ARTICLE

A New Method to Model and Predict Progression Free Survival Based on Tumor Growth Dynamics

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Progression-free survival (PFS) has been increasingly used as a primary endpoint for early clinical development to evaluate efficacy of different cancer treatments. Although overall survival (OS) remains the gold standard for evaluating new oncology therapies, using OS as the primary endpoint can be challenging, requiring a larger sample size and longer follow-up time, and increasing line of therapies may confound the OS result.1 In contrast, PFS can be accessed in a relatively short follow-up time, avoiding any confounding effects of subsequent lines of therapy. Therefore, as an important surrogate endpoint for OS, PFS has been increasingly used in early clinical development stages as the primary endpoint to accelerate drug approval, particularly in disease areas where treatment options are limited.1

In parallel, efforts have been made to use longitudinal tumor size data as a biomarker to quantitatively predict clinical endpoints, such as OS.2–6 There has been an increasing interest in applying the approach in the clinical development of oncology products from both the industry and regulatory agencies.7 This quantitative modeling approach linking tumor growth dynamics to OS could potentially inform early decision making in clinical development and subsequently guide the design of pivotal trials.4–6 However, most of the previous works have aimed at modeling and predicting OS with limited focus on PFS.3,7–9

Platinum-resistant ovarian cancer is defined as disease progression during or within 6 months after completion of prior platinum-based chemotherapy. Patients with platinum-resistant ovarian cancer have a poor prognosis with limited treatment options. Current standard of care, such as pegylated liposomal doxorubicin (doxorubicin), has a < 20% overall response rate and a median PFS of 3.7 months.10,11 In this setting, PFS currently is an acceptable endpoint for

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✔ There has been an increasing interest toward using tumor size data as a biomarker to predict clinical outcomes. The focus has primarily been on overall survival, whereas predicting progression-free survival (PFS) has not been thoroughly investigated.

WHAT QUESTION DID THIS STUDY ADDRESS?

✔ Is there a way to predict PFS based on a joint model where progression is either derived from target lesion growth or predicted from a nontarget progression hazard?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✔ The study suggests PFS could be jointly modeled as target lesion and nontarget progressions. The target lesion progression could be derived from tumor growth dynamics following the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The nontarget progression could be predicted by modeling nontarget progression hazard as a function of tumor growth dynamics metrics. The PFS time would be determined by the first occurring progression event.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

✔ The proposed method can be used to provide early predictions of PFS before the PFS data are mature, hence supporting early decision making in future oncology studies.
regulatory decisions. The risk of a PFS event can be linked to tumor growth dynamics using a hazard function, which is similar to what has been done for predicting OS. However, PFS events are often triggered by growth of target lesions. Hence, once a tumor dynamics model has been developed, it can be used to predict target lesion progressions directly by applying the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. To fully account for PFS, however, the PFS events not be related to the target lesions need to be modeled using the time-to-event methodology. In this work, using a pooled platinum-resistant ovarian cancer data set, we investigated whether PFS could be jointly modeled as target lesion progression and nontarget progression, where target lesion progression was directly derived from tumor growth dynamics. Our goal was to develop a modeling approach that not only utilizes available information from tumor growth dynamics but also applies the RECIST criteria. The method can be considered for early decision making in future studies when PFS is deemed to be critical.

METHODS
Platinum-resistant ovarian cancer data set
A pooled data set was created from three phase I and one phase II studies conducted by Genentech among patients with platinum-resistant ovarian cancer over the last decade. The three phase I studies were dose-escalating studies of anti-MUC16 antibody-drug conjugate (ADC; NCT01355958), anti-MUC16 THIOMAB-drug conjugate (TDC; NCT02146313), and anti-NaPi2b ADC (NCT01363947). The phase II study compared the safety and activity of anti-NaPi2b ADC to doxorubicin (NCT01991210). Besides patients with platinum-resistant ovarian cancer, the phase I studies had also enrolled patients with pancreatic cancer and patients with non-small cell lung cancer, which were excluded from the pooled data set. Additionally, 23 subjects had been evaluated with a weekly dosing schedule (Q1W) during the anti-MUC16 ADC phase I study; and one subject in anti-NaPi2b ADC phase II study had data errors in PFS information. These 24 subjects were also excluded from the pooled data set. In the final pooled data set, a total of 230 subjects were included, where 43 subjects received anti-MUC16 ADC, 65 received anti-MUC16 TDC, 76 received anti-NaPi2b ADC, and 62 received doxorubicin. The ADC and TDC were dosed i.v. every 3 weeks (Q3W), whereas doxorubicin was dosed i.v. every 4 weeks (Q4W) with a 40 mg/m² single dose level. Because the data set contained three phase I studies, it presented a wide range of dose levels ranging from 0.2 to 5.6 mg/kg for ADCs (Table S1). Tumor assessments were scheduled at screening and then every 6 weeks after the starting of the study treatment in the phase I studies or every 8 weeks after the starting of the study treatment in the phase II study. All clinical trials were conducted in accordance with the Declaration of Helsinki and in compliance with good clinical practice guidelines and quality assurance procedures. More details on the studies included in the data set can be found in the previous clinical publications.

Modeling software
The model was developed using the nonlinear mixed-effects modeling software (NONMEM), version 7.4 (ICON Development Solutions, Ellicott City, MD). The first-order conditional estimation with interaction combined with the Laplace method was used for parameter estimations. Perl-speaks-NONMEM version 4.8.1 (https://uupharmacometrics.cs.github.io/PsN/) and Pirana version 2.9.9 (Certara USA, Princeton, NJ) were used to manage NONMEM runs. The R software package version 3.5.1 (http://www.r-project.org/) was used to assemble the pooled data set and perform model diagnosis.

Model evaluation
The likelihood ratio test was used to select between nested models based on the principle that the difference in NONMEM objective function values (ΔOFV) between two nested models approximately follows a χ² distribution. The model performance was evaluated using the visual predictive check (VPC) technique. For tumor growth dynamics VPC, the 5th percentiles, median, 95th percentiles, and proportion of data that are below the lower limit of quantification (LLOQ) were compared between observed values of longitudinal sum of the longest diameter (SLD) and 95% confidence interval (CI) of model simulation. For PFS Kaplan–Meier VPC, 95% CI of model simulation was compared with observed PFS Kaplan–Meier result.

General method for modeling PFS
A modeling approach was developed in which three possible outcomes defined PFS: (1) target lesion progression, (2) nontarget related progression (or death), and (3) dropout. For target lesions, as per the RECIST criteria version 1.1, progression was defined as at least a 20% increase in the SLD, taking as reference the smallest observed SLD (including baseline) in the study. Additionally, the absolute increase of SLD must be at least 5 mm.

(Figure 1a)

A patient was considered to have a nontarget progression when the target lesion progression criteria were not met, but any of following conditions were present: growth of nontarget lesion, new lesion, symptomatic deterioration, or death (Figure 1b).

PFS information would be censored if a patient withdrew from the study before having either target lesion progression or nontarget progression (Figure 1c). When simulating from the model, the PFS time would be determined by target lesion progression or nontarget progression, whichever occurs first.

Model of the tumor growth dynamic
The longitudinal tumor size data were described based on a modified version of the model developed by Claret et al. The model assumes that the tumor growth dynamics are governed by a first-order tumor growth, a drug exposure related tumor killing, and a time-dependent resistance to the drug treatment. The final model equations are listed below:

\[
\frac{d\text{SLD}}{dt} = \text{kg} \times \text{SLD} - \text{ks} \times \text{DOSE}_{\text{adj}} \times \text{SLD}
\]

\[
\text{ks} = \text{kS}_{0} \times e^{-\text{Gammaxt}}
\]
where, SLD is the sum of the longest diameters of target lesions measured according to the RECIST criteria version 1.1. The SLD value at screening was used as the baseline. The kg is the tumor growth rate constant, whereas ks is the drug-induced tumor killing rate. The value of ks decreases exponentially with time (t) from the initial value (ks₀), the rate of decrease being controlled by the parameter Gamma. Consistent with the baseline.

DOSE_{adj} = DOSE \times \text{POT}_{\text{drug}}

Figure 1 Illustration of progression-free survival (PFS) components in the model. (a) Patients having target lesion progression as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) guidance. (b) Patients having nontarget progression. (c) Patient dropout (censored). SLD, sum of the longest diameter.

Figure 2 Visual predictive check of tumor growth dynamics based on 100 simulations. (a) Longitudinal sum of the longest diameter (SLD) data with shaded areas showing 95% confidence interval (CI) of 95th, median, and 5th percentiles of simulated data. Dashed and solid line represent 95th percentile, median, and 5th percentiles of observations. The red horizontal line represents the lower limit of quantification of SLD value. (b) Proportion of SLD data that are below the lower limit of quantification (BLOQ) over time with solid line representing observations and shaded area representing 95% CI of model simulations. Simulated SLD data were included up to the first PFS events (target progression, nontarget progression, or dropout).
cytotoxic mechanism of action for the drugs included in the analysis, the drug effect was introduced on the killing parameter \( k_s \). Due to differences in drug-antibody ratios (DARs), pharmacokinetics, and dosing frequency among ADC, TDC, and doxorubicin, a drug-specific relative potency parameter (\( P_{OT, drug} \)) was used to account for the tumor killing difference between different treatments. Because anti-NaPi2b ADC had the greatest number of subjects, it was used as the reference drug with a relative potency value set to 1. The adjusted dose level (\( DOSE_{adj} \)) is the product of nominal dose level that each patient received (DOSE) and drug-specific relative potency. Tumor killing has a linear relationship with the drug exposure, which is represented by the potency-adjusted dose level that each patient received (\( DOSE_{adj} \)). The growth rate constant \( kg \) and the resistance parameter Gamma were shared across all treatments. Per RECIST criteria version 1.1, the lower limit of quantification (LLOQ) of SLD is 5 mm.\(^{13} \) The probability of SLD being BLOQ was estimated using the NONMEM M3 method.\(^{23} \) The interindividual variability of model parameters was assumed to follow a log-normal distribution as follows:

\[
P_i = \theta_p \times \exp(\eta_p)
\]

where, \( \eta_p \) denotes the difference between the parameter \( (\theta_p) \) of individual \( i \) and the typical value in the population \( (\theta_p) \), and is assumed normally distributed with mean zero and variance \( \sigma_p^2 \). Additive, proportional, and combined additive plus proportional error models were tested to explain the residual error.

**Time to event analysis**

The hazard for nontarget lesion progression (\( HZ_{NTLP} \)) was linearly associated with the first derivative of the tumor growth dynamics as:

\[
HZ_{NTLP} = \frac{dSLD}{dt} \times \text{slope} + \text{intercept} \\
HZ_{NTLP} \geq 0.
\]

When a patient has an increase in target lesion tumor growth rate over time, the hazard for the nontarget progression also increases. When a patient has target lesion shrinkage with negative \( \frac{dSLD}{dt} \), the hazard for nontarget progression decreases with a lower bound set to zero. Several other models and covariates were also tested, including constant hazard, SLD relative to baseline, relative SLD change over time (\( \frac{dSLD}{df} \)), baseline albumin level, baseline Eastern Cooperative Oncology Group status, and baseline total protein level. The survival model for nontarget lesion progression was implemented in NONMEM, and parameter values were simultaneously fitted with the tumor growth dynamic model parameters.

A parametric survival model for patient dropout was developed in R. The exponential, Weibull, logistic, log-normal, and log-logistic accelerated failure time models were fitted to the patient dropout data, and the model selection was based on the Akaike Information Criterion. The dropout model was used in the simulations for VPC and diagnostic plots.

**RESULTS**

The Claret et al. model with a treatment-specific relative potency parameter was able to adequately describe the longitudinal SLD profile over time for the population (Figure 2) and for individual patients (Figure S1). The proportional residual error model with interindividual variability was selected based on OFV and VPCs. For SLD measurement, the LLOQ is 5 mm per RECIST criteria version 1.1. The BLOQ data seemed to be adequately captured using the M3 method with a slight underprediction of the fraction below 5 mm. This is consistent with the slight overprediction of SLD as indicated by the VPC for the tumor dynamics (Figure 2).

To model the hazard for the patients having nontarget progression, a linear model linking the first derivative of the SLD over time to nontarget progression hazard was the best model to describe the data. Adding baseline albumin level, baseline Eastern Cooperative Oncology Group status, or baseline total protein level as a covariate in the model did not improve the model fit. The final parameter estimates of the joint model fit are presented in Table 1. Relative standard errors obtained from bootstrap suggested that parameters were estimated with good precision. In order to simulate realistic clinical outcomes, patient dropout was modeled using the exponential time to event model (Figure S2). The same dropout rate was assumed for different drugs as there was no statistically significant difference in patient dropout between treatments (Figure S3).

The final model performance was also evaluated by a PFS Kaplan–Meier plot VPC (Figure 3) showing a good agreement between overall simulated and observed data. Patient

| Table 1 Final parameter estimates |
|----------------------------------|
| **Parameter name (unit)** | Model estimate | SE by bootstrap (%) | Shrinkage (%) |
|-----------------------------|----------------|---------------------|---------------|
| kg (day\(^{-1}\)) | 0.002 | 7.01 | – |
| \( k_s \) (day\(^{-1}\)) | 0.00151 | 5.31 | – |
| Gamma | 0.00421 | 7.95 | – |
| Proportional error | 0.129 | 5.68 | – |
| Relative potency doxorubicin to NaPi2b | 0.048 | 8.25 | – |
| Relative potency MUC16-TDC to NaPi2b ADC | 0.571 | 9.44 | – |
| Relative potency MUC16-ADC to NaPi2b ADC | 0.705 | 10.9 | – |
| Non target progression hazard slope | 0.0556 | 29.1 | – |
| Nontarget progression hazard slope intercept | 0.00352 | 16.2 | – |
| IIV kg | 0.204 | 12.1 | 52.5 |
| IIV \( k_s \) | 0.406 | 14.0 | 31.6 |
| IIV on proportional error | 0.82 | 12.1 | 10.5 |

ADC, antibody-drug conjugate; IIV, interindividual variability; kg, tumor growth rate constant; \( k_s \), drug-induced tumor killing rate.

Bootstrap standard errors were obtained based on 500 simulations.
dropout was incorporated by using the exponential model in the simulation. In addition, the PFS Kaplan–Meier VPC were stratified by treatments (Figure 4) as well as dose levels (Figure S4) to verify that the model can capture the treatment difference as well as the dose response. The triggers for patients having a PFS event have also been compared between the model simulation and observed data (Figure 5). In general, model simulation is consistent with the actual clinical outcome, not only in overall PFS but also in terms of PFS event triggers. The overall frequency for patients having target lesion progression (105 of 230 subjects) and nontarget lesion progression (80 of 230 subjects) are similar between simulated and observed data, which suggests that the model has adequately captured the clinical outcome.

**DISCUSSION**

Although previous works have successfully modeled and predicted OS using different metrics derived from tumor growth dynamics as significant covariates,\(^2,^3\) predicting
Predicting PFS based on Tumor Growth Dynamics

Yu et al.

PFS in a similar setting has been less investigated. In this work, we proposed a method to predict PFS by categorizing disease progression into target lesion progression and nontarget progression. By this approach, we modeled the tumor growth dynamics based on longitudinal SLD data and directly obtained target lesion progression based on the RECIST criteria. The hazard for nontarget progression was modeled as a function of tumor growth dynamics. This joint model successfully described the treatment response in patients with platinum-resistant ovarian cancer in terms of both tumor growth dynamics and PFS outcome. During the model development process, several crucial steps were identified to ensure modeling success. Based on the RECIST criteria, the LLOQ of SLD is 5 mm. A BLOQ sample is clinically meaningful because it suggests that the patient’s SLD meets the complete response criteria at the time. Therefore, treating the BLOQ samples as categorical data is useful for not only improving the model fit, but also the clinical interpretation of the modeling result. In the simulations, it also proved important to ensure that target lesion progression was triggered according to the RECIST criteria. Previously, an additive error model has been frequently used when modeling tumor growth dynamics to predict OS. In this study, using an additive error model induced unrealistically large numbers of target lesion progressions during the simulation, particularly for patients with low baseline SLD values. Therefore, the proportional error model was selected as the appropriate error model.

It should be noted that death events defining PFS are different than the death events defining OS. For PFS, only death events occurring before any other disease progression events are relevant. In this work, death was treated as nontarget progression, because in the pooled data set there were only three subjects having PFS time defined by death. For simplicity, nominal dose was used as the exposure metric in this work without accounting for dose interruptions/reductions. For model predictions, the nominal dose can be used under the assumption that dosing pattern will be similar in the new study, as in the study which the analysis was based on.

Two generations of ADCs were included in the pooled data set. The anti-MUC16 ADC and anti-NaPi2b ADC are traditional ADCs with heterogeneous mixtures of DAR ranging from 0 to 8. The anti-MUC16 TDC was generated by THIOMAB™ specific conjugation technology that yielded a homogeneous DAR ratio of 2. Although both MUC16 and NaPi2b are reported to be highly expressed on ovarian cancer cells, expression levels can be different and patient-specific in clinical studies. The fitted relative potency value in the model suggests that a 1 mg/kg Q3W dose of MUC16-ADC may provide similar tumor killing efficacy as 0.7 mg/kg Q3W NaPi2b ADC. Similarly, 1 mg/kg Q3W MUC16-ADC dose...
may have an equivalent efficacy of around 0.8 mg/kg Q3W MUC16-TDC. However, this kind of interpretation should be performed with caution because the data set was pooled from separate clinical trials.

The results suggest that the risk of nontarget progression is correlated to the rate of target lesion growth over time. Although drug exposure and potency-related parameters were necessary to describe treatment effects on target lesion tumor growth dynamics, a direct drug effect on nontarget lesion progression was not needed in the model. Therefore, for future studies in the same disease setting, it may be possible to predict patient PFS time based on tumor growth dynamics data alone, before the PFS data are fully mature. The tumor growth dynamics model needs to be developed and used to derive target lesion progression time for each patient. The time to nontarget progression can be predicted based on the nontarget lesion progression survival model developed in this work under the assumption that the correlation between tumor growth dynamics and nontarget progression is drug independent. The PFS time can be predicted based on target lesion progression and nontarget progression time, whichever occurs first. The proposed method accounts for the full time course of tumor dynamics, and, hence, has the potential to improve PFS predictions over simpler approaches that focus on early response (e.g., overall response rate or tumor size ratio at an early time point). This will be of particular importance if the difference between drugs is more related to durability of response rather than the initial tumor size reduction. Further evaluation of the predictive power of the proposed method including comparisons with other approaches would be important to understand in what situations the proposed method would be most useful. The present results also support the notion that comparisons between drugs in this patient population can be focusing on target lesions, because they seem to capture the treatment effect on PFS.

In summary, we have proposed a new method to predict the PFS based on tumor growth dynamics, where PFS can be modeled based on target lesion and nontarget progressions. The model successfully captures both tumor growth dynamics and PFS of a pooled platinum-resistant ovarian cancer data set. The method can potentially be used to provide earlier predictions of PFS and, hence, support early decision making for indications where PFS is an important clinical endpoint.

Supporting Information. Supplementary information accompanies this paper on the CPT: Pharmacometrics & Systems Pharmacology website (www.psp-journal.com).

Figure S1. Diagnostic plot of individual SLD fit for first 56 subjects in the data set.

Figure S2. Exponential model fit (green dashed line) overlaid with Kaplan–Meier plot for patient dropout.

Figure S3. Kaplan–Meier plot for patient dropout stratified by treatments.

Figure S4. Visual predictive check of PFS Kaplan–Meier plot stratified by dose level based on 100 simulations showing observations (solid line) and 95% CI (shaded line) of model simulations. Dose levels are listed in mg/kg unit, except for doxorubicin (40 mg/m²).

Table S1. Number of subjects by study and treatment groups.

| Study | Treatment | Subjects |
|-------|-----------|----------|
| RTOG 2001 | 337 | 337 |
| RTOG 2002 | 337 | 337 |
| RTOG 2003 | 337 | 337 |

Supplemental Material.

Supplemental Figure Legends.

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Conflict of Interest. J.Y., N.W., and M.K. are all current or former employees of Genentech and own or owned Genentech stocks.

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