Prediction of the haematological effects of a new combination of anticancer drugs, BI 2536 and pemetrexed, using a semi-mechanistic model for neutropenia

Elena Soto[1], Alexander Staab[2], Matthias Freiwald[2], Gerd Munzert[2], Holger Fritsch[2], Christiane Tillmann[2] and Iñaki F. Trocóniz[1]

[1] University of Navarra (Pamplona, Spain)

[2] Boehringer Ingelheim Pharma GmbH & Co.KG (Biberach, Germany)

Universidad de Navarra

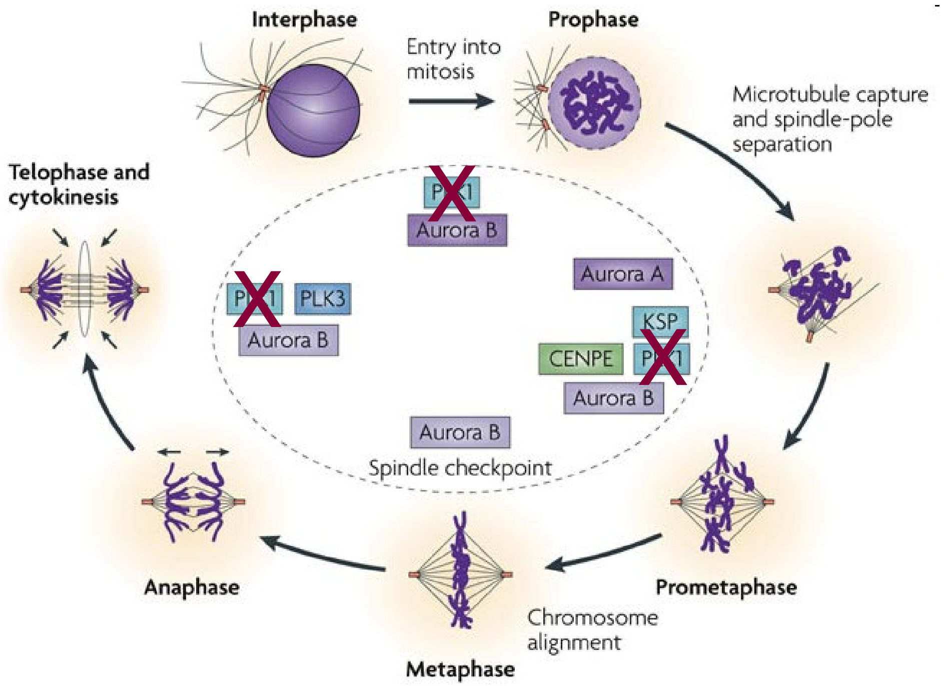
Boehringer Ingelheim

Outline

- Introduction
- Objective
- Modelling Strategy
- Modelling Steps
  - Step 1
  - Step 2
  - Step 3
- Conclusions

Introduction

- BI 2536 is an inhibitor of Polo-like kinase 1 (Plk1)



Jackson *et al*. (February 2007) **Nature Reviews** | **Cancer**

Induction of apoptosis

Neutropenia is the dose limiting toxicity

Introduction

- Administration of BI 2536 + Pemetrexed being evaluated

  - BI 2536

    PK and Neutropenic effects have been characterized previously in 104 advanced cancer patients (Soto et al, 2008)

  - Pemetrexed

    PK and Neutropenic effects of pemetrexed have been described (Latz et al, 2006)

Objective

To **predict** the neutropenic effects for the novel combination of **BI 2536** and **pemetrexed** in an ongoing study performed in non-small-cell lung cancer (NSCLC) patients, using a semi-mechanistic modeling approach

Combination study

Phase I dose escalation study in NSCLC patients (n=40)

A. BI 2536 1 hour infusion (doses 100 to 325mg)

+

B. Pemetrexed 15 minutes infusion (doses 375 to 500mg/m^2)

+

C. Concomitant therapy

- Folic Acid
- Vitamin B12

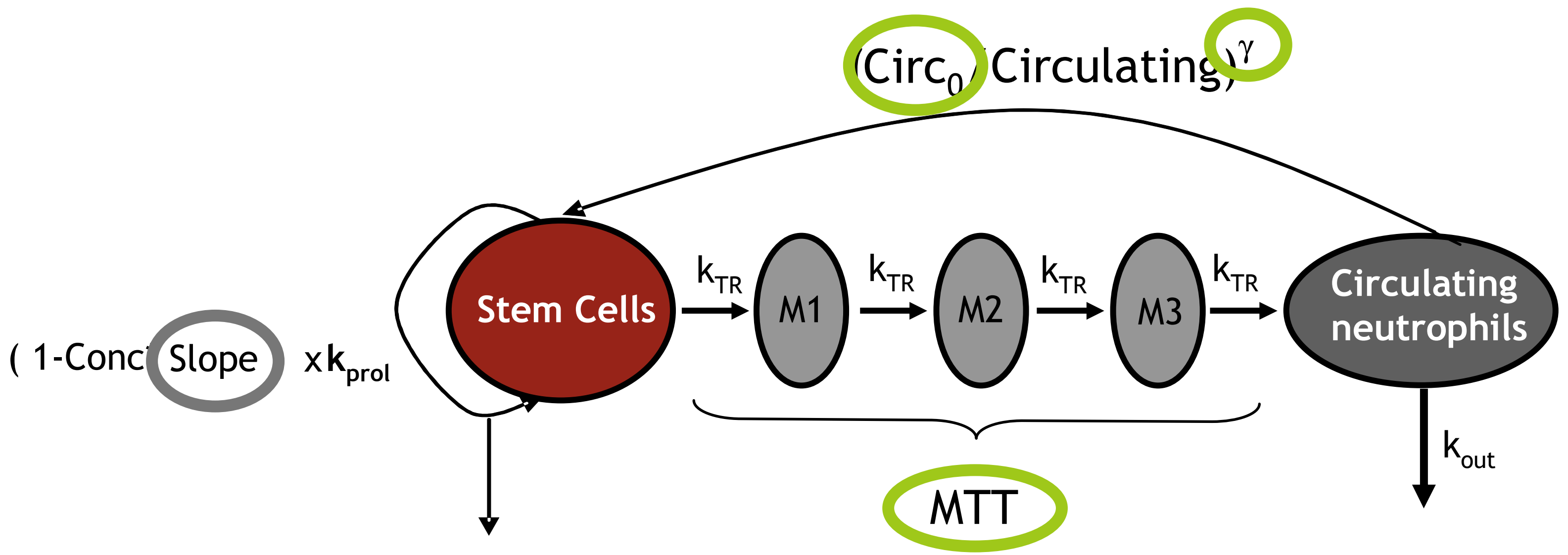
↓ Haematological toxicity of pemetrexed

- Dexamethasone

To prevent other adverse effects but produces a temporary INCREASE in neutrophils

Modelling strategy

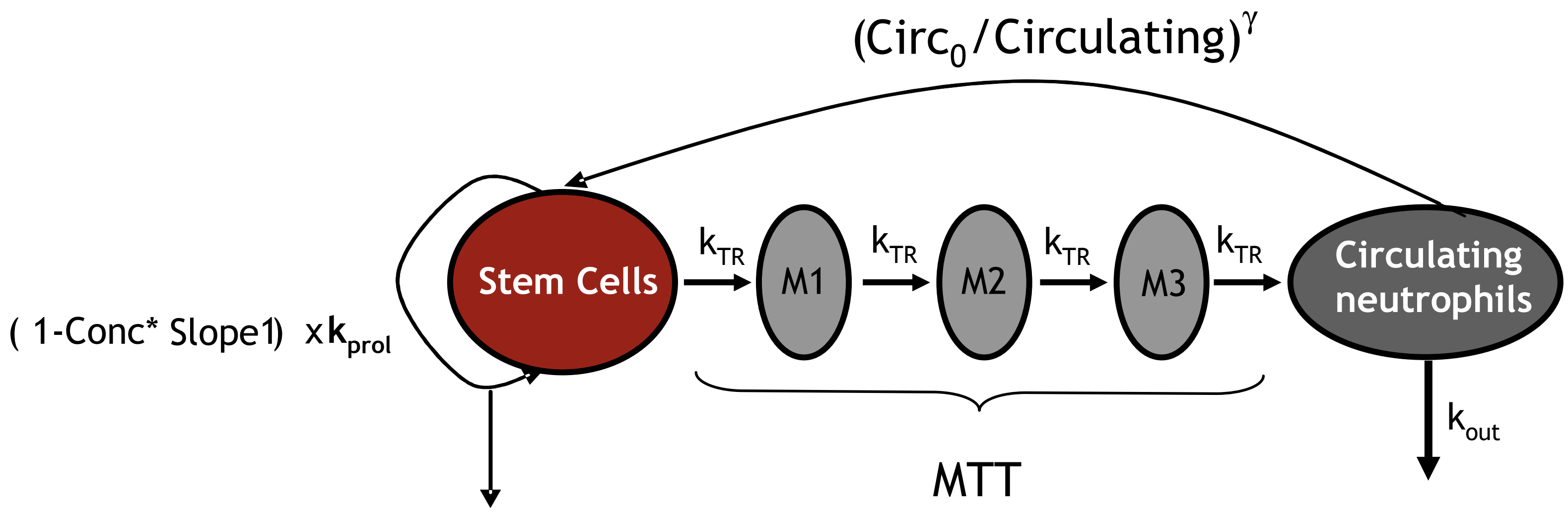
Based on Semi-mechanistic model (Friberg, et al 2002)



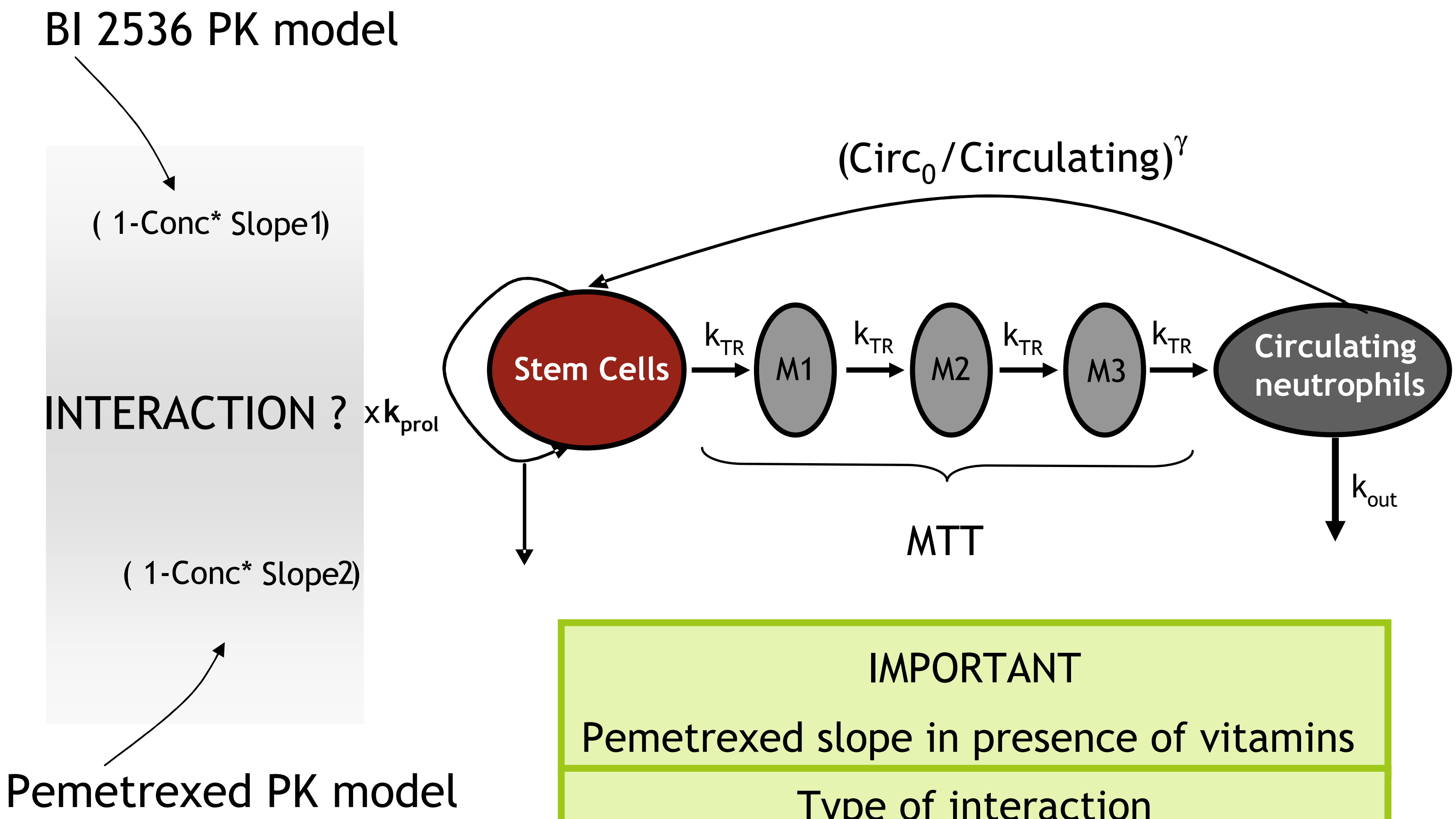
$K_{prol}=k_{TR}=k_{out}$

Modelling strategy

Based on Semi-mechanistic model (Friberg, et al 2002)



Modelling strategy



IMPORTANT
Pemetrexed slope in presence of vitamins
Type of interaction

Modelling steps

1. Obtain missing information
   - PK/PD model for pemetrexed + co-medication
   - Type of interaction
2. Simulations
3. PK/PD combination model refinement
   - Response surface analysis
   - Use of PRIORS subroutine

Modelling steps

1. Obtain missing information
   - PK/PD model for pemetrexed + co-medication
     - Type of interaction
2. Simulations
3. PK/PD combination model refinement
   - Response surface analysis
   - Use of PRIORS subroutine

Pemetrexed model

Phase I dose escalation study in NSCLC patients (n=26)

A. BIBF 1120 ES → NO EFFECT on absolute neutrophil counts

+

B. Pemetrexed doses 375 to 500mg/m^2

+

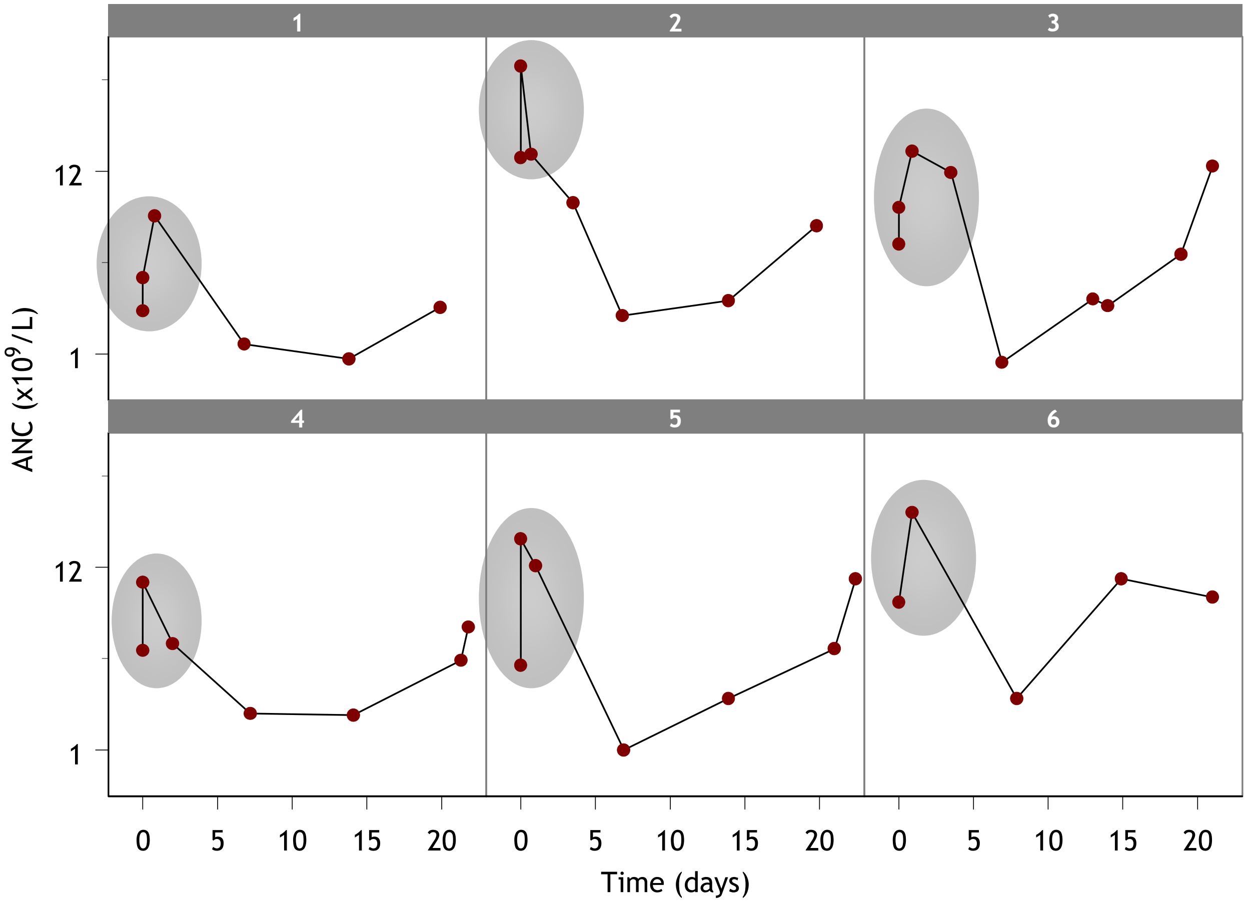
C. Concomitant therapy

- Folic Acid
- Vitamin B12
- Dexamethasone

Effect on absolute neutrophil counts

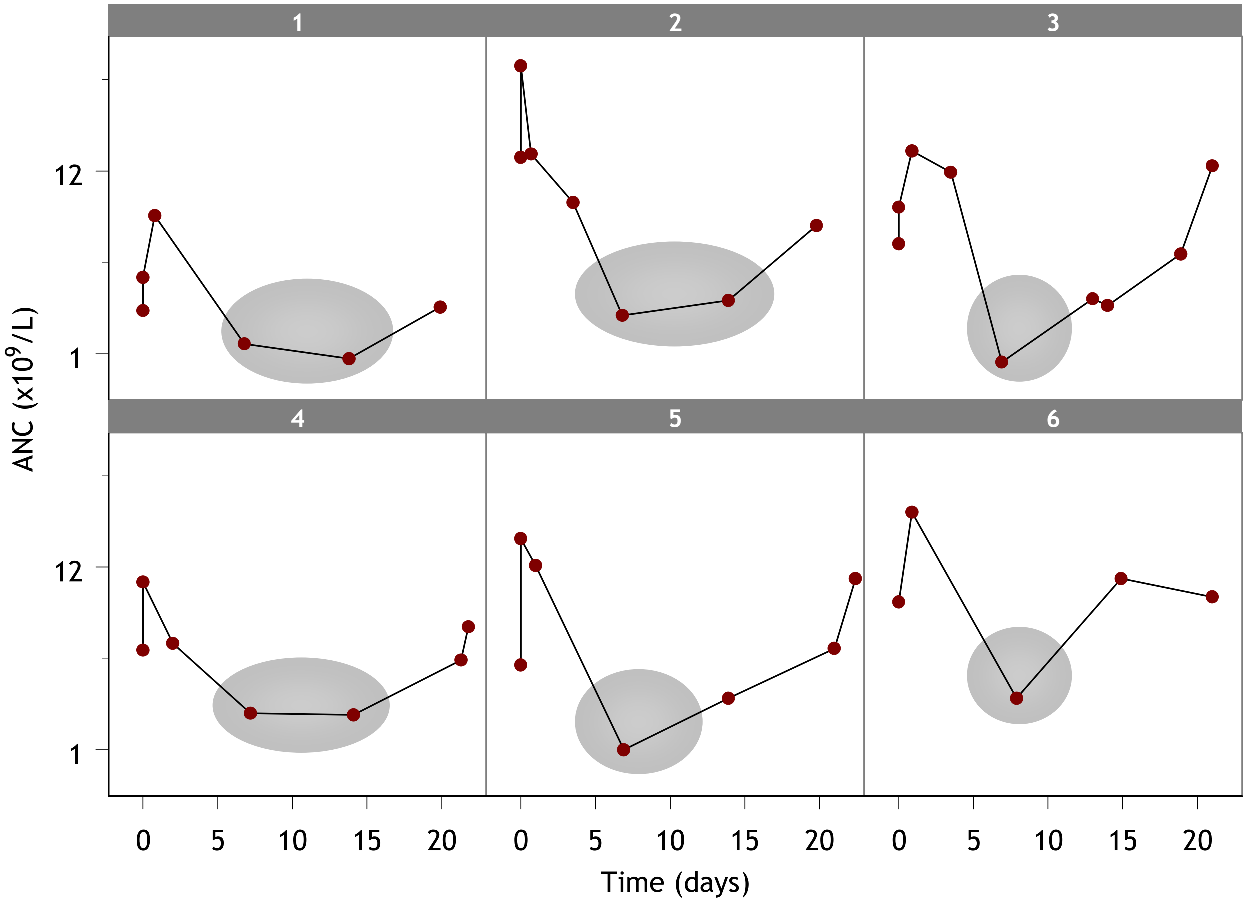
Pemetrexed model

Temporary increase in neutrophils → Dexamethasone Effect

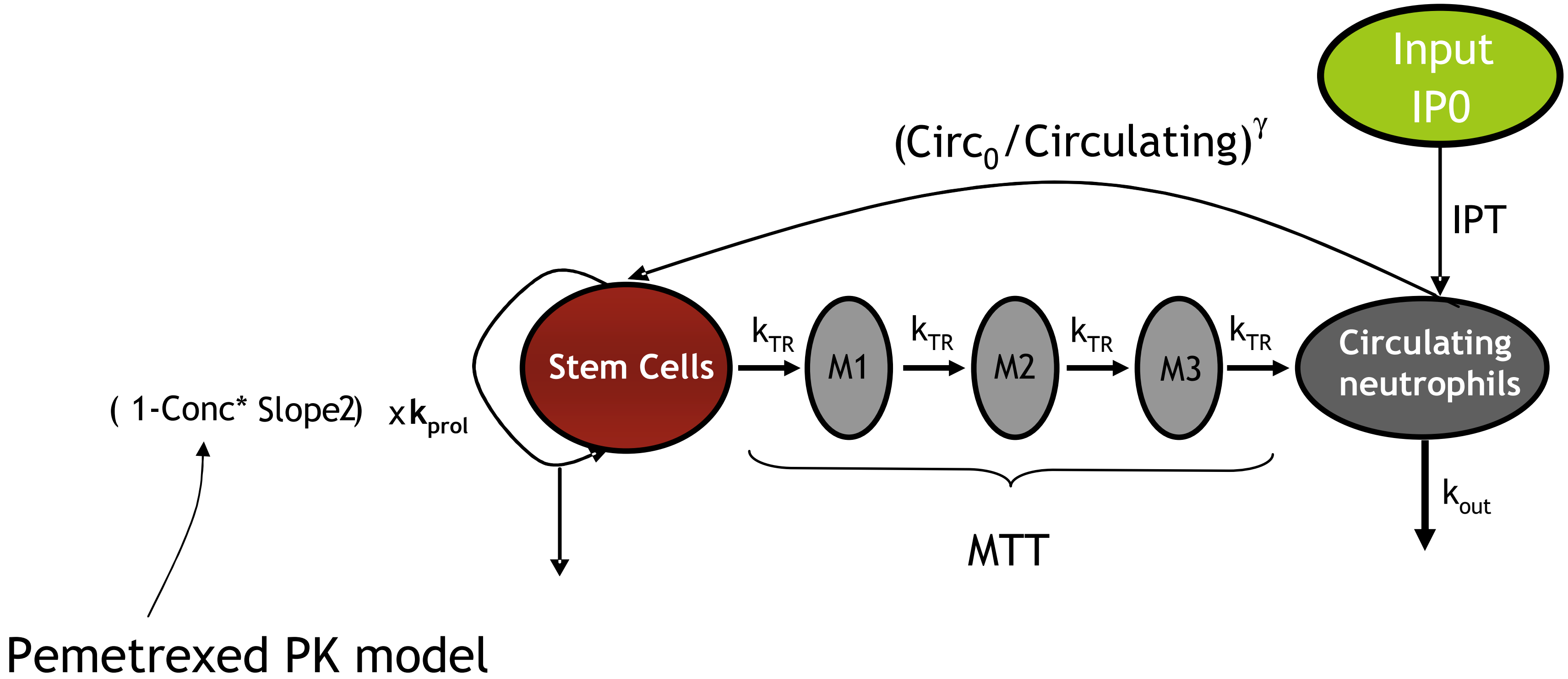


Pemetrexed model

Later decrease in neutrophils → Pemetrexed (+ vitamins) Effect



Pemetrexed model



To describe dexamethasone effect*

*Ozawa et al, 2007

Pemetrexed model

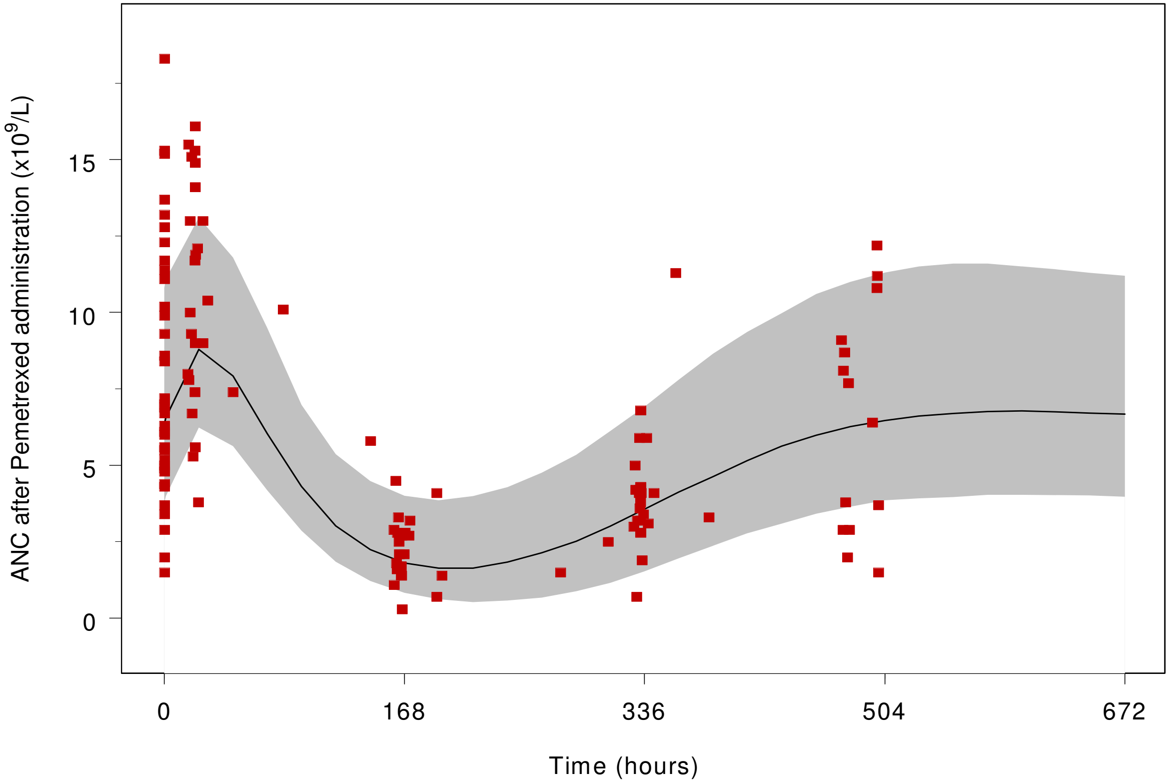
Parameter	Estimate	IPV
Pharmacokinetics		
CL (L/h)	5.15 (7.24)	30.1 (29.2)
V_1 (L)	3.68 (23.60)	85.0 (67.0)
Q_2 (L/h)	1.58 (14.60)	-
V_2 (L)	3.94 (9.59)	21.3 (43.3)
Q_3 (L/h)	22.6 (6.11)	-
V_3 (L)	6.03 (4.74)	-
Proportional error (ng/mL)	8.45 (12.1)	-
Pharmacodynamics		
$Circ_0$ (cells x10^9/L)	6.29 (8.87)	31.9 (26.9)
MTT (h)	87.8 (7.80)	-
Slope (mL/ng)	0.000191 (12.1)	31.0 (57.2)
γ	0.129 (14.1)	-
IPT (h)	46.2 (43.7)	-
IP0 (cells x10^9/L)	10.9 (42.3)	-
Residual error (1)	0.16 (14.94)	-

(1) Additive error in logarthmic scale

Pemetrexed model

Internal Validation

VPC 500mg/m² dose



Pemetrexed model

External Validation

DOSE (mg/m^2)	HDFA (Intermittent high dose Folic Acid)		MVI (Continues daily multivitamins with nutritional doses of folic acid)	
	HPT n=28	LPT n=34	HPT n=20	LPT n=23
600	9	7	3	3
700	3	3	0	0
800	9	4	11	5
925	6	7	6	3
1050	0	5	0	9
1200	0	6	0	3
1400	0	3	0	0
% Grade 3 obs	32	21	50	30
% Grade 4 obs	18	24	15	13

HPT: Heavily pretreated, LPT: Lightly pretreated

Takimoto et al, 2007

Pemetrexed model

External Validation

DOSE (mg/m²)	HDFA (Intermittent high dose Folic Acid)		MVI (Continues daily multivitamins with nutritional doses of folic acid)	
	HPT n=28	LPT n=34	HPT n=20	LPT n=23
600	9	7	3	3
700	3	3	0	0
800	9	4	11	5
925	6	7	6	3
1050	0	5	0	9
1200	0	6	0	3
1400	0	3	0	0
% Grade 3 obs	32	21	50	30
% Grade 3 sim	30 (15-44)	30 (17-43)	35 (15-50)	30 (17-48)
% Grade 4 obs	18	24	15	13
% Grade 4 sim	15 (4-26)	29 (20-43)	15 (5-30)	30 (17-48)

HPT: Heavily pretreated, LPT: Lightly pretreated

Takimoto et al, 2007

Modelling steps

1. Obtain missing information
    - PK/PD model for pemetrexed + co-medication
    - Type of interaction
2. Simulations
3. PK/PD combination model refinement
    - Response surface analysis
    - Use of PRIORS subroutine

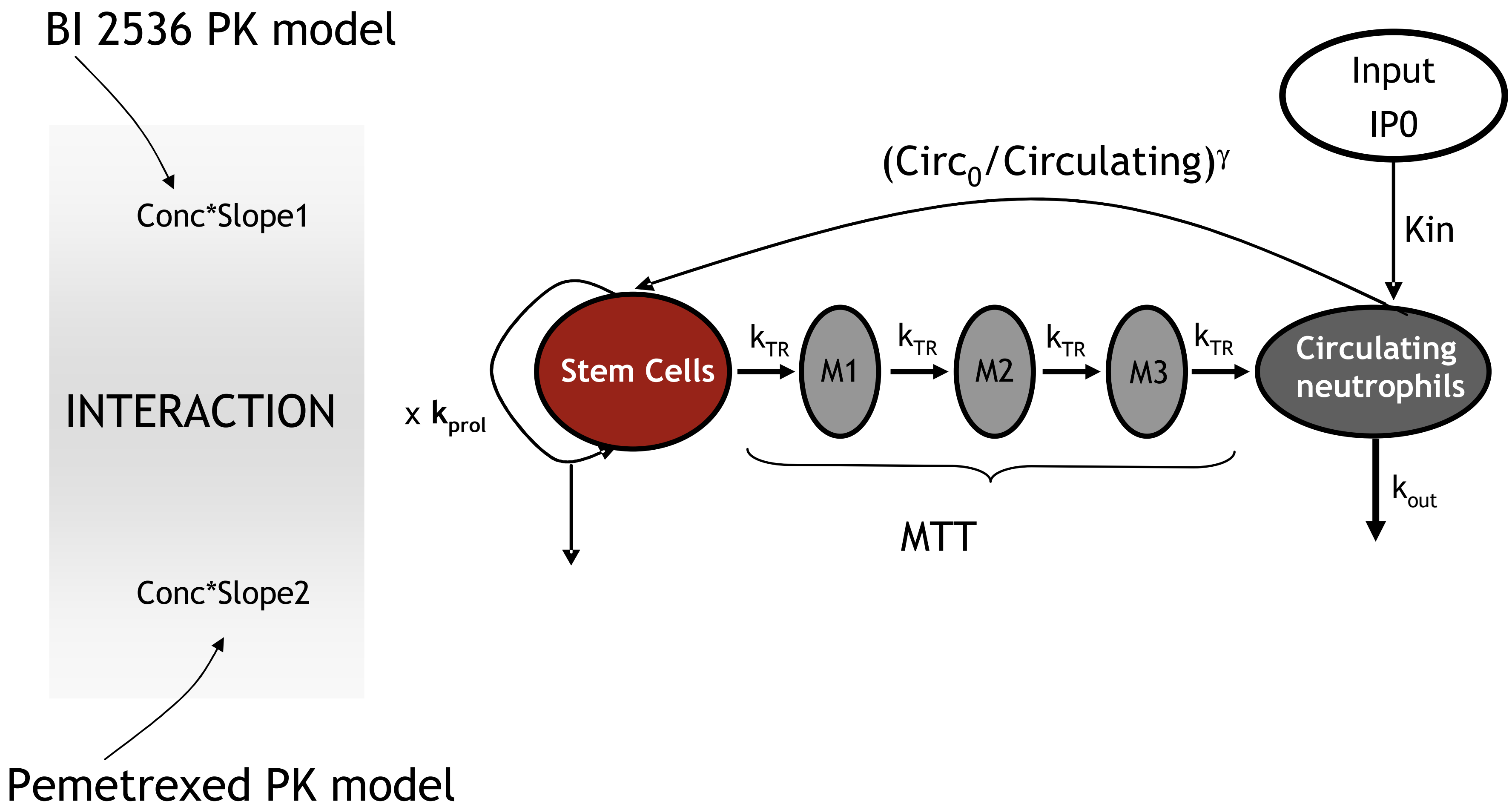
Type of interaction

Interaction models described in literature

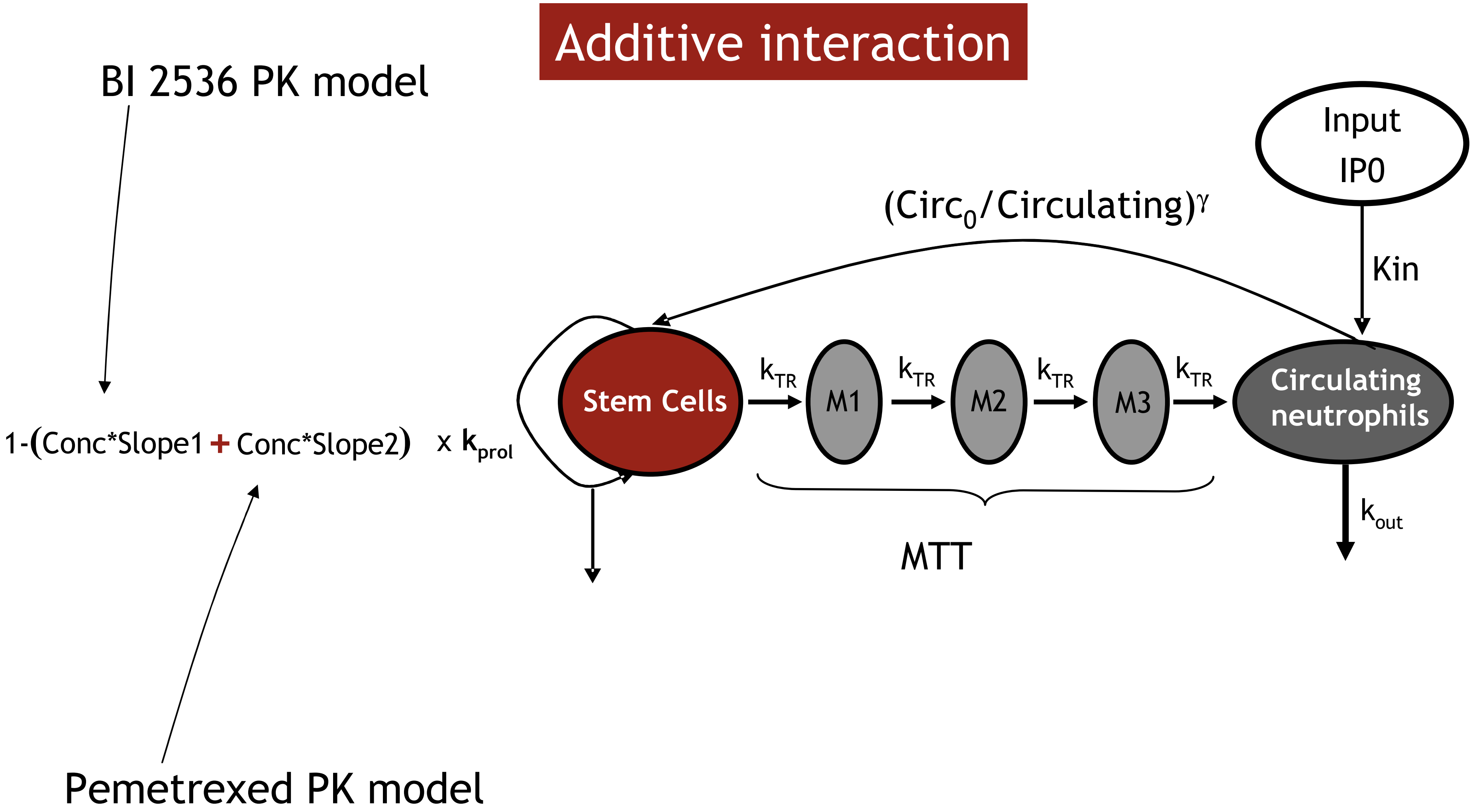
	Sandstrom et al, 2005	Sandstrom et al, 2006	Zandvliet et al, 2007	Kathman et al, 2007
Drugs	Docetaxel Epirubicin	Fluoroucil Epirubicin Cyclophosphamide	Indisulam Capecitabine (oral)	Ispinesib Docetaxel
Patients	44	140	34 (pk & pd data)	24
Model	Additive	Additive	Additive	Additive

Additive effect

Type of interaction



Type of interaction



Modelling steps

1. Obtain missing information
   - PK/PD model for pemetrexed + co-medication
   - Type of interaction
2. Simulations
3. PK/PD combination model refinement
   - Response surface analysis
   - Use of PRIORS subroutine

Simulations

What would be needed for simulations?

1. Study design characteristics
2. PK parameters
3. Neutropenia parameters

Source	Parameter	Estimates	IIV
From Combination Study	E0 ($x10^9$/L)	6.53	42%
From previous BI 2536 study	MTT (hours)	107	22%
	γ	0.161	-
	BI slope (mL/ng)	0.0147	65%
From previous Pemetrexed study	PTX slope (mL/ng)	0.00019	31%
	IPT (hours)	49.5	-
	IP0 (mL/ng)	11.6	-
	Residual error [(1)]	0.16	-

[(1)] Additive error in logarithmic scale

Simulations

Model performance was evaluated using predictive checks

- 500 simulations for the combination study
  - Calculation of
    - Nadir
    - %G3 and %G4 Neutropenia
    - %G4 Neutropenia
- Simulation of 1000 individual profiles
  - Visual Predictive Checks

Simulations

Numerical Predictive Checks

Cycle 1 (all doses)

	Nadir	% G4	%G3 & %G4
Observation	1.37	40	50
Prediction	1.28 (0.99-1.61)*	34 (28-48)*	58 (48-70)*

Cycle 2 (all doses)

	Nadir	% G4	%G3 & %G4
Observation	1.8	27	42
Prediction	1.23 (0.89-1.69)*	33 (21-48)*	58 (45-69)*

* Median (2.5% and 97.5% percentiles)

Simulations

Numerical Predictive Checks

Cycle 1 (BI 2536 250mg dose, n=16)

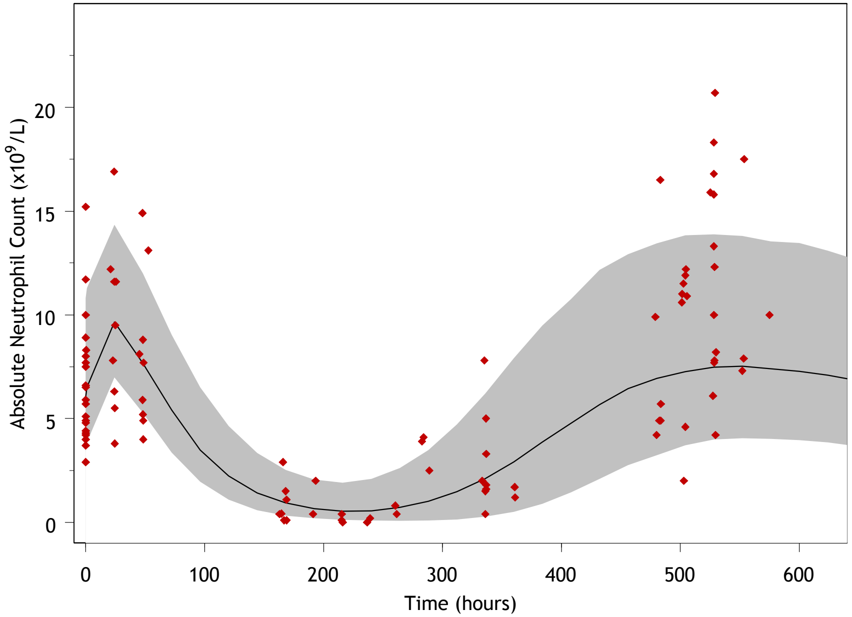
	Nadir	% G4	%G3 & %G4
Observation	0.93	63	63
Prediction	1.02 (0.62-1.51)*	41 (25-63)*	63 (44-81)*

* Median (2.5% and 97.5% percentiles)

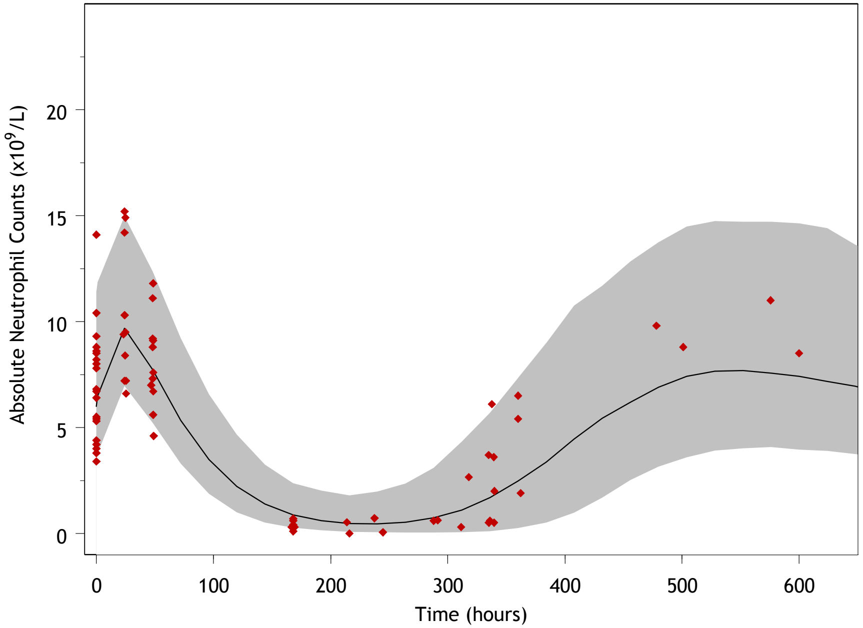
Simulations

Visual Predictive Checks

250 mg BI2536 + 945 mg PTX



300 mg BI2536 + 945 mg PTX



Modelling steps

1. Obtain missing information
   - PK/PD model for pemetrexed + co-medication
   - Type of interaction
2. Simulations
3. PK/PD combination model refinement
   - Response surface analysis
   - Use of PRIORS subroutine

PK/PD combination model

Response surface modeling to evaluate interaction

$$\text{Drug} = \frac{\text{Conc}_{BI2536} \times \text{Slope}_{BI2536} + \text{Conc}_{PTX} \times \text{Slope}_{PTX}}{E_{50}}$$

$$E_{50} = 1 - \boxed{\mathit{PAR}} \times \frac{CP_{BI2536} \times SLP_{BI2536}}{CP_{BI2536} \times SLP_{BI2536} + CP_{PTX} \times SLP_{PTX}} + \boxed{\mathit{PAR}} \left(\frac{CP_{BI2536} \times SLP_{BI2536}}{CP_{BI2536} \times SLP_{BI2536} + CP_{PTX} \times SLP_{PTX}} \right)^2$$

PAR=Interaction parameter

- $E_{50}=1$ → Additive interaction
- $E_{50}<1$ → Sinergistic interaction
- $E_{50}>1$ → Antagonistic interaction

(Minto et al, 2000)

Modelling steps

1. Obtain missing information
   - PK/PD model for pemetrexed + co-medication
   - Type of interaction
2. Simulations
3. PK/PD combination model refinement
   - Response surface analysis
   - ➢ Use of PRIORS subroutine

PK/PD combination model

Use of prior knowledge

- NWPRIOR = Normal / Wishart⁻

- Priors (from previous studies) on:
  - BI 2536 slope parameter (and IIV)
  - Pemetrexed slope parameter (and IIV)

(Gisleskog et al, 2002)

Modelling steps

1. Obtain missing information
   - PK/PD model for pemetrexed + co-medication
   - Type of interaction
2. Simulations
3. PK/PD combination model refinement
   - Response surface analysis
   - Use of PRIORS subroutine

PK/PD combination model

Final parameters	estimate	IIV (%)
$Circ_0$ (cells $x10^9/L$)	6.02	36
MTT (h)	97.8	37
PTX slope (mL/ng)	0.000118	34
BI 2536 slope (mL/ng)	0.0162	55
γ	0.172	-
IP0 (cells $x10^9/L$)	9.07	-
IPT (h)	19.3	-
PAR	Not significantly different from 0	
Residual error [(1)]	0.31	-

[(1)] Additive error in logarthmic scale

Additive interaction

PK/PD combination model

Final parameters	estimate	IIV (%)	Previous
$Circ_0$ (cells x10^9/L)	6.02 (7)	36 (26)	
MTT (h)	97.8 (3)	37 (32)	
PTX slope (mL/ng)	0.000118 (36)	[illegible]	0.000191
BI 2536 slope (mL/ng)	0.0162 (16)	[illegible]	0.0147
γ	0.172 (5)	-	
IP0 (cells x10^9/L)	9.07 (22)	-	
IPT (h)	19.3 (44)	-	
Residual error [(1)]	0.31 (16)	-	

[(1)] Additive error in logarthmic scale

PK/PD combination model

Final parameters	estimate	IIV (%)	Published
$Circ_0$ (cells x10^9/L)	6.02 (7)	36 (26)	
MTT (h)	97.8 (3)	37 (32)	
PTX slope (mL/ng)	0.000118 (36)		0.00012
BI 2536 slope (mL/ng)	0.0162 (16)	55 (18)	
γ	0.172 (5)	-	
IP0 (cells x10^9/L)	9.07 (22)	-	
IPT (h)	19.3 (44)	-	
Residual error (1)	0.31 (16)	-	

(1) Additive error in logarthmic scale

Latz et al, 2009

PK/PD combination model

Summary of the results

Cycle 1 (all doses)

	Nadir	% G4	%G3 and %G4
Observation	1.37	40	50
Step 2	1.28 (0.99-1.61)*	34 (28-48)*	58 (48-70)*
Step 3	1.27 (0.98-1.69)*	33 (18-45)*	58 (41-72)*

Cycle 2 (all doses)

	Nadir	% G4	%G3 and %G4
Observation	1.59	30	48
Step 2	1.23 (0.89-1.69)*	33 (21-48)*	58 (45-69)*
Step 3	1.80 (1.35-2.60)*	27 (16-41)*	51 (38-65)*

* Median (2.5% and 97.5% percentiles)

PK/PD combination model

Summary of the results

Cycle 1 (250mg BI 2536 dose)

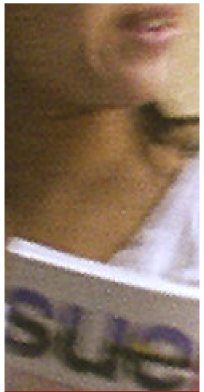
	Nadir	% G4	%G3 and %G4
Observation	0.93	63	63
Parameters monotherapy	1.02 (0.62-1.51)*	41 (25-63)*	65 (44-81)*
Parameters update	0.99 (0.59-1.54)*	38 (19-63)*	69 (44-88)*

* Median (2.5% and 97.5% percentiles)

Conclusions

1. The neutropenic effects of the combination of BI 2536 and pemetrexed were adequately predicted using information from previous single drug studies and assuming an additive interaction between the drugs.

2. The drug related parameters in this model are consistent between studies and independent of study type (single drug or combination therapy) suggesting a promising opportunity for predicting future trial outcomes.



Acknowledgements

Department of Drug Metabolism & Pharmacokinetics

Boehringer Ingelheim Pharma GmbH & Co.KG

Department of Pharmacy and Pharmaceutical Technology

University of Navarra