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ARTICLE

Clinical Studies

Association of immune-related adverse events with durvalumab efficacy after chemoradiotherapy in patients with unresectable Stage III non-small cell lung cancer

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BACKGROUND: Immune-related adverse events (irAEs) have been found to predict PD-L1 inhibitor efficacy in metastatic NSCLC. However, the relation of irAEs to clinical outcome for nonmetastatic NSCLC has remained unknown.
METHODS: In this multicenter prospective study of Stage III NSCLC treated with PACIFIC regimen, the relation of irAEs to PFS was evaluated by 8-week landmark analysis to minimise lead-time bias as well as by multivariable analysis adjusted for baseline factors. irAEs were categorised as mild or nonmild according to whether they were treated with systemic steroid.
RESULTS: Median PFS was 16.0 months, not reached, and 9.7 months for patients without (85 cases) or with mild (21 cases) or nonmild (21 cases) irAEs, respectively. Multivariable analysis indicated that nonmild irAEs were associated with poor PFS, with HRs of 3.86 (95% CI, 1.31–11.38) compared with no irAEs and 11.58 (95% CI, 2.11–63.63) compared with mild irAEs. This pattern was consistent after irAE grade, the number of durvalumab doses and immune profiles (PD-L1 score, $CD8^+$ tumour-infiltrating lymphocyte density, and tumour mutation burden) were taken into consideration.
CONCLUSIONS: The development of mild irAEs might predict a better survival outcome, whereas immunosuppressive steroid–treated irAEs were associated with a worse outcome, regardless of baseline clinical and immune profiles.

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BACKGROUND

Immune checkpoint inhibitors (ICIs) such as antibodies to programmed cell death-1 (PD-1) or to its ligand PD-L1 have become a cornerstone in the treatment of solid malignancies [1]. ICI treatment achieves long-term disease control in some patients, even those with tumours at an advanced stage, by promoting adaptive immunity [1]. However, this immune-related mode of action is often associated with the development of immune-related adverse events (irAEs) with clinicopathologic features reminiscent of autoimmune disease [2–5]. Evidence has suggested that the development of irAEs is associated with ICI efficacy for metastatic malignancies [3–5]. Although the underlying mechanism remains ill defined, a better understanding of this association would be expected to improve daily clinical practice [3–5].

A direct relation between irAEs and ICI efficacy has been well described for non-small cell lung cancer (NSCLC). With the use of landmark analysis, we previously showed that the early occurrence of irAEs was associated with a better survival outcome in patients with Stage IV NSCLC treated with the PD-1 inhibitor

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nivolumab [6], with subsequent studies obtaining similar results [7, 8]. Even patients with NSCLC at earlier stages are now becoming potential targets of ICI therapy [9], but the relation of irAEs to clinical outcome in such patients remains poorly investigated. In particular, the impact of irAEs on survival outcome in the context of multimodality treatment involving radiotherapy and cytotoxic chemotherapy in addition to ICI therapy requires clarification. The PACIFIC regimen, which comprises consolidation with the PD-L1 inhibitor durvalumab following definitive concurrent chemoradiotherapy (dCCRT), has become a dominant standard of care for Stage III NSCLC [10]. However, this regimen is associated with the development of pneumonitis as a serious irAE requiring steroid treatment, likely as a result of the preceding intensive thoracic radiotherapy [11–14]. Given that a study of Stage IV NSCLC suggested that concomitant administration of immunosuppressive steroid treatment might compromise ICI efficacy [15], this distinctive toxicity profile of the PACIFIC regimen raises doubt as to a potential survival advantage of irAE development in this context. In addition, the relation of baseline clinical features to irAE development remains unclear in this setting.

Given this background, we have now assessed the relation between irAEs and survival outcome in patients with Stage III NSCLC treated with the PACIFIC regimen in a nationwide multi-institutional prospective observational study (WJOG11518L/SUBMARINE). We adopted multiple landmark analyses to minimise immortal lead-time bias caused by the time-dependent nature of irAE development [16]. In addition, the relation of irAE development to baseline clinicopathologic features as well as to immune profiles was also interrogated.

METHODS

Study design

WJOG11518L/SUBMARINE is a multi-institutional prospective observational study (trial identifier, UMIN000035916) conducted at 41 sites of West Japan Oncology Group (WJOG). It was performed in accordance with the protocol and the Declaration of Helsinki. The full protocol and informed consent form were approved by the ethics committee of each institution. The required sample size was calculated as 129 patients in order to ensure that the lower bound of the 95% confidence interval (CI) for the 1-year progression-free survival (PFS) rate would be >47%, assuming that the 1-year PFS rate for durvalumab would be 56% on the basis of the PACIFIC trial data [17]. The final planned sample size was 135 patients, taking into account potential dropouts and withdrawals. The primary objective of the study was to evaluate the association of tumour microenvironment profiles with treatment outcome in order to explore mechanisms of resistance to the PACIFIC regimen, with this analysis being published separately [18]. The data for and irAE profiles collected for a secondary objective of the WJOG11518L/SUBMARINE study are presented here. A total of 142 patients who provided written consent before study entry was prospectively enrolled between April 2019 and February 2020. Eligibility criteria included an age of ≥20 years, a pathological diagnosis of NSCLC according to cytology or histology, a disease stage of unresectable Stage III according to the 8th edition of the TNM classification, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, treatment history of dCCRT with two cycles of platinum-based chemotherapy and thoracic radiotherapy of ≥54 Gy for the Stage III NSCLC, and no evidence of disease progression after dCCRT. Preplanned durvalumab treatment (10 mg/kg every 2 weeks for up to 1 year) in clinical practice within 42 days after the last dose of radiation as well as consent to provision of archival tumour tissue were also necessary before study entry. Individuals presenting with postoperative recurrence and those with a history of PD-1 inhibitor or PD-L1 inhibitor treatment were not eligible. Patients were treated with durvalumab in clinical practice, with a minimum follow-up period of 1 year. Radiological assessment of tumour response every 8 weeks was recommended. Data regarding clinicopathologic features and treatment history were prospectively extracted from medical records by investigators at each institution before any analyses and were independently managed by a central data centre (WJOG).

Data collection

Three patients did not receive durvalumab treatment because they experienced disease progression or severe pneumonitis after study entry. For the remaining 139 patients who received at least one dose of durvalumab, clinical features and irAE data were obtained as a safety-analysis set (SAS) as preplanned in the study protocol. Durvalumab efficacy including survival outcome was evaluated for 135 patients as a full-analysis set, from which 4 patients were omitted because they turned out not to meet all eligibility criteria at the time of data collection (2 patients received only one cycle of platinum-based chemotherapy, 1 patient received <54 Gy of radiotherapy, and 1 patient did not have a sufficient amount of tumour tissue), according to the preplanned definition in the study protocol.

The response was assessed by investigators according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. PFS was defined as the time from enrollment to clinical or radiographic progression or death from any cause; patients without documented clinical or radiographic disease progression or who were still alive were censored on the date of the last radiological follow-up. Overall survival (OS) was measured from enrollment to death from any cause; patients who were still alive were censored on the date of the last follow-up.

irAEs were predefined as adverse events with a potential immunologic basis that required frequent monitoring and potential intervention with immune suppression, including topical corticosteroid therapy as well as systemic corticosteroid therapy or hormone replacement [6]. As predefined in the study protocol, asymptomatic and transient abnormalities of laboratory findings—such as increases in thyroid-stimulating hormone, aspartate aminotransferase, or alanine aminotransferase levels that resolved spontaneously without intervention—were not regarded as irAEs [6]. Adverse events that occurred >30 days after the last dose of durvalumab therapy were also not counted, according to the predesigned protocol. All adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and the American Society of Clinical Oncology Clinical Practice Guideline [19]. All irAEs were classified into two subgroups (mild or nonmild) according to whether immunosuppressive systemic steroid therapy was administered for their treatment, given that previous studies have suggested a reduction in ICI efficacy in association with such steroid therapy [15, 20]. The irAEs that were not treated with systemic steroid or those treated with physiological steroid replacement for adrenal insufficiency were thus defined as mild irAEs.

Archival formalin-fixed, paraffin-embedded (FFPE) tumour tissue obtained before dCCRT was subjected to immunohistochemistry (IHC) and targeted next-generation sequencing (NGS). In addition, where available, peripheral blood mononuclear cells were obtained within 2 weeks before or 4–6 weeks after the start of durvalumab treatment for flow cytometry (FCM) analysis.

IHC

Sections of FFPE tumour tissue (thickness of 4 μm) were depleted of paraffin and stained with monoclonal antibodies to PD-L1 (Ventana PD-L1 [SP263] assay, Roche Diagnostics), to CD8 (clone C8/144B, 1:200 dilution, Agilent Technologies), and to forkhead box P3 (FOXP3) (clone 236A/E7, 1:100, Abcam) with the use of an autostainer (BenchMark XT [Roche Diagnostics] or Bond III [Leica Biosystems]). Staining for PD-L1 was performed according to the instructions of the assay manufacturer and that for CD8 and FOXP3 according to our previous studies [21–23]. The immunostained sections were scanned with a NanoZoomer instrument (Hamamatsu Photonics) at ×40 magnification, and were reviewed by three board-certified pathologists who were blinded to the clinical data. Sections for which the number of cancer cells was <100 were excluded from final analyses.

Evaluation of IHC staining was performed in accordance with our previous studies [21–23]. The percentage of cancer cells positive for PD-L1 at any intensity was determined as the tumour proportion score (TPS). Tumour-infiltrating lymphocytes (TILs) were evaluated on the basis of staining for CD8 or FOXP3 (for regulatory T cells [Tregs]). The number of TILs was determined as the absolute count of cells positive for each marker at any staining intensity in intratumoral regions. At least one and a maximum of five fields of tumour regions were randomly chosen for each TIL count. The TIL density in the tumour was then calculated as the number of TILs divided by the sum of the area (mm^2) of the viewed fields. Expression of PD-L1 and CD8 was determined on the basis of cytomembranous staining, whereas that of FOXP3 was determined on the basis of nuclear staining. Tissue obtained by transbronchial needle

aspiration and cell block specimens were excluded from the analysis of TIL counts in order to avoid contamination by non-tumour-infiltrating immune cells.

Targeted NGS

Genomic DNA was extracted from the tumour lesions of FFPE tissue with an AllPrep DNA/RNA FFPE Kit (Qiagen). The quality and quantity of the DNA were determined with the use of a PicoGreen dsDNA Assay Kit (Thermo Fisher Scientific). At least 5 ng of total DNA from tissue samples with a cancer cell content of ≥5% were analysed. Tumour mutation burden (TMB [mutations/Mb]) was determined with the Oncomine Tumour Mutation Load Assay (Thermo Fisher Scientific) and Ion Reporter Software version 5.10 (Thermo Fisher Scientific) as the number of nonsynonymous mutations including single nucleotide variants and frameshift mutations [24, 25]. Germline mutations were excluded with the use of the Human Genetic Variation Database (http://www.genome.med.kyoto-u.ac.jp/SnpDB). Samples with a deamination score (the number of C-to-T or G-to-A variant calls with an allele frequency of ≤15%) of ≥15 were removed from final analyses to avoid artifactual variant calls due to formalin fixation.

Flow cytometry

Whole blood (16 ml) obtained within 2 weeks before or 4–6 weeks after the start of durvalumab treatment was processed for isolation of peripheral blood mononuclear cells (PBMCs) with a CPT vacutainer (BD Biosciences). PBMCs were stored at −80 °C or in a liquid nitrogen tank until analysis.

Frozen PBMCs were thawed, washed with and then incubated for 45 min at 37 °C in RPMI-1640 medium supplemented with 10% foetal bovine serum (FBS), washed with ice-cold phosphate-buffered saline, stained with the use of a Zombie UV Fixable Viability Kit (BioLegend) at a 1:500 dilution for 5 min at room temperature, and treated with Fc Block Human (Fc1, BD Pharmingen) at a 1:40 dilution in Staining Buffer containing FBS (BD Biosciences) for 10 min at 4 °C. The cells were then stained with antibodies to CD3 (BioLegend 317332, 1:40 dilution), to CD4 (BioLegend 317438, 1:100), to CD8 (BioLegend 301046, 1:100), and to CD45RA (BioLegend 304138, 1.5:100). They were fixed and permeabilized with the use of a FOXP3 Transcription Factor Staining Buffer Set (eBioscience) before staining with antibodies to FOXP3 (eBioscience 12-4777-42, 2.5:100). FCM was performed with an LSRFortessa X-20 instrument (BD Biosciences), and data were analysed with FlowJo software (BD Biosciences). Fluorescence minus one (FMO) controls, and corresponding isotype controls were used as negative controls [26]. Effector Tregs ($CD3^+CD8^-CD4^+CD45RA^-FOXP3^+$ cells) were considered as circulating Tregs in this study [27]. For all readouts, nonsinglet cells and dead cells were removed beforehand. Samples were excluded from the final analysis if the total number of live cells was <5000.

Statistical analysis

Fisher's exact test was applied to compare categorical variables, and continuous variables were compared with the Kruskal–Wallis test or Steel–Dwass test for multiple comparisons. Logistic regression models were applied to calculate crude and adjusted odds ratios. Differences in PFS or OS curves constructed by the Kaplan–Meier method were assessed with the log-rank test. Univariable and multivariable Cox proportional hazards regression models were adopted to determine hazard ratios (HRs). Age (≥75 versus <75 years), sex (male versus female), ECOG PS (1 versus 0), mutational status (positive for activating *EGFR* mutations or *ALK* fusion genes versus negative for these gene alterations), time from last radiation exposure to first durvalumab dose (>14 versus ≤14 days), smoking history (current or former smoker versus never-smoker), histology (squamous versus non-squamous), Stage (IIIB or IIIC versus IIIA), derived neutrophil-to-lymphocyte ratio (dNLR, >3 versus ≤3), serum C-reactive protein (>1.0 versus ≤1.0 mg/dl), serum albumin (≤3.5 versus >3.5 g/dl), and response to preceding dCCRT (stable disease versus partial response or complete response) were predefined as covariables for multivariable analysis of survival outcome according to predesigned criteria in the study protocol [18]. Cutoff values for the clinical factors were predefined before any analyses. The dNLR was calculated as absolute neutrophil count/(white blood cell count minus absolute neutrophil count), as described previously [28].

The association of irAEs with survival taking into account the time-related bias was evaluated with an 8-week landmark analysis including only patients who achieved disease control or those who were alive at 56 days after enrollment for PFS ($n = 127$) or OS ($n = 133$), respectively. Eight weeks were chosen as the primary landmark time point because the first formal evaluation of tumour response was expected to be performed around 8 weeks after the onset of treatment (see above), similar to the case for our previous study of Stage IV NSCLC [6]. The PFS and OS analyses were performed on the basis of this landmark assessment of irAEs that developed within the first 8 weeks. Any irAE that occurred after the landmark date was therefore not counted in the corresponding landmark-based analysis (patients were thus assigned to the group without irAEs if they developed an irAE only after the landmark date). We carried out the landmark analysis according to the development of any irAE. The same landmark analyses were also performed according to severities such as the use of systemic steroid treatment (mild vs nonmild) or CTCAE grades (≤2 versus ≥3), because whether such irAE severities are associated with survival outcomes was a primary clinical question. In addition, 6-week and 10-week landmark analyses were performed as complementary evaluations in the same manner. Missing data were not imputed. All *P* values were based on the two-tailed hypothesis. Given that this investigation was originally designed as an exploratory biomarker study, no threshold *P* value was defined for statistical significance. Statistical analysis was performed with SAS version 9.4 (SAS Institute), JMP software version 14.3.0 (SAS Institute), or GraphPad Prism 9.0.1 (GraphPad Software).

RESULTS

Patient characteristics and irAE profiles

The baseline clinical features of the 139 patients in the SAS are shown in Supplementary Table 1. Thirty-one patients (22%) were aged ≥75 years at the onset of durvalumab treatment. Preexisting autoimmune disease and preexisting pulmonary disease were apparent for 7 patients (5%) and 16 patients (12%), respectively. Twenty-one patients (15%) developed radiation pneumonitis before durvalumab treatment, with all cases being of grade 1 with the exception of one case of grade 2.

The median follow-up time was 15.6 months in the SAS. The irAE profiles in the SAS are shown in Table 1. At least one irAE was observed in 81 patients (58%), including 23 patients (17%) who developed multiple irAEs. The median time to onset of the first irAE was 57 days. The most common irAE type was pulmonary, which was apparent in 38 patients (27%), followed by endocrine (17%) and skin (14%). Thirty-six patients (26%) developed irAEs that were treated with systemic corticosteroid (nonmild irAEs), most of which were pneumonitis. Pneumonitis as an irAE resulted in treatment-related death in one patient.

Association of irAE development with durvalumab efficacy

To minimise the immortal time bias associated with the time-dependent nature of irAE development during the treatment course, we performed an 8-week landmark analysis for evaluation of the association of irAE development with the efficacy of the PACIFIC regimen. Such analysis of PFS according to the development of any irAE did not show a clear association, with a HR of 1.22 (95% CI, 0.71–2.09). However, similar analysis revealed that median PFS was longer in patients with mild irAEs and shorter in those with nonmild irAEs than in those without any irAE (median, not reached [NR] vs. 9.7 months vs. 16.0 months, respectively), and this pattern was confirmed by multivariable analysis (Fig. 1a, b). Additional 6-week and 10-week landmark analyses also yielded similar results (Supplementary Fig. 1). Of note, the relation between PFS and irAE development according to event severity was less clear when such severity was determined solely on the basis of CTCAE grade (≤2 vs. ≥3) (Supplementary Fig. 2A, B). Given that some irAEs of grade 2 were treated with systemic steroid therapy, however, a further 8-week landmark analysis was performed only for patients with irAEs of grade 2 according to the administration of such treatment. This analysis showed that PFS was clearly better for the patients not receiving systemic steroid treatment (HR, 0.09 [95% CI, 0.01–0.70]) (Fig. 1c). We further noted that 13 patients initiated systemic steroid treatment during durvalumab therapy for non-irAE disease—all of which were non-irAE radiation pneumonitis—in the 106 patients without

Table 1. Immune-related adverse events (irAEs) according to category and grade in the safety-analysis set.

Category	No. of patients (%)[a]					Median (range) days to onset of first irAE
	Total ($n = 139$)	Grade 1 or 2	Grade 3 or 4	Grade 5	Systemic steroid therapy[b]	
Any	81 (58)	65 (47)	15 (11)	1 (1)	36 (26)	57 (1–358)
Skin[c]	20 (14)	20 (14)				67.5 (8–199)
Rash	12 (9)	12 (9)				
Pruritus	12 (9)	12 (9)				
Pneumonitis	38 (27)	28 (20)	9 (7)	1 (1)	30 (22)	49.5 (1–358)
Endocrine	23 (17)	22 (16)	1 (1)		2 (1)	91 (17–338)
Thyroiditis	21 (15)	21 (15)			1 (1)	
Adrenal insufficiency	2 (1)	2 (1)			1 (1)	
Hypophysitis	1 (1)	1 (1)				
Hyperglycaemia	1 (1)		1 (1)			
Gastrointestinal	7 (5)	5 (4)	2 (1)		2 (1)	71 (2–252)
Stomatitis	1 (1)	1 (1)				
Diarrhoea/colitis	6 (4)	4 (3)	2 (1)		2 (1)	
Hepatobiliary	4 (4)	3 (2)	1 (1)		2 (1)	68 (4–404)[d]
Hepatitis	4 (4)	3 (2)	1 (1)		2 (1)	
Neurological	1 (1)	1 (1)				57 (57–57)
Peripheral neuropathy	1 (1)	1 (1)				
Other	19 (14)	17 (12)	2 (1)		4 (3)	15 (1–251)
Fever	8 (6)	8 (6)			2 (1)	
Fatigue	7 (5)	7 (5)				
Immune thrombocytopenic purpura	1 (1)	1 (1)				
Arthritis	1 (1)	1 (1)				
Infusion reaction	1 (1)	1 (1)				
Miscellaneous	3 (2)	1 (1)	2 (1)		2 (1)	

[a]Percentages may add up to >100 because 23 patients (17%) experienced more than one event.
[b]Physiological replacement for adrenal insufficiency not included.
[c]Thirteen patients were treated with topical corticosteroid therapy.
[d]One patient experienced a first irAE (pneumonitis) at day 22 and presented with hepatitis at day 404.

nonmild irAE in the 8-week landmark analysis, where such systemic steroid treatment was also associated with early disease progression (HR, 1.75 [95% CI, 0.78–3.95]; median PFS, 9.0 [5.6–NR] months vs 17.0 [14.9–NR] months).

We next examined whether this apparently negative effect of nonmild irAEs on survival outcome might be attributable to discontinuation of durvalumab during systemic steroid treatment. Patients with nonmild irAEs in 8-week landmark analysis of PFS indeed received fewer doses of durvalumab than did those with mild irAEs or those without any irAE (median of 3 vs. 19 vs. 16, respectively) (Supplementary Fig. 2C), consistent with clinical practice guidelines to withhold durvalumab administration while patients undergo systemic steroid treatment for irAEs [19, 29]. Nevertheless, nonmild irAEs remained strongly associated with a poor PFS even when the number of durvalumab doses was adjusted for in multivariable analysis, whereas patients with mild irAEs still showed a longer PFS (Fig. 1d).

We also performed 8-week landmark analysis of OS, which revealed a tendency for OS to be shorter in patients with than in those without any irAE (HR, 1.54 [95% CI, 0.66–3.57]). Again, however, nonmild irAEs were associated with a shorter OS, whereas mild irAEs were not (Fig. 1e). Indeed, multivariable analysis revealed a strong association of nonmild irAEs with a shorter OS in comparison with patients with no or mild irAEs combined (HR, 15.88 [95% CI, 2.54–99.36]).

Overall, our findings thus suggested that the development of mild irAEs may be predictive of better durvalumab efficacy, whereas that of nonmild irAEs was strongly associated with a worse survival outcome, possibly as a result of a negative impact of systemic steroid therapy on durvalumab efficacy.

Relation between clinicopathologic factors and irAE development

Patient characteristics according to the development of irAEs for the 8-week landmark PFS analysis cohort are shown in Table 2. Logistic regression analysis indicated that no baseline clinical feature was clearly associated with irAE development (Supplementary Fig. 3). Of note, preexisting autoimmune disease did not increase the risk for the development of any irAE or nonmild irAE. Data for basic features of the tumour microenvironment (TME) such as PD-L1 TPS, $CD8^+$ TIL density, and TMB were available, allowing us to evaluate the relation of these features to irAE development (Supplementary Fig. 4A, B). Intratumoral inflammation characterised by PD-L1 TPS or $CD8^+$ TIL density was also not clearly associated with early irAE development, whereas a higher antigenicity of cancer cells as predicted by a higher TMB was negatively associated with irAE development. Adjusted odds ratios for multivariable logistic regression analysis are shown in Fig. 2a, b. The pattern of association of irAEs with PFS persisted even if these TME features were adopted for multivariable analysis (Fig. 2c and

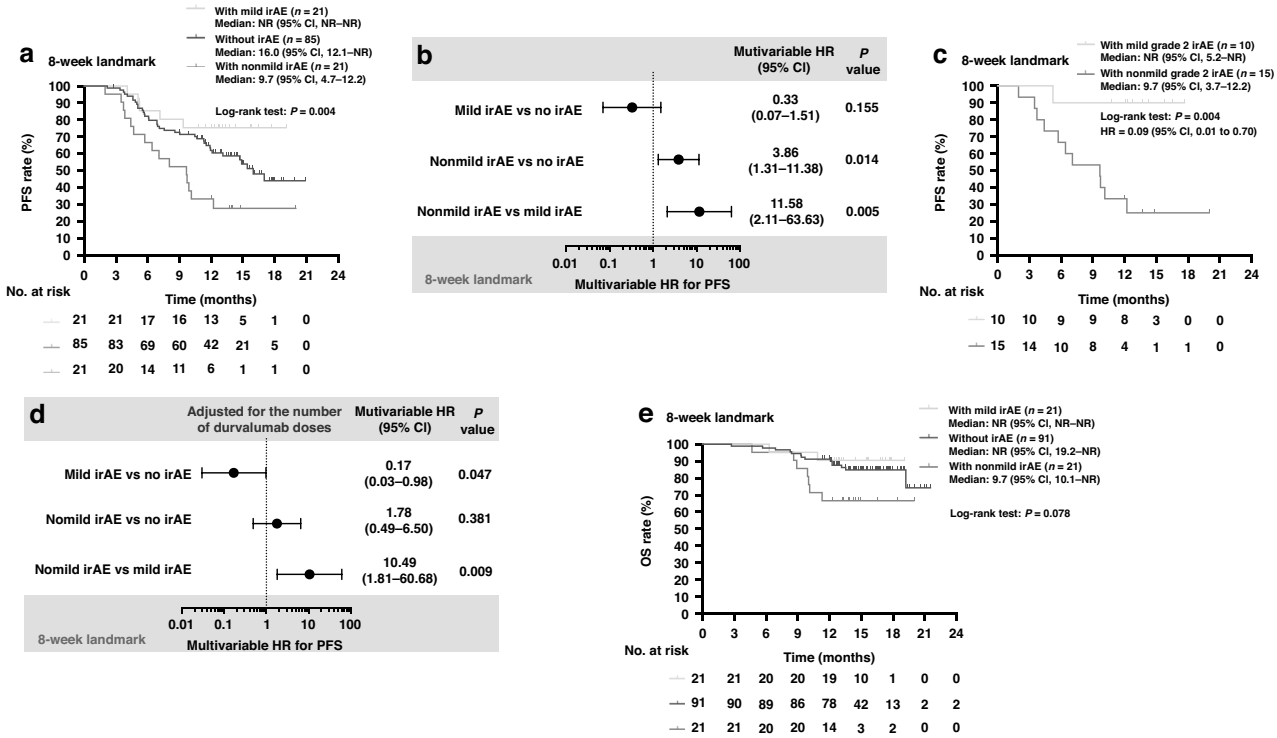

Fig. 1 Survival outcome according to immune-related adverse event (irAE) profiles in 8-week landmark analysis. a Kaplan–Meier curves of progression-free survival (PFS) in patients with mild, nonmild, or no irAEs. Vertical bars denote censoring in all survival curves. NR not reached, CI confidence interval. **b** Forest plot showing adjusted hazard ratios (HRs) for PFS estimated by multivariable Cox hazard regression models based on irAE profiles. Adopted covariables were predetermined as described in METHODS. **c** Kaplan–Meier curves of PFS in patients with irAEs of grade 2 according to whether immunosuppressive systemic steroid therapy was administered (nonmild irAEs) or not (mild irAEs). **d** Forest plot showing adjusted HRs for PFS estimated by multivariable Cox hazard regression models based on irAE profiles. Adopted covariables included the number of durvalumab doses (as a continuous variable) in addition to those predetermined as described in METHODS. **e** Kaplan–Meier curves of overall survival (OS) in patients with mild, nonmild or no irAEs.

Supplementary Fig. 4C, D). The relation of Tregs to irAE development was also evaluated, but no association was apparent for either intratumoral or circulating Tregs (Fig. 2d and Supplementary Fig. 5).

In addition, several respiratory clinical factors of interest were investigated for their potential relation to nonmild pulmonary irAEs (Fig. 2e), given that pneumonitis accounted for most nonmild irAEs. Radiation type (intensity-modulated radiation therapy [IMRT] vs. non-IMRT) and field (involved-field radiation therapy [IFRT] vs. non-IFRT) were not associated with the early development of nonmild pneumonitis as an irAE. Preexistence of radiation pneumonitis also did not increase the risk of early nonmild pneumonitis as an irAE. Even a patient with radiation pneumonitis of grade 2 that developed before the start of durvalumab treatment did not experience pneumonitis as an irAE during durvalumab therapy. However, this patient experienced early tumour relapse at 2.3 months after the first dose of durvalumab despite a definitive tumour response to preceding dCCRT. Note that the patient did receive systemic steroid treatment for the preexisting radiation pneumonitis at the time of the first dose of durvalumab.

irAE profiles in patients with preexisting autoimmune disease

The safety of PD-1/PD-L1 inhibitors in patients with preexisting autoimmune disease remains a clinical concern, particularly for those who also receive aggressive therapy such as dCCRT. We therefore further probed treatment outcome in the seven patients with preexisting autoimmune disease in our study. The irAE profiles, survival outcome, and clinical background of these patients are summarised in Table 3. Among these seven patients, one individual experienced rheumatoid arthritis that previously required methotrexate treatment, one had active rheumatoid arthritis, one experienced idiopathic thrombocytopenia previously requiring systemic steroid therapy, and one had active psoriasis. Only one patient (with a history of active hypothyroidism) experienced a flare of the preexisting autoimmune disease. Two patients developed nonmild irAEs that appeared to be unrelated to their preexisting autoimmune disease. Of note, however, all seven patients were alive at the end of follow-up for the present investigation, indicating that irAEs were controllable and not life-threatening for these individuals.

DISCUSSION

Knowledge of toxicity profiles of anticancer treatment is essential for best clinical practice in oncology. However, recent advances in immunotherapy involving multiple treatment modalities have complicated patient care [30]. In our nationwide study, we prospectively collected real-world treatment data for patients with Stage III NSCLC who received the PD-L1 inhibitor durvalumab after dCCRT, allowing us to dissect the relations among baseline clinical features, irAEs, and survival outcome in this complex treatment setting. Our results indicate that the early development of mild irAEs was associated with a better survival outcome, whereas that of irAEs requiring immunosuppressive steroid therapy was associated with a worse survival outcome. The impact of irAE development on survival outcome thus appeared to differ according to irAE profile. We also investigated how the clinical background of patients might be related to irAE development, with such insight being likely to inform the selection of patients for treatment with the PACIFIC regimen. As far as we are aware, this is the first large multi-institutional study

Table 2. Characteristics of the study cohort for 8-week landmark analysis of PFS ($n = 127$).

Characteristic	No. of patients (%)[a]			
	Without irAE ($n = 85$)	With mild irAE ($n = 21$)	With nonmild irAE ($n = 21$)	*P* value[b]
Age, years				
Median (range)	69 (44–82)	69 (54–83)	71 (55–82)	0.761]
≥75	17 (20)	3 (14)	7 (33)	0.306
<75	68 (80)	18 (86)	14 (67)	
Sex				
Male	67 (79)	13 (62)	14 (67)	0.214
Female	18 (21)	8 (38)	7 (33)	
ECOG PS				
0	49 (58)	11 (52)	11 (52)	0.895
1	36 (42)	10 (48)	10 (48)	
Smoking history[c]				
Never	8 (9)	3 (15)	1 (5)	0.470
Current or former	77 (91)	17 (85)	20 (95)	
Histology				
Squamous	38 (45)	7 (33)	8 (38)	0.617
Nonsquamous	47 (55)	14 (67)	13 (62)	
Stage				
IIIA	38 (45)	8 (38)	10 (48)	0.635
IIIB	40 (47)	9 (43)	10 (48)	
IIIC	7 (8)	4 (19)	1 (5)	
EGFR mutation or *ALK* fusion gene				
Positive	11 (13)	0 (0)	2 (10)	0.348
Negative	41 (48)	11 (52)	9 (43)	
Unknown	33 (39)	10 (48)	10 (48)	
Preexisting autoimmune disease				
Yes	4 (5)	1 (5)	1 (5)	1.000
No	81 (95)	20 (95)	20 (95)	
Preexisting pulmonary disease				
Yes	7 (8)	2 (10)	3 (14)	0.668
No	78 (92)	19 (90)	18 (86)	
Serum albumin level, mg/dl				
Median (range)	3.8 (2.8–4.7)	3.7 (2.7–4.2)	3.6 (3.0–4.4)	0.180]
Not decreased (>3.5)	58 (68)	11 (52)	11 (52)	0.207
Decreased (≤3.5)	27 (32)	10 (48)	10 (48)	
Serum C-reactive protein, mg/dl				
Median (range)	0.32 (0.02–6.51)	0.17 (0.04–7.99)	0.68 (0.06–4.78)	0.089]
Elevated (>1.0)	20 (24)	3 (14)	8 (38)	0.249
Not elevated (≤1.0)	64 (76)	18 (86)	13 (62)	
Radiation pneumonitis before durvalumab				
Yes	12 (14)	3 (14)	4 (19)	0.817
No	73 (86)	18 (86)	17 (81)	
Radiation dose, Gy				
Median (range)	60 (60–70)	60 (56–60)	60 (60–66)	0.760]
>60	8 (9)	0 (0)	3 (14)	0.259
≤60	77 (91)	21 (100)	18 (86)	
Radiation type				
IMRT	18 (21)	4 (19)	4 (19)	1.000
Not IMRT	67 (79)	17 (81)	17 (81)	
Radiation field				
IFRT	25 (29)	3 (14)	4 (19)	0.331
Not IFRT	60 (71)	18 (86)	17 (81)	
Last radiation to first durvalumab				
≤14 days	42 (49)	9 (43)	11 (52)	0.866
>14 days	43 (51)	12 (57)	10 (48)	

Table 2. continued

Characteristic	No. of patients (%)[a]			
	Without irAE ($n = 85$)	With mild irAE ($n = 21$)	With nonmild irAE ($n = 21$)	*P* value[b]
Cytotoxic chemotherapy regimen				
Cisplatin-based	59 (69)	15 (71)	14 (67)	0.959
Carboplatin-based	26 (31)	6 (29)	7 (33)	
Best response to dCCRT				
Complete response	2 (2)	0 (0)	0 (0)	0.817
Partial response	55 (65)	15 (71)	13 (62)	
Stable disease	28 (33)	6 (29)	8 (38)	
irAE grade				
Grade 1		10 (48)	0 (0)	0.001
Grade 2		10 (48)	15 (71)	0.208
Grade 3		1 (5)	6 (29)	0.093
Grade ≥4		0 (0)	0 (0)	
irAE category[d]				
Skin		6 (29)	0 (0)	0.021
Pneumonitis		3 (14)	19 (91)	<0.001
Endocrine		7 (33)	1 (5)	0.045
Gastrointestinal		2 (10)		0.488
Hepatobiliary		2 (10)		0.488
Neurological		1 (5)		>0.999
Other		7 (33)	2 (10)	0.130
PD-L1 TPS				
Median (range)	0 (0–100)	5 (0–100)	10 (0–95)	0.508
≥1.0	38 (45)	13 (62)	12 (57)	0.304
<1.0	40 (47)	8 (38)	6 (29)	
Unknown[e]	7 (8)	0 (0)	3 (14)	
$CD8^+$ TIL density, cells/mm^2				
Median (range)	41.1 (0.4–223.6)	33.6 (0.4–149)	40.05 (3.2–137.5)	0.666
≥median	31 (37)	6 (29)	8 (38)	0.367
<median	25 (29)	11 (52)	8 (38)	
Unknown[d]	29 (34)	4 (19)	5 (24)	
Tumour mutation burden, muts/Mb				
Median (range)	9.18 (0.84–24.29)	6.67 (1.67–85.04)	4.46 (0.00–14.99)	0.065
≥median	43 (51)	6 (29)	5 (24)	0.023
<median	29 (34)	12 (57)	12 (57)	
Unknown[d]	13 (15)	3 (14)	4 (19)	

PFS progression-free survival, *irAE* immune-related adverse event, *ECOG PS* Eastern Cooperative Oncology Group performance status, *IMRT* intensity-modulated radiation therapy, *IFRT* involved-field radiation therapy, *dCCRT* definitive concurrent chemoradiotherapy, *PD-L1 TPS* programmed cell death-ligand 1 tumour proportion score, *TIL* tumour-infiltrating lymphocyte, *muts* mutations, *Mb* megabase.

[a]Percentages may not add up to 100 because of rounding.

[b]Differences were tested with Fisher's exact test for categorical and nominal variables, or with the Kruskal–Wallis test for continuous variables.

[c]Current smokers were defined as individuals who had smoked ≥100 cigarettes including at least one within the year prior to diagnosis; former smokers as those who had smoked ≥100 cigarettes but had quit >1 year prior to diagnosis; and never-smokers as those who had smoked <100 cigarettes.

[d]Percentages may add up to >100 because of multiple irAEs experienced by the same patients.

[e]Data for PD-L1 TPS, $CD8^+$ TIL density, and tumour mutation burden were not obtained from these patients due to the sample quality criteria (see 'Methods').

to evaluate the association of irAEs with survival outcome for NSCLC patients treated with multimodality immunotherapy, including dCCRT.

Our study was designed to collect irAE data in a prospective manner according to a predetermined definition and thereby to provide solid clinical evidence. Comprehensive irAE profiles for the PACIFIC regimen had not previously been well described for the real-world setting. We found that pneumonitis was the most common irAE, the incidence of which was markedly higher than that for PD-1 inhibitor treatment of Stage IV NSCLC determined in our previous study (27% vs. 4%), which adopted the same irAE definition [6]. This difference was probably due to the preceding intensive thoracic radiotherapy administered for the present cohort [13]. A substantial proportion of patients in the present study thus experienced serious irAEs that required immunosuppressive systemic steroid therapy.

Numerous studies have suggested that irAE development is associated with a better survival outcome in patients with various cancer types treated with PD-1/PD-L1 inhibitors, with this association having received further support from several systematic reviews combined with meta-analyses [7, 16, 31–35]. This association remained apparent even when only studies based on landmark analysis (the reduction in time-related bias resulting in an appropriate loss of statistical power [16]) were selected for meta-analysis [16, 32, 34]. Of note, however, a subgroup analysis for one study suggested that irAEs of higher grade were not

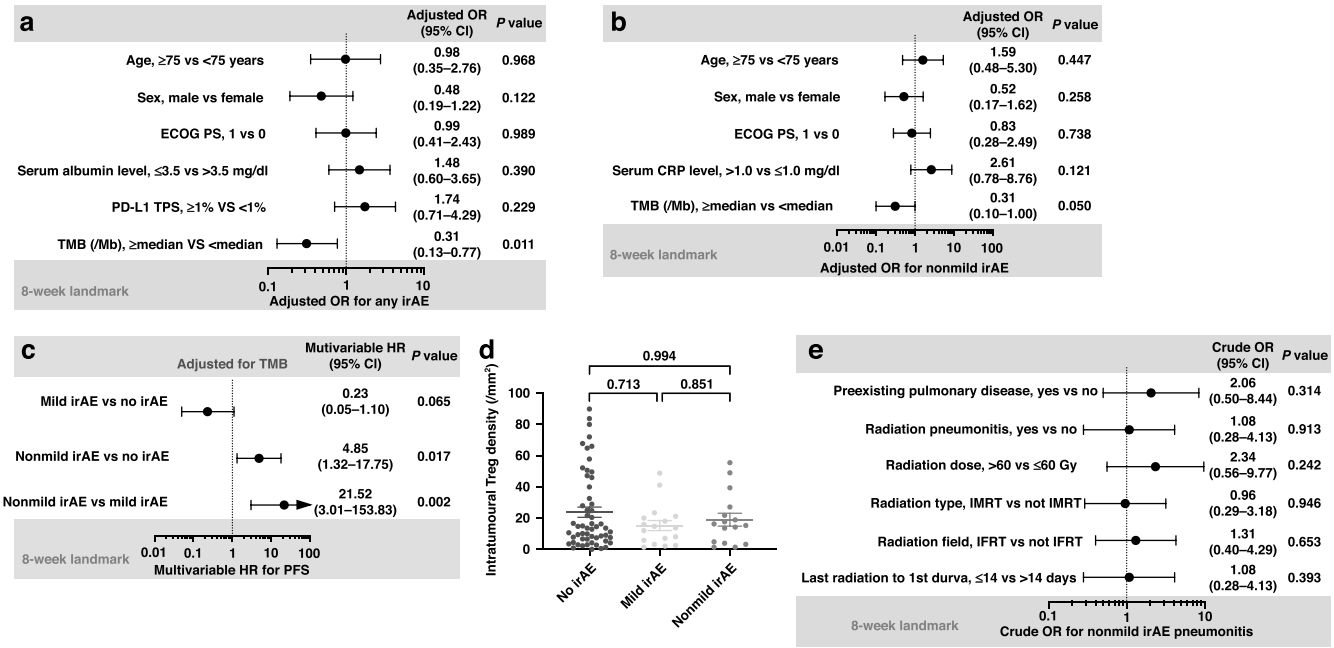

Fig. 2 Relation between the development of immune-related adverse events (irAEs) and baseline clinical features or tumour microenvironment (TME) profiles. a, **b** Forest plots showing adjusted odds ratios (ORs) for the development of any irAE (**a**) or a nonmild irAE (**b**) as estimated by multivariable logistic regression models based on clinical features and TME profiles in the cohort for 8-week landmark analysis of progression-free survival (PFS). Adopted covariables were cardinal clinical factors (age, sex, and Eastern Cooperative Oncology Group performance status [ECOG PS]) as well as factors for which the *P* value for the crude OR was <0.2 (see Supplementary Figs. 3 and 4A, B). See Table 2 for the numbers of patients in individual subgroups. **c** Forest plot showing adjusted hazard ratios (HRs) for PFS estimated by multivariable Cox hazard regression models based on irAE profiles for the 8-week landmark analysis. Adopted covariables included tumour mutation burden (TMB [/Mb], ≥median vs. <median) in addition to those predetermined as described in METHODS. **d** Dot plots for intratumoral regulatory T-cell (Treg) density according to irAE profiles for the 8-week landmark PFS analysis cohort. Each dot represents one patient. The mean and standard error of the mean (SEM) are indicated, and *P* values determined with the Steel–Dwass test are shown above the horizontal lines. **e** Forest plot showing crude ORs for the development of pneumonitis as a nonmild irAE as estimated by logistic regression models based on clinical features for the 8-week landmark PFS analysis cohort. Multivariable analysis was not performed because no variable showed a *P* value of <0.2. See Table 2 for the numbers of patients in individual subgroups. CI confidence interval, CRP C-reactive protein, IMRT intensity-modulated radiation therapy, IFRT involved-field radiation therapy, durva durvalumab.

associated with a better survival outcome [30], consistent with our findings. The reason underlying such a difference between severe and mild irAEs has remained unclear, although several factors have been proposed, including a decline in general condition caused by severe irAEs, a decrease in total drug exposure due to discontinuation of ICI treatment during severe irAEs, and a negative effect of immunosuppressive steroid treatment on ICI-induced immune activation [30]. We addressed this issue by detailed analysis taking these factors into consideration. Subgroup analysis including only patients with irAEs of grade 2 implicated systemic steroid treatment rather than event severity per se as a key determinant of the negative association of nonmild irAEs with survival outcome. In addition, complementary multivariable analysis taking into account the number of durvalumab doses implicated systemic steroid treatment as a contributor to the subsequent poor survival outcome of patients experiencing nonmild irAEs. Of note, these findings were all based on landmark analysis, rendering them robust. Our clinical findings are also consistent with previous experimental studies. A pharmacokinetics study thus indicated that durvalumab is retained in the body at an effective concentration for several months after the last administration of multiple doses [36]. The temporary discontinuation of durvalumab would therefore not be expected to immediately compromise treatment efficacy. Furthermore, a preclinical study revealed that immunosuppressive systemic steroid therapy hampered ICI-induced activation of antitumor T cells [20]. This previous study also suggested that the impact of corticosteroid therapy on T-cell function might be dependent on the affinity of the T-cell receptor (TCR) for antigenic epitopes. The impact of nonmild irAEs on ICI efficacy might therefore vary depending on individual patient characteristics such as cancer type, tumour antigenicity, and T-cell repertoire.

The mechanism underlying the association of early irAE development with ICI efficacy remains unsettled. This association has been attributed to cross-reactivity of antitumor adaptive immunity with self-antigens of normal tissue [5]. Indeed, an individual TCR has been estimated to be reactive with more than a million different epitopes [37], thus possibly allowing tumour-reactive T cells to attack normal tissue, especially after the proliferative burst elicited by PD-1/PD-L1 blockade. This hypothesis suggests that TME profiles that are indirect markers of tumour immunogenicity might be predictive of irAE development. However, we found that neither PD-L1 expression on cancer cells nor $CD8^+$ TIL density was related to the development of early irAEs. A high TMB actually tended to be associated with a low risk of early irAEs, in contrast to previous findings of a positive correlation between TMB and irAE incidence [38, 39]. This discrepancy might be explained by differences in methodology regarding whether to consistently address lead-time bias. Collectively, our results suggest that these clinical biomarkers of tumour response may not be informative for estimation of the risk for irAE development. In addition, the apparent independence of early irAE development from these conventional biomarkers emphasises the usefulness of such irAEs for prediction of ICI efficacy. Tregs are immunosuppressive cells and have been proposed to contribute to prevention of irAEs [5, 27]. However, we found that neither intratumoral nor circulating Tregs were associated with early irAE development. The immunologic

Table 3. Baseline clinical features and treatment outcome for seven patients with preexisting autoimmune disease.

Age (yrs)	PS	SH	AID	AID status	AID treatment	Radiation dose (Gy)	Response to dCCRT	Durvalumab doses	Best response to durvalumab	PFS (mos)	Disease control	OS (mos)	Survival status	irAE	irAE grade	Systemic steroid treatment
60 s	1	Cu	Hypothyroidism	Active	Yes, but uncertain	60	PR	3	PR	17.7	O	17.7	Alive	Thyroiditis	≤2	No
50 s	0	Cu	RA	Inactive	Previously on MTX	60	PR	24	PR	17.0	O	17.1	Alive	Thyroiditis	≤2	No
70 s	0	Fo	Hypothyroidism	Active	Thyroid hormone	60	PR	25	PR	11.7	O	16.6	Alive	Thyroiditis	≤2	No
60 s	1	Fo	RA	Active	Yes, but uncertain	60	PR	2	SD	3.8	P	14.8	Alive	Rash Pneumonitis	≤2 ≥3	No Yes
60 s	1	Ne	ITP	Inactive	Previously on systemic steroid therapy	60	SD	3	PD	1.6	P	14.3	Alive	None		
70 s	0	Cu	Psoriasis	Active	None	60	PR	10	PR	12.9	O	12.9	Alive	Hypophysitis	≤2	Yes
70 s	1	Fo	Hypothyroidism	Active	Thyroid hormone	60	SD	11	SD	5.7	P	12.2	Alive	Pneumonitis	≤2	No

PS Eastern Cooperative Oncology Group performance status, *SH* smoking history, *AID* autoimmune disease, *dCCRT* definitive concurrent chemoradiation therapy, *PFS* progression-free survival, *OS* overall survival, *irAE* immune-related adverse event, *Cu* current smoker, *Fo* former smoker, *Ne* never-smoker, *RA* rheumatoid arthritis, *ITP* idiopathic thrombocytopenia, *MTX* methotrexate, *PR* partial response, *SD* stable disease, *PD* progressive disease, *O* ongoing, *P* progressed.

complexity generated by human leukocyte antigen variability or TCR diversity warrants further investigation with regard to its contribution to early irAEs.

The identification of risk factors for drug-related toxicity is of clinical importance. None of the clinical features examined in our study was found to be clearly associated with the risk of irAE development for the PACIFIC regimen. In particular, feasibility for consolidation therapy with durvalumab in patients with preceding radiation pneumonitis of grade 1 or a well-controlled autoimmune disease was indicated. A previous noncomparative study also suggested that patients with radiation pneumonitis of grade 1 did not present serious complications during durvalumab therapy after dCCRT [40]. Our study provided further evidence in this regard by directly comparing patients with or without radiation pneumonitis. Clinical evidence for the safety and efficacy of the PACIFIC regimen for patients with autoimmune disease has been lacking, with only nine cases reported to date in a retrospective study that included a different spectrum of autoimmune disease compared with our study [41]. Our data should therefore reinforce the clinical rationale for treatment of this clinical trial-ineligible subset of patients with durvalumab even after intensive thoracic radiotherapy. Whether durvalumab is appropriate for more seriously ill individuals such as those with an Eastern Cooperative Oncology Group performance status of 2 or radiation pneumonitis of grade 2 remains to be determined.

This study has several limitations. First, it was designed as an exploratory study. Second, the follow-up time was not long enough, particularly with regard to the collection of sufficient OS data. Third, this study mainly focused on early-onset irAEs, where landmark analyses were consistently performed, and the predetermined study protocol did not allow the collection of adverse events occurring after 30 days from a last dose of durvalumab as also adopted by other historical irAE studies [42, 43]. Fourth, information about several radiotherapy dosimetric parameters such as V5, V20, and mean lung dose—which were previously reported to be risk factors for pneumonitis after thoracic radiotherapy [44]—are missing. However, this study was conducted as a nationwide prospective study that was able to collect clinical data at various institutions. Data collection was based on stringent predetermined criteria, and lead-time bias, a key concern related to this type of study, was consistently addressed by landmark analysis. Late-onset irAEs need to be interrogated in future studies. Given that pneumonitis was revealed as a main aetiology of nonmild irAE by our study, further investigation of other potential risk factors for irAE pneumonitis during PACIFIC regimen is encouraged to maximise the clinical benefit of this therapy.

In conclusion, our results suggest that the early development of mild irAEs predicts better disease control, whereas that of irAEs treated with immunosuppressive systemic steroid is a risk factor for early disease progression, in patients with Stage III NSCLC treated with the PACIFIC regimen. Our examination of clinical profiles and immunologic biomarkers suggested that irAEs development is independent of these general features. Further effort is warranted to clarify the mechanisms of irAE development so as to improve clinical outcome. Our study provides a better understanding of irAEs and should thereby facilitate proper clinical management in this setting.

DATA AVAILABILITY

The data generated in this study are not publicly available as restricted by the study protocol due to the possibility that could compromise patient privacy or consent, but are possibly available upon reasonable request from the corresponding author.

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AUTHOR CONTRIBUTIONS

K Haratani developed the hypothesis, designed the overall study concept, wrote the study protocol, provided clinical data and samples, supervised IHC experiments, performed FCM experiments, performed data analysis and interpreted the data, wrote the manuscript, and supervised the project. A Nakamura, N Mamesaya, K Sawa, Y Shiraishi, R Saito, J Tanizaki, Y Tamura, A Hata, K Tsuruno, T Sakamoto, S Teraoka, M Oki, H Watanabe, T Tokito, K Nagata and T Masuda provided clinical data and samples. Y Nakamura supervised IHC experiments and evaluated IHC staining. K Sakai performed genomic sequencing and processed genomic data. Y Chiba wrote the study protocol and supervised the statistical analysis. A Ito supervised IHC experiments, evaluated IHC staining, and provided administrative support. K Nishio, N Yamamoto, K Nakagawa and H Hayashi provided administrative support and supervised the project. All authors critically revised the manuscript for important intellectual content and approved the final version.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was performed in accordance with the protocol and the Declaration of Helsinki. The full protocol and informed consent form were approved by the ethics committee of each institution. All participants provided written consent before study entry.

CONSENT FOR PUBLICATION

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