Oncologic Drugs Advisory Committee (ODAC) Meeting

July 25, 2024

BLA# 761069/Supplement 43

Drug name: durvalumab

Applicant: AstraZeneca UK Limited

Combined FDA and Applicant ODAC Briefing Document

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Applicant and the Food and Drug Administration (FDA) for the panel members of the advisory committee. We have brought the drug durvalumab (BLA# 761069 Supplement 43) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Advisory Committee Briefing Materials: Available For Public Release

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Glossary

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
BICR	Blinded independent central review
cCRT	Concurrent chemoradiotherapy
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTEP	Cancer Therapy Evaluation Program
CTx	Chemotherapy
DCO	Data cut-off
DFS	Disease-free survival
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor mutation(s)
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
ETOP	European Thoracic Oncology Platform
FA	Final Analysis
FDA	Food and Drug Administration
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
IA	Interim Analysis
IASLC	International Association for the Study of Lung Cancer
ICH	International Conference on Harmonisation
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IMLD	Immune-mediated lung disease
ITT	Intent-to-treat

Abbreviation or special term	Explanation
mITT	Modified intent-to-treat
MPR	Major pathological response
MRD	Minimal residual disease
MTP	Multiple testing procedure
NCCN	National Comprehensive Cancer Network
NR	Not reached
NSCLC	Non-small cell lung cancer
ODAC	Oncologic Drugs Advisory Committee
ORR	Objective response rate
OS	Overall survival
Pbo	Placebo
PD-1	Programmed cell death-protein 1
PD-L1	Programmed cell death-ligand 1
PD-L2	Programmed cell death-ligand2
PFS	Progression-free survival
PRO	Patient-reported outcomes
QLQ-C30	30-item Core Quality of Life Questionnaire
QLQ-LC13	13-item Lung Cancer Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety analysis set
sBLA	Supplemental Biologics License Application
SWOG	Southwest Oncology Group
TC	Tumor cells
UC	Urothelial carcinoma
US	United States (of America)

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1. Introduction

1.1 Proposed Indication(s)

IMFINZI™ (durvalumab) is a programmed death ligand-1 (PD-L1) blocking antibody indicated in combination with platinum-containing chemotherapy as neoadjuvant treatment, followed by IMFINZI™ as monotherapy after surgery, for the treatment of adult patients with resectable (tumors ≥ 4 cm and/or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements.

1.2 Purpose of the Meeting

FDA's Summary of the Purpose of the meeting:

The U.S. Food and Drug Administration (FDA) is convening the Oncologic Drugs Advisory Committee (ODAC) to discuss two issues concerning evidence generation in perioperative immune checkpoint inhibitor (ICI) trials for patients with resectable non-small cell lung cancer (NSCLC).

To clarify the terminology used by FDA in this briefing document, we discuss three common trial designs that have been conducted to assess anti-PD-(L)1 antibodies, hereafter referred to as immune checkpoint inhibitors (ICIs), as part of the treatment approach for early-stage NSCLC. A **neoadjuvant approach** investigates ICI given only prior to surgery, an **adjuvant approach** investigates ICI given only after surgery, and a **perioperative approach** investigates ICI both prior to surgery and after surgery. This ODAC discussion focuses on trials seeking to provide evidence to support a perioperative approach; investigating ICI given both before and after surgery; in both the neoadjuvant and adjuvant "phases" of therapy.

There are two discussion topics for this meeting: one product specific, and the other non-product specific. The committee will first discuss results from the AEGEAN trial submitted to the FDA to support the use of neoadjuvant durvalumab in combination with platinum-containing chemotherapy, followed by adjuvant durvalumab as monotherapy after surgery, for the treatment of adult patients with resectable NSCLC. The discussion will consider the adequacy of the efficacy and safety data from the AEGEAN trial to support the proposed perioperative indication taking into account: (1) Accumulating uncertainty from emerging data across trials on the potential for overtreatment for perioperative ICI regimens; and (2) The inability of the two-arm AEGEAN trial to distinguish whether the efficacy of durvalumab is related to use in the neoadjuvant phase, the adjuvant phase, or both phases.

For the second topic of discussion, the committee will focus on design of new trials developing novel systemic treatments for resectable NSCLC moving forward. The committee will be presented with two-arm study designs being proposed to FDA that combine novel drugs with ICI onto standard of care perioperative regimens. As with AEGEAN, these proposed two-arm

designs are unable to evaluate contribution of phase, further magnifying the risk of potential overtreatment. Given the inability of two-arm trial designs to establish the contribution of each phase of the regimen to the overall treatment effect, the ODAC will discuss strategies to address this limitation in future proposed trial designs and be asked whether contribution of the phase of treatment in a perioperative regimen should be supported within a single trial.

Contribution of Treatment Phase in AEGEAN

On July 25, 2023, AstraZeneca UK Ltd. (hereafter referred to as "the Applicant") submitted a supplemental biologics license application (sBLA) for durvalumab for the above indication based on the results of the AEGEAN trial (NCT03800134). AEGEAN is a two-arm, randomized, placebo-controlled trial evaluating the efficacy and safety of neoadjuvant durvalumab in combination with histology-specific platinum-based chemotherapy, followed by surgery and adjuvant durvalumab, versus neoadjuvant platinum-based chemotherapy in combination with placebo, followed by surgery and adjuvant placebo in patients with stage IIA-IIIB(N2) resectable NSCLC. The dual primary endpoints were pathologic complete response (pCR) per central pathology review and event-free survival (EFS) as assessed by blinded independent central review (BICR). Overall survival (OS) was a key secondary endpoint. In a protocol amendment, the Applicant modified the eligibility criteria to require confirmation of negative genetic tests for sensitizing *EGFR* mutations and *ALK* gene rearrangements. Therefore, the modified intention-to-treat (mITT) population includes only patients whose tumors did not harbor *EGFR* or *ALK* gene aberrations.

The first interim analysis of the primary endpoint of pCR took place after the data cutoff (DCO) date of January 14, 2022. In this interim analysis, the durvalumab arm had a pCR rate of 18% (95% confidence interval [CI]: 13%, 24%) compared with 5% (95% CI: 2.4%, 9%) for the control arm. The absolute difference in pCR rate was 13% (95% CI: 7%, 20%), which was statistically significant (p-value = 0.000036).

The first interim analysis (IA1) of the primary endpoint of EFS took place after the DCO date of November 10, 2022. AEGEAN met its primary endpoint of EFS by demonstrating a hazard ratio (HR) of 0.68 (95% CI: 0.53, 0.88) favoring the durvalumab arm, which was statistically significant (p-value = 0.0039). The median EFS was not reached (NR) in the durvalumab arm (95% CI: 31.9, NR) compared with 25.9 months (95% CI: 18.9, NR) in the control arm. The effect of perioperative durvalumab on EFS was generally consistent across patient subgroups.

AEGEAN's statistical analysis plan specifies hierarchical testing of disease-free survival (DFS) and then OS; specifically, a statistically significant difference in the endpoint of DFS is required to formally test OS. As the first interim analysis of DFS was not statistically significant, the analysis of OS at IA1 was descriptive. An additional descriptive analysis of OS that included follow up for deaths up to the time of the 120-day safety update (DCO date: August 14, 2023) was submitted

to the BLA during the review period. A total 212 death events had occurred in both trial arms, with 99 events occurring in the durvalumab arm and 113 events occurring in the placebo arm. The OS HR was 0.91 (95% CI: 0.69, 1.19) and the median OS was NR (95% CI: NR, NR) in the durvalumab arm and NR (95% CI: 40.3, NR) in the control arm.

Safety data from AEGEAN showed a similar incidence of grade 3-4 adverse events (AEs) between the trial arms for the entire perioperative regimens, with an incidence of 42% in the durvalumab arm and 43% in the placebo arm. The incidence of fatal AEs was numerically higher in the durvalumab at 6%, compared with 3.8% in the placebo arm. The incidence of serious AEs (SAEs) was also numerically higher in the durvalumab arm at 38%, compared with 31% in the placebo arm. The toxicity profile in the durvalumab arm was generally consistent with the described individual toxicities for platinum-based chemotherapy and anti-PD-1 / anti-PD-L1 antibodies. Of note, of the 265 patients who received adjuvant durvalumab, 9% had unresolved immune-related AEs (irAEs) at the end of the study period. The most frequent unresolved irAEs were hypothyroidism (3.8%) and rash (1.5%). Other unresolved irAEs occurred in individual patients, including diarrhea, musculoskeletal pain, adrenal insufficiency, and pneumonitis.

FDA acknowledges the AEGEAN trial met its primary endpoint with demonstration of a statistically significant and clinically meaningful improvement in EFS, an endpoint generally considered suitable for traditional approval in this disease setting. However, the design of AEGEAN does not allow for a within-trial assessment of the individual contributions of durvalumab given concurrently with chemotherapy in the neoadjuvant phase and durvalumab given in the adjuvant phase to the effect of the overall regimen. In addition, emerging data from completed trials of neoadjuvant only, adjuvant only, and perioperative ICI regimens across other drugs in the class contribute to the uncertainty regarding the need for ICI in both perioperative phases of therapy. This raises concern for potential overtreatment and its attendant toxicities. For example, if the clinical benefit of durvalumab is derived primarily from its use in the neoadjuvant phase, the use of durvalumab in the adjuvant phase would expose patients to overtreatment and its attendant safety risks and additional treatment burden without added clinical benefit.

Demonstration of Contribution of Treatment Phase in Future Perioperative Trials

The second discussion topic will focus on how future trial designs can be constructed to provide stronger evidence of the contribution of each phase of a perioperative regimen when investigating new therapies for the treatment of resectable NSCLC. With several FDA approved options incorporating ICI into the treatment of resectable NSCLC, there is interest in adding new therapies onto these approved ICI backbone treatments. Where intensification of only one phase is being studied, a two-arm trial design can be appropriate. This would include studies adding a new therapy to only the adjuvant or neoadjuvant phase.

One available FDA approved therapy for resectable NSCLC is a perioperative ICI treatment regimen (ICI administered in neoadjuvant and adjuvant phases). FDA has seen proposals for two-arm trials designs adding a new therapy to both the neoadjuvant and adjuvant phases of treatment. This includes proposals to randomize patients to an experimental arm consisting of the new therapy added to the neoadjuvant and adjuvant phases of a perioperative ICI backbone compared to a control arm that consists of an approved perioperative ICI regimen. As previously stated, emerging data has led to increasing uncertainty regarding whether the use of ICI in both phases of therapy is necessary to achieve the observed clinical benefit. Even if one considers a standard of care backbone incorporating ICI in both the neoadjuvant and adjuvant phases of therapy appropriate, a two-arm trial design incorporating a new therapy into both phases of treatment will only lead to additional uncertainty as to whether each intensified phase is necessary, and increase the risks associated with potential for overtreatment. As treatment regimens are intensified with the addition of new agents to an anti-PD-(L)1 backbone, this can be expected to result in additional toxicity and treatment burden.

Like AEGEAN, more recent two-arm add-on trial designs proposed to FDA will not allow for an assessment of the contribution of the new therapy given in the neoadjuvant phase versus the contribution of the new therapy given in the adjuvant phase to the overall treatment effect. Intensification of perioperative add-on designs only exacerbates concerns for overtreatment. To address the issue of contribution of treatment phase, alternative trial designs are increasingly necessary to evaluate the efficacy of novel drugs in each treatment phase of a perioperative regimen. Potential trial designs may include multi-arm trials (e.g., trials with more than two arms or factorial randomized trials) or trials that incorporate re-randomization (e.g., Sequential Multiple Assignment Randomized Trial [SMART] designs). In addition to a perioperative arm that includes the new therapy in both phases and a control arm, multi-arm or factorial trials would include additional arms that consist of the new therapy added to either the neoadjuvant or adjuvant phase only. Comparison of the perioperative arm to an arm containing the new therapy in only one treatment phase will enable a direct assessment of contribution of phase. In SMART designs, patients undergo a first randomization to receive the experimental drug versus standard of care in the neoadjuvant setting. After surgery, patients undergo a second randomization to receive the experimental drug versus standard of care in the adjuvant setting, therefore allowing the estimation of the experimental drug's effect when given in each of the phases, neoadjuvant and adjuvant. Section 5.2 discusses these alternative trial designs in greater detail.

1.3 Regulatory History

The Applicant's Position:

Durvalumab is a human monoclonal IgG1 antibody that selectively blocks the interaction of PD-L1 with the PD-1 and CD80 (B7.1) receptors expressed on immune cells, and has been

engineered to remove the Fc effector function. Durvalumab has approved indications in the US and in more than 70 countries globally as a single agent or in combination, across various tumor types, namely: unresectable Stage III NSCLC after chemoradiation, metastatic NSCLC with no sensitizing EGFR mutation or ALK genomic tumor aberrations, extensive stage small cell lung cancer, metastatic biliary tract cancer, and hepatocellular carcinoma.

On 25 July 2023, the Sponsor (AstraZeneca) submitted an sBLA to the FDA to seek approval of the proposed indication for the use of durvalumab in combination with chemotherapy as neoadjuvant treatment, followed by durvalumab monotherapy after surgery, in adult patients with resectable NSCLC and no known EGFR mutations or ALK rearrangements (see Section 1.1). This submission was based on data from the interim and final analyses of pCR, and the first interim analysis of EFS, of the ongoing Phase III AEGEAN study (interim analyses are defined in Section 2.2.4). Before submission, AstraZeneca met with the FDA on 9 May 2023 to discuss the acceptability of efficacy and safety data from the AEGEAN study to support an sBLA in the proposed indication. Overall, FDA agreed that efficacy and safety data from EFS IA1 were sufficient to initiate review of the benefit-risk profile of durvalumab in the proposed indication. Additionally, FDA agreed with AstraZeneca's proposal for provision of updated safety and OS data during the sBLA review to confirm no detriment to overall survival.

Formal interactions held with the FDA for the development of durvalumab in the proposed indication are summarized in Appendix 1.

The FDA's Position:

FDA generally agrees with the Applicant's position. As described in Appendix 1, in a Type B meeting held on November 01, 2018, FDA stated the design of AEGEAN would not isolate the effect of the treatment phases and recommended that the Applicant should consider a factorial study design, potentially with adaptive design elements. The Applicant opted to proceed with a two-arm trial. In a Type B meeting held on May 09, 2023, FDA reiterated that the trial design does not isolate the effect of neoadjuvant durvalumab with chemotherapy from the effect of adjuvant durvalumab. FDA also recommended that the Applicant provide a method to assess the contribution of durvalumab in the pre-surgery and post-surgery treatment phases to the treatment effect of the overall regimen.

2. Efficacy

2.1 Description of Clinical Setting

2.1.1 Overview of Resectable NSCLC

The Applicant's Position:

Lung cancer is the second most common cancer worldwide, with approximately 2.5 million new

cases reported in 2022 [1]. In the US, lung cancer is the leading cause of cancer-related deaths. In the US in 2024, it is estimated that 234,580 new cases of lung cancer will be diagnosed, and 125,070 people will die because of the disease [2].

Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers [3, 4], and is classified into 2 main subtypes: non-squamous (~70% of new cases) and squamous cell carcinoma (~30% of new cases) [5, 6]. Approximately 20% to 25% of NSCLC patients present with resectable lung cancer at diagnosis [7], a proportion that is expected to increase following the rollout of lung cancer screening in high-risk populations [8]. In the US, from 2010 to 2017, while the annual NSCLC incidence per 100,000 people decreased from 46.4 to 40.9 overall, the incidence of Stages II, IIIA, and IIIB NSCLC remained more stable [9].

Resectable NSCLC is an aggressive disease. Despite surgical resection with curative intent, 30% to 76% of patients experience recurrence, most commonly at distant locations, ultimately leading to death from the disease [10, 11]. The prognosis of resectable NSCLC therefore remains poor, with 5-year survival rates of 56% to 65% for patients with Stage II disease, and 24% to 41% for patients with Stage III disease [12].

The FDA's Position:

FDA agrees with the Applicant's position.

2.1.2 Current Treatment Options in Resectable NSCLC

The Applicant's Position:

At the time AEGEAN was initiated (first patient enrolled on 06 December 2018), the global and US standard of care for patients with resectable NSCLC was surgical resection, with or without 4 cycles (neoadjuvant or adjuvant) of platinum-based doublet chemotherapy [13, 14]. Platinum-based (cisplatin/carboplatin) doublet chemotherapy remains integral to current global and US treatment guidelines for patients with resectable NSCLC [15].

After AEGEAN was initiated, immunotherapy has since become an important part of the therapeutic landscape for patients with resectable NSCLC. Several Phase III studies have demonstrated the clinical benefit of anti-PD-L1/PD-1 immunotherapy in the neoadjuvant, adjuvant, and perioperative settings, and have been included in the US NCCN Clinical Practice Guidelines [15]. Resulting FDA approvals are summarized below, with further details provided in Appendix 2:

- **IMpower010** [16]: Atezolizumab (anti-PD-L1) was approved in October 2021 as adjuvant monotherapy for patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression ≥ 1%, after complete resection and adjuvant platinum-based chemotherapy (NCCN evidence category 2A).
- **CheckMate-816** [10]: Nivolumab (anti-PD-1) was approved in March 2022 for neoadjuvant

treatment, given in combination with platinum-doublet chemotherapy before surgery for patients with resectable NSCLC (tumors ≥ 4 cm or node positive) (NCCN evidence category 2A).

- **PEARLS/KEYNOTE-091** [17]: Pembrolizumab (anti-PD-1) was approved in January 2023 as adjuvant monotherapy for patients with Stages IB to IIIA NSCLC, after complete resection and optional adjuvant platinum-based chemotherapy (NCCN evidence category 2A).
- **KEYNOTE-671** [18, 19]: Pembrolizumab was approved in October 2023 in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as adjuvant monotherapy after surgery, in patients with Stages II to IIIB[N2] NSCLC (NCCN evidence category 1; of note, NCCN guidelines recommend pembrolizumab with cisplatin-based doublet chemotherapy only).

The presence of tumoral EGFR mutations (EGFRm) or ALK gene rearrangements has been associated with less benefit from anti-PD-L1/PD-1 inhibitors [20-22]. Tumoral EGFR mutations are found in approximately 10% of white patients and up to 50% of Asian patients with NSCLC [23]. Tumoral ALK gene rearrangements are found in about 5% of patients with NSCLC [24]. In these subpopulations, biomarker-targeted therapies have become preferred treatment approaches [15]: adjuvant osimertinib is recommended for patients with completely resected EGFRm NSCLC, with or without prior adjuvant chemotherapy [22]; and adjuvant alectinib is recommended for patients with completely resected NSCLC with ALK gene rearrangements [25].

The FDA's Position:

FDA generally agrees with the Applicant's position with one clarification. Based on results of the PEARLS/KEYNOTE-091 trial, FDA approved pembrolizumab as a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC. See Table 1 for a listing of FDA-approved ICI therapies for patients with resectable NSCLC.

Table 1: Approved Immune Checkpoint Inhibitors (ICIs) for Patients with Resectable NSCLC

	Adjuvant Only		Neoadjuvant Only	Neoadjuvant followed by Adjuvant
ICI	**Atezolizumab**	**Pembrolizumab**	**Nivolumab**	**Pembrolizumab**
Date of approval	October 2021	January 2023	March 2022	October 2023
Stage	II-IIIA	IB[a]-IIIA	IB[a]-IIIA	II-IIIB

Indication	PD-L1 ≥1%, following adjuvant chemotherapy	Following adjuvant chemotherapy	Concurrently with platinum-based chemotherapy x3 cycles	Concurrently with neoadjuvant platinum-based chemotherapy x4 cycles → adjuvant pembrolizumab x13 cycles
Pivotal Trial	IMpower-010	KEYNOTE-091	CHECKMATE-816	KEYNOTE-671
Primary Endpoint(s)	DFS	DFS	EFS/pCR	EFS/OS
HR (95% CI)	**0.66 (0.50, 0.88)**	**0.73 (0.60, 0.89)**	**0.63 (0.45, 0.87)**	**EFS: 0.58 (0.46, 0.72) OS: 0.72 (0.56, 0.93)**

2.1.3 Unmet Medical Need in Resectable NSCLC

The Applicant's Position:

At the time of the Phase III AEGEAN study designed (protocol version 1.0, dated 31 August 2018), the standard-of-care in this setting was surgery with curative intent, with or without 4 cycles (neoadjuvant or adjuvant) of platinum-doublet chemotherapy. However, the 5-year survival rate for these patients treated with platinum-doublet therapy remained low at 56% to 65% for patients with Stage II, and 24% to 41% for patients with Stage III disease [12], highlighting an urgent unmet medical need for patients with early-stage NSCLC. Furthermore, disease recurrence post-surgery remained common, with 5-year recurrence-free survival rates ranging from 50% for Stage II disease to 34% for Stage III disease (based on data published between 2011 and 2021) [26]. These data further highlighted the need for therapeutic strategies that can improve postoperative disease control and long-term survival in this patient population.

AEGEAN was designed to address this unmet need, building on the clinical benefit of chemoimmunotherapy in the metastatic NSCLC setting [27-29], as well as the proven benefit of durvalumab monotherapy after cCRT in Stage III unresectable NSCLC in the PACIFIC trial [30]. AEGEAN assessed the efficacy and safety of durvalumab when given in combination with neoadjuvant platinum-based chemotherapy, followed by adjuvant durvalumab monotherapy, in patients with resectable Stage II-IIIB[N2] NSCLC. The rationale for the overall study design is provided in Section 2.1.4. To avoid potentially suboptimal treatment of patients with EGFR mutations or ALK gene rearrangements, the protocol was later amended (protocol version 4.0, dated 15 April 2021) to exclude these patients from further enrollment and from efficacy analysis sets (Section 2.2.2).

Since the start of the AEGEAN study, positive results from contemporaneous Phase III trials in resectable NSCLC have validated the clinical utility of immunotherapy in this setting, leading to

the regulatory approval of neoadjuvant chemoimmunotherapy, adjuvant immunotherapy, and perioperative chemoimmunotherapy options for patients with resectable/resected early-stage NSCLC (see Appendix 2) [10, 16-19]. Outcomes from AEGEAN add to the body of evidence supporting the value of immunotherapy when given perioperatively.

However, there are no data that formally compare neoadjuvant, adjuvant and perioperative treatment approaches, and it is notable that the relevant Phase III trials that have reported outcomes to date have important differences in the staging systems employed, patient eligibility (including prior surgery and chemotherapy, clinical/pathological disease stage, and EGFRm/ALK gene rearrangement status), on-study treatments used (including the type and number of cycles of neoadjuvant chemotherapy), blinding and use of placebo, and other permitted anti-cancer treatments (including radiotherapy) [10, 16-19]. As such, the heterogeneity of trial designs, platinum-chemotherapy backbones used, and enrolled patient populations precludes direct cross-trial comparisons of overall outcomes.

Of note, in US clinical practice, most patients with resectable NSCLC treated with chemotherapy are treated with carboplatin-based regimens [31]. Cisplatin is an important alternative, and is also widely used, but since it is associated with significant side effects and increased patient morbidity [32, 33], it is therefore usually reserved for the fittest, least comorbid patients. Carboplatin is considered a more tolerable alternative for patients who are ineligible for cisplatin treatment [34]. AEGEAN permitted the use of either cisplatin- or carboplatin-based doublets, in alignment with US clinical practice (see Section 2.2 and Section 2.3 for further details).

In conclusion, the AEGEAN trial is an important addition that significantly adds to the growing evidence base for anti-PD-L1/PD-1 immunotherapy in resectable NSCLC. Perioperative durvalumab, used in combination with a flexible chemotherapy backbone, has the potential to become an important new treatment option for patients with resectable NSCLC, a patient population that continues to have a poor prognosis.

The FDA's Position:

FDA acknowledges that resectable NSCLC remains a serious condition with unmet medical need; however, given the available therapies described in Section 2.1.2, the AEGEAN regimen provides an additional option rather than directly addressing a current high unmet medical need. Although other perioperative ICI trials for resectable NSCLC (Table 6) have utilized cisplatin as part of the neoadjuvant regimen and the regimen specified in AEGEAN allowed for either cisplatin or carboplatin, we note that use of carboplatin instead of cisplatin is not expected to improve the efficacy of ICI therapy. In addition, clinical practice providers may use carboplatin as an alternative to cisplatin in many contexts, and it is likely that this will be the case here regardless of the choice of ICI.[51]

2.1.4 Scientific Rationale for the Perioperative Design of the AEGEAN Study

The Applicant's Position:

The AEGEAN trial design builds on the longstanding concept of induction-maintenance that has been established across multiple disease settings and tumor types, including metastatic NSCLC [35]. Lessons learned from pivotal trials and approved regimens in NSCLC and other disease settings, where important paradigms were established for combination treatments with chemotherapy, as well as immunotherapy treatment duration, were instrumental to determining how perioperative immunotherapy was applied in AEGEAN.

In the metastatic NSCLC setting (in patients without EGFRm or ALK gene rearrangements), chemoimmunotherapy has been firmly established as an important standard of care, providing important clinical benefit for patients regardless of PD-L1 expression [27-29]. Chemoimmunotherapy combines the cytotoxic effect of chemotherapy and stimulation of anti-tumor immunity in the induction phase of treatment, with sustained anti-tumor immunity achieved through continued inhibition of the PD-L1/PD-1 axis in the maintenance phase of treatment. This latter mechanism is important, because any tumor cells present may continue to express, or develop expression of, PD-L1, thus inhibiting anti-tumor effector T-cell function ([36]; data on file). Ongoing immunotherapy is given in order to overcome this important resistance mechanism and sustain anti-tumor immunity in the long term.

The goal of treatment in patients with early-stage NSCLC is to eradicate locoregional disease (achieved through surgery, with or without systemic treatment) and to eradicate/suppress micrometastatic disease (for which detection methods are not currently available). At the time of the AEGEAN trial initiation, standard-of-care treatment for patients with resectable NSCLC comprised surgical resection with or without 4 cycles of (neoadjuvant or adjuvant) platinum-based chemotherapy. When considering the investigation of anti-PD-L1/PD-1 immunotherapy in the resectable NSCLC setting, this could be achieved through adjuvant only, neoadjuvant only or perioperative treatment regimens in the study design.

At the time, adjuvant only approaches (after complete surgical resection with or without platinum-based chemotherapy) were already being investigated in Phase III registrational studies IMpower010 [16], KEYNOTE-091 [17], and BR.31 [37]. In these studies, immunotherapy is given as monotherapy in an attempt to delay the progression of, or to eliminate, micrometastatic disease and commences after macroscopic disease and locoregional lymph nodes have been removed and thus are no longer available for stimulation of systemic anti-tumor immunity.

Starting immunotherapy in the neoadjuvant setting offers important potential advantages over adjuvant only treatment, namely: the presence of the locoregional disease in situ can serve as an antigen source for expansion/activation of tumor-specific T-cells (resulting in improved anti-tumor response); the fact that vasculature and tumor-draining lymph nodes remain intact with preservation of locoregional immunity; and the early introduction of systemic treatment, which may allow for rapid locoregional and distant disease control. At the time of AEGEAN initiation, neoadjuvant approaches were being investigated for resectable NSCLC, with Phase II clinical

trial data demonstrating promising clinical activity (in terms of pCR and MPR) for neoadjuvant immunotherapy/chemoimmunotherapy in patients with resectable NSCLC [38-40].

It is important to note, however, that at the time of the AEGEAN trial design, there was no robust clinical evidence to support any expectation that neoadjuvant immunotherapy or chemoimmunotherapy alone would be sufficient to substantially improve and optimize long-term outcomes for patients with resectable NSCLC, in the absence of maintenance treatment. Therefore, utilizing a neoadjuvant-only approach in an AEGEAN investigational arm was not considered optimal. While data have since emerged demonstrating important clinical benefits for patients receiving 3 cycles of neoadjuvant chemoimmunotherapy over 3 cycles of chemotherapy alone [10], it remains unclear how patients treated with such a regimen would have additionally benefited from adjuvant immunotherapy. In the metastatic setting, immunotherapy is usually given for a total of 2 years or until progression (with the CheckMate-153 trial demonstrating inferior outcomes for a shorter course of 1 year [41]). Lessons from the metastatic disease setting are relevant because the goal of treatment in the curative disease setting is both to effectively manage locoregional disease and to suppress or eliminate micrometastatic disease. Distant disease recurrence, resulting from undetected tumor cells remaining following surgery, affects a sizeable proportion of patients with resected NSCLC, ranging from 28-46% of patients with Stage II disease and 30-63% of patients with Stage III disease [26].

In AEGEAN, in the neoadjuvant phase, a maximum of 4 cycles of durvalumab given Q3W in combination with platinum doublet chemotherapy before surgery was employed, in an attempt to minimize any potential risk to patients' ability to achieve surgical resection, while at the same time maximizing the potential benefit from this combination (mirroring efficacious chemoimmunotherapy induction regimens used in the metastatic setting, eg., KEYNOTE-189 and KEYNOTE-407 [27, 28]). This was also a practical approach, aligning the number of neoadjuvant cycles of durvalumab with the duration of the standard-of-care chemotherapy regimen that was already known to have an acceptable benefit-risk profile in patients with resectable NSCLC.

After intervening surgery in AEGEAN, adjuvant immunotherapy was then applied in order to consolidate anti-tumor immunity initiated in the neoadjuvant induction phase, and thus eradicate or maintain effective control of micrometastatic disease. Note that durvalumab clearance is expected to result in significant waning of PD-L1/PD-1 axis inhibition post-surgery in the absence of further exposure. The favorable safety and tolerability profile of durvalumab allows for the investigation of more prolonged treatment exposure (in the perioperative setting) than with chemotherapy, which is usually limited by cumulative toxicity.

At the time of the design of the AEGEAN study, the best evidence regarding duration of maintenance treatment came from the stage III unresectable NSCLC setting, where data from the Phase III PACIFIC trial established curative intent chemoradiation followed by one year of durvalumab in patients who had not progressed post chemoradiation as an important standard of care [30]. The adjuvant treatment duration chosen in AEGEAN aligns with that in the PACIFIC trial, where durvalumab treatment has been shown to be both effective (demonstrating clinically meaningful benefits in PFS and OS) and have a tolerable and manageable safety

profile. This also aligns with the duration of treatment chosen in pivotal adjuvant only trial designs, which have since led to regulatory approvals [16, 17], further supporting that this is an appropriate treatment duration for the disease setting.

Since AEGEAN was designed, other registrational studies investigating anti-PD-L1/PD-1 immunotherapy have employed perioperative designs across multiple tumor types and reported clinically meaningful improvement in patient outcomes. These include the Phase III KEYNOTE-671 and KEYNOTE-522 studies, which have led to the regulatory approval of perioperative pembrolizumab in resectable NSCLC [19] and in early-stage, triple-negative breast cancer [42], respectively. Other ongoing registrational studies investigating perioperative immunotherapy in resectable NSCLC include CheckMate-77T [43] and IMpower030 [44].

In summary, based on the strength of prevailing data, AEGEAN was designed as a perioperative study, assessing durvalumab (or placebo) given in combination with platinum-based chemotherapy in the neoadjuvant phase, followed by adjuvant durvalumab (or placebo) monotherapy after surgery. The rationale for perioperative immunotherapy is to combine the advantages afforded by neoadjuvant treatment, in terms of optimal immune response stimulation, early locoregional disease control, and early elimination/suppression of micrometastatic disease, with the advantages of post-surgical adjuvant treatment, in terms of antitumor immunity consolidation and elimination/suppression of residual cancer cells in patients who are not cured by surgery, with the aim of improving long-term patient outcomes [45].

The FDA's Position:

FDA disagrees with the Applicant's position. At the time of the design of AEGEAN, the available clinical evidence did not support the Applicant's statement that "…utilizing a neoadjuvant-only approach in an AEGEAN investigational arm was not considered optimal", given the absence of evidence showing inferior clinical efficacy of neoadjuvant chemoimmunotherapy alone relative to ICI-containing perioperative therapy in both the neoadjuvant and adjuvant treatment phases. Although the use of "maintenance" immunotherapy improves clinical outcomes in metastatic NSCLC, this observation alone does not support the Applicant's rationale that the adjuvant durvalumab phase is necessary after neoadjuvant durvalumab in combination with chemotherapy. The majority of patients with metastatic NSCLC will have residual macroscopic disease after induction chemoimmunotherapy, whereas few patients will have residual macroscopic disease after completion of neoadjuvant chemoimmunotherapy followed by surgery in the resectable setting. These differences in tumor burden following completion of surgery for resectable NSCLC compared with completion of chemoimmunotherapy for metastatic NSCLC may be expected to result in differential benefit for additional immunotherapy in these populations.

The Applicant notes, "at the time of the AEGEAN trial design, there was no robust clinical evidence to support any expectation that neoadjuvant immunotherapy or chemoimmunotherapy alone would be sufficient to substantially improve and optimize long-

term outcomes for patients with resectable NSCLC, in the absence of maintenance treatment." The uncertainty around whether neoadjuvant alone would be effective and the additional uncertainty regarding whether adjuvant adds to a neoadjuvant chemoimmunotherapy approach is the very reason why FDA recommended that the contribution of the phases of the perioperative regimen be characterized within the AEGEAN trial. Indeed, given the strong biologic rationale of neoadjuvant treatment in the setting of an intact tumor, and shorter duration of neoadjuvant treatment, support for the additional year of additional adjuvant ICI is particularly important.

Given the trial design of AEGEAN, we are forced to look to external data to support the need for both phases of perioperative treatment with durvalumab. While we have allowed external results to support contribution of components of a regimen, external data are currently not supportive given results supporting the use of ICI (nivolumab) as a neoadjuvant chemoimmunotherapy alone regimen, as well as new information that durvalumab alone in the adjuvant setting does not appear effective. Finally, acknowledging the challenges with cross-trial comparison, the existing perioperative approval (pembrolizumab) does not appear to have results that are far superior to either neoadjuvant or adjuvant alone results.

In conclusion, given its two-arm study design, AEGEAN does not allow for within-trial assessment of the individual contribution of durvalumab in the neoadjuvant and adjuvant phases of therapy to the treatment effect of the perioperative regimen. Contribution of phase is reliant on cross-trial comparisons and their attendant limitations, with emerging results not providing support for the need of both phases. What is clear is that administration of ICI therapy in both phases increases overall treatment burden and toxicity, and the AEGEAN trial as designed does not allow for determination of whether or not it is necessary to administer durvalumab in both the neoadjuvant treatment phase and for an additional 1 year after surgery to achieve clinical benefit.

2.2 Summary of Clinical Trials Supporting Efficacy

2.2.1 AEGEAN Study Design

The Applicant's Position:

AEGEAN is an ongoing, Phase III, double-blind, placebo-controlled, randomized, multicenter, international study assessing the efficacy and safety of durvalumab in combination with neoadjuvant platinum-based chemotherapy followed by adjuvant durvalumab monotherapy (D + CTx), compared with placebo in combination with neoadjuvant platinum-based chemotherapy followed by adjuvant placebo alone (Pbo + CTx), for the treatment of patients with resectable NSCLC (Stages IIA to IIIB[N2], per the AJCC 8th edition staging system; squamous or non-squamous) (Figure 1) [46].

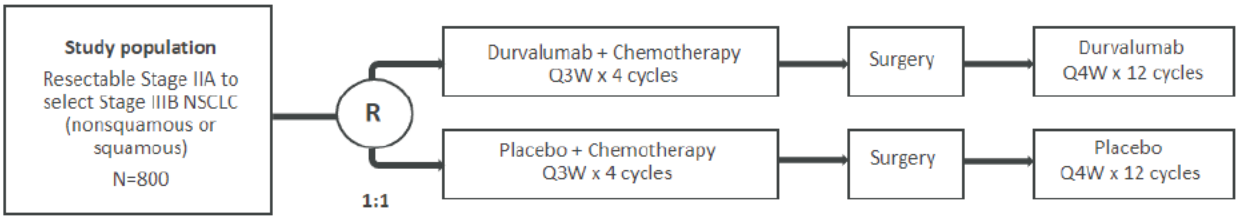
A total of 802 patients were randomized in a 1:1 ratio to the D + CTx arm or the Pbo + CTx arm. Patients were stratified by disease stage (Stage II vs Stage III) and by tumor PD-L1 expression (TC < 1% vs TC ≥ 1%; assessed with the VENTANA SP263 PD-L1 immunohistochemistry assay) at

baseline. Patients were randomized into the study by a total of 183 study centers in 28 countries, with sites across North America (including 20 sites in the US), Central and South America, Europe, and Asia-Pacific. Study centers in the US included 18 urban (90%) and 2 rural (10%) locations, 12 being community cancer centers (60%) and 8 being academic centers (40%).

Permitted chemotherapy options included both cisplatin- and carboplatin-based doublets, consistent with real-world clinical practice. The ESMO and NCCN criteria for the resectability of NSCLC were followed. NCCN guidelines were also followed for margins evaluation and nodal assessment. Following surgery, patients with negative resection margins (R0) or microscopically positive resection margins (R1) were allowed to continue to adjuvant treatment.

An independent data and safety monitoring committee reviewed safety data on a regular basis, and efficacy data at pre-defined efficacy analyses, during the conduct of the study. Blinded independent central review (BICR) was used to assess the dual primary endpoint of EFS and the key secondary endpoint of DFS. Blinded central pathology review was used to evaluate the dual primary endpoint of pCR and the key secondary endpoint of MPR (see Section 2.2.3). Major protocol amendments are summarized in Appendix 3.

Figure 1 AEGEAN Study Design



Stratification factors: Disease stage (Stage II vs Stage III) and PD-L1 expression status (TC <1% vs TC ≥1%)

Note: In total, the study randomized 802 patients (planned enrollment: 800 patients) in a 1:1 ratio to the D + CTx arm or the Pbo + CTx arm. Durvalumab (or placebo) was given at a fixed dose of 1500 mg Q3W in combination with chemotherapy prior to surgery for up to 4 cycles, followed by durvalumab monotherapy 1500 mg Q4W (or placebo) post-surgery for up to 12 cycles.

The FDA's Position:

FDA agrees with the Applicant's position.

2.2.2 Patient Selection

The Applicant's Position:

Eligibility criteria ensured the selection of a patient population that is representative of the real-world patient population with resectable NSCLC in the US and globally: adult patients (at least 18 years of age) with newly diagnosed, previously untreated, histologically- or cytologically-confirmed NSCLC with resectable disease (Stages IIA to IIIB[N2], per the AJCC 8th edition staging system). At screening, patients had to be candidates for lobectomy, sleeve resection, or bilobectomy (and not be planned to undergo pneumonectomy), have an ECOG

performance status of 0 or 1, and have adequate cardiac, lung, hematological, renal, and hepatic function.

From protocol version 4.0 (dated 15 April 2021), patients with EGFRm or ALK gene rearrangements were excluded from enrollment, based on data external to the AEGEAN study suggesting that such patients may have a limited response to immunotherapy, and patients with resected EGFRm NSCLC being shown to achieve significant clinical benefit from adjuvant targeted therapy [20-22]. Patients with known EGFRm or ALK gene rearrangements already enrolled in the study were excluded from efficacy evaluations via the introduction of the modified intent-to-treat (mITT) analysis set, but were included in safety analysis set if they received any study treatment.

The FDA's Position:

FDA agrees with the Applicant's position.

2.2.3 Study Endpoints

The Applicant's Position:

AEGEAN had two primary objectives: to compare D + CTx administered prior to surgery with Pbo + CTx administered prior to surgery in terms of pCR; and to compare the efficacy of the perioperative D + CTx regimen with perioperative Pbo + CTx in terms of EFS. Table 1 defines the primary endpoints of pCR and EFS, the key secondary endpoints of MPR, DFS, and OS, and a supplemental analysis of ORR.

In addition, the study collected patient-reported outcomes using the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires and collected safety data through adverse event reporting.

Table 2 Primary and key secondary efficacy endpoints in AEGEAN

Efficacy Endpoint	Definition
Dual Primary Endpoints	
Pathological complete response (pCR)	Absence of any residual viable tumor at the time of surgical resection in the primary lung lesion, without R1 or R2 margins, and without carcinoma in any examined lymph nodes based on a blinded central pathology review according to IASLC criteria [47].
Event-free survival (EFS)	Time from the date of randomization to the first of any of the following events: • Local or distant recurrence as determined by BICR using RECIST 1.1 assessment; • Death due to any cause; • Disease progression that precludes surgery, or for patients who do not have surgery for a reason other than progression, the date of disease progression per RECIST 1.1 assessment after the surgery eligibility decision date; • Disease progression discovered upon first attempt at surgery that resulted in the surgery not being completed, or for patients who do not complete surgery for a reason other than progression, the date of disease progression per RECIST 1.1 assessment after the surgery date.
Key Secondary Endpoints (included in the multiple testing procedure)	
Major pathological response (MPR)	10% or less residual viable tumor tissue in the primary lung lesion at the time of surgical resection based on a blinded central pathology review according to IASLC criteria [47].
Disease-free survival (DFS) [a]	Time from the date of surgery until the first of any of the following events: • Local or distant recurrence as determined by BICR using RECIST 1.1 assessment; • Death due to any cause. DFS is only to be evaluated for patients who had surgical resection following neoadjuvant period and whose first post-surgical RECIST scan shows no disease (resected and modified resected analysis sets).
Overall survival (OS)	Time from the date of randomization until death due to any cause, regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy.
Supplemental Analyses of Efficacy	
Objective response rate (ORR)	Percentage of patients with BICR-assessed visit response of complete response or partial response at their latest assessment prior to surgery. All data obtained prior to surgery was considered in the assessment of ORR, including unscheduled assessments.

[a] At the time of submission, the sponsor remained blinded to DFS and the study continued in a blinded manner, with patients and Investigators blinded to treatment assignment (see Section 2.2.4).

Note: AEGEAN is an ongoing study. Per the multiple testing procedure (see Appendix 4), DFS and OS will be formally assessed at a subsequent IA or FA. EFS efficacy data will continue to be collected.

The FDA's Position:

FDA agrees with the Applicant's position.

2.2.4 Statistical Methods

The Applicant's Position:

Two pre-planned interim analyses have been completed as of the date of finalization of the Applicant's sections of this briefing document (27 May 2024):

- **pCR IA (DCO of 14 January 2022):** primary analysis of pCR and MPR, which declared statistical significance for both endpoints. The pCR IA was pre-specified to occur after all patients had been randomized to the study and when approximately 400 patients in the mITT population had the opportunity for at least 7 months of follow-up, to allow time for surgery (where applicable) and for completion of pCR and MPR assessments by central pathology review.
- **EFS IA1 (DCO of 10 November 2022):** first interim and primary analysis of EFS (using BICR per RECIST 1.1), which was declared to be statistically significant. EFS IA1 was pre-specified to occur when approximately 224 EFS events had been reported across both treatment arms in the mITT population (approximately 30% maturity). The final analysis of pCR and MPR was also performed at this DCO date, but they were not re-tested for statistical significance.

DFS was also tested at the EFS IA1 DCO but did not meet the pre-specified boundary to declare statistical significance. DFS will be analyzed again at the next pre-specified IA (EFS IA2), when approximately 296 EFS events have been reported in the mITT population (approximately 40% maturity). Following the MTP, OS was not formally tested for statistical significance at EFS IA1 and will only be formally tested following a positive DFS result.

In addition, to fulfill an agreement with FDA for provision of updated data 120 days after the date of application, safety and descriptive OS data were reported at a DCO of 14 August 2023 (referred to as the Safety Update in this document), which corresponds to approximately 9 months of additional study follow-up since the EFS IA1 DCO.

Efficacy evaluations were conducted in analysis sets that followed the intent-to-treat (ITT) principle and excluded patients with EGFRm/ALK gene rearrangements. Safety analyses were performed in the safety analysis set, defined as all randomized patients in the ITT population who received at least one dose (any amount) of study treatment.

Details of the pre-specified MTP and statistical methodology are summarized in Appendix 4. Major changes to the statistical analysis plan (SAP) are summarized in Appendix 5.

The FDA's Position:

FDA agrees with the Applicant's position with additional clarifications. AEGEAN was designed to evaluate the dual primary endpoints of EFS and pCR, and the key secondary endpoints DFS and OS. The study was sized to achieve >90% power for EFS with 371 events, 73% power for DFS with 277 events and 74% power for OS after accruing 232 events, when evaluated in that order.

The statistical analysis plan (SAP) for AEGEAN included two interim analyses (IA) and one final analysis (FA) for EFS. According to the SAP, the DFS and OS endpoints were to be evaluated at the same timepoints as EFS and the timing of these analyses were to be determined after observation of a pre-determined number of events and maturity for EFS (EFS IA1, EFS IA2 and EFS FA at 60%, 80% and 100% information fraction, respectively).

AEGEAN met statistical significance for its primary endpoint of EFS at IA1. Typically, when a primary endpoint is met at an interim analysis, that analysis is considered the final analysis for the endpoint and subsequent analysis timing for remaining secondary endpoints are guided by the number of events needed for the interim and/or final analysis of each endpoint in the prespecified testing order. However, the AEGEAN SAP relies on maturity of EFS, which has reached statistical significance, to determine the timing of the DFS and OS analyses. Additionally, the OS events in AEGEAN are accumulating faster than the expected rate, while fewer than expected DFS events have accrued due to smaller than initially predicted analysis population for this endpoint. As a result, even if the number of OS events observed at EFS IA2 surpasses the planned number of events needed for the final analysis, OS will not qualify for testing unless DFS reaches statistical significance. The current trend in DFS is unknown as this endpoint remains blinded. Based on the current data, it is likely that formal testing of OS will not have occurred at the time of regulatory action on this BLA.

Of note, additional follow up may provide more clarity on the DFS and OS outcomes for this study. Importantly, FDA acknowledges that the study already provides a statistically significant and meaningful effect on EFS, an endpoint suitable for traditional approval for marketing applications evaluating neoadjuvant and perioperative approaches. The purpose of this ODAC is to discuss whether the high uncertainty around the contribution of phases (particularly the need for adjuvant treatment in addition to neoadjuvant chemoimmunotherapy) precludes our ability to adequately assess the benefit in light of potential overtreatment.

2.3 Efficacy Summary

2.3.1 AEGEAN Patient Population

The Applicant's Position:

2.3.1.1 Patient Disposition

A total of 1480 patients were enrolled in the AEGEAN study, with 802 patients randomized in a 1:1 ratio to the D + CTx arm (400 patients) or Pbo + CTx arm (402 patients), forming the ITT population. Randomization was complete before the pCR IA database lock (22 April 2022).

At the pCR IA (DCO of 14 January 2022), 402 patients were included in the interim mITT population: 196 patients in the D + CTx arm and 206 patients in the Pbo + CTx arm.

At the EFS IA1 (DCO of 10 November 2022), a total of 740 randomized patients were included in the mITT population: 366 patients in the D + CTx arm and 374 patients in the Pbo + CTx arm. At this DCO: no patient was ongoing with neoadjuvant treatment; all 4 cycles of neoadjuvant durvalumab/placebo were completed by 318 patients (86.9%) in the D + CTx arm and 331 patients (88.5%) in the Pbo + CTx arm; on-study surgery was completed by 284 patients (77.6%) in the D + CTx arm and 287 patients (76.7%) in the Pbo + CTx arm. Adjuvant durvalumab/placebo treatment was started by 241 patients (65.8%) in the D + CTx arm and 237 patients (63.4%) in the Pbo + CTx arm; among these patients, at EFS IA1 DCO, adjuvant treatment was ongoing for 85/241 patients (35.3%) in the D + CTx arm and 88/237 patients (37.1%) in the Pbo + CTx arm.

At the Safety Update (DCO of 14 August 2023), one more patient started adjuvant treatment in the D + CTx arm compared to EFS IA1 (for a total of 242 patients [66.1%] in this arm [mITT population]). Among patients who had started adjuvant treatment by the Safety Update DCO, adjuvant treatment was ongoing for 4/242 patients (1.7%) in the D + CTx arm and 3/237 patients (1.3%) in the Pbo + CTx arm. A total of 76/242 patients (31.4%) in the D + CTx arm and 86/237 patients (36.3%) in the Pbo + CTx arm discontinued adjuvant durvalumab/placebo treatment prior to completing all 12 cycles; the most common reason was radiological progression according to RECIST 1.1 in both treatment arms (30/242 patients [12.4%] for D + CTx vs 60/237 patients [25.3%] for Pbo + CTx).

See Appendix 6 for an overview of patient disposition at EFS IA1 and Safety Update. Adverse events (AEs) leading to study treatment discontinuation are summarized in Section 3.

2.3.1.2 Demographics and Baseline Characteristics

Overall, demographics and baseline disease characteristics of patients in the mITT population were generally well-balanced between treatment arms and were representative of the intended patient population with resectable NSCLC. Consistent with real-world practice, the majority of patients in the mITT population (73.5%) were planned to receive carboplatin, while the remaining 26.5% of patients were planned to receive cisplatin (see detailed breakdown in Appendix 7).

US-specific demographics and patient characteristics are summarized in Appendix 16 and are discussed in Section 5.1.

2.3.1.3 Important Protocol Deviations

The number of patients in the mITT population with important protocol deviations was low (< 5% overall) and balanced between treatment arms. Their nature did not suggest an impact on the overall quality of the study, including its conduct and the collection of data.

The FDA's Position:

FDA agrees with the Applicant's position.

2.3.2 Overview of AEGEAN Efficacy Results

The Applicant's Position:

2.3.2.1 Dual Primary Endpoint: Pathological Complete Response (pCR)

The AEGEAN study met the primary endpoint of pCR (per central pathology review) at the pCR IA DCO (14 January 2022; interim mITT population). At this DCO, a higher pCR rate was observed for patients in the D + CTx arm compared to the Pbo + CTx arm (17.86% vs 4.85%, respectively), which resulted in a statistically significant and meaningful 13.03% improvement (95% CI: 7.11, 19.52) in pCR rate in favor of the D + CTx arm (2-sided p-value = 0.000036) (Table 2).

At the EFS IA1 DCO (10 November 2022; mITT population), the final analysis of pCR was consistent with that observed at the pCR IA, with a meaningful 12.96% improvement (95% CI: 8.67, 17.57) in pCR rate between treatment arms in favor of D + CTx (Table 2). At this DCO, improvement in pCR rate in favor of D + CTx was also demonstrated across all pre-specified subgroups, including race, age, sex, and geographic region (see Appendix 8).

Table 3 Pathological complete response: primary analysis (interim mITT population at pCR IA) and final analysis (mITT population at EFS IA1)

pCR IA DCO (14 January 2022): Interim (primary) analysis of pCR		
Interim mITT cohort	**D + CTx (N = 196)**	**Pbo + CTx (N = 206)**
Number of patients with pCR	35	10
pCR rate, % (95% CI)	17.86 (12.76, 23.95)	4.85 (2.35, 8.75)
Difference in proportions, % (95% CI)	13.03 (7.11, 19.52)	
2-sided p-value [a]	0.000036	
EFS IA1 DCO (10 November 2022): Final analysis of pCR		
mITT cohort	**D + CTx (N = 366)**	**Pbo + CTx (N = 374)**
Number of patients with pCR	63	16
pCR rate, % (95% CI)	17.21 (13.49, 21.48)	4.28 (2.46, 6.85)
Difference in proportions, % (95% CI)	12.96 (8.67, 17.57)	

[a] The boundary for declaring statistical significance was 0.0082% for a total 0.5% 2-sided alpha.

Statistical analysis methods are summarized in Appendix 4.
Source: Tables 14.2.1.1.IA and 14.2.1.1.FA.

2.3.2.2 Dual Primary Endpoint: Event-free Survival (EFS)

The AEGEAN study met the primary endpoint of EFS at the EFS IA1 DCO (10 November 2022; mITT population), based on a 31.9% maturity of data and a 63.6% information fraction. EFS is a validated and internationally accepted endpoint for patients with resectable NSCLC [48], and provides important prognostic information regarding the likelihood of disease recurrence, progression, or death.

EFS IA1 demonstrated a statistically significant and clinically meaningful 32% reduction in the risk of an EFS event (using BICR assessment per RECIST 1.1) for patients in the D + CTx arm compared to the Pbo + CTx arm (HR = 0.68 [95% CI: 0.53, 0.88]; p-value = 0.003902). Median EFS was not reached for the D + CTx arm, compared to a median EFS of 25.9 months in the Pbo + CTx arm (Table 3).

The EFS Kaplan-Meier curves overlapped until approximately 3 months post-randomization, after which there was a clear and sustained separation that favored the D + CTx arm (Figure 2), as shown by a greater proportion of patients in the D + CTx arm who were alive and event-free at 12 months and 24 months post-randomization compared to the Pbo + CTx arm (Table 3). This delayed separation was expected given the first planned disease assessment was scheduled approximately 3 months after randomization (ie, pre-surgery). A pre-planned analysis of piecewise HRs suggested improvement in the EFS HR over time (Table 3).

Of note, there was a lower proportion of patients in the D + CTx arm vs the Pbo + CTx arm experiencing EFS events of "progression that precluded surgery" and "progression discovered upon attempting surgery", which directly reflect efficacy of treatment during the neoadjuvant phase of the study (Table 3). The proportion of patients with EFS events of "RECIST recurrence after surgery" was also lower in the D + CTx arm, providing evidence of efficacy during the post-surgery phase of the study (Table 3).

Improvement in EFS favoring the D + CTx arm was observed across all pre-specified subgroups, including race, age, geographic region, disease stage, and PD-L1 TC expression status. Of note, EFS benefit was observed for D + CTx regardless of the platinum chemotherapy agent used (see Appendix 9).

Robustness of the treatment effect was also demonstrated by the results of the pre-specified EFS sensitivity analyses, which were consistent with the primary analysis (see Appendix 10).

Collectively, data from the evaluations of EFS in the AEGEAN study provide evidence of the benefits of perioperative durvalumab in the target patient population, which is likely to be predictive of improved long-term survival benefits.

Table 4 Event-free survival (using BICR per RECIST 1.1) (mITT population; EFS IA1)

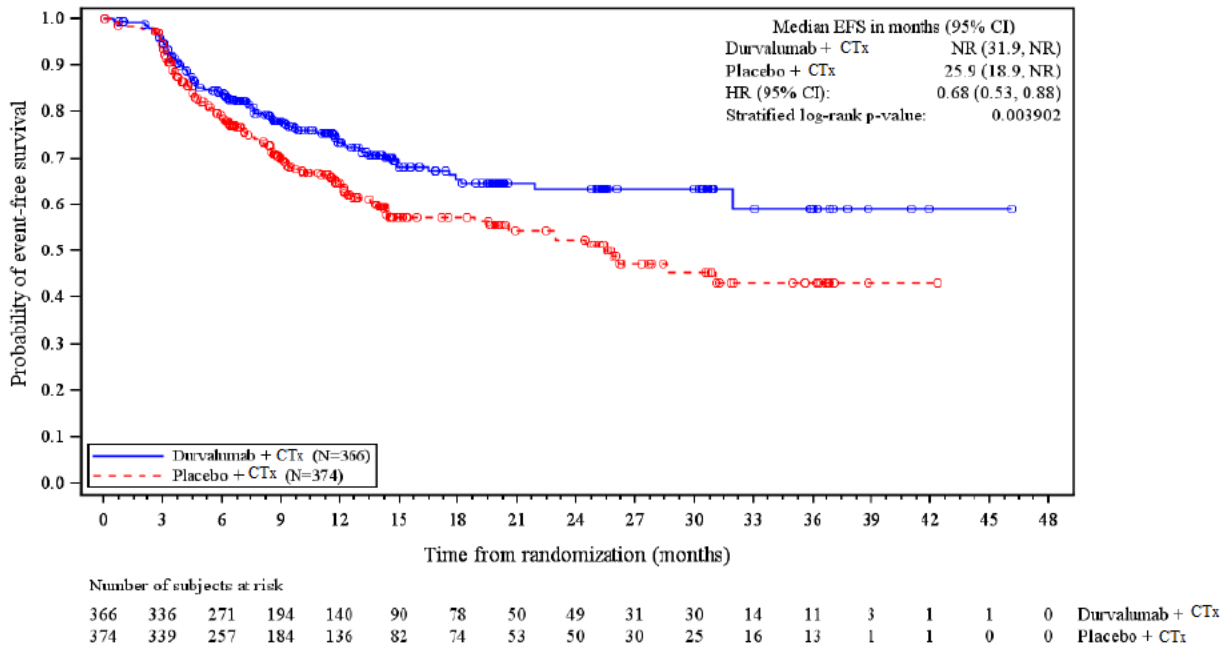
	D + CTx (N = 366)	Pbo + CTx (N = 374)
Patients with events, n (%)	**98 (26.8)**	**138 (36.9)**
Progression that precluded surgery	26 (7.1)	35 (9.4)
Progression discovered upon attempting surgery	5 (1.4)	13 (3.5)
RECIST recurrence after surgery	38 (10.4)	60 (16.0)
Death due to any cause	29 (7.9)	30 (8.0)
Censored patients, n (%)	**268 (73.2)**	**236 (63.1)**
Median EFS (95% CI) (months) [a]	**NR (31.9, NR)**	**25.9 (18.9, NR)**
EFS rate at 12 months, % (95% CI) [a]	73.4 (67.9, 78.1)	64.5 (58.8, 69.6)

	D + CTx (N = 366)	Pbo + CTx (N = 374)
EFS rate at 24 months, % (95% CI) [a]	63.3 (56.1, 69.6)	52.4 (45.4, 59.0)
Median (range) duration of follow-up in censored patients (months)	11.66 (0 to 46.1)	11.73 (0 to 42.4)
Hazard ratio (95% CI)	**0.68 (0.53, 0.88)**	
2-sided p-value	**0.003902**	
Piecewise hazard ratios (95% CI)		
0 to 3 months	0.90 (0.47, 1.70)	
3 to 6 months	0.69 (0.45, 1.05)	
6 to 12 months	0.63 (0.39, 1.02)	
12 to 36 months	0.58 (0.30, 1.10)	

[a] Calculated using the Kaplan-Meier technique.

Statistical analysis methods are summarized in Appendix 4.
DCO: 10 November 2022.
Source: Tables 14.2.3.1.IA1 and 14.2.3.13.IA1.

Figure 2 **Kaplan-Meier plot of EFS (using BICR per RECIST 1.1) (mITT population, EFS IA1)**



A circle indicates a censored observation. DCO: 10 November 2022.
Source: Figure 14.2.3.2.IA1.

2.3.2.3 Key Secondary Endpoint: Major Pathological Response (MPR)

At the pCR IA DCO (interim mITT population), the AEGEAN study met the key secondary endpoint of MPR (per central pathology review): the MPR rate was 34.18% (95% CI: 27.57, 41.28) in the D + CTx arm compared to 14.08% (95% CI: 9.64, 19.59) in the Pbo + CTx arm. This corresponded to a meaningful 20.07% difference in proportions in favor of the D + CTx arm, which was statistically significant (95% CI: 11.85, 28.26; 2-sided p-value = 0.000002).

The MPR findings at the final analysis (EFS IA1; mITT population) were consistent with the MPR findings at the interim analysis: the MPR rate in D + CTx arm was 33.33% (95% CI: 28.52, 38.42) vs 12.30% (95% CI: 9.15, 16.06) in the Pbo + CTx arm. This corresponded to a 21.03% difference in proportions in favor of the D + CTx arm (95% CI: 15.14, 26.93).

2.3.2.4 Supplemental Analysis of Efficacy: Objective Response Rate (ORR)

In the mITT population at EFS IA1, treatment with D + CTx resulted in a meaningful improvement in ORR (using BICR per RECIST 1.1) prior to surgery, compared with Pbo + CTx: 206 patients (56.3%) in the D + CTx arm vs 142 patients (38.0%) in the Pbo + CTx arm (difference in proportions: 18.26 [95% CI: 11.16 to 25.18]). Objective response includes both complete response and partial response, with complete response reported for 4 patients (1.1%) in the D + CTx arm vs 1 patient (0.3%) in the placebo + CTx arm.

2.3.2.5 Key Secondary Endpoint: Overall Survival (OS)

At the EFS IA1 DCO (10 November 2022; mITT population), OS was not eligible for statistical testing per the MTP (see Section 2.2.4). At this DCO, OS data had a 22.1% maturity, with a comparable number of deaths occurring in each treatment arm: 81 patients (22.1%) in the D + CTx arm and 82 patients (21.9%) in the Pbo + CTx arm (Table 4).

At the Safety Update DCO (14 August 2023), an updated descriptive analysis of OS was conducted with approximately 9 months of additional study follow-up since the EFS IA1 DCO and an overall OS maturity of 28.6%. This included 49 new OS events (for a total of 212 OS events) in the mITT population: 18 new OS events in the D +CTx arm and 31 new OS events in the Pbo + CTx arm (Table 4). The median duration of follow-up in censored patients increased from 15.90 months at the EFS IA1 DCO to 24.80 months at the Safety Update DCO.

At the EFS IA1 DCO, the OS HR was 1.02 (95% CI: 0.75, 1.39) (Table 4). At the Safety Update DCO, with a small increase in data maturity, a trend toward improved OS favoring the D + CTx arm was observed (OS HR was 0.91 [95% CI: 0.69, 1.19]). At both DCOs, the median OS had not been reached for either treatment arm (Table 4).

At the Safety Update, the Kaplan-Meier OS curves were similar until approximately 20 months post-randomization (Figure 3), after which there was a sustained separation that favored D + CTx, as reflected in a greater proportion of patients who were alive at 24 months and 36 months post-randomization in the D + CTx arm compared to the Pbo + CTx arm (Table 4).

Table 5 Overall survival (mITT Population; EFS IA1 and Safety Update)

	EFS IA1 DCO (10 Nov 2022)		Safety Update DCO (14 Aug 2023)	
	D + CTx (N = 366)	Placebo + CTx (N = 374)	D + CTx (N = 366)	Placebo + CTx (N = 374)
Death, n (%)	81 (22.1)	82 (21.9)	99 (27.0)	113 (30.2)
Censored patients, n (%)	285 (77.9)	292 (78.1)	267 (73.0)	261 (69.8)
Median OS (95% CI) (months) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (40.3, NR)
OS rate at 12 months, % (95% CI) [a]	83.6 (79.2, 87.2)	85.9 (81.7, 89.1)	84.3 (80.1, 87.7)	85.2 (81.2, 88.5)
OS rate at 24 months, % (95% CI) [a]	71.7 (65.2, 77.2)	72.0 (65.5, 77.5)	74.6 (69.5, 79.0)	72.2 (67.0, 76.8)
OS rate at 36 months, % (95% CI) [a]	NR	NR	66.2 (59.3, 72.2)	63.2 (56.5, 69.2)
Median (range) duration of follow-up in censored patients (months)	15.87 (0.8 to 46.3)	15.90 (0.7 to 43.3)	24.61 (0.8 to 55.4)	25.00 (0.7 to 52.4)
Hazard ratio (95% CI)	1.02 (0.75, 1.39)		0.91 (0.69, 1.19)	

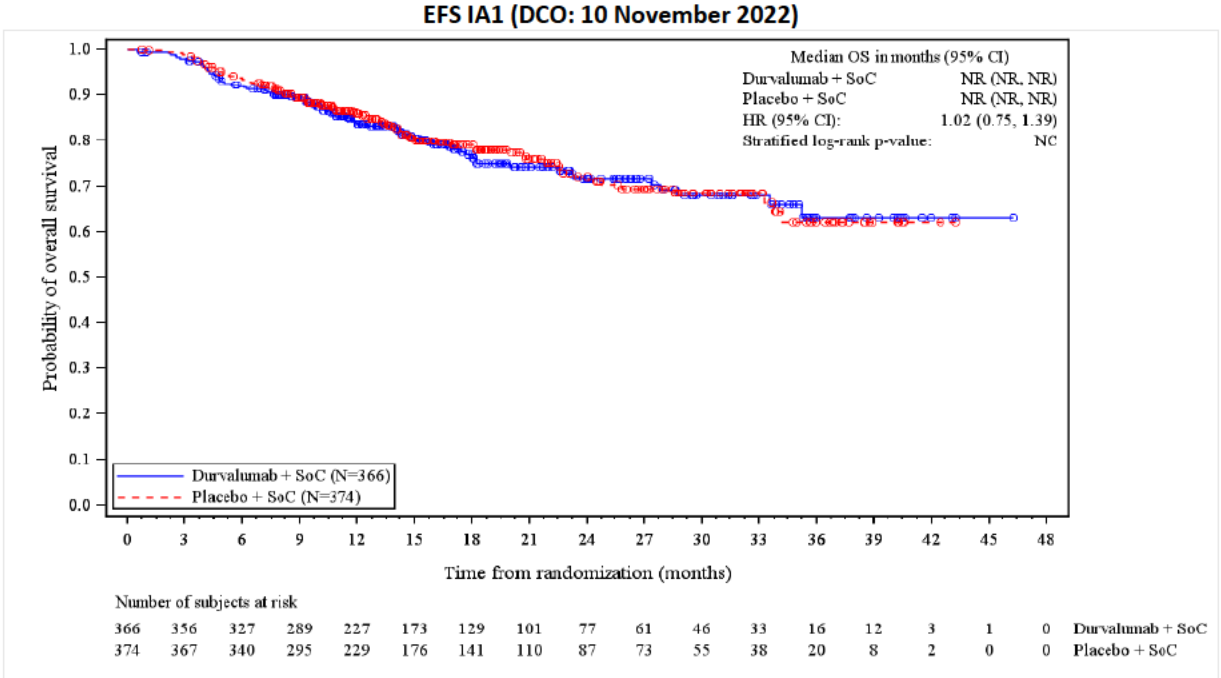
[a] Calculated using the Kaplan-Meier technique.

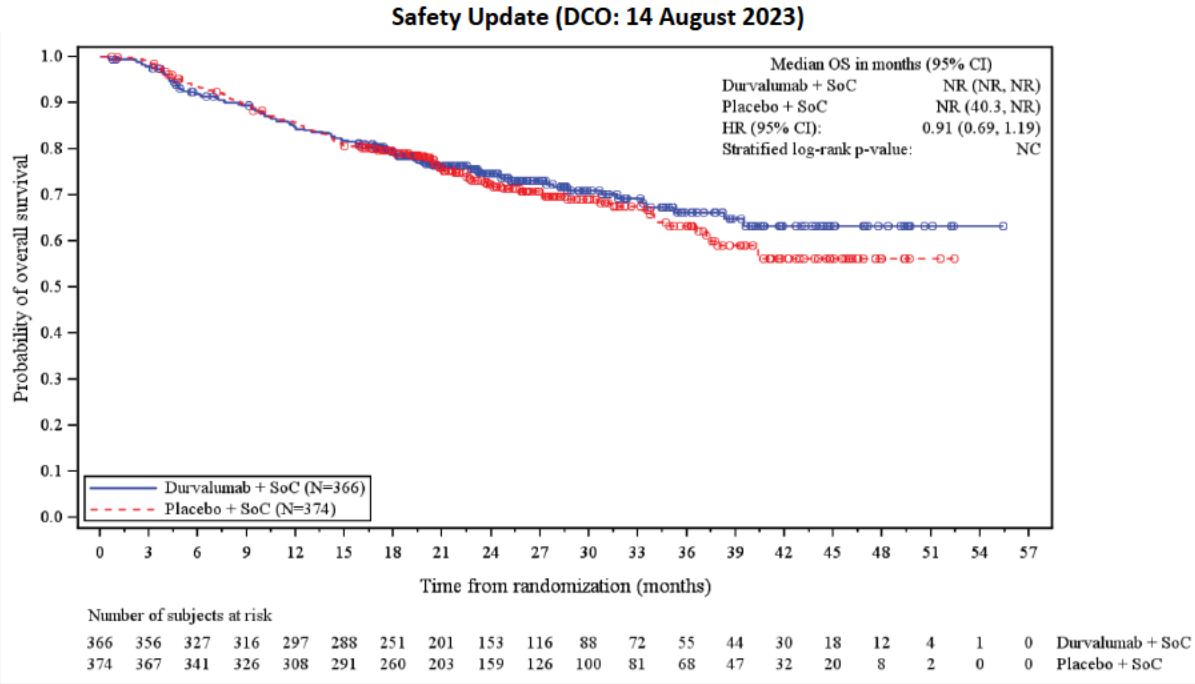
Statistical analysis methods are summarized in Appendix 4.

DCO: 10 November 2022 (EFS IA1) and 14 August 2023 (Safety Update).

Source: Table 14.2.5.1.IA1, Table 14.2.5.9.IA1, Table 14.2.5.1.120DSU, and Table 14.2.5.9.120DSU.

Figure 3 Kaplan-Meier plots of OS (mITT population; EFS IA1 and Safety Update)





A circle indicates a censored observation.
DCO: 10 November 2022 (EFS IA1) and 14 August 2023 (Safety Update).
Source: Figure 14.2.5.2.IA1 and Figure 14.2.5.2.120DSU.

Of note, the AEGEAN study enrolled patients during the COVID-19 pandemic, including the period where COVID-19 vaccines were unavailable. It is known that patients with NSCLC were at a higher risk of mortality from COVID-19 in this period [49]. A pre-defined sensitivity analysis of OS, which censored on the date of death patients whose primary cause of death was COVID-19, suggested that deaths due to COVID-19 potentially impacted the OS analysis: at EFS IA1, the sensitivity analysis resulted in an HR of 0.94 (95% CI: 0.69 to 1.29); and at the Safety Update DCO, this resulted in a numerically improved HR of 0.85 (95% CI: 0.64, 1.12). The corresponding Kapan-Meier OS curves are shown in Appendix 11.

OS remains eligible for statistical testing per the MTP and will be re-evaluated at future timepoints.

2.3.3 Efficacy Conclusions

The Applicant's Position:

The Phase III AEGEAN study demonstrated that neoadjuvant treatment with D + CTx resulted in statistically significant and meaningful improvements in pCR and MPR rates, as well as a

numerical increase in ORR prior to surgery, as compared to Pbo + CTx. These results represent a substantial improvement in pathological regression rate and locoregional tumor eradication with the addition of durvalumab to standard-of-care chemotherapy when given prior to surgery.

Additionally, AEGEAN demonstrated that perioperative treatment with D + CTx resulted in a statistically significant and clinically meaningful 32% reduction in the risk of an EFS event as compared to Pbo + CTx, as well as a trend for improved OS favoring D + CTx. The EFS benefit seen with D + CTx treatment was sustained over time and translates to a substantial reduction in the risk of neoadjuvant disease progression precluding surgical resection, disease recurrence post-surgery, or death. These data suggest that durvalumab in combination with chemotherapy prior to surgery, followed by durvalumab monotherapy post-surgery, has a beneficial impact on patients' long-term disease control and overall prognosis.

Notably, improvements in pCR and EFS favoring the D + CTx arm were observed across all pre-specified subgroups, providing reassurance that the proposed treatment regimen is beneficial across a broad patient population, irrespective of demographics, geographic region, tumor histology, disease stage, ECOG performance status, PD-L1 TC expression status, and platinum chemotherapy agent (cisplatin or carboplatin).

The totality of efficacy results reported herein support the conclusion that the proposed treatment regimen of durvalumab in combination with chemotherapy prior to surgery, followed by durvalumab monotherapy post-surgery, led to a substantial enhancement of pathological regression and clinically meaningful improvement of long-term efficacy outcomes in patients with resectable NSCLC (stages IIA-IIIB[N2]) and no known EGFRm or ALK gene rearrangements.

The FDA's Position:

FDA generally agrees with Applicant's description of the efficacy results with additional considerations. FDA acknowledges that the AEGEAN trial met its primary endpoint and demonstrated a statistically significant and clinically meaningful improvement in EFS. In general, EFS is considered an acceptable endpoint to support approval in the disease setting of early-stage resectable NSCLC, with the ability to support approval dependent on the magnitude of effect, the toxicity profile, and reassurance of no detrimental effect on OS.

While FDA concurs that AEGEAN demonstrated an EFS benefit of perioperative durvalumab that extends into the post-surgery period, FDA clarifies that the AEGEAN trial design does not allow the ability to determine if the benefit observed in the post-surgery period requires the addition of the adjuvant durvalumab phase. Since the experimental arm of AEGEAN included durvalumab in both the neoadjuvant and adjuvant phases, the post-surgery EFS benefit could reflect the effect of neoadjuvant chemotherapy in combination with durvalumab. FDA also clarifies that the OS analysis conducted at the 120-day safety update suggests there is no detrimental effect of the experimental regimen on OS rather than supporting the claim that there is a "trend for improved OS" favoring the durvalumab arm, as stated by the Applicant. While AEGEAN provides evidence of benefit as measured by EFS for patients receiving

perioperative durvalumab, to date there is no evidence of an overall survival benefit, and the improvement in EFS cannot be interpreted as a predictor for an improvement in long term survival.

FDA reiterates the focus of this ODAC is not on the EFS result, but rather to discuss whether the high uncertainty around the contribution of phases (particularly the need for adjuvant treatment in addition to neoadjuvant chemoimmunotherapy) precludes our ability to adequately assess the EFS benefit in light of potential overtreatment. Given the inability to use AEGEAN to support contribution of phases, the review team has had to look at external data.

At present, four randomized trials have supported approvals of ICIs for the treatment of resectable NSCLC. One of the four trials led to approval of a neoadjuvant indication (CHECKMATE-816 [NCT02998528]); two trials led to approvals of adjuvant indications (IMpower-010 [NCT02486718], KEYNOTE-091 [NCT02504372]); and one trial led to approval of a perioperative indication (KEYNOTE-671 [NCT03425643]). Table 6 shows the available data for these approved treatment options, AEGEAN, and publicly available results for another multiregional perioperative trial, CheckMate-77T.

Table 6: Randomized Trials of Immune Checkpoint Inhibitors (ICIs) for Patients with Resectable NSCLC

	Neoadjuvant Only	Adjuvant Only		Perioperative (Neoadjuvant followed by Adjuvant)		
ICI	**Nivolumab**	**Atezolizumab**	**Pembrolizumab**	**Pembrolizumab**	**Durvalumab**	**Nivolumab**
Stage	IB[a]-IIIA	II-IIIA	IB[a]-IIIA	II-IIIB	II-IIIB	II-IIIB
Trial	CHECKMATE-816	IMpower-010	KEYNOTE-091	KEYNOTE-671	AEGEAN	CHECK MATE-77T
Primary Endpoint(s)	EFS/pCR	DFS	DFS	EFS/OS	EFS/pCR	EFS
DFS/EFS HR (95% CI)	**0.63 (0.45, 0.87)**	**0.66 (0.50, 0.88)**	**0.73 (0.60, 0.89)**	**0.58 (0.46, 0.72)**	**0.68 (0.53, 0.88)**	**0.58 (0.42, 0.81)**

While we acknowledge that cross trial comparisons limit the ability to draw definitive conclusions from this data, the AEGEAN design requires us to use external data with its attendant limitations to support contribution of each phase of this perioperative regimen. Rather than support the need for the addition of adjuvant treatment to neoadjuvant chemoimmunotherapy, the observation of similar treatment effect sizes across trials raises concerns for the possibility of overtreatment when using a regimen approach incorporating ICI in both phases of treatment and challenges the notion that the perioperative regimen approach is needed for all patients.

As discussed, in meetings with the Applicant held during the design and conduct of AEGEAN, FDA recommended using alternative design options including an adaptive or factorial trial design to address durvalumab's contribution to each treatment phase. The Applicant opted to proceed with a two-arm trial comparing the perioperative regimen to neoadjuvant chemotherapy followed by surgery. A randomized within trial comparison that directly evaluates the contribution of each phase of therapy would have removed the many uncertainties related to cross-trial comparison.

Thus, as designed, AEGEAN does not distinguish whether the effect on the primary endpoint of EFS is due to durvalumab given in the neoadjuvant phase, in the adjuvant phase, or in both treatment phases. Particularly concerning is the additional year of adjuvant treatment if exposure to ICI and its toxicities does not add additional efficacy to neoadjuvant chemoimmunotherapy. This potential overtreatment comes with increased treatment burden and additional toxicities for patients, some of whom may be cured following surgery. The uncertainty of the contribution of the adjuvant component of the perioperative durvalumab regimen is heightened by accumulating data across trials of ICIs in resectable NSCLC. In addition, the Applicant recently released a statement regarding high-level results from Study BR.31 (NCT02273375), a large multi-center trial of adjuvant durvalumab for patients with resected NSCLC, conducted by the Canadian Cancer Trials Group (CCTG).[52] The trial did not achieve statistical significance for the primary endpoint of DFS in patients whose tumors express PD-L1 on 25% or more tumor cells. These results add to the uncertainty regarding the contribution, if any, of adjuvant durvalumab to the treatment effect observed in AEGEAN.

Finally, even if a statistically significant improvement in OS is eventually demonstrated in the AEGEAN trial, the inability to demonstrate contribution of phase would remain problematic. While demonstration of an overall survival benefit might mitigate some concerns over severe toxicities from addition of adjuvant ICI, the fundamental deficiency in trial design does not address the core issue of whether both phases of therapy are necessary to achieve the observed EFS benefit. It can provide reassurance that treatment is not resulting in a number of deaths due to toxicity that exceeds the number of deaths in the control arm, but it does not capture long-term toxicities or patient burden, and leaves open the question of potentially exposing patients to unnecessary therapy.

3. Safety

The Applicant's Position:

Safety results generated from the AEGEAN study demonstrated that durvalumab in combination with chemotherapy prior to surgery, followed by durvalumab monotherapy post-surgery, in adult patients with resectable (Stage IIA-IIIB[N2]) NSCLC has a tolerable and

manageable safety profile that is consistent with the established safety profiles of the individual agents, i.e., durvalumab monotherapy and chemotherapy.

The safety profile of durvalumab is well-characterized based on an extensive clinical development program and post-marketing experience. More than 5825 patients have been treated in the clinical development program, and the exposure of durvalumab in the post-marketing setting is approximately 144,273 patient-years (DCO 31 October 2023).

The safety of durvalumab in AEGEAN was compared with data pooled from 13 completed studies (N = 4045), including data from patients with NSCLC, breast cancer, bladder cancer, HNSCC, and HCC, among other tumor types.

The exposure and safety analyses from the AEGEAN study presented in this briefing document were performed on the SAS population from the most recent update of exposure and safety data (DCO 14 August 2023).

Overall, based on the review of data from the AEGEAN study, no new safety concerns have been identified for durvalumab when given in combination with chemotherapy, as compared to durvalumab monotherapy, and no evidence of increased risk of known chemotherapy toxicities was observed in the D + CTx arm as compared to the Pbo + CTx arm.

The majority of AEs reported for the study overall were observed during the neoadjuvant period. The majority of imAEs in the D + CTx arm were non-serious, low in severity (CTCAE Grade 1 or 2), manageable, and resolved at the time of the DCO.

3.1 Overall Extent of Exposure

The median overall actual duration of durvalumab/placebo exposure was comparable in the D + CTx and Pbo + CTx arms (Table 5). The median number of treatment cycles of durvalumab/placebo was 11.0 cycles (range: 1 to 16) in the D + CTx arm and 10.0 cycles (range: 1 to 16) in the Pbo + CTx arm.

During the neoadjuvant period, 86.5% of patients in the D + CTx arm and 89.2% of patients in the Pbo + CTx arm completed 4 treatment cycles of durvalumab/placebo.

In the adjuvant period, the median number of durvalumab cycles in the D + CTx arm was 12.0 (range: 1 to 12), and the median number of placebo cycles in the Pbo + CTx arm was also 12.0 (range: 1 to 12). 66.5% of patients in the D + CTx arm and 62.6% of patients in the Pbo + CTx arm who received adjuvant treatment had completed all 12 adjuvant treatment cycles (Table 5). Only 4 patients (1.7%) in the D + CTx arm and 3 patients (1.3%) in the Pbo + CTx arm were still receiving adjuvant treatment.

Table 7 Duration of exposure to study treatment (durvalumab / placebo / chemotherapy) (SAS population; Safety Update DCO)

	Neoadjuvant Period [a]	Adjuvant Period [a]	Overall [b]

	D + CTx (N = 401)	Pbo + CTx (N = 398)	D + CTx (N = 266)	Pbo + CTx (N = 254)	D + CTx (N = 401)	Pbo + CTx (N = 398)
Actual duration of exposure to D/Pbo: Median (min, max) (weeks)	12.00 (0.0, 13.3)	12.00 (3.0, 13.0)	48.00 (4.0, 52.4)	47.86 (4.0, 50.4)	40.14 [c] (2.0, 64.6)	36.14 [c] (3.0, 62.9)
Completed 4 neoadjuvant cycles of D/Pbo (%)	86.5%	89.2%	NA	NA	86.5%	89.2%
Completed 4 neoadjuvant cycles of at least 1 CTx component (%)	87.3%	89.7%	NA	NA	87.3%	89.7%
Completed 4 cycles of neoadjuvant treatment of both CTx components	86.5%	89.4%	NA	NA	86.5%	89.4%
Completed 12 adjuvant cycles of D/Pbo (%)	NA	NA	66.5%	62.6%	44.1% [c]	39.9 [c]
Median number of D/Pbo treatment cycles	4.0	4.0	12.0	12.0	11.0 [c]	10.0 [c]

[a] The actual treatment duration = total treatment duration minus the total duration of dose delays for each period.
[b] The actual treatment duration overall = total treatment duration of both neoadjuvant and adjuvant periods minus the total duration of dose delays for both periods.
[c] Note that the duration of exposure and the median number of cycles in the overall period is lower than for the adjuvant period, since the overall SAS population includes patients who did not start adjuvant treatment.
Source: Table 14.3.1.1.1.1.120DSU, Table 14.3.1.3.2.120DSU, Table 14.3.1.3.3.1.120DSU, Table 14.3.1.3.1.IA1

3.2 Summary of Adverse Events

AEs were assessed in all randomized patients who received at least one dose of study treatment during each of the protocol-specified study periods:

- **Neoadjuvant period:** from the date of the first dose of neoadjuvant study treatment until the date of surgery, or in subjects without surgery until the date of the last dose of treatment + 90 days, or until the start of subsequent therapy, whichever comes first.
- **Surgical period [1]:** from the surgery date to 90 days after surgery or until the start of subsequent therapy, whichever comes first.
- **Adjuvant period [1]:** from the date of the first dose of adjuvant study treatment until the last dose of adjuvant treatment + 90 days or until the start of subsequent therapy, whichever comes first.
- **Overall period:** from the date of the first dose of study treatment until the date of the last dose of study treatment + 90 days or until the start of subsequent therapy, whichever comes first.

AEs were recorded throughout the study and graded according to the National Cancer Institute CTCAE v5.0, categorizing AEs into CTCAE Grades 1-5 based on their severity.

[1] Note that these 2 periods may overlap (since the surgical period may extend beyond the start of adjuvant study treatment).

3.2.1 Adverse Events

An overview of AEs by category and treatment period is provided in Table 6. The most common AEs in the overall study period are shown in Figure 4, and the most common AEs in the neoadjuvant, surgical, and adjuvant periods are shown in Figure 5. These results are summarized by the treatment period in the sections below. Given that some patients were still receiving treatment at the Safety Update DCO, with a larger proportion remaining in safety follow up, updated AE and imAE resolution summaries will be provided at the next pre-specified interim analysis (EFS IA2).

3.2.1.1 Overall Period

In the overall period, a similar proportion of patients in each arm reported AEs: 96.5% in the D + CTx arm vs. 95.2% in the Pbo + CTx arm (Table 6). The majority of AEs reported were non-serious, low in severity (CTCAE Grade 1-2), and resolved in both treatment arms.

The most commonly reported AEs (reported by ≥ 10% of patients in both arms), as well as maximum CTCAE Grade 3 or 4 AEs and SAEs, were hematological and gastrointestinal in nature and were consistent with known toxicities from chemotherapy. A similar proportion of patients in each arm had AEs of anemia, nausea, constipation, decreased appetite, neutropenia/neutrophil count decreased, and alopecia (Figure 4).

Importantly, no new safety concerns were identified for durvalumab in combination with chemotherapy, as compared to durvalumab monotherapy in the pooled safety dataset, and no evidence of increased chemotherapy toxicities was observed with D + CTx treatment compared to Pbo + CTx treatment (Figure 4).

The proportions of patients with AEs of maximum CTCAE Grade 3 or 4 (any causality) were similar in both treatment arms: 174 patients (43.4%) in the D + CTx arm vs. 172 patients (43.2%) in the Pbo + CTx arm) (Table 6). A similar proportion of patients across treatment arms reported AEs of maximum CTCAE Grade 3 or 4 possibly related to durvalumab/placebo (60 patients [15.0%] in the D + CTx arm and 47 patients [11.8%] in the Pbo + CTx arm) and AEs of maximum CTCAE Grade 3 or 4 possibly related to at least 1 chemotherapy component (112 patients [27.9%] in the D + CTx arm and 126 patients [31.7%] in the Pbo + CTx arm).

The frequency of maximum CTCAE Grade 3-4 events of neutropenia, leukopenia, anemia, and thrombocytopenia were similar between the D + CTx and Pbo + CTx arms. Overall, the most commonly reported AEs of maximum CTCAE Grade 3-4 were either consistent with known hematological chemotherapy toxicities or with the known safety profile of durvalumab (see Appendix 15).

Among patients who reported any AE (any grade, any causality), the AEs were resolved in 368/387 patients (95.1%) in the D + CTx arm and in 361/379 patients (95.3%) in the Pbo + CTx arm. AEs (any grade, any causality) were resolved with sequelae in 3 patients in the D + CTx arm and in 4 patients in the Pbo + CTX arm.

Table 8 Overview of adverse events by category and by study treatment period (SAS population; Safety Update DCO)

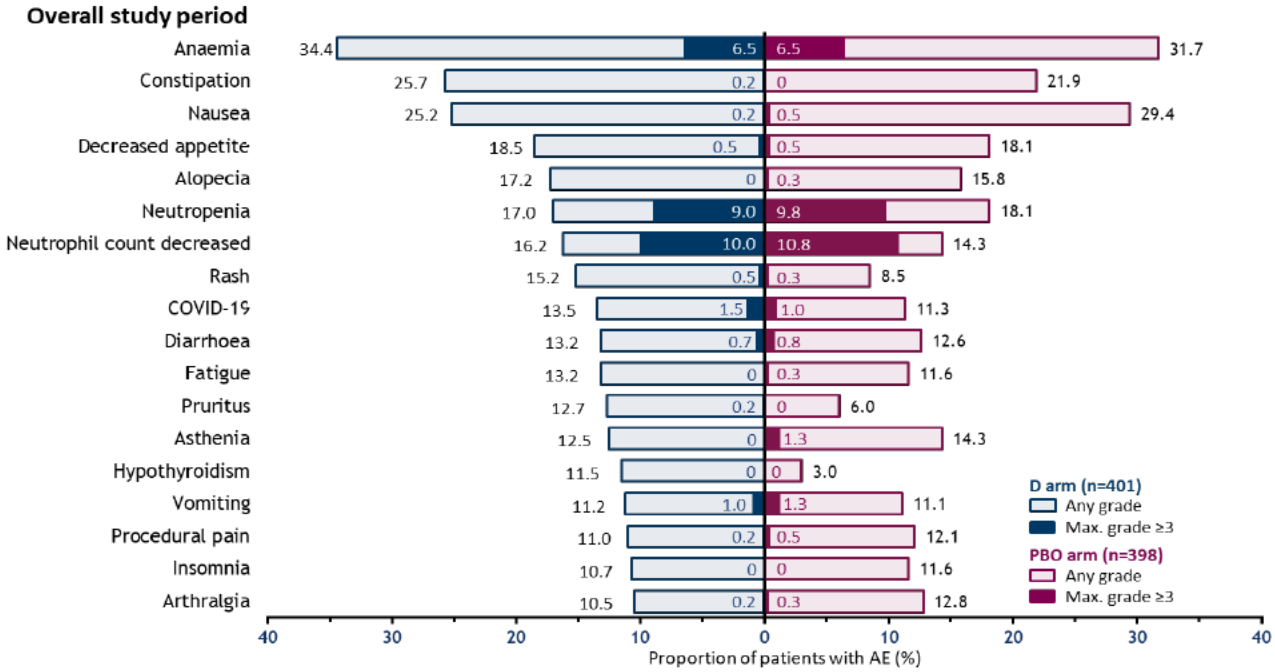
N (%)	Neoadjuvant period †		Surgical period ‡		Adjuvant period §		Overall ¶		Pooled D Safety Data (N = 4045)
	D + CTx (N = 401)	Pbo CTx (N = 398)	D + CTx (N = 325)	Pbo CTx (N = 326)	D + CTx (N = 266)	Pbo + CTx (N = 254)	D + CTx (N = 401)	Pbo + CTx (N = 398)	
Any-Grade all-causality AEs	**365 (91.0)**	**357 (89.7)**	**235 (72.3)**	**219 (67.2)**	**223 (83.8)**	**190 (74.8)**	**387 (96.5)**	**379 (95.2)**	**3825 (94.6)**
Max. CTCAE Grade 3 or 4	130 (32.4)	145 (36.4)	55 (16.9)	41 (12.6)	41 (15.4)	27 (10.6)	174 (43.4)	172 (43.2)	1600 (39.6)
SAEs	83 (20.7)	66 (16.6)	61(18.8)	51 (15.6)	40 (15.0)	26 (10.2)	156 (38.9)	126 (31.7)	1447 (35.8)
Outcome of **death**	8 (2.0)	4 (1.0)	11 (3.4)	9 (2.8)	4 (1.5)	2 (0.8)	23 (5.7)	15 (3.8)	231 (5.7)
AEs Leading to discontinuation of Any Treatment	54 (13.5)	31 (7.8)	N/A	N/A	26 (9.8)	10 (3.9)	78 (19.5)	40 (10.1)	397 (9.8)
AEs leading to discontinuation of D/Pbo	26 (6.5)	15(3.8)	2(0.6)	2(0.6)	26(9.8)	10(3.9)	51 (12.7)	25(6.3)	397 (9.8)
AEs leading to discontinuation of CTx	48(12.8)	31(7.8)	N/A	N/A	N/A	N/A	48(12.0)	31(7.8)	N/A
AEs leading to discontinuation of both D/Pbo and CTx	20(5.0)	15(3.8)	N/A	N/A	N/A	N/A	20(5.0)	15(3.8)	N/A
AEs Leading to on-study surgery not done	7 (1.7)	4 (1.0)	N/A	N/A	N/A	N/A	7 (1.7)	4 (1.0)	N/A
Any-Grade AEs possibly related to any study treatment	**330 (82.3)**	**313 (78.6)**	**83 (25.5)**	**36 (11.0)**	**128 (48.1)**	**74 (29.1)**	**350 (87.3)**	**325 (81.7)**	**2340 (57.8)**
Max. Grade 3 or 4	117 (29.2)	129 (32.4)	11 (3.4)	3 (0.9)	20 (7.5)	9 (3.5)	133 (33.2)	132 (33.2)	459 (11.3)
Outcome of death	3 (0.7)	1 (0.3)	3 (0.9)	0	1 (0.4)	1 (0.4)	7 (1.7)	2 (0.5)	27 (0.7)
Any-Grade imAEs #	33 (8.2)	19 (4.8)	19 (5.8)	2 (0.6)	60 (22.6)	20 (7.9)	102 (25.4)	40 (10.1)	705 (17.4)
imAEs Max. CTCAE Grade 3-4	6 (1.5)	5 (1.3)	6 (1.8)	1 (0.3)	6 (2.3)	4 (1.6)	18 (4.5)	10 (2.5)	175 (4.3)

† First dose of Study Tx (D/Pbo/CT) until the date of surgery or, for patients without surgery, up to the earliest of: last dose of neoadjuvant Tx (D/Pbo/CT) + 90 days, first dose of subsequent anti-cancer Tx, or the DCO date; for assessments recorded on the day of surgery, time was used to determine if it was pre- or post-surgery (if time was not available, it was assumed to occur post-surgery). ‡ Date of surgery (inclusive) to the earliest of 90 days post-surgery, first dose of subsequent anti-cancer Tx, or DCO date. § Date of first dose of Study Tx post-surgery until earliest of: last Study Tx post-surgery + 90 days, date of first dose of subsequent anti-cancer Tx, or DCO date. ¶ First dose of Study Tx (D/Pbo/CT) until the earliest of: the last dose of Study Tx or surgery (taking the latest dose of D/Pbo/CTx/date of surgery) + 90 days, date of the first dose of subsequent anti-cancer Tx, or DCO date. # 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. One patient assigned to the Pbo arm erroneously received a single cycle of D (in the adjuvant phase) and was included in the D arm for the safety analyses.

All reported percentages are based on the total number of patients in each column header as the denominator (i.e., patients who received Tx during that period).

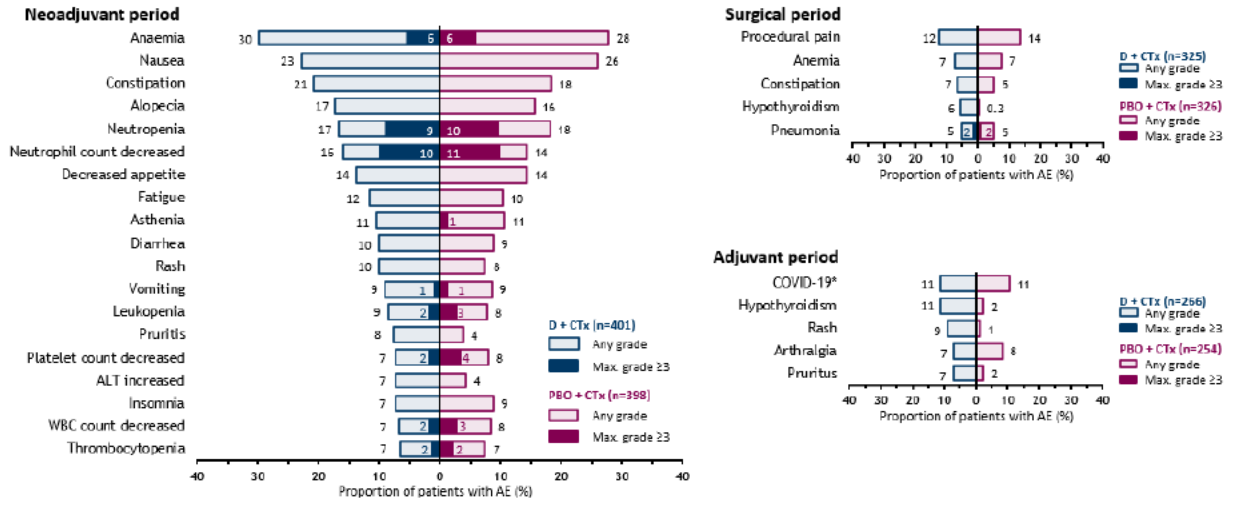
Source: Table 14.3.6.2.1.1.120DSU, iemt 0617.21, iemt 0617.69, Table 14.3.6.2.1.120DSU, Table 14.3.2.1.4.120DSU, Table 14.3.6.2.1.1.120DSU, Table 14.3.2.1.1.120DSU, Table 14.3.2.1.3.120DSU, iemt0617_021, iemt0617.108, Table 14.3.2.2.2.120DSU and Table 14.3.4.1.1.2.120DSU.

Figure 4 Most frequent adverse events in the overall study period (≥ 10% of patients in the D + CTx arm) (SAS population; Safety Update DCO)



Source: Table 14.3.2.3.120DSU.

Figure 5 Most frequent adverse events by study period (≥ 5% of patients in the D + CTx arm) (SAS population; Safety Update DCO



* COVID-19 is summarized as a grouped term comprising the 'COVID-19' and 'COVID-19 pneumonia' preferred terms.
Source: iemt0617.59, iemt0617_020, and iemt0617_101, Table 14.3.2.3.120DSU.

Among patients who reported AEs of maximum CTCAE Grade 3 or 4, the AEs were resolved in 166/174 patients (95.4%) in the D + CTx arm and 159/172 patients (92.4%) in the Pbo + CTx arm. AEs of maximum CTCAE Grade 3 or 4 were resolved with sequelae in 1 patient in the D + CTx arm and in 3 patients in the Pbo + CTX arm.

The proportion of patients with SAEs was 38.9% in the D + CTx arm and 31.7% in the Pbo + CTx arm. The SAEs reported were consistent with the established safety profile of the individual agents, i.e., durvalumab and chemotherapy. Pneumonia was the most frequently reported SAE in the D + CTx arm (5.7% of patients); its incidence was also similar in the Pbo + CTx arm (4.5%) (see Appendix 12).

Overall, 23 (5.7%) patients in the D + CTx arm vs. 15 (3.8%) patients in the Pbo + CTx arm had fatal AEs. Further information regarding AEs with an outcome of death during the overall period is provided in Section 3.4.1.

3.2.1.2 Neoadjuvant Period

In the neoadjuvant period, the proportions of patients with AEs (any Grade, any causality) were similar between arms: 91.0% in the D + CTx arm vs. 89.7% in the Pbo + CTx arm (Table 6).

The most frequent AEs (reported by ≥ 5% of patients in both arms) in the neoadjuvant period were similar in both arms, and included anemia, nausea, constipation, alopecia, neutropenia/neutrophil count decreased, decreased appetite, fatigue, and asthenia (Figure 5). These events are consistent with the known chemotherapy toxicities and occurred at similar frequencies and severities in both arms (Table 6). The majority of these AEs were CTCAE Grade 1-2 in severity. There were no AEs reported with a difference in frequency > 5% between the two arms (Figure 5), and no new safety concerns were observed in either treatment arm.

The proportions of patients with AEs of maximum CTCAE Grade 3-4 in the neoadjuvant period were comparable between arms: 130 (32.4%) in the D + CTx arm vs. 145 (36.4%) in the Pbo + CTx arm (Table 6).

Most AEs leading to discontinuation of any study treatment (durvalumab, or placebo, or any chemotherapy) in the study occurred during the neoadjuvant period: 54 patients (13.5%) in the D + CTx arm and 31 patients (7.8%) in the Pbo + CTx arm (Table 6).

SAEs in the neoadjuvant period were reported by 83 patients (20.7%) in the D + CTx arm and 66 patients (16.6%) in the Pbo + CTx arm (Table 6).

Fatal AEs during the neoadjuvant period were reported for 8 patients (2.0%) in the D + CTx arm and 4 patients (1.0%) in the Pbo + CTx arm (Table 6). Further information regarding AEs with outcome of death is provided in Section 3.4.2.

The addition of durvalumab to chemotherapy as neoadjuvant treatment did not affect the proportion of patients undergoing on-study surgery and did not increase the risk of surgical resection being delayed or not performed: AEs that led to a delay in on-study surgery were reported for a similar proportion of patients in the D + CTx and Pbo + CTx arms (15 patients [3.7%] vs 16 patients [4.0%], respectively); AEs leading to on-study surgery not being performed were reported for a similar proportion of patients in the D + CTx and Pbo + CTx arms (7 patients [1.7%] vs 4 patients [1.0%], respectively) (Table 6). Similar proportions of patients in each arm

experienced a delay in proceeding to surgery, with the majority being delays of less than 2 weeks, and the most common reason for delay being logistical reasons.

3.2.1.3 Surgical Period

A similar proportion of patients underwent on-study surgery in each treatment arm: 81.0% in the D + CTx arm and 81.3% in the Pbo + CTx arm.

Among patients who underwent surgery, 325 patients (72.3%) in the D + CTx arm and 326 patients (67.2%) in the Pbo + CTx arm had an AE. The most frequently reported AEs in the surgical period were procedural pain, anemia, constipation, hypothyroidism, and pneumonia (Figure 5). Hypothyroidism was the only event that was reported with a difference in frequency > 5% between the D + CTx and Pbo + CTx arms (D + CTx: 5.5% vs. Pbo + CTx: 0.3%); all hypothyroidism events in the surgical period were CTCAE Grade 1 or 2 (Figure 5).

AEs related to any study treatment were reported in the surgical period by 83 patients (25.5%) in the D + CTx arm vs. 36 patients (11.0%) in the Pbo + CTx arm. AEs of maximum CTCAE Grade 3 or 4 were reported in 55 patients (16.9%) in the D + CTx arm vs. 41 patients (12.6%) in the Pbo + CTx arm. The proportion of patients with SAEs in the surgical period was 18.8% in the D + CTx arm and 15.6% in the Pbo + CTx arm (Table 6).

During the surgical period, there were 11 patients with fatal AEs in the D + CTx arm and 9 patients in the Pbo + CTx arm. Further details on AEs with outcome of death are provided in Section 3.4.3. The total number of perioperative deaths (deaths occurring within 30 days of surgery) was 4 (1.0%) in the D + CTx arm and 8 (2.0%) in the Pbo + CTx arm.

Among patients who underwent surgery, AEs assessed as possibly related to surgery were reported in 134 patients (41.2%) in the D + CTx arm vs. 135 patients (41.4%) in the Pbo + CTx arm. The most frequently reported AE assessed as possibly related to surgery was procedural pain (11.7% of patients in each arm).

Maximum CTCAE Grade 3 or 4 AEs assessed as possibly related to surgery were reported for similar numbers of patients in each arm: 27 patients (8.3%) in the D + CTx arm vs 29 patients (8.9%) in the Pbo + CTx arm.

Fatal AEs assessed as possibly related to surgery were reported for 6 patients (1.8%) in the D + CTx arm and 4 patients (1.2%) in the Pbo + CTx arm. The only fatal AE possibly related to surgery reported for ≥ 2 patients in either arm was pneumonia (2 patients in the D + CTx arm and 1 patient in the Pbo + CTx arm).

3.2.1.4 Adjuvant Period

Durvalumab monotherapy during the adjuvant period was well-tolerated and had a safety profile consistent with the established safety profile of durvalumab. Adverse events (any Grade, any causality), SAEs, AEs of maximum CTCAE Grade 3-4, AEs leading to discontinuation of study treatment, and fatal AEs were less frequent during the adjuvant period compared to the neoadjuvant period in both treatment arms (Table 6).

Within the adjuvant period, AEs (any Grade, any causality), SAEs, AEs of maximum CTCAE Grade 3-4, AEs leading to discontinuation of study treatment, and imAEs were reported by

numerically higher proportions of patients in the D + CTx arm compared to the Pbo + CTx arm, as expected given the active mechanism of action of durvalumab and patients in the comparator arm receiving placebo alone (Table 6). However, the incidence of these events in the D + CTx arm was either similar to, or lower than, those reported for the pooled durvalumab safety data (Table 6) despite much longer median duration of exposure to durvalumab/placebo during the adjuvant period (48 weeks) compared to the median duration of exposure to durvalumab in the pooled safety data (16.4 weeks).

The majority of AEs reported in the adjuvant period were non-serious, low in severity (CTCAE Grade 1-2), and resolved in both treatment arms. The most frequent AEs of any CTCAE Grade (reported by ≥ 5% of patients in either arm) were COVID-19 and arthralgia, which were similar in frequency in both treatment arms. Hypothyroidism, rash, and pruritus were more commonly reported in the D + CTx arm than in the Pbo + CTx arm (Figure 5).

The proportion of patients with SAEs in the adjuvant period was 15.0% in the D + CTx arm and 10.2% in the Pbo + CTx arm (Table 6).

Fatal AEs in the adjuvant period were reported for 4 patients in the D + CTx arm and 2 patients in the Pbo + CTx arm. Further information regarding AEs with outcome of death is provided in Section 3.4.4.

3.3 Immune-mediated Adverse Events

Consistent with the durvalumab immune-mediated mechanism of action, more patients experienced any imAE in the D + CTx arm (25.4%) than in the Pbo + CTx arm (10.1%) during the overall period. The majority of imAEs in the D + CTx arm were CTCAE Grade 1 or 2 in severity, were non-serious, were generally manageable, and were resolved by the time of the DCO (see Appendix 14).

3.3.1 Overall Period

In the overall period, the most common imAEs occurring in ≥ 5% of patients were hypothyroidism and rash/dermatitis (Table 7). All hypothyroid events and the majority of rash/dermatitis events were low Grade (Grade 1 or 2). Pneumonitis imAEs were reported at a higher frequency in the D + CTx arm (4.5%) than in the Pbo + CTx arm (1.8%). However, maximum Grade 3-4 pneumonitis imAEs were reported at a comparable frequency in both treatment arms (1.5% in the D + CTx arm vs. 1.0% in the Pbo + CTx arm).

ImAEs leading to discontinuation of any study treatment were low in frequency in both treatment arms: 19 patients (4.7%) in the D + CTx arm and 4 patients (1.0%) in the Pbo + CTx arm.

Table 9 Immune-mediated adverse events (SAS population; Safety Update DCO)

Category	Number (%) of patients							
	Neoadjuvant Period †		Surgical Period ‡		Adjuvant Period §		Overall ¶	
	D + CTx (n = 401)	Pbo + CTx (n = 398)	D + CTx (n = 325)	Pbo + CTx (n = 326)	D + CTx (n = 266)	Pbo + CTx (n = 254)	D + CTx (n = 401)	Pbo + CTx (n = 398)
Any imAE #	33 (8.2)	19 (4.8)	19 (5.8)	2 (0.6)	60 (22.6)	20 (7.9)	102 (25.4)	40 (10.1)
Grade 3 or 4 imAE	6 (1.5)	5 (1.3)	6 (1.8)	1 (0.3)	6 (2.3)	4 (1.6)	18 (4.5)	10 (2.5)
Pneumonitis	3 (0.7)	1 (0.3)	6 (1.8)	1 (0.3)	9 (3.4)	5 (2.0)	18 (4.5)	7 (1.8)
Grade 3-4	1 (0.2)	0	3 (0.9)	1 (0.3)	2 (0.8)	3 (1.2)	6 (1.5)	4 (1.0)
Hypothyroid events	6 (1.5)	5 (1.3)	8 (2.5)	0	28 (10.5)	5 (2.0)	42 (10.5)	10 (2.5)
Grade 3-4	0	0	0	0	0	0	0	0
Rash/dermatitis	9 (2.2)	7 (1.8)	1 (0.3)	0	12 (4.5)	0	22 (5.5)	7 (1.8)
Grade 3-4	1 (0.2)	1 (0.3)	0	0	1 (0.4)	0	2 (0.5)	1 (0.3)
Colitis/diarrhea	1 (0.2)	3 (0.8)	0	0	2 (0.8)	2 (0.8)	3 (0.7)	5 (1.3)
Grade 3-4	0	1 (0.3)	0	0	0	2 (0.8)	0	3 (0.8)
Hepatic events	8 (2.0)	2 (0.5)	2 (0.6)	0	4 (1.5)	2 (0.8)	13 (3.2)	4 (1.0)
Grade 3-4	4 (1.0)	1 (0.3)	2 (0.6)	0	2 (0.8)	0	8 (2.0)	1 (0.3)

† First dose of Study Tx (D/Pbo/CT) until the date of surgery or, for patients without surgery, up to the earliest of: last dose of neoadjuvant Tx (D/Pbo/CT) + 90 days, first dose of subsequent anti-cancer Tx, or the DCO date; for assessments recorded on the day of surgery, time was used to determine if it was pre- or post-surgery (if time was not available, it was assumed to occur post-surgery).

‡Date of surgery (inclusive) to the earliest of 90 days post-surgery, first dose of subsequent anti-cancer Tx, or DCO date.

§ Date of first dose of Study Tx post-surgery until earliest of: last Study Tx post-surgery + 90 days, date of first dose of subsequent anti-cancer Tx, or DCO date.

¶ First dose of Study Tx (D/Pbo/CT) until the earliest of: the last dose of Study Tx or surgery (taking the latest dose of D/Pbo/CTx/date of surgery) + 90 days, date of the first dose of subsequent anti-cancer Tx, or DCO date.

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. One patient assigned to the Pbo arm erroneously received a single cycle of D (in the adjuvant phase) and was included in the D arm for the safety analyses.

All reported percentages are based on the total number of patients in each column header as the denominator (i.e., patients who received Tx during that period).

Source: Table 14.3.6.2.1.120DSU, Table 14.3.6.2.2.120DSU, Table 14.3.6.2.3.120DSU, Table 14.3.6.2.4.120DSU, Table 14.3.6.2.10.120DSU, Table 14.3.6.2.12.120DSU, Table 14.3.6.2.13.120DSU, Table 14.3.6.2.1.1.120DSU, iemt0617.43 a,b,c,i,k,l, iemt0617.21, iemt0617_022 a,b,c,i,k,l, iemt 0617.69, iemt0617_086: a,b,c,i,k,l.

Among the patients with imAEs (in total: 102 patients [25.4%] in the D + CTx arm; 40 patients [10.1%] in the Pbo + CTx arm), imAEs had resolved for 56 patients (54.9%) in the D + CTx arm vs. 19 patients (47.5%) in the Pbo + CTx arm. At the time of the DCO, these were ongoing for 41 patients (40.1%) in the D + CTx arm vs. 21 patients (52.5%) in the Pbo + CTx arm. Only 1 patient, in the D + CTx arm, had an imAE that resolved with sequelae.

The majority of unresolved imAEs reported in the D + CTx arm (32 out of 41 patients) were hypothyroid events that required endocrine therapy. All hypothyroid imAEs reported in the D + CTx arm were low in severity (CTCAE Grade 1-2), non-serious, and none of these events resulted in discontinuation of study treatment. The remaining unresolved imAEs in the D + CTx arm reported in >2 patients included pneumonitis (4 patients) and rash (3 patients). The

majority of unresolved imAEs reported in the Pbo + CTx arm were hypothyroid events that required endocrine therapy (6 patients) or pneumonitis events (5 patients). All hypothyroid events in the Pbo + CTx arm were low in severity (Grade 1-2), non-serious, and none of these events resulted in discontinuation of study treatment.

In the pooled safety dataset (N = 4045), imAEs were reported in 705 patients (17.4%); the higher incidence of imAEs in the D + CTx arm of AEGEAN (25.4%) may be explained by the markedly longer median duration of durvalumab exposure compared to the pooled safety dataset (approximately 40 weeks [overall period] vs. 16.4 weeks, respectively). The incidence of imAEs of CTCAE Grade 3-4 in the AEGEAN D + CTx arm (4.5%) was consistent with that observed in the pooled safety dataset (4.3%).

The nature, severity, and manageability of imAEs in the D + CTx arm of AEGEAN were consistent with those previously reported for the pooled safety dataset. No new safety findings were identified for durvalumab treatment for patients with resectable NSCLC.

3.3.2 Neoadjuvant Period

In the neoadjuvant period, the proportion of patients reporting any imAEs was higher in the D + CTx arm (8.2%) than in the Pbo + CTx arm (4.8%) (Table 7). Maximum CTCAE Grade 3-4 imAEs were reported for a similar proportion of patients in the D + CTx arm (1.5%) vs. the Pbo + CTx arm (1.3%). The most common imAEs on both arms were rash/dermatitis, hypothyroid events, and hepatic events.

3.3.3 Surgical Period

In the surgical period, the proportion of patients reporting any imAEs was higher in the D + CTx arm (5.8%) than in the PbO + CTx arm (0.6%) (Table 7). Maximum CTCAE Grade 3-4 imAEs were reported for a higher proportion of patients in the D + CTx arm (6 patients [1.8%]) compared to the Pbo + CTx arm (1 patient [0.3%]). The most common imAEs on the D + CTx arm were hypothyroid events and pneumonitis.

3.3.4 Adjuvant Period

In the adjuvant period, the proportion of patients reporting any imAEs was higher in the D + CTx arm (22.6%) than in the Pbo + CTx arm (7.9%) (Table 7). Maximum CTCAE Grade 3-4 imAEs were reported for a similar proportion of patients in the D + CTx arm (2.3%) vs. the Pbo + CTx arm (1.6%) (Table 7). The most commonly reported imAEs in the adjuvant period were hypothyroid events (10.5% of patients in the D + CTx arm and 2.0% of patients in the Pbo + CTx arm), rash/dermatitis (4.5% of patients in the D + CTx arm and 0% in the Pbo + CTx arm), and pneumonitis events (3.4% of patients in the D + CTx arm and 2.0% of patients in the Pbo + CTx arm) (Table 7).

All hypothyroid imAEs and the majority of rash/dermatitis events were low Grade (Grade 1-2). Pneumonitis imAEs of maximum Grade 3-4 were reported in 0.8% of patients in the D + CTx arm and 1.2% of patients in the Pbo + CTx arm (Table 7).

3.4 Adverse Events with Outcome of Death (Fatal AEs)

In the ITT population, the overall number of all cause deaths reported was lower in the D + CTx arm (105 patients [26.3%]) than in the Pbo + CTx arm (122 patients [30.3%]). In both study

arms, most deaths were due to the disease under investigation only, as determined by the Investigator, affecting 66 patients (16.5%) in the D + CTx arm and 94 patients (23.4%) in the Pbo + CTx arm (see Appendix 13).

3.4.1 Overall Period

Overall, 23 patients (5.7%) in the D + CTx arm vs. 15 patients (3.8%) in the Pbo + CTx arm had fatal AEs. The majority of these events in both arms were unrelated to any study treatment. The most frequent AEs with outcome of death in both arms were infections (13 vs. 7 patients in the D + CTx and Pbo + CTx arms, respectively). None of these were assessed as possibly related to durvalumab or chemotherapy. The most common fatal infection in the D + CTx arm was COVID-19 (5 patients) vs 1 patient in the Pbo + CTx arm. Non-COVID-19 fatal infections were reported in 8 patients vs. 6 patients in the D + CTx arm and Pbo + CTx arm, respectively.

3.4.2 Neoadjuvant Period

Eight (2.0%) patients in the D + CTx arm vs. 4 (1.0%) patients in the Pbo + CTx arm had fatal AEs during the neoadjuvant period. Events reported in > 1 patients were COVID-19 pneumonia and sepsis (2 patients each on the D + CTx arm); none of these events was assessed as related to durvalumab or chemotherapy.

There were 4 fatal AEs possibly related to any study treatment in the neoadjuvant period. In the D + CTx arm there were 3 such events: myocarditis, assessed as related to durvalumab and not to chemotherapy; hemoptysis, assessed as related to both durvalumab and chemotherapy; and decreased appetite, assessed as related to chemotherapy only.

In the Pbo + CTx arm there was one such fatal AE: pneumonia, which was assessed as related to chemotherapy by the Investigator.

3.4.3 Surgical Period

Eleven patients (3.4%) in the D + CTx arm and 9 patients (2.8%) in the Pbo + CTx arm had fatal AEs during the surgical period. Fatal AEs reported for > 1 patient were COVID-19, pneumonia, and septic shock in the D + CTx arm, and pneumonia in the Pbo + CTx arm.

There were 3 fatal AEs in the D + CTx arm which were assessed to be related to durvalumab (and not to chemotherapy) by the Investigator during the surgical period: pneumonitis (6 days after surgery); ILD (22 days after surgery); and immune-mediated lung disease (14 days after surgery).

In 2 of these 3 patients with fatal AEs possibly related to durvalumab (pneumonitis and ILD events), the investigator assessed the fatal AE to also be related to surgery. There were no fatal AEs assessed as possibly related to any study treatment in the Pbo + CTx arm.

The total number of perioperative deaths (ie., all deaths occurring within 30 days post-surgery) was 4 (1.0%) in the D + CTx arm and 8 (2.0%) in the Pbo + CTx arm. No patient in either arm had an AE with outcome of death occurring within 1-day post-surgery.

3.4.4 Adjuvant Period

AEs with outcome of death occurring in the adjuvant period were reported in 4 patients (1.5%) in the D + CTx arm vs. 2 patients (0.8%) in the Pbo + CTx arm.

Fatal AEs considered possibly related to study treatment in the adjuvant period occurred in one patient in each treatment arm. In the D + CTx arm, one patient had a fatal AE of ILD considered possibly related to durvalumab that occurred 56 days after surgery and 13 days after the first dose of adjuvant durvalumab. In the Pbo + CTx arm, one patient had a fatal AE of infection considered possibly related to chemotherapy.

3.5 Safety Summary and Conclusions

The AEGEAN study has demonstrated a tolerable and manageable safety profile for durvalumab given in combination with chemotherapy prior to surgery, followed by durvalumab monotherapy post-surgery, for patients with resectable NSCLC. The safety profile is consistent with the established safety profile of the individual agents (ie., durvalumab and platinum-based chemotherapy) and no new safety concerns were observed.

- Overall, the incidences of any AEs and AEs of maximum CTCAE Grade 3-4 were similar between the D + CTx and Pbo + CTx arms.
- The addition of durvalumab to neoadjuvant platinum-based chemotherapy did not lead to an increase in the frequency or severity of known chemotherapy-related toxicities, or adversely affect standard-of-care surgical resection.
- The incidence of AEs leading to discontinuation of any study treatment was low overall, with a numerically higher incidence in D + CTx arm compared to the Pbo + CTx arm.
- The majority of AEs with outcome of death were considered unrelated to any study treatment by the Investigator. Infections were the most frequent AE with outcome of death in both treatment arms (with none of the fatal events of infection reported in the D + CTx arm being considered related to durvalumab by the Investigator).
- The majority of imAEs in the D + CTx arm were non-serious, low in severity (CTCAE Grade 1 or 2), manageable, and resolved at the time of the DCO. The most common imAEs were hypothyroidism and skin reactions.
- Overall, the majority of AEs reported in the study were observed during the neoadjuvant period. The incidences of any AEs, SAEs, and AEs of maximum CTCAE Grade 3-4 were lower during the adjuvant period when compared to the neoadjuvant and overall periods.
- Durvalumab monotherapy during the adjuvant period had an acceptable safety and tolerability profile. The nature of the AEs reported during adjuvant durvalumab treatment was consistent with the established safety profile of durvalumab monotherapy. Despite longer exposure, AE frequencies during adjuvant durvalumab treatment in AEGEAN were either similar to, or lower than, those reported in the pooled durvalumab safety dataset.

The FDA's Position:

FDA generally agrees with the Applicant's position with additional considerations related to the incidence of immune-related adverse events (irAEs). Based on FDA analyses of 265 patients that received adjuvant durvalumab, 31% developed irAEs during treatment with adjuvant durvalumab (Table 9). Approximately 9% of patients had unresolved irAEs at the end of study period (Table 10).

Table 10: Immune-related adverse events (irAEs) during the Adjuvant Phase

	Durvalumab + Chemotherapy N=265 n (%)	Placebo + Chemotherapy N=254 n (%)
All-Grade irAEs	83 (31)	27 (11)
Grade 3-4 irAEs	10 (3.8)	5 (2)
Grade 5 (Deaths due to irAEs)	1 (0.4)	0 (0)
Study drug withdrawn due to irAEs	14 (5)	3 (1.2)
Study drug interrupted due to irAEs	14 (5)	3 (1.2)

Table 11: Outcome of Immune-related adverse events (irAEs) with durvalumab in the adjuvant phase

irAE Status	Durvalumab + Chemotherapy N=265 n (%)
Resolved	48 (18)
Resolved with sequalae	1 (0.4)
Resolving	18 (7)
Unresolved	23 (9)
Death	1 (0.4)

Although most irAEs were Grade 1 or 2, persistent Grade 2 events may be bothersome or negatively impact patients' health-related quality of life and may require additional care, thereby increasing treatment burden. Unresolved irAEs that occurred with durvalumab during the adjuvant phase included hypothyroidism (3.8%) and rash (1.4%), as well as individual cases of adrenal insufficiency, diarrhea, pneumonitis, and musculoskeletal pain that may have long-term effects on patients' health status and quality of life (Table 11). There are other potential irAEs associated with ICI therapy which could also negatively impact patients' health status and quality of life in the long-term, such as nephritis and diabetes mellitus.

Table 12: Unresolved immune-related adverse events (irAEs) with durvalumab that developed in the adjuvant phase.

Unresolved Adjuvant irAEs	Durvalumab + Chemotherapy N=265 n (%)
Hypothyroidism	10 (3.8)
Rash (GT)	4 (1.5)
Adrenal Insufficiency	1 (0.4)
Aspartate Aminotransferase Increased	1 (0.4)
Blood Alkaline Phosphatase Increased	1 (0.4)
Diarrhea	1 (0.4)

Gamma-glutamyltransferase Increased	1 (0.4)
Hyperthyroidism	1 (0.4)
Immune-mediated Lung Disease	1 (0.4)
Musculoskeletal Pain	1 (0.4)
Pneumonitis	1 (0.4)
Transaminases Increased	1 (0.4)
Vitiligo	1 (0.4)

Group Rash (GT) includes PT terms RASH, ECZEMA, DERMATITIS, PEMPHIGOID, RASH MACULAR, DERMATITIS ACNEIFORM, RASH MACULO-PAPULAR, URTICARIAL DERMATITIS

Given the potential for such toxicities with adjuvant durvalumab, a demonstration of the contribution of adjuvant therapy to the observed efficacy of the perioperative regimen would allow for better characterization of the benefit-risk profile of perioperative durvalumab. These lower grade but persistent AEs are particularly important in a population where some patients may experience cure following surgery.

4 Clinical Outcome Assessment Analyses

The Applicant's Position:

At the EFS IA1 DCO, the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires were assessed only in the neoadjuvant period (mITT population). PRO data for the adjuvant period remained blinded and will be reported for the resected set and modified resected set alongside DFS (see Section 2.2.3 and Section 2.2.4 for details of planned DFS analyses).

At neoadjuvant baseline, overall questionnaire compliance rates were high across the two treatment arms (> 90%) for both EORTC QLQ-C30 and EORTC QLQ-LC13. Compliance rates decreased similarly in both arms throughout the neoadjuvant period, reaching > 63% in both treatment arms at neoadjuvant Week 12.

Mean baseline EORTC QLQ-C30 scores indicated a moderate-to-high quality of life and high functioning for patients in both treatment arms. Throughout the neoadjuvant period, some deterioration of patients' perception of global health status and/or quality of life was noted in both treatment arms, with decreases in each functional domain consistently reported between treatment arms. Clinically meaningful improvements (ie, a change from baseline score of ≥ 10 points) in the overall perception of quality of life and global health status were also reported in a notable proportion of patients in the neoadjuvant period, which was generally similar between treatment arms (range: 21% to 25% of patients in the D + CTx arm and 20% to 25% of patients in the Pbo + CTx arm).

Based on patient feedback collected via EORTC QLQ-LC13, an improvement from baseline in coughing throughout the neoadjuvant period, and pain in the chest at Week 12, was observed in both treatment arms, with no differences between arms. Conversely, an incremental worsening from baseline to Week 12 was observed for dyspnea, pain in other parts, peripheral

neuropathy, and alopecia, with no differences across arms. However, the majority of patients did not report clinically meaningful changes from baseline in the assessed symptoms.

In conclusion, while some impact on patients' perception of health and/or quality of life was observed in both treatment arms in the neoadjuvant period of the AEGEAN study, this is not unexpected for a patient population with early-stage cancer receiving chemoimmunotherapy, and data were generally similar between treatment arms.

The FDA's Position:

While the FDA appreciates the incorporation of patient generated data in this application, there are a few substantive concerns with the applicant's position. Most notably, the PRO strategy magnifies the design flaw related to the inability to assess the impact of each of the two phases of this perioperative treatment regimen. As discussed throughout the briefing document, the most substantive concern for overtreatment is with the adjuvant phase, and the applicant did not assess PRO during this period of treatment; opting instead to assess PRO data only in the neoadjuvant period. In the neoadjuvant assessments, PRO data compliance rate fell below 70% after week 9 resulting in only three post-baseline PRO assessments with reasonable data quality. Lastly, although we commend the sponsor for selection of symptomatic side effects using the PRO-CTCAE item library in PRO assessments for AEGEAN, the frequency of patient-reported symptomatic AEs was sparse (every 3 weeks) and could have been more frequent (e.g., weekly) for the first few cycles to capture periods of higher toxicity that may occur between cycles as is typically the case with cytotoxic chemotherapy regimens.

5. Other Significant Issues Pertinent to Clinical Conclusions on Efficacy and Safety

5.1 Applicability of the AEGEAN Study Results to the U.S. Population

The Applicant's Position:

AEGEAN was conducted following ICH E17 principles, and the results of this large, multiregional clinical trial generally apply to the US population. This conclusion is based on the similarities between the demographics of the patients randomized in the mITT population and that of real-world patients with stage II to III NSCLC in the US (see Appendix 16), and the use of neoadjuvant platinum chemotherapy in alignment with US medical practice. Therefore, treatment effect data from the AEGEAN study are deemed generalizable to the US patient population.

The statistically significant and clinically meaningful improvement in EFS (HR = 0.68 [95% CI: 0.53, 0.88]; p-value = 0.003902; see Section 2.3.2.2) was consistent across geographic regions, including North America, with confidence intervals overlapping with the results of the primary

analysis in the mITT population (see subgroup analyses of EFS in Appendix 9) further supporting the applicability of AEGEAN study results to the US population.

The FDA's Position:

FDA generally agrees with the Applicant's position with some additional considerations. Relative to the patient sample from CancerLinQ reported in Appendix 16, the patient population in AEGEAN underrepresented patients aged 75 or older (11% in AEGEAN vs 21% in CancerLinQ), female patients (28% vs 46%), and patients who were Black or African American (0.9% vs 10%). In addition, tumor stage distribution differed between AEGEAN and the CancerLinQ samples, as 29% and 71% of patients in AEGEAN had stage II and III NSCLC, compared with 61% and 39% in CancerLinQ. The AEGEAN patient population had a higher proportion of squamous NSCLC compared with CancerLinQ (49% vs 33%). Given that the effect sizes for EFS were consistent across subgroups, the results of AEGEAN appear applicable to the U.S. patient population, despite these observed demographic and clinical differences between the AEGEAN and CancerLinQ patient samples.

5.2 Considerations Regarding Future Clinical Trials in Resectable NSCLC

The Applicant's Position:

Pivotal trial results for patients with resectable NSCLC have demonstrated the benefit of anti-PD-L1/PD-1 inhibition in neoadjuvant only, adjuvant only, and perioperative settings. As with many important therapeutic advances, additional questions remain regarding optimized treatment for individual patients. In the context of the current approvals in resectable NSCLC (see Section 2.1.2 and Appendix 2), a question of debate is whether, and for which patients, a neoadjuvant chemoimmunotherapy strategy followed by surgical resection (with or without adjuvant immunotherapy) is preferred versus pursuing upfront surgery followed by adjuvant immunotherapy only.

Clinical challenges that remain to be explored in the coming years therefore include further practice-informing studies, as well as establishing reliable biomarkers to accurately identify patients who benefit most from adjuvant immunotherapy post-surgery. Monitoring of ctDNA and minimal residual disease in the perioperative setting continues to be an area of active research [50], and such methods may play a future role in determining which patients may require continued treatment in the adjuvant phase after neoadjuvant treatment and surgery, and/or treatment intensification. Notably, no such methods are currently approved for these purposes.

The Sponsor has committed to working collaboratively with cooperative oncology groups to optimize trial designs for early-stage NSCLC moving forward, and to address questions that have emerged following the success of perioperative, neoadjuvant and adjuvant trials of immunotherapy. The Sponsor is currently working with the Southwest Oncology Group (SWOG)

Cancer Research Network and the European Thoracic Oncology Platform (ETOP) in support of two randomized Phase III studies, as follows:

- **INSIGHT:** the Sponsor will supply drug product and funding for a Cancer Therapy Evaluation Program (CTEP)-sponsored study that will randomize patients with pCR after neoadjuvant chemoimmunotherapy to either adjuvant durvalumab or to observation, with DFS as the primary endpoint.
- **ADOPT:** the Sponsor will supply drug product and funding for an ETOP-sponsored study that will randomize patients after neoadjuvant chemoimmunotherapy to either adjuvant durvalumab or to observation, with DFS in patients without pCR as the primary endpoint. Secondary endpoints include DFS in patients achieving a pCR and OS.

In addition, the Sponsor has engaged with the FDA to discuss plans to conduct a diagnostic study (Lung MRD Assessment, or LUMA), in which ctDNA will be used to identify patients at high-risk of recurrence after curative intent surgery for early-stage NSCLC.

The Sponsor is exploring options for future trial designs to elucidate the contribution of phase for novel combinations that add new agents onto a perioperative therapy backbone.

The FDA's Position:

The Applicant describes partnering with cooperative groups to conduct post-marketing trials, such as the INSIGHT and ADOPT-Lung (NCT06284317) trials, as attempts to optimize therapy by demonstrating the contribution of treatment phase, in all patients or patients selected based on pathologic response status. FDA acknowledges the planned efforts to conduct trials to address questions related to contribution of phase and believes these trials are important and will provide valuable information to help clinicians determine how to best incorporate ICIs into treatment.

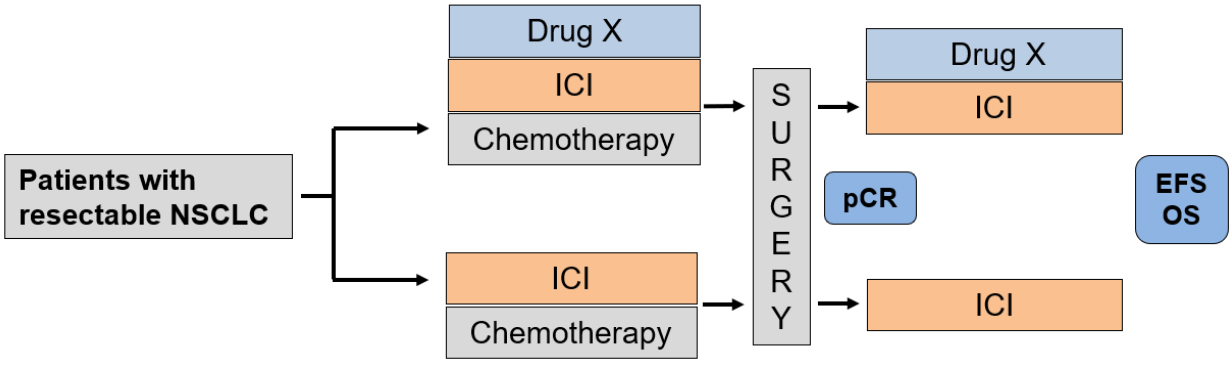
Unfortunately, these trials are not designed to answer the question of contribution of phase for each phase of treatment in all patients eligible to receive the perioperative therapy proposed in the Applicants indication statement. Additionally, while these trials may inform the benefit of ICIs when given in each phase of a perioperative regimen, some limitations apply to the conduct of such trials in the post-marketing setting. First, the oncology community may adopt perioperative regimens as the treatment of choice after approval, leading to a perceived loss of equipoise to enroll patients in post-marketing cooperative group trials. Second, the cooperative group trials will take years to complete. By the time the results of cooperative trials become available, the treatment landscape may have evolved, limiting the application of the trials' conclusions to clinical practice.

While the Applicant discusses designs looking to refine perioperative ICI regimens, FDA has received proposals to add new therapies on to a perioperative ICI backbone. There are options for study designs for which a two-arm trial design may be appropriate. This would include studies adding a new therapy to only one phase of treatment, as either neoadjuvant or

adjuvant therapy. As discussed, FDA recommended within trial evaluation of contribution of phase for AEGEAN and other trials designed at the time. Sponsors elected to perform two arm trials against this advice. Given that add on regimens will increase toxicity, and in light of the significant uncertainty related to potential overtreatment, FDA believes it is even more important to move away from two-arm trial designs when proposing to add a new therapy to both the neoadjuvant and adjuvant phases of treatment.

This issue is relevant now, as FDA has received proposals for two-arm trials adding a new therapy to both the neoadjuvant and adjuvant phases of treatment. The figure below provides an example.

Figure 6: Two-arm trial designs for add-on therapies



As FDA has previously stated in this document, there is uncertainty regarding whether the use of ICI in both phases of therapy is necessary to achieve the observed clinical benefit. Even if one considers a standard of care backbone incorporating ICI in both the neoadjuvant and adjuvant phases of therapy appropriate, a two-arm trial design incorporating a new therapy into both phases of treatment will only add to the uncertainty and the potential for overtreatment. As treatment regimens are intensified with the addition of new agents or new mechanisms of action added to an anti-PD-(L)1 backbone, this can be expected to result in additional toxicity, increasing the potential for harm associated with overtreatment. This expectation of additional toxicity with intensification of therapy makes it even more important to have evidence that the addition of new therapy to each phase of treatment is necessary to achieve benefit.

To address the need to demonstrate contribution of treatment phase, alternative trial designs are necessary. Such trials should evaluate the efficacy of new therapies, while simultaneously demonstrating their contribution to each treatment phase of a perioperative regimen. Potential examples of alternative designs include multi-arm or factorial randomized trials, including those that implement features such as adaptive designs or re-randomization of patients after surgery.

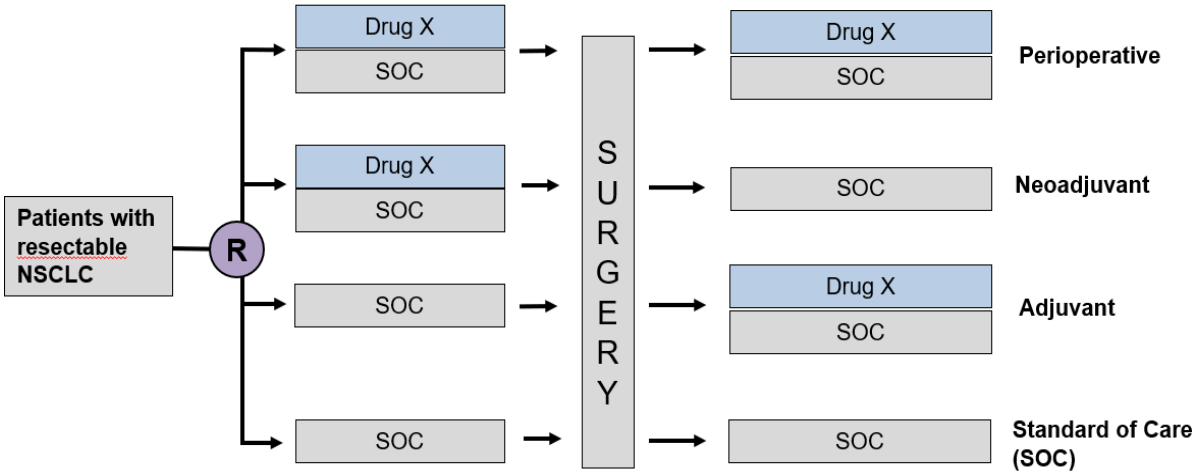
Statistical considerations for the alternative trials

In the perioperative setting, FDA believes it is critical that study designs going forward provide evidence of the contribution of the phases of therapy to the overall treatment effect. The best way to accomplish this is with additional trial arms that explore the effect of the drug added to neoadjuvant or adjuvant treatment alone.

Add-on Trial: Four-arm trial design

Ideally, a factorial design is needed to assess contribution of the neoadjuvant and adjuvant phases of the perioperative treatment regimen. Such a trial would have three experimental treatment arms and a control arm (***Figure 7***).

Figure 7 Four-arm factorial trial design



The primary comparison of interest would be between the Perioperative arm and the SOC arm. This comparison should be performed with type I error rate control and be adequately powered based on expected treatment effect of the add-on therapy. The secondary analyses should include comparisons of the Neoadjuvant arm and the Adjuvant arm with the SOC arm. There should be a careful consideration of power and type I error control for these secondary analyses as they may provide basis for the approval of single-phase regimens should the primary comparison fail, or contribution of phases not be adequately established. Additional analyses should include comparisons between the Perioperative arm and the Neoadjuvant arm and the Perioperative arm and the Adjuvant arm. These analyses provide the main supportive evidence for the assessment of contribution of effect for the adjuvant and neoadjuvant phases, respectively, and may be considered as a distinct family of hypotheses to be tested separately.

Although such factorial trials include two additional experimental arms, the sample size may not be substantially larger and accrual/follow-up durations may not be inordinately longer for disease settings such as resectable NSCLC. ***Table 13*** provides sample sizes required for three sets of hypothetical scenarios, assuming at least 80% power for each comparison to the SOC arm and employing the Hochberg method for control of Type I error for testing of multiple experimental arms against the control. Although these scenarios are hypothetical, the assumptions made are informed by the historical ICI perioperative trials and a currently proposed trial that adds another drug to the previously approved perioperative regimen to treat early-stage NSCLC.

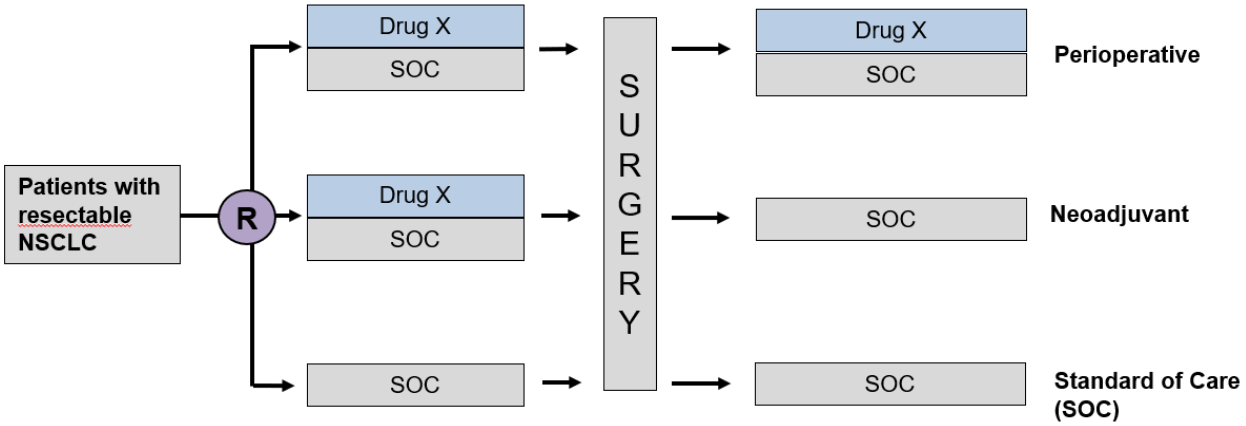
Table 13 Sample size required for hypothetical four-arm trial designs.

Scenario	Assumed EFS Hazard Ratios			Total number of events	Total number of patients
	Perioperative vs. SoC	Neoadjuvant vs. Soc	Adjuvant vs. Soc		
1	0.60	0.65	0.70	460	960
2	0.60	0.70	0.70	485	1000
3	0.70	0.80	0.80	1256	2420

Add-on Trial: Three-arm trial design

While a 4-arm factorial design is the optimal design to evaluate each individual phase of a perioperative approach, the largest concern for overtreatment is focused on the adjuvant phase. Designs that clarify whether the adjuvant phase adds sufficient efficacy to outweigh its additional toxicity and treatment burden would be a practical alternative. ***Figure 8*** illustrates an example of three-arm trial that excludes the Adjuvant arm from the factorial design described above. This design will allow the assessment of the contribution of the addition of drug X in the adjuvant phase.

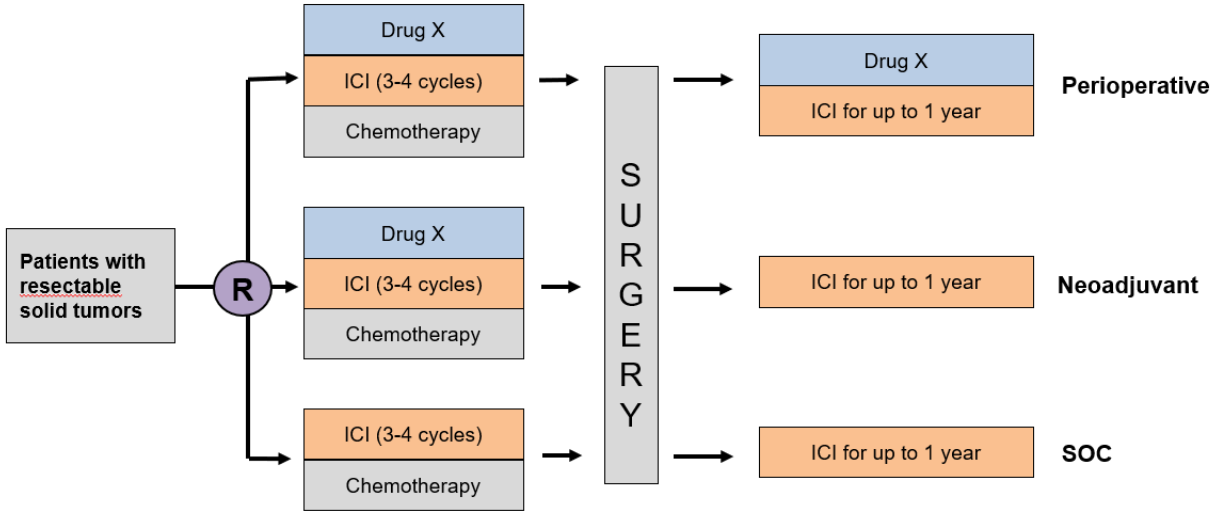
Figure 8 Three-arm trial design



The incorporation of a new therapy into the neoadjuvant phase only rather than incorporation into the adjuvant phase only as the third arm in a 3-arm trial may be preferable because: (1) there may be stronger biologic rationale for antitumor activity in an intact tumor environment, (2) there are concerns for increased toxicities with longer duration adjuvant therapy relative to neoadjuvant therapy, and (3) some patients may achieve cure with neoadjuvant therapy and surgery alone. Thus, inclusion of an arm incorporating a new therapy in the neoadjuvant phase only may be the most reasonable choice to provide within trial information on the contribution of adjuvant treatment while preserving the ability to statistically test a potentially safe and effective addition of a new drug to only the neoadjuvant phase of therapy.

For example, applying this 3-arm trial design to the example in *Figure 6* would result in the study design shown in the figure below (Figure 9).

Figure 9 A specific example of three-arm trial design with ICI perioperative backbone



While formal testing of the comparison between the perioperative arm and the neoadjuvant experimental arm may not be required, it is strongly recommended that the analysis plan ensures formal testing of comparison of both the Perioperative and Neoadjuvant arms to the standard of care control arm. This hypothesis testing approach is advisable because the trial can then support approval of either the perioperative regimen or the neoadjuvant regimen depending on the trial results if both arms are significantly superior to control. For instance, if results do not support a substantive difference between the Perioperative arm and the Neoadjuvant Arm, a new neoadjuvant regimen could be approved.

Table 14 provides sample sizes for three different hypothetical three-arm trial design scenarios, assuming at least 80% power for each comparison to the SOC arm and the Hochberg method for control of Type I error for testing of multiple experimental arms against the control. As in all trial designs, the sample size is largely driven by the assumptions regarding design parameters.

Table 14 Sample size required for hypothetical three-arm trial designs.

Scenario	Assumed EFS Hazard Ratios		Total number of events	Total number of patients
	Perioperative vs. SOC	Neoadjuvant vs. SOC		
1	0.60	0.70	352	657
2	0.65	0.75	547	990

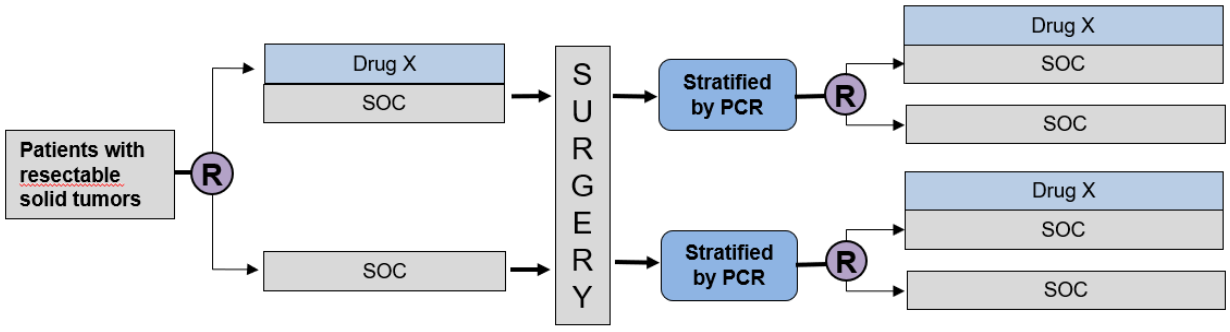
3	0.70	0.80	908	1740

Comparison of the Perioperative arm to the Neoadjuvant arm is critical for the direct assessment of contribution of effect for the adjuvant phase of therapy. However, the sample size needed to formally test these two experimental arms may be prohibitive given the effect size is not expected to be as large as either arm compared to control. Even a descriptive comparison of randomized patients is far superior to relying on cross-trial external data. Therefore, an alternative approach, such as prespecifying a comprehensive descriptive evaluation of data from these two arms in the context of the totality of the evidence may be considered. This approach and any other alternative approaches aimed at providing persuasive evidence of contribution of phases should be discussed with FDA when planning such a trial.

Other trial designs

Finally, other innovative and more complex trial design options may also be considered, including adaptive trial designs or those with re-randomization. For example, designs that re-randomize patients after definitive surgery provide an opportunity to answer finer clinical questions (***Figure 5***). Such re-randomization allows direct comparison between the patients treated and not treated with the adjuvant therapy following the neoadjuvant phase. This type of study design could also directly answer questions regarding a treatment regimen guided by pCR status after neoadjuvant treatment. Depending on the granularity of questions to be answered, the sample size required for such a trial design could be similar or larger than the full factorial design. However, these complex designs can be more challenging operationally and must be conducted with care to preserve data integrity and interpretability.

Figure 10 Trial design with re-randomization for resectable NSCLC



6. Points for the Advisory Committee to Consider

The Applicant's Position:

Resectable NSCLC is an aggressive disease with a poor prognosis. Despite surgical resection with curative intent, 30% to 76% of patients experience disease recurrence [10, 11], and 5-year survival rates remain low (56% to 65% for patients with Stage II, and 24% to 41% for patients with Stage III disease) [12].

Despite recent approvals of immunotherapy for resectable NSCLC in the neoadjuvant, adjuvant, and perioperative settings [10, 16-19], the outlook for a substantial proportion of patients remains poor. AEGEAN was designed to address high unmet need in this setting which remains relevant today. The clinical community is now presented with questions regarding how patients might be best selected for specific neoadjuvant, adjuvant, and perioperative immunotherapy strategies. However, there are no data from Phase III studies that formally compare these treatment approaches, and cross-trial comparisons are confounded by important study design and patient population differences.

AEGEAN was a robustly designed and well-controlled study that enrolled a large patient population across geographic regions that is representative of patients with resectable NSCLC in the US and globally, both in terms of demographics and disease characteristics. In alignment with US clinical practice, both cisplatin and carboplatin chemotherapy doublets were permitted in the study.

AEGEAN demonstrated that perioperative durvalumab is safe and effective for the treatment of patients with resectable NSCLC. The study met its dual primary endpoints of pCR and EFS at pre-specified interim analyses, met its key secondary endpoint of MPR (at pCR IA), demonstrated improving OS with increased maturity, and was associated with a manageable safety and tolerability profile.

AEGEAN demonstrated that treatment with D + CTx in the neoadjuvant phase resulted in a statistically significant and meaningful improvement in locoregional tumor eradication compared to Pbo + CTx, as determined by the assessment of pCR and MPR.

The benefits of perioperative durvalumab are demonstrated by the results of the primary endpoint of EFS, which is a well-established regulatory endpoint in early-stage NSCLC. While demonstration of OS benefit remains the gold standard in oncology studies, EFS can represent direct clinical benefit in early-disease settings, provided the magnitude of benefit outweighs the toxicity of the treatment [48]; EFS has been used as a surrogate endpoint to support regulatory approval in resectable NSCLC (see Appendix 2) and across other tumor types.

AEGEAN demonstrated that perioperative D + CTx elicited a statistically significant and clinically meaningful improvement in EFS as compared to Pbo + CTx, based on 31.9% data maturity at EFS IA1. Of note, AEGEAN demonstrated statistical significance for EFS with less data maturity

and less follow-up time than other Phase III studies of anti-PD-L1/PD-1 immunotherapy in resectable NSCLC [10, 19].

OS was immature in AEGEAN, as would be expected, but an updated analysis demonstrated a trend for improved OS favoring D + CTx. Time to a survival event, and subsequent therapies in the relapsed/metastatic setting, make OS a challenging endpoint in early disease, and therefore a trend in survival improvement has been considered sufficient to support EFS.

Collectively, efficacy data suggest that perioperative durvalumab in combination with neoadjuvant chemotherapy results in early tumor cell elimination and the priming of anti-tumor immunity before surgery (while the primary tumor and lymph nodes are present), combined with and a durable and sustained suppression/elimination of residual micrometastatic disease after surgery, resulting in improved event-free survival. These benefits were consistently observed regardless of demographics, disease characteristics, or platinum chemotherapy agent (cisplatin or carboplatin).

Durvalumab as monotherapy and in combination with chemotherapy has a well-established and manageable safety profile, and safety results from AEGEAN are consistent with the established safety profiles of the individual treatment agents (ie., durvalumab and platinum-based chemotherapy).

The majority of imAEs in the D + CTx arm were non-serious, low in severity (CTCAE Grade 1-2), did not lead to discontinuation of study treatment, and were resolved by the DCO date. The most common imAEs reported in both treatment arms were hypothyroidism and rash/dermatitis.

Durvalumab monotherapy during the adjuvant period had an acceptable safety and tolerability profile as compared to the placebo arm. Overall, the nature of the AEs reported during adjuvant durvalumab treatment was consistent with the established safety profile of durvalumab monotherapy, with AE frequencies that were either similar to, or lower than, those reported in the pooled safety dataset.

In conclusion, the Sponsor considers that the totality of efficacy and safety data summarized herein confirm a strongly favorable benefit-risk profile for neoadjuvant durvalumab in combination with platinum doublet chemotherapy given prior to surgery, followed by adjuvant durvalumab monotherapy post-surgery, for adult patients with resectable NSCLC whose tumors have no known EGFRm/ALK gene rearrangements.

The FDA's Position:

AEGEAN efficacy results demonstrated a statistically significant and clinically meaningful improvement in EFS favoring perioperative durvalumab. At present, the analysis of DFS is not statistically significant, precluding formal testing of OS due to the hierarchical design. Descriptive analyses of OS do not suggest a detrimental effect of perioperative durvalumab.

The safety analysis revealed a risk profile consistent with described toxicities of platinum-based chemotherapy and immune checkpoint inhibitors. Additional safety findings in the prolonged

adjuvant setting, while consistent with the known toxicity profile of durvalumab, are concerning given that the contribution of this phase of treatment to the efficacy of the regimen remains unclear. Grade 1 and 2 toxicities, while not life threatening, can affect patient function and quality of life and PRO data were not captured in the adjuvant period to further characterize this possibility. Importantly, 9% of patients who received adjuvant durvalumab had unresolved irAEs at the end of study treatment, raising concerns for lasting adverse events from adjuvant durvalumab in a patient population that may achieve cure or long-term survival.

The critical review issue for this application is the inability of AEGEAN to assess the contribution of durvalumab in the neoadjuvant phase or the adjuvant phase to the efficacy of the overall perioperative regimen. The two-arm design of AEGEAN forces the FDA to consider external data to attempt to assess the contribution of phase. Available external trial data do not appear to provide clear support for the perioperative regimen having substantively higher efficacy than either neoadjuvant or adjuvant treatment alone. This raises the concern for potential patient overtreatment, most impactful in the adjuvant setting, if the observed EFS benefit is due to treatment effect from the neoadjuvant phase alone.

The advisory committee will be asked to discuss the available evidence from AEGEAN and provide their thoughts on whether the benefits outweigh the risks for the AEGEAN regimen and whether additional data on contribution of sequence should be provided prior to approval of this perioperative indication.

The second topic of discussion will be focused on future trial designs investigating new agents added to existing NSCLC regimens in the curative intent setting. FDA is currently receiving proposals from sponsors for two-arm, add-on trials of novel drugs combined with perioperative ICI backbones for patients with resectable NSCLC. These designs would replicate the uncertainties we have seen with other two-arm trials like AEGEAN, including inability to determine whether intensification of both the neo-adjuvant and adjuvant phases is necessary. This exacerbates concerns for overtreatment due to treatment intensification and its attendant increased toxicities.

While FDA has recommended within trial evaluation of contribution of sequence, including for AEGEAN, sponsors have not heeded this advice. The committee will discuss trial design options that can assess the efficacy of novel drugs in resectable NSCLC, while simultaneously demonstrating the contribution of these drugs when given in each phase of a perioperative regimen. Multi-arm, factorial, and re-randomization trials represent alternative designs that may address the issue of contribution of treatment phase while assessing efficacy of the novel drug. FDA remains open to other alternative drug development plans that are designed to adequately characterize the efficacy of a novel drug and its contribution to treatment effect when given in different phases of a perioperative regimen.

FDA feels this approach is increasingly necessary and seeks the advisory committee's advice on whether to require future trials be designed to allow for within trial evaluation of the phases of a perioperative regimen to avoid potential toxicities due to overtreatment without additional clinical benefit.

7. Draft Topics for Discussion by the Advisory Committee

- In light of the uncertainty around the need for both phases of treatment, discuss whether an additional trial should be conducted to clarify the contribution of treatment phase for the durvalumab perioperative regimen prior to approval.

- Should FDA require that new trial design proposals for perioperative regimens include adequate within trial assessment of contribution of treatment phase?

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9. Appendices

9.1 Applicant's Appendices

Appendix 1: Key Regulatory Interactions With the FDA

Relevant formal interactions held with the FDA for the development of durvalumab in the proposed indication are summarized in Table 8. At the time of the initial regulatory interactions, the AEGEAN study protocol version 1.0 (dated 31 August 2018) was effective. The study design at the time of this early advice was therefore based on a primary endpoint of MPR, with pCR as a secondary endpoint. For a summary of important changes to study design over time (including changes to endpoints), see Appendix 3.

Table 15 Summary of key regulatory interactions with the FDA

01 Nov 2018:	**Type B/End-of-Phase II Meeting**
• The FDA recommended powering the study for EFS or DFS as a primary endpoint. • FDA noted that, as designed, the AEGEAN study does not isolate the benefit of neoadjuvant durvalumab from post-surgical adjuvant durvalumab, to consider an adaptive or factorial study design, and that the product label based on this study would need to specify that both neoadjuvant therapy and adjuvant therapy are necessary to provide clinical benefit. • Stratification factors, comparator, and standard-of-care background therapy were deemed acceptable.	
16 Dec 2020:	**Type C Meeting**
• FDA did not consider MPR to be a candidate surrogate endpoint, and stated pCR was a clearer endpoint to be assessed pathologically. • FDA would not consider an application for neoadjuvant durvalumab based on a primary analysis of pCR to be fileable in the absence of statistically significant EFS data. • Statistically significant improvement in EFS would likely be required to support a marketing application but magnitude of improvement in EFS required may also be dependent on magnitude of pCR observed.	
09 May 2023:	**Type B Pre-BLA Meeting**
• The FDA acknowledged the AEGEAN study was positive and that the data were sufficient for submission. However, given the limitations with the study design and its inability to isolate the contributions of durvalumab in the pre-surgery phase and durvalumab given in the post-surgery phase to the overall treatment effect, FDA requested a thorough, scientific discussion of the AEGEAN study design within the submission. • The FDA agreed with AstraZeneca's proposal to provide updated OS during the sBLA review to confirm that there is no detriment to survival demonstrated with neoadjuvant durvalumab with chemotherapy followed by adjuvant durvalumab compared to placebo with chemotherapy in this curative intent setting.	

Appendix 2: Anti-PD-L1/PD-1 Therapies Approved in the US for Resectable NSCLC

Table 16 Anti-PD-L1/PD-1 therapies approved in the US for resectable NSCLC

Product name	Pivotal study (approval date)	Indication	Dosing and administration	Efficacy information per label	Important safety issues per label
Neoadjuvant setting					
OPDIVO (nivolumab)	**CheckMate-816** (March 2022)	Adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.	Nivolumab 360 mg with platinum-doublet chemotherapy on the same day every 3 weeks for 3 cycles.	Nivolumab + chemotherapy vs chemotherapy alone: **EFS:** • Median: 31.6 vs 20.8 months • HR: 0.63 (95% CI: 0.45 to 0.87); p-value = 0.0052 **pCR:** • 24.0% vs 2.2% • Estimated treatment difference: 21.6 (95% CI: 15.1 to 28.2); p-value < 0.0001	Nivolumab + chemotherapy: • Most common adverse reactions (> 20% of patients): nausea, constipation, fatigue, decreased appetite, and rash. • Serious adverse reactions occurred in 30% of patients. • Adverse reactions led to permanent discontinuation of treatment in 10% of patients. • No fatal adverse reactions.
Adjuvant setting					
TECENTRIQ (atezolizumab)	**IMpower010** (October 2021)	As adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II-IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test.	Following resection and up to 4 cycles of platinum-based chemotherapy, give atezolizumab as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year.	Atezolizumab vs best supportive care: **DFS:** • Median: not reached vs 35.3 months • HR: 0.66 (95% CI: 0.50 to 0.88); p-value = 0.004	Atezolizumab: • Most common adverse reactions (≥ 10% of patients): rash, pruritus, hypothyroidism, cough, pyrexia, fatigue, peripheral neuropathy, musculoskeletal pain, and arthralgia. • Serious adverse reactions occurred in 18% of patients. • Adverse reactions led to permanent discontinuation of treatment in 18% of patients. • Fatal adverse reactions occurred in 1.8% of patients.

Product name	Pivotal study (approval date)	Indication	Dosing and administration	Efficacy information per label	Important safety issues per label
KEYTRUDA (pembrolizumab)	**KEYNOTE-091** (January 2023)	As a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC.	Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks for up to 12 months.	Pembrolizumab vs placebo: **DFS:** • Median: 58.7 vs 34.9 months • HR: 0.73 (95% CI: 0.60 to 0.89); p-value not reported	Adverse reactions were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (22%), hyperthyroidism (11%), and pneumonitis (7%). There were 2 fatal adverse reactions of myocarditis.
Perioperative setting					
KEYTRUDA (pembrolizumab)	**KEYNOTE-671** (October 2023)	Treatment of patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery	Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks. Give neoadjuvant treatment in combination with chemotherapy for up to 12 weeks; followed by adjuvant treatment as a single agent after surgery for up to 39 weeks.	Pembrolizumab + chemotherapy, followed by pembrolizumab vs placebo + chemotherapy, followed by placebo: **OS:** • Median: not reached vs 52.4 months • HR: 0.72 (95% CI: 0.56 to 0.93); p-value = 0.0103 **EFS:** • Median: not reached vs 17.0 months • HR: 0.58 (95% CI: 0.46 to 0.72); p-value < 0.0001 **pCR:** • 18.1% vs 4.0% • Estimated treatment difference: p-value < 0.0001 **MPR:** • 30.2% vs 11.0% • Estimated treatment difference: p-value < 0.0001	Adverse reactions were generally similar to those occurring in patients across tumor types receiving KEYTRUDA in combination with chemotherapy. **Pembrolizumab + chemotherapy in the neoadjuvant phase:** • Serious adverse reactions occurred in 34% of patients. • Adverse reactions led to permanent discontinuation of treatment in 18% of patients. • Fatal adverse reactions occurred in 1.3% of patients. **Pembrolizumab as single agent in the adjuvant phase:** • Serious adverse reactions occurred in 14% of patients. • Adverse reactions led to permanent discontinuation of treatment in 12% of patients. • One fatal adverse reaction occurred.

Appendix 3: Major Protocol Amendments

All study protocol amendments were made prior to the DCO date of the interim pCR analysis (14 January 2022), and CSP Version 5.0 (dated 10 December 2021) was current at the pCR IA and EFS IA1 DCO dates. Consequently, no internal AEGEAN data were used as a rationale to modify study design, therefore preserving the trial integrity. The key changes to the study protocol are summarized in Table 10.

Table 17 Summary of key amendments to the AEGEAN study protocol

Amendment Number/Date	Key details of amendment
Amendments made *before* the start of patient randomization	
Protocol version 2.0 (Amendment 1) 04 December 2018	The pre-surgery chemotherapy treatment regimen was revised from 3 neoadjuvant cycles (with an optional fourth cycle post-surgery based on local practice and Investigator's judgment) to 4 neoadjuvant cycles for all patients.
Amendments made *after* the start of patient randomization (prior to the DCO date of the pCR interim analysis, and the first EFS interim analysis)	
Protocol version 3.0 (Amendment 2) 26 November 2019	Changes to the study objectives and endpoints and their respective analysis populations were made: • EFS (previously a secondary endpoint) was added as a new primary endpoint (in addition to the existing primary endpoint of MPR) • DFS (previously a secondary endpoint) was added as a key secondary endpoint (in addition to the existing key secondary endpoint of pCR). Aligned with this update, the number of planned patients to be enrolled and randomized was increased to 1333 and 800, respectively, and the MTP was updated.
	The definitions of EFS and DFS were updated to the following: • EFS is defined as the time from randomization to the first of the following: a) documented disease progression of lung cancer as determined by BICR using RECIST 1.1 assessments; b) death due to any cause (event date is the date of death); or c) PD that precludes surgery as assessed by a multidisciplinary evaluation before surgery (event date is the date of this determination), or discovered upon attempting surgery (event date is the date of the first attempt at surgery). • DFS is defined as the time from the date of surgery until the first date of disease recurrence as determined by BICR using RECIST 1.1 assessments (local or distant), or date of death due to any cause, whichever occurs first.
Protocol version 4.0 (Amendment 3) 15 April 2021	The secondary objective of pCR was changed to be a primary objective and the primary objective of MPR was changed to be a key secondary objective. The existing secondary endpoint of OS was reclassified as a key secondary endpoint. Updated definitions of pCR and MPR: • Specimens demonstrating a lack of any viable tumor cells upon complete evaluation of resected lung cancer specimen(s), including all sampled lymph nodes, will be considered to have pCR • Resected lung cancer specimens in which there is ≤ 10% residual viable TCs will be considered to have MPR. Additional text was added stating that central pathology assessment of pCR and MPR will be performed according to the recommended methods and definitions described by IASLC.

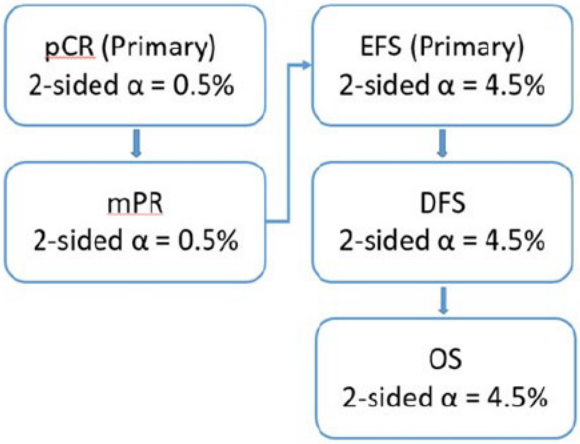
Amendment Number/Date	Key details of amendment
	A new exclusion criterion was added to clarify that patients with EGFRm/ALK gene rearrangement were no longer eligible for the study. In relation to this update, efficacy analysis sets were also modified to include only patients whose tumors do not contain EGFRm or ALK gene rearrangements.
	The guidance for proceeding to adjuvant treatment following surgery was updated to permit this only for patients with R0/1 margins (not R2).
	Previous reference to the IA of MPR was updated to reflect the IA of pCR (as the updated primary endpoint) after approximately 400 patients (previously 300 patients) with no known EGFRm/ALK gene rearrangement had been randomized and completed approximately 7 months of follow-up.
	The general AstraZeneca guidance relating to study conduct during study disruptions due to COVID-19 were added to the protocol.
Protocol version 5.0 (Amendment 4) 10 December 2021	The definition of EFS was updated to the following: • EFS is defined as the time from randomization to the first of the following: a) local or distant recurrence (using BICR per RECIST 1.1); b) death due to any cause (event date is the date of death); c) PD that precludes surgery (event date is the date of this determination) or PD discovered and reported by the Investigator upon attempting surgery that prevents completion of surgery (event date is the date of the first attempt at surgery).

Appendix 4: Multiple Testing Procedure and Summary of Statistical Methodology

Multiple Testing Procedure (MTP):

In order to strongly control the type I error at 5% (2-sided), an MTP was utilized across the primary (pCR and EFS) and key secondary endpoints (MPR, DFS, and OS) (Figure 6). The MTP is hierarchical, starting with testing the 2 primary endpoints of pCR and EFS. The overall 2-sided 5% type I error was split between the 2 primary endpoints pCR and EFS, with an alpha level of 0.5% allocated to the pCR analysis and an alpha level of 4.5% allocated to the EFS analysis.

Figure 11 Pre-planned MTP utilized in the AEGEAN study



The pre-planned alpha recycling strategy was as follows:

1) If pCR was declared statistically significant, the 0.5% alpha would be recycled to MPR. If both pCR and MPR were declared statistically significant, the 0.5% alpha would be recycled to EFS, such that a total alpha level of 5% will be allocated to the EFS analyses.
2) If EFS was declared statistically significant, then the alpha level utilized for the EFS analysis (either 4.5% alpha or 5% alpha) would be recycled to DFS.
3) If DFS was declared statistically significant, then the alpha level utilized (either 4.5% alpha or 5% alpha) would be recycled again to OS.

Since the pre-planned pCR IA (DCO of 14 January 2022) demonstrated a statistically significant improvement in pCR and MPR in favor of the D + CTx arm, the 0.5% alpha assigned to pCR (and MPR) was recycled to EFS, such that EFS was tested with a total of 5% 2-sided alpha level.

Based on the pre-planned EFS IA1 (DCO of 10 November 2022), EFS was also declared statistically significant. Per the MTP, DFS was also tested at EFS IA1, however it did not meet the pre-specified boundary for declaring statistical significance (overall maturity of DFS data was 21%). As DFS was not statistically significant at EFS IA1, OS was not formally tested based on the MTP; however, OS data are reported descriptively herein to support the benefit-risk-assessment of the proposed treatment regimen.

Summary of Statistical Methodology for Efficacy Endpoints:

Table 18 Efficacy endpoints and analysis methods relevant to this briefing document

Endpoint	Analysis methodology
Primary endpoints	
EFS	EFS (based on BICR assessment per RECIST 1.1) was analyzed in the mITT population using a stratified log-rank test stratified by disease stage (Stage II vs Stage III) and PD-L1 expression status (TC < 1% vs TC ≥ 1%) at baseline. The effect of treatment was estimated by the HR together with its corresponding 95% CI, a CI with confidence level adjusted for the relevant alpha level, and p-value. The HR and CI was estimated from the stratified Cox proportional hazards model (using the Efron method to control for ties and a profile likelihood approach to calculate the CI). **EFS subgroup analyses:** For each subgroup, the HR and 95% CI were calculated from an unstratified Cox proportional hazards model with treatment as the only covariate. If too few events were available for a meaningful analysis of a particular subgroup (ie, less than 20 events across both treatment arms), the relationship between that subgroup and EFS was not analyzed. No adjustment was made to the significance level for testing of the subgroup analyses. **EFS sensitivity analyses:** Evaluation-time bias, attrition bias, ascertainment bias, non-proportional hazards, and for the primary treatment comparison using PD-L1 expression status at baseline (TC < 1% vs TC ≥ 1%) and disease stage (Stage II vs Stage III) as defined by source data (instead of IXRS) as stratification factors. **EFS piecewise analysis:** The analysis was performed using a stratified Cox regression model, with time-dependent covariate for each piecewise estimate. Stratification factors include disease stage and PD-L1 expression status at baseline.

Endpoint	Analysis methodology
pCR	The analysis of pCR (by blinded central pathology review) was performed on the mITT population using a Cochran-Mantel-Haenszel test, stratified by disease stage (Stage II vs Stage III) and PD-L1 expression status (TC < 1% vs TC ≥ 1%) at baseline. The effect of treatment was estimated by the difference in proportions between treatment arms, together with its corresponding 95% CI, a CI with confidence level adjusted for the relevant alpha level, and p-value. The CIs were computed using stratified Miettinen and Nurminen's confidence limits. **pCR subgroup analyses:** For each subgroup, the difference in proportions between treatment arms and 95% CI was calculated using unstratified Miettinen and Nurminen's confidence limits. No adjustment was made to the significance level for testing of the subgroup analyses.
Key secondary endpoints	
MPR	The analysis of MPR (by blinded central pathology review) was performed on the mITT population using a Cochran-Mantel-Haenszel test, stratified by disease stage (Stage II vs Stage III) and PD-L1 expression status (TC < 1% vs TC ≥ 1%) at baseline. The effect of treatment was estimated by the difference in proportions between treatment arms, together with its corresponding 95% CI, alpha-adjusted CI, and p-value. The CIs for the difference in proportions between groups was computed using stratified Miettinen and Nurminen's confidence limits.
DFS	DFS was to be evaluated for patients who had surgical resection following neoadjuvant period and whose first post-surgical RECIST scan (scheduled at 5 weeks [± 2 weeks] following the date of surgery) shows no disease (ie., resected and modified resected analysis set). DFS was to be analyzed in the modified resected set, using the same methodology as described for EFS. DFS was to be analyzed using a log-rank test (using BICR per RECIST 1.1) stratified by disease stage (Stage II vs Stage III) and by PD-L1 expression status (TC < 1% vs TC ≥ 1%) at baseline.
OS	OS was analyzed in the mITT population using the same methodology as described for EFS. However, as DFS was not statistically significant at EFS IA1, according to the MTP, OS could not be formally tested for statistical significance. The effect of treatment was estimated by the HR together with its corresponding 95% CI. A pre-specified sensitivity analysis to assess the impact of COVID-19 deaths was performed.
Supplemental analyses of efficacy	
ORR	Whilst ORR was not a pre-defined study endpoint in the CSP, ORR summaries have been produced as a potentially supportive endpoint for pCR, as per the Statistical Analysis Plan. The analysis of ORR was performed on the mITT population using a Cochran-Mantel-Haenszel test, stratified by disease stage (Stage II vs Stage III) and PD-L1 expression status (TC < 1% vs TC ≥ 1%) at baseline. The effect of treatment was estimated by the difference in proportions between treatment arms, together with their corresponding CI and p-value. The CIs for the difference in proportions between groups was computed using stratified Miettinen and Nurminen's confidence limits.

Appendix 5: Major Changes to the Statistical Analysis Plan (SAP)

Key changes to the planned analyses that are reflected in the SAP but were not described as part of a protocol amendment are summarized in Table 12. All major changes to planned analyses were made prior to the DCO date of pCR IA (14 January 2022).

Table 19 Key changes to the planned statistical analyses

Key details of change	SAP amendment
• Time to deterioration analyses for PRO were updated to be analyzed for the adjuvant period only. As surgery will have an impact on these data, this variable will only be derived for EORTC QLQ-C30, using the first measurement post-surgery and pre-dose of the first adjuvant treatment as baseline.	**SAP Version 2.0** 16 July 2020
• Updated pCR definition to exclude patients with carcinoma present in any examined lymph nodes, ie, consider them a non-response. • Clarified for MPR that patients will be assigned MPR response regardless of any carcinoma present in any examined lymph nodes. • ORR added as a supportive variable to facilitate comparison of the clinical outcome prior to surgery with pathological response. • Planned summaries of nodal downstaging and disease stage downstaging added. • The on-treatment definition was updated to include the surgery date in addition to last dose of durvalumab/placebo + CTx or durvalumab/placebo monotherapy, to ensure AEs occurring in the surgical period are captured in safety summaries. • mITT population definition clarified to include unknown EGFR/ALK, and inclusion of post-baseline EGFR/ALK data to determine status. • Addition of sensitivity analyses for study endpoints eg, OS, in which patients who had a death due to COVID-19 were censored (using their death date as the censor date).	**SAP Version 3.0** 22 December 2021
• Changes to RMST models to report unadjusted models for all RMST analyses. Adjusted models may be considered post hoc as further exploratory analysis. • Update to perform unstratified analyses on the EGFRm/ALK gene rearrangement subgroups. • Additional subgroups for analysis added: ▪ Further PD-L1 and Stage categories added due to clinical interest. ▪ PORT added as a post-baseline subgroup for survival endpoints, following interaction with regulatory bodies. • Update interaction test analyses to specify use of source data rather than IXRS data, to avoid downward bias caused by errors in stratification (if any). • Addition of summaries of duration of follow-up for EFS, DFS and OS added. • Addition of new output to AE analyses to describe number of patients with AEs of maximum CTCAE Grade 3 or 4, by SOC and PT. • Baseline Characteristic summaries and surgery detail summaries to be repeated on mITT population and ITT population.	**SAP Addendum Version 1.0** 10 November 2022

Appendix 6: Patient Disposition

Table 20 Overview of patient disposition (mITT population; EFS IA1 and Safety Update)

Study period		Number (%) patients [a]			
		EFS IA1 (mITT population)		Safety Update (mITT population)	
		D + CTx (N = 366)	Pbo + CTx (N = 374)	D + CTx (N = 366)	Pbo + CTx (N = 374)
Pre-treatment	Randomized	366 (100)	374 (100)	366 (100)	374 (100)
Neoadjuvant	Received neoadjuvant treatment	366 (100)	371 (99.2)	366 (100)	371 (99.2)
	Completed 4 cycles of neoadjuvant treatment of both (doublet) CTx	310 (84.7)	326 (87.2)	310 (84.7)	326 (87.2)
	Completed 4 cycles of neoadjuvant durvalumab/placebo	318 (86.9)	331 (88.5)	318 (86.9)	331 (88.5)
Surgery	Underwent on-study surgery [b]	295 (80.6)	302 (80.7)	295 (80.6)	302 (80.7)
	Did not undergo surgery on study	71 (19.4)	72 (19.3)	71 (19.4)	72 (19.3)
	Completed on-study surgery	284 (77.6)	287 (76.7)	284 (77.6)	287 (76.7)
	Did not complete on-study surgery	11 (3.0)	15 (4.0)	11 (3.0)	15 (4.0)
Adjuvant	Started adjuvant durvalumab/placebo [c]	241 (65.8)	237 (63.4)	242 (66.1)	237 (63.4)
	Discontinued adjuvant durvalumab/placebo	68 (18.6)	70 (18.7)	76 (20.8)	86 (23.0)
	Completed adjuvant durvalumab/placebo	88 (24.0)	79 (21.1)	162 (44.3)	148 (39.6)
	Ongoing adjuvant durvalumab/placebo	85 (23.2)	88 (23.5)	4 (1.1)	3 (0.8)

[a] All percentages are calculated from number of randomized patients in each arm (EFS IA1 mITT, and Safety Update mITT respectively).
[b] Excludes patients with surgery done outside the study.
[c] Includes 3 patients who did not complete surgery in the mITT population (1 patient for D + CTx vs 2 patients for Pbo + CTx).
DCO: 10 November 2022 (EFS IA1) and 14 August 2023 (Safety Update).
Source: Tables iemt0577.21 and iemt0617.4

Appendix 7: Patient Demographics and Baseline Characteristics

Table 21 Demographics and baseline patient characteristics (ITT and mITT populations; EFS IA1)

Characteristic	Number (%) patients			
	ITT population		mITT population	
	D + CTx (N = 400)	Placebo + CTx (N = 402)	D + CTx (N = 366)	Placebo + CTx (N = 374)
Age (years) [a]				
Median (min, max)	65.0 (30, 88)	65.0 (39, 85)	65.0 (30, 88)	65.0 (39, 85)
Age group [a]				
< 50 years	22 (5.5)	22 (5.5)	17 (4.6)	20 (5.3)
≥ 50 to < 65 years	170 (42.5)	177 (44.0)	158 (43.2)	163 (46.3)
≥ 65 to < 75 years	160 (40.0)	165 (41.0)	147 (40.2)	155 (41.4)
≥ 75 years	48 (12.0)	38 (9.5)	44 (12.0)	36 (9.6)
Sex				
Male	262 (65.5)	291 (72.4)	252 (68.9)	278 (74.3)
Female	138 (34.5)	111 (27.6)	114 (31.1)	96 (25.7)
Race				
White	216 (54.0)	196 (48.8)	206 (56.3)	191 (51.1)
Asian	165 (41.3)	187 (46.5)	143 (39.1)	164 (43.9)
American Indian or Alaska Native	7 (1.8)	4 (1.0)	6 (1.6)	4 (1.1)
Black or African American	5 (1.3)	3 (0.7)	4 (1.1)	3 (0.8)
Other	7 (1.8)	12 (3.0)	7 (1.9)	12 (3.2)
Ethnic group				
Not Hispanic or Latino	332 (83.0)	344 (85.6)	303 (82.8)	318 (85.0)
Hispanic or Latino	68 (17.0)	58 (14.4)	63 (17.2)	56 (15.0)
Region				
Asia	164 (41.0)	186 (46.3)	142 (38.8)	163 (43.6)
Europe	147 (36.8)	144 (35.8)	141 (38.5)	140 (37.4)
North America	47 (11.8)	44 (10.9)	43 (11.7)	43 (11.5)
South America	42 (10.5)	28 (7.0)	40 (10.9)	28 (7.5)
Smoking history				
Never-smoker	72 (18.0)	74 (18.4)	51 (13.9)	56 (15.0)
Current smoker	96 (24.0)	97 (24.1)	95 (26.0)	95 (25.4)
Former smoker	232 (58.0)	231 (57.5)	220 (60.1)	223 (59.6)
ECOG performance status				
(0) Normal activity	278 (69.5)	277 (68.9)	251 (68.6)	255 (68.2)
(1) Restricted in physically strenuous activity	122 (30.5)	125 (31.1)	115 (31.4)	119 (31.8)

Characteristic	Number (%) patients			
	ITT population		mITT population	
	D + CTx (N = 400)	Placebo + CTx (N = 402)	D + CTx (N = 366)	Placebo + CTx (N = 374)
Disease stage at baseline (per source data) [b]				
IIA	19 (4.8)	28 (7.0)	18 (4.9)	24 (6.4)
IIB	100 (25.0)	92 (22.9)	86 (23.5)	86 (23.0)
III (not otherwise specified)	0	1 (0.2)	0	1 (0.3)
IIIA	186 (46.5)	178 (44.3)	173 (47.3)	165 (44.1)
IIIB	94 (23.5)	103 (25.6)	88 (24.0)	98 (26.2)
IV (not otherwise specified)	1 (0.3)	0	1 (0.3)	0
TNM classification at baseline [b]				
T1	53 (13.3)	48 (11.9)	44 (12.0)	43 (11.5)
T2	108 (27.0)	119 (29.6)	97 (26.5)	108 (28.9)
T3	141 (35.3)	136 (33.8)	128 (35.0)	129 (34.5)
T4	98 (24.5)	99 (24.6)	97 (26.5)	94 (25.1)
N0	118 (29.5)	110 (27.4)	110 (30.1)	102 (27.3)
N1	83 (20.8)	94 (23.4)	75 (20.5)	87 (23.3)
N2	199 (49.8)	198 (49.3)	181 (49.5)	185 (49.5)
Histology				
Squamous	173 (43.3)	192 (47.8)	169 (46.2)	191 (51.1)
Non-squamous	226 (56.5)	206 (51.2)	196 (53.6)	179 (47.9)
PD-L1 expression				
TC < 1%	133 (33.3)	134 (33.3)	122 (33.3)	125 (33.4)
TC 1 to 49%	151 (37.8)	158 (39.3)	135 (36.9)	142 (38.0)
TC ≥ 50%	116 (29.0)	110 (27.4)	109 (29.8)	107 (28.6)
Planned neoadjuvant platinum agent				
Cisplatin	110 (27.5)	105 (26.1)	100 (27.3)	96 (25.7)
Carboplatin	290 (72.5)	297 (73.9)	266 (72.7)	278 (74.3)

[a] Age was calculated using date of randomization.

[b] According to AJCC Cancer Staging Manual, 8th Edition.

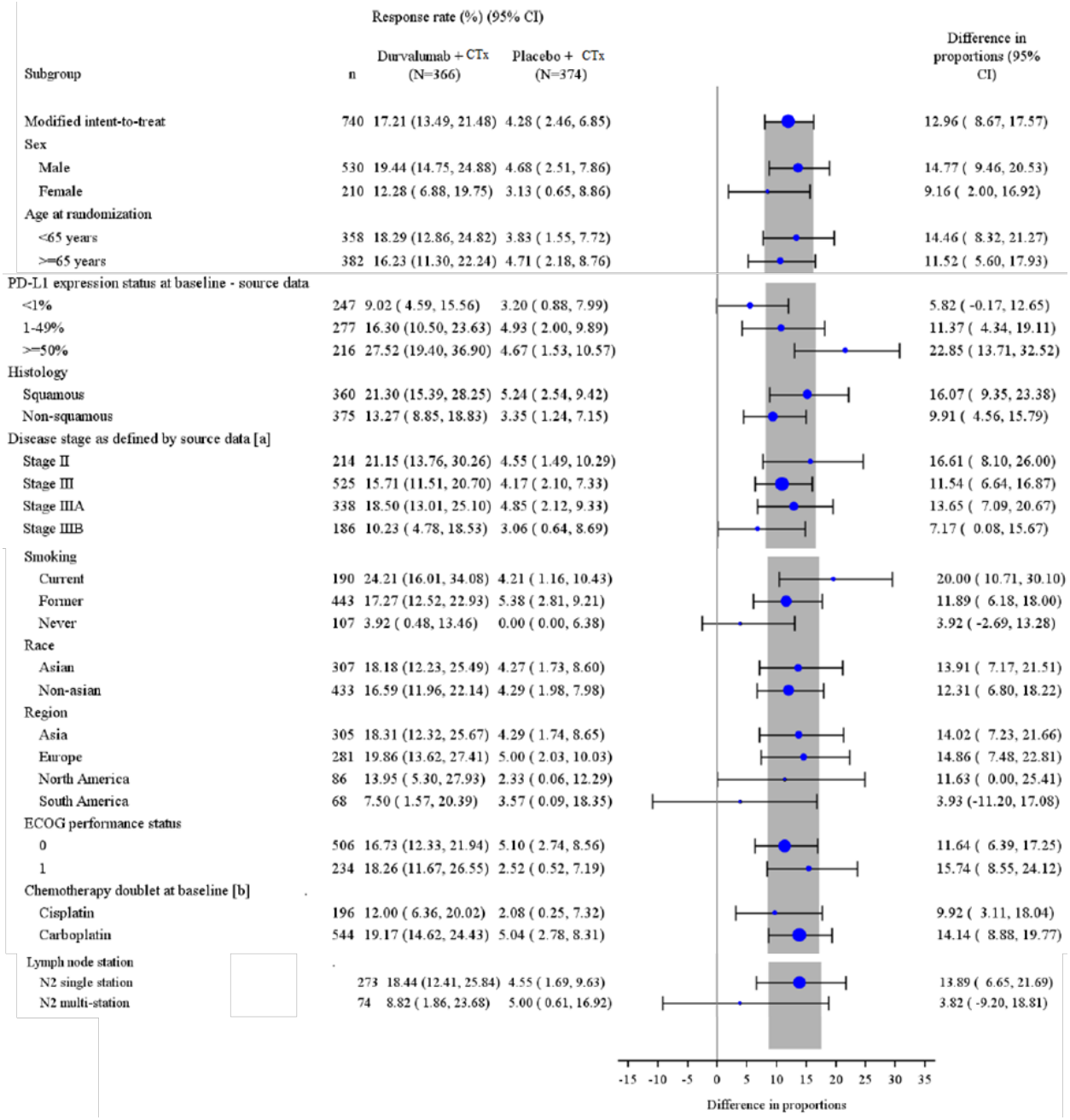
Baseline was defined as the last observation prior to randomization if available, or otherwise, an observation after randomization but before the first dose of randomized treatment.

DCO: 10 November 2022.

Source: Tables 14.1.5.1.IA1, 14.1.5.2.IA1, 14.1.6.1.IA1, 14.1.6.2.IA1, 14.1.10.1.IA1, 14.1.10.2.IA1, 14.1.11.1.IAI, 14.1.11.2.IA1.14.1.14.1.IA1, 14.1.14.2.IA1, iemt0578.015, and iemt0578.016.

Appendix 8: Subgroup Analysis of Pathological Complete Response

Figure 12 Pathological complete response at final analysis: forest plot by subgroup (mITT population, EFS IA1)



[a] One patient who had disease stage IV at baseline was excluded from the analysis.

[b] Refers to the platinum agent of the chemotherapy doublet (planned treatment).

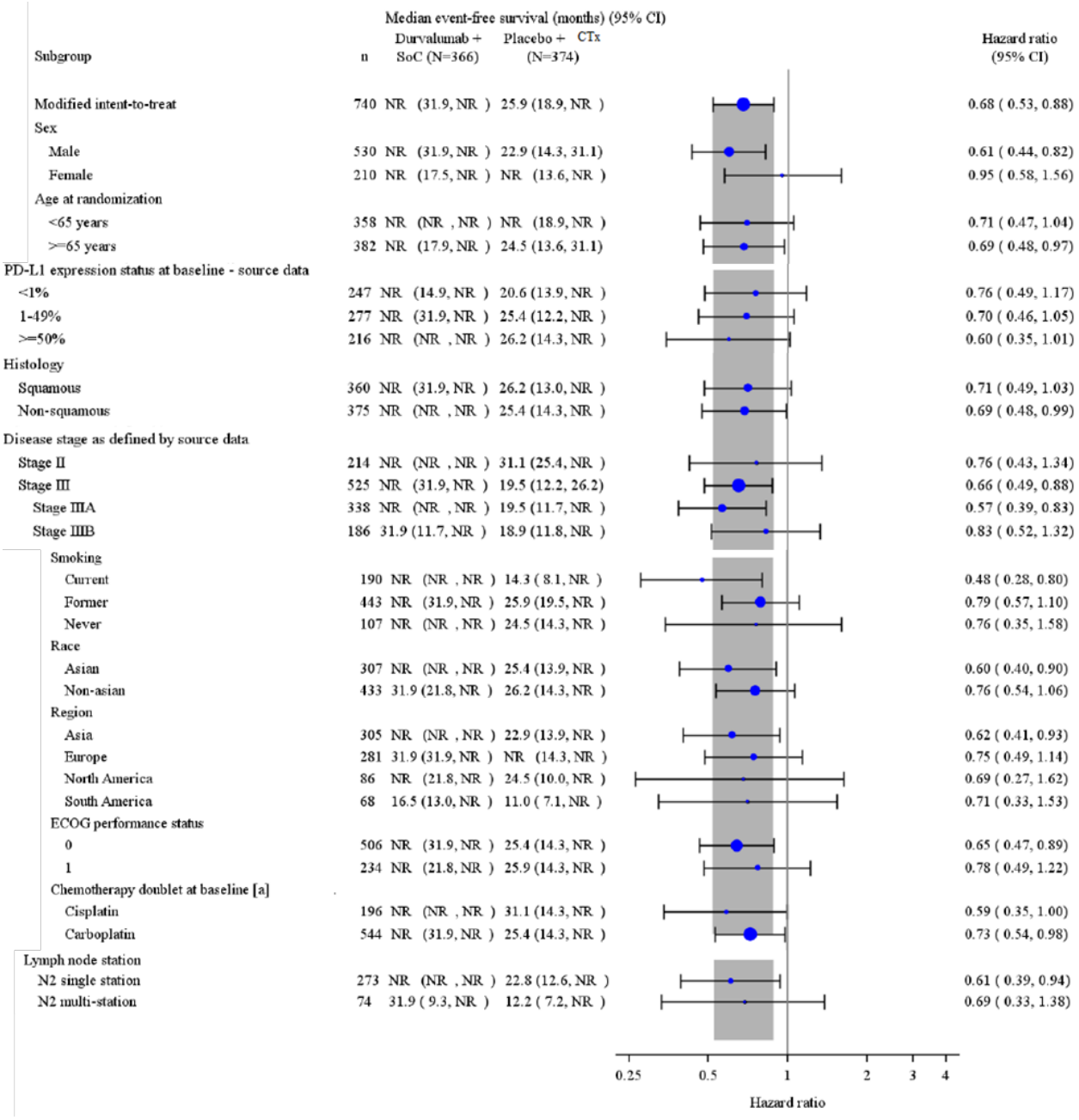
Results show the difference in proportions (%) and corresponding 95% CI. A difference > 0 favors D + CTx.

Size of circle is proportional to the number of patients in the subgroup. Grey band represents the 95% confidence interval for the difference in proportions in the overall mITT population.

DCO: 10 November 2022. Source: Figure 14.2.1.7.FA.

Appendix 9: Subgroup Analysis of Event-free Survival

Figure 13 EFS (using BICR per RECIST 1.1): forest plot by subgroup (mITT population, EFS IA1)



[a] Refers to the platinum agent of the chemotherapy doublet (planned treatment).

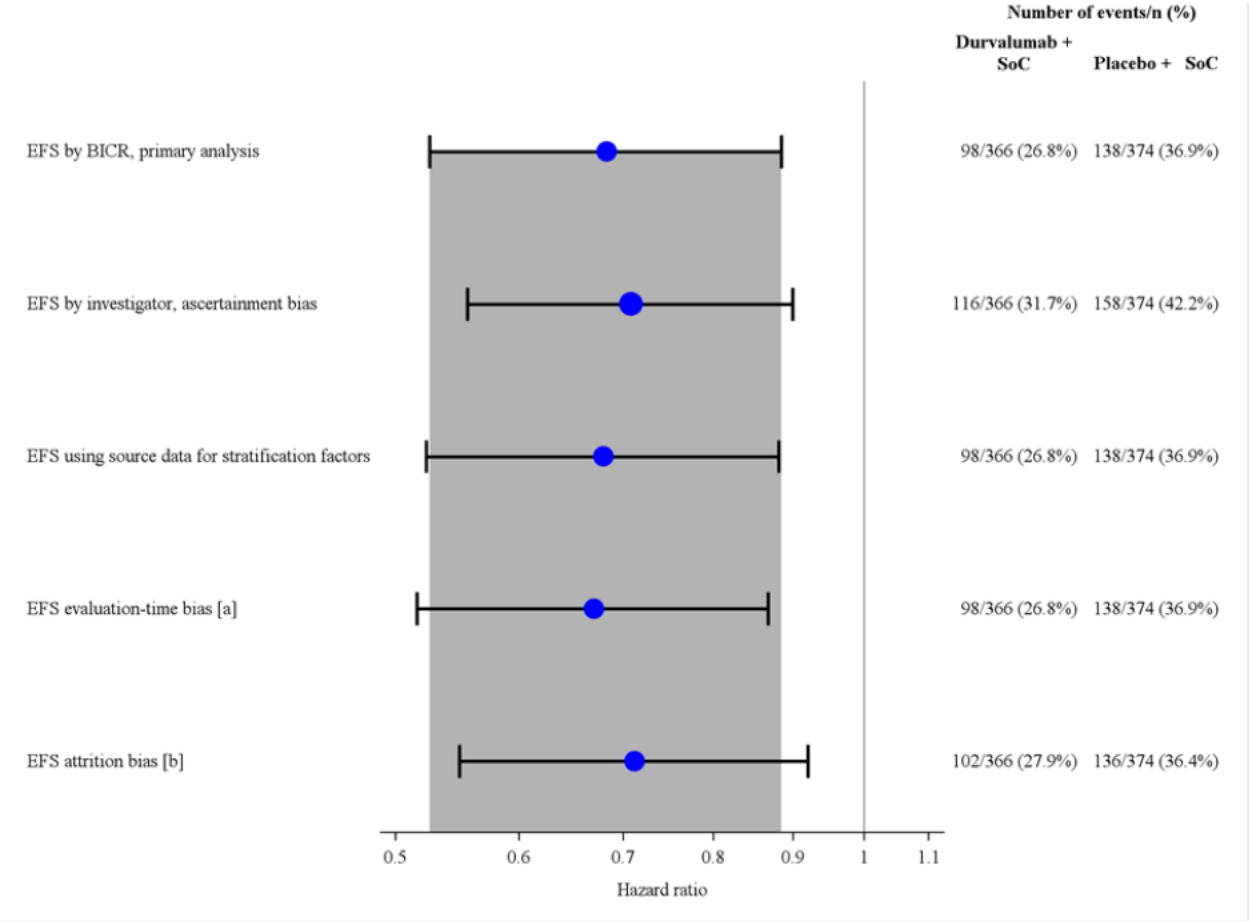
An HR < 1 favors D + CTx. Median EFS was calculated using Kaplan-Meier method, and the HR using a stratified Cox proportional hazards model for the mITT population and unstratified Cox proportional hazards models for the subgroups.

Size of circle is proportional to the number of patients in the subgroup. Grey band represents the 95% confidence interval for the HR in the overall mITT population.

DCO: 10 November 2022. Source: Figure 14.2.3.12.IA1.

Appendix 10: Sensitivity Analyses of Event-free Survival

Figure 14 Event-free survival (using BICR per RECIST 1.1): forest plot of primary and sensitivity analyses (mITT population; EFS IA1)



[a] Event time is the midpoint between time of progression and previous evaluable disease assessments, or for those whose death was treated as an EFS event, date of death is used to derive the EFS time used in analysis.

[b] Analysis uses actual event times, rather than censored times, for patients with an EFS event immediately following ≥ 2 non-evaluable disease assessments are included. Patients who take subsequent therapy prior to their last evaluable RECIST assessment, progression that precludes surgery/results in incomplete surgery or death are censored at their last evaluable assessment prior to taking subsequent therapy.

A HR < 1 favors durvalumab + CTx. Size of circle is proportional to the number of events. Grey band represents the 95% CI for the primary analysis HR in the mITT population.

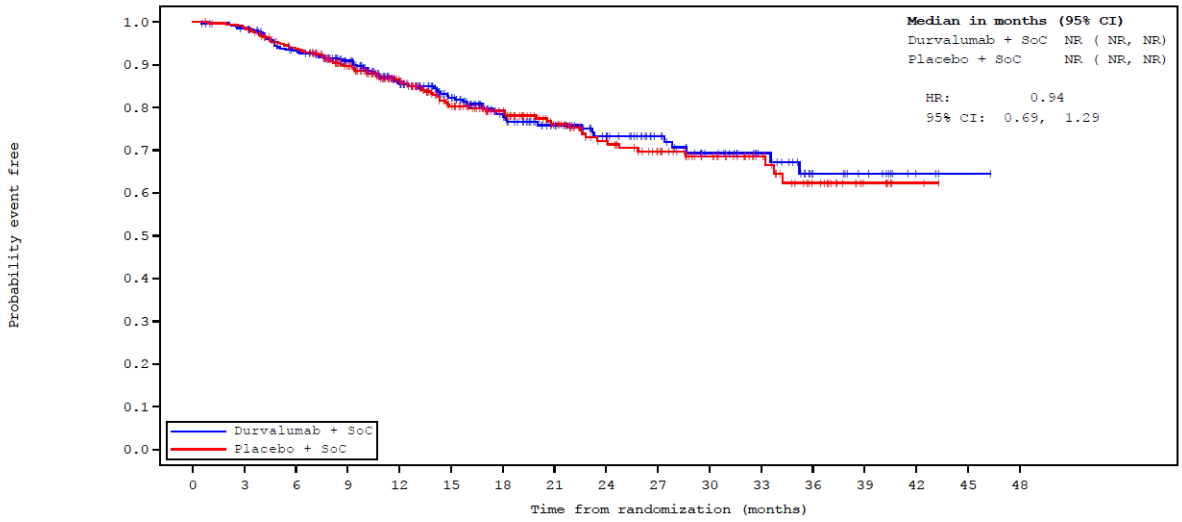
DCO: 10 November 2022.

Source: Figure 14.2.3.16.6.IA1.

Appendix 11: Sensitivity Analysis of Overall Survival, Censoring for COVID-19 Deaths

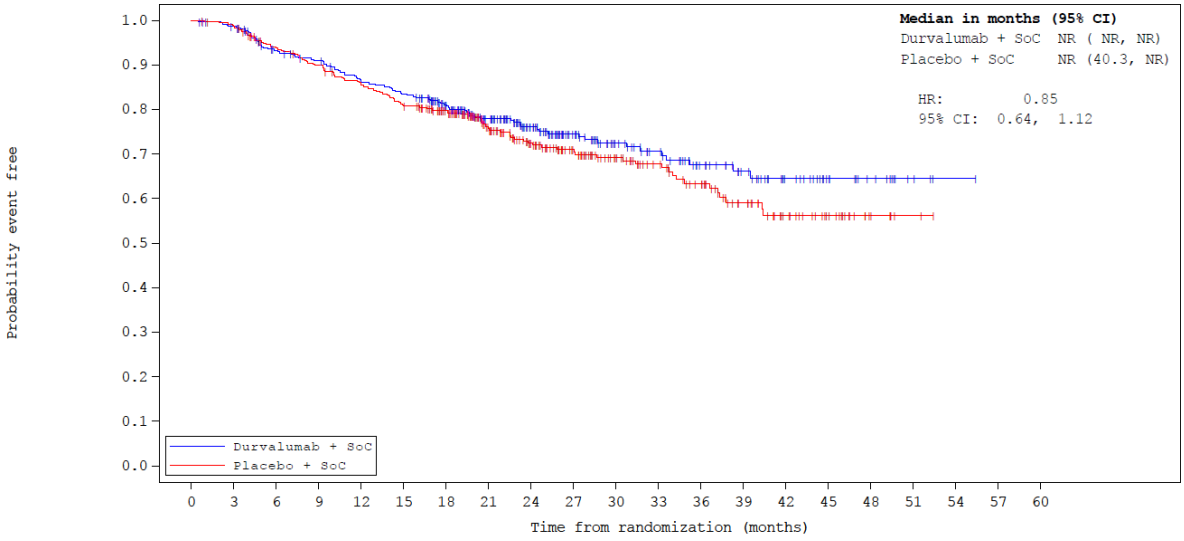
Figure 15 Kaplan-Meier plots of OS: sensitivity analysis censoring for COVID-19 deaths (mITT population; EFS IA1 and Safety Update)

EFS IA1 (DCO: 10 November 2022)



Number of patients at risk																	Events/Randomized
Durvalumab + SoC	366	356	327	289	227	173	129	101	77	61	46	33	16	12	3	1	0	74/366
Placebo + SoC	374	367	340	295	229	176	141	110	87	73	55	38	20	8	2	0	0	81/374

Safety Update (DCO: 14 August 2023)



Number of patients at risk																					Events/Randomized
Durvalumab + SoC	366	356	327	316	297	288	251	201	153	116	88	72	55	44	30	18	12	4	1	0	0	92/366
Placebo + SoC	374	367	341	326	308	291	260	203	159	126	100	81	68	47	32	20	8	2	0	0	0	112/374

Patients whose primary cause of death was reported as COVID-19 were censored on their date of death. A circle indicates a censored observation. DCO: 10 November 2022 (EFS IA1) and 14 August 2023 (Safety Update).
Source: Figure iemt0579.47 and Figure iemt0617.009.

Appendix 12: Summary of SAEs in the Overall Study Period

Table 22 Summary of SAEs in the overall study period (> 1% patients in either treatment arm) (SAS population; Safety Update DCO)

MedDRA PT	Number (%) patients [a]	
	D + CTx (N = 401)	Pbo + CTx (N = 398)
Patients with any SAE	**156 (38.9)**	**126 (31.7)**
Pneumonia	23 (5.7)	18 (4.5)
Anemia	7 (1.7)	5 (1.3)
COVID-19	7 (1.7)	5 (1.3)
Myelosuppression	6 (1.5)	2 (0.5)
Vomiting	5 (1.2)	2 (0.5)
Drug-induced liver injury	5 (1.2)	1 (0.3)
Pneumonitis	7 (1.7)	1 (0.3)
Pneumothorax	4 (1.0)	9 (2.3)

[a] Number (%) of patients with an SAE, sorted by descending frequency of PT in the D arm at the SU DCO. Patients with multiple SAEs are counted once for each PT.

Overall period refers to the neoadjuvant period, surgical period, and adjuvant period, ie, D + CTx followed by surgery and D monotherapy, and Pbo + CTx followed by surgery and Pbo. Includes AEs between date of first dose and the earliest of: maximum date of (last dose or surgery) + 90 days, date of first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
MedDRA version 26.0. DCO: 14 August 2023 (SU).

Appendix 13: Summary of All Deaths

Table 23 Summary of all deaths (ITT population; Safety Update DCO)

Category	Number (%) patients	
	D + CTx (N = 400)	Pbo + CTx (N = 402)
Total number of deaths	**105 (26.3)**	**122 (30.3)**
Death related to disease under investigation only [a]	66 (16.5)	94 (23.4)
TEAE with outcome of death only [b]	19 (4.8)	12 (3.0)
Death related to disease under investigation and with TEAE with an outcome of death [a,b]	4 (1.0)	3 (0.7)
AE with outcome of death only (AE start date falling after safety follow-up period) [c]	3 (0.8)	1 (0.2)
Death related to disease under investigation (AE start date falling after safety follow-up period) [c]	0	1 (0.2)
Patients with unknown reason for death	4 (1.0)	1 (0.2)
Other deaths [d]	9 (2.3)	10 (2.5)
Total number of perioperative deaths [e]	4 (1.0)	8 (2.0)

[a] Death related to disease under investigation is determined by the Investigator as recorded on the DEATH form.
[b] Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increased in severity and resulted in an outcome of death on or after the date of first dose up to and including the earliest of: maximum date of (last dose or surgery) + 90 days, date of first dose of subsequent anti-cancer therapy.
[c] Includes AEs with outcome of death on or after the earliest of: maximum date of (last dose or surgery) + 90 days, or date of first dose of subsequent anti-cancer therapy.
[d] Patients who died and are not captured in the earlier categories.
[e] Includes deaths within 30 days of surgery.
Rows within the "Total number of deaths" section are mutually exclusive; patients are only reported in one category.
DCO: 14 August 2023 (SU). Source: Table 14.3.3.1.1.1.120DSU.

Appendix 14: Summary of imAEs in Any Category in the Overall Study Period

Table 24 Summary of imAEs in any category in the overall study period (SAS population; Safety Update DCO)

AE Category [b]	Number (%) patients [a]	
	D + CTx (N = 401)	Pbo + CTx (N = 398)
Any AE	102 (25.4)	40 (10.1)
Any AE, possibly related to study treatment [c]	98 (24.4)	32 (8.0)
Any AE of CTCAE Grade 3 or 4 [d]	18 (4.5)	10 (2.5)
Any AE of CTCAE Grade 3 or 4, possibly related to study treatment [c, d]	18 (4.5)	10 (2.5)
Any SAE (including events with outcome = death)	21 (5.2)	10 (2.5)
Any SAE, possibly related to study treatment [c]	21 (5.2)	10 (2.5)
Any AE with outcome of death	5 (1.2)	0
Any AE with outcome of death, possibly related to study treatment [c]	5 (1.2)	0
Received systemic corticosteroids	62 (15.5)	25 (6.3)
Received high-dose steroids	45 (11.2)	18 (4.5)
Received endocrine therapy	47 (11.7)	17 (4.3)
Received other immunosuppressants	5 (1.2)	1 (0.3)
Any AE leading to discontinuation of study treatment [e]	19 (4.7)	4 (1.0)
Event outcome resolved	56 (14.0)	19 (4.8)
Event outcome not resolved	41 (10.2)	21 (5.3)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
[b] Includes only AESIs, AEPIs, and AEs adjudicated as imAEs (see the Durvalumab and Tremelimumab Global ImAE Characterization Charter in AEGEAN CSR, Appendix 16.1.9).
[c] Possibly related to any of the study treatments, as assessed by the Investigator. Missing responses are counted as related.
[d] Any AEs of CTCAE Grade 3 or 4 in this period (regardless of the grade of any other AE they may also have had in this period). CTCAE grades are assigned from the maximum toxicity grade within each event.
[e] Adverse events on the AE eCRF page with Action taken = "Drug permanently discontinued" for at least one treatment.
Overall period refers to the neoadjuvant period, post-surgery and adjuvant period, ie, D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.
Includes AEs between date of first dose and the earliest of: maximum date of (last dose or surgery) + 90 days, date of first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period. Adverse event of special interest terms of Infusion/Hypersensitivity reactions are not included in this table.
Reasons of not recovered/not resolved, recovering/resolving, unknown map to an outcome of not resolved.
Reasons of recovered/resolved, recovered/resolved with sequelae map to an outcome of Resolved.
Percentages were calculated from number of patients in the arm (N).
MedDRA Version 25.1 (EFS IA1) and version 26.0 (SU). CTCAE Version 5.0. AESI version 17.0 (EFS IA1) and version 18.1 (SU).
DCO: 14 August 2023 (SU). Source: Table 14.3.6.2.1.120DSU.

Appendix 15: Summary of AEs of Maximum CTCAE Grade 3 or 4 in the Overall Study Period

Table 25 Summary of AEs of maximum CTCAE Grade 3 or 4 by MedDRA preferred term (> 1% in either treatment arm) in the overall study period (SAS population; Safety Update DCO)

	Number (%) patients [a]	
	D + CTx (N = 401)	Pbo + CTx (N = 398)
Patients with any AE of maximum CTCAE Grade 3 or 4	**174 (43.4)**	**172 (43.2)**
Neutrophil count decreased	40 (10.0)	43 (10.8)
Neutropenia	36 (9.0)	39 (9.8)
Anaemia	26 (6.5)	26 (6.5)
Pneumonia	12 (3.0)	10 (2.5)
Leukopenia	9 (2.2)	12 (3.0)
Platelet count decreased	9 (2.2)	14 (3.5)
Myelosuppression	8 (2.0)	3 (0.8)
White blood cell count decreased	8 (2.0)	12 (3.0)
Pulmonary embolism	7 (1.7)	4 (1.0)
Hypokalaemia	6 (1.5)	3 (0.8)
Thrombocytopenia	6 (1.5)	9 (2.3)
Hypertension	4 (1.0)	6 (1.5)
Vomiting	4 (1.0)	5 (1.3)
Febrile neutropenia	3 (0.7)	5 (1.3)
Pneumothorax	3 (0.7)	8 (2.0)
Interstitial lung disease	1 (0.2)	4 (1.0)
Asthenia	0	5 (1.3)

[a] Number (%) of patients with AE of maximum CTCAE Grade 3 or 4, sorted in descending frequency of PTs in the D arm for the SU DCO. Patients with multiple AEs are counted once for each PT. Overall period refers to the neoadjuvant period, surgical, and adjuvant period, ie, D + CTx followed by surgery and D monotherapy, and Pbo + CTx followed by surgery and Pbo.

Maximum CTCAE Grade of 3 or 4 is derived per patient and PT (regardless of other PTs the patient may have had). PTs of Grade 3 or 4 for patients who have also experienced the same PT at Grade 5 are excluded from this table. Includes AEs between date of first dose and the earliest of: maximum date of (last dose or surgery) + 90 days, date of first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

Appendix 16: Demographic and Disease Characteristic Comparison Between the AEGEAN Study and US Patients with Resected NSCLC

Table 26 Demographic and disease characteristic comparison between the AEGEAN study and US patients with resected NSCLC

		Global AEGEAN mITT Population (N = 740) [a]	US Patients in the AEGEAN mITT Population (N = 52) [a]	Prevalence of Stages II–III NSCLC in the US (CancerLinQ [2014 to 2019] [b]) (N = 1404) [c]
Age group (years), n (%)	< 50	37 (5.0)	1 (1.9)	62 (4.4)
	≥ 50 to < 65	321 (43.4)	20 (38.5)	516 (36.8)
	≥ 65 to < 75	302 (40.8)	27 (51.9)	525 (37.4)
	≥ 75	80 (10.8)	4 (7.7)	301 (21.4)
Sex, n (%)	Male	530 (71.6)	34 (65.4)	755 (53.8)
	Female	210 (28.4)	18 (34.6)	649 (46.2)
Race, n (%)	Black or African American	7 (0.9)	5 (9.6)	141 (10.2)
	American Indian or Alaska Native	10 (1.4)	0	3 (0.2)
	Asian	307 (41.5)	4 (7.7)	28 (2.0)
	White	397 (53.6)	36 (69.2)	1106 (80.0)
	Other	19 (2.6)	7 (13.5)	126 (9.0)
Ethnic group, n (%)	Hispanic or Latino	119 (16.1)	5 (9.6)	41 (2.9)
Smoking status, n (%)	Current or former	633 (85.5)	49 (94.2)	895 (90.8) [d]
	Never smokers	107 (14.5)	3 (5.8)	91 (9.2) [d]
Disease stage, n (%)	Stage II	214 (28.9) [e]	11 (21.2) [e]	853 (60.8)
	Stage III	525 (70.9) [e]	40 (76.9) [e]	551 (39.2)
NSCLC histology, n (%)	Squamous	360 (48.6)	18 (34.6)	323 (32.6) [f]
	Non-squamous	375 (50.7)	33 (63.5)	536 (54.1) [f]
	Other	5 (0.7)	1 (1.9)	132 (13.3) [f]

[a] All percentages are calculated based on the total number of patients in the respective dataset, unless otherwise stated.
[b] Data were obtained from the ASCO CancerLinQ database using the following inclusion criteria: patients diagnosed with Stage II–III NSCLC from 01 January 2014 to 31 August 2020, who underwent surgical resection within 140 days after initial diagnosis. Initial diagnosis was defined as the first curated diagnosis in the CancerLinQ database; patients may have had an earlier diagnosis that was either not recorded or could not be verified. Staging was prioritized from surgical tissue when available; or, if not available staging was performed via medical imaging.
[c] Some demographic/disease characteristics categories may not add up to the total number of patients due to rounding, or because unknown values or minor demographic/disease characteristics categories are excluded for brevity.
[d] The denominator for this category is 986 patients (based on missing data for 418 patients).
[e] Of note, one additional US patient was randomized into the AEGEAN study with Stage IV disease at baseline.
[f] The denominator for this category was 991 patients (based on missing data for 413 patients).
Source: ASCO CancerLinQ 2014 to 2019, and Table IEMT0531.002.