Radiotherapy and Oncology 196 (2024) 110294

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Durvalumab impacts progression-free survival while high-dose radiation >66 Gy improves local control without excess toxicity in unresectable NSCLC stage III: Real-world data from the **A**ustrian radio-oncological **l**ung cancer **s**tudy **a**ssociation **r**egistry (ALLSTAR)

Franz Zehentmayr [a,*], Petra Feurstein [b], Elvis Ruznic [a], Brigitte Langer [b], Brane Grambozov [a], Marisa Klebermass [b], Herbert Hüpfel [c], Johann Feichtinger [d], Danijela Minasch [e], Martin Heilmann [f], Barbara Breitfelder [g], Claudia Steffal [h], Gisela Gastinger-Grass [i], Karoline Kirchhammer [j], Margit Kazil [k], Heidi Stranzl [l], Karin Dieckmann [f], on behalf of the ALLSTAR group

[a] *Paracelsus Medical University, Salzburg, Austria*
[b] *Klinikum Ottakring, Vienna, Austria*
[c] *Klinikum Hietzing-Rosenhügel, Vienna, Austria*
[d] *Ordensklinikum Linz, Linz, Austria*
[e] *Medical University Innsbruck, Innsbruck, Austria*
[f] *Medical University Vienna, Department of Radiation Oncology, Comprehensive Cancer Centre, Vienna, Austria*
[g] *Klinikum Krems, Krems, Austria*
[h] *Klinikum Favoriten, Vienna, Austria*
[i] *Donauspital, Vienna, Austria*
[j] *Klinikum Klagenfurt, Klagenfurt, Austria*
[k] *Klinikum Feldkirch, Feldkirch, Austria*
[l] *Medizinische Universität Graz, Graz, Austria*

ARTICLE INFO

Keywords:
Non-operable NSCLC
Durvalumab
Local control
Total radiation dose
Toxicity

ABSTRACT

Background: Chemo-radioimmunotherapy with total radiation doses of 60–66 Gy in 2 Gy fractions is the standard of care for non-small cell lung cancer (NSCLC) UICC stage III. The Austrian radio-oncological lung cancer study association registry (ALLSTAR) is a prospective multicentre registry intended to document clinical practice at the beginning of the Durvalumab era.

Patients and methods: Patients were eligible if they had pathologically verified unresectable NSCLC stage III with a curative treatment option. Chemo-radiation combined with immunotherapy was performed according to local treatment practices. The endpoints were local control (LC), progression-free survival (PFS) and toxicity.

Results: Between 2020/03 and 2023/04, 12/14 (86 %) Austrian radiation-oncology centres recruited 188 patients (median 17, range: 1–89). PD-L1 testing was performed in 173/188 (93 %) patients. The median interval between the end of chemoradiotherapy and start of Durvalumab was 14 days (range: 1–65). About 40 % (75/188) of the patients received a total radiation dose of > 66 Gy (range: 67.1–100), which improved 2-year LC (86 % versus 60 %, HR = 0.41; 95 %-CI: 0.17–0.98; log-rank p-value < 0.05). Median PFS for patients with Durvalumab was 25.8 months (95 %-CI: 21.9-not reached) compared to 15.7 months (95 %-CI: 13.2–27.8) for those without (HR = 1.88; 95 %-CI: 1.16–3.05; log-rank p-value < 0.01). The rates of esophageal and pulmonary toxicities were

Abbreviations: AESI, adverse events of special interest; ALLSTAR, **A**ustrian radio-oncological **l**ung cancer **s**tudy **a**ssociation **r**egistry; cCRT, concomitant chemoradiotherapy; EAP, early access programme; EMA, European Medicines Agency; EQD2, biologically equivalent dose in 2 Gy fractions; GTV, gross tumor volume; ICI, immune checkpoint inhibition; IMRT, intensity modulated radiotherapy; LC, local control; MVA, multivariate analysis; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression free survival; PFT, pulmonary function test; RCT, randomized control trial; RT, radiotherapy; RWD, real-world data; SABR, stereotactic body radiotherapy; SCC, squamous cell carcinoma; sCRIT, sequential chemoradioimmunotherapy; sCRT, sequential chemoradiotherapy; SoC, standard of care; VMAT, volumetric arc therapy; WBDC, web-based data capture system.

* Corresponding author at: Müllner Haupstrasse 48 A-5020 Salzburg, Austria.
E-mail address: f.zehentmayr@salk.at (F. Zehentmayr).

https://doi.org/10.1016/j.radonc.2024.110294
Received 20 February 2024; Received in revised form 10 April 2024; Accepted 17 April 2024
Available online 21 April 2024

34.6 % and 23.9 %, respectively, including one case of grade 4 pneumonitis. In the subcohort of 75 patients who received > 66 Gy, 19 (25 %) cases of pulmonary toxicity grades 1–3 were observed.
Conclusion: While Durvalumab impacts PFS, LC can be improved by total radiation doses > 66 Gy without excess toxicity.

Introduction

Lung cancer is still the most prominent cause for cancer-related deaths worldwide [1]. The majority of patients are diagnosed with non-small cell lung cancer (NSCLC), 30 % of which present in locally advanced stage III [2]. Since the landmark publication by Antonia et al. the standard of care (SoC) for unresectable NSCLC stage III is concomitant chemoradiotherapy (cCRT) 60 – 66 Gy in 2 Gy fractions followed by Durvalumab for one year [3–6]. Although cCRT is preferably recommended by multiple prospective trials [7–11] and one *meta*-analysis [12], sequential regimens are still frequently used, especially in elderly patients and those deemed unfit for concomitant treatment [5–6]. The 5-year update of the results of the PACIFIC trial showed improved clinical outcome compared to CRT alone, resulting in median overall (OS) and progression free survival (PFS) rates of 47.5 and 16.9 months, respectively, for patients treated with Durvalumab regardless of their programmed death ligand-1 (PD-L1) status [13].

In this respect the question arises in how far these trial data translate into clinical practice even more so as NSCLC UICC III comprises a heterogeneous group of diseases, which entails a wide range of treatment approaches. Therefore, real-world data (RWD) are important as they include patients who usually do not qualify for prospective randomized control trials (RCT). In fact, only 2 % patients participate in trials, hence RWD are able to fill the knowledge gap between RCT and clinical practice [14]. A multinational RWD study from the pre-immunotherapy era with over 3000 patients listed more than 25 treatment regimens for unresectable NSCLC stage III [15]. With the widespread use of Durvalumab and other immunotherapies nowadays, the treatment landscape evolves rapidly so that reliable data representing real world practice are needed. Despite recent publications [14,16–18], the current registry together with the German early access program (EAP) study [19] is the first to focus not only on PFS but also on LC. The data presented in this analysis may gain additional importance as PACIFIC – in spite of the clear PFS and OS benefit achieved by Durvalumab – could not demonstrate any improvement in LC compared to the 60–70 % in historic series [8–10]. In this respect, radiation dose escalation might be of interest, although RTOG 0617 came to the conclusion that total radiation doses of 74 Gy in conventional fractionation yield no advantage compared to 60 Gy [11]. In contrast, a *meta*-analysis including approximately 2000 patients [21] demonstrated improved OS for accelerated or hyperfractionated RT. Likewise, two small series combining dose escalation regimens with Durvalumab revealed enhanced LC rates compared to the standard of care (SoC) [22–23].

The aim of ALLSTAR, a prospective registry for unresectable NSCLC stage III, was to document the use of immunotherapy, especially Durvalumab, together with cCRT and sCRT regimens in Austria. As for the current analysis, the primary endpoints were LC together with PFS and toxicity.

Methods

Study design and patients

ALLSTAR was designed as a multicentre prospective registry for patients with unresectable stage III NSCLC with the aim to document and compare the diversity of treatment schedules for this disease used in daily clinical practice. This analysis differs from other RWD studies [16,17,19], in as far as it is prospective and the patients did not form part of an EAP. By collecting data on the heterogeneity of this patient population, this registry sheds light on the variety of treatment regimens throughout Austria. In this regard, several issues should be addressed: First, since Durvalumab maintenance for one year after CRT is a cornerstone of therapeutic advances in recent years, the question arises, whether it is widely used in clinical practice and if not, what the systemic treatment alternatives are. Secondly, is CRT primarily administered in the sequential mode or concomitantly with RT? Thirdly, what radiation treatment schedules are in clinical use aside from the conventionally accepted 60–66 Gy in 2 Gy fractions?

Treatment decisions were consensually taken in the local tumor boards consisting of radiation oncologists, pulmonologist, medical oncologists, thoracic surgeons, radiologists and pathologists. At each centre one local investigator certified by the Austrian board of radiation-oncologist was responsible for entering the data in the web-based data capture (WBDC) system. The study was approved by the ethics committee of the federal state of Salzburg on the 20th of March 2020 (Ethikkommission Land Salzburg Nr. 1002/2019). Patients aged 18 years or older were included if they had histologically or cytologically verified unresectable NSCLC UICC stage III (TNM version 8) with a curatively intended treatment option. All patients provided written informed consent. As opposed to PACIFIC [3,4], patients with poor performance score, i.e. ECOG > 1 were also allowed to participate. The diagnostic work-up consisted of a contrast enhanced whole body CT scan or – preferably – an [18]F-FDG-PET-CT scan together with a cranial MRI as well as bronchoscopy or transthoracic needle aspiration with endobronchial ultrasound for mediastinal lymph node staging and pulmonary function tests (PFT). Follow-up was performed at each study site with a clinical check-up, contrast enhanced thoracic CT and PFT three months after the end of RT and on a biannual basis thereafter.

Radiochemoimmunotherapy

Radiation treatment was performed according to daily clinical practice in each centre. The minimum technical requirement in dose delivery was 3D radiotherapy (RT) or – preferably – advanced radiation techniques such as intensity modulated radiotherapy (IMRT), volumetric arc therapy (VMAT) or stereotactic body radiotherapy (SABR). As for total radiation dose, 60 – 66 Gy in 2 Gy fractions was regarded as the SoC but other treatment schedules, such as hypofractionated-accelerated or twice-daily fractionation were also allowed. Patients who received > 66 Gy were analyzed separately as a dose-escalation subgroup. For reasons of comparability total irradiation doses were recalculated as biologically equivalent dose in 2 Gy fractions (EQD2) using the formalism below with D for total dose, d for single dose and α/β assumed as 10 for tumor tissue [24,25]:

$$EQD_2 = \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

Several prospectively RCTs showed that chemotherapy administered simultaneously with RT was beneficial in terms of outcome compared to sequential CRT [7–10,12], which is reflected by international guidelines [5–6]. In the current study however, CRT was either administered concomitantly or sequentially according to specific practice at each centre. In general, patients who had a PD-L1 status of 1 % or more were considered positive and therefore amenable to immunotherapy. Patients were treated with immunotherapy at the discretion of the local tumor board.

Endpoints and statistics

The primary endpoints were LC, PFS and treatment related toxicity graded according to CTCAEv5. Data were extracted on the 11th of April 2023, which is slightly longer than three years after the first patient was entered in the registry. LC was defined according to Machtay, which was the basis for the investigator at each centre to determine whether a patient had loco-regionally failed [26]. For the current analysis adverse events of special interest (AESI) were pulmonary and esophageal toxicities. The first term comprises pneumonitis either caused by immunotherapy or chemoradiation, fibrosis, interstitial lung disease and pneumonia. The second term, i.e. esophageal toxicity, comprises dysphagia, esophagitis and fibrotic stricture.

Time-to-event analyses were calculated with the Kaplan-Meier-method using the date of diagnosis, i.e. histological or cytological confirmation of disease, as index date. The comparison between subgroups was performed with the log-rank test. Multivariate analysis (MVA, Cox Regression, forward stepwise) included parameters that might have an impact on LC such as $EQD2_{Tumour}$, GTV size, histology (non-SCC versus SCC), Durvalumab (yes or no). As for baseline and treatment characteristics as well as for side effects, the comparison between immunotherapy and non-immunotherapy groups was done by non-parametric testing with the Mann-Whitney-*U* test for each variable.

Results

Between March 21st 2020 and April 11th 2023, 12/14 (86 %) Austrian radiation oncology centres recruited 243 patients for the current study. Patients who had at least one follow-up visit three months after the end of CRT were eligible so that 200 individuals remained (supplementary Fig. 1). In 11 patients (5.5 %) follow-up data were missing and one patient (0.5 %), who was treated during the study period, had been diagnosed with NSCLC before the study was approved by the lead ethics committee in Salzburg. Finally, 188 patients with a median follow-up of 15.1 months (range: 3.3–37.6) were eligible for this analysis. The median number of patients per centre was 17 (range: 1–89). Approximately 60 % of the patients in both groups were male ($p = 0.955$) with a median age of 67 (range: 41–84) and 68 (range 36–91) years, respectively ($p = 0.903$). More than 90 % of the patients in each group had a good performance score, i.e. ECOG 0–1 ($p = 0.378$). Tumor specific characteristics, such as histology ($p = 0.089$) and disease stage ($p = 0.795$) were also distributed equally in both groups. As expected, a significant difference was found between the two groups with regard to PDL-1 status ($p < 0.001$), which was known in 173/188 (93 %) patients (Table 1).

CRT was administered sequentially in 129/188 (69 %) patients with VMAT/IMRT as the radiation treatment technique of choice in 182/188 (97 %) of cases. Of the remaining 6/188 (3 %) patients, one was treated with SABR in three fractions of 15 Gy (65 %-isodose), whereas the other five received conventional 3D-planning (Table 2). With a median of 44.7 ml (range: 0.24–483.8) the gross tumor volume (GTV) was significantly ($p = 0.004$) smaller in the immunotherapy group than in the non-immunotherapy group (median: 79.2 ml, range: 1–784.1). The total median EQD2 to the primary tumour was 66 Gy (range: 32.5–100) compared to 60 Gy (range: 24.8–100) and therefore significantly higher in the first group (<0.001). The total radiation dose both to involved and electively irradiated lymph nodes did not differ significantly between groups (Table 2). Chemotherapy was administered as a platinum-doublet (carboplatinum or cisplatinum) combined with one of the following substances in dependence of histology: pemetrexed, taxane, gemcitabine or vinorelbine. In the immunotherapy group 92/130 (71 %) and 35/130 (27 %) patients, respectively, received chemotherapy prior and concomitantly to radiation. In the non-immunotherapy group 37/58 (64 %) and 12/58 (21 %) patients, respectively, had chemotherapy prior and concomitantly to radiation. Details on chemotherapy regimens are provided in supplementary Table 1.

Table 1
Patient characteristics (AC = adenocarcinoma, SCC = squamous cell carcinoma, NOS = not otherwise specified).

Patients N = 188				
		Immunotherapy n = 130 (%)	No immunotherapy n = 58 (%)	p-Value
Sex	male	78 (60)	36 (62)	0.788
	female	52 (40)	22 (38)	
Age (years)	median	67	68	0.955
	range	41–84	36–91	
Smoking status	never	10 (8)	3 (5)	0.556
	ex	75 (58)	33 (57)	
	current	45 (35)	22 (38)	
ECOG	0–1	123 (95)	53 (91)	0.403
	2–3	7 (5)	5 (9)	
Histology	AC	72 (55)	26 (45)	0.089
	SCC	52 (40)	26 (45)	
	NOS	5 (4)	6 (10)	
PDL-1	< 1 %	17 (13)	26 (45)	<0.001
	> 1 %	105 (81)	25 (43)	
	unknown	8 (6)	7 (12)	
T-stage	Tis	1 (1)	1 (2)	0.179
	1	21 (16)	5 (9)	
	2	15 (12)	8 (14)	
	3	41 (32)	15 (26)	
	4	50 (38)	29 (50)	
	unknown	2 (2)	0 (0)	
N-stage	0	9 (7)	6 (10)	0.428
	1	7 (5)	9 (16)	
	2	86 (66)	28 (48)	
	3	28 (22)	15 (26)	
M-stage	0	130 (100)	58 (100)	n.a.
	1	0 (0)	0 (0)	
UICC	IIIa	45 (35)	22 (38)	0.795
	IIIb	59 (45)	24 (41)	
	IIIc	26 (20)	12 (21)	

While 81 % (105/130) of the patients who received immunotherapy were PD-L1 positive, 13 % (17/130) were negative and in 6 % (8/130) the status was unknown (Table 1). Twenty-five patients who were PDL1 positive did not receive immunotherapy because of one of the following reasons: pulmonary toxicity from previous CRT (8), death shortly after completion of CRT (4), osimertinib treatment (1). In 12/188 (6 %) patients the reason was unknown. Durvalumab was administered in 113/130 patients (87 %). The other 17 patients received either Pembrolizumab (13), Nivolumab (1) or Atezolizumab (3) (Table 2). The median time interval between the end of CRT and the start of Durvalumab was 14 days (range: 1–65) with 5/113 (4 %) patients having a delay of more than 42 days. The median number of cycles was nine (range: 1–30). While in 61/113 (54 %) patients 1 to 10 cycles were administered, 32/113 (28 %) individuals received 11–20 cycles. Only 20/113 (18 %) patients had 21 or more cycles. We used the number of cycles and the administration of cortisone as proxies for finishing therapy as well as treatment discontinuation due to pulmonary toxicity. Twenty of 113 (18 %) patients had 21 to 30 cycles and therefore stopped treatment. Additionally, 22/113 (19 %) had cortisone treatment for one of the following reasons: pneumonitis (15), COPD exacerbation (3), lung fibrosis (2), joint pain (1), pancreatitis (1).

With 25 local failures the LC rates were 93 % and 74 % at 12 and 24 months, respectively (Fig. 1). Patients who recieved > 66 Gy, had a 2-year LC rate of 86 % compared to the 60 % in the SoC group (Fig. 2; HR = 0.41; 95 %-CI: 0.17–0.98; $p = 0.038$). Additionally, we applied the same stratification criteria as PACIFIC-R, i.e. CRT sequence, PDL1 status, UICC disease stage and histology, in order to test their influence on LC. Patients with non-SCC tumors showed better 2-year LC rates than those with squamous cell histology (supplementary Fig. 2; 85 % versus 59 %; HR = 2.60; 95 %-CI: 1.16–5.83; $p = 0.016$). Multivariate analysis (Cox regression, forward stepwise) revealed that $EQD2_{Tumour}$ (HR 0.378; 95 %-CI: 0.157–0.911; $p = 0.030$) and histology (HR 2.721; 95 %-CI: 1.208–6.128; $p = 0.016$) impacted LC, whereas Durvalumab and GTV

Table 2
Treatment characteristics (CRT = chemoradiotherapy, VMAT = volumetric arc therapy, IMRT = intensity modulated radiotherapy, EQD2 = biologically equivalent dose in 2 Gy fractions, GTV = gross tumour volume).

Treatment N = 188			Immunotherapy n = 130 (%)	No immunotherapy n = 58* (%)	p-Value
Treatment sequence	concomitant CRT		35 (27)	12 (21)	0.501
	sequential CRT		92 (71)**	37 (64)***	
	radio(immuno)therapy		3 (3)	9 (16)	
Immune Checkpoint inhibitors	Durvalumab		113 (87)	x	n.a.
	Pembrolizumab		13 (10)	x	
	Nivolumab		1 (1)	x	
	Atezolizumab		3 (2)	x	
RT Technique	VMAT/IMRT		125 (96)	57 (98)	0.446
	3-D		5 (4)	1 (2)	
Tumor	EQD2	median	66	60	<0.001
		range	32.5–100	24.8–100	
	GTV	median	44.7	79.2	0.004
		range	0.24–483,8	1 – 784.1	
Lymph nodes	EQD2	median	57.3	50	0.179
		range	31.3–70	24 – 81.3	
	GTV	median	33,75	53	0.209
		range	1–408,1	1,9–473	
Elective nodal irradiation	EQD2	median	32.5	51.6	0.242
		range	32.5–60	32.5–54	
	GTV	median	86	137	0.374
		range	2–429	83.5–265	

* This group includes one patient who received osimertinib.
** Two patients in this group received chemotherapy after radiotherapy.
*** One patient in this group received chemotherapy after radiotherapy.

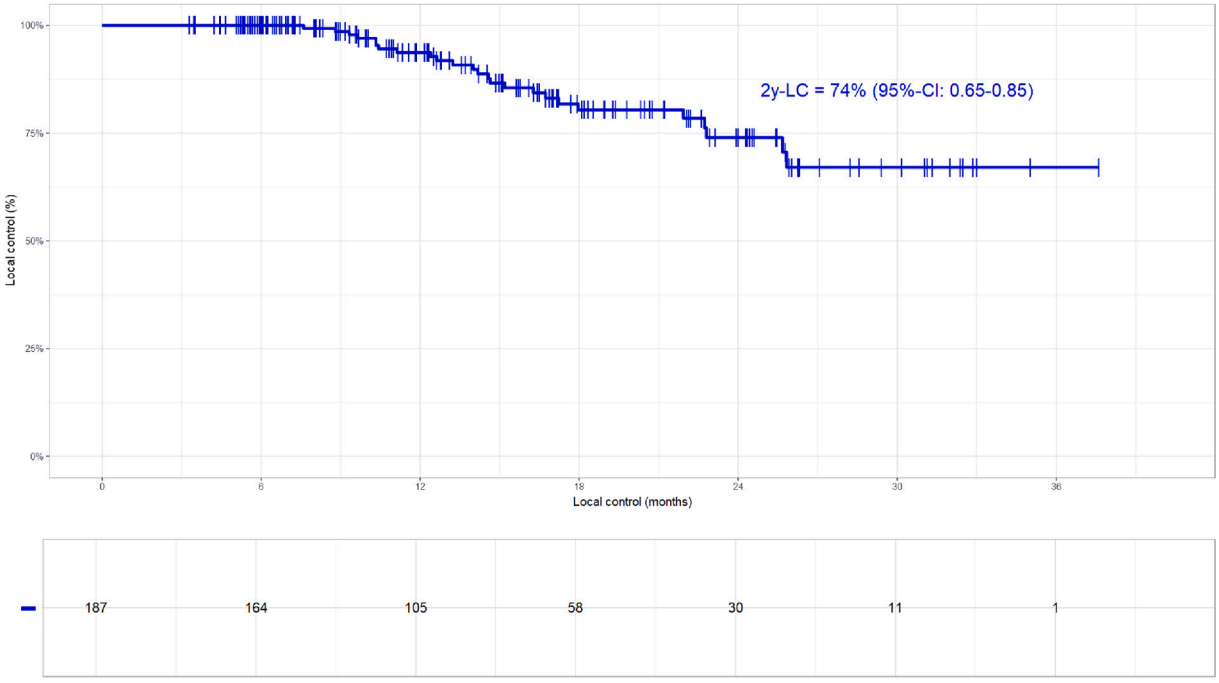

Fig. 1. The 2-year local control rate was 74 % (95 %-CI: 0.65–0.85; N = 25/187 events).

did not. The risk of higher local relapse due to enhanced local invasiveness with SCC [27] became insignificant with higher total radiation doses > 66 Gy (supplementary Fig. 3). Likewise, the time to event analysis revealed that Durvalumab had no influence on LC (supplementary Fig. 4). In the whole cohort of 188 patients 67 had progressive disease. As shown in Fig. 3, the median PFS was 22.7 months (95 %-CI: 17.7–30.7). The 12- and 24-months PFS were 77 % and 47 %, respectively. Patients who received CRT followed by Durvalumab (N = 113), had better mPFS (Fig. 4; HR = 1.88; 95 %-CI: 1.16–3.05; p = 0.009) than those without Durvalumab (N = 75): 25.8 months (95 %-CI: 21.9-not reached; 35 progressions) versus 15.7 months (95 %-CI: 13.2–27.8; 32 progressions). Again, we applied the same stratification variables to the current cohort as PACIFIC-R [16], which revealed better mPFS for UICC IIIa patients (mPFS not reached) compared to 17.2 months (95 %-CI: 15.2–26.8) in UICC IIIb/c (supplementary Fig. 5; HR = 1.99, 95 %-CI: 1.13–3.51; p = 0.015). Overall, 50/188 (27 %) deaths occurred. The preliminary median overall survival (OS) was 33 months (95 %-CI: 30.8–35.2). The estimated 24-months OS rate was 65 %.

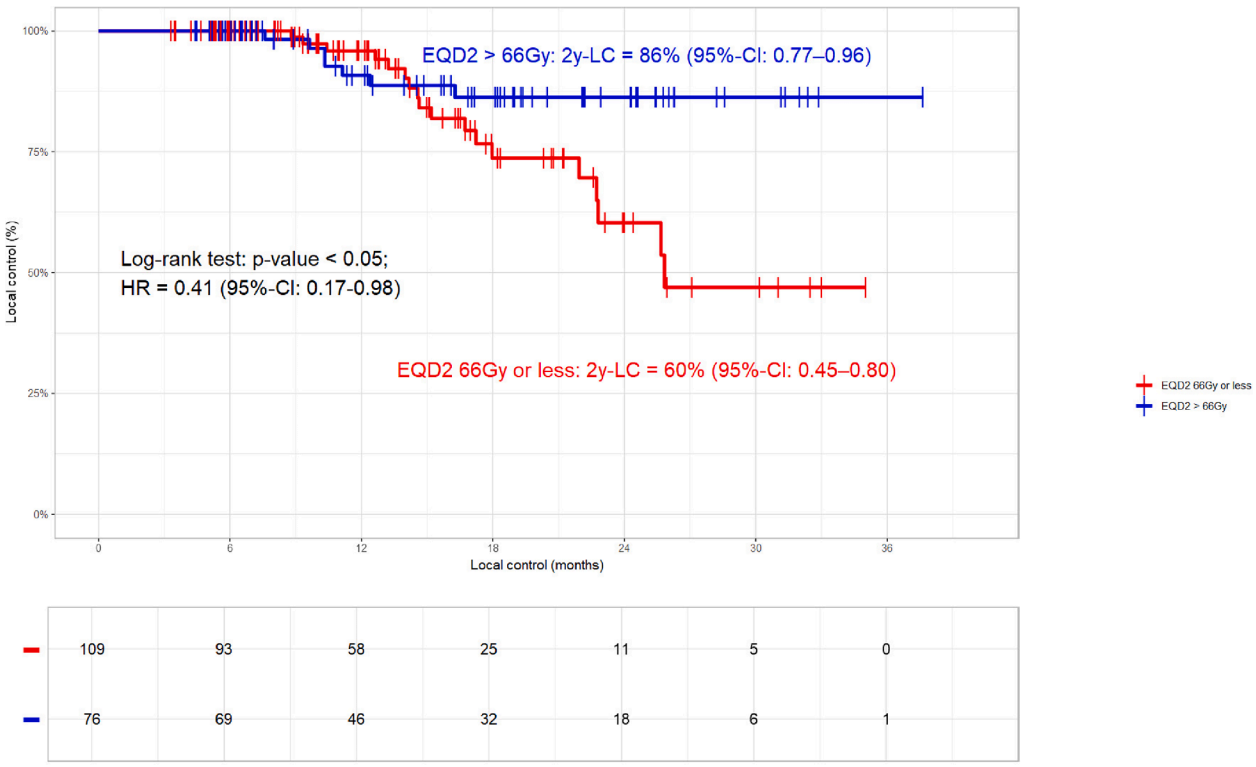

Fig. 2. Local control (LC) stratified by biologically equivalent dose (EQD_2) to the tumor. The 2-year LC rates were 86 % (95 %-CI: 0.77–0.96; n = 7/75 events) and 60 % (95 %-CI: 0.45–0.80; n = 18/110 events) in the high-dose and SoC groups, respectively (log-rank p-value = 0.038).

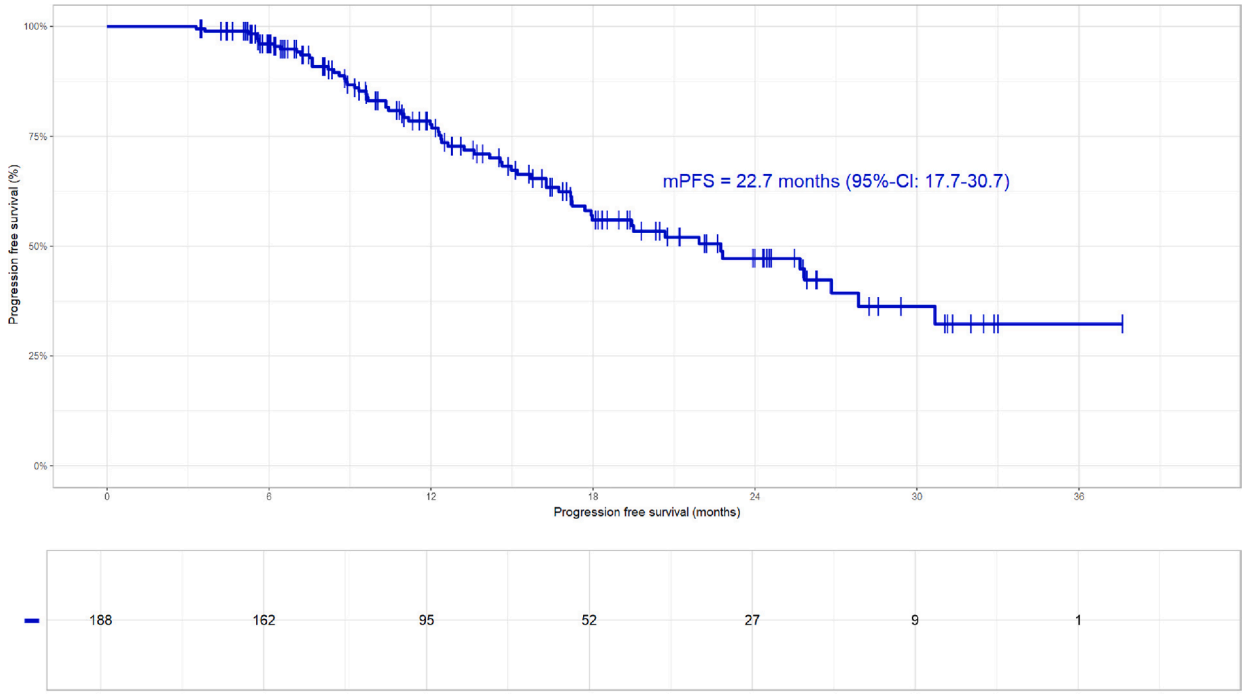

Fig. 3. The median progression free survival (mPFS) was 22.7 months (95 %-CI: 17.7 – 30.7; N = 67/188 events).

Altogether, 65/188 (34.6 %) and 45/188 (23.9 %) cases of esophageal and pulmonary toxicities were observed. These main side effects of thoracic chemoradio(immuno)therapy were equally distributed between immunotherapy and non-immunotherapy groups: grade 1 to 3 esophageal toxicity 27 % versus 52 % (p = 0.841) and grade 1 to 3 pulmonary toxicity 26 % versus 24 % (p = 0.902). One case of grade 4 pneumonitis (0.6 %) was observed in a patient who received Osimertinib for metastatic progression in the brain. This patient had completed thoracic chemoradiation with a total dose of 60.5 Gy six months before (Table 3). Since the administration of high radiation doses together with Durvalumab may have a supra-additive effect in terms of pulmonary toxicity, we tried to model its incidence in dependence of volume

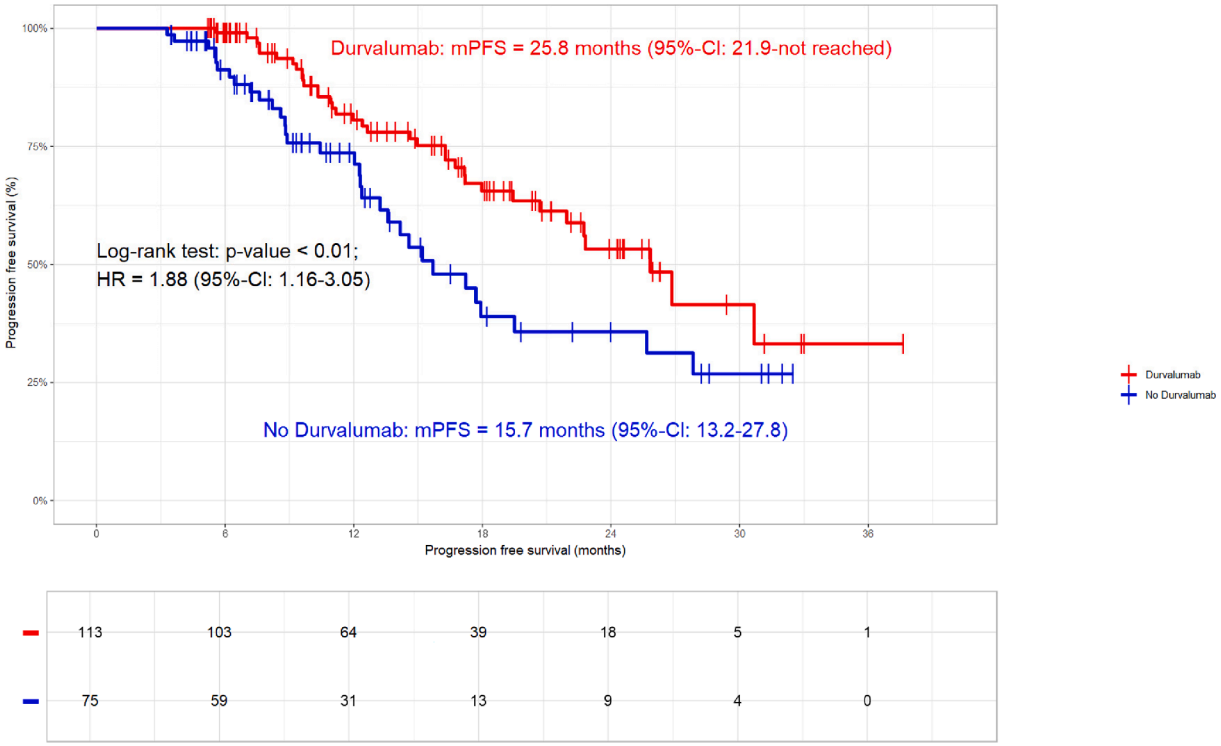

Fig. 4. Progression free survival stratified by Durvalumab. The median PFS for patients with and without Durvalumab were 25.8 months (95 %-CI: 21.9 – not reached; n = 35/113 events) and 15.7 months (95 %-CI: 13.2 – 27.8; n = 32/75 events), respectively (log-rank p-value = 0.009).

Table 3
Toxicity.

Toxicity N = 188				
		Immunotherapy n = 130 (%)	No immunotherapy n = 58 (%)	p-Value
Esophagitis	Grade 1	10 (8)	7 (12)	0.842
	Grade 2	24 (18)	22 (38)	
	Grade 3	1 (1)	1 (2)	
	Grade 4	0 (0)	0 (0)	
	Grade 5	0 (0)	0 (0)	
Pneumonitis	Grade 1	13 (10)	5 (9)	0.902
	Grade 2	19 (15)	5 (9)	
	Grade 3	1 (1)	1 (2)	
	Grade 4	0 (0)	1 (2)	
	Grade 5	0 (0)	0 (0)	
Hematologic	any grade	2 (2)	2 (3)	n.a.
Other	any grade	9 (7)	5 (9)	n.a.

(Fig. 5). Of the 75 patients who received high dose irradiation, 19 developed pneumonitis grade 1 to 3 (25 %). The subcohort was divided by volume increments of 10 ml up to 99 ml for the GTV and – due to the small patient numbers – in a 100–200 ml and > 200 ml group. A significant volume-toxicity correlation could not be established (Fig. 5). Similarly, the administration of Durvalumab in the 57/75 (76 %) patients did not correlate with the incidence of pneumonitis.

Discussion

ALLSTAR is a multi-institutional prospective registry for unresectable NSCLC stage III patients treated with chemoradioimmunotherapy. We could show that with total radiation doses beyond 66 Gy, which was the upper limit in the PACIFIC trial [3,4], LC improved significantly compared to SoC (Fig. 2). We could also demonstrate that Durvalumab prolonged PFS (Fig. 4) but had no impact on LC (supplementary Fig. 4).

The median follow-up was 15.1 months, which is in the range of prospective trials [3,4,28], but shorter than other RWD sets [16,17]. In the whole cohort 25/188 (13 %) local failures were observed (Fig. 1), which is similar to the German EAP study [19]. This very same study and ALLSTAR are the only ones to report LC as an endpoint, which gains additional importance since a pattern of failure analysis from the PACIFIC [20] trial showed that Durvalumab did not improve LC rates compared to historic series [7–11]. With 86 % the 2-year LC rates in the dose escalation group in ALLSTAR were significantly higher than the 60 % in patients who received SoC (Fig. 2). A single centre analysis on patterns of failure by Friedes revealed a loco-regional control rate of 81 % at two years, which is similar to ours [29]. Of note, the median total dose in this retrospective analysis was 66.6 Gy emphasizing the potentially beneficial effect of dose-escalation in terms of local control. A systematic review lists only one small study with 31 patients, 26 % of which were treated with total doses beyond 66 Gy [14], whereas in ALLSTAR the proportion of patients receiving 66 Gy or more was 39.8 %. It must be pointed out that this result has to be taken with a grain of salt since tumor size was smaller in the high dose group although on MVA it did not impact LC. Also, the curves in the Kaplan-Meier-plot for LC intersect twice during the first year. Since most patients received Durvalumab, this could be interpreted as an early – but not long-lasting – ICI effect on the primary tumor, which blurs the impact of high dose radiation during the first year after RT. In the long run, however, acquired immunotherapeutic resistance to Durvalumab may play a role [30]. Hence the effect of radiation dose escalation becomes visible as a plateau in the Kaplan-Meier plot (Fig. 2). Although it appears rewarding to combine ICI with high dose thoracic radiation [22,23], we agree with Girard that the optimal radiation dose together with ICI remains an open question [16], which can only be addressed in prospectively randomized phase III trials.

In accordance with PACIFIC [4], mPFS in patients receiving Durvalumab was better than in those without (Fig. 4). The 25.8 months is almost exactly the same number as in the Korean RWD study [17] and slightly above the 24.9 months for PD-L1 positive patients treated with Durvalumab in the PACIFIC trial [4]. This slight superiority in our non-

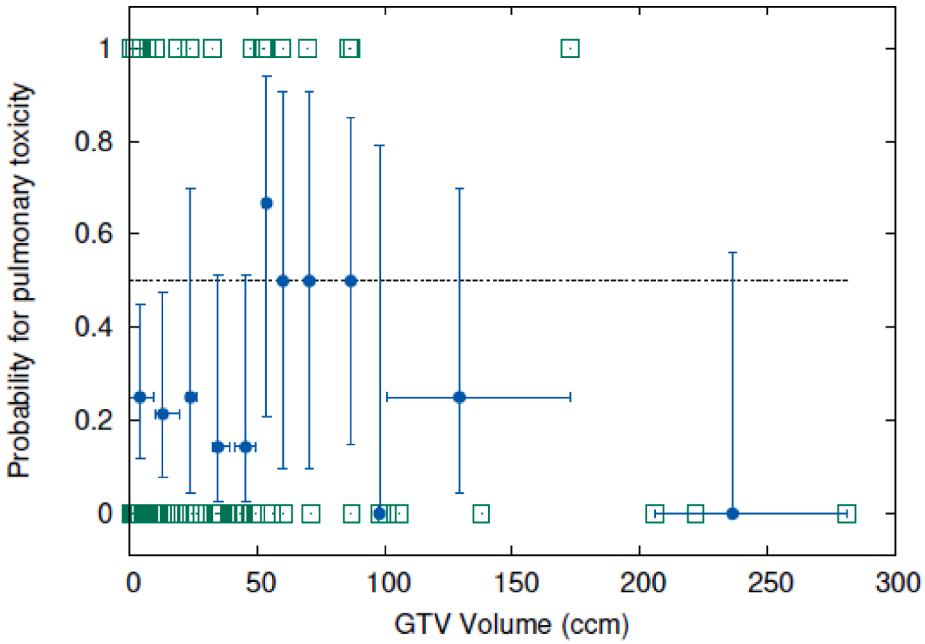

Fig. 5. Pulmonary toxicity in dependence of gross tumor volume (GTV).

selected patient population may have to do with the fact that we calculated mPFS from the date of pathological diagnosis, whereas PACIFIC, PACIFIC-R and the German EAP study used the date of randomization or first dose of Durvalumab for indexing [4,16,19]. The comparatively short delay for Durvalumab start [14] could be another reason for this favourable PFS, which corroborates the notion that maintenance therapy should be preferably initiated within 14 days completion of CRT [4]. In contrast to PACIFIC-R [16], but similar to the German [19] and Korean [17] RWD studies, our analysis revealed no difference in PFS when the cohort was stratified according to PDL-1 status, which questions the EMA decision to exclude PDL1 negative patients from Durvalumab treatment in Europe [31].

Overall, pulmonary toxicity rates were in the range of previous RWD publications with 15 – 36 % [14,16–19] and the placebo arm of the PACIFIC trial [4]. As opposed to our dataset, at least one case of lethal pneumonitis was reported in each of these RWD studies [16–19] with a pooled incidence of 6 % grade 3 or higher pulmonary toxicity [14]. Although high dose radiation together with Durvalumab is said to increase toxicity supra-additively, we could neither establish a GTV nor Durvalumab dependent correlation with the incidence of pulmonary toxicity in our data. This partly contradicts published reports [32]. A possible explanation for this finding could be the fact that VMAT/IMRT was the predominant radiation technique. A post-hoc analysis of the RTOG0617 trial by Chun et al. concluded that VMAT/IMRT reduced the incidence of pneumonitis $>$ G2 [33]. This may lead to an underestimation of clinically less relevant pulmonary toxicities, thereby hampering an exact modelling of this AESI. As for toxicity during chemoradiation, esophagitis was predominant with a cumulative rate of 42 %, which resembles the approximately 45 % reported in RTOG 0617 from the pre-immunotherapy era [11].

PD-L1 testing and immunotherapy administration in ALLSTAR reflect close adherence to treatment guidelines [5,6]. In 93 % of the patients the PD-L1 status was known, which is on the upper edge of the published range between 60 % and 91 % [4,14,16–17,19,28,34–35]. Almost 90 % of the patients who received immunotherapy were treated with Durvalumab. Of note, 17 PD-L1 negative patients and eight patients with unknown PD-L1 status received Durvalumab. This is in accordance with administration practices in the PACIFIC study [3,4] but contradicts the much disputed European Medicines Agency (EMA) decision [31]. The median interval between the end of CRT and the start of Durvalumab was 14 days compared to 26 to 56 days in PACIFIC-6 [28] and prior RWD studies [16–18,35,36]. In PACIFIC-R, immunotherapy was initiated within 42 days in less than one third of the patients, which prompted commentators on this largest RWD series to question the applicability of this limit in clinical practice [37]. In our study however, 96 % of the patients received the first dose of Durvalumab within 42 days, so that in this respect we cannot agree with O'Leary's criticism [37]. In 4 % of the patients treated at two centres, immunotherapy was commenced before finishing RT, which is done in very rare cases as reported also by PACIFIC-R [16]. The median number of nine Durvalumab cycles in our patient population was comparable to the prospective trial on sequential chemoradioimmunotherapy (sCRIT) [28] and most RWD studies (summarized by Wang [14]) but less than half in the original PACIFIC trial [4]. Reasons for Durvalumab treatment discontinuation were therapy completion (18 %), progressive disease (31 %) and adverse events (19 %). The latter is especially important since this is a prognosticator for worse OS [38]. The 18 % treatment completion are very similiar to recent RWD data from the US [36] but markedly lower than the 43 % in other RWD studies [16,19]. A major reason could be a certain degree of inaccuracy in the definition of therapy completion. Patients who completed therapy had received 21 or more cycles. But if we assume that a whole year of Durvalumab maintenance therapy would entail 26 cycles on a bi-weekly basis without interruptions [16], only 7/113 (6 %) patients in ALLSTAR could be regarded as having finished the full course of Durvalumab maintenance therapy. This is in the same order of magnitude as PACIFIC-6 with 3 % fulfilling the whole treatment schedule as defined per protocol [28]. Girard also observed a more variable use of Durvalumab outside the strictly regulated protocol of a randomized control trial, which might mean that sometimes patients are declared as having finished treatment before reaching the above indicated 26 cycles and – on the other hand – some patients would continue therapy at the discretion of the treating physician longer than one year. This would also explain the variance in cycle numbers up to 65 in PACIFIC-R [16].

Registries like this are limited by several inherent biases concerning patient selection and data measurement. First, the patient population may not entirely respresent the landscape of unresectable NSCLC stage III disease in Austria since recruiting sites that contribute a higher number of patients are potentially more interested in adopting new strategies and questioning own approaches within scientific discussions.

Although 12/14 (86 %) of the Austrian radiation-oncology centres participated, 73.5 % of the study population were contributed by two centres. Secondly, patients in prospectively designed RCTs are followed up more stringently than in RWD studies so that LC and PFS may appear longer. As the initiation of the current study coincided with the first nationwide COVID-19 lock-down in Austria by the end of March 2020, this restriction may have been aggravated.

Conclusion

ALLSTAR, a prospective multi-institutional registry for unresectable NSCLC stage III, shows the diversity of treatment approaches at the beginning of the widespread clinical use of immunotherapy in Austria. While Durvalumab impacts PFS, LC improves with total radiation dose escalation beyond 66 Gy.

Disclaimer

The publication was supported by AstraZeneca. AstraZeneca had no influence on the manuscript and the authors are responsible for all content and editorial decisions.

CRediT authorship contribution statement

Franz Zehentmayr: Writing – original draft, Project administration, Methodology, Data curation, Conceptualization. **Petra Feurstein:** Writing – review & editing, Project administration, Investigation, Data curation. **Elvis Ruznic:** Software, Methodology, Data curation. **Brigitte Langer:** Writing – review & editing, Project administration, Investigation, Data curation. **Brane Grambozov:** Writing – review & editing, Resources, Formal analysis, Data curation. **Marisa Klebermass:** Project administration, Methodology, Investigation, Data curation. **Herbert Hüpfel:** Methodology, Investigation, Formal analysis, Data curation. **Johann Feichtinger:** Project administration, Investigation, Formal analysis, Data curation. **Danijela Minasch:** Methodology, Investigation, Formal analysis, Data curation. **Martin Heilmann:** Methodology, Investigation, Formal analysis, Data curation. **Barbara Breitfelder:** Project administration, Investigation, Formal analysis, Data curation. **Claudia Steffal:** Writing – review & editing, Methodology, Investigation, Data curation. **Gisela Gastinger-Grass:** Methodology, Investigation, Formal analysis, Data curation. **Karoline Kirchhammer:** Project administration, Investigation, Formal analysis, Data curation. **Margit Kazil:** Project administration, Investigation, Formal analysis, Data curation. **Heidi Stranzl:** Project administration, Investigation, Formal analysis, Data curation. **Karin Dieckmann:** .

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110294.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA: a Cancer J Clin 2021;71:7–33. https://doi.org/10.3322/caac.21654.
[2] Gridelli C, Rossi A, Carbone DP, et al. Non-small-cell lung cancer (In English) ARTN 15009 Nat Rev Dis Primers 2015;1. https://doi.org/10.1038/nrdp.2015.9.
[3] Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379:2342–50. https://doi.org/10.1056/NEJMoa1809697.
[4] Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017;377:1919–29. https://doi.org/10.1056/NEJMoa1709937.
[5] Daly ME, Singh N, Ismaila N, et al. Management of stage III non-small-cell lung cancer: ASCO guideline. J Clin Oncol 2022;40(12). https://doi.org/10.1200/Jco.21.02528. 1356-+. (In English).
[6] Remon J, Soria JC, Peters S, Comm EG. Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy (In English) Ann Oncol 2021;32:1637–42. https://doi.org/10.1016/j.annonc.2021.08.1994.
[7] Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 1999;17:2692–9. Clinical Trial Clinical Trial, Phase III Randomized Controlled TrialResearch Support, Non-U.S. Gov't) (In eng) (http://www.ncbi.nlm.nih.gov/pubmed/10561343.
[8] Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer 2004;46:87–98. https://doi.org/10.1016/j.lungcan.2004.03.004.
[9] Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95–01 Study. J Clin Oncol 2005;23:5910–7. Clinical Trial Clinical Trial, Phase III Multicenter Study Randomized Controlled TrialResearch Support, Non-U.S. Gov't) (In eng). DOI: 10.1200/JCO.2005.03.070.
[10] Curran WJ. Sequential vs concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410 (vol 103, pg 1452, 2011). J Natl Cancer Inst 2012;104(1). https://doi.org/10.1093/jnci/djr487. 79-79. (In English).
[11] Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16:187–99. https://doi.org/10.1016/S1470-2045(14)71207-0 (In English).
[12] Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181–90. https://doi.org/10.1200/JCO.2009.26.2543.
[13] Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes from the PACIFIC trial: Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. J Clin Oncol 2022. https://doi.org/10.1200/JCO.21.01308.
[14] Wang Y, Zhang T, Huang YL, et al. Real-world safety and efficacy of consolidation durvalumab after chemoradiation therapy for stage III non-small cell lung cancer: A systematic review and meta-analysis. Int J Radiat Oncol 2022;112:1154–64. https://doi.org/10.1016/j.ijrobp.2021.12.150 (in English).
[15] Jazieh AR, Onal HC, Tan DSW, et al. Real-world treatment patterns and clinical outcomes in patients with stage III NSCLC: Results of KINDLE, a multicountry observational study. J Thorac Oncol 2021;16:1733–44. https://doi.org/10.1016/j.jtho.2021.05.003 (in English).
[16] Girard N, Bar J, Garrido P, et al. Treatment characteristics and real-world progression-free survival in patients with unresectable stage III NSCLC who received durvalumab after chemoradiotherapy: findings from the PACIFIC-R study (In English) J Thorac Oncol 2023;18:181–93. https://doi.org/10.1016/j.jtho.2022.10.003.
[17] Park CK, Oh HJ, Kim YC, et al. Korean real-world data on patients with unresectable stage III NSCLC treated with durvalumab after chemoradiotherapy: PACIFIC-KR. J Thorac Oncol 2023;18:1042–54. https://doi.org/10.1016/j.jtho.2023.04.008 (In English).
[18] Preti BTB, Sanatani MS, Breadner D, et al. Real-world analysis of durvalumab after chemoradiation in stage III non-small-cell lung cancer. Curr Oncol 2023;30:7713–21. https://doi.org/10.3390/curroncol30080559 (In English).
[19] Faehling M, Schumann C, Christopoulos P, et al. Durvalumab after definitive chemoradiotherapy in locally advanced unresectable non-small cell lung cancer (NSCLC): Real-world data on survival and safety from the German expanded-access program (EAP) (In English) Lung Cancer 2020;150:114–22. https://doi.org/10.1016/j.lungcan.2020.10.006.
[20] Raben D, Rimner A, Senan S, et al. Patterns of disease progression with durvalumab in stage III non-small cell lung cancer (PACIFIC) (In English) Int J Radiat Oncol 2019;105:683. https://doi.org/10.1016/j.ijrobp.2019.08.034.
[21] Mauguen A, Le Pechoux C, Saunders MI, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. J Clin Oncol 2012;30:2788–97. https://doi.org/10.1200/JCO.2012.41.6677 (Meta-Analysis Research Support, Non-U.S. Gov't) (In eng).
[22] Landman Y, Jacobi O, Kurman N, et al. Durvalumab after concurrent chemotherapy and high-dose radiotherapy for locally advanced non-small cell lung cancer (In English) Artn 1959979 Oncoimmunology 2021;10. https://doi.org/10.1080/2162402x.2021.1959979.
[23] Wass R, Hochmair M, Kaiser B, et al. Durvalumab after Sequential High Dose Chemoradiotherapy versus Standard of Care (SoC) for Stage III NSCLC: A Bi-Centric Trospective Comparison Focusing on Pulmonary Toxicity (In English) ARTN 3226 Cancers 2022;14. https://doi.org/10.3390/cancers14133226.
[24] Bentzen SM, Dorr W, Gahbauer R, et al. Bioeffect modeling and equieffective dose concepts in radiation oncology–terminology, quantities and units. Radiother Oncol 2012;105:266–8. https://doi.org/10.1016/j.radonc.2012.10.006.

[25] Fowler JF, Tome WA, Fenwick JD, Mehta MP. A challenge to traditional radiation oncology. Int J Radiat Oncol Biol Phys 2004;60:1241–56. https://doi.org/10.1016/j.ijrobp.2004.07.691 (In eng).
[26] Machtay M, Paulus R, Moughan J, et al. Defining local-regional control and its importance in locally advanced non-small cell lung carcinoma. J Thorac Oncol 2012;7:716–22. https://doi.org/10.1097/JTO.0b013e3182429682.
[27] Kishi N, Matsuo Y, Shintani T, et al. Recurrence patterns and progression-free survival after chemoradiotherapy with or without consolidation durvalumab for stage III non-small cell lung cancer. J Radiat Res 2023;64:142–53. https://doi.org/10.1093/jrr/rrac057.
[28] Garassino MC, Mazieres J, Reck M, et al. Durvalumab After Sequential Chemoradiotherapy in Stage III, Unresectable NSCLC: The Phase 2 PACIFIC-6 Trial. J Thorac Oncol 2022;17:1415–27. https://doi.org/10.1016/j.jtho.2022.07.1148 (In English).
[29] Friedes C, Iocolano M, Lee SH, et al. Patterns of failure, low-volume relapse, and subsequent ablative management in locally advanced non-small cell lung cancer treated with definitive chemoradiation and consolidation immune checkpoint inhibitors. Int J Radiat Oncol Biol Phys 2024;118:1435–44. https://doi.org/10.1016/j.ijrobp.2023.10.005.
[30] Syn NL, Teng MWL, Mok TSK, Soo RA. De-novo and acquired resistance to immune checkpoint targeting. Lancet Oncol 2017;18:e731–41. https://doi.org/10.1016/S1470-2045(17)30607-1.
[31] Peters S, Dafni U, Boyer M, et al. Position of a panel of international lung cancer experts on the approval decision for use of durvalumab in stage III non-small-cell lung cancer (NSCLC) by the Committee for Medicinal Products for Human Use (CHMP) (In English) Ann Oncol 2019;30:161–5. https://doi.org/10.1093/annonc/mdy553.
[32] Jung HA, Noh JM, Sun JM, et al. Real world data of durvalumab consolidation after chemoradiotherapy in stage III non-small-cell lung cancer. Lung Cancer 2020;146:23–9. https://doi.org/10.1016/j.lungcan.2020.05.035 (In English).
[33] Chun SG, Hu C, Choy H, 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 2017;35:56–62. https://doi.org/10.1200/JCO.2016.69.1378.
[34] Borghetti P, Volpi G, Facheris G, et al. Unresectable stage III non-small cell lung cancer: could durvalumab be safe and effective in real-life clinical scenarios? Results of a single-center experience. Front (In English). ARTN 1208204 Oncol 2023;13. https://doi.org/10.3389/fonc.2023.1208204.
[35] Wang CC, Chiu L, Ju JS, et al. Durvalumab as consolidation therapy in post-concurrent chemoradiation (CCRT) in unresectable stage III non-small cell lung cancer patients: A multicenter observational study (In English). ARTN 1122 Vaccines-Basel 2021;9. https://doi.org/10.3390/vaccines9101122.
[36] Waterhouse D, Yong CDC, Frankart A, et al. Durvalumab real-world treatment patterns and outcomes in patients with stage III non-small-cell lung cancer treated in a US community setting. Future Oncol 2023;19:1905–16. https://doi.org/10.2217/fon-2023-0117 (In English).
[37] O'Leary C, Naidoo J. PACIFIC in the Real World. J Thorac Oncol 2023;18:133–5. https://doi.org/10.1016/j.jtho.2022.11.015 (In English).
[38] Xu T, Wu LR, Gandhi S, et al. Treatment-related pulmonary adverse events induced by chemoradiation and Durvalumab affect survival in locally advanced non-small cell lung cancer. Radiother Oncol 2022;176:149–56. https://doi.org/10.1016/j.radonc.2022.10.002 (In English).