ORIGINAL ARTICLE

Korean Real-World Data on Patients With Unresectable Stage III NSCLC Treated With Durvalumab After Chemoradiotherapy: PACIFIC-KR

Cheol-Kyu Park, MD, PhD,[a] Hyung-Joo Oh, MD,[a] Young-Chul Kim, MD, PhD,[a] Yong-Hyub Kim, MD, PhD,[b] Sung-Ja Ahn, MD, PhD,[b] Won Gi Jeong, MD,[c] Jeong Yeop Lee, MD,[c] Jae Cheol Lee, MD, PhD,[d] Chang Min Choi, MD, PhD,[e] Wonjun Ji, MD, PhD,[e] Si Yeol Song, MD, PhD,[f] Juwhan Choi, MD, PhD,[g] Sung Yong Lee, MD, PhD,[g] Hakyoung Kim, MD, PhD,[h] Shin Yup Lee, MD, PhD,[i] Jongmoo Park, MD, PhD,[j] Seong Hoon Yoon, MD,[k] Ji Hyeon Joo, MD,[l] In-Jae Oh, MD, PhD[a,*]

[a]*Department of Internal Medicine, Chonnam National University Medical School and Hwasun Hospital, Jeonnam, Republic of Korea*
[b]*Department of Radiation Oncology, Chonnam National University Medical School and Hwasun Hospital, Jeonnam, Republic of Korea*
[c]*Department of Radiology, Chonnam National University Medical School and Hwasun Hospital, Jeonnam, Republic of Korea*
[d]*Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*
[e]*Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*
[f]*Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*
[g]*Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea*
[h]*Department of Radiation Oncology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea*
[i]*Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea*
[j]*Department of Radiation Oncology, School of Medicine, Kyungpook National University, Daegu, Republic of Korea*
[k]*Department of Internal Medicine, Pusan National University School of Medicine, Yangsan Hospital, Gyeongnam, Republic of Korea*
[l]*Department of Radiation Oncology, Pusan National University School of Medicine, Yangsan Hospital, Gyeongnam, Republic of Korea*

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ABSTRACT

Introduction: This study aimed to investigate real-world evidence for efficacy and safety of durvalumab consolidation (DC) after chemoradiotherapy (CRT) in patients with unresectable stage III NSCLC.

Methods: Patients with stage III NSCLC who started DC after CRT between September 2018 and December 2020 and were treated at five tertiary hospitals in the Republic of Korea were included. The primary end point was real-world progression-free survival (rwPFS). Secondary end points were overall survival, objective response rate, and adverse events including radiation pneumonitis (RP) and immune-related adverse events (irAEs).

Results: A total of 157 patients were enrolled. At the median follow-up of 19.1 months, median rwPFS of DC was 25.9 months (95% confidence interval: 16.5–35.4) and the 1-, 2-, and 3-year rwPFS rates were 59.4%, 51.8%, and 43.5%, respectively. The median overall survival was not mature, and objective response rate of DC was 51.0%. High programmed death-ligand 1 expression (≥50%) and development of RP requiring steroid treatment were

*Corresponding author.

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Address for correspondence: In-Jae Oh, MD, PhD, Department of Internal Medicine, Chonnam National University Medical School and Hwasun Hospital, 322 Seoyang-ro, Hwasun, Jeonnam 58128, Republic of Korea. E-mail: droij@jnu.ac.kr

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significantly associated with longer ($p = 0.043$) and shorter rwPFS ($p = 0.036$), respectively. RP, RP requiring steroid treatment, and irAEs developed in 57 (36.3%), 42 (26.8%), and 53 (33.8%) patients, respectively. Among peripheral blood cell counts at the initiation of DC, a high derived monocyte-to-lymphocyte ratio was the most significant risk factor for the development of RP requiring steroid treatment (OR 44.76, 95% CI: 8.89–225.43, $p < 0.001$) and irAEs (OR 2.85, 95% CI: 1.27–6.41, $p = 0.011$).

Conclusions: Compared with the outcome of the PACIFIC trial, these real-world data revealed favorable survival benefits of DC after CRT in patients with unresectable stage III NSCLC. Blood-based biomarkers could predict higher-grade RP and irAEs before the initiation of DC.

Keywords: Real-world data; Chemoradiotherapy; Durvalumab; Non–small cell lung cancer

Introduction

In patients with unresectable stage III NSCLC with favorable performance status, definitive chemoradiotherapy (CRT) including radical radiation therapy (RT) plus platinum-doublet chemotherapy has been the historic standard of care for several decades. Recent preclinical and clinical evidence has suggested a synergistic antitumor effect of the combination of CRT and immune checkpoint inhibitors (ICIs).[1] The PACIFIC trial revealed overall survival (OS) benefits of durvalumab, a programmed death-ligand 1 (PD-L1) inhibitor, after concurrent CRT (cCRT) in patients with unresectable stage III NSCLC.[2,3] Durvalumab consolidation (DC) after cCRT improved the 5-year OS rate compared with the placebo. DC for up to 12 months has been the new standard of care for patients who received CRT without disease progression during the treatment.[4]

Owing to its poor prognosis and the variability in real-world multidisciplinary discussions originating from the heterogeneity of unresectable stage III NSCLC,[5] real-world data (RWD) on the efficacy and safety of the PACIFIC regimen are needed. RWD from clinical experiences of DC after CRT have been reported worldwide in recent years.[6–12] In a meta-analysis of RWD regarding DC, studies revealed generally better survival rates than the results of the PACIFIC trial.[11] The pooled 12-month OS and progression-free survival (PFS) rates were 90% (95% confidence interval [CI]: 83%–98%) and 62% (95% CI: 56%–68%), respectively. Nevertheless, there is insufficient real-world evidence (RWE) of predictive biomarkers for DC.

Furthermore, compared with randomized clinical trials (RCTs), RWD have advantages in evaluating the actual incidence and risk of adverse events (AEs) in a wide range of patients who are ineligible for RCTs. Nevertheless, an exploratory evaluation of treatment-related factors or biomarkers predicting AEs is considerably limited except for age, dose or extent of RT, and baseline chest computed tomography (CT) findings. On the basis of these unmet needs, this study (PACIFIC-KR) aimed to provide RWE for the efficacy and safety of durvalumab after CRT.

Material and Methods

Study Population and Treatment

The PACIFIC-KR trial is the first multicenter, retrospective, observational study of patients who participated in an early access program (EAP) for durvalumab or who received durvalumab as part of their usual treatment in South Korea. Between September 2018 and December 2020, patients with unresectable locally advanced stage III NSCLC who started durvalumab after completion of CRT without progression were recruited from five tertiary medical centers in South Korea. The clinical stage was defined by the Union for International Cancer Control TNM classification (eighth edition).[13] Patients who underwent radical surgery before CRT were excluded.

The completion of CRT was the main inclusion criterion of the PACIFIC trial[3]: patients who received platinum-based chemotherapy concurrently or sequentially with RT and received a total dose of radiation of at least 60 Gy (54–66 Gy) were included. Given the therapeutic dose intensity of the three-week interval regimen and weekly regimen, patients who received at least two cycles (3-wk interval) or five cycles (weekly) of chemotherapy were included. After completion of CRT, durvalumab (10 mg/kg) was administered every two weeks and continued for a maximum of 12 months until confirmed progression, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue the drug occurred. The initial chest CT scan was performed before the start of CRT, and a follow-up scan was performed four to eight weeks after completion of CRT and repeated every eight to 12 weeks thereafter. Clinical responses to treatment were defined according to Response Evaluation Criteria in Solid Tumors version 1.1.[14]

This study was conducted in accordance with the Declaration of Helsinki (2013 revision). The study was approved by the institutional review boards of the relevant institutions: Chonnam National University Hwasun Hospital Institutional Review Board (IRB) (CNUHH-2021-156), Asan Medical Center IRB (2021-1700), Kyungpook National University Chilgok Hospital IRB (2021-09-015), Pusan National University Yangsan

Hospital IRB (04-2021-036), and Korea University Guro Hospital IRB (2021GR0414). Individual informed consent was received from all participants.

Data Collection

The patient demographic and clinical characteristics were retrospectively reviewed using electric medical records from five hospitals, and the anonymized data sources were collected using a supported electronic data capture system. Data on PD-L1 tumor proportional score (TPS, %), *EGFR* mutation status, *ALK* alterations, pulmonary function before the start of CRT, and laboratory findings were collected based on the tests conducted by each institution. Laboratory tests using the peripheral blood were investigated based on the results at the start of CRT (C0) and durvalumab (C1).

Data on RT plans were analyzed based on total dose, fraction, techniques, and sequence between RT and chemotherapy (concurrent or sequential). Dose-volume parameters of radiation exposure to the lung were also assessed in terms of the percentage of total lung volume exceeding 50 Gy (V50), 40 Gy (V40), 30 Gy (V30), 20 Gy (V20), 10 Gy (V10), 5 Gy (V5), mean lung dose (MLD), and initial planning target volume.

Safety profiles of special interest included radiation pneumonitis (RP) and immune-related AEs (irAEs) that caused interruption or withdrawal of treatment or required interventions. RP and irAEs were diagnosed clinically based on the presence of classic symptoms, timing and history of RT or durvalumab, imaging findings, and exclusion of alternative causes. To investigate the association between baseline lung fibrosis and the development of RP, we measured the pulmonary fibrosis score from the initial chest CT scan images, declared by Kazerooni et al.[15] and modified by Tsujino et al.[16] The definition of pulmonary fibrosis score is described in Appendix 1,[10] and the scores were independently measured and reviewed by two expert radiologists blinded to the patients' medical records. Treatment profiles included chemotherapy regimens, objective response rates of CRT and DC, duration of durvalumab treatment, time to discontinuation of durvalumab, and time to next treatment.

Outcomes and Statistical Analyses

The primary end points were the median real-world PFS (rwPFS) and 1-, 2-, and 3-year rwPFS rates. The rwPFS was measured from the first date of durvalumab treatment to the date of objective recurrence, death from any cause, or data cutoff and was censored at the date of the last patient contact. The secondary end points were the median OS, 1-, 2-, and 3-year OS rates, safety profiles, and treatment profiles. The OS was measured from the first date of durvalumab treatment to the date of death from any reason or data cutoff and was censored at the date of the last patient contact.

The derived neutrophil-to-lymphocyte ratio (dNLR) was calculated as follows: absolute neutrophil count [ANC]/(white blood cell [WBC] count − ANC).[17] The absolute monocyte count was not initially included in the survey, and the derived monocyte count was defined and calculated as follows: WBC count − ANC − absolute lymphocyte count (ALC). The derived monocyte-to-lymphocyte ratio (dMLR) was calculated as follows: derived monocyte count/ALC. The cutoff values of NLR, dNLR, platelet-to-lymphocyte ratio (PLR), and dMLR at C1 for the development of RP requiring steroid treatment and irAEs were calculated based on receiver operating characteristic (ROC) curve analysis and area under the curve. The cutoff values of dose-volume parameters of radiation exposure to the lung for the development of RP and RP requiring steroid treatment were also calculated by ROC curve analysis. AEs were graded based on severity using Common Terminology Criteria for Adverse Events (version 4.03). The calculation of the sample size in the present study is described in Appendix 2.

All data are expressed as median (range) for continuous variables and as numbers (percentages) for categorical variables. Intergroup comparisons of responses were performed using *t* test or Mann-Whitney *U* test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. Survival times were estimated for each group using Kaplan-Meier method. The time to RP was defined as the time interval from the start of CRT to the diagnosis of RP and was calculated using the Kaplan-Meier method. Univariate and multivariate analyses of survival were performed using Cox proportional hazards models. Statistical analysis was performed using IBM SPSS statistics version 25 (IBM Corp., Armonk, NY) and R statistics.[18] A p value of less than 0.05 was considered significant.

Results

Patient Characteristics and Treatment-Related Factors Associated With CRT and Durvalumab

A total of 157 patients were enrolled, and the baseline patient characteristics are summarized in Table 1. Pulmonary comorbidities were detected in 57 patients (36.3%), and most patients did not have pulmonary fibrosis (score 0, 82.8%) on the baseline chest CT scan. *EGFR* mutation and *ALK* fusion were detected in 21 patients (13.4%) and two patients (1.3%), respectively. The results of PD-L1 immunohistochemistry with SP263 antibody were confirmed in 143 patients (91.1%), and PD-L1 expression (TPS $\geq$ 1%) was present in 124 patients (79.0%).

Table 1. Baseline Characteristics of Patients Treated With Durvalumab After CRT

Characteristics	No. of Patients, N = 157
Age	65 (36-82)
Sex	
Male	134 (85.4)
Female	23 (14.6)
Smoking	
Never smoker	31 (19.7)
Ex-smoker	75 (47.8)
Current smoker	51 (32.5)
Pack x years	40.0 (1.5-160.0)
ECOG PS	
0/1	43 (27.4)/97 (61.8)
2/3	14 (8.9)/3 (1.9)
Comorbidity: yes	114 (72.6)
Pulmonary	57 (36.3)
COPD	50 (31.8)
ILD	1 (0.6)
Radiation pneumonitis	2 (1.3)
Pulmonary fibrosis score: 0/1/2/3/4/5	130 (82.8)/19 (12.1)/5 (3.2)/3 (1.9)/0 (0.0)/0 (0.0)
Cardiovascular	66 (42.0)
Hypertension	58 (36.9)
Angina or myocardial infarction	8 (5.1)
Stroke	1 (0.6)
Other primary cancer[a]	16 (10.2)
Previous medication (within a month)	
Antibiotics	12 (7.6)
Steroids	12 (7.6)
Daily dose, mg/d	13.5 (2.0-30.0)
Histology	
ADC	64 (40.8)
SQC	82 (52.2)
Others[b]	11 (7.0)
Stage (TNM eighth)	
IIIA	53 (33.8)
IIIB	73 (46.5)
IIIC	31 (19.7)
T0/T1/T2	1 (0.6)/27 (17.2)/35 (22.3)
T3/T4	50 (31.8)/44 (28.0)
N0/N1	10 (6.4)/16 (10.2)
N2/N3	64 (40.8)/67 (42.7)
EGFR mutation	
Mutant	21 (13.4)
Wild type	70 (44.6)
Unknown	66 (42.0)
ALK translocation	
Positive	2 (1.3)
Negative	75 (47.8)
Unknown	80 (51.0)
PD-L1 IHC (SP263)	
TPS $<$ 1%	19 (12.1)
TPS $\geq$ 1%	124 (79.0)
TPS $<$ 25%	75 (47.8)
TPS $\geq$ 25%	68 (43.3)
TPS $<$ 50%	91 (58.0)
TPS $\geq$ 50%	52 (33.1)
Unknown	14 (8.9)
Pulmonary function (before CRT), n = 142	
FEV1, %	76.0 (36.5-119.0)
FVC, %	81.0 (43.0-128.0)
DLCO, %	76.0 (35.6-141.0)
Laboratory findings (before initiation of durvalumab)	
WBC count, $\times 10^3/\mu$L	4.9 (2.3-20.6)
ANC, $\times 10^3/\mu$L	2.4 (0.6-15.7)
Lymphocyte count, $\times 10^3/\mu$L	0.8 (0.0-11.6)
Platelet count, $\times 10^3/\mu$L	220 (89-536)
Derived monocyte count, $\times 10^3/\mu$L	0.9(0.1-19.5)
NLR	3.6 (0.27-111.0)
dNLR	1.3 (0.1-12.7)
PLR	294.7 (24.7-20,170.9)
dMLR	1.0 (0.1-221.3)
T3, ng/mL	1.03 (0.48-2.88)
Free T4, ng/dL	1.08 (0.0-1.72)
TSH, uIU/mL	1.48 (0.0-21.8)
CRT sequence	
Concurrent	153 (97.5)
Sequential	4 (2.5)
Radiation therapy	
Total dose, Gy	60.0 (0.6-86.0)
$<$54 Gy	3 (1.9)
$\geq$54 to $\leq$66 Gy	152 (96.8)
$>$66 Gy	2 (1.3)
Fractions	30 (3-35)
Radiation field	
Intrathoracic lesion	115 (73.2)
Intrathoracic lesion plus supraclavicular LN	42 (26.8)
Modality (technique)	
Conventional	44 (28.0)
3D-CRT	14 (8.9)
IMRT	90 (57.3)
Unknown	9 (5.7)
Chemotherapy regimen	
Paclitaxel-Cisplatin	108 (68.8)
Paclitaxel-Carboplatin	38 (24.2)
Etoposide-Cisplatin	4 (2.5)
Etoposide-Carboplatin	3 (1.9)
Gemcitabine-Carboplatin	3 (1.9)
Vinorelbine-Cisplatin	1 (0.6)
Chemotherapy cycle	
Weekly	146 (93.0)
Every 3 wk	9 (5.7)
Unknown	2 (1.3)
CRT best response	
CR	0 (0.0)
PR	104 (66.2)
SD	49 (31.2)
NE	4 (2.5)
Objective response rate (%)	104/157 (66.2)

(continued)

Table 1. Continued

Characteristics	No. of Patients, N = 157
CRT completion	
Yes	151 (96.2)
No	5 (3.2)
Unknown	1 (0.6)

Note: Values are presented as medians (ranges) or numbers (%).
[a]Thyroid (n = 5), stomach (n = 3), bladder (n = 2), prostate (n = 2), esophagus (n = 1), liver (n = 1), ureter (n = 1), kidney (n = 1), skin (n = 1).
[b]NSCLC, NOS (n = 6), large-cell neuroendocrine carcinoma (n = 1), sarcomatoid carcinoma (n = 2), hepatoid adenocarcinoma (n = 1), pleomorphic carcinoma (n = 1).
3D-CRT, three-dimensional conformal radiation therapy; ADC, adenocarcinoma; ANC, absolute neutrophil count; COPD, chronic obstructive pulmonary disease; CR, complete response; CRT, chemoradiotherapy; DLCO, diffusing capacity of carbon monoxide; dMLR, derived monocyte-to-lymphocyte ratio; dNLR, derived NLR; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiration volume within 1 second; FVC, forced vital capacity; IHC, immunohistochemistry; ILD, interstitial lung disease; IMRT, intensity-modulated radiotherapy; LN, lymph node; NE, not evaluable; NLR, neutrophil-to-lymphocyte ratio; NOS, not otherwise specified; PD-L1, programmed cell death ligand-1; PLR, platelet-to-lymphocyte ratio; PR, partial response; PS, performance status; SD, stable disease; SQC, squamous cell carcinoma; TPS, tumor proportional score; TSH, thyroid-stimulating hormone; WBC, white blood cell count.

The treatment-related factors associated with CRT are described in Table 1. Most patients received chemotherapy concurrently with RT (97.5%). Most patients received platinum-based chemotherapy weekly (93.0%). Most patients (96.8%) received 54 to 66 Gy of RT. In terms of RT techniques, most patients (66.2%) received three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy. In addition, most patients (96.2%) completed CRT based on the criteria of the PACIFIC trial.

The outcomes of DC treatment are described in Table 2. Most patients (81.5%) received durvalumab within 42 days after the last date of RT. At the time of data cutoff (December 15, 2021), 63 patients (40.1%) had completed the 12-month course of durvalumab, 65 patients (41.4%) experienced progression during DC, and 15 patients (9.6%) discontinued the treatment due to AEs associated with durvalumab.

Survival Outcomes With DC and Post-Progression Treatment

At the median follow-up of 19.1 months, the median rwPFS was 25.9 months and the 1-, 2-, and 3-year rwPFS rates were 59.4%, 51.8%, and 43.5%, respectively (Fig. 1*A*). The median OS data were not mature, and the 1-, 2-, and 3-year OS rates were 87.8%, 71.0%, and 69.2%, respectively (Fig. 1*B*, Table 2). The Kaplan-Meier curves for rwPFS and OS are found in Figure 1.

In the subgroup analysis for rwPFS, stage IIIA (versus IIIB–C), N0-1 (versus N2–3), and PD-L1 TPS greater than or equal to 25% (versus <25%) and greater than or equal to 50% (versus <50%) were favorable factors for survival, whereas RP requiring steroid treatment was a risk factor for a shorter rwPFS (Supplementary Fig. 1*A*). In the multivariate analysis, PD-L1 greater than or equal to 50% and RP requiring steroid treatment were independent factors associated with longer and shorter rwPFS, respectively. Patients with RP requiring steroid treatment also had a shorter median time-to-next treatment (12.4 mo, 95% CI: 3.6–21.1) than those without RP or those with RP who did not require steroid treatment (30.6 mo, 95% CI: 22.7–38.5; $p = 0.031$). In the subgroup analysis for OS, Eastern Cooperative Oncology Group performance status of 2 to 3 (versus 0–1) was the only risk factor for a shorter OS (hazards ratio [HR] = 2.65, 95% CI: 1.21–5.82) (Supplementary Fig. 1*B*).

At the time of data cutoff (December 15, 2021), progression was confirmed in 73 patients (46.5%) and 66 patients (42.0%) received subsequent treatment (Supplementary Table 1). Locoregional progression (56.2%) was the predominant type of relapse, and the lungs (60.3%) and lymph nodes (35.6%) were the most common sites of progression, followed by the brain (13.7%) and bones (13.7%).

Safety Profile of Durvalumab and Risk Factors for the Development of RP

Overall AEs developed in 126 patients (80.3%), and 77 patients (49.0%) experienced treatment-related AEs (Supplementary Table 2). Treatment interruption and withdrawal were reported in 25 (15.9%) and 15 patients (9.6%), respectively. Pneumonitis was the most common AE, and grade 5 toxicity was reported in one patient. RP developed in 57 patients (36.3%), and RP was found in three patients before the initiation of durvalumab. The median interval from the end of RT to the development of RP was 4.2 months (95% CI: 4.0–4.4). Steroid treatment for RP was required in 42 patients (26.8%).

Peripheral blood cell (PBC) count parameters, such as NLR, dNLR, PLR, and dMLR, were calculated at the start of CRT (C0) and durvalumab (C1). The median interval from C0 sampling to the start of RT was 1.0 days (range: −6 to 43), and the C0 sampling after the start of RT was performed in only one patient. The median interval from C1 sampling to the start of durvalumab was 0.0 day (range: −14 to 44), and the C1 sampling after the start of durvalumab was performed in only one patient.

There was no significant difference in PBC count parameters at C0 and C1 between patients with RP and those without RP (Supplementary Fig. 2*A* and *B*). Nevertheless, NLR, PLR, and dMLR at C0 and C1 were significantly higher in patients with RP requiring steroid treatment than in patients without RP or those with RP who did not require steroid treatment. In contrast, dNLR

Table 2. Treatment-Related Factors Associated With Patients Treated With Durvalumab After CRT

Variables	No. of Patients, N = 157
Last radiotherapy to initiation of durvalumab, d	32 (0-86)
<14	15 (9.6)
≥14	142 (90.4)
<28	54 (34.4)
≥28	103 (65.6)
<42	128 (81.5)
≥42	29 (18.5)
Durvalumab cycle	19 (1-32)
Reason for cessation of durvalumab treatment	
Completion (1 y)	63[a] (40.1)
Progression during treatment	65 (41.4)
Adverse events (toxicity)	15 (9.6)
Patient refusal	4 (2.5)
Lost to follow-up or transferred to another clinic	2 (1.3)
Unknown	5 (3.2)
Ongoing	8 (5.1)
Best response of durvalumab	
CR	0 (0.0)
PR	80 (51.0)
SD: ≥24 wk/<24 wk	43 (27.4)/14 (8.9)
PD	14 (8.9)
NE	6 (3.8)
Objective response rate (%)	80/157 (51.0)
Progression	
Confirmed	73 (46.5)
No progression	81 (51.6)
Unknown	3 (1.9)
Follow-up duration, mo (median, 95% CI)	19.1 (17.0-21.2)
rwPFS, mo (median, 95% CI)	25.9 (16.5-35.4)
1-y rwPFS rate, % (95% CI)	59.4 (52.1-67.7)
2-y rwPFS rate, % (95% CI)	51.8 (43.8-61.2)
3-y rwPFS rate, % (95% CI)	43.5 (33.5-56.5)
Duration of treatment, mo (median, 95% CI)	12.0 (10.8-13.3)
TTNT, mo (median, 95% CI)	26.4 (16.4-36.3)
OS, mo (median, 95% CI)	NR
1-y OS rate, % (95% CI)	87.8 (82.8-93.1)
2-y OS rate, % (95% CI)	71.0 (62.6-80.5)
3-y OS rate, % (95% CI)	69.2 (60.5-79.2)
Alive	121 (77.1)
Death	21 (13.4)
Lost to follow-up or transferred to another clinic	15 (7.5)

Note. Values are presented as medians (ranges) or numbers (%).
[a]Included progression after completion (n = 3), ongoing beyond one year (n = 1), transferred to another clinic after completion (n = 1).
CR, complete response; CRT, chemoradiotherapy; NE, not evaluable; OS, overall survival; PD, progressive disease; PR, partial response; rwPFS, real-world progression-free survival; SD, stable disease;TTNT, time-to-next treatment.

at C1 was significantly lower in patients with RP requiring steroid treatment than in patients without RP or those with RP who did not require steroid treatment (Fig. 2*A* and *B*). When dividing subgroups by the cutoff values of PBC count parameters at C1 (Supplementary Fig. 3*A*), high NLR, PLR, and dMLR and low dNLR at C1 were significantly associated with the development of RP requiring steroid treatment (Fig. 2*C* and Table 3).

In the univariate analysis using ROC curve analysis (Supplementary Table 3) and logistic regression methods (Table 3), the development of RP and RP requiring steroid treatment was associated with conventional RT (versus 3D-CRT or intensity-modulated radiotherapy), a high total lung volume (%) exposed to radiation, and a high MLD. In the multivariate analysis including PBC count parameters, variables of RT, baseline pulmonary function, and pulmonary fibrosis score, a high dMLR at C1 (OR 44.76, 95% CI: 8.89–225.43, $p < 0.001$) was the most significant parameter for predicting the development of RP requiring steroid treatment, and V10 greater than 46.4% (OR 15.03, 95% CI: 2.39–94.51, $p = 0.004$) and MLD greater than 11.5 Gy (OR 6.09, 95% CI: 1.40–26.477, $p = 0.016$) were other independent risk factors.

irAEs of Durvalumab and Correlation With PBC Count Parameters

irAEs developed in 53 patients (33.8%), and grade greater than or equal to 3 irAEs were reported in five patients (3.2%). Pneumonitis and thyroid dysfunction were the most common irAEs. In patients with irAEs, NLR, PLR, and dMLR at C0 were significantly higher in patients with irAE than in those without irAEs (Fig. 2*D*). The dMLR at C1 was significantly higher in patients with irAEs than in those without irAEs, whereas the dNLR at C1 was lower in patients with irAEs (Fig. 2*E*). When dividing subgroups by the cutoff values of PBC count parameters at C1 (Supplementary Fig. 3*B*), low dNLR and high dMLR at C1 were significantly associated with the development of irAEs (Fig. 2*F* and Table 4). In the multivariate analysis, a high dMLR at C1 (OR 2.85, 95% CI: 1.27–6.41, $p = 0.011$) was the most significant parameter for predicting the development of irAEs.

Discussion

The PACIFIC-KR trial is the first multicenter, real-world study involving patients who received DC after completion of CRT in South Korea. The median rwPFS with DC was 25.9 months, and approximately half of the patients (51.8%) did not have disease progression until two years after the initiation of durvalumab treatment. The median OS data were not mature, and 77.7% of the patients were alive at the time of data cutoff, with a median follow-up of 19.1 months. During DC for a median of 12.0 months, DC was well-tolerated, and several PBC count parameters were found to be predictive

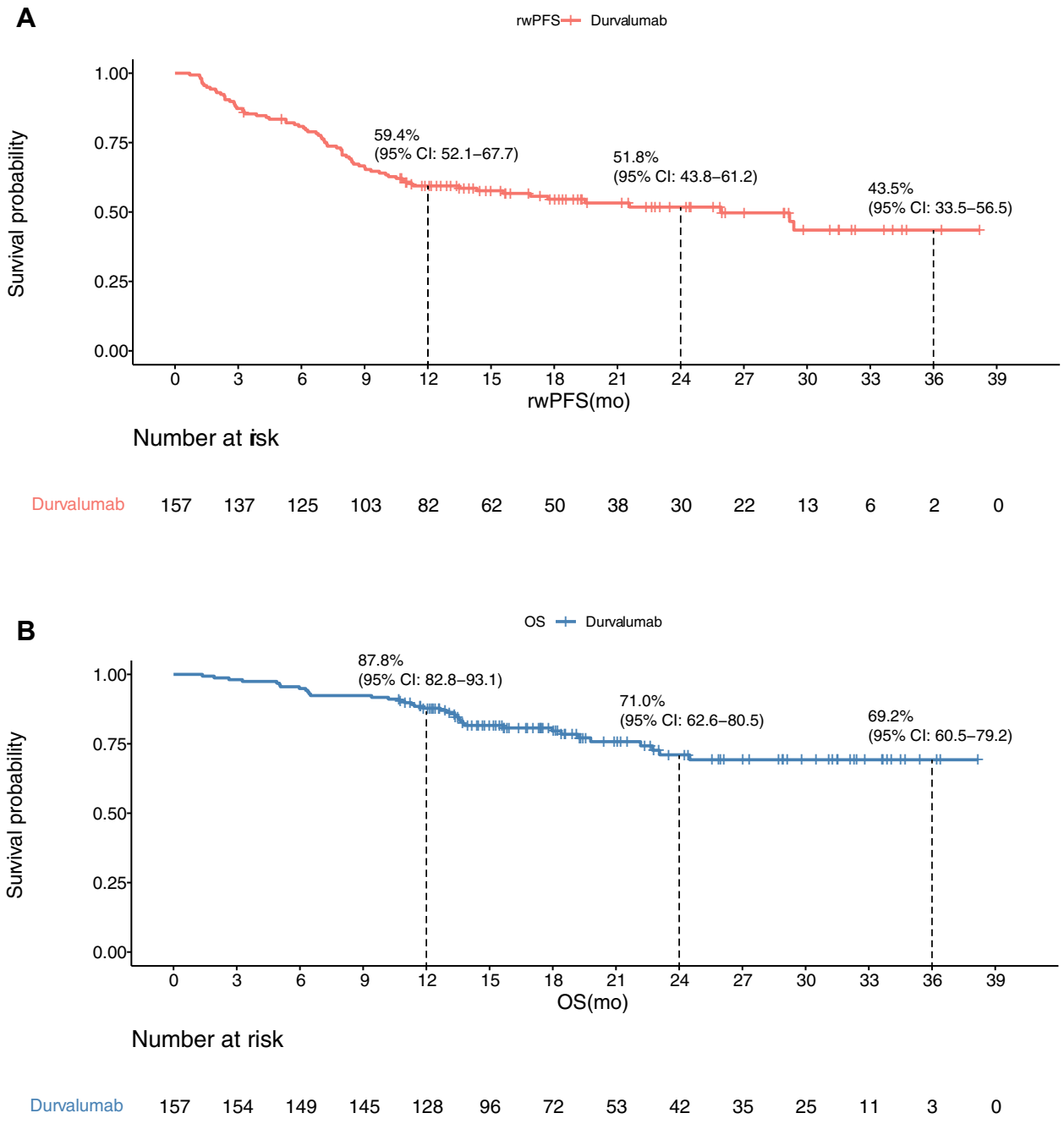

Figure 1. rwPFS and OS in patients treated with durvalumab. (*A*) Kaplan-Meier curve for the rwPFS and 1-, 2-, and 3-year rwPFS rates. (*B*) Kaplan-Meier curve for OS and the 1-, 2-, and 3-year OS rates. CI, confidence interval; OS, overall survival; rwPFS, real-world progression-free survival.

biomarkers for the development of RP requiring steroid treatment and irAEs.

The survival rates in the present study were numerically superior to those in the PACIFIC trial. In the PACIFIC trial,[2] the median PFS was 16.9 months, and the 1-, 2-, and 3-year PFS rates were 55.7%, 45.0%, and 39.7%, respectively. The higher rwPFS rates in the present study than in the PACIFIC trial are aligned with the results of recent real-world studies. In a large European cohort study of patients who participated in an EAP for durvalumab (PACIFIC-R),[12] the median rwPFS was 21.7 months, and the 1- and 2-year rwPFS rates were 62.2% and 48.2%, respectively. Although the OS data from real-world studies need to mature, these favorable outcomes from RWD suggest that the impact of the PACIFIC trial can be steadily translated to real-world clinical practice.

Nevertheless, several factors could affect this overestimation of survival in RWD. RCTs have strict schedules for response assessment compared with surveillance in real-world practice, which may cause delayed detection of disease progression. In addition, disease progression is confirmed radiologically by blinded independent central review in RCTs; in contrast, in real-world studies, progression is determined based on either radiologic evidence or investigators' clinical assessments.

In the PACIFIC trial, the PFS benefit favored DC across all subgroups, except for the *EGFR* mutation-positive group and PD-L1 TPS less than 1% group.[19] In the real-world study of the PACIFC-R, the rwPFS time was numerically longer in the subgroups with PD-L1 greater than or equal to 1%, stage IIIA, nonsquamous histology, cCRT, cisplatin-based chemotherapy, durvalumab initiation less than or equal to 42 days after completion of RT, and wild-type *EGFR* status; however, the differences were not statistically significant.[12] In the present study, although there was no comparator for durvalumab, patients with higher PD-L1 expression ($\geq$25% and $\geq$50%) had a better rwPFS than those with lower PD-L1 expression. Nevertheless, there was no significant difference in rwPFS between patients with PD-L1 greater than or equal to 1% and less than 1%. The European Medicines Agency and Korean Ministry of Food and Drug Safety have restricted the use of DC to a specific population with PD-L1 expression greater than or equal to 1%. Most patients with PD-L1 less than 1% in the present study belonged to the population who participated in an EAP for durvalumab, and the considerable difference in the number of patients between subgroups (124 versus 19) may have affected the significance of the rwPFS benefit. Furthermore, there were no significant differences in OS between other subgroups, except for Eastern Cooperative Oncology Group performance status. The subgroup of patients with RP requiring steroid treatment had a shorter rwPFS, whereas there was no difference in OS between those subgroups. Further subgroup analysis for OS needs to be performed based on sufficiently mature survival data.

DC can lead to additional long-term exposure to AEs, especially irAEs. In recent studies, several potential biomarkers have been identified to predict the development of irAEs.[20] Among blood-based biomarkers, the pretreatment PBC count (ANC, ALC, NLR, PLR, MLR, and platelet and eosinophil counts) and dynamic changes in the PBC count have drawn attention due to several advantages of liquid biopsy[21–25]; however, the optimal cutoff values for these factors are variable, and the comparative results of subgroups according to their levels are inconsistent from study to study. In the present study, low dNLR and high dMLR at C1 were associated with the development of irAEs, and a high dMLR at C1 was the strongest predictive factor (OR: 2.85). Furthermore, such a pattern had already been observed even before CRT (C0). When inferred from the formula for producing the value, low dNLR and high dMLR refer to relative increases in monocytes compared with lymphocytes. In a recent preclinical report on single-cell RNA sequencing (scRNA-seq) of peripheral blood mononuclear cells from patients who developed skin irAEs, the percentage of CD14+ and CD16+ monocytes increased among patients with irAEs, and macrophage cell population-related pathways were upregulated in a gene set enrichment analysis.[26] Even considering that PBC counts only crudely reflect the body's immune state, the absolute monocyte count or MLR might be promising parameters to predict the development of irAEs.

In the PACIFIC trial, the incidence of pneumonitis or RP was higher in the DC group than in the placebo group (33.9% versus 24.8%), whereas grade 3 or 4 events were similar between groups (3.4% versus 2.6%).[3] According to real-world studies of DC after CRT, the risk factors for the development of (symptomatic) RP are as follows: DC treatment per se, MLD greater than or equal to 20 Gy, lung V20 greater than or equal to 35% or 18.3 Gy, lung V40 greater than or equal to 10%, and pulmonary fibrosis score.[7,10,27] In the present study, all the dose-volume parameters of radiation exposure to the lung were associated with the development of RP and RP requiring steroid treatment, except initial planning target volume and pulmonary fibrosis score. Indeed, the distinguishing point between immune-related pneumonitis and RP in the setting of DC after CRT may be ambiguous, and those two categories were not described separately in the safety profile of the PACIFIC trial.[3] Thus, in addition to treatment-related or radiologic factors, peripheral blood biomarkers have been suggested as predictors of the development and severity of pneumonitis or RP. Tang et al.[28] suggested that post-RT WBC counts were significantly associated with RP and correlated with its severity. In a cohort study of ICI-related pneumonitis in lung cancer, Lin et al.[29] revealed that increases in the NLR and PLR and decreases in the ALC relative to baseline were associated with the occurrence of pneumonitis.

In the present study, high NLR, PLR, and dMLR and low dNLR at C1 were significantly associated with the development of RP requiring steroid treatment, which can be considered a severe manifestation of pneumonitis. Furthermore, even after adjusting for variables related to RT, a high dMLR at C1 was the most powerful biomarker for predicting RP requiring steroid treatment (OR: 44.76). In the same manner as for irAEs, monocyte counts might have a crucial role in the pathogenesis of

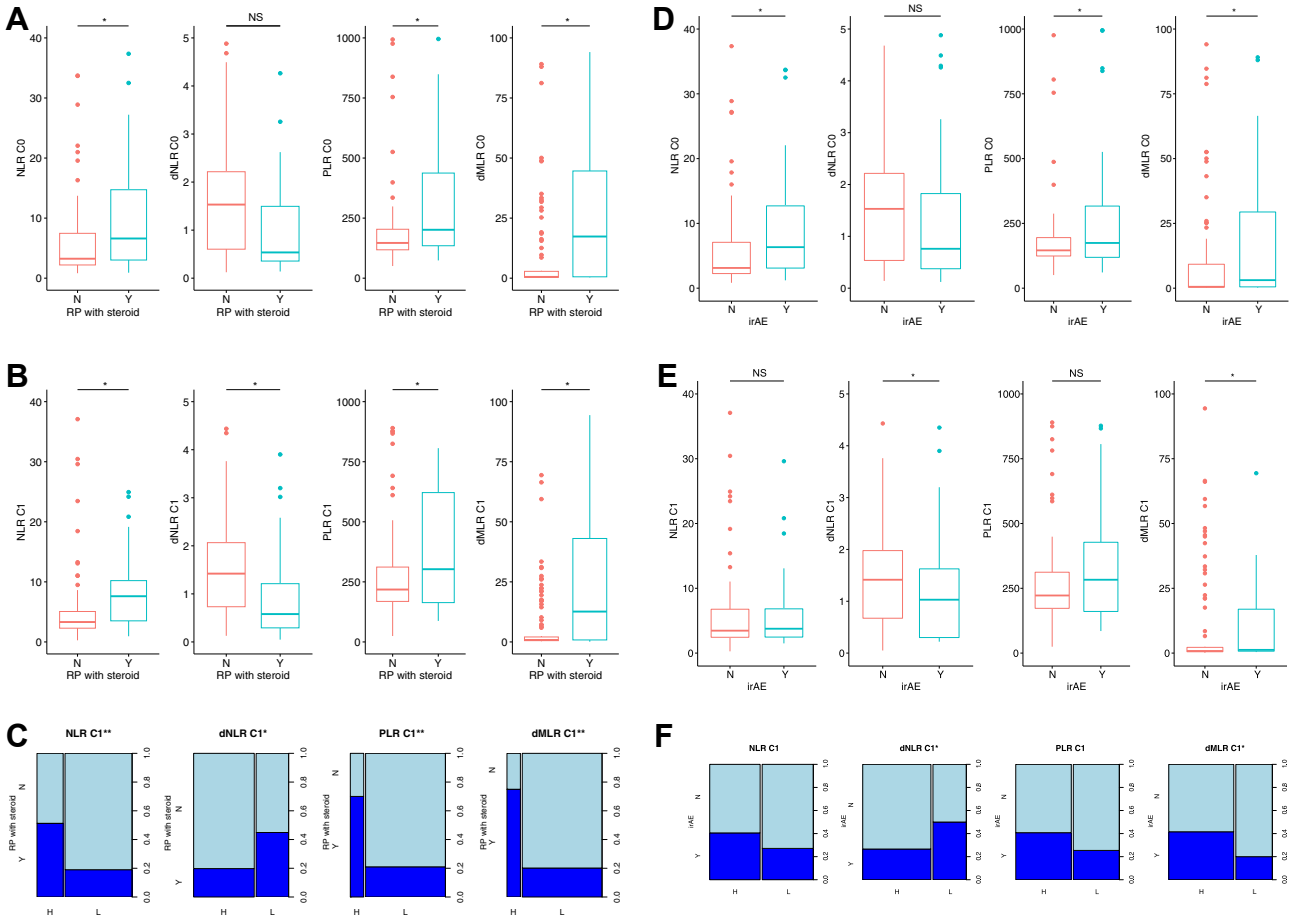

Figure 2. Development of RP with or without steroid treatment and irAEs after initiation of durvalumab and PBC count parameters. (*A*) PBC counts at C0 (before the first cycle of CRT) according to RP requiring steroid treatment. (*B*) PBC counts at C1 (before the first cycle of durvalumab) according to RP requiring steroid treatment. (*C*) Development of RP requiring steroid treatment according to PBC counts at C1. (*D*) PBC counts at C0 according to irAEs. (*E*) PBC counts at C1 according to irAEs. (*F*) Development of irAEs according to PBC counts at C1. *p value less than 0.05, **p value less than 0.001. CRT, chemoradiotherapy; dMLR, derived monocyte-to-lymphocyte ratio; dNLR, derived NLR; H, high; irAEs, immune-related adverse events; L, low; NLR, neutrophil-to-lymphocyte ratio; PBC, peripheral blood cell; PLR, platelet-to-lymphocyte ratio; RP, radiation pneumonitis; N, no; NS, not significant; Y, yes.

pneumonitis in patients treated with ICIs, and the activity of monocytes might be exaggerated by CRT. In a cohort study using NSCLC surgical specimen, the CIBERSORT analysis revealed significantly up-regulated memory B cells, CD8+ T cells, and M1 macrophages in the ICI-related pneumonitis group.[30] As innate immune cells, monocyte-derived pulmonary macrophages are known to play a key role in the inflammatory response, causing acute respiratory distress syndrome (ARDS) and severe coronavirus disease 2019 (COVID-19).[31,32] Monocytes are likely recruited from the blood to the lower airway during COVID-19,[33] and a report of scRNA-seq using bronchoalveolar lavage cells has revealed higher frequencies of proinflammatory monocyte-derived macrophages in patients with severe COVID-19 than in those with moderate disease.[34] In a retrospective cohort study of ARDS, the MLR was significantly associated with 28-day mortality (OR: 2.956), and a combination of MLR and NLR was the most predictive indicator for mortality (area under the curve 0.750).[35] In the present study, more importantly, such a pattern in the differences in blood biomarkers had already been observed even before CRT (C0). Therefore, the present study suggests that pretreatment risk prediction of severe RP or irAEs using these relevant blood-based biomarkers may be warranted in patients with unresectable stage III NSCLC planning to undergo CRT and DC.

This study has several limitations. First, this study involved an enriched population, which could have affected the results of the subgroup analysis, especially for OS. All the patients in this study received DC treatment, and patients with PD-L1 greater than or equal to 1% were selected to receive DC due to the reimbursement policy for DC of the Korean National Health Insurance System. In addition, the incidence of driver mutations (15% versus 6%) and the unknown results of

Table 3. Risk Factors for the Development of RP Requiring Steroid Treatment After CRT

Variables	RP Without Steroid or No RP	RP With Steroid	*p*	Univariate OR (95% CI)	*p*	Multivariate OR (95% CI)	*p*
NLR C1[a] ($n = 139$)			<0.001		<0.001		0.312
≤6.8	81 (81.0)	19 (48.7)		1 (reference)		1 (reference)	
>6.8	19 (19.0)	20 (51.3)		4.49 (2.01-10.01)		1.97 (0.53-7.31)	
dNLR C1[a] ($n = 140$)			0.002		0.002		0.276
>0.8	73 (73.0)	18 (45.0)		1 (reference)		1 (reference)	
≤0.8	27 (27.0)	22 (55.0)		3.31 (1.54-7.09)		2.05 (0.56-7.47)	
PLR C1[a] ($n = 138$)			<0.001		<0.001		0.838
≤1582.5	94 (94.9)	25 (64.1)		1 (reference)		1 (reference)	
>1582.5	5 (5.1)	14 (35.9)		10.53 (3.46-32.02)		0.73 (0.04-14.19)	
dMLR C1[a] ($n = 139$)			<0.001		<0.001		< 0.001
≤31.2	95 (95.0)	24 (61.5)		1 (reference)		1 (reference)	
>31.2	5 (5.0)	15 (38.5)		11.88 (3.93-35.92)		44.76 (8.89-225.43)	
RT technique[b]			<0.001		<0.001		0.439
3D-CRT or IMRT	87 (78.4)	17 (45.9)		1 (reference)		1 (reference)	
Conventional	24 (21.6)	20 (54.1)		4.27 (1.94-9.39)		0.36 (0.03-4.72)	
V50 ($n = 153$), %			<0.001		<0.001		0.789
≤5.4	72 (64.9)	13 (31.0)		1 (reference)		1 (reference)	
>5.4	39 (35.1)	29 (69.0)		4.12 (1.92-8.82)		1.37 (0.14-13.58)	
V40 ($n = 153$), %			0.001		0.001		0.407
≤9.6	75 (67.6)	16 (38.1)		1 (reference)		1 (reference)	
>9.6	36 (32.4)	26 (61.9)		3.39 (1.62-7.09)		2.09 (0.37-11.87)	
V30 ($n = 153$), %			<0.001		<0.001		0.707
≤14.9	78 (70.3)	15 (35.7)		1 (reference)		1 (reference)	
>14.9	33 (29.7)	27 (64.3)		4.26 (2.01-9.02)		1.66 (0.12-23.34)	
V20 ($n = 153$), %			0.010		0.011		0.069
≤21.6	73 (65.8)	18 (42.9)		1 (reference)		1 (reference)	
>21.6	38 (34.2)	24 (57.1)		2.56 (1.24-5.29)		0.22 (0.04-1.13)	
V10 ($n = 153$), %			0.007		0.009		0.004
≤46.4	99 (89.2)	30 (71.4)		1 (reference)		1 (reference)	
>46.4	12 (10.8)	12 (28.6)		3.30 (1.34-8.10)		15.03 (2.39-94.51)	
MLD ($n = 153$), Gy			0.001		0.002		0.016
≤11.5	50 (45.0)	7 (16.7)		1 (reference)		1 (reference)	
>11.5	61 (55.0)	35 (83.3)		4.10 (1.68-10.02)		6.09 (1.40-26.48)	
FEV1[c] ($n = 142$), %			0.494		0.494		0.768
>76.0	56 (53.8)	18 (47.4)		1 (reference)		1 (reference)	
≤76.0	48 (46.2)	20 (52.6)		1.30 (0.62-2.73)		0.78 (0.15-4.15)	
FVC[c] ($n = 142$), %			0.579		0.579		0.390
>81.0	52 (50.0)	21 (55.3)		1 (reference)		1 (reference)	
≤81.0	52 (50.0)	17 (44.7)		0.81 (0.38-1.71)		1.65 (0.53-5.16)	
DLCO[c] ($n = 139$), %			0.808		0.808		0.637
>76.0	52 (51.0)	18 (48.6)		1 (reference)		1 (reference)	
≤76.0	50 (49.0)	19 (51.4)		1.10 (0.52-2.33)		1.37 (0.37-5.02)	
Pulmonary fibrosis score[d]			1.000		0.909		0.642
0-1	109 (94.8)	40 (95.2)		1 (reference)		1 (reference)	
2-5	6 (5.2)	2 (4.8)		0.91 (0.18-4.69)		0.71 (0.16-3.08)	

Note: Values are presented as numbers (%).
[a]Measured before the first cycle of durvalumab.
[b]Unknown cases were excluded.
[c]Measured before the start of CRT and subgroups divided by median values.
[d]Measured before the start of CRT.
3D-CRT, three-dimensional conformal radiation therapy; CI, confidence interval; CRT, chemoradiotherapy; DLCO, diffusing capacity of carbon monoxide; DMLR, derived monocyte-to-lymphocyte ratio; dNLR, derived NLR; FEV1, forced expiration volume within 1 second; FVC, forced vital capacity; IMRT, intensity-modulated radiotherapy; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RP, radiation pneumonitis; RT, radiotherapy.

their tests (42% versus 26%) were higher than in the PACIFIC trial, and this is a limitation of this real-world retrospective study. Second, although the diagnosis of RP and immune-mediated pneumonitis was determined by the investigators' assessments, differentiation between those categories might have been incomplete. In

Table 4. Correlation Between the PBC Count and the Development of irAEs After Durvalumab Treatment

Variables	No irAE	irAE	*p*	Univariate OR (95% CI)	*p*	Multivariate OR (95% CI)	*p*
NLR C1[a] ($n = 139$)					0.096		0.908
≤3.7	51 (55.4)	19 (40.4)	0.094	1 (reference)		1 (reference)	
>3.7	41 (44.6)	28 (59.6)		1.83 (0.90-3.74)		1.05 (0.43-2.59)	
dNLR C1[a] ($n = 140$)					0.013		0.216
>0.7	69 (75.0)	26 (54.2)	0.012	1 (reference)		1 (reference)	
≤0.7	23 (25.0)	22 (45.8)		2.54 (1.21-5.31)		1.69 (0.74-3.90)	
PLR C1[a] ($n = 140$)					0.075		0.728
≤279.1	46 (50.0)	16 (34.0)	0.073	1 (reference)		1 (reference)	
>279.1	46 (50.0)	31 (66.0)		1.94 (0.94-4.02)		0.83 (0.29-2.37)	
dMLR C1[a] ($n = 139$)					0.011		0.011
≤0.7	40 (43.5)	10 (21.3)	0.010	1 (reference)		1 (reference)	
>0.7	52 (58.4)	37 (78.7)		2.85 (1.27-6.41)		2.85 (1.27-6.41)	

Note. Values are presented as numbers (%).
[a]Measured before the first cycle of durvalumab.
CI, confidence interval; dMLR, derived monocyte-to-lymphocyte ratio; dNLR, derived NLR; irAE, immune-related adverse event; NLR, neutrophil-to-lymphocyte ratio; PBC, peripheral blood cell; PLR, platelet-to-lymphocyte ratio.

the present study, ten of 57 patients with RP had irAEs and three of 10 irAEs were RP. Finally, the pretreatment PBC counts can be affected by various conditions, such as infection, comorbidities, and prior chemotherapy or RT. Therefore, the cutoff values for blood-based biomarkers need to be verified in a larger cohort.

In conclusion, the PACIFIC-KR trial, which is the first multicenter study with RWD regarding DC conducted in South Korea, revealed longer rwPFS and OS than those reported in the PACIFIC trial and a tolerable safety profile of DC after completion of CRT in patients with unresectable stage III NSCLC. A favorable rwPFS was observed regardless of age, prior CRT sequence, driver mutation, and duration from the last RT to DC. This RWE supports the continued use of the PACIFIC regimen (DC after CRT) as the standard of care for patients with unresectable stage III NSCLC. This study revealed that several pretreatment blood-based biomarkers, especially monocyte-related parameters (dMLR), were associated with the development of severe RP and irAEs even before the initiation of CRT. These findings could provide valuable insights into the clinical vigilance and management of treatment-related AEs. Future prospective studies with larger cohorts are warranted to verify the clinical significance of blood-based biomarkers and to explore the predictive potential of the MLR in patients treated with CRT and ICIs.

CRediT Authorship Contribution Statement

Cheol-Kyu Park: Data curation, Formal analysis, Methodology, Software, Visualization, Writing—original draft.

In-Jae Oh: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Software, Visualization.

Cheol-Kyu Park, Hyung-Joo Oh, Young-Chul Kim, Yong-Hyub Kim, Sung-Ja Ahn, Won Gi Jeong, Jeong Yeop Lee, Jae Cheol Lee, Chang Min Choi, Wonjun Ji, Si Yeol Song, Juwhan Choi, Sung Yong Lee, Hakyoung Kim, Shin Yup Lee, Jongmoo Park, Seong Hoon Yoon, Ji Hyeon Joo, In-Jae Oh: Investigation, Resources, Supervision, Validation, Writing—review and editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2023.04.008.

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