A Modelling Framework to Simulate Xeloda Dose Intensity and Survival in Colorectal Cancer

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Background and objectives

Selection of optimal dose to maximize patient benefit (side effects, survival) is challenging in oncology

Capecitabine (Xeloda®) is approved for colorectal cancer ("CRC") as a monotherapy at 1250 mg/m^2 BID x 14 days every 3 weeks

A reduced starting dose has frequently been used in clinical practice and is recommended for the combination with oxaliplatin and irinotecan

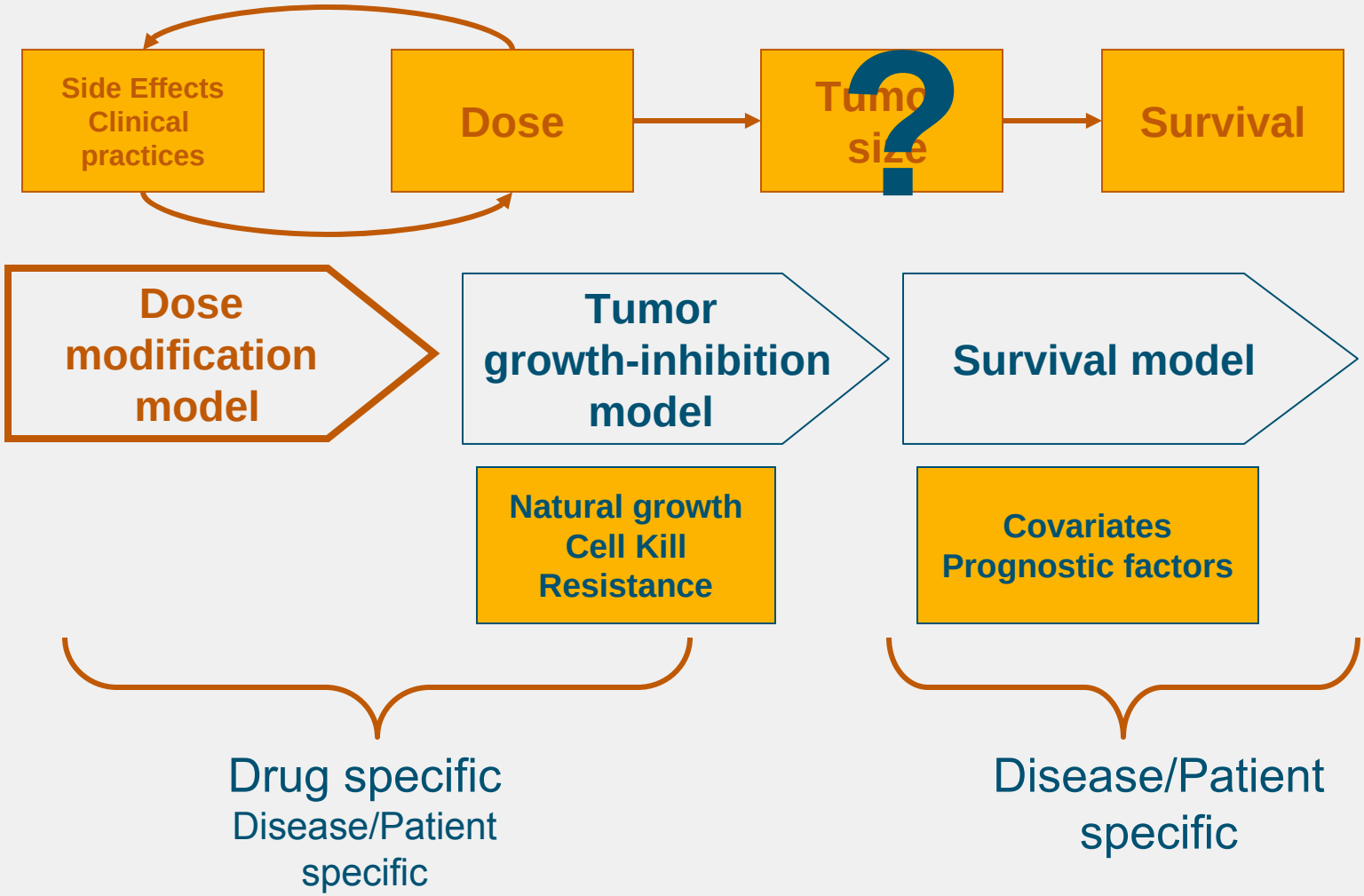
The objectives were:

- To demonstrate through simulations to what extent a 850 mg/m^2 starting dose is comparable with 1000 mg/m^2 with respect to drug treatment efficacy in terms of overall survival

A modeling framework has been developed to simulate the impact of lower starting doses of Xeloda on:

- overall median dose intensity
- response to treatment
- patient survival

The modelling framework



Claret L et al. Proc ASCO, # 6025, 2006.

The tumor growth inhibition model describes the sum of tumor longest diameters, y, as a function of time and dose

Tumor growth rate

Cell-kill rate

$$\frac{dy(t)}{dt} = K_L \cdot y(t) - K_D(t) \cdot Dose(t) \cdot y(t)$$

$$K_D(t) = K_{D,0} \cdot e^{-\lambda t}$$

Resistance: exponential decrease of kill rate

λ: rate constant for resistance appearance, $K_D(0)=K_{D,0}$

$$y(0) = y_0$$

Baseline tumor size

$$Dose(t)$$

Step function of daily dose

K_L, K_D and λ were estimated in NONMEM with a random effect on each parameter

Claret L et al. PAGE 15, (Abstract 1004), 2006.

Survival model

Survival time distribution was estimated as a function of predicted change in tumor size at week 6 and tumor size at baseline

Parametric (lognormal distr.) model needed for simulations

$$T \sim pdf(t)$$

$$\log T \sim N(\alpha, \sigma^2)$$

- α is a function of covariates:
  - Tumor size at baseline (patient characteristics)
  - Tumor shrinkage at week 6 after start of treatment (drug effect)

Tumor growth inhibition and survival models were qualified previously (PAGE and ASCO, 2006)

Dose modification model

Numerous adverse events require dose adaptations

One approach would consist in modeling the probability of all dose-limiting side effects and simulate dose intensity using the dosing algorithm

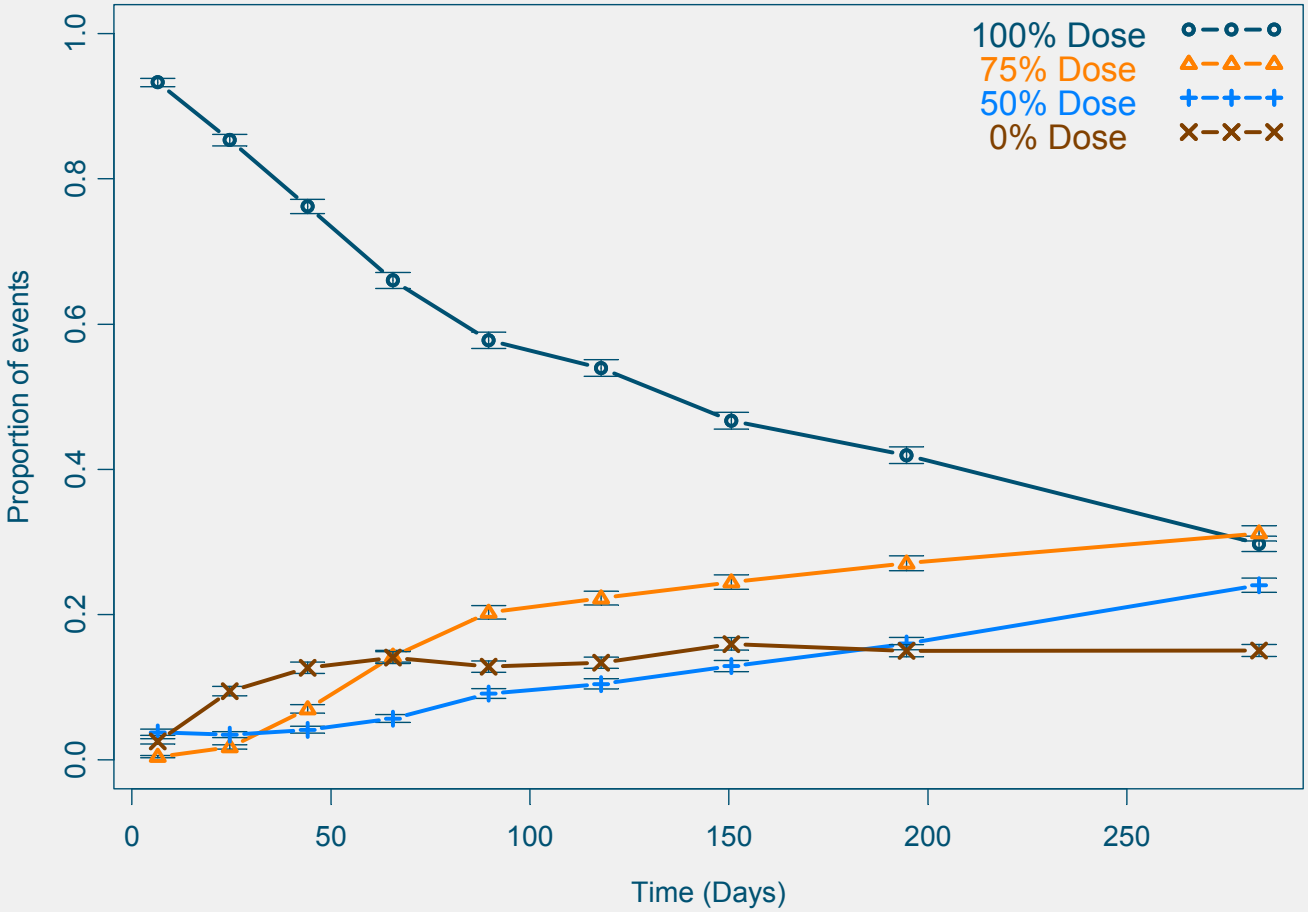
To avoid these complexities, we considered a model of the occurrence of dose reductions and delays as a function of time and (previous) doses

We developed an ordered categorical model for the probability of dosing events (daily doses) :

- 100% of starting dose [100 ; 87.5],
- 75% of starting dose [87.5 ; 60],
- 50% of starting dose [60 ; 35],
- 0% of starting dose [35 ; 0]

596 patient dosing histories coming from two Xeloda monotherapy Phase III arms (1250 mg/m^2 BID)

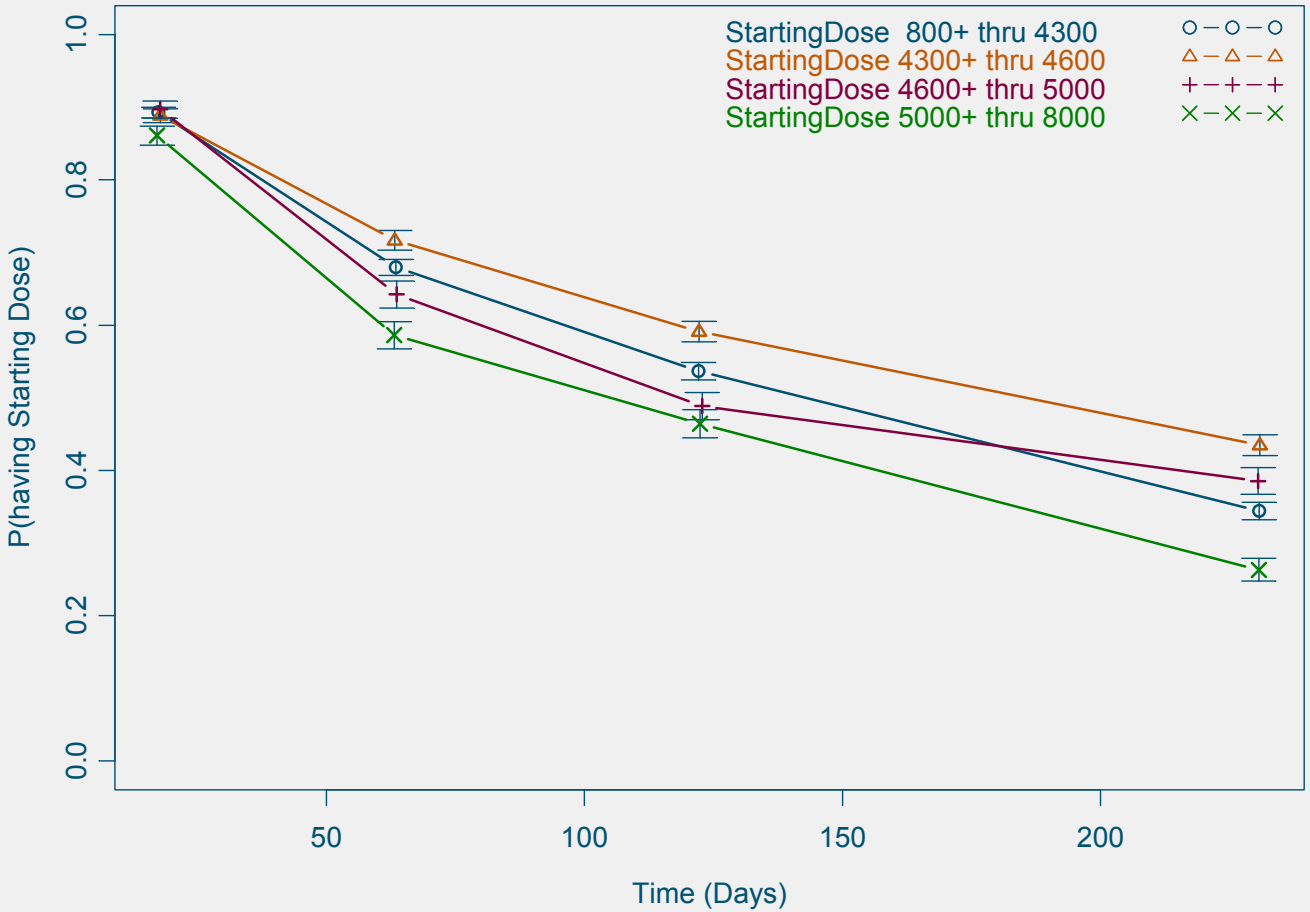
Observed proportion of dose modification events as a function of time for the 4 categories



Starting dose: 1250 mg/m^2

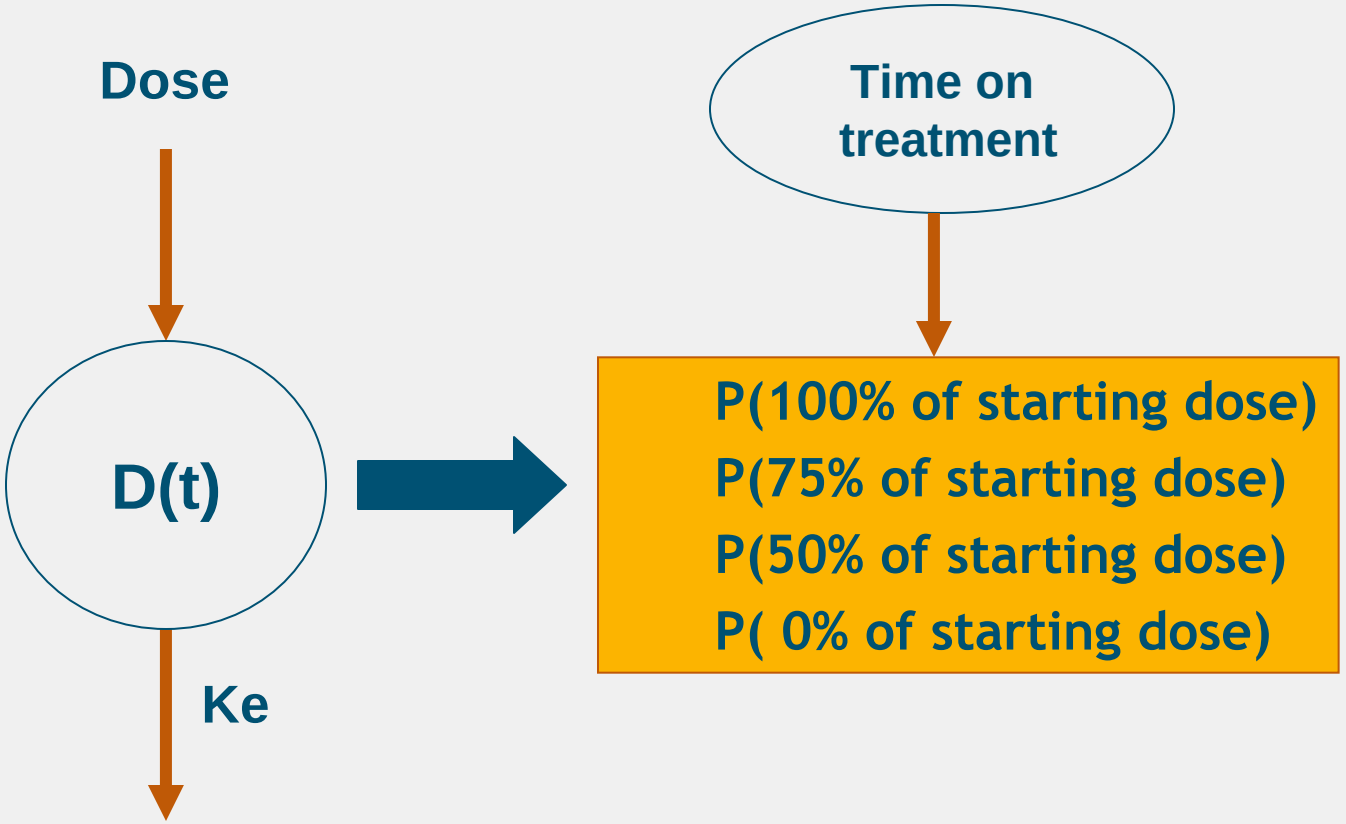
Influence of starting dose (in mg/day) on dose modifications as a function of time

The probability to stay at the starting dose is lower in patients receiving larger starting doses (larger body surface area)



Dose modification model scheme

Accumulation of effect on underlying probability of daily dose event is modelled by a “biophase” compartment



Ordered categories were modelled as logit functions of dose and time

$$\mathrm{logit}\left[P_i(Y \geq k)\right] = Int_k + E(t) + \eta_i$$

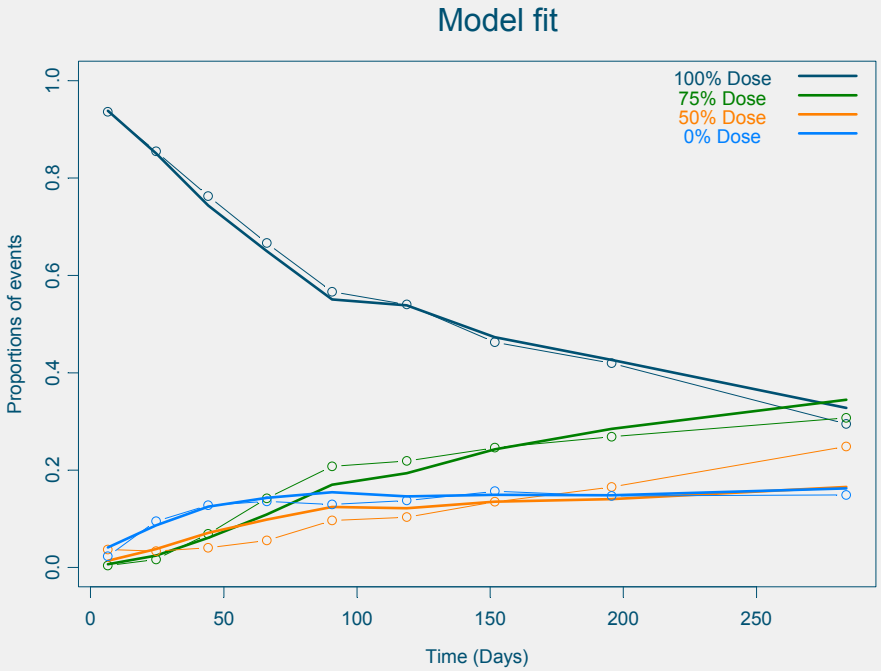
$$E(t) = Sl_{drug} \cdot D(t) + f(t)$$

$$\frac{dD(t)}{dt} = -K_e \cdot D(t)$$

$$f(t) = Int_t\left[1 - \exp\left(-K_t \cdot t\right)\right]$$

$$\eta_i \rightarrow N(0, \Omega)$$

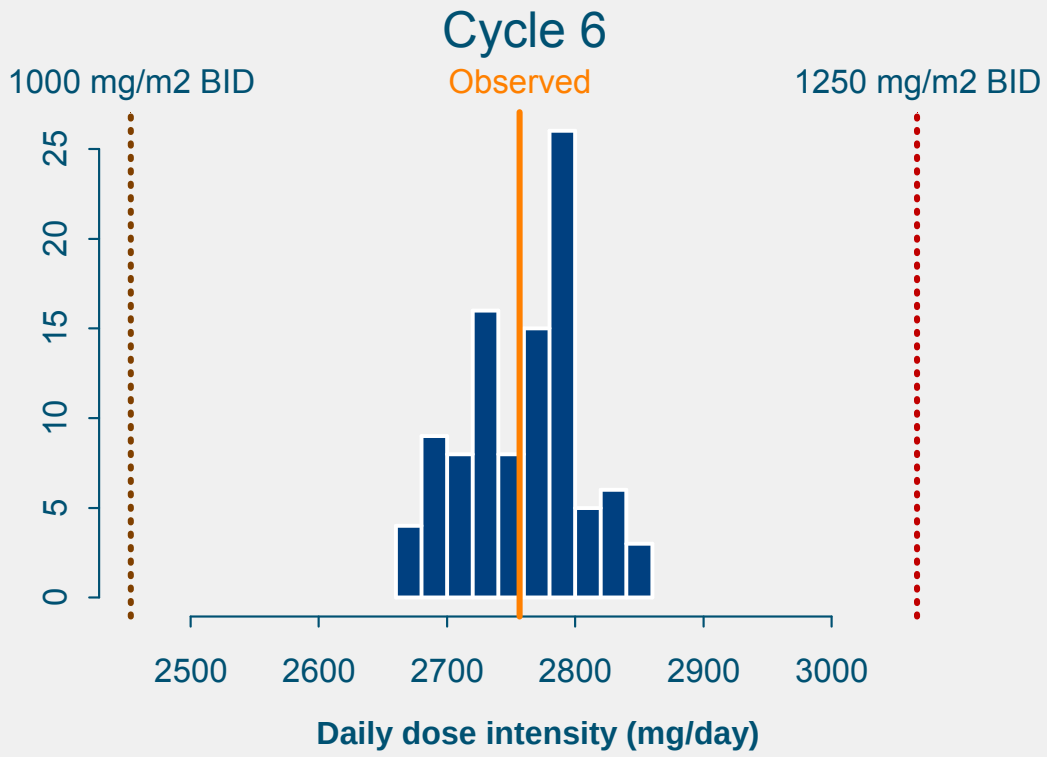
$$\mathrm{logit}(x) = \log\frac{x}{1-x}$$



Model parameters Int_k, Sl_{drug}, K_e, K_t, Ω were estimated in NONMEM V

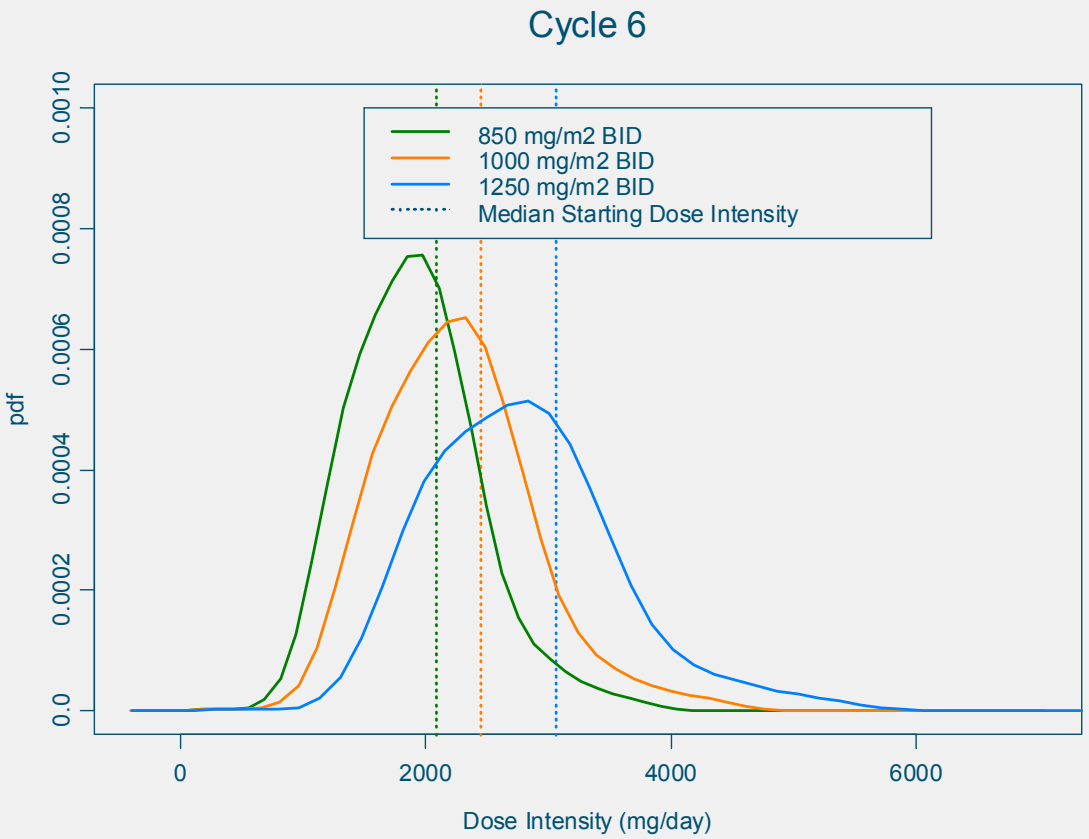
Model qualification

Posterior distribution (across 100 replicates) of median dose intensity (mg/day) at cycle 6 vs. observed values



Similar performances at cycle 4 and 8

Dose intensity simulations

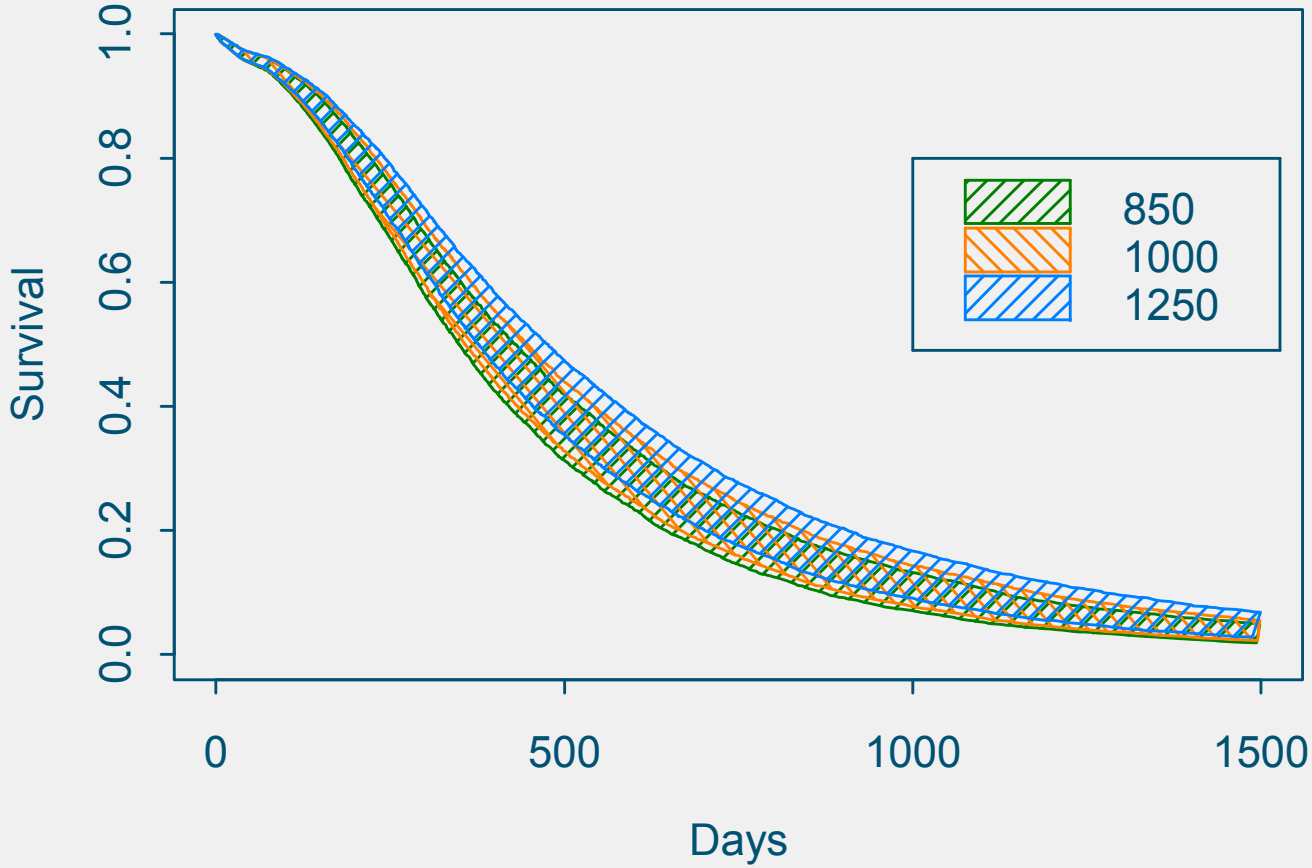


Nearly proportional reductions of median dose intensity at all starting doses

- **With a 10% reduction of starting dose intensity at cycle 6**

Distributions of individual dose intensities overlap for different starting dose levels

Survival simulations



Large overlap of the predictive distribution (90% PI) of survival for different starting dose levels

- **A minor difference concerning median overall survival at 1000 (-23 days) and 850 mg/m^2 (-36 days) respectively compared to 1250 mg/m^2**

Conclusion

The modeling framework is a useful tool to simulate expected clinical response and support dosing decisions for Xeloda monotherapy

The minor impact on median survival time support tailoring Xeloda dose in case of toxicity, older age or impaired performance status to retain a favorable therapeutic ratio in clinical practice

The modelling framework supports dose selection for Xeloda in combination with other cytotoxic agents

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Backups

Dose-reduction model: Parameter estimates (-2LL: 84775.8)

	Parameter	Estimated	SE	CV (%)
Int1	th1	-3.39	0.545	16
Int2	th2	1.27	0.105	8
Int3	th3	1.46	0.061	4
Ke (day-1)	th4	0	NA	NA
Deff	th5	0.0151	0.0048	32
log(SD(eta1))	th6	1.23	0.0388	3
Intt	th7	-5.67	0.575	10
Kt (day-1)	th8	0.020	0.0025	12

The probability of dose modifications increases with dose

- Cumulative dose (Kd = 0)

The time component f(t) describes the probability of dose-independent adjustments increasing with time up to a plateau after ~ 80 days

- If removed from the model objective function increase by 3050

The probability of dose-dependent adjustments increase with dose and time. No saturation with time could be estimated (Kd=0).

Tumor size model parameters for CRC population

Same Population ↓ **Same Drug** ↓

Parameter	Phase III 5-FU Value	Phase III 5-FU cv%	Phase II Xeloda Value	Phase II Xeloda cv%
K_L	**0.015**	18%	0.021	28%
K_D	0.052	13%	**0.025**	20%
λ	0.040	18%	**0.053**	58%
$\Omega 11$	**0.548**	24%	0.499	37%
$\Omega 22$	0.956	26%	**0.388**	67%
$\Omega 33$	0.619	36%	**1.260**	126%

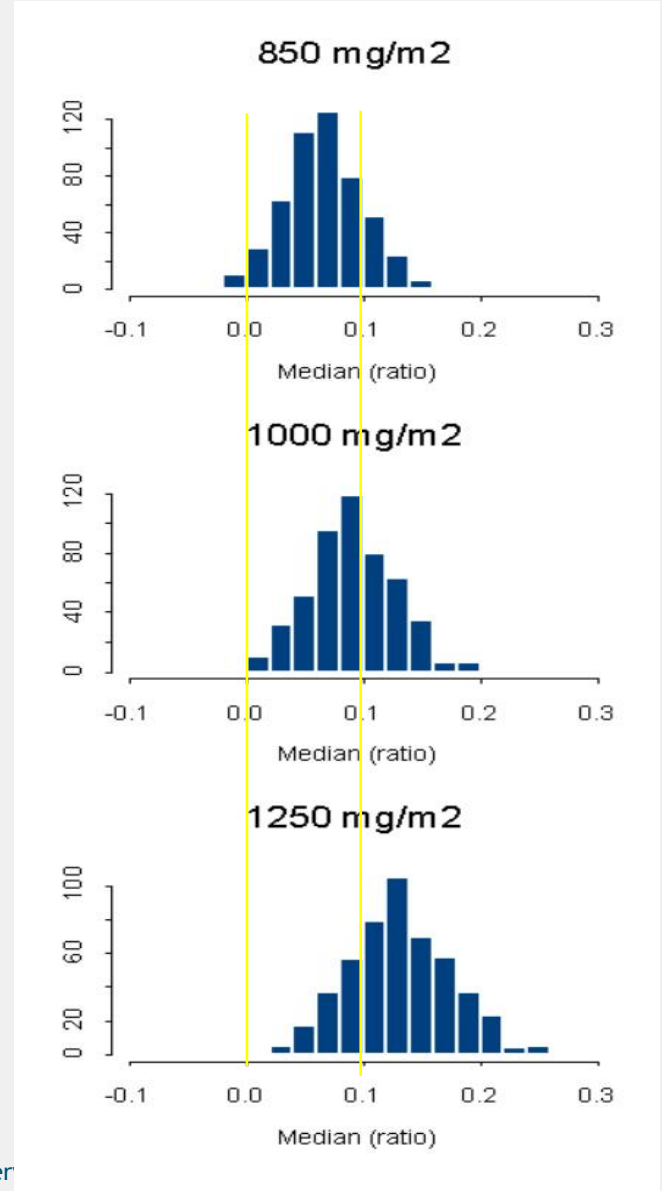
Population specific: K_L, $\Omega 11$

Drug specific: K_D, λ, $\Omega 22$, $\Omega 33$

Simulated tumor size reductions (DELTA) at week 6

A reduced starting dose results in less reduction of tumor sizes from baseline.

Dose (mg/m^2)	DELTA (median)
850	**6.6 %**
1000	**9.0 %**
1250	**13.1 %**



Survival model for CRC population

Lognormal distribution achieved the best fit (log-likelihood)

	Value	Std Error
Intercept	6.2028	0.0523
DELTA.T	1.2866	0.1511
Tumor Base	-0.0028	0.0004
Log(scale)	-0.4055	0.0319

where DELTA.T is the model predicted change in tumor size at week 6 and TUMOR.BASE is the baseline tumor size (mm).