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ORIGINAL ARTICLE

Outcomes of Patients with Unresectable Stage III Non–Small-Cell Lung Cancer Treated with Durvalumab After Chemoradiotherapy

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ABSTRACT

Introduction: *This study evaluated the efficacy and safety of durvalumab in unresectable stage III non–small-cell lung cancer (NSCLC) at a tertiary centre in Hong Kong.*

Methods: *Cases of stage III NSCLC treated with radical-intent chemoradiotherapy (CRT), with or without durvalumab, from December 2017 to June 2023 were included. Outcomes, including progression-free survival (PFS) and overall survival, were analysed using the Kaplan–Meier method. Adverse events, including any-grade pneumonitis and the Common Terminology Criteria for Adverse Events grade ≥3 immune-related adverse events, were reviewed.*

Results: *A total of 113 cases were analysed (51 cases of durvalumab plus CRT and 62 cases of CRT). The durvalumab plus CRT cohort demonstrated a significantly longer median PFS compared to the CRT cohort (34.9 vs. 10.5 months; p = 0.01), while median overall survival remained immature at the time of analysis. Among patients with epidermal growth factor receptor (EGFR) mutations, the estimated PFS also favoured the durvalumab plus CRT cohort. A significantly higher incidence of any-grade pneumonitis was observed in the durvalumab plus CRT cohort (31% vs. 8%; p = 0.002), with most cases occurring within the initial 3 months of durvalumab use.*

Conclusion: *Durvalumab following CRT significantly benefitted patients with unresectable stage III NSCLC, including those with EGFR mutations. Symptomatic pneumonitis tended to occur in the first 3 months of durvalumab therapy and was generally manageable. Close follow-up during this period is recommended to facilitate early detection and intervention. Further research is warranted to understand the complex interplay among EGFR mutation status, programmed death ligand 1 expression, and treatment outcomes with and without durvalumab in NSCLC.*

Key Words: *Carcinoma, non–small-cell lung; Chemoradiotherapy; ErbB receptors; Progression-free survival*

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中文摘要

無法切除的第三期非小細胞肺癌患者在同步化學放射治療後接受度伐魯單抗治療的療效分析

梁詩雅、林美瑩、劉芷珊

引言：本研究旨在評估香港一所三級醫院針對無法切除的第三期非小細胞肺癌患者採用度伐魯單抗作為鞏固治療的效益及安全性。

方法：本研究回溯性納入於2017年12月至2023年6月期間接受根治性同步化學放射治療（放化療）的無法切除第三期非小細胞肺癌患者，依據後續是否接受度伐魯單抗治療分組。我們使用Kaplan-Meier法分析疾病無惡化存活期及整體存活期，並系統性評估不良事件，涵蓋各級別非感染性肺炎及符合「常見不良事件評價標準」【CTCAE】第3級或以上免疫相關不良反應。

結果：本研究共分析了113例患者，包括51例放化療合併度伐魯單抗及62例僅接受放化療。放化療合併度伐魯單抗組的疾病無惡化存活期中位數顯著較單獨放化療組長（34.9個月與10.5個月；p = 0.01），整體存活期中位數則在分析時尚未成熟。在表皮生長因子受體（EGFR）基因突變患者中，放化療合併度伐魯單抗組也呈現較長的預估疾病無惡化存活期。安全性方面，放化療合併度伐魯單抗組在非感染性肺炎總發生率顯著較高（31%與8%；p = 0.002），且多數病例集中於治療起始3個月內發生。

結論：同步放化療後接續度伐魯單抗治療對於第三期非小細胞肺癌患者（包括EGFR基因突變患者）具顯著臨床效益。症狀性肺炎雖易於治療初期首3個月出現，但整體可控。我們建議在此段期間密集隨訪，以監察非感染性肺炎的早期徵狀。EGFR基因突變狀態、細胞程式死亡—配體1（PD-L1）表現量及度伐魯單抗的治療效益存在複雜相互作用，有待未來研究作進一步釐清。

INTRODUCTION

The PACIFIC trial[1] showed that 1 year of durvalumab consolidation therapy following chemoradiotherapy (CRT) significantly improves the progression-free survival (PFS) and overall survival (OS) in unresectable stage III non–small-cell lung cancer (NSCLC), with a median PFS of 16.9 months and OS of 47.5 months.[2] The PACIFIC-R study[3] substantiated these findings, suggesting that real-world outcomes align with the drug's registration trial results.[4]

In Hong Kong, durvalumab has been a registered drug since October 2018 and included in the Community Care Fund Medical Assistance Programme since May 2020.[5] Given the emerging concern that patients harbouring epidermal growth factor receptor (*EGFR*) mutations may derive less benefit from immune checkpoint inhibitors, including maintenance durvalumab, studies have been conducted to review the outcomes in this subgroup.[6-8] Pneumonitis, a major adverse event associated with durvalumab, is of particular concern in patients who have undergone thoracic radiotherapy.

This study aimed to evaluate the real-world efficacy and safety of durvalumab in unresectable stage III NSCLC in a population with a high prevalence of *EGFR* mutations and to assess pneumonitis incidence relative to radiation dose, enabling early toxicity detection and optimising follow-up protocols to ensure that local patients achieve maximal therapeutic benefit with minimised risks.

METHODS

Inclusion Criteria and Data Collection

This retrospective study included patients with stage III NSCLC who were treated with chemoradiotherapy (CRT) between December 2017 and June 2023 in Princess Margaret Hospital, Hong Kong. The durvalumab cohort was drawn from the Clinical Data Analysis and Reporting System of Hospital Authority, comprising all patients who received durvalumab during the specified period. The CRT cohort—patients who received CRT only—was drawn from our department's ARIA Oncology Information System. Each case was screened via the Electronic Patient Record system for eligibility. Inclusion criteria were adult patients aged

≥18 years, diagnosed with stage III NSCLC and treated with CRT with curative intent. All patients were restaged using the 8th edition of the American Joint Commission on Cancer TNM (tumour, node and metastasis) Classification.[9] Patients who had commenced treatment in other centres must have received at least one dose of durvalumab in our hospital to be included in the analysis. Cases of proven disease progression within 2 months of CRT completion were excluded. Patient and disease demographics, details of chemoradiotherapy treatment regimens, and response to treatment were documented. Treatment-related toxicities were graded according to the CTCAE (Common Terminology Criteria for Adverse Events) version 5.0.[10]

Treatment and Follow-up

Standard radical-intent CRT in the stage III NSCLC study population involved three-dimensional conformal radiotherapy of 60 to 66 Gy at 2 Gy per fraction, typically paired with etoposide/cisplatin for two cycles once every 3 weeks. For non-squamous cases, pemetrexed/cisplatin was an alternative, especially for patients with poor venous access or concerns about tolerance. Patients unsuitable for cisplatin (e.g., creatinine clearance <50 mL/min or congestive heart failure) received weekly paclitaxel/carboplatin. Induction chemotherapy was planned on a case-by-case basis. Optimal organs-at-risk dose constraints were: (1) the percentage of lung receiving ≥20 Gy (lung V_{20Gy}) ≤30%; (2) lung V_{5Gy} ≤55%; and (3) mean lung dose (MLD) ≤15 Gy.

Durvalumab consolidation was offered to eligible patients without progression after CRT as self-funded treatment since October 2018, or with financial assistance from the Community Care Fund for those with programmed death ligand 1 (PD-L1) expression of tumour proportion score ≥1% since May 2020.[5] Durvalumab at 10 mg/kg biweekly for up to 12 months was usually started within 42 days post-radiotherapy, though this was not mandatory. Pre-cycle chest radiographs (CXR) and laboratory tests, including complete blood count, liver/renal/thyroid function, cortisol level, and fasting glucose level were taken to monitor for adverse events. Post-treatment, patients were followed up every 4 to 6 months with CXR, and carcinoembryonic antigen was also measured in cases of adenocarcinoma. Computed tomography scans were performed subject to availability and clinical judgement.

Statistical Analyses

Baseline characteristics and dosimetric parameters of the two cohorts were compared using Chi squared or Fisher's exact tests. PFS and OS were measured from the last day of radiotherapy to disease progression or death. The data cut-off was 15 June 2024. The Kaplan-Meier method was utilised to estimate PFS and OS. Subgroup analysis explored outcomes in *EGFR*-mutated (*EGFR*m) and *EGFR*–wild-type (*EGFR*wt) patients. Univariate logistic regression analysis was employed to evaluate any significant predictive factors (clinical or dosimetric) for the incidence of any-grade pneumonitis, with only significant univariate factors further analysed by multivariate analysis. Statistical analyses were conducted using commercial software SPSS (Windows version 29.0; IBM Corp, Armonk [NY], US), each with a significance level of 0.05. For missing data, a listwise deletion approach was employed to analyse cases with complete data only. Receiver operating characteristic (ROC) analysis was conducted as an exploratory measure to identify an optimal cut-off value for lung V_{20Gy} associated with pneumonitis occurrence.

RESULTS

Patient Characteristics

This study included 113 cases, with 51 in the durvalumab plus CRT cohort and 62 in the CRT cohort (Table 1). Both cohorts had a predominance of male and smoker/ex-smoker patients. The median ages were 65 years and 66.5 years in the durvalumab plus CRT and CRT cohorts, respectively. Baseline characteristics were similar, except for a higher proportion of patients with no PD-L1 expression in the CRT cohort compared with the durvalumab plus CRT cohort. Histology was mainly adenocarcinoma (41% in the durvalumab plus CRT cohort and 48% in the CRT cohort) and squamous cell carcinoma (27% and 37%, respectively). NSCLC of no specific type was reported in 27% of the durvalumab plus CRT cohort and 6% of the CRT cohort. Approximately 70% of patients had their *EGFR* status tested; 7 (14%) and 15 (24%) patients in the durvalumab plus CRT and CRT cohorts, respectively, were confirmed as *EGFR*m. Commonly used CRT chemotherapy regimens were etoposide/platinum (37% and 48%), paclitaxel/carboplatin (35% and 37%), and pemetrexed/platinum (12% and 10%) in the durvalumab plus CRT and CRT cohorts, respectively. The median duration from CRT completion to durvalumab initiation was 45 days (range, 8-172); 59% (n = 30) of patients completed the planned 26 cycles of biweekly durvalumab (median: 13.8 months). Treatment discontinuation was attributed to disease progression, adverse events, patient decision, or death (Table 2).

Table 1. Baseline characteristics (n = 113).*

	Durvalumab plus CRT cohort (n = 51)	CRT cohort (n = 62)	p Value
Patient demographics			
Sex			0.32
Male	39 (76%)	52 (84%)	
Female	12 (24%)	10 (16%)	
Age, y	65 (46-82)	66.5 (48-76)	0.67
≤60	14 (27%)	13 (21%)	
61-70	25 (49%)	31 (50%)	
>70	12 (24%)	18 (29%)	
ECOG PS score			0.19
0	45 (88%)	49 (79%)	
1	6 (12%)	13 (21%)	
Smoking status			0.43
Smoker/Ex-smoker	38 (75%)	50 (81%)	
Non-smoker	13 (25%)	12 (19%)	
Disease demographics			
Overall staging (AJCC 8th edition)			0.47
IIIA	23 (45%)	26 (42%)	
IIIB	18 (35%)	28 (45%)	
IIIC	10 (20%)	8 (13%)	
Histology			0.02
NSCLC, no specific type	14 (27%)	4 (6%)	
Squamous cell carcinoma	14 (27%)	23 (37%)	
Adenocarcinoma	21 (41%)	30 (48%)	
Others	2 (4%)	5 (8%)	
LELC	2 (4%)	1 (2%)	
Large cell carcinoma	0	2 (3%)	
Poorly differentiated carcinoma	0	2 (3%)	
EGFR status			0.27
EGFR mutated	7 (14%)	15 (24%)	
EGFR wild-type	28 (55%)	26 (42%)	
Unknown	16 (31%)	21 (34%)	
PD-L1 expression			< 0.01
<1% (negative)	4 (8%)	30 (48%)	
1%-49% (low)	21 (41%)	5 (8%)	
≥50% (high)	24 (47%)	10 (16%)	
Unknown	2 (4%)	17 (27%)	
CRT treatment			
CRT†	48 (94%)	59 (95%)	1.00‡
With induction chemo	28 (55%)	30 (48%)	0.49
With consolidation chemo	5 (10%)	36 (58%)	< 0.01
Unknown§	1 (2%)	0	0.45‡
Platinum agent with radiotherapy			0.36
Cisplatin	21 (41%)	33 (53%)	
Carboplatin	24 (47%)	26 (42%)	
Cisplatin and Carboplatin	5 (10%)	3 (5%)	
Unknown§	1 (2%)	0	
Radiotherapy			0.02
60 Gy/30 Fr	32 (63%)	49 (79%)	
66 Gy/33 Fr	14 (27%)	13 (21%)	
Others (64 Gy/30 Fr, 62 Gy/31 Fr, 60 Gy/25 Fr, 54 Gy/18 Fr, and unknown§)	5 (10%)	0	
Best response on CT			0.81
Stable disease	11 (22%)	11 (18%)	
Partial response	27 (53%)	30 (48%)	
Complete response	2 (4%)	3 (5%)	
Not available‖	11 (22%)	18 (29%)	

Abbreviations: AJCC = American Joint Committee on Cancer; chemo = chemotherapy; CRT = chemoradiotherapy; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; *EGFR* = epidermal growth factor receptor; LELC = lymphoepithelioma-like carcinoma; NSCLC = non–small-cell lung carcinoma; PD-L1 = programmed death ligand 1; PS = performance status.

* Data are shown as No. (%) or median (range).

† Defined as at least two cycles of 3-weekly chemo or five cycles of weekly treatment used concurrent with radiotherapy.

‡ Fisher's exact test was used instead of the Chi squared test.

§ One patient received CRT in the private sector and subsequent maintenance durvalumab in our hospital; a detailed treatment record could not be retrieved.

‖ CT scans were not performed, but other methods such as chest radiographs and carcinoembryonic antigen levels were used to assess the response and conclude non–disease progression.

Table 2. Reasons for and timing of durvalumab discontinuation (n = 51).*

		No. of cycles to discontinuation
Completed treatment	30 (59%)	Not applicable
Disease progression	12 (24%)	12.5 (2-19)
Adverse events	6 (12%)	5 (2-17)
Patient decision	1 (2%)	7
Death	2 (4%)	12 (5-19)

* Data are shown as No. (%) or median (range), unless otherwise specified.

At the time of analysis, all patients in the durvalumab plus CRT cohort had either discontinued or completed 26 cycles of durvalumab consolidation treatment. 94% and 95% patients in the durvalumab plus CRT and CRT cohorts, respectively, had completed CRT, defined as either having received chemotherapy once every 3 weeks for 2 cycles or a concurrent regimen once a week for 5 cycles. All patients, except for one treated in the private sector with missing data, received a radical dose of at least 60 Gy (equivalent dose in 2 Gy fractions).

Efficacy Outcomes

The median follow-up was 25.6 months for the durvalumab plus CRT cohort and 31.0 months for the CRT cohort. The median PFS was significantly longer in the durvalumab plus CRT cohort, at 34.9 months (95% confidence interval [CI] = 17.8-52.0) compared to 10.5 months (95% CI = 7.1-14.0) in the CRT cohort (p = 0.01) [Figure 1]. The median OS was 50.8 months (95% CI = 26.6-75.0) in the durvalumab plus CRT cohort and 41.5 months (95% CI = 22.2-60.7) in the CRT cohort, which was not statistically significant (p = 0.32) [Figure 2].

The estimated PFS for *EGFR*m patients was not reached in the durvalumab plus CRT cohort, compared to 7.8 months (95% CI = 3.4-12.1) in the CRT cohort. OS analysis was not performed due to the limited number of events (one in the durvalumab plus CRT cohort and 8 in the CRT cohort). Notably, all *EGFR*m patients in the durvalumab plus CRT cohort had either unknown or low PD-L1 expression, while those in the CRT cohort had either unknown or negative PD-L1 expression. No *EGFR*m patients had high PD-L1 expression.

Pneumonitis

A significantly higher incidence of any-grade pneumonitis was observed in the durvalumab plus CRT cohort compared to the CRT cohort (31% vs. 8%; p = 0.002) [Table 3]. In total, 57% of *EGFR*m patients and 27% of *EGFR*wt/*EGFR*-unknown patients in the durvalumab plus CRT cohort developed pneumonitis, compared to 0% and 10%, respectively, in the CRT cohort. Of the 16 patients in the durvalumab plus CRT cohort who developed pneumonitis, the majority (87.5%) experienced their first episode during the initial six biweekly cycles (range, 2-12). Approximately 80% of cases were grade 1 to 2 and responded to appropriate management strategies including corticosteroids, except one grade 4 pneumonitis (Table 4). Overall, 12% discontinued durvalumab treatment due to pneumonitis. In the CRT cohort, five patients (8%) developed any grade of radiation pneumonitis (RP), with onset ranging from 6 to 91 days after the last day of radiotherapy. All improved clinically after a course of steroids.

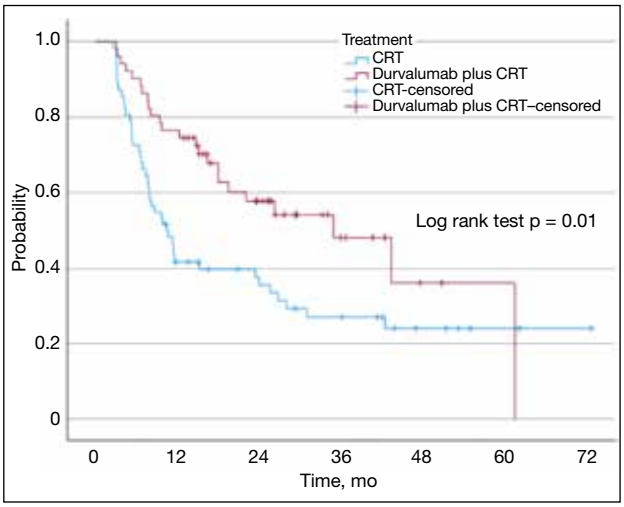

Figure 1. Progression-free survival.
Abbreviation: CRT = chemoradiotherapy.

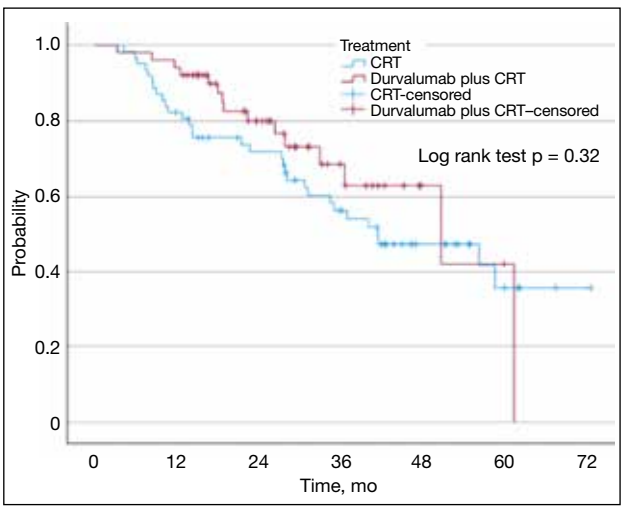

Figure 2. Overall survival.
Abbreviation: CRT = chemoradiotherapy.

The single case of grade 4 pneumonitis in the durvalumab plus CRT cohort was a patient with a history of rectal and hepatocellular carcinoma in remission, who was diagnosed with a third primary, T4N0 poorly differentiated NSCLC with focal squamous differentiation. The patient received two cycles of induction 3-weekly paclitaxel/carboplatin followed by CRT and subsequently three weekly cycles of paclitaxel/carboplatin due to neutropenia and thrombocytopenia. A computed tomography scan performed 1 day after CRT completion showed stable disease, leading to durvalumab initiation on day 22. He developed grade 2 pneumonitis before cycle 4 of durvalumab, leading to treatment suspension and initiation of a 1-month tapering course of prednisolone at 1 mg/kg. After radiological and clinical improvement, cycle 4 of durvalumab was resumed 43 days after its original planned date. Seven days later, he was admitted for respiratory failure requiring high-flow oxygen. Intravenous methylprednisolone 2 mg/kg was administered for 5 days, but there was further consolidation on CXR treated with one dose of infliximab on day 6. He was subsequently transitioned to oral prednisolone on day 54, with clinical improvement and reduced oxygen requirement. He became deconditioned 3 months later after steroid weaning, developing brain metastases and hospital-acquired pneumonia, and succumbed after 140 days of hospitalisation.

Table 3. Occurrence of pneumonitis in the two cohorts.*

	Durvalumab plus CRT cohort (n = 51)	CRT cohort (n = 62)	p Value	
None	35 (69%)	57 (92%)	0.002†	0.005‡
Any grade	16 (31%)	5 (8%)		
Grade 1-2	13 (25%)	3 (5%)		
Grade 3-4	3 (6%)	2 (3%)		

Abbreviation: CRT = chemoradiotherapy.
* Data are shown as No. (%), unless otherwise specified.
† Fisher's exact test looking into the statistical difference in 'None' or 'Any grade' pneumonitis occurrence in the two cohorts.
‡ Chi squared test looking into the statistical difference in 'None', 'Grade 1-2' or 'Grade 3-4' pneumonitis occurrence in the two cohorts.

No significant differences were observed in lung V_{5Gy}, lung V_{20Gy}, MLD, or planning target volume between the two cohorts (Table 5). Among these parameters, only lung V_{20Gy} demonstrated a significant correlation with any grade pneumonitis in univariate logistic analysis, with an odds ratio of 1.11 (95% CI = 1.013-1.213; p = 0.03), indicating that for each 1% increase in the volume of lung receiving ≥20 Gy, the odds of developing pneumonitis increased by approximately 11% (Table 6). Focusing on the durvalumab plus CRT cohort, ROC analysis identified an optimal lung V_{20Gy} threshold of 22.76% for predicting pneumonitis, with a Youden's index of 0.469, optimising sensitivity (0.92) and specificity (0.46). The area under the curve of the ROC analysis was 0.71, indicating moderate discriminatory power.

Grade 3 or 4 Immunotherapy-Related Adverse Events Within the Durvalumab Cohort

The overall incidence of grade 3 or 4 immune-related

Table 4. Detailed account of pneumonitis occurrence in the durvalumab plus chemoradiotherapy cohort.

Study code	Sex	Age, y	Ex-/current smoker	*EGFR* status	PD-L1 expression	Days from CRT to durvalumab	Completed durvalumab	Reason for discontinuation	Steroid use	Grade	Post-durvalumab cycle, No.
1	M	69	Y	Unknown	Low	22	N	AR	Y	2,4	3,4
2	M	60	Y	*L858R*	Unknown	55	Y	N/A	N	2	9
6	M	48	Y	Neg	High	41	N	PD	N	2	2
7	F	67	N	Neg	High	22	Y	N/A	Y	2	6
11	M	68	Y	Neg	Low	42	N	PD	Y	2	3
14	M	61	Y	*Exon19del*	Unknown	12	N	PP	Y	1	7
23	M	63	Y	Neg	High	45	Y	N/A	N	1	4
25	M	75	Y	Unknown	Low	35	N	AR	Y	2,2,2	5,10,12
28	F	67	N	*L858R*	Low	45	N	PD	Y	2	4
29	M	76	Y	Neg	Low	45	Y	N/A	Y	2,2	2,3
31	F	65	N	Unknown	High	112	Y	N/A	Y	2	3
35	F	68	N	*Exon19del*	Low	62	N	AR	Y	2,1,1,2	2,3,5,7
36	M	53	Y	Neg	High	60	Y	N/A	Y	2	4
38	F	56	N	Unknown	High	39	N	AR	Y	2	2
50	M	65	Y	Neg	Low	29	N	AR	Y	3,2	3,4
51	M	55	Y	Neg	High	78	N	AR	Y	3	6

Abbreviations: AR = adverse reactions; CRT = chemoradiotherapy; *Exon19del* = exon 19 deletion; F = female; M = male; N = no; N/A = not available; Neg = negative; PD = progressive disease; PD-L1 = programmed death ligand 1; PP = patient preference; Y = yes.

Table 5. Radiation dosimetry of radical chemoradiotherapy.*

	Durvalumab plus CRT cohort (n = 51)	CRT cohort (n = 62)	p Value†
Lung V_{5Gy}, %‡	60.35 (50.27-63.45)	57.61 (51.73-66.69)	0.94
Lung V_{20Gy}, %‡	25.08 (20.20-28.20)	25.13 (21.42-29.85)	0.94
Mean lung dose, Gy	14.16 (11.42-16.04)	15.27 (12.71-17.38)	0.44
PTV, cm^3	436.9 (274.49-670.79)	476.28 (350.95-721.79)	0.23

Abbreviations: CRT = chemoradiotherapy; PTV = planning target volume.
* Data are shown as median (interquartile range).
† Independent-samples median test with Yates' continuity corrected asymptotic significance.
‡ Expressed as the percentage of lung receiving at least the dose as specified.

Table 6. Univariate analysis for predictive factors of pneumonitis.

	Odds ratio (95% CI)	p Value
Age	0.99 (0.924-1.051)	0.65
Male sex	1.38 (0.444-4.284)	0.58
Ex-/current smoker	0.89 (0.290-2.724)	0.84
ECOG PS score 1	0.46 (0.099-2.186)	0.33
Lung V_{5Gy}, %*	1.04 (0.993-1.082)	0.10
Lung V_{20Gy}, %*	1.11 (1.013-1.213)	0.03
PTV, cm^3	1.00 (0.998-1.002)	0.74
Mean lung dose, Gy	1.11 (0.941-1.317)	0.21
*EGFR*m	1.02 (0.284-3.681)	0.97

Abbreviations: 95% CI = 95% confidence interval; ECOG = Eastern Cooperative Oncology Group; *EGFR*m = epidermal growth factor receptor mutated; PS = performance status; PTV = planning target volume.
* Expressed as the percentage of lung receiving at least the dose as specified.

adverse events was 13.7% (7/51). Three patients (6%) had RP, with one concurrently developing grade 3 hepatitis after 6 cycles that resolved over 2 months of corticosteroid treatment. For the remaining four patients, two (3.9%) developed grade 3 hyperglycaemia without a baseline history of diabetes, one (2%) experienced grade 3 skin rash after 17 cycles of durvalumab, and one (2%) developed grade 3 pneumonia. No patients discontinued durvalumab due to adverse events other than pneumonitis.

DISCUSSION

Our durvalumab plus CRT cohort demonstrated superior PFS to the CRT cohort, consistent with findings from the PACIFIC trial and real-world studies.[2,11-13] The disparity in median follow-up times between the CRT cohort (31 months) and the durvalumab plus CRT cohort (25.6 months) may be attributed to delayed availability of durvalumab funding, resulting in more patients receiving CRT alone between 2018 to 2020. This complicates PFS and OS interpretation, especially with the survival curve of the durvalumab plus CRT cohort plateauing.

Our mean PFS durations of 34.9 months (the durvalumab plus CRT cohort) and 10.5 months (the CRT cohort) exceeded those of the PACIFIC trial results,[2] nearly doubling their reported numbers. While real-world follow-up variability might underestimate early progression, prognostic advantages in our cohort likely contributed. These included a higher proportion with Eastern Cooperative Oncology Group performance status score of 0 (88% vs. 50% in the PACIFIC trial[14]) and more never-smokers (25% vs. 9%). PD-L1 status showed dual roles: in the CRT cohort, the higher proportion of PD-L1-negative patients (~50%) aligns with its known favourable prognostic value in the pre-immunotherapy era, supported by multiple meta-analyses.[15-18] Conversely, the PD-L1–enriched population in the durvalumab plus CRT cohort (~90% positive, ~50% with ≥ 50% expression) reflect its predictive value, consistent with the PACIFIC subgroup analysis showing enhanced immunotherapy benefit with higher PD-L1 expression.[2] Additionally, approximately half of the cohort received at least one cycle of induction chemotherapy, compared to only a quarter in the PACIFIC trial.[2] Any potentiation of immunotherapy with induction chemotherapy, through neoantigen release and tumour microenvironment modulation, is a theoretical consideration. Further elucidation, however, is required to determine the application of PD-L1 for risk stratification and to optimise treatment sequencing and combination, including toxicity risks.[19,20]

The incidence of any-grade pneumonitis in our durvalumab plus CRT cohort (31%) was similar to the figure reported in the PACIFIC study (34%),[2] where it was the most common adverse event leading to treatment discontinuation (6.3%).[2] It was higher than in the CRT cohort (8%), though the majority (~80%) were grade 1 to 2 per the CTCAE version 5.0 criteria.[10] Differentiating between immunotherapy-induced pneumonitis (IP) and RP, especially in the early cycles, proved challenging. Radiologically, RP is more likely if the consolidative changes are seen only within the irradiated field.

Observation from our study reinforced this diagnostic difficulty as the majority of events occurred within the first 3 months in both groups (87.5% in the durvalumab plus CRT cohort vs. all within 91 days in the CRT cohort). This aligns with other studies reporting median pneumonitis onset around 3 to 4 months,[21,22] emphasising the importance of close monitoring during early durvalumab treatment.

Fortunately, treatment is mostly similar for both conditions with corticosteroids as the mainstay, although IP may require longer treatment. In cases of steroid-refractory IP, immunosuppressive agents such as mycophenolate mofetil or infliximab can be considered.[23] Supportive management such as symptom-relieving medications and oxygen support should always be given where clinically indicated. Vigilance for concomitant infection due to the immunosuppressive effects of the cancer treatments and high-dose steroids is also essential. The decision to rechallenge with durvalumab after resolution of low-grade pneumonitis should be made after ensuring patients are well informed of recurrent or higher-grade pneumonitis risks. Among patients in the durvalumab plus CRT cohort who developed pneumonitis, 31% experienced recurrence of events after treatment resumption. Overall, 12% discontinued durvalumab due to pneumonitis, similar to the reported 9.5% in the PACIFIC-R study.[4]

There is no doubt that RP could compromise patients' outcomes and quality of life, therefore continuous efforts have been put to identify any clinical and dosimetric factors that are predictive and/or preventive. Lung V_{20Gy} is the most representative among the commonly reported parameters. However, it is uncertain whether the traditional dose constraints used in CRT are equally applicable to patients also receiving immunotherapy. In our cohort, lung V_{20Gy} was the only radiation dose parameter that correlated with pneumonitis, with an optimal threshold at 22.76% based on ROC analysis. However, the low specificity (0.46) suggests that lung V_{20Gy} alone is not a strong predictor due to its high false positive rate. Of note, this threshold is lower than the commonly reported 30% for normofractionated thoracic radiotherapy in the preimmunotherapy era. Even lower thresholds, such as 18.77% in a Japanese study[21] and 15.8% in the Mayo Clinic, have been proposed for predicting grade≥2 pneumonitis.[22] All these highlight a change in regulation of immune and/or lung homeostasis after exposure to immunotherapy and radiotherapy; this could possibly lead to different lung parenchymal susceptibilities. The high incidence of any-grade (88%) and grade ≥3 pneumonitis (12%) in the Japanese study involving 91 patients,[21] and Asian predominance in pneumonitis after CRT with or without immunotherapy in a recent meta-analysis over 20,000 patients[24] and in the PACIFIC subgroup analysis[25] raise further research questions with regard to any ethnic and/or genetic contributing factors. Although direct comparison across trials to derive the optimal dose constraint is not possible due to varying radiotherapy planning techniques, chemotherapy regimens, and patient factors, efforts to reduce the lung V_{20Gy} to as low as possible are reasonable.

Practically, applying more stringent lung dose constraints while maintaining target coverage in radiotherapy planning for stage III NSCLC, where tumours are often bulky, is challenging. Advanced technology, including intensity-modulated radiation therapy and proton therapy, may offer benefits over conventional techniques.[26] However, uncertainty remains regarding any interplay between low radiation exposure (e.g., lung V_{5Gy} and MLD) and immunotherapy in modulating pneumonitis risk. Moreover, the labour-intensive nature of planning and treatment delivery warrants careful patient selection, especially in high-workload or resource-limited settings.

In addition to pneumonitis, our study also examined all-cause immune-related grade 3 or 4 adverse events. The incidence in our cohort (13.7% grade 3 and 3% grade 4) were higher than in the PACIFIC trial (3.4% in the durvalumab plus CRT cohort and 2.6% in the CRT group),[2] but a solid conclusion on differences in safety cannot be made due to the small sample size and variable documentation of our study. Reassuringly, a similar proportion of patients required durvalumab discontinuation due to adverse events (12% in our study vs. 15.4% in the PACIFIC trial).[2] This underpins the fact that adequate patient education together with team-based engagement remain the key to ensuring timely recognition and effective management of immune-related adverse events.

When focusing on *EGFR*m patients, the estimated PFS was not reached in the durvalumab plus CRT cohort, compared with 7.8 months in the CRT cohort, suggesting a potential benefit of adjuvant durvalumab. This contrasts with the lack of benefit in the post-hoc analysis of *EGFR*m subgroups in the PACIFIC trial[6] and another retrospective review involving multiple academic medical centres in the US.[7] However, caution

should be exercised when interpreting these results due to the small sample size, the low treatment completion rates (15%-50%) reported in the abovementioned studies, and the short follow-up interval of our study.

Another notable observation from our durvalumab plus CRT cohort is the higher occurrence of pneumonitis in *EGFR*m patients (57%) compared to *EGFR*wt/unknown patients (27%), though the difference was not statistically significant. While the exact mechanism underlying this difference remains unknown, this observation carries important clinical implications as initiating *EGFR* tyrosine kinase inhibitors (TKIs) after CRT is a relatively common post-radical treatment for *EGFR*m stage III disease due to the high risk of progression. There is already growing recognition of the increased risk of pneumonitis with sequential immunotherapy followed by early TKI treatment.[27] Prior RP and IP may exacerbate this risk through increased lung tissue sensitivity, cumulative lung injuries, and/or shared mechanisms such as immune response dysregulation. Although none of our three *EGFR*m patients who received erlotinib immediately upon disease progression during durvalumab plus CRT treatment developed pneumonitis, this should not over-reassure clinicians given the safety alert reported in other studies[28,29] when using immunotherapy and TKIs in close intervals. Optimal timing to guide safe use of immunotherapy and TKIs is undefined, but the premature terminations of the TATTON[28,30] and CAURAL trials[29,31] due to the higher incidence of interstitial lung disease–like events with osimertinib and durvalumab provided important information, leading to the consensus that concurrent use should be avoided outside clinical trials. Common practice to reduce pneumonitis risk is to defer the TKI initiation for at least 1 month, preferably 3 months for less aggressive diseases, after the last use of immunotherapy.[7,32] Extra caution is needed with the third-generation TKI osimertinib compared to first- or second-generation TKIs, especially in patients with preexisting lung injuries.[32]

Limitations

Limitations of our study included small sample size, variable follow-up, and assessment tools, leading to inconsistent evaluations of efficacy and toxicities. The unexpectedly low *EGFR* mutation rate (~30%) among those tested makes it challenging to draw statistically significant conclusions about the benefits for the controversial *EGFR*m subgroup, despite an observed improvement in PFS. Retrospective *EGFR* analysis of the 37 untested cases could enhance understanding, though further *EGFR* population enrichment may be limited due to the expected low mutation rates based on histology[33] (70.3% squamous, 8.1% lymphoepithelioma-like carcinoma, 5.4% large cell, and 13.5% NSCLC of no specific type). The imbalance and deviation in PD-L1 expression pattern, probably due to small sample size, may also confound results. Collaborative multi-centre analysis, adoption of universal *EGFR* testing for non-squamous NSCLC, and increased accessibility of PD-L1 test in Hong Kong oncology centres could enhance the statistical value of future similar studies by reducing the untested population and increasing the overall sample size.

CONCLUSION

This study provides compelling evidence that durvalumab consolidation therapy following CRT improves PFS in unresectable stage III NSCLC, with manageable adverse effects. Pneumonitis, occurring mainly within the first 3 months, underscores the need for close monitoring and timely management, especially at the start of durvalumab. Lung V_{20Gy} may predict pneumonitis and should be kept as low as possible after balancing a reasonable target coverage, but its low specificity suggests it should be used alongside other clinical factors for individual risk assessment and planning.

As the treatment landscape for locally advanced NSCLC is evolving, therapies effective in metastatic disease are applied earlier in the treatment pathway. The recently published LAURA study,[34,35] which demonstrated a highly encouraging PFS benefit from 5.6 months to 39.1 months with adjuvant osimertinib in *EGFR*m patients, is probably just the start. With increasing evidence, both PD-L1 and *EGFR* status are expected to be critical in the near future to guide treatment selection. Further large-scale studies and uniform follow-up are needed to validate the roles of different biomarkers in tailoring treatments for patients with unresectable stage III NSCLC, similar to the approach in stage IV disease.

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