influence durvalumab discontinuation through lung toxicity, and multiple studies have found MHD of approximately  $\geq 9 - 10$  Gy predicts Grade 2+ pneumonitis [41–44,46,47].

Unexpectedly, the current study did not show that extent of lung irradiation predicted durvalumab discontinuation from lung toxicity. Several studies have suggested a range of lung parameters predict pneumonitis during durvalumab maintenance after CRT[48–53], sometimes causing durvalumab discontinuation[46,47,54]. This emerging data, as well as the current study, illustrate the need for high-quality, real-world data to better define lung parameters in the immunotherapy era.

Effect 4.1 is likely a key factor in the established association between cardiac irradiation and mortality risk in patients treated with CRT for LA-NSCLC. It is likely that effects 4.2 and 4.3 will amplify the deleterious effects of cardiac irradiation in modern LA-NSCLC patients who are treated with CRT followed by immunotherapy, and it is possible that one or a combination of the three effects contributed to this study's findings.

The current study's median OS and PFS values were below those in the PACIFIC 5-year update[3], likely due to difference in patients discontinuing durvalumab (69% in the current study, 46.4% in PACIFIC), worse outcomes for patients who discontinued durvalumab, and our inclusion of patients with ECOG performance status of 2 +. This study reflects the 5-year PACIFIC update in that the main reason for durvalumab discontinuation was progression, and our landmark analyses confirm the survival advantages of completing durvalumab seen in PACIFIC[3].

As adjuvant immunotherapy reduces the risk of recurrence and distant metastases following CRT for LA-NSCLC, there will be increased

opportunity for direct cardiac toxicity to become clinically relevant. These considerations suggest that minimizing cardiac irradiation should be a priority when treating LA-NSCLC with CRT, also to not compromise tolerance of adjuvant durvalumab.

Avoiding elective nodal irradiation[55] and employing intensity-modulated radiotherapy[56] are now common practices that reduce cardiac irradiation. Treatment with proton radiotherapy in the ongoing RTOG 1308 trial (NCT01993810)[57] and dose-painted or de-escalated radiotherapy[10,58] are being studied as techniques to reduce heart parameters.

There are several limitations to this hypothesis-generating study. It is retrospective, sample size is modest, and follow-up is limited. This real-world analysis included patients who would not have been eligible for PACIFIC, which established durvalumab as adjuvant therapy after CRT, including 3 oligometastatic Stage IV patients (5%), although the number of these patients was small enough to likely not drive statistical analysis. Causes for durvalumab discontinuation were identified using clinicians' notes rather than formal toxicity scoring or objective physiologic data, due to missing real-time adverse-event grading and to represent a real-world experience. Our patients did not obtain routine electrocardiograms or echocardiograms in follow-up. We are evolving our practices to include these measures for current-day patients based on cardiac irradiation and risk factors for heart disease. A larger multi-institutional analysis to validate our findings and address these concerns is underway, as well as incorporate more detailed parameters such as cardiac subsites, immune-cell counts, more lung volumetric parameters, tumor location, first progression location, RIL prediction models[59], causes of death, and chemotherapy regimens contributing to lung toxicity[39,60].

### Conclusion

For LA-NSCLC patients treated with chemoradiotherapy followed by immunotherapy, extent of cardiac irradiation may be an important risk factor for affecting early immunotherapy discontinuation via progression or lung toxicity, disease recurrence, and death, and should be further explored in multi-institutional, prospective, and randomized studies.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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