BRIEF REPORT

Brief Report: Durvalumab After Chemoradiotherapy in Unresectable Stage III *EGFR*-Mutant NSCLC: A Post Hoc Subgroup Analysis From PACIFIC

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ABSTRACT

Introduction: Consolidation durvalumab (the "PACIFIC regimen") is standard of care for patients with unresectable stage III NSCLC who have not progressed after chemoradiotherapy, on the basis of data from the phase 3 placebo-controlled PACIFIC study (NCT02125461). Nevertheless, the benefit of immunotherapy in patients with stage III *EGFR*-mutant (*EGFR*m) NSCLC is not well characterized. Here, we report a post hoc exploratory efficacy and safety analysis from a subgroup of patients with *EGFR*m NSCLC from the PACIFIC.

Methods: Patients with stage III unresectable NSCLC and no progression after more than or equal to two cycles of platinum-based concurrent chemoradiotherapy were randomized (2:1) to receive durvalumab (10 mg/kg intravenously every 2 weeks [wk], for up to 1 y) or placebo; stratified

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by age, sex, and smoking history. Enrollment was not restricted by oncogenic driver gene mutation status or programmed death-ligand 1 expression. Patients with NSCLC with an *EGFR* mutation, determined by local testing only, were included in this subgroup analysis. The primary end points were progression-free survival (PFS; assessed by blinded independent central review) and overall survival (OS). Secondary end points included objective response rate and safety. Statistical analyses for the subgroup of patients with *EGFR*m NSCLC were post hoc and considered exploratory.

Results: Of 713 patients randomized, 35 had locally confirmed *EGFR*m NSCLC (durvalumab, n = 24; placebo, n = 11). At data cutoff (January 11, 2021), median duration of follow-up for survival was 42.7 months (range: 3.7–74.3 mo) for all randomized patients in the subgroup. Median PFS was 11.2 months (95% confidence interval [CI]: 7.3–20.7) with durvalumab versus 10.9 months (95% CI: 1.9–not evaluable [NE]) with placebo; hazard ratio = 0.91 (95% CI: 0.39–2.13). Median OS was 46.8 months (95% CI: 29.9–NE) with durvalumab versus 43.0 months (95% CI: 14.9–NE) with placebo; hazard ratio = 1.02 (95% CI: 0.39–2.63). The safety profile of durvalumab was generally consistent with the overall population and known profile for durvalumab.

Conclusions: PFS and OS outcomes with durvalumab were similar to placebo for patients with *EGFR*m tumors, with wide CIs. These data should be interpreted with caution owing to small patient numbers and lack of a prospective study that evaluates clinical outcomes by tumor biomarker status. Further research to determine the optimal treatment for unresectable stage III *EGFR*m NSCLC is warranted.

Keywords: NSCLC; EGFR; Durvalumab; Chemoradiotherapy

Introduction

Consolidation durvalumab ("PACIFIC regimen") is standard of care for patients with unresectable stage III NSCLC after chemoradiotherapy (CRT).[1] In the PACIFIC study, durvalumab improved overall survival (OS) and median progression-free survival (PFS) in all-comers versus placebo.[2,3] An updated 5-year analysis reinforced this benefit: OS hazard ratio (HR) = 0.72 (95% confidence interval [CI]: 0.59–0.89); PFS HR equal to 0.55 (95% CI: 0.45–0.68).[4]

Osimertinib is the preferred first-line therapy in advanced *EGFR*m NSCLC, on the basis of significant improvements in PFS (HR = 0.46, 95% CI: 0.37–0.57; $p < 0.001$) and OS (HR = 0.80, 95.05% CI: 0.64–1.00; $p = 0.046$) versus first-generation EGFR tyrosine kinase inhibitors (TKIs) in the FLAURA study.[5–8] Osimertinib is also approved as an adjuvant treatment in resected stages IB to IIIA *EGFR*m NSCLC, on the basis of significantly improved disease-free survival (DFS) versus placebo (median 65.8 versus 28.1 mo, HR = 0.27, 95% CI: 0.21–0.34) in ADAURA.[9]

The benefit of immunotherapy in *EGFR*m NSCLC is not well characterized. In resectable NSCLC, adjuvant atezolizumab is approved post-chemotherapy, on the basis of the IMpower010 trial, revealing a significant DFS improvement versus best supportive care (n = 476, HR = 0.66, 95% CI: 0.50–0.88; $p = 0.039$) in patients with stages II to IIIA NSCLC with programmed death-ligand 1 (PD-L1) expressed on greater than or equal to 1% of tumor cells (TCs).[10] In patients with *EGFR*m NSCLC and PD-L1 TC greater than or equal to 1% (n = 43) in this trial, the HR was 0.57 (95% CI: 0.26–1.24).[10] Interestingly, in the KEYNOTE-091/PEARLS trial, adjuvant pembrolizumab had a significant DFS benefit versus placebo for stages IB to IIIA NSCLC without PD-L1 selection (n = 1177, HR = 0.76, 95% CI 0.63–0.91; $p = 0.0014$)[11] and a HR of 0.44 (95% CI 0.23–0.84) in the *EGFR*m subgroup (n = 73).[12]

In unresectable stage III NSCLC, two small retrospective studies have reported data on consolidation durvalumab post-CRT in patients with *EGFR*m tumors.[13,14] Aredo et al.[13] reported a median PFS (mPFS) of 10.3 months with CRT and durvalumab (n = 13) versus 6.9 months with CRT (n = 16). Hellyer et al.[14] reported a median DFS of 7.5 months (n = 14) for patients with tumors harboring *EGFR*m/*ERBB2* mutations receiving the PACIFIC regimen versus not reached (n = 22) for *ERBB2*/*EGFR* wild-type tumors (HR = 2.8, 95% CI: 1.02–7.67).[14]

In first-line advanced NSCLC, a phase 2 trial investigating the utility of single-agent pembrolizumab in patients with newly diagnosed *EGFR*m NSCLC (n = 11) was stopped early for futility, with investigators concluding this was not an appropriate therapy for these patients.[15] A study of first-line nivolumab reported a 14% objective response rate (ORR) and mPFS of 1.8 months for patients with advanced *EGFR*m NSCLC (n = 7).[16] In the IMpower150 trial, the combination of first-line carboplatin or paclitaxel or bevacizumab plus atezolizumab numerically improved OS (n = 697, HR = 0.80, 95% CI: 0.67–0.95) versus carboplatin or paclitaxel or bevacizumab in patients with wild-type chemotherapy-naive metastatic disease.[17] In the *EGFR*m subgroup, who had received prior EGFR TKIs, the HR was 0.74, with wide CIs (n = 50, 95% CI: 0.38–1.46).[18] Separately, the phase 3 IMpower130 study found improvements in OS (HR= 0.79, 95% CI: 0.64–0.98) and PFS (HR = 0.64, 95% CI: 0.54–0.77) with first-line atezolizumab plus chemotherapy versus chemotherapy in all patients with stage IV wild-type NSCLC (n = 451). Nevertheless, no benefit was observed in the subset of patients whose tumors harbored *EGFR/ALK* alterations (n = 44; OS HR = 0.98, 95% CI: 0.41–2.31).[19] In addition, a meta-analysis of a

Table 1. Baseline Demographics and Characteristics for the PACIFIC *EGFR*m Subgroup

Demographic or Characteristic	Durvalumab (n = 24)	Placebo (n = 11)	Total (N = 35)
Age (y): median (range)	65 (42-83)	69 (57-90)	67 (42-90)
Sex: male/female, n (%)	13 (54)/11 (46)	8 (73)/3 (27)	21 (60)/14 (40)
Race: Asian/non-Asian, n (%)	15 (63)/9 (38)[c]	6 (55)/5 (45)	21 (60)/14 (40)
Disease stage[a] IIIA/IIIB, n (%)	11 (46)/13 (54)	7 (64)/4 (36)	18 (51)/17 (49)
WHO PS: 0/1, n (%)	13 (54)/11 (46)	7 (64)/4 (36)	20 (57)/15 (43)
Tumor history: Squamous/nonsquamous	3 (13)/21 (88)[c]	1 (9)/10 (91)	4 (11)/31 (89)
Smoking history Yes/no, n (%)	13 (54)/11 (46)	5 (45)/6 (55)	18 (51)/17 (49)
Best response to previous CRT: CR/PR/stable disease, n (%)	0/11 (46)/13 (54)	0/4 (36)/7 (64)	0/15 (43)/20 (57)
Positive *EGFR* mutation status: exon 19 del/L858R/other,[b] n (%)	10 (42)/6 (25)/8 (33)	3 (27)/5 (45)/3 (27)[c]	13 (37)/11 (31)/11 (31)[c]
PD-L1 status ≥25%/<25%/unknown, n (%)	4 (17)/16 (67)/4 (17)[c]	3 (27)/4 (36)/4 (36)[c]	7 (20)/20 (57)/8 (23)
Primary tumor stage T1a-b/T2a-b/T3/T4, n (%)	6 (25)/9 (38)/4 (17)/5 (21)[c]	2 (18)/6 (55)/1 (9)/2 (18)	8 (23)/15 (43)/5 (14)/7 (20)
Regional lymph nodes N0/N2/N3, n (%)	2 (8)/10 (42)/12 (50)	1 (9)/7 (64)/3 (27)	3 (9)/17 (49)/15 (43)[c]
Previous induction chemotherapy, n (%)	2 (8)	4 (36)	6 (17)

Note: DCO: February 13, 2017.
[a]According to AJCC seventh edition staging.
[b]EGFR other includes the following: Durvalumab: exon 18 mutation, exon 18 mutation + exon 19 deletion, >3 mutations; T790M, L858R + S768I, other, n = 1 (4%) each; exon 18 mutation + other, n = 2 (8%). Placebo: exon 19 deletion + other, T790M + other, other, n = 1 (9%) each.
[c]Percentages do not add up to 100 owing to rounding.
AJCC, American Joint Committee on Cancer; CR, complete response; CRT, chemoradiotherapy; DCO, data cutoff; del, deletion; *EGFR*m, *EGFR* mutant; PD-L1, programmed death-ligand 1; PR, partial response; PS, performance status; WHO, World Health Organization.

single-agent immune checkpoint inhibitor therapy (nivolumab, pembrolizumab, or atezolizumab) versus docetaxel as second/later-line treatment in *EGFR*m NSCLC did not find a benefit for immunotherapy, with a HR for OS of 1.11 (95% CI: 0.80–1.53).[20]

Here, we report a post hoc exploratory efficacy and safety analysis from a subgroup of 35 patients with unresectable stage III *EGFR*m NSCLC enrolled in the PACIFIC trial (NCT02125461).[2,3]

Materials and Methods

Patients

Study methodology has been reported previously.[2,3] Eligible patients had histologically/cytologically documented stage III unresectable NSCLC, WHO performance status (PS) 0/1, and no progression after more than or equal to two cycles of platinum-based concurrent CRT (total radiotherapy dose typically 60–66 Gy in 30–33 fractions).[3,4] Enrollment was not restricted by oncogenic driver gene mutation status or PD-L1 expression. Patients whose tumors harbored an *EGFR* mutation, on the basis of local testing only, were included in this subgroup analysis.

Study Design

Patients were randomized 2:1 (1–42 days [d] post-CRT) to receive durvalumab (10 mg/kg intravenously every 2 wk, for up to 1 y) or placebo; stratified by age (<65 y versus ≥65 y), sex (male versus female), and smoking history (yes versus no).[3] The study was designed by representatives of the sponsor (AstraZeneca) and academic advisors. The study was performed in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice and the Declaration of Helsinki. All patients provided informed written consent.

End Points and Assessments

Primary end points were PFS, per Response Evaluation Criteria in Solid Tumors version 1.1, by blinded independent central review, and OS, measured from the time of randomization after CRT. Secondary end points included ORR and safety.[3] Safety assessments and statistical methods are reported in the Supplementary Methods. Baseline characteristics and safety analysis data cutoff: February 13, 2017. Efficacy analysis data cutoff: January 11, 2021.

Results

Patients and Treatment

Of 713 patients randomized, 35 had *EGFR*m NSCLC at baseline (durvalumab n = 24, placebo n = 11),

excluding eight patients whose tumors harbored *ALK* rearrangements, previously reported as part of this subgroup. In the *EGFR*m subgroup, 69% of the patients had EGFR TKI sensitizing exon 19 deletion or L858R mutations and 31% had other *EGFR* mutations or combinations (Table 1). More patients in the placebo arm were male (73% versus 54%), had stage IIIA disease (64% versus 46%), WHO PS 0 (64% versus 54%), and

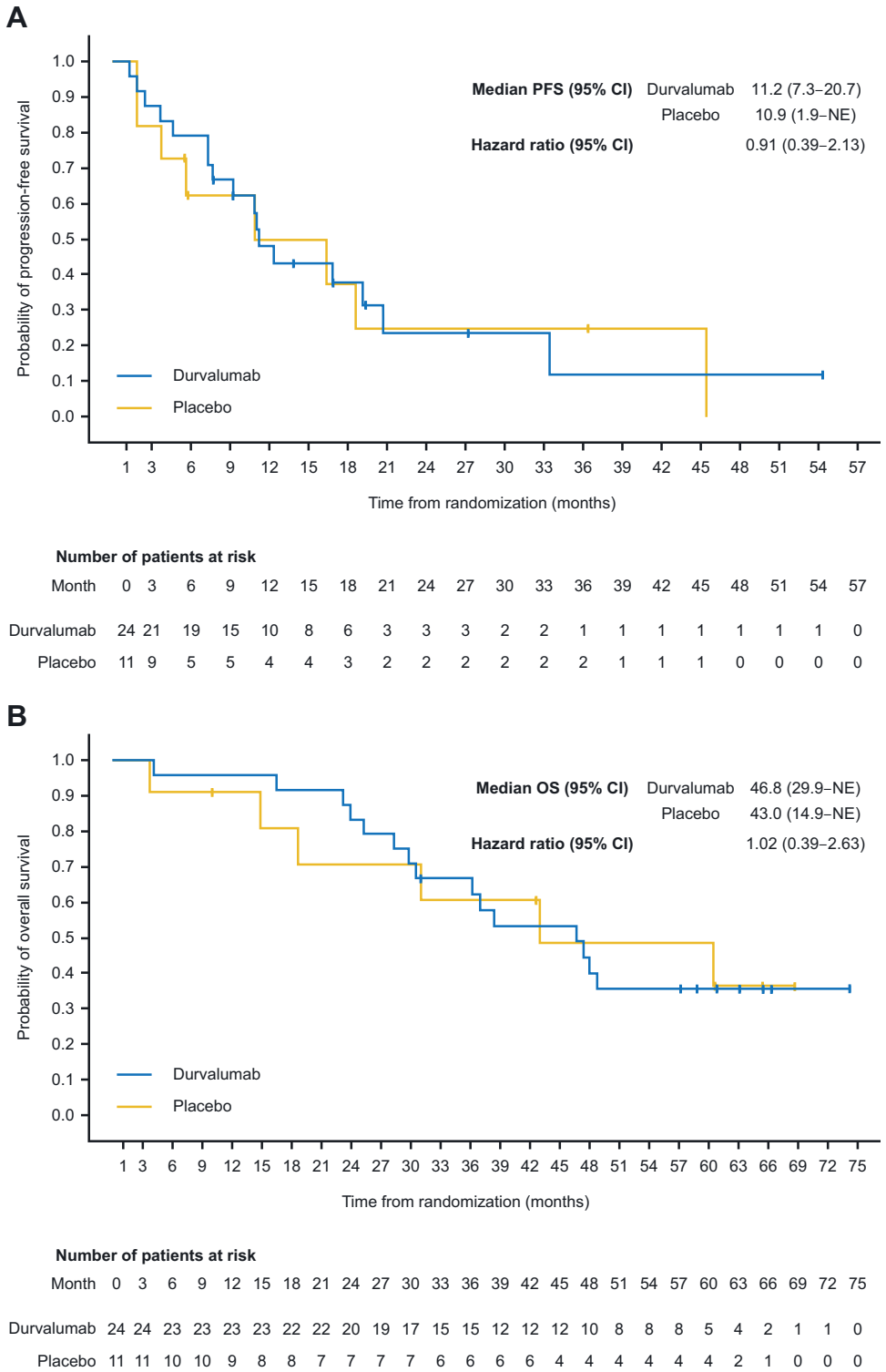

Figure 1. PFS and OS in the PACIFIC *EGFR*m subgroup (assessed by blinded independent central review). DCO: January 11, 2021. Tick marks indicate censored data. CI, confidence interval; DCO, data cutoff; *EGFR*m, EGFR-mutant; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

received pre-CRT induction chemotherapy (36% versus 8%), compared with the durvalumab arm. More patients in the durvalumab versus placebo arm were Asian (63% versus 55%) and had tumors with PD-L1 TC less than 25% (67% versus 36%). These differences should be interpreted with caution as patient numbers for these demographic subgroups are small.

Efficacy

Median duration of follow-up for survival was 42.7 months (range: 3.7–74.3 mo) for all randomized patients in the *EGFR*m subgroup. mPFS was 11.2 months (95% CI: 7.3–20.7) with durvalumab versus 10.9 months (95% CI: 1.9–not evaluable [NE]) with placebo; HR = 0.91 (95% CI: 0.39–2.13; Fig. 1*A*). Median OS was 46.8 months (95% CI: 29.9–NE) with durvalumab versus 43.0 (95% CI: 14.9–NE) with placebo; HR = 1.02 (95% CI: 0.39–2.63; Fig. 1*B*). ORR was 26.1% (95% CI: 10.2–48.4) and 18.2% (95% CI: 2.3–51.8) with durvalumab and placebo, respectively.

In the *EGFR*m subgroup, 12 (50%) and four patients (36%) receiving durvalumab and placebo, respectively, completed one year of treatment; 12 (50%) and seven patients (64%) discontinued treatment, all of whom were alive and eligible to receive subsequent treatments. Nineteen (79%) and eight patients (73%) who received durvalumab and placebo, respectively, received a subsequent treatment. Most received an EGFR TKI (54% from the durvalumab arm and 64% from the placebo arm) as subsequent treatment (described in the Supplementary Results and Supplementary Table 1).

Safety

In the *EGFR*m subgroup, median treatment duration was 36 weeks (range: 4–52 wk) with durvalumab and 46 weeks (range: 8–52 wk) with placebo. With durvalumab and placebo, adverse events (AEs) of any cause and grade occurred in 100% and 82% of patients, grade 3/4 AEs occurred in 17% and 18% of patients, AEs leading to dose delay occurred in 71% and 18% of patients, and AEs leading to dose discontinuation occurred in 8% and 9% of patients, respectively (Supplementary Table 2).

The most common AEs reported with durvalumab versus placebo were radiation pneumonitis (Fig. 2; 42% versus 36%; grade 1, 21% versus 27%; grade 2, 21% versus 9%; no cases being grade 3 or greater), cough (38% versus 18%), and pruritus (25% versus 0%). Pneumonitis occurred in 17% of patients with durvalumab (none grade 3 or above) versus 18% with placebo (one patient grade 3; Fig. 2).

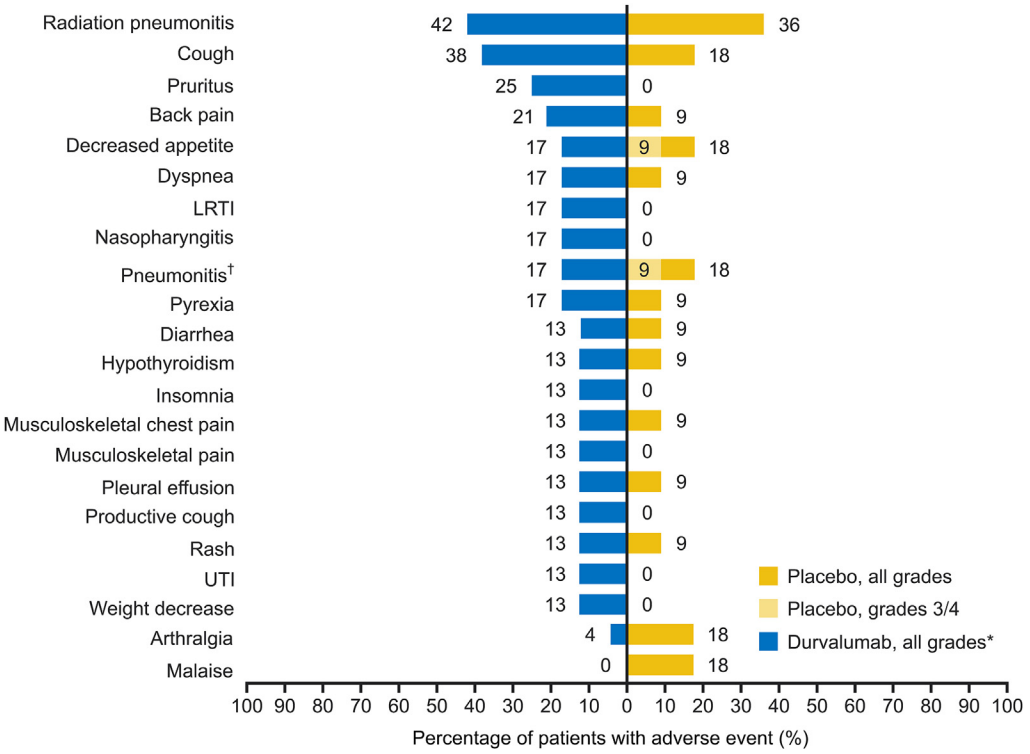

Figure 2. All causality adverse events reported in more than or equal to 10% of patients. DCO: February 13, 2017. *No grade 3/4 AEs were reported in the durvalumab arm for the AEs reported in more than or equal to 10% of patients found in this figure. †All pneumonitis events regardless of steroid or immunosuppressive use underwent adjudication before unblinding the study. AE, adverse event; DCO, data cutoff; LRTI, lower respiratory tract infection; UTI, urinary tract infection.

Discussion

In this exploratory subgroup analysis, PFS and OS with durvalumab were similar to placebo in patients with *EGFR*m NSCLC, with wide CIs. These data should be interpreted with caution owing to small patient numbers, imbalances in selected baseline characteristics between treatment arms, and the study not being designed to prospectively evaluate clinical outcomes according to tumor biomarker status. It should also be noted that the overall *EGFR*m subgroup included 60% males, 51% smokers, and 11% with squamous tumors, not typically characteristic of an *EGFR*m cohort of patients.

Safety findings in the *EGFR*m subgroup were consistent with the overall PACIFIC study population and durvalumab monotherapy profile.[2] Although the proportion of AEs leading to a dose delay was considerably higher in the durvalumab versus the placebo arm (71% versus 18%), grade 3/4 causally related AEs were low in both arms (4% versus 9%). The proportion of patients with radiation pneumonitis (42% versus 36%, no cases being grade 3 or greater) or pneumonitis (17% versus 18%) was similar in both arms. All pneumonitis events with durvalumab were of low grade.

Given these results and that there is no approved EGFR TKI for these patients, further research into the optimal choice of treatments for unresectable stage III *EGFR*m NSCLC is warranted. On the basis of data in the advanced and resectable settings, EGFR TKIs may provide an effective treatment for these patients post-CRT, but prospective data are needed.

Several phase 3 studies are planned or currently underway, including LAURA (NCT03521154), investigating maintenance osimertinib versus placebo in locally advanced stage III *EGFR*m unresectable NSCLC (primary end point: PFS by independent review; key secondary end points: PFS by EGFRm, central nervous system PFS, and OS), and a study (NCT04951635) that will investigate aumolertinib (third-generation EGFR TKI) versus placebo in Chinese patients with stage III EGFRm unresectable disease (primary end point: PFS by independent review; key secondary end points: PFS by investigators, central nervous system PFS, and OS).

CRediT Authorship Contribution Statement

Jarushka Naidoo: Methodology, Conceptualization, Formal analysis, Investigation, Resources, Data curation.

Scott Antonia: Methodology, Conceptualization, Formal analysis, Investigation, Resources, Data curation, Visualization.

Yi-Long Wu: Conceptualization, Formal analysis, Investigation.

Byoung Chul Cho: Methodology, Conceptualization, Formal analysis, Investigation, Resources, Data curation.

Piruntha Thiyagarajah: Methodology, Formal analysis.

Helen Mann: Methodology, Formal analysis.

Michael Newton: Methodology, Conceptualization, Formal analysis, Supervision.

Corinne Faivre-Finn: Conceptualization, Visualization.

All authors wrote the original draft and reviewed and edited the manuscript.

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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.2023.02.009.

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