Oncologic Drugs Advisory Committee (ODAC) Meeting

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Drug name: durvalumab

Applicant: AstraZeneca UK Limited

Addendum to the Combined FDA and Applicant ODAC Briefing Document

Advisory Committee Briefing Materials: Available For Public Release

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1. Purpose of this Addendum

The Applicant's Position:

The combined FDA and AstraZeneca ODAC briefing document presented data from the first three DCOs of the AEGEAN study:

- DCO1 (14 January 2022): a pre-specified and primary analysis of pCR and MPR (also designated as pCR IA in the statistical analysis plan).
- DCO2 (10 November 2022): a pre-specified and primary analysis of EFS using BICR per RECIST 1.1 (also designated as EFS IA1 in the statistical analysis plan).
- DCO3 (14 August 2023): an ad hoc updated analysis of safety data and descriptive OS data which was provided to fulfill an agreement with FDA (also designated as Safety Update DCO).

The purpose of this addendum is to provide updated efficacy and safety results from the third pre-planned analysis of the AEGEAN study (DCO4), corresponding to a DCO date of 10 May 2024.

The DCO4 data reported in this addendum include an updated descriptive analysis of EFS and OS, a descriptive analysis of DFS, updated exposure and safety data, and an analysis of patient-reported outcomes and health-related quality of life in the adjuvant phase of the study. These updated results confirm the positive benefit-risk profile of durvalumab in combination with chemotherapy prior to surgery, followed by durvalumab monotherapy post-surgery, in patients with resectable NSCLC (stages IIA-IIIB[N2]) and no known EGFRm or ALK gene rearrangements, and may support the ODAC discussion for Question 1.

The FDA's Position:

FDA agrees that this addendum provides updated efficacy and safety results from the third pre-planned analysis of AEGEAN. The updated results based on the DCO date of May 10, 2024 include: (1) a descriptive analysis of EFS, given that the previously reported first interim analysis of EFS met statistical significance and became the primary analysis of EFS; (2) the second interim analysis of DFS; (3) a descriptive analysis of OS given that DFS did not meet statistical significance at the second interim analysis; and (4) an updated safety analysis. FDA did not review patient-level data to verify the safety results reported in this addendum. Therefore, FDA's positions regarding safety in this addendum are based on the Applicant's reported results and the review of safety results provided for the previous data cutoff (see main combined ODAC briefing document).

These updated results do not change the FDA's position as detailed in the main combined ODAC briefing document.

2. Updated Efficacy Summary

2.1 AEGEAN Patient Population

The Applicant's Position:

2.1.1 Updated Patient Disposition (DCO4)

As provided in the ODAC briefing document, at DCO2 (EFS IA1; 10 November 2022), 64.6% of patients overall in the mITT population had started adjuvant treatment and 23.4% of patients remained on adjuvant treatment. At DCO3 (Safety Update; 14 August 2023), one additional patient (in the D + CTx arm) had started adjuvant treatment, and 7 patients (1.0%) overall remained on adjuvant treatment.

At DCO4 (10 May 2024), with 9 months of additional study follow-up since DCO3, all patients in both treatment arms had completed adjuvant treatment and the safety follow-up period. Of those patients who started adjuvant treatment (242 patients in the D + CTx arm vs. 237 patients in the Pbo + CTx arm), 166 patients (68.6%) in the D + CTx arm and 151 patients (63.7%) in the Pbo + CTx arm completed all 12 planned cycles of adjuvant treatment. Radiological progression according to RECIST 1.1 continued to be the most common reason for discontinuation of adjuvant treatment in both treatment arms (30/242 patients [12.4%] for the D + CTx arm vs. 59/237 patients [24.9%] for the Pbo + CTx arm).

The subset of the mITT population used for evaluation of the key secondary endpoint of DFS and adjuvant period PROs is known as the modified resected set (mRS) in the study protocol. For simplicity, in this document, it is hereafter referred to as "resected mITT population". This analysis set comprised patients in the mITT population who had received neoadjuvant treatment, completed surgical resection, and whose first post-surgical RECIST scan showed no disease, and excluded patients with R2 resection margins.

At DCO4, a total of 473 randomized patients were included in the resected mITT population: 242 patients in the D + CTx arm and 231 patients in the Pbo + CTx arm. Adjuvant durvalumab/placebo treatment was started by 223 patients (92.1%) in the D + CTx arm and 214 patients (92.6%) in the Pbo + CTx arm; among these patients, all 12 cycles of adjuvant durvalumab/placebo were completed by 158 patients (70.9%) in the D + CTx arm and 139 patients (65.0%) in the Pbo + CTx arm.

See Appendix 1 for an overview of patient disposition at DCO4 for the mITT population and resected mITT population. Adverse events (AEs) leading to study treatment discontinuation are summarized in Section 3.

2.1.2 Demographics and Baseline Characteristics in the Resected mITT Population

Overall, demographics and baseline disease characteristics of patients in the resected mITT population were generally similar to those in the mITT population. See detailed breakdown of baseline patient and disease characteristics in Appendix 2.

Within the resected mITT population, baseline characteristics were generally balanced between the two treatment arms. Imbalances ≥ 5% between treatment arms within the resected mITT

population were noted for: female sex, ECOG performance status 0, white race, and disease Stage IIIA, which were enriched in the D + CTx arm (differences of 5.1% to 8.7% between arms); and patients enrolled in Asia, which were enriched in the Pbo + CTx arm (7.6% difference between arms) (see Appendix 2).

2.1.3 Anti-cancer Therapy Post-treatment Discontinuation (DCO4)

At DCO4 (mITT population), subsequent anti-cancer therapy was received by 19.4% of patients in the D + CTx arm vs 29.7% of patients in the Pbo + CTx arm. Systemic therapies were most frequently cytotoxic chemotherapy (12.8% of patients in the D + CTx arm vs. 13.6% of patients in the Pbo + CTx arm) and immunotherapy-based regimens (7.1% vs. 16.8% of patients, by respective treatment arm). Radiotherapy (as a subsequent therapy) was received by 12.0% of patients in the D + CTx arm vs. 17.6% of patients in the Pbo + CTx arm, including concomitant chemoradiotherapy (6.0% vs. 5.3% of patients, respectively).

See Appendix 3 for a detailed breakdown of anti-cancer therapies received after discontinuation of study treatment.

2.2 Updated Efficacy Results of AEGEAN (DCO4)

The Applicant's Position:

2.2.1 Updated Event-free Survival

As described in the ODAC briefing document, the AEGEAN study met the primary endpoint of EFS at DCO2 (10 November 2022; mITT population), demonstrating a statistically significant and clinically meaningful 32% reduction in the risk of an EFS event (assessed by BICR 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) (Table 1).

At the pre-planned DCO4 (10 May 2024; approximately 18 months after DCO2), an updated descriptive analysis of EFS (assessed by BICR per RECIST 1.1) was conducted with an overall EFS data maturity of 39%. This included 53 new EFS events in the mITT population (for a total of 289 EFS events): 26 new EFS events in the D + CTx arm and 27 new EFS events in the Pbo + CTx arm. Overall, the majority of EFS events in both treatment arms were due to RECIST recurrence after surgery: 53 patients (14.5%) in the D + CTx arm vs. 83 patients (22.2%) in the Pbo + CTx arm (Table 1). The median duration of follow-up in censored patients increased from 11.7 months at DCO2 to 25.9 months at DCO4.

At DCO4, the EFS HR was 0.69 (95% CI: 0.55, 0.88), which is consistent with DCO2 results, despite improved performance of the Pbo + CTx arm (reflected in increased median EFS from 25.9 months at DCO2 to 30.0 months at DCO4). Median EFS was not reached for the D + CTx arm (Table 1). The separation in the EFS Kaplan-Meier curves favoring the D + CTx arm, which was observed from approximately 3 months post-randomization, was maintained over time, as shown by the greater proportions of patients in the D + CTx arm who were alive and event-free at 12 months, 24 months, and 36 months post-randomization compared to the Pbo + CTx arm (Figure 1 and Table 1).

Improvement in EFS favoring the D + CTx arm was maintained across all pre-specified subgroups at DCO4, including race, age, geographic region, disease stage, PD-L1 TC expression status, and platinum chemotherapy agent (see Appendix 4). Robustness of the treatment effect was also demonstrated by the results of the pre-specified EFS sensitivity analyses, which remained consistent with the main EFS analysis at DCO4 (see Appendix 5).

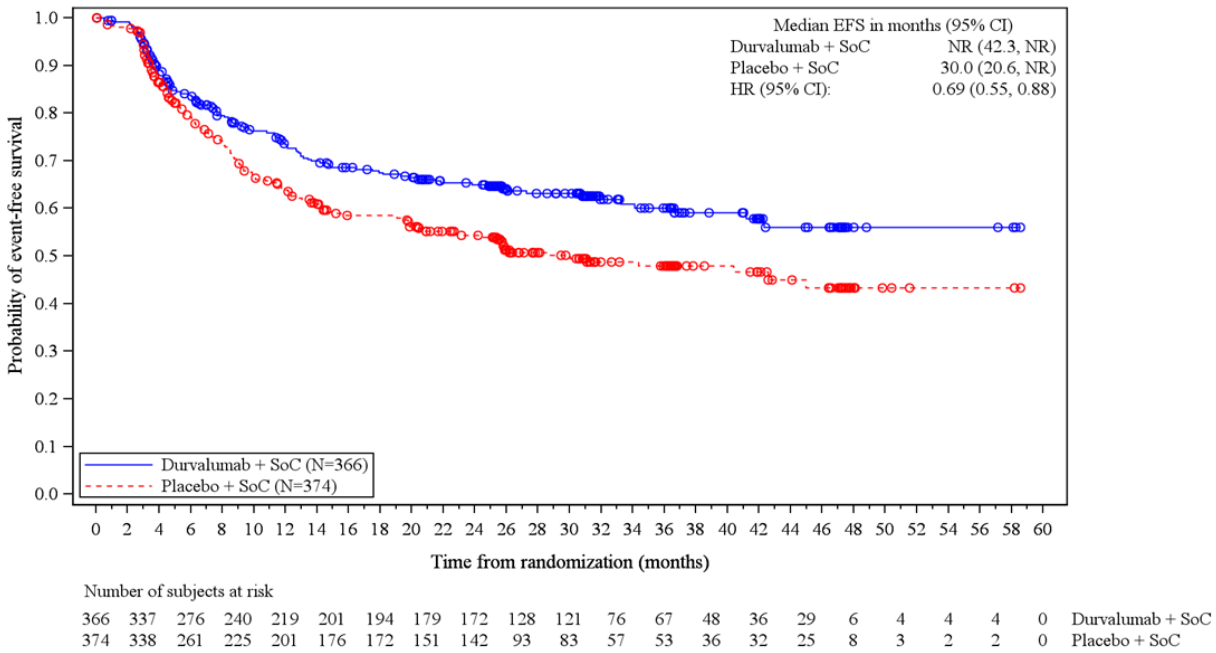
Collectively, these data demonstrate that the EFS benefits of perioperative durvalumab in the target patient population, that were first demonstrated at DCO2, were maintained with an additional 18 months of study follow-up at DCO4.

Table 1 Event-free survival assessed by BICR per RECIST 1.1 (mITT population; DCO2 and DCO4)

	DCO2 (10 Nov 2022)		DCO4 (10 May 2024)	
	D + CTx (N = 366)	Pbo + CTx (N = 374)	D + CTx (N = 366)	Pbo + CTx (N = 374)
Patients with events, n (%)	**98 (26.8)**	**138 (36.9)**	**124 (33.9)**	**165 (44.1)**
Progression that precluded surgery	26 (7.1)	35 (9.4)	28 (7.7)	36 (9.6)
Progression discovered upon attempting surgery	5 (1.4)	13 (3.5)	5 (1.4)	13 (3.5)
RECIST recurrence after surgery	38 (10.4)	60 (16.0)	53 (14.5)	83 (22.2)
Death due to any cause	29 (7.9)	30 (8.0)	38 (10.4)	33 (8.8)
Censored patients, n (%)	**268 (73.2)**	**236 (63.1)**	**242 (66.1)**	**209 (55.9)**
Median EFS (95% CI) (months) [a]	**NR (31.9, NR)**	**25.9 (18.9, NR)**	**NR (42.3, NR)**	**30.0 (20.6, NR)**
EFS rate at 12 months post-randomization, % (95% CI) [a]	73.4 (67.9, 78.1)	64.5 (58.8, 69.6)	73.3 (68.1, 77.7)	64.1 (58.7, 69.0)
EFS rate at 24 months post-randomization, % (95% CI) [a]	63.3 (56.1, 69.6)	52.4 (45.4, 59.0)	65.0 (59.4, 70.0)	54.4 (48.7, 59.6)
EFS rate at 36 months post-randomization, % (95% CI) [a]	NR	NR	60.1 (53.9, 65.8)	47.9 (41.8, 53.8)
Median (range) duration of follow-up in censored patients (months)	11.66 (0 to 46.1)	11.73 (0 to 42.4)	26.68 (0 to 58.6)	25.69 (0 to 58.5)
Hazard ratio (95% CI)	**0.68 (0.53, 0.88)**		**0.69 (0.55, 0.88)**	
2-sided p-value	**0.003902**		*Formally analyzed at DCO2*	

[a] Calculated using the Kaplan-Meier technique.
Statistical analysis methods are summarized in Appendix 4 of the ODAC briefing document.
DCO: 10 November 2022 (DCO2) and 10 May 2024 (DCO4).
Source: Tables 14.2.3.1.IA1 and 14.2.3.13.IA1, 14.2.3.1.IA2, and 14.2.3.13.IA2.

Figure 1 Kaplan-Meier plot of event-free survival (assessed by BICR per RECIST 1.1) (mITT population; DCO4)



A circle indicates a censored observation. DCO: 10 May 2024 (DCO4).
Source: Figure 14.2.3.2.IA2.

2.2.2 Disease-free Survival

At DCO4 (10 May 2024), based on an overall DFS data maturity of 30%, DFS results (using BICR assessment per RECIST 1.1) were not statistically significant. Results indicate a trend toward improved DFS in favor of the D + CTx arm compared to the Pbo + CTx arm, with a HR of 0.66 (95% CI: 0.47, 0.92; p-value = 0.013652). A p-value of < 0.012303 was required to declare statistical significance at this interim analysis. Median DFS was not reached for either treatment arm (Table 2).

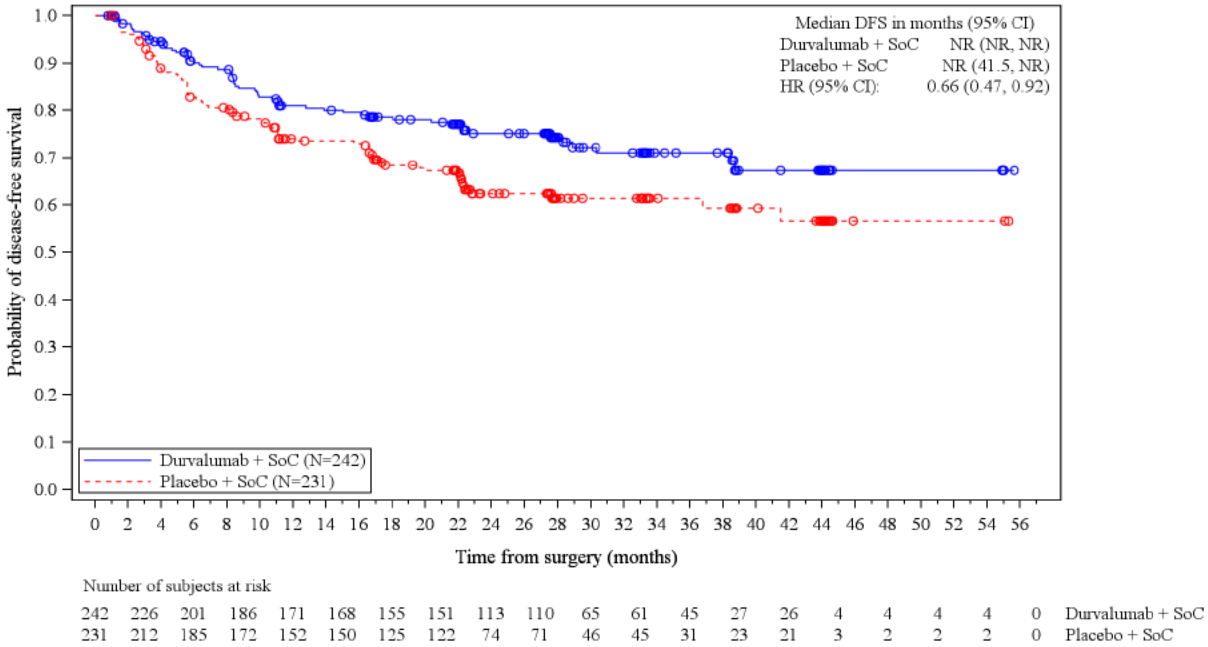
The DFS Kaplan-Meier curves overlapped until approximately 2 months post-surgery, after which there was a clear and sustained separation that favored the D + CTx arm (Figure 2), as shown by a greater proportion of patients in the D + CTx arm who were alive and recurrence-free at 12 months, 24 months, and 36 months post-surgery compared to the Pbo + CTx arm (Table 2).

Table 2 Disease-free survival (assessed by BICR per RECIST 1.1) (resected mITT population; DCO4)

	D + CTx (N = 242)	Pbo + CTx (N = 231)
Patients with events, n (%)	**60 (24.8)**	**81 (35.1)**
Disease recurrence	44 (18.2)	69 (29.9)
Death due to any cause	16 (6.6)	12 (5.2)
Censored patients, n (%)	**182 (75.2)**	**150 (64.9)**
Median DFS (95% CI) (months) [a]	**NR (NR, NR)**	**NR (41.5, NR)**
DFS rate at 12 months post-surgery, % (95% CI) [a]	81.0 (75.2, 85.5)	74.1 (67.8, 79.3)
DFS rate at 24 months post-surgery, % (95% CI) [a]	75.1 (68.7, 80.4)	62.4 (55.2, 68.8)
DFS rate at 36 months post-surgery, % (95% CI) [a]	71.2 (63.8, 77.3)	61.4 (54.0, 68.0)
Median (range) duration of follow-up in censored patients (months)	27.50 (0.8 to 55.7)	22.77 (0.9 to 55.3)
Hazard ratio (95% CI)	**0.66 (0.47, 0.92)**	
2-sided p-value	**0.013652**	

[a] Calculated using the Kaplan-Meier technique.
Statistical analysis methods are summarized in Appendix 4 of the ODAC briefing document.
DCO: 10 May 2024 (DCO4). Source: Tables 14.2.4.1.IA2, 14.2.4.13.IA2, and iemt0666_011.

Figure 2 Kaplan-Meier plot of disease-free survival (using BICR per RECIST 1.1) (resected mITT population; DCO4)



A circle indicates a censored observation. DCO: 10 May 2024 (DCO4).
Source: Figure 14.2.4.2.IA2.

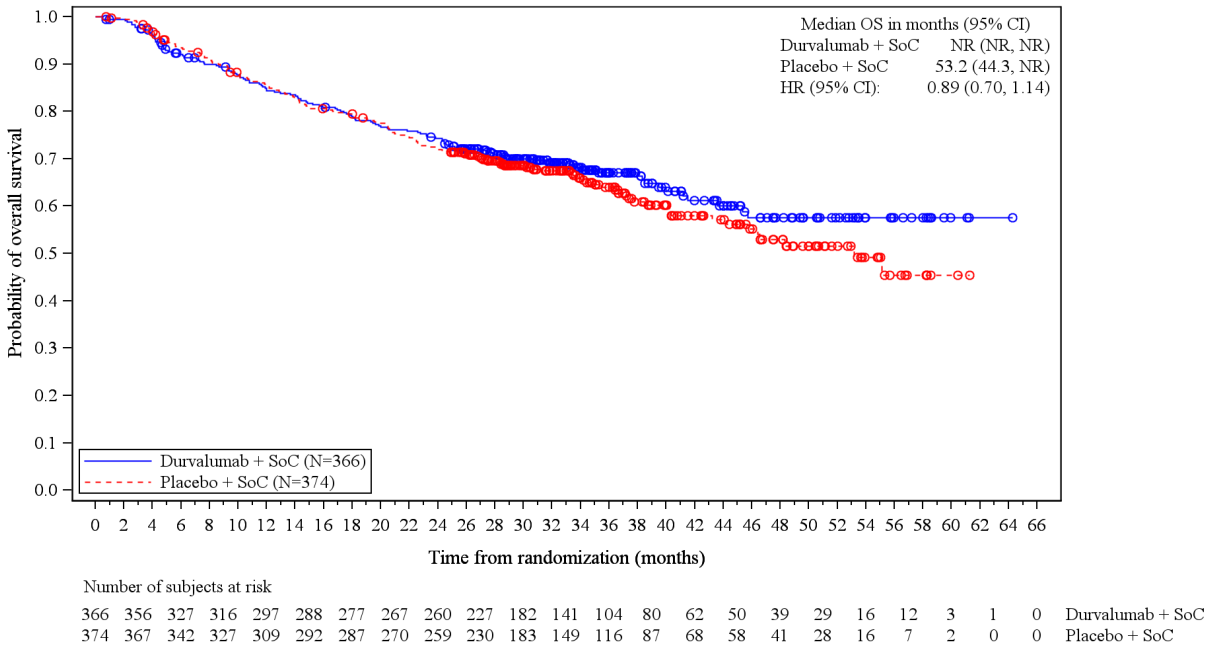
2.2.3 Updated Overall Survival

As described in the ODAC briefing document, a descriptive analysis of OS at the DCO2 (10 November 2022; mITT population) showed an OS HR of 1.02 (95% CI: 0.75, 1.39). At DCO3 (14 August 2023), with 9 months of additional study follow-up, a trend toward improved OS favoring the D + CTx arm was observed, with an OS HR of 0.91 (95% CI: 0.69, 1.19) (Table 3).

At DCO4 (10 May 2024), an updated descriptive analysis of OS (with 35% data maturity) provided a HR of 0.89 (95% CI: 0.70, 1.14). This updated analysis included 49 new OS events since DCO3 (for a total of 261 OS events in the mITT population): 22 new OS events in the D + CTx arm and 27 new OS events in the Pbo + CTx arm (Table 3). Median OS was not reached for the D + CTx arm, compared to a median OS of 53.2 months in the Pbo + CTx arm (Table 3 and Figure 3). The majority of death events in both arms were due to the disease under investigation: 76 patients (20.8%) in the D + CTx arm vs. 113 patients (30.2%) in the Pbo + CTx arm (see summary of all deaths in the mITT population in Appendix 8).

A pre-defined sensitivity analysis of OS, which censored patients whose primary cause of death was COVID-19 on their date of death, showed a numerically improved OS HR in favor of the D + CTx arm at DCO4 (HR of 0.84 [95% CI: 0.66, 1.08]). The corresponding Kaplan-Meier OS curves are shown in Appendix 6.

Figure 3 Kaplan-Meier plot of overall survival (mITT population; DCO4)



A circle indicates a censored observation. DCO: 10 May 2024 (DCO4).
Source: Figure 14.2.5.2.IA2.

Table 3 Overall survival (mITT population; DCO2, DCO3, and DCO4)

	DCO2 (10 Nov 2022)		DCO3 (14 Aug 2023)		DCO4 (10 May 2024)	
	D + CTx (N = 366)	Pbo + CTx (N = 374)	D + CTx (N = 366)	Pbo + CTx (N = 374)	D + CTx (N = 366)	Pbo + CTx (N = 374)
Death, n (%)	81 (22.1)	82 (21.9)	99 (27.0)	113 (30.2)	121 (33.1)	140 (37.4)
Censored patients, n (%)	285 (77.9)	292 (78.1)	267 (73.0)	261 (69.8)	245 (66.9)	234 (62.6)
Median OS (95% CI) (months) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (40.3, NR)	NR (NR, NR)	53.2 (44.3, 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)	84.3 (80.1, 87.7)	85.3 (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)	74.4 (69.5, 78.6)	72.2 (67.3, 76.5)
OS rate at 36 months, % (95% CI) [a]	NR	NR	66.2 (59.3, 72.2)	63.2 (56.5, 69.2)	67.1 (61.6, 71.9)	63.9 (58.4, 69.0)
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)	33.48 (0.8 to 64.3)	33.87 (0.7 to 61.3)
Hazard ratio (95% CI)	**1.02 (0.75, 1.39)**		**0.91 (0.69, 1.19)**		**0.89 (0.70, 1.14)**	

[a] Calculated using the Kaplan-Meier technique.

Statistical analysis methods are summarized in Appendix 4 of the ODAC briefing document.

DCO: 10 November 2022 (DCO2), 14 August 2023 (DCO3), and 10 May 2024 (DCO4).

Source: Tables 14.2.5.1.IA1, 14.2.5.9.IA1, 14.2.5.1.120DSU, 14.2.5.9.120DSU, 14.2.5.1.IA2, and 14.2.5.9.IA2.

2.3 Updated Efficacy Conclusions

The Applicant's Position:

With 18 months of additional study follow-up, the efficacy data from AEGEAN at DCO4 are supportive of the data presented in the ODAC briefing document, where it was shown that the primary endpoints of the study (pCR and EFS) were met at their first respective interim analyses (DCO1 and DCO2, respectively). In addition, positive trends toward improved DFS and OS were shown in favor of the D + CTx arm, as compared to the Pbo + CTx arm.

In conclusion, the totality of efficacy data from the AEGEAN study have demonstrated that the proposed treatment regimen of durvalumab in combination with platinum-doublet chemotherapy prior to surgery, followed by durvalumab monotherapy post-surgery, led to 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 agrees that the efficacy data from AEGEAN at DCO4 are supportive of the data presented in the main combined ODAC briefing document, with some additional considerations regarding the data noted below. As noted in the main combined ODAC briefing document, FDA also clarifies that the DFS and OS analyses suggest there is no detrimental effect of the experimental regimen on DFS and OS, rather than supporting the claim that there are "positive trends toward improved DFS and OS" favoring the durvalumab arm, as stated by the Applicant above.

The Applicant evaluated DFS in a modified resected set, a subset of the mITT population comprising patients who underwent surgery and had no evidence of recurrence at a post-surgery radiographic disease assessment. Since surgery and post-surgical tumor assessments occur after randomization, the patient population represented in the modified resected set may have imbalances between arms in measured and unmeasured characteristics that could be associated with the DFS endpoint, resulting in bias in the assessment of treatment effect on DFS.

While the analysis of DFS was not statistically significant, FDA acknowledges a numerical increase in DFS favoring the durvalumab arm. This numerical improvement in DFS may reflect lasting effects of neoadjuvant chemoimmunotherapy rather than a direct effect of adjuvant durvalumab on DFS. Therefore, the finding of a numerically improved DFS does not necessarily demonstrate an effect of adjuvant durvalumab on DFS.

Although the Applicant describes OS data maturity to be 35%, the current 261 OS events has far exceeded the 232 OS events anticipated to be available at the time of the final analysis of OS. Therefore, OS data have surpassed the maturity that was considered sufficient, per initial trial design, for the definitive final analysis of OS. Nonetheless, the OS result is and will remain statistically inconclusive unless DFS eventually attains statistical significance.

3. Updated Safety Summary

The updated exposure and safety analyses from the AEGEAN study presented in this briefing document addendum were performed on the SAS population from the most recent update of exposure and safety data (DCO4).

At DCO4 (10 May 2024), all patients in the study were off treatment and had completed the 90-day safety follow-up period. Conclusions from safety data at DCO4 are consistent with those of DCO3 (14 August 2023) presented in the ODAC briefing document. Overall, no new safety concerns have been identified for durvalumab when given in this treatment setting. The overall and adjuvant phases of the perioperative D + CTx treatment regimen were well-tolerated.

As observed previously at DCO3, most AEs reported for the study overall were reported during the neoadjuvant period. The majority of imAEs reported for the D + CTx arm in the overall, neoadjuvant, surgical, and adjuvant treatment periods were non-serious, low grade (CTCAE Grade 1 or 2), manageable, and resolved at the time of DCO4.

3.1 Overall Extent of Exposure at DCO4

The Applicant's Position:

At DCO4, all patients had completed the study treatment and the 90-day safety follow-up period. Similar to exposure data from DCO3 (when 7 patients remained on adjuvant study treatment), at DCO4, the median actual duration of exposure to durvalumab/placebo continued to be longer in the D + CTx arm at 40 weeks compared to the Pbo + CTx arm at 36 weeks (Table 9). Among patients in the SAS population who received adjuvant treatment (266 patients in the D + CTx arm and 254 patients in the Pbo + CTx arm), 68.4% of patients in the D + CTx arm and 63.4% in the Pbo + CTx arm completed all 12 planned adjuvant treatment cycles (Table 9).

3.2 Summary of Adverse Events (DCO4)

The Applicant's Position:

3.2.1 Overall Period

The safety profile of durvalumab reported at DCO4 was consistent with that reported at DCO3.

The proportions of patients in each arm with AEs in the categories reported in Table 4 remained similar to those observed at DCO3. Most of the AEs reported were non-serious and low in severity (CTCAE Grade 1-2) in both treatment arms.

At DCO4, the most commonly reported AEs (reported by ≥ 10% of patients in either treatment arm) and AEs of maximum CTCAE Grade 3 or 4 were similar in nature and frequency to those reported at DCO3 (Table 13 and Table 14). The safety profile of durvalumab remained consistent with that reported at DCO3. Of note, one additional patient in the D+ CTx arm reported an AE of maximum Grade 3-4 (neutrophil count decreased) at DCO4.

Since the DCO3 date, no new AEs leading to discontinuation of durvalumab/placebo were reported in either treatment arm for the overall period at DCO4 (Table 4).

The proportions of patients with SAEs in the D + CTx arm (39.2%) and the Pbo + CTx arm (31.7%) remained similar to those reported at DCO3, with one additional patient with an SAE reported in the D + CTx arm at DCO4 (Table 4 and Table 10); this was an event of transient amnesia which was considered unrelated to any study treatment and resolved by the DCO4 date.

No additional AEs with an outcome of death were reported at DCO4 (see Section 3.4.1). The number of AEs with an outcome of death has remained unchanged since DCO2 (10 November 2022), when approximately 23% of patients in each treatment arm were still ongoing with adjuvant durvalumab/placebo treatment.

Since DCO3, although the overall number of patients with imAEs in the D + CTx arm did not change (102 patients), there was one patient who reported an additional imAE of hypothyroidism in the adjuvant period at DCO4. In the Pbo + CTx arm, one additional patient reported an imAE of hyperthyroidism at DCO4 (Table 4). See Section 3.3 for further details pertaining to imAEs.

3.2.2 Adjuvant Period

During the adjuvant period, durvalumab monotherapy continued to be well-tolerated, and its safety profile continued to be consistent with the established safety profile of durvalumab.

At DCO4, AEs (any-Grade, any causality), AEs of maximum CTCAE Grade 3-4, AEs leading to discontinuation of study treatment, SAEs, and fatal AEs continued to be less frequent in both treatment arms during the adjuvant period (among patients who received adjuvant treatment: 266 patients in the D + CTx arm and 254 patients in the Pbo + CTx arm) as compared to the neoadjuvant period and overall period of the study (among 401 patients in the D + CTx arm and 398 patients in the Pbo + CTx arm) (Table 4).

At DCO4, the most common AEs reported in the adjuvant period for both treatment arms were consistent with those reported at DCO3 (Table 15).

Consistent with the previous DCO3 results, at DCO4, the proportions of patients with AEs (any-Grade, any causality), AEs of maximum CTCAE Grade 3-4, AEs leading to discontinuation of study treatment, and SAEs in the adjuvant period were higher in the D + CTx arm compared to the Pbo + CTx arm (Table 4). Most AEs reported during the adjuvant period were non-serious, low in severity (CTCAE Grade 1-2), and the majority resolved by the DCO4 date in both treatment arms.

The incidences of AEs (any-Grade, any causality), AEs of maximum CTCAE Grade 3-4, AEs leading to discontinuation of study treatment, and SAEs for the adjuvant period in the D + CTx arm continued to be similar to, or lower than, those reported for the pooled durvalumab safety data (Table 4), despite a much longer median duration of exposure to durvalumab during the adjuvant period (48.0 weeks) compared to the median duration of exposure to durvalumab in the pooled safety data (16.4 weeks).

Consistent with the proportions of patients with SAEs in the adjuvant period reported at DCO3 (15.0% in the D + CTx arm vs. 10.2% in the Pbo + CTx arm), at DCO4, the proportion of patients

in the adjuvant period with SAEs was 15.4% in the D + CTx arm vs. 10.2% in the Pbo + CTx arm (Table 4).

Table 4 Overview of adverse events by category and by study treatment period (SAS population; DCO4)

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 any causality AEs	**365 (91.0)**	**357 (89.7)**	**239 (73.5)**	**227 (69.6)**	**224 (84.2)**	**195 (76.8)**	**387 (96.5)**	**379 (95.2)**	**3825 (94.6)**
AEs of max. CTCAE Grade 3 or 4	131 (32.7)	145 (36.4)	56 (17.2)	43 (13.2)	41 (15.4)	27 (10.6)	175 (43.6)	172 (43.2)	1600 (39.6)
SAEs	83 (20.7)	66 (16.6)	61 (18.8)	51 (15.6)	41 (15.4)	26 (10.2)	157 (39.2)	126 (31.7)	1447 (35.8)
AEs with outcome of death	**8 (2.0)**	**4 (1.0)**	**13 (4.0)**	**9 (2.8)**	**4 (1.5)**	**2 (0.8)**	**23 (5.7)**	**15 (3.8)**	**231 (5.7)**
AEs Leading to discontinuation of any study treatment	54 (13.5)	30 (7.5)	2 (0.6)	2 (0.6)	26 (9.8)	10 (3.9)	78 (19.5)	39 (9.8)	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 any CTx	48 (12.0)	30 (7.5)	NA	NA	NA	NA	48 (12.0)	30 (7.5)	NA
AEs leading to discontinuation of both D/Pbo and any CTx	20 (5.0)	15 (3.8)	NA	NA	NA	NA	20 (5.0)	15 (3.8)	NA
AEs Leading to on-study surgery not done	7 (1.7)	4 (1.0)	NA	NA	NA	NA	7 (1.7)	4 (1.0)	NA
Any-Grade AEs possibly related to any study treatment	**330 (82.3)**	**313 (78.6)**	**86 (26.5)**	**38 (11.7)**	**131 (49.2)**	**76 (29.9)**	**350 (87.3)**	**325 (81.7)**	**2340 (57.8)**
AEs of max. CTCAE Grade 3 or 4 possibly related to any study treatment	118 (29.4)	130 (32.7)	11 (3.4)	3 (0.9)	20 (7.5)	9 (3.5)	134 (33.4)	133 (33.4)	459 (11.3)
AEs with outcome of death possibly related to any study treatment	3 (0.7)	1 (0.3)	4 (1.2)	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)**	**61 (22.9)**	**21 (8.3)**	**102 (25.4)**	**41 (10.3)**	**705 (17.4)**
imAEs of max. CTCAE Grade 3 or 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 treatment (D/Pbo/CTx) until the date of surgery or, for patients without surgery, up to the earliest of: last dose of neoadjuvant treatment (D/Pbo/CTx) + 90 days, first dose of subsequent anti-cancer therapy, 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 therapy, or DCO date.

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

¶ First dose of study treatment (D/Pbo/CTx) until the earliest of: the last dose of Study treatment or surgery (taking the latest dose of D/Pbo/CTx/date of surgery) + 90 days, date of the first dose of subsequent anti-cancer therapy, 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 treatment during that period).
DCO: 10 May 2024 (DCO4).
Source: Table 14.3.2.1.1.IA2, Table 14.3.2.1.2.IA2, Table 14.3.2.1.3.IA2, Table 14.3.2.1.4.IA2, Table 14.3.6.2.1.IA2, Table 14.3.6.2.1.1.IA2, Table 14.3.6.2.1.2.IA2, Table 14.3.6.2.1.3.IA2, Table iemt0617.180, Table iemt0673.048, Table iemt0673.049, Table iemt0673.050.

3.3 Immune-mediated Adverse Events (DCO4)

The Applicant's Position:

3.3.1 Overall Period

Since DCO3, although the overall number of patients with imAEs in the D + CTx arm did not change (102 patients), there was one patient who reported an additional imAE of hypothyroidism in the adjuvant period at DCO4. In the Pbo + CTx arm 1 additional patient reported an imAE of hyperthyroidism at DCO4 (Table 5).

Similar to the previous DCO3 results, at DCO4, more patients experienced any imAE in the D + CTx arm (25.4%) than in the Pbo + CTx arm (10.3%) in the overall period of the study (Table 5). The majority of imAEs reported were non-serious, low in severity (CTCAE Grade 1-2), generally manageable, and resolved by the DCO4 date in both treatment arms (see Table 12). There were no new imAEs with outcome of death at DCO4. Overall, there were 5 imAEs with outcome of death in the D + CTx arm (1.2%) and none in the Pbo + CTx arm.

The most common imAEs occurring in ≥ 1% of patients overall are presented in Table 5.

There were no major differences in the nature, severity, and manageability of imAEs at DCO4 compared with the imAEs previously reported at DCO3. ImAEs leading to discontinuation of any study treatment continued to be low in frequency in both treatment arms at DCO4: 19 patients (4.7%) in the D + CTx arm and 4 (1.0%) in the Pbo + CTx arm (see Table 12).

Similar to the results observed at DCO3, at DCO4, among patients with imAEs (any-Grade) in the overall period: 59/102 patients (57.8%) in the D + CTx arm vs. 21/41 patients (51.2%) in the Pbo + CTx arm had imAEs that were resolved; 38/102 patients in the D + CTx arm (37.3%) vs. 20/41 patients (48.8%) in the Pbo + CTx arm had imAEs that were unresolved [1].

The majority of unresolved imAEs reported in the D + CTx arm (30 out of 38 patients) were hypothyroid events that required endocrine therapy. All hypothyroid imAEs reported in the D + CTx arm were low in severity (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 included pneumonitis (3 patients), dermatitis/rash (3 patients), and events that were each reported in a single patient: diarrhea, arthralgia, nephritis, adrenal insufficiency, thyroiditis, and AST increased. All unresolved imAEs in the D + CTx arm were low grade (CTCAE grade 1-2) except for 1 pneumonitis case, which was CTCAE Grade 2 at onset (for 7 days), then increased to CTCAE Grade 4 (for 5 days), before improving to CTCAE Grade 2.

The unresolved imAEs in the Pbo + CTx arm were pneumonitis events (5 patients), hypothyroid events (5 patients), hyperthyroid events (3 patients), and thyroiditis events (2 patients) requiring endocrine therapy. Additional unresolved imAEs were reported in a single patient each: diarrhea, arthralgia, immune-mediated pancreatitis, arthritis, hypertransaminasemia, and rash maculopapular. Of the unresolved imAEs, events of CTCAE Grade 3-4 were reported for 2 patients: 1 patient with CTCAE Grade 3 pneumonitis event and 1 patient with a CTCAE Grade 4

[1] Note that imAEs with a fatal outcome are not included in either of these categories.

pneumonitis event and a CTCAE Grade 3 diarrhea/colitis event (both imAEs) at DCO. The remaining unresolved imAEs in the Pbo + CTx arm were CTCAE Grade 1-2 [2].

The proportion of patients with resolved/unresolved imAEs in the D + CTx arm at DCO4 remained consistent with those reported in the established safety pool for durvalumab: 254 patients (36.0%) with imAE event outcome resolved; and 451 patient (64.0%) with imAE event outcome not resolved.

At DCO4, the nature, severity, and manageability of imAEs in the D + CTx arm remained consistent with the established safety profile of durvalumab.

Table 5 Immune-mediated adverse events by study period (SAS population; DCO4)

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)	61 (22.9)	21 (8.3)	102 (25.4)	41 (10.3)
Grade 3-4 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)
ImAE categories reported in ≥ 1% of patients								
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	29 (10.9)	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 treatment (D/Pbo/CT) until the date of surgery or, for patients without surgery, up to the earliest of: last dose of neoadjuvant treatment (D/Pbo/CT) + 90 days, first dose of subsequent anti-cancer treatment, 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 treatment, or DCO date.

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

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

[2] Note: A patient may experience more than one imAE.

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 treatment during that period).

DCO: 10 May 2024 (DCO4). Source: Table 14.3.6.2.1.IA2, Table 14.3.6.2.1.1.IA2, Table 14.3.6.2.1.2.IA2, Table 14.3.6.2.1.3.IA2, Table 14.3.6.2.2.IA2, Table 14.3.6.2.3.IA2, Table 14.3.6.2.4.IA2, Table 14.3.6.2.10.IA2, Table 14.3.6.2.13.IA2, iemt0673_023, iemt0673_024, and iemt0673_032.

3.3.2 Adjuvant Period

Similar to the results from DCO3, at DCO4, the proportion of patients in the adjuvant period reporting any imAEs remained higher in the D + CTx arm (61 patients [22.9%]) than in the Pbo + CTx arm (21 patients [8.3%]) (Table 5). The proportion of patients with imAEs of maximum CTCAE Grade 3-4 remained similar between treatment arms: 6 patients (2.3%) in the D + CTx arm vs. 4 patients (1.6%) in the Pbo + CTx arm (Table 5).

At DCO4, the most commonly reported imAEs in the adjuvant period remained similar in nature and severity to those reported at DCO3 (Table 5), with the exception of 1 additional patient in the D + CTx arm who reported a low-Grade hypothyroid event and 1 additional patient in the Pbo + CTx arm who reported a low-Grade imAE of hyperthyroidism.

The number of patients with unresolved imAEs (any category) in the adjuvant period was 29 (10.9%) in the D + CTx arm vs. 12 (4.7%) in the Pbo + CTx arm. The majority of unresolved imAEs reported in the D + CTx arm (23 out of 29 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 reported for the D + CTx arm in the adjuvant period included pneumonitis (2 patients), dermatitis/rash (2 patients) and events that were reported in one patient each: diarrhea, arthralgia, adrenal insufficiency, thyroiditis, and AST increased. All unresolved imAEs in the D + CTx arm were low grade (CTCAE grade 1-2).

The unresolved imAEs reported for the Pbo + CTx arm in the adjuvant period were pneumonitis (3 patients), hypothyroid events (3 patients), hyperthyroid events (2 patients), thyroiditis (2 patients), and events that were reported in one patient each: diarrhea, arthralgia, and arthritis. Of the unresolved imAEs, events of CTCAE Grade 3-4 were reported for 2 patients: 1 patient with CTCAE Grade 3 pneumonitis event and 1 patient with a CTCAE Grade 4 pneumonitis event and a CTCAE Grade 3 diarrhea/colitis event (both imAEs) at DCO. The remaining unresolved imAEs in the Pbo + CTx arm were CTCAE Grade 1-2[3].

3.4 All Deaths (DCO4)

The Applicant's Position:

The total number of deaths reported at DCO4 in the ITT population continued to be lower in the D + CTx arm (128 patients [32%]) vs. the Pbo + CTx arm (150 patients [37.3%]). In both study arms, most deaths continued to be attributed to the disease under investigation only

[3] Note: A patient may experience more than one imAE.

(83/128 patients [64.8%] in the D + CTx arm and 121/150 [80.7%] in the Pbo + CTx arm). A summary of all deaths in the ITT population is provided in Table 11.

3.4.1 Adverse Events with Outcome of Death in the SAS Population (DCO4)

The Applicant's Position:

No new fatal AEs were reported in the study between the DCO2 and the DCO4 dates. Overall, the total number of patients in the SAS population who reported AEs with an outcome of death remained the same as reported at DCO2 and DCO3: 23 patients (5.7%) in the D + CTx arm vs. 15 patients (3.8%) in the Pbo + CTx arm.

3.5 Updated Safety Conclusions

The Applicant's Position:

All patients in AEGEAN had completed all study treatments and the safety follow-up period by the DCO4 date. The safety and tolerability profile of perioperative D + CTx treatment at DCO4 remained consistent with that previously summarized in the ODAC briefing document (based on data from DCO3).

The FDA's Position:

FDA acknowledges that the safety data for durvalumab reported in the addendum is generally consistent with previous analyses.

In the text above, the Applicant notes that 11% of patients who received adjuvant durvalumab had unresolved immune-related adverse events (irAEs) at the end of study treatment. Although most irAEs were Grade 1 and 2, persistent Grade 2 irAEs such as diarrhea or rash may have lasting negative impacts. As noted by FDA in the main combined ODAC briefing document, there are other potential irAEs associated with ICI therapy which could also negatively impact patients' long-term health status, such as nephritis and diabetes mellitus.

4. Updated Clinical Outcome Assessment Analyses

The Applicant's Position:

4.1 Patient-reported Outcomes in the Adjuvant Period (DCO4)

At DCO4 (10 May 2024), the following patient-reported outcome variables were assessed for the adjuvant period of AEGEAN in the resected mITT population:

- EORTC QLQ-C30 (secondary endpoint): Assessed at adjuvant baseline and then every 4 weeks until adjuvant Week 44 (cycle 12 of planned adjuvant durvalumab/placebo) or until discontinuation of study treatment.
- Patients' Global Impression of Severity (PGIS) of cancer symptoms (exploratory endpoint): Assessed at baseline then at adjuvant Week 20 (cycle 6 of planned adjuvant durvalumab/placebo) and adjuvant Week 44 or until discontinuation of study treatment.

- PRO-CTCAE (exploratory endpoint): Assessed at adjuvant baseline and then every 4 weeks until adjuvant Week 44 or until discontinuation of study treatment.

Results are summarized below.

4.1.1 EORTC QLQ-C30

Throughout the adjuvant period, EORTC QLQ-C30 questionnaire compliance rates remained high (> 82%) for both treatment arms (resected mITT population).

Mean EORTC QLQ-C30 scores at the start of the adjuvant period indicated a moderate-to-high quality of life, high functioning, and low-to-moderate symptom burden for patients in both treatment arms, with scores that were generally comparable to those reported for the general population within a similar age group (60-69 years) [1].

At the group level, throughout the adjuvant period, patients' perception of global health status/quality of life and all functioning domain scores (physical, role, emotional, cognitive, and social) remained stable over time in both treatment arms, with small numerical improvements observed for both treatment arms in some functioning domains. Similar trends toward stability/minor improvements were observed for the symptom scales of fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties throughout the adjuvant period for both treatment arms.

At the individual patient level, most patients in both treatment arms reported either no change or clinically meaningful improvement from adjuvant baseline (i.e., change from baseline score of ≥ 10 points) in global health status/quality of life throughout the adjuvant period (proportion of patients reporting no change or clinically meaningful improvement from adjuvant baseline varied between 77% to 88% of patients in the D + CTx arm vs. 83% to 88% of patients in the Pbo + CTx arm, across all adjuvant visits). Similar results at the individual patient level were observed for physical functioning, role functioning, fatigue, and appetite loss, with the majority of patients in both treatment arms reporting either no change or clinically meaningful improvement from adjuvant baseline for each of these domains at all adjuvant period visits.

Adjusted mean change from adjuvant baseline over time in global health status/quality of life, physical functioning, role functioning, fatigue, and appetite loss are shown in Appendix 14.

Overall, EORTC QLQ-C30 data collected after surgery indicate that adjuvant durvalumab treatment did not have a detrimental effect on patients' perception of global health status/quality of life, functioning, and disease/treatment-related symptoms. All questionnaire domain scores remained stable or improved slightly in both treatment arms throughout the adjuvant period of AEGEAN and were comparable to those observed in the general population.

4.1.2 PGIS

PGIS questionnaire compliance rates in the adjuvant period were high (> 82%) for both treatment arms (resected mITT population).

Most patients in both treatment arms reported no cancer symptoms, very mild cancer symptoms, or mild cancer symptoms in the adjuvant period (range: 85% to 89% of patients in

the D + CTx arm vs. 83% to 95% of patients in the Pbo + CTx arm). The proportion of patients reporting severe or very severe cancer symptoms was very low in both arms (range: 0% to 3% of patients in the D + CTx arm vs. 1% to 3% of patients in the Pbo + CTx arm).

4.1.3 PRO-CTCAE (Selected Items)

Patient-reported treatment tolerability was explored using 7 pre-defined symptoms for a total of 13 items from the PRO-CTCAE item library that were considered relevant for the AEGEAN study: difficulty swallowing (severity), nausea (frequency/severity/interference), pain in the abdomen (frequency/severity), rash (occurrence), itchy skin (severity), numbness or tingling in the hands or feet (severity/interference), and aching joints (frequency/severity/interference).

At the start of adjuvant treatment, the overall compliance rates for the selected PRO-CTCAE items were high in both treatment arms (> 82%) and remained high (80% to 90%) throughout the adjuvant period (resected mITT population).

The proportion of patients reporting PRO-CTCAE items was comparable between the two treatment arms throughout the adjuvant period, with the exception of a greater proportion of patients reporting itchy skin in the D + CTx arm than the Pbo + CTx arm, as would be expected based on the well-characterized safety profile of durvalumab monotherapy. Of note, events of itchy skin were rarely reported as “severe” or “very severe” in either treatment arm.

Overall, descriptive PRO-CTCAE results indicate that, from the patients’ perspective, adjuvant durvalumab treatment and adjuvant placebo were similarly well-tolerated in terms of the frequencies of patient-reported treatment-related symptoms. The majority of patient-reported symptoms were mild or moderate in both treatment arms and/or had a limited degree of interference with patients' usual or daily activities.

The FDA’s Position:

FDA continues to note substantive concerns with the applicant’s position regarding patient generated data from AEGEAN. Although data quality appeared to be reasonable (e.g., compliance rate >80%) during the adjuvant period, the assessment frequency of patient-reported outcomes was sparse (every 4 weeks). Although the Applicant observed that patient-reported symptoms and function were similar between arms, FDA did not have the opportunity to review source datasets and relies on the Applicant’s presentation of the data. Regardless, these data as presented do not mitigate the concerns outlined elsewhere in this document regarding efficacy. Furthermore, comparable rates of patient-reported symptoms assessed sparsely are not sufficient evidence to demonstrate comparative tolerability. Please see The FDA’s Position from the main combined ODAC briefing document for more information.

5. Updated Benefit-Risk Conclusion

The Applicant’s Position:

Updated efficacy results from AEGEAN at DCO4 show that the clinically meaningful improvement in EFS demonstrated at DCO2 in favor of the D + CTx arm was maintained through DCO4, which provided increased data maturity with 18 months of additional study follow-up. These clinical benefits were observed across all pre-specified subgroups, providing reassurance

that the proposed treatment regimen is beneficial across a broad patient population, irrespective of demographics, disease characteristics, or platinum chemotherapy agent (cisplatin or carboplatin). Furthermore, trends toward improved DFS and OS were shown for the D + CTx arm, as compared to the Pbo + CTx arm, at DCO4.

Overall, the updated efficacy results at DCO4 are supportive of the data presented in the ODAC briefing document, where it was shown that the primary endpoints of the study (pCR and EFS) were met at their first respective interim analyses and reinforce the conclusion that perioperative durvalumab in combination with neoadjuvant chemotherapy provides a clinically meaningful improvement of long-term efficacy outcomes for patients with resectable NSCLC.

Updated safety results from DCO4 show consistency with the safety and tolerability profile of the perioperative D + CTx treatment regimen previously summarized in the ODAC briefing document (based on data from DCO3). Overall, no new safety concerns have been identified for durvalumab when given in this treatment setting. The overall and adjuvant phases of the perioperative D + CTx treatment regimen remained well-tolerated.

Patient-reported outcomes collected after surgery demonstrate that adjuvant durvalumab treatment appeared to be well-tolerated overall and did not have a detrimental effect on patients' perception of disease/treatment-related symptoms, functioning, and overall health-related quality of life, which remained stable throughout the adjuvant period.

In conclusion, the totality of efficacy and safety results of the AEGEAN study summarized in the ODAC briefing document and in this addendum 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 (stages IIA-IIIB[N2]) whose tumors have no known EGFRm or ALK gene rearrangements.

The FDA's Position:

FDA notes that despite the updated data from AEGEAN DCO4, concern remains that the design of AEGEAN does not allow for an assessment of the contribution of durvalumab in the neoadjuvant phase or the adjuvant phase to the efficacy of the overall perioperative regimen. Please refer to FDA's position on this issue detailed in the combined ODAC briefing document.

6. References

The Applicant's References:

1. Nolte S, Liegl G, Petersen MA, Aaronson NK, Costantini A, Fayers PM, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. Eur J Cancer 2019;107:153-163.

FDA's References:

2. Fujiwara Y, Horita N, Adib E, Zhou S, Nassar AH, Asad ZUA, et al. Treatment-related adverse events, including fatal toxicities, in patients with solid tumours receiving neoadjuvant and adjuvant immune checkpoint blockade: a systematic review and meta-analysis of randomised controlled trials. Lancet Oncol. 2024 Jan;25(1):62-75.

7. Appendices

7.1 Applicant's Appendices

Appendix 1: Patient Disposition

Table 6 Overview of patient disposition (mITT and resected mITT populations; DCO4)

Study period		Number (%) patients [a]			
		mITT population		Resected mITT population	
		D + CTx (N = 366)	Pbo + CTx (N = 374)	D + CTx (N = 242)	Pbo + CTx (N = 231)
Pre-treatment	Randomized	366 (100.0)	374 (100.0)	242 (100.0)	231 (100.0)
Neoadjuvant	Received neoadjuvant treatment	366 (100.0)	371 (99.2)	242 (100.0)	231 (100.0)
	Completed 4 cycles of neoadjuvant treatment of both (doublet) CTx	310 (84.7)	326 (87.2)	217 (89.7)	215 (93.1)
	Completed 4 cycles of neoadjuvant durvalumab/placebo	318 (86.9)	331 (88.5)	222 (91.7)	220 (95.2)
Surgery	Underwent on-study surgery [b]	295 (80.6)	302 (80.7)	242 (100.0)	231 (100.0)
	Did not undergo surgery on study	71 (19.4)	72 (19.3)	0	0
	Completed on-study surgery	284 (77.6)	287 (76.7)	242 (100.0)	231 (100.0)
	Did not complete on-study surgery	11 (3.0)	15 (4.0)	0	0
Adjuvant	Started adjuvant durvalumab/placebo [c]	242 (66.1)	237 (63.4)	223 (92.1)	214 (92.6)
	Discontinued adjuvant durvalumab/placebo	76 (20.8)	86 (23.0)	65 (26.9)	75 (32.5)
	Completed adjuvant durvalumab/placebo	166 (45.4)	151 (40.4)	158 (65.3)	139 (60.2)
	Ongoing adjuvant durvalumab/placebo	0	0	0	0

[a] All percentages are calculated from number of patients in each arm in the corresponding analysis set (mITT and resected mITT populations, as shown in the table).
[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 May 2024 (DCO4).
Source: Tables iemt0667.001 and iemt0667.003.

Appendix 2: Patient Demographics and Baseline Characteristics

Table 7 Demographics and baseline patient characteristics (mITT and resected mITT populations)

Characteristic	Number (%) patients			
	mITT population		Resected mITT population	
	D + CTx (N = 366)	Pbo + CTx (N = 374)	D + CTx (N = 242)	Pbo + CTx (N = 231)
Age (years) [a]				
Median (min, max)	65.0 (30, 88)	65.0 (39, 85)	65.0 (32, 88)	64.0 (40, 85)
Age group [a]				
< 50 years	17 (4.6)	20 (5.3)	10 (4.1)	14 (6.1)
≥ 50 to < 65 years	158 (43.2)	163 (46.3)	108 (44.6)	102 (44.2)
≥ 65 to < 75 years	147 (40.2)	155 (41.4)	95 (39.3)	87 (37.7)
≥ 75 years	44 (12.0)	36 (9.6)	29 (12.0)	28 (12.1)
Sex				
Male	252 (68.9)	278 (74.3)	161 (66.5)	167 (72.3)
Female	114 (31.1)	96 (25.7)	81 (33.5)	64 (27.7)
Race				
White	206 (56.3)	191 (51.1)	133 (55.0)	107 (46.3)
Asian	143 (39.1)	164 (43.9)	99 (40.9)	111 (48.1)
American Indian or Alaska Native	6 (1.6)	4 (1.1)	4 (1.7)	2 (0.9)
Black or African American	4 (1.1)	3 (0.8)	2 (0.8)	1 (0.4)
Other	7 (1.9)	12 (3.2)	4 (1.7)	10 (4.3)
Ethnic group				
Not Hispanic or Latino	303 (82.8)	318 (85.0)	206 (85.1)	192 (83.1)
Hispanic or Latino	63 (17.2)	56 (15.0)	36 (14.9)	39 (16.9)
Region				
Asia	142 (38.8)	163 (43.6)	98 (40.5)	111 (48.1)
Europe	141 (38.5)	140 (37.4)	98 (40.5)	76 (32.9)
North America	43 (11.7)	43 (11.5)	24 (9.9)	26 (11.3)
South America	40 (10.9)	28 (7.5)	22 (9.1)	18 (7.8)
Smoking history				
Never-smoker	51 (13.9)	56 (15.0)	38 (15.7)	43 (18.6)
Current smoker	95 (26.0)	95 (25.4)	67 (27.7)	48 (20.8)
Former smoker	220 (60.1)	223 (59.6)	137 (56.6)	140 (60.6)
ECOG performance status				
(0) Normal activity	251 (68.6)	255 (68.2)	182 (75.2)	162 (70.1)
(1) Restricted in physically strenuous activity	115 (31.4)	119 (31.8)	60 (24.8)	69 (29.9)

Characteristic	Number (%) patients			
	mITT population		Resected mITT population	
	D + CTx (N = 366)	Pbo + CTx (N = 374)	D + CTx (N = 242)	Pbo + CTx (N = 231)
Disease stage at baseline (per source data) [b]				
IIA	18 (4.9)	24 (6.4)	13 (5.4)	16 (6.9)
IIB	86 (23.5)	86 (23.0)	63 (26.0)	63 (27.3)
III (not otherwise specified)	0	1 (0.3)	0	1 (0.4)
IIIA	173 (47.3)	165 (44.1)	114 (47.1)	96 (41.6)
IIIB	88 (24.0)	98 (26.2)	52 (21.5)	55 (23.8)
IV (not otherwise specified)	1 (0.3)	0	0	0
TNM classification at baseline [b]				
T1	44 (12.0)	43 (11.5)	29 (12.0)	21 (9.1)
T2	97 (26.5)	108 (28.9)	66 (27.3)	70 (30.3)
T3	128 (35.0)	129 (34.5)	85 (35.1)	89 (38.5)
T4	97 (26.5)	94 (25.1)	62 (25.6)	51 (22.1)
N0	110 (30.1)	102 (27.3)	80 (33.1)	64 (27.7)
N1	75 (20.5)	87 (23.3)	51 (21.1)	67 (29.0)
N2	181 (49.5)	185 (49.5)	111 (45.9)	100 (43.3)
Histology				
Squamous	169 (46.2)	191 (51.1)	107 (44.2)	113 (48.9)
Non-squamous	196 (53.6)	179 (47.9)	134 (55.4)	117 (50.6)
PD-L1 expression				
TC < 1%	122 (33.3)	125 (33.4)	72 (29.8)	79 (34.2)
TC 1% to 49%	135 (36.9)	142 (38.0)	90 (37.2)	86 (37.2)
TC ≥ 50%	109 (29.8)	107 (28.6)	80 (33.1)	66 (28.6)
Planned neoadjuvant platinum agent				
Cisplatin	100 (27.3)	96 (25.7)	72 (29.8)	60 (26.0)
Carboplatin	266 (72.7)	278 (74.3)	170 (70.2)	171 (74.0)

[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.
Source: Tables iemt0578.015, iemt0578.016, 14.1.5.5.IA2, 14.1.10.5.IA2, 14.1.11.5.IA2, and iemt0665_007.

Appendix 3: Anti-cancer Therapy Post-treatment Discontinuation

Table 8 Subsequent anti-cancer therapy (mITT population; DCO4)

Anti-cancer therapy regimen [a]	Number (%) patients	
	D + CTx (N = 366)	Placebo + CTx (N = 374)
Number of patients with post-discontinuation anticancer therapy	**71 (19.4)**	**111 (29.7)**
Systemic therapy	70 (19.1)	111 (29.7)
Cytotoxic chemotherapy	47 (12.8)	51 (13.6)
Single agent	15 (4.1)	16 (4.3)
Platinum doublet	30 (8.2)	32 (8.6)
Other combination	10 (2.7)	9 (2.4)
Immunotherapy	26 (7.1)	63 (16.8)
Immunotherapy only	6 (1.6)	32 (8.6)
Immunotherapy + CTx	19 (5.2)	31 (8.3)
Immunotherapy + other	1 (0.3)	1 (0.3)
Targeted therapy	7 (1.9)	8 (2.1)
Other	2 (0.5)	6 (1.6)
Radiotherapy	44 (12.0)	66 (17.6)
Concomitant chemoradiotherapy	22 (6.0)	20 (5.3)
Line of subsequent therapy		
1st subsequent therapy	71 (19.4)	111 (29.7)
2nd subsequent therapy	19 (5.2)	26 (7.0)
≥ 3rd subsequent therapy	6 (1.6)	6 (1.6)
Intent of subsequent therapy		
Neoadjuvant	4 (1.1)	4 (1.1)
Adjuvant	7 (1.9)	13 (3.5)
Definitive	9 (2.5)	5 (1.3)
Maintenance	10 (2.7)	6 (1.6)
Palliative	53 (14.5)	87 (23.3)
Not applicable	1 (0.3)	0

[a] Therapies post discontinuation of study treatment. Regimen categories and line of subsequent therapy identified from medical review of preferred terms using treatment start dates.

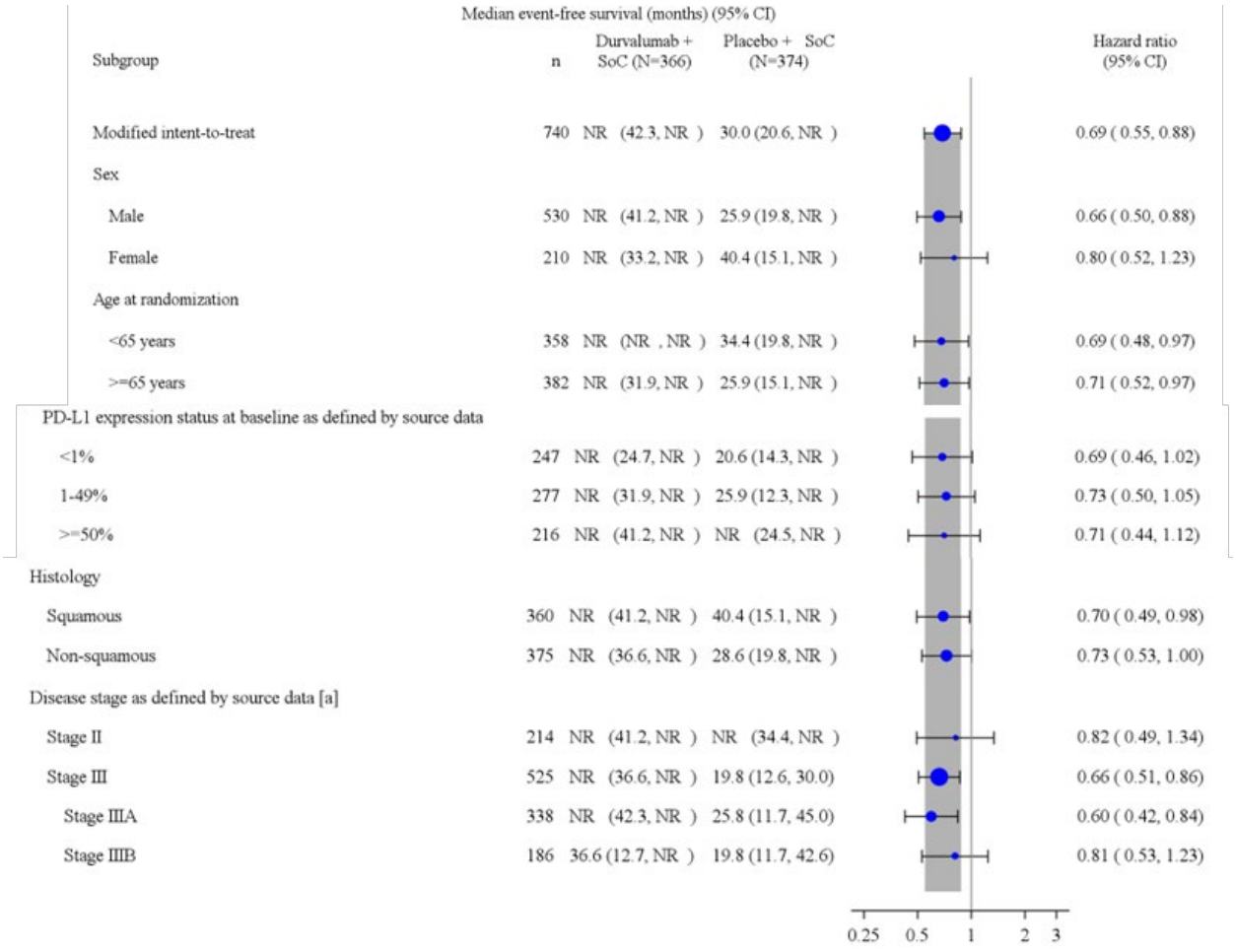
Patients with therapies in more than one category are counted once in each of those categories. Percentages are calculated from number of patients in the modified intent-to-treat in that treatment arm.

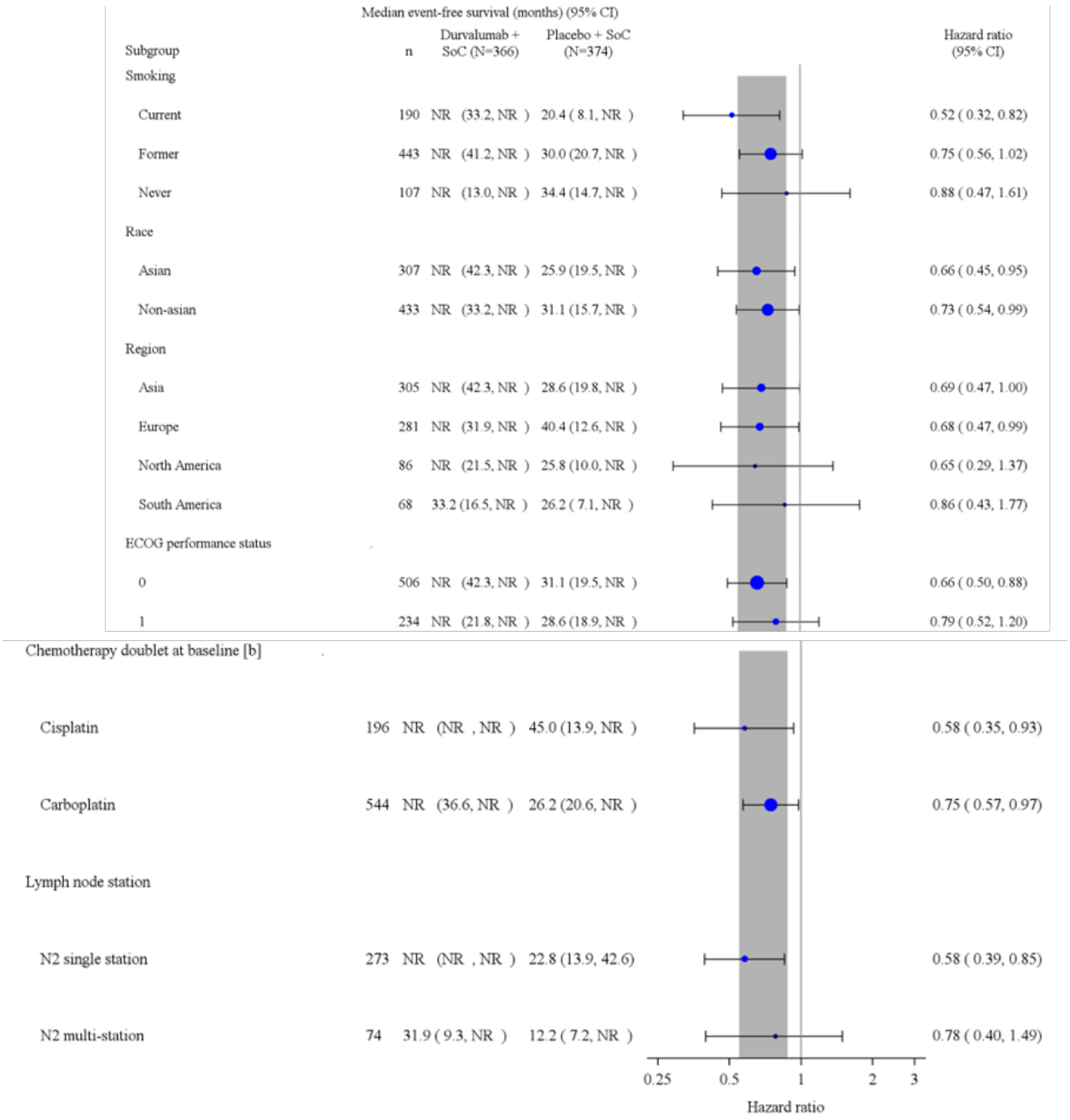
DCO: 10 May 2024 (DCO4).

Source: Table 14.1.15.IA2.

Appendix 4: Subgroup Analysis of Event-free Survival

Figure 4 **Event-free survival (using BICR per RECIST 1.1): forest plot by subgroup (mITT population; DCO4)**



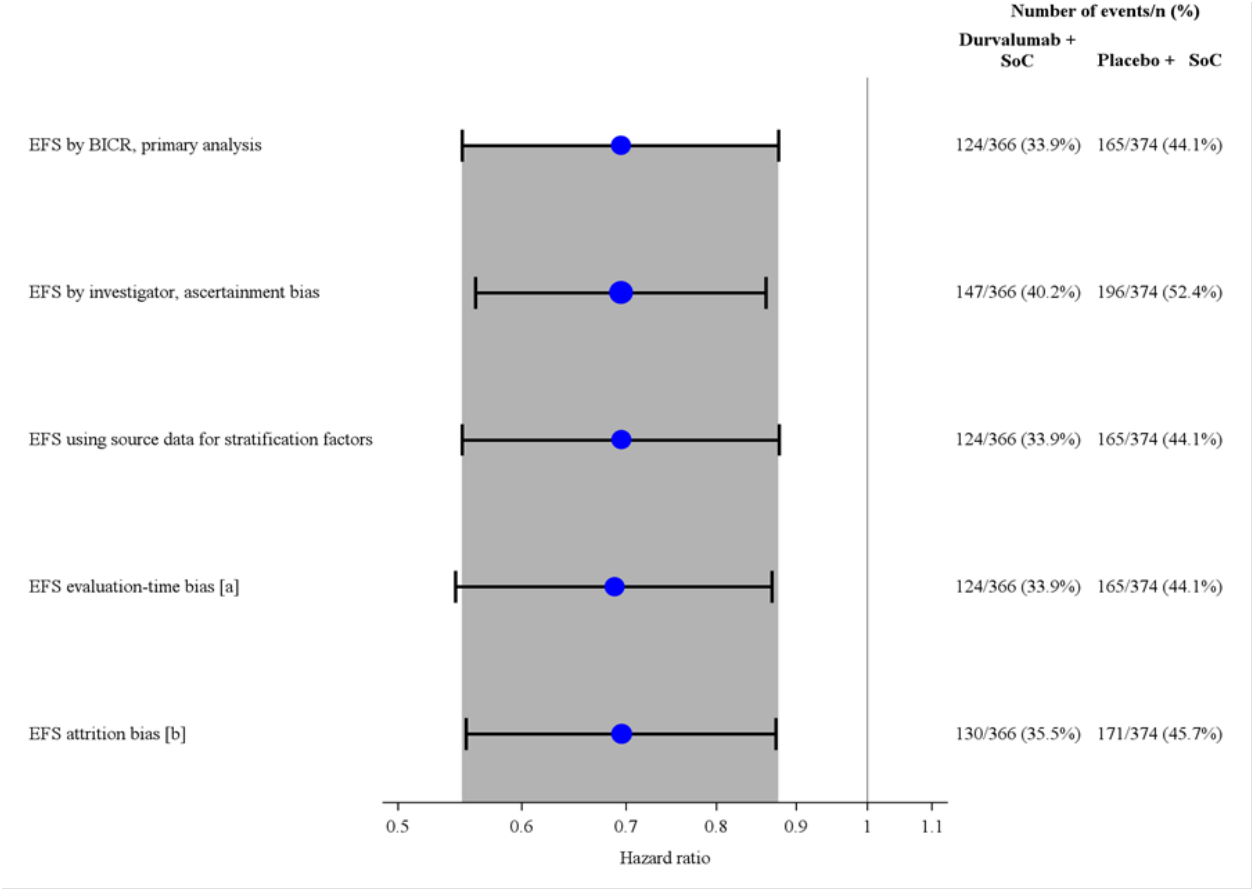


[a] According to AJCC Cancer Staging Manual, 8th Edition.
[b] Refers to the platinum agent of the chemotherapy doublet (planned treatment).

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 events in the subgroup. Grey band represents the 95% confidence interval for the HR in the overall mITT population.
DCO: 10 May 2024 (DCO4).
Source: Figure 14.2.3.12.IA2.

Appendix 5: Sensitivity Analyses of Event-free Survival

Figure 5 Event-free survival (using BICR per RECIST 1.1): forest plot of primary and sensitivity analyses (mITT population; DCO4)



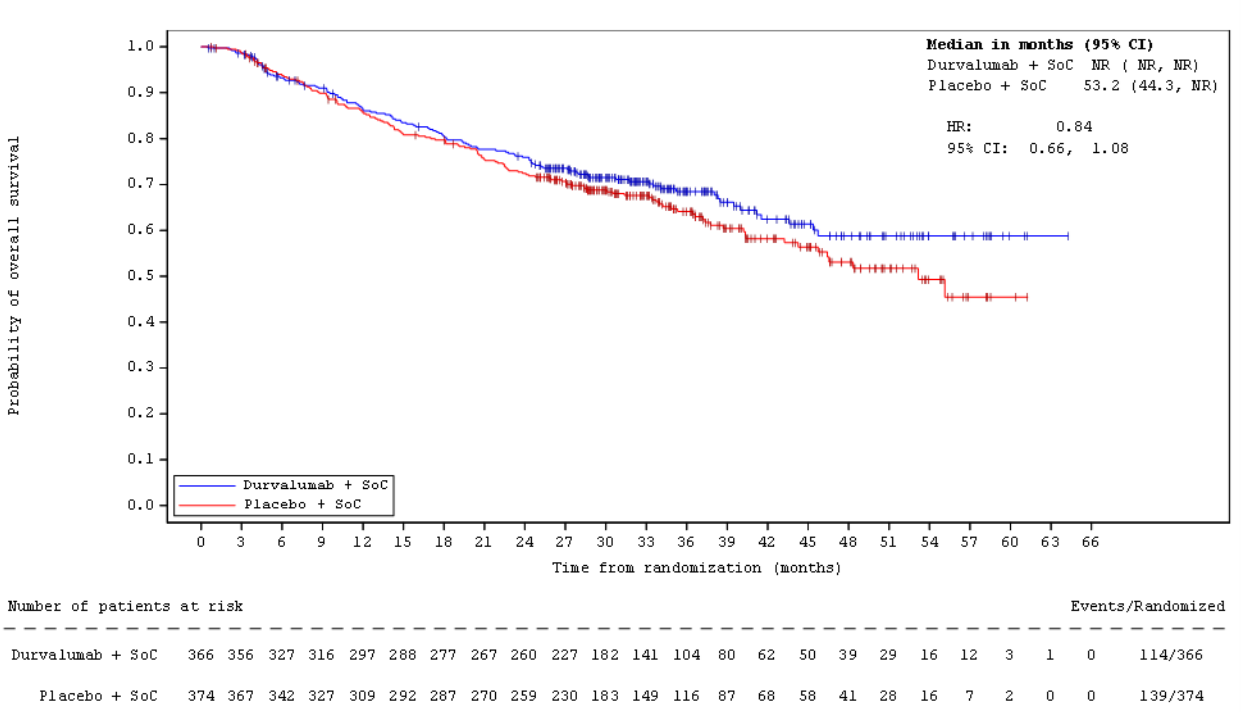
[a] Event time is the midpoint between time of progression and previous evaluable disease assessments, or for those whose death was treated as an EFS event, date of death is used to derive the EFS time used in analysis.

[b] Analysis uses actual event times, rather than censored times, for subjects with an EFS event immediately following ≥ 2 non-evaluable disease assessments are included. Subjects 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 hazard ratio < 1 favors the D + CTx arm, to be associated with longer EFS than Pbo + CTx. Size of circle is proportional to the number of events. Grey band represents the 95% CI for the primary analysis hazard ratio in the mITT population.
DCO: 10 May 2024 (DCO4).
Source: Figure 14.2.3.16.6.IA2.

Appendix 6: Sensitivity Analysis of Overall Survival, Censoring for COVID-19 Deaths

Figure 6 **Kaplan-Meier plots of overall survival: sensitivity analysis censoring for COVID-19 deaths (mITT population; DCO4)**



Patients whose primary cause of death was reported as COVID-19 were censored on their date of death. A vertical line indicates a censored observation.
DCO: 10 May 2024 (DCO4).
Source: Figure iemt0666_020.

Appendix 7: Duration of Exposure to Study Treatment

Table 9 Duration of exposure to study treatment (durvalumab / placebo / chemotherapy) (SAS population; DCO3 and DCO4)

	Adjuvant Period [a]				Overall [b]			
	DCO3 (14 Aug 2023)		DCO4 (10 May 2024)		DCO3 (14 Aug 2023)		DCO4 (10 May 2024)	
	D + CTx (N = 266)	Pbo + CTx (N = 254)	D + CTx (N = 266)	Pbo + CTx (N = 254)	D + CTx (N = 401)	Pbo + CTx (N = 398)	D + CTx (N = 401)	Pbo + CTx (N = 398)
Actual duration of exposure to D/Pbo: Median (min, max) (weeks)	48.00 (4.0, 52.4)	47.86 (4.0, 50.4)	48.00 (4.0, 52.3)	47.93 (4.0, 50.4)	40.14 [c] (2.0, 64.6)	36.14 [c] (3.0, 62.9)	40.14 (2.0, 64.4)	36.14 (3.0, 62.9)
Completed 4 cycles of neoadjuvant D/Pbo, n (%)	NA	NA	NA	NA	346 (86.3)	355 (89.2)	346 (86.3)	355 (89.2)
Completed 4 cycles of at least one neoadjuvant CTx component, n (%)	NA	NA	NA	NA	350 (87.3)	357 (89.7)	350 (87.3)	357 (89.7)
Completed 4 cycles of neoadjuvant treatment of both CTx components, n (%)	NA	NA	NA	NA	347 (86.5)	356 (89.4)	347 (86.5)	356 (89.4)
Completed 12 cycles of adjuvant D/Pbo, n (%)	177 (66.5)	159 (62.6)	182 (68.4)	161 (63.4)	177 (44.1)	159 (39.9)	182 (45.4)	161 (40.5)
Median number of D/Pbo treatment cycles	12.0	12.0	12.0	12.0	11.0 [c]	10.0 [c]	11.0 [c]	11.0 [c]

[a] 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.

DCO: 14 August 2023 (DCO3) and 10 May 2024 (DCO4).
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 iemt0617.179, Table 14.3.1.1.1.1.IA2, Table 14.3.1.3.3.1.IA2, Table iemt0673.107, and Table iemt0673.113.

Appendix 8: Summary of SAEs in the Overall Study Period

Table 10 Summary of SAEs in the overall study period (> 1% patients in either treatment arm) (SAS population; DCO4)

MedDRA PT	Number (%) patients [a]	
	D + CTx (N = 401)	Pbo + CTx (N = 398)
Patients with any SAE	**157 (39.2)**	**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)
Pneumonitis	7 (1.7)	1 (0.3)
Myelosuppression	6 (1.5)	2 (0.5)
Vomiting	5 (1.2)	2 (0.5)
Drug-induced liver injury	5 (1.2)	1 (0.3)
Pneumothorax	4 (1.0)	9 (2.3)

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

Overall period refers to the neoadjuvant period, surgical period, and adjuvant period, i.e., 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.

DCO: 10 May 2024 (DCO4)

Source: Table 14.3.4.1.1.1.IA2.

Appendix 9: Summary of All Deaths

Table 11 Summary of all deaths (ITT and mITT populations; DCO4)

Category	Number (%) patients			
	ITT population		mITT population	
	D + CTx (N = 400)	Pbo + CTx (N = 402)	D + CTx (N = 366)	Pbo + CTx (N = 374)
Total number of deaths	**128 (32.0)**	**150 (37.3)**	**121 (33.1)**	**140 (37.4)**
Death related to disease under investigation only [a]	83 (20.8)	121 (30.1)	76 (20.8)	113 (30.2)
TEAE with outcome of death only [b]	19 (4.8)	12 (3.0)	19 (5.2)	11 (2.9)
Death related to disease under investigation and with TEAE with an outcome of death [a, b]	4 (1.0)	3 (0.7)	4 (1.1)	3 (0.8)
AE with outcome of death only (AE start date falling after safety follow-up period) [c]	3 (0.8)	1 (0.2)	3 (0.8)	1 (0.3)
Death related to disease under investigation (AE start date falling after safety follow-up period) [c]	0	1 (0.2)	0	1 (0.3)
Patients with unknown reason for death	7 (1.8)	3 (0.7)	7 (1.9)	3 (0.8)
Other deaths [d]	12 (3.0)	9 (2.2)	12 (3.3)	8 (2.1)
Total number of perioperative deaths [e]	4 (1.0)	8 (2.0)	4 (1.1)	8 (2.1)

[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: 10 May 2024 (DCO4).
Source: Table 14.3.3.1.1.1.IA2 and Table 14.3.3.1.1.2.IA2.

Appendix 10: Summary of imAEs in Any Category in the Overall Study Period

Table 12 Summary of imAEs in any category in the overall study period and in the pooled durvalumab safety data (SAS population; DCO4)

imAE Category [b]	Number (%) patients [a]	
	D + CTx (N = 401)	Pbo + CTx (N = 398)
Any imAE	102 (25.4)	41 (10.3)
Any imAE, possibly related to study treatment [c]	98 (24.4)	32 (8.0)
Any imAE of CTCAE Grade 3 or 4 [d]	18 (4.5)	10 (2.5)
Any imAE of CTCAE Grade 3 or 4, possibly related to study treatment [c, d]	18 (4.5)	10 (2.5)
Any serious imAE (including events with outcome of death)	21 (5.2)	10 (2.5)
Any serious imAE, possibly related to study treatment [c]	21 (5.2)	10 (2.5)
Any imAE with outcome of death	5 (1.2)	0
Any imAE with outcome of death, possibly related to study treatment [c]	5 (1.2)	0
Any imAE leading to discontinuation of study treatment [e]	19 (4.7)	4 (1.0)
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)	18 (4.5)
Received other immunosuppressants	5 (1.2)	1 (0.3)
Event outcome resolved	59 (14.7)	21 (5.3)
Event outcome not resolved	38 (9.5)	20 (5.0)

[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 (according to the Durvalumab and Tremelimumab Global ImAE Characterization Charter).
[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, i.e., 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 the number of patients in the respective treatment arm (N).
DCO: 10 May 2024 (DCO4) Source: Table 14.3.6.2.1.IA2.

Appendix 11: Summary of AEs of Maximum CTCAE Grade 3 or 4 in the Overall Study Period

Table 13 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; DCO4)

	Number (%) patients [a]	
	D + CTx (N = 401)	Pbo + CTx (N = 398)
Patients with any AE of maximum CTCAE Grade 3 or 4	**175 (43.6)**	**172 (43.2)**
Neutrophil count decreased	42 (10.5)	45 (11.3)
Neutropenia	36 (9.0)	39 (9.8)
Anemia	26 (6.5)	26 (6.5)
Pneumonia	12 (3.0)	10 (2.5)
Platelet count decreased	9 (2.2)	14 (3.5)
Leukopenia	9 (2.2)	13 (3.3)
White blood cell count decreased	8 (2.0)	12 (3.0)
Pulmonary embolism	7 (1.7)	4 (1.0)
Myelosuppression	7 (1.7)	3 (0.8)
Thrombocytopenia	6 (1.5)	9 (2.3)
Hypokalemia	6 (1.5)	3 (0.8)
Hypertension	4 (1.0)	6 (1.5)
Vomiting	4 (1.0)	5 (1.3)
Pneumothorax	3 (0.7)	8 (2.0)
Febrile neutropenia	3 (0.7)	5 (1.3)
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 EFS IA2 DCO. Patients with multiple AEs are counted once for each PT. Overall period refers to the neoadjuvant period, surgical, and adjuvant period, i.e., 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.

DCO: 10 May 2024 (DCO4).

Source: Table 14.3.2.5.1.IA2 and iemt 0673.099.

Appendix 12: Most Common AEs of Any-Grade in the Overall Study Period

Table 14 Most common AEs of Any CTCAE Grade (in ≥ 10% of patients in either treatment arm), by PT in the overall study period (SAS population; DCO4)

MedDRA Preferred term	Number (%) of subjects [a]	
	D + CTx (N = 401)	Pbo + CTx (N = 398)
Patients with any AE	**387 (96.5)**	**379 (95.2)**
Anemia	140 (34.9)	128 (32.2)
Constipation	104 (25.9)	90 (22.6)
Nausea	103 (25.7)	119 (29.9)
Decreased appetite	74 (18.5)	72 (18.1)
Alopecia	69 (17.2)	64 (16.1)
Neutropenia	68 (17.0)	72 (18.1)
Neutrophil count decreased	66 (16.5)	59 (14.8)
Rash	63 (15.7)	33 (8.3)
Fatigue	56 (14.0)	47 (11.8)
COVID-19	54 (13.5)	45 (11.3)
Diarrhea	53 (13.2)	51 (12.8)
Pruritus	51 (12.7)	26 (6.5)
Asthenia	49 (12.2)	58 (14.6)
Hypothyroidism	47 (11.7)	12 (3.0)
Procedural pain	46 (11.5)	49 (12.3)
Vomiting	45 (11.2)	44 (11.1)
Arthralgia	43 (10.7)	51 (12.8)
Insomnia	43 (10.7)	48 (12.1)
Cough	36 (9.0)	43 (10.8)

[a] Number (%) of subjects with AEs, sorted in descending frequency of preferred term in the durvalumab treatment group. Includes AEs with an onset date prior to dosing which worsen during this period.
Most common is defined as a total frequency of >10% in either treatment group.
Percentages are based on the total numbers of subjects in the treatment group (N).
MedDRA version 26.1.
AE = Adverse event. N = Number of subjects in treatment group, within each period. SoC = Standard of Care.
DCO: 10 May 2024 (DCO4).
Source: Table iemt0673.099.

Appendix 13: Most Common AEs of Any-Grade in the Adjuvant Study Period

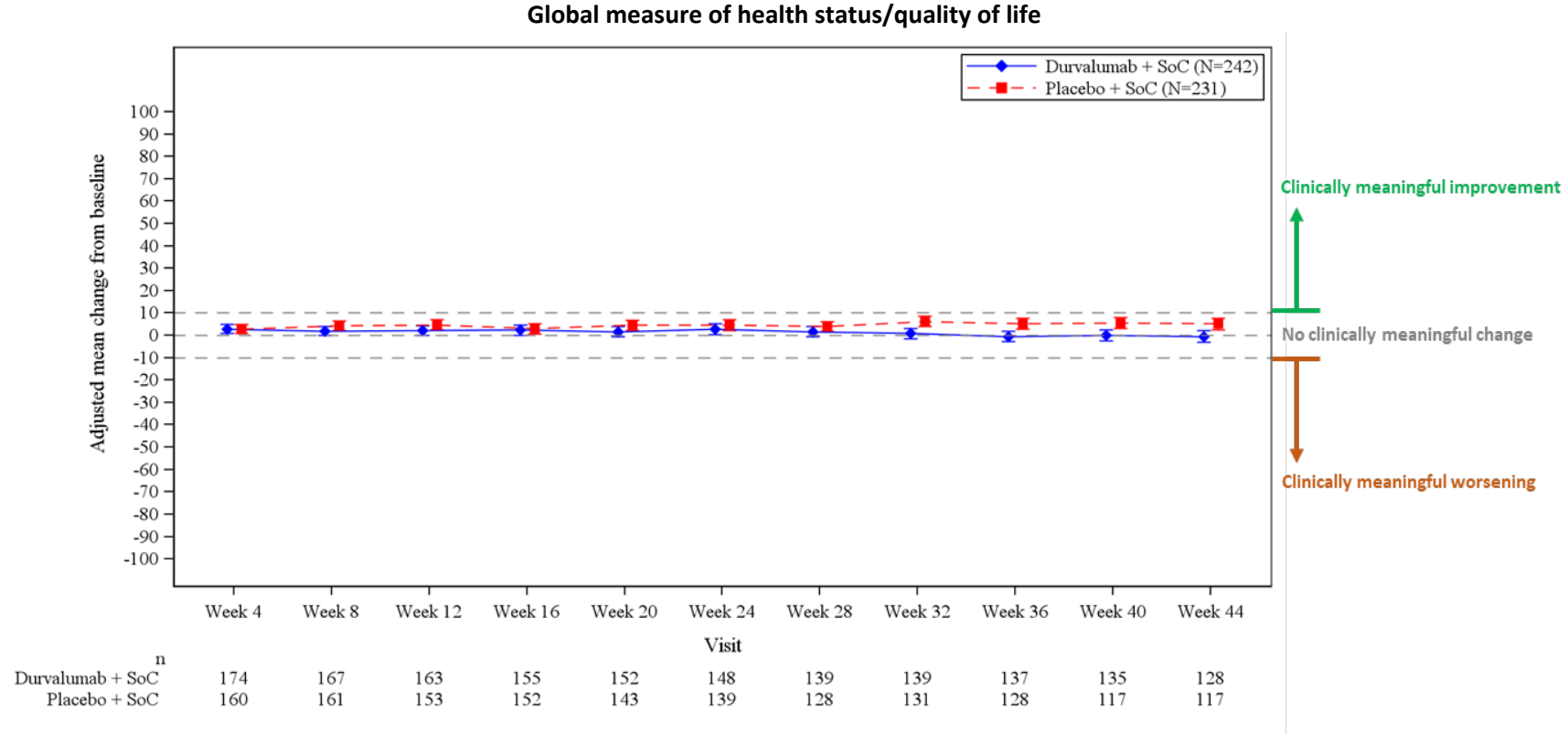
Table 15 Most common AEs of Any CTCAE Grade (in > 5% of patients in either treatment arm), by PT in the adjuvant study period (SAS population; DCO4)

MedDRA Preferred term	Number (%) of subjects [a]	
	D + CTx (N = 266)	Pbo + CTx (N = 254)
Patients with any AE	224 (84.2)	195 (76.8)
COVID-19	34 (12.8)	30 (11.8)
Hypothyroidism	32 (12.0)	6 (2.4)
Rash	26 (9.8)	3 (1.2)
Arthralgia	20 (7.5)	21 (8.3)
Pruritus	19 (7.1)	6 (2.4)
Anemia	14 (5.3)	8 (3.1)
Constipation	14 (5.3)	11 (4.3)
Diarrhea	13 (4.9)	15 (5.9)

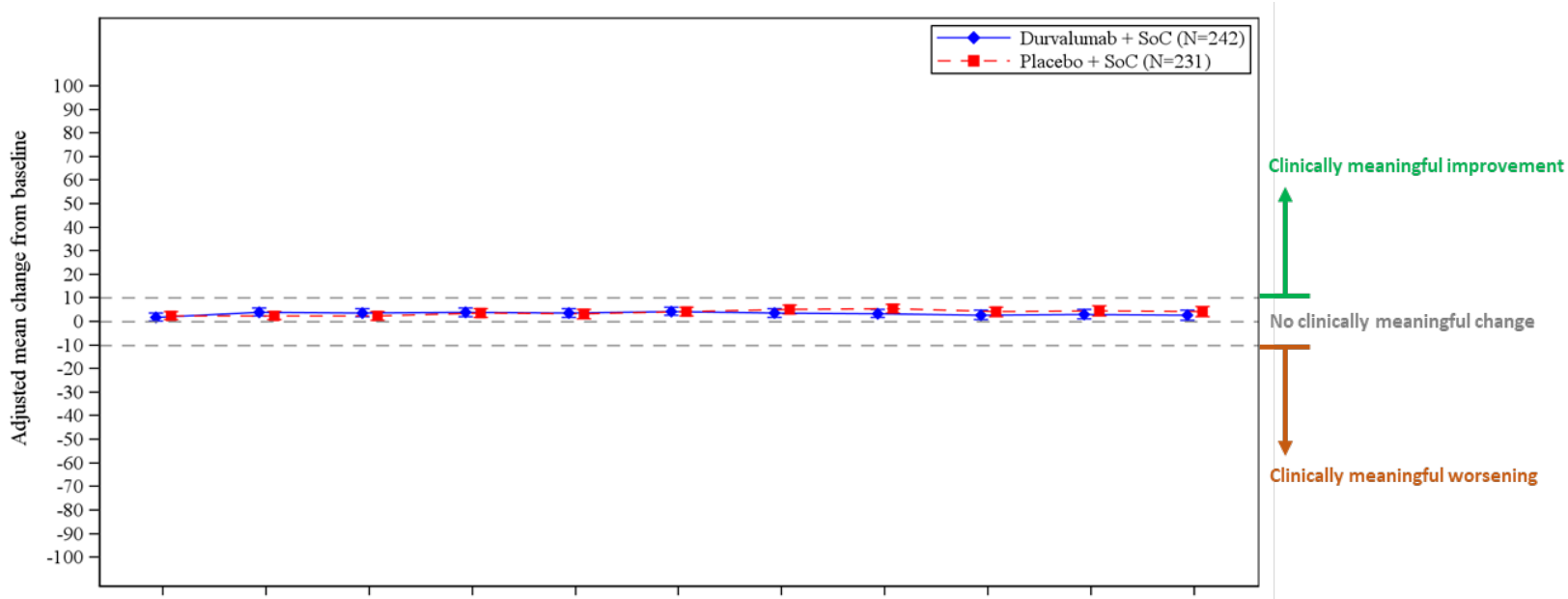
[a] Number (%) of subjects with AEs, sorted in descending frequency of preferred term in the durvalumab treatment group.
Includes AEs with an onset date prior to dosing which worsen during this period.
Most common is defined as a total frequency of > 5% in either treatment group.
Percentages are based on the total numbers of subjects in the treatment group (N).
MedDRA version 26.1.
AE = Adverse event. N = Number of subjects in treatment group, within each period. SoC = Standard of Care.
DCO: 10 May 2024 (DCO4).
Source: Table iemt0673.099.

Appendix 14: Adjusted Mean Change from Adjuvant Baseline in EORTC QLQ-C30 Scores (Selected Items)

Figure 7 **Adjusted mean change from adjuvant baseline in EORTC QLQ-C30 scores (selected items) by MMRM analysis (resected mITT population; DCO4)**

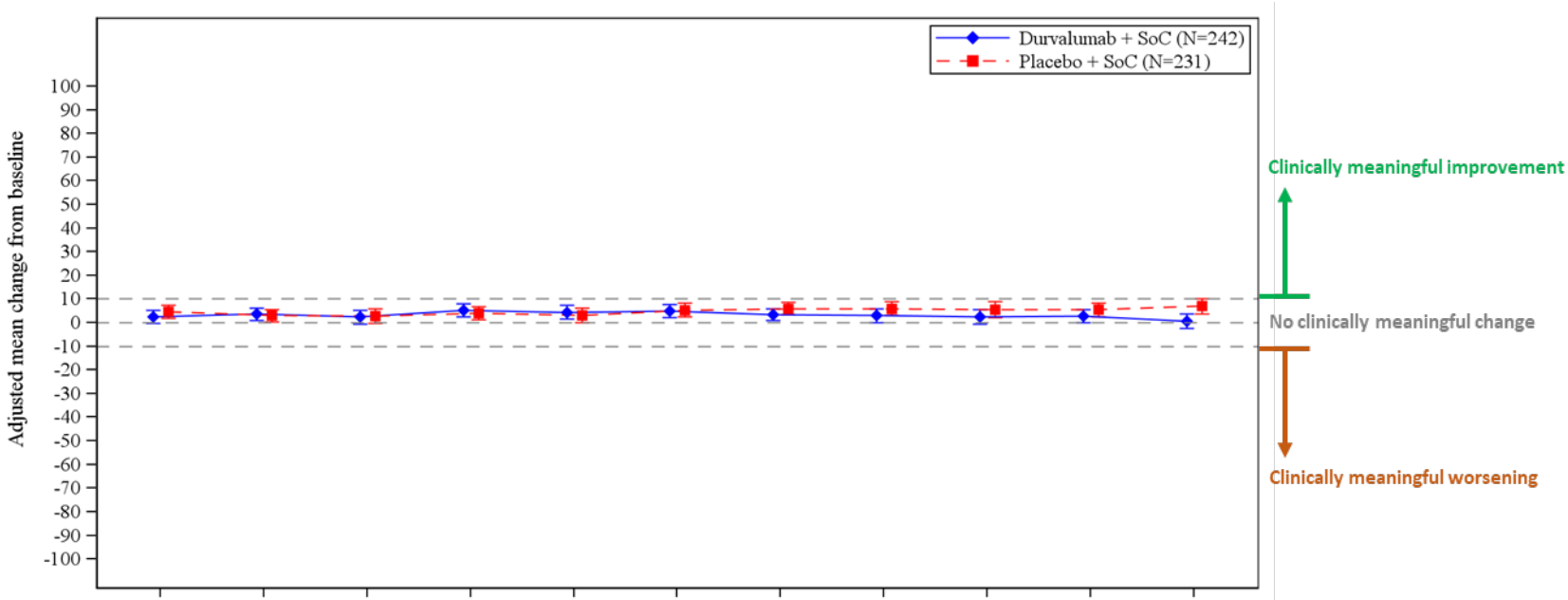


Function – Physical



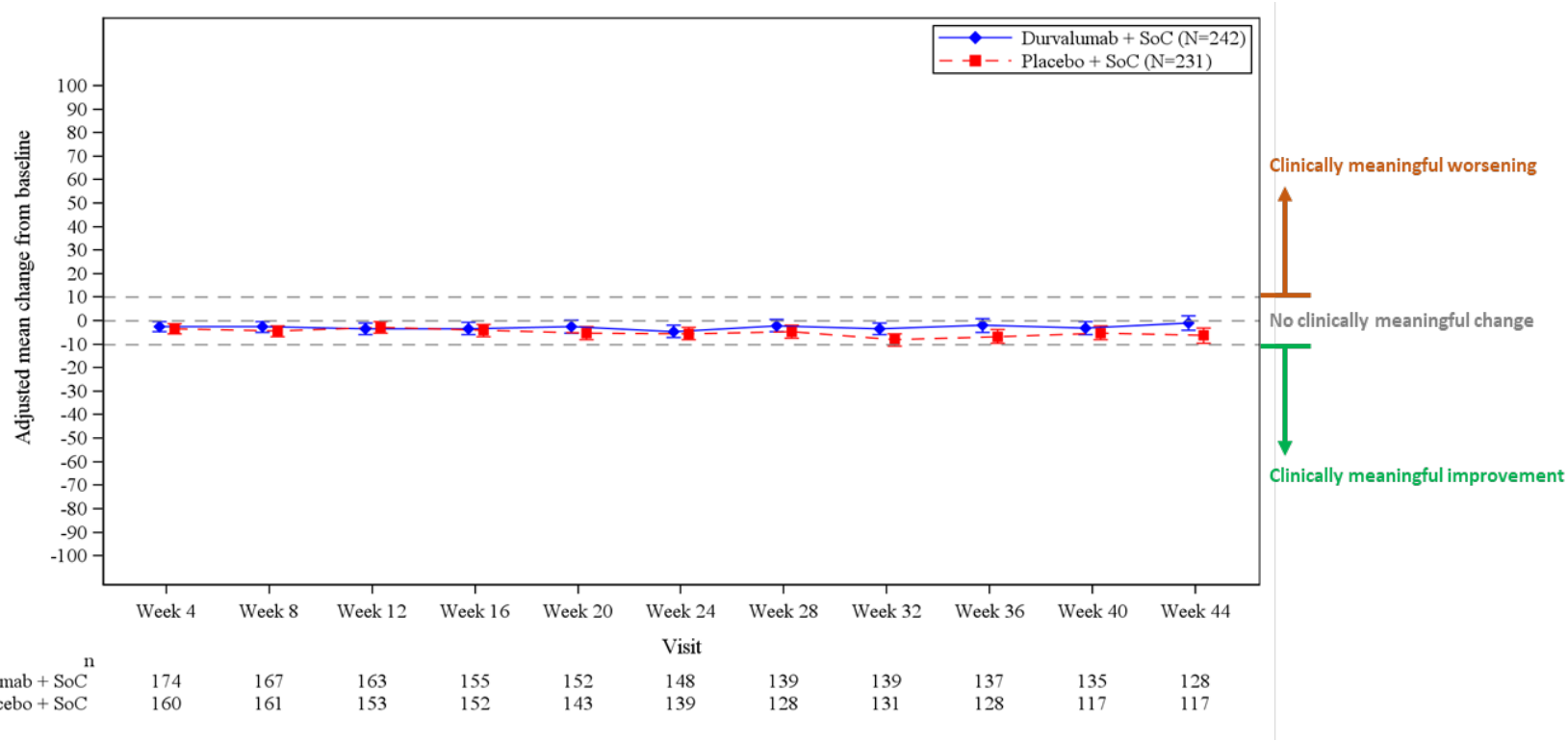
n										
Durvalumab + SoC	174	167	163	155	152	148	139	139	137	135	128
Placebo + SoC	160	161	153	152	143	139	128	131	128	117	117

Function – Role



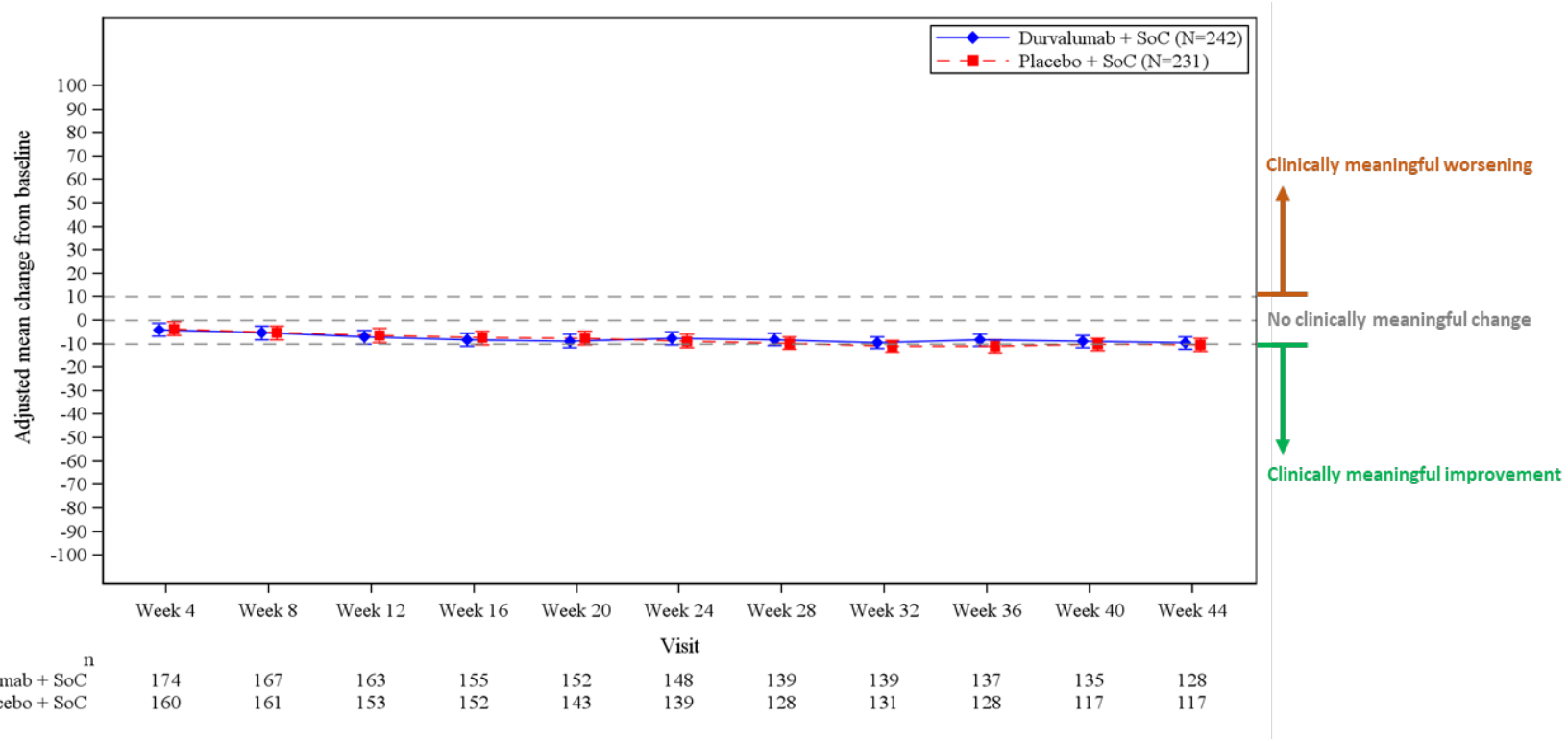
n	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44
Durvalumab + SoC	174	167	163	155	152	148	139	139	137	135	128
Placebo + SoC	160	161	153	152	143	139	128	131	128	117	117

Symptom – Fatigue



n										
Durvalumab + SoC	174	167	163	155	152	148	139	139	137	135	128
Placebo + SoC	160	161	153	152	143	139	128	131	128	117	117

Symptom – Appetite loss



The analysis was performed using a mixed model for repeated measures (MMRM) analysis of change from baseline for all post-baseline adjuvant visits, with treatment, visit, and treatment by visit interaction included as explanatory variables and the baseline score as a covariate. Adjuvant baseline measurement is the latest measurement after surgery but before the first dose of adjuvant treatment. Error bars represent the 95% confidence interval for each respective adjusted mean change from adjuvant baseline. Timepoints are only included if at least 20 patients are present in each treatment group. No adjustments were made for multiplicity in these analyses.
A clinical meaningful change from adjuvant baseline score corresponds to a difference of ≥ 10 points (in either direction, ie. improvement or worsening). Yellow shaded area corresponds to non-meaningful change from adjuvant baseline (difference of < 10 points in either direction).
A higher score on the global measure of health status/quality of life and functioning scales indicates better health status/function, ie. an increase in score is favorable.
Higher scores on symptom scales/items represent greater symptom severity, ie. a decrease in score is favorable.
EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire.
DCO: 10 May 2024 (DCO4).
Source: Figure 14.2.7.11.IA2.