ORIGINAL ARTICLE

Durvalumab for Stage III *EGFR*-Mutated NSCLC After Definitive Chemoradiotherapy

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ABSTRACT

Introduction: In 2018, durvalumab was approved by the U.S. Food and Drug Administration as consolidation immunotherapy for patients with stage III NSCLC after definitive chemoradiotherapy (CRT). However, whether durvalumab benefits patients with *EGFR*-mutated NSCLC remains unknown.

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Methods: We conducted a multi-institutional retrospective analysis of patients with unresectable stage III *EGFR*-mutated NSCLC who completed concurrent CRT. Kaplan-Meier analyses evaluated progression-free survival (PFS) between patients who completed CRT with or without durvalumab.

Results: Among 37 patients, 13 initiated durvalumab a median of 20 days after CRT completion. Two patients completed 12 months of treatment, with five patients discontinuing durvalumab owing to progression and five owing to immune-related adverse events (irAEs). Of 24 patients who completed CRT without durvalumab, 16 completed CRT alone and eight completed CRT with induction or consolidation EGFR tyrosine kinase inhibitors (TKIs). Median PFS was 10.3 months in patients who received CRT and durvalumab versus 6.9 months with CRT alone (log-rank $p = 0.993$). CRT and EGFR TKI was associated with a significantly longer median PFS (26.1 mo) compared with CRT and durvalumab or CRT alone (log-rank $p = 0.023$). Six patients treated with durvalumab initiated EGFR TKIs after recurrence, with one developing grade 4 pneumonitis on osimertinib.

Conclusions: In this study, patients with *EGFR*-mutated NSCLC did not benefit with consolidation durvalumab and experienced a high frequency of irAEs. Patients who initiate osimertinib after durvalumab may be susceptible to incident irAEs. Consolidation durvalumab should be approached with caution in this setting and concurrent CRT with induction or consolidation EGFR TKIs further investigated as definitive treatment.

Keywords: EGFR mutation; Durvalumab; Concurrent chemoradiotherapy; Osimertinib; EGFR TKI

Introduction

Approximately one-third of patients with NSCLC are diagnosed with having locally advanced disease. For patients with unresectable stage III NSCLC, the standard of care is platinum-based concurrent chemoradiotherapy (CRT) followed by 1 year of consolidation durvalumab (anti–programmed death-ligand 1 [PD-L1] immunotherapy) on the basis of the results of the PACIFIC trial.[1] Historically, median progression-free survival (PFS) after CRT alone has been low despite its administration with curative intent, ranging from 9 to 12 months after CRT initiation.[2–4] Furthermore, PFS after CRT alone may be even lower among patients with tumors that harbor activating *EGFR* mutations, ranging from 6 to 9 months in retrospective studies.[5–7] Studies have also shown that patients with *EGFR*-mutated NSCLC experience recurrence with higher rates of distant metastases,[5,6] underscoring the need for definitive treatments that enhance both local and systemic control.

The PACIFIC trial was a phase 3 clinical trial in which 713 patients with unresectable stage III NSCLC who completed platinum-based concurrent CRT were randomized to receive consolidation durvalumab versus placebo every 2 weeks for up to 12 months.[1,8] The trial met its coprimary end points, with durvalumab demonstrating a 45% reduction in risk of recurrence and a 29% reduction in risk of overall mortality compared with placebo.[9] Within the trial population, only 43 patients (6%) had tumors harboring confirmed *EGFR* mutations. Accordingly, the subset analyses evaluating PFS (hazard ratio [HR] = 0.84, 95% confidence interval [CI]: 0.40–1.75) and overall survival (OS) (HR = 0.97, 95% CI: 0.40–2.33) between durvalumab and placebo were inconclusive in these patients.[9] As a result, the impact of durvalumab remains unknown in patients with *EGFR*-mutated NSCLC.

To further complicate this assessment, recent data have raised concerns on the safety of EGFR tyrosine kinase inhibitors (TKIs) after recent immunotherapy administration. TATTON was a phase 1b clinical trial evaluating the concurrent administration of osimertinib, a third-generation EGFR TKI, and durvalumab in patients with *EGFR*-mutated NSCLC.[10] The trial was halted owing to 38% and 15% of patients experiencing any grade and grade 3 to 4 interstitial lung disease, respectively. Subsequently, a retrospective review of patients with advanced *EGFR*-mutated NSCLC found that 15% of patients who received sequential immunotherapy followed by osimertinib experienced severe immune-related adverse events (irAEs), which most often occurred if osimertinib was initiated within 3 months of immunotherapy.[11] As patients with stage III *EGFR*-mutated NSCLC remain at high risk of recurrence after definitive treatment, a fair proportion may need to initiate EGFR TKIs soon after durvalumab. Thus, the long-term safety and efficacy of durvalumab for these patients need to be elucidated.

In this multi-institutional retrospective study, we describe the experiences of patients with unresectable stage III *EGFR*-mutated NSCLC who received consolidation durvalumab after concurrent CRT. We evaluated the clinical outcomes of patients who completed CRT and durvalumab compared with CRT alone and a subset of patients who received CRT with induction or consolidation EGFR TKIs. Finally, we evaluated the impact of durvalumab on toxicities and outcomes with subsequent EGFR TKI treatment in patients who experienced disease recurrence.

Materials and Methods

Study Design

Patients with unresectable stage III NSCLC with activating *EGFR* mutations who completed concurrent

Table 1. Patient Characteristics

Characteristics	All N = 37	CRT + Durvalumab n = 13	CRT Wo Durvalumab n = 24	*p* Value[a]
Age at CRT completion (y), mean (SD)	68.1 (9.6)	67.6 (12.1)	68.3 (8.3)	0.832
Sex, n (%)				0.158
Male	8 (21.6)	5 (38.5)	3 (12.5)	
Female	29 (78.4)	8 (61.5)	21 (87.5)	
Race/ethnicity, n (%)				0.038
White	22 (59.5)	5 (38.5)	17 (70.8)	
Asian	13 (35.1)	8 (61.5)	5 (20.8)	
Hispanic/Latino	2 (5.4)	0 (0.0)	2 (8.3)	
Smoking status, n (%)				0.992
Never	27 (73.0)	10 (76.9)	17 (70.8)	
Former	10 (27.0)	3 (23.1)	7 (29.2)	
Histology, n (%)				0.340
Adenocarcinoma	34 (91.9)	11 (84.6)	23 (95.8)	
Squamous	1 (2.7)	1 (7.7)	0 (0.0)	
Adenosquamous	2 (5.4)	1 (7.7)	1 (4.2)	
Stage at CRT initiation, n (%)				0.756
IIIA	16 (43.2)	5 (38.5)	11 (45.8)	
IIIB	17 (45.9)	7 (53.8)	10 (41.7)	
IIIC	4 (10.8)	1 (7.7)	3 (12.5)	
EGFR mutation, n (%)				0.484
Exon 19 deletion	14 (37.8)	4 (30.8)	10 (41.7)	
L858R	18 (48.6)	8 (61.5)	10 (41.7)	
Other	5 (13.5)	1 (7.7)	4 (16.7)	
PD-L1 expression, n (%)				0.002
Negative (0% TPS)	7 (18.9)	2 (15.4)	5 (20.8)	
Low (1%–49% TPS)	8 (21.6)	4 (30.8)	4 (16.7)	
High (≥50% TPS)	9 (24.3)	7 (53.8)	2 (8.3)	
Not tested	13 (35.1)	0 (0.0)	13 (54.2)	
Induction therapy before CRT, n (%)				
EGFR TKI	4 (10.8)	0 (0.0)	4 (16.7)	0.315
CRT chemotherapy regimen, n (%)				0.880
Cisplatin/etoposide	4 (10.8)	2 (15.4)	2 (8.3)	
Cisplatin/pemetrexed	7 (18.9)	2 (15.4)	5 (20.8)	
Carboplatin/pemetrexed	15 (40.5)	5 (38.5)	10 (41.7)	
Carboplatin/paclitaxel	10 (27.0)	4 (30.8)	6 (25.0)	
Carboplatin/nab-paclitaxel	1 (2.7)	0 (0.0)	1 (4.2)	
Radiotherapy dose (Gy), n (%)				0.443
44	1 (2.7)	0 (0.0)	1 (4.2)	
45	1 (2.7)	0 (0.0)	1 (4.2)	
50	1 (2.7)	1 (7.7)	0 (0.0)	
54	2 (5.4)	0 (0.0)	2 (8.3)	
60	19 (51.4)	6 (46.2)	13 (54.2)	
66	12 (32.4)	6 (46.2)	6 (25.0)	
69.6	1 (2.7)	0 (0.0)	1 (4.2)	
ECOG PS at CRT completion, n (%)				0.142
0–1	32 (86.5)	10 (76.9)	22 (91.7)	
2	2 (5.4)	2 (15.4)	0 (0.0)	
Unknown	3 (8.1)	1 (7.7)	2 (8.3)	
Consolidation therapy after CRT, n (%)				
Chemotherapy	10 (27.0)	1 (7.7)	9 (37.5)	0.118
EGFR TKI	4 (10.8)	0 (0.0)	4 (16.7)	0.315
Follow-up (mo), median (IQR)	21.8 (11–37)	18.6 (15–27)	23.0 (11–39)	0.324

Note: Percentages may not sum to 100% owing to rounding.

[a]*p* value was calculated across treatment groups for categorical data using Fisher's exact test and for continuous data using the *t* test or Wilcoxon ranked sum test.

CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD-L1, programmed death-ligand 1; PS, performance status; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score; Wo, without.

platinum-based CRT between January 2017 and November 2020 were identified from the following four academic medical centers: Stanford Cancer Institute, City of Hope, University of California, San Francisco, and University of California, Davis. All sites obtained local Institutional Review Board approval for participating in this study. Patients had *EGFR* molecular testing performed in their standard-of-care evaluation at baseline through next-generation sequencing panels or targeted gene assays (Supplementary Table 1). Patients were classified as receiving durvalumab if they received at least one cycle of durvalumab after completing CRT. All other patients who did not receive durvalumab were classified as completing CRT without durvalumab. In a subgroup analysis, patients who received EGFR TKIs for the purposes of induction or consolidation treatment with CRT were further distinguished from those who received CRT alone (without durvalumab or EGFR TKI).

Baseline demographic, clinical, and pathologic data were abstracted from patients' electronic health records. NSCLC histology was classified according to WHO criteria.[12] Disease staging was based on the eighth edition of the American Joint Committee on Cancer and International Union Against Cancer TNM stage classification for lung cancer.[13] The PD-L1 tumor proportion score (TPS) was ascertained from pathological or molecular sequencing reports in patients who had anti–PD-L1 immunohistochemistry performed.

Study Outcomes

PFS was measured from the date of CRT completion (unless otherwise stated) to the date of recurrence, death from any cause, or last follow-up, whichever came first. Recurrence was evaluated pathologically or radiographically on the basis of the Response Evaluation Criteria in Solid Tumors version 1.1.[14] OS was measured from the date of CRT completion to the date of death from any cause or last follow-up. Adverse events (AEs) owing to durvalumab were classified according to the Common Terminology Criteria for Adverse Events version 5.0. We defined severe irAEs as AEs that were attributed to durvalumab by the treating clinician, required immunosuppression (i.e., oral corticosteroids), and were treated as irAEs according to standard oncologic guidelines.[15,16] High-dose corticosteroids were defined as greater than 20 mg/day of oral prednisone.

Statistical Analysis

Kaplan-Meier survival curves were generated to evaluate PFS and OS across treatment groups, and the log-rank test was used for subgroup comparisons. Survival analyses were supplemented with Cox proportional hazards regression models which estimated HRs for PFS in treatment group comparisons. The proportional hazards assumption was confirmed for all Cox models. Patient characteristics were evaluated between treatment groups using Fisher's exact test for categorical variables and the *t* test or Wilcoxon ranked sum test for continuous variables. Statistical significance was defined at a two-sided p value less than 0.05. All statistical analyses were performed using R version 4.0.2 (Vienna, Austria).

Results

Patient Characteristics

In total, 37 patients were included in the cohort (Table 1). The mean age at CRT completion was 68.1 years, and most patients were of female sex (78.4%) and never smoking (73.0%). The lung cancers were predominantly adenocarcinoma (91.9%), and most patients had stage IIIA (43.2%) or IIIB (45.9%) disease at CRT initiation. Eastern Cooperative Oncology Group performance status was 0 to 1 at CRT completion in most cases (86.5%). Patients who received CRT without durvalumab compared with CRT and durvalumab were more likely to be white (70.8% versus 38.5%) and of female sex (87.5% versus 61.5%), otherwise the baseline characteristics were similar between the two groups.

Overall, 18 patients (48.6%) had *EGFR* L858R mutations and 14 (37.8%) had exon 19 deletions (Table 1 and Fig. 1). Uncommon *EGFR* driver mutations included exon 20 insertions (n = 2), G719A (n = 1), exon 19 insertion (n = 1), and L747P (n = 1). No significant differences in *EGFR* mutation subtypes were observed between the CRT treatment groups ($p = 0.484$). Co-occurring mutations most often occurred in *TP53* and *CTNNB1*, and the frequencies did not substantially differ among those tested between treatment groups. Among patients with available PD-L1 expression (N = 24), nine (37.5%) had high (≥50% TPS), eight (33.3%) had low (1%–49% TPS), and seven (29.2%) had no PD-L1 expression. There were no significant differences in PD-L1 expression between CRT treatment groups among those tested for PD-L1 ($p = 0.141$). However, PD-L1 expression significantly differed between CRT treatment groups overall as all patients who completed CRT and durvalumab had PD-L1 testing performed whereas most patients who had CRT without durvalumab did not have PD-L1 testing (Table 1).

Most patients received carboplatin/pemetrexed (40.5%) as their chemotherapy regimen during CRT (Table 1). Furthermore, most patients completed a radiotherapy dose totaling 60 Gy (51.4%) or 66 Gy (32.4%). There were no major differences in CRT treatment regimens between the CRT treatment groups. As expected, a higher frequency of patients who completed CRT without durvalumab versus with durvalumab

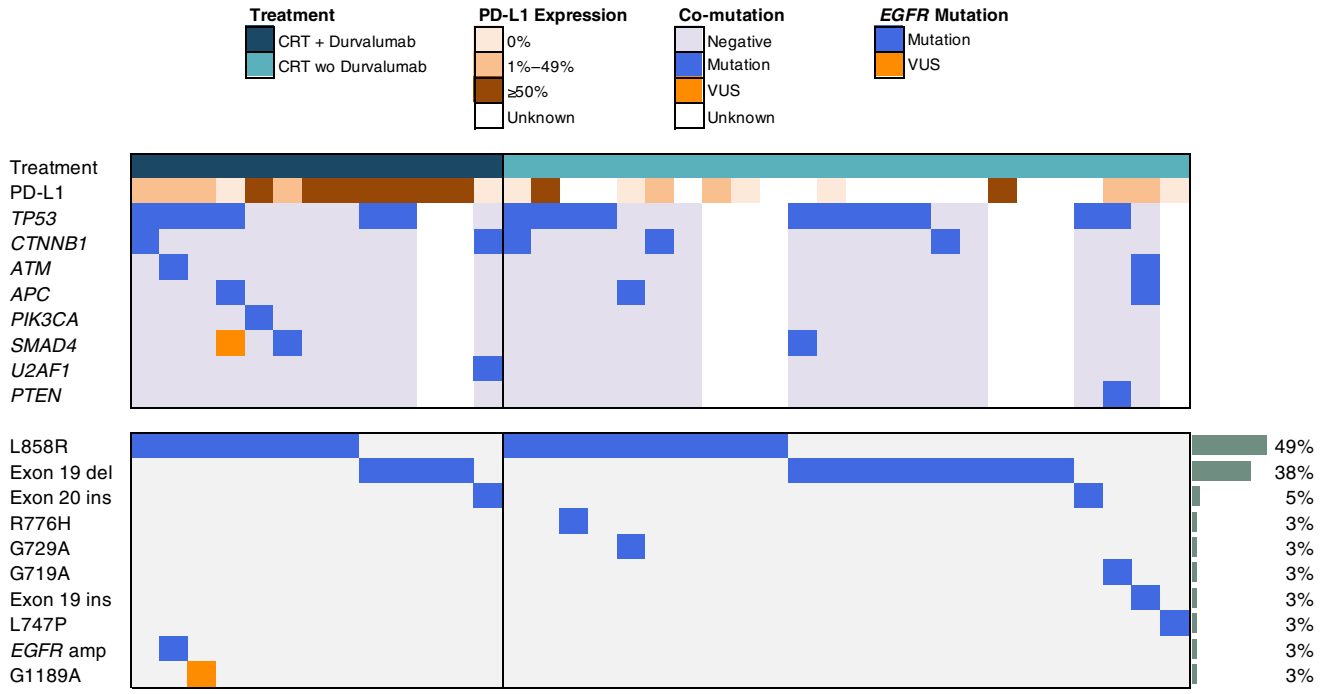

Figure 1. Molecular features of the *EGFR*-mutated NSCLC cohort (N = 37). OncoPrint summarizes the definitive treatment regimen that patients received, PD-L1 expression, and co-occurring mutations in the upper panel and *EGFR* mutation subtypes or copy number variation in the lower panel. Each column represents one patient. The bar graphs and percentages correspond to the frequencies of the *EGFR* mutations across the cohort. Amp, amplification; CRT, chemoradiotherapy; del, deletion; ins, insertion; PD-L1, programmed death-ligand 1; VUS, variant of unknown significance; wo, without.

received consolidation chemotherapy, though the difference was not statistically significant (37.5% versus 7.7%, $p = 0.118$). Four patients who completed CRT without durvalumab received induction EGFR TKIs before CRT, and another four patients received EGFR TKIs as consolidation treatment after CRT per the standard practice of their treating physicians. None who received CRT and durvalumab had induction or consolidation EGFR TKIs.

CRT With Consolidation Durvalumab

A total of 13 patients initiated consolidation durvalumab a median of 20 days (interquartile range [IQR]: 17–49) after completing CRT (Fig. 2*A*). Patients received a median of six cycles (IQR: 4–14) of durvalumab (Fig. 2*B*), with one patient (7.7%) receiving durvalumab every 4 weeks and all others receiving durvalumab every 2 weeks. Only two patients (15.4%) completed 12 months of durvalumab. Reasons for durvalumab discontinuation included severe irAEs (n = 5, 38.5%), disease progression (n = 5, 38.5%), and cognitive decline (n = 1, 7.7%). One patient developed a severe irAE at the time of disease progression (patient no. 3), but the primary reason for durvalumab discontinuation was owing to progression.

Among 12 assessable patients, all experienced AEs (Supplementary Table 2). The most common all-grade AEs included fatigue (n = 7, 58.3%), cough (n = 6, 50.0%), dyspnea (n = 3, 25.0%), and pneumonitis (n = 3, 25.0%). Severe irAEs occurred in six patients overall (46.2%), with three patients experiencing pneumonitis (one grade 2, two grade 3) and one patient each developing myocarditis (grade 3), hepatitis (grade 2), and colitis (grade 3) (Table 2). The median time from durvalumab initiation to onset of the severe irAE was 95 days (IQR: 33–151; Fig. 2*C*). Although two patients experienced severe irAEs within 1 month of starting durvalumab, most had these events after multiple cycles of treatment. All patients with severe irAEs were hospitalized for their symptoms, where the irAEs were adjudicated by specialists (Table 2). Although it is possible that the grade 3 pneumonitis in the patient who initiated durvalumab 2 days before (patient no. 2) was radiation induced,[17,18] the patient's records indicate that the onset of symptoms was distinctly after the infusion, suggesting at least a component of the pneumonitis was due to durvalumab. All initiated oral corticosteroids for treatment, with all except one patient requiring high-dose corticosteroids. No additional forms of immunosuppression were administered. None had obvious risk factors, such as a history of autoimmune disease. *EGFR* mutations, co-occurring alterations, and PD-L1 expression varied within this group. All recovered from the severe irAE, and none resumed further treatment with durvalumab.

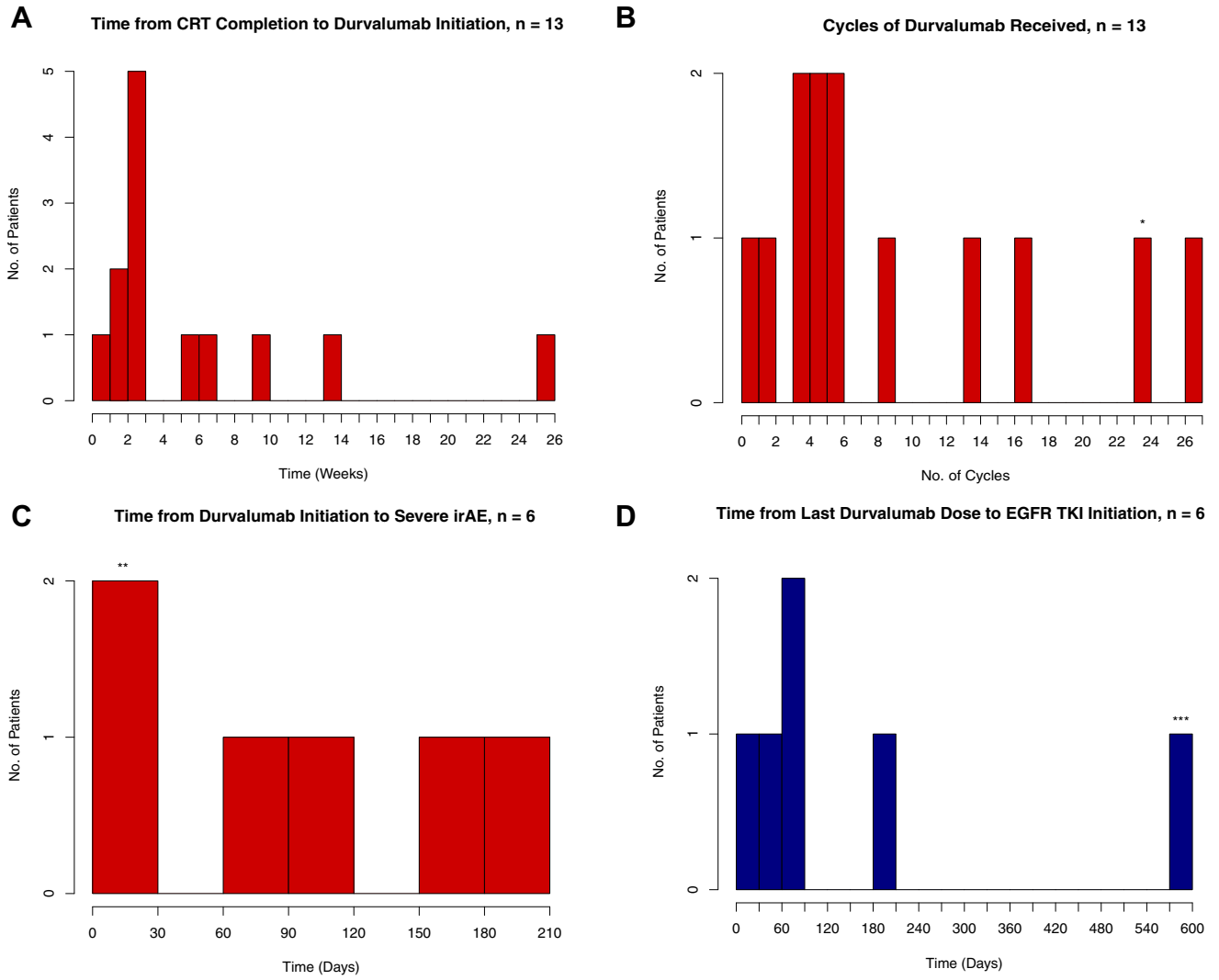

Figure 2. Time intervals surrounding consolidation durvalumab and EGFR TKI initiation. (*A*) The median time from CRT completion to durvalumab initiation was 20 days (IQR: 17–49; 2.9 wk). (*B*) Patients received a median of six cycles (IQR: 4–14) of durvalumab. (*C*) Median time from durvalumab initiation to severe irAE was 95 days (IQR: 33–151). (*D*) Median time from the last durvalumab dose to EGFR TKI initiation was 71 days (IQR: 51–168). *Patient completed 12 months of consolidation durvalumab but only 24 cycles were recorded in the available documentation. **One patient experienced a severe irAE (colitis) a few days after completing the second cycle of durvalumab; thus, the patient was included in the 0- to 30-day bin and a close approximation (20 d) was used when calculating the median time to severe irAE. ***One patient initiated osimertinib 588 days after the last dose of durvalumab and experienced an incident grade 4 pneumonitis while on osimertinib. CRT, chemoradiotherapy, IQR, interquartile range, irAE, immune-related adverse event; TKI, tyrosine kinase inhibitor.

CRT Alone or With EGFR TKI

A total of 24 patients completed concurrent CRT without durvalumab. The two most common documented reasons for withholding durvalumab included the oncologist's concerns on the efficacy or safety of durvalumab with *EGFR*-mutated NSCLC (n = 9) and because patients received consolidation EGFR TKIs instead per the physician's standard treatment preference (n = 4; Supplementary Fig. 1).

Within this group, eight patients completed CRT with EGFR TKIs as either induction (n = 4) or consolidation (n = 4) therapy (Supplementary Table 3). As induction therapy, patients received either osimertinib (n = 3) or erlotinib (n = 1) for a median of 4.5 months (IQR: 3–7) and one patient received consolidation chemotherapy after CRT. As consolidation therapy, patients received erlotinib (n = 2), gefitinib (n = 1), or afatinib (n = 1) for a median of 17 months (IQR: 8–30), with one patient continuing erlotinib after progression.

Progression-Free Survival

In the overall cohort, the median follow-up time was 21.8 months (IQR: 11–37) after concurrent CRT. A total of 23 patients (62.2%) experienced recurrence after

Table 2. Characteristics of Patients Who Developed Severe irAEs While Receiving Durvalumab (n = 6)

Patient No.	*EGFR* Mutation	Coalterations	PD-L1 Expression (% TPS)	Cycle(s) of Durvalumab	Time From First Cycle of Durvalumab to irAE Onset, d	irAE	CTCAE Grade	Required Hospitalization?	Required High-Dose Steroids?	PFS From CRT Completion, mo
1	L858R	$TP53^{mut}$, APC^{mut}	0	9	120	Pneumonitis	3	Yes	Yes	21.5
2	Exon 20 insertion	$CTNNB1^{mut}$, $U2AF1^{mut}$	0	1	2	Pneumonitis	3	Yes	Yes	12.0
3	L858R	$TP53^{mut}$, ATM^{mut}, EGFR amp	20	6[a]	161	Pneumonitis	2	Yes	No[b]	7.6
4	L858R	$SMAD4^{mut}$	1	5	70	Myocarditis	3	Yes	Yes	16.3 (censored)
5	Exon 19 deletion	$TP53^{mut}$	100	14	201	Hepatitis	2	Yes	Yes	8.5
6	Exon 19 deletion	Not tested	60	2	~20[c]	Colitis	3	Yes	Yes	10.3

Note: Severe irAEs were defined as AEs attributed to durvalumab, required oral corticosteroids, and were treated as irAEs according to standard oncologic guidelines. High-dose steroids were defined as greater than 20 mg/day of oral prednisone.

[a]Patient received one cycle of durvalumab every 4 weeks. All other patients received one cycle of durvalumab every 2 weeks.

[b]Patient initiated oral corticosteroids for the treatment of pneumonitis but did not initiate high-dose corticosteroids (>20 mg/d of oral prednisone).

[c]Patient experienced grade 3 colitis a few days after receiving the second cycle of durvalumab. Exact date of event was unavailable; thus, a close approximation was provided.

AE, adverse event; amp, amplification; CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events version 5.0; irAE, immune-related adverse event; mut, mutated; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

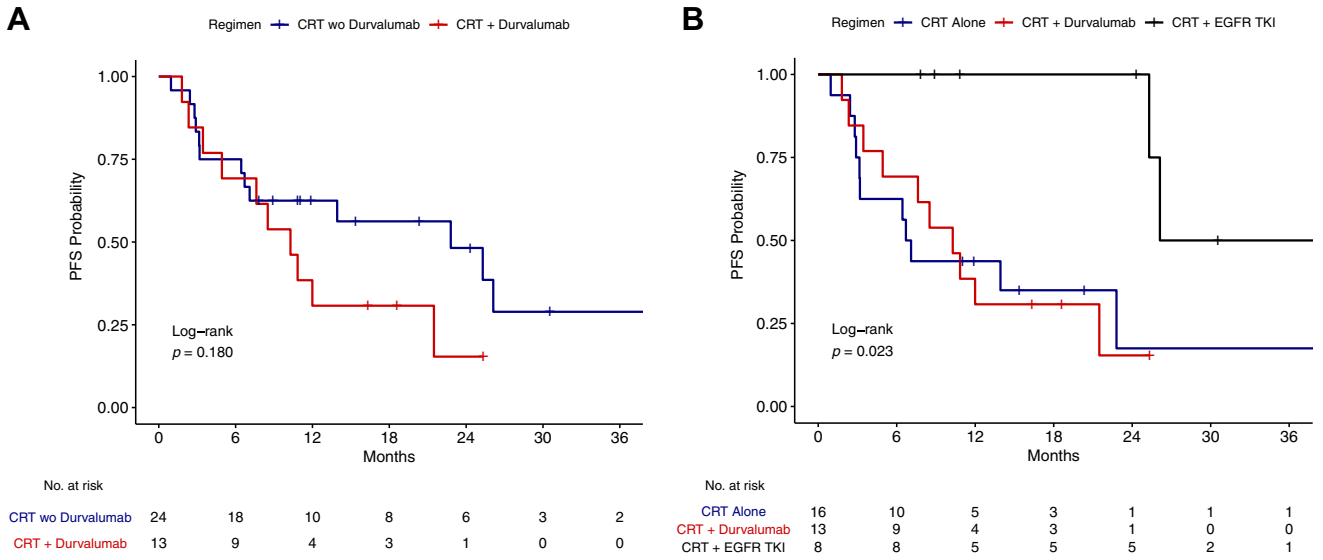

Figure 3. PFS after chemoradiotherapy with or wo durvalumab. (*A*) Median PFS among patients who completed CRT and durvalumab versus CRT wo durvalumab was 10.3 months versus 22.8 months (log-rank $p = 0.180$). (*B*) Median PFS among patients who completed CRT alone versus CRT and durvalumab versus CRT and induction or consolidation EGFR TKI was 6.9 months versus 10.3 months versus 26.1 months (log-rank $p = 0.023$). CRT, chemoradiotherapy; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; wo, without.

concurrent CRT. Median PFS was 12.0 months (95% CI: 7.6–not reached [NR]), and OS data were immature at data cutoff (Supplementary Fig. 2). Median PFS among patients who received CRT and durvalumab compared with CRT without durvalumab (but with or without EGFR TKI) was 10.3 months versus 22.8 months (HR = 1.78, 95% CI: 0.76–4.16, log-rank $p = 0.180$; Fig. 3*A*). Recurrence occurred most frequently in the ipsilateral lung (29.7%) followed by the brain (27.0%) and contralateral lung (21.6%) among all patients (Supplementary Table 4). Patients who received CRT and durvalumab experienced recurrence most frequently in the brain (38.5%), whereas patients who received CRT without durvalumab (but some with EGFR TKI) had relatively higher recurrence in the ipsilateral and contralateral lungs than in the brain (29.2% versus 25.0% versus 20.8%).

When distinguishing patients who received induction or consolidation EGFR TKIs from those who completed CRT alone (Supplementary Table 5), median PFS did not significantly differ between those who received CRT and durvalumab and CRT alone (10.3 mo versus 6.9 mo, log-rank $p = 0.993$; Supplementary Fig. 3), whereas those who received CRT and EGFR TKI had a significantly longer median PFS (26.1 mo) than the other two CRT treatment groups (log-rank $p = 0.023$; Fig. 3*B*). Cox analysis confirmed the negligible difference in recurrence risk between CRT and durvalumab and CRT alone (HR = 1.06, 95% CI: 0.44–2.52). However, treatment with CRT and EGFR TKI was associated with a significantly reduced risk of recurrence compared with CRT alone (HR = 0.16, 95% CI: 0.03–0.73) and CRT and durvalumab (HR = 0.15, 95% CI: 0.03–0.72).

Among the 13 patients who received CRT and durvalumab, exploratory analyses were conducted to identify factors associated with differences in PFS (Supplementary Fig. 4). From the date of durvalumab initiation, the overall median PFS was 8.0 months (95% CI: 2.3–NR). There were no significant differences in median PFS in these patients when stratified by PD-L1 expression, severe irAEs, and *EGFR* mutation subtype. However, given the small sample size of this subset analysis, further validation of these results is required.

EGFR TKIs After CRT

Among six patients who progressed on CRT and durvalumab and subsequently initiated EGFR TKIs, the median time from the last durvalumab dose to EGFR TKI initiation was 71 days (IQR: 51–168; Fig. 2*D*). EGFR TKIs included osimertinib (n = 5) and erlotinib (n = 1). With a median follow-up of 15.3 months (IQR: 14–18), one patient (16.7%) experienced an incident grade 4 pneumonitis 17 days after initiating osimertinib. Notably, this patient had previously experienced a grade 3 pneumonitis while on durvalumab (Table 2, patient no. 1) and had a nearly 20-month treatment-free interval between durvalumab and osimertinib (Fig. 2*D*).

Within the CRT alone group, 11 patients initiated EGFR TKIs after progression on CRT (osimertinib n = 6,

erlotinib n = 3, afatinib n = 2), and these treatments were distinct from the consolidation EGFR TKIs administered to some patients. There were no significant PFS differences from EGFR TKI initiation between patients who received CRT and durvalumab versus CRT without durvalumab (median = 16.1 mo versus NR; HR = 1.39, 95% CI: 0.30–6.31, log-rank $p = 0.655$; Supplementary Fig. 5), though a definitive conclusion is limited owing to the small sample sizes.

Discussion

In this study, we presented an in-depth assessment of patients with unresectable stage III *EGFR*-mutated NSCLC who received consolidation durvalumab after concurrent CRT. These patients experienced a high frequency of severe irAEs and did not obtain improvements in PFS when compared with those who completed CRT alone, in line with the negligible PFS difference in the PACIFIC trial subset analysis.[1] To the best of our knowledge, this retrospective analysis is also the first to suggest that EGFR TKIs administered as induction or consolidation therapy with concurrent CRT may achieve a greater PFS compared with CRT with durvalumab or alone in patients with *EGFR*-mutated NSCLC. Altogether, these data suggest that an alternative definitive treatment approach may be more appropriate for patients with *EGFR*-mutated NSCLC.

The PACIFIC trial has revolutionized the treatment of patients with locally advanced NSCLC. Yet, the median PFS of 10.3 months among *EGFR*-mutated NSCLC patients treated with durvalumab in this cohort was lower than the 17.2 months among those in PACIFIC.[9] The PFS in this study was also lower than that reported in retrospective analyses of unselected patients, which reached at least 14 months.[19–21] Although the median PFS with CRT and durvalumab was numerically higher than that with CRT alone, the Kaplan-Meier plot reveals that the survival curves are largely overlapping, indicating a lack of benefit with durvalumab. This finding is in accordance with previous assessments of anti–PD-(L)1 immunotherapy among patients with *EGFR*-mutated NSCLC, which have consistently revealed suboptimal outcomes.[22] Although the exact cause for this response pattern remains unknown, studies suggest that low rates of PD-L1 expression and $CD8^+$ tumor-infiltrating lymphocytes may play a role.[23,24] After recurrence, PFS with first-line EGFR TKIs did not significantly differ between patients who received CRT with or without durvalumab, suggesting EGFR TKIs could have similar effects as salvage therapy after either approach. As the OS data were immature, we were unable to compare the OS between treatment groups, which would provide a more definitive answer on the clinical benefit with durvalumab or the absence thereof in this setting.

When considering the administration of any immune checkpoint inhibitor, the potential benefits must always be balanced with the risks of irAEs. In PACIFIC, 30% of patients experienced grade 3 or 4 AEs with durvalumab (3% with grade 3 or 4 pneumonitis) and 15% discontinued treatment owing to AEs,[1] consistent with previous studies of immunotherapy for advanced NSCLC.[25–27] In this study, 42% of assessable patients experienced grade 3 AEs and 39% discontinued durvalumab owing to AEs. In addition, 25% of assessable patients developed a grade greater than or equal to 2 pneumonitis and required oral corticosteroids. A PACIFIC trial subgroup analysis revealed that all-grade pneumonitis (including radiation pneumonitis) occurred more frequently in patients treated with durvalumab who were *EGFR*-positive versus *EGFR*-negative (59% versus 36%).[28] In a separate analysis, all-grade nonpneumonitis irAEs occurred at similar frequencies in the *EGFR*-positive and *EGFR*-negative durvalumab subgroups (14% versus 15%).[29] However, small retrospective studies have revealed higher rates of toxicity with durvalumab overall,[19,21,30] suggesting outside of a selected clinical trial population, the risk of irAEs may be higher. Previous data have indicated that patients who experience high-grade irAEs may derive greater clinical benefit from immunotherapy[31–33]; however, we did not observe this pattern in our cohort. As the number of *EGFR*-positive patients who received durvalumab was relatively small, we cannot definitively conclude that these patients are at a higher risk of irAE development with durvalumab, only that nearly half experienced severe irAEs and most had negligible PFS benefits compared with patients receiving CRT alone.

The question of whether to administer durvalumab to patients with *EGFR*-mutated NSCLC is compounded by the concerns of irAEs when initiating osimertinib after immunotherapy.[11] In this study, one patient who developed pneumonitis while on durvalumab unfortunately redeveloped a grade 4 pneumonitis shortly after initiation of osimertinib. Previous analyses have revealed that anti–PD-(L)1 antibodies may persist in the bloodstream for months after treatment and can cause delayed onset of irAEs[11,34]; however, it is unlikely that the durvalumab antibodies persisted after the patient's 20-month treatment-free interval. It is possible that the patient's previous episode of pneumonitis had "primed" the immune system to overactivation on exposure to osimertinib, which would raise additional concerns given the frequency of pneumonitis associated with CRT and durvalumab.[28] None of the other five patients who initiated EGFR TKIs after durvalumab experienced irAEs despite having shorter between-treatment time intervals. In one retrospective study, four of six patients who developed severe irAEs received osimertinib within

30 days of their last immunotherapy dose and only one of our patients fit within this 30-day between-treatment time interval.[11]

Finally, this retrospective analysis suggests that there may be a significant PFS benefit among patients who receive EGFR TKIs as induction or consolidation therapy with CRT. Previous investigations of EGFR TKIs in the locally advanced setting have been limited. The phase 2 RTOG-1306 trial sought to evaluate erlotinib hydrochloride as induction therapy for 12 weeks followed by concurrent CRT for patients with stage III *EGFR*-mutated NSCLC (NCT01822496), but unfortunately it terminated early owing to slow accrual. Maintenance gefitinib was evaluated after CRT in the randomized phase 3 SWOG 0023 trial, which revealed that gefitinib was associated with poorer OS compared with placebo (23 mo versus 35 mo, $p = 0.013$) in a molecularly unselected population.[35] However, recent data from the phase 3 ADAURA trial indicate that EGFR TKIs may have a role in the definitive treatment of early-stage *EGFR*-mutated NSCLC.[36] Currently, the randomized phase 3 LAURA trial is underway which will evaluate osimertinib administered until progression, toxicity, or other reasons for discontinuation in patients with stage III *EGFR*-mutated NSCLC after CRT (NCT03521154). Whether the optimal definitive strategy for these patients involves EGFR TKIs as induction or consolidation therapy with CRT remains to be determined. Although the subgroup analysis was small, the induction EGFR TKI data in this study are provocative in that none of these patients had recurrence over 7 months and this strategy could enable EGFR TKI rechallenge in case of recurrence.

Although this retrospective analysis has inherent limitations, this design enabled us to evaluate a spectrum of patient experiences during CRT and with EGFR TKIs after recurrence. The multi-institutional nature of this study could introduce heterogeneity but found consistent results between institutions. The sample size of this study was small, especially in the subset analyses; yet, the main findings corroborated those observed in PACIFIC. Nonetheless, further investigation with larger cohorts will be insightful. Although all patients in the CRT and durvalumab group had PD-L1 testing performed, PD-L1 expression was missing for more than half of the patients in the CRT-alone group. As oncologists may be more likely to recommend consolidation durvalumab for patients with high PD-L1 expression, this could potentially induce a selection bias. Patients with high PD-L1 expression had better outcomes after CRT and durvalumab in PACIFIC[37]; however, whether this applies to patients with *EGFR*-mutated NSCLC remains unknown.

In summary, patients with *EGFR*-mutated NSCLC did not derive PFS benefits with consolidation durvalumab and experienced a high frequency of severe irAEs. Although most patients did not experience incident irAEs when initiating EGFR TKIs after recurrence, one patient who had pneumonitis on durvalumab redeveloped severe pneumonitis on osimertinib, suggesting potentially multiple mechanisms for increased susceptibility to irAEs with EGFR TKIs after immunotherapy. Given the growing body of literature suggesting a lack of benefit and the current evidence of harm, consolidation durvalumab in the setting of *EGFR*-mutated NSCLC should be approached with caution. Alternatively, induction or consolidation EGFR TKIs may offer a more durable definitive treatment strategy for these patients and further investigation of these approaches is warranted.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.01.1628.

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