Prediction of tumour response induced by chemotherapy using modelling of CA-125 kinetics in recurrent ovarian cancer patients

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Background: The main objective of the present study was to establish the relationships between CA-125 kinetics and tumour size changes during treatment.

Methods: The data from the CALYPSO-randomised phase III trial, comparing two platinum-based regimens in recurrent ovarian cancer (ROC) patients, was randomly split into a 'learning data set' to estimate model parameters and a 'validation data set' to validate model performances. A kinetic–pharmacodynamic semi-mechanistic model was built to describe tumour size and CA-125 kinetics during chemotherapy. The ability of the model to predict tumour response induced by chemotherapy, based on CA-125 values, was assessed.

Results: Data from 535 ROC patients were used to model CA-125 kinetics and tumour size changes during the first 513 days after treatment initiation. Using the validated model, we could predict with accuracy the tumour size changes induced by chemotherapy based on the baseline imaging assessment and longitudinal CA-125 values (mean prediction error: 0.3%, mean absolute prediction error: 10.6%).

Conclusions: Using a semi-mechanistic model, the dynamic relationships between tumour size changes and CA-125 kinetics induced by chemotherapy were established in ROC patients. A modelling approach allowed CA-125 to be assessed as a biomarker for tumour size dynamics, to predict treatment efficacy for research and clinical purposes.

Worldwide, ovarian cancer is the leading cause of death among all invasive cancers of the female gynaecological system (Jemal *et al*, 2011). The asymptomatic features of early-stage disease lead to frequent diagnosis at later stages in most patients, thereby contributing to the poor prognosis of this cancer. Metastases, mainly located in the peritoneal cavity, are found in 61% of patients

at diagnosis, and the 5-year survival is less than 30% (Lengyel, 2010; Howlader *et al*, 2012). CA-125 is the serum marker established for the post-treatment follow-up of ovarian cancer patients. It is secreted by tumour cells and healthy normal cells into the plasma.

Strategies combining platinum-based chemotherapies, meant to reduce tumour burden, and interval debulking surgeries in cases of

peritoneal carcinomatosis, have been developed to cure patients, or at least to slow down disease progression (Vergote *et al*, 2010). Such approaches require proper evaluation of the disease extent before and during treatment to estimate the potential benefit of surgery. However, due to the microinfiltrative feature of peritoneal carcinomatosis, the disease is not measurable by imaging in many patients with advanced ovarian cancers. Therefore, tumour response cannot be frequently assessed using Response Evaluation Criteria in Solid Tumors, and strategies are still being developed to help characterise tumour size changes easily during treatment (Rustin *et al*, 2004). Moreover, imaging tests, such as CT scanner and MRI, are not available in all parts of the world. Assessment of tumour response to chemotherapy based on CA-125 kinetics would be cheap and helpful in low-resource countries.

Monitoring of the declining profile of CA-125 during chemotherapy has been extensively investigated as a way of predicting treatment efficacy. However, numerous studies reported inconsistent outcomes for the prognostic values of different kinetic parameters and, despite the official definition of CA-125 response by the Gynecologic Cancer InterGroup, the optimal methodology to assess CA-125 kinetics remains undetermined (Lee *et al*, 2011).

An intuitive direct link between tumour size changes and tumour marker kinetics has been the basic hypothesis sustaining all studies on the prognosis of tumour marker kinetics. If this assumption was confirmed, it might be of high relevance as a rational strategy for predicting tumour burden changes induced by chemotherapy and for evaluating the potential benefit of surgical intervention or surgical resection of the tumour in the treatment of ovarian cancer patients. In the present study, we developed a kinetic–pharmacodynamic (K–PD) semi-mechanistic model to characterise the relationships between CA-125 kinetics and tumour size changes induced by chemotherapy.

MATERIALS AND METHODS

Data and objectives. The CALYPSO trial was a randomised, multicentre, phase III non-inferiority trial to test the efficacy and safety of the combination of carboplatin and pegylated liposomal doxorubicin (CD) compared with the standard combination of carboplatin and paclitaxel (CP) in patients with platinum-sensitive recurrent ovarian cancer (ROC). A total of 976 patients were randomised, 467 to CD and 509 to CP. Patients were excluded from the study if they had received prior radiotherapy, and simultaneous administration of other anticancer therapy was not allowed (Pujade-Lauraine *et al*, 2010). Pujade-Lauraine *et al* (2010) reported the superiority of CD regarding PFS and safety. The details of this study are provided elsewhere (Pujade-Lauraine *et al*, 2010).

The present study aimed at the following: (1) building a population K–PD semi-mechanistic model, which may enable accurate investigation of the relationships between drug kinetics, tumour dynamics, and tumour marker production and elimination; (2) evaluating model performance in an advanced internal validation; and (3) assessing the possibility of predicting tumour response based on CA-125 concentration kinetics in patients with and without measurable disease.

Data management. A semi-mechanistic model was built using the available CA-125 concentrations and tumour size values along with the chemotherapy treatments and dates. For our analysis, only patients with at least four measurements of CA-125 and two tumour size values were retained. In a first intent, patients with non-measurable lesions were excluded. Then, the patient data set was randomly split into two: a learning data set including two-third of patients to build the model and estimate parameters, and a validation data set with the remaining one-third of patients for an

advanced evaluation of the model. Owing to the magnitude of observed values for the dependent variables, CA-125 concentrations were Box–Cox transformed, as described in the Supplementary Material 1, and tumour size values were log transformed (Box and Cox, 1964).

Tumour size corresponded to the sum of the longest dimensions of all target lesions. The limit of quantification (LOQ) for tumour size data was 10 mm (Eisenhauer *et al*, 2009). Tumour sizes below the LOQ were set to LOQ/2 (5 mm) and the s.d., associated with the imprecision of this measure, was fixed at LOQ/4, as previously described (M5 method; Beal, 2001).

Model development and qualification. A semi-mechanistic model, defined as a compartmental model with minimal physiological components, was built to describe CA-125 concentrations and tumour size kinetics during chemotherapy treatment (Figure 1). A K–PD approach was used to describe the kinetics of the drug action in the absence of PK data (Jacqmin *et al*, 2007). The model contained three outputs: the drug kinetics, the tumour dynamics, and the CA-125 kinetics.

The drug kinetics were described by a two-compartment K–PD model: a central compartment (A_1) receiving the treatment and a transit compartment (A_2) allowing a lag time before the drug effect, typical of anticancer drugs (Savic *et al*, 2007). As no doses or concentrations were available, an arbitrary value (equal to 1) was set for the dose of each chemotherapy cycle. A K–PD model, with two different kinetics for each chemotherapy combinations (CP and CD), was tested. As parameters were not significantly different, a model with the same drug kinetics for both treatments was retained.

Tumour dynamics were dependent on the treatment effect, acting as an inhibitor of tumour growth in a saturable manner. Different models of tumour growth inhibition were tested as described in the Supplementary Material 2; Supplementary Table S1). A constant tumour growth rate with a linear decrease rate fitted the best. In order to enable the tumour growth, the baseline tumour size was constrained to be less than the steady-state condition using the logit function as described in the Supplementary Material 3).

CA-125 kinetics were described with an indirect model including production and elimination rates. To account for CA-125 production by both normal tissues and cancer tissues, two additive production rates were considered: KPROD1, the CA-125 basal production rate by normal tissue, and KPROD2, the CA-125 production rate by a stationary tumour. The key models tested to link CA-125 with tumour size or variations in tumour size are described in the Supplementary Material 2; Supplementary Table S2).

The final model was described with the following equations:

$$\begin{cases} \frac{dA_1}{dt} = -K \times A_1 \\ \frac{dA_2}{dt} = K \times A_1 - K \times A_2 \\ \frac{d\text{Tumoursize}}{dt} = K_{\text{PROL}} \times \left(1 - \frac{A_2}{A_{50} + A_2}\right) - K_{\text{REDUC}} \times \text{Tumoursize} \\ \frac{d\text{CA125}}{dt} = K_{\text{PROD1}} + K_{\text{PROD2}} \times \exp(K2 \times VAR_{\text{TS}}) - K_{\text{ELIM}} \times \text{CA125} \end{cases}$$

The initial conditions at time 0 were:

$$\begin{cases} A_1(0) = 0 \\ A_2(0) = 0 \\ \text{Tumoursize}(0) = \text{TS}_0 \\ \text{CA125}(0) = \text{CA}_0 \end{cases}$$

A_1 and A_2 represent drug amounts in the central compartment and the transit compartment, respectively. K is the treatment kinetic rate constant. K_{PROL} is the tumour growth rate. A_{50} is the amount producing 50% of the maximum effect. K_{REDUC} is the tumour size decrease rate constant. K_{PROD1} is the CA-125 basal production rate. K_{PROD2} represents the CA-125 production rate by
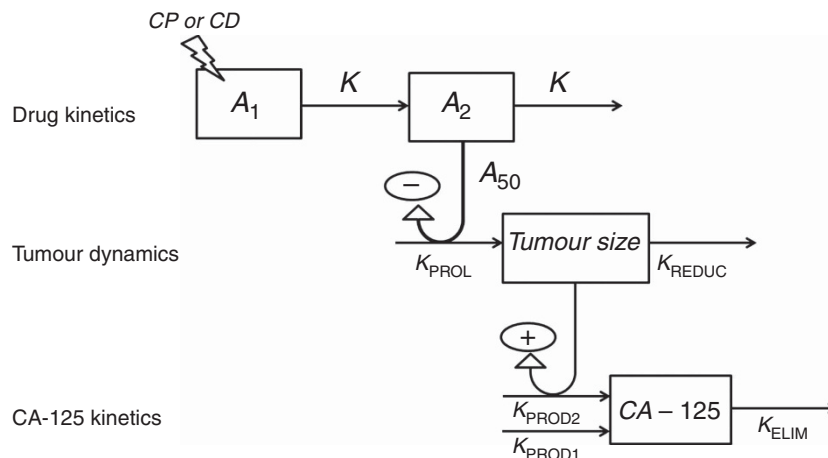
Figure 1. K–PD semi-mechanistic model describing tumour size and CA-125 kinetics in ROC patients during chemotherapy. A_1 and A_2 represent drug amounts in the central compartment and transit compartment (arbitrary unit; a.u.), respectively. K is the treatment kinetic rate constant (day^{-1}). K_{PROL} is the tumour growth rate (mm per day). A_{50} is the amount producing 50% of the maximum inhibitory effect of A_2 on K_{PROL} (a.u.). K_{REDUC} is the tumour size decrease rate constant (day^{-1}). K_{PROD1} is the CA-125 basal production rate (U ml^{-1} per day). K_{PROD2} represents the CA-125 production rate by a stationary tumour (U ml^{-1} per day). $K2$ is a proportional factor (day mm^{-1}). K_{ELIM} is the CA-125 elimination rate constant (day^{-1}). TS_0 is the initial tumour size value (mm) and CA_0 is the initial CA-125 concentration (U ml^{-1}).

a stationary tumour. $K2$ is a proportional factor linking K_{PROD2} to VAR_{TS}; VAR_{TS} is the tumour size variation ($\frac{dTumoursize}{dt}$). K_{ELIM} is the CA-125 elimination rate constant. TS_0 is the initial tumour size value and CA_0 is the initial CA-125 concentration.

To estimate the model parameters, population analysis was performed using the non-linear mixed effects modelling approach as commonly done, where data from all patients are analysed simultaneously (described in the Supplementary Material 4; Sheiner, 1984). Log-normal parameter distributions within the population were assumed, and an additive error model was used to reflect residual variability (including measurement errors) in tumour size and CA-125. As 50% of patients had discontinued the study in the first 513 days after randomisation (or the first treatment day), we limited modelling analysis to this time frame to reduce potential biases.

We searched for covariates able to reduce the unexplained variability of model parameters using a stepwise forward selection–backward deletion (Jonsson and Karlsson, 1998).

The best model was selected using criteria based on the maximisation of the likelihood (or minimisation of the objective function value), Akaike criteria, classical goodness-of-fit plots (GOF), and the normalised prediction distribution errors (NPDE) (FDA, 1999). In addition, the model's predictive capacity was tested using the visual predictive check (VPC) (FDA, 1999; Yano et al, 2001). One hundred simulations of CA-125 and tumour size profiles from the learning data set were performed using the final individual parameters estimated from the model. The observed CA-125 values and tumour sizes were compared with the median and 90% confidence intervals of the CA-125 concentrations and tumour sizes, respectively, from the simulated replicates (Yano et al, 2001).

Advanced internal evaluation. The ability of the final model to predict tumour size and CA-125 values was evaluated using the validation data set. The metric used was the NPDE, computed after 100 simulations of the validation data set (Brendel et al, 2006). The model and population parameters were considered correct if the NPDE followed a standard normal distribution.

Tumour size prediction to estimate the test's clinical performance. The ability of the model to predict tumour size changes based on CA-125 was tested. From the validation data set, all CA-125 observations up to 200 days (nine cycles of chemotherapy) and

the initial tumour size value for each patient were used. The final model structure and population parameter distributions, obtained from the learning data set, were used for predicting tumour size changes for the following 200 days, in validation data set patients. The maximum a posteriori bayesian method was used (Supplementary Material 4). Predictions were compared with observations graphically and the performance of predictions was evaluated numerically. The mean prediction error (MPE) was used to assess prediction bias, whereas the mean absolute prediction error (MAE) was computed to estimate prediction accuracy as described in the Supplementary Material 5.

In the same way, the model was used to predict latent tumour response induced by chemotherapy based on CA-125 kinetics in patients with non-measurable disease, excluded from the model building and the advanced internal validation.

Computing process. The NONMEM 7.2 software (ICON Development Solutions, Ellicott City, MD, USA) and PsN suite were used to fit CA-125 and tumour size kinetics to the semi-mechanistic model (Lindbom et al, 2004; Beal et al, 2009). Estimations were made by maximising the likelihood of the data, using the Stochastic Approximation Expectation Maximization algorithm followed by an important sampling to obtain the objective function value for hypothesis testing by the likelihood ratio test (Beal et al, 2009). The covariate model was built using the PsN's scm programme (Jonsson and Karlsson, 1998; Lindbom et al, 2004). Data handling and graphical representations were performed in R, using the Xpose package (Jonsson and Karlsson, 1999; R Development Core Team, 2010). The Box–Cox power parameter λ was calculated in R, using the powertransform function of the car package (R Development Core Team, 2010).

RESULTS

Data. Two hundred and ninety-seven patients with tumour size missing data owing to non-measurable disease were excluded. As a consequence, the data from 535 patients were available for modelling analysis (Figure 2), with a median of 10 CA-125 values and four tumour size observations per subject. Distributions of continuous and discrete covariates are described in Table 1. After random data splitting, the learning data set contained 357 patients

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┌─────────────────────┐
│   CALYPSO trial     │
│  N = 974 enrolled   │
│      patients       │
└─────────────────────┘
           │
           │          ┌──────────────────────────────────────────────┐
           │          │ Exclusions:                                  │
           │          │  - 16 Patients with missing data on time     │
           │          │  - 297 Patients with missing data on tumour  │
           │          │    size                                      │
           ▼          └──────────────────────────────────────────────┘
┌─────────────────────┐
│  N = 661 patients   │
│  with no missing    │
│       data          │
└─────────────────────┘
           │          ┌──────────────────────────────────────────────────────┐
           │          │ Exclusions:                                          │
           │          │  - 39 Patients with < 4 CA-125 observations          │
           │          │  - 35 Patients with < 2 tumour size values           │
           │          │  - 52 Patients with CA-125 values consistently       │
           ▼          │    < 25 U ml⁻¹                                        │
┌─────────────────────┐ └──────────────────────────────────────────────────┘
│  N = 535 patients   │
│  with data available│
│    for modelling    │
│      analyses       │
└─────────────────────┘
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Randomisation

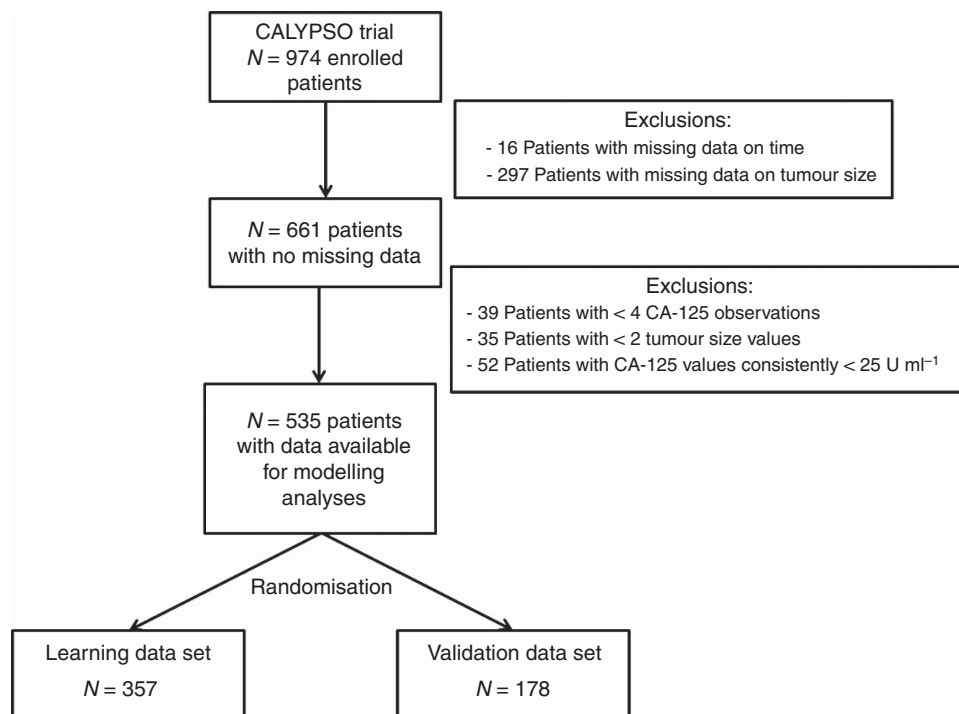| Learning data set	Validation data set
$N = 357$	$N = 178$

Figure 2. Selection of patients included in the present study (CONSORT diagram).

and the validation data set contained 178 patients. Patients' characteristics were similar in both data sets. The value of the power parameter λ for the CA-125 Box–Cox transformation was estimated at -0.16.

K–PD model. Typical parameter and inter-individual variability (IIV) estimates of the joint model for tumour size and CA-125 kinetics are presented in Table 2. The CA-125 half-life was estimated at 52.5 days. Relative s.e. (RSE) of typical mean parameters and IIV, representative of estimation precision, were all less than 25%. Because of the heterogeneity of the data, IIV were large, but they were supported by satisfactory RSE and shrinkage values. None of the tested covariates, summarised in Table 1, were found to significantly reduce the unexplained IIV of model parameter estimates.

Model evaluation. The GOFs demonstrate that both individual CA-125 kinetics and tumour change profiles were properly fitted by the model (Supplementary Material 6; Supplementary Figure S1A–D). The NPDE, which followed a standard normal distribution as expected, suggested no bias or trends in the residual error models (Supplementary Material 6; Supplementary Figure S1E and F). The VPCs, which were used to assess the internal validity of the model, demonstrated that most of the observed CA-125 values and tumour size predictions were included within the 90% confidence interval boundaries of simulated CA-125 and tumour size predictions, suggesting good predictive performance of the model (Figure 3).

For advanced internal evaluation purposes, the kinetic parameters derived from the learning data set were used to predict CA-125 kinetics and tumour size changes in the validation data set patients. The NPDE did not deviate from a standard normal distribution, indicating that the model and population parameter distributions were correct (Supplementary Material 7; Supplementary Figure S2).

Tumour size prediction based on CA-125 kinetics in the validation data set. After integrating the initial radiological tumour size at treatment initiation, our model was used to predict

the subsequent variations of tumour sizes (above the 10-mm LOQ) induced by chemotherapy on the basis of longitudinal values of CA-125 only over a period of 200 days. There was good graphical agreement between the observed and predicted tumour sizes, without bias (MPE = 0.3%) and with an acceptable precision (MAE = 10.6%). The kinetics profiles of the observed CA-125 and predicted tumour sizes for two patients are shown in the Figure 4A.

Finally, latent tumour response was predicted, based on longitudinal CA-125 assessments, in the 297 patients with non-measurable disease. Two individual profiles for the kinetics of CA-125 kinetics and latent tumour response are shown in the Figure 4B.

More individual kinetics profiles are available in the Supplementary Material 8.

DISCUSSION

The proof of a direct relationship between CA-125 kinetics and tumour burden changes may have important clinical consequences in ovarian cancer patients treated with chemotherapy. Such results would mean it may be used as a complement tool to overcome the limitations of imaging in advanced ovarian cancer patients, or facilitate assessment of tumour response to treatment in countries where modern imaging tests are not available. Our mathematical model is the first, to our knowledge, to link tumour size changes and CA-125 kinetics to cytotoxic effects in ROC patients receiving chemotherapy. The results of the present modelling suggest that there are quantifiable relationships between CA-125 kinetics and tumour size changes. The assumption, that the tumour size variation will drive the rate of change for CA-125, results from the non-heterogeneity of the tumours in term of vascularisation. Internal and advanced internal validation demonstrated the strong prediction ability of the model. Some results such as CA-125 half-life (52.5 days) were in agreement with literature data (Riedinger et al, 2008). We used a K–PD approach because of the absence of PK data. The integration of already published population PK

Table 1. Patient characteristics			
	Total ($n = 535$)	Learning data set ($n = 357$)	Validation data set ($n = 178$)
Characteristics			
CA-125 values number per patient	9 (4–15)	9 (4–15)	9 (4–15)
CA-125 values (U ml^{-1})	43 (1–13 235)	41 (1–10 079)	45 (3–13 235)
Tumour size values number per patient	4 (2–6)	4 (2–6)	4 (2–6)
Tumour size values (mm)	34 (5–400)	33 (5–400)	34 (5–395)
Dropout times (day)	424 (59–513)	424 (59–513)	425 (93–512)
Continuous covariates			
Age (year)	61 (27–82)	62 (30–80)	61 (27–82)
Weight (kg)	69 (41–150)	69 (45–121)	70 (41–150)
Height (cm)	162 (139–183)	162 (139–183)	162 (143–178)
Body surface area (m^2)	1.73 (1.32–2.59)	1.72 (1.34–2.3)	1.73 (1.32–2.59)
Creatinine (μmol l^{-1})	71 (6.2–154)	71 (6.2–154)	71 (6.2–143)
PFS 1st chemo (month)	20 (2.8–144)	20.5 (2.9–144)	21.6 (2.8–83)
Patient therapy free interval (month)	12 (6–12)	12 (6–12)	12 (6–12)
Categorical covariates			
Treatment			
CP	284	190	94
CD	251	167	84
Any surgery within 28 days			
Yes	43	23	20
No	492	334	158
FIGO stage			
I	24	16	8
II	38	24	14
III	395	269	126
IV	66	39	27
NAs	12	9	3
Primary tumour site			
Fallopian	19	13	6
Ovary	475	316	159
Peritoneal	41	28	13
Elevated white blood cells			
Yes	342	226	116
No	193	131	62
Ascite involvement			
Yes	531	355	176
No	4	2	2
Measurable lesion			
Yes	494	332	162
No	41	25	16
Lesion sites number			
$= 1$	163	115	48
> 1	372	242	130
Target lesion size			
< 5	390	251	139
> 5	145	106	39
Number of cycles			
(1–3)	33	26	7
(4–6)	376	247	129
(7–9)	107	72	35
(10–14)	19	12	7
Abbreviations: CD = carboplatin-pegylated liposomal doxorubicin; CP = carboplatin–paclitaxel; PFS = progression-free survival. Data are presented as median (min–max) or number of patients (%).			

Table 2. Estimates of typical parameters and IIV					
Parameter (unit)	Estimate	RSE estimate (%)	IIV (%CV)	RSE IIV (%)	Shrinkage (%)
K (day^{-1})	0.019	17.4	72.1	7.1	22.1
K_{PROL} (mm per day)	0.869	10.2	153.6	4.7	25.7
A_{50} (a.u.)	0.162	23.7	167.0	12.8	23.9
K_{REDUC} (day^{-1})	0.013	6.5	140.4	2.7	15.2
K_{PROD1} (U ml^{-1} per day)	0.452	10.9	87.0	16.6	31.7
K_{PROD2} (U ml^{-1} per day)	0.615	7.1	225.8	10.7	8.7
$K2$ (day mm^{-1})	21.4	3.8	108.6	8.1	15.8
K_{ELIM} (day^{-1})	0.037	7.2	63.6	15.8	21.7
TS_0 (mm)	57.8	2.8	75.6	14.5	4.3
CA_0 (U ml^{-1})	167	16.9	112.7	4.3	4.7
Residual error for tumour size above LOQ (mm)	0.273	6.6	—	—	—
Residual error for tumour size below LOQ (mm)	0.576 FIX	—	—	—	—
CA-125 residual error (U ml^{-1})	0.165	11.3	—	—	—

Abbreviations: CA_0 = baseline CA-125 value; CV = coefficient of variation; FIX = fixed parameter; IIV = inter-individual variability; LOQ = limit of quantification; RSE = relative s.e.; TS_0 = baseline tumour size.
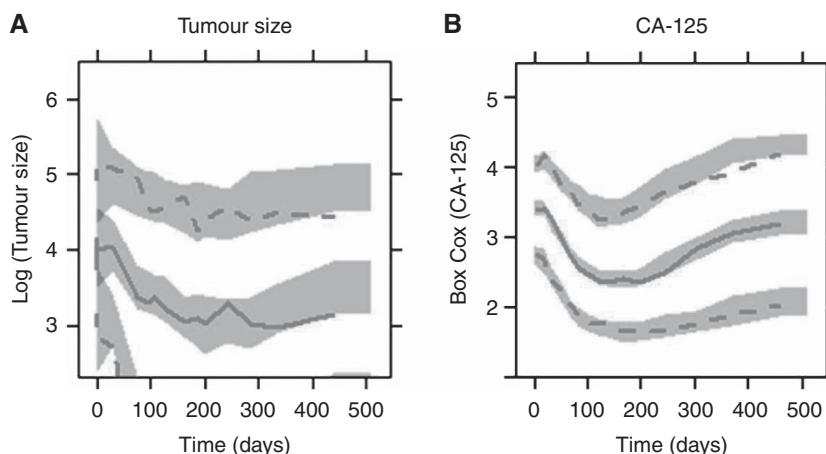

Figure 3. Visual predictive check of (**A**) tumour size and (**B**) CA-125. Transformed tumour size and CA-125 values are plotted *vs* time. Blue areas represent the 95% confidence intervals of the 10th, 50th, and 90th percentiles of simulated data. Red lines represent the median (solid line), and the 10th and 90th percentiles (dashed lines) of the observations. Values below the LOQ are not drawn. The full colour version of this figure is available at *British Journal of Cancer* online.

model would be useful only if the model had a covariate model explaining the major part of the IIV. Development of resistance was also evaluate in the model, but as a few tumour regrowth under treatment were observed, data did not contain enough information to support the estimation of a treatment resistance.

The second main finding of the present study is our potential ability to predict, with limited bias and correct precision, individual tumour size changes induced by chemotherapy based on CA-125 kinetics. We could monitor individual tumour size kinetic profiles on the basis of longitudinal CA-125 values and the initial tumour size. Practically, these outcomes mean that prediction of tumour size changes based on CA-125 kinetics may be a useful complementary tool for surgeons when assessing the resectability of residual lesions after three or six cycles of chemotherapy.

Some limitations may reduce the impact of the outcomes presented here. First, this work is an unplanned retrospective study of the CALYPSO phase III trial and results will have to be validated in another cohort of patients. Second, CA-125 concentrations were assessed in patients from different countries using different tests.

Variability related to the use of different immunoassays might have contributed to increase inter- and IIV and to scatter kinetic parameter results.

Moreover, there are limitations while extrapolating the present outcomes to clinical situations, as our results are bound to the patient population enrolled in the CALYPSO trial and its primary objective, that is, to compare two platinum-based chemotherapy regimens on progression-free survival in ROC patients. As a result, our outcomes may not necessarily be applicable to patients who are potential candidates for primary or interval debulking surgery. Moreover, we had no data for investigating the predictive value of forecasted tumour size on tumour resectability. Thus, we have planned to investigate the value of our predictions in a study specifically designed to assess the role of surgery.

Despite these limitations, the present model-based study suggests a quantifiable link between CA-125 kinetics and tumour size changes and the potential prediction of tumour burden based on CA-125 variations. If these results are confirmed, relevant information may be derived for management of ovarian cancer
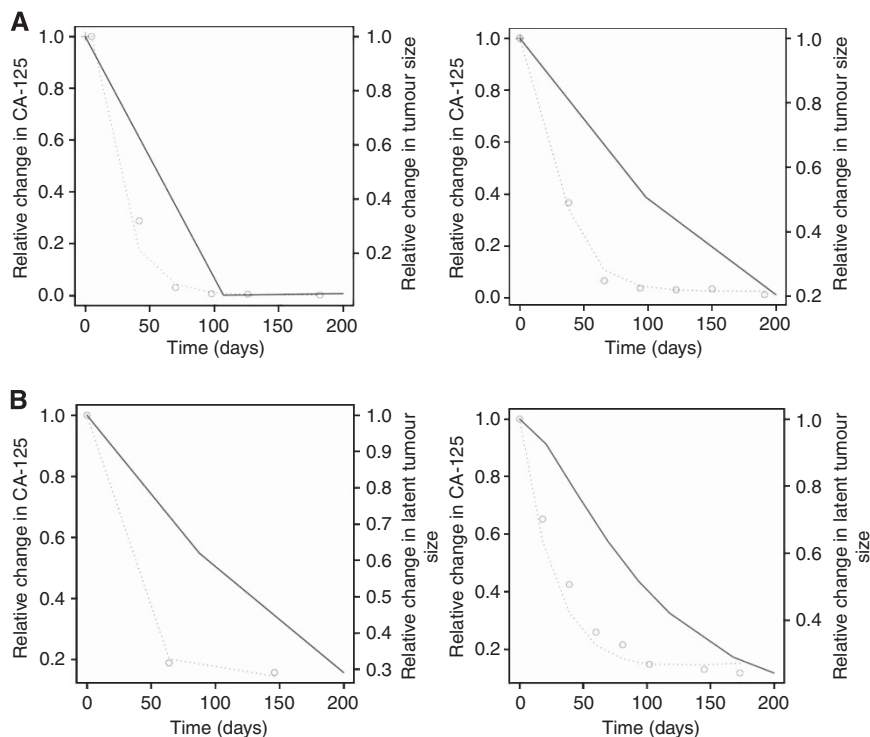
Figure 4. Prediction of tumour response and latent tumour response for the first 200 days of the study in patients with measurable (A) and non-measurable disease (B). Dotted red lines are the predicted kinetics of the relative change in CA-125, red circles are the observed relative change in CA-125, blue lines represent the dynamics of the relative change in predicted tumour size and latent tumour size, and blue crosses are the observed relative change in tumour size. The full colour version of this figure is available at *British Journal of Cancer* online.

patients, particularly by guiding surgical decision making in a setting where imaging has limited utility. Although model building is a complex process, models could be easily implemented on routine settings. An online programme integrating the models could automatically calculate individually modelled kinetic parameters of interest, and thus predict tumour response, based on a few CA-125 time points measured during treatment. Furthermore, this model-based approach may have other applications such as analysis of other tumour markers for different groups of cancer patients, or as a predictor of drug efficacy for drug development.

Quantification of the links between survival and early changes in tumour size and/or CA-125 (predicted with the present model), analogous to the work of Claret *et al* (2009), has been planned.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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