Modelization of a categorical toxicity score :

Application to colorectal cancer patients treated with capecitabine

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Capecitabine
Oral pro-drug of 5-Fluorouracile

- Oral cytotoxic treatment for breast and colorectal cancer
- Metabolized to 5-Fluorouracile predominantly in tumour cells

- **Main toxicities:** Hand and Foot Syndrome (HFS), Diarrhoea, Nausea, Vomiting, Fatigue

Capecitabine
Oral pro-drug of 5-Fluorouracile

In case of severe toxicities:

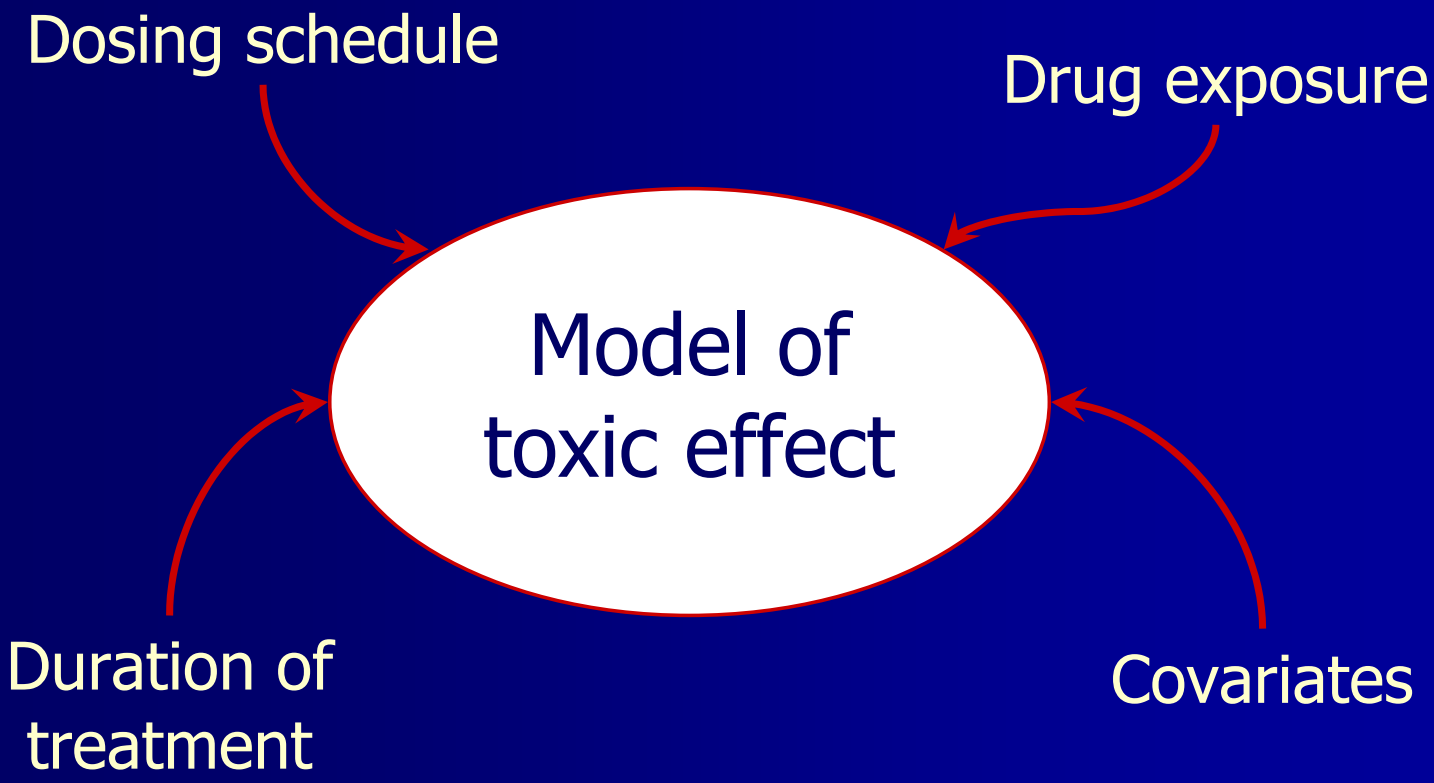
- Need to adapt the dosage regimen using rational quantitative based information
- Patients may modify themselves their compliance

A dynamic longitudinal model for toxicities would help:

→ to understand potential compliance issues

→ to adapt dosage regimen in clinical routine

Objectives


Dosing schedule
Drug exposure
Model of toxic effect
Duration of treatment
Covariates

PATIENTS & METHODS

Patients

2 large phase III studies[1,2]

Capecitabine (oral)
2500mg/m²/day
14 days on / 7 days off
603 patients

5FU/Leucovorin (IV)
LV 20mg/m² + 5FU 425mg/m²
daily for 5 days in 4-week cycles
604 patients

30 weeks or until disease progression

EFFICACY ?

TOXICITY ?

[1] Hoff et al., *J Clin Oncol*, 2001; 19(8):2282-2292
[2] VanCutsem et al., *J Clin Oncol*, 2001; 19(21):4097-4106

Patients Characteristics

inclusions from October 1996 to March 1998

		Capecitabine	5-FU/LV
Age *		62 (23 – 86)	62 (24 – 87)
Height (cm) *		168 (142 – 196)	168 (142 – 195)
Weight (kg) *		72.6 (35.8 – 208.7)	72.5 (36.4 – 152)
Sex	*Male*	58%	61%
	Female	42%	39%

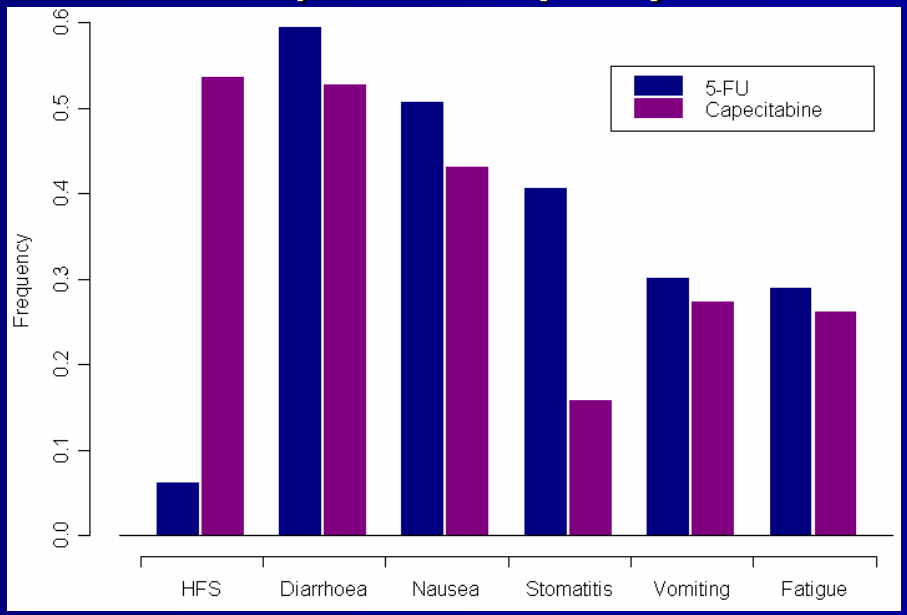
Patients randomized	603	604
Patients treated	595	593
Treatment duration (days) *	153 (4 – 507)	126 (2 – 397)

* *mean (min – max)*

Main toxicities

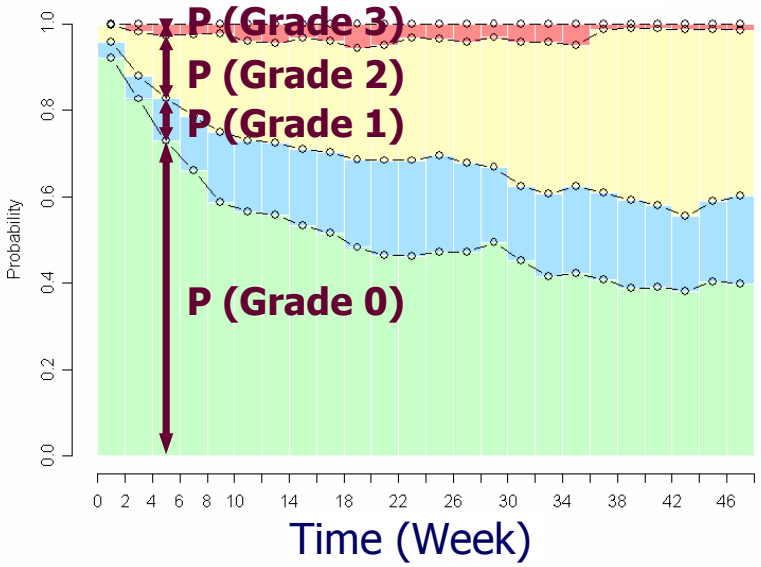
- Less toxicity in the Capecitabine group than in the 5FU group
  - Except for the Hand-and-Foot Syndrome (HFS)

Proportion of patients experiencing at least once an adverse events with grade>0

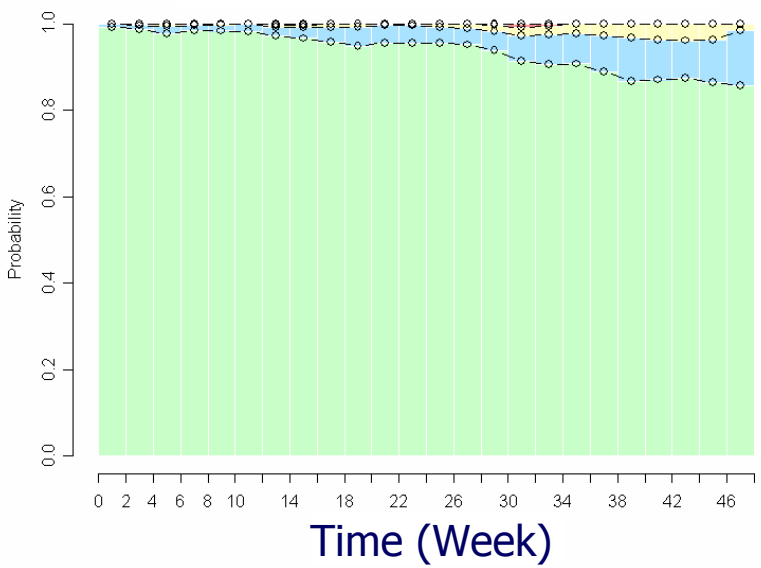


Evolution of HFS

Capecitabine



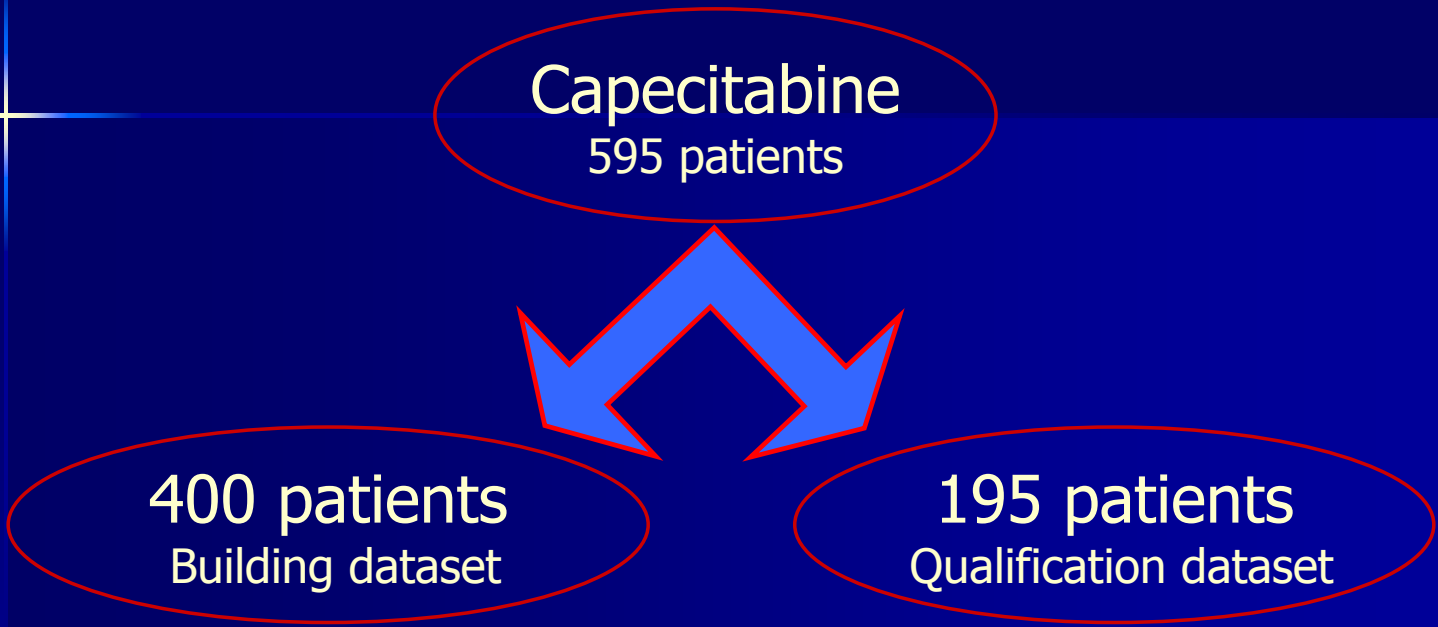
5-FluoroUracile



Only Hand-and-Foot Syndrome seems to be clearly related to drug exposure

- HFS: cutaneous toxicity, characterised by pain, redness, peeling of the skin of palms and soles
  - Measured by a score representing its severity, scaling from 0 (none) to 3 (severe)
- In the data set:
  - Only responding patients after 30 weeks
  - ➔ Data of HFS will be modelled only for the first 30 weeks
  - Very few observations of HFS grade 3 (<3%)
  - ➔ Occurrences of grade 2 and 3 grouped in the same category (painful toxicity)

Model building



Categorical data ➔proportional odds ratio model

- Model the probability of experiencing a score of HFS
- Use of the logistic transformation

Structural model for Logit

$$p = \frac{e^{\text{Logit}(p)}}{1 + e^{\text{Logit}(p)}} \quad \textit{with} \quad \text{Logit}(p) \in \Re$$

- Combination of several components:
  - Transitional model
  - Dose accumulation model

Transitional Model

- Score at time *t* dependent of score at time *t -1*
- Conditional probabilities on score transitions

$$\underset{m=0,1,2}{p(Score_t = m)} = p(Score_t = m \mid \underset{n=0,1,2}{Score_{t-1} = n})$$

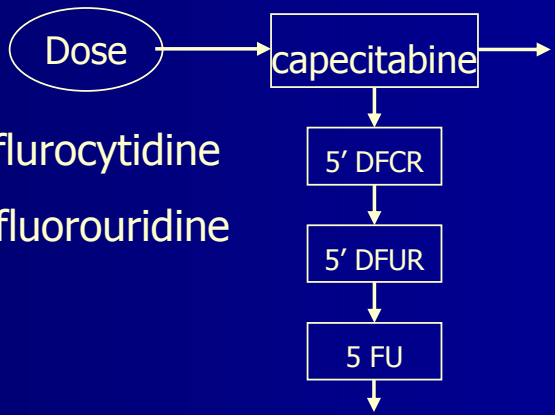
At time t:

Logit (p_t) = f($Score_{t-1}$)

Zingmark PH. et al, J Pharmacokinet Pharmacodyn , 32(2), 2005

Dose accumulation Model

- PK model of Capecitabine



5' DFCR: 5'-deoxy-5-flurocytidine

5' DFUR: 5'-deoxy-5-fluorouridine

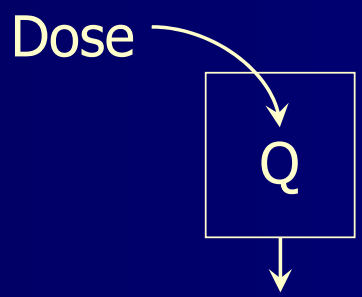
5 FU: 5-fluorouracile

In our data, no PK information !

Urien S. et al, J Pharmacokinet Pharmacodyn , 32(6), 2005

Dose accumulation Model
simplifications thanks to KPD[1] approach

- Assume accumulation of drug in the body during the treatment, and mono-exponential elimination



$K \sim \log\mathcal{N}(K_{POP}, \omega_K)$

At time t:

$\text{Logit}(p_t) = f(Q_t)$

[1] *Jacqmin P. et al, PAGE 10 (2001) Abstract 232*

Model building

- Parameters estimated by the Laplacian Method implemented in NONMEM V

- Building of the model guided by predictive checks and internal goodness-of-fit:
  - "Building dataset" simulated 100 times
  - Goodness-of-fit plots (PRED *vs.* OBS)
  - Predictive confidence interval of observed probabilities

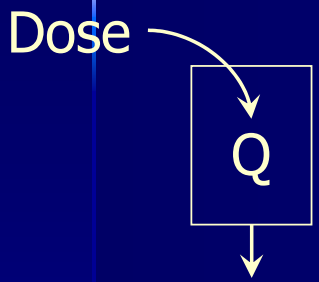
Covariate inclusion

- Following covariates tested:
  - age, sex, height, weight, body surface area, karnofsky status, type of cancer, race…
  - alkaline phosphatase, transaminase, creatinine clearance
- Likelihood ratio test for covariates (α=0.01)
- Correlation between inter-individual variabilities to be tested

RESULTS

Model Building

Final HFS Model:
Model characteristics

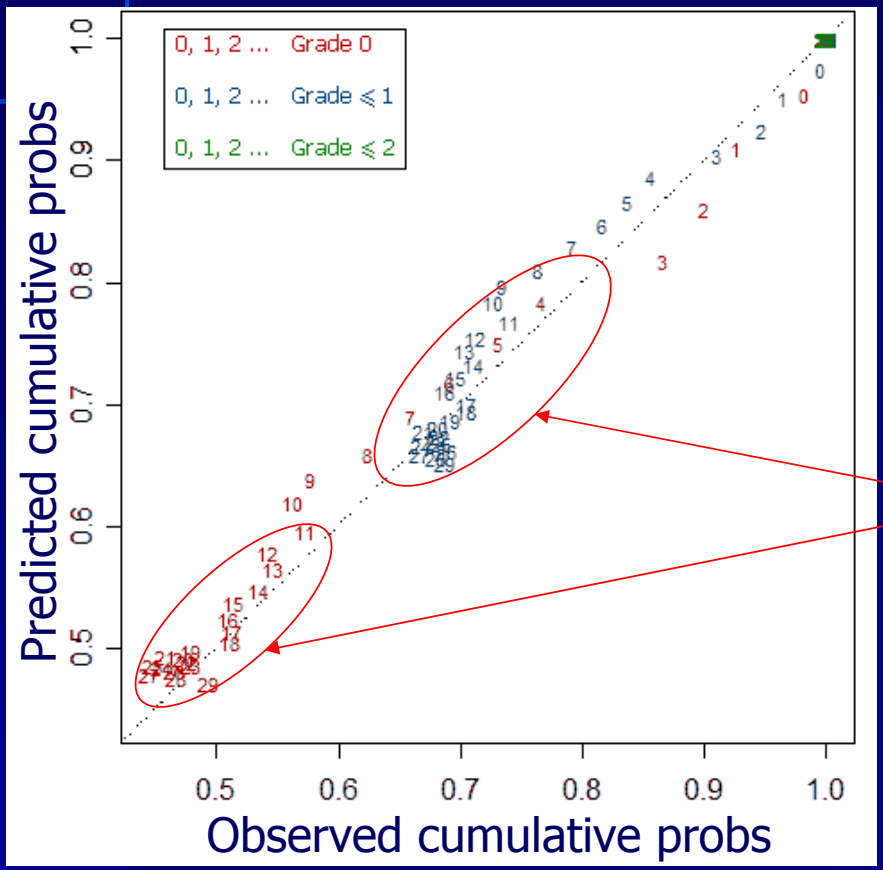


$$\begin{cases} Logit\{P(Y=0)\} = B_0 - \dfrac{E_{MAX}\cdot(Q\cdot K)}{(Q\cdot K)+ED_{50}} + \theta_{CLCR_b}\cdot(CLCR_b - 75.5) + \eta_i \\ Logit\{P(Y\le 1)\} = B_0 + B_1 - \dfrac{E_{MAX}\cdot(Q\cdot K)}{(Q\cdot K)+ED_{50}} + \theta_{CLCR_b}\cdot(CLCR_b - 75.5) + \eta_i \\ P(Y=2) = 1 - P(Y\le 1) \end{cases}$$

$K \sim \log\mathcal{N}(K_{POP}, \omega_K)$

- B_0, B_1 and E_{MAX} dependent of the score at the previous time
- ($CLCR_b$-75.5) the difference of the basal creatinine clearance with the population median
- η_K, η_i the inter-individual variabilities with corr(η_K, η_i)≠0

Final HFS Model:
Observed vs. Predicted Cumulative Probabilities



Predicted cumulative probs
vs.
Observed cumulative probs

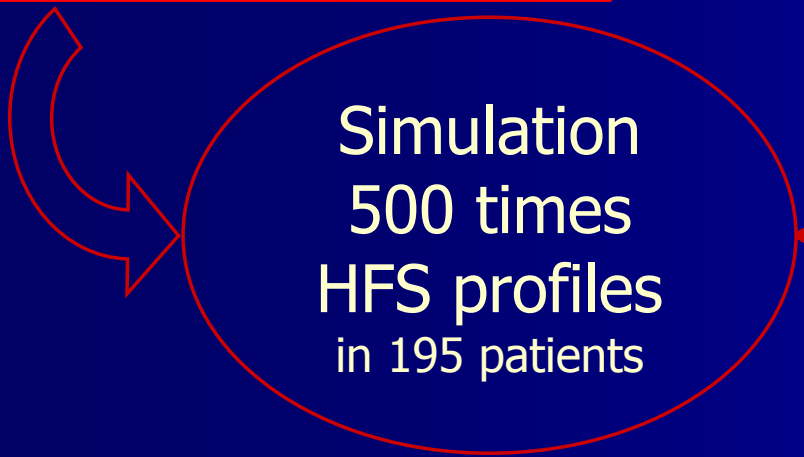
Good estimation at the end of period

RESULTS

Model qualification

Model qualification:
Predictive Check

HFS Model
+
Parameter estimates
(on 400 patients)

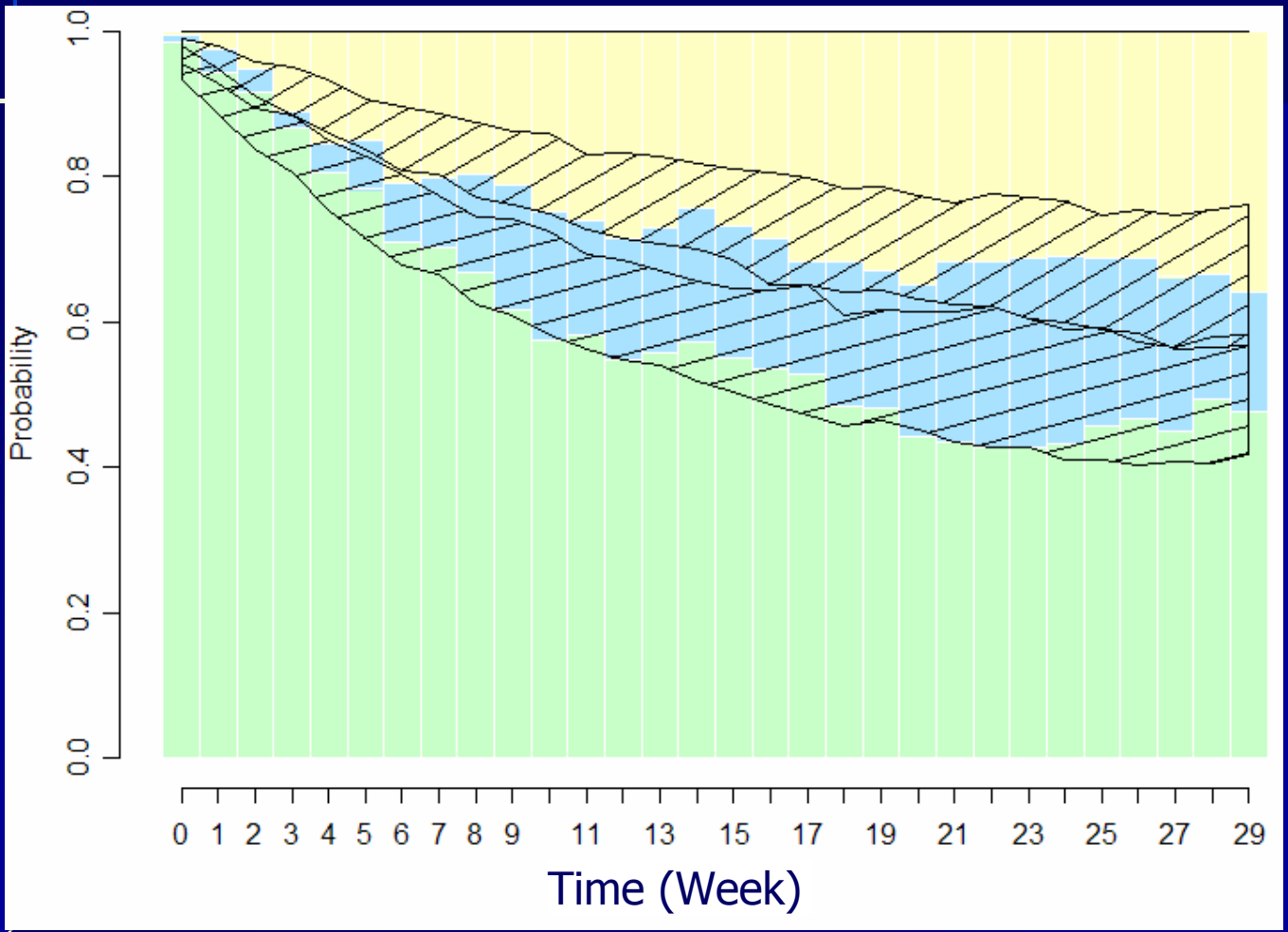


Visual predictive check

Qualification criteria

Do we accept the HFS Model ?

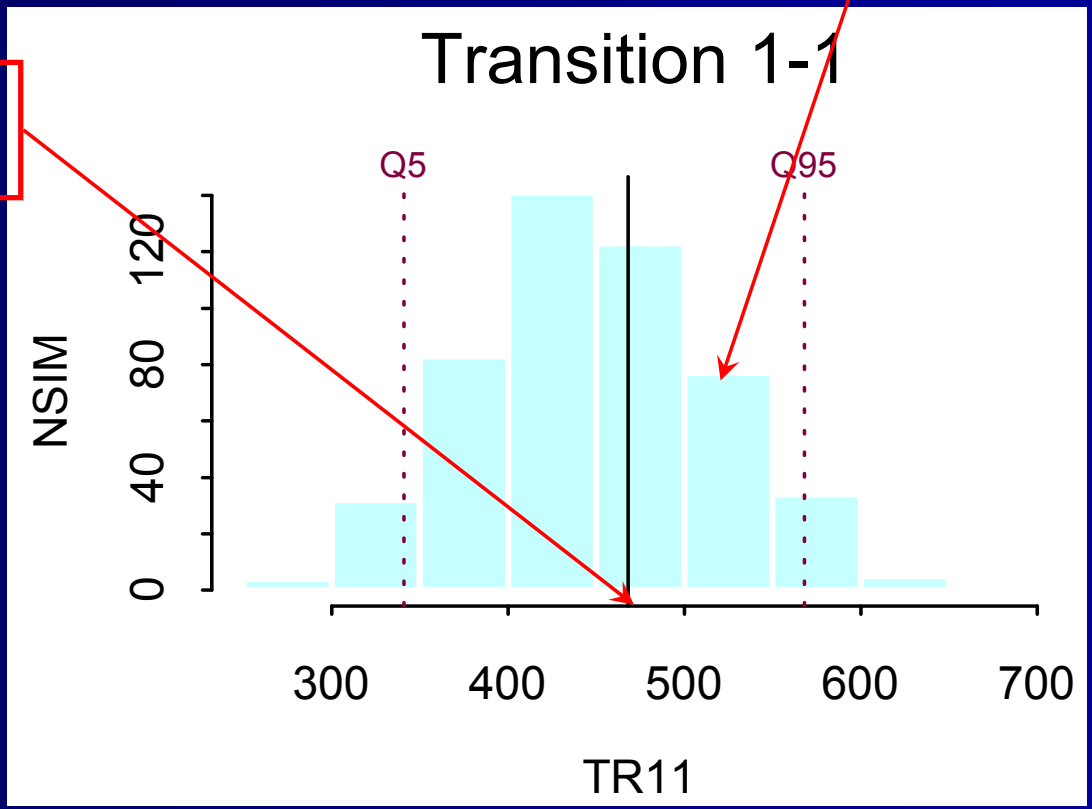
Model qualification:
Visual Predictive checks on qualification dataset



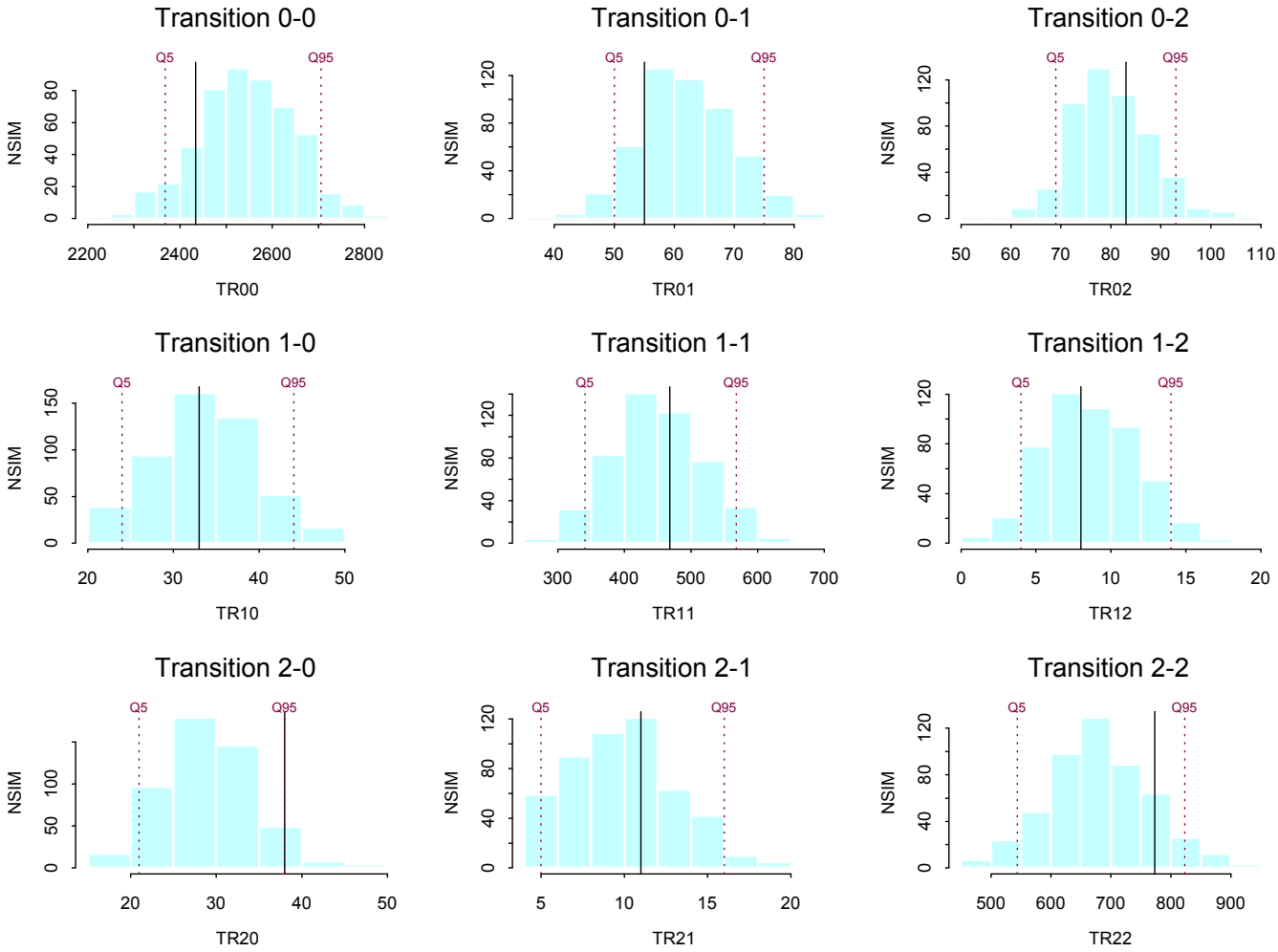
Number of Transitions

Predicted distribution of number of transitions 1-1 across 500 simulated datasets

#tr 1-1 observed: 468

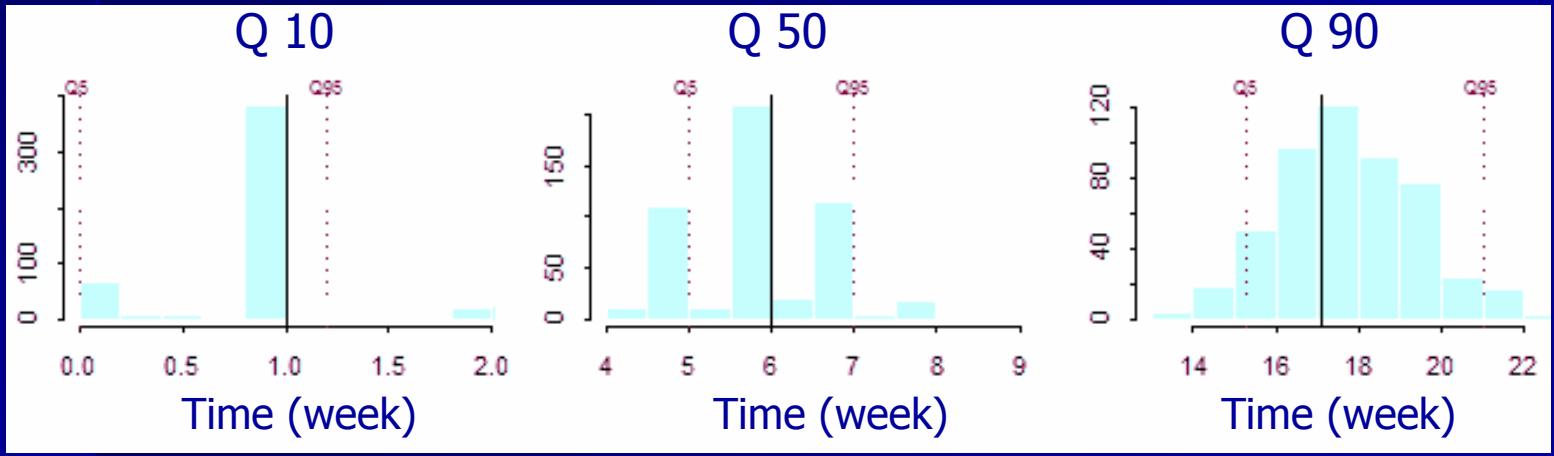


Number of Transitions



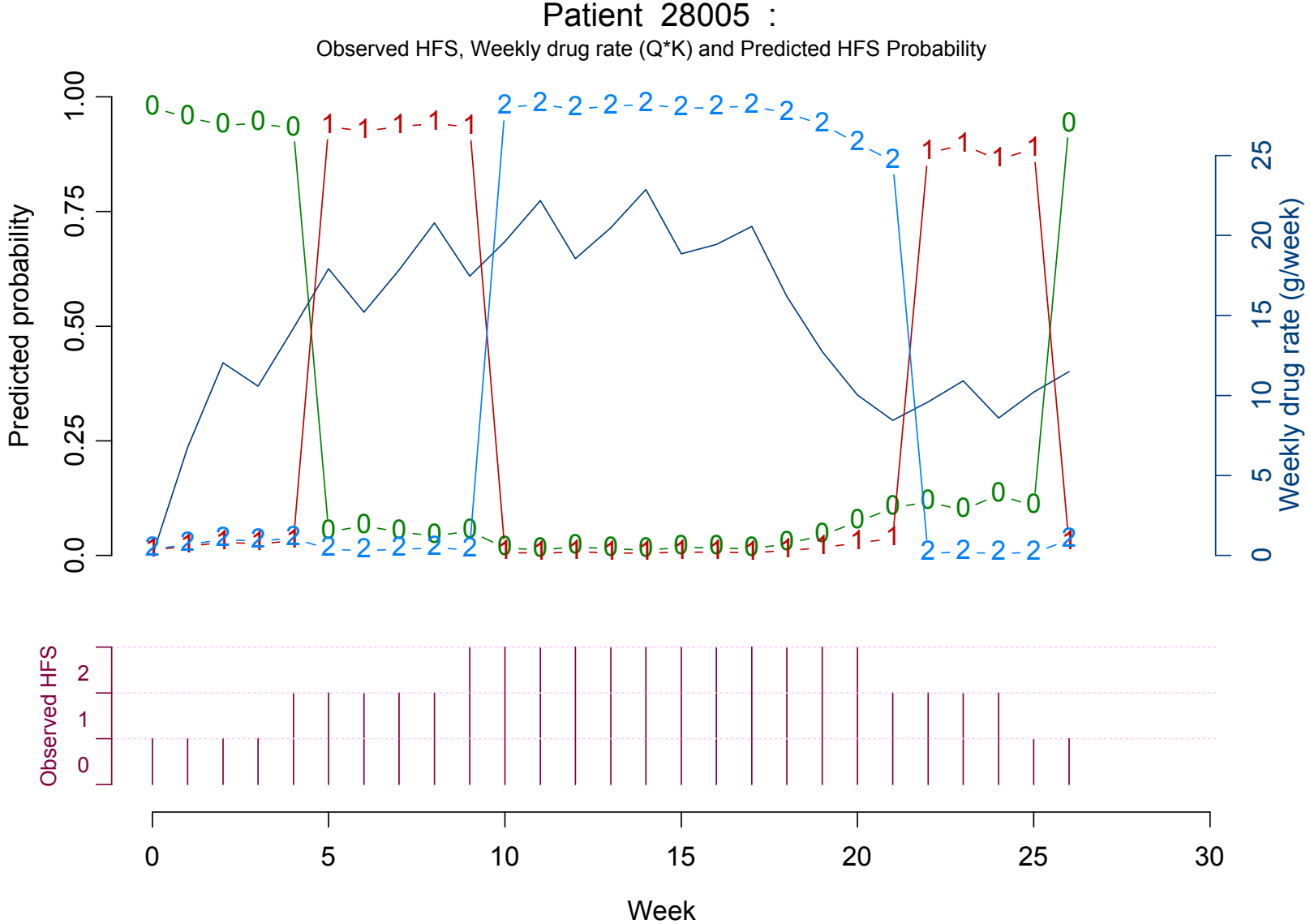
Time to the first occurrence of HFS (grade≥1)

- Population quantiles of distribution of time before the first occurrence of HFS (Grade≥1)



Individual HFS profiles

According to individual data and POSTHOC estimates

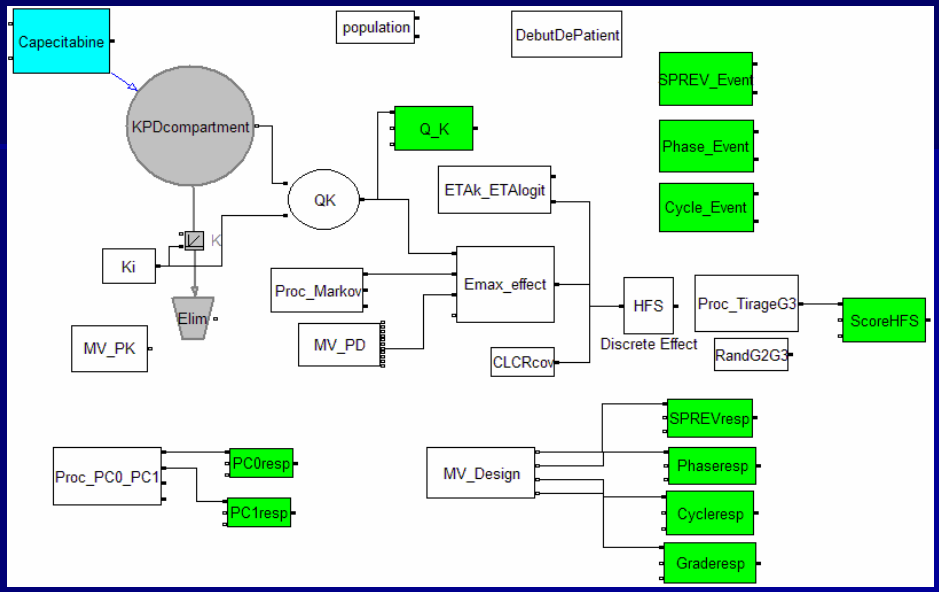

Patient 28005 :
Observed HFS, Weekly drug rate (Q*K) and Predicted HFS Probability
Predicted probability
0.0
0.25
0.50
0.75
1.00
Weekly drug rate (g/week)
0
5
10
15
20
25
Observed HFS
0
1
2
0
5
10
15
20
25
30
Week

PERSPECTIVES

HFS Model: Simulations to…

- Compare several dosing regimen
- Compare several dose reduction policies
- Study impact of non-compliance

HFS Model: Simulations
implementation in TSII (Pharsight)



Virtual patients defined by:
- body surface area
- basal creatinine clearance

Drug regimen:
- 2500 mg/m²/day
- 14 days on / 7 days off

Dose Modification:

	Grade 2	Grade 3
1st appearance of HFS	Interrupt until resolved to grade 0-1 then continue at **100%**	Interrupt until resolved to grade 0-1 then continue at **75%**
2nd appearance of HFS	Interrupt until resolved to grade 0-1 then continue at **75%**	Interrupt until resolved to grade 0-1 then continue at **50%**
3rd appearance of HFS	Interrupt until resolved to grade 0-1 then continue at **50%**	Discontinue treatment
4th appearance of HFS	Discontinue treatment	

Perspectives (1/2)

- Adaptation of individual dosing regimen using the model:
  - How should a clinician modify dosing regimen in case of a severe HFS toxicity ?

→ reduce dose?

→ shorten treatment cycles?

→ lengthen "wash-out periods"?

Perspectives (2/2)

- Study of the impact of non-compliance on HFS:
  - No patient compliance data available for treatment of cancer by an oral cytotoxic chemotherapy

    ⟶ *in silico* study

  - Future clinical study OCTO (Compliance to an oral anticancer chemotherapy):

    Assessing simultaneously patient compliance and efficacy/toxicity in patients treated with Capecitabine