Lung Cancer 161 (2021) 86–93

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Real-world survey of pneumonitis and its impact on durvalumab consolidation therapy in patients with non-small cell lung cancer who received chemoradiotherapy after durvalumab approval (HOPE-005/CRIMSON)

Go Saito [a], Yuko Oya [b,*], Yoshihiko Taniguchi [c], Hayato Kawachi [d], Fujimoto Daichi [e], Hirotaka Matsumoto [f], Shunichiro Iwasawa [a,g], Hidekazu Suzuki [h], Takayuki Niitsu [i], Eisaku Miyauchi [j], Takashi Yokoi [k], Toshihide Yokoyama [l], Takeshi Uenami [m], Yoshihiko Sakata [n], Daisuke Arai [o], Asuka Okada [p], Kenji Nagata [q], Shunsuke Teraoka [r], Masaki Kokubo [s]

[a] Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan
[b] Department of Thoracic Oncology, Aichi Cancer Center, Aichi, Japan
[c] Department of Internal Medicine, Kinki-chuo Chest Medical Center, Osaka, Japan
[d] Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan
[e] Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Hyogo, Japan
[f] Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Hyogo, Japan
[g] Medical Sciences Department, Medical Affairs Division, Chugai Pharmaceutical Co., Ltd, Japan
[h] Department of Thoracic Oncology, Osaka Habikino Medical Center, Osaka, Japan
[i] Department of Respiratory Medicine, Osaka General Medical Center, Osaka, Japan
[j] Department of Respiratory Medicine, Tohoku University Hospital, Miyagi, Japan
[k] Department of Thoracic Oncology, Hyogo College of Medicine, Hyogo, Japan
[l] Department of Respiratory Medicine, Kurashiki Central Hospital, Okayama, Japan
[m] Department of Thoracic Oncology, National Hospital Organization, Toneyama National Hospital, Osaka, Japan
[n] Division of Respiratory Medicine, Saiseikai Kumamoto Hospital, Kumamoto, Japan
[o] Pulmonary Division, Department Internal Medicine, Saiseikai Utsunomiya Hospital, Tochigi, Japan
[p] Department of Respiratory Medicine, Saiseikai Suita Hospital, Osaka, Japan
[q] Department of Respiratory Medicine, Itami City Hospital, Hyogo, Japan
[r] Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan
[s] Department of Radiation Oncology, Kobe City Medical Center General Hospital, Hyogo, Japan

ARTICLE INFO

Keywords:
Non-small cell lung cancer
Chemoradiotherapy
Durvalumab
Consolidation
Pneumonitis
Rechallenge

ABSTRACT

Objectives: The incidence of real-world pneumonitis and durvalumab rechallenge during chemoradiotherapy and durvalumab consolidation for non-small cell lung cancer is unknown.
Materials and methods: We retrospectively evaluated the medical records of 302 consecutive patients diagnosed with non-small cell lung cancer who started chemoradiotherapy between May 2018 and May 2019.
Results: Median age was 70 (range: 40–87) years. Volume of lung parenchyma that received 20 Gy (V20) exceeded 35% in 2% and mean lung dose exceeded 20 Gy in 1% of patients. Durvalumab consolidation was delivered to 225 patients (75%). Overall, 83% (n = 251), 34% (n = 103), 7% (n = 21), and 1% (n = 4) of the patients developed any grade of pneumonitis, symptomatic pneumonitis, ≥grade 3 pneumonitis, and fatal (grade 5) pneumonitis, respectively. Corticosteroids were administered to 25% of the patients to treat pneumonitis. Multivariate analysis identified the predictive factors for the development of symptomatic pneumonitis: V20 Gy or more ≥ 25% (odds ratio [OR]: 2.37, $P = 0.008$) and mean lung dose (MLD) ≥ 10 Gy (OR: 1.93, $P < 0.0047$). Of the 52 patients who received corticosteroids for pneumonitis after durvalumab initiation, 21 were rechallenged

* Corresponding author at: Department of Thoracic Oncology, Aichi Cancer Center, 1-1 Kanokoden, Chikusa-ku Nagoya 464-8681, Japan.
E-mail address: yshima@aichi-cc.jp (Y. Oya).

https://doi.org/10.1016/j.lungcan.2021.08.019
Received 17 July 2021; Received in revised form 24 August 2021; Accepted 30 August 2021
Available online 5 September 2021

with durvalumab. Overall, 81% of patients met the PACIFIC study's rechallenge criteria and did not experience a severe pneumonitis relapse.
Conclusion: High V20 and MLD were independent risk factors of symptomatic pneumonitis. More than 80% of the patients who were rechallenged with durvalumab after pneumonitis met the PACIFIC study's rechallenge criteria. Consequently, severe relapse did not occur. Cooperation between radiation and medical oncologists is important for safe chemoradiotherapy and the safe completion of durvalumab consolidation therapy.

1. Introduction

Approximately 20% of patients with non-small cell lung cancer (NSCLC) are diagnosed with locally advanced disease with only 18% undergoing surgery, indicating that most of them are treated with chemotherapy and/or radiation [1,2]. Based on the phase 3 PACIFIC study [3,4], durvalumab consolidation therapy has become a standard of care for those patients.

However, there are safety concerns with the clinical application of durvalumab consolidation therapy. First, the PACIFIC study included patients who completed chemoradiotherapy and did not develop ≥ grade 2 pneumonitis from previous chemoradiotherapy. Second, the study stated that the radiation dose should not exceed 66 Gy (Gy), and the participating sites should adhere to a mean organ radiation dose with the V20 (the volume of lung parenchyma that receives 20 Gy or more) not exceeding 35%. In addition, it has been reported that 36% of patients who received definitive concurrent chemoradiotherapy were ineligible for the PACIFIC study because of non-radiotherapeutic reasons (i.e., performance status ≥ 2) in clinical practice [5]; therefore, only selected patients who received well-designed radiation therapy and were in good physical condition were included in the study. The extent of pneumonitis may have been underestimated compared with the frequency and severity seen in clinical practice. Given the high rate of radiation pneumonitis in clinical practice [6–8] and that pneumonitis caused by immune checkpoint inhibitors (ICIs) for advanced NSCLC in clinical practice was reported to be higher than that in clinical trials [9], durvalumab consolidation therapy after chemoradiotherapy may lead to more frequent and severe pneumonitis in clinical settings. In addition, patients were registered for the PACIFIC study after chemoradiotherapy was completed, and there was little information on the patient's condition before chemoradiotherapy or irradiation in the PACIFIC study. Thus, the risk factors for pneumonitis at the time of initiation of chemoradiotherapy are unknown. Furthermore, there is also the issue of durvalumab rechallenge. In the PACIFIC study, durvalumab rechallenge was an option for patients who developed ≤ grade 2 pneumonitis after the initiation of durvalumab, which resolved to grade 1, and who achieved reduction in prednisone or an equivalent to a dose of ≤ 10 mg/day. However, the clinical course of durvalumab rechallenge after chemoradiotherapy and pneumonitis is unknown. Rechallenge with checkpoint inhibitors following immune-related adverse events are highly controversial [10]. Thus, describing the details of durvalumab rechallenge in real-world practice is important for optimizing concurrent chemoradiotherapy.

Therefore, we conducted a retrospective study to investigate the details of pneumonitis and risk factors for symptomatic pneumonitis among patients with NSCLC during chemoradiotherapy after the approval of durvalumab. Additionally, we described the impact of pneumonitis on the clinical course of durvalumab consolidation therapy.

2. Methods

2.1. Study population

This observational, retrospective cohort study was conducted at 17 sites throughout Japan, and the institutions at these sites comprised the Hanshin Oncology Clinical Problem Evaluation group (HOPE). All the participating institutions were radiotherapy centers. Consecutive patients diagnosed with NSCLC who started chemoradiotherapy between May 1, 2018 and May 31, 2019 following the approval of durvalumab in Japan were enrolled. Staging was based on the American Joint Committee on Cancer Staging Manual, version 8. All the treatments, including radiotherapy, were at the clinician's discretion. Patients who did not receive platinum-based chemoradiotherapy and those who received definitive surgery after chemoradiotherapy or non-concurrent chemoradiotherapy were excluded. Cases in which chemotherapy and radiation therapy started more than a week apart were also excluded.

The study protocol was approved by the Institutional Review Board of Aichi Cancer Center, Aichi, Japan (Approval Number; No. 2019–1-228) and all the participating facilities. Informed consent was not required owing to the retrospective nature of the study.

2.1.1. Data collection and statistical analysis

All the data of the registered patients were retrieved from the medical records. With respect to the dosimetric parameters for lung toxicity, V5 (%) (volume of lung parenchyma that received ≥ 5 Gy) and V20 were calculated. The total lung volume was defined as the volume of both lungs minus the gross tumor volume. The endpoint of this study was the occurrence of pneumonitis during the whole course of concurrent chemoradiotherapy and durvalumab consolidation therapy. The grade of pneumonitis was classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Data were presented as medians and ages for continuous variables and as numbers (percentages) for categorical variables. For two-group comparisons of the categorical variables, we used the Chi-square test. Univariate and multivariate analyses using logistic regression models were conducted to assess the risk factors for symptomatic pneumonitis (≥grade 2). Candidates for risk factors of symptomatic pneumonitis were listed with reference to previous studies [3,6,11,12]. All tests were two-sided, and a P value < 0.05 was considered significant. Statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients' characteristics

The selection of patients is shown in Fig. 1. From May 2018 to May 2019, chemoradiotherapy was initiated in a total of 329 patients. Of them, 10 patients who received definitive surgery after chemoradiotherapy, 2 platinum-free chemotherapy, and 15 sequential chemoradiotherapy were excluded; thus, 302 patients were analyzed. At the time of data cutoff, all patients had completed chemoradiotherapy. The median (range) follow-up time was 8.4 months (range: 1.5–15.7), and 26 (9%) patients had died at the point of data cutoff.

The patients' characteristics are summarized in Table 1. In terms of radiotherapy, the median total dose delivered was 60 Gy, most often in fractionated doses of 2 Gy per day (83%). The median V20 was 19%, and 2% of patients deviated from the PACIFIC criterion "V20 must be<35%". The median V5 was 36%. The mean lung dose (MLD) was 11 Gy, and 1% of patients deviated from the PACIFIC criterion "MLD must be less than 20 Gy". Of the 302 patients who were analyzed, 225 received durvalumab consolidation therapy (75%). The most frequent cause of durvalumab-administration-avoidance was radiation

pneumonitis (n = 20).

At the point of cutoff, 111 of 225 (49%) patients were still on durvalumab consolidation therapy, 15 (7%) had completed one year of durvalumab consolidation therapy, and 49 (22%) had discontinued consolidation therapy due to adverse events, 36 (16%) due to disease progression, and 14 (6%) due to other reasons.

3.2. Onset, frequency, and CTCAE grade of pneumonitis

The incidence of pneumonitis after chemoradiotherapy and severity are shown in Table 2. Overall (n = 302), 83% (n = 251), 34% (n = 103), 7% (n = 21), and 1% (n = 4)of the patients developed any grade of pneumonitis, symptomatic pneumonitis, ≥grade 3 pneumonitis, and fatal (grade 5) pneumonitis, respectively. Of the 251 cases of pneumonitis, 217 were determined to be radiation pneumonitis, 7 were considered immune-related pneumonitis, and 27 were a combination of both. Corticosteroids were administered to 25% of patients (n = 74) for pneumonitis and home oxygen therapy to 5% (n = 16). The time from the initiation of chemoradiotherapy to the onset of pneumonitis and the severity of the disease are shown in Figs. 2A-C. The median time from the initiation of chemoradiotherapy to the onset of pneumonitis was 92 days. None of the patients who developed ≥ grade 2 pneumonitis before the initiation of durvalumab received durvalumab. Of the 225 patients who received durvalumab consolidation therapy, 213 received a response evaluation of chemoradiotherapy via computed tomography before the initiation of durvalumab consolidation therapy. Of the 213 patients, 20% (n = 43) developed pneumonitis prior to/on the day of response evaluation of chemoradiotherapy.

3.3. Risk factors for symptomatic pneumonitis (≥grade 2)

The results from the univariate and multivariate analyses in the log-rank test for symptomatic pneumonitis (≥grade 2) are shown in Table 3. From multivariate analysis, the predictive factors for the development of symptomatic pneumonitis were V20 ≥ 25% (odds ratio [OR]: 2.37, $P = 0.008$) and MLD ≥ 10 Gy (OR: 1.93, $P < 0.0047$).

Further examination of the incidence of symptomatic pneumonitis by V20 revealed that the incidence of symptomatic pneumonitis increased with increase in V20 (V20 < 15%: 13/67 (19%), 15% ≤ V20 < 25%: 46/142 (32%), 25% ≤ V20 < 35%: 32/68 (47%), V20 ≥ 35%: 5/5 (100%)) (Supplementary Fig. 1). In addition, the incidence of symptomatic pneumonitis with V20 increased as the MLD increased; 22% (21/96) of the patients with MLD < 10 Gy, 41% (70/172) of the patients with 10 Gy ≤ MLD < 20 Gy, and 75% (3/4) of the patients with 20 Gy ≤ V20 < 30 Gy developed symptomatic pneumonitis (Supplementary Fig. 2).

3.4. Characteristics and clinical outcome of patients treated with corticosteroids against pneumonitis after durvalumab initiation

The characteristics and clinical outcomes of patients treated with corticosteroids for pneumonitis after durvalumab initiation are shown in Table 4. Overall, 52 of 225 patients (23%) who received durvalumab consolidation therapy were treated with corticosteroids for pneumonitis after durvalumab initiation. Of the 52 patients, 30 (58%) were not rechallenged with durvalumab after treatment with corticosteroids. The most frequent cause of durvalumab-rechallenge-avoidance was ≥ grade 3 pneumonitis (n = 10). Although one patient continued with durvalumab after the initiation of corticosteroids, the remaining 21 were rechallenged with durvalumab after the resolution of the pneumonitis (Table 4). Of the 21 patients, none experienced > grade 3 pneumonitis. The pneumonitis had resolved to ≤ grade 1 in 81% of patients, and 90% of patients had achieved a reduction in prednisone or equivalent to a dose of ≤ 10 mg/day by the time of rechallenge. The relapse of pneumonitis was seen in 6 of 21 patients (29%). Of the six patients who had relapsed pneumonitis, 34% had not resolved the first pneumonitis to ≤

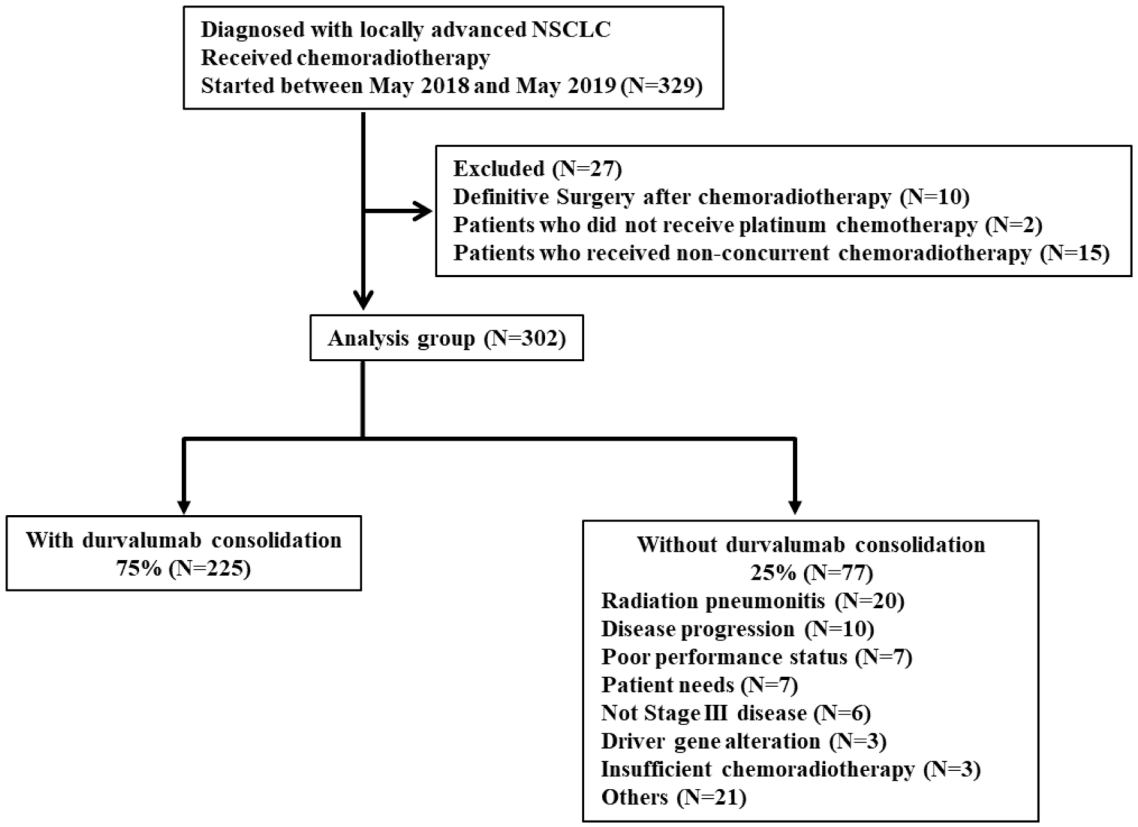

Fig. 1. Flowchart outlining the selection of patients NSCLC, non-small cell lung cancer.

Table 1
Patient characteristics.

Characteristics	All Patients (N = 302)
Age, yr.	
Median (range)	70 (40–87)
Sex – n (%)	
Male	247 (82%)
Female	55 (18%)
PS	
0	139 (46%)
1	156 (52%)
2	7 (2%)
Disease stage	
I-II	15 (5%)
IIIA	127 (42%)
IIIB	99 (33%)
IIIC	28 (9%)
IVA	3 (1%)
Recurrent	30 (10%)
Histologic subtype	
Squamous	118 (39%)
Adeno	153 (51%)
NSCLC NOS	29 (10%)
LCNEC	2 (<1%)
Driver gene status	
EGFR mutation	28 (9%)
ALK fusion	4 (1%)
PD-L1 status	
≥50%	98 (33%)
1%–49%	88 (29%)
<1%	64 (21%)
Unknown	52 (17%)
Comorbid COPD	77 (26%)
Comorbid Interstitial pneumonia	17 (6%)
Chemotherapy	
Carboplatin + Paclitaxel	155 (51%)
Cisplatin + Vinorelbine	67 (22%)
Carboplatin	26 (9%)
Cisplatin + Docetaxel	16 (5%)
Cisplatin + S-1	14 (5%)
Cisplatin + Pemetrexed	9 (3%)
Carboplatin + nab-Paclitaxel	9 (3%)
Carboplatin + Pemetrexed	3 (1%)
Cisplatin + Etoposide	1 (<1%)
Carboplatin + Etoposide	1 (<1%)
Carboplatin + S-1	1 (<1%)
Radiotherapy methods	
3D-CRT	211 (70%)
IMRT	91 (30%)
Irradiation type	
Elective nodal (ENI)	117 (39%)
Involved-field (IFRT)	185 (61%)
Radiation Dose (Gy)	
Median (range)	60 (14–70.4)
< 54 Gy	8 (3%)
≥ 54 and ≤ 66 Gy	271 (90%)
>66 Gy	23 (8%)
V_{20} (%)	
Median (range)	19.65(1.4–37.9)
V_5 (%)	
Median (range)	35.4 (3.1–92.9)
MLD (Gy)	
Median (range)	11.2 (1.4–31.3)

PS, performance status; NSCLC, non-small-cell lung cancer; NOS, not otherwise specified; LCNEC, large cell neuroendocrine carcinoma; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, Programmed death-ligand 1; S-1, Oral-Tegafur, Gimeracil, Oteracil Potassium; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; COPD, chronic obstructive pulmonary disease; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy; Gy, gray; V20, the volume of lung parenchyma that received 20 Gy or more; V5, the volume of lung parenchyma that received 5 Gy or more; MLD, mean lung dose.

Table 2
Incidence of pneumonitis and CTCAE grade (N = 302).

Characteristics	All patients (N = 302)	Patients who received durvalumab (n = 225)	Patients who did not receive durvalumab (n = 77)
No pneumonitis	51 (17%)	34 (15%)	17 (22%)
Patients developed pneumonitis, grade			
1	148 (49%)	114 (51%)	34 (44%)
2	82 (27%)	62 (28%)	20 (26%)
3	12 (4%)	9 (4%)	3 (4%)
4	5 (2%)	4 (2%)	1 (1%)
5	4 (1%)	2 (1%)	2 (3%)
Numbers of pneumonitis treated with corticosteroid	74 (25%)	52 (23%)	22 (29%)
Numbers of pneumonitis resulted in HOT	16 (5%)	12 (5%)	4 (5%)

CTCAE, Common Terminology Criteria for Adverse Events; HOT, home oxygen therapy.

grade 1 or had not achieved a reduction in prednisone or equivalent to a dose of ≤ 10 mg/day by the time of the rechallenge. Durvalumab discontinuation due to relapse of pneumonitis was seen in 3 of 21 patients who were rechallenged with durvalumab. However, no case of relapsed pneumonitis was severe (≥grade 3).

4. Discussion

To the best of our knowledge, this is the first large, multicenter cohort study that described the details of radiotherapy, pneumonitis, and durvalumab rechallenge among patients with NSCLC who received chemoradiotherapy after the approval of durvalumab.

After durvalumab was approved, there were three reports on the frequency of pneumonitis among patients who received durvalumab consolidation therapy after chemoradiotherapy [13–15]. The differences between these reports and our study are shown in the detailed description of the frequency and severity of pneumonitis. We included all patients regardless of whether they received durvalumab consolidation therapy. A previous study reported that the incidence of severe grade 3 pneumonitis was 14% higher than the incidence observed in the PACIFIC study [13], whereas another reported that no severe (≥grade 3) pneumonitis was seen [16]. These heterogeneities were thought to be related to the differences in V20 and MLD. Many previous reports have shown a correlation between V20/MLD and the incidence/severity of pneumonitis [6,11,17]. The NCCN guidelines recommend that V20 should not exceed 35%–40% and that the MLD should not exceed 20 Gy [18]. Based on the recommendations, the PACIFIC study encouraged trial sites to adhere to the mean organ radiation dose, stating “MLD must be < 20 Gy and V20 must be < 35%” [3]. Of the patients enrolled in the study on highly frequent and severe pneumonitis, 28% had a MLD of 20 Gy or more and 50.9% had V20 of more than 35% [13]. Of the patients who did not have severe ≥ grade 3 pneumonitis, none had an MLD of 20 Gy or more, or a V20 of more than 35% [14]. V20 also exceeded 35% in 2% and MLD exceeded 20 Gy in 1% of patients in our study. These findings suggested that it is very important to suppress V20 and MLD after the approval of durvalumab. In particular, V20 correlated with the frequency of symptomatic pneumonitis in both the previous [6] study and ours. Therefore, V20 should be kept as low as possible. In addition, in this cohort, none of the patients with ≥ grade 2 pneumonitis received durvalumab consolidation therapy. Although 75% of patients in this

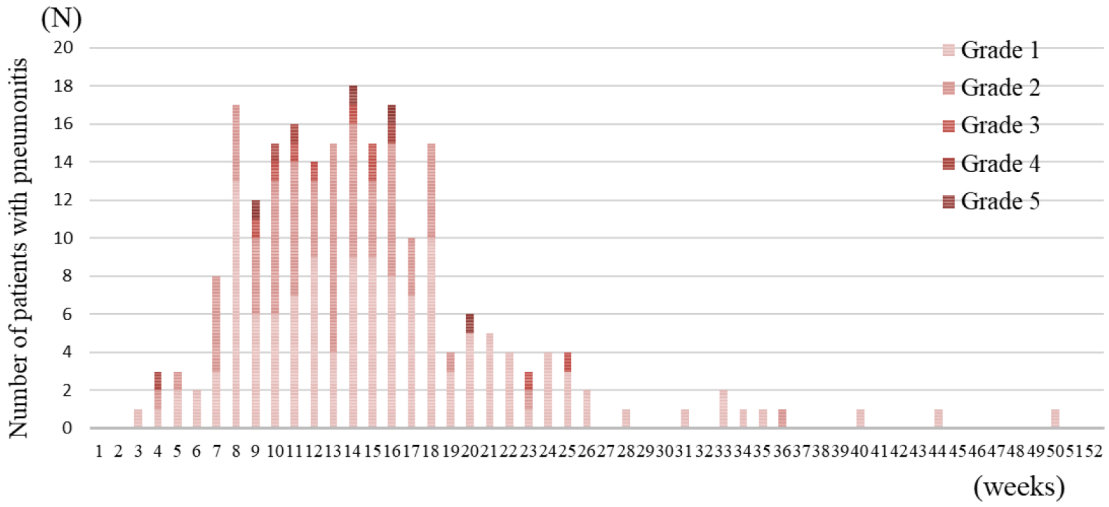

Fig. 2A. Onsets and grades of pneumonitis in all patients (N = 302).

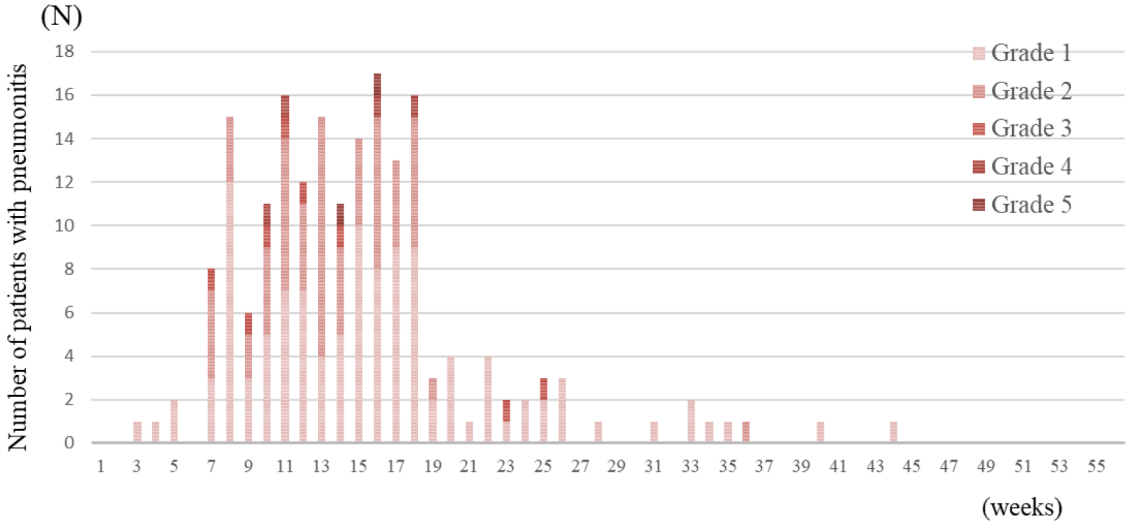

Fig. 2B. Onset and grades of pneumonitis in patients with durvalumab consolidation (N = 225).

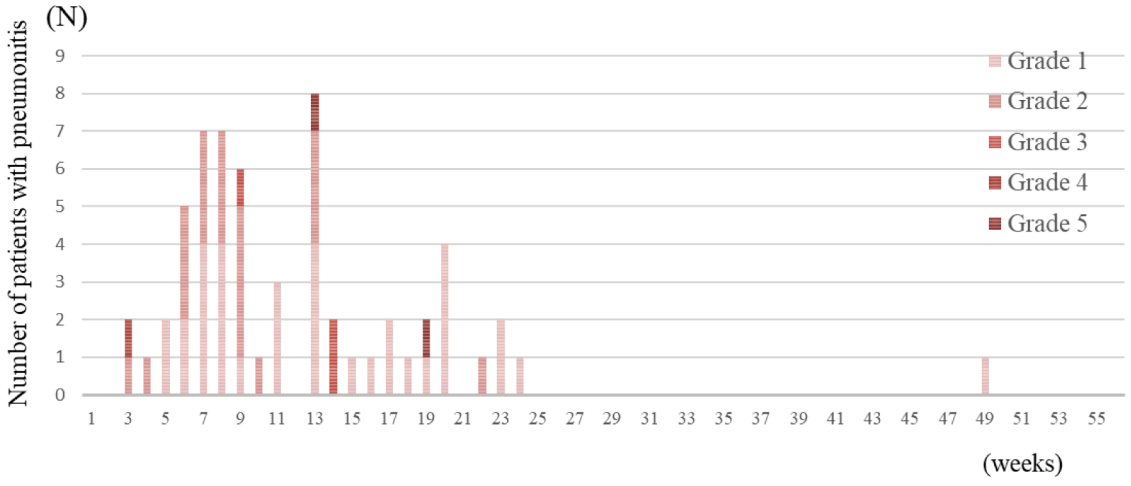

Fig. 2C. Onsets and grades of pneumonitis in patients without durvalumab consolidation (N = 77).

Table 3
Risk factors for symptomatic pneumonitis (≥Grade 2).

Characteristics	Risk Factors	Univariate			Multivariate		
		HR	95% CI	p value	HR	95% CI	p value
Sex	Female (vs male)	1.24	0.68–2.28	0.48	1.47	0.74–2.90	0.27
Age	< 65 yr. (vs. ≥ 65)	1.00	0.60–1.68	0.99	1.29	0.70–2.38	0.41
COPD	Yes (vs. no)	1.14	0.67–1.96	0.63	1.18	0.64–2.18	0.58
Radiotherapy technique	3D-CRT (vs. IMRT)	1.15	0.68–1.95	0.59	1.12	0.61–2.04	0.70
V_{20}	≥25% (vs. < 25%)	2.54	1.47–4.39	0.0008	2.37	1.23–4.48	0.008
MLD	≥10 Gy (vs. < 10 Gy)	2.56	1.45–4.53	0.0008	1.93	1.01–3.67	0.047
Chemotherapy	Taxane + (vs. -)	1.44	0.89–2.33	0.14	1.41	0.81–2.46	0.22
Durvalumab	With (vs. without)	1.02	0.59–1.76	0.94	1.34	0.72–2.60	0.34

HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy; Gy, gray; V20, the volume of lung parenchyma that received 20 Gy or more; MLD, mean lung dose.

Table 4
Characteristics and clinical outcomes of patients treated for pneumonitis with corticosteroids after durvalumab initiation.

Characteristics	All patients (n = 52) *	Patients never rechallenged (n = 30)	Patients rechallenged (n = 21)		
			All	Rechallenge without relapse of pneumonitis (n = 15)	Rechallenge with Relapse of pneumonitis (n = 6)
Median age, yr.	70.95	72	66	70.1	60.5
Sex – n (%)					
Male	38 (73%)	24 (80%)	13 (62%)	12 (80%)	1 (17%)
Female	14 (27%)	6 (20%)	8 (38%)	3 (20%)	5 (83%)
Comorbid COPD	18 (35%)	14 (47%)	4 (19%)	4 (27%)	0 (0%)
Histologic subtype					
Squamous	24 (46%)	15 (50%)	8 (38%)	7 (47%)	1 (17%)
Adenocarcinoma	24 (46%)	12 (40%)	12 (57%)	7 (47%)	5 (83%)
NSCLC NOS	4 (8%)	3 (10%)	1 (5%)	1 (6%)	0
Radiotherapy methods					
3D-CRT	39 (75%)	22 (73%)	16 (76%)	11 (73%)	5 (83%)
IMRT	13 (25%)	8 (27%)	5 (24%)	4 (27%)	1 (17%)
Median Radiation Dose	60 Gy	60 Gy	60 Gy	60 Gy	60 Gy
Median V_{20}	21.37%	20.575%	22.62%	22.62%	21.60%
Median MLD	11.9 Gy	11.1 Gy	12.1 Gy	11.95 Gy	12.81 Gy
Grades of first pneumonitis					
1	4 (8%)	1 (3%)	3 (14%)	1 (6%)	2 (33%)
2	34 (65%)	15 (50%)	18 (86%)	14 (94%)	4 (67%)
3	8 (15%)	8 (27%)	0	0	0
4	4 (8%)	4 (13%)	0	0	0
5	2 (4%)	2 (7%)	0	0	0
Numbers whose pneumonitis achieved improvement to G1 before the rechallenge	N/A	N/A	17 (81%)	13 (87%)	4 (66%)
Numbers whose corticosteroids were reduced to 10 mg or less before the rechallenge	N/A	N/A	19 (90%)	15 (100%)	4 (66%)
Reasons for no rechallenge					
≥ G3 pneumonitis	N/A	10	N/A	N/A	N/A
disease progression	N/A	9	N/A	N/A	N/A
relapsed pneumonitis after corticosteroid reduction / never resolved to G1	N/A	4	N/A	N/A	N/A
Infection	N/A	3	N/A	N/A	N/A
patients' needs	N/A	3	N/A	N/A	N/A
others	N/A	1	N/A	N/A	N/A
Grades of relapsed pneumonitis					
2	N/A	N/A	6 (29%)	N/A	6 (100%)
Durvalumab discontinuation due to pneumonitis relapse	N/A	N/A	3 (14%)	N/A	3 (50%)

*One patient continued with durvalumab after the initiation of corticosteroid therapy.
COPD, chronic obstructive pulmonary disease; NSCLC, non-small-cell lung cancer; NOS, not otherwise specified; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy; Gy, gray; V20, the volume of lung parenchyma that received 20 Gy or more; MLD, mean lung dose; G1, grade 1; G3 grade 3; N/A, not applicable.

study received durvalumab despite the development pneumonitis prior to/upon response evaluation of chemoradiotherapy in 20%, the prevalence of severe pneumonitis was comparable to other real data [15] or the findings of the PACIFIC study. Taken together, we believe that the PACIFIC-protocol-based or guideline-recommended radiation therapy is important to reduce the frequency of symptomatic or severe pneumonitis in clinical practice. Thus, cooperation between medical and radiation oncologists is an important step towards safe chemoradiotherapy.

Although 41% of patients who experienced pneumonitis and required corticosteroid treatment were rechallenged with durvalumab, there were no severe relapses of pneumonitis. There were several reports on rechallenge with ICIs after immune-related adverse events (irAEs) [19–23], but all were among cases of advanced cancer. Although the largest cohort study of ICI rechallenge reported that pneumonitis was associated with a higher recurrence rate than other types of irAEs [21], it was reported that the severity of irAEs at the time of relapse was lower than the severity at the time of the first irAEs. Thus, a high relapse rate did not necessarily mean a high number of serious relapses [20]. In our cohort, 71% of patients were able to continue durvalumab after rechallenge without relapses of pneumonitis, and serious relapse did not occur in patients who had relapses of pneumonitis. Considering that continuing nivolumab provided a prognostic benefit compared with stopping treatment at one year in patients with previously treated NSCLC [22] and a short duration of durvalumab consolidation therapy after chemoradiotherapy due to adverse events was reported to result in poor prognosis [24], we believe that durvalumab rechallenge after pneumonitis should be considered. However, although most (81%) of the patients who underwent rechallenge in our cohort also complied with the rechallenge criteria of the PACIFIC study (the initial pneumonitis was less than grade 3 and improved to grade 1 before rechallenge, and steroid intake was reduced to less than 10 mg/day before rechallenge), two out of six patients who experienced a relapse after rechallenge did not meet the rechallenge criteria of the PACIFIC study. Hence, durvalumab rechallenge in patients who have experienced $\geq$ grade 3 severe pneumonitis, whose pneumonitis did not improve to grade 1, and who received $\geq$ 10 mg/day of corticosteroid therapy, is not recommended.

There were some limitations in this study. First, this was a retrospective cohort study which may have distorted the results because of unmeasured confounders. However, we attempted to minimize bias by including the registration of consecutive patients from 17 institutions all over Japan. Second, we did not conduct third-party audits. To control the quality and accuracy of data, all data, excluding personal information, were shared among the research institutions to ensure that there were no inconsistencies in the data. Third, the median follow-up time, 8.4 months, was shorter than that of the PACIFIC study. However, our study focused on pneumonitis, and considering that the median duration in our cohort from the initiation of chemoradiotherapy to the onset of pneumonitis (92 days) was comparable to the median duration from the initiation of durvalumab to the onset of pneumonitis in the PACIFIC study (55 days), we considered that the duration of the follow-up was sufficient to evaluate the details of radiation pneumonitis in clinical settings. However, it is likely that immune-related pneumonitis was underestimated. In addition, there were few cases which durvalumab rechallenge, and the follow-up period was short; thus, the outcome of durvalumab rechallenge must be interpreted with caution. In terms of chemoradiotherapy, a wide diversity of chemotherapy schedules, including regimens for which no phase III trials had been conducted, was concurrently used with radiotherapy. Moreover, 70% of the patients received three-dimensional conformal radiation therapy (3D-CRT) and 39% received elective nodal irradiation (ENI). However, the latest National Comprehensive Cancer Network guideline recommends intensity modulated radiation therapy (IMRT) and involved-field radiotherapy (IFRT) [18], considering their safety and survival advantage. The techniques used in this study, namely, 3D-CRT and ENI, may have influenced the occurrence of pneumonitis and made the results less applicable to others.

5. Conclusion

Pneumonitis of any grade was observed in 83% of all patients with NSCLC who received chemoradiotherapy after the approval of durvalumab and symptomatic pneumonitis in 34%. V20 and MLD were independent risk factors for symptomatic pneumonitis. Over 80% of the patients who were rechallenged with durvalumab after pneumonitis complied with the rechallenge criteria of the PACIFIC study; consequently, severe relapse did not occur. Cooperation between radiation and medical oncologists, and adherence to radiotherapy standards and the PACIFIC study criteria is important for safe chemoradiotherapy and the safe completion of durvalumab consolidation therapy.

CRediT authorship contribution statement

Go Saito: Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **Yuko Oya:** Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Yoshihiko Taniguchi:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Hayato Kawachi:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Fujimoto Daichi:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Hirotaka Matsumoto:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Shunichiro Iwasawa:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Hidekazu Suzuki:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Takayuki Niitsu:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Eisaku Miyauchi:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Takashi Yokoi:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Toshihide Yokoyama:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Takeshi Uenami:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Yoshihiko Sakata:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Daisuke Arai:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Asuka Okada:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Kenji Nagata:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Shunsuke Teraoka:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Masaki Kokubo:** Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Dr. Saito reports personal fees from Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., Novartis Pharma K.K., and Taiho Pharmaceutical Co., Ltd., outside the submitted work.

Dr. Oya reported receiving personal fees from AstraZeneca, Daiichi Sankyo, Ono Pharmaceutical, Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly Japan K.K., Bristol-Myers Squibb and Amgen.

Dr. Taniguchi reports personal fees from Ono Pharmaceutical Co., LTD., Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., outside the submitted work.

Dr. Kawachi reports personal fees from Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co, Merck Sharp and Dohme, and Taiho Pharmaceutical Co, and AstraZeneca K.K., outside the submitted work.

Dr. Fujimoto reports receiving grants and personal fees from AstraZeneca K.K.; Boehringer Ingelheim Japan Inc.; and personal fees from Ono Pharmaceutical Co., Ltd.; Bristol-Myers Squibb Co., Ltd.; Taiho Pharmaceutical Co.,Ltd.; Chugai Pharmaceutical Co., Ltd.; MSD K.K.; Eli Lilly Japan K.K.; Novartis Pharma K.K., outside the submitted work.

Dr. Matsumoto reports personal fees from Chugai Pharma, AstraZeneca, Eli Lilly Japan K.K., Taiho Pharmaceutical, Ono Pharmaceutical and Boehringer Ingelheim, outside the submitted work.

Dr. Iwasawa reports personal fees from ONO PHARMACEUTICAL CO., LTD., Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., MSD K.K., Bristol-Myers Squibb K.K., and Taiho Pharmaceutical Co., Ltd., outside the submitted work.

Dr. Suzuki reports personal fees from Chugai Pharmaceutical, MSD,

and AstraZeneca, outside the submitted work

Dr. Niitsu has nothing to decleare.

Dr. Miyauchi reports receiving grants and personal fees from Chugai Pharma, Eli Lilly Japan K.K., and personal fees from AstraZeneca K.K., Taiho Pharmaceutical, Daiichi Sankyo, Boehringer Ingelheim Japan Inc, Bristol-Myers Squibb, Novartis Pharma K.K., MSD K.K., Kyowa Kirin Co Ltd, Merck Biopharma Daiichi Sankyo, Pfizer and Ono Pharmaceutical outside the submitted work.

Dr. Yokoi reports receiving personal fees from Ono Pharmaceutical Co., Ltd.; Chugai Pharmaceutical Co., Ltd.; AstraZeneca K.K.; and Bristol-Myers Squibb Company.

Dr. Yokoyama reported receiving grants and personal fees from Eli Lilly Japan K.K.; Takeda Pharmaceutical Co. Ltd.; MSD K.K.; Ono Pharmaceutical; Chugai Pharmaceutical; AstraZeneca K.K.; Novartis Pharma K.K.; Bristol-Myers Squibb; Boehringer Ingelheim Japan Inc.; and Taiho Pharmaceutical Co., Ltd., outside the submitted work.

Dr. Uenami reports receiving personal fees from Chugai Pharmaceutical and AstraZeneca K.K.

Dr. Sakata reports receiving personal fees from Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly Japan K.K., MSD, and Taiho Pharmaceutical outside the submitted work.

Dr. Arai reported receiving personal fees from Taiho Pharmaceutical, AstraZeneca K.K., and Pfizer Japan Inc, outside the submitted work.

Dr. Okada reports personal fees from AstraZeneca K.K., Boehringer Ingelheim Japan Inc, Eli Lilly Japan K.K., MSD K.K., outside the submitted work.

Dr. Nagata has nothing to declare.

Dr. Teraoka reports personal fees from Chugai Pharma, Novartis Recipient, AstraZeneca, Taiho Pharmaceutical, Ono Pharmaceutical Boehringer Ingelheim, and Eli Lilly Japan K.K., outside the submitted work.

Dr. Kokubo reports personal fees from AstraZeneca K.K.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2021.08.019.

References

[1] K.D. Miller, L. Nogueira, A.B. Mariotto, J.H. Rowland, K.R. Yabroff, C.M. Alfano, A. Jemal, J.L. Kramer, R.L. Siegel, Cancer treatment and survivorship statistics, 2019, CA Cancer J. Clin. 69 (2019) 363–385, https://doi.org/10.3322/caac.21565.

[2] R.L. Siegel, K.D. Miller, A. Goding Sauer, et al., Colorectal cancer statistics, 2020, CA: Cancer J. Clin. 70 (2020) 145–164, https://doi.org/10.3322/caac.21601.

[3] S.J. Antonia, A. Villegas, D. Daniel, et al., Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer, N. Engl. J. Med. 377 (2017) 1919–1929, https://doi.org/10.1056/NEJMoa1709937.

[4] S.J. Antonia, A. Villegas, D. Daniel, et al., Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC, N. Engl. J. Med. 379 (2018) 2342–2350, https://doi.org/10.1056/NEJMoa1809697.

[5] K. Hosoya, D. Fujimoto, H. Kawachi, et al., Ineligibility for the PACIFIC trial in unresectable stage III non-small cell lung cancer patients, Cancer Chemother. Pharmacol. 84 (2019) 275–280, https://doi.org/10.1007/s00280-019-03885-4.

[6] D.A. Palma, S. Senan, K. Tsujino, et al., Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis, Int. J. Radiat. Oncol. Biol. Phys. 85 (2013) 444–450, https://doi.org/10.1016/j.ijrobp.2012.04.043.

[7] I. Sekine, M. Sumi, Y. Ito, et al., Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients, Radiother. Oncol. 80 (2006) 93–97, https://doi.org/10.1016/j.radonc.2006.06.007.

[8] H. Horinouchi, S. Atagi, S. Oizumi, et al., Real-world outcomes of chemoradiotherapy for unresectable Stage III non-small cell lung cancer: The SOLUTION study, Cancer Med. 9 (2020) 6597–6608, https://doi.org/10.1002/cam4.3306.

[9] Y. Suzuki, M. Karayama, T. Uto, et al., Assessment of immune-related interstitial lung disease in patients with NSCLC treated with immune checkpoint inhibitors: a multicenter prospective study, J. Thorac. Oncol. 15 (2020) 1317–1327, https://doi.org/10.1016/j.jtho.2020.04.002.

[10] J. Haanen, M. Ernstoff, Y. Wang, et al., Rechallenge patients with immune checkpoint inhibitors following severe immune-related adverse events: review of the literature and suggested prophylactic strategy, J. Immunother. Cancer 8 (2020) e000604, https://doi.org/10.1136/jitc-2020-000604.

[11] S.G. Chun, C. Hu, H. Choy, et al., Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial, J. Clin. Oncol. 35 (2017) 56–62, https://doi.org/10.1200/JCO.2016.69.1378.

[12] Z. Zhou, X. Song, A. Wu, et al., Pulmonary emphysema is a risk factor for radiation pneumonitis in NSCLC patients with squamous cell carcinoma after thoracic radiation therapy, Sci. Rep. 7 (2017), https://doi.org/10.1038/s41598-017-02739-4.

[13] H.A. Jung, J.M. Noh, J.-M. Sun, et al., Real world data of durvalumab consolidation after chemoradiotherapy in stage III non-small-cell lung cancer, Lung Cancer 146 (2020) 23–29, https://doi.org/10.1016/j.lungcan.2020.05.035.

[14] T. Zhang, K. Xu, N. Bi, et al., Efficacy and safety of immune checkpoint inhibitor consolidation after chemoradiation in patients of Asian ethnicity with unresectable stage III non-small cell lung cancer: Chinese multicenter report and literature review, Thorac. Cancer 11 (2020) 2916–2923, https://doi.org/10.1111/1759-7714.13631.

[15] A. Desilets, F. Blanc-Durand, S. Lau, et al., Durvalumab therapy following chemoradiation compared with a historical cohort treated with chemoradiation alone in patients with stage III non-small cell lung cancer: a real-world multicentre study, Eur. J. Cancer 142 (2021) 83–91, https://doi.org/10.1016/j.ejca.2020.10.008.

[16] Z. Zhang, T. Wang, J. Zhang, et al., Prognostic value of epidermal growth factor receptor mutations in resected non-small cell lung cancer: a systematic review with meta-analysis, PLoS ONE 9 (2014) e106053, https://doi.org/10.1371/journal.pone.0106053.

[17] M.V. Graham, J.A. Purdy, B. Emami, et al., Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC), Int. J. Radiat. Oncol. Biol. Phys 45 (1999) 323–329, https://doi.org/10.1016/S0360-3016(99)00183-2.

[18] D.S. Ettinger, D.E. Wood, D.L. Aisner, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Non-Small Cell Lung Cancer Version 3.2020-February 11, 2020. 2020; https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 27th March, 2020.

[19] M.H. Pollack, A. Betof, H. Dearden, et al., Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma, Ann. Oncol. 29 (2018) 250–255, https://doi.org/10.1093/annonc/mdx642.

[20] A. Simonaggio, J.M. Michot, A.L. Voisin, et al., Evaluation of readministration of immune checkpoint inhibitors after immune-related adverse events in patients with cancer, JAMA Oncol. 5 (2019) 1310, https://doi.org/10.1001/jamaoncol.2019.1022.

[21] C. Dolladille, S. Ederhy, M. Sassier, et al., Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer, JAMA Oncol. 6 (2020) 865, https://doi.org/10.1001/jamaoncol.2020.0726.

[22] D.M. Waterhouse, E.B. Garon, J. Chandler, et al., Continuous versus 1-year fixed-duration nivolumab in previously treated advanced non-small-cell lung cancer: CheckMate 153, J. Clin. Oncol. 38 (2020) 3863–3873, https://doi.org/10.1200/JCO.20.00131.

[23] M. Allouchery, T. Lombard, M. Martin, et al., Safety of immune checkpoint inhibitor rechallenge after discontinuation for grade ≥2 immune-related adverse events in patients with cancer, J. Immunother. Cancer 8 (2020) e001622, https://doi.org/10.1136/jitc-2020-001622.

[24] N. Shaverdian, M. Offin, A.F. Shepherd, et al., Association between the early discontinuation of durvalumab and poor survival in patients with stage III NSCLC, JTO Clin. Res. Rep. 2 (2021) 100197, https://doi.org/10.1016/j.jtocrr.2021.100197.