ORIGINAL ARTICLE

Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Neoadjuvant or adjuvant immunotherapy can improve outcomes in patients with resectable non–small-cell lung cancer (NSCLC). Perioperative regimens may combine benefits of both to improve long-term outcomes.

METHODS

We randomly assigned patients with resectable NSCLC (stage II to IIIB [N2 node stage] according to the eighth edition of the *AJCC Cancer Staging Manual*) to receive platinum-based chemotherapy plus durvalumab or placebo administered intravenously every 3 weeks for 4 cycles before surgery, followed by adjuvant durvalumab or placebo intravenously every 4 weeks for 12 cycles. Randomization was stratified according to disease stage (II or III) and programmed death ligand 1 (PD-L1) expression (≥1% or <1%). Primary end points were event-free survival (defined as the time to the earliest occurrence of progressive disease that precluded surgery or prevented completion of surgery, disease recurrence [assessed in a blinded fashion by independent central review], or death from any cause) and pathological complete response (evaluated centrally).

RESULTS

A total of 802 patients were randomly assigned to receive durvalumab (400 patients) or placebo (402 patients). The duration of event-free survival was significantly longer with durvalumab than with placebo; the stratified hazard ratio for disease progression, recurrence, or death was 0.68 (95% confidence interval [CI], 0.53 to 0.88; P=0.004) at the first interim analysis. At the 12-month landmark analysis, event-free survival was observed in 73.4% of the patients who received durvalumab (95% CI, 67.9 to 78.1), as compared with 64.5% of the patients who received placebo (95% CI, 58.8 to 69.6). The incidence of pathological complete response was significantly greater with durvalumab than with placebo (17.2% vs. 4.3% at the final analysis; difference, 13.0 percentage points; 95% CI, 8.7 to 17.6; P<0.001 at interim analysis of data from 402 patients). Event-free survival and pathological complete response benefit were observed regardless of stage and PD-L1 expression. Adverse events of maximum grade 3 or 4 occurred in 42.4% of patients with durvalumab and in 43.2% with placebo. Data from 62 patients with documented *EGFR* or *ALK* alterations were excluded from the efficacy analyses in the modified intention-to-treat population.

CONCLUSIONS

In patients with resectable NSCLC, perioperative durvalumab plus neoadjuvant chemotherapy was associated with significantly greater event-free survival and pathological complete response than neoadjuvant chemotherapy alone, with a safety profile that was consistent with the individual agents. (Funded by AstraZeneca; AEGEAN ClinicalTrials.gov number, NCT03800134.)

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Lung cancer is the leading cause of cancer-related death worldwide, with non–small-cell lung cancer (NSCLC) accounting for over 80% of cases.[1-3] Approximately 25 to 30% of patients with NSCLC present with resectable disease,[4,5] a proportion that is expected to increase with the growing use of lung-cancer screening programs.[6] Surgery remains the primary curative-intent treatment for eligible patients with early-stage NSCLC.[7,8] However, many patients have tumor recurrence within 5 years after surgery (approximately 30 to 55%, depending on the disease stage at diagnosis), a factor that increases the likelihood of disease-related death.[9-14] Chemotherapy administered in the neoadjuvant or adjuvant period offers only a modest 5% improvement in 5-year survival as compared with surgery alone.[15-17]

After positive results from phase 3 trials, inhibitors of programmed death-1 (PD-1) and programmed death ligand 1 (PD-L1) have received approval for use as a component of either neoadjuvant treatment (in combination with platinum-based chemotherapy) or adjuvant treatment (following resection and platinum-based chemotherapy) for patients with resectable NSCLC.[18-23] Perioperative regimens that combine the benefits of neoadjuvant and adjuvant immunotherapy could further improve long-term outcomes (as suggested by results of recent melanoma and NSCLC trials[24-26]) by priming antitumor immunity while the primary tumor and lymph nodes are present and eradicating residual micrometastases both before and after surgery.[27]

Durvalumab is a selective, high-affinity, human IgG1 monoclonal antibody that inhibits interaction of PD-L1 with PD-1 and CD80 by binding to PD-L1.[28] Findings from the PACIFIC trial have established consolidation therapy with durvalumab for up to 12 months as an international standard for patients with unresectable, stage III NSCLC and no disease progression after platinum-based chemoradiotherapy.[29-31] In addition, encouraging activity has been shown with durvalumab administered as neoadjuvant therapy in phase 2 trials.[32-35] Here, we report the primary analyses of event-free survival and pathological complete response from the phase 3, international, double-blind, placebo-controlled AEGEAN trial, which investigated the use of durvalumab administered perioperatively (i.e., as neoadjuvant and adjuvant therapy) along with neoadjuvant chemotherapy in patients with resectable NSCLC.

Methods

Patients

Eligible patients had newly diagnosed, previously untreated, histologically or cytologically documented, resectable NSCLC (stage IIA to stage IIIB [N2 node stage] disease, according to the eighth edition of the *AJCC Cancer Staging Manual*[36]), with mediastinal lymph-node staging performed pathologically at the discretion of the investigator. At enrollment, patients had to be at least 18 years of age and be candidates for planned surgical treatment with lobectomy, sleeve resection, or bilobectomy. Additional inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a scale of 0 to 5, with higher numbers reflecting greater disability); estimated life expectancy of at least 12 weeks; documented tumor PD-L1 status (assessed at a central laboratory using the VENTANA PD-L1 [SP263] immunohistochemistry assay); and the presence of at least one lesion that qualified as a target lesion according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1.

Key exclusion criteria were previous exposure to anti–PD-L1, anti–PD-1, or anti–cytotoxic T-lymphocyte antigen 4 antibodies, uncontrolled intercurrent illness, specific active or previously documented autoimmune disorders, and sublobar resections as planned surgery at the time of enrollment. With enrollment ongoing, the protocol was amended to exclude patients with tumors classified as T4 for any reason other than size (>7 cm), whose planned surgery at enrollment was pneumonectomy, or who had documented test results that confirmed the presence of an *EGFR* mutation (confirmed by central testing) or *ALK* translocation (confirmed by local or central testing). Complete eligibility criteria are provided in the protocol, available with the full text of this article at NEJM.org.

Trial Design

Patients were randomly assigned in a 1:1 ratio to receive four cycles of platinum-based chemotherapy (administered according to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology[37]) plus either fixed-dose durvalumab (at a dose of 1500 mg) or placebo administered intravenously every 3 weeks, followed by surgery. After surgery, patients continued to receive durvalumab or placebo intrave-

nously every 4 weeks for up to 12 cycles (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Randomization was stratified according to disease stage (II or III) and PD-L1 expression (<1% or ≥1%).

In a treatment approach that was consistent with general practice, the chemotherapy regimen was determined by histologic findings and administered at the investigator's discretion (details of permitted regimens are provided in the Supplementary Appendix). Surgery was prespecified to take place no more than 40 days after the administration of the last dose of neoadjuvant treatment. The initiation of adjuvant treatment was scheduled as soon as clinically feasible and within 10 weeks after surgery or within 3 weeks after completion of postoperative radiotherapy, which was permitted if indicated and according to local guidance; if indicated, postoperative radiotherapy had to begin within 8 weeks after surgery. To be eligible to receive adjuvant durvalumab or placebo, patients must have had a resection margin of R0 or R1 after surgery, and a postsurgical scan must have been performed before adjuvant treatment began.

The trial was designed by the sponsor, AstraZeneca. All the patients provided written informed consent, and an independent data and safety monitoring committee monitored efficacy and safety. The protocol and all amendments were approved by the relevant ethics committees or institutional review boards, and the trial was performed in accordance with the Declaration of Helsinki, the International Council for Harmonization Good Clinical Practice guidelines, and all applicable laws and regulations. All the investigators were responsible for the collection of data. All the authors participated in writing the manuscript and provided approval to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Medical writing assistance, including development of the initial draft of the manuscript, was funded by the sponsor.

END POINTS AND ASSESSMENTS

The primary end points were event-free survival (evaluated in a blinded fashion by independent central review) and pathological complete response (evaluated centrally). Key secondary end points were major pathological response, disease-free survival, and overall survival. Other secondary end points included pharmacokinetics and immunogenicity, patient-reported outcomes, and safety. Additional secondary objectives included evaluation of the primary and key secondary end points in patients with PD-L1 expression of 1% or more.

Event-free survival was defined as the time from randomization to the earliest of the following: progressive disease that precluded surgery, progressive disease that was discovered and reported by the investigator when attempting surgery and that prevented completion of the surgery, local or distant recurrence assessed independently according to RECIST (as described in the Supplementary Appendix), or death from any cause. All patients were included in the analysis of event-free survival, regardless of surgery status; however, not undergoing or completing surgery for reasons other than progressive disease was not considered to be an event in the analysis of event-free survival, and these patients continued to be followed for event-free survival until RECIST-defined progression or death.

Primary tumors and sampled lymph nodes were assessed for pathological response to neoadjuvant treatment by central review.[38] Patients were considered to have had no response if they were not eligible for assessment (including those with resection margins of R2 according to local assessment) or if a surgical specimen was not available. Pathological complete response was defined as the absence of any viable tumor cells after complete evaluation of the resected lung-cancer specimen and all sampled regional lymph nodes, and major pathological response was defined as the presence of 10% or less of viable tumor cells in the primary tumor.

Safety was monitored throughout the trial. Adverse events were documented according to the *Medical Dictionary for Regulatory Activities*, version 25.1, and graded with the use of National Cancer Institute Common Toxicity Criteria for Adverse Events, version 5.0.

STATISTICAL ANALYSIS

We planned that 800 eligible patients would undergo randomization in the intention-to-treat population, including 740 patients in the modified intention-to-treat population, which excluded patients with documented *EGFR* or *ALK* alterations who were enrolled before a protocol amendment. We would consider trial findings to be positive if either event-free survival or patho-

logical complete response in the modified intention-to-treat population was significantly better in the durvalumab group than in the placebo group. Complete statistical analysis methods are described in the Supplementary Appendix.

Efficacy analyses were performed in the modified intention-to-treat population, and safety was assessed in all the patients who had undergone randomization and received at least one dose of any trial treatment (i.e., durvalumab or chemotherapy) or placebo (the safety analysis set). Interim and final analyses of pathological complete response and the interim analysis of event-free survival (all reported here) were triggered by prespecified criteria.

To strongly control the two-sided type I error rate at 0.05, a hierarchical multiple testing procedure that included a gatekeeping strategy was used across the primary end points and alpha-controlled secondary end points, with alpha allocation and recycling between end points and the interim and final analyses (Fig. S2 and Table S1 in the Supplementary Appendix). As a result, the planned interim analysis of pathological complete response (based on a modified intention-to-treat population of 400 patients) had a 55% power to detect a between-group difference of 12 percentage points at a two-sided significance level of 0.008%, and the first planned interim analysis of event-free survival (based on 740 patients in the modified intention-to-treat population with 224 events) had a 50% power to show a hazard ratio for disease progression, recurrence, or death of 0.69 with a two-sided significance level of 0.665%.

For event-free survival, the P value was calculated with the use of a stratified log-rank test and compared against a significance boundary of 0.990% (on the basis of a total 5% alpha with adjustment for interim analysis). For the pathological response end points, P values were calculated by means of a stratified Cochran–Mantel–Haenszel test and compared against an adjusted significance boundary of 0.008%. Significance boundaries were calculated with the use of a Lan–DeMets alpha spending function with an O'Brien–Fleming boundary.

RESULTS

PATIENTS

Between January 2, 2019, and April 19, 2022, a total of 1480 patients from 28 countries were enrolled; of these patients, 802 were randomly assigned to receive durvalumab (400) or placebo (402), representing the intention-to-treat population (Fig. S3). The characteristics of this population (Table S2) were generally representative of an international population of patients with resectable NSCLC who were recruited across Asia, Europe, North America, and South America (Table S3). Overall, 16.1% of the patients who had undergone randomization were Hispanic or Latino, and less than 1% were Black. The modified intention-to-treat population (which excluded 62 patients with known *EGFR* or *ALK* alterations) was made up of 740 patients (366 in the durvalumab group and 374 in the placebo group).

At baseline, the demographic and clinical characteristics of the patients and their planned neoadjuvant platinum therapies were largely balanced between the groups in the modified intention-to-treat population (Table 1). The median age of the patients was 65 years, and most were male (71.6%), had an ECOG performance-status score of 0 (68.4%), and were current or former smokers (85.5%). More than 70% of the patients had stage III disease, and approximately half had N2 disease. Approximately equal proportions of the patients had disease with squamous and nonsquamous histologic characteristics. Overall, 33.4% of the patients had tumor PD-L1 expression of less than 1%, and carboplatin was the planned neoadjuvant platinum agent in 73.5% of the patients.

In the modified intention-to-treat population, as of November 10, 2022 (the date of the data cutoff for the first planned interim analysis of event-free survival), the median duration of follow-up among patients without an event in the event-free-survival analysis was 11.7 months (range, 0.0 to 46.1). Approximately 85% of the patients had completed four cycles of both chemotherapy agents in each group, and more than 60% had started receiving adjuvant durvalumab or placebo (Table 2; see Table S4 for details of neoadjuvant treatment exposure). Only 6.4% of the patients received postoperative radiotherapy, which was allowed under the protocol. Overall, 24.0% of the patients in the durvalumab group and 21.1% of the patients in the placebo group had completed 12 cycles of adjuvant durvalumab or placebo at the time of data cutoff; 18.6% and 18.7%, respectively, had prematurely discontinued the adjuvant trial regimen, most commonly due to disease progression (Fig. S3); and 23.2%

and 23.5%, respectively, were still receiving adjuvant durvalumab or placebo. Among patients in the safety analysis set who had received adjuvant treatment, the first cycle of durvalumab or placebo was delayed in 21 patients (7.9%) and 15 patients (5.9%), respectively, with the most common reason for the delay being adverse events (in 8 patients and 5 patients, respectively), followed by logistic reasons (in 5 and 4 patients) and patient decision (in 4 and 3 patients).

SURGERY

As of the data-cutoff date, approximately 81% of the patients in each group in the modified intention-to-treat population had undergone surgery (i.e., curative-intent thoracic surgery attempted, regardless of whether it was completed) (Table 2). In total, 77.6% of the patients in the durvalumab group and 76.7% of those in the placebo group had completed surgery (i.e., curative-intent thoracic surgery that was deemed completed by the investigator), among whom a slightly higher proportion of patients in the durvalumab group than in the placebo group had R0 resection (94.7% vs. 91.3%); 4.2% of patients in the durvalumab group had R1 resection as compared with 7.7% of patients in the placebo group. See the Supplementary Appendix for a summary of the most common reasons that surgery was not performed or completed in patients in the intention-to-treat population (Table S5), details of surgical delays in the safety analysis set (Table S6), and details of surgery and surgical outcomes in the modified intention-to-treat population (Table S7).

EFFICACY

At the first interim analysis of event-free survival (with 31.9% data maturity), event-free survival in the modified intention-to-treat population was of significantly longer duration in the durvalumab group than in the placebo group (Fig. 1A); the stratified hazard ratio for disease progression, recurrence, or death was 0.68 (95% confidence interval [CI], 0.53 to 0.88; P=0.004). At the 12-month landmark analysis, the percentage of patients with event-free survival was 73.4% in the durvalumab group (95% CI, 67.9 to 78.1) and 64.5% in the placebo group (95% CI, 58.8 to 69.6); at 24 months, event-free survival was 63.3% in the durvalumab group (95% CI, 56.1 to 69.6) and 52.4% in the placebo group (95% CI, 45.4 to 59.0). Event-free survival benefit with durvalumab as compared with placebo was maintained across most subgroups prespecified at baseline (Fig. 1B). See the Supplementary Appendix for outcomes across subgroups defined by the planned neoadjuvant platinum agent (Fig. S4), disease stage (Fig. S5), PD-L1 expression (Fig. S6), and histologic characteristics of the tumor (Fig. S7).

At the final analysis of pathological complete response (at data cutoff on November 10, 2022), for which no formal statistical testing was performed, pathological complete response was seen in a higher proportion of patients in the durvalumab group (17.2%; 95% CI, 13.5 to 21.5) than in the placebo group (4.3%; 95% CI, 2.5 to 6.9) (Fig. 2). Results for pathological complete response and major pathological response were consistent (P<0.001 for both) at the interim analysis of pathological complete response (among 402 patients at data cutoff on January 14, 2022) (Fig. S8 and Fig. S9). Pathological regression in the primary tumor was greater overall in the durvalumab group than in the placebo group (Fig. S10). The independently assessed objective response rate before surgery was 56.3% (95% CI, 51.0 to 61.4) in the durvalumab group and 38.0% (95% CI, 33.0 to 43.1) in the placebo group (Table S8).

A total of 51 patients who had known *EGFR* mutations were enrolled before the adoption of a protocol amendment but were not included in the modified intention-to-treat population. Preplanned subgroup analyses suggested that there was no clear evidence of clinical benefit with the use of durvalumab as compared with placebo in this subgroup (Fig. 1B and Fig. 2C).

SAFETY

Adverse events of any cause occurred in 96.5% of the patients who received durvalumab and 94.7% of the patients who received placebo (Table 3); adverse events of any cause occurred in 91.0% and 89.2%, respectively, during the neoadjuvant treatment phase. Adverse events possibly related to any trial-related treatment (durvalumab or chemotherapy) or placebo occurred in 86.8% of patients in the durvalumab group and 80.7% of patients in the placebo group. The incidence of maximum grade 3 or 4 adverse events of any cause was similar in the two groups (42.4% in the durvalumab group and 43.2% in the placebo group, with 32.2% and 36.2% of patients in the respective groups having such events during the neoadjuvant treatment phase).

Table 1. Characteristics at Baseline and Planned Treatment, Modified Intention-to-Treat Population.*

Characteristic†	Durvalumab Group (N=366)	Placebo Group (N=374)
Age		
Median (range) — yr	65 (30–88)	65 (39–85)
≥75 yr — no. (%)	44 (12.0)	36 (9.6)
Sex — no. (%)		
Male	252 (68.9)	278 (74.3)
Female	114 (31.1)	96 (25.7)
ECOG performance-status score — no. (%)‡		
0	251 (68.6)	255 (68.2)
1	115 (31.4)	119 (31.8)
Race — no. (%)§		
Asian	143 (39.1)	164 (43.9)
White	206 (56.3)	191 (51.1)
Other	17 (4.6)	19 (5.1)
Ethnic group — no.(%)		
Hispanic or Latino	63 (17.2)	56 (15.0)
Not Hispanic or Latino	303 (82.8)	318 (85.0)
Geographic region — no. (%)		
Asia	142 (38.8)	163 (43.6)
Europe	141 (38.5)	140 (37.4)
North America	43 (11.7)	43 (11.5)
South America	40 (10.9)	28 (7.5)
Smoking status — no. (%)		
Current	95 (26.0)	95 (25.4)
Former	220 (60.1)	223 (59.6)
Never	51 (13.9)	56 (15.0)
Disease stage — no. (%)¶		
II	104 (28.4)	110 (29.4)
IIIA	173 (47.3)	165 (44.1)
IIIB	88 (24.0)	98 (26.2)
TNM classification, primary tumor — no. (%)‖		
T1	44 (12.0)	43 (11.5)
T2	97 (26.5)	108 (28.9)
T3	128 (35.0)	129 (34.5)
T4	97 (26.5)	94 (25.1)
TNM stage, regional lymph nodes — no. (%)		
N0	110 (30.1)	102 (27.3)
N1	75 (20.5)	87 (23.3)
N2	181 (49.5)	185 (49.5)
Single-station	141 (38.5)	132 (35.3)
Multistation	34 (9.3)	40 (10.7)

Table 1. (Continued.)

Characteristic†	Durvalumab Group (N = 366)	Placebo Group (N = 374)
Histologic classification — no. (%)		
Squamous	169 (46.2)	191 (51.1)
Nonsquamous	196 (53.6)	179 (47.9)
PD-L1 expression — no. (%)		
Tumor cell <1%	122 (33.3)	125 (33.4)
Tumor cell 1 to 49%	135 (36.9)	142 (38.0)
Tumor cell ≥50%	109 (29.8)	107 (28.6)
Planned neoadjuvant platinum agent — no. (%)		
Cisplatin	100 (27.3)	96 (25.7)
Carboplatin	266 (72.7)	278 (74.3)

* The modified intention-to-treat population included all patients who had undergone randomization, excluding patients with documented *EGFR* or *ALK* alterations. PD-L1 denotes programmed cell death ligand 1, and TNM tumor–node–metastasis.

† Characteristics for which there were missing or other responses were histologic classification (0.3% of the patients in the durvalumab group and 1.1% of those in the placebo group had other histologic classification), disease stage (0.3% in the durvalumab group had stage IV disease and 0.3% in the placebo group had stage III [not otherwise specified] disease, as reported on the electronic case-report form), and N2 lymph node station stage (1.6% in the durvalumab group and 3.5% in the placebo group had N2 disease with missing data on single-station vs. multistation classification).

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

§ Race was reported by the patients.

¶ Patients with stage IIA disease to stage IIIB (N2 node stage) disease according to the eighth edition of the *AJCC Cancer Staging Manual* were enrolled.[36]

‖ All patients had disease that was classified as M0 except for one patient in the durvalumab group who had disease that was classified as M1 (not otherwise specified).

The incidence of maximum grade 3 or 4 adverse events that were possibly related to any trial treatment or placebo was also similar in the two groups (32.4% and 32.9%).

Adverse events of any cause that led to the discontinuation of durvalumab or placebo occurred in 12.0% and 6.0% of patients, respectively (in 6.7% vs. 3.8% of patients during the neoadjuvant treatment phase). Adverse events with an outcome of death possibly related to any trial treatment or placebo were uncommon, with occurrences in 1.7% of patients in the durvalumab group and 0.5% of those in the placebo group. The most common adverse events of any cause largely reflected the safety profile of the chemotherapy agents used in the trial (Table S9); the incidence of the most common adverse events was largely similar across both groups. There were more occurrences of rashes of any grade in the durvalumab group than in the placebo group (14.0% vs. 8.5%) and more occurrences of pruritus (11.7% vs. 5.5%); however, grade 3 or 4 rash and pruritus events were uncommon and occurred with similar frequency in the two groups (see Table S10 for a summary of the most common adverse events possibly related to trial treatment or placebo).

Immune-mediated adverse events of any grade were reported in 23.7% of patients who received durvalumab and 9.3% of patients who received placebo (Table S11); most were grade 1 or 2 adverse events, with grade 3 or 4 immune-mediated adverse events reported in 4.2% and 2.5%, respectively, in the two groups. Immune-mediated pneumonitis of any grade was reported in 3.7% of patients in the durvalumab group and 1.8% of those in the placebo group; grade 3 or 4 immune-mediated pneumonitis was reported in 1.2% and 1.0%, respectively.

DISCUSSION

In patients with resectable NSCLC, perioperative durvalumab plus neoadjuvant chemotherapy, as compared with neoadjuvant chemotherapy alone,

Table 2. Treatment Summary in the Modified Intention-to-treat Population.

Trial Phase	Durvalumab Group (N=366)	Placebo Group (N=374)
Neoadjuvant phase — no. (%)		
Underwent randomization	366 (100)	374 (100)
Received chemotherapy plus durvalumab or placebo	366 (100)	371 (99.2)
Completed four cycles of both chemotherapy agents	310 (84.7)	326 (87.2)
Completed four cycles of durvalumab or placebo	318 (86.9)	331 (88.5)
Surgery*		
Underwent surgery — no. (%)	295 (80.6)	302 (80.7)
Did not undergo surgery — no. (%)†	71 (19.4)	72 (19.3)
Completed surgery — no. (%)	284 (77.6)	287 (76.7)
R0 resection — no./total no. (%)	269/284 (94.7)	262/287 (91.3)
R1 resection — no./total no. (%)	12/284 (4.2)	22/287 (7.7)
Did not complete surgery — no. (%)	11 (3.0)	15 (4.0)
Adjuvant phase, ongoing — no. (%)		
Started durvalumab or placebo‡	241 (65.8)	237 (63.4)
Completed durvalumab or placebo	88 (24.0)	79 (21.1)
Discontinued durvalumab or placebo	68 (18.6)	70 (18.7)
Ongoing durvalumab or placebo	85 (23.2)	88 (23.5)

* Surgery status was assessed by the investigator. Patients who underwent surgery were those for whom curative-intent thoracic surgery was attempted, regardless of whether it was completed. Patients who completed surgery were those for whom curative-intent thoracic surgery was completed.
† Numbers include patients who had surgery outside the trial.
‡ For patients to have been eligible for adjuvant durvalumab or placebo, they must have had an R0 or R1 margin after surgery, and a postsurgical scan must have been performed before adjuvant treatment began.

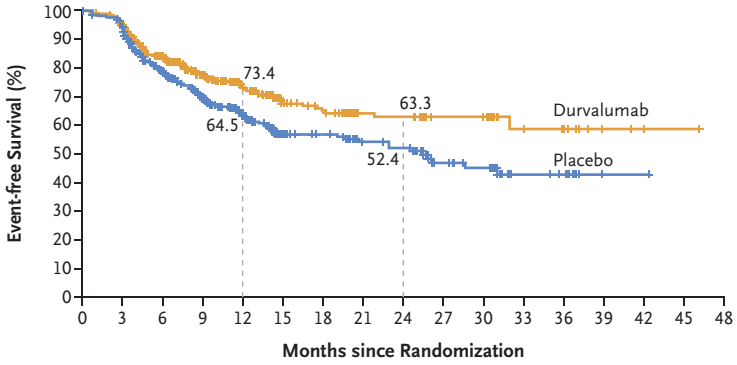
was associated with significantly better results with regard to the two primary end points of event-free survival (hazard ratio for disease progression, recurrence, or death, 0.68; P=0.004) and pathological complete response (difference in proportions, 13.0 percentage points; P<0.001), with a safety profile that was consistent with the individual agents, and had no detrimental effect on the completion of neoadjuvant chemotherapy or surgery. A significant benefit with regard to event-free survival was noted at the first planned interim analysis with 31.9% data maturity and a median follow-up of 1 year (among patients who had not had an event in the event-free survival analysis), when approximately one fourth of patients were still receiving adjuvant durvalumab or placebo.

Improvements in event-free survival and pathological complete response with durvalumab were broadly observed across subgroups, including in patients with PD-L1 expression of less than 1%, although the magnitude of benefit was greater in patients with PD-L1 expression of at least 50%. Although benefit was seen across all

Figure 1 (facing page). Event-free Survival in the Modified Intention-to-Treat Population.

Shown are the results of analyses of data from 740 patients as of the data cutoff of November 10, 2022. Panel A shows Kaplan–Meier estimates of event-free survival among the patients in the modified intention-to-treat population (i.e., all the patients who had undergone randomization without documented *EGFR* or *ALK* alterations). Dashed lines indicate the 12-month and 24-month event-free survival landmark points. Panel B shows a forest plot of event-free survival in prespecified baseline subgroups; all are subgroups of the modified intention-to-treat population except the *EGFR*-mutation–positive subgroup, which is a subgroup of the intention-to-treat population. The size of the data point is proportional to the number of events in each subgroup. Shading indicates the hazard ratio and 95% confidence interval for the modified intention-to-treat population. Race was reported by the patients. (The *ALK*-translocation–positive subgroup was also excluded; owing to the small number of patients in that subgroup [11], those results are not shown here.) Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Disease stage was defined according to the eighth edition of the *AJCC Cancer Staging Manual*. CI denotes confidence interval, NR not reached, and PD-L1 programmed death ligand 1.

A Event-free Survival



	No. of Events/ No. of Patients	Median Event-free Survival (95%CI)
		mo
Durvalumab	98/366 (26.8)	NR (31.9–NR)
Placebo	138/374 (36.9)	25.9 (18.9–NR)

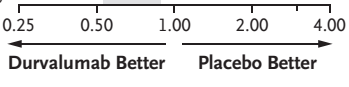
Stratified hazard ratio for disease progression, recurrence, or death, 0.68 (95% CI, 0.53–0.88)
P=0.004 by stratified log-rank test

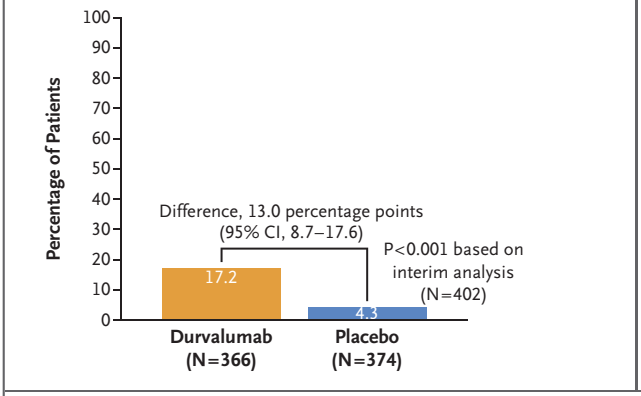
No. at Risk

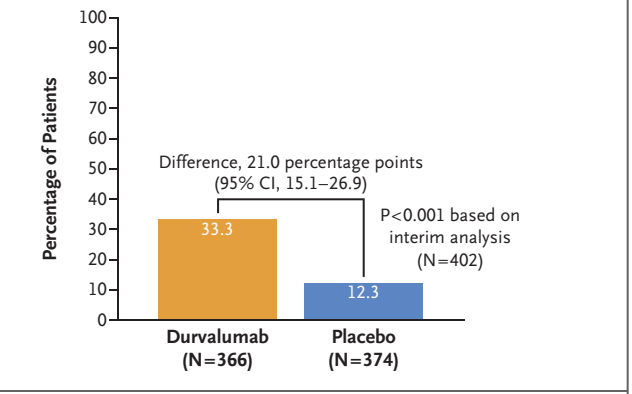
Durvalumab	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
Placebo	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

B Subgroup Analysis

Subgroup	No. of Patients	Median Event-free Survival (95% CI)		Hazard Ratio for Disease Progression, Recurrence, or Death (95% CI)
		Durvalumab	Placebo	
		mo		
All patients	740	NR (31.9–NR)	25.9 (18.9–NR)	0.68 (0.53–0.88)
Age at randomization				
<65 yr	358	NR (NR–NR)	NR (18.9–NR)	0.71 (0.47–1.04)
≥65 yr	382	NR (17.9–NR)	24.5 (13.6–31.1)	0.69 (0.48–0.97)
Sex				
Male	530	NR (31.9–NR)	22.9 (14.3–31.1)	0.61 (0.44–0.82)
Female	210	NR (17.5–NR)	NR (13.6–NR)	0.95 (0.58–1.56)
ECOG performance-status score				
0	506	NR (31.9–NR)	25.4 (14.3–NR)	0.65 (0.47–0.89)
1	234	NR (21.8–NR)	25.9 (14.3–NR)	0.78 (0.49–1.22)
Race				
Asian	307	NR (NR–NR)	25.4 (13.9–NR)	0.60 (0.40–0.90)
Non-Asian	433	31.9 (21.8–NR)	26.2 (14.3–NR)	0.76 (0.54–1.06)
Geographic region				
Asia	305	NR (NR–NR)	22.9 (13.9–NR)	0.62 (0.41–0.93)
Europe	281	31.9 (31.9–NR)	NR (14.3–NR)	0.75 (0.49–1.14)
North America	86	NR (21.8–NR)	24.5 (10.0–NR)	0.69 (0.27–1.62)
South America	68	16.5 (13.0–NR)	11.0 (7.1–NR)	0.71 (0.33–1.53)
Smoking status				
Current smoker	190	NR (NR–NR)	14.3 (8.1–NR)	0.48 (0.28–0.80)
Former smoker	443	NR (31.9–NR)	25.9 (19.5–NR)	0.79 (0.57–1.10)
Never smoked	107	NR (NR–NR)	24.5 (14.3–NR)	0.76 (0.35–1.58)
Histologic features				
Squamous	360	NR (31.9–NR)	26.2 (13.0–NR)	0.71 (0.49–1.03)
Nonsquamous	375	NR (NR–NR)	25.4 (14.3–NR)	0.69 (0.48–0.99)
Disease stage				
II	214	NR (NR–NR)	31.1 (25.4–NR)	0.76 (0.43–1.34)
IIIA	338	NR (NR–NR)	19.5 (11.7–NR)	0.57 (0.39–0.83)
IIIB	186	31.9 (11.7–NR)	18.9 (11.8–NR)	0.83 (0.52–1.32)
Lymph node station				
N2 single	273	NR (NR–NR)	22.8 (12.6–NR)	0.61 (0.39–0.94)
N2 multi	74	31.9 (9.3–NR)	12.2 (7.2–NR)	0.69 (0.33–1.38)
PD-L1 expression at baseline				
Tumor cell <1%	247	NR (14.9–NR)	20.6 (13.9–NR)	0.76 (0.49–1.17)
Tumor cell 1–49%	277	NR (31.9–NR)	25.4 (12.2–NR)	0.70 (0.46–1.05)
Tumor cell ≥50%	216	NR (NR–NR)	26.2 (14.3–NR)	0.60 (0.35–1.01)
Planned neoadjuvant platinum agent				
Cisplatin	196	NR (NR–NR)	31.1 (14.3–NR)	0.59 (0.35–1.00)
Carboplatin	544	NR (31.9–NR)	25.4 (14.3–NR)	0.73 (0.54–0.98)
EGFR-mutation positive	51	30.8 (11.4–NR)	19.6 (14.3–NR)	0.86 (0.35–2.19)







C Subgroup Analysis for Pathological Complete Response

Subgroup	No. of Patients	Pathological Complete Response (95% CI)		Difference in Pathological Complete Response (95% CI)
		Durvalumab	Placebo	
		percent		*percentage points*
All patients	740	17.2 (13.5 to 21.5)	4.3 (2.5 to 6.9)	13.0 (8.7 to 17.6)
Age at randomization				
<65 yr	358	18.3 (12.9 to 24.8)	3.8 (1.6 to 7.7)	14.5 (8.3 to 21.3)
≥65 yr	382	16.2 (11.3 to 22.2)	4.7 (2.2 to 8.8)	11.5 (5.6 to 17.9)
Sex				
Male	530	19.4 (14.7 to 24.9)	4.7 (2.5 to 7.9)	14.8 (9.5 to 20.5)
Female	210	12.3 (6.9 to 19.7)	3.1 (0.6 to 8.9)	9.2 (2.0 to 16.9)
ECOG performance-status score				
0	506	16.7 (12.3 to 21.9)	5.1 (2.7 to 8.6)	11.6 (6.4 to 17.3)
1	234	18.3 (11.7 to 26.5)	2.5 (0.5 to 7.2)	15.7 (8.6 to 24.1)
Race				
Asian	307	18.2 (12.2 to 25.5)	4.3 (1.7 to 8.6)	13.9 (7.2 to 21.5)
Non-Asian	433	16.6 (12.0 to 22.1)	4.3 (2.0 to 8.0)	12.3 (6.8 to 18.2)
Geographic region				
Asia	305	18.3 (12.3 to 25.7)	4.3 (1.7 to 8.6)	14.0 (7.2 to 21.7)
Europe	281	19.9 (13.6 to 27.4)	5.0 (2.0 to 10.0)	14.9 (7.5 to 22.8)
North America	86	14.0 (5.3 to 27.9)	2.3 (0.1 to 12.3)	11.6 (0.0 to 25.4)
South America	68	7.5 (1.6 to 20.4)	3.6 (0.1 to 18.3)	3.9 (–11.2 to 17.1)
Smoking status				
Current smoker	190	24.2 (16.0 to 34.1)	4.2 (1.2 to 10.4)	20.0 (10.7 to 30.1)
Former smoker	443	17.3 (12.5 to 22.9)	5.4 (2.8 to 9.2)	11.9 (6.2 to 18.0)
Never smoked	107	3.9 (0.5 to 13.5)	0.0 (0.0 to 6.4)	3.9 (–2.7 to 13.3)
Histology				
Squamous	360	21.3 (15.4 to 28.3)	5.2 (2.5 to 9.4)	16.1 (9.3 to 23.4)
Nonsquamous	375	13.3 (8.9 to 18.8)	3.4 (1.2 to 7.2)	9.9 (4.6 to 15.8)
Disease stage				
II	214	21.2 (13.8 to 30.3)	4.5 (1.5 to 10.3)	16.6 (8.1 to 26.0)
IIIA	338	18.5 (13.0 to 25.1)	4.8 (2.1 to 9.3)	13.6 (7.1 to 20.7)
IIIB	186	10.2 (4.8 to 18.5)	3.1 (0.6 to 8.7)	7.2 (0.1 to 15.7)
Lymph node station				
N2 single	273	18.4 (12.4 to 25.8)	4.5 (1.7 to 9.6)	13.9 (6.6 to 21.7)
N2 multi	74	8.8 (1.9 to 23.7)	5.0 (0.6 to 16.9)	3.8 (–9.2 to 18.8)
PD-L1 expression at baseline				
Tumor cell <1%	247	9.0 (4.6 to 15.6)	3.2 (0.9 to 8.0)	5.8 (–0.2 to 12.7)
Tumor cell 1–49%	277	16.3 (10.5 to 23.6)	4.9 (2.0 to 9.9)	11.4 (4.3 to 19.1)
Tumor cell ≥50%	216	27.5 (19.4 to 36.9)	4.7 (1.5 to 10.6)	22.9 (13.7 to 32.5)
Planned neoadjuvant platinum agent				
Cisplatin	196	12.0 (6.4 to 20.0)	2.1 (0.3 to 7.3)	9.9 (3.1 to 18.0)
Carboplatin	544	19.2 (14.6 to 24.4)	5.0 (2.8 to 8.3)	14.1 (8.9 to 19.8)
EGFR-mutation positive	51	3.8 (0.1 to 19.6)	0.0 (0.0 to 13.7)	3.8 (–10.0 to 19.1)

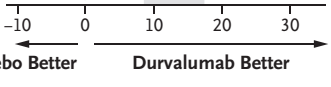


Figure 2 (facing page). Pathological Response in the Modified Intention-to-Treat Population.

Shown are the results of analyses of data from 740 patients as of the data-cutoff date of November 10, 2022. Pathological response was assessed by central review with the use of recommendations from the International Association for the Study of Lung Cancer (2020).[38] Pathological complete response (Panel A) was defined as a lack of viable tumor cells after complete evaluation of the resected lung-cancer specimen and all sampled regional lymph nodes. Major pathological response (Panel B) was defined as 10% or less of viable tumor cells in the lung primary tumor after complete evaluation of the resected lung-cancer specimen. Patients were considered to have had no response if they were not eligible for assessment (including those with R2 resection margins by local assessment) or if a surgical specimen was not available. Pathological complete response in prespecified baseline subgroups is shown in a forest plot (Panel C); all are subgroups of the modified intention-to-treat population except the *EGFR*-mutation–positive subgroup, which is a subgroup of the intention-to-treat population. The size of the data point is proportional to the number of events in each subgroup. Shading indicates the hazard ratio and 95% confidence interval for the modified intention-to-treat population. Disease stage was defined according to the eighth edition of the *AJCC Cancer Staging Manual*.

smoking-status subgroups, the greatest benefit was in current and former smokers, a finding consistent with the results of other immunotherapy trials.[39] Although improvements in event-free survival and pathological complete response were greater among patients who received durvalumab, the magnitude of benefit varied, with patients with stage II disease having a relatively larger benefit with regard to pathological complete response and patients with stage IIIA disease (the largest subgroup) having a relatively larger benefit with regard to event-free survival.

Our trial was designed and began enrollment before approval of adjuvant osimertinib for patients with *EGFR*-mutated resectable NSCLC. The results of the phase 3 ADAURA trial were published during the period in which AEGEAN was enrolling patients and established a new treatment standard for patients with *EGFR*-mutated disease.[40] In light of this new standard as well as emerging data from external trials that suggest patients with *EGFR* or *ALK* alterations have a limited response to immunotherapy,[41] the AEGEAN protocol was amended to exclude these patients from further enrollment and from efficacy analyses in the modified intention-to-treat population. No clear evidence of benefit with perioperative durvalumab was noted in the subgroup of patients with documented *EGFR* mutations who were enrolled before this amendment, although this subgroup analysis had limited statistical power given the small patient numbers.

The use of perioperative durvalumab plus neoadjuvant chemotherapy in the AEGEAN trial was associated with a safety profile that was consistent with the known profiles of durvalumab and chemotherapy. The incidence of maximum grade 3 or 4 adverse events of any cause was similar in the two groups, occurring in 42.4% of patients who received durvalumab and 43.2% of those who received placebo. Adverse events that were possibly related to a trial treatment or to placebo that resulted in death were rare in both groups. As expected, immune-mediated adverse events were more common in the durvalumab group than in the placebo group (23.7% vs. 9.3%); however, most immune-mediated adverse events were grade 1 or 2. Also, although differences in the populations and designs of the AEGEAN and PACIFIC trials confound cross-trial comparisons (particularly the use of chemoradiotherapy in the PACIFIC trial), it is notable that the incidence of any-grade and grade 3 or 4 immune-mediated adverse events was similar in the two trials.[29]

With regard to resectable NSCLC, findings from the AEGEAN trial and other recent trials (i.e., CheckMate-816, IMpower010, KEYNOTE-091, Neotorch, and KEYNOTE-671)[18-20,25,26] have confirmed the benefits of immunotherapy given as neoadjuvant treatment in combination with chemotherapy, as adjuvant treatment, or both. However, differences in trial design and patient populations confound cross-trial comparisons. Results from the AEGEAN trial and other trials[24-26] reinforce the importance of perioperative treatment approaches that combine the benefits of neoadjuvant and adjuvant immunotherapy, priming antitumor immunity while the primary tumor and lymph nodes are present, and eradicating residual micrometastases before and after surgery.[27] Although the relative contributions of the neoadjuvant and adjuvant immunotherapy components cannot be directly determined from the current trial, cross-trial comparisons in all-comer

Table 3. Summary of Adverse Events in the Safety Analysis Set.*

Event	Durvalumab Group (N = 401)	Placebo Group (N = 398)
	no. of patients (%)	
Adverse events of any grade and any cause	387 (96.5)	377 (94.7)
Maximum grade 3 or 4	170 (42.4)	172 (43.2)
Serious adverse events	151 (37.7)	125 (31.4)
Events leading to death	23 (5.7)	15 (3.8)
Leading to discontinuation of durvalumab or placebo	48 (12.0)	24 (6.0)
Leading to cancellation of surgery	7 (1.7)	4 (1.0)
Adverse events of any grade possibly related to durvalumab, placebo, or chemotherapy	348 (86.8)	321 (80.7)
Maximum grade 3 or 4	130 (32.4)	131 (32.9)
Events leading to death†	7 (1.7)	2 (0.5)

* The safety analysis set includes all patients who underwent randomization and received at least one dose of trial treatment or placebo; one patient assigned to the placebo group erroneously received a single cycle of durvalumab (in the adjuvant phase) and was included in the durvalumab group for the safety analysis set. Safety data is shown for the overall trial period, which spans the time from the first dose of any trial treatment or placebo until the earliest of the last dose of any trial treatment or placebo or surgery plus 90 days, the data-cutoff date, or the date of the first dose of subsequent anticancer treatment.

† Adverse events with an outcome of death included deaths assessed by the investigator as possibly related to any systemic trial treatment and include interstitial lung disease (in two patients) and immune-mediated lung disease, pneumonitis, hemoptysis, myocarditis, and decreased appetite (one patient each) in the durvalumab group and pneumonia and infection (one patient each) in the placebo group.

PD-L1 populations suggest that regimens that included a neoadjuvant immunotherapy component (both neoadjuvant-only and perioperative immunotherapy)[18,25,26] appear to confer benefit that is at least similar to, if not greater than, that with adjuvant immunotherapy alone.[19,20] Future trials may focus on comparing and tailoring these different approaches (i.e., neoadjuvant vs. adjuvant vs. perioperative immunotherapy).

Findings from the AEGEAN trial show a clear clinical benefit with perioperative immunotherapy in patients with resectable NSCLC. On the basis of the current findings, perioperative durvalumab plus neoadjuvant chemotherapy should be considered as a potential new treatment option for patients with resectable NSCLC.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Supplementary Appendix

Supplement to: Heymach JV, Harpole D, Mitsudomi T, et al. Perioperative durvalumab for resectable non–small-cell lung cancer. N Engl J Med. DOI: 10.1056/NEJMoa2304875

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

Table of contents

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Supplementary Methods

Trial Oversight

The study was designed by the sponsor (AstraZeneca). All patients provided written informed consent for participation, and an independent data monitoring committee (IDMC) monitored efficacy and safety. Specifically, the IDMC performed an early safety evaluation when ~40 patients across both arms had undergone surgery with at least 21 days of follow-up. The IDMC then met regularly at approximately 6-month intervals, until all patients had the opportunity to undergo surgery, with at least 6 months follow-up for those who had surgery, to review safety in an unblinded manner. The IDMC also reviewed the efficacy results at the interim analyses to advise if the primary and key secondary endpoints had met statistical significance. The study protocol and all amendments were approved by the relevant ethics committees/institutional review boards, and the study was performed in accordance with the Declaration of Helsinki, the International Conference for Harmonization Good Clinical Practice Guidelines, and all applicable laws and regulations. All the investigators (listed above) were responsible for the collection of data. Data analyses were completed and vouched for by the sponsor. All the authors participated in writing the manuscript and provided approval to submit the manuscript for publication. Medical writing support, including development of the initial draft of the manuscript, was funded by the sponsor.

Permitted Chemotherapy Regimens

The choice of platinum-based chemotherapy regimen was determined by tumor histology and at the investigator's discretion. For patients with squamous tumor histology, the options were carboplatin AUC 6 plus paclitaxel 200 mg/m2 on Day 1 of each 3-week cycle for 4 cycles or cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Day 1 and Day 8 of each 3-week cycle for 4 cycles (or carboplatin plus gemcitabine for patients who had comorbidities or who are unable to tolerate cisplatin per the investigator's judgment); for patients with non-squamous tumor histology, the

options were pemetrexed 500 mg/m^2 plus either cisplatin 75 mg/m^2 or carboplatin AUC 5 on Day 1 of each 3-week cycle for 4 cycles.

Tumor Imaging

Tumors were evaluated per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) using imaging collected at the following timepoints: baseline (≤28 days before randomization); after completing neoadjuvant treatment and before surgery; 5 weeks (±2 weeks) after surgery and before starting adjuvant treatment; every 12 weeks (±1 week) until Week 48 after surgery; every 24 weeks (±2 weeks) until Week 192 (i.e., ~4 years post-surgery); and every 48 weeks (±2 weeks) thereafter until local/distant recurrence, consent withdrawal, or death.

Statistical Analysis

AEGEAN was to be considered positive if either of the two primary endpoints, event-free survival or pathological complete response (pCR), was significantly improved in the durvalumab arm versus the placebo arm. We planned to randomize approximately 800 eligible patients to the intent-to-treat (ITT) population (Figure S1), including 740 patients in the modified ITT (mITT) population, which excluded patients with documented *EGFR* or *ALK* aberrations. Efficacy analyses were performed on the mITT population. Safety was assessed in all randomized patients who received at least one dose of study treatment (safety analysis set).

An interim analysis of pCR was scheduled to occur once (1) approximately 400 patients in the mITT population had approximately 7 months follow-up to allow time for surgery to occur, where applicable, and have complete central pathology assessment for pCR (inclusive of patients not eligible for surgery), and (2) approximately 800 patients had been randomized to the ITT population. The final analysis of pCR was scheduled to occur once all patients in the ITT population had the opportunity to undergo surgery (i.e., had ~7 months follow-up) and complete central pathology

assessment. The first interim analysis of event-free survival was scheduled to occur at approximately 30% maturity for this endpoint (~224 events) in the mITT population; this ultimately coincided with the final analysis of pCR (data cut-off, November 10, 2022).

To strongly control the type I error at 5% (two-sided), a hierarchical multiple testing procedure with gatekeeping strategy was used across the primary endpoints and alpha-controlled secondary endpoints (Figure S2 and Table S1). Initially, 0.5% alpha and 4.5% alpha were allocated to pCR and event-free survival, respectively. The alpha was split between the interim and final analyses (IA and FA, respectively) using the Lan-DeMets spending function that approximates an O'Brien Fleming approach to account for multiple time point assessments.[2] Positivity for pCR enabled alpha recycling to the key secondary endpoint MPR, which in turn could be recycled to event-free survival (to provide a total 5% alpha). Based on a total of 0.5% alpha allocated to the pCR endpoint, the planned IA of pCR (assuming 400 patients in the modified intent-to-treat [mITT] population at the IA, 740 patients in the mITT population at the FA) had 55% power to detect a between-arm difference of 12% with a two-sided significance level of 0.008%; MPR (an alpha-controlled secondary endpoint) was also formally analyzed at the IA. For event-free survival, a 33-month nonlinear (k=2) accrual was assumed with a 3-month delay in hazard, whereby the assumed hazard ratio for the first 3 months was 1.0 and a hazard ratio of 0.63 was assumed after 3 months to give an approximate overall hazard ratio of 0.67 at the time of the FA. Based on a total of 4.5% alpha allocated to the event-free survival endpoint, for the first interim analysis of event-free survival (reported here), if the true overall hazard ratio is 0.69, with 224 event-free survival events (per blinded independent central review) in the mITT population (N=740) the study would provide 50% power to demonstrate an event-free survival effect with a two-sided significance level of 0.665%. Since pCR and MPR were statistically significant, event-free survival was tested with a total 5% alpha allocated. The actual significance level was calculated based on the observed number of patients or events at the interim

analysis compared with the planned number of patients or events at the final analysis for each endpoint, respectively.

For pathological endpoints, response rates were compared between treatment arms using a stratified Cochran-Mantel-Haenszel test; the treatment effect was estimated by the differences in response rates, with their corresponding 95% confidence intervals (CIs) calculated by the stratified Miettinen and Nurminen method. Event-free survival was compared between the treatment arms using a stratified log-rank test; the treatment effect was estimated by hazard ratios and 95% CIs calculated with stratified Cox-proportional-hazards models. Medians and landmark rates for event-free survival were estimated using the Kaplan–Meier method. Stratification for the primary and key secondary endpoints was by disease stage and PD-L1 expression. Planned analyses of the primary endpoints in predefined baseline subgroups were performed. For pCR, the differences in response rates were calculated for each subgroup, with corresponding 95% CIs estimated using an unstratified Miettinen and Nurminen method; for event-free survival, hazard ratios and 95% CIs were calculated for each subgroup using a Cox-proportional-hazards model with treatment as the only covariate.

Figure S1. Study Design.

*The protocol was amended while enrollment was ongoing to exclude (1) patients with tumors classified as T4 for any reason other than size; (2) patients with planned pneumonectomies (in addition to the exclusion of patients with planned segmentectomies or wedge resections); and (3) patients with a documented test result confirming the presence of an *EGFR* mutation or *ALK* translocation. †Determined using the Ventana PD-L1 (SP263) immunohistochemistry assay. ‡Choice of chemotherapy regimen was determined by histology and at the investigator's discretion; for patients with squamous histology, the options were carboplatin AUC 6 plus paclitaxel 200 mg/m^2 on Day 1 of each 3-week cycle for 4 cycles or cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Day 1 and Day 8 of each 3-week cycle for 4 cycles (or carboplatin plus gemcitabine for patients who had comorbidities or who are unable to tolerate cisplatin per the investigator's judgment); for patients with non-squamous histology, the options were pemetrexed 500 mg/m^2 plus either cisplatin 75 mg/m^2 or carboplatin AUC 5 on Day 1 of each 3-week cycle for 4 cycles. §Surgery was expected within 40 days of the last dose of neoadjuvant treatment; PORT was permitted, if indicated, according to local guidance, and had to start within 8 weeks of surgery. Adjuvant treatment was expected to commence as soon as clinically feasible and within 10 weeks from surgery (or within 3 weeks of completing PORT). ¶All efficacy analyses reported here were performed on the mITT population, which includes all randomized patients who did not have documented *EGFR* or *ALK* aberrations. AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; DFS, disease-free survival; EFS, event-free survival; IASLC, International Association for the Study of Lung Cancer; MPR, major pathological response; NSCLC, non-small-cell lung cancer; OS, overall survival; pCR, pathological complete response; PD-L1, programmed cell death-ligand 1; PORT, post-operative radiotherapy; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

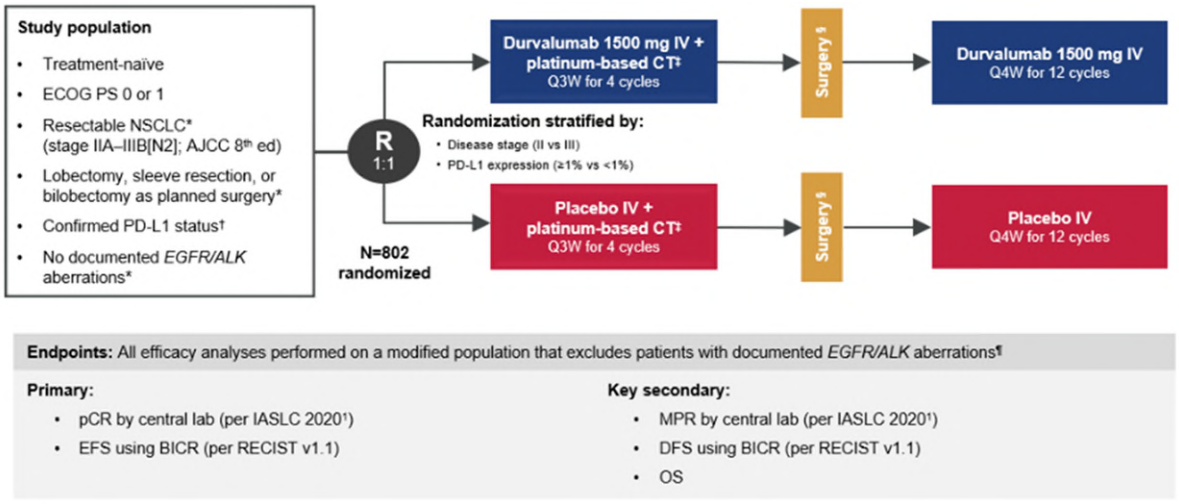


Figure S2. Multiple Testing Procedure and Alpha Recycling.

DFS, disease-free survival; EFS, event-free survival; MPR, major pathological response; OS, overall survival; pCR, pathological complete response.

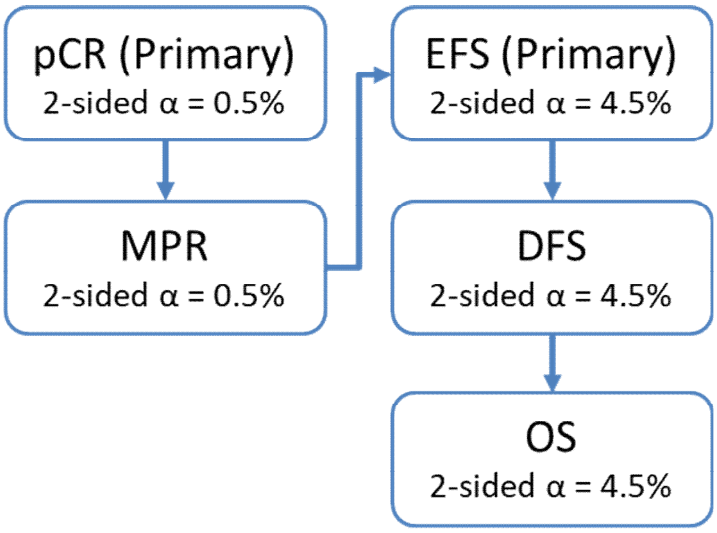


Table S1. Planned Interim and Final Analyses for Primary Endpoints.

Endpoint	Timepoint	No. of patients (information fraction)
pCR	IA	N=400 (54%)
	Final	N=740 (100%)
Endpoint	**Timepoint**	**Maturity of events (information fraction)**
Event-free survival	IA1	~30% maturity (60%)
	IA2	~40% maturity (80%)
	Final	~50% maturity (100%)

Analyses for MPR will be performed at the planned pCR interim and final analyses. As per multiple testing procedure, MPR is only tested if pCR is successful. Analyses of disease-free survival and overall survival will be performed at the planned interim and final analyses for event-free survival. As per multiple testing procedure, disease-free survival is only tested if event-free survival is successful; overall survival is only tested if event-free survival and disease-free survival are successful. IA, interim analysis; MPR, major pathological response; ND, not disclosed; pCR, pathological complete response.

Supplementary Results

Figure S3. CONSORT Flow Diagram.

*Signed informed consent received. †One patient assigned to the placebo arm erroneously received a single cycle of durvalumab (in the adjuvant phase); this patient is included in the placebo arm for the ITT/mITT populations, and in the durvalumab arm for the safety analysis set. ‡The mITT population comprises the ITT population minus patients with documented *EGFR* (durvalumab arm, n=26; placebo arm, n=25) or *ALK* (durvalumab arm, n=8; placebo arm, n=3) aberrations. §The safety analysis set includes all randomized patients who received at least one dose of any study Tx. AE, adverse event; CT, computerized tomography; DCO, data cut-off; MDT, multidisciplinary team; (m)ITT, (modified) intent-to-treat; PD, progressive disease; PET, positron emission tomography; Tx, treatment.

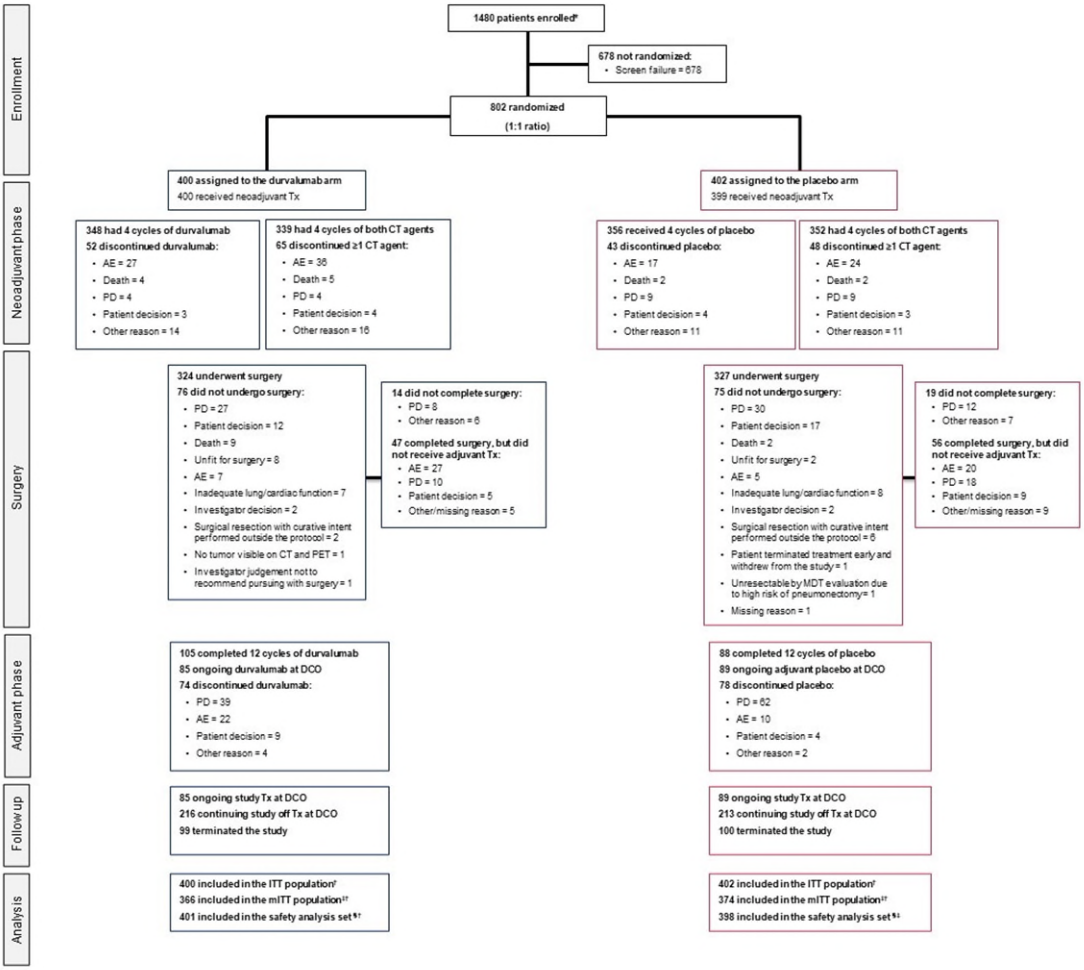


Figure S4. Event-free Survival According to Blinded Independent Central Review by Planned Neoadjuvant Platinum Agent in the Modified Intent-to-treat Population (Predefined Subgroup Analysis).

Data cut-off of November 10, 2022 (N=740). Panel A shows EFS among the subgroup of patients with planned cisplatin-based chemotherapy, and Panel B shows EFS among the subgroup of patients with planned carboplatin-based chemotherapy (at study baseline). EFS was defined as the time from randomization to the earliest of: progressive disease that precludes surgery; progressive disease discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; local or distant recurrence using blinded independent central review according to Response Evaluation Criteria in Solid Tumors version 1.1; or death from any cause. CI, confidence interval; D, durvalumab; EFS, event-free survival; HR, hazard ratio; mEFS, median EFS; PBO, placebo.

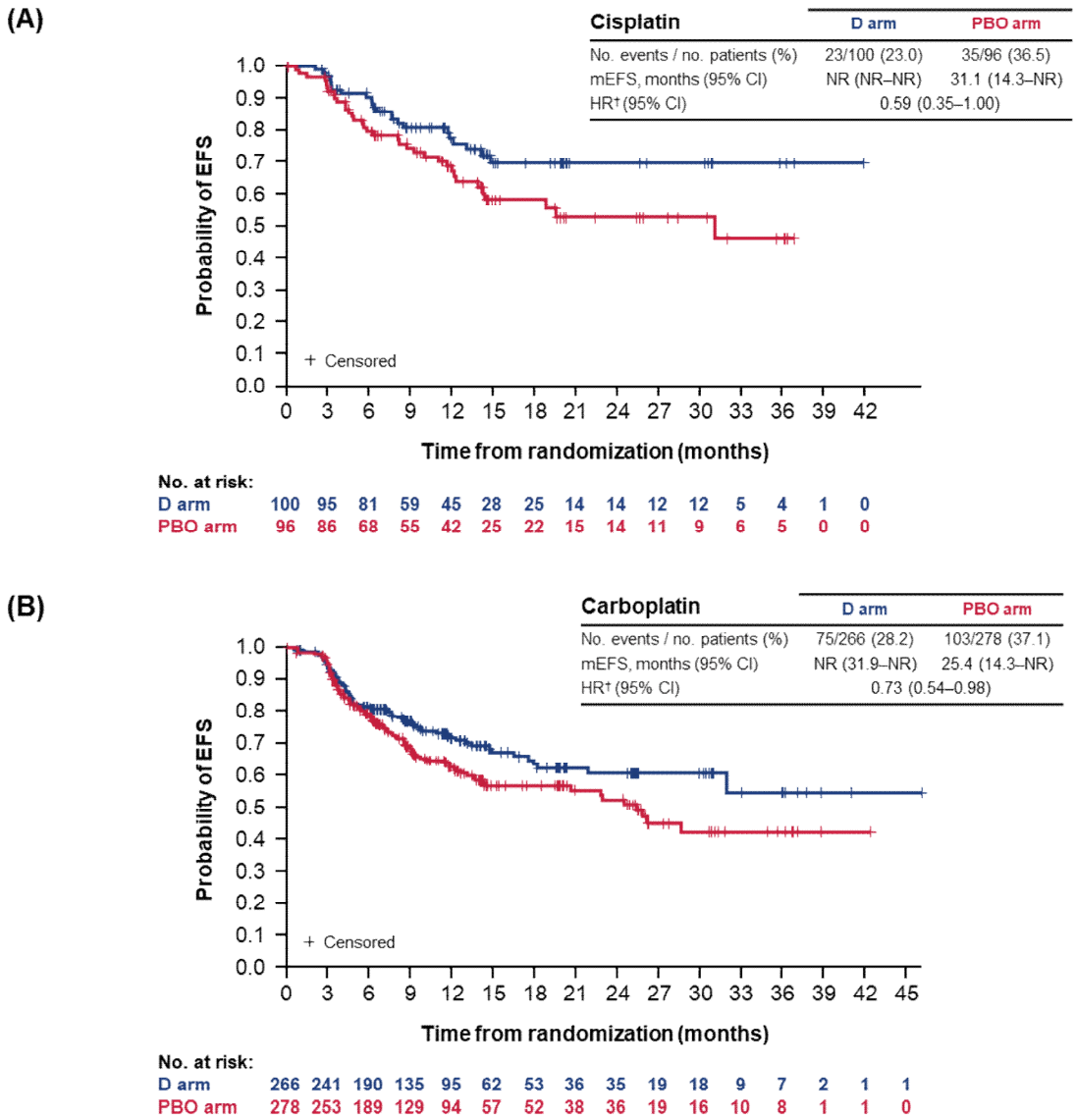


Figure S5. Event-free Survival According to Blinded Independent Central Review by Disease Stage in the Modified Intent-to-treat Population (Predefined Subgroup Analysis).

Data cut-off of November 10, 2022 (N=740). Panel A shows EFS among the subgroup of patients with stage II disease, and Panel B shows EFS among the subgroup of patients with stage III disease (at study baseline). EFS was defined as the time from randomization to the earliest of: progressive disease that precludes surgery; progressive disease discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; local or distant recurrence using blinded independent central review according to Response Evaluation Criteria in Solid Tumors version 1.1; or death from any cause. CI, confidence interval; D, durvalumab; EFS, event-free survival; HR, hazard ratio; mEFS, median EFS; PBO, placebo.

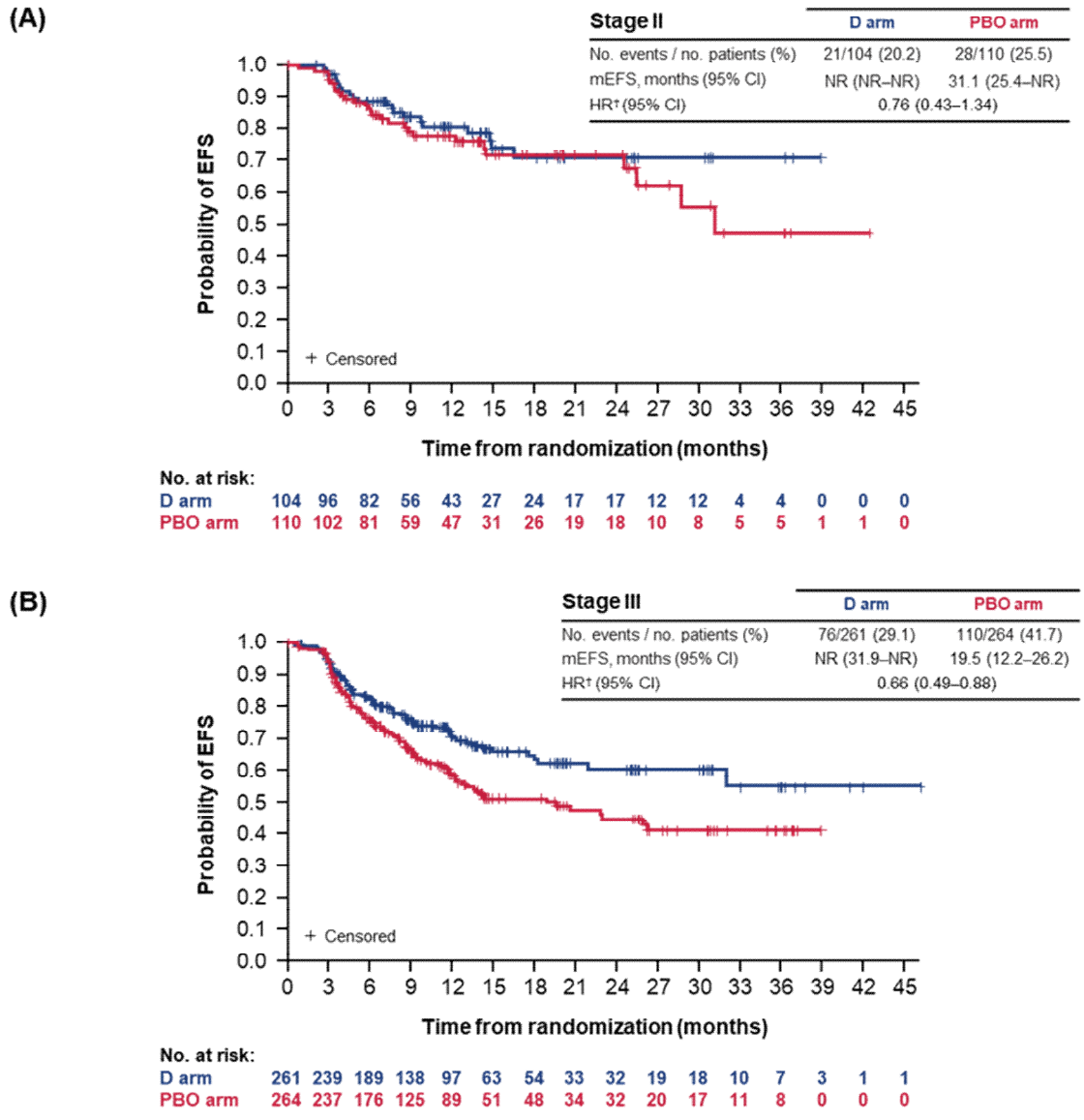


Figure S6. Event-free Survival According to Blinded Independent Central Review by PD-L1 Tumor Cell Expression in the Modified Intent-to-treat Population (Predefined Subgroup Analysis).

Data cut-off of November 10, 2022 (N=740). Panel A shows EFS among the subgroup of patients with PD-L1 tumor cell expression <1%, Panel B shows EFS among the subgroup of patients with PD-L1 tumor cell expression 1–49%, and Panel C shows EFS among patients with PD-L1 tumor cell expression ≥50% (at study baseline). PD-L1 expression level was determined using the Ventana PD-L1 (SP263) immunohistochemistry assay. EFS was defined as the time from randomization to the earliest of: progressive disease that precludes surgery; progressive disease discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; local or distant recurrence using blinded independent central review according to Response Evaluation Criteria in Solid Tumors version 1.1; or death from any cause. CI, confidence interval; D, durvalumab; EFS, event-free survival; HR, hazard ratio; mEFS, median EFS; PBO, placebo; PD-L1, programmed cell death-ligand-1; TC, tumor cell.

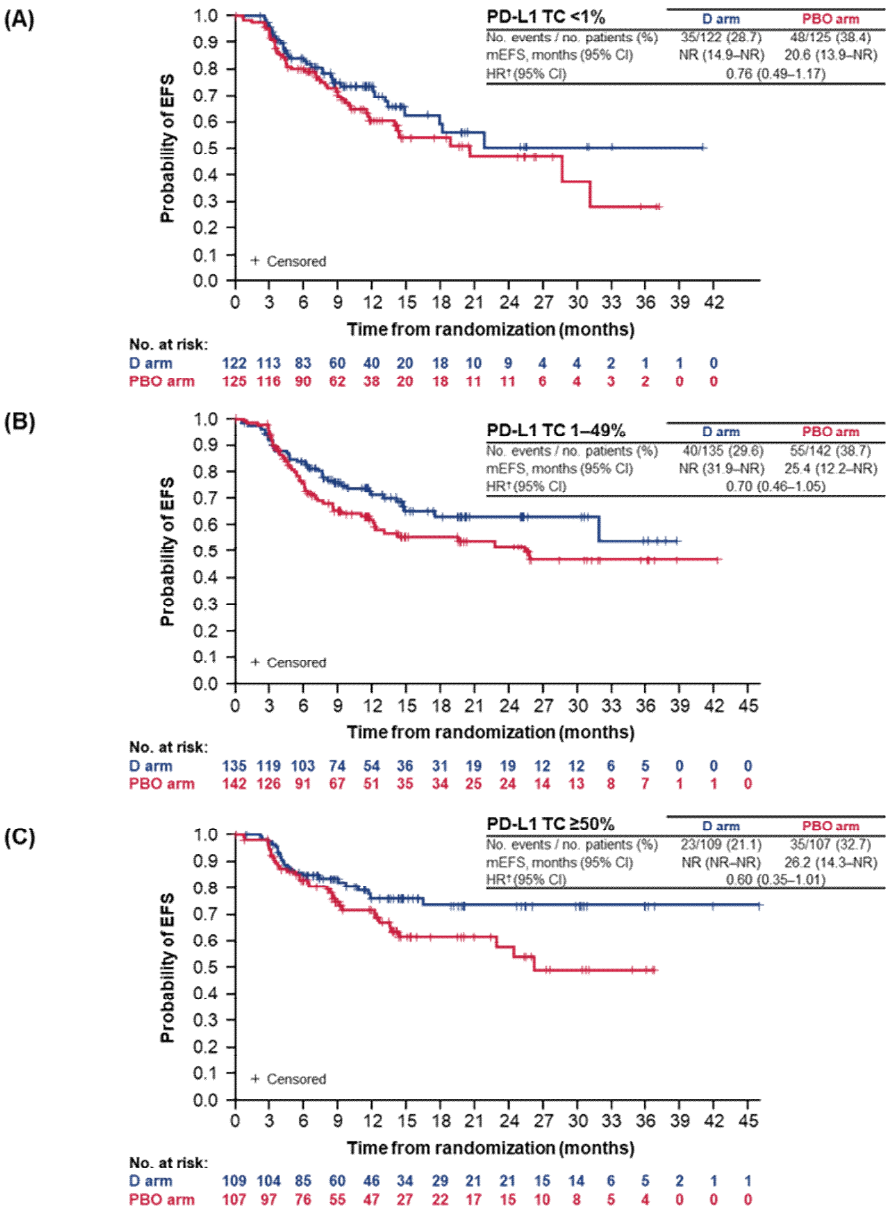


Figure S7. Event-free Survival According to Blinded Independent Central Review by Tumor Histology in the Modified Intent-to-treat Population (Predefined Subgroup Analysis).

Data cut-off of November 10, 2022 (N=740). Panel A shows EFS among the subgroup of patients with squamous tumor histology, and Panel B shows EFS among the subgroup of patients with non-squamous tumor histology (at study baseline). EFS was defined as the time from randomization to the earliest of: progressive disease that precludes surgery; progressive disease discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; local or distant recurrence using blinded independent central review according to Response Evaluation Criteria in Solid Tumors version 1.1; or death from any cause. CI, confidence interval; D, durvalumab; EFS, event-free survival; HR, hazard ratio; mEFS, median EFS; PBO, placebo.

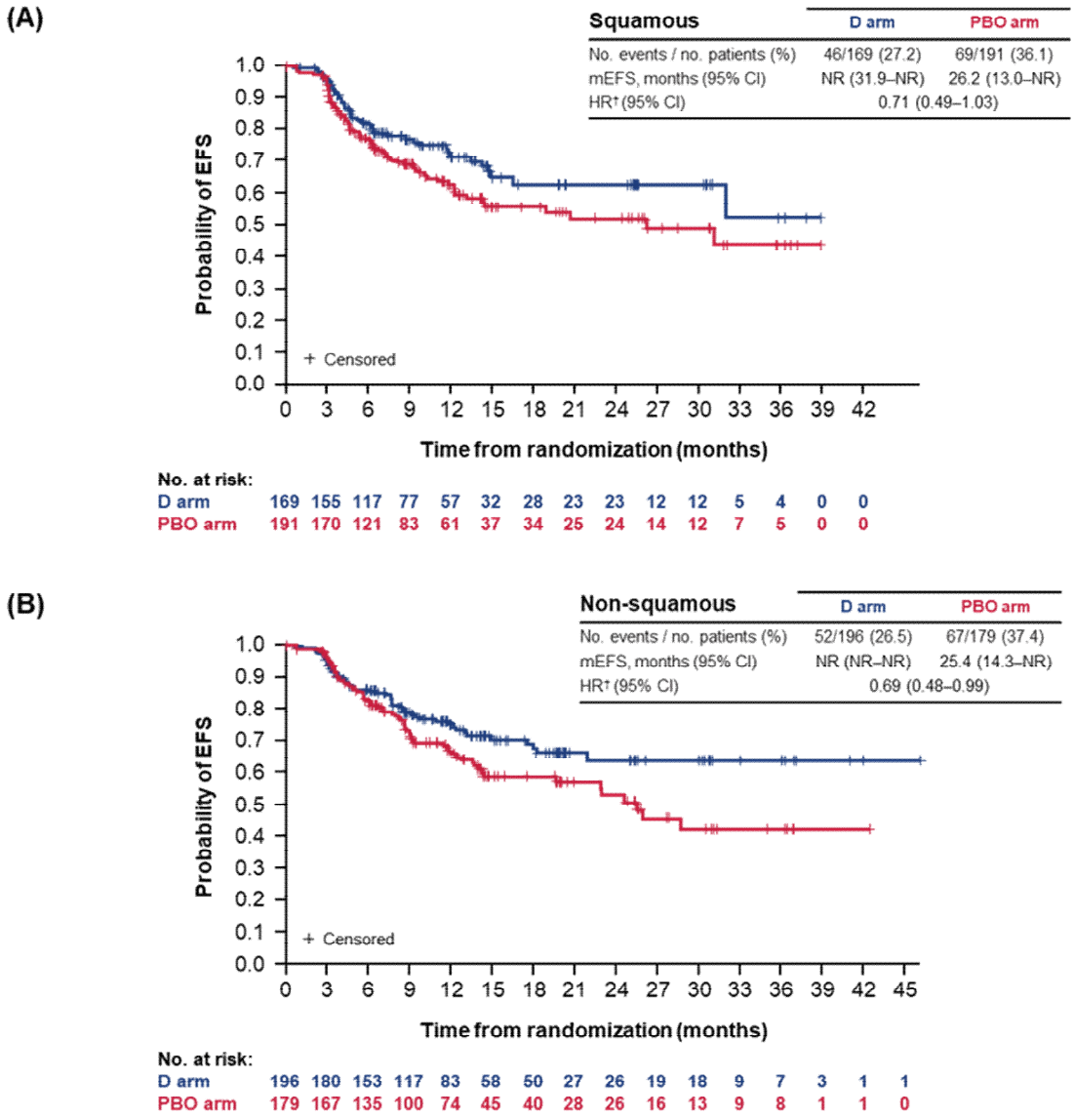


Figure S8. Interim Analyses of Pathological Response According to Central Review in the Modified Intent-to-treat Population.

Data cut-off of January 14, 2022 (n=402). Panel A shows pCR and Panel B shows MPR in the pCR interim analysis cohort (the first ~400 patients in the mITT population who had the opportunity to undergo surgery and complete central pathology assessment for pCR [inclusive of patients not eligible for surgery]). Pathological response was assessed using recommendations from the International Association for the Study of Lung Cancer (2020).[1] pCR was defined as a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes. MPR was defined as ≤10% of viable tumor cells in the lung primary tumor after complete evaluation of the resected lung cancer specimen. Patients were classified as non-responders if they were not eligible for assessment (including those with R2 resection margins by local assessment) or they did not have a surgical specimen. The P-values were calculated using a stratified Cochran-Mantel-Haenszel test with a significance boundary <0.001 calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary. CI, confidence interval; D, durvalumab; MPR, major pathological response; PBO, placebo; pCR, pathological complete response.

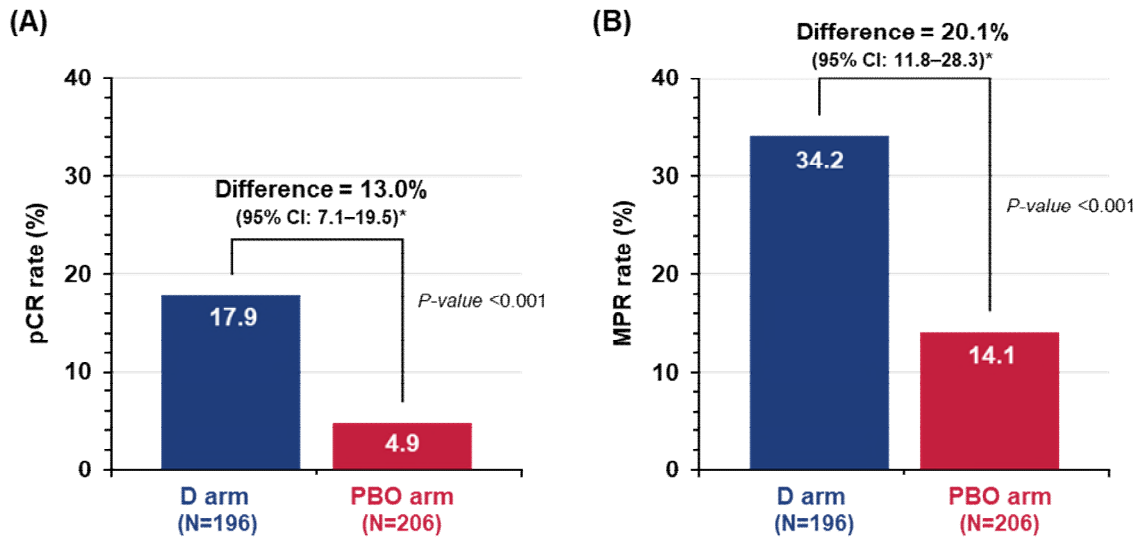


Figure S9. Subgroup Analysis of Major Pathological Response According to Central Review in the Modified Intent-to-treat Population.

Data cut-off of November 10, 2022 (N=740). The figure shows a forest plot of MPR in predefined baseline subgroups (in which the size of the circles is proportional to number of patients for each subgroup, and the horizontal bars represent the 95% confidence intervals). Pathological response was assessed using recommendations from the International Association for the Study of Lung Cancer (2020).[1] MPR was defined as ≤10% of viable tumor cells in the lung primary tumor after complete evaluation of the resected lung cancer specimen. Patients were classified as non-responders if they were not eligible for assessment (including those with R2 resection margins by local assessment) or they did not have a surgical specimen. *Race was self-reported per the electronic case report form. †Determined using the Ventana PD-L1 (SP263) immunohistochemistry assay. AJCC, American Joint Committee on Cancer; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; MPR, major pathological response; PBO, placebo; PD-L1, programmed cell death-ligand 1; TC, tumor cell.

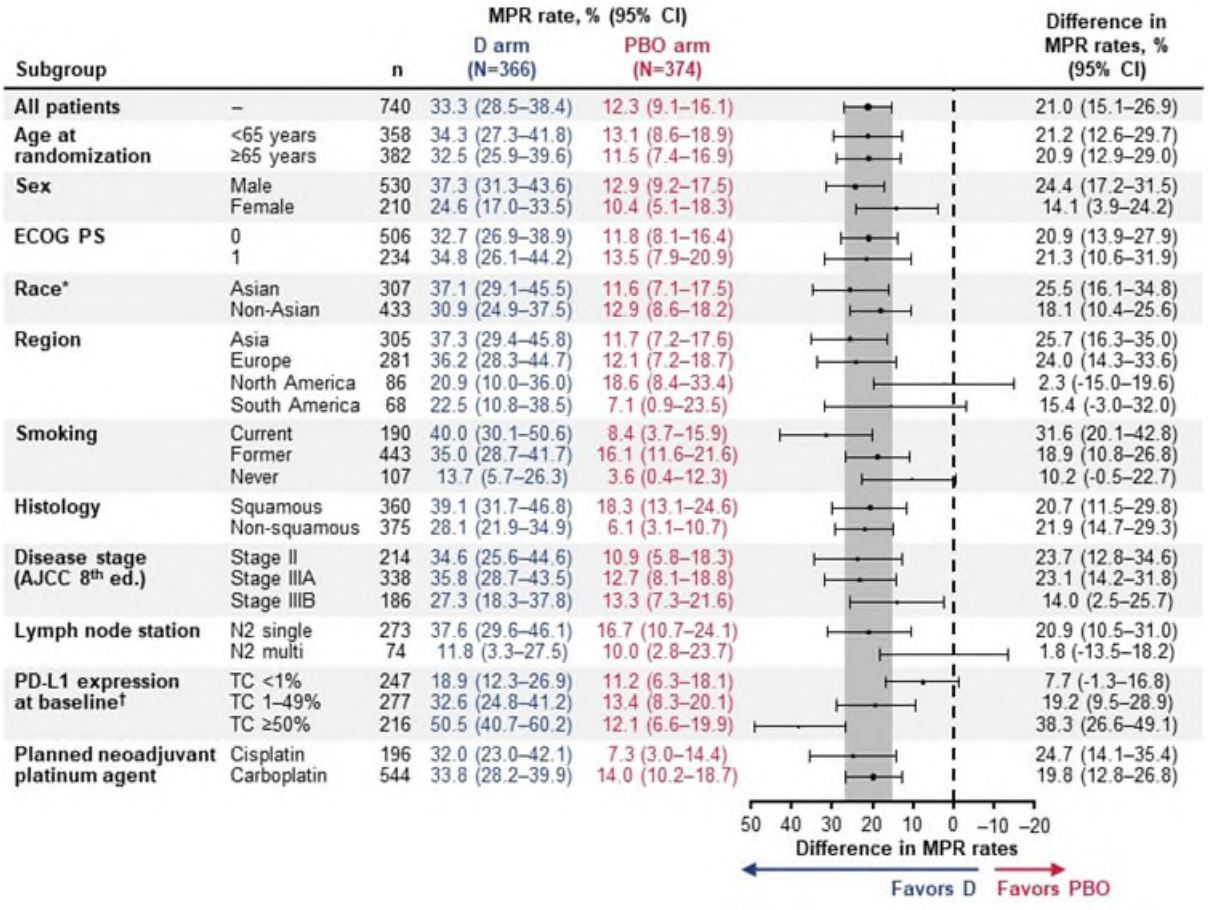


Figure S10. Pathological Regression in the Modified Intent-to-treat Population.

Data cut-off of November 10, 2022 (N=740). Pathological regression is summarized based on patients with evaluable % RVT (and specifically defined as % viable tumor cells minus 100%). The waterfall plots show pathological regression of the primary tumor in the durvalumab arm (left panel) and placebo arm (right panel). *Indicates patients with evidence of carcinoma present in any examined lymph nodes or whose lymph nodes are not evaluable. Pathological response was assessed using recommendations from the International Association for the Study of Lung Cancer (2020).[1] pCR was defined as a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes. MPR was defined as ≤10% of viable tumor cells in the lung primary tumor after complete evaluation of the resected lung cancer specimen. †Patients with no viable tumor cells in the primary tumor, but with evidence of carcinoma present in examined lymph nodes, or whose lymph nodes are not evaluable, are classified as responders for MPR and non-responders for pCR, in accordance with the definitions of these endpoints. MPR, major pathological response; pCR, pathological complete response; RVT, residual viable tumor.

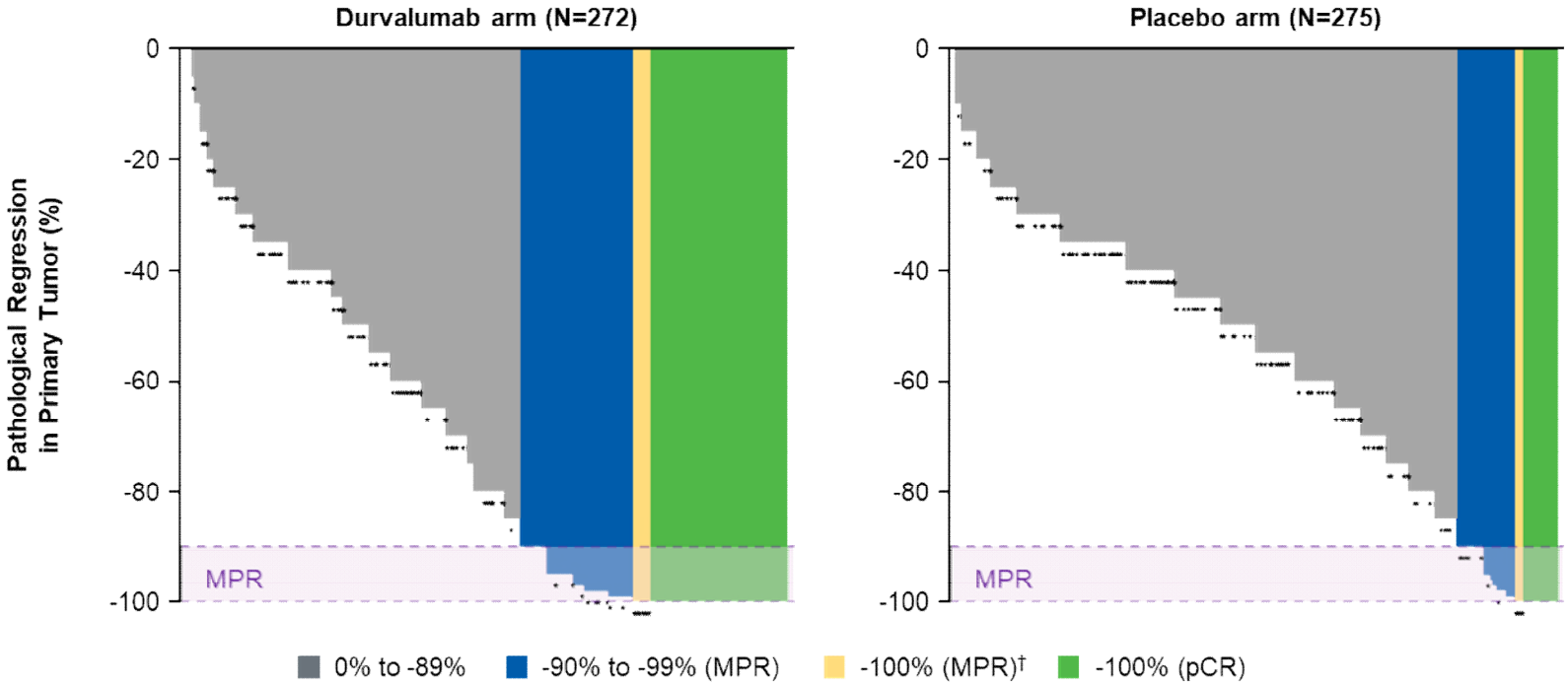


Table S2. Baseline Characteristics in the Intent-to-treat Population.

Characteristics*		Durvalumab arm (N=400)	Placebo arm (N=402)
Age	Median (range), years ≥75 years, n (%)	65.0 (30–88) 48 (12.0)	65.0 (39–85) 38 (9.5)
Sex, n (%)	Male Female	262 (65.5) 138 (34.5)	291 (72.4) 111 (27.6)
ECOG PS, n (%)	0 1	278 (69.5) 122 (30.5)	277 (68.9) 125 (31.1)
Race[†], n (%)	Asian White Other	165 (41.3) 216 (54.0) 19 (4.8)	187 (46.5) 196 (48.8) 19 (4.7)
Ethnicity, n (%)	Hispanic or Latino Not Hispanic or Latino	68 (17.0) 332 (83.0)	58 (14.4) 344 (85.6)
Region, n (%)	Asia Europe North America South America	164 (41.0) 147 (36.8) 47 (11.8) 42 (10.5)	186 (46.3) 144 (35.8) 44 (10.9) 28 (7.0)
Smoking status, n (%)	Current Former Never	96 (24.0) 232 (58.0) 72 (18.0)	97 (24.1) 231 (57.5) 74 (18.4)
Disease stage (AJCC 8th ed.)[£], n (%)	II IIIA IIIB	119 (29.8) 186 (46.5) 94 (23.5)	120 (29.9) 178 (44.3) 103 (25.6)
TNM classification[‡]: primary tumor, n (%)	T1 T2 T3 T4	53 (13.3) 108 (27.0) 141 (35.3) 98 (24.5)	48 (11.9) 119 (29.6) 136 (33.8) 99 (24.6)
TNM classification[‡]: regional lymph nodes, n (%)	N0 N1 N2 Single-station Multi-station	118 (29.5) 83 (20.8) 199 (49.8) 151 (37.8) 38 (9.5)	110 (27.4) 94 (23.4) 198 (49.3) 140 (34.8) 45 (11.2)
Histology, n (%)	Squamous Non-squamous	173 (43.3) 226 (56.5)	192 (47.8) 206 (51.2)
PD-L1 expression, n (%)	TC <1% TC 1–49% TC ≥50%	133 (33.3) 151 (37.8) 116 (29.0)	134 (33.3) 158 (39.3) 110 (27.4)
Patients excluded from the modified ITT population, n (%)	*EGFR* mutation detected *ALK* translocation detected	26 (6.5) 8 (2.0)	25 (6.2) 3 (0.7)

Data cut-off of November 10, 2022 (N=802). *Characteristics with missing or other responses were histology (0.3% in the durvalumab arm and 1.0% in the placebo arm had 'other' histology), disease stage (0.3% in the durvalumab arm had stage IV disease and 0.2% in the placebo arm had stage III [NOS] disease, as reported per the eCRF), and N2 lymph node station status (2.5% in the durvalumab arm and 3.2% in the placebo arm had N2 disease with missing data on single-station vs. multi-station classification). [†]Race was self-reported per the eCRF. [£]Patients with stage IIA to select (N2) stage IIIB disease according to the AJCC Cancer Staging Manual (version 8)[3]. [‡]All patients were M0 except one patient in the durvalumab arm who was classified as M1 (NOS). AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form; ITT, intent-to-treat; NOS, not otherwise specified; PD-L1, programmed cell death-ligand 1; TC, tumor cell; TNM, tumor, [lymph] nodes, metastasis.

Table S3. Representativeness of Study Participants.

Demographics	AEGEAN Study mITT, N=740	Observations
Age, median (range) **Age, mean ± SD**	65.0 (30–88) 64.0 ±8.8	• Patients with resectable NSCLC are on average approximately 65 years of age across geographies. The age of patients in the AEGEAN study was representative of a real-world population.
Sex Male Female	 71.6% 28.4%	• Globally, NSCLC affects more men than women. The gender balance in the AEGEAN study was representative of a real-world population.
ECOG performance status 0 1	 68.4% 31.6%	• Most patients diagnosed with NSCLC who are eligible for curative-intent surgery have good performance status, as reflected in the population enrolled in the AEGEAN study.
Smoking Status Current smoker/ Former smoker Never smoker	 85.5% 14.5%	• Lung cancer is strongly associated with smoking, with approximately 80% of patients having a history of smoking. This was also reflected in the AEGEAN study population.
Region Asia Europe North America South America	 41.2% 38.0% 11.6% 9.2%	• The race and ethnicity composition of the AEGEAN study is indicative of a large, global clinical trial that enrolled patients across 28 countries in Asia, Europe, North America, and South America; 16.1% of randomized patients were Hispanic/Latino and <1% of randomized patients were Black.
Race Asian White Black / African American Other	 41.5% 53.6% 0.9% 3.9%	
Ethnicity Hispanic/Latino Not Hispanic/Latino	 16.1% 83.9%	
Planned Neoadjuvant Platinum Backbone Carboplatin Cisplatin	 73.5% 26.5%	• In general clinical practice, many patients may have contraindications to cisplatin-based chemotherapy. The AEGEAN study allowed for flexibility in the choice of platinum agent, and as such is reflective of a real-world treatment regimen.

ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat; NSCLC, non-small-cell lung cancer; SD, standard deviation.

Table S4. Neoadjuvant Treatment Exposure in the Safety Analysis Set.*

	Durvalumab arm (N=401)	Placebo arm (N=398)
Patients receiving neoadjuvant treatment, n (%)	401 (100)	398 (100)
Type of SoC chemotherapy, n (%)		
Cisplatin + Gemcitabine	46 (11.5)	43 (10.8)
Cisplatin + Paclitaxel	0	1 (0.3)
Cisplatin + Pemetrexed	63 (15.7)	60 (15.1)
Carboplatin + Gemcitabine	11 (2.7)	9 (2.3)
Carboplatin + Paclitaxel	122 (30.7)	139 (34.9)
Carboplatin + Pemetrexed	158 (39.4)	146 (36.7)
Total duration of treatment (weeks):†		
Any SoC chemotherapy, median (range)	12.1 (2.0–20.7)	12.1 (3.0–22.7)
Durvalumab / placebo, median (range)	12.1 (2.0–19.0)	12.1 (3.0–22.7)

Data cut-off of November 10, 2022 (N=799). *The safety analysis set includes all randomized patients who received at least one dose of study treatment; one patient assigned to the placebo arm erroneously received a single cycle of durvalumab (in the adjuvant phase) and was included in the durvalumab arm for the safety analysis set. †Total duration of treatment is inclusive of the total duration of dose delays. SoC, standard of care.

Table S5. Summary of Reasons for Not Undergoing or Completing Surgery in the Intent-to-treat Population.*

	Durvalumab arm (N=400)	Placebo arm (N=402)
Patients who underwent surgery†, n (%)	324 (81.0)	327 (81.3)
Patients who did not undergo surgery†, n (%)	76 (19.0)	75 (18.7)
Disease progression	27 (6.8)	30 (7.5)
Unfit for surgery‡	15 (3.8)	10 (2.5)
Patient decision	12 (3.0)	17 (4.2)
Death	9 (2.3)	2 (0.5)
Adverse event	7 (1.8)	5 (1.2)
Surgical resection with curative intent performed outside of the protocol	2 (0.5)	6 (1.5)
Investigator decision	2 (0.5)	2 (0.5)
Other/missing	2 (0.5)	3 (0.7)
Patients who completed surgery†, n (%)	310 (77.5)	308 (76.6)
Patients who did not complete surgery†, n (%)	14 (3.5)	19 (4.7)
Disease progression	8 (2.0)	12 (3.0)
Patient not sufficiently fit to tolerate completion of surgery	1 (0.3)	1 (0.2)
Other	5 (1.3)	6 (1.5)

Data cut-off of Nov 10, 2022 (N=802). *The intent-to-treat population included all patients who were randomized. †As per the investigator's assessment. Patients who 'underwent' surgery were those for whom curative-intent thoracic surgery was attempted regardless of whether it was completed. Patients who 'completed' surgery were those for whom curative-intent thoracic surgery was completed (assessed by the investigator at the time of surgery). ‡Includes responses of 'unfit for surgery', inadequate lung function', and 'inadequate cardiac function'.

Table S6. Details of Surgical Delays in the Safety Analysis Set.*

Surgical detail	Durvalumab arm (N=401)	Placebo arm (N=398)
Patients with delayed surgery, n (%)	58 (14.5)	67 (16.8)
Reason for surgical delay, n (%)†		
Unresolved toxicity from neoadjuvant Tx	5 (1.2)	4 (1.0)
Durvalumab / Placebo	2 (0.5)	2 (0.5)
SoC	3 (0.7)	2 (0.5)
Logistical reasons	31 (7.7)	37 (9.3)
Adverse event	11 (2.7)	12 (3.0)
Other	14 (3.5)	13 (3.3)
Length of delay in surgery, n (%)		
<2 weeks	31 (7.7)	39 (9.8)
2 to <4 weeks	15 (3.7)	21 (5.3)
4 to <6 weeks	7 (1.7)	3 (0.8)
≥6 weeks	5 (1.2)	4 (1.0)

Data cut-off of November 10, 2022 (N=799). *The safety analysis set includes all randomized patients who received at least one dose of study treatment; one patient assigned to the placebo arm erroneously received a single cycle of durvalumab (in the adjuvant phase) and was included in the durvalumab arm for the safety analysis set. †A surgical delay is defined as surgery occurring more than 40 days after the last dose of study treatment in the neoadjuvant period. The length of delay is the time beyond the per-protocol window of 40 days after the last dose of study treatment to the date of surgery. Reasons for surgical delay are not mutually exclusive for patients with multiple reasons per delay or subjects with multiple delays (although a patient can only be counted once per category). SoC, standard of care; Tx, treatment.

Table S7. Details of Surgery and Surgical Outcomes in the Modified Intent-to-treat Population.*

Surgical detail	Durvalumab arm (N=366)	Placebo arm (N=374)
Patients who underwent surgery, n (%)	295 (80.6)	302 (80.7)
Patients who completed surgery, n (%)	284 (77.6)	287 (76.7)
Margins, n (%)†		
R0†	269 (94.7)	262 (91.3)
R1†	12 (4.2)	22 (7.7)
R2†	2 (0.7)	2 (0.7)
Missing†	1 (0.4)	1 (0.3)
Surgery procedure performed, n (%)		
Lobectomy	238 (65.0)	221 (59.1)
Sleeve resection	7 (1.9)	14 (3.7)
Bilobectomy	13 (3.6)	20 (5.3)
Pneumonectomy	27 (7.4)	29 (7.8)
Sleeve resection (bronchial)	2 (0.5)	2 (0.5)
Sleeve resection (arterial)	0	1 (0.3)
Wedge resection	1 (0.3)	2 (0.5)
Other	7 (1.9)	13 (3.5)
Surgical approach, n (%)		
Open Procedure	145 (39.6)	153 (40.9)
Minimally invasive	145 (39.6)	142 (38.0)
Other	4 (1.1)	6 (1.6)
Missing	1 (0.3)	1 (0.3)
Days from last neoadjuvant Tx dose to surgery, median (range)‡	34.0 (12–91)	34.0 (13–103)
Days from surgery to first dose of adjuvant Tx, median (range)¶	50.0 (22–136)	52.0 (21–141)

Data cut-off of November 10, 2022 (N=740). *The modified intent-to-treat population included all patients who were randomized, excluding patients with documented *EGFR* or *ALK* aberrations. †For the summary of resection margin status only the percentages are calculated using the number of patients who completed surgery as the denominator. ‡Based on the number of patients who underwent surgery (durvalumab arm, n=295; placebo arm, n=279). ¶Based on the number of patients in the modified intent-to-treat population who started adjuvant treatment (durvalumab arm, n=241; placebo arm, n=237). Tx, treatment.

Table S8. Objective Response Prior to Surgery According to Blinded Independent Central Review (RECIST v1.1) in the Modified Intent-to-treat Population.*

	Durvalumab arm (N=366)	Placebo arm (N=374)
Objective response rate, n (%)	206 (56.3)	142 (38.0)
95% CI	51.0–61.4	33.0–43.1
Patients with a response, n (%)		
Complete response	4 (1.1)	1 (0.3)
Partial response	202 (55.2)	141 (37.7)
Patients with no response, n (%)		
Stable disease	124 (33.9)	189 (50.5)
Progression	11 (3.0)	15 (4.0)
Not evaluable†	25 (6.8)	28 (7.5)

Data cut-off of November 10, 2022 (N=740). *The modified intent-to-treat population included all patients who were randomized, excluding patients with documented *EGFR* or *ALK* aberrations. †Includes patients with missing baseline scans or missing pre-surgery scans. CI, confidence interval; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

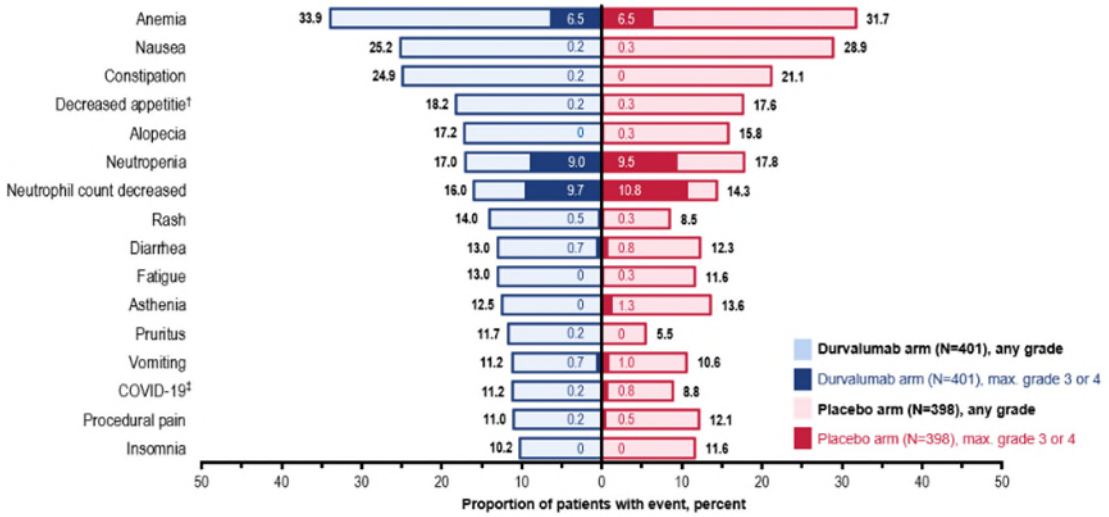
Table S9. Most Common Adverse Events of Any Cause in the Safety Analysis Set.*

Data cut-off of November 10, 2022 (N=799). Panel A and Panel B show a table and tornado plot, respectively, of the most common adverse events of any cause in the safety analysis set.

(A)

Event	Durvalumab arm (N=401)		Placebo arm (N=398)	
	Any Grade	Max. Grade 3 or 4	Any Grade	Max. Grade 3 or 4
	Number of patients with event (percent)			
Anemia	136 (33.9)	26 (6.5)	126 (31.7)	26 (6.5)
Nausea	101 (25.2)	1 (0.2)	115 (28.9)	1 (0.3)
Constipation	100 (24.9)	1 (0.2)	84 (21.1)	0
Decreased appetite[†]	73 (18.2)	1 (0.2)	70 (17.6)	1 (0.3)
Alopecia	69 (17.2)	0	63 (15.8)	1 (0.3)
Neutropenia	68 (17.0)	36 (9.0)	71 (17.8)	38 (9.5)
Neutrophil count decreased	64 (16.0)	39 (9.7)	57 (14.3)	43 (10.8)
Rash	56 (14.0)	2 (0.5)	34 (8.5)	1 (0.3)
Diarrhea	52 (13.0)	3 (0.7)	49 (12.3)	3 (0.8)
Fatigue	52 (13.0)	0	46 (11.6)	1 (0.3)
Asthenia	50 (12.5)	0	54 (13.6)	5 (1.3)
Pruritis	47 (11.7)	1 (0.2)	22 (5.5)	0
Vomiting	45 (11.2)	3 (0.7)	42 (10.6)	4 (1.0)
COVID-19[‡]	45 (11.2)	1 (0.2)	35 (8.8)	3 (0.8)
Procedural pain	44 (11.0)	1 (0.2)	48 (12.1)	2 (0.5)
Insomnia	41 (10.2)	0	46 (11.6)	0

(B)



*The safety analysis set includes all randomized patients who received at least one dose of study treatment; one patient assigned to the placebo arm erroneously received a single cycle of durvalumab (in the adjuvant phase) and was included in the durvalumab arm for the safety analysis set; adverse events were graded using Common Terminology Criteria for Adverse Events version 5.0. Included are adverse events reported with an any-grade incidence of at least 10% in the durvalumab arm during the overall study period, which spans from the first dose of study treatment (durvalumab or placebo or chemotherapy) until the earliest of: the last dose of study treatment or surgery + 90 days (taking the latest dose of durvalumab or placebo or chemotherapy or the date of surgery, + 90 days); the data cut-off date; or the date of the first dose of subsequent anti-cancer treatment. †Two patients (one in each arm) had decreased appetite with an outcome of death (max. grade 5); the fatal event in the durvalumab arm was assessed as possibly related to study treatment by the investigator. ‡Six patients had COVID-19 events of max. grade 5 (durvalumab arm, n=5; placebo arm, n=1); all COVID-19 deaths were assessed by the investigator as unrelated to study treatment (note: COVID-19 is summarized as a grouped term comprising the 'COVID-19' and 'COVID-19 pneumonia' adverse event preferred terms).

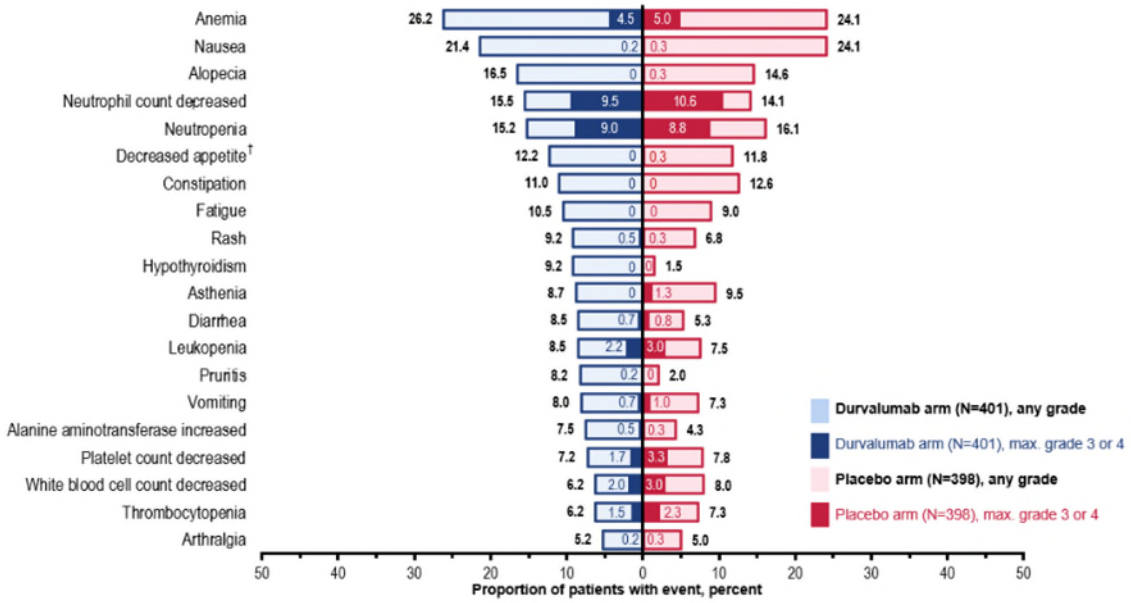
Table S10. Most Common Adverse Events Possibly Related to Study Treatment in the Safety Analysis Set.*

Data cut-off of November 10, 2022 (N=799). Panel A and Panel B show a table and tornado plot, respectively, of the most common adverse events possibly related to study treatment in the safety analysis set.

(A)

Event	Durvalumab arm (N=401)		Placebo arm (N=398)	
	Any Grade	Max. Grade 3 or 4	Any Grade	Max. Grade 3 or 4
	Number of patients with event (percent)			
Anemia	105 (26.2)	18 (4.5)	96 (24.1)	20 (5.0)
Nausea	86 (21.4)	1 (0.2)	96 (24.1)	1 (0.3)
Alopecia	66 (16.5)	0	58 (14.6)	1 (0.3)
Neutrophil count decreased	62 (15.5)	38 (9.5)	56 (14.1)	42 (10.6)
Neutropenia	61 (15.2)	36 (9.0)	64 (16.1)	35 (8.8)
Decreased appetite[†]	49 (12.2)	0	47 (11.8)	1 (0.3)
Constipation	44 (11.0)	0	50 (12.6)	0
Fatigue	42 (10.5)	0	36 (9.0)	0
Rash	37 (9.2)	2 (0.5)	27 (6.8)	1 (0.3)
Hypothyroidism	37 (9.2)	0	6 (1.5)	0
Asthenia	35 (8.7)	0	38 (9.5)	5 (1.3)
Diarrhea	34 (8.5)	3 (0.7)	21 (5.3)	3 (0.8)
Leukopenia	34 (8.5)	9 (2.2)	30 (7.5)	12 (3.0)
Pruritis	33 (8.2)	1 (0.2)	8 (2.0)	0
Vomiting	32 (8.0)	3 (0.7)	29 (7.3)	4 (1.0)
Alanine aminotransferase increased	30 (7.5)	2 (0.5)	17 (4.3)	1 (0.3)
Platelet count decreased	29 (7.2)	7 (1.7)	31 (7.8)	13 (3.3)
White blood cell count decreased	25 (6.2)	8 (2.0)	32 (8.0)	12 (3.0)
Thrombocytopenia	25 (6.2)	6 (1.5)	29 (7.3)	9 (2.3)
Arthralgia	21 (5.2)	1 (0.2)	20 (5.0)	1 (0.3)

(B)



*The safety analysis set includes all randomized patients who received at least one dose of study treatment; one patient assigned to the placebo arm erroneously received a single cycle of durvalumab (in the adjuvant phase) and was included in the durvalumab arm for the safety analysis set; adverse events were graded using Common Terminology Criteria for Adverse Events version 5.0. Included are adverse events assessed by the investigator as possibly related to any study treatment (durvalumab or placebo or chemotherapy) reported with an any-grade incidence of at least 5% in the durvalumab arm during the overall study period, which spans from the first dose of study treatment until the earliest of: the last dose of study treatment or surgery + 90 days (taking the latest dose of durvalumab or placebo or chemotherapy or the date of surgery, + 90 days); the data cut-off date; or the date of the first dose of subsequent anti-cancer treatment.
†One patient in the durvalumab arm had decreased appetite with an outcome of death (grade 5) that was assessed as possibly related to study treatment by the investigator.

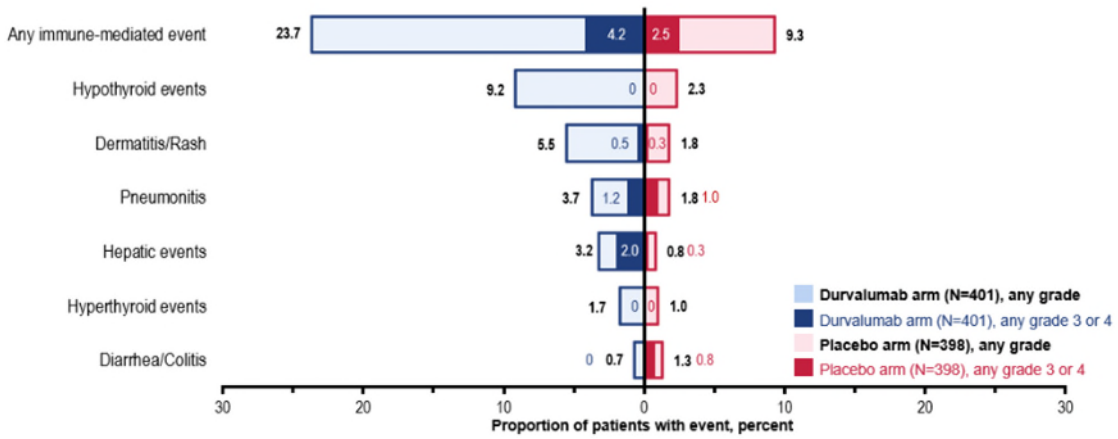
Table S11. Immune-mediated Adverse Events (Grouped Terms) Occurring in >1% of Patients in Either Treatment Arm in the Safety Analysis Set.*

Data cut-off of November 10, 2022 (N=799). Panel A and Panel B show a table and tornado plot, respectively, of immune-mediated adverse events occurring in >1% of patients in either treatment arm in the safety analysis set.

(A)

	Durvalumab Arm (N=401)		Placebo Arm (N=398)	
	Any Grade	Any Grade 3 or 4	Any Grade	Any Grade 3 or 4
	Number of patients with event (percent)			
Any immune-mediated event	95 (23.7)	17 (4.2)	37 (9.3)	10 (2.5)
Hypothyroid events	37 (9.2)	0	9 (2.3)	0
Dermatitis/Rash	22 (5.5)	2 (0.5)	7 (1.8)	1 (0.3)
Pneumonitis	15 (3.7)	5 (1.2)	7 (1.8)	4 (1.0)
Hepatic events	13 (3.2)	8 (2.0)	3 (0.8)	1 (0.3)
Hyperthyroid events	7 (1.7)	0	4 (1.0)	0
Diarrhea/Colitis	3 (0.7)	0	5 (1.3)	3 (0.8)

(B)



*The safety analysis set includes all randomized patients who received at least one dose of study treatment; one patient assigned to the placebo arm erroneously received a single cycle of durvalumab (in the adjuvant phase) and was included in the durvalumab arm for the safety analysis set; AEs were graded using Common Terminology Criteria for Adverse Events version 5.0. An immune-mediated AE was defined as an AE of special interest consistent with an immune-mediated

mechanism of action, where there is no clear alternate etiology, and requiring the use of systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy. AE, adverse event.

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