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ORIGINAL ARTICLE

Population pharmacokinetics and exposure–response of anti-programmed cell death protein-1 monoclonal antibody dostarlimab in advanced solid tumours

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Aim: Develop a population pharmacokinetic (PopPK) model to characterise the pharmacokinetics (PK) of anti-programmed cell death protein-1 (PD-1) antibody dostarlimab, identify covariates of clinical relevance, and investigate efficacy/safety exposure–response (ER) relationships.

Methods: A PopPK model was developed using Phase 1 GARNET (NCT02715284) trial data for dostarlimab (1, 3 or 10 mg kg^{-1} every 2 wk; 500 mg every 3 wk or 1000 mg every 6 wk; 500 mg every 3 wk × 4 then 1000 mg every 6 wk [recommended regimen]) serum concentrations over time. Concentration–time data were analysed using nonlinear mixed effects modelling with standard stepwise covariate modelling. ER was explored for treatment-related adverse events and overall response rate (ORR) using logistic regression.

Results: PopPK model/adverse event ER analyses included 546 patients (ORR ER analysis $n = 362$). Dostarlimab PK was well described by a 2-compartment model with time-dependent linear elimination. Time-dependent clearance decreased over time to a maximum of 14.9%. At steady state, estimated dostarlimab geometric mean coefficient of variation % clearance was 0.179 (30.2%) L d^{-1}; volume of distribution was 5.3 (14.2%) L; terminal elimination half-life was 23.5 (22.4%) days. Statistically significant covariates were age, body weight, sex, time-varying albumin and alanine aminotransferase for clearance; body weight, albumin and sex for volume of distribution of the central compartment. Hepatic or renal impairment did not affect PK. There were no clinically significant ER relationships.

Conclusion: Dostarlimab PK parameters are similar to other anti-programmed cell death protein-1 antibodies. The clinical impact of covariates on exposure was limited-to-moderate, supporting recommended dostarlimab monotherapy therapeutic dosing.

KEYWORDS
clinical pharmacology (drug safety), oncology (anticancer drugs), pharmacokinetics, therapeutics

The GARNET trial does not have a designated study PI.

1 | INTRODUCTION

Dostarlimab (JEMPERLI) is a humanised anti-**programmed cell death protein-1 (PD-1)** immunoglobulin G4 monoclonal antibody (mAb) that binds with high affinity to the PD-1 receptor and effectively blocks its interaction with **programmed death ligand-1 (PD-L1)** and PD-L2.[1] The ongoing, multicohort, open-label Phase 1 GARNET study (NCT02715284) is evaluating the antitumour activity and safety of dostarlimab in patients with advanced solid tumours. Based on promising response rates and durability of response observed in GARNET, dostarlimab has received accelerated and conditional approval in the USA and Europe as monotherapy for the treatment of patients with mismatch repair-deficient (dMMR) and dMMR/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC), respectively, that has progressed on or after treatment with platinum-based chemotherapy and received accelerated approval in the USA in dMMR recurrent or advanced solid tumours following progression.[2–5] Data from the GARNET trial are consistent with reports that dMMR/MSI-H is a predictive biomarker of response to anti-PD (L)-1 agents;[6–10] however, dostarlimab has also shown clinical activity in EC and nonsmall cell lung cancer (NSCLC) regardless of MMR status,[9,11,12] with an acceptable tolerability profile across tumour types that is similar to other anti-PD-1 mAbs.[4,9,12–14] Clinical trials in patients with advanced or metastatic solid tumours also are underway evaluating dostarlimab in combination with other agents.[15–27]

Full characterisation of pharmacokinetics (PK) and exposure–response (ER) relationships of new agents is vital to inform the selection of dosing regimens to optimise the risk–benefit profile for each agent.[28] The PK profiles of other approved PD-1 inhibitors share common features of other therapeutic mAbs (long half-life, limited extravascular diffusion and minimal impact of hepatic or renal function impairment on PK). Time-varying drug clearance (CL) is also common to the anti-PD-1 class.[28,29] There are some differences in PK properties between anti-PD-1 agents, however, which may reflect target-mediated drug disposition.[28] Both fixed and body weight dosing regimens are recommended for the PD-1 inhibitors pembrolizumab and nivolumab depending on their licensed indications[30,31]; PD-1 inhibitor cemiplimab has a fixed dosing regimen.[32,33]

Here, we present PK and ER analyses of dostarlimab in patients with recurrent/advanced solid tumours using data from the GARNET trial.[34] The objectives were to develop a population PK (PopPK) model of dostarlimab, identify covariates of clinical relevance and evaluate ER relationships for overall response rate (ORR) and the occurrence of relevant adverse events (AEs).

What is already known about this subject

- In the GARNET study, dostarlimab showed durable clinical activity and acceptable safety in recurrent/advanced solid tumours, consistent with other anti- programmed cell death protein-1 (PD-1) monoclonal antibodies.
- Approved anti-PD-1 inhibitors typically display linear pharmacokinetics (PK) and time-varying clearance at relevant doses.
- Full characterisation of dostarlimab PK and exposure–response relationships supported the therapeutic dose recommendation.

What this study adds

- Dostarlimab PK was well described by a 2-compartment model with time-dependent linear elimination, like other anti-PD-1 monoclonal antibodies.
- Patient covariates/disease characteristics had limited clinically relevant effects on exposure.
- No clinically significant efficacy/safety exposure–response relationships were identified, supporting dostarlimab recommended therapeutic regimen (500 mg every 3 wk × 4 cycles, then 1000 mg every 6 wk).

2 | METHODS

2.1 | Study design and patients

Details of the GARNET study design have been published previously.[9] Briefly, GARNET is an ongoing, Phase 1, multicentre, open-label, multicohort, first-in-human, 2-part trial evaluating the efficacy and safety of dostarlimab in recurrent/advanced solid tumours (Figure S1). Part 1 evaluated weight-based doses of dostarlimab monotherapy in a dose-escalation manner. Part 2A was a fixed-dose safety phase to determine the recommended Phase 2 dose of dostarlimab, and Part 2B enrolled patients into 4 expansion cohorts based on tumour type and mutation status: Cohort A1: dMMR/MSI-H EC; Cohort A2: mismatch repair-proficient (MMRp)/microsatellite stable (MSS) EC; Cohort E: NSCLC; Cohort F: non-EC dMMR/MSI-H and polymerase ϵ (*POLE*)-mutant tumours; Cohort G: platinum-resistant ovarian cancer without *BRCA* mutation. Dostarlimab weight-based and flat dose regimens are described in the methods below. Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

The GARNET study involves human participants and the ethics committee at each investigational site approved the protocol. Participants gave informed consent to participate in the study before taking part.

2.2 | Patients

Patients eligible for GARNET were aged ≥18 years, with proven recurrent or advanced solid tumour and disease progression after

treatment with available anticancer therapies (further eligibility criteria previously published).[4]

2.3 | Dose regimens and sample analyses

The dostarlimab dose regimens included in PopPK model development were 1, 3 or 10 mg every 2 weeks (Q2W; Part 1); 500 mg Q3W or 1000 mg Q6W (Part 2A); 500 mg Q3W × 4 cycles followed by 1000 mg Q6W thereafter (Part 2B). All patients who received ≥1 dose of dostarlimab and had ≥1 PK sample (sampling schedule in Supplementary Methods) were included in the PK population used for model development. Serum samples were analysed for dostarlimab PK using enzyme-linked immunosorbent assay. Biomarker status was determined from archival and baseline tumour tissue samples. The presence of dostarlimab anti-drug antibodies (ADAs) was assessed using electrochemiluminescence using serum samples obtained predose and at/after 96 hours of the corresponding dose.

2.4 | PopPK model development

Starting with a preliminary model tested on data from a previous GARNET data cut, models were developed in order of increasing complexity proceeding until further improvement in fit was not supported by the data. This principle was applied to the search for structural model components including parameter variability components and residual error structure.

During model development, a difference in objective function value (OFV) of 6.63 was used to differentiate between 2 nested models differing in 1 parameter (corresponding to a nominal $P < .01$).

The effect of body weight was modelled based on the principles of allometry and included as a covariate for CL, volume of distribution of the central compartment (V_c) and volume of distribution of peripheral compartment (V_p) on the structural model.

Once the final structural model was identified, the predictive value of individual patient characteristics was assessed using an automated covariate search.[35] Covariates were assessed on CL, V_c, V_p and maximum decrease in clearance relative to baseline (I_{max}). To evaluate the impact of patient covariates, an automated forward inclusion followed by backward elimination procedure was followed through use of stepwise covariate modelling.[35] Additional preselected covariates of interest included age, race, sex, ethnicity, creatinine clearance, renal impairment (mild, moderate, normal), liver function markers, liver impairment (mild, moderate, normal), albumin (ALB), tumour diagnosis, use of corticosteroids, sum of diameters of measurable target lesions per immune-related (ir) Response Evaluation Criteria in Solid Tumors (RECIST) and presence of ADAs (yes/no). ADA effect was defined as either time-invariant (never positive or if ever positive), time-variant as positive or negative as observed at each measurement and time-variant as negative until first positive, then carried forward as positive for the rest of the study. Responder *vs.* nonresponder was also evaluated as a covariate on I_{max}. For stepwise covariate modelling, a difference in OFV of 6.63 ($P < .01$) was used for an effect to be included in the model during forward inclusion, and OFV of 10.8 ($P < .001$) for retention during backward elimination.

Model selection criteria are described in Supplementary Methods. The final PopPK model was determined based on the lowest stable OFV, physiological plausibility of parameter values, successful numerical convergence, parameter precision and acceptable prediction-corrected (pc)-visual predictive checks (VPC).[36]

Individual dostarlimab concentration *vs.* time profiles were simulated using *posthoc* PK parameter estimates from the final model and planned dose. For predictions of exposure at steady state, enough doses were simulated to ensure steady state was reached (dosing for approximately a year of the recommended therapeutic dose [RTD]; 500 mg Q3W × 4 cycles then 1000 mg Q6W).

To illustrate the impact of the statistically significant covariates, forest plots were constructed using the reference patient who was female with a body weight of 70 kg, aged 64.0 years, and with baseline ALB 39 g dL^{-1} and alanine aminotransferase (ALT) of 18 U L^{-1}. The PopPK analysis was carried out using nonlinear mixed effects modelling (NONMEM; Version 7.4, ICON Development Solutions, Ellicott City, MD, USA) under Windows 7 Professional and the GNU gfortran compiler (Version 4.5.0). Postprocessing of NONMEM analysis was carried out in R version 3.6.2 (The R Foundation).[37] NONMEM run execution (with parallelisation), VPC and stepwise covariate modelling was carried out using Perl-speaks-Nonmem, version 4.8.0.[35]

2.5 | ER analysis

The ER efficacy analysis was performed for all patients in Cohorts A1, A2 and F from Part 2B (full efficacy dataset) and for 2 overlapping patient subgroups (EC patients, with dMMR or MMRp as covariate, and dMMR pan-tumour patients, with EC or non-EC as covariate). The ER safety analysis was performed for all patients from Parts 1, 2A and 2B. Relationships between dostarlimab exposure, ORR (per RECIST v1.1) and the 5 most frequent treatment-related AEs reported by investigators (fatigue [26.4% of patients], nausea [25.6%], diarrhoea [22.2%], asthenia [18.1%] and hypothyroidism [9.5%]) were explored. ORR was defined as the proportion of patients achieving a best overall response of complete response or partial response per RECIST v1.1[38] over the entire study period. AEs were coded according to the Medical Dictionary for Regulatory Activities v23.0.[39]

For the ER analysis of efficacy, Cycle 1 (Day 21) predictions of area under the concentration–time curve (AUC), maximum concentration (C_{max}) and minimum concentration (C_{min}) were generated based on planned dose and individual *posthoc* PK parameters. The ER of safety used AUC (cumulative $AUC_{0-6weeks}$) and C_{max}, simulated using planned dosing and individual *posthoc* parameters from the final PopPK model for the first 6 weeks of treatment. ORR and AE data were initially analysed using univariate logistic regression with exposure as the independent predictor. Covariates included in the ORR multivariate logistic regression analysis were neutralising ADA status

(ADNAS), baseline Eastern Cooperative Oncology Group performance status (ECOG PS), baseline tumour mutational burden status (TMBST) and total prior lines of therapy (TOTPLA). These were analysed for the full ER dataset and by tumour subgroup (EC patients, with dMMR or MMRp as covariate, and dMMR pan-tumour patients, with EC or non-EC as covariate; Tables S1 and S2).

2.5.1 | 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 2019/20.[40]

3 | RESULTS

3.1 | Analysis dataset

In total, 4804 PK observations from 546 patients were used in the development of the PopPK model (Table 1; Figure S2). Twenty-one observations with absolute conditional weighted residual (CWRES) > 5 were excluded from the analysis, resulting in 4783 PK observations used in the final model.

Baseline demographics and clinical characteristics for the analysis set are shown in Table 2. Median age of patients was 64.0 years (range: 24–86) and 77% were female. Overall, 23.4% of patients had dMMR/MSI-H EC, 29.3% had MMRp/MSS EC, 12.3% had NSCLC and 28.8% had non-EC dMMR/MSI-H or POLE-mutant tumours. At baseline, 11% of patients had mild-to-moderate hepatic impairment and 61% had mild-to-moderate renal impairment.

3.2.Dostarlimab PopPK model development

The PK profile of dostarlimab was well described by a 2-compartment model with time-dependent linear elimination. The time-dependency in CL was best described empirically by a sigmoid-I_{max} function with a maximum reduction of 14.9%. Time-dependent CL was also tested on a model with linear and nonlinear elimination components but did not result in any significant improvement in the model fit. Body weight was added allometrically and was found to be statistically significant for dostarlimab PK during structural model building.

3.3.Stepwise covariate analysis

Stepwise covariate modelling found that the baseline covariates of age, sex, time-varying ALB and time-varying ALT had a statistically significant impact on CL. Both time-varying ALB and sex were found to be predictors of V_c. The effect of time-varying sum of diameters of measurable target lesions on CL and tumour type on V_c were found to be significant in the forward inclusion step but were not significant in the backward elimination step and were removed. The presence of ADAs had no impact on dostarlimab CL. Response (responder *vs.* nonresponder) was not a significant covariate on I_{max}.

Body weight was included as a covariate for CL, V_c and V_p with the exponents estimated to 0.47 for CL and 0.419 for volumes V_c and V_p in the final model. The final model incorporated interindividual variability (IIV) on CL, V_c and I_{max} and were estimated to be 29.2% coefficient of variation (CV), 17.4% CV and 82.0% CV, respectively. The addition of covariates reduced the IIV to 23.5% CV for CL, 16.1% for V_c and 73.3% CV for I_{max}.

The final PopPK model is mathematically described by the following equations:

$$\frac{dA_{central}}{dt} = -k_{10}\cdot A_{central} - k_{12}\cdot A_{central} + k21\cdot A_{peripheral}$$

$$\frac{dA_{peripheral}}{dt} = k_{12}\cdot A_{central} - k_{21}\cdot A_{peripheral}$$

with time-dependent elimination:

$$CL_{timebase} = \mathrm{CL_{base}}\cdot exp\left[\frac{\left(I_{max}\cdot Time^{Hill}\right)}{T50^{Hill} + Time^{Hill}}\right]$$

TABLE 1 Number of patients and PK observations by study part and dosage regimen in the analysis dataset

GARNET study part	Dose/dosage regimen	Patients, *n*	PK observations, *n*[a]
Part 1	1 mg kg^{-1} Q2W	6	168
	3 mg kg^{-1} Q2W	3	115
	10 mg kg^{-1} Q2W	12	273
Part 2A	500 mg Q3W	6	118
	1000 mg Q6W	7	118
Part 2B	500 mg Q3W × 4 cycles followed by 1000 mg Q6W	512	4012
Total	-	546	4804 [a]

CWRES, conditional weighted residual; PK, pharmacokinetics; PopPK, population pharmacokinetic; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

[a]21 observations with CWRES>5 were excluded from the analysis, resulting in 4783 observations in the final PopPK model.

TABLE 2 Baseline demographics and clinical characteristics

	Analysis set ($n = 546$)
Age, y	
Mean (SD)	62.5 (11.0)
Median (range)	64.0 (24.0–86.0)
Female, *n* (%)	422 (77.3)
Race, *n* (%)	
White	410 (75.1)
Black/African American	19 (3.5)
Asian	13 (2.4)
Other	6 (1.1)
Unknown	5 (0.9)
Not reported	89 (16.3)
Weight, kg [a]	
Mean (SD)	74.4 (20.0)
Median (range)	71.4 (34.0–182.0)
Tumour diagnosis	
MMRp/MSS EC	160 (29.3)
Non-EC MSI-H and POLE-Mut	157 (28.8)
dMMR/MSI-H EC	128 (23.4)
NSCLC	67 (12.3)
Missing	34 (6.2)
Hepatic impairment, *n* (%)	
None	486 (89.0)
Mild	55 (10.1)
Moderate	5 (0.9)
Severe	0 (0)
Renal impairment	
None	209 (38.3)
Mild	235 (43.0)
Moderate	100 (18.3)
Severe	2 (0.4)
Concomitant medications, *n* (%) [b]	
Immunomodulators	1 (0.2)
Immunostimulants	3 (0.5)
Corticosteroids	206 (37.7)
ADAs, n (%)	
Ever positive	101 (18.5)
Never positive	445 (81.5)
eGFR (mL/min/m^2)	
Mean (SD)	84.6 (29.0)
Median (range)	83.4 (19.5–336.0)
Creatinine clearance (mL min^{-1})	
Mean (SD)	90.3 (30.0)
Median (range)	86.4 (19.3–150.0)
Alanine aminotransferase (U L^{-1})	
Mean (SD)	20.9 (15.0)
Median (range)	17.0 (2.9–120.0)

TABLE 2 (Continued)

	Analysis set ($n = 546$)
Aspartate aminotransferase (U L^{-1})	
Mean (SD)	24.3 (15.0)
Median (range)	20.0 (5.0–163.0)
Alkaline phosphate (U L^{-1})	
Mean (SD)	117.0 (88.0)
Median (range)	94.0 (33.0–855.0)
Albumin (g L^{-1})	
Mean (SD)	38.2 (5.1)
Median (range)	39.0 (19.0–51.0)
Bilirubin (μmol L^{-1})	
Mean (SD)	7.8 (4.0)
Median (range)	6.8 (1.7–31.0)
Lactate dehydrogenase (U L^{-1})	
Mean (SD)	348 (570)
Median (range)	222 (86.0–11700.0)

ADA, antidrug antibodies; dMMR, deficient mismatch repair; EC, endometrial cancer; eGFR, estimated glomerular filtration rate; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NSCLC, nonsmall cell lung cancer; POLE-Mut, polymerase ϵ mutated; SD, standard deviation.

[a] $n = 2$ patients with missing body weight were imputed to sex median value;

[b] Only concomitant medications relevant to these analyses are presented, and this is not exhaustive list of all concomitant medications received by patients.

where time is in days and where the microconstants of the mass transfer are defined as:

$$k_0 = \frac{CL}{V_c}\ k_{12} = \frac{Q}{V_c}\ k_{21} = \frac{Q}{V_p}.$$

The age, ALB, ALT and sex effects are given by (body weight defined as WT):

$$CL = CL_{timebase} \cdot \left(\frac{WT}{70}\right)^{\theta_{CL,WT}} \cdot \left(\frac{AGE}{64}\right)^{\theta_{CL,AGE}} \cdot \left(\frac{ALB}{39}\right)^{\theta_{CL,ALB}} \cdot \left(\frac{ALT}{18}\right)^{\theta_{CL,ALT}} \cdot (1 + \theta_{CL-SEX}),$$

$$V_c = V_{cbase} \cdot \left(\frac{WT}{70}\right)^{\theta_{Vcp,WT}} \cdot \left(\frac{ALB}{39}\right)^{\theta_{Vc,ALB}} \cdot (1 + \theta_{Vc-SEX}),$$

$$V_p = V_{pbase} \cdot \left(\frac{WT}{70}\right)^{\theta_{Vcp;WT}}$$

where θ_{CL-SEX} and θ_{Vc-SEX} are equal to 0 for females (most common) and estimated for males.

3.4.PopPK model performance

Across the range of dostarlimab doses, including the clinically relevant doses of 500 mg Q3W and 1000 mg Q6W, the final model demonstrated appropriate agreement between observed and model prediction values (Figure S3), demonstrating that the model estimated PK parameters with sufficient precision. The CWRES were randomly scattered around predicted range and across time. The pc-VPCs (Figure S4) showed that the final model predicted the dostarlimab concentration *vs*. time profile reasonably well across doses. For the lowest dose group (1 mg kg^{-1}, $n = 6$), the observed concentrations appeared to be slightly lower than predicted, but acceptable for simulations.

Parameter estimates for the final PopPK model are shown in Table 3. The dostarlimab CL (at start of treatment), V_c and V_p were estimated to be 0.179 L day^{-1}, 2.98 L and 2.10 L, respectively. At steady state, estimated dostarlimab geometric mean CL (CV%) was 0.179 (30.2%) L day^{-1} and volume of distribution (V_{ss}; CV%) was 5.3 (14.2%) L. Terminal half-life ($t_{1/2}$) at steady state was 23.5 (22.4%) days and α half-life at steady state was 1.51 (11.9%) days. The Hill parameter in the sigmoid I_{max}-function (describing the time dependency in CL) was 5.29.

3.2 | Clinical relevance of covariates

The impact of the statistically significant covariates on exposure at steady state (AUC_{ss} and $C_{max;ss}$) is presented in Figure 1. Time-varying ALB demonstrated the largest impact on exposure with 25.9% lower AUC_{ss} in a patient with the 5th percentile of the baseline covariate value and 15.5% higher AUC_{ss} in a patient with the 95th percentile of the baseline covariate value, independent of any time-varying CL (based on the typical value of the covariate effect). The impact of body weight on exposure at steady state was moderate, at approximately 0.8–1.2 fold at the 5th and 95th percentiles of the baseline covariate distribution compared to the reference patient. All other identified covariates also had limited impact on exposure.

TABLE 3 Parameter estimates of final PopPK model[a]

Parameter (units)	Estimate [b]	Relative SE (%)	95% CI
CL (L d^{-1})[a]	0.179	1.57	0.173, 0.184
V_c (L)[a]	2.98	0.871	2.93, 3.03
Q (L d^{-1})	0.547	9.18	0.461,0.650
V_p (L)	2.10	2.00	2.02, 2.18
I_{max}[a]	−0.161	8.53	−0.187, −0.134
T50 (d)	108	7.47	92.6, 124.0
Hill	5.29	9.12	4.34, 6.23
Effect of WT on CL	0.470	6.12	0.414, 0.527
Effect of WT on V_c and V_p	0.419	5.29	0.376, 0.463
Effect of age on CL	−0.227	29.7	−0.360, −0.0951
Effect of ALB on CL	−1.01	8.64	−1.18, −0.835
Effect of ALT on CL	−0.0585	32.4	−0.0956, −0.0213
Effect of male on CL	0.165	18.4	0.106, 0.225
Effect of ALB on V_c	−0.153	35.8	−0.261, −0.0461
Effect of male on V_c	0.162	12.6	0.122, 0.202
ω^2CL	0.0551 (0.235)	7.51	0.0470, 0.0632
ω^2CL, V_c	0.0210 (0.557)	11.1	0.0164, 0.0255
ω^2V_c	0.0258 (0.161)	7.48	0.0220, 0.0296
ω^2I_{max}	0.537 (0.733)	16.4	0.365, 0.710
Proportional residual variability	0.133	2.45	0.126, 0.139
Additive residual variability (mg L^{-1})	2.79	14.7	1.98, 3.59

ALB, albumin; ALT, alanine aminotransferase; CI, confidence interval; CL, apparent systemic clearance; I_{max}, maximal decrease in clearance relative to baseline; IIV, interindividual variability; PopPK, population pharmacokinetics; Q, apparent intercompartment clearance; SE, standard error; T50, time at which 50% of I_{max} is reached; Vc, apparent central volume of distribution; Vp, apparent peripheral volume of distribution; WT, body weight.

[a]Shrinkage in individual deviations (ETA)1(CL), ETA2(V_c) and ETA5(I_{max}) were 16.2, 7.4 and 49.2%, respectively;

[b]Random effects parameter estimates are shown as variance (standard deviation) for diagonal elements and covariance (correlation) for off-diagonal elements; ω^2, IIV of parameter X is derived from variance according to $\sqrt{(\omega^2)} \times 100$.

C_{max} and $AUC_{0\text{-}21d}$ (1st or 5th dose) values for patients with impaired renal or hepatic function were within 10% of the values for patients with normal function, except for $AUC_{0\text{-}21d}$ at 5th dose for hepatic impairment, for which the value observed for patients with moderate impairment was 21% higher than the value for patients with normal function (Table S3).

3.3 | Predicted exposure

Predicted dostarlimab concentration *vs*. time profiles for the patients from GARNET Part 2B were simulated using individual *posthoc* PK parameter estimates from the final model and planned RTD (Figure S5). Geometric mean (CV%) AUC_{ss} and $C_{max,ss}$ were estimated to 147 000 (30.1%) mg*h L^{-1} and 434 (21.0%) mg L^{-1} following the RTD (Table S4). Dostarlimab showed approximately a 2-fold dose-adjusted accumulation for both area under the concentration *vs*. time curve for a dosing interval (AUC_{tau}) and C_{max} when comparing predicted exposure after the first 500-mg Q3W dose with steady state exposure following a 1000-mg Q6W dose.

3.4 | ER analysis

3.4.1 | Efficacy

Ranges of Cycle 1 exposure metrics for patients included in the efficacy ER analysis ($n = 362$; Part 2B only) are shown in Table 4. The univariate logistic regression of ORR showed no statistically significant ER relationship, with *P*-values of 0.19, 0.319 and 0.187 for AUC, C_{max} and C_{min}, respectively (Figure S6). The odds ratios of the multivariate logistic regression with covariates added linearly is shown in Figure S7 for the full dataset. The 95% confidence intervals (CIs) of ECOG PS and TMBST did not include 1 for any of the tested exposure metrics while the 95% CIs for the other tested covariates (ADNAS, TOTPLA and AUC, C_{min} and C_{max} during the first 21 days) included 1;

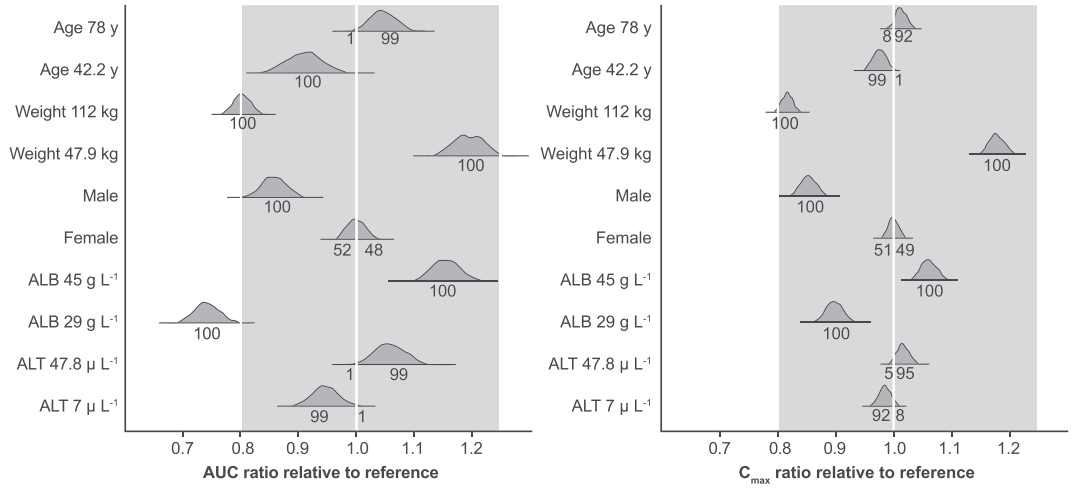

FIGURE 1 Forest plots illustrating the covariate effects on AUC_{ss} and $C_{max;ss}$ ratios as compared with median reference patient. The distribution represents the ratios based on 1000 sets of parameter estimates re-sampled from the variance covariance matrix. Numbers indicate actual percent of each distribution in a bounded region (central reference line). The grey area represents the 0.8 and 1.25 boundaries. ALB, albumin; ALT, alanine aminotransferase; AUC, area under the curve; AUC_{ss}, area under the curve at steady state; C_{max}, maximum concentration; $C_{max;ss}$, maximum concentration at steady state

TABLE 4 Summary of C_{min}, C_{max} and AUC for patients in the efficacy ER analysis ($n = 362$; Cycle 1 exposure) and safety ER analysis ($n = 546$, first 6 wks' exposure)

Metric (units)	Min	Max	Mean	SD
Efficacy analysis				
C_{min} (mg L^{-1})	13.7	70.2	41.3	10.5
C_{max} (mg L^{-1})	103.0	284.0	177.0	32.8
AUC (mg*h L^{-1})	19100.0	51000.0	34400.0	6090.0
Safety analysis				
C_{min} (mg L^{-1})	8.32	253.0	61.6	22.5
C_{max} (mg L^{-1})	27.1	556.0	216.0	54.5
AUC (mg*h L^{-1})	10600.0	260000.0	83800.0	21900.0

AUC, area under the curve; C_{min}, minimum concentration; C_{max}, maximum concentration; ER, exposure–response; max, maximum; min, minimum; SD, standard deviation; T1, first tertile cut (~33rd percentile); T2, second tertile cut (~67th percentile).

the 95% CIs for AUC, C_{max} and C_{min}, respectively were 0.326–0.879, 0.32–0.856 and 0.327–0.885 for ECOG PS and 3.04–9.04, 3.05–9.08 and 3.02–8.97 for TMBST.

Univariate logistic regression of ORR in the subgroup of patients with EC tumours ($n = 249$) demonstrated that none of the tested exposure metrics had a statistically significant relationship with ORR, with *P*-values of 0.502, 0.717 and 0.449 for AUC, C_{max}, and C_{min}, respectively. Multivariate logistic regression with covariates added linearly was performed for the EC subgroup, and the 95% CIs of TMBST did not include for any of the tested exposure metrics (1.37–8.92, 1.35–8.81, 1.36–8.9 for AUC, C_{max} and C_{min}, respectively (Figure 2); for ECOG PS, the 95% CIs included 1 for AUC (0.274–1.01) and C_{min} (0.277–1.03) but not for C_{max} (0.266–0.979). The 95% CIs for all the other tested covariates included 1. Tumour subtype (dMMR *vs.* MMRp) was also tested and did not have a statistically significant relationship with ORR (odds ratio 95% CI: 0.185–1.22).

Subgroup analysis of patients with dMMR tumours ($n = 217$) by univariate analysis showed that Cycle 1 AUC and C_{min} had a statistically significant relationship with ORR, with *P*-values of 0.0395 and 0.0451. However, the ER relationship for ORR was no longer significant after inclusion of additional covariates Following multivariate logistic regression for the dMMR subgroup (Figure 2), the odds ratio 95% CIs for AUC, C_{max} and C_{min}, respectively were 0.186–0.609, 0.181–0.589 and 0.187–0.612 for ECOG and 1.08–10.9, 1.07–10.8 and 1.07–10.8 for ADNAS. The 95% CIs of the other tested covariates included 1. Tumour type (EC *vs.* non-EC) did not have a statistically significant relationship with ORR.

3.4.2 | Safety

Table 4 shows ranges of exposure metrics (over the first 6 wk) for the patients included in the ER analysis of safety ($n = 546$; Parts 1, Part 2A, Part 2B). There was no statistically significant ER relationship ($P > .05$) for AUC, C_{max} or C_{min} for any of the 5 most prevalent drug-related AEs (asthenia, diarrhoea, fatigue, hypothyroidism and nausea; Figure 3). Although the ER relationship was not flat for fatigue and started to increase at approximately 350 mg L^{-1} for C_{max} and 15 000 mg*h L^{-1} for AUC, there was uncertainty in this measure as only 8 and 7 patients had exposure levels above these values, respectively.

4 | DISCUSSION

This analysis is the first to evaluate the PopPK of dostarlimab and used interim data collected in the ongoing Phase 1 GARNET trial evaluating dostarlimab in patients with recurrent or advanced solid tumours.

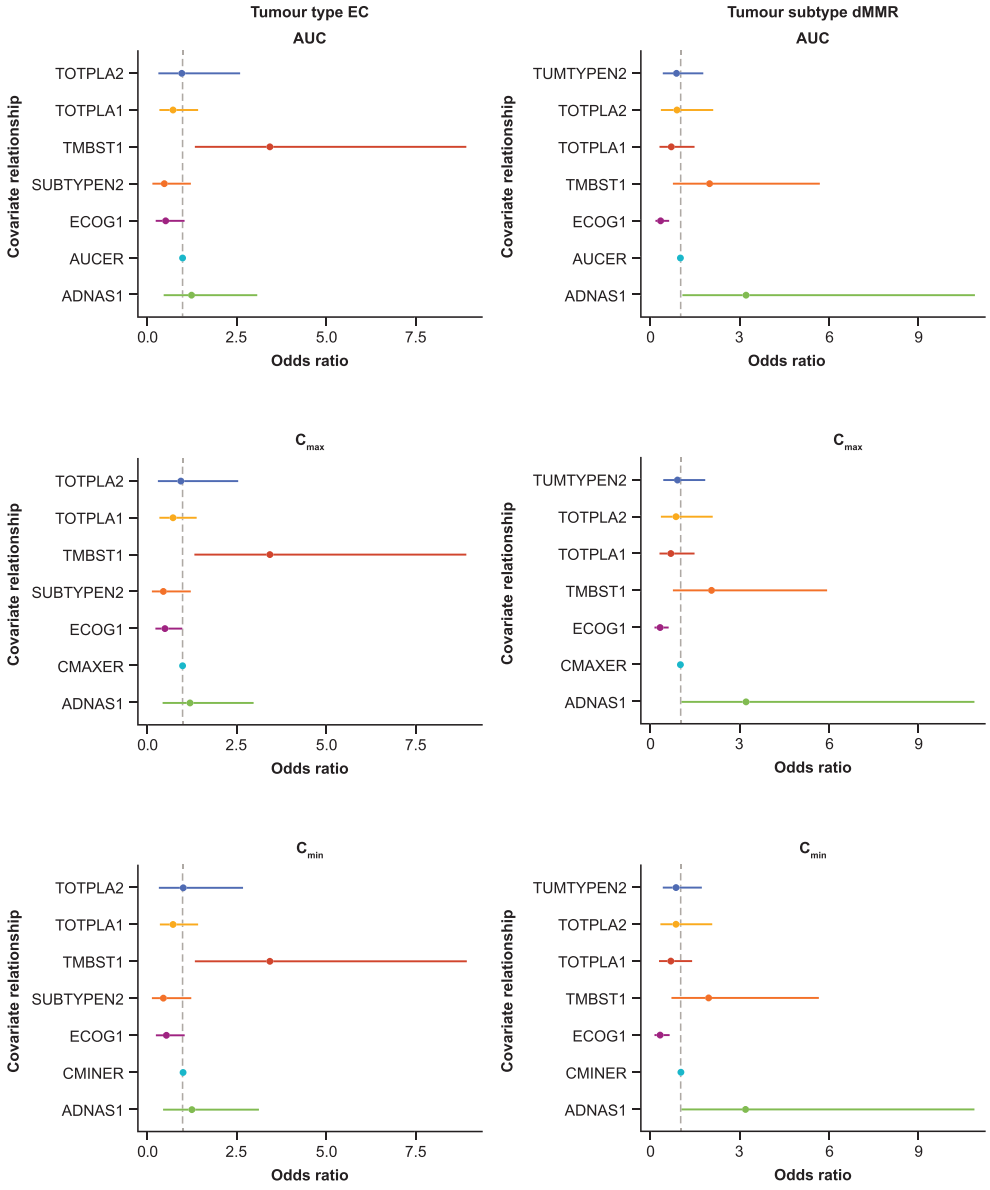

FIGURE 2 Odds ratio for multivariate logistic regression with covariates added linearly for tumour type endometrial cancer (EC) and tumour subtype mismatch repair-deficient (dMMR). ADNAS, neutralising antibody status, reference ADNAS = 0 (no ADNAS); AUC, area under the curve; AUCER, AUC during first 21 days; C_{max}, maximum concentration; CMAXER, concentration max during first 21 days; C_{min}, minimum concentration; CMINER, concentration at 21 days after first dose; ECOG, Eastern Cooperative Oncology Group performance status, reference ECOG = 0; TMBST, tumour mutational burden status, reference TMBST = 0 (TMBST <10); TOTPLA, total prior lines of therapy, reference TOTPLA = 0 (no TOTPLA)

The dostarlimab PK profile was well described by a 2-compartment model, with a time-dependent linear elimination. Time-dependent CL was described by a sigmoid–I_{max} function, decreasing over time. Dostarlimab geometric mean (CV%) CL at steady state and V_{ss} were estimated to 0.179 (30.2%) L d^{-1} and 5.3 (14.2%) L, respectively, and the geometric mean (CV%) $t_{1/2}$ at steady state was estimated to be 23.5 (22.4%) days.

Model evaluation demonstrated that the model described the dostarlimab PK data adequately well. The slight overprediction for the 1 mg kg^{-1} dose group may be due to the low number of patients who received this dose. Overall, the PopPK model showed that dostarlimab exposure is approximately dose-proportional at clinically relevant doses. The dostarlimab PK profile is generally consistent with that of other approved PD-1 inhibitors, pembrolizumab, nivolumab and cemiplimab, as PK parameters were similar and both time-varying CL and a linear elimination pattern have previously been observed for these agents within their therapeutic dose ranges.[28,29,41–44]

Whilst dostarlimab demonstrating time-varying CL is consistent with observations for other PD-1 inhibitors, the typical maximum reduction in CL over time was estimated at 14.9%, which is lower than that reported for pembrolizumab (20–30%), nivolumab (~25%) or cemiplimab (35.9%).[28,29,42,45] Further, the Hill parameter (5.29) was estimated to be slightly higher than other PD-1 inhibitors,[29,41,42] but results suggest generally that the time–CL relationship is relatively steep. The apparent difference between agents in maximum CL change over time may be due to differences in study sampling schema and proportion of patients with long term samples available,[28] rather than being a dostarlimab-specific finding. In Part 2B of GARNET, PK samples were infrequent and 25% of patients included in this analysis did not have any trough sample beyond the second dose. Additionally, it is not clear whether the lower estimated magnitude of decrease in CL over time for dostarlimab compared with other PD-1 inhibitors could reflect the patient population; previously reported data indicate that time-dependent CL observed with anti-PD-1 mAbs may vary

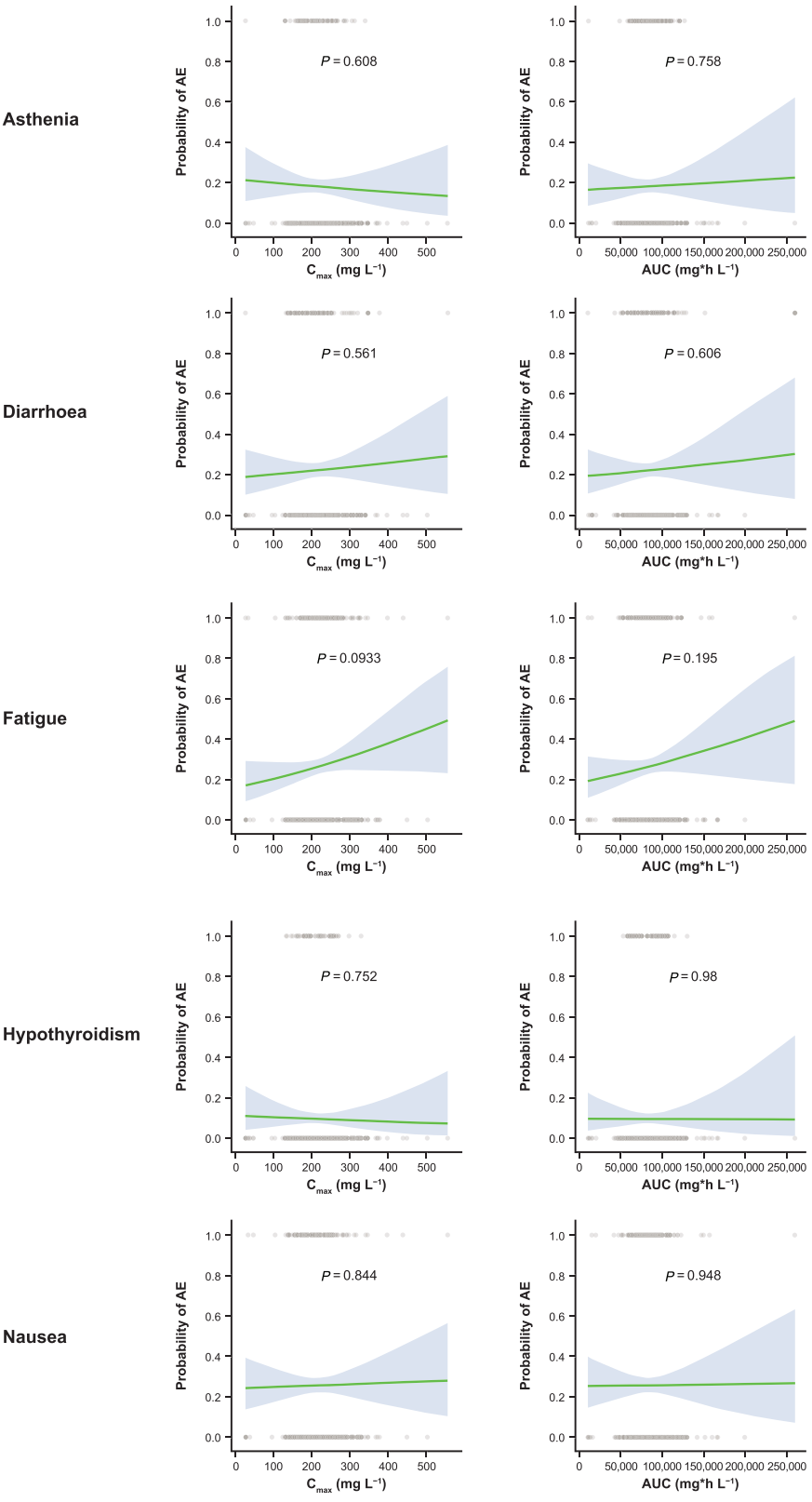

FIGURE 3 AEs *vs*. exposure metrics. Line represents predicted probability. Shaded area corresponds to 95% CIs. AE, adverse event; AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration; C_{min}, minimum concentration

depending on tumour type, although this may not be clinically relevant.[28,41,42] Tumour type (EC [dMMR/MSI-H or MSS/MMRp], NSCLC or MSI-H, and POLE-mutated non-EC) was not found to be a statistically significant covariate and did not impact dostarlimab PK parameters in stepwise covariate modelling.

In line with previous reports for other PD-1 inhibitors, body weight and time-varying ALB were found to impact dostarlimab PK.[28,41,42] Body weight had a statistically significant influence and this was accounted for in model development, with exponents comparable to those utilised for pembrolizumab and nivolumab.[28,41,42] It has been

shown that fixed dosing of mAbs results in less variability in AUC compared with body weight dosing when an exponent of <0.5 is used to normalise the body weight effect on CL during PK modelling.[46,47] Overall, the impact of body weight on exposure (AUC_{ss} and $C_{max;ss}$) was moderate (within 0.8–1.2 fold) and deemed not clinically relevant, further supporting fixed dosing for dostarlimab. Sex was a covariate identified as having an impact on dostarlimab PK during stepwise covariate modelling; however, this effect is consistently reported for anti-PD-(L)1 agents and other therapeutic antibodies, and its clinical relevance may be limited.[28,41,42,48] An inverse relationship between time-varying ALB and CL for dostarlimab was observed (also seen with pembrolizumab, nivolumab and durvalumab),[41,42,49] which may reflect an underlying catabolic rate associated with progression or improvement of disease, rather than a causative effect between the 2. That is, low serum ALB signals hypermetabolism in cancer, with higher protein turnover and loss of muscle mass; this state of cachexia indicates increased CL of therapeutic antibodies, as they share protein catabolism as an elimination mechanism with ALB.[41,42,48,49] Time-varying ALB had the largest impact on dostarlimab exposure but is not expected to be clinically relevant.

Sex, age and time-varying ALT had only limited clinical effects on exposure metrics. Mild hepatic and mild or moderate renal impairment did not influence dostarlimab PK, suggesting no dose adjustment is needed in these patient populations. This is in line with other analyses of anti-PD-1 agents,[29,41,42] and would be anticipated given that the degradation of immune-checkpoint inhibitors is predominantly nonspecific within plasma and tissue.[28] Whilst the presence of ADAs has been demonstrated to have a modest impact on CL for certain PD-L1 inhibitors and nivolumab (e.g. increasing CL by 14% for nivolumab),[28,42] ADAs did not have an effect on dostarlimab CL.

No significant ER relationship between any dostarlimab exposure metric and ORR were observed in the full analysis population, although significant relationships were observed for the subgroup of patients with dMMR tumours. There is a correlation between TMBST and dMMR/MSI status in some tumour types, including in EC and colorectal cancer,[50] and multivariate logistic regression analysis showed that the impact of TMBST on ORR was significant for the full dataset and for the EC subgroup, and such a correlation between TMBST and ORR has previously been reported for immune-checkpoint inhibitors.[51] Additionally, improved ECOG PS was a clinically relevant predictor of ORR across the full dataset and both the EC and dMMR subgroups. However, interpreting ER relationships for efficacy can be challenging due to potential confounding effects such as baseline patient characteristics, tumour type, tumour progression and the effect of disease status (e.g. cancer-associated cachexia) on PK (particularly time-dependent CL).[52,53] Previous studies of efficacy ER relationships for anti-PD-1 agents have produced discrepant findings.[28,45,53–56] However, a previous modelling analysis for nivolumab based on simulated and clinical data demonstrated that using exposure metrics derived from an early stage of the trial provided an estimate of the ER relationship that was less affected by response to treatment, as patients with better response showed greater reduction of CL.[57] Our ER analyses therefore used Cycle 1 (Day 21) exposures for efficacy to avoid this confounding (i.e. reduce the impact of time-dependent CL on the ER relationship)[52] and the relatively high IIV and shrinkage estimates for I_{max} observed did not have any significant impact on the exposure estimates derived for this analysis, due to Cycle 1 exposures being used.

Exposure over the first 6 weeks (cumulative $AUC_{0-6weeks}$) was used in the ER analysis of safety to obtain a complete dosing interval for all patients. The analysis indicated that the tested exposure metrics were not significant predictors for the AEs evaluated. Whilst the ER relationship for fatigue appeared to not be flat, this observation was considered inconclusive, due to limited number of patients in the upper range of exposures. Similarly, exposure or dose level has been found not to be a significant predictor of safety for pembrolizumab, nivolumab or cemiplimab previously.[28,29,54,55]

The strengths of our PopPK and ER analyses include the inclusion of patients across multiple tumour types, inclusion of covariates of clinical interest, including those that may have confounding effects on ER efficacy relationships, the multiple exposure metrics tested and the evaluation of exposure data for specific time periods (Cycle 1 for efficacy [Day 21], and during the first 6 wk for AEs).[52] However, this analysis applies only to the exposure range evaluated, with most data arising from the therapeutic dose regimen of 500 mg Q3W followed by 1000 mg Q6W, as used in GARNET Part 2B, and no extrapolation is possible beyond the dose range evaluated.

In conclusion, in this analysis, a PopPK model describing dostarlimab PK was developed, demonstrating similar PK properties to other anti-PD-1 mAbs. The impact of covariates on dostarlimab exposure was judged to be limited-to-moderate within the dose range evaluated in this study. The PopPK model was able to adequately describe the data, as judged by graphical goodness-of-fit including pc-VPCs. These PK and ER analyses support the recommended therapeutic dosing regimen for dostarlimab monotherapy of 500 mg Q3W for 4 cycles followed by 1000 mg Q6W in recurrent/advanced EC,[2,3] and exposures achieved with this regimen are expected to result in maximal peripheral PD-1 suppression throughout the dosing cycle.[34]

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COMPETING INTERESTS

M.M., S.V. and Y.G. are employees of GSK and hold stock/ownership interests; S.L. is a former employee of GSK. E.H. and O.A. are employees of qPharmetra and report consultancy fees from GSK.

CONTRIBUTORS

M.M., S.L., S.V. and Y.G. contributed to study conception/design and data analysis or interpretation. O.A. and E.H. contributed to data analysis or interpretation.

ClinicalTrials.gov: NCT02715284.

DATA AVAILABILITY STATEMENT

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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