Pharmacometric Models for Antibody Drug Conjugates and Taxanes in HER2+ and HER2-Breast Cancer

BRENDAN BENDER
Abstract

In oncology, there is a need to optimize drug treatment for efficient eradication of tumors, minimization of adverse effects (AEs), and prolonging patient survival. Pharmacometric models can be developed to streamline information between drug development phases, describe and quantify response to treatment, and determine dose regimens that balance toxicity and efficacy. In this thesis, data from trastuzumab emtansine (T-DM1) and taxane drug treatment were used to develop pharmacometric models of pharmacokinetics (PK), AEs, anti-tumor response, and survival, supporting drug development.

T-DM1 is an antibody-drug conjugate (ADC) for treatment of human epidermal growth factor receptor 2 (HER2)–positive breast cancer. ADCs are a relatively new class of oncologic agents, and contain multiple drug-to-antibody ratio (DAR) moieties in their dose product. The complex distribution of T-DM1 was elucidated through PK models developed using in vitro and in vivo rat and cynomolgus monkey DAR data. Mechanism–based PK/pharmacodynamic (PKPD) models were also developed for T-DM1 that described the AEs thrombocytopenia (TCP) and hepatotoxicity in patients receiving T-DM1. Variable patterns of platelet and transaminase (ALT and AST) response were quantified, including an effect of Asian ethnicity that was related to higher incidences of TCP. Model simulations, comparing dose intensities (DI) and Grade 3/4 incidences between the approved T-DM1 dose (3.6 mg/kg every three weeks) and weekly regimens, determined that 2.4 mg/kg weekly provided the highest DI.

Docetaxel and paclitaxel are taxane treatment options for HER2–negative breast cancer. Tumor response data from these treatments were used to develop a mechanism–based model of tumor quiescence and drug–resistance. Subsequently, a parametric survival analysis found that tumor baseline and the model–predicted time to tumor growth (TTG) were predictors of overall survival (OS). This tumor and OS modeling approach can be applied to other anticancer treatments with similar patterns of drug–resistance.

Overall, the pharmacometric models developed within this thesis present new modeling approaches and provide understanding on ADC PK and PKPD (TCP and hepatotoxicity), as well as drug–resistance tumor response. These models can inform simulation strategies and clinical study design, and be applied towards dose finding for anticancer drugs in development, especially ADCs.

Keywords: pharmacometric, PKPD, model, breast cancer, T-DM1, thrombocytopenia, hepatotoxicity, HER2

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV. **Bender BC**, Jin J, Friberg LE. A mechanism–based model of tumor quiescence and drug–resistance in HER2–negative metastatic breast cancer patients receiving docetaxel or paclitaxel. (In manuscript)

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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>adverse effects</td>
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<tr>
<td>ALT</td>
<td>alanine transaminase</td>
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<td>AST</td>
<td>aspartate transaminase</td>
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<tr>
<td>AUC</td>
<td>area under the curve</td>
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<td>AUC&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>steady state area under the curve</td>
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<tr>
<td>BM</td>
<td>biomarker</td>
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<tr>
<td>BSL</td>
<td>baseline</td>
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<tr>
<td>C</td>
<td>concentration</td>
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<td>Ce</td>
<td>effect compartment concentration</td>
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<tr>
<td>Circ</td>
<td>circulation</td>
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<td>CL</td>
<td>clearance</td>
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<td>CLd</td>
<td>distributional clearance</td>
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<tr>
<td>C&lt;sub&gt;max,ss&lt;/sub&gt;</td>
<td>steady state maximum concentrations</td>
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<tr>
<td>Cp</td>
<td>central compartment concentration</td>
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<tr>
<td>C/P</td>
<td>carboplatin/paclitaxel</td>
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<td>CRC</td>
<td>colorectal cancer</td>
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<tr>
<td>DAR</td>
<td>drug-to-antibody ratio</td>
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<tr>
<td>DEC</td>
<td>deconjugation</td>
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<tr>
<td>DI</td>
<td>dose intensity</td>
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<tr>
<td>ECD</td>
<td>extracellular domain</td>
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<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
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<td>Emax</td>
<td>maximum effect</td>
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<td>ELISA</td>
<td>enzyme linked immunosorbent assay</td>
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<tr>
<td>Exp</td>
<td>exponential</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FO</td>
<td>first order</td>
</tr>
<tr>
<td>FOCE</td>
<td>first order conditional estimate</td>
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<tr>
<td>FnR</td>
<td>fraction resistant</td>
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<tr>
<td>GIST</td>
<td>gastro-intestinal stromal tumor</td>
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<tr>
<td>HER2</td>
<td>human epidermal growth factor receptor 2</td>
</tr>
<tr>
<td>IACUC</td>
<td>Institutional Animal Care and Use Committee</td>
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<tr>
<td>IIV</td>
<td>interindvidual variability</td>
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<tr>
<td>L</td>
<td>liter</td>
</tr>
<tr>
<td>LC–MS</td>
<td>liquid chromatography mass spectrophotometry</td>
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</tbody>
</table>
LDH  lactate dehydrogenase
LLN  lower level of normal
log(G)  log of the tumor growth rate
MOA  mechanism of action
MTT  mean transit time
NONMEM  nonlinear mixed effects modeling
NSCLC  non-small cell lung carcinoma
OFV  objective function value
ORR  overall response rate
OS  overall survival
PD  pharmacodynamic
PK  pharmacokinetic
PFS  progression–free survival
PKPD  pharmacokinetic–pharmacodynamic
PLT  platelet compartment
PP  platelet proliferation
PPC  posterior predictive check
Prol  proliferation
q1w, q3w, q4w  weekly, every 3 weeks, every 4 weeks
R  resistant
RCC  renal cell carcinoma
RDI  relative dose intensity
RECIST  Response Evaluation Criteria in Solid Tumors
RSE  relative standard error
sKIT  soluble stem cell factor
SLD  sum of longest diameter
SMCC  N–succinimidyl–4–(N–maleimidomethyl)–cyclohexane–1–carboxylate
sVEGFR-3  soluble vascular endothelial growth factor receptor 3
T  transit
t  time–course
TCP  thrombocytopenia
TGI  tumor growth inhibition
TT  total trastuzumab
TTE  time-to-event
TSR  tumor size ratio
TTG  time to tumor growth
μL  microliter
ULN  upper level of normal
V1  central volume of distribution
V2  peripheral volume of distribution 2
V3  peripheral volume of distribution 3
VPC  Visual Predictive Check
Introduction

Cancer remains an unmet medical need [1]. Not only is there a need to develop new drugs in oncology, but also to improve the speed and efficiency of preclinical to clinical oncology drug development [2]. In oncology, optimizing drug treatment to effectively kill tumors, minimize adverse effects (AE), and prolong patient survival is paramount. Pharmacometric models and strategies can be developed based on anti-cancer drug treatment data, and then applied to new anti-cancer drugs and their effects (e.g. for efficacy, biomarker, and toxicity endpoints), in order to improve the speed and efficiency of analysis. Pharmacometric models are also powerful tools towards the design of clinical trials (e.g. the most informative doses, relevant variables, data collection time points, number of patients, etc.), to ultimately determine the dose regimen that will provide the best balance between desired effects and side–effects.

Model–based framework for drug development in oncology

Figure 1 illustrates a proposed framework for pharmacometric drug development in oncology. As shown, pharmacometric models may be developed early and used to inform Phase I–III study design and target endpoints. From development of a population pharmacokinetic (PK) model, PK metrics may be tested and implemented into PK–pharmacodynamic (PKPD) models describing various responses, such as adverse effects, tumor and biomarker response, and also be assessed as predictors for survival. Once developed, these data–driven PKPD models can be used to explore and support dose and regimen changes, as well as to provide model–based metrics that can be assessed as “drivers” for other PD responses and as predictors for survival.

The similarity among measurements and endpoints in oncology, regardless of cancer type, makes this an applicable framework for oncologic drug development programs. For example: 1) anti–tumor treatment efficacy is typically established using tumor bearing mice; 2) in the clinic, tumor sum of longest diameter (SLD) measurements are used as an indication of treatment
Figure 1. Model–based framework for drug development in oncology, adapted from publications [3, 4]. Δ Baseline: change from baseline; AUC: area under the drug concentration–time curve; AUCBM: area under the biomarker–time curve; $k_{GROW}$: tumor growth rate constant; OS: overall survival; PFS: progression–free survival; PKPD: pharmacokinetic–pharmacodynamic; (t): time–course ; TSR: tumor size ratio; TTG: time to tumor growth.
effect for solid tumors; 3) circulating biomarkers, associated with drug mechanism of action, may be assessed as early indicators of treatment effect; 4) adverse effects, such as chemotherapy–induced myelosuppression, are noted across many cancer treatments; and 5) progression–free survival (PFS) and overall survival (OS) are primary clinical endpoints for evaluating treatment success.

This pharmacometric framework serves as a template to introduce analyses within this thesis work of pharmacometric models for antibody drug conjugates (ADCs) and taxanes in human epidermal growth factor receptor 2 (HER2)–positive and HER2–negative breast cancer. The following models have been developed: 1) a PKPD model describing platelet response to T-DM1 treatment in HER2–positive breast cancer patients; 2) a PKPD model simultaneously describing platelet, ALT, and AST response to T-DM1 treatment in HER2–positive breast cancer patients; 3) PK models elucidating and conceptualizing T-DM1 disposition based on preclinical experimental data; and 4) a model for tumor response to taxane treatment in HER2–negative breast cancer patients, and a subsequent parametric time-to-event analyses of survival data.

Pharmacometric Background in Oncologic Drug Development

Pharmacometrics is the science of quantitative drug development, and includes concepts utilized in this thesis work regarding population PK [5], PKPD [6-9], and model–based drug development [3, 10]. In the following sections, general pharmacometric concepts and analyses are introduced that have guided this thesis work. Specifically: 1) population PK and PKPD modeling; 2) preclinical PK and PKPD models in oncology; 3) pharmacometric models of continuous type data in oncology; and 4) time-to-event (TTE) modeling in oncology.

Population PK and PKPD modeling

In drug development, pharmacometricians develop and fit PK models to drug plasma concentration–time data so that typical PK parameters and their variabilities can be estimated. Patient characteristics (covariates), such as weight, creatinine clearance, disease status, etc., can be tested and implemented into the model to explain the between patient PK variability [11]. Development of a population PK model that well describes the drug concentration–time data implies an understanding of how the body is processing the drug.
Following this analysis, pharmacometricians may attempt to incorporate PK model–based metrics to describe the drug concentration–effect, or “PKPD”, relationship. In oncology, PD measurements are typically associated with how the patient responds to treatment, such as the tumor burden, a biomarker, or the development of adverse effects. Shown in Figure 2 is a general PKPD model structure, in which predicted drug concentrations over time (Cp(t)) from a PK model are directly linked to PD responses.

**Figure 2. Compartmental representation of a general PKPD system.** CL: drug clearance; CLd: distributional clearance; Kin: zero–order rate constant for production of response; kout: first–order rate constant for loss of the response; Slope: drug effect scaling parameter; V1: central volume of distribution; V2: peripheral volume of distribution

As shown, the PK portion of the model system is a two compartmental model, developed from drug concentration–time data, and the typical population PK parameters (i.e. clearances (CL, CLd) and volumes of distribution (V1 and V2)) and their variabilities are estimated. The PK parameters for each individual subject can be obtained in a ‘posthoc’ step.

In the PD portion of the model, a direct link using the model–predicted drug concentration–time curve (Cp(t)), from the central compartment (V1), acts to stimulate the production of PD Response1 and inhibit the production of PD Response2. Slope1 and Slope2 are drug–related scaling parameters to be estimated by the PKPD model when fit to the PD data. Kin and kout are system–related parameters which are also estimated by the model [12]. Following development of a PKDP model, simulations can be done as illustrated in Figure 3.
Preclinical PK and PKPD modeling

As shown in Figure 1, pharmacometric models in oncology may be developed and applied early in preclinical drug development. For PK modeling, the approach is the same as described in the previous section, though covariates are typically not explored; in vivo animal experiments typically do not have the heterogeneity in body composition or physiological function as seen in the healthy human or diseased patient population.

Most relevant for clinical support, preclinical PKPD models for efficacy and toxicity may be developed to support and inform Phase I–III dose selection. In oncology, myelosuppression is one of the most common adverse effects (AE) following chemotherapy. Notably, Friberg et al. [13] has proposed a strategy for scaling myelosuppression data from rats to humans via PKPD modeling. For efficacy, PKPD modeling of tumor response from tumor-bearing mice has been used to derive a tumorstatic concentration—the drug concentration at which there is no net tumor growth, thereby providing a target exposure that may be used to support clinical dose selection [14, 15].

Figure 3. Model–predicted curves for a general PKPD system. Model–predicted time–courses of PD response for stimulation of $k_{in}$ (stippled line) and inhibition of $k_{in}$ (solid line); the model–predicted drug concentration time–course (bottom curve) is shown for once every 3 week (q3w) dose regimen.
Pharmacometric Models of Continuous Type Data in Oncology

For this thesis work, platelet counts, liver enzyme levels (e.g. alanine transaminase (ALT) and aspartate transaminase (AST)), and tumor SLD were the measurements available for development of PKPD models. Prior to model development, literature searches were done to establish starting points.

Elevations in ALT and AST levels provide indication of liver damage, and PKPD models have not been readily applied, and only two models were found for consideration. Fetterly et al. [16] presented a precursor–dependent mechanism-based model for ALT response to the anti-tumor drug trabedectin. Pollak et al. [17] presented a linear effect compartment approach to predict ALT response to amiodarone, a treatment for atrial fibrillation. In contrast to ALT and AST, PKPD models for platelet and tumor SLD have been routinely applied in oncologic drug development and are discussed further here: 1) the myelosuppression model and 2) the clinical tumor growth inhibition (TGI) model.

**Pharmacometric Model for Myelosuppression**

For chemotherapy, myelosuppression is one of the most common adverse effects (AE). Myelosuppression is a condition in which the normal production of blood cells in the bone marrow is reduced, resulting in fewer circulating red blood cells, leukocytes (60–70% neutrophils), and/or platelets. Given the importance for neutrophils and platelets in fighting infections and in maintenance of blood clotting, respectively, myelosuppression is dose limiting for many anticancer agents.

In 2002, a myelosuppression PKPD model was presented by Friberg et al. [18] based on leukocyte and neutrophil data from six chemotherapeutic agents. This model has been used to characterize neutrophil [19-25], leukocyte [24], and platelet [20, 26] responses. As shown in Figure 4, the myelosuppression model is a physiological–based model, with components of myelocyte proliferation, maturation, blood circulation, and feedback.
Figure 4. Compartmental representation of the myelosuppression model. Prol: proliferation cell pool compartment; T1, T2, and T3: transit compartments of cell maturation; Circ: blood circulation compartment; Drug effect: Slope • Exposure; Exposure: e.g., the drug–concentration time–course; kel: elimination rate constant; kPROL: proliferation rate constant; ktr: intercompartmental transit rate constant; Circ0: baseline cell count; MTT: mean transit time, derived as ktr/(n+1), where n is the number of transit compartments.

The model consists of a proliferation cell pool (Prol) compartment, three transit compartments (T1, T2, and T3) mimicking the maturation of the non-proliferative cells, and a blood circulation compartment (Circ) where the measurements (e.g. neutrophil counts) have been observed over time. The feedback process is governed by the parameter (γ), which stimulates the proliferation rate as circulating cell levels are depleted and slows down proliferation when the circulating neutrophil counts are above the baseline value. The drug effect is the product of the Slope parameter and the individual exposure metric, where exposure can be AUC, Dose, or concentration (t), etc.

The mechanism–based nature of the myelosuppression model readily allows modifications to the structure. For example, Quartino et al. [27] incorporated granulocyte stimulating colony factor (G–CSF) measurements. A turnover model of G–CSF, where G–CSF elimination was dependent on the circulating neutrophil counts, replaced the feedback function and provided a more mechanistic interpretation which may allow for improved predictive capacity.

With regard to platelets, van Kesteren et al. [20] presented a PKPD model based on this myelosuppression structure to describe platelet response to the anti-cancer agent indisulam. Chalret du Rieu et al. [26] also added modifica-
tions to the myelosuppression model, using an extra feedback term and alter-
nate platelet baseline parameterization, to describe platelet response to abexintostat.

Figure 5 illustrates components of the myelosuppression model, showing simulations of neutrophil and drug effect time-course (Slope• concentration (t) in this example), for a once every 3 week intravenous drug treatment.

As shown, neutrophil counts oscillate in response to drug treatment, reaching a nadir between 6–9 days before rebounding towards baseline prior to the next dose.

**Pharmacometric Model for Tumor Response**

In oncologic drug development for solid tumors, the tumor sum of longest diameter (SLD) measurement is used as an indication of treatment effect. These measurements are sparse, typically once every 6–8 weeks. The Response Evaluation Criteria in Solid Tumors (RECIST; currently version 1.1) is then used to categorize tumor response to treatment [28]. However, RECIST 1.1 is not an optimal assessment of drug efficacy, as information is lost when the continuous tumor SLD data is categorized.

In 2009, the tumor growth inhibition (TGI) model was presented by Claret et al. [29] on data from colorectal cancer patients receiving capecitabine. The
TGI model offered an improved understanding for response versus the standard RECIST criteria, by modeling longitudinal tumor SLD data on a continuous scale. This structural model (Figure 6) has been applied by investigators to several cancer types and drugs.

Figure 6. Compartmental representation of the TGI model. \( k_{\text{GROW}} \): tumor growth rate constant; Exposure: drug exposure metric; \( k_{\text{KILL}} \): tumor kill rate constant; \( \lambda \): drug resistance parameter; \( k \): drug exposure elimination rate constant—the \( k \) parameter was not applied in the original publication (\( k=0 \)) [29].

The TGI model predicts that, in the absence of treatment, tumor SLD increases exponentially according to a disease–specific first–order growth rate constant \( k_{\text{GROW}} \). The tumor SLD doubling rate is derived as \( \ln(2)/k_{\text{GROW}} \). Drug–related tumor shrinkage is accounted for by a metric for drug exposure (e.g. Dose, AUC) and a drug–specific cell kill rate constant \( (k_{\text{KILL}}) \). Loss of drug effect is described by a time–dependent mono–exponential function defined by the parameter \( (\lambda) \). Figure 7 shows a representative plot of drug effect and tumor SLD time–courses simulated using the TGI model.
Figure 7. Model–predicted PKPD curves for the TGI model. TGI model–predicted tumor SLD (top curve) and drug effect (bottom curve) time–courses for a once every 3 week (q3w) drug treatment. TSR: tumor size ratio from baseline, typically assessed after 1 or 2 treatment cycles (6–8 weeks); TTG: time to tumor growth.

In this simulation, the drug exposure decreases mono–exponentially within treatment cycles via the k parameter, and tumor begins regrowth around week 9 as the drug effect diminishes.

Several tumor metrics can be derived from the TGI model for assessment as predictors for OS. These metrics include the tumor time–course (red line), the tumor size ratio (TSR), and the time to tumor growth (TTG). TSR reflects the relative change in tumor SLD from baseline at a certain time point, e.g. after one or two treatment cycles (6–8 weeks). There are drawbacks with TSR in that it is determined at a fixed time point, irrespective of the ongoing tumor response. TSR can thereby be the same value for two patients, where both patients initially respond to treatment, but one patient develops tumor regrowth; it is not possible to ascertain whether tumor SLD is in a declining or increasing phase at week 6–8.

TTG corresponds to the time of a patient’s tumor SLD nadir, at which there is no net tumor growth. The TTG metric shares some limitations with TSR; it is a constant value metric that is also used to predict the hazard of survival time–points before the metric has occurred, and TTG can have the same value for patients with vastly different tumor responses. Time-varying pre-
dictors, such as the tumor time–course may have advantages, especially if the model is to be used prospectively [3, 30].

Time-to-Event Modeling in Oncology

In the current paradigm for oncology, overall survival (OS) – the time from randomization until death from any cause, is the preferred endpoint to evaluate treatment benefit [31]. However, it may take many years for OS data to reach the number of events so that statistical conclusions can be drawn, and thus preliminary drug approval may be granted based on an improvement in progression-free survival (PFS) [31]. “Progression” refers to tumor growth, and is defined as a >20% increase in tumor SLD over baseline (or from best response), with a minimum 5 mm absolute increase, or appearance of any new lesions [28].

As illustrated in Figure 1, pharmacometricians may evaluate and implement “metrics” from PK and PKPD models into parametric TTE models as predictors for OS, in order to improve the assessment of treatment efficacy. Concepts regarding parametric modeling of survival are presented below. A recent tutorial on TTE analysis for pharmacometricians [32] and a textbook on modeling survival data [33] provide further background.

Shown in the following equation is the hazard function, h(t), which describes the instantaneous rate at which an event (in oncology = death) occurs:

\[ h(t) = h_0(t) \cdot e^{\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n} \]

The baseline hazard \( h_0(t) \) is defined by one or more estimated parameters, and \( x_1, x_2, \ldots, x_n \) represent a set of predictors that affect the hazard. As shown in Figure 1, these predictors may be a derived constant value for each patient (e.g. TSR, TTG), a model parameter estimate (e.g. \( k_{\text{GROW}} \)), or a model–predicted time varying metric (e.g. Tumor(t), Biomarker(t)). Additionally, patient baseline characteristics (e.g. ECOG status, observed tumor SLD at baseline, number of lesions, etc.) are frequently assessed as predictors. The impact of the predictors is determined by the size of the respective coefficients \( \beta_1, \beta_2, \ldots, \beta_n \), which are estimated from the data [34].

Pharmacometric analyses incorporating tumor SLD and TTE modeling

Table 1 shows representative analyses [29, 35-43], for a diversity of solid tumor types and treatment drugs, in which the time–course of longitudinal tumor SLD was described by population models, and metrics therefrom were assessed as predictors for survival.
<table>
<thead>
<tr>
<th>Table 1. Pharmacometric analyses incorporating tumor SLD and TTE</th>
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<tr>
<td><strong>Tumor type</strong></td>
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<td>NSCLC</td>
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| Thyroid cancer | Motesanib | tumor SLD | AUCss | TGI | -- | ECOG, tumor SLD<sub>0</sub> | Lu 2010 [37]
| Thyroid cancer | Motesanib | tumor SLD | AUCss | TGI | -- | ECOG, tumor SLD<sub>0</sub> | Claret 2010 [38] |
| Metastatic breast cancer | Capecitabine + docetaxel | tumor SLD | Dose | TGI | TSR (week 6) | tumor SLD<sub>0</sub>, ECOG, number of metastases, study effect | Bruno 2012 [39] |
| GIST           | Sunitinib | tumor SLD | Daily AUC, sVEGFR-3(t), sKIT(t) | TGI | -- | tumor SLD<sub>0</sub> | Hansson 2013 [40] |
| CRC            | Bevacizumab + chemotherapy | tumor SLD | Constant exposure | TGI with constant exposure | TTG, TSR (week 6), log(G)(*), | ECOG, tumor SLD<sub>0</sub>, treatment arm(*), number of organs | Claret 2013 [41] |
| NSCLC          | Motesanib | tumor SLD | Dose | TGI with constant exposure | Log(TTG) | Asian ethnicity, Smoking history, tumor SLD<sub>0</sub> | Claret 2014 [42] |
| RCC            | Temsirolimus, sunitinib, axitinib, interferon, or sorafenib | tumor SLD | Dose | TGI with constant exposure | TTG, TSR (week 8) | ECOG, number of metastases, LDH<sub>0</sub>, hemoglobin, corrected calcium | Claret 2015 [43] |

AUCss: steady state area under the drug concentration curve; C/P: carboplatin/paclitaxel; CRC: colorectal cancer; ECOG: Eastern Cooperative Oncology Group; exp: exponential; GIST: gastro-intestinal stromal tumor; LDH<sub>0</sub>: baseline lactate dehydrogenase; log(G): log of the tumor growth rate; NSCLC: non-small-cell lung carcinoma; PD: pharmacodynamic; RCC: renal cell carcinoma; sKIT: soluble stem cell factor; SLD: sum of longest diameters; SLD<sub>0</sub>: baseline sum of longest diameters; sVEGFR-3: soluble vascular endothelial growth factor receptor 3; TGI: tumor growth inhibition model; TSR: tumor size ratio; TTG: time to tumor regrowth. (*) Survival analysis was performed using non-parametric methods.
As shown in Table 1, most published tumor modeling incorporating TTE analyses since 2009 have utilized the TGI. Other than the TGI model, Wang et al. [35] presented a simple empirical model with exponential drug–dependent shrinkage and linear growth with time to describe tumor SLD data from four clinical trials of patients with NSCLC treated with various chemotherapies or placebo. This model structure was also used to describe data from NSCLC patients treated with carboplatin/paclitaxel alone or in combination with bevacizumab or motesanib [36].

In contrast to the model first presented by Wang et al., the TGI model typically includes dose or drug exposure as PK drivers, and therefore has the potential to simulate tumor response at other dose levels. In addition, metrics derived from biomarker PKPD models have been implemented as “drivers” for tumor response and OS. For example, Hansson et al. [40] found that biomarkers time–courses of sVEGFR–3 and sKIT were drivers of tumor response, and sVEGFR-3 response was the best predictor of OS. Biomarker analyses such as these can confirm or drive new hypotheses as to how the drug is reducing tumor burden and may provide an early indication of anti–tumor efficacy.

From Table 1, the tumor baseline SLD (SLD_0) and ECOG status are consistent patient characteristics predictive for OS in most tumor types. The model–based metric of TSR (at week 6–8) was identified as a predictor for OS in NSCLC [35, 36], colorectal cancer [29, 41], and metastatic breast cancer [39]. In addition to TSR, the relatively new model–based metric of TTG was shown as a predictor for survival in a parametric TTE analysis of colorectal cancer data [41] and renal cell cancer [43]. The interpretation of these survival predictors is as follows: 1) an increased tumor baseline (SLD_0), reflective of higher initial tumor burden, is associated with poorer survival prognosis; 2) a smaller TSR (week 6–8) and a shorter TTG, reflective of treatment efficacy, is associated with poorer survival prognosis; and 3) an increased ECOG status, reflective of poorer health, is associated with poorer survival prognosis.

Utility of a modeling and simulation framework in oncology
Development of population PKPD and TTE models within the modeling framework aid in the understanding of the link between drug exposure, PD response, and survival, and provide a tool for optimizing drug treatment. The application of this modeling framework has been demonstrated, with notable examples: 1) the long–term clinical outcome in Phase III studies was predicted based on short–term Phase II data [29, 36]; 2) PFS and overall response rate (ORR) were predicted for thyroid cancer patients treated with motasenib [37, 38]; and 3) the capecitabine dose that would show non–
inferiority to the dose currently registered, when used in combination with docetaxel, was predicted [39].
Metastatic Breast Cancer Treatment

Shown in Figure 8 is a timeline of the US Food and Drug Administration (FDA) approval of drugs for metastatic breast cancer, adapted from Cortazar et al. [44]. In this thesis work, pharmacometric model have been developed from clinical trials of paclitaxel [45], docetaxel [46], and trastuzumab emtansine (T-DM1) [47-51] from metastatic breast cancer patients.

Figure 8. FDA approval timeline of drugs for metastatic breast cancer

Paclitaxel and Docetaxel

Paclitaxel and docetaxel are members of the taxane drug class, anti–mitotic chemotherapies that work by interfering with spindle microtubules leading to cell cycle arrest and apoptosis. Paclitaxel (Taxol®, Abraxane®) is a drug approved for treatment of ovarian, breast, lung, pancreatic and other cancers. Docetaxel (Taxotere®, Docecad®) is approved for treatment of locally advanced or metastatic breast cancer, head and neck cancer, gastric cancer, hormone–refractory prostate cancer and non-small cell lung cancer. Shown in Figure 9 are the chemical structures for docetaxel and paclitaxel.
T-DM1 (trastuzumab emtansine, Kadcyla®) is an ADC approved by the FDA in 2013 for the treatment of HER2–positive cancers [52, 53]. ADCs are a relatively new promising class of compounds in clinical development for the treatment of cancer [54-57]. ADCs harness the targeting capability and long half–life of antibodies to deliver potent small molecule cytotoxins that may be too toxic to directly administer and/or have poor PK properties. Shown in Figure 10 is a schematic of T-DM1.

T-DM1 is composed of 1) trastuzumab, a humanized monoclonal antibody directed against the extracellular region of the HER2 antigen, 2) DM1, an anti–microtubule agent derived from the plant extract maytansine which inhibits cell division through tubulin binding, and 3) a lysine–SMCC linker—a thioether bond linker molecule used to conjugate DM1 to trastuzumab.
Trastuzumab

The antibody backbone of T-DM1 is trastuzumab (Herceptin®), a recombinant, humanized anti-HER2 monoclonal IgG antibody approved in 1998 for the treatment of HER2–positive metastatic breast cancer. HER2 is a protein overexpressed in approximately 30% of breast cancer patients, and these patients are denoted as HER2–positive. HER2 overexpression is associated with uncontrolled cell growth, poor prognosis, and shorter survival time [58]. Trastuzumab targets the HER2 receptor, and binding inhibits downstream signaling associated with tumor growth. HER2–positive breast cancers can have up to 25–50 copies of the HER2 gene and up to 40–100–fold increase in HER2 protein resulting in 2 million receptors expressed at the tumor cell surface [59].

DM1

DM1 is a potent, small molecule cytotoxic derivative of the microtubule inhibitor maytansine, which was abandoned as a chemotherapeutic due to a narrow therapeutic index [56]. DM1 is chemically linked to lysine residues on trastuzumab via a stable non–reducible (“non–cleavable”) thioether bond using the SMCC (N–succinimidyl–4–(N–maleimidomethyl)–cyclohexane–1–carboxylate) linker.

T-DM1 Dose Product

ADCs made by conventional drug conjugation strategies (using antibody lysine side–chain amines or sulfhydryl groups for conjugation) are complex, heterogeneous mixtures of various drug–to–antibody ratio (DAR) moieties. During the manufacturing process for T-DM1, DM1 may conjugate to one or more lysine residues on trastuzumab, yielding a T-DM1 dose product containing a mixture of different numbers of DM1 (from 0 to 8) per trastuzumab antibody. Understanding the PK underlying these ADCs has been elusive, primarily due to the lack of analytical techniques capable of measuring the individual DAR moieties comprising the ADCs. Shown in Figure 11 is an illustration of the T-DM1 dose product contain from 0–8 DAR moieties.
Figure 11. T-DM1 dose product containing multiple DARs. DAR: drug–to–antibody ratio; The total trastuzumab concentration is the sum of each individual DAR moiety and free trastuzumab (i.e., unconjugated DAR_0) concentrations; The T-DM1 concentration is sum of DAR moieties with at least one DM1 conjugated to trastuzumab.

T-DM1 Mechanism of Action

Following uptake via the HER2 receptor, T-DM1 is degraded in the lysosome. DM1, and DM1–containing catabolites, are released intracellularly and bind tubulin, thereby disrupting microtubule assembly/disassembly and selectively killing HER2–overexpressing tumor cells [60]. Notably, HER2+ patients may benefit from a dual pharmacologic effect as T-DM1 retains the anti–tumor mechanism of trastuzumab [61].

Figure 12. T-DM1 Mechanism of Action. HER2: human epidermal growth factor receptor 2; Mab: monoclonal antibody
Aims

The aim of this thesis work was to develop pharmacometric models and strategies for analyzing 1) antibody drug conjugate (ADC) disposition, 2) ADC–driven hepatotoxicity and thrombocytopenia, and 3) clinical tumor response/survival from taxane treatment. The developed models and strategies, derived from HER2–positive and HER2–negative metastatic breast cancer breast cancer treatment and data, provide important pharmacometric tools to apply within the modeling and simulation framework proposed for oncologic drug development.

The specific aims were:

1. To develop a pharmacokinetic–pharmacodynamic (PKPD) model describing platelet response to T-DM1 treatment in HER2–positive breast cancer patients.

2. To develop a PKPD model describing simultaneous platelet, ALT, and AST response to T-DM1 treatment in HER2–positive breast cancer patients.

3. To develop a PKPD model simulation strategy of alternative T-DM1 dose regimens, incorporating dose modification rules for platelet, ALT, and AST responses, towards supporting T-DM1 dose and scheduling.

4. To develop PK models elucidating and conceptualizing T-DM1 disposition from preclinical experiments, that may guide study design, PKPD modeling, and drug development for other ADCs.

5. To develop models for tumor response to taxane treatment in HER2–negative breast cancer patients, characterizing patterns of tumor quiescence and drug–resistance, and apply results into a parametric time-to-event analyses of survival data.
Data and Methods

In this thesis, clinical trial data from T-DM1 (trastuzumab emtansine, Kadcyla®), docetaxel (Taxotere®, Docecad®), and paclitaxel (Taxol®, Abraxane®) were used for the development of pharmacometric models.

For the five T-DM1 clinical studies used in this thesis, protocols were approved by the institutional review boards of all participating institutions and were carried out in accordance with the Declaration of Helsinki, current US FDA Good Clinical Practices, and applicable local laws. Patients provided written informed consent.

The docetaxel and paclitaxel studies were conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, and the laws and regulations of the countries involved. The protocol was approved by local ethics committees; written informed consent was obtained from all patients before screening.

The T-DM1 PK studies in rats were approved by Institutional Animal Care and Use Committee (IACUC) and conducted at Genentech, Inc. The T-DM1 PK studies in cynomolgus monkeys were approved by IACUC and conducted by Covance Laboratories, Inc. (Covance; Madison, WI)

Table 2 outlines the study designs and data for Papers I–IV within this thesis.
<table>
<thead>
<tr>
<th>Paper</th>
<th>Drug Treatment</th>
<th>Species / Matrix</th>
<th>n</th>
<th>Drug Dose Level</th>
<th>Route of administration</th>
<th>Measurements</th>
</tr>
</thead>
</table>
| I     | T-DM1          | Human            | 164 | q3w regimens: 0.3 (n=3), 0.6 (n=1), 1.2 (n=1), 2.4 (n=1), 3.6 (n=127), and 4.8 mg/kg (n=3)  
|       |                |                  |     | q1w regimens: 1.2 (n=3), 1.6 (n=2), 2.0 (n=1), 2.4 (n=13), and 2.9 mg/kg (n=2) | Intravenous infusion; 0.5–1.5 hr | Platelets                  |
| II    | T-DM1          | Human            | 658 | q3w regimens: 0.3 (n=3), 0.6 (n=1), 1.2 (n=1), 3.6 (n=629), and 4.8 mg/kg (n=3)  
|       |                |                  |     | q1w regimens: 1.2 (n=3), 1.6 (n=2), 2.0 (n=1), 2.4 (n=13), and 2.9 mg/kg (n=2) | Intravenous infusion 0.5–1.5 hr | Platelets, ALT, AST        |
| III   | T-DM1          | Plasma           | –   | 100 μg/mL       |                                          | in vitro incubation          | T-DM1, Total trastuzumab, Drug:Antibody Ratios |
|       |                | Rat              | 34  | 0.3 (n=7), 3.0 (n=8), 10.0 (n=10), and 20.0 mg/kg (n=9) | Intravenous                 |                            |
|       |                | Cynomolgus Monkey| 4   | 30.0 mg/kg (n=4) | Intravenous                 |                            |
|       |                | Cynomolgus Monkey| 14  | 10.0 mg/kg q3w (n=14) | Intravenous                 |                            |
| IV    | Docetaxel      | Human            | 185 | 100 mg/m² q3w (maximum 9 cycles) | Intravenous Infusion; 1 hr | Tumor SLD                  |
|       | Paclitaxel     | Human            | 242 | 90 mg/m² on days 1, 8, and 15 q4w | Intravenous Infusion; 1 hr | Tumor SLD                  |

q1w: weekly; q3w: every 3 weeks; q4w: every 4 weeks; ALT: alanine transaminase; AST: aspartate transaminase; SLD: sum of longest diameter
Clinical Data

T-DM1

As shown in Table 2, data was used from 164 HER2–positive breast cancer patients for the development of a PKPD model of platelet response to T-DM1 treatment in Paper I. These patients were from the Phase I TDM3569g [48] and the Phase II TDM4258g [51] clinical trials and received doses ranging from 0.3–4.8 mg/kg.

In Paper II, a PKPD model of simultaneous ALT, AST, and platelet response to T-DM1 was developed. This PKPD modeling analysis was extended from Paper I to include ALT and AST data, as well as additional patient data from the Phase II TDM4374g [49], the Phase III TDM4370g [50], and the Phase II TDM4450g [47] studies. The final dataset therefore included 658 HER2–positive breast cancer patients from 5 clinical T-DM1 trials. This dataset consisted of 99% females, with a median age of 53 years. Sixty percent of patients had ECOG status of 0, 39% ECOG 1, and 1% ECOG 2. Eleven percent of patients were Asian, 44% had liver metastases, and 88% had measurable disease.

Docetaxel and Paclitaxel

In Paper IV, tumor SLD data and survival times were available from 185 of 241 HER2–negative breast cancer patients in the docetaxel treatment group of the Phase III AVADO trial [46]. In this modeling dataset, 59% of patients were ECOG=0 and 41% were ECOG=1. Patients were women with a median age of 55 years (range 29–83 years).

For paclitaxel, tumor SLD data and survival times were available from 242 of 326 HER2–negative breast cancer patients in the paclitaxel treatment group of the Phase III E2100 trial [45]. In this dataset, patients were women with a median age of 55 years (range 27–85 years); ECOG status was not available.

Preclinical Data

In Paper III, for the development of PK models of T-DM1 disposition, two different T-DM1 dose products were dosed to rats and cynomolgus monkeys (T-DM1\textsubscript{DAR3.1} and T-DM1\textsubscript{DAR1.5}).
Preparation of T-DM1$_{\text{DAR 3.1}}$ and T-DM1$_{\text{DAR 1.5}}$ Dose Products

The two preclinical T-DM1 dose products were prepared by regulating the amount of SMCC linker added during the manufacturing process. Specifically, less SMCC linker was added to generate the T-DM1$_{\text{DAR 1.5}}$ dose product compared to more SMCC linker added to generate the T-DM1$_{\text{DAR 3.1}}$ dose product.

As shown in Figures 13 and 14 below, the T-DM1$_{\text{DAR 3.1}}$ dose product (average DAR=3.1) and T-DM1$_{\text{DAR 1.5}}$ (average DAR=1.5) dose products contained various DAR moieties with the following percentages as measured by affinity capture liquid chromatography mass spectrophotometry (LC–MS).

![Figure 13. T-DM1$_{\text{DAR 3.1}}$ dose product](image1)

![Figure 14. T-DM1$_{\text{DAR 1.5}}$ dose product](image2)

Rats

Two PK studies were conducted in vivo in rats. In the first study, 10 naïve Sprague–Dawley rats (n=5 rats/group) were administered a single intravenous dose of 10 mg/kg T-DM1$_{\text{DAR 3.1}}$ or 10 mg/kg T-DM1$_{\text{DAR 1.5}}$. Blood samples were collected up to 21 days post–dose. T-DM1 DAR concentrations and total trastuzumab concentrations were determined.

For the second PK study, T-DM1$_{\text{DAR 3.1}}$ was administered as a single IV dose at 0.3, 3.0, and 20.0 mg/kg (n=7–9 Sprague Dawley rats/group). Blood samples were collected up to 42 days post–dose. Blood samples were processed for total trastuzumab and T-DM1 concentrations. Rats weighed between 193–283 g.
Cynomolgus Monkeys

T-DM1\textsubscript{DAR 3.1} was administered to cynomolgus monkeys both as a single IV dose (30 mg/kg; \(n=4\)), as well as every 3 weeks (10 mg/kg q3w \(n=14\)). Animals were approximately 3–5 years old and weighed 2.6–4.5 kg. Blood samples were collected via the femoral vein. Blood samples were processed for total trastuzumab, DAR, and T-DM1 concentrations.

Measurements

Platelet, ALT, and AST

In Papers I and II, laboratory data were collected at different time points following T-DM1 dosing and typically within a day before each new cycle treatment. For patients receiving q3w regimens in study TDM3569g, measurements were assessed on day 1, 2, 4, 7–8, 11, and 18 post-dose in cycle 1. Typical collection times in subsequent cycles included days 1, 4, and 7–8 post-dose. For patients receiving q1w regimens, measurements were assessed on day 1, 2, 4, 7–8, 11, 14–15, and 18 post–dose in cycle 1, with pre–dose weekly sampling beginning day 21. For TDM4258g, measurements were assessed every 7 days. For TDM4374g, measurements were assessed weekly during cycle 1 and on day 1 and day 8 post-dose of all subsequent cycles. For TDM4370g and TDM4450g, measurements were assessed weekly. For Grade 3/4 assessment of ALT and AST, measurements were normalized to the upper level of normal (ULN) from the respective analytical lab; the median ALT ULN value was 45 units/L (range 22–85 units/L) and the median AST ULN value was 39 units/L (range 20–66 units/L).

Platelet, ALT, and AST Toxicity Grades

Toxicity grades were based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>ALT increased</td>
<td>&gt;ULN – 3.0 • ULN</td>
</tr>
<tr>
<td>AST increased</td>
<td>&gt;ULN – 3.0 • ULN</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>&lt;LLN – 75 (&lt;1000/μL)</td>
</tr>
</tbody>
</table>

LLN: lower level of normal; ULN: upper level of normal
T-DM1 and Total Trastuzumab Concentrations

Enzyme–linked immunosorbent assays (ELISA) were used to measure T-DM1 concentrations (trastuzumab bearing at least one T-DM1) and total trastuzumab concentrations (trastuzumab with or without DM1). T-DM1 concentrations were measured for Papers I–III, and total trastuzumab concentrations were measured for Paper III. Figure 15 illustrates the ELISA process for T-DM1 and total trastuzumab.

![Diagram of ELISA process](image)

Figure 15. ELISA format for T-DM1 and total trastuzumab, adapted from [62]. (Left panel): The total trastuzumab assay uses capture of ADC antibody (T-DM1 with or without DM1) via an antigen or target extracellular domain (ECD), with detection using labeled antibody to ADC antibody. (Right panel): The T-DM1 antibody assay uses capture of ADC via an anti–DM1 antibody, with detection using labeled antigen or ECD.

T-DM1 Drug-to-antibody Ratio (DAR) Concentrations

In Paper III, measurement of individual DAR moieties in plasma was done using an affinity capture liquid chromatography mass spectrophotometry (LC–MS) assay recently developed [63, 64]. The percentage of each DAR (DAR₀–DAR₇) moiety was calculated by its relative signal intensity. The DAR plasma concentrations were then obtained by multiplying these individual percentages by the total trastuzumab concentration (from ELISA) at the respective time. Shown in Figure 16 is a representative LC–MS chromatogram illustrating the signal intensities from individual T-DM1 DARs.
Tumor Sum of Longest Diameter (SLD)

In Paper IV, planned tumor SLD measurements were performed by investigators every 9 weeks until week 36 and every 12 weeks thereafter until disease progression occurred. The docetaxel dataset contained 879 tumor SLD measurements (2–13 measurements/patient collected up to a maximum 138 weeks). The paclitaxel dataset contained 784 tumor SLD measurements (2–9 measurements/patient collected up to a maximum 105 weeks). For docetaxel, the median patient tumor baseline SLD was 69mm (range 10 – 308mm). For paclitaxel, the median patient tumor baseline SLD was 83mm (range 12 – 391mm).

Model Building and Data Analysis

Post-hoc Bayesian estimates

Two population PK models have previously been developed for T-DM1 by other investigators, and the post–hoc Bayesian estimates of the individual patient PK parameters were used for PKPD model development in Papers I and II. In the first PK analysis, T-DM1 plasma concentration–time data from the Phase I TDM3569g [48], the Phase II TDM4258g [51], and the Phase II study TDM4374g [49] were used to develop a linear two–compartment PK
model with first–order elimination from the central compartment [65]. In the second population PK analysis [66], the modeling was extended to include data from the Phase III TDM4370g [50], and the Phase II TDM4450g [47] studies. Table 4 outlines results from these population PK analyses.

Table 4. Summary of Post-hoc Bayesian estimates for PKPD model development

<table>
<thead>
<tr>
<th>Paper</th>
<th>Data Source</th>
<th>Typical Population Parameter Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Phase I TDM3569g, Phase II TDM4258g, Phase II TDM4374g</td>
<td>CL (L/day) (IIV%), V₁ (L) (IIV%), CLd (L/day) (IIV%), V₂ (L) (IIV%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.70 (21), 3.33 (13.2), 0.78, 0.89 (50)</td>
</tr>
<tr>
<td>II</td>
<td>Phase I TDM3569g, Phase II TDM4258g, Phase II TDM4374g, Phase III TDM4370g, Phase II TDM4450g</td>
<td>0.676 (19.1), 3.13 (11.7), 1.53 (181), 0.66 (75)</td>
</tr>
</tbody>
</table>

**Paper I: T-DM1 PKPD Model of TCP**

In Paper I, a PKPD model describing platelet response to T-DM1 treatment was developed. Model development started by considering the PKPD model of myelosuppression presented by Friberg et al. [18] (see Figure 4).

During model development, modifications to the myelosuppression model (i.e., the addition of structural components and parameters) were made taking into account two notable observations from the clinical studies.

- First, in some patients, platelet–time profiles drifted slowly down over multiple cycles of T-DM1.
- Second, platelet count nadirs were generally lowest after the first T-DM1 dose.

From 1–5 transit compartments were considered, as well as T-DM1 concentrations acting directly on the platelet compartment. Shown in Figure 17 is a schematic of the final PKPD model for platelets.
Figure 17. Schematic of PKPD model for platelet response to T-DM1 treatment. BASE: baseline platelet count at time = 0, modeled as BASE₁ + BASE₂; BASE₁: amount of baseline proliferating PP that is nondepletable; BASE₂: amount of baseline proliferating PP that is depletable by the C_avg • k_deplete rate; C_avg: average T-DM1 concentration over dosing intervals; CL: clearance; CLd: intercompartmental clearance; &‡6ORSH T-DM1 drug effect; GAM: feedback parameter that increases the proliferation rate when PLT count drops below BASE; k_deplete: rate of depletion of BASE₂; kel: rate of physiologic elimination of circulating platelets; k_PROL: rate of PP proliferation; ktr: intercompartmental transit rate constant; MTT: mean transit time, equal to the number of intercompartmental transits divided by the transit rate constant (4/ktr); PLT: circulating platelet compartment; PP: platelet proliferation compartment; Slope: T-DM1 drug effect; Slope: feedback parameter that increases the proliferation rate when PLT count drops below BASE; &‡6ORSH RQWKHSUROLIH &‡6ORSH r- &‡6ORSH™ BSL(t) = (BASE – BASE₁ – C_avg • k_deplete – C_avg • k_deplete – WLPH) + BASE₁.

As shown in Figure 17, individual patient PK parameters from the population PK model [65] provided T-DM1 central compartment concentrations (C), which acted as a linear inhibitory drug effect (C • Slope) on the proliferation rate (k_PROL) of the PP compartment.

The downward drift in some patient platelet–time profiles was modeled by the introduction of an additional slow T-DM1–related drug effect on a depletable fraction of the PP pool. Specifically, the PP compartment was modeled as a nondepletable (BASE₁) proliferating pool and as a depletable (BASE₂ derived by BASE - BASE₂) proliferating pool of platelets. The drug effect (C_avg • k_deplete) was incorporated to slowly deplete the BASE₂ pool over time. The following equation was applied: BSL(t) = (BASE - BASE₁) • exp(-C_avg • k_deplete • time) + BASE₁.
Two separate Slope parameters were used to capture the lower platelet nadir in the first cycle—Slope$_1$ for the first dose, and Slope$_2$ for all subsequent doses. System–related parameters that were estimated included MTT, BASE, BASE$_1$, and GAM. Drug–related parameters that were estimated included Slope$_1$, Slope$_2$, and $k_{\text{deplete}}$.

Paper II: T-DM1 PKPD Model of TCP and Hepatotoxicity

In Paper II, a PKPD model describing platelet, ALT, and AST response to T-DM1 treatment was developed. For ALT and AST, only two published models were available for consideration: 1) a precursor–dependent PKPD model for ALT response to trabectedin presented by Fetterly et al. [16], and 2) a linear effect compartment model predicting ALT response to amiodarone presented by Pollak et al. [17]. The following patterns were also noted in the data.

- Similar to the platelet–time profiles, some ALT–time and AST–time profiles gradually increased over multiple cycles of T-DM1.
- Similar to the platelet count nadirs, ALT and AST levels were generally highest after the first T-DM1 dose.

Ultimately, for ALT and AST modeling, the model structure and parameterization developed for platelets in Paper I was used as a starting point. This model utilizes a delay in maximum drug effect through transit compartments, and also a drug-induced drift in baseline. Employing structural similarities between platelet, ALT, and AST readily allows incorporation of parameter correlations between PD responses.

The additional 494 patients, and longer time–courses, available for Paper II provided robust data to refine the original modeling approach for platelets, and apply to ALT and AST. Shown in Figure 18 is a schematic of the final PKPD model for ALT, AST, and platelet response to T-DM1.
Figure 18. Schematic of PKPD model for platelet, ALT, and AST response to T-DM1. ALT: alanine transaminase; ALTcirc (pool): ALT circulating or pool compartment; AST: aspartate transaminase; ASTcirc (pool): AST circulating or pool compartment; BSL0: baseline measurement at time = 0; BSL2: secondary baseline value; BSL(t): baseline time-course; CL: clearance; CLd: distributional clearance; Cp(t): T-DM1 central compartment concentrations time-course; Ce(t): T-DM1 EC concentration time-course; CEC50: T-DM1 EC concentration at 50% Emax; EC: effect compartment; Emax: maximum drug effect; GAM: feedback parameter; kEC: EC rate constant; kOUT: output rate; kPROL: rate of PLTprog proliferation; ktr: intercompartmental transit rate; n: Hill factor; PLTcirc: circulating platelet compartment; PLTprog: proliferative progenitor platelet pool compartment; Slope0: initial drug effect; SlopeSS: steady state drug effect; Slope(t): Slope time-course; T1, T2, and T3: transit compartments; TDEC: half-life decay parameter; V1: T-DM1 central volume of distribution; V2: T-DM1 peripheral volume of distribution.

As shown in Figure 18, the final model consisted of ALT, AST, and platelets submodels. For each PD response, the individually predicted T-DM1 central compartment concentrations (Cp(t)), based on parameter PK results from the extended population PK analysis [66], were used to drive the platelet, ALT, and AST responses. For platelets, Cp(t) acted as a linear inhibitory drug effect (Cp(t) • Slope0) on the proliferation rate (kPROL) of the PLTprog compartment. For ALT and AST, Cp(t) acted as a linear stimulation of the ALT or AST production rate (kIN = kOUT • BSL(t)), where BSL(t) is the baseline measurement at time=t.
In this analysis, the baseline time–course , \( (BSL_{(t)}) \), for each PD response was described using an effect compartment (EC) approach in which theoretical T-DM1 EC concentrations \( (C_{e(t)}) \) typically either reduced (platelets), or increased (ALT and AST) baseline values slowly over time. Specifically, pretreatment baseline values at time = 0 (BSL0), slowly transitioned to a minimum (platelets) or maximum (ALT and AST) baseline (BSL_{min/max}) upon repeated T-DM1 dosing.

This cumulative dose effect was saturable and modeled using a sigmoidal Emax model. The following equation was applied for platelet, ALT, and AST BSL(t): \( \text{BSL}(t) = (\text{BSL}_0 - \text{BSL}_2) \times \exp((-\text{Emax} \times \text{C}_{e(t)}^{n}) / (\text{C}_{e,50}^{n} + \text{C}_{e(t)}^{n})) + \text{BSL}_2. \) BSL2 is a secondary baseline parameter for model fitting purposes. C_{e(t)} was predicted from the central compartment using an EC input rate of k_{EC} \times C_p(t), and a first order output rate of k_{EC}. This readily allowed assessment and implementation of correlations between platelet, ALT, and AST cumulative effects.

In Paper I PKPD platelet model, a Slope1 and Slope2 parameterization captured the phenomenon of increased drug effect after the first dose. In Paper II, the modeling approach was refined and applied to ALT and AST responses. The drug effect time–course , \( (\text{Slope}_{(t)}) \), was modeled as an initial drug effect \( (\text{Slope}_0) \) decaying to a steady state drug effect \( (\text{Slope}_{SS}) \), with a half–life decay parameter \( (T_{DEC}) \). Correlations between platelet, ALT, and AST acute dose response were assessed and implemented.

After model building, dose modification rules for T-DM1 were incorporated into the PKPD model code to provide relevant simulations and VPCs. During the model simulation process, a predose assessment, immediately before the scheduled dose, checked whether a Grade \( \geq 3 \) ALT, AST, or platelet was predicted, and model code incorporated the following dose modifications:

<table>
<thead>
<tr>
<th>ALT or AST</th>
<th>Platelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Delay the next dose until concentrations recover to Grade ( \leq 2 )</td>
<td>Discontinue T-DM1 Dosing</td>
</tr>
<tr>
<td>Dose reduce by 0.6 mg/kg for q3w regimens, and by 0.4 mg/kg for q1w regimens</td>
<td>Do not dose reduce</td>
</tr>
<tr>
<td>Discontinue T-DM1 treatment if more than 2 dose reductions are necessary</td>
<td></td>
</tr>
</tbody>
</table>
Paper III: T-DM1 PK Models

In Paper III, PK models elucidating and conceptualizing T-DM1 disposition from preclinical experiments in rat and cynomolgus monkeys were developed. Initially, a three–compartmental PK model was developed to best describe total trastuzumab concentrations. Subsequently, the mechanistic T-DM1 PK model was fit simultaneously to total trastuzumab and DAR₀–DAR₇ concentration–time data from both in vitro plasma stability and in vivo experiments. DM1 deconjugation occurring in V₁, V₂, and V₃ compartments was considered. A model parameterization was also tested which assumed that DM1 deconjugation rates were independent of the number of DM1s attached or the conjugations site as described by Gibiansky et al. [67]; in this approach, k₁→₀ was the single deconjugation parameter, and the other intercompartmental deconjugation rate constants were factors of k₁→₀, i.e., k₂→₁ = 2 • k₁→₀, k₃→₂ = 3 • k₁→₀, etc.

From the mechanistic PK model, a reduced T-DM1 PK model was developed by fitting the model simultaneously to ELISA measurements of total trastuzumab and T-DM1 concentration–time data. Shown in Figure 19 are schematics of the final T-DM1 PK models.

Figure 19. Schematic of the T-DM1 PK Models. (Left panel): Mechanistic model describing concentration time–courses of individual DAR₀–DAR₇ moieties and total trastuzumab (TT). CLₜₜ: TT clearance from the central compartment; CLₜᵥᵥ: in vivo antibody clearance from the central compartment; CLd₂, CLd₃: distributional clearances; DARₙ: n DM1 molecules bound to trastuzumab (drug-to-antibody ratio); Kₚₚₚₚ: antibody degradation rate in plasma; K₁→₀: DM1 deconjugation rate from higher to next DAR moiety; V₁, V₂, V₃: volumes of distribution of central and peripheral compartments; (Right panel): Reduced T-DM1 PK model describing time–courses of T-DM1 and TT. T-DM1 is any trastuzumab molecule with at least one DM1 molecule. CL_DEC: deconjugation rate from T-DM1 to unconjugated trastuzumab (DAR₀).
As shown in the mechanistic PK model approach, individual DAR moieties are linked together through a catenary chain of sub–compartments within the central compartment ($V_1$) of a 3–compartment model. DAR moieties undergo distributional clearance ($\text{CL}_{\text{d}_2}$ and $\text{CL}_{\text{d}_3}$) into two peripheral compartments ($V_2$ and $V_3$) and are cleared from the central compartment through antibody clearance ($\text{CL}_{\text{TT}}$) processes. $\text{CL}_{\text{TT}}$ was parameterized as composed of a first order antibody degradation rate ($K_{\text{plasma}}$), supported by the in vitro plasma stability data, and other in vivo antibody clearance processes ($\text{CL}_{\text{in vivo}}$). Individual rates of DM1 deconjugation from DAR moieties were modeled as first order rate constants ($K_{n\rightarrow n-1}$), where $n$ is the higher DAR moiety, and $n-1$ is the subsequent DAR moiety in the catenary chain.

In the reduced PK model, T-DM1 is represented by a single compartment within the central compartment ($V_1$) of a 3–compartment model. A single deconjugation parameter ($\text{CL}_{\text{DEC}}$) described the conversion of T-DM1 to unconjugated trastuzumab (DAR$_0$). T-DM1 and DAR$_0$ distribute into peripheral compartments and are cleared by antibody clearance ($\text{CL}_{\text{TT}}$) processes.

**Paper IV: Taxane Tumor Model**

**Tumor Model**

In Paper IV, a general model for tumor response was developed base on taxane treatment, and results were applied in parametric TTE analyses of survival data. Tumor model development began by first considering the TGI model of tumor SLD proposed by Claret et al. [29] (see Figure 6). However, the TGI model did not adequately fit certain patterns of tumor response, primarily those in patients exhibiting long periods of tumor quiescence and regrowth. Therefore, modifications to the TGI model (i.e., the addition of structural components and parameters) were made. The schematic for the final tumor model is shown in Figure 20.
Figure 20. Schematic of the tumor model. SLD₀: tumor SLD at time=0; FnR: fraction of tumor SLD₀ quiescent at time=0; 1–FnR: fraction of tumor SLD₀ sensitive to drug treatment; k_{Grow,Sens}: growth rate constant of drug–sensitive tumor fraction; k_{Grow,Resist}: growth rate constant of drug–resistant tumor fraction; k_{Kill}: tumor kill rate constant; k_{Delay}: transit compartment delay rate constant from quiescent tumor to drug–resistant tumor; k_{Drug}: drug effect elimination rate constant; R₁, R₂, and R₃: transit delay compartments of nonproliferating drug–resistant tumor cells. The overall tumor SLD is the sum of all six tumor compartments. The drug–resistant tumor SLD is the sum of the Tumor Quiescent, R₁, R₂, R₃ and Proliferating Tumor Drug–Resistant compartments.

The final tumor model consisted of a chain of five compartments mimicking tumor drug–resistance, and a tumor drug–sensitive compartment susceptible to drug treatment. The resistant tumor compartments consisted of an initial tumor quiescent compartment, 3 transit compartments (R₁, R₂, and R₃), and a proliferative drug–resistant tumor compartment. During model building, from 1–5 transit compartments were considered. The total tumor SLD is represented as the sum of all 6 compartments.

At time = 0, the tumor quiescent SLD was determined by FnR • SLD₀, where SLD₀ equals the observed tumor baseline and FnR is a model parameter describing the fraction of SLD₀ which transitions to proliferative drug–resistant tumor; the drug–sensitive tumor SLD was derived by (1– FnR) • SLD₀. The drug–sensitive tumor and drug–resistant tumor compartments proliferate according to first order growth rate constants, k_{Grow,Sens} and k_{Grow,Resist}, respectively. The antitumor taxane drug effect was described by
first order tumor kill rate \( (k_{\text{Kill}}) \) multiplied by the predicted taxane time-course Drug\( (t) \). Drug\( (t) \) was based on the administration schedule and a first order drug loss rate \( (k_{\text{Drug}}) \). Lastly, the first order \( k_{\text{Delay}} \) rate parameter described the transition time from tumor quiescence to proliferative drug-resistant tumor.

**Overall Survival (OS) Model**

In Paper IV, TTE survival models were developed according to the following equation for the hazard function:

\[
h(t) = h_0(t) \cdot e^{\sum_{i=1}^{n} \beta_i \cdot X_i}
\]

The baseline hazard function, \( h_0(t) \), was first determined considering exponential, Weibull, and log-normal distributions. The best model, determined by the lowest objective function value and VPCs, was carried forward in the covariate analysis where \( X_1, X_2, \ldots, X_n \) represent covariates and \( \beta_1, \beta_2, \ldots, \beta_n \) were parameters to be estimated [3, 34].

**Model building methods**

For PK and PKPD model building, the First Order Conditional Estimation (FOCE) method with INTERACTION using NONMEM 7.3.0 was used [68]. Platelet, ALT, AST, and tumor SLD data were log-transformed. Log-normal parameter distributions were typically used for IIV, where the parameter value for the \( i^{th} \) patient was represented by Parameter\( _i = \text{Typical Value} \cdot \exp(\eta_i) \), where the CV of \( \eta_i \) represents the IIV. The residual error was modeled as a proportional error, which is additive in the log domain. For the \( k_{\text{p Elite}} \) (Paper I), platelet \( k_{\text{eo}} \) (Paper II), and \( k_{\text{delay}} \) (Paper IV) parameters, the distributions were bimodal and the mixture model implementation in NONMEM was used. A difference in OFV of >6.63, corresponding to a significance level of \( P < 0.01 \), was used for discrimination between two nested models that differed in one parameter.

OS model building was performed using the FO method in NONMEM 7.3.0. A difference in OFV of >6.63, corresponding to a significance level of \( P < 0.01 \), was used for discrimination between two nested models that differed in one parameter.

**Covariate Analyses**

For Papers I, II, and IV, analyses were used to identify covariates (e.g. patient baseline characteristics, model-based metrics) that might explain sources of IIV on model parameters. Shown in the Table 5 are the covariates assessed for each paper.
In Papers I and II, the covariate analysis was first performed using the linearized FOCE method with stepwise covariate model building [69], to screen the considered covariates for significance on any parameter. If significant covariate parameter correlations were found (p<0.01), these were assessed using the nonlinear FOCE method for inclusion into the model. In Paper IV, covariates were first screened separately for significance, and the most significant covariate by OFV was retained in the model. This procedure was repeated adding covariates stepwise until no significance remained.

Model Evaluation and Simulation

For Papers I, II, and III, model simulations were done for model evaluation, dose comparison, and illustration of PK concepts. Table 6 introduces specifics of model simulations.

<table>
<thead>
<tr>
<th>Covariate Type</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical</td>
<td>Race, Prior myelosuppressive chemotherapies (paclitaxel, docetaxel, or carboplatin) (Yes/No)</td>
<td>ECOG status (0 / ≥1), Race=Asian (Yes/No), Liver metastases (Yes/No), Measurable disease (Yes/No)</td>
<td>ECOG status (0 / ≥1)</td>
</tr>
<tr>
<td>Continuousa</td>
<td>Age, Weight, Creatinine clearance, Serum creatinine, Albumin, Total protein, Platelet count, ALT, AST count, Total bilirubin, Tumor SLD, HER2 ECD</td>
<td>Age, Albumin, HER2 ECD, Bilirubin, Tumor SLD, Number of disease sites</td>
<td>Age, Tumor SLD</td>
</tr>
<tr>
<td>Model–Basedb</td>
<td>—</td>
<td>—</td>
<td>k_{Drug}, k_{Kill}, k_{Delay}, k_{Grow,Sens}, k_{Grow,Resist}, FnR, TSR_{6}, TTG</td>
</tr>
</tbody>
</table>

ALT: Alanine transaminase; AST: Aspartate transaminase; SLD: sum of longest diameter; ECD: extracellular domain; ECOG: Eastern Cooperative Oncology Group; HER2: human epidermal growth factor receptor 2; TSR_{6}: tumor size ratio at week 6; TTG: time to tumor growth

a Baseline values
b See Figure 20 for description of model–based covariates

Table 5. List of covariates assessed in Papers I, II, and IV

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b See Figure 20 for description of model–based covariates
<table>
<thead>
<tr>
<th>Paper</th>
<th>Model</th>
<th>T-DM1 Dose(s) Simulated</th>
<th>Purpose</th>
<th>Simulation Notes</th>
</tr>
</thead>
</table>
| I     | Platelet T-DM1 PKPD | 3.6 mg/kg q3w | • External evaluation dataset TDM4374g  
• Stratification of Grade 3 TCP by platelet baseline, T-DM1 AUC, and T-DM1 C_{max} | • 100 simulated replicates  
• 110 patients/replicate  
• 10 dose cycles simulated  
• Simulations stratified by k_{deplete} |
| II    | ALT, AST, and Platelet T-DM1 PKPD | 3.6 mg/kg q3w; 2.4 mg/kg q1w; 1.2 mg/kg q1w | • Internal evaluation dataset TDM4370g  
• PPCs  
• Comparison of Dose Regimens for % Grade 3 AEs, DI, and RDI | • 200 simulated replicates  
• 338 patients/replicate  
• 10 dose cycles simulated  
• Model includes dose modification rules per T-DM1 prescribing information |
| III   | Mechanistic T-DM1 PK | DAR, 3.1: 3.6 mg/kg and 3.6 mg/kg q3w  
DAR, 1.5: 3.6, 5.16, 5.8, 7.1, and 8.0 mg/kg q3w | • Illustration of PK system  
• Support hypothesis testing for efficacy and toxicity MOA | • DAR_{AVG}, T-DM1, and Conjugated DM1 time courses were elucidated |

AE: adverse effect; ALT: Alanine transaminase; AST: Aspartate transaminase; AUC: area under the curve; C_{max}: maximal concentration; DAR_{AVG}: average drug:antibody ratio; DI: dose intensity; MOA: mechanism of action; PPC: posterior predictive check; TCP: thrombocytopenia; q1w: weekly; q3w: every 3 weeks; RDI: relative dose intensity
Model Evaluation

Posterior Predictive Checks (PPCs) for Grade 3 and Grade 4 Toxicities

As shown in Table 6, an external evaluation was performed in Paper I using platelet data from the TDM4374 trial. 100 simulation replicates were generated from the PKPD model using the TDM4374g patient number (N=110; 3.6 mg/kg q3w). The ability of the model to predict the incidence of Grade ≥3 TCP by day 63 was evaluated. Day 63 was chosen as the end point since most patients were still on study, and Grade ≥3 TCP (when observed) was usually reached within three treatment cycles. The observed incidence of Grade ≥3 TCP from the model dataset and evaluation dataset were overlaid with the simulated predictions. These probabilities were further separated by quartiles of observed baseline platelet count, T-DM1 Cmax (calculated by Dose/V1), and T-DM1 area under the curve (AUC) (calculated by Dose/CL).

In Paper II, an internal evaluation was done using the TDM4370g portion of the model building dataset (~ 50% of total patients); 200 simulation replicates were generated using the TDM4374g dataset as the template (N=338; 3.6 mg/kg q3w). PPC histograms of percentages of model–predicted Grade 3 and Grade 4 toxicities in the 200 datasets were compared with observed toxicities.

Visual Predictive Checks (VPCs)

For VPCs, 90% prediction intervals with 95% confidence intervals were obtained by simulating 100 datasets from the model using the original datasets as templates. For Papers I, II, and IV, the model–predictions were examined to determine whether observed 5th, 50th, and 95th percentiles of data fell within the 95% confidence intervals of the corresponding percentiles derived from model simulations. For Paper III, due to the relatively small number of animals used, the model–predictions were examined to determine whether the observed 50th prediction of data fell within the 95% confidence intervals of the corresponding prediction derived from model simulations.

For OS model evaluation, VPCs were done by comparing 100 simulated Kaplan–Meier curves, based on the final OS model estimates, to the observed docetaxel and paclitaxel survival data [70].

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Results/Discussion

Papers I and II
This impetus for the original analysis in Paper I was the fact that thrombocytopenia (TCP), a reduction in platelet counts, is the dose–limiting toxicity for T-DM1. Therefrom, a PKPD model was developed describing platelet response to T-DM1 treatment in HER2–positive breast cancer patients, and patient covariates were investigated in attempts of explaining factors that may contribute to TCP. In Paper II, the model was updated with data from 494 additional patients to simultaneously describe platelet, ALT, and AST response. Hepatotoxicity, in the form of elevated ALT and AST enzymes, is also a common Grade 3/4 AE for T-DM1 [71].

For PKPD modeling, there was a clear concentration-effect relationship and thus the time-course of T-DM1 was used to drive platelet, ALT, and AST responses. For platelet response, this has mechanistic support as trastuzumab, as a single agent, has not been associated with myelosuppressive effects [72]. Secondly, maytansine, the parent drug of DM1 and of similar structure, showed no substantial myelosuppressive effects in Phase I [73] and Phase II [74] studies. Thirdly, TCP has not been reported as a significant toxicity with other DM1–containing antibody drug conjugates (ADCs) [75, 76]. A T-DM1 effect acting on the platelet progenitor compartment was chosen as the best model. Experimental support for this recently been shown by Uppal et al. [77], who concluded that T-DM1 is internalized into megakaryocytes (i.e. platelet precursors) in a HER2–independent, FcgRIIa–dependent manner, resulting in the intracellular cytotoxic release of DM1. Experimental support for T-DM1 concentrations as the PK driver for ALT and AST responses has been shown in vivo by Poon et al. [78], who determined that elevations were driven by T-DM1 in a HER2 antigen–independent manner. Similarly, this drug effect was applied to the “presystemic” pool compartment.
In Figures 21–23, VPCs and model simulations show that the PKPD models developed in Papers I and II well–described the data and incidences of Grade ≥ 3 toxicities. The model in Paper I well–predicted the platelet time–course data, as well as the ~8% incidence of Grade ≥3 TCP determined in the model building and evaluation datasets (Figure 21). Patients with lower platelet baseline were more likely to experience Grade ≥3 TCP, as a higher incidence (~25%) occurs when baseline platelet counts are <201•1000/μL.

Figure 21. VPC and model simulations from Paper I (T-DM1 3.6 mg/kg q3w). (Left panel): VPC: The solid red line represents the median of the observed platelet data (open circles). The red shaded region represents the 95% confidence interval of the model simulated median. The outer blue shaded regions represent the 95% confidence interval around the model simulated 5th and 95th percentiles. The stippled red lines represent the 5th and 95th percentiles of the observed platelet observations. (Right panel): Grade ≥3 TCP probabilities are stratified by “All” baseline platelet counts, and by quartiles of observed baseline platelet counts (lower 25%, 25–75%, and upper 25%).

In Figure 22, Paper I model simulations show that the model also well–described the two patterns of platelet response in the evaluation dataset: 1) those patients with “stable” platelet nadirs (k_deplete,POP1 patients), and 2) those patients with a downward drift in platelet nadirs and post nadir counts over time (k_deplete,POP2 patients).
Figure 22. Model simulations (T-DM1 3.6 mg/kg q3w) stratified by the two patterns of platelet response to T-DM1. (Left panel): \(k_{\text{deplete,POP1}}\) patients, i.e. those with a stable platelet count nadir over time; (Right panel): \(k_{\text{deplete,POP2}}\) patients, i.e. those with a downward drift in nadir and post nadir counts over time. In each plot, the solid black line represents the median of the model–building platelet data. The solid red line represents the median of the evaluation dataset platelets (open circles). The light blue shaded region represents the 95% confidence interval of the model simulated median. Blue lines represent the 90th prediction interval. The stippled grey lines represent the 95% confidence interval around the model simulated 5th and 95th percentiles. Horizontal grey line indicates the cutoff for Grade 3 TCP (50•1000/μL).

Shown in Figure 23 are the Paper II VPCs and posterior predictive checks (PPCs) for platelet, ALT, and AST responses. As shown for the VPCs, the model well–predicted the longitudinal ALT, AST, and platelet data simultaneously. PPCs show that the model also predicted the incidences of Grade ≥3 events for platelet (~17%), ALT (~4%), and AST (~6%) in the evaluation dataset simultaneously.
Figure 23. Paper II VPCs and PPCs. VPCs (Left panels): The solid black line represents the median of the platelet, ALT, and AST observations (black circles). The red shaded region represents the 95% confidence interval of the model simulated median. The outer blue shaded regions represent the 95% confidence intervals of the model simulated 5th and 95th percentiles. The stippled black lines represent the 5th and 95th percentiles of the observed platelet, ALT, or AST observations. Vertical lines indicate binning intervals for VPCs. (Right panels): PPC histograms showing the distribution of the model predicted percentages of patients ZLWK*UDGHWLRQ$ZLWK*UDGHWLRQ from 200 simulated trials. The solid blue line is the 50th percentile of the model predicted percentages. The stippled blue lines represent the 5th and 95th percentiles of the model predicted percentages. The solid red line is the observed incidence of toxicity in the TDM4370g study as an internal evaluation dataset.

The VPCs also show that the higher drug effect after the first T-DM1 dose is well-described by the model. Most evident is the lowest platelet nadir occurring ~Day 8 (Figure 23). Similarly, ALT and AST concentrations are slightly higher at ~Day 8. Final parameter estimates from the two PKPD models developed in Paper I and II have been integrated into Table 7.
Table 7. Final PKPD Model Estimates for Paper I and Paper II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Unit</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper II</th>
<th>Paper II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Platelet</td>
<td>Platelet</td>
<td>ALT</td>
<td>AST</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Value</td>
<td>Value</td>
<td>Value</td>
<td>Value</td>
</tr>
<tr>
<td>Slope1</td>
<td>Slope for first dose</td>
<td>L/mg</td>
<td>2.97</td>
<td>36.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Slope2</td>
<td>Slope for subsequent doses</td>
<td>L/mg</td>
<td>1.82</td>
<td>56.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Slope0</td>
<td>Initial Slope value</td>
<td>L/mg</td>
<td>—</td>
<td>—</td>
<td>52.0</td>
<td>23.1</td>
</tr>
<tr>
<td>SlopeSS</td>
<td>Initial Slope at steady state</td>
<td>L/mg</td>
<td>2.08</td>
<td>47.9</td>
<td>4.28</td>
<td>83.0</td>
</tr>
<tr>
<td>TDEC</td>
<td>Half-life for Slope0 --- SlopeSS</td>
<td>week</td>
<td>—</td>
<td>—</td>
<td>1.39</td>
<td>53.7</td>
</tr>
<tr>
<td>BASE</td>
<td>Baseline at time = 0</td>
<td>count</td>
<td>255</td>
<td>32.3</td>
<td>264</td>
<td>28.2</td>
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<tr>
<td>BASE1</td>
<td>Nondepletable platelet baseline</td>
<td>count</td>
<td>118</td>
<td>37.4</td>
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<tr>
<td>BASE2</td>
<td>Depletable platelet baseline</td>
<td>count</td>
<td>137</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BSL2</td>
<td>Secondary baseline</td>
<td>count</td>
<td>—</td>
<td>1.41</td>
<td>52.9</td>
<td>43.7</td>
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<tr>
<td>(1)</td>
<td>Probability for Population 1</td>
<td>—</td>
<td>0.554</td>
<td>—</td>
<td>0.840</td>
<td>—</td>
</tr>
<tr>
<td>k_{MAX,POP1}</td>
<td>DEP depletion rate; POP1</td>
<td>L/mg\cdot week(^{-1})</td>
<td>6.25</td>
<td>88.1 ^a</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>k_{MAX,POP2}</td>
<td>DEP depletion rate; POP2</td>
<td>L/mg\cdot week(^{-1})</td>
<td>84.2</td>
<td>88.1 ^a</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>kEC,POP1</td>
<td>EC rate constant; POP1</td>
<td>hr(^{-1})</td>
<td>0.889</td>
<td>86.9</td>
<td>0.917</td>
<td>84.6</td>
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<tr>
<td>kEC,POP2</td>
<td>EC rate constant; POP2</td>
<td>hr(^{-1})</td>
<td>7.64</td>
<td>51.0</td>
<td>—</td>
<td>—</td>
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<tr>
<td>C_{EC,50}</td>
<td>T-DM1 [EC] at 50% Emax</td>
<td>mg/L</td>
<td>0.900</td>
<td>0</td>
<td>0.303</td>
<td>0.156</td>
</tr>
<tr>
<td>Emax</td>
<td>Maximum drug effect from EC</td>
<td>L/mg</td>
<td>0.635</td>
<td>54.2</td>
<td>1.20</td>
<td>111</td>
</tr>
<tr>
<td>n</td>
<td>Hill factor</td>
<td>—</td>
<td>—</td>
<td>2.67</td>
<td>2.67</td>
<td>1.66</td>
</tr>
<tr>
<td>GAM</td>
<td>Platelet feedback parameter</td>
<td>—</td>
<td>0.135</td>
<td>—</td>
<td>0.150</td>
<td>—</td>
</tr>
<tr>
<td>k_{tr}</td>
<td>Intecompartmental transit rate</td>
<td>hr(^{-1})</td>
<td>2.35</td>
<td>31.6</td>
<td>3.29</td>
<td>28.5</td>
</tr>
<tr>
<td>MTT</td>
<td>Mean transit time</td>
<td>hr</td>
<td>37.4</td>
<td>24.5</td>
<td>37.4</td>
<td>24.5</td>
</tr>
<tr>
<td>Res. Err.</td>
<td>Residual error</td>
<td>—</td>
<td>18.4%</td>
<td>19.2%</td>
<td>15.1%</td>
<td>9.85%</td>
</tr>
</tbody>
</table>

EC = effect compartment; [EC] = effect compartment concentration; POP = population

^a Asian ethnicity was a significant covariate for Platelet Slopes

^b Shared ETA implemented due to approximately 100% correlation; scaled values = 1.93, 1.58, and 1.24 for ALT Slope0, ALT SlopeSS, and ALT TDEC, respectively (see Paper II for details)

^c units = LIL for ALT and AST; ^d units = count\(\times 1000\) \(\mu\)L for platelets

Residual error fixed to 0

^e k_{EC,50} set equivalent to k_{tr} (MTT/4) for platelet submodel; k_{OUT} set equivalent to k_{tr} for ALT and AST submodels

^f OMEGA SAME option used for IIV

---

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Unit</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper II</th>
<th>Paper II</th>
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<td></td>
<td></td>
<td></td>
<td>Platelet</td>
<td>Platelet</td>
<td>ALT</td>
<td>AST</td>
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<td></td>
<td></td>
<td></td>
<td>Value</td>
<td>Value</td>
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<tr>
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<td>Slope for subsequent doses</td>
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<td>Initial Slope value</td>
<td>L/mg</td>
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<td>—</td>
<td>52.0</td>
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<tr>
<td>SlopeSS</td>
<td>Initial Slope at steady state</td>
<td>L/mg</td>
<td>2.08</td>
<td>47.9</td>
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<td>Half-life for Slope0 --- SlopeSS</td>
<td>week</td>
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<td>—</td>
<td>1.39</td>
<td>53.7</td>
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<td>BASE</td>
<td>Baseline at time = 0</td>
<td>count</td>
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<td>BASE1</td>
<td>Nondepletable platelet baseline</td>
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<td>BASE2</td>
<td>Depletable platelet baseline</td>
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<td>137</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td>BSL2</td>
<td>Secondary baseline</td>
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<td>1.41</td>
<td>52.9</td>
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<td>(1)</td>
<td>Probability for Population 1</td>
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<td>0.840</td>
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<td>k_{MAX,POP1}</td>
<td>DEP depletion rate; POP1</td>
<td>L/mg\cdot week(^{-1})</td>
<td>6.25</td>
<td>88.1 ^a</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>k_{MAX,POP2}</td>
<td>DEP depletion rate; POP2</td>
<td>L/mg\cdot week(^{-1})</td>
<td>84.2</td>
<td>88.1 ^a</td>
<td>—</td>
<td>—</td>
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<td>kEC,POP1</td>
<td>EC rate constant; POP1</td>
<td>hr(^{-1})</td>
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<td>84.6</td>
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<tr>
<td>kEC,POP2</td>
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<td>hr(^{-1})</td>
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<tr>
<td>C_{EC,50}</td>
<td>T-DM1 [EC] at 50% Emax</td>
<td>mg/L</td>
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<td>0</td>
<td>0.303</td>
<td>0.156</td>
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<tr>
<td>Emax</td>
<td>Maximum drug effect from EC</td>
<td>L/mg</td>
<td>0.635</td>
<td>54.2</td>
<td>1.20</td>
<td>111</td>
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<td>n</td>
<td>Hill factor</td>
<td>—</td>
<td>—</td>
<td>2.67</td>
<td>2.67</td>
<td>1.66</td>
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<tr>
<td>GAM</td>
<td>Platelet feedback parameter</td>
<td>—</td>
<td>0.135</td>
<td>—</td>
<td>0.150</td>
<td>—</td>
</tr>
<tr>
<td>k_{tr}</td>
<td>Intecompartmental transit rate</td>
<td>hr(^{-1})</td>
<td>2.35</td>
<td>31.6</td>
<td>3.29</td>
<td>28.5</td>
</tr>
<tr>
<td>MTT</td>
<td>Mean transit time</td>
<td>hr</td>
<td>37.4</td>
<td>24.5</td>
<td>37.4</td>
<td>24.5</td>
</tr>
<tr>
<td>Res. Err.</td>
<td>Residual error</td>
<td>—</td>
<td>18.4%</td>
<td>19.2%</td>
<td>15.1%</td>
<td>9.85%</td>
</tr>
</tbody>
</table>

EC = effect compartment; [EC] = effect compartment concentration; POP = population

^a Asian ethnicity was a significant covariate for Platelet Slopes

^b Shared ETA implemented due to approximately 100% correlation; scaled values = 1.93, 1.58, and 1.24 for ALT Slope0, ALT SlopeSS, and ALT TDEC, respectively (see Paper II for details)

^c units = LIL for ALT and AST; ^d units = count\(\times 1000\) \(\mu\)L for platelets

Residual error fixed to 0

^e k_{EC,50} set equivalent to k_{tr} (MTT/4) for platelet submodel; k_{OUT} set equivalent to k_{tr} for ALT and AST submodels

^f OMEGA SAME option used for IIV
In both Paper I and II, a higher drug effect for platelets was noted after the first T-DM1 dose. In Paper I, a simple Slope₁ (for the first dose) and Slope₂ (for all subsequent doses) parameterization was used. Paper II refined this approach, using a Slope₀ transitioning to SlopeₙSS according to the Tₐ₀ parameter. For both approaches, the initial Slope value (Slope₀ and Slope₁) was highest, effectively capturing the low platelet nadir after the first dose. Most patients in the model–building dataset demonstrated this pattern of lowest platelet nadir in the first cycle, with variable degrees of increased nadir counts in the second and subsequent cycles.

Paper II also described the phenomena that ALT and AST show the highest responses after the first dose (i.e. SlopeₙSS > Slope₀). Parameters of Slope₀, SlopeₙSS, and Tₐ₀ were highly correlated between ALT and AST, but not with platelets. These correlations are supported by physiology, given that both AST and ALT are likely released into circulation upon cellular damage from T-DM1 treatment. Slope₀ was not correlated with SlopeₙSS for platelets, ALT, or AST, suggesting that the steady state treatment response cannot be predicted from the initial dose response.

In Paper II, the downward drift in platelet nadir was also refined from Paper I, utilizing BSL₀ and BSL₂ instead of BASE₁ and BASE₂. In Paper I, the following equation was applied for BSLₙ(t):

\[
BSLₙ(t) = (BASE - BASE₁) \times \exp(-C_{avg} \times k_{deplete} \times time) + BASE₁
\]

In Paper II, the equation for BSLₙ(t) was updated to:

\[
BSLₙ(t) = (BSL₀ - BSL₂) \times \exp((-E_{max} \times Cₙ(t)^n)/(C_{e,50} + Cₙ(t)^n)) + BSL₂
\]

In this approach, the model more appropriately predicted data following dose delays that had been built into the model, as “time” was replaced by an effect compartment approach. Ce(t) was predicted from the EC compartment, using an input rate of kEC \times C_{p(t)}, and first order elimination of kEC.

In each approach for BSLₙ(t), a population approach on a key parameter (k_{deplete} in Paper I, and kEC in Paper II) determined the probability of a patient belonging to 1) a population (POP1) with a stable platelet nadir, and 2) a population (POP2) with a downward drift in platelet nadir and post-nadir counts over time. In each modeling analyses, the platelet–time profiles for the typical patient in POP2 was shown to stabilize after 24 weeks (eight treatment cycles), and above Grade 3 TCP.

In addition to Slope₀, SlopeₙSS, and Tₐ₀, kEC was also highly correlated between ALT and AST, but not with platelets. Thus, patients showing gradual elevations in ALT concentrations over time coincided with AST elevations,
but not with platelet decline. The mixture model was not supported for ALT and AST, and patient profiles were typically stable over time.

In the covariate analysis, the Paper II analysis revealed that Asian patients are more sensitivity than non-Asians with regard to platelet response. Asian ethnicity was a significant covariate for platelet $\text{Slope}_{SS}$, the steady state drug effect parameter which describes the extent of platelet nadir in the later T-DM1 dosing cycles. This ethnic difference has previously been reported by Dieras et al. [71]. In this dataset, 38% of Asian patients had Grade 3 TCP and 5% Grade 4 TCP versus 12.5% Grade 3 TCP and 2% Grade 4 TCP in non-Asians. The covariate analysis did not find any significant predictor for ALT or AST response, and therefore an individual ALT or AST response to T-DM1 cannot be predicted a priori from any baseline characteristics tested.

Overall, the PKPD modeling analysis quantified the T-DM1 concentration-effect relationship simultaneously for platelet, ALT, and AST responses. The correlations that were found and implemented for model simulations, in addition to the dose modification rules, was instrumental for accurate model evaluation and simulation.

Figure 24 illustrates additional seminal conclusions, with regard to platelets, from the Paper I and Paper II modeling results: 1) the typical Asian patient (top panel) has lower platelet nadirs versus Non–Asian patients (bottom panel); 2) there are two typical patterns of platelet response in patients receiving T-DM1; 3) typical patient platelet responses stabilize above Grade 3 TCP; and 4) the first-dose drug effect corresponds to a typical platelet count nadir of $115 \times 1000/\mu L$ in the first cycle and then a higher platelet nadir of $145 \times 1000/\mu L$ in the second cycle (for Non–Asians).
Figure 24. Typical platelet–time profiles following T-DM1 administration (3.6 mg/kg q3w). Black lines show the model–predicted platelet response for the typical Asian versus Non–Asian patient (k$_{EC,POP1}$ patients). Blue lines are the corresponding model–predicted platelet responses for the patient subpopulation (k$_{EC,POP2}$ patients) with faster platelet nadir decline. Grey points indicate the individual patient platelet data from the model building dataset. The solid red line indicates the Grade 3 threshold for platelets.

**Paper II Simulations**

In Paper II, a PKPD model simulation strategy was developed towards supporting T-DM1 dose and scheduling. The simultaneous modeling approach, parameter correlations, and incorporation of T-DM1 dose modification rules, allowed for prediction of dose intensity (DI) and relative dose intensity (RDI), which may be used as endpoints for overall treatment safety assessment and as a target drug exposure for clinical decision–making. The matching of T-DM1 steady state exposure (AUC$_{SS}$; 1.2 mg/kg q1w) and steady
state maximum concentrations ($C_{\text{max,SS}}$; 2.4 mg/kg q1w) to the approved dose (3.6 mg/kg q3w) may be relevant to consider for drug development, in which a target exposure or concentration may direct dose optimization. Shown in Figure 25 are the model predictions for PK and PD for these dose regimens based on the typical PKPD parameter estimates (see Tables 4 and 7).

![Model-predicted T-DM1 concentration time-courses](image)

**Figure 25.** Model–predicted T-DM1 concentration time–courses (top) and ALT, AST, and platelet time–courses (bottom) for the typical patient receiving 1.2 mg/kg q1w, 2.4 mg/kg q1w, and 3.6 mg/kg q3w T-DM1. q1w: weekly; q3w: every 3 weeks
As shown in Figure 25, the shortened dose interval with T-DM1 q1w dosing prevents full return towards baseline prior to the next dose for ALT, AST, and platelets, in contrast to T-DM1 q3w dosing. As dose interruptions are based on predose measurements, more dose interruptions may be expected for q1w dosing. With q3w dosing, more Grade 3 events may be expected during the treatment cycle compared to q1w, but the recovery to baseline prevents the need for dose modifications. Shown in Table 8 are the results of T-DM1 PKPD model simulations, comparing the percentages of simulated patients with Grade 3/4 events, based on weekly assessments, and dose modifications for these dose regimens.
Table 8. PKPD Model Simulations of Grade 3/4 Adverse Events and Dose Modifications

<table>
<thead>
<tr>
<th>Event</th>
<th>Description</th>
<th>T-DM1 Dose Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3.6 mg/kg q3w</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median %</td>
</tr>
<tr>
<td>Grade ≥ 3 Events</td>
<td>Platelet, ALT, or AST b</td>
<td>33.0 (28.6–37.2)</td>
</tr>
<tr>
<td></td>
<td>Platelet</td>
<td>23.6 (19.7–27.7)</td>
</tr>
<tr>
<td></td>
<td>ALT</td>
<td>4.42 (2.64–6.19)</td>
</tr>
<tr>
<td></td>
<td>AST</td>
<td>10.9 (8.26–13.6)</td>
</tr>
<tr>
<td></td>
<td>ALT or AST</td>
<td>12.4 (9.72–15.1)</td>
</tr>
<tr>
<td>Grade 4 Events</td>
<td>Platelet, ALT, or AST</td>
<td>5.31 (3.24–7.09)</td>
</tr>
<tr>
<td></td>
<td>Platelet</td>
<td>5.01 (3.24–7.08)</td>
</tr>
<tr>
<td></td>
<td>ALT</td>
<td>0 (0–0.295)</td>
</tr>
<tr>
<td></td>
<td>AST</td>
<td>0 (0–0.295)</td>
</tr>
<tr>
<td></td>
<td>ALT or AST</td>
<td>0 (0–0.590)</td>
</tr>
<tr>
<td>Dose Modifications</td>
<td>≥ 1 Dose Reduction</td>
<td>2.07 (0.885–3.25)</td>
</tr>
<tr>
<td></td>
<td>≥ 1 Dose Delay</td>
<td>4.87 (3.24–6.80)</td>
</tr>
<tr>
<td></td>
<td>Dose discontinuations</td>
<td>0.295 (0–0.885)</td>
</tr>
<tr>
<td></td>
<td>Dose Intensity</td>
<td>(mg/kg/wk) c</td>
</tr>
<tr>
<td></td>
<td>Relative (%) d</td>
<td>98.3 (97.5–99.0)</td>
</tr>
</tbody>
</table>

a The incidences of Grade 3/4 events are based on weekly assessments. Dose modification and dose intensity calculations derive from predose assessments per clinical guidelines.

b Platelet, ALT, or AST Grade 3/4 events may be less than the sum of the individual incidences (i.e. ALT+AST+Platelet), as Grade 3 events may occur simultaneously.

c Dose intensity is calculated by the total dose given divided by the treatment duration.

d Relative dose intensity is calculated by the ratio of the total dose received and the total dose intended during the treatment duration.
Table 8 shows that, as expected, the 2.4 mg/kg q1w regimen resulted in the highest dose intensity (2.07 mg/kg/wk) compared to the 1.2 mg/kg q1w regimen (1.15 mg/kg/wk) and the approved dose (1.18 mg/kg/wk). The q1w dose regimens are associated with more dose modifications due to more frequent Grade 3 events predose. This leads to the lower RDIs of 95.7% and 86.2% for the weekly regimens, versus the approved dose (98.3%). These simulations may provide guidance when considering alternative dose regimens for T-DM1.

Paper III

For Paper III, an LC-MS assay provided the crucial analytical measurements of the individual T-DM1 drug-to-antibody ratio (DAR) moieties. Two PK models, elucidating and conceptualizing T-DM1 disposition, were developed from preclinical in vitro and in vivo rat and cynomolgus monkey data: 1) a mechanistic PK model simultaneously fit to total trastuzumab and individual DAR concentrations, and 2) a reduced PK model simultaneously fit to total trastuzumab and T-DM1 concentrations.

T-DM1 Mechanistic PK Model

As shown in the following VPCs, the mechanistic PK model well-described the total trastuzumab and DAR0–DAR7 concentration–time data from the in vitro and in vivo studies in rats (Figure 26) and monkeys (Figure 27). Table 9 presents the final parameter estimates for the mechanistic PK model.
Figure 26. VPCs of total trastuzumab (TT) and DAR₇–DAR₉ concentrations for the mechanistic PK model fit to data from: (Top Panel) in vitro rat plasma stability study with 100 μg/mL T-DM1_{DAR, 3.1}; (Middle Panel) Rat PK study with 10 mg/kg T-DM1_{DAR, 3.1}; (Bottom Panel) Rat PK study with 10 mg/kg T-DM1_{DAR, 1.5}. The shaded area is the model-predicted median with 95% confidence interval, and the solid line is the median of the observed data (circles). Both axes are shown on log scale for visualization purposes. DARn = n DM1 molecules bound to trastuzumab.
Figure 27. VPCs of total trastuzumab (TT) and DAR₀−DAR₇ concentrations for the mechanistic deconjugation model fit to data from: (Top Panel) *in vitro* cynomolgus monkey plasma stability study with 100 μg/mL T-DM1roatDAR 3.1; (Bottom Panel) Cynomolgus monkey PK study with 30 mg/kg T-DM1roatDAR 3.1. The shaded area is the model–predicted median with 95% confidence interval, and the solid line is the median of the observed data (circles). Both axes are shown on log scale for visualization purposes; DARₙ = n DM1 molecules bound to trastuzumab
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Unit</th>
<th>Value</th>
<th>RSE (%)</th>
<th>IIV %</th>
<th>RSE (%)</th>
<th>Value</th>
<th>RSE (%)</th>
<th>IIV %</th>
<th>RSE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLTT</td>
<td>Total trastuzumab clearance</td>
<td>mL/day</td>
<td>2.42</td>
<td>(5.7)</td>
<td>24.0</td>
<td>(18)</td>
<td>17.4</td>
<td>(13)</td>
<td>24.8</td>
<td>(22)</td>
</tr>
<tr>
<td>V1</td>
<td>Central volume</td>
<td>mL</td>
<td>11.0</td>
<td>(4.3)</td>
<td>18.5</td>
<td>(11)</td>
<td>148</td>
<td>(4.8)</td>
<td>11.7</td>
<td>(12)</td>
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<td>CLd2</td>
<td>Distributional Clearance 2</td>
<td>mL/day</td>
<td>49.0</td>
<td>(35)</td>
<td>—</td>
<td>—</td>
<td>25.5</td>
<td>(35)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>V2</td>
<td>Peripheral volume 2</td>
<td>mL</td>
<td>3.44</td>
<td>(58)</td>
<td>49.4</td>
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<td>57.2</td>
<td>(38)</td>
<td>46.8</td>
<td>(33)</td>
</tr>
<tr>
<td>CLd3</td>
<td>Distributional Clearance 3</td>
<td>mL/day</td>
<td>12.0</td>
<td>(16)</td>
<td>—</td>
<td>—</td>
<td>81.2</td>
<td>(19)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>V3</td>
<td>Peripheral volume 3</td>
<td>mL</td>
<td>16.7</td>
<td>(6.2)</td>
<td>16.8</td>
<td>(21)</td>
<td>127</td>
<td>(15)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kplasma</td>
<td>Plasma degradation rate constant</td>
<td>day⁻¹</td>
<td>0.156</td>
<td>(1.2)</td>
<td>—</td>
<td>—</td>
<td>0.0939</td>
<td>(3.0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cin vivo</td>
<td>in vivo antibody clearance</td>
<td>mL/day</td>
<td>0.704</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3.50</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>K7–6, K8–5, K5–3, K3–2</td>
<td>DAR7–DAR3 deconjugation rate constants</td>
<td>day⁻¹</td>
<td>0.543</td>
<td>(15)</td>
<td>21.8</td>
<td>(40)</td>
<td>0.341</td>
<td>(7.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>K2–1, K1–0</td>
<td>DAR2–DAR1 deconjugation rate constants</td>
<td>day⁻¹</td>
<td>0.388</td>
<td>(7.1)</td>
<td>—</td>
<td>—</td>
<td>0.255</td>
<td>(6.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Res. Err.</td>
<td>Residual error</td>
<td>%</td>
<td>11.1</td>
<td>(6.1)</td>
<td>—</td>
<td>—</td>
<td>15.3</td>
<td>(3.3)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

IIV: interindividual variability; RSE: relative standard error; a Composed of Cin vivo and Kplasma * V1; b Derived by: Cin vivo = CLtrastuzumab * Kplasma * V1; c Rates were determined to be equal from model building
As shown, values for typical compartmental PK parameters (CL\textsubscript{TT}, V\textsubscript{1}, CL\textsubscript{d2}, V\textsubscript{2}, CL\textsubscript{d3}, and V\textsubscript{3}) were estimated. The conjugation of DM1 (Mol. wt.=737 Da) does not appear to alter the disposition of the trastuzumab antibody (Mol. wt.=146 kDa), as the individual DAR\textsubscript{1}–DAR\textsubscript{7} moieties are well described using the same distributional volumes and clearance pathways as DAR\textsubscript{0} (unconjugated trastuzumab).

Notably, DM1 deconjugation rates were fastest for DAR moieties with ≥ 3 DM1 per trastuzumab in both rats and cynomolgus monkeys. It can be hypothesized that 1) higher conjugated DAR moieties have more probability to lose DM1 than less conjugated DAR moieties, or 2) that they have DM1 molecules that are conjugated to more solvent–accessible lysine residues on trastuzumab, making them less resistant to deconjugation [79, 80]. DM1 deconjugation from DAR\textsubscript{1} was the slowest step in the deconjugation chain, approximately 3.4–fold and 2.7–fold slower than DAR\textsubscript{2} in rats and cynomolgus monkeys, respectively.

Following development of the mechanistic model, simulations were done to illustrate all components of the PK system. In addition to total trastuzumab and the individual DAR moieties, the T-DM1 concentration, conjugated DM1 concentration, and the DAR\textsubscript{AVG} time–courses were derived (see Paper III for details). Shown in Figure 28 are simulations of the PK system following a T-DM1 single dose of 3.6 mg/kg T-DM1\textsubscript{DAR 3.1} and the cynomolgus monkey parameter estimates.
Figure 28. Mechanistic PK model predictions of total trastuzumab (TT), T-DM1, conjugated DM1, and DAR0–DAR7 concentration–time curves, and DARavg–time curve, based on the final parameter estimates from cynomolgus monkeys analysis. The T-DM1 curve is the composite of the 7 curves representing DAR1–DAR7 moieties. The TT curve is the composite of the 8 curves representing DAR0–DAR7 moieties. Predictions are for a single dose of 3.6 mg/kg T-DM1DAR 3.1.

The development of the mechanistic PK model provides guidance when considering experimental designs regarding PD responses from T-DM1 treatment. For example, with regard to T-DM1 anti–tumor efficacy, potential PK drivers include: 1) T-DM1 concentrations, where the binding of the anti–HER2 region of T-DM1 drives response, such that the anti–tumor effects between DAR moieties are equal; 2) the individual DAR moiety concentrations, where more heavily loaded DARs have more anti–tumor effect; 3) conjugated DM1 concentrations, where the overall DM1 drug load still attached to antibody may more appropriately drive response.

Reduced T-DM1 PK Model

The reduced model, based on T-DM1 and total trastuzumab, is more practical analytically in the clinical setting, as only ELISA measurements are necessary. As shown in the Figure 29 VPCs, the reduced PK model well–described both the total trastuzumab and T-DM1 concentration–time data from the in vivo rat and cynomolgus monkey studies. Final parameter estimates are shown in Table 10.
Figure 29. VPCs of total trastuzumab (TT) and T-DM1 concentrations for the reduced PK model fit to data, from (top panel) rat PK study with 0.3, 3.0, and 20 mg/kg T-DM\text{DAR}_{3.1} and (bottom panels) cynomolgus monkey PK study with 10 mg/kg q3w and 30 mg/kg T-DM1\text{DAR}_{3.1}. For each VPC, the shaded area is the model–predicted median with 95% confidence interval, and the solid line is the median of the observed data (circles).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Unit</th>
<th>Value</th>
<th>RSE (%)</th>
<th>IIV %</th>
<th>RSE (%)</th>
<th>Value</th>
<th>RSE (%)</th>
<th>IIV %</th>
<th>RSE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL(_{TT})</td>
<td>Total trastuzumab clearance</td>
<td>mL/day</td>
<td>2.37</td>
<td>(4.9)</td>
<td>24.6</td>
<td>(19)</td>
<td>19.9</td>
<td>(9.8)</td>
<td>19.8</td>
<td>(23)</td>
</tr>
<tr>
<td>(V_1)</td>
<td>Central volume</td>
<td>mL</td>
<td>10.7</td>
<td>(4.0)</td>
<td>19.8</td>
<td>(12)</td>
<td>154</td>
<td>(4.8)</td>
<td>7.65</td>
<td>(18)</td>
</tr>
<tr>
<td>CL(_{d2})</td>
<td>Distributional Clearance 2</td>
<td>mL/day</td>
<td>59.7</td>
<td>(32)</td>
<td>–</td>
<td>–</td>
<td>56.8</td>
<td>(46)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>(V_2)</td>
<td>Peripheral volume 2</td>
<td>mL</td>
<td>2.52</td>
<td>(28)</td>
<td>68.0</td>
<td>(39)</td>
<td>50.0</td>
<td>(60)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CL(_{d3})</td>
<td>Distributional Clearance 3</td>
<td>mL/day</td>
<td>13.9</td>
<td>(11)</td>
<td>–</td>
<td>–</td>
<td>60.4</td>
<td>(35)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>(V_3)</td>
<td>Peripheral volume 3</td>
<td>mL</td>
<td>15.5</td>
<td>(4.9)</td>
<td>16.5</td>
<td>(18)</td>
<td>84.7</td>
<td>(50)</td>
<td>27.3</td>
<td>(43)</td>
</tr>
<tr>
<td>CL(_{DEC})</td>
<td>Deconjugation clearance</td>
<td>mL/day</td>
<td>2.24</td>
<td>(3.4)</td>
<td>15.3</td>
<td>(18)</td>
<td>22.0</td>
<td>(6.9)</td>
<td>11.9</td>
<td>(28)</td>
</tr>
<tr>
<td>CL(_{T-DM1})(^a)</td>
<td>T-DM1 clearance</td>
<td>mL/day</td>
<td>4.61</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>41.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TT (t_{1/2})(^b)</td>
<td>Total trastuzumab terminal (t_{1/2})</td>
<td>day</td>
<td>8.84</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>T-DM1 (t_{1/2})(^b)</td>
<td>T-DM1 terminal (t_{1/2})</td>
<td>day</td>
<td>4.77</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5.21</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Res Err</td>
<td>Residual error</td>
<td>%</td>
<td>10.9</td>
<td>(5.6)</td>
<td>–</td>
<td>–</td>
<td>9.64</td>
<td>(16)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

IIV, interindividual variability; RSE, relative standard error

\(^a\) Derived by: CL\(_{T-DM1}\) = CL\(_{trastuzumab}\) + CL\(_{DEC}\)

\(^b\) Derived by 3-compartment PK equation for terminal half-life
As shown in Tables 9 and 10, the two modeling approaches yielded similar estimates for CLTT and V₁ in both rats and cynomolgus monkeys but slightly different estimates for CLd₂, V₂, CLd₃, and V₃; the difference between the distributional parameters was attributed to the different data used for each analysis.

The reduced PK model employed T-DM1 clearance via 2 mechanisms: antibody clearance mechanisms (CLTT) and deconjugation clearance mechanisms (CLDEC). Notably, CLDEC is approximately 50% of CLT-DM1 in both rats and cynomolgus monkeys, indicating that the overall T-DM1 deconjugation is similar between species. For both species, CLDEC was approximately equal to that of CLTT, indicating that deconjugation is a major pathway of T-DM1 clearance. Overall, deconjugation is supported as the mechanism for the increased clearance of T-DM1 over its parent trastuzumab antibody. For antibodies, allometric scaling of clearance from cynomolgus monkeys to humans has been successful given that cynomolgus monkeys are a similar antibody binding species [15, 81]. The reduced PK model can also be utilized towards allometric scaling for T-DM1, investigating approaches for scaling of clearance (e.g. CLTT and CLDEC) to human data.

For ADCs, efficacy and toxicity is influenced in part by the stability of the linker, in which systemic cytotoxin release from less stable linkers results in loss of efficacy and potential for toxicity. CLDEC can be viewed as a quantitative measure of linker stability, where higher CLDEC values describe a less stable linker, and can inform ADC design. Shown in Figure 30 is an illustration using the reduced PK model, with CLDEC values of 22 mL/day (for T-DM1₁) and a higher 44 mL/day (for T-DM1₂) predictions. In this prediction, higher CLDEC values (T-DM1₂) in patients may correlate with higher incidence of free DM1-related toxicities, and lower anti-tumor efficacy.
The reduced T-DM1 PK model has clinical implications and utility. An optimal sampling strategy for the ELISA analyses (i.e., for antibody, ADC, or both) can be used streamline clinical development [82]. T-DM1 may also be considered for front–line treatment of metastatic breast cancer, as HER2+ patients may benefit from a dual pharmacologic effect given that T-DM1 retains the anti–tumor mechanism of trastuzumab [61]. Here, the measurement of both total trastuzumab and T-DM1 concentrations is warranted, and a single population model of these two analytes can be developed using the reduced PK modeling approach. Moreover, total trastuzumab and T-DM1 concentrations can be evaluated as dual PK drivers of anti–tumor response.

Paper IV

In Paper IV, a model describing tumor response following taxane treatment in HER2–negative breast cancer patients was developed. This model characterized various patterns of tumor quiescence and resistance, and results were applied into a parametric time-to-event analyses of survival data. This tumor model provides an alternative approach for modeling tumor data, and shows advantages over the TGI model (Figure 6), especially when fitting patterns of tumor quiescence followed by tumor regrowth. Tumor model VPCs (Figure 31) for docetaxel and paclitaxel treatments show that the tumor model developed well–predicted the longitudinal tumor SLD measurements. Final parameter estimates are presented in Table 11.
Figure 31. VPCs of the final tumor model simulations for docetaxel (left panel) and paclitaxel (right panel). The solid black line represents the median of the observed tumor SLD measurements (circles). The inner shaded region represents the 95% confidence interval of the model simulated median. For docetaxel, the outer shaded regions represent the 95% confidence intervals of the model simulated 5th and 95th percentiles, and the stippled black lines represent the 5th and 95th percentiles of the observed tumor SLD measurements. For paclitaxel, the outer shaded regions represent the 95% confidence intervals of the model simulated 10th and 90th percentiles, and the stippled lines represent the 10th and 90th percentiles of the observed tumor SLD measurements. Vertical lines indicate binning intervals for VPCs.
Table 11. Final Parameter Estimates for the Tumor Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Unit</th>
<th>Value</th>
<th>RSE (%)</th>
<th>IIV %</th>
<th>Value</th>
<th>RSE (%)</th>
<th>IIV %</th>
<th>RSE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{\text{Grow, Sens}}$</td>
<td>growth rate sensitive tumor fraction</td>
<td>week$^{-1}$</td>
<td>0.0506</td>
<td>29.2</td>
<td>0</td>
<td>—</td>
<td>0.113</td>
<td>23.4</td>
<td>130</td>
</tr>
<tr>
<td>$k_{\text{Grow, Resist}}$</td>
<td>growth rate resistant tumor fraction</td>
<td>week$^{-1}$</td>
<td>1.19</td>
<td>21.1</td>
<td>118</td>
<td>28.0</td>
<td>0.121</td>
<td>25.5</td>
<td>176</td>
</tr>
<tr>
<td>$k_{\text{Kill}}$</td>
<td>tumor kill rate</td>
<td>mg$^{-1}$ week$^{-1}$</td>
<td>0.714</td>
<td>15.9</td>
<td>164</td>
<td>21.6</td>
<td>0.806</td>
<td>20.1</td>
<td>141</td>
</tr>
<tr>
<td>$k_{\text{Drug}}$</td>
<td>drug elimination rate</td>
<td>week$^{-1}$</td>
<td>0.248</td>
<td>22.5</td>
<td>391</td>
<td>24.9</td>
<td>0.498</td>
<td>26.2</td>
<td>253</td>
</tr>
<tr>
<td>$\text{FnR}_{\logit}$</td>
<td>Logit transformation $\text{FnR}$</td>
<td>—</td>
<td>0.0163</td>
<td>35.9</td>
<td>109</td>
<td>17.6</td>
<td>0.600</td>
<td>21.3</td>
<td>103</td>
</tr>
<tr>
<td>$\text{FnR}^b$</td>
<td>fraction tumor resistant</td>
<td>—</td>
<td>0.504</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.646</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$1-\text{FnR}$</td>
<td>fraction tumor sensitive</td>
<td>—</td>
<td>0.496</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.354</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$k_{\text{Delay, pop1}}$</td>
<td>transit delay rate constant; Population 1</td>
<td>week$^{-1}$</td>
<td>0.00426</td>
<td>31.2</td>
<td>239</td>
<td>30.3</td>
<td>0.699</td>
<td>32.2</td>
<td>0</td>
</tr>
<tr>
<td>$k_{\text{Delay, pop2}}$</td>
<td>transit delay rate constant; Population 2</td>
<td>week$^{-1}$</td>
<td>0.0209</td>
<td>24.4</td>
<td>239</td>
<td>25.9</td>
<td>0.0525</td>
<td>23.4</td>
<td>211</td>
</tr>
<tr>
<td>$P(1)$</td>
<td>probability</td>
<td>—</td>
<td>0.629</td>
<td>14.5</td>
<td>—</td>
<td>—</td>
<td>0.532</td>
<td>19.5</td>
<td>—</td>
</tr>
<tr>
<td>Res. Err.</td>
<td>residual error</td>
<td>%</td>
<td>15.2</td>
<td>4.40</td>
<td>—</td>
<td>5.37</td>
<td>6.34</td>
<td>5.37</td>
<td>—</td>
</tr>
</tbody>
</table>

IIV = interindividual variability; RSE = relative standard error

$^a$ additive error

$^b$ Derived parameter; $\text{FnR} = \exp(\text{FnR}_{\logit}) / (\exp(\text{FnR}_{\logit}) + 1)$
Model predictions for the two typical tumor patient responses ($k_{\text{Delay, pop1}}$ and $k_{\text{Delay, pop2}}$) as reported in Table 1 are illustrated for patients receiving docetaxel treatment in Figure 32. As shown, the typical docetaxel patient had a tumor baseline SLD equal to 70mm, consisting of ~35mm (0.496 • 70mm) drug-sensitive tumor SLD and ~35mm (0.504 • 70mm) of quiescent drug-resistant tumor SLD. The drug-sensitive tumor fraction was estimated to grow at the $k_{\text{Grow, Sens}}$ rate of 0.00506 week$^{-1}$ (tumor SLD doubling rate = 137 weeks). Docetaxel had a typical elimination rate of 0.248 week$^{-1}$ (2.8 week half-life) that was scaled by a tumor kill constant ($k_{\text{Kill}} = 0.000714 \text{ mg}^{-1} \cdot \text{week}^{-1}$), and this drug effect acted to eliminate the drug-sensitive tumor fraction as shown by 24 weeks.

The transition rate from quiescent drug-resistant tumor cells to a proliferating state was quantified using the $k_{\text{Delay}}$ parameter. The $k_{\text{Delay}}$ parameter was bimodal, with one probability (0.629; P(1)) of having a much slower rate ($k_{\text{Delay, pop1}} = 0.0000426 \text{ week}^{-1}$) compared to a faster $k_{\text{Delay, pop2}}$ rate of 0.0209 week$^{-1}$. As shown in Figure 32, patients were stratified into a stable response group (Population 1), and into a group initially responding and then developing resistance (Population 2). For the $k_{\text{Delay, pop1}}$ group, the slower rate predicted no tumor regrowth over the study length. The tumor SLD profile for the typical patient in the $k_{\text{Delay, pop2}}$ group was predicted to begin to regrow at the $k_{\text{Grow, Resist}}$ rate (0.119 week$^{-1}$; tumor SLD doubling = 5.8 weeks) after the predicted tumor nadir at ~30 weeks. A similar figure and discussion for paclitaxel is presented in Paper IV.
Figure 32. Model predictions for the two typical tumor patient responses ($k_{\text{Delay, pop1}}$ and $k_{\text{Delay, pop2}}$) receiving docetaxel treatment, derived from population parameter estimates shown in Table 11. The typical tumor SLD for each group is shown in the solid red line. The solid green line is the time–course of drug–sensitive tumor. The solid blue line is the time–course of drug–resistant tumor. The tumor SLD (red line) is the sum of the drug–resistant and drug–sensitive tumor time–courses. Observed data (black circles) are connected for each patient by grey lines.

Shown in the Figure 33 are Kaplan–Meier VPCs for docetaxel and paclitaxel datasets. The observed docetaxel and paclitaxel survival data fall within the simulated 95th confidence interval.
Figure 33. Kaplan–Meier VPC of the Overall Survival (OS) model for Docetaxel and Paclitaxel. The shaded regions represent the 95% confidence intervals of the model simulated data. The solid line is the observed survival data, and the vertical lines indicate censored patients.
Table 12 presents the parameter estimates for the survival models. In the survival analysis, an increased tumor baseline, reflective of higher tumor burden, and a shorter TTG, reflective of treatment efficacy, was associated with poorer survival prognosis. This aligns with results from other cancer treatments and indications as shown in Table 1. Notably, TSR and ECOG status were not statistically significant predictors for OS.

Table 12. Parameter Estimates for Survival Models

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Survival Model</th>
<th>Parameter</th>
<th>Value (RSE)</th>
<th>Covariate Search</th>
<th>OFV Drop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>Log-Normal</td>
<td>SD</td>
<td>0.894 (8.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mu</td>
<td>2.64 (7.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\beta_{TTG})</td>
<td>0.134 (18.1)</td>
<td>TTG —</td>
<td>-51.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\beta_{BSL})</td>
<td>-0.00447 (28.9)</td>
<td>TTG BSL</td>
<td>-12.9</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Weibull</td>
<td>Lambda</td>
<td>0.0350 (10.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shape</td>
<td>1.49 (6.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\beta_{TTG})</td>
<td>-0.0342 (20.4)</td>
<td>TTG —</td>
<td>-18.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\beta_{BSL})</td>
<td>0.00398 (24.8)</td>
<td>TTG BSL</td>
<td>-12.0</td>
</tr>
</tbody>
</table>

OFV: objective function value; RSE: relative standard error; TTG: time to tumor growth; BSL: tumor baseline
Conclusions

In this thesis work, pharmacometric models and methodology, from HER2–positive and HER2–negative metastatic breast cancer treatment, were developed. These pharmacometric tools can be applied within the modeling and simulation framework proposed for oncologic drug development, with primary applications to antibody-drug conjugates (ADCs) and anticancer treatments exhibiting tumor drug–resistance.

Specifically:

- A PKPD model describing longitudinal platelet response to T-DM1 treatment in HER2–positive breast cancer patients was developed. The model successfully predicts rates of Grade 3 thrombocytopenia (TCP).

- A PKPD model describing simultaneously the time–course of platelet, ALT, and AST response to T-DM1 treatment in HER2–positive breast cancer patients was developed. Correlations between parameters were implemented, and the model determined that Asian ethnicity was related to higher incidences of TCP due an increased drug effect on platelet production.

- Dose modification rules were incorporated into the PKPD model, and successfully predicted incidences of Grade ≥3 TCP, ALT, and AST. Model simulations of alternative T-DM1 dose regimens quantified the difference in the incidences of Grade ≥3 events and dose intensities, as compared to the approved dose, supporting T-DM1 drug development.

- Two PK models were developed from preclinical experiments and elucidated the underlying pharmacokinetics (PK) of T-DM1. The modeling approaches describe and quantify the T-DM1 PK system, and provide modeling flexibility given available analytical techniques for ADCs.

- A model for tumor response to taxane treatment in HER2–negative breast cancer patients was developed. This model shows advantages over the standard TGI modeling approach, primarily in characterizing patterns of tumor quiescence and drug–resistance. Time-to-event analysis indicates that tumor size at baseline and TTG are predictors for OS.
Future perspectives

ADCs are emerging as novel, exciting therapeutics in oncology [83, 84]. In a recent review on the preclinical and clinical toxicities of 35 ADCs, TCP was reported for 5 ADCs, elevated aminotransferases in 6 ADCs, and neutropenia in 13 ADCs [85]. In this thesis work, the model approaches developed for T-DM1 PKPD of AE (Papers I and II), and for T-DM1 PK to elucidate its complex disposition (Paper III), may be applicable to other ADCs given the similarity in the synthesis, antibody properties, and mechanism of action of these drugs. Specifically:

- The modeling work described and quantified particular response patterns of AE for T-DM1— a “first dose” effect and the cumulative dose effect. These phenomena may not be specific to T-DM1.
- Regarding hepatotoxicity, models for ALT and AST are not routinely applied in pharmacometrics as yet, and the PKPD models developed herein may provide guidance.
- The mechanistic and reduced PK models can be applied to any ADC given the analytical measurements of DAR, ADC, and total antibody.

Tumor drug–resistance is a primary obstacle for cancer treatment, and this was described in Paper IV using a mechanism–based approach. The tumor model, developed based on taxane treatment in HER2–negative breast cancer, can be applied to any drug treatment and indication showing patterns of tumor quiescence and drug–resistance. Results from this analysis add to the growing body of literature for predictors of OS in various cancers and cancer treatments (Table 1).

Ultimately, PKPD model development in oncology should encompass both AE and efficacy, in order to provide simulations balancing both risk and benefit. Within this thesis work, the pharmacometric analyses presented can be expanded. For example,

- A tumor model (preferably incorporating individual dose exposure) describing tumor response to T-DM1 treatment can be integrated into the current T-DM1 PKPD model of AEs.
PKPD models of docetaxel and paclitaxel AE, e.g. neutropenia from taxane treatment [24, 25]), can be integrated with the developed models of taxane tumor response.

Tumor model metrics and AE metrics can simultaneously be assessed as predictors for OS in a parametric TTE analysis, as illustrated in Figure 1.

With more complete models describing both AE and tumor response, model–based simulation strategies can developed to weigh different toxicity and efficacy outcomes. For example, 1) comparing outcomes between AUCss–matched and Cmax,SS–matched dose regimens to an approved dose, or 2) comparing standard population drug treatment to a model–based dose adaptation approach, in which doses are titrated within an individual to provide maximum acceptable exposure, as has been described [86].

A recently conducted T-DM1 clinical trial illustrates applications for the models developed within this thesis work. Shown in Table 13 are treatment arm details for a clinical T-DM1 trial in patients with gastric cancer.

<table>
<thead>
<tr>
<th>ARM A</th>
<th>ARM B</th>
<th>ARM C</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM1 3.6 mg/kg q3w</td>
<td>T-DM1 2.4 mg/kg q1w</td>
<td>docetaxel or paclitaxel (standard taxane therapy per investigator choice)</td>
</tr>
</tbody>
</table>

Table 13. Phase II/III Study To Evaluate The Efficacy And Safety Of T-DM1 Versus Taxane (Docetaxel Or Paclitaxel) In Patients With Previously Treated Locally Advanced Or Metastatic Her2-Positive Gastric Cancer

q1w: weekly; q3w: every 3 weeks

Using the pharmacometric models developed herein, and their proposed extensions, the following predictions may have been used to support clinical decision making: 1) predictions of Grade 3/4 platelet, ALT, and AST for ARM A vs ARM B; 2) the relative differences in toxicity rates between ARM A and B, given that Gastric cancer patients may respond differently than MBC patients; 3) expected PFS and OS between ARMS A, B, and C. Results from the clinical trial in HER2–positive gastric cancer may serve as a model evaluation dataset for the model predictions based on HER2–positive and HER2–negative breast cancer (e.g. toxicity incidences, DI and RDI, tumor growth rates, OS predictors).

Overall, the pharmacometric models developed within this thesis work have supplemented the available methodologies for application within the model–based framework for drug development in oncology (Figure 1), especially for ADCs. The population PK, PKPD, and TTE modeling analyses support
efforts to link drug exposure with PD response, and PK and PD response with survival. This, in order to explain and forecast patient response to drug treatment in oncology, with the ultimate goal of predicting and improving survival by bringing the “right drug to the right patient at the right dose”.
Acknowledgements

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I would like to first and foremost thank

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AND

The many breast cancers patients who allowed their data to be shared…

Thank you to Prof. Mats Karlsson, for creating and leading such a world class group, and for being a fierce competitor to push me past my limits… for the ski weekends, go-karting, egg races, sponsoring my attendance at TACA, and for volunteering me for numerous events.

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Thanks to the organizers of PEGS, AAPS, and SUP Meetings for the invited speakerships.

Now some random thoughts, thanks, and shout outs for some pepes I ran into in the last 5.4 years.

Thank you to Karin, Ulrica, and Marina R. for all the administrative help through the years! …but more importantly for all the party entertainment (with Jessica), we had back in the day, and hopefully one more time.

Thanks all my officemates for the good times, with some managing longer than others: Agneta, Bettan, Emma, Angelica, Anne-Gaelle, Salim, Rob-in, Benjamin, and Gustaf. Hmmm…this seems like a lot.

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To all the babies I will never meet again but I got you a gift anyway. To my mother from another mother Britt, thanks for diagnosing my crystals and showing me that life can be fun forever.

And now, since I know I neglected some of you, or maybe you are fortunate enough to get a copy of my thesis, here’s a little extra:

Dear ________________, I will never forget the time when ________________

__________________________________________________________________________

I hope that ___________________________________________________________________

__________________________________________________________________________

P.S., Apologies for ___________________________________________________________________
References


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