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ORIGINAL RESEARCH

Durvalumab after concurrent chemotherapy and high-dose radiotherapy for locally advanced non-small cell lung cancer

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ABSTRACT

The standard of care for stage III non-small cell lung cancer (NSCLC) is chemoradiotherapy (CRT) followed by durvalumab. Although doses higher than 66 Gy are standard in our center, they were used in only 6.9% of patients in the PACIFIC trial. We report our experience with durvalumab after high-dose radiotherapy. The database of a tertiary hospital for patients with stage III NSCLC who were treated with CRT and adjuvant durvalumab was evaluated. Progression-free survival (PFS), overall survival (OS), and local-regional failure (LRF) were measured from the administration of durvalumab. Thirty-nine patients were included. All were treated with intensity-modulated radiation (mean dose 69.9 Gy); Median follow-up time was 20.4 months (range 1–35.4). At 12 months, PFS was 49%, OS 79%, and LRF 14%. Intrathoracic failure at first progression was demonstrated in 8 (21%) patients. Adverse events requiring corticosteroids occurred in 10(25.6%) patients: pneumonitis – 6 (15.4%), hepatitis – 2 (5.1%), and arthralgia and pericarditis – 1 (2.6%). One patient (2.6%) died of pneumonitis. The occurrence of pneumonitis was significantly associated with lung V5 (55% vs. 42%, $p = .04$) and V20 (28% vs. 19%, $p = .01$) and mean lung dose (14.8 Gy vs.11.6 Gy, $p = .05$). The similar 12-month PFS and OS rates of our cohort and the PACIFIC trial support the use of high-dose radiotherapy in patients with stage III NSCLC. Treatment-related mortality was similar to the PACIFIC results. The intrathoracic failure rate in our cohort was lower than that reported from the PACIFIC trial, suggesting that radiation dose escalation may improve local control.

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Introduction

The treatment of locally advanced non-small cell lung cancer (NSCLC) has been rigorously debated. Early multiple phase II and one small randomized phase III trial suggested that chemotherapy concurrent with dose-escalated radiotherapy, made possible with the introduction of advanced technologies such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), yielded an improved outcome compared to combined chemotherapy and standard-dose radiotherapy.[1–4] However, these claims were reversed in the RTOG 0617 trial of Bradley et al.[5] wherein 60 Gy of concurrent chemoradiotherapy not only provided improved local control over the higher 74 Gy dose but also led to better overall survival. As a consequence of these disappointing results, the standard of care for stage III NSCLC remained unchanged for 15 y. PD and PD-L1 blockers were shown in a number of trials to be effective in metastatic NSCLC.[6,7] In 2017, this data led to a breakthrough, when the PACIFIC trial demonstrated an absolute 17% improvement in 18-months PFS with the administration of durvalumab as adjuvant treatment to standard concurrent chemoradiotherapy.[8] Later updates have shown similar improvements in OS which was durable up to 4 y after randomization.[9] Nevertheless, the intrathoracic response rate was not significantly increased over historical controls and intrathoracic progression was up to 38.5% of the durvalumab arm,[10] indicating that the majority of the benefit of durvalumab was in the prevention of distant disease.[9]

Thus, it remains unclear if there is an interaction or an improvement in outcome with dose-escalated radiotherapy in the setting of adjuvant durvalumab. The aim of the present institutional study was to evaluate the effect of radiotherapy of >66 Gy followed by durvalumab on the outcome of patients with stage III NSCLC.

Patients and methods

Study cohort and setting

The pharmacy registry of a tertiary university-affiliated medical center was retrospectively searched for all patients treated with durvalumab following definitive radiotherapy for biopsy-proven AJCC stage III NSCLC, with or without concurrent chemotherapy, from January 2018 to June 2020. Patient data were collected from the complete electronic medical records. Each case had been reviewed by a multidisciplinary tumor board prior to treatment. Patients underwent standard fluorodeoxyglucose (FDG)-positron emission tomography (PET), magnetic resonance imaging (MRI) of the brain, and mediastinal staging with endobronchial ultrasound (EBUS) when appropriate. Patients with recurrent disease or malignant pleural effusion were excluded from the study as were patients

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who had prior antineoplastic systemic therapy or were scheduled for surgical resection.

The study was approved by the institutional regulatory board.

Systemic chemotherapy

Concurrent chemotherapy was given at the discretion of the treating oncologist. The predominate regimen used was a combination of cisplatin and etoposide (SWOG), as previously published.[11]

Radiotherapy

All patients underwent computed tomography (CT) simulation with intravenous contrast when appropriate. T-bar and Vac-Lok bags were used for immobilization. Planning was done on Eclipse™, v. 13.5 (Varian, Palo Alto, CA, USA). The gross tumor volume (GTV) included all gross disease identified on FDG-PET. As the dose was escalated in these patients, a very minimal clinical target volume (CTV) of 2–3 mm was used. Expansion of the planning treatment volume (PTV) was based on four-dimensional CT or other respiratory excursion assessment. IMRT treatment plans were generated in all cases utilizing standard thoracic dose volume. PTV was optimized such that 95% of the planned dose covered 95% of the planned volume.

IGRT

All patients were treated with daily image-guided radiation therapy (IGRT) using daily kilo-voltage (KV) imaging and, with time, daily cone beam CT (CBCT).

Restaging and durvalumab therapy

In view of the results of the PACIFIC trial which encouraged a minimal time lag between completion of radiotherapy and initiation of durvalumab, patients underwent CT scanning 2–4 weeks after radiotherapy was completed to ensure lack of progressive disease (PD) and were then started on durvalumab therapy. Durvalumab was delivered intravenously per protocol at a dose of 10 mg/kg every 2 weeks for up to 12 months or to disease progression or unacceptable toxicity.

Patient follow-up and toxicity reporting

All patients were followed for local control and survival outcome until death or end of follow-up. Toxicity, both acute and late, was recorded and graded based on the Common Terminology Criteria for Adverse Events (CTCAE), v.5.0.

Statistical analysis

Oncological outcomes of progression-free survival (PFS), overall survival (OS), and locoregional failure (LRF) were analyzed using the Kaplan–Meier method and competing risks analysis, as needed. Cox regression analysis was used to assess associations between oncological outcomes and clinical characteristics. For associations between dosimetric parameters and treatment-related adverse events, the Mann–Whitney *U*-test was used.

Results

According to pharmacy registry, a total of 67 patients received durvalumab at our center during the study period. We identified 39 patients that were treated following definitive radiotherapy for stage III. The clinical characteristics of the patients and the treatment parameters are presented in Tables 1 and 2, respectively. The chemotherapy regimen consisted of platinum doublets, with 25 (64%) and 13 (33%) with cisplatin and carboplatin doublets, respectively. Only one patient was treated without concurrent chemotherapy due to comorbidities, and two switched or stopped their chemotherapy due to toxicity. Mean radiation dose was 69.9 Gy. Prior stereotactic body radiotherapy (SBRT) for suspected lung lesions was given to two patients. Only one patient stopped the radiotherapy after a 56 Gy dose was given due to esophagitis. Median time to initiation of durvalumab was 2.2 months (range 0.6–5.3), and median number of cycles and duration of treatment were 21 (range 1–26) cycles and 10.2 (0.5–15.8) months. At the end of follow-up, 15 (38%) patients finished 1 y of adjuvant durvalumab, and 2 (5%) were still ongoing.

Figure 1 shows the oncological outcomes of the cohort. Median follow-up time was 20.4 months (range 1–35.4). The respective 1- and 2-y survival rates were as follows: PFS, 49% and 43%; OS, 79% and 68%; and LRF, 14% and 17%. Median PFS was 11.8 months; median OS was not reached. The complete metabolic response rate as defined by no viable tumor on PET CT was 18%. Univariate Cox regression analysis did not show a significant association of survival outcomes with any of the patient or treatment characteristics examined. The only exception was number of durvalumab cycles received (HR of 0.86 and 0.83 for PFS and OS, respectively, $p < .001$). Details are provided in Table 3.

Table 1. Baseline characteristics of 39 patients with stage III NSCLC

Characteristic	Value
Sex (male)	25 (64%)
Age (y), median (range)	66.5 (48.8–85.1)
Performance status	
ECOG 0	9 (23%)
ECOG 1	30 (77%)
Smoking history (yes)	33 (85%)
Histology	
Non-squamous	28 (72%)
Squamous	11 (28%)
Stage	
IIIA	27 (69%)
IIIB	12 (32%)
PDL1 expression TPS	
>1%	18 (46%)
<1%	11 (28%)
Unknown	10 (26%)
Driver mutation status (only EGFR or ALK alterations)	
Yes	3 (8%)
No	26 (66%)
Unknown	10 (26%)

NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group [score]; PDL1, programmed death ligand 1; TPS, tumor proportion score; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Imaging demonstrated first disease progression in 17 patients (43%): in the lung in 8 patients (47%), the brain in 5 (29%), and other sites in 4 (24%). Local therapy was administered in 9/17 patients (53%) and consisted of brain resection in 1, stereotactic radiosurgery in 4, and SBRT in 4. Median time to progression after local therapy was 8.6 months. A full explanation of patterns of failure is included in Table 4.

The adverse events are detailed in Table 5. The most common reported toxicities (any grade) during durvalumab therapy were fatigue in 30 patients (77%), dyspnea in 28 (72%), and endocrine abnormalities in 18 (46%). Treatment-related adverse events requiring discontinuation of durvalumab and corticosteroids occurred in 10/39 (27%) patients after a median of 8 (1–21) cycles. Only 3/10 (30%) were able to successfully resume durvalumab and complete the full year of therapy. Patients without treatment-related toxicities received a significantly higher number of cycles of treatment (19.2 vs 14, p = .05). Occurrence of treatment-related toxicity was found to be non-significantly associated with poorer PFS and OS (HR 1.4, p = .45 and HR 2.4, p = .18) respectively.

One patient (3%) patient died of pneumonitis. The occurrence of pneumonitis during durvalumab maintenance after chemoradiotherapy was significantly associated with a higher percentage of the lung volume receiving at least 5 Gy (V5) and 20 Gy (V20) relative to no pneumonitis (55% vs. 42%, p = .04 and 28% vs. 19%, p = .01, respectively), and higher mean lung dose (MLD) values (14.8 Gy vs.11.6 Gy, p = .05). The full dosimetry data are found in Table 2.

Table 2. Treatment of 39 patients with stage III NSCLC

Treatment parameter	Value
Radiation dosimetrics, mean ± SD	
Dose (Gy)	69.9 ± 3.1
GTV (cc)	118.2 ± 95.8
Lung V5 (%)	45.7 ± 15.1
Lung V20 (%)	21 ± 9.4
MLD (Gy)	12.2 ± 4.6
Heart V5 (%)	20.7 ± 2.7
Heart V20 (%)	4.2 ± 6
MHD (Gy)	5 ± 5.5
Type of chemotherapy:	n (%)
Cisplatin doublet	25(64%)
Carboplatin doublet	13(33%)
No chemotherapy	1(3%)
Response to chemoradiotherapy	
Complete response	7 (18%)
Partial response	30 (77%)
Stable disease	2 (5%)
Durvalumab therapy	
Months to initiation, median (range)	2.2 (0.6–5.3)
Number of cycles, median (range)	21 (1–26)
Duration of therapy, months, median (range)	10.4 (0.5–15.6)
Completed a full year	17(44%)
Reason for durvalumab discontinuation	
Disease progression	12 (31%)
Immune-related toxicity	7 (18%)
Patient preference	2 (5%)
Death from other causes	2 (5%)

Values are presented as n(%), unless otherwise stated.
GTV, gross tumor volume, V5, lung volume receiving at least 5 Gy; V20, lung volume receiving at least 20 Gy, MLD, mean lung dose; MHD, mean heart dose.

Discussion

Recent advances in active systemic treatments have led to an increasing importance of local therapy in breast, prostate, and other cancers, including NSCLC,[12–14] not only for local control but also for survival. The present study sought to answer the question raised by the results of the PACFIC trial: Does the decrease in distant failure rates with adjuvant immunotherapy serve as a rationale for aggressive local therapy?

A previous study in our institution showed that a radiation dose of 72 Gy with concurrent chemotherapy was safe and was associated with a remarkable 64% complete pathologic response rate.[15] Therefore, in the present trial, we chose to continue our in-house regimen followed by durvalumab, based on the consolidation of our own data with the data from the PACIFIC trial. Certainly, the question of high-dose radiotherapy in stage III NSCLC is controversial. The data from RTOG 0617 showed not only decreased overall survival with higher dose radiotherapy but also decreased local control.[5] This study is very important; however, it is not the only randomized trial asking this question. A previous smaller study by Yuan et al.[16] was positive for higher dose radiotherapy. In addition, other works have shown potential for improved outcome with higher doses as long as cardiac toxicity is minimized.[17,18] Combining these data with our own results regarding metabolic CR as mentioned above, we felt it was highly important to examine the PACIFIC regimen with higher radiation doses.

Our findings demonstrated that the toxicity with this combination is acceptable. Treatment-related pneumonitis occurred in only 15% of cases with only one grade 5 event. These data are consistent with both the results of the PACIFIC trial as well as recently published real-world data from Memorial Sloan Kettering Cancer Center.[19] In addition, as expected, the standard dose volume metrics such as V20 and MLD correlated with the occurrence of pneumonitis in our cohort, suggesting that the classic relationship between dose volume metrics and toxicity was preserved and that durvalumab was not an additive factor.

The PACIFIC trial demonstrated 55.9% 1-y progression-free survival an 81.6% overall survival[8,9] in the experimental arm. Since the publication of those results, a number of groups have reported real-world data on the same patient population. Diselets et al.[20] recently reported a multicenter cohort study that demonstrated an impressive 92% 1-y overall survival. They specifically emphasized the importance of PDL >50%, which may be confirmed in future studies. Other groups have shown similar results in outcome with future concerns mainly for learning to manage toxicity associated with this regimen.[21–23]

The 12-month outcome results in this study, namely, PFS 49%, OS 79%, and LRF 14%, are similar to other published studies using chemoradiotherapy and adjuvant durvalumab. What is noteworthy in our study is the 18% complete metabolic response rate compared to 1.5% in the PACIFIC trial.[10] This finding could suggest that in selected patients, high-dose radiotherapy combined with the PACIFIC regimen may lead to improved outcome. Further studies are needed to confirm this hypothesis.

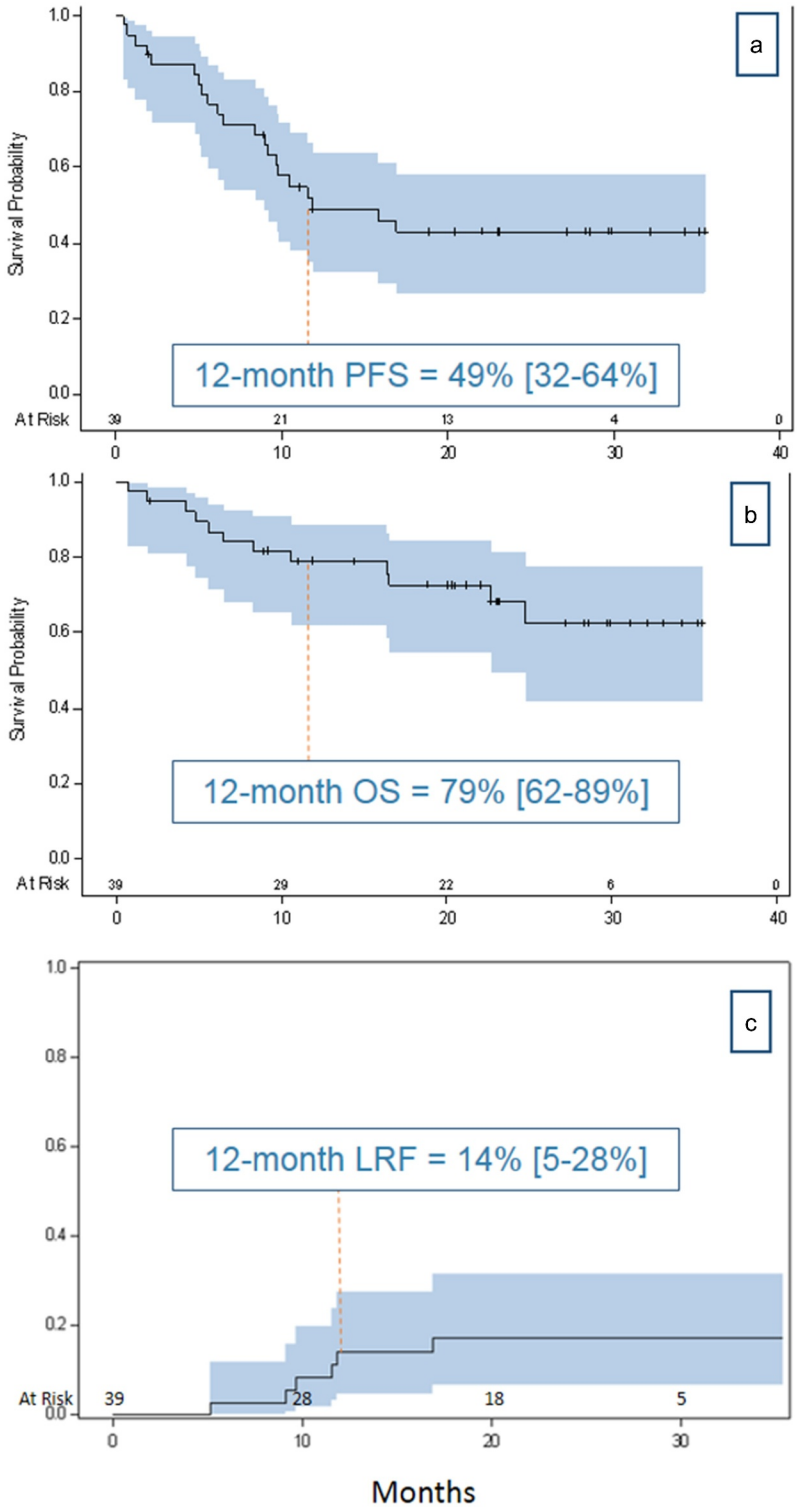

Figure 1. Kaplan–Meier graphs of PFS (a) and OS (b) and a competing risks graph of LRF (c) with 95% confidence intervals. The competing risk for LRF is death.

Table 3. Univariate analysis of patient and treatment parameters and survival outcomes

Characteristic	*N* (%)	PFS				OS			
	Unless otherwise specified	HR	P-value	CI LL	CI UL	HR	*P*-value	CI LL	CI UL
Age, y, median (range)	66.5 (48.8–85.1)	1.01	0.78	0.96	1.06	1.05	0.18	0.98	1.13
Sex									
Male	25 (64%)	1.00				1.00			
Female	14 (36%)	1.45	0.40	0.61	3.45	1.37	0.59	0.43	4.34
Performance status									
ECOG 0	9 (23%)	1.00				1.00			
ECOG 1	30 (77%)	1.81	0.29	0.61	5.38	1.89	0.41	0.41	8.71
Smoking history									
No	6 (15%)	1.00				1.00			
Yes	33 (85%)	0.94	0.92	0.32	2.82	0.99	0.99	0.21	4.53
Histology									
Non-squamous	28 (72%)	1.00				1.00			
Squamous	11 (28%)	1.78	0.20	0.73	4.33	2.11	0.21	0.66	6.77
Stage									
IIIA	27 (69%)	1.00				1.00			
IIIB	12 (32%)	1.99	0.13	0.82	4.82	1.36	0.62	0.41	4.54
Primary side									
Right lung	25 (64%)	1.00				1.00			
Left lung	11(28%)	0.74	0.54	0.29	1.92	0.65	0.51	0.17	2.40
Midline	3(8%)								
PDL1 expression									
>1%	18 (46%)	1.00							
<1%	11 (28%)	1.08	0.88	0.38	3.06	2.33	0.30	0.47	11.55
Unknown	10 (26%)								
Driver mutation status (only EGFR or ALK alterations)									
No	26 (66%)	1.00				1.00			
Yes	3 (8%)	1.25	0.77	0.28	5.56	1.49	0.71	0.18	12.45
Unknown	10 (26%)								
Type of chemotherapy									
Cisplatin doublet	25(64%)	1.00				1.00			
Carboplatin doublet	13(33%)	0.79	0.63	0.31	2.04	1.63	0.41	0.52	5.14
No chemotherapy	1(3%)								
Durvalumab therapy									
Months to initiation, median (range)	2.2 (0.6–5.3)	0.68	0.11	0.43	1.09	1.00	0.99	0.52	5.14
Number of cycles, median (range)	21 (1–26)	0.86	<0.001	0.81	0.91	0.83	<0.001	0.76	0.91
Immune-related G3+ toxicity occurrence									
No	29 (74%)	1.00				1.00			
Yes	10 (26%)	1.45	0.45	0.56	3.75	2.38	0.18	0.67	8.48

Table 4. Reported adverse events in 39 patients with stage III NSCLC during durvalumab therapy

Adverse event	Value
Fatigue	30 (77%)
Dyspnea	28 (72%)
Endocrine changes	18 (46%)
Hepatitis	14 (36%)
Diarrhea	5 (13%)
Nausea	4 (10%)
Patients with any grade 3–5 adverse event	14 (36%)
Immune related	
Pneumonitis	6 (15%)
Hepatitis	2 (5%)
Arthralgia	1 (3%)
Pericarditis	1 (3%)
Immune-related mortality – 1(3%) grade 5 pneumonitis	
Nonimmune related	
Pneumonia 2 – grade 3 Anemia 1 – grade 3 Acute myocardial infarction 1 – grade 5 Massive hemoptysis 1 – grade 5	

Table 5. Patterns of failure

Failure patterns	*N*	%
Alive without progression	18	46.2
Dead without progression	4	10.3
Site of first progression		
Intrathoracic	8	20.5
In-field	4	10.3
Out-of-field	4	10.3
Extrathoracic	9	23.1
Brain	5	12.8
Liver	2	5.1
Lymph nodes	2	5.1
Bones	2	5.1
Combined	3	7.7
Total out-of-field failures	13	33.4
Total in-field failures (including later progression)	6	15.4

Interestingly, thoracic failures in our cohort (both intrathoracic only and combined intra- and extra-thoracic) occurred in 8/39 (21%) patients and 8/17 (47%) of patients with evaluable progression. These are much lower than the pacific thoracic failure rates, which were reported by Raben et al.,[10] to be 38.5% in the entire intention-to-treat duravalumab arm, and 84% of patients with evaluable progression. While the in-field vs. out-of-field data are currently unpublished, this difference might suggest that better local control can be achieved with higher radiation doses as demonstrated in our cohort.

The present study was limited by the retrospective design and its inherent biases and the small size of the cohort which restricts the generalizability of the results. Nevertheless, our real-life results based on consecutive patients attending a large tertiary cancer center are hypothesis-generating.

In conclusion, the combination of high-dose chemoradiotherapy and adjuvant durvalumab is tolerable and leads to good results, warranting further investigation.

Disclosure statement

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