original reports

COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non–Small-Cell Lung Cancer

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abstract

PURPOSE Durvalumab significantly improves overall survival for patients with unresectable stage III non–small-cell lung cancer and no progression after concurrent chemoradiotherapy (cCRT). Building upon that standard of care, COAST is a phase II study of durvalumab alone or combined with the anti-CD73 monoclonal antibody oleclumab or anti-NKG2A monoclonal antibody monalizumab as consolidation therapy in this setting.

METHODS Patients with unresectable stage III non–small-cell lung cancer, Eastern Cooperative Oncology Group performance status 0/1, and no progression after cCRT were randomly assigned 1:1:1, ≤ 42 days post-cCRT, to durvalumab alone or combined with oleclumab or monalizumab for up to 12 months, stratified by histology. The primary end point was investigator-assessed confirmed objective response rate (ORR; RECIST v1.1).

RESULTS Between January 2019 and July 2020, 189 patients were randomly assigned. At this interim analysis (data cutoff, May 17, 2021), median follow-up was 11.5 months (range, 0.4-23.4 months; all patients). Confirmed ORR was numerically higher with durvalumab plus oleclumab (30.0%; 95% CI, 18.8 to 43.2) and durvalumab plus monalizumab (35.5%; 95% CI, 23.7 to 48.7) versus durvalumab (17.9%; 95% CI, 9.6 to 29.2). Progression-free survival (PFS) was prolonged with both combinations versus durvalumab (plus oleclumab: hazard ratio, 0.44; 95% CI, 0.26 to 0.75; and plus monalizumab: hazard ratio, 0.42; 95% CI, 0.24 to 0.72), with higher 12-month PFS rates (plus oleclumab: 62.6% [95% CI, 48.1 to 74.2] and plus monalizumab: 72.7% [95% CI, 58.8 to 82.6] *v* durvalumab alone: 33.9% [95% CI, 21.2 to 47.1]). All-cause grade ≥ 3 treatment-emergent adverse events occurred in 40.7%, 27.9%, and 39.4% with durvalumab plus oleclumab, durvalumab plus monalizumab, and durvalumab, respectively.

CONCLUSION Both combinations increased ORR and prolonged PFS versus durvalumab alone. Safety was similar across arms with no new or significant safety signals identified with either combination. These data support their further evaluation in a phase III trial.

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ASSOCIATED CONTENT

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Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Durvalumab is a selective, high-affinity, human immunoglobulin G1 monoclonal antibody (mAb) that blocks programmed cell death ligand-1 (PD-L1) binding to programmed cell death-1 (PD-1) and CD80, allowing T cells to recognize and kill tumor cells.[1] In the placebo-controlled phase III PACIFIC trial, durvalumab significantly improved progression-free survival (PFS) and overall survival (OS) in patients with unresectable, stage III non–small-cell lung cancer (NSCLC) and no progression after concurrent chemoradiotherapy (cCRT).[2-4] Thus, the PACIFIC regimen (durvalumab after CRT) is now the standard of care in this setting.[4-6] Furthermore, recent 5-year data from PACIFIC demonstrated robust and sustained OS benefit plus durable PFS with durvalumab, with 5-year OS and PFS rates of 42.9% and 33.1%, respectively.[7]

Despite progress, additional work remains to further improve outcomes for this patient population. Therefore, immunotherapy combination strategies that build upon the durvalumab standard of care are being

CONTEXT

Key Objective

Consolidation treatment with the programmed cell death ligand-1 inhibitor durvalumab after chemoradiotherapy is the standard of care for patients with unresectable, stage III non–small-cell lung cancer. Additional immunomodulation through combination therapy, however, may extend benefit to more patients. The signal-finding phase II COAST study is assessing durvalumab alone or combined with the anti-CD73 monoclonal antibody oleclumab or anti-NKG2A monoclonal antibody monalizumab as consolidation therapy in this setting.

Knowledge Generated

Confirmed objective response rate was numerically higher with durvalumab plus oleclumab (30.0%) and durvalumab plus monalizumab (35.5%) versus durvalumab (17.9%), and progression-free survival was prolonged with both combinations (hazard ratios, 0.44 and 0.42, respectively). In addition, safety was similar across the arms with no new or significant safety signals identified.

Relevance

To our knowledge, COAST is the first randomized phase II study to show improved clinical outcomes with novel immunotherapy combinations in this setting, supporting their further evaluation in a planned phase III study (PACIFIC-9; ClinicalTrials.gov identifier: NCT05221840).

explored to expand the number of patients who respond and remain progression-free.

Oleclumab (MEDI9447) is a human IgG1λ mAb that inhibits the function of cluster of differentiation 73 (CD73).[8] CD73 is an enzyme found on the surfaces of cancer and immune cells and is involved in conversion of adenosine monophosphate to extracellular adenosine, which has an immunosuppressive effect on the tumor environment.[9] CD73 upregulation by tumors has been shown to increase extracellular adenosine production and result in subsequent local immunosuppression in multiple cancers.[10-12] Preclinical models have demonstrated additive antitumor immunity when oleclumab is combined with other immunotherapies, including PD-1/PD-L1 inhibitors.[9] In addition, a phase I study of oleclumab combined with durvalumab produced durable responses with manageable safety in patients with advanced epidermal growth factor receptor (*EGFR*)–mutated NSCLC.[13]

Monalizumab (IPH2201) is a first-in-class, humanized, IgG4 mAb that specifically binds to and blocks the inhibitory receptor NKG2A from binding to the major histocompatibility complex E (HLA-E), thereby reducing inhibition of natural killer and CD8+ T cells.[14] HLA-E is overexpressed in multiple tumor types and, once bound to NKG2A, triggers inhibitory signals that suppress cytokine secretion and direct cytotoxicity of T lymphocytes and natural killer cells.[15] Monalizumab binds specifically and with high affinity to NKG2A, thereby suppressing inhibitory signals and enhancing antitumor immunity.[14,16] In a phase I/II trial of patients with recurrent/metastatic head-and-neck squamous cell carcinoma, monalizumab combined with the anti-EGFR mAb cetuximab showed promising activity with manageable safety.[17]

Radiotherapy is known to increase tumoral expression of CD73, HLA-E (NKG2A ligand), and PD-L1; therefore, combining blockade of these immune checkpoints with CRT is a promising means of improving responses.[18-21] In preclinical models, radiotherapy combined with anti-CD73 or anti-NKG2a (with/without anti–PD-[L]1) have increased antitumor activity versus either alone.[18,20,21] Therefore, we hypothesized that combining anti-CD73 or anti-NKG2A mAbs with anti–PD-L1 could improve outcomes in patients with unresectable, stage III NSCLC who have undergone CRT.

Here, we report the results from an interim analysis of COAST, a global, open-label, randomized, phase II, multidrug platform study of durvalumab alone or in combination with oleclumab or monalizumab, as consolidation therapy in patients with unresectable, stage III NSCLC who had not progressed following cCRT. The goal of this signal-finding study was early identification of novel durvalumab combinations that are more active than durvalumab alone for validation in a phase III study.

METHODS

Patients

Eligible patients were age ≥ 18 years, with histologically/cytologically documented unresectable, stage III NSCLC, without progression following definitive platinum-based cCRT (total radiotherapy dose: ≥ 60 Gy at 1.8 Gy/fraction or bioequivalent dose), completed within 42 days before random assignment. Patients had ≥ 1 previously irradiated tumor lesion measurable per RECIST v1.1, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0/1, adequate organ and marrow function, and life expectancy ≥ 12 weeks. Exclusion criteria and additional patient details are described in Appendix 1 (online only).

Study Design and Treatments

Patients were randomly assigned (1:1:1), stratified by histology (adenocarcinoma and nonadenocarcinoma), 1-42 days post cCRT, to one of three arms (Appendix Fig A1, online only). Patients in the control arm received 1,500 mg durvalumab once every 4 weeks (Q4W) on day 1 of each treatment cycle. Patients in arm A received 1,500 mg durvalumab Q4W on day 1 of each cycle and 3,000 mg oleclumab every 2 weeks (Q2W) on days 1 and 15 for cycles 1 and 2, then Q4W starting on day 1 of cycle 3. Patients in arm B received 1,500 mg durvalumab Q4W on day 1 of each cycle and 750 mg monalizumab Q2W on days 1 and 15 of each cycle. Dosing regimens for oleclumab and monalizumab were based on prior phase I, combination studies.[13,22] All study drugs were administered intravenously up to 12 months or until progression or unacceptable toxicity.

End Points and Assessments

The primary end point was confirmed objective response rate (ORR) by investigator assessment per RECIST v1.1 (with imaging scheduled as described in Appendix 1). Key secondary end points included safety, duration of response, disease control rate, PFS by investigator assessment (RECIST v1.1), 12-month PFS rate, and OS. Preplanned exploratory analyses included PFS analyses on the basis of tumoral expression of clinically relevant biomarkers including CD73, NKG2A, HLA-E and PD-L1. Archival (pre-cCRT) tumor specimens (not mandatory) were obtained for immunohistochemistry biomarker analysis as described in Appendix 1. Unplanned exploratory subgroup analyses of PFS were also performed.

Statistical Analyses

This phase II study was not designed to test a specific hypothesis around the primary end point. A sample size of 60 patients per arm was chosen to provide an acceptable level of precision as described in Appendix 1 for this ad hoc interim analysis.

Efficacy end points were assessed in the intent-to-treat population (all patients randomly assigned). For analyses involving comparison between an experimental arm and a control arm, only control arm patients concurrently enrolled with the experimental arm were included. ORR rates (RECIST v1.1) were summarized with 95% CIs on the basis of Clopper-Pearson exact method. Time-to-event end points were analyzed using Kaplan-Meier estimates, with each experimental arm compared with the control arm (PFS censored as described in Appendix 1). Comparison of PFS between each experimental arm and control arm used a Cox-regression model, stratified by histology (adenocarcinoma and nonadenocarcinoma), to estimate hazard ratios (HRs) and 95% CIs. There were no formal statistical comparisons between experimental arms. For exploratory PFS subgroup analyses, HRs and 95% CIs were estimated by using a Cox regression model, stratified by histology.

Safety end points were summarized for the as-treated population (patients who received ≥ 1 dose of study treatment). Adverse events (AEs) were graded by National Cancer Institute Common Terminology Criteria for Adverse Events v5.0, and safety data were analyzed using descriptive statistics.

Twelve-month PFS rates and 95% CIs were estimated by using Kaplan-Meier method. PFS according to tumoral PD-L1 expression (≥ 1% or < 1%) was analyzed by using Kaplan-Meier method. PFS on the basis of tumoral expression of CD73 (tumor cell [TC] ≥ 10% or TC < 10%), NKG2A (≥ median or < median) or HLA-E (≥ median or < median) was analyzed using a stratified Cox regression model to estimate HRs and 95% CIs.

Data analyses used SAS System, version 9.3 or above.

RESULTS

Patients

Between January 2019 and July 2020, 189 patients were randomly assigned; 186 received ≥ 1 dose of study drug. Sixty-six patients received durvalumab alone (control arm), whereas 59 and 61 patients received durvalumab plus oleclumab (arm A) and durvalumab plus monalizumab (arm B), respectively (Fig 1). As of May 17, 2021 (data cutoff for this interim analysis), overall median follow-up in all patients was 11.5 months (range, 0.4-23.4 months). Baseline characteristics were generally well balanced between arms (Table 1). Most patients were White (84.1%), male (68.3%), and current/former smokers (93.1%); median age was 65 years (range, 37-87 years); almost half had squamous cell histology (42.9%); 45.5% had unresectable, stage IIIA disease and 54.5% had stage IIIB/C disease; approximately a third had prior cisplatin (34.9%); and most were randomly assigned ≥ 14 days after RT (89.9%). Tumoral PD-L1 expression was available for 68.7%, 50.0%, and 51.6% of patients in the durvalumab, durvalumab plus oleclumab, and durvalumab plus monalizumab arms, respectively.

Efficacy

The primary end point of confirmed ORR by investigator assessment was numerically higher with both combinations versus durvalumab alone (Table 2). Among all randomly assigned patients, confirmed ORR was 30.0% (n = 18 responders; 95% CI, 18.8 to 43.2) with durvalumab plus oleclumab and 35.5% (n = 22 responders; 95% CI, 23.7 to 48.7) with durvalumab plus monalizumab versus 17.9% (n = 12 responders; 95% CI, 9.6 to 29.2) with durvalumab only (differences of 12.1% [95% CI, –2.7 to 26.9] and 16.7% [95% CI, 1.5 to 32.0], respectively). The secondary end point of disease control rate at 16 weeks was 81.7% (95% CI, 69.6 to 90.5) with durvalumab plus oleclumab, 77.4% (95% CI, 65.0 to 87.1) with durvalumab plus monalizumab, and 58.2% (95% CI, 45.5 to 70.2) with durvalumab only (Table 2).

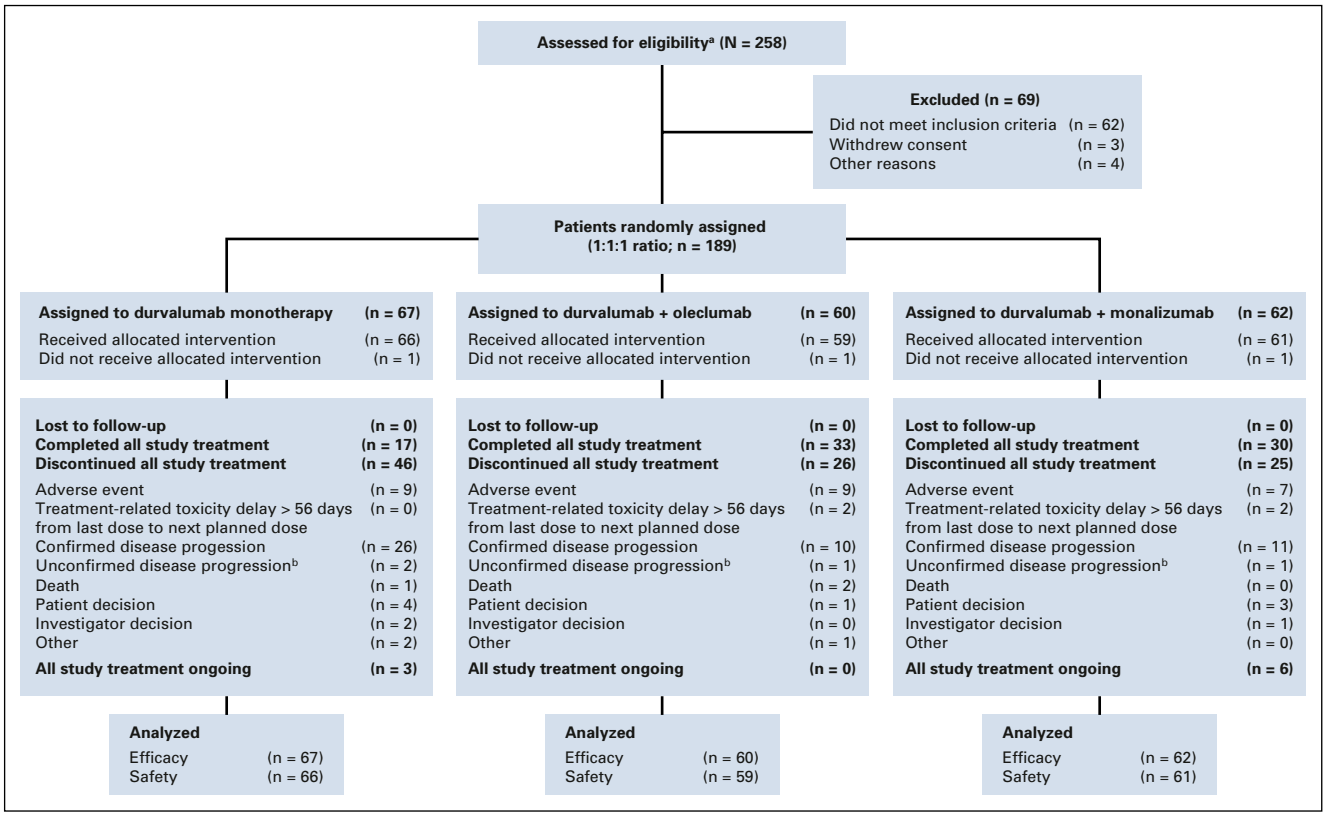


FIG 1. CONSORT diagram. [a]Informed consent received. [b]Unconfirmed disease progression and investigator determination that the patient was not eligible for a confirmation scan.

PFS was prolonged with both combinations versus durvalumab alone (stratified HR of 0.44 [95% CI, 0.26 to 0.75] for durvalumab plus oleclumab and stratified HR of 0.42 [95% CI, 0.24 to 0.72] for durvalumab plus monalizumab versus durvalumab alone; Fig 2). The 12-month PFS rate was higher with both combinations (62.6% [95% CI, 48.1 to 74.2] with durvalumab plus oleclumab and 72.7% [95% CI, 58.8 to 82.6] with durvalumab plus monalizumab versus 33.9% [95% CI, 21.2 to 47.1] with durvalumab alone; Fig 2). Median PFS was not reached with durvalumab plus oleclumab, 15.1 months (95% CI, 13.6 to not estimable) with durvalumab plus monalizumab, and 6.3 months (95% CI, 3.7 to 11.2) with durvalumab alone (Fig 2).

In exploratory subgroup analyses (Fig 3), PFS benefit was observed with both combinations across a range of clinically important subgroups, including those on the basis of histology, type of prior platinum-based chemotherapy, and ECOG PS, although patient numbers in these subgroups were small (Fig 3). Evidence of benefit from the combinations appeared persistent among patients with unknown PD-L1 status and PD-L1 TC $\geq$ 1% (Kaplan-Meier curves of PFS by tumoral PD-L1 expression provided in Appendix Fig A2, online only). However, analysis of patients with PD-L1 TC $<$ 1% was limited by the numbers of patients available. On the basis of exploratory biomarker analyses, PFS benefit was consistently demonstrated with both combinations versus durvalumab alone, irrespective of tumor CD73, NKG2A, or HLA-E expression (Appendix Fig A3, online only).

Safety

The safety profiles of both combination regimens were similar to that of durvalumab alone, with similar rates of any-cause treatment-emergent AEs and grade $\geq$ 3 treatment-emergent AEs (Table 3). Among the most common any-grade (grade 3/4) treatment-emergent AEs across the combination arms were cough, dyspnea, pneumonitis, asthenia, and pruritus, which occurred in 30.5% (1.7%), 25.4% (1.7%), 18.6% (0%), 16.9% (0%), and 16.9% (0%), respectively, of patients in the durvalumab plus oleclumab arm and 44.3% (0%), 23.0% (1.6%), 16.4% (1.6%), 23.0% (0%), and 24.6% (0%), respectively, of patients in the durvalumab plus monalizumab arm, whereas dyspnea, cough, pneumonitis, and arthralgia were the most common any-grade (grade 3/4) treatment-emergent AEs in the durvalumab only arm, occurring in 25.8% (3.0%), 18.2% (0%), 16.7% (0%), and 16.7% (0%), respectively (Table 4). The any-grade (grade 3/4) rate of radiation pneumonitis was 11.9% (0%), 4.9% (0%) and 4.5% (1.5%) in durvalumab plus oleclumab, durvalumab plus monalizumab, and durvalumab only arms, respectively. The most common any-grade (grade 3/4) durvalumab-related AEs in the combination arms were hypothyroidism, pneumonitis,

TABLE 1. Baseline Characteristics and Prior CRT

Characteristic[a]	Durvalumab (n = 67)	Durvalumab + Oleclumab (n = 60)	Durvalumab + Monalizumab (n = 62)
Median age, years (range)	66.0 (46-81)	65.0 (37-83)	65.0 (44-87)
Male, %	67.2	70.0	67.7
Race, No. (%)[b]			
American Indian or Alaska Native	0	1 (1.7)	0
Asian	5 (7.7)	4 (6.8)	5 (8.1)
Black or African American	1 (1.5)	5 (8.5)	2 (3.2)
Native Hawaiian or Other Pacific Islander	1 (1.5)	0	0
White	57 (87.7)	47 (79.7)	55 (88.7)
Other	1 (1.5)	2 (3.4)	0
ECOG PS, No. (%)[b]			
0	30 (45.5)	33 (55.9)	27 (44.3)
1	36 (54.5)	26 (44.1)	34 (55.7)
Ever smoked, No. (%)	63 (94.0)	54 (90.0)	59 (95.2)
Histology, No. (%)			
Squamous	30 (44.8)	24 (40.0)	27 (43.5)
Nonsquamous	37 (55.2)	36 (60.0)	35 (56.5)
Disease stage at study entry, No. (%)			
IIIA	27 (40.3)	27 (45.0)	32 (51.6)
IIIB	34 (50.7)	29 (48.3)	27 (43.5)
IIIC	6 (9.0)	4 (6.7)	3 (4.8)
PD-L1 status, No. (%)[c]			
TC ≥ 1%	30 (44.8)	23 (38.3)	20 (32.3)
TC < 1%	16 (23.9)	7 (11.7)	12 (19.4)
Unknown	21 (31.3)	30 (50.0)	30 (48.4)
Prior RT dose, Gy, No. (%)			
54-66	62 (92.5)	54 (90.0)	57 (91.9)
> 66	5 (7.5)	6 (10.0)	5 (8.1)
Time from last RT to random assignment, days, No. (%)			
< 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 CT, No. (%)[d]			
Cisplatin	23 (34.3)	28 (46.7)	15 (24.2)
Carboplatin	43 (64.2)	28 (46.7)	44 (71.0)

NOTE. Data cutoff: May 17, 2021.

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death ligand-1; RT, radiotherapy; TC, tumor cell.

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

[b]Race was missing for two patients in the durvalumab arm and one patient in the durvalumab + oleclumab arm, and ECOG PS was missing for one patient in each arm (reported percentages are based on patients with available data).

[c]28, 30, and 32 patients in the durvalumab, durvalumab + oleclumab, and durvalumab + monalizumab arms, respectively, were not evaluable for PD-L1 TC expression.

[d]In addition, 1, 4, and 3 patients in the durvalumab, durvalumab + oleclumab, and durvalumab + monalizumab arms, respectively, received cisplatin and carboplatin combined.

TABLE 2. Antitumor Activity by Investigator Assessment (ITT population)

Antitumor Activity	Durvalumab (n = 67)	Durvalumab + Oleclumab (n = 60)	Durvalumab + Monalizumab (n = 62)
Confirmed ORR, % (95% CI)[a] (No.)	17.9 (9.6 to 29.2) (12)	30.0 (18.8 to 43.2) (18)	35.5 (23.7 to 48.7) (22)
Difference in confirmed ORR, % (95% CI)[b]	—	12.1 (–2.7 to 26.9)	16.7 (1.5 to 32.0)
Best overall response by RECIST,[c,d] No. (%)			
CR	2 (3.0)	1 (1.7)	3 (4.8)
PR	10 (14.9)	17 (28.3)	19 (30.6)
SD	37 (55.2)	32 (53.3)	31 (50.0)
PD	11 (16.4)	6 (10.0)	4 (6.5)
NE	7 (10.4)	4 (6.7)	4 (6.5)
DCR at 16 weeks, % (95% CI)[c,e] (No.)	55.2 (42.6 to 67.4) (37)	80.0 (67.7 to 89.2) (48)	77.4 (65.0 to 87.1) (48)
Median DoR, months (95% CI)[c] Range	NR (7.4 to NA) 1.9+ to 17.5+	NR (12.9 to NA) 1.8+ to 16.9+	NR (9.0 to NA) 1.9+ to 18.4+

NOTE. Data cutoff: May 17, 2021.

Abbreviations: CR, complete response; DCR, disease control rate; DoR, duration of response; ITT, intent-to-treat; NA, not applicable; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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

[b]Compared with the 67 and 64 patients in the durvalumab arm enrolled concurrently with patients in the durvalumab + oleclumab and durvalumab + monalizumab arms, respectively.

[c]Confirmed responses.

[d]One patient did not have a postbaseline disease assessment and is, therefore, missing a best overall response.

[e]DCR at 16 weeks = CR + PR + SD for ≥ 16 weeks.

and pruritus, which occurred in 13.6% (0%), 16.9% (0%), and 16.9% (0%), respectively, of patients in the durvalumab plus oleclumab arm, and 18.0% (0%), 9.8% (1.6%), and 16.4% (0%), respectively, of patients in the durvalumab plus monalizumab arm, whereas hypothyroidism was the most common any-grade (grade 3/4) durvalumab-related AE in the durvalumab only arm, occurring in 15.2% (0%; Appendix Table A1, online only).

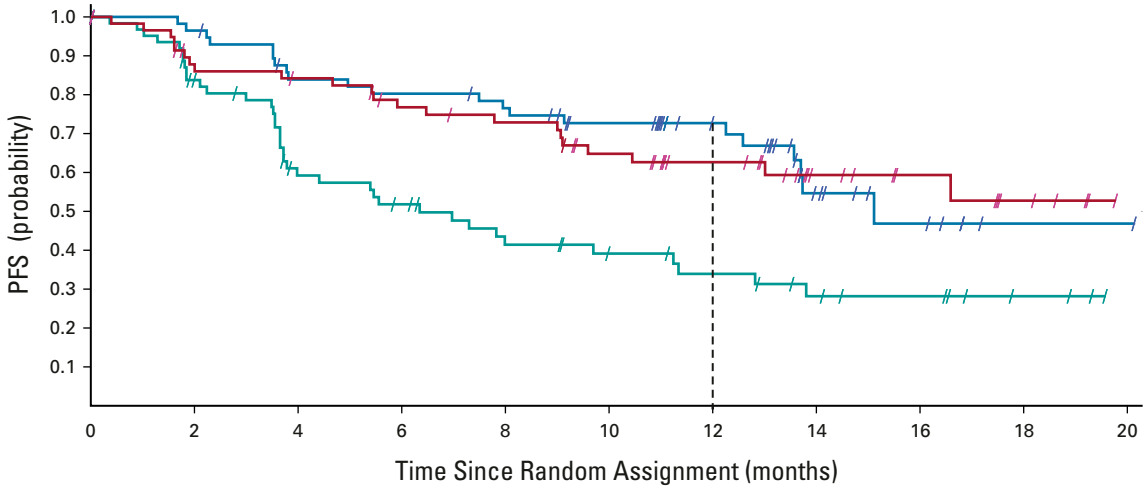
The proportions of patients with treatment-emergent AEs leading to treatment discontinuation were similar between arms (15.3%, 14.8%, and 16.7% of patients in the durvalumab plus oleclumab, durvalumab plus monalizumab, and durvalumab only arms, respectively). The most common treatment-emergent AE leading to discontinuation was pneumonitis (among 5.1%, 4.9%, and 6.1% of patients in the durvalumab plus oleclumab, durvalumab plus monalizumab, and durvalumab only arms, respectively). Overall, 6.8%, 4.9%, and 10.6% of patients, respectively, died within 90 days of last dose of study drug (regardless of the relationship to study drug; Table 3). In total, 4 deaths were related to 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.

The incidence of AEs of special interest (AESIs) related to durvalumab was similar between arms (Appendix Table A2, online only). Overall, AESIs were reported in 61.0%, 67.2%, and 56.1% of patients in the durvalumab plus oleclumab, durvalumab plus monalizumab, and durvalumab only arms, respectively, including pneumonitis in 20.3%, 18.0%, and 18.2% of patients in each arm, respectively. The incidence of rash was slightly higher in the combination arms (20.3% with durvalumab plus oleclumab and 23.0% with durvalumab plus monalizumab *v* 9.1% with durvalumab only).

DISCUSSION

The COAST trial is, to our knowledge, the first randomized phase II study to show evidence of improved clinical outcomes with novel immunotherapy combinations in the unresectable, stage III NSCLC setting, specifically combining anti-CD73 or anti-NKG2A treatment with standard-of-care anti–PD-L1 therapy in this setting, supporting their further evaluation in a planned phase III study (PACIFIC-9; ClinicalTrials.gov identifier: NCT05221840).[18-21,23] Interim data indicate that combining oleclumab or monalizumab with durvalumab can provide additional clinical benefit, versus durvalumab alone. Both combination regimens increased ORR and prolonged PFS versus durvalumab alone. Importantly, the PFS curves showed an early separation at approximately 2-4 months that was sustained over time. In addition, PFS benefit was observed with both combinations across a range of clinically important subgroups, including histology, ECOG PS, and prior

Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–



No. at risk:

Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab	67	50	32	27	20	16	13	9	7	3	0

FIG 2. Progression-free survival (ITT population). Data cutoff: May 17, 2021 (median follow-up of 11.5 months; range, 0.4-23.4 months). [a]Interim analysis was performed when all patients had a 10-month minimum potential follow-up; Kaplan-Meier estimates for PFS, PFS rate, and 95% CIs. [b]PFS HR and 95% CI estimated by Cox regression model, stratified by histology (adenocarcinoma and nonadenocarcinoma). [c]Compared with the 67 and 64 patients in the durvalumab arm enrolled concurrently with patients in the durvalumab + oleclumab and durvalumab + monalizumab arms, respectively. HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; NR, not reached; PFS, progression-free survival.

platinum-based chemotherapy, although the patient numbers in these subgroups were small.

The tumoral PD-L1 status was available for a subset of patients (50.0%-68.7% across all arms). With the caveat of limited sample sizes in the different PD-L1 subgroups, evidence of benefit from the combinations appeared persistent among patients with unknown PD-L1 status and PD-L1 TC $\geq$ 1% (Fig 3). However, the number of patients with PD-L1 TC $<$ 1% was limited and, thus, no definitive conclusions can be drawn for this subgroup on the basis of this study. Similarly, further analysis of patients with PD-L1 TC $\geq$ 1% will require a larger study. The phase III PACIFIC-9 study requires provision of tumor tissue samples and documented tumor PD-L1 status as part of the eligibility criteria.[23]

The safety profiles were consistent across all three arms and consistent with the safety profile of durvalumab in PACIFIC, with similar rates of discontinuation because of AEs.[2] Both combination arms displayed manageable safety profiles, with no new or significant safety signals identified in either; the incidences of any AESIs, including pneumonitis, were similar across all three arms and also consistent with the durvalumab arm in PACIFIC.[2] Immune-related AEs, specifically, rash and pruritus, were slightly more frequent in the combination arms compared with the control arm; however, all events were grade 1 or 2. A larger study will be required to better understand any differences in the incidences of specific AESIs and immune-related AEs across the different combinations versus durvalumab alone.

Several studies are investigating alternative combination regimens in unresectable, stage III NSCLC, including anti–PD-[L]1 therapies combined with anti-T cell immunoreceptor with immunoglobulin and ITIM domains immunotherapy and PARP or CTLA-4 inhibitors,[24-27] anti–PD-[L]1 therapies given concurrently with cCRT (eg, durvalumab in the phase III PACIFIC-2 study[28]), or bifunctional fusion proteins that target both the transforming growth factor-β and PD-L1 pathways (eg, bintrafusp alfa), also given concurrently with cCRT.[29] The COAST study is the first randomized study to demonstrate improved clinical outcomes by additional immunomodulation through combination therapy, suggesting that the clinical benefit of the standard-of-care PACIFIC regimen can be further improved by addressing mechanisms of treatment resistance and relapse, such as the CD73 and NKG2A pathways. The results of the COAST study also provide further support for targeting these pathways with oleclumab and

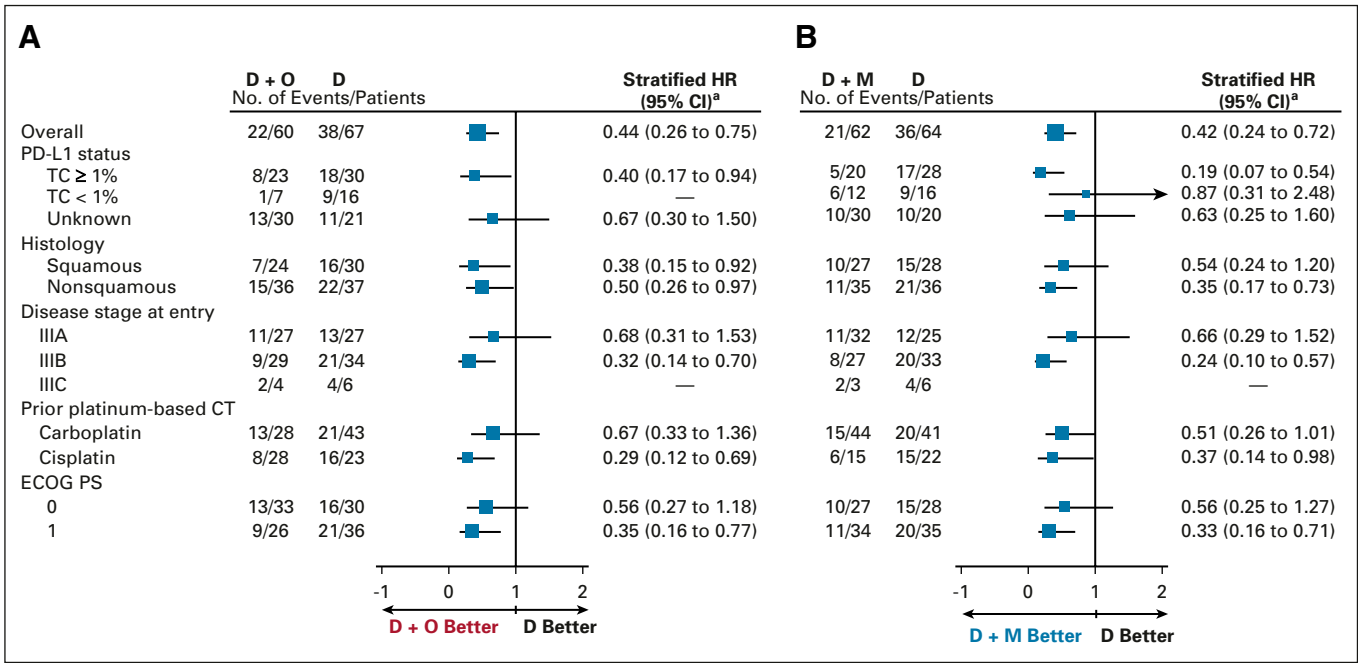


FIG 3. Exploratory PFS subgroup analyses by investigator assessment (ITT population): (A) durvalumab + oleclumab versus durvalumab alone and (B) durvalumab + monalizumab versus durvalumab alone. Data cutoff: May 17, 2021 (median follow-up of 11.5 months; range, 0.4-23.4 months). [a]PFS HR and 95% CI estimated by Cox regression model, stratified by histology (adenocarcinoma and nonadenocarcinoma), for these unplanned exploratory analyses. CT, chemotherapy; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; M, monalizumab; O, oleclumab; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; TC, tumor cell.

monalizumab in other tumor types. Additionally, this model could represent a new way to test novel combinations in an immunotherapy-naïve setting.

Despite the inherent challenges associated with naïve cross-trial comparisons, when compared with the PACIFIC study,[2-4] the ORR and PFS observed with the durvalumab (control) arm of this study appeared to be lower. To better understand these disparities, we reviewed the baseline characteristics of patients in this trial against those in PACIFIC for any clinically meaningful differences. Specifically, there was a lower proportion of patients who were Asian, received prior cisplatin, and were randomly assigned < 14 days after radiotherapy in this trial versus PACIFIC[2]; in addition, this trial enrolled a higher number of patients who were older or had stage IIIB/C disease, all of which are factors that might be associated with either a poorer prognosis or reduced clinical benefit with durvalumab in this trial, relative to PACIFIC.[2,3,7] Furthermore, although the three arms in COAST were fairly well balanced, there were a few imbalances in the baseline characteristics between them. For example, within the durvalumab plus oleclumab arm, higher proportions of patients had ECOG PS 0 and prior cisplatin-based chemotherapy and a lower proportion were randomly assigned < 14 days after radiotherapy, relative to the other

TABLE 3. Safety Summary (as-treated population)

Incidence	Durvalumab	Durvalumab + Oleclumab	Durvalumab + Monalizumab
Any TEAEs, No. (%)	65 (98.5)	57 (96.6)	61 (100)
Grade ≥ 3 TEAEs, No. (%)	26 (39.4)	24 (40.7)	17 (27.9)
Study drug-related AEs, No. (%)	49 (74.2)	46 (78.0)	50 (82.0)
Study drug-related SAEs, No. (%)	6 (9.1)	7 (11.9)	5 (8.2)
TEAEs leading to treatment discontinuation, No. (%)	11 (16.7)	9 (15.3)	9 (14.8)
Deaths[a,b], No. (%)	7 (10.6)	4 (6.8)	3 (4.9)

NOTE. Data cutoff: May 17, 2021.

Abbreviations: AEs, adverse events; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events.

[a]All reported deaths within 90 days after last dose, regardless of relationship to study drug.

[b]In total, four deaths were related to study drug, two (pneumonitis and radiation pneumonitis) in the durvalumab arm, one (pneumonitis) in the durvalumab + oleclumab arm, and one (myocardial infarction) in the durvalumab + monalizumab arm.

TABLE 4. TEAEs Occurring in ≥ 10% of Patients in Any Arm (all causality; as-treated population)

	Durvalumab (n = 66)		Durvalumab + Oleclumab (n = 59)		Durvalumab + Monalizumab (n = 61)	
Preferred Term	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Patients with at least 1 TEAE, No. (%)	65 (98.5)	23 (34.8)	57 (96.6)	21 (35.6)	61 (100)	16 (26.2)
Cough	12 (18.2)	0	18 (30.5)	1 (1.7)	27 (44.3)	0
Dyspnea	17 (25.8)	2 (3.0)	15 (25.4)	1 (1.7)	14 (23.0)	1 (1.6)
Asthenia	10 (15.2)	0	10 (16.9)	0	14 (23.0)	0
Pneumonitis	11 (16.7)	0	11 (18.6)	0	10 (16.4)	1 (1.6)
Pruritus	7 (10.6)	0	10 (16.9)	0	15 (24.6)	0
Hypothyroidism	10 (15.2)	0	9 (15.3)	0	12 (19.7)	0
Arthralgia	11 (16.7)	0	9 (15.3)	0	10 (16.4)	0
Diarrhea	7 (10.6)	1 (1.5)	7 (11.9)	0	12 (19.7)	0
Fatigue	7 (10.6)	0	8 (13.6)	0	9 (14.8)	0
Pyrexia	6 (9.1)	0	8 (13.6)	0	10 (16.4)	0
Rash	6 (9.1)	0	9 (15.3)	0	8 (13.1)	0
Back pain	7 (10.6)	2 (3.0)	5 (8.5)	0	9 (14.8)	0
Hyperthyroidism	8 (12.1)	0	6 (10.2)	0	6 (9.8)	0
Pneumonia	9 (13.6)	6 (9.1)	5 (8.5)	4 (6.8)	4 (6.6)	1 (1.6)
Productive cough	7 (10.6)	0	6 (10.2)	0	5 (8.2)	0
Decreased appetite	6 (9.1)	0	6 (10.2)	0	5 (8.2)	0
Constipation	10 (15.2)	0	4 (6.8)	0	2 (3.3)	0
Amylase increased	7 (10.6)	1 (1.5)	4 (6.8)	0	4 (6.6)	1 (1.6)
Insomnia	7 (10.6)	0	3 (5.1)	0	4 (6.6)	0
Nausea	8 (12.1)	0	1 (1.7)	0	5 (8.2)	0
Lymphocyte count decreased	4 (6.1)	2 (3.0)	8 (13.6)	4 (6.8)	1 (1.6)	0
Radiation pneumonitis	3 (4.5)	1 (1.5)	7 (11.9)	0	3 (4.9)	0
Hyperglycemia	2 (3.0)	0	6 (10.2)	0	3 (4.9)	0
Anxiety	0	0	1 (1.7)	0	7 (11.5)	0

NOTE. Data cutoff: May 17, 2021.
Abbreviation: TEAE, treatment-emergent adverse event.

arms. However, the implications of such imbalances remain uncertain, and the promising results reported here support further evaluation.

Exploratory analyses across a range of tumor biomarkers demonstrated PFS benefit with both combination regimens versus durvalumab alone, irrespective of biomarker expression; however, given the small sample sizes for these analyses, the results should be interpreted with caution, requiring confirmation in larger studies. Moreover, tumor biopsies were collected before CRT, which may upregulate tumor tissue expression of biomarkers, such as CD73 and HLA-E,[18-21] potentially rendering these pre-CRT–based biomarkers inaccurate predictors of clinical benefit. Obtaining evaluable biopsies after cCRT is challenging in large studies. Nonetheless, additional translational analyses (eg, circulating tumor DNA) are warranted and ongoing to better understand which patients may derive benefit from these unique combination strategies. The planned phase III PACIFIC-9 study should provide further insights into the patient selection approach.[23]

Additional limitations of this study include that it was an open-label study with response data on the basis of investigator assessment (rather than central review) and the sample sizes were not powered to assess superiority of the combination arms.

In conclusion, interim data indicate that the addition of either novel agent oleclumab or monalizumab to durvalumab provided additional clinical benefit over durvalumab alone in patients with unresectable, stage III NSCLC without disease progression following cCRT. The safety profiles were similar across arms with no new or significant safety signals identified with either combination. These findings support further evaluation of these combinations in the larger, registration-intent PACIFIC-9 study.[23]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non–Small-Cell Lung Cancer

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APPENDIX 1. SUPPLEMENTARY METHODS

Exclusion Criteria

Patients with mixed small-cell and non–small-cell histology, current or prior use of immunosuppressants within 14 days of first dose of study drug, prior exposure to any anti–programmed cell death-1, anti–programmed cell death ligand-1 (PD-L1), or anticytotoxic T-lymphocyte–associated antigen-4 therapy for non–small-cell lung cancer, any unresolved grade > 2 toxicity (per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [NCI CTCAE v5.0]) from prior chemoradiotherapy (CRT), or history of venous thrombosis within 3 months before random assignment were excluded. Further exclusion criteria included history of active primary immunodeficiency, history of grade ≥ 2 pneumonitis following CRT, active or prior documented autoimmune disorders, and major surgery within 28 days before the first dose of study drug.

All patients provided written informed consent. The study was carried out in accordance with protocols and principles set out in the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines, as well as any applicable local laws and requirements.

Tumor Assessment Imaging

Imaging scans were taken during screening; within 28 days of cycle 1 day 1; from cycle 1 day 1, every 8 weeks (± 7 days) for the first 12 months (treatment period); then every 12 weeks (± 7 days) until 24 months; and, thereafter, every 6 months (± 4 weeks) until 60 months.

Immunohistochemistry

Archival (preconcurrent CRT) tumor specimens (which were not mandatory for enrollment) were obtained and a pathologist examined a hematoxylin and eosin–stained slide from each tissue block for the presence of tumor. Sections of 4-μm thickness were cut from a representative tumor block, selected from each patient for immunohistochemistry (IHC) analysis. The IHC tests used for each biomarker were as follows (using previously optimized conditions): PD-L1 expression was tested using the Ventana antibody clone SP263 IHC assay (specific antibody concentration of 1.61 μg/mL; Roche Diagnostics, Ventana Medical Systems; Tucson, AZ); CD73, Cell Signaling Technology antibody clone D7F9A IHC assay (specific antibody concentration of 0.5 μg/ml; Cell Signaling Technology; Danvers, MA); histocompatibility complex E (HLA-E), Abcam antibody clone MEM-E/02 IHC assay (specific antibody concentration of 0.75 μg/mL; Abcam, Cambridge, United Kingdom); and NKG2A, Abcam antibody clone EPR23737-127 (specific antibody concentration of 0.2 μg/mL; Abcam). All of the IHC-stained slides were converted into high-resolution digital images of the whole section (e-slide) using Aperio AT Turbo or Aperio XT scanners (Leica Biosystems; Buffalo Grove, IL) with a 20× objective magnification. Digital images were manually annotated by a pathologist to designate the tumor areas. Marker quantification was performed by Definiens AG (Munich, Germany) via image analysis using Definiens Developer software program, employing customized algorithms for NKG2A and HLA-E, which were reported as marker-positive cells/mm^2 of tumor area and the percentage of HLA-E+ cells in tumor epithelium, respectively. PD-L1 and CD73 were reported as the percentage of positive tumor cells as scored by a pathologist. The number of patients with evaluable samples for each marker was PD-L1 (n = 108), CD73 (n = 107), NKG2A (n = 105), and HLA-E (n = 103).

Statistical Analyses

This phase II study was not designed to test a specific hypothesis around the primary end point. A sample size of 60 patients per arm was chosen to provide an acceptable level of precision for the estimated difference in objective response rate between the control and experimental arms, being approximately ± 18% based upon an exact 2-sided 95% CI. This ad hoc interim analysis reported here was conducted after all patients had a minimum follow-up of 10 months to support further development of the experimental arms.

For progression-free survival, patients with no progressive disease or death at the time of analysis, or those lost to follow-up, were censored at the date of their last evaluable progression-free disease assessment. Patients with a death or progressive disease, immediately after two or more consecutively missed or nonevaluable disease assessments, were censored at the date of last progression-free disease assessment (before the missed or nonevaluable assessments) or random assignment, whichever occurred last.

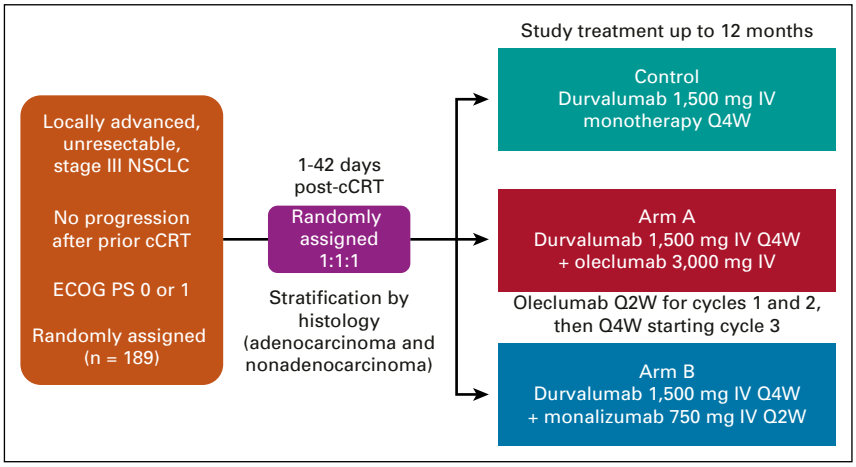
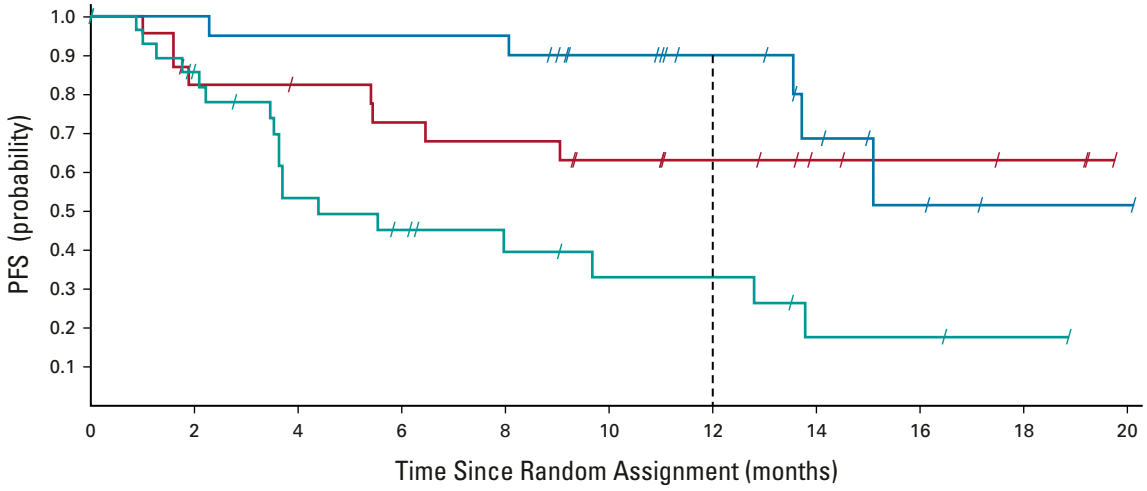


FIG A1. COAST study design. cCRT, concurrent chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; NSCLC, non–small-cell lung cancer; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

A **PD-L1 TC ≥ 1%**

Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b]
Durvalumab + monalizumab	5/20 (25.0)	NR (13.6 to NE)	90.0 (65.6 to 97.4)	0.19 (0.07 to 0.54)
Durvalumab + oleclumab	8/23 (34.8)	NR (5.5 to NE)	63.0 (39.3 to 79.6)	0.40 (0.17 to 0.94)
Durvalumab	18/30 (60.0)	4.4 (3.5 to 12.8)	32.9 (14.4 to 52.9)	—

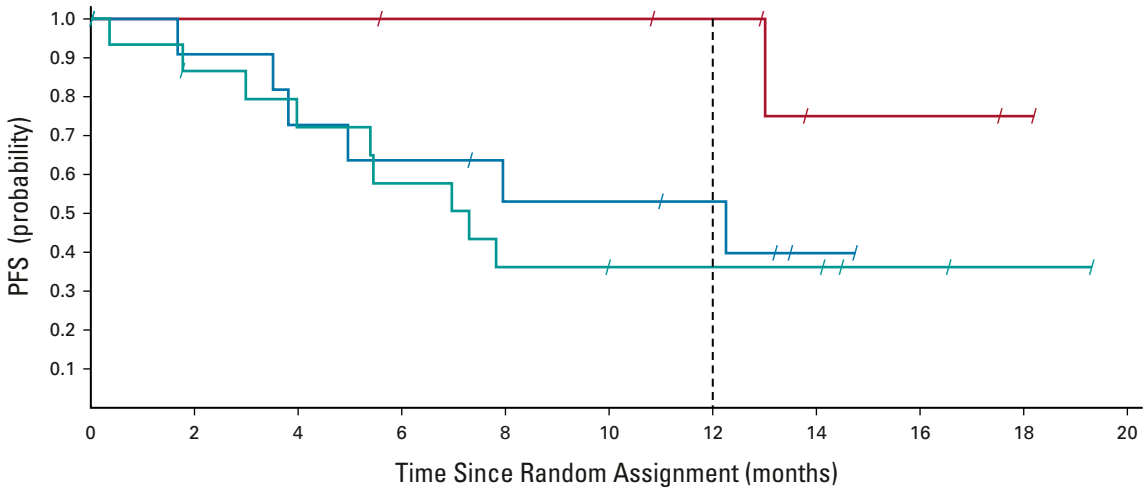


No. at risk:

Durvalumab + monalizumab	20	20	19	19	19	14	10	6	3	1	1
Durvalumab + oleclumab	23	18	17	15	14	11	8	5	4	3	0
Durvalumab	30	23	13	10	7	5	5	2	2	1	0

B **PD-L1 TC < 1%**

Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b]
Durvalumab + monalizumab	6/12 (50.0)	12.3 (3.5 to NE)	53.0 (20.9 to 77.3)	0.87 (0.31 to 2.48)
Durvalumab + oleclumab	1/7 (14.3)	NR (13.0 to NE)	100.0 (100.0 to 100.0)	NE
Durvalumab	9/16 (56.3)	7.3 (3.0 to NE)	36.1 (13.2 to 59.9)	—



No. at risk:

Durvalumab + monalizumab	12	10	8	7	5	5	4	1	0	0	0
Durvalumab + oleclumab	7	7	7	6	6	6	5	2	2	1	0
Durvalumab	16	12	10	8	5	4	4	4	2	1	0

FIG A2. Exploratory PFS in patients with tumoral PD-L1 expression (A) ≥1% and (B) <1%. Data cutoff: May 17, 2021 (median follow-up of 11.5 months; range, 0.4-23.4 months). [a]Kaplan-Meier estimates for PFS, PFS rate, and 95% CIs. [b]PFS HR and 95% CI estimated by Cox regression model, stratified by histology (adenocarcinoma and nonadenocarcinoma). HR, hazard ratio; ITT, intention to treat; NE, not estimable; NR, not reached; PD-L1, programmed cell death ligand-1; PFS, progression-free survival.

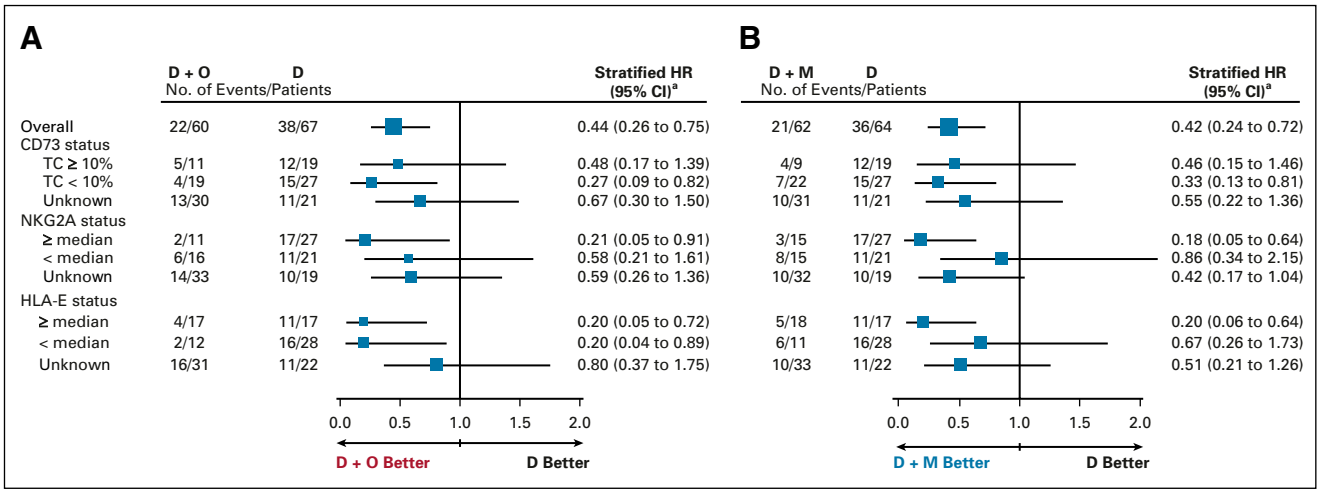


FIG A3. Exploratory PFS analysis by tumor CD73, NKG2A, and HLA-E expression per investigator assessment (ITT population): (A) durvalumab + oleclumab versus durvalumab alone and (B) durvalumab + monalizumab versus durvalumab alone. Data cutoff: May 17, 2021 (median follow-up of 11.5 months; range, 0.4-23.4 months). [a]HR calculations were performed using Cox regression models in patients with evaluable biomarker expression. CD73, cluster of differentiation 73; D, durvalumab; HLA-E, histocompatibility complex E; HR, hazard ratio; ITT, intention-to-treat; M, monalizumab; NE, not evaluable; O, oleclumab; PFS, progression-free survival; TC, tumor cell.

TABLE A1. Durvalumab-Related TEAEs Occurring in ≥10% of Patients in Any Arm (as-treated population)

	Durvalumab (n = 66)		Durvalumab + Oleclumab (n = 59)		Durvalumab + Monalizumab (n = 61)	
Preferred Term	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Patients with at least one durvalumab-related TEAE, No. (%)	49 (74.2)	5 (7.6)	45 (76.3)	2 (3.4)	47 (77.0)	7 (11.5)
Asthenia	6 (9.1)	0	7 (11.9)	0	7 (11.5)	0
Pneumonitis[a]	7 (10.6)	0	10 (16.9)	0	6 (9.8)	1 (1.6)
Pruritus	6 (9.1)	0	10 (16.9)	0	10 (16.4)	0
Hypothyroidism	10 (15.2)	0	8 (13.6)	0	11 (18.0)	0
Diarrhea	2 (3.0)	1 (1.5)	3 (5.1)	0	8 (13.1)	0
Rash	4 (6.1)	0	7 (11.9)	0	6 (9.8)	0

NOTE. Data cutoff: May 17, 2021.
Abbreviation: TEAE, treatment-emergent adverse event.
[a]In addition, radiation pneumonitis of any grade (grade 3/4) occurred in two (1) patients in the durvalumab arm.

TABLE A2. AESIs Related to Durvalumab (as-treated population).

	Durvalumab (n = 66)	Durvalumab + Oleclumab (n = 59)	Durvalumab + Monalizumab (n = 61)
Grouped Term	**Any Grade**	**Any Grade**	**Any Grade**
Any AESI[a], No. (%)	37 (56.1)	36 (61.0)	41 (67.2)
Pneumonitis[b]	12 (18.2)	12 (20.3)	11 (18.0)
Rash	6 (9.1)	12 (20.3)	14 (23.0)
Hypothyroid events	10 (15.2)	9 (15.3)	12 (19.7)
Diarrhea	7 (10.6)	7 (11.9)	12 (19.7)
Hyperthyroid events	8 (12.1)	6 (10.2)	6 (9.8)
Dermatitis	4 (6.1)	4 (6.8)	2 (3.3)
Hepatic events	3 (4.5)	1 (1.7)	0
Other rare/miscellaneous[c]	0	0	2 (3.3)
Renal events	0	1 (1.7)	0
Infusion-related reaction	0	1 (1.7)	0
Type 1 diabetes mellitus	0	0	1 (1.6)
Colitis	1 (1.5)	0	0
Hypersensitivity/anaphylactic reactions	1 (1.5)	0	0
Myositis	1 (1.5)	0	0

NOTE. Data cutoff: May 17, 2021.

Abbreviation: AESI, adverse event of special interest.

[a]Patients with multiple events in the same category were counted once in that category; patients with events in more than one category were counted once in each of those categories.

[b]Includes immune-mediated lung disease, interstitial lung disease, and pneumonitis.

[c]Includes iridocyclitis and pericarditis.