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ORIGINAL ARTICLE

Population pharmacokinetics and exposure–response analysis of durvalumab in patients with resectable stage II to IIIB (N2) NSCLC in the phase III AEGEAN study

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Aims: In the AEGEAN study, perioperative durvalumab plus platinum-based neoadjuvant chemotherapy for patients with resectable stage II to IIIB (N2) non-small-cell lung cancer (NSCLC) demonstrated a favourable benefit–risk profile. This study evaluated population pharmacokinetics (PopPK) and exposure–response (ER) relationships of durvalumab in patients with resectable NSCLC.

Methods: The durvalumab PopPK model was updated by integrating PK data from the AEGEAN study. Individual exposure metrics were derived from empirical Bayes estimates for ER analyses relating to safety (adverse events [AEs]) and efficacy (pathological complete response [pCR] and event-free survival [EFS]).

Results: A two-compartment model with a time-dependent clearance adequately characterized durvalumab PK data. The typical parameter estimates clearance, central and peripheral volume of distribution were 0.285 L/day (relative standard error: 1.68%), 3.42 L (0.962%) and 2.30 L (2.09%), respectively. All identified covariates caused ≤21% of change on durvalumab PK parameters, indicating no meaningful impact on durvalumab exposure. At the plateaued dose level of durvalumab 1500 mg, a flat relationship was observed between durvalumab PK exposure and EFS, confirmed by Cox proportional hazards analysis, and pCR, confirmed by logistic regression analysis. Logistic regression analysis indicated that no clinically relevant relationships were observed between durvalumab PK exposure and safety endpoints, including grade ≥3 treatment-related AEs, grade ≥3 treatment-related AEs of special interest, and AEs leading to treatment discontinuation.

Conclusions: These results support the novel perioperative durvalumab regimen for patients with resectable NSCLC from the AEGEAN study, and no dose adjustment is necessary based on the PopPK and ER analyses.

KEYWORDS
anticancer drugs, clinical trials, immunotherapy, pharmacokinetics, population analysis

1 | INTRODUCTION

While the primary treatment for resectable early-stage non-small-cell lung cancer (NSCLC; stage I to IIIB) is curative surgery, the 5-year survival rate for patients treated with surgery alone remains low, ranging from 67% (stage IA) to 23% (stage IIIA).[1] Studies of adjuvant chemotherapy in this setting have demonstrated modest but clinically meaningful improvement in overall survival (OS), with toxicities of grade ≥3 observed in over half of patients.[2,3] Other studies have demonstrated the clinical benefit of neoadjuvant chemotherapy in early-stage NSCLC.[4–7] Despite these encouraging results, further improvement is needed. Early studies of immunotherapy with or without chemotherapy in the neoadjuvant setting in patients with resectable NSCLC have shown promising clinical activity and acceptable safety profiles.[8–10]

Durvalumab (IMFINZI®), a monoclonal antibody targeting **programmed death-ligand 1** (PD-L1), is an immunotherapy approved as a single agent for treatment of adults with unresectable stage III NSCLC or limited-stage small-cell lung cancer (SCLC); in combination with tremelimumab and platinum-based chemotherapy in patients with metastatic NSCLC without sensitizing **epidermal growth factor receptor** (*EGFR*) mutations or **ALK receptor tyrosine kinase** (*ALK*) genomic tumour aberrations; in combination with etoposide and carboplatin or cisplatin for extensive-stage SCLC in adults; in combination with gemcitabine and cisplatin for treatment of adults with locally advanced or metastatic biliary tract cancer (BTC); in combination with tremelimumab for treatment of adults with unresectable hepatocellular carcinoma; and in combination with carboplatin and paclitaxel followed by durvalumab as a single agent for treatment of adults with primary advanced or recurrent endometrial cancer that is mismatch repair deficient.[11] One goal of combining immunotherapy with chemotherapy is to utilize agents that affect cancer cells by different mechanisms, thus reducing risk of developing resistance.

AEGEAN was a phase III randomized, double-blind, placebo-controlled, global study evaluating the addition of perioperative durvalumab *vs.* placebo to neoadjuvant chemotherapy and surgery for patients with resectable stage II to IIIB (N2) NSCLC.[12] The addition of durvalumab to neoadjuvant chemotherapy resulted in statistically significant improvement in pathological complete response (pCR) *vs.* placebo plus neoadjuvant chemotherapy (pCR final analysis: 17.2% *vs.* 4.3%). AEGEAN also demonstrated that treatment with neoadjuvant chemotherapy plus perioperative durvalumab resulted in a statistically significant, clinically meaningful and sustained improvement in event-free survival (EFS; using blinded independent central review per Response Evaluation Criteria in Solid Tumors version 1.1) *vs.* neoadjuvant chemotherapy plus perioperative placebo; the hazard ratio (HR) corresponded to a 32% overall reduction in the risk of an EFS event (stratified HR = 0.68; 95% confidence interval [CI], 0.53, 0.88), with consistent results at the second interim analysis.[13] Subsequently, perioperative durvalumab for patients with resectable NSCLC has been approved in many countries and regions including the US, UK, Switzerland, China, Taiwan, South Korea and India.[11]

What is already known about this subject

- In the AEGEAN study, the combination of perioperative durvalumab plus neoadjuvant chemotherapy demonstrated a favourable risk–benefit profile *vs.* perioperative placebo plus neoadjuvant chemotherapy among patients with resectable stage II to IIIB (N2) non-small-cell lung cancer (NSCLC).
- Previous studies have characterized the population pharmacokinetics (PopPK) of durvalumab monotherapy.
- Given existing and anticipated approvals for combination regimens that include durvalumab, updated analyses addressing the PopPK of durvalumab in combination with other agents are warranted.

What this study adds

- The previous PopPK model was updated to include data from the AEGEAN study.
- At the plateaued dose level of durvalumab 1500 mg every 3 weeks, a flat relationship was observed between durvalumab PK exposure and event-free survival, and no clinically relevant relationships were observed between durvalumab PK exposure and selected safety endpoints.
- These results support the novel perioperative durvalumab regimen for patients with resectable NSCLC from the AEGEAN study, and no dose adjustment is necessary based on the PopPK and exposure–response analyses.

Understanding the human pharmacokinetics of agents like durvalumab is crucial to optimizing doses, thereby achieving improved clinical outcomes, and minimizing adverse events. To this end, a population pharmacokinetics (PopPK) model for durvalumab monotherapy was first developed and validated based on data from two durvalumab monotherapy studies (Study 1108 [NCT01693562][14] and ATLANTIC [NCT02087423][15]). A two-compartment PopPK model with both linear and nonlinear eliminations was initially developed; this initial model adequately described durvalumab PK profiles from these two studies and was documented in the original durvalumab PopPK report.[16] Several statistically significant covariates were identified with this model, most notably a positive association between tumour burden and durvalumab clearance potentially driven by the effects of cancer-related inflammation on non-specific protein catabolism.[16] However, none of these associations, including for tumour burden, were considered clinically relevant, as their effects on PK parameters did not exceed a predefined threshold of ≥30% change.[16] Importantly, while the data used to create this model were derived from studies using weight-based dosing, simulations showed that a flat-dosing regimen provided comparable median steady-state exposure to the

weight-based regimens approved at the time, suggesting that flat dosing could be a practical alternative in clinical practice.[16]

The durvalumab PopPK model was later amended to a two-compartment model with linear elimination and a time-varying clearance (CL) equation at doses ≥10 mg/kg every 2 weeks (Q2W) or equivalent intravenous (IV) infusion in a post hoc analysis. Subsequently, this amended model was externally validated against data from PACIFIC (NCT02125461[17]) and CASPIAN (NCT03043872[18]). The durvalumab PopPK model was then updated by including all studies in previous PopPK models (Study 1108, ATLANTIC, PACIFIC and CASPIAN) and data from POSEIDON (NCT03164616).[19,20] Notably, this version of the model was based on both weight-based and fixed-dosing regimens.[20] As with the original model, several statistically significant covariates were identified using this model, but none were considered clinically relevant given effects on exposure metrics of <20% change.[20] Furthermore, exposure–response (ER) analyses found that none of the studied durvalumab exposure metrics showed a relationship with either OS or progression-free survival (PFS) at the doses studied.[20] In the current study, the most recent durvalumab PopPK model, based on five previous clinical studies, was further updated by including data from the AEGEAN study.[12,20]

The objective of the analysis reported here was to evaluate the PK of durvalumab, any covariates that might impact PK, and the relationships between durvalumab PK exposure and efficacy and safety in patients treated with four cycles of durvalumab 1500 mg + platinum-based chemotherapy (Q3W) before surgery followed by 12 cycles of durvalumab 1500 mg (Q4W) post-surgery in the AEGEAN trial.

2 | METHODS

2.1 | Study design and patients

AEGEAN was a phase III randomized, double-blind, placebo-controlled, global study for patients with resectable stage II to IIIB (N2) NSCLC (ClinicalTrials.gov identifier: NCT03800134). Patients were planned to receive four cycles of durvalumab 1500 mg or placebo plus platinum-based chemotherapy Q3W (neoadjuvant treatment) followed by surgery, and an additional 12 cycles of durvalumab 1500 mg or placebo Q4W post-surgery (adjuvant treatment). AEGEAN was conducted in accordance with the Declaration of Helsinki and was consistent with International Conference on Harmonization and Good Clinical Practice guidelines and applicable regulatory requirements. The protocol and all amendments were approved by the relevant ethics committees or institutional review boards, as previously described.[12] Written informed consent from participants was obtained before performing any protocol-related procedures.

2.2 | Bioanalytical methods

Serum samples for determination of durvalumab concentrations in the AEGEAN study were analysed by validated bioanalytical methods BAL-17-078-230 (BioAgilytix Labs, Durham, NC, USA) and ICSH 16–032 (Labcorp-Shanghai, Shanghai, China) utilizing an electrochemiluminescence (ECL) assay format with a lower limit to upper limit of quantification (LLOQ–ULOQ) range of 0.05–3.2 μg/mL for durvalumab. The cross-validation was conducted between methods, and all results had a coefficient of variation percentage of <20%, which meets the requirements from health authorities.

A three-tiered testing approach, which consisted of validated assays for detection (screening assay), specificity (confirmation assay) and characterization (titre assay), was used for the assessment of anti-drug antibody (ADA) responses to durvalumab. Confirmed ADA-positive samples were subsequently tested for in vitro neutralizing activity, as assessed by neutralizing antibody assay(s). For all assays, cut points were derived using treatment-naïve individual human serum from indications for the study, as appropriate.

2.3 | Population PK model

The durvalumab PopPK model was developed based on studies in which durvalumab was administered in patients with urothelial carcinoma, NSCLC, SCLC and other solid tumours. The dataset included five phase I/II/III studies (Study 1108 [NCT01693562],[14] ATLANTIC [NCT02087423],[15] PACIFIC [NCT02125461],[17] CASPIAN [NCT03043872][18] and POSEIDON [NCT03164616][19] used in previous PopPK analyses,[16,20] with the addition of AEGEAN. Individuals were defined as evaluable for PopPK analysis if they had at least one post-dose sample that was above the LLOQ. An overview of studies and PK sampling included in the pooled durvalumab PK dataset is provided in Table S1.

The previously developed durvalumab PopPK model[20] was developed using a stepwise covariate search, adding or removing covariates including demographic factors (bodyweight [WT], age, sex, race and region), renal (creatinine clearance [CRCL]) and hepatic (NCI-ODWG criteria [HINCI]) function, performance status (Eastern Cooperative Oncology Group [ECOG]), and other lab variables. This previously developed model[20] was used as a starting model, with the same structure and covariate relationships (initial full covariate model), and was further updated with additional data from AEGEAN. As the first step in the covariate model building, all covariates included in the initial full covariate model were removed one by one to assess their significance ($P < 0.001$) to reach a statistically parsimonious model. In the second step, additional covariates of interest (race [White, Asian and others; Non-Asian, Asian; Chinese *vs.* non-Chinese], region and tumour type) were tested by including them via stepwise addition. Model refinements were considered as needed and indicated through goodness-of-fit (GOF) plots, parameter precision and model stability. Model discrimination was based on inspection of graphical diagnostics and changes in objective function value, approximated via chi-square distribution ($P < 0.001$). The first-order conditional estimation method with interaction (FOCE-I) was used to estimate parameters. The adequacy of the final model and parameter estimates was investigated with a prediction-corrected visual predictive check (pcVPC) method. A

non-parametric bootstrap, with replacement and stratification by study, with 1000 replicates, was generated for the final model to obtain an alternative measure of uncertainty in population parameter estimates.

Exposure metrics were derived using simulated durvalumab time course PK profiles based on individual empirical Bayes' estimates (EBEs) following administration of 1500 mg durvalumab Q3W for four cycles. The following exposure metrics were calculated for durvalumab: area under the serum concentration *vs*. time curve from time 0 to the end of dosing interval following the first dose (AUC_{1d}) and at steady state (AUC_{ss}), maximum concentration following the first dose (C_{max}, dose 1) and at steady state (C_{max},ss), and trough concentration following the first dosing cycle (C_{min}, dose 1) and at steady state (C_{min},ss). The first dose was defined as the first administered dose prior to surgery and steady state at neoadjuvant phase was defined as the fourth Q3W administered dose prior to surgery (i.e., the last administered dose prior to surgery). AUC values were obtained by integrating concentrations over time by dosing intervals. The simulated exposure metrics described above were merged into the efficacy and safety datasets for the exposure–response analysis.

2.4 | Exposure–response models

The relationship between durvalumab exposure (AUC_{1d}, AUC_{ss}, C_{max}, dose 1, C_{max},ss, C_{min}, dose 1 and C_{min},ss) and efficacy/safety variables were explored only for data obtained from the AEGEAN study. All patients in AEGEAN for which durvalumab exposure information could be computed from the PopPK model were included in the efficacy/safety population.

2.4.1 | Exposure–efficacy (EFS) model

EFS (EFS interim analysis 2 [IA2]; 39% maturity; data cutoff [DCO] date of 10 May 2024) was evaluated with Kaplan–Meier (KM) plots stratified by quartiles of exposure to durvalumab in all patients. Placebo treatment was included in KM plots as control. Cox proportional hazard (Cox PH) models without exposure metrics or covariates were developed for EFS as the base model, and stepwise selection was performed on the durvalumab arm only ($n = 353$). The factors considered for inclusion in the base model included durvalumab exposure metrics (listed above), as well as covariates of clinical interest (e.g., race, region), baseline covariates and development of treatment-emergent anti-drug antibody (TEADA). Exposure metrics and covariates of clinical interest were tested using a forward-addition and backward-elimination method, with significance thresholds of $P < 0.01$ and $P < 0.001$, respectively, when tested univariately (likelihood ratio test).

2.4.2 | Exposure–efficacy (pCR) model

The relationship between durvalumab exposure and pCR (pCR final analysis; DCO date of 10 November 2022) was evaluated using boxplots by pCR category. The probability of response was plotted *vs*. exposure quantiles. Binary logistic regression was used to further characterize the relationship between durvalumab exposure and pCR.

2.4.3 | Exposure–safety models

The relationships between durvalumab exposure and safety endpoints (grade ≥3 treatment-related adverse events [AEs], grade ≥3 treatment-related AEs of special interest [AESI], and AEs leading to treatment discontinuation; DCO date of 10 May 2024) were evaluated using boxplots by AE category. The probability for each AE category was plotted *vs*. exposure, after grouping patients according to durvalumab exposure quartiles. Binary logistic regression was used to characterize durvalumab exposure–safety relationships. All predefined exposure metrics were evaluated on all safety variables.

2.5 | Software

PopPK analysis was implemented by nonlinear mixed effects modelling software (NONMEM) version 7.3.0 (Icon Development Solutions, Ellicott City, MD, USA). R version 4.1.0 and above (R project, www.rproject.org) and the R package Xpose (xpose.sourceforge.net), as well as Perl speaks NONMEM (PsN) version 4.4.8 (psn.sourceforge.net), were used for exploratory analysis, executing NONMEM runs and post processing of NONMEM output (e.g., to assess goodness of fit). R was used for the exposure–response analysis.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.[21]

3 | RESULTS

3.1 | Datasets and patient characteristics

There were 2827 and 385 evaluable patients from previous datasets and AEGEAN, respectively, resulting in 3212 patients in the current dataset. Seven patients were excluded due to physiologically impossible covariate values in previous analyses. A total of 145 below the LLOQ samples (1.16%) were excluded from the current analysis. Eventually, 12 466 PK samples from 3205 patients treated with durvalumab were available in the final dataset for analysis.

Tables 1 and 2 summarize the continuous and categorical characteristics of the population in the PopPK analysis dataset, including from AEGEAN and previous studies. Summary statistics of the covariates showed consistency between AEGEAN and previous clinical studies,

TABLE 1 Summary of continuous covariates.

	Total	Previous studies[a]	AEGEAN
Sample size			
N	3212	2827	385
Age (years)			
Mean (SD)	62.2 (10.3)	61.9 (10.4)	63.9 (9.19)
Median (IQR)	63.0 (56.0–69.0)	63.0 (56.0–69.0)	65.0 (58.0–70.0)
Min-max	19.0–96.0	19.0–96.0	30.0–88.0
Missing	0 (0%)	0 (0%)	0 (0%)
Bodyweight (kg)			
Mean (SD)	71.3 (16.7)	71.2 (16.7)	71.5 (16.3)
Median (IQR)	69.6 (59.4–81.0)	69.4 (59.3–81.0)	70.0 (60.0–81.0)
Min-max	31.0–175	31.0–175	39.0–152
Missing	4 (0.125%)	4 (0.141%)	0 (0%)
Creatinine clearance (mL/min)			
Mean (SD)	90.7 (33.2)	90.5 (31.6)	91.9 (43.0)
Median (IQR)	85.5 (68.7–107)	85.7 (68.4–106)	84.0 (71.2–108)
Min-max	25.7–718	25.7–279	32.3–718
Missing	65 (2.02%)	63 (2.23%)	2 (0.519%)
Albumin (g/L)			
Mean (SD)	38.4 (5.35)	38.1 (5.31)	40.7 (5.03)
Median (IQR)	39.0 (35.0–42.0)	39.0 (35.0–42.0)	41.0 (38.0–43.4)
Min-max	3.70–78.0	4.10–57.1	3.70–78.0
Missing	72 (2.24%)	71 (2.51%)	1 (0.260%)
Lactate dehydrogenase (U/L)			
Mean (SD)	341 (460)	359 (487)	215 (102)
Median (IQR)	235 (179–368)	247 (186–387)	184 (163–223)
Min-max	4.00–15 800	18.0–15 800	4.00–826
Missing	122 (3.80%)	121 (4.28%)	1 (0.260%)
Aspartate transaminase (AST) (IU/L)			
Mean (SD)	25.0 (18.8)	25.6 (19.7)	21.2 (9.38)
Median (IQR)	20.0 (16.0–27.0)	20.4 (16.0–28.0)	19.0 (15.9–24.0)
Min-max	0–322	0–322	6.00–74.0
Missing	65 (2.02%)	65 (2.30%)	0 (0%)
Alanine transaminase (ALT) (IU/L)			
Mean (SD)	23.0 (18.9)	23.2 (19.5)	21.2 (13.6)
Median (IQR)	18.0 (12.0–27.0)	18.0 (12.0–27.0)	18.0 (13.0–24.0)
Min-max	0–245	0–245	3.60–112
Missing	60 (1.87%)	60 (2.12%)	0 (0%)
Total bilirubin (mg/dL)			
Mean (SD)	0.501 (0.281)	0.495 (0.283)	0.543 (0.265)
Median (IQR)	0.420 (0.300–0.600)	0.410 (0.300–0.600)	0.487 (0.354–0.718)
Min-max	0.0215–3.72	0.0600–3.72	0.0215–1.43
Missing	60 (1.87%)	59 (2.09%)	1 (0.260%)
Neutrophil-to-lymphocyte ratio			
Mean (SD)	4.21 (3.37)	4.41 (3.62)	3.65 (2.46)
Median (IQR)	3.30 (2.37–5.00)	3.46 (2.50–5.20)	2.76 (2.15–4.26)
Min-max	0.00600–58.8	0.00600–58.8	0.744–17.5
Missing	2044 (63.6%)	1968 (69.6%)	76 (19.7%)

Abbreviations: IQR, interquartile range; SD, standard deviation.

[a]Includes Study 1108 (NCT01693562), ATLANTIC (NCT02087423), PACIFIC (NCT02125461), CASPIAN (NCT03043872) and POSEIDON (NCT03164616).

TABLE 2 Summary of categorical covariates.

	Total	Previous studies[a]	AEGEAN
Sample size			
N	3212	2827	385
Sex			
Male	2087 (65.0%)	1837 (65.0%)	250 (64.9%)
Female	1125 (35.0%)	990 (35.0%)	135 (35.1%)
Race			
White	2163 (67.3%)	1956 (69.2%)	207 (53.8%)
Black	75 (2.33%)	70 (2.48%)	5 (1.30%)
Asian	805 (25.1%)	646 (22.9%)	159 (41.3%)
Native Hawaiian or Other Pacific Islander	8 (0.249%)	8 (0.283%)	-
American Indian/Alaskan Native	37 (1.15%)	30 (1.06%)	7 (1.82%)
Other	122 (3.80%)	115 (4.07%)	7 (1.82%)
Multiple	2 (0.0623%)	2 (0.0707%)	-
Region of enrolment			
South America	116 (3.61%)	76 (2.69%)	40 (10.4%)
Africa	25 (0.778%)	25 (0.884%)	-
Asia	726 (22.6%)	568 (20.1%)	158 (41.0%)
Europe	1237 (38.5%)	1096 (38.8%)	141 (36.6%)
North America	1076 (33.5%)	1030 (36.4%)	46 (11.9%)
Other	32 (0.996%)	32 (1.13%)	-
Tumour type			
Other	471 (14.7%)	471 (16.7%)	-
Lung	2550 (79.4%)	2165 (76.6%)	385 (100%)
Bladder	191 (5.95%)	191 (6.76%)	-
Age group			
<65	1781 (55.4%)	1596 (56.5%)	185 (48.1%)
65–75	1109 (34.5%)	954 (33.7%)	155 (40.3%)
≥75	322 (10.0%)	277 (9.80%)	45 (11.7%)
Renal status[b]			
Normal	1380 (43.0%)	1217 (43.0%)	163 (42.3%)
Mild	1305 (40.6%)	1136 (40.2%)	169 (43.9%)
Moderate	464 (14.4%)	411 (14.5%)	53 (13.8%)
Severe	63 (1.96%)	63 (2.23%)	-
ECOG performance status			
Normal activity	1302 (40.5%)	1030 (36.4%)	272 (70.6%)
Restricted activity	1903 (59.2%)	1790 (63.3%)	113 (29.4%)
In bed less than or equal to 50% of the time	3 (0.0934%)	3 (0.106%)	-
Missing	4 (0.125%)	4 (0.141%)	-
Smoking status			
Never	765 (23.8%)	695 (24.6%)	70 (18.2%)
Former	1881 (58.6%)	1659 (58.7%)	222 (57.7%)
Current	557 (17.3%)	464 (16.4%)	93 (24.2%)
Missing	9 (0.280%)	9 (0.318%)	-
Treatment-emergent anti-drug antibody status post-baseline			
Negative	3097 (96.4%)	2737 (96.8%)	360 (93.5%)
Positive	115 (3.58%)	90 (3.18%)	25 (6.49%)

TABLE 2 (Continued)

	Total	Previous studies[a]	AEGEAN
Primary indication			
NSCLC	2269 (70.6%)	1884 (66.6%)	385 (100%)
Advanced solid tumour	662 (20.6%)	662 (23.4%)	-
SCLC	281 (8.75%)	281 (9.94%)	-
NCI Scale: hepatic function			
Normal	2775 (86.4%)	2433 (86.1%)	342 (88.8%)
Mild	379 (11.8%)	337 (11.9%)	42 (10.9%)
Moderate	14 (0.436%)	14 (0.495%)	-
Severe	1 (0.0311%)	1 (0.0354%)	-
Missing	43 (1.34%)	42 (1.49%)	1 (0.260%)

Abbreviations: CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; NCI, National Cancer Institute; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

[a]Includes Study 1108 (NCT01693562), ATLANTIC (NCT02087423), PACIFIC (NCT02125461), CASPIAN (NCT03043872) and POSEIDON (NCT03164616).

[b]Renal status: "Normal" = CrCl ≥90 mL/min, "Mild" = CrCl ≥60–<90 mL/min, "Moderate" = CrCl ≥30–<60 mL/min and "Severe" = CrCl <30 mL/min.

except for lactate dehydrogenase (LDH); patients in AEGEAN had slightly lower LDH levels than those in previous studies. In addition, a higher percentage of Asian patients and patients with ECOG performance status of 0 were enrolled in AEGEAN *vs*. previous studies.

Table S2 summarizes time-varying covariates of interest in patients from AEGEAN who had covariates information from both neoadjuvant and adjuvant phases. Among 385 evaluable patients in the PK dataset, only 264 patients continued with the adjuvant phase. Summary statistics of time-varying covariates from AEGEAN showed no major difference between the neoadjuvant and adjuvant phase.

Exposure metrics were derived using simulated durvalumab time course PK profiles based on individual EBEs following administration of 1500 mg durvalumab Q3W for four cycles, consistent with the neoadjuvant phase of the AEGEAN regimen.[12] A total of 385 PK evaluable patients in durvalumab arm were analysed in the ER analysis, including 353 who were included in the modified intention-to-treat (mITT) analysis set and were eligible for exposure–efficacy analysis, and 385 who were included in the safety analysis set and were eligible for exposure–safety analysis. Generally, patient characteristics were comparable between the two treatment arms (perioperative durvalumab plus chemotherapy *vs*. placebo plus chemotherapy). Only the durvalumab arm was assessed in this ER analysis, while the placebo arm was included in certain plots for comparison purposes only.

3.2 | Population PK model

A two-compartment model with time-varying clearance that was previously demonstrated to describe concentration–time profiles of durvalumab well was also appropriate for analysis of the pooled PK data, including data from AEGEAN. As the first step in building the covariate model, the significance of all covariates in the previous model except for LDH was confirmed. Then the covariates of race, region and/or tumour type were further tested on selected model parameters, and results suggested that none of them had a significant impact on durvalumab clearance or central volume of distribution (V1). The final model removed the LDH covariate and retained the other covariates from the previous model.

Albumin levels (ALB), CRCL, ECOG performance status, sex, WT and combination therapy were identified as statistically significant covariates on CL. WT and sex had a statistically significant impact on V1.

The relationships between covariates and model parameters are described in the following equations:

$$\begin{aligned} CL_{cat.cov} &= 1_{comb=0}\cdot(1-0.0701_{comb=1})\cdot(1-0.0578_{comb=2})\cdot 1_{ECOGbin=0} \\ &\quad\cdot(1-0.0604_{ECOGbin=1})\cdot 1_{male}\cdot(1-0.166_{female})CL_{cont.cov} \\ &= \left(\frac{alb_i}{39}\right)^{-0.526}\cdot\left(\frac{CrCL_i}{85.66}\right)^{0.112}\cdot\left(\frac{WT_i}{69.4}\right)^{0.378} CL_{T,i} \\ &= 0.285\cdot CL_{cat.cov}.CL_{cont.cov}\cdot exp\left(\frac{-0.412\cdot t}{48+t}\right)\cdot\exp(\eta_i) \end{aligned}$$

where $CL_{cat.cov}$, $CL_{cont.cov}$ and $CL_{T,i}$ represent the impact of categorical and continuous covariates and the individual total CL, including the time-dependent decrease of CL, respectively.

$$V_{c,i} = 3.42\cdot\left(\frac{WT_i}{69.4}\right)^{0.503}\cdot 1_{male}\cdot(1-0.144_{female})$$

Note: alb_i = albumin concentration at baseline in the *i*th individual, $CrCL_i$ = creatinine clearance at baseline in the *i*th individual, WT_i = bodyweight at baseline in the *i*th individual. Definitions for categorical covariates are combination therapy: comb = 0 is durvalumab monotherapy, comb = 1 is durvalumab + standard-of-care (SOC) chemotherapy, comb = 2 is durvalumab + tremelimumab + SOC chemotherapy; ECOG status at baseline: $ECOG_{bin}$ = 0 is normal activity, $ECOG_{bin}$ = 1 is restricted activity or in bed ≤50% of the time; sex: male and female. The reference subject is defined as durvalumab

monotherapy (comb = 0), ECOG normal ($ECOG_{bin} = 0$), male, and with median parameter estimates for continuous covariates.

Parameter estimates for the final model are reported in Table 3. Parameters were well estimated with good precision, and the typical parameter estimates CL, V1 and peripheral volume of distribution (V2) were 0.285 L/day, 3.42 L and 2.30 L, respectively. The relative standard error for model parameters was small overall, and shrinkage was acceptable at <30% except for T_{max}. A non-parametric bootstrap with 1000 replicates was conducted, and results are presented in Table 3. The non-parametric distribution of parameter estimates showed good agreement with the NONMEM estimates.

The goodness of fit plots indicated an adequate description of the data by the model observations *vs.* population, and individual predictions were generally symmetrically distributed around the line of identity (Figure 1A). In addition, the pcVPC showed good agreement between the model prediction and the observed durvalumab concentration (Figure 1B); the limited number of high-concentration observations are due to data variability and had minimal impact on modelling. In summary, the final durvalumab PopPK model described observed durvalumab concentrations adequately for the AEGEAN study and could be reliably used to predict individual durvalumab exposure parameters (AUC, C_{min} or C_{max}) for exposure–response analysis.

The impact of the selected covariates on clearance at steady-state (CL_{ss}) and V1 based on univariate assessment are presented as tornado plots in Figure 1C. Overall, no covariate showed a substantial impact on model parameters CL_{ss} and V1, with the covariate effect being ≤21%. For example, ALB had the most pronounced impact on CL_{ss}, with a maximum change of +21.3% for the 5th percentile of ALB level. The impact of WT on CL_{ss} and V1 was also small, with a maximum change of +15.6% and +21.3% for the 95th percentile of WT, respectively.

TABLE 3 Population PK model parameter estimates.

Parameter	Estimate	RSE (%)	Bootstrap median	Bootstrap 95% CI	Shrinkage (%)	Unit
Population parameter						
CL	0.285	1.68	0.285	[0.270; 0.303]	-	L/day
V1	3.42	0.962	3.42	[3.38; 3.48]	-	L
V2	2.30	2.09	2.30	[2.15; 2.44]	-	L
$Q_{intercompartmental}$	0.381	4.90	0.381	[0.297; 0.465]	-	L/day
T_{max} change CL	−0.412	4.91	−0.414	[−0.465; −0.360]	-	L/day
TC_{50} change CL	48.0	10.9	47.4	[32.8; 71.9]	-	day
LAM change CL	1.00	-	-	-	-	-
Covariate						
Albumin on CL	−0.526	2.88	−0.537	[−0.776; −0.389]	-	-
Creatinine clearance on CL	0.112	19.1	0.111	[0.0699; 0.153]	-	-
ECOG status on CL	−0.0604	19.1	−0.0590	[−0.0836; −0.0325]	-	-
Sex on CL	−0.166	7.40	−0.165	[−0.189; −0.139]	-	-
COMB1 on CL	−0.0701	17.9	−0.0694	[−0.0984; −0.0406]	-	-
COMB 2 on CL	−0.0578	29.0	−0.0561	[−0.108; −0.00867]	-	-
Bodyweight on CL	0.378	9.31	0.382	[0.311; 0.453]	-	-
Sex on V1	−0.144	8.27	−0.143	[−0.166; −0.121]	-	-
Bodyweight on V1	0.503	5.73	0.502	[0.446; 0.558]	-	-
Interindividual variability						
ETA CL	0.0845	3.43	0.0832	[0.0737; 0.0942]	19.4	-
Cov CL-V1	0.0408	5.77	0.0407	[0.0345; 0.0471]	-	-
ETA V1	0.0563	3.74	0.0563	[0.0482; 0.0644]	28.9	-
ETA T_{max}	0.0534	9.53	0.0537	[0.0341; 0.0772]	56.5	-
Residual variability						
Proportional component	0.253	0.627	0.253	[0.245; 0.261]	13.5	-
Additive component	5.38	6.38	5.35	[4.16; 6.80]	13.5	μg/mL

Abbreviations: CI, confidence interval; CL, clearance; COMB1, durvalumab + SOC; COMB2, durvalumab + tremelimumab + SOC; Cov, covariance; ECOG, Eastern Cooperative Oncology Group; ETA, random effect; LAM, Hill factor; PK, pharmacokinetics; $Q_{intercompartmental}$ = intercompartmental clearance; RSE, relative standard error; SOC, standard of care; TC50, time to 50% change of CL over time; T_{max}, maximum change of CL over time; V1, central volume of distribution; V2, peripheral volume of distribution.

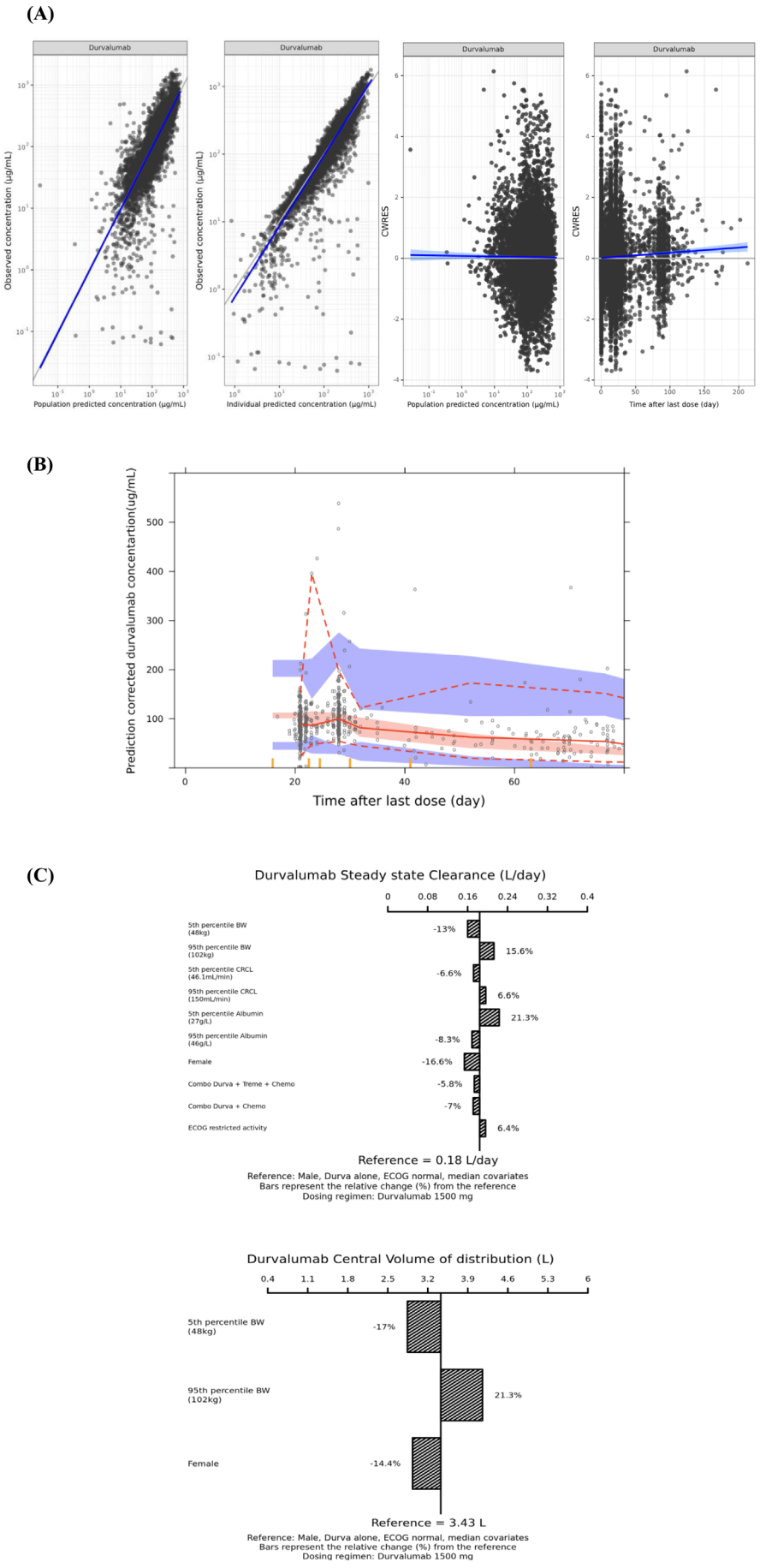

FIGURE 1 Diagnostic plots. (A) Basic goodness of fit plots (all studies). Blue line = trend line through the data points, the blue area is the 95% confidence interval around it. Abbreviations: CWRES, conditional weighted residuals; pcVPC, prediction corrected visual predictive check. (B) pcVPC of the final model *vs.* time after last dose in AEGEAN. Solid and dashed lines = the median, 5th, and 95th percentiles of the observations. Shaded red and blue areas = the 95% confidence interval of the median, 5th and 95th percentiles predicted by the model. Abbreviations: pcVPC, prediction-corrected visual predictive check. (C) Impact of covariates on durvalumab clearance and central volume at steady state – tornado plot. Dashed area = the percentage change of model parameter for the 5th and 95th percentile of the relevant covariates relative to the median parameter estimates (for continuous covariates), or relative to the most frequent category (for categorical covariates). Abbreviations: BW, bodyweight; Chemo, chemotherapy; CRCL, creatinine clearance; Durva, durvalumab; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; Treme, tremelimumab.

3.3 | Covariates of clinical interest

The distributions of AUC_{ss}, C_{max},ss and C_{min},ss were further investigated in AEGEAN patients by covariates of clinical interest, such as TEADA status, WT quartile and Chinese *vs.* non-Chinese race. The number of TEADA-positive patients was small (3.58%) in the PopPK dataset, and TEADA was not evaluated as a covariate. A total of 25 patients were identified as TEADA-positive in the PK dataset from AEGEAN, and their durvalumab exposure, derived from empirical Bayes estimates, was generally comparable to that of TEADA-negative patients with the difference <20% (Figure S3), indicating that durvalumab PK is unlikely to be affected by ADA status. The limited change in AUC per WT quartile (< 25% change as median change for each quartile) illustrated a limited impact of WT on AUC (Table S3). In addition, pcVPC plots stratified by Chinese *vs.* non-Chinese race from AEGEAN showed overall good coverage of simulated 95% prediction intervals to the observed 5th, 50th (median) and 95th percentiles of durvalumab concentrations (Figure S4). PK exposures, as specified by AUC_{ss}, C_{max},ss and C_{min},ss in Chinese patients ($n = 42$) were slightly higher than those in non-Chinese patients ($n = 343$) with the difference <8% (Figure 2 and Table S4), which was partly related to lower WT (Chinese: 66.1 kg *vs.* non-Chinese: 70.2 kg); this difference was not considered clinically relevant. The impact of other covariates, including age categories (<65 years, between 65 and 75 years, >75 years), renal and hepatic function (normal, mild and moderate), race, region, sex and ECOG performance status, on durvalumab exposure were also investigated. Overall, none of the investigated covariates were considered to have a significant effect on durvalumab exposure.

3.4 | Exposure–response analysis

Figure 3 shows EFS KM curves in patients receiving durvalumab stratified by model-predicted exposure metrics and overlaid with data from patients in the placebo arm. In these plots, there was separation between the durvalumab and placebo arms. There was no clear trend between EFS and durvalumab exposure at the effectively plateaued dose level of durvalumab 1500 mg, and the exposure quartiles overlapped with each other. Furthermore, a Cox PH model for EFS was developed based on durvalumab-treated patients from AEGEAN. Covariates of clinical interest such as demographic characteristics (e.g., race, region), baseline covariates, development of TEADA and exposure metrics were tested using a forward inclusion method and with a significance threshold of $P < 0.01$. Detailed steps can be found in Table S5. Following the likelihood ratio test, none of the investigated covariates were identified as significant covariates in the model. Overall, no covariate was found to be related to EFS in this analysis.

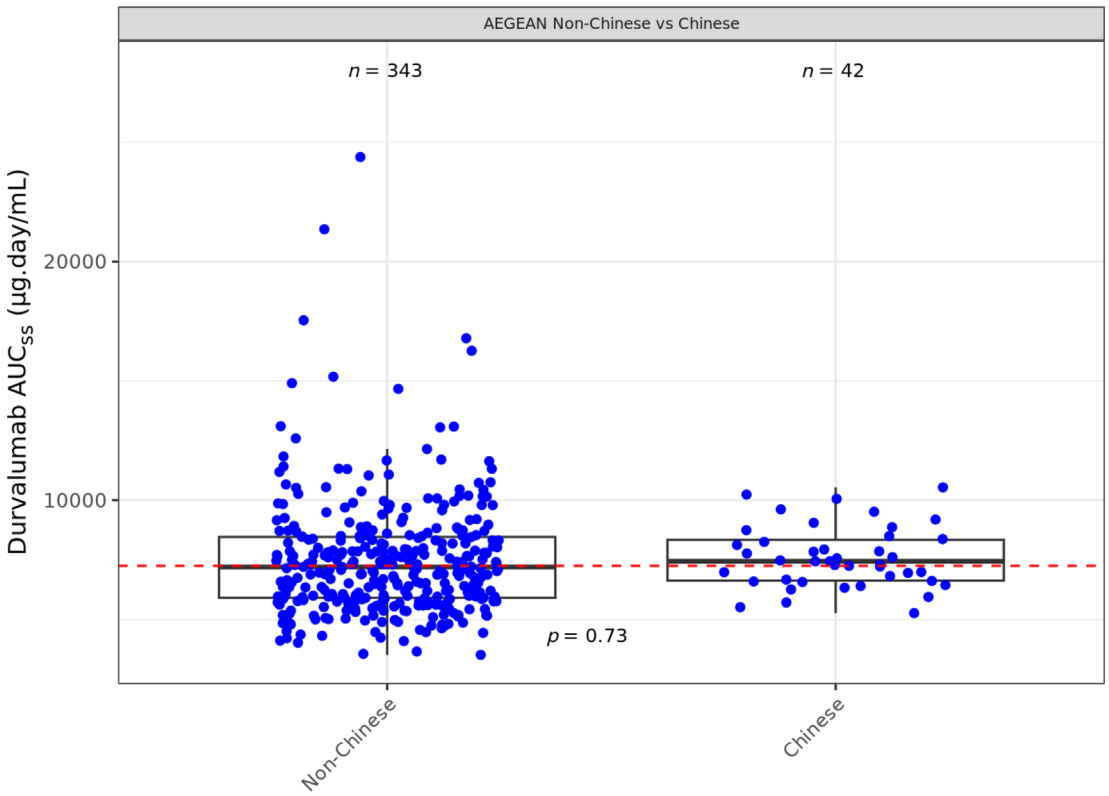

FIGURE 2 Durvalumab exposure by non-Chinese and Chinese patients (AEGEAN study). Blue dots = the simulated PK exposure parameter based on PopPK model. Black solid lines = the median of the observations, the lower and upper parts of the boxplot are 25% and 75% of the distribution. Lower and upper lines = the median −1.5 IQR and median + 1.5 IQR, respectively. *P*-value calculated from *t*-test. Abbreviations: AUC, area under the serum concentration–time curve; PK, pharmacokinetic; PopPK, population pharmacokinetics.

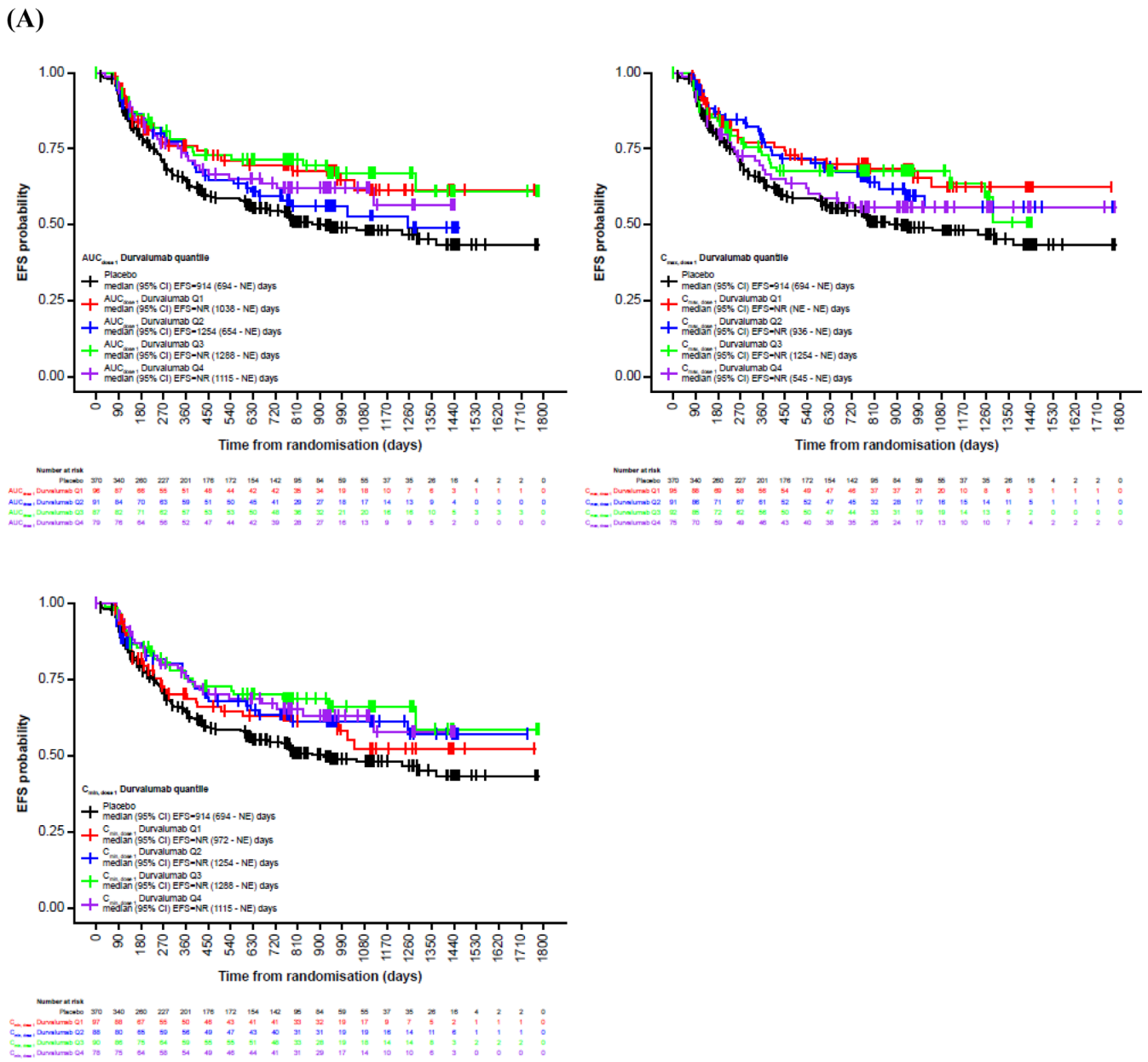

FIGURE 3 EFS Kaplan–Meier plots for durvalumab exposure metrics by quartiles at dose 1 (A) and steady state (B). Abbreviations: AUC, area under the serum concentration–time curve; AUC, dose 1, AUC from time 0 to the end of dosing interval following the first dose; AUC_{ss}, AUC at steady state; C_{max}, maximum concentration; C_{max}, dose 1, C_{max} following the first dose; C_{max},ss, C_{max} at steady state; C_{min}, trough concentration; C_{min}, dose 1, C_{min} following the first dosing cycle; C_{min},ss, C_{min} at steady state; CI, confidence interval; EFS, event-free survival; QX, quartile X.

Overall, 62 of 353 evaluable patients were considered to have pCR. Safety endpoints of interest were grade ≥3 treatment-related AEs, grade ≥3 treatment-related AESIs, and AEs leading to durvalumab discontinuation. Distribution of AUC1d of durvalumab in patients with and without pCR/safety endpoints are shown in Figure 4. Distributions of AUC_{ss} for durvalumab in patients with and without pCR/safety endpoints are presented in Figure S1. These distribution plots suggested a flat relationship between durvalumab exposure and pCR at the effectively plateaued dose level of durvalumab 1500 mg. All these distribution plots suggested no clear relationship between durvalumab exposure and safety parameters.

Relationships between durvalumab exposure and pCR/safety endpoints were further analysed using a logistic regression model relating the probability of being a responder or experiencing a particular safety endpoint to durvalumab exposure metrics. The probabilities of pCR or having grade ≥3 treatment-related AEs, calculated in quartiles of the AUC1d and AUC_{ss} for durvalumab, are shown in Figure 5. Relationships between having grade ≥3 treatment-related AESIs or having AEs leading to durvalumab treatment discontinuation and AUC1d or AUC_{ss} for durvalumab are shown in Figure S2. Logistic regression results assessing the impact of exposure on the probability of pCR or safety parameters demonstrated that *P*-values associated

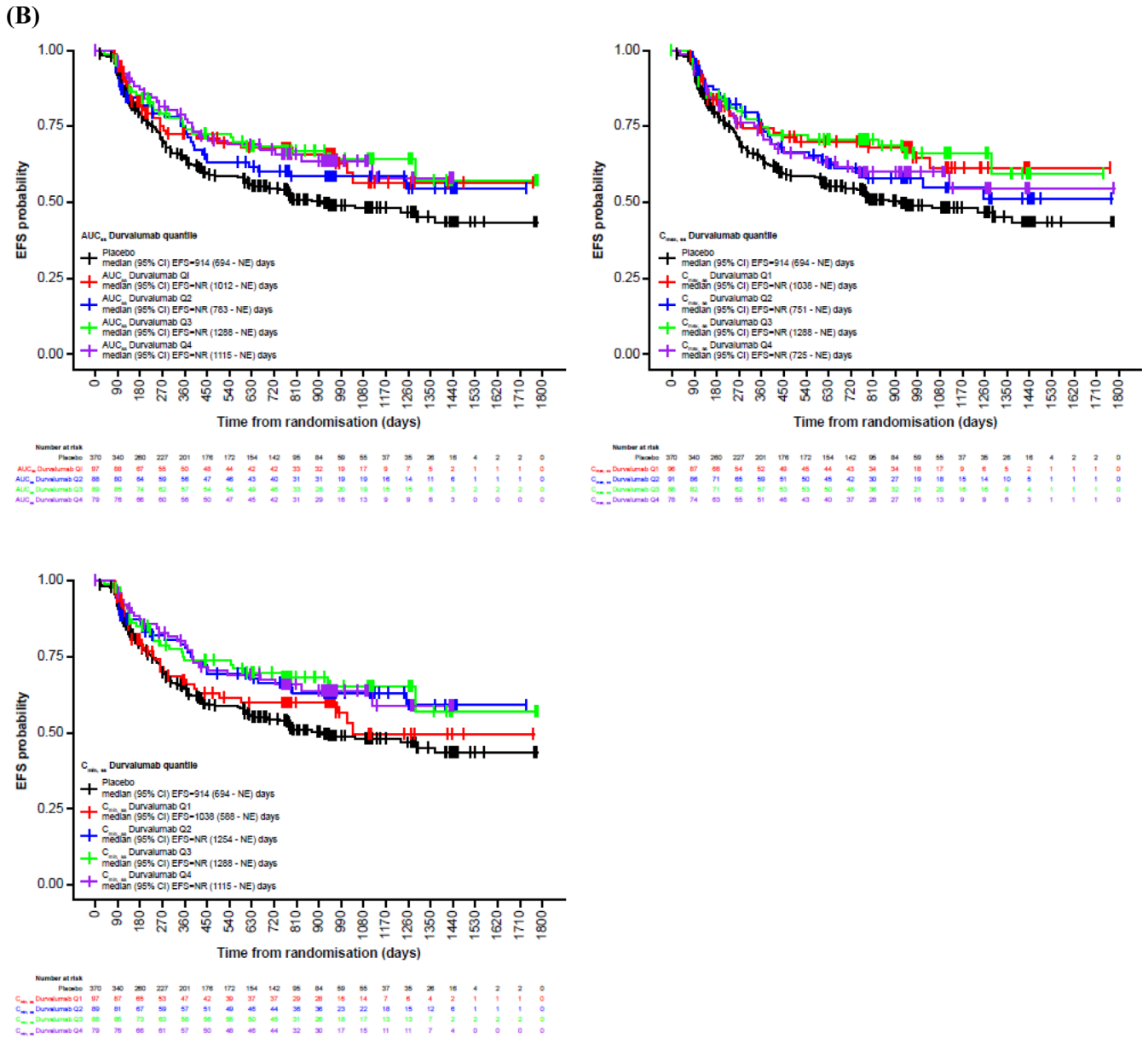

FIGURE 3 (Continued)

with exposure effects were relatively large (*vs.* the pre-specified significance level of $\alpha = 0.001$), with the *P*-values range being 0.202–0.971 for pCR (Table S6) and 0.210–0.979 for safety endpoints (Tables S7, S8 and S9), indicating that the relationship(s) were not statistically significant. Other exposure matrices (e.g., C_{max}, C_{min}) were also included in the ER analysis and demonstrated the same outcomes as AUC (data not shown).

4 | DISCUSSION

This analysis evaluated the PopPK and ER relationships of durvalumab in patients with stage II to IIIB (N2) NSCLC from the phase III AEGEAN study. A two-compartmental model with time-varying clearance that was previously demonstrated to describe concentration–time profiles of durvalumab well was also appropriate for the analysis of the pooled PK data, including data from AEGEAN. In this PopPK analysis, the typical clearance and V1 were 0.285 L/day and 3.42 L, respectively, close to those of the previous model (0.297 L/day and 3.40 L).[20] The time-dependent clearance suggests that clearance could decrease by a maximum of 34%, which is still similar to the previous model (37%).[20] ALB, CRCL, ECOG performance status, sex, WT and combination therapy were identified as statistically significant covariates for clearance. WT and sex had a statistically significant impact on V1. When assessing the impact of the included covariates using a univariate approach, the magnitude of covariate effects on CL_{ss} and V1 were ≤21%. The most pronounced covariate effects were ALB (5th percentile value) on CL_{ss} (+21.3%), and WT

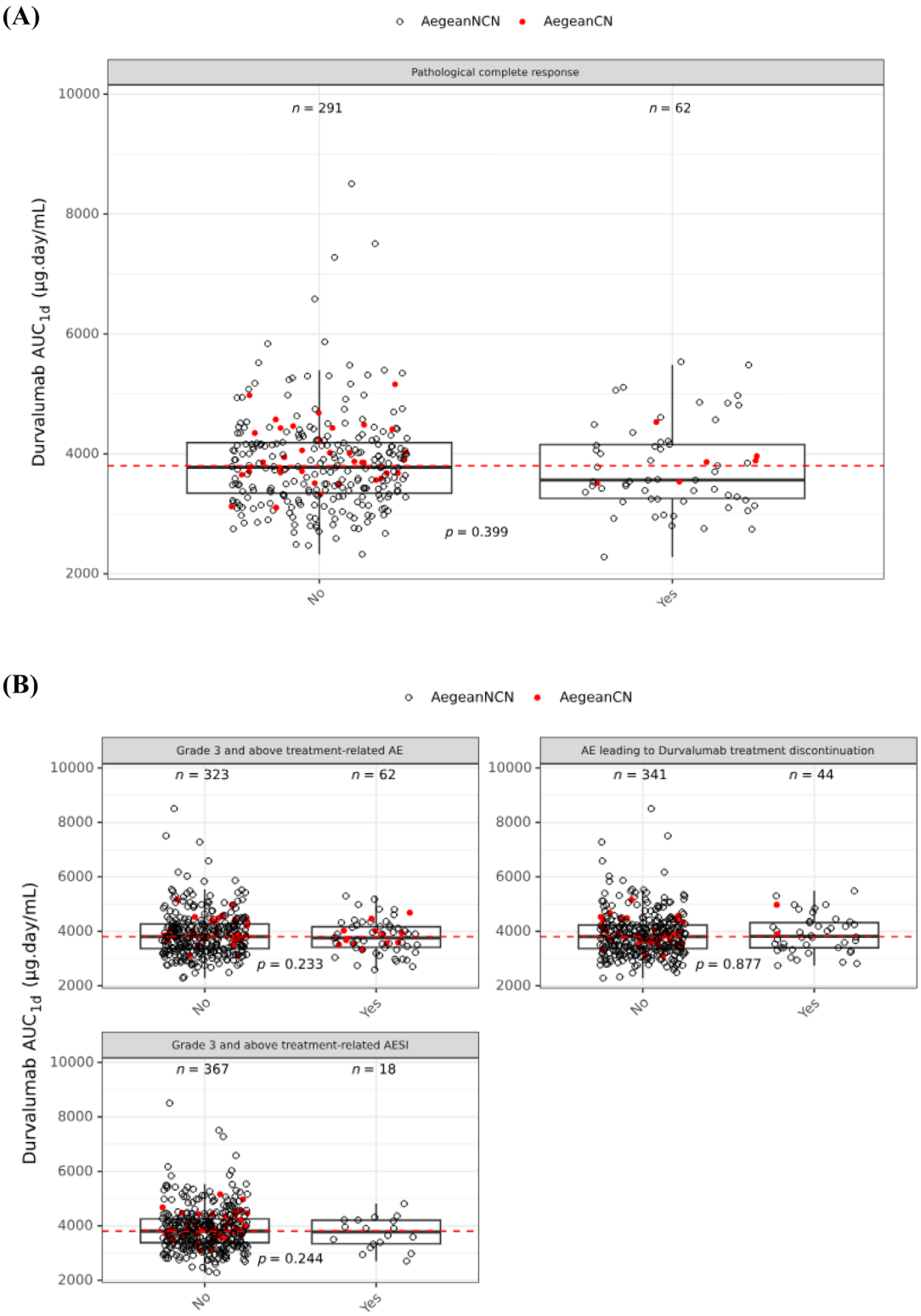

FIGURE 4 Distribution of AUCdose 1 (AUC1d) after first dose of durvalumab in patients with (yes) and without (no) pCR (A) /specified AEs (B). Black hollow circles = values observed in non-Chinese (NCN) patients. Red dots = values observed in Chinese (CN) patients. The dark line is the median, the lower and upper part of the box are 25% and 75% percentile of the distribution, and the lower and upper whiskers are the median−1.5 IQR and median+1.5 IQR. *P*-values calculated from *t*-test. Abbreviations: AE, adverse event; AUC, area under the serum concentration−time curve; AUC1d, AUC from time 0 to the end of dosing interval following the first dose; pCR, pathological complete response; IQR, interquartile range.

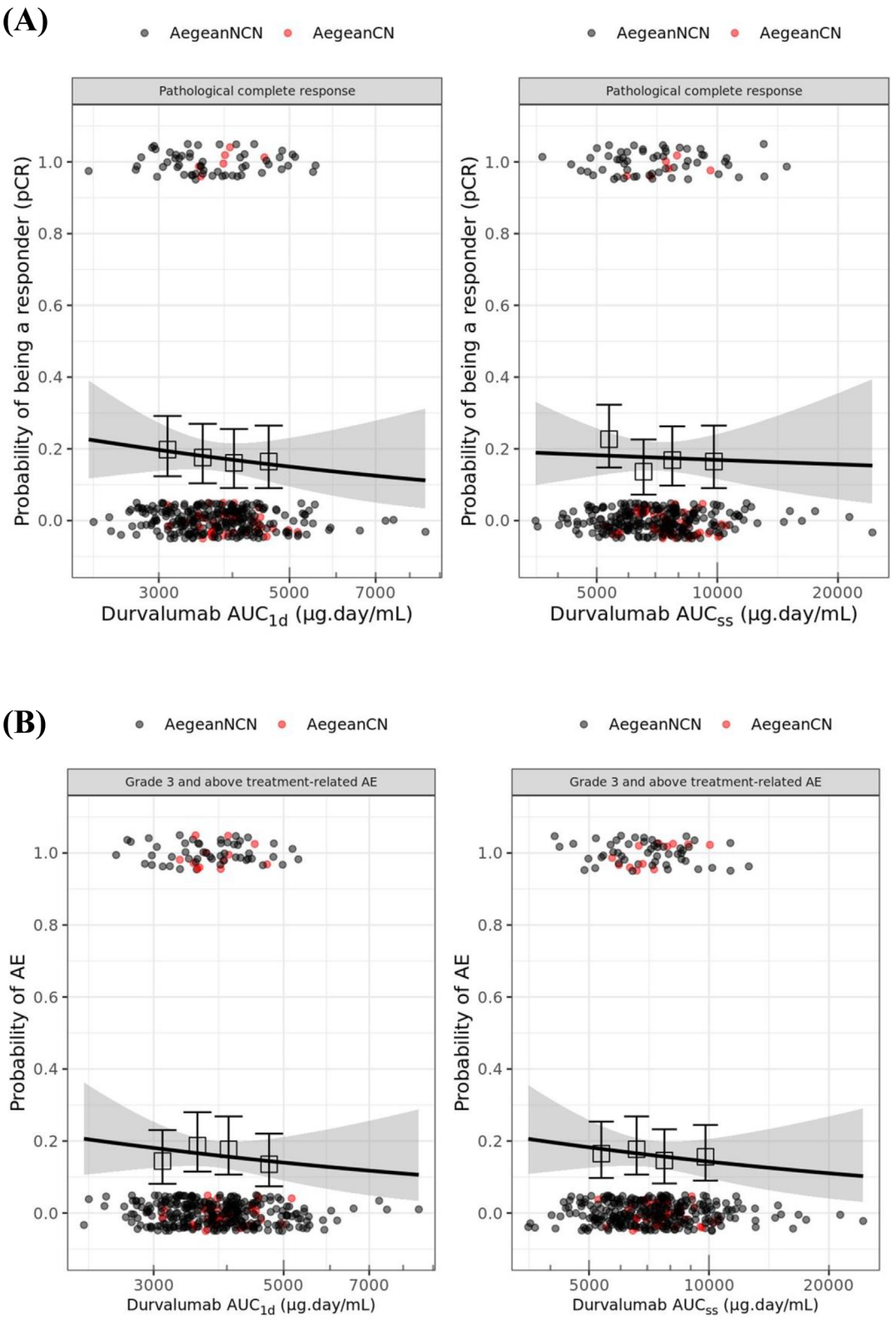

FIGURE 5 Relationship between the probability of pCR (A) /having grade ≥3 treatment-related AEs (B) and AUCdose 1 (AUC1d) or steady state (AUC_{ss}) for durvalumab. Black solid circles = observed pCR/AE in non-Chinese (NCN) patients. Red solid circles = the observed pCR/AE in Chinese (CN) patients. Open squares with error bars are the observed probability of response at each exposure quartile. Black lines = the logistic regression between two variables. The grey area represents the associated confidence interval. Abbreviations: AE, adverse event; AUC, area under the serum concentration–time curve; AUC1d, AUC from time 0 to the end of dosing interval following the first dose; AUC_{ss}, AUC at steady state; pCR, pathological complete response.

(95th percentile value) on V1 (+21.3%). Based on this finding, despite the statistical significance of these covariates, no covariate was regarded as of clinical relevance as the covariate effects on durvalumab PK exposure were ≤21% and there were no apparent exposure–efficacy/safety relationships at the effectively plateaued dose level of durvalumab 1500 mg in multiple studies.

The dosing regimen of durvalumab 1500 mg Q3W during the neoadjuvant phase aligns with the standard chemotherapy schedule for this disease setting (Q3W for four cycles), and PopPK modelling predicted that a Q3W regimen would yield similar exposures to Q4W; durvalumab is expected to yield a slightly higher C_{max} and C_{min} on a 3-week schedule, but a lower AUC_{tau} (data on file). Therefore, PK modelling suggests that when durvalumab 1500 mg Q3W is used for limited cycles in combination with other agents (e.g., chemotherapies), a Q3W schedule does not impose a significant increased safety risk based on expected durvalumab exposures.[22] Consistent with this finding, similar dosing regimens (e.g., durvalumab 1500 mg Q3W combined with chemotherapy) have already been approved in other settings such as early-stage SCLC and locally advanced or metastatic BTC.[11,23]

In the AEGEAN study, for patients randomized to the durvalumab arm, the dosing regimen was 1500 mg durvalumab Q3W for four cycles prior to surgery (neoadjuvant phase in combination with platinum-based chemotherapy), then 1500 mg Q4W for 12 cycles post-surgery (adjuvant phase as monotherapy). After receiving four cycles of 1500 mg durvalumab Q3W prior to surgery, patients had no further neoadjuvant durvalumab treatment and instead proceeded to surgical resection. Only patients who completed surgery and met certain criteria after surgery were eligible to receive adjuvant durvalumab or placebo. Thus, fewer patients started adjuvant treatment than neoadjuvant treatment. Among 385 patients in the PK dataset, 264 continued with durvalumab treatment in the adjuvant phase. Therefore, we considered neoadjuvant phase data when simulating AUC_{ss}. We defined the 4th Q3W administered dose prior to surgery (i.e., the last dose prior to surgery) as the steady state in the neoadjuvant phase to simulate AUC_{ss}.

Exposure–efficacy relationships of EFS in AEGEAN were explored by KM curves stratified by durvalumab exposure quartiles. None of the exposure metrics showed a significant signal for any exposure–response relationship. For EFS outcomes, Cox PH models were developed, and none of the investigated covariates, including durvalumab exposure, had a significant impact on EFS hazard. The KM-estimated median EFS for the durvalumab arm was not reached based on data with only 39% maturity,[13] which may reduce our ability to observe the potential impact of covariates related to EFS. Additional EFS analyses are planned with increased maturity at future prespecified points, which may provide a more comprehensive understanding of the durvalumab exposure–EFS relationship.

The relationship between durvalumab exposure and pCR was explored based on data from the durvalumab treatment arm from AEGEAN. Graphical exploration of exposure metrics by pCR status (responder *vs.* non-responder) did not reveal any significant relationship between durvalumab exposure and pCR. This was further confirmed by logistic regression analysis, which showed a flat exposure–pCR relationship. Hence, a flat exposure–pCR relationship was observed based on the selected efficacy endpoint (pCR) at the effectively plateaued dose level of durvalumab 1500 mg from the AEGEAN study.

Relationships between durvalumab exposure and clinical safety endpoints were explored based on data from the durvalumab treatment arm from AEGEAN. Graphical exploration of exposure metrics for patients with an AE and patients without any AEs did not reveal any significant relationship. This initial result was confirmed by logistic regression analysis, which did not identify any significant impact of durvalumab exposure on the incidence of grade ≥3 treatment-related AEs, grade ≥3 treatment-related AESIs, or AEs leading to durvalumab treatment discontinuation. Hence, no clinically relevant exposure–safety relationship was observed based on selected safety endpoints from the AEGEAN study.

When considering ER relationships in the context of steady-state measures, it is important to consider potential confounding due to the effect of changes in disease state on durvalumab CL, as previously discussed.[16,24] Briefly, a decrease in tumour burden is associated with decreased durvalumab CL, likely due primarily to nonspecific changes in antibody catabolism associated with inflammation rather than changes in target-mediated clearance.[16] Thus, higher exposure in patients with tumours that respond to treatment may be an "effect" rather than a "cause". Such confounding would be expected to be most impactful during later phases of treatment. The potential for such bias is partially mitigated in the current study by the fact that the steady-state exposure metrics were derived from measurements taken before surgical resection (the 4th Q3W administered dose prior to surgery) and that analyses based on single-dose exposure metrics were also performed.[24] Moreover, in a previous PopPK analysis of durvalumab, the impact of baseline tumour burden was not considered clinically relevant based on an a priori threshold of <30% change in PK parameters, and the amount of interindividual variability for CL attributable to time-dependent changes in tumour size and ALB concentration (which inversely correlates with CL of monoclonal antibodies like durvalumab[16,25–27]) was only 4% and 11%, respectively.[16]

Dose-escalation and dose-expansion of durvalumab was assessed in a previous study (Study 1108); target engagement was assessed by measuring free soluble PD-L1 (sPD-L1) in serum.[14] The extent and duration of sPD-L1 suppression was dose-dependent, with complete suppression around the dose of ≥0.3 mg/kg. PK modelling indicated that 10 mg/kg Q2W would maintain trough exposure above 50 μg/mL (target exposure level) throughout the dosing interval, with approximately 97% of patients showing complete sPD-L1 suppression throughout the dosing interval. Suppression of free sPD-L1 was similar among 10 mg/kg Q2W, 15 mg/kg Q3W, and 20 mg/kg Q4W cohorts. PopPK modelling predicted similar overall PK exposures following WT-based (10 mg/kg Q2W) and fixed dosing regimens (1500 mg Q4W or 750 mg Q2W), with all regimens expected to maintain target trough exposure of ~50 μg/mL in ≥95% patients.[28] It follows that durvalumab 1500 mg is considered the dose for reaching

efficacy plateau. All the efficacy and safety data in the AEGEAN study were derived from the single dose level (1500 mg) of durvalumab, which is likely the reason for no ER relationships identified at this dose level in the current analysis.

In conclusion, durvalumab PK was adequately characterized using a two-compartment model with time-dependent clearance. Flat exposure–efficacy relationships were observed between durvalumab PK exposure and EFS and pCR at the effectively plateaued dose level of durvalumab 1500 mg. No clinically relevant exposure–safety relationships were observed between durvalumab PK exposure and safety endpoints in patients treated with durvalumab 1500 mg. Overall, no dose adjustment for the fixed-dose durvalumab regimen in patients with resectable stage II to IIIB (N2) NSCLC is considered necessary based on PopPK covariates analyses or exposure–response analyses, thus simplifying clinical decision-making and potentially decreasing risk of drug spillage and medication errors.[29] This analysis also highlights the robustness of the 1500 mg durvalumab regimen across different patient populations.

AUTHOR CONTRIBUTIONS

Xiaoying Zhao, Junjie Ding, Jiajia Zhao, Aburough Abegesah, Gary J. Doherty, Allen Chen, KyoungSoo Lim, Song Ren, Peiming Ma and Diansong Zhou conceptualized the study. Xiaoying Zhao and Cathy O'Brien curated the data. Formal analysis was conducted by Xiaoying Zhao, Junjie Ding, Jiajia Zhao, Ling Zhang, Yu-qian Zhang and Diansong Zhou. Xiaoying Zhao was responsible for the methodology. Song Ren, Peiming Ma and Diansong Zhou supervised the study. Xiaoying Zhao and Diansong Zhou wrote the original draft of the article and all authors reviewed and edited it. All the authors approved the final draft.

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CONFLICT OF INTEREST STATEMENT

X.Z., J.Z., L.Z., A.A., C.O. and A.C. report employment with AstraZeneca. J.D. reports former employment with AstraZeneca. Y.Z., G.J.D., K.L., S.R., P.M. and D.Z. report employment with and ownership of stock/shares in AstraZeneca.

DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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