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PK/PD modeling and optimization of eltrombopag dose and regimen for treatment of chemotherapy-induced thrombocytopenia in cancer patients

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Introduction

Eltrombopag

- Orally administered small molecule
- Thrombopoietin receptor (TPO-R) agonist
- Induces differentiation of normal marrow progenitors and increases platelet counts
- Approved for the treatment of thrombocytopenia in patients with chronic idiopathic thrombocytopenic purpura (ITP)
- Study in cancer patients for chemotherapy–induced thrombocytopenia (CIT)
  - eltrombopag administered **after** chemotherapy in each cycle
- Studies with rhTPO suggested that platelet response is dependent on timing of dosing relative to chemotherapy (Vadhan-Raj et al, 2003)

➡ PKPD model is needed to predict platelet response for alternative dosing regimens

Prior Eltrombopag Modeling

- Population PK/PD model (Hayes et al, 2011)
  - in healthy subjects
  - in ITP patients
- Population PK model in patients with cancer (Gibiansky et al, 2009)

Data

Phase 2, randomized, blinded, placebo-controlled, parallel group design

- 172 patients with advanced solid tumors naive to chemotherapy
- Chemotherapy with carboplatin/paclitacel (CP) every 21 days up to 8 cycles
- 0 (placebo), 50, 75 or 100 mg eltrombopag once-a-day for **10 days following** each CP administration
- Measurements:
  - Platelet counts
    - ✓ 7 samples in cycles 1 and 2
    - ✓ 4 samples in cycles 3 - 8
  - Eltrombopag plasma concentrations

Modeling Approach

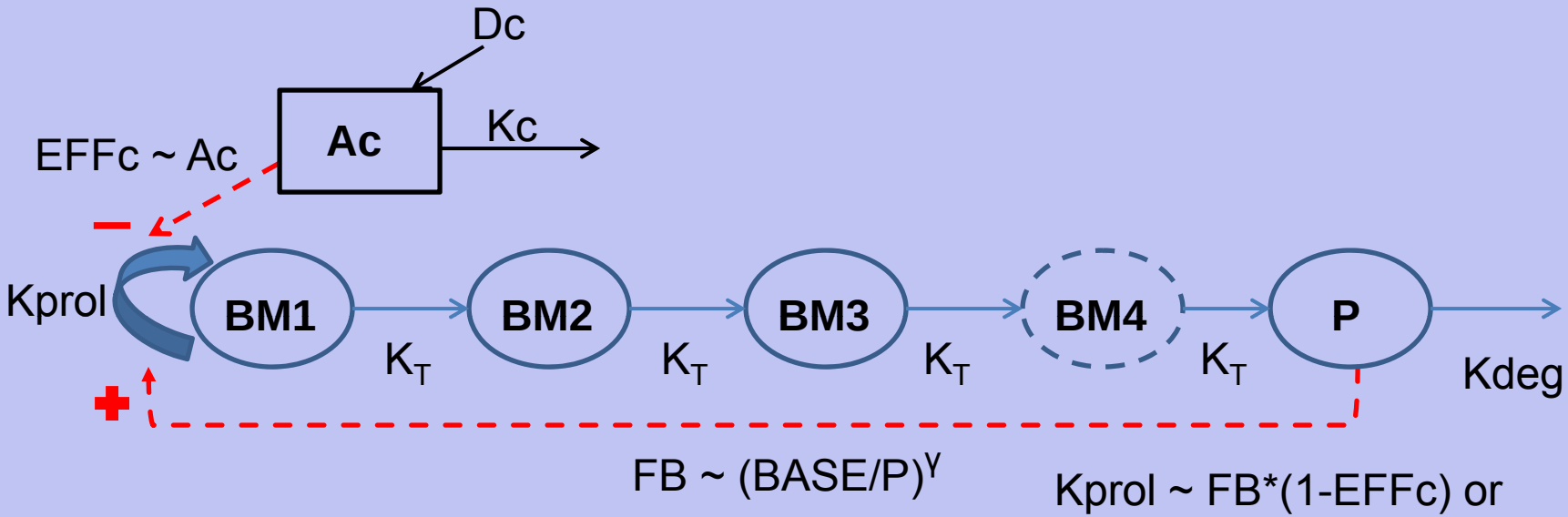
- Modeling performed in 2 stages
  - Population PD model of platelet counts (PLT) in placebo patients receiving carboplatin/paclitaxel (CP)
  - PK/PD model of PLT for eltrombopag + CP without the placebo data
    - ✓ Using population parameters of the placebo model (except residual variability)
- Nonlinear mixed effects modeling using NONMEM
  - FOCEI

Stage 1 Carboplatin/paclitaxel modeling

- According to (Joerger et al, 2007) paclitaxel does not have a significant effect on PLT
  - ➡ decrease in PLT following chemotherapy was attributed to carboplatin
- Concentrations of carboplatin were not measured
  - ➡ KPD approach was used
    - ✓ Hypothetical 1-compartment with bolus input
- Assumption
  - Carboplatin decreases production rate of platelet precursors in bone marrow

Carboplatin models

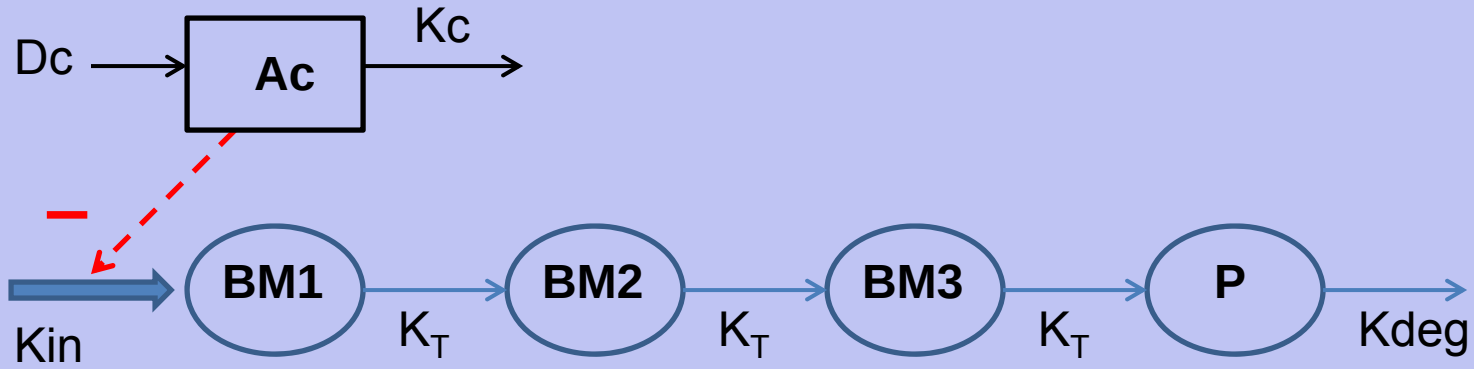
"Conventional" model of myelosuppression (Friberg et al, 2002)



Kprol ~ FB*(1-EFFc) or

Kprol ~ FB - EFFc

"Eltrombopag" model



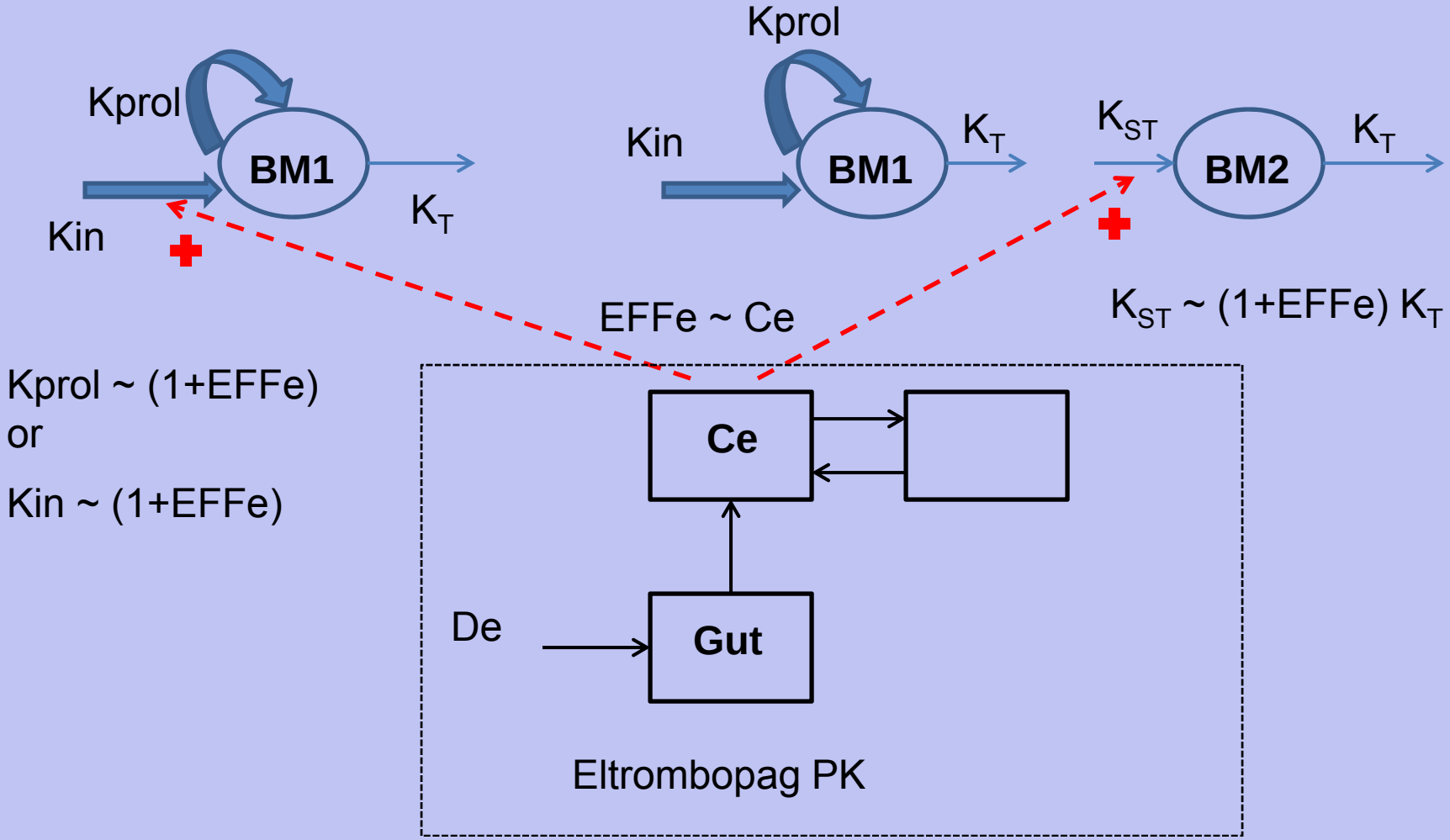
Carboplatin models: Results

- Both models gave similar population and individual predictions
- Not all parameters were identifiable
  - Thrombopoesis parameters in the absence of chemotherapy (Kin, K_T, their variability, number of transit compartments) fixed to their values in healthy subjects

Stage 2 Eltrombopag modeling

- Fixed population parameters of carboplatin + placebo models and added effect of eltrombopag
- Individual PK parameters computed using earlier developed population PK model of eltrombopag in cancer patients
- Assumptions
  - Eltrombpag linearly increases production rate of platelet precursors (as in ITP and healthy subjects)
  - Eltrombpag influences Kprol (Kin) or differentiation downstream

Eltrombopag models (fragment)



Results: Eltrombopag + Carboplatin model

- Only one model was able to describe the combined effect of carboplatin and eltrombopag on PLT
  - Zero-order production rate Kin
  - No feedback
  - Both, carboplatin and eltrombopag affect Kin

    $Kin \sim (1-EFFc)*(1+EFFe)$
  - Effect depends on cycle
    - ✓ Increases for carboplatin: $EFFc \sim Ac * CYCLE^{\gamma_1}, \quad \gamma_1 > 0$
    - ✓ Decreases for eltrombopag: $EFFe \sim Ce * CYCLE^{\gamma_2}, \quad \gamma_2 < 0$

Model Parameters

Parameter [Units]	Point Estimate	%RSE	95% CI	CV%, R, or SD
K_C [hr^{-1}]	0.0176	20.7	0.0104-0.0248	
SLPc [g^{-1}]	3.01	17.9	1.96-4.06	
γ_1	0.253	12.6	0.190-0.316	
Kin [10^9/L/hr]	1.43 FIXED			
K_T [hr^{-1}]	0.0253 FIXED			
SLPe [mL/μg]	0.190	11.5	0.147-0.233	
γ_2	-0.611	28.3	-0.950- -0.272	
ω^2_{KC}	0.797	29.9	0.331-1.26	CV= 89.3%
ω^2_{Kin}	0.762 FIXED			CV= 87.3%
ω^2_{KT}	0.161 FIXED			CV= 40.1%
ω^2_{BASE}	0.00969	25.5	0.00485-0.0145	CV= 9.84%
ω^2_{SLPE}	1.03	26.6	0.493-1.57	CV=101%
σ_{prop}	0.153	8.50	0.128-0.178	CV= 15.3%
σ_{add}	31.0	13.5	22.8-39.2	SD=31.0

Parameters from eltrombopag model in healthy subjects

Parameters estimated in the carboplatin + placebo model

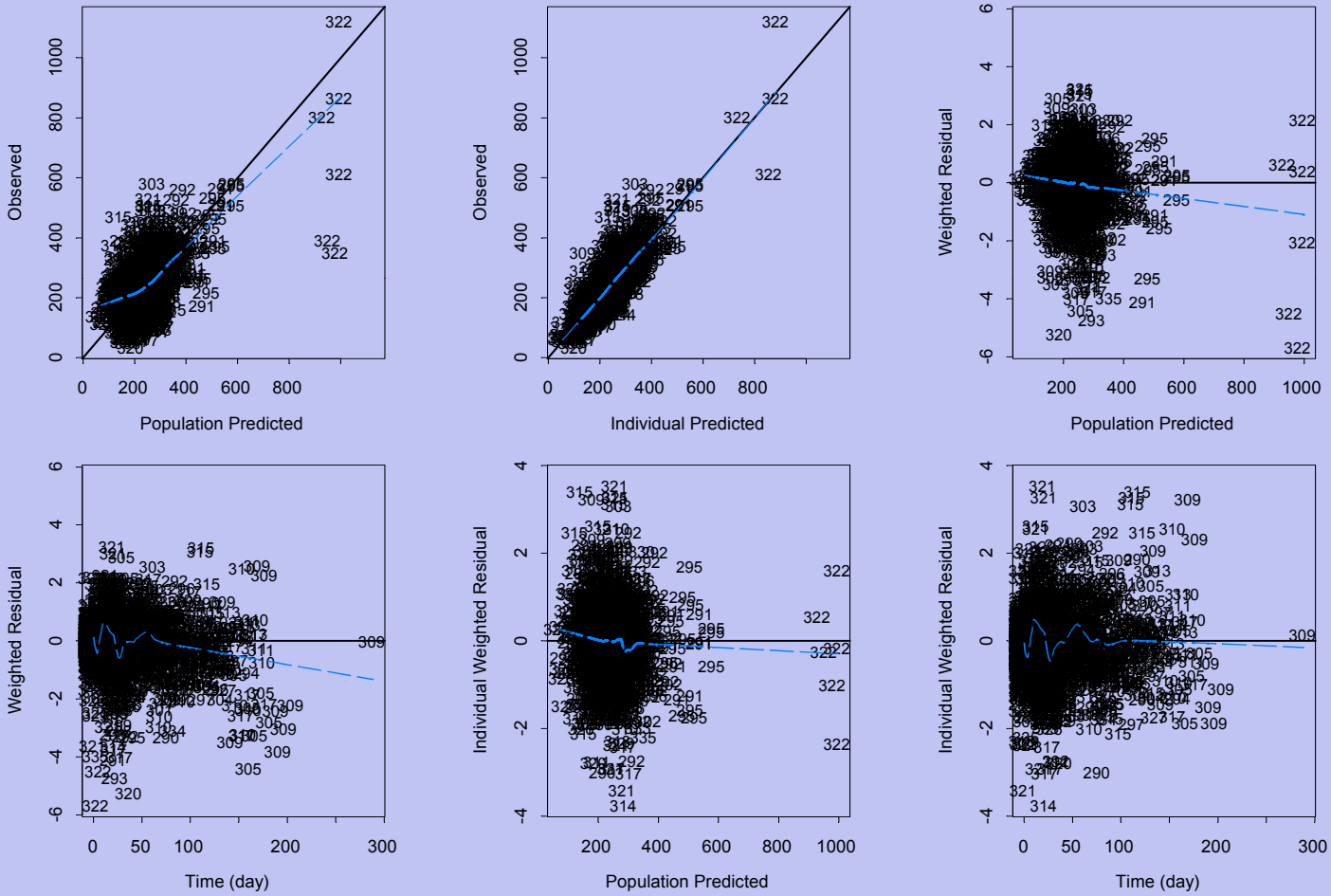
Results

- Carboplatin lowered platelet production rate proportionally to dose
  - Cycle 1: by 18.1% at dose of 536 mg (median carboplatin dose)
  - Cycle 8: by 31.4% at the same carboplatin dose
- Eltrombopag increased production rate, linearly with plasma concentration
  - Cycle 1: by 133% at 7 μg/mL (median average concentration at steady state at 100 mg dose)
  - Cycle 8: by 37%

Results

Goodness-of-fit

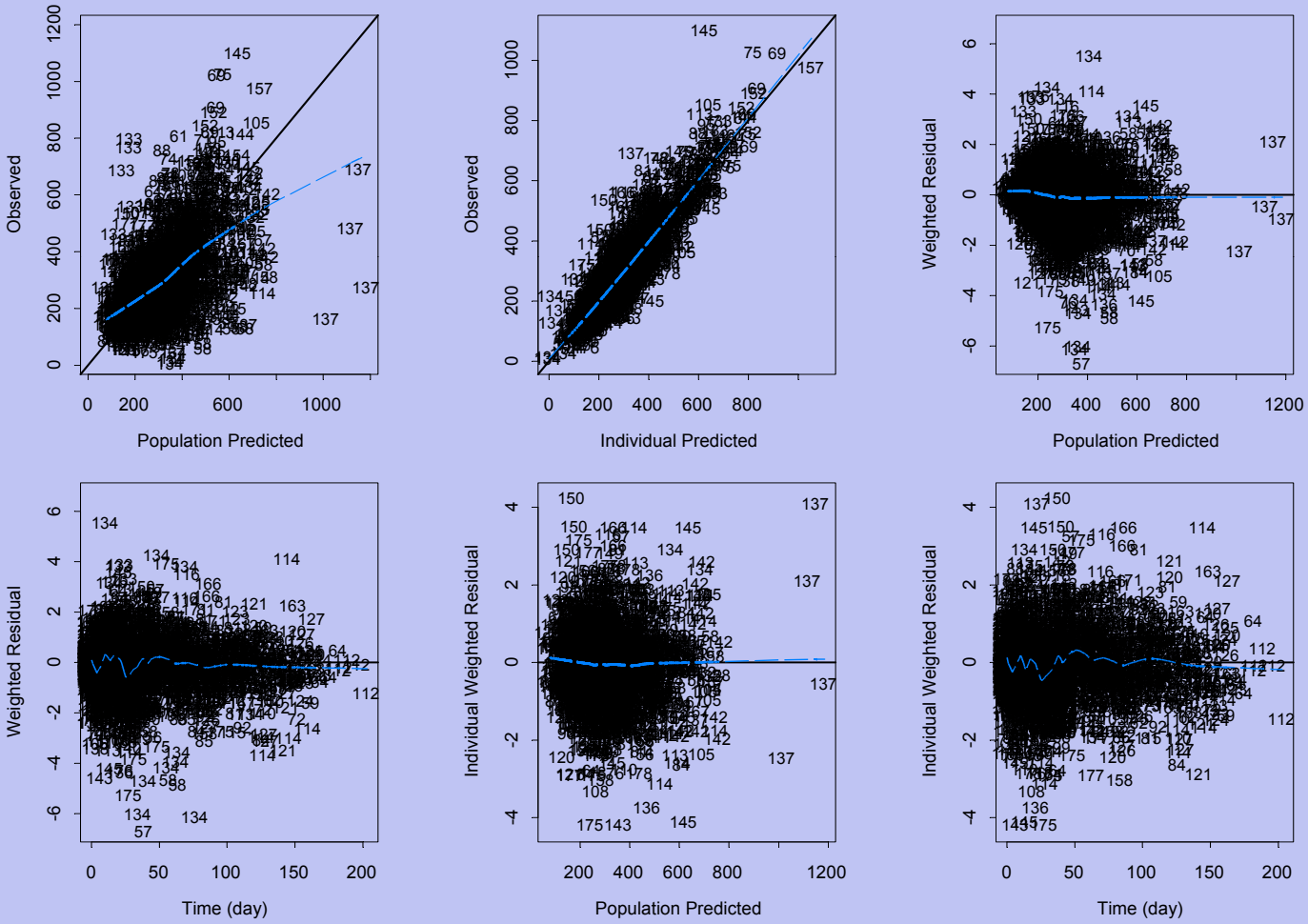
Carboplatin model



Results

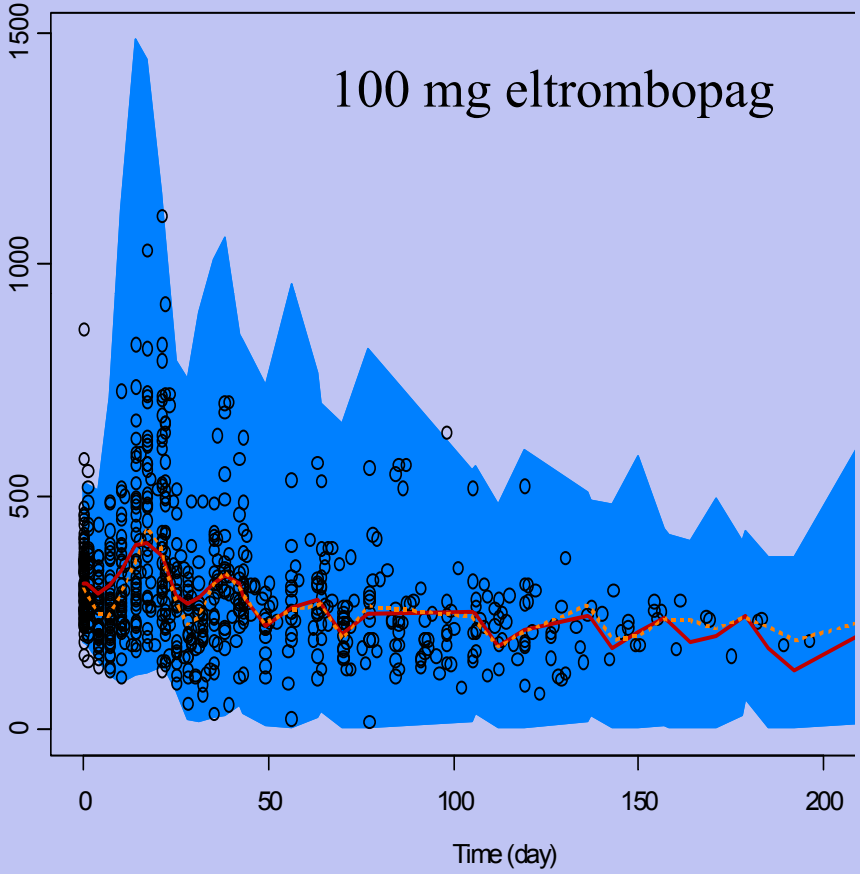
Goodness-of-fit

Eltrombopag + carboplatin model



Results

Visual Predictive Check



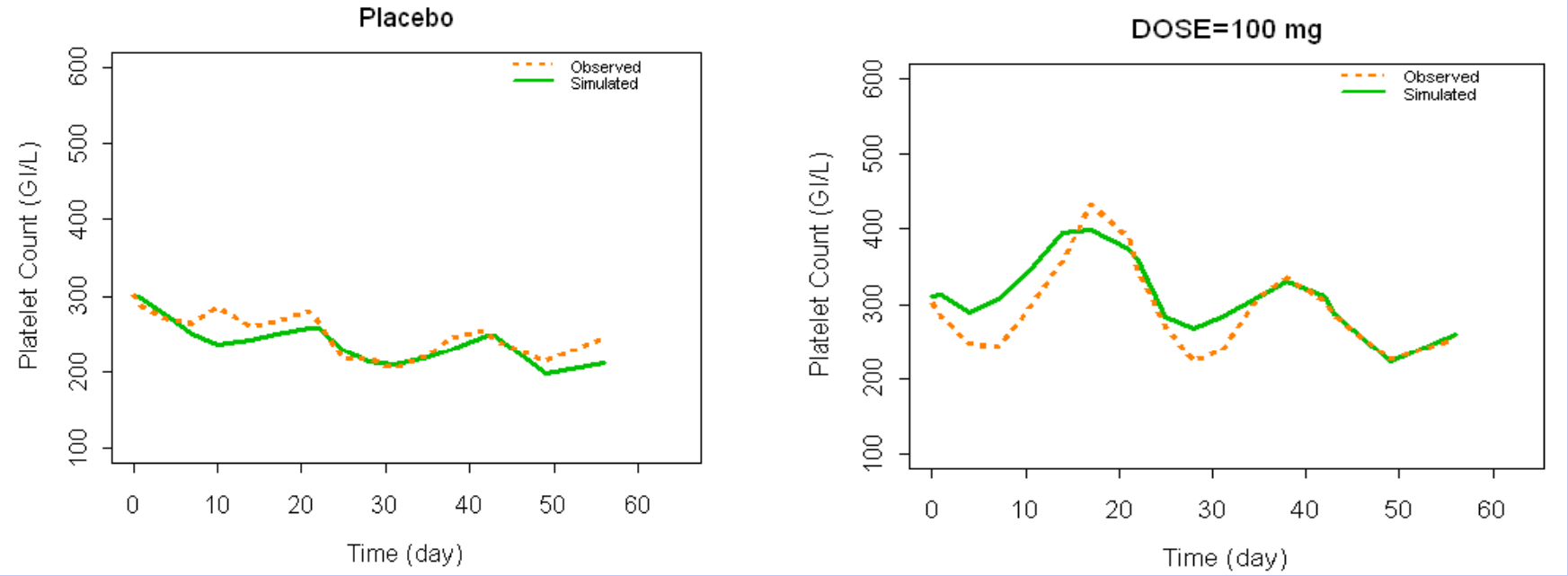
Overestimated variability:

- 1.7 – 3.8% points outside 90% prediction intervals
- 60% prediction interval provided coverage for 80% of the observed PLT data

Results

Visual Predictive Check

Median Observed and Simulated (VPC) Platelet Counts (over 3 cycles)



Modeling Summary

- Platelet counts for patients on chemotherapy can be described by several models, therefore caution is needed in mechanistic interpretation of the results
- "Conventional" model of myelosuppression described platelet response to carboplatin therapy, but was not able to describe addition of eltrombopag
- "Eltrombopag" model was able to describe both, PLT response to carboplatin alone and to carboplatin + eltrombopag therapy
  - Carboplatin decreases production rate, linearly with dose. The effect increases with each cycle
  - Eltrombopag increases production rate, linearly with eltrombopag concentrations (and dose). The effect decreases with each cycle
- "Eltrombopag" model describes PLT across populations and therapies
  - Response to eltrombopag in healthy subjects, in ITP patients, response to carboplatin, and response to both carboplatin and eltrombopag in cancer patients
    - ✓ Common structure and thrombopoesis parameters
    - ✓ Differential effects on production rate of platelet precursors

Simulations of Dosing Regimens

Goal: To inform future study designs

Regimens

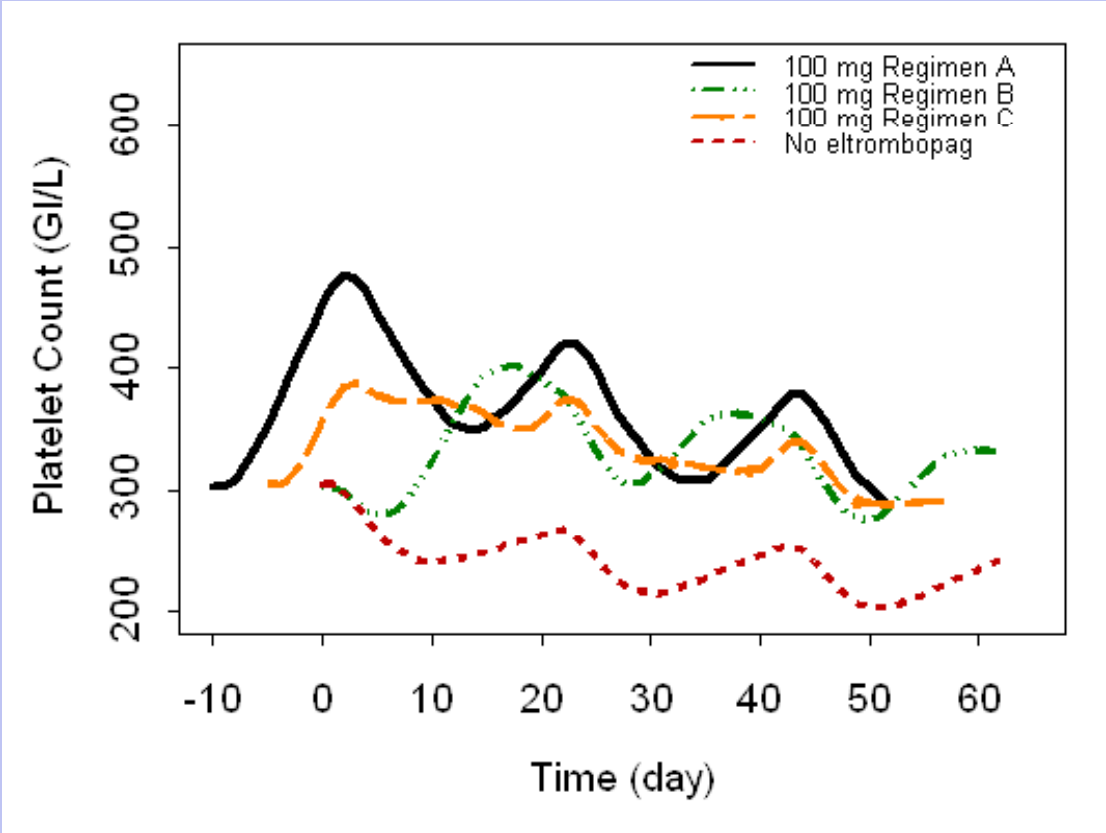
- A – 10 days **prior** each CP administration
- B - 10 days **after** each CP administration (current study)
- C – 5 days **prior** and 5 days **after** each CP administration

Setup

- Patients from all treatment groups
- Each patient replicated 100 times (CP dosing, covariates, baseline PLT)
- PLT simulated for each patient, dosing regimen, and eltrombopag doses of 50, 100, and 200 mg
- Additionally, for regimen C simulations performed for fixed baseline PLT of 100 and 150 10^9/L

Simulations 100 mg Eltrombopag

Median Simulated Platelet Count versus Time

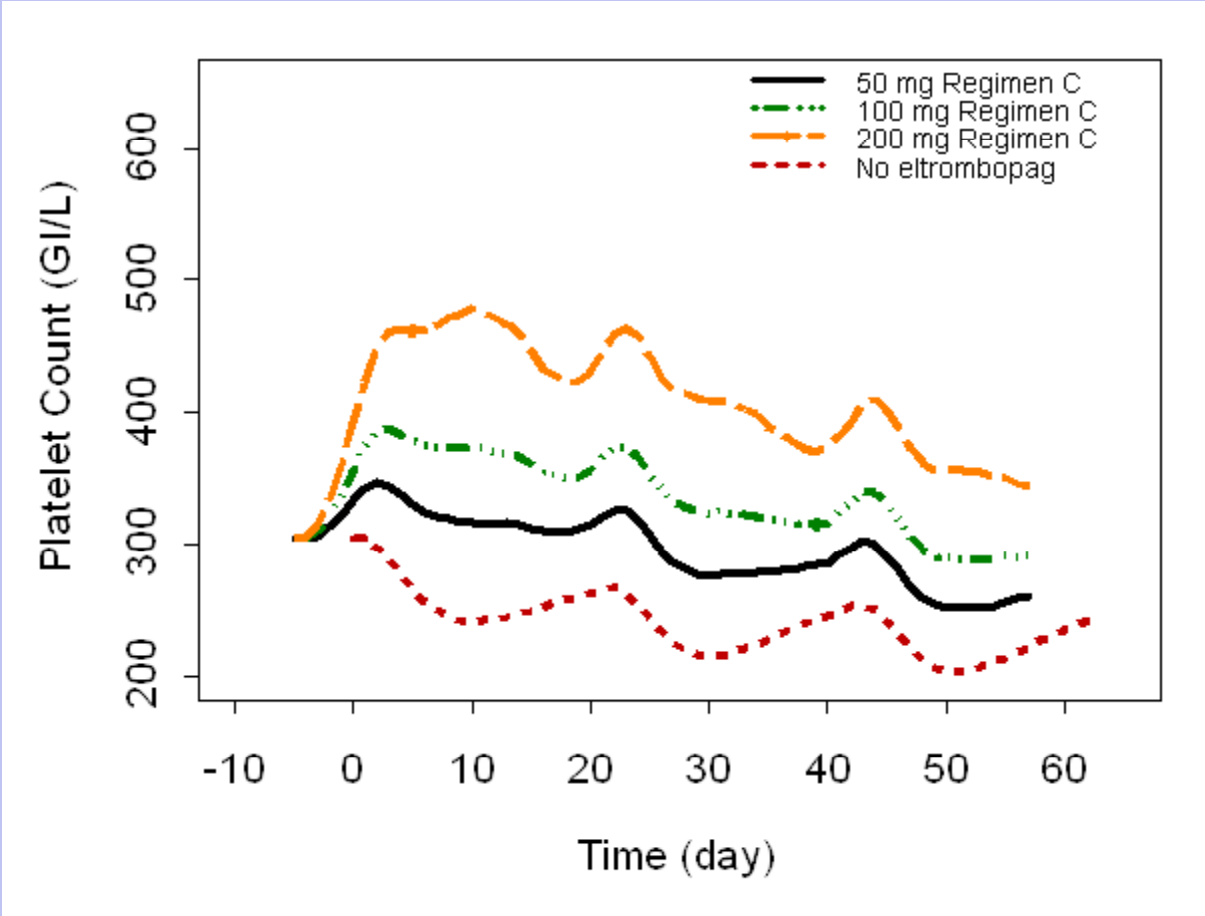


- Nadir similar for A and C for 50, 100 and 200 mg eltrombopag, but lower for B
- Maximum PLT are highest in A, and lowest in C

Regimen C stabilized platelet counts, minimized nadir

Simulations Regimen C

Median Simulated Platelet Count versus Time



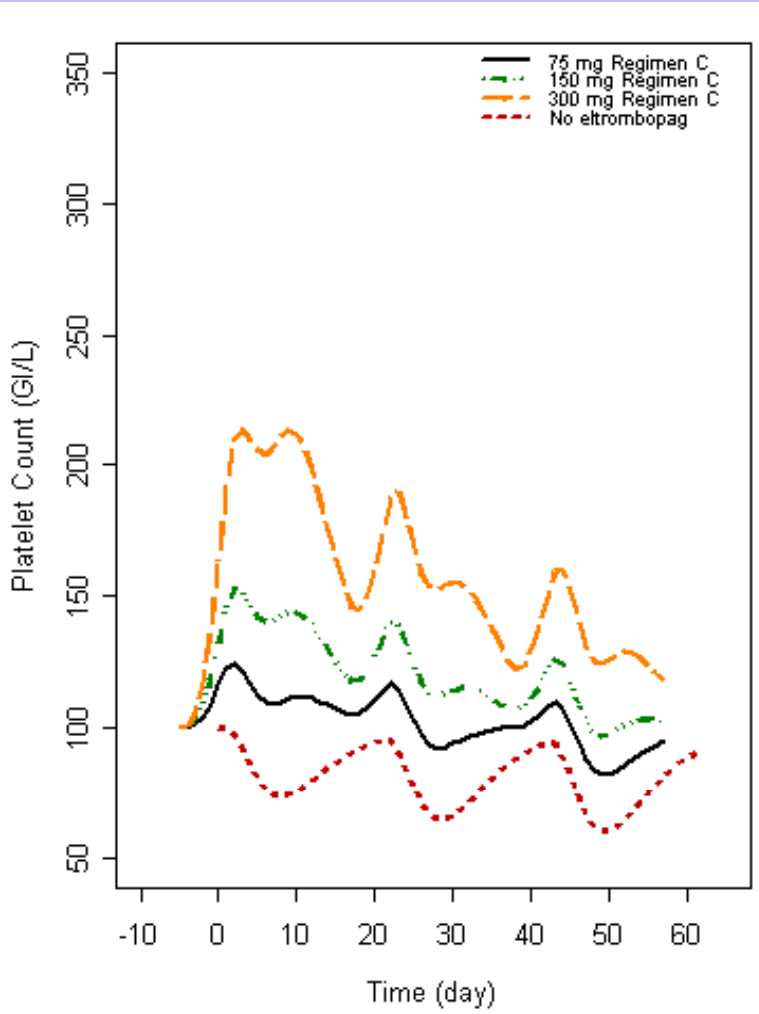
Median baseline PLT of 305 10^{-9}/L

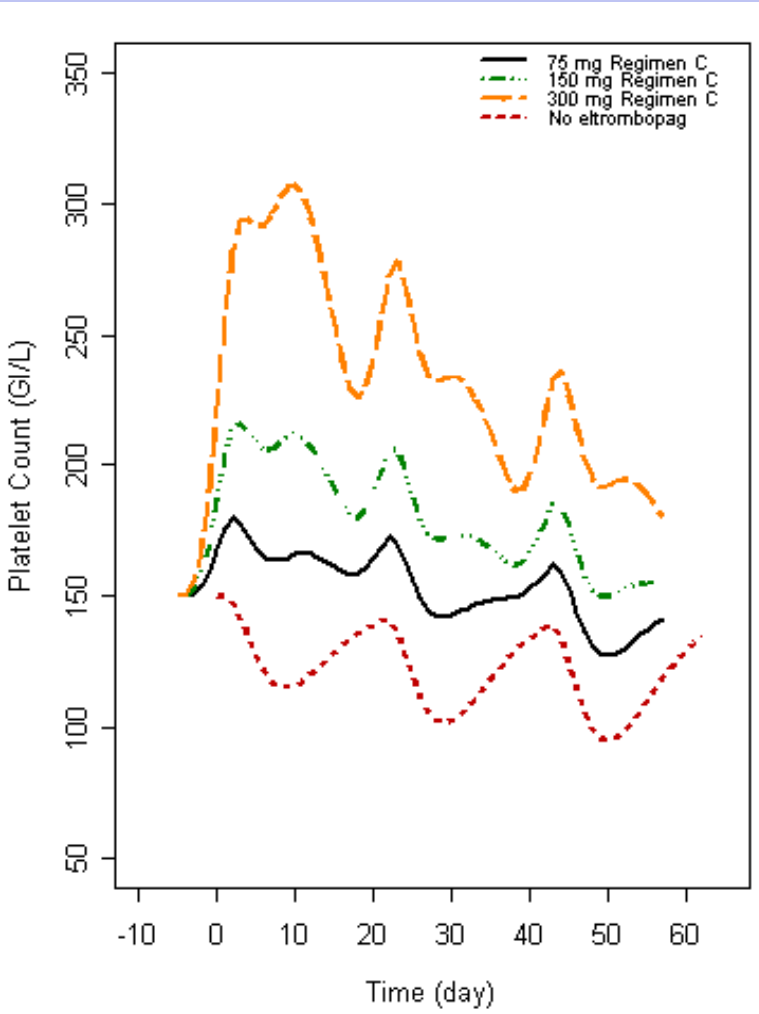
Starting at dose of 50 mg looks best

Possibly increasing dose at later cycles

Simulations Low Baseline PLT

Regimen C Median Simulated Platelet Count versus Time





Baseline PLT: 100 10^9/L

Baseline PLT: 150 10^9/L

Simulations Impact of Variability

Regimen C Predicted nadir values for different baseline platelet counts

Eltrombopag Dose (mg)	Baseline Median (80% PI) (10^9/L)	Nadir (10^9/L) Median (80% PI)		
		Cycle 1	Cycle 2	Cycle 3
Placebo	305 (229, 398)	240 (159, 336)	214 (124, 315)	203 (108, 305)
50 mg	305 (229, 398)	baseline value	276 (156, 439)	251 (129, 402)
Placebo	150	115 (76, 136)	102 (48, 130)	95 (33, 127)
150 mg	150	baseline value	166 (93, 276)	150 (52, 272)
Placebo	100	73 (46, 89)	64 (26, 85)	60 (16, 83)
150 mg	100	baseline value	109 (62, 177)	96 (29, 177)

Normal PLT range: 150 – 400 10^9/L

Simulation Summary

- Eltrombopag started **5 days before** carboplatin/paclitaxel therapy and continued **5 days after** in each cycle minimizes the reduction and fluctuation of PLT
- Eltrombopag dose should be increased across cycles to overcome the impact of chemotherapy
- Higher starting doses are required in patients with low baseline counts
- Inter-individual variability in response suggests that titration strategy may be based on response and baseline PLT

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