JAMA Network Open

Original Investigation | Oncology

Durvalumab Alone or Combined With Novel Agents for Unresectable Stage III Non–Small Cell Lung Cancer

Update From the COAST Randomized Clinical Trial

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Abstract

IMPORTANCE The PACIFIC trial established durvalumab as the standard-of-care therapy for unresectable, stage III non–small cell lung cancer (NSCLC) without progression following concurrent chemoradiotherapy (cCRT). Novel immunotherapy combinations involving the anti-CD73 monoclonal antibody oleclumab or the anti-NKG2A monoclonal antibody monalizumab have the potential to build on the durvalumab standard of care.

OBJECTIVE To report updated results from the phase 2 COAST trial of consolidation durvalumab alone or combined with oleclumab or monalizumab in patients with unresectable, stage III NSCLC and no progression following cCRT.

DESIGN, SETTING, AND PARTICIPANTS COAST was an open-label, phase 2, multidrug platform randomized clinical trial conducted across 73 sites globally. Patients with an Eastern Cooperative Oncology Group Performance Status of 0 or 1 and no progression following definitive platinum-based cCRT were enrolled between January 2019 and July 2020. The data cutoff for this final analysis was July 18, 2023. Data were analyzed from September 2023 to March 2024.

INTERVENTION Patients were randomized 1:1:1, stratified by histologic type within 42 days after cCRT, to durvalumab alone or durvalumab combined with oleclumab or monalizumab for up to 12 months.

MAIN OUTCOMES AND MEASURES The primary end point was investigator-assessed confirmed objective response rate (ORR). Key secondary end points included investigator-assessed progression-free survival (PFS), overall survival (OS), and safety. Efficacy end points were assessed in the intention-to-treat population. Safety was assessed in the as-treated population.

RESULTS Of 189 randomized patients (median [range] age, 65 [37-87] years; 129 males [68.3%]; 176 [93.1%] current or former smokers), 186 received treatment consisting of durvalumab plus oleclumab (n = 59), durvalumab plus monalizumab (n = 61), or durvalumab alone (n = 66). Of these patients, 1 (0.5%) self-reported as American Indian or Alaska Native, 14 (7.5%) as Asian, 8 (4.3%) as Black or African American, 1 (0.5%) as Native Hawaiian or Other Pacific Islander, 159 (85.5%) as White, and 3 (1.6%) as other race. After a median (range) follow-up in all patients of 30.1 (0.4-48.9) months, confirmed ORR was numerically higher with durvalumab plus oleclumab (35.0%; 95% CI, 23.1%-48.4%) or monalizumab (40.3%; 95% CI, 28.1%-53.6%) than with durvalumab alone (23.9%; 95% CI, 14.3%-35.9%). However, the difference in ORR for durvalumab plus oleclumab (11.1 [-6.4 to 28.1] percentage points) and durvalumab plus monalizumab (16.9 [-0.8 to 33.4] percentage points)

(continued)

Key Points

Question Can combining standard-of-care consolidation durvalumab with oleclumab or monalizumab further improve outcomes in patients with unresectable, stage III non–small cell lung cancer without progression following chemoradiotherapy?

Findings Final analyses from this phase 2 randomized clinical trial of 189 patients showed that confirmed objective response rates were numerically higher but not statistically significantly higher with durvalumab plus oleclumab or monalizumab than with durvalumab alone.

Meaning These findings support further evaluation of these combinations in an ongoing, larger, phase 3 trial (PACIFIC-9).

+ Visual Abstract

+ Supplemental content

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Abstract (continued)

was not statistically significant compared with durvalumab alone. Both combinations prolonged PFS vs durvalumab alone (plus oleclumab: hazard ratio [HR], 0.59 [95% CI, 0.37-0.93]; plus monalizumab: HR, 0.63 [95% CI, 0.40-0.99]) but did not demonstrate nominal associations with longer OS (plus oleclumab: HR, 0.69 [95% CI, 0.40-1.20]; plus monalizumab: HR, 0.77 [95% CI, 0.44-1.33]). Safety was comparable across arms, without new or notable safety signals.

CONCLUSIONS AND RELEVANCE In the COAST trial, combining consolidation durvalumab with oleclumab or monalizumab provided additional clinical benefit over durvalumab alone. This finding supports further investigation of these novel combinations in the phase 3 PACIFIC-9 trial.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03822351

JAMA Network Open. 2025;8(7):e2518440. doi:10.1001/jamanetworkopen.2025.18440

Introduction

The PACIFIC trial established durvalumab, a programmed death ligand-1 (PD-L1) inhibitor, as standard-of-care therapy for patients with unresectable, stage III non–small cell lung cancer (NSCLC) without progression following concurrent chemoradiotherapy (cCRT).[1-3] Subsequent phase 3 studies failed to show improved outcomes with simultaneous anti–PD-L1 or programmed cell death 1 therapy plus cCRT in this setting.[4,5] Alternatively, novel immunotherapy combinations that build on consolidation durvalumab are being investigated.[6-8] Radiotherapy can suppress antitumor immune responses by promoting tumoral expression of cluster of differentiation 73 (CD73), human leukocyte antigen E (HLA-E, ligand of inhibitory receptor natural killer group 2 member A [NKG2A]), and PD-L1, providing rationale for blockade of these immune checkpoints following cCRT.[9-11]

Oleclumab is a human IgG1λ monoclonal antibody (mAb) that selectively binds to and inhibits CD73, an enzyme found on the surface of cancer and immune cells.[12] By inhibiting CD73, oleclumab reduces extracellular adenosine production and promotes antitumor immunity.[13] In a phase 1 study, oleclumab combined with durvalumab showed promising antitumor activity, with a manageable safety profile, in patients with epidermal growth factor receptor (*EGFR*)-mutant NSCLC.[14]

Monalizumab is a first-in-class, humanized IgG4 mAb that specifically binds to and blocks NKG2A from binding to HLA-E, thereby reducing inhibition of natural killer and $CD8^+$ T cells and enhancing antitumor immunity.[15] In a phase 1b study, monalizumab in combination with durvalumab demonstrated modest clinical activity, with a manageable safety profile, in patients with recurrent ovarian cancer.[16]

COAST was a global, randomized, phase 2, signal-finding trial of consolidation durvalumab alone or combined with oleclumab or monalizumab in patients with unresectable, stage III NSCLC without progression following cCRT. Interim results (median [range] follow-up, 11.5 [0.4-23.4] months) showed that both combinations numerically increased objective response rate (ORR) and prolonged progression-free survival (PFS) compared with durvalumab alone, without adversely impacting safety and tolerability.[8] We report final analyses of ORR and key secondary and exploratory end points, including safety, from the COAST trial.

Methods

Study Design

The study design, which has been reported previously,[8] is summarized in eFigure 1 in Supplement 2. The COAST trial was conducted in accordance with International Council for Harmonization Good Clinical Practice guidelines, the principles of the Declaration of Helsinki,[17] and all applicable country

and local regulations. The trial protocol (Supplement 1) was approved by the institutional review board or independent ethics committee at each of the 73 study sites. All patients provided written informed consent. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Eligible patients were enrolled from January 2019 to July 2020. The data cutoff for this final analysis was July 18, 2023. Patients were adults (aged ≥18 years) with unresectable, stage III NSCLC, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 (range: 0-5, with the higher value indicating greater adverse impact of disease on patient functioning), and no progression following definitive platinum-based cCRT. These patients were randomized 1:1:1—stratified by histologic type (adenocarcinoma and nonadenocarcinoma)—up to 42 days after cCRT to receive durvalumab alone (control arm) or durvalumab combined with oleclumab or monalizumab (intervention arms) for up to 12 months (eFigure 1 in Supplement 1).

Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or other) was self-reported by patients. This variable was collected as part of standard demographic characterization of study patients. Disease characteristics and results analyzed by histologic type are reported here in squamous vs nonsquamous subgroups to align with current research standards.

The primary end point was confirmed ORR by investigator assessment, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Key secondary end points included duration of response, disease control rate at 16 weeks, PFS by investigator assessment (per RECIST version 1.1), 12-month PFS rate, overall survival (OS), and safety. Efficacy end points were assessed in the intention-to-treat population (all patients who were randomized). Safety was assessed in the as-treated population (patients who received ≥1 dose of study treatment).

Statistical Analysis

Statistical analysis has been reported previously.[8] This trial was not designed to test a specific hypothesis for the primary endpoint. A sample size of 60 patients per arm was chosen to provide an acceptable level of precision. For analytical comparisons between an experimental arm and the control arm, only control-arm patients concurrently enrolled with the experimental-arm patients were included. Due to drug supply availability, the durvalumab plus monalizumab arm opened later than the other 2 arms, so the first few patients could only be randomized to durvalumab monotherapy or durvalumab plus oleclumab. Three patients were randomized to durvalumab monotherapy at this time, and thus were not concurrently randomized with the durvalumab plus monalizumab arm. Therefore, they were not included in the analytical comparisons between these two arms; for these comparisons, the durvalumab monotherapy arm comprised 64 patients.

Efficacy endpoints were assessed in the intent-to-treat population (all randomized patients) and safety was assessed in the as-treated population (patients who received ≥1 dose of study treatment). Treatment-emergent adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, and safety data were analyzed using descriptive statistics.

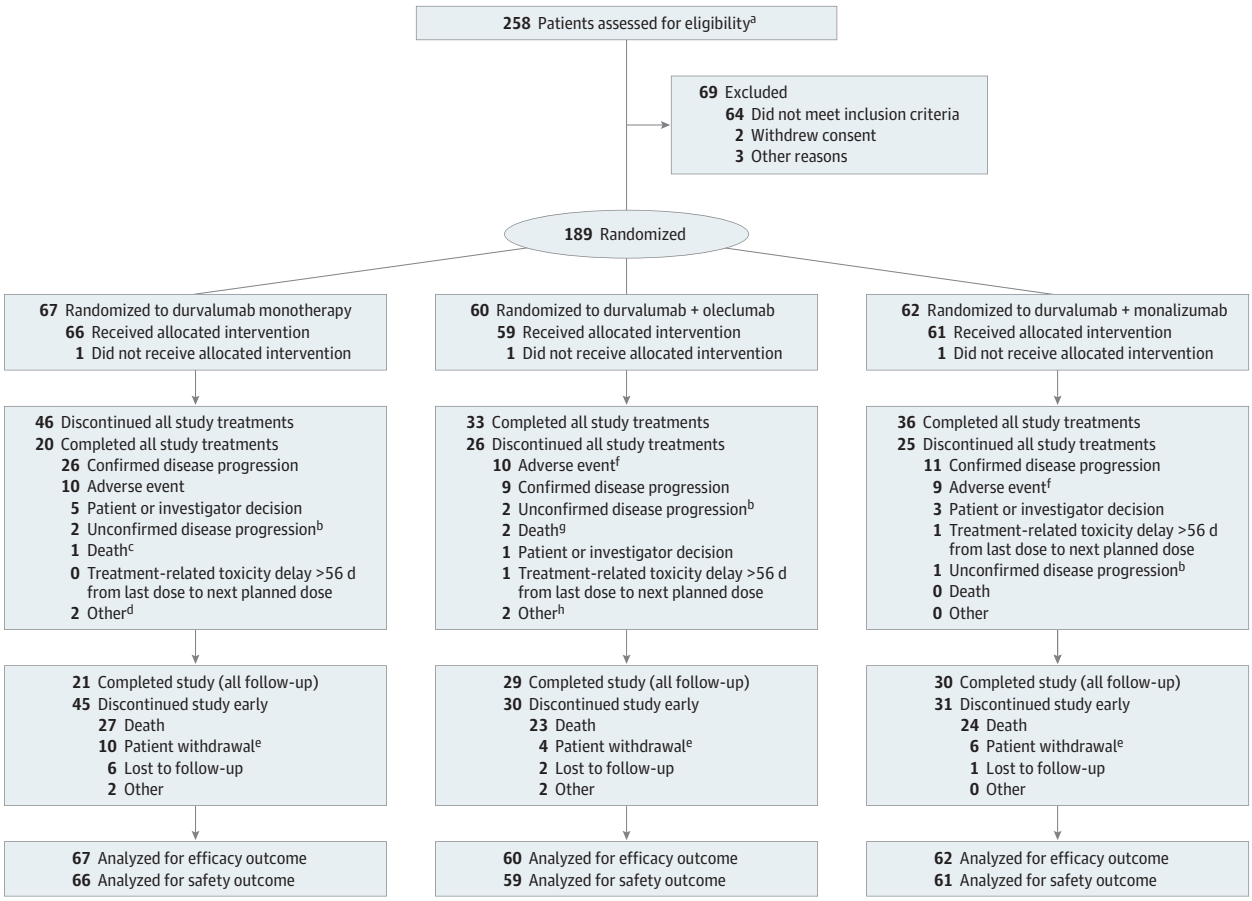
Time-to-event endpoints were analyzed by Kaplan–Meier methodology, with each experimental arm compared with the control arm; comparisons of PFS and OS between each experimental arm and the control arm used a Cox regression model, stratified by histology, to estimate hazard ratios (HRs) and 95% CIs. Confirmed overall response rates were summarized with 95% CIs calculated on the basis of the Clopper–Pearson exact method. Formal statistical comparisons between experimental arms were not performed. For exploratory subgroup analyses, HRs and 95% CIs were estimated using a Cox regression model, stratified by histology (adenocarcinoma and non-adenocarcinoma) (eMethods in Supplement 2). Nominal associations were indicated based on 2-sided 95% CIs. Data were analyzed September 2023 to March 2024 using SAS System, version 9.3 or higher (SAS Institute).

Results

Between January 2019 and July 2020, 189 patients were randomized, of whom 186 received durvalumab plus oleclumab (n = 59), durvalumab plus monalizumab (n = 61), or durvalumab alone (n = 66) (**Figure 1**). At data cutoff for this final analysis (July 18, 2023), the median (range) follow-up in all patients was 30.1 (0.4-48.9) months. All patients are now off the study, which is closed. Median (range) treatment exposure (28-day cycles) was 13 (1-13) cycles for both combination arms and 7 (1-13) cycles for durvalumab alone.

Baseline characteristics, as reported previously,[8] were generally balanced across arms (**Table 1**). The intention-to-treat population included 60 females (31.7%) and 129 males (68.3%), with a median (range) age of 65 (37-87) years. Among the 186 patients for whom data on race were available, 1 (0.5%) self-reported as American Indian or Alaska Native, 14 (7.5%) as Asian, 8 (4.3%) as Black or African American, 1 (0.5%) as Native Hawaiian or Other Pacific Islander, 159 (85.5%) as White, and 3 (1.6%) as other race. Overall, most patients were current or former smokers (176 of 189

Figure 1. CONSORT Flow Diagram



[a] Informed consent received.

[b] Unconfirmed disease progression and investigator determination that the patient was not eligible for a confirmation scan.

[c] Pneumonitis.

[d] Ineligibility after 56 days since last treatment due to patient unwillingness to visit the hospital due to the COVID-19 pandemic (n = 1) and clinical deterioration (n = 1).

[e] There was no option in the electronic data collection form to record the specific reason for patient withdrawal.

[f] One patient discontinued oleclumab due to an adverse event, but treatment with durvalumab alone in combination arms was not allowed per protocol.

[g] Death at home (n = 1) and radiation pneumonitis (n = 1).

[h] Non–study medication–related delay of more than 56 days from the last administration of study drug to the next planned dose (n = 1).

[93.1%]). There were some imbalances in ECOG PS, PD-L1 tumor cell (TC) expression, and prior platinum-based chemotherapy subgroups (Table 1).

Efficacy

Investigator-assessed confirmed ORR was 35.0% (95% CI, 23.1%-48.4%) with 21 responders in the durvalumab plus oleclumab arm, 40.3% (95% CI, 28.1%-53.6%) with 25 responders in the durvalumab plus monalizumab arm, and 23.9% (95% CI, 14.3%-35.9%) with 16 responders in the durvalumab only arm. However, the difference in ORR for durvalumab plus oleclumab (11.1 [−6.4 to 28.1] percentage points) and durvalumab plus monalizumab (16.9 [−0.8 to 33.4] percentage points) was not statistically significant compared with durvalumab alone (**Table 2**). Disease control rate at 16 weeks and median duration of response are presented in Table 2.

Table 1. Baseline Characteristics and Prior Chemoradiotherapy in the Intention-to-Treat Population

Characteristic[a]	Patients, No. (%)		
	Durvalumab alone (n = 67)	Durvalumab plus oleclumab (n = 60)	Durvalumab plus monalizumab (n = 62)
Age, median (range), y	66.0 (46-81)	65.0 (37-83)	65.0 (44-87)
Sex			
Female	22 (32.8)	18 (30.0)	20 (32.3)
Male	45 (67.2)	42 (70.0)	42 (67.7)
Race[b]			
Asian	5 (7.7)	4 (6.8)	5 (8.1)
Black or African American	1 (1.5)	5 (8.5)	2 (3.2)
White	57 (87.7)	47 (79.7)	55 (88.7)
Other[c]	2 (3.1)[d]	3 (5.1)[e]	0
ECOG PS[f]			
0	30 (45.5)	33 (55.9)	27 (44.3)
1	36 (54.5)	26 (44.1)	34 (55.7)
Current or former smoker	63 (94.0)	54 (90.0)	59 (95.2)
Histologic type			
Adenocarcinoma	31 (46.3)	26 (43.3)	31 (50.0)
Nonadenocarcinoma	36 (53.7)	34 (56.7)	31 (50.0)
Squamous	30 (44.8)	25 (41.7)	27 (43.5)
Nonsquamous	37 (55.2)	35 (58.3)	35 (56.5)
Disease stage at study entry			
IIIA	27 (40.3)	27 (45.0)	32 (51.6)
IIIB	35 (52.2)	29 (48.3)	27 (43.5)
IIIC	5 (7.5)	4 (6.7)	3 (4.8)
PD-L1 status			
TC expression ≥1%	30 (44.8)	23 (38.3)	20 (32.3)
TC expression <1%	16 (23.9)	7 (11.7)	12 (19.4)
Unknown (not evaluable)	21 (31.3)	30 (50.0)	30 (48.4)
Prior RT dose, Gy			
54-66	62 (92.5)	55 (91.7)	57 (91.9)
>66	5 (7.5)	5 (8.3)	5 (8.1)
Time from last RT to randomization, d			
<14	9 (13.4)	4 (6.7)	6 (9.7)
14-28	27 (40.3)	27 (45.0)	30 (48.4)
29-42	31 (46.3)	29 (48.3)	26 (41.9)
Prior platinum-based chemotherapy			
Cisplatin	23 (34.3)	28 (46.7)	15 (24.2)
Carboplatin	43 (64.2)	28 (46.7)	44 (71.0)
Cisplatin and carboplatin	1 (1.5)	4 (6.7)	3 (4.8)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed death-ligand 1; RT, radiotherapy; TC, tumor cell.

[a] One randomized patient in each arm did not receive treatment.

[b] Race was self-reported by patients. Data were missing for 2 patients in the durvalumab arm and 1 patient in the durvalumab plus oleclumab arm.

[c] Other race included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and other.

[d] Identified as Native Hawaiian or Other Pacific Islander (n = 1) and other (n = 1).

[e] Identified as American Indian or Alaska Native (n = 1) and other (n = 2).

[f] Baseline ECOG PS (range: 0-5, with the higher value indicating greater adverse impact of disease on patient functioning) was reported for randomized patients who received treatment; reported percentages are based on patients with available data.

Overall PFS data maturity was 60.8% (calculated by dividing the number of patients with a PFS event [n = 115] by the number of randomized patients in all 3 arms [n = 189]). PFS was prolonged with both combinations vs durvalumab alone (stratified HR, 0.59 [95% CI, 0.37-0.93] with durvalumab plus oleclumab and 0.63 [95% CI, 0.40-0.99] with durvalumab plus monalizumab). Median PFS was 21.1 (95% CI, 10.4-30.9) months with durvalumab plus oleclumab, 19.8 (95% CI, 13.6-31.3) months with durvalumab plus monalizumab, and 7.3 (95% CI, 4.0-13.8) months with durvalumab alone (**Figure 2**A; eTable 1 in Supplement 2). The 12-month PFS rates were 63.5% (95% CI, 49.2%-74.7%) with durvalumab plus oleclumab, 73.2% (95% CI, 59.6%-82.9%) with durvalumab plus monalizumab, and 37.6% (95% CI, 24.7%-50.4%) with durvalumab alone. The 24-month PFS rates are also shown in Figure 2A and eTable 1 in Supplement 2. In exploratory subgroup analyses, PFS benefit was observed with 1 or both combinations vs durvalumab alone across a range of subgroups (eFigure 2 in Supplement 2), including patients with nonsquamous histologic type (eFigure 3 in Supplement 2) or PD-L1 TC expression of 1% or greater (eFigure 4 in Supplement 2); analysis of patients with PD-L1 TC expression less than 1% was limited by a small sample size (eFigure 4 in Supplement 2). In exploratory biomarker analyses, PFS benefit was observed with both combinations vs durvalumab alone among patients with median or higher NKG2A or HLA-E expression and with durvalumab plus oleclumab in patients with low CD73 or HLA-E expression (eFigure 2 in Supplement 2).

Data maturity for OS was 39.7% (75 of 189 patients had died). OS appeared to favor both combinations vs durvalumab alone (stratified HR, 0.69 [95% CI, 0.40-1.20] with durvalumab plus oleclumab and 0.77 [95% CI, 0.44-1.33] with durvalumab plus monalizumab) (Figure 2B; eTable 2 in Supplement 2), although these differences did not demonstrate nominal associations. Median OS was not reached for the combination arms and was 40.9 (95% CI, 22.6 to not estimable) months with durvalumab alone; the 12- and 24-month OS rates are shown in eTable 2 in Supplement 2. Exploratory subgroup analyses also appeared to show OS benefit with both combinations vs durvalumab alone among patients with nonsquamous histologic type (stratified HR, 0.54 [95% CI, 0.26-1.13] with durvalumab plus oleclumab and 0.44 [95% CI, 0.19-0.99] with durvalumab plus monalizumab), PD-L1 TC expression of 1% or greater (stratified HR, 0.43 [95% CI, 0.18-1.01] with durvalumab plus oleclumab and 0.20 [95% CI, 0.07-0.61] with durvalumab plus monalizumab), and stage IIIB or IIIC disease (stratified HR, 0.44 [95% CI, 0.22-0.91] with durvalumab plus oleclumab and 0.53 [95% CI, 0.26-1.09] with durvalumab plus monalizumab) (eFigure 5 in Supplement 2).

Table 2. Antitumor Activity by Investigator Assessment in the Intention-to-Treat Population

Antitumor activity	Treatment arms		
	Durvalumab alone (n = 67)	Durvalumab plus oleclumab (n = 60)	Durvalumab plus monalizumab (n = 62)
Confirmed ORR (95% CI), %[a]	23.9 (14.3 to 35.9)	35.0 (23.1 to 48.4)	40.3 (28.1 to 53.6)
Difference in confirmed ORR, percentage points (95% CI), [b]	NA	11.1 (−6.4 to 28.1)	16.9 (−0.8 to 33.4)
Best overall response by RECIST, No. (%)[c]			
Complete response	2 (3.0)	0	3 (4.8)
Partial response	14 (20.9)	21 (35.0)	22 (35.5)
Stable disease	33 (49.3)	29 (48.3)	28 (45.2)
Progressive disease	11 (16.4)	6 (10.0)	4 (6.5)
Not evaluable	7 (10.4)	4 (6.7)	5 (8.1)
DCR at 16 wk (95% CI), %[c,d]	58.2 (45.5 to 70.2)	80.0 (67.7 to 89.2)	79.0 (66.8 to 88.3)
Difference in DCR at 16 wk, percentage points (95% CI)[b]	NA	21.8 (4.4 to 38.2)	22.8 (5.6 to 39.4)
Median DOR (95% CI), mo[c,e]	NR (14.1 to NE)	29.9 (17.1 to NE)	23.0 (10.2 to NE)
Range, mo	2.7 to 43.4[f]	3.7 to 35.4[f]	1.9 to 38.8[f]

Abbreviations: DCR, disease control rate; DOR, duration of response; NA, not applicable; NE, not estimable; NR, not reached; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors, version 1.1.

[a] 95% CIs calculated by Clopper-Pearson exact method.

[b] Differences are shown between patients enrolled in the durvalumab plus oleclumab arm and 67 patients enrolled concurrently in the durvalumab arm and between patients enrolled in the durvalumab plus monalizumab arm and 64 patients enrolled concurrently in the durvalumab arm.

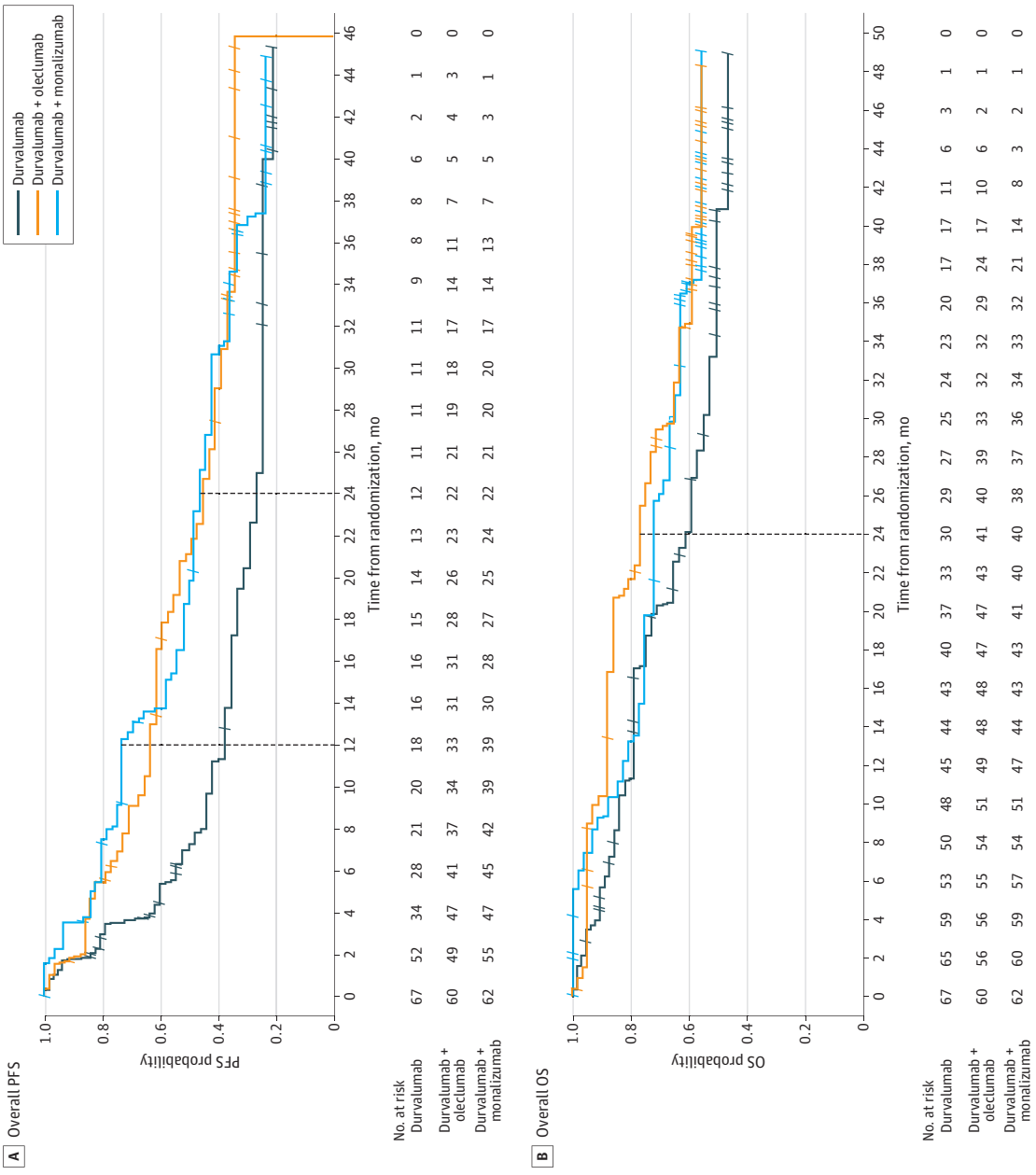
[c] Confirmed responses.

[d] DCR at 16 weeks = Complete response + Partial response + Stable disease for at least 16 weeks.

[e] Median DOR was assessed using Kaplan-Meier methods.

[f] Response was ongoing at data cutoff.

Figure 2. Kaplan-Meier Estimates for Progression-Free Survival (PFS) and Overall Survival (OS) for the Intention-to-Treat Population



A, Overall PFS maturity was 60.8%. Patients who were alive and progression free at data cutoff (July 18, 2023) were censored on the date of their last evaluable tumor assessment. B, Overall OS maturity was 39.7%. Patients who were alive or lost to follow-up at data cutoff were censored on the last date they were known to be alive.

Safety

Safety profiles were consistent with the interim analysis, and safety profiles for both combinations were generally comparable with that for durvalumab alone (**Table 3**).[8] At this final analysis, grade 3 or higher treatment-emergent adverse events (AEs) were reported in 24 patients (40.7%) in the durvalumab plus oleclumab arm, 21 patients (34.4%) in the durvalumab plus monalizumab arm, and 30 patients (45.5%) in the durvalumab monotherapy arm, compared with 24 patients (40.7%), 17 patients (27.9%), and 26 patients (39.4%), respectively, at the interim analysis. Incidences of treatment-emergent AEs remained largely unchanged (eTable 3 in Supplement 2). The incidence of any grade immune-mediated AEs was 25.4% (n = 15, including 0% grade 3 or 4 events) with durvalumab plus oleclumab, 34.4% (n = 21, including 3.3% [n = 2] grade 3 or 4 events) with durvalumab plus monalizumab, and 34.8% (n = 23, including 3.0% [n = 2] grade 3 or 4 events) with durvalumab alone.

Discussion

Consolidation durvalumab after cCRT is standard-of-care treatment for patients with unresectable, stage III NSCLC.[2] However, as many patients experience disease progression, unmet need remains. COAST was the first randomized phase 2 trial to demonstrate improved outcomes when combining

Table 3. Safety Summary in the As-Treated Population

Incidence[a]	Patients in as-treated population, No. (%)		
	Durvalumab alone (n = 66)	Durvalumab plus oleclumab (n = 59)	Durvalumab plus monalizumab (n = 61)
Any TEAE	65 (98.5)	57 (96.6)	61 (100)
Any TEAE of maximum grade 3 or 4	23 (34.8)	20 (33.9)	20 (32.8)
Any study drug-related AE	49 (74.2)	46 (78.0)	52 (85.2)
Any study drug-related AE of maximum grade 3 or 4	3 (4.5)	1 (1.7)	8 (13.1)
Any SAE[b]	23 (34.8)	20 (33.9)	17 (27.9)
Any study drug-related SAE[b]	6 (9.1)	7 (11.9)	6 (9.8)
Any TEAE leading to discontinuation of			
Durvalumab	9 (13.6)	9 (15.3)[c]	9 (14.8)
Oleclumab	NA	10 (16.9)[c]	NA
Monalizumab	NA	NA	9 (14.8)
Death[d,e]	7 (10.6)	4 (6.8)	4 (6.6)
Any AESI for durvalumab	35 (53.0)	36 (61.0)	43 (70.5)
Pneumonitis	11 (16.7)	12 (20.3)	11 (18.0)
Any imAE	23 (34.8)	15 (25.4)	21 (34.4)
Pneumonitis	9 (13.6)	7 (11.9)	7 (11.5)

Abbreviations: AE, adverse event; AESI, AE of special interest; imAE, immune-mediated AE; NA, not applicable; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a] Patients were counted once for each applicable category regardless of the number of events.

[b] SAE criteria: death, life threatening, required inpatient hospitalization or prolongation of existing inpatient hospitalization, persistent or substantial disability or incapacity, important medical event, or congenital anomaly or birth defect in the offspring of the patient.

[c] One patient who discontinued oleclumab due to a TEAE was also required to discontinue durvalumab (but not due to a TEAE) because treatment with durvalumab alone in combination arms was not allowed per protocol.

[d] All reported deaths (due to any cause) within 90 days after last dose. In the durvalumab and durvalumab plus oleclumab arms, all deaths within 90 days after last dose were reported as TEAEs. In the durvalumab plus monalizumab arm, 1 death was reported as a TEAE (myocardial infarction), and 3 other deaths within 90 days after last dose were due to the disease under investigation. One additional death was reported in the durvalumab plus monalizumab arm since the previous interim analysis.[1]

[e] In total, four grade 5 TEAEs were related to the study drug: 2 (pneumonitis and radiation pneumonitis) in the durvalumab arm, 1 (pneumonitis) in the durvalumab plus oleclumab arm, and 1 (myocardial infarction) in the durvalumab plus monalizumab arm. Data cutoff date was July 18, 2023.

novel immunotherapies (anti-CD73 or anti-NKG2A mAbs) with standard-of-care anti–PD-L1 therapy in this setting.[8] At this final analysis, durvalumab plus oleclumab or monalizumab continued to be nominally associated with higher ORR and prolonged PFS compared with durvalumab alone. Additionally, OS appeared to be longer with both combinations (although the data did not demonstrate nominal associations) despite OS maturity of only 39.7%. The safety profiles of all 3 regimens were consistent with that of durvalumab monotherapy in the PACIFIC trial, including similar rates of discontinuation due to AEs.[1]

Subgroup analyses demonstrated improved outcomes with 1 or both combinations in a range of clinically important patient subgroups. However, while randomization was stratified by histologic type, results should be interpreted with caution given the imbalances in characteristics (eg, prior platinum-based chemotherapy and PD-L1 status) between arms and high proportions of unknown values for CD73, NKG2A, and HLA-E status.

Although cross-trial comparisons have inherent limitations and should be interpreted cautiously, the ORR was lower and PFS was shorter at this final analysis of the COAST trial compared with durvalumab monotherapy in the PACIFIC trial, in which the ORR was 28.4% and median (range) PFS was 16.8 (13.0-18.1) months in the durvalumab arm.[1,8] Median PFS in the PACIFIC-R study, which evaluated durvalumab after CRT in patients with unresectable stage III NSCLC, also appeared to be longer than in the durvalumab arm of the COAST trial (24.1 vs 7.3 months, respectively).[8,18] Potential reasons for these observed differences could be the lower proportions of patients of Asian race, who received prior cisplatin, or who were randomly assigned less than 14 days after radiotherapy in the COAST vs the PACIFIC trial. Furthermore, the study population in the COAST trial had a higher median age and a higher proportion of enrolled patients with stage IIIB or IIIC disease compared with patients in the PACIFIC trial and PACIFIC-R study.[1,8,18] However, definitive reasons for these differences remain unclear.

Limitations

Limitations of this study include the small sample sizes, which were not powered to assess superiority of the combination arms, and the limited diversity of the study population. The impact of oncogenic driver alterations (*EGFR* or *ALK*) was also not assessed. Although patients with *EGFR* or *ALK* alterations were not excluded, sequence variation status could only be retroactively determined in approximately 40% of patients, and there were not enough archival tumor samples to perform a full next-generation sequencing analysis. Nevertheless, when compared with the control arm, the combination arms in this phase 2, signal-finding trial performed better, although both combination treatments did not demonstrate nominal associations with longer OS.

Conclusions

In this final analysis of the COAST randomized clinical trial of durvalumab alone or durvalumab combined with oleclumab or monalizumab for the treatment of patients with unresectable, stage III NSCLC and no disease progression following cCRT, both combination treatments provided additional clinical benefit over durvalumab alone. Final analyses showed durvalumab plus oleclumab and durvalumab plus monalizumab continued to be nominally associated with higher ORR and prolonged PFS compared with durvalumab alone, while OS also appeared to be longer with both combinations (although the data did not demonstrate nominal associations). These findings support further evaluation of durvalumab plus oleclumab or monalizumab in the ongoing larger, registrational-intent PACIFIC-9 trial.[7]

ARTICLE INFORMATION

Accepted for Publication: April 17, 2025.

Published: July 15, 2025. doi:10.1001/jamanetworkopen.2025.18440

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Author Contributions: Drs Aggarwal and Herbst had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Aggarwal, Camidge, Cooper, Kumar, Herbst.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Aggarwal, Martínez-Martí, Dowson, Cooper, Kumar, Herbst.

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Statistical analysis: Aggarwal, Pillet, Brown, Cooper, Herbst.

Obtained funding: Herbst.

Administrative, technical, or material support: Aggarwal, Chu, Camidge, Brown, Paliompeis, Dowson, Herbst.

Supervision: Aggarwal, Carcereny, Monnet, Sánchez-Hernández, Paliompeis, Kumar, Herbst.

Include patients: Martínez-Martí.

Conflict of Interest Disclosures: Dr Aggarwal reported receiving personal fees from AstraZeneca, Daiichi Sankyo/AstraZeneca, Sanofi/Regeneron, Pfizer, Boehringer Ingelheim, Takeda, Arcus Biosciences, Gilead Sciences, Novocure, AbbVie, Merck Sharp & Dohme, and Loxo@Lilly outside the submitted work. Dr Martínez-Martí reported receiving personal fees from AstraZeneca/MedImmune, Bristol Myers Squibb, F. Hoffmann La Roche AG, MSD, Pfizer, Janssen, Amgen, Lilly, and Fuchigec outside the submitted work. Dr Majem reported receiving personal fees from AstraZeneca, Roche, Pfizer, MSD, Immedica, BeiGene, and Johnson & Johnson; grants from AstraZeneca and Roche; and travel support from MSD and Roche outside the submitted work. Dr Barlesi reported receiving institutional fees from AbbVie, ACEA, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer-Ingelheim, Eisai, Eli Lilly Oncology, F. Hoffmann La Roche Ltd, Genentech, Ipsen, Ignyta, Innate Pharma, Loxo@Lilly, Novartis, Medimmune, Merck, MSD, Pierre Fabre, Pfizer, Sanofi-Aventis, Summit Therapeutics, and Takeda outside the submitted work. Dr Chu reported receiving personal fees from AstraZeneca during the conduct of the study and personal fees from AbbVie, Amgen, AnHeart, Astellas, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Genprex, GSK, Janssen, Merck, Merck KGaA, Novartis, Ocellaris, Pfizer, Roche, and Takeda Pharmaceuticals outside the submitted work. Dr Monnet reported receiving meeting support from Pfizer, MSD, Oxyvie, Takeda, and Regeneron outside the submitted work. Dr Camidge reported receiving personal fees from AstraZeneca during the conduct of the study and personal fees from Apollomics, AstraZeneca/Daiichi Sankyo, AbbVie, Anheart, Aveo, Beigene, Betta, BMS, Coherus, Eli Lilly, Ellipses, Gallapagos, Genesis, Gilead, Hengrui, Imagene, Immunocore, Indupro, Janssen, Kestrel, Lianbio, Merck KGaA, Mirati (IDMC), Nalo, Newsoara, Nextcure, Prelude, Pfizer, Roche, Sanofi, Seattle Genetics, Sutro, Takeda Pharmaceuticals, Triana, Valence, and Xencor outside the submitted work. Ms Pillet reported being employed by Fortrea Inc (contracted to AstraZeneca) outside the submitted work. Mr Dowson reported being employed by AstraZeneca during the conduct of the study. Dr Cooper reported owning stock in and being employed by AstraZeneca during the conduct of the study. Dr Kumar is an employee of AstraZeneca and reported holding a patent for anti-CD73 antibodies pending (AstraZeneca) outside the submitted work. Dr Herbst reported receiving personal fees from AstraZeneca during the conduct of the study; personal fees from Immunocore, Junshi Pharmaceuticals, Amgen, ArriVent, Bristol Myers Squibb,

Candel Therapeutics, Catalym, Checkpoint Therapeutics, Cybrexa Therapeutics, Eli Lilly and Company, Genentech, Gilead, I-Mab Biopharma, Janssen, Mediflix, Merck and Company, Neuvogen, NextCure, Normunity, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, and Sanofi outside the submitted work; and travel support from the Friends of Cancer, the American Association for Cancer Research, the International Association for the Study of Lung Cancer, and the Southwest Oncology Group outside the submitted work. No other disclosures were reported.

Funding/Support: This study was sponsored by AstraZeneca.

Role of the Funder/Sponsor: AstraZeneca was involved, in conjunction with the authors, in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: Medical writing support, under the direction of the authors, was provided by Susanne Gilbert, MA; Andrew Gannon, MS, MA; and Eric Exner, MD, PhD, of Ashfield MedComms (New York, NY), an Inizio company, and was funded by AstraZeneca.

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SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
eFigure 1. COAST Study Design
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SUPPLEMENT 3.
Data Sharing Statement