Updated results from COAST, a Phase 2 study of durvalumab ± oleclumab or monalizumab in patients with Stage III unresectable non-small-cell lung cancer

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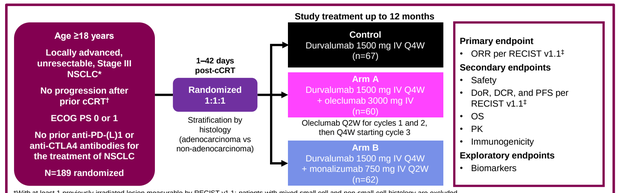
Background

- The PACIFIC trial established consolidation durvalumab after chemoradiotherapy (CRT) as the standard of care for patients with unresectable, Stage III non-small-cell lung cancer (NSCLC) who have not progressed after CRT.[1–3]
  - At 5 years of follow up, median progression free survival (PFS) was 16.9 vs 5.6 months (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.45, 0.68) and median overall survival (OS) was 47.5 vs 29.1 months (HR, 0.72; 95% CI, 0.59, 0.89) for patients who received consolidation durvalumab vs placebo in PACIFIC, respectively.[3]
- Rational immunotherapy combinations that build upon the foundation of consolidation durvalumab may further improve outcomes.
- As radiotherapy (RT) can induce expression of CD73, HLA-E (NKG2A ligand) and programmed cell death ligand-1 (PD-L1) in tumor cells, each of which suppress antitumor immunity, there is a rationale for combined blockade of these immune checkpoints after CRT.[4–7]
- COAST is a global, open-label, phase 2 study of durvalumab alone or combined with the anti-CD73 monoclonal antibody (mAb) oleclumab or anti-NKG2A mAb monalizumab as consolidation therapy in this setting.
  - Interim results from COAST (median follow-up 11.5 months) suggested that treatment with durvalumab + oleclumab or durvalumab + monalizumab increased objective response rate (ORR) and prolonged PFS versus durvalumab alone.[8]
- Here, we present updated efficacy, including the final analysis of ORR, and safety from COAST.

Methods

- Detailed methods have been published previously,[8] and the study design is summarized in **Figure 1**.

Figure 1. Study design



*With at least 1 previously irradiated lesion measurable by RECIST v1.1; patients with mixed small cell and non-small-cell histology are excluded.
†Completed definitive cCRT (≥60 Gy at 1.8 Gy per fraction, or bioequivalent dose) without progression within 42 days prior to randomization.
‡By investigator assessment.
cCRT, concurrent chemoradiotherapy; CTLA4, cytotoxic T-lymphocyte associated protein 4; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; Gy, gray; IV, intravenously; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PK, pharmacokinetics; PS, performance status; Q2W, every 2 weeks; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumours.

Results

Patients and treatment

- At the data cutoff (July 18, 2023), median follow-up was 30.1 months (range, 0.4–48.9).
- Baseline characteristics and details of prior CRT were generally balanced across arms (**Table 1**), though imbalances were noted for the Control Arm vs Arm A vs Arm B in the prevalence of ECOG PS 0 (45.5% vs 55.9% vs 44.3%), PD-L1 TC ≥1% (44.8% vs 38.3% vs 32.3%), and receipt of prior carboplatin (64.2% vs 46.7% vs 71.0%).
- All but one randomized patient in each group received treatment; disposition and exposure are presented in **Table 2**.

Table 1. Baseline characteristics and prior CRT (ITT population)

	Control Arm (D; n=67)	Arm A (D+O; n=60)	Arm B (D+M; n=62)
Median age (range), years	66.0 (46–81)	65.0 (37–83)	65.0 (44–87)
Female / male, %	32.8 / 67.2	30.0 / 70.0	32.3 / 67.7
Race, %*			
American Indian or Alaska Native	0	1.7	0
Asian	7.7	6.8	8.1
Black or African American	1.5	8.5	3.2
Native Hawaiian or Other Pacific Islander	1.5	0	0
White	87.7	79.7	88.7
Other	1.5	3.4	0
ECOG PS 0 / 1, %*	45.5 / 54.5	55.9 / 44.1	44.3 / 55.7
Current or former smoker, %	94.0	90.0	95.2
Squamous / non-squamous, %	44.8 / 55.2	41.7 / 58.3	43.5 / 56.5
PD-L1 TC ≥1% / <1% / Unknown, %†	44.8 / 23.9 / 31.3	38.3 / 11.7 / 50.0	32.3 / 19.4 / 48.4
Stage IIIA / IIIB / IIIC disease at study entry, %	40.3 / 52.2 / 7.5	45.0 / 48.3 / 6.7	51.6 / 43.5 / 4.8
Prior RT dose 54–66 / >66–74 Gy, %	92.5 / 7.5	91.7 / 8.3	91.9 / 8.1
Time from last RT to randomization <14 / 14–28 / >28 days, %	13.4 / 40.3 / 46.3	6.7 / 45.0 / 48.3	9.7 / 48.4 / 41.9
Prior cisplatin / carboplatin / cisplatin and carboplatin, %	34.3 / 64.2 / 1.5	46.7 / 46.7 / 6.7	24.2 / 71.0 / 4.8

*Race was missing for two patients in the D arm and one patient in the D+O arm, and baseline ECOG PS was reported for randomized patients who received treatment (reported percentages are based on patients with reported data).
†21, 30, and 30 patients in the D, D+O, and D+M arms, respectively, were not evaluable for PD-L1 TC expression.
CRT, chemoradiotherapy; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; Gy, gray; ITT, intention to treat; M, monalizumab; O, oleclumab; PD-L1, programmed cell death ligand-1; PS, performance status; RT, radiotherapy; TC, tumor cell expression.

Table 2. Disposition and exposure (ITT population)

	Control Arm (D; n=67)	Arm A (D+O; n=60)	Arm B (D+M; n=62)
Received treatment, n (%)	66 (98.5)	59 (98.3)	61 (98.4)
Median duration of exposure to study treatment (range), cycles	7.0 (1–13)	13.0 (1–13)	13.0 (1–13)
Completed planned study treatment, n (%)*	20 (30.3)	33 (55.9)	36 (59.0)
Discontinued all study treatment, n (%)*	46 (69.7)	26 (44.1)	25 (41.0)
Adverse event	10 (15.2)	10 (16.9)†	9 (14.8)
Treatment-related toxicity delay‡	0	1 (1.7)	1 (1.6)
Confirmed disease progression	26 (39.4)	9 (15.3)	11 (18.0)
Unconfirmed disease progression§	2 (3.0)	2 (3.4)	1 (1.6)
Death	1 (1.5)	2 (3.4)	0
Patient decision	4 (6.1)	1 (1.7)	3 (4.9)
Investigator decision	1 (1.5)	0	0
Other	2 (3.0)¶	1 (1.7)‖	0

*The denominator for percentages is the number of patients who received treatment in each group.
†One patient discontinued D due to an adverse event, and treatment with D alone in combination arms was not allowed, per protocol.
‡Treatment-related toxicity delay >56 days from last dose to next planned dose.
§Unconfirmed disease progression and investigator determination that the patient was not eligible for a confirmation scan.
¶Clinical deterioration (n=1) and patient did not want to come into the hospital due to the COVID-19 pandemic, so became ineligible 56 days after last treatment (n=1).
‖Non-study medication-related delay of >56 days from last administration of study drug to the next planned dose (n=1).
D, durvalumab; ITT, intention to treat; M, monalizumab; O, oleclumab.

Results, cont'd

Objective response rate (ORR)

- Confirmed ORR was higher in Arms A (35.0%) and B (40.3%) vs the Control Arm (23.9%; **Table 3**).

Table 3. Antitumor activity by investigator assessment (ITT population)

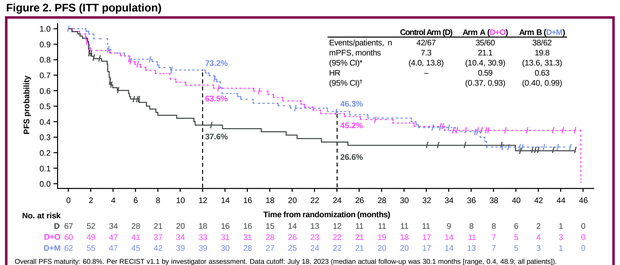
Antitumor activity	Control Arm (D; n=67)	Arm A (D+O; n=60)	Arm B (D+M; n=62)
ORR, % (95% CI)*	23.9 (14.3, 35.9)	35.0 (23.1, 48.4)	40.3 (28.1, 53.6)
Difference in ORR, % (95% CI)†	-	11.1 (−6.4, 28.1)	16.9 (−0.8, 33.4)
Best overall response, n (%)*			
CR	2 (3.0)	0	3 (4.8)
PR	14 (20.9)	21 (35.0)	22 (35.5)
SD	33 (49.3)	29 (48.3)	28 (45.2)
PD	11 (16.4)	6 (10.0)	4 (6.5)
NE	7 (10.4)	4 (6.7)	5 (8.1)
DCR at 16 weeks, % (95% CI)*	58.2 (45.5, 70.2)	80.0 (67.7, 89.2)	79.0 (66.8, 88.3)
Difference in DCR at 16 weeks, % (95% CI)†	-	21.8 (4.4, 38.2)	22.8 (5.6, 39.4)
Median DoR, months (95% CI)‡	NC (14.1, NC)	29.9 (17.1, NC)	23.0 (10.2, NC)

*Confirmed responses. The one-sample exact CI is calculated by the Clopper-Pearson method. Disease control is defined as a best overall response of CR or PR, or SD maintained for ≥16 weeks.
†Compared with 67 and 64 patients in the Control Arm enrolled concurrently with patients in Arms A and B, respectively. Exact unconditional confidence limits for rate difference are computed.
‡Median DoR is assessed via Kaplan-Meier methods.
CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; D, durvalumab; ITT, intention to treat; M, monalizumab; NC, not calculable; NE, not evaluable; O, oleclumab; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Progression-free survival (PFS)

- In the ITT population, PFS favored Arms A and B vs the Control Arm, with HRs of 0.59 (95% CI: 0.37, 0.93) and 0.63 (0.40, 0.99), respectively (**Figure 2**).
- Analysis of patients with PD-L1 TC <1% was limited by small sample size (**Figure 3A**), while patients with PD-L1 TC ≥1% in Arms A and B appeared to have a PFS benefit vs the Control Arm (**Figure 3B**).
- Among patients with non-squamous histology, a PFS benefit was observed for both Arms A and B vs the Control Arm (**Figure 3C**), whereas no difference was observed among patients with squamous histology (**Figure 3D**).
- Exploratory subgroup analyses for PFS are presented in **Figure 4**.
  - HRs trended in favor of Arms A and B (vs the Control Arm) among patients who received cisplatin and patients with non-squamous histology, ECOG PS 1, PD-L1 tumor cell expression (TC) ≥1%, Stage IIIB/C disease, and NKG2A or HLA-E status ≥ than the median value.
  - HRs also trended in favor of Arm A (vs the Control Arm) among patients with known CD73 status, regardless of expression level, and HLA-E status lower than the median value.

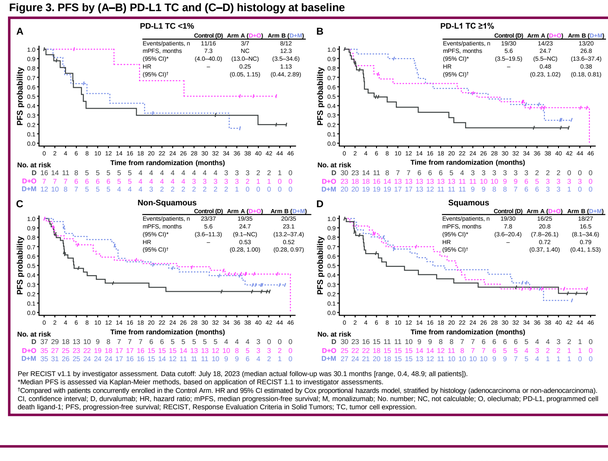
Figure 2. PFS (ITT population)



	Control Arm (D)	Arm A (D+O)	Arm B (D+M)
Events/patients, n	42/67	35/60	38/62
mPFS, months (95% CI)*	7.3 (4.0, 13.8)	21.1 (10.4, 30.9)	19.8 (13.6, 31.3)
HR (95% CI)†	–	0.59 (0.37, 0.93)	0.63 (0.40, 0.99)

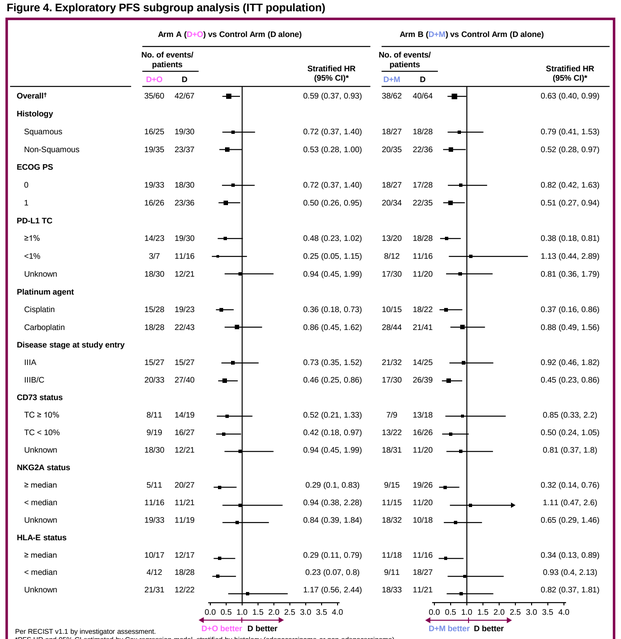
Overall PFS maturity: 60.8%. Per RECIST v1.1 by investigator assessment. Data cutoff: July 18, 2023 (median actual follow-up was 30.1 months [range, 0.4, 48.9; all patients]).
*Median PFS is assessed via Kaplan-Meier methods, based on application of RECIST 1.1 to investigator assessments.
†Compared with 67 and 64 patients in the Control Arm enrolled concurrently with patients in Arms A and B, respectively. HR and 95% CI estimated by Cox proportional hazards model, stratified by histology (adenocarcinoma or non-adenocarcinoma).
CI, confidence interval; D, durvalumab; HR, hazard ratio; ITT, intention to treat; M, monalizumab; mPFS, median progression-free survival; No., number; O, oleclumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 3. PFS by (A–B) PD-L1 TC and (C–D) histology at baseline



Per RECIST v1.1 by investigator assessment. Data cutoff: July 18, 2023 (median actual follow-up was 30.1 months [range, 0.4, 48.9; all patients]).
*Median PFS is assessed via Kaplan-Meier methods, based on application of RECIST 1.1 to investigator assessments.
†Compared with patients concurrently enrolled in the Control Arm. HR and 95% CI estimated by Cox proportional hazards model, stratified by histology (adenocarcinoma or non-adenocarcinoma).
CI, confidence interval; D, durvalumab; HR, hazard ratio; mPFS, median progression-free survival; M, monalizumab; No. number; NC, not calculable; O, oleclumab; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cell expression.

Figure 4. Exploratory PFS subgroup analysis (ITT population)

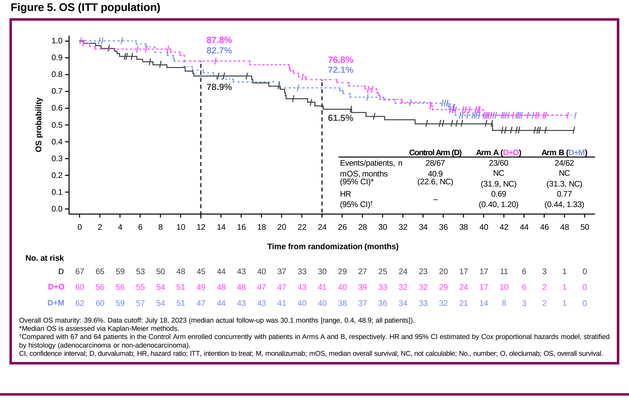


Per RECIST v1.1 by investigator assessment.
*PFS HR and 95% CI estimated by Cox regression model, stratified by histology (adenocarcinoma or non-adenocarcinoma).
†Compared with 67 and 64 patients in the Control Arm enrolled concurrently with patients in Arms A and B, respectively.
CD73, cluster of differentiation 73; CI, confidence interval; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; HLA-E, human leukocyte antigen E; HR, hazard ratio; M, monalizumab; NKG2A, natural killer group 2 member A; No., number; O, oleclumab; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cell expression.

Overall survival (OS)

- In the ITT population, OS trended in favor of Arms A and B vs the Control arm, with HRs of 0.69 (95% CI: 0.40, 1.20) and 0.77 (0.44, 1.33), respectively (**Figure 5**).
- Exploratory subgroup analyses for OS are presented in **Figure 6**.
  - HRs trended in favor of Arms A and B (vs the Control Arm) among patients with non-squamous histology, PD-L1 TC ≥1%, and Stage IIIB/C disease.

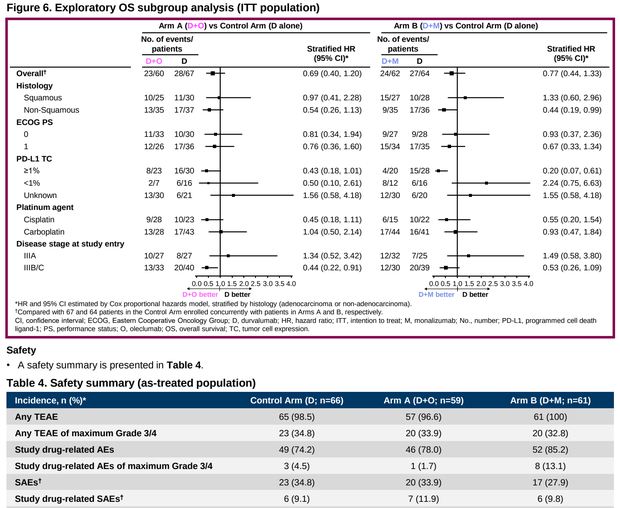
Figure 5. OS (ITT population)



	Control Arm (D)	Arm A (D+O)	Arm B (D+M)
Events/patients, n	28/67	23/60	24/62
mOS, months (95% CI)*	40.9 (22.6, NC)	NC (31.9, NC)	NC (31.3, NC)
HR (95% CI)†	–	0.69 (0.40, 1.20)	0.77 (0.44, 1.33)

Overall OS maturity: 39.6%. Data cutoff: July 18, 2023 (median actual follow-up was 30.1 months [range, 0.4, 48.9; all patients]).
*Median OS is assessed via Kaplan-Meier methods.
†Compared with 67 and 64 patients in the Control Arm enrolled concurrently with patients in Arms A and B, respectively. HR and 95% CI estimated by Cox proportional hazards model, stratified by histology (adenocarcinoma or non-adenocarcinoma).
CI, confidence interval; D, durvalumab; HR, hazard ratio; ITT, intention to treat; M, monalizumab; mOS, median overall survival; NC, not calculable; No., number; O, oleclumab; OS, overall survival.

Figure 6. Exploratory OS subgroup analysis (ITT population)



*HR and 95% CI estimated by Cox proportional hazards model, stratified by histology (adenocarcinoma or non-adenocarcinoma).
†Compared with 67 and 64 patients in the Control Arm enrolled concurrently with patients in Arms A and B, respectively.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; D, durvalumab; HR, hazard ratio; ITT, intention to treat; M, monalizumab; No., number; PD-L1, programmed cell death ligand-1; PS, performance status; O, oleclumab; OS, overall survival; TC, tumor cell expression.

Safety

- A safety summary is presented in **Table 4**.

Table 4. Safety summary (as-treated population)

Incidence, n (%)*	Control Arm (D; n=66)	Arm A (D+O; n=59)	Arm B (D+M; n=61)
Any TEAE	65 (98.5)	57 (96.6)	61 (100)
Any TEAE of maximum Grade 3/4	23 (34.8)	20 (33.9)	20 (32.8)
Study drug-related AEs	49 (74.2)	46 (78.0)	52 (85.2)
Study drug-related AEs of maximum Grade 3/4	3 (4.5)	1 (1.7)	8 (13.1)
SAEs†	23 (34.8)	20 (33.9)	17 (27.9)
Study drug-related SAEs†	6 (9.1)	7 (11.9)	6 (9.8)
TEAEs leading to discontinuation of:			
Durvalumab	9 (13.6)	9 (15.3)‡	9 (14.8)
Oleclumab	NA	10 (16.9)	NA
Monalizumab	NA	NA	9 (14.8)
Death§¶	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)

*Patients are counted once for each applicable category regardless of the number of events.
†SAE criteria: death, life-threatening, required inpatient hospitalization or prolongation of existing inpatient hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the patient).
‡One subject that discontinued O (but not D) due to an adverse event also discontinued D, as treatment with D alone in combination arms was not allowed, per protocol.
§All reported deaths within 90 days after last dose, regardless of relationship to study drug.
¶In total, four grade 5 AEs were related to study drug: two (pneumonitis and radiation pneumonitis) in the D+O arm, one (pneumonitis) in the D+O arm, and one (myocardial infarction) in the D+M arm.
AE, adverse event; AESI, AE of special interest; D, durvalumab; imAE, immune-mediated AE; M, monalizumab; NA, not applicable; O, oleclumab; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Conclusions

- In this analysis of updated results from COAST, the combination of durvalumab plus oleclumab or monalizumab increased ORR, prolonged PFS, and trended toward improved OS compared to durvalumab alone.
- Both combinations improved PFS and numerically improved OS versus durvalumab alone.
  - PFS benefit with one or both combinations was observed in various subgroups based on histology, ECOG PS, prior platinum-based chemotherapy, PD-L1 status, NKG2A status, and HLA-E status.
  - OS HRs trended in favor of both combinations among patients with stage IIIB/C disease, non-squamous histology, and PD-L1 TC ≥1%.
- Randomization was stratified by histology; however, results should be interpreted with caution given imbalances in prognostic characteristics (e.g., prior cisplatin, PD-L1 status) between arms and the high number of unknown values for CD73, NKG2A, and HLA-E status.
- Safety profiles were consistent across arms, with no new safety signals in either combination arm.
  - The incidence of pneumonitis was similar across arms.
- Further investigation of these combinations in this population is ongoing in the Phase 3 PACIFIC-9 study (NCT05221840), which will stratify patients by disease stage, histology, and PD-L1 status.[9]

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Disclosures

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