Individual prediction-based dose adaptation of capecitabine:

in silico comparison with the standard method,
impact on limiting toxicity and on **antitumour efficacy**

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EMR 3738 "TherapeutiC Targeting in Oncology"
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20 th PAGE meeting, Athens, 9 June 2011

Introduction

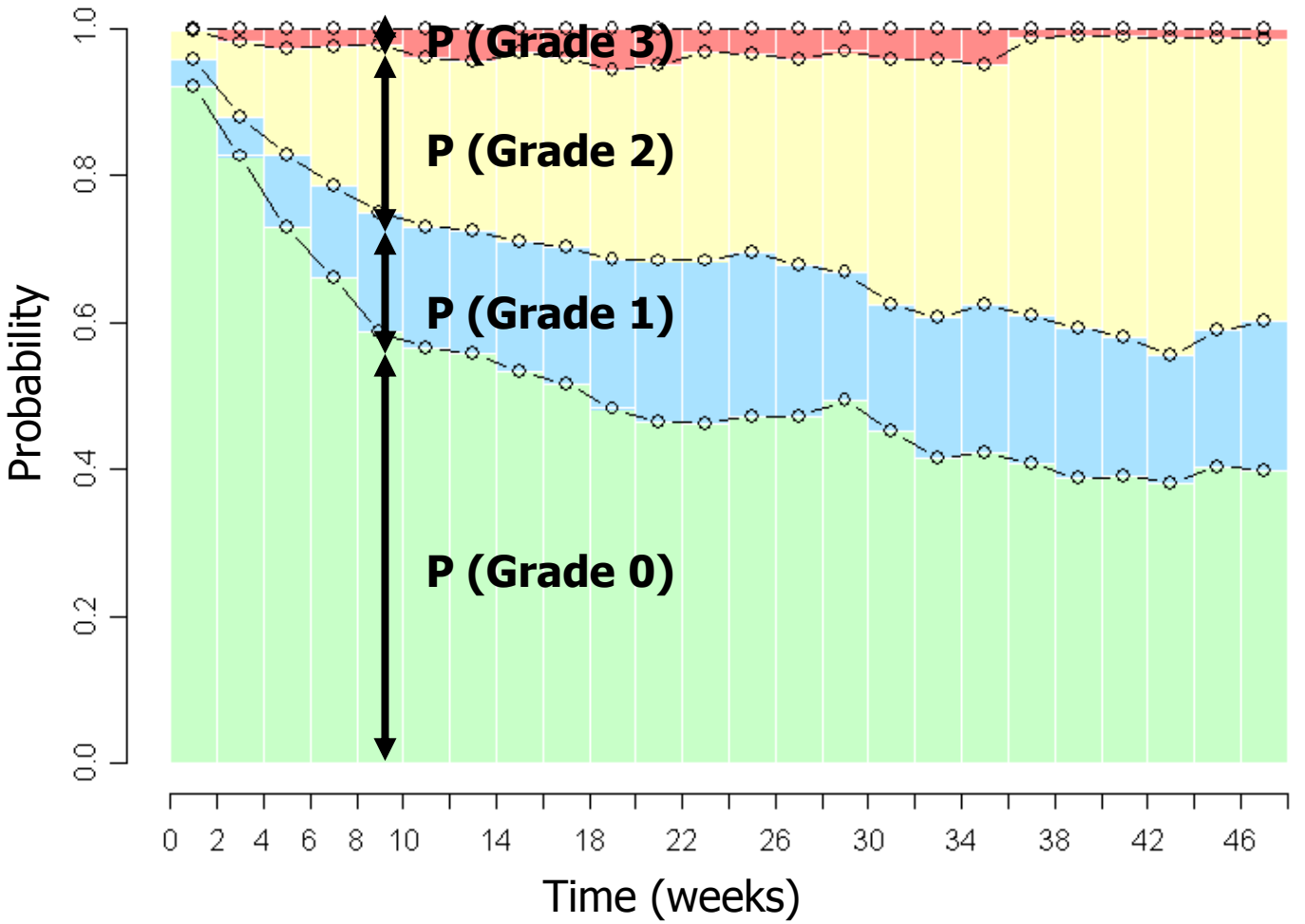
- **5-FU**:
  - inhibitor of cell cycle
  - one of the most used anticancer drugs for the treatment of solid tumors (colorectal, breast) (since 1957)

- **Capecitabine** (Xeloda®, Roche):
  - prodrug of 5-FU taken orally (a blockbuster since 2002)
  - main toxicity: **hand-and-foot syndrome** (54% patients) (redness, peeling, numbness, pain of the skin of palms and soles)

Grade		**0**	**1**	**2**	**3**
Symptoms	**Pain**	None	Tingling or burning	**Pain**	**Severe pain**
	Skin damage	None	Mild redness, swelling; skin intact	Redness, swelling; skin intact	**Blisters, peeling, loss of function**

Evolution of the Hand-and-foot syndrome

600 patients, 2500 mg/m²/day, 1 year



[Hénin *et al.,* A dynamic model of hand-and-foot syndrome in patients receiving capecitabine, *Clin Pharmacol Ther*, *2009]*

Dose adaptation strategies

Standard:

If grade ≥2, treatment stopped until HFS returns to grade ≤1.

Subsequent doses are changed according to the table:

Grade	Occurrences			
	1	2	3	4
2	100%	75%	50%	0
3	75%	50%	0	0

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Alternative:

individualized adaptation according to **model-based prediction** of patient-specific toxicity **risk**

Objectives of this work

Develop an individual prediction-based dose adaptation method using a model for **ordinal** observations that results in **less toxicity** without reducing **efficacy** as compared to the standard dose reductions

Compare its performance to that of the standard practice:

- impact on HFS toxicity
- impact on antitumour efficacy

➔ by randomized ***in silico*** clinical trials

Individual prediction-based dose adaptation

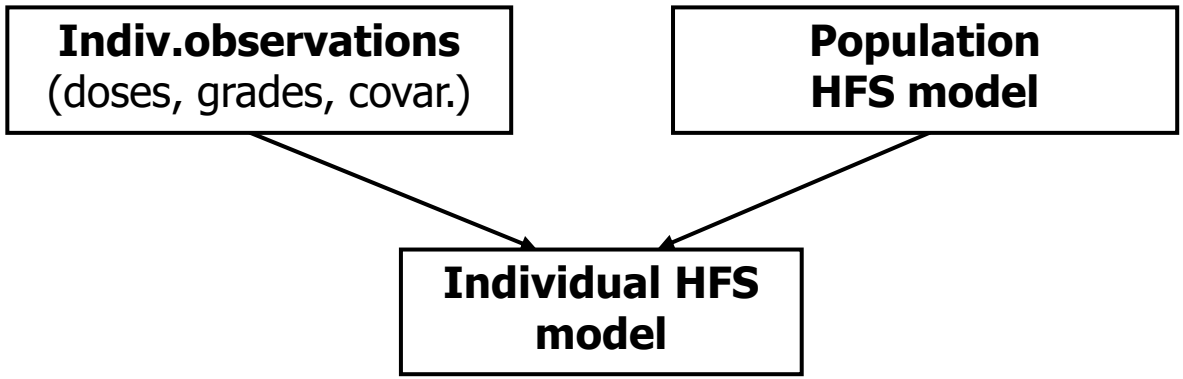
Population
HFS model

Individual prediction-based dose adaptation

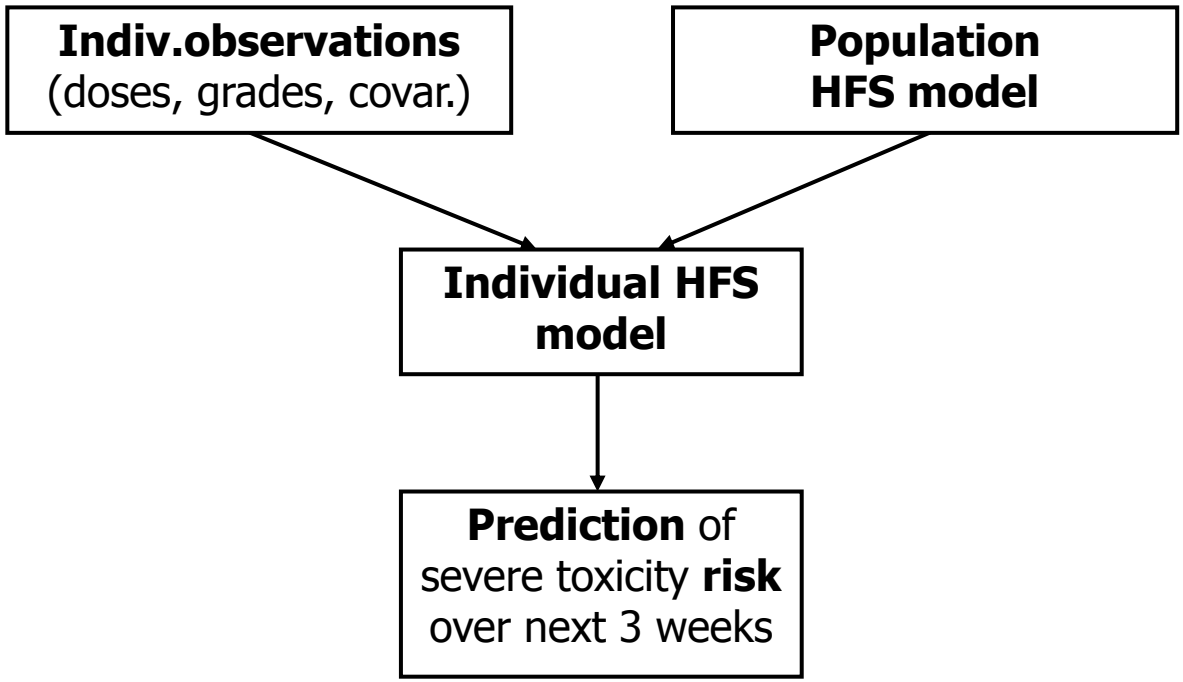
Indiv.observations
(doses, grades, covar.)

Population
HFS model

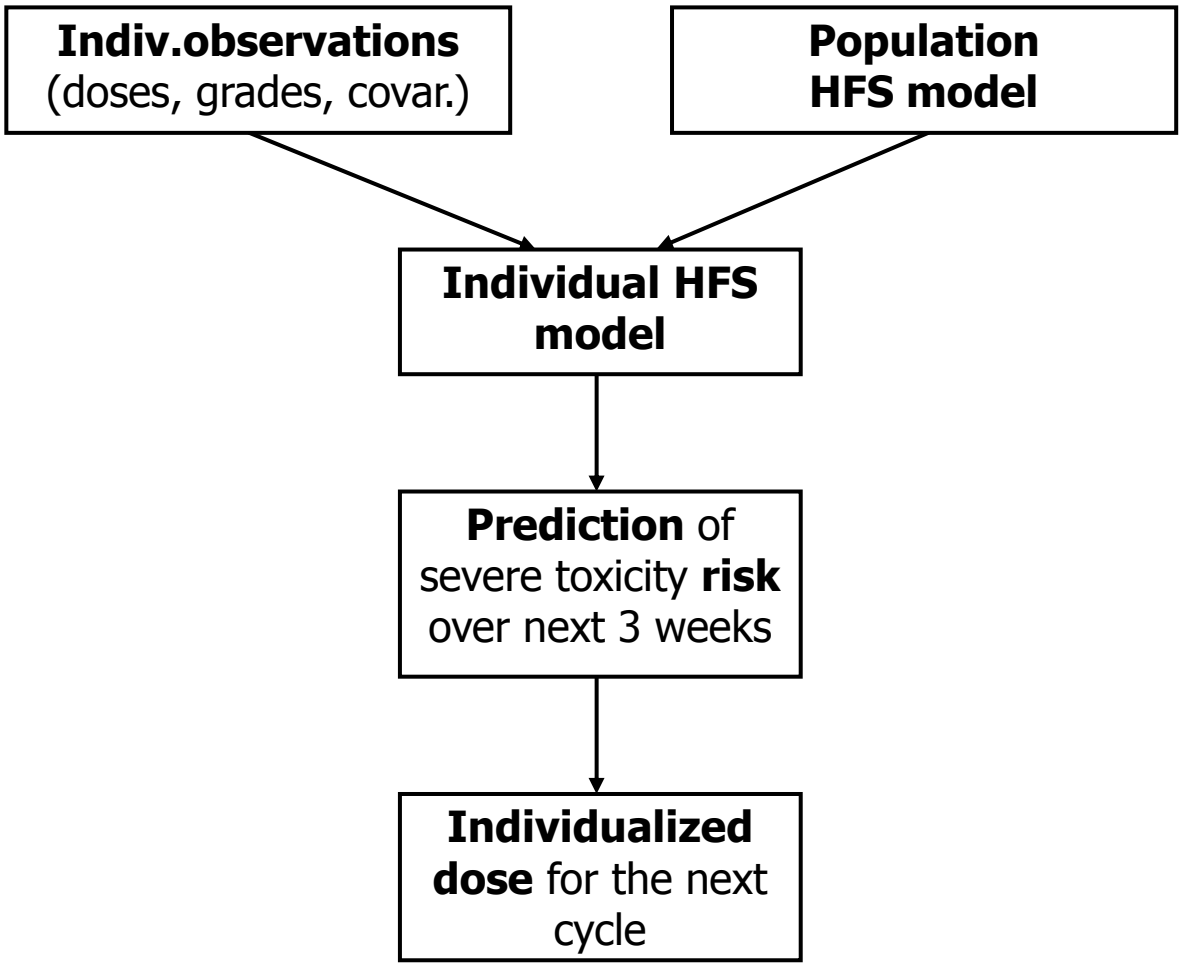
Individual prediction-based dose adaptation



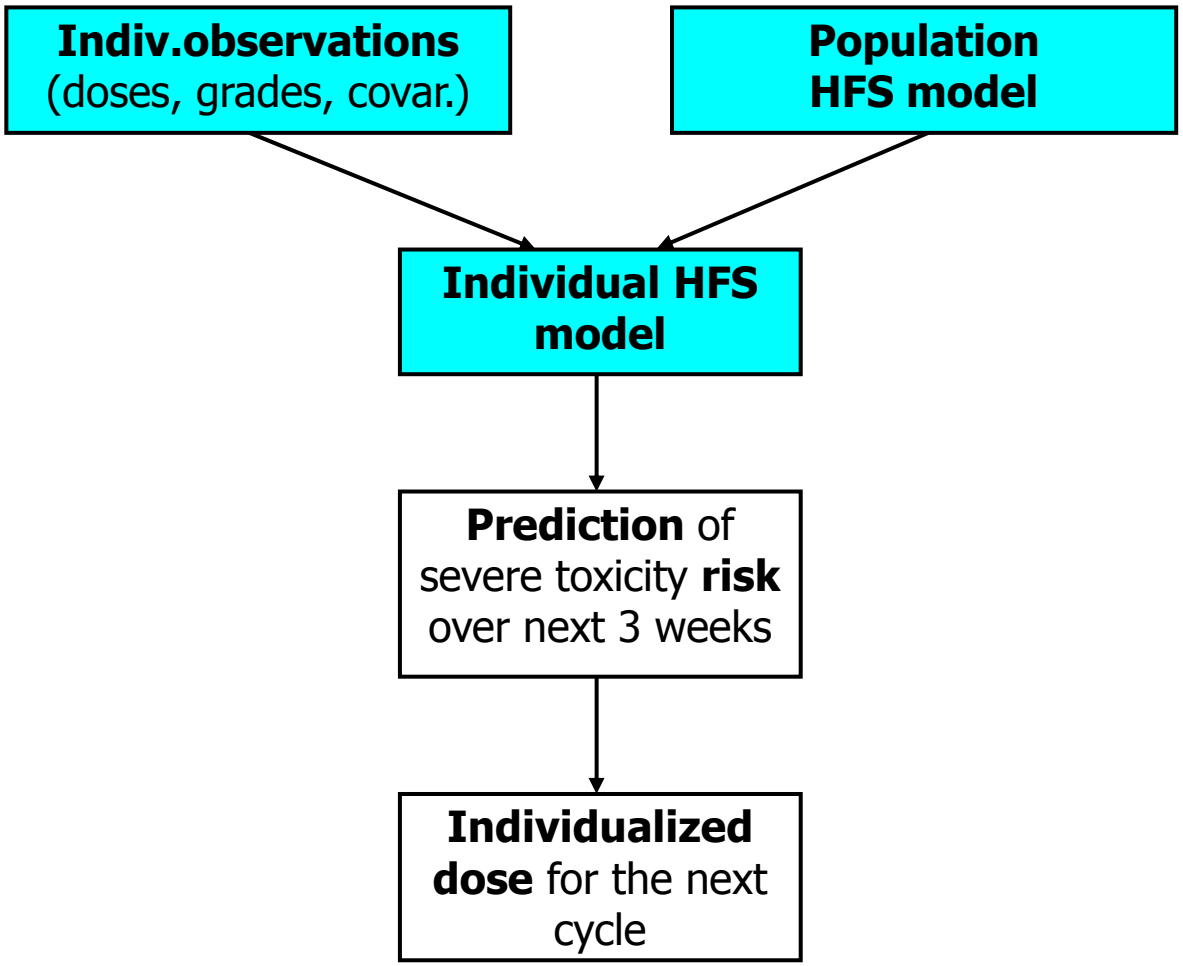
Individual prediction-based dose adaptation



Individual prediction-based dose adaptation

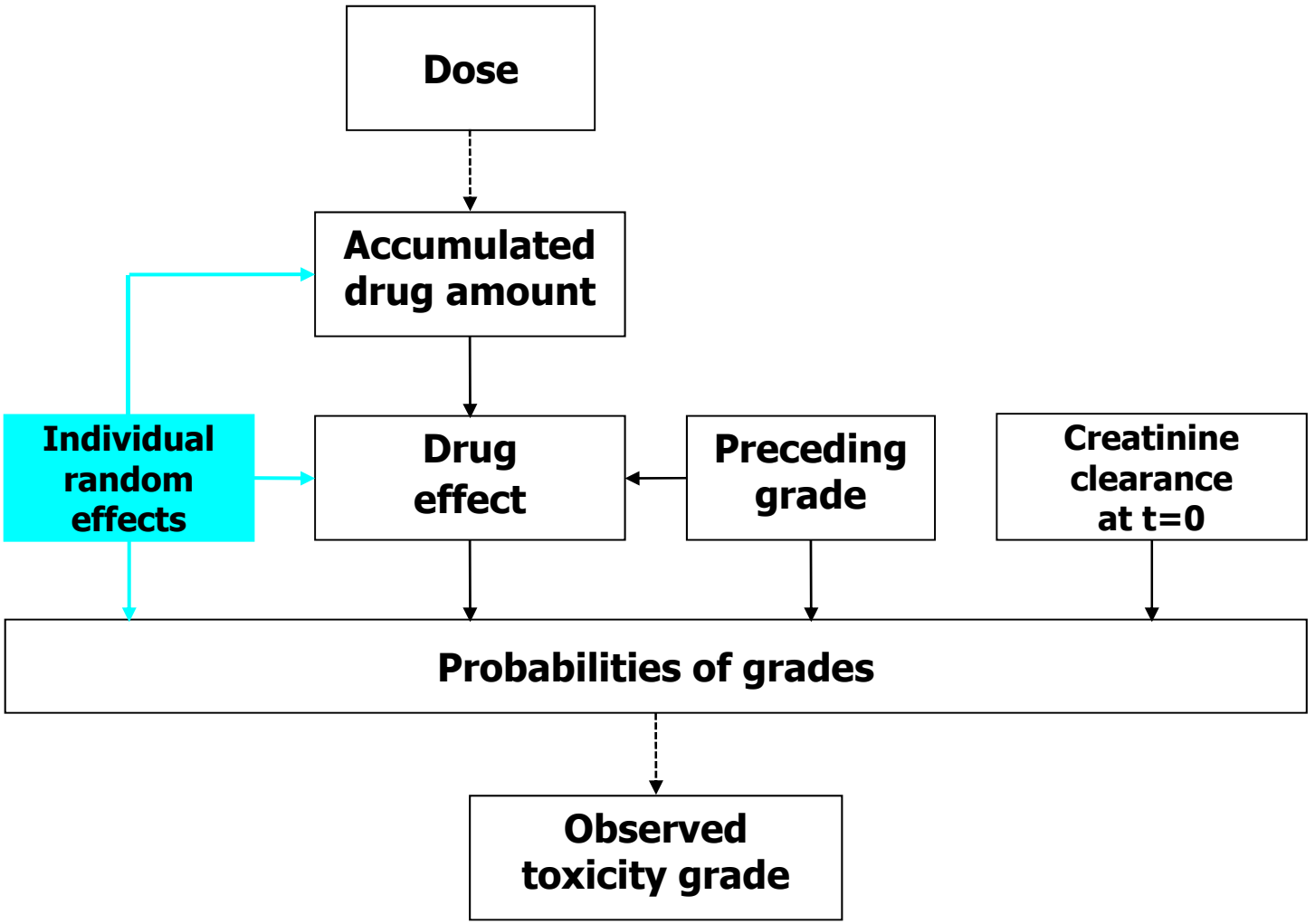


Individual prediction-based dose adaptation

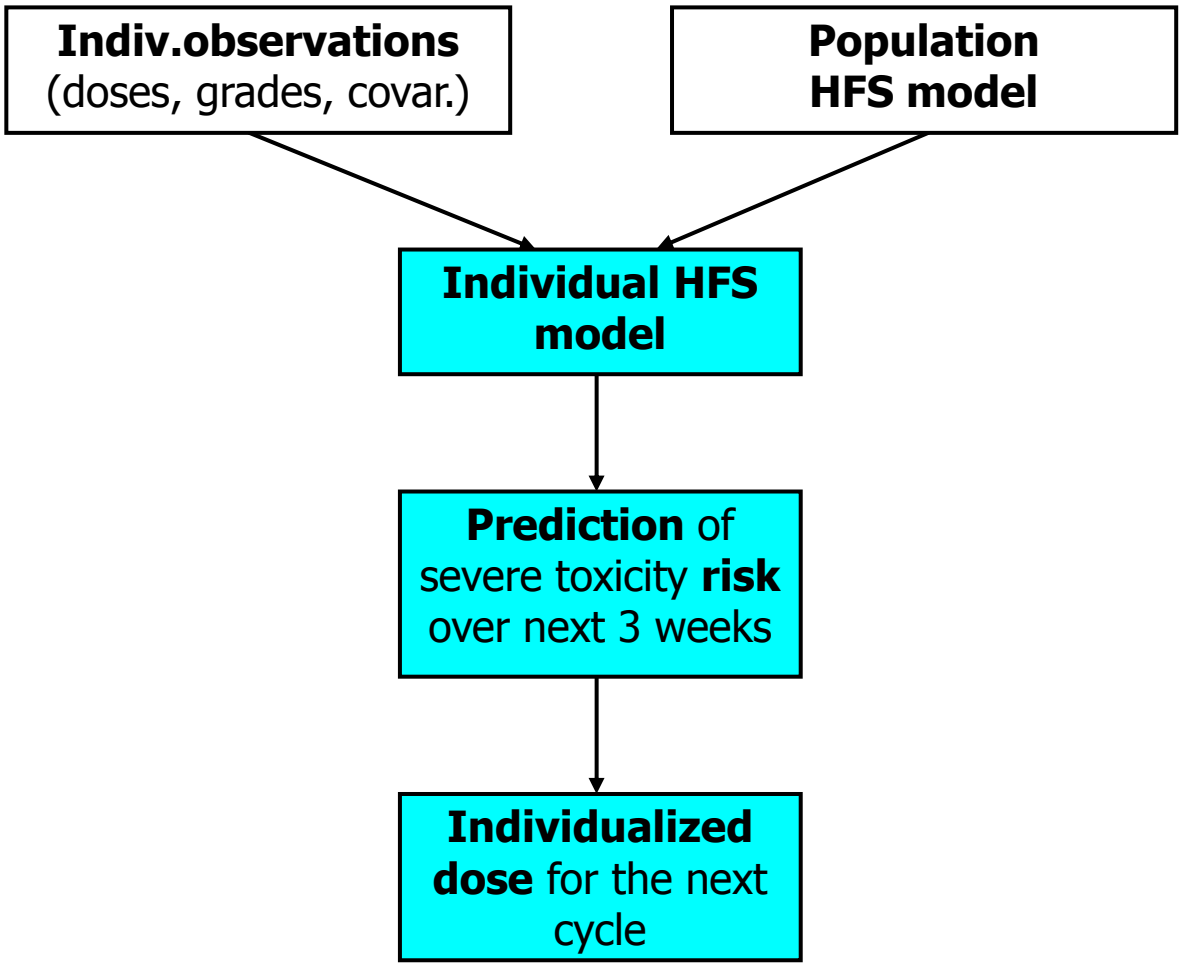


Dose-toxicity model: the principle

[Hénin *et al.,* A dynamic model of hand-and-foot syndrome in patients receiving capecitabine, *Clin Pharmacol Ther*, *2009*]



Individual prediction-based dose adaptation



Dose determination rules

Target:
Average predicted probability of HFS grade ≥2 over next cycle (3 weeks) **≤ Target Risk**

"Individualized" dose:
Daily dose closest to this target,

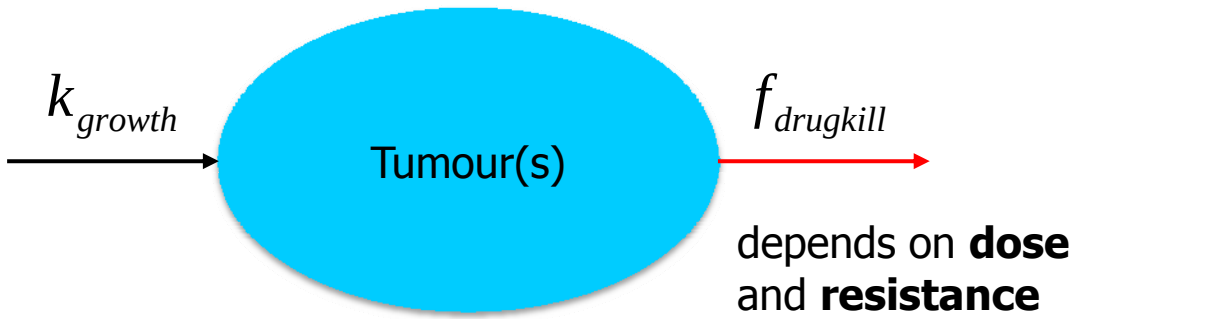
constrained to be at least 50%
and at most 100% or 150% of the nominal dose
(depending on the protocol and HFS history)

The second side of a coin

Reducing the severity and frequency of adverse effects is desirable, but what if the anticancer effect is reduced as well?

→ Need to incorporate a model of **effect on tumours**

Colorectal tumour inhibition model



depends on **dose**
and **resistance**
which develops over time

Tumour(s) measure: sum of largest tumour diameters (mm)

[*Claret et al. J Clin Oncol. 2009 27(25):4103-8*]

In silico clinical trial

3 parallel **arms** according to **dose adaptation** method:

- **Standard**
- **Basic** individual risk prediction-based
- **Advanced** individual risk prediction-based

Common features for all arms:

- **50,000** virtual patients per arm.
- **Dosing regimen**: 2500 mg/m²/day for 2 weeks, 1 week rest.
- Max **30 weeks** (10 cycles of 3 weeks).
- **Interruption** of treatment in case of grade ≥2 HFS, until recovery to grade ≤1.
- Next doses are reduced according to the corresponding protocol.
- Definitive **end of treatment**:
  - if HFS grade ≥2 lasts for more than 6 consecutive weeks,
  - if HFS grade ≥2 appears for the 4th time,
  - if disease progression is observed,
  - if complete response is observed and the patient has received 6 treatment cycles.
- HFS is monitored for 4 weeks after the treatment is ended.

In silico clinical trial: simulation of tumour and HFS observations

- **Covariate** values were simulated from distribution estimated from clinical trial data used to build the corresponding models
- **HFS grade observations** were obtained for **each week** by random sampling according to grade probabilities defined by the model
- **Tumour observations** were obtained **every 6 weeks**

Disease status (similar to RECIST*)	**Criteria**
Partial response (PR)	>30% reduction from baseline
Complete response (CR)	<10 mm
Progressive disease (PD)	>20% and at least 5 mm increase above lowest observed value
Stable disease (SD)	all other cases

*RECIST: Response Evaluation Criteria In Solid Tumours

Dose adaptation protocols

Protocols	Dose reductions	Dose increases	Dose adaptation rule	Dose limits
Standard	After the 2nd occurrence of G≥2	-	-25% after 2nd occurrence of G≥2 -50% after the 3rd 0% after the 4th	[50%, 100%]

Dose adaptation protocols

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Basic prediction-based	After the 1st occurrence of at least G1, if the risk of G≥2 exceeds the TR		Corresponding to predicted average risk of G≥2 over next 3 weeks ≤ **6**%	

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Standard	After the 2nd occurrence of G≥2	-	-25% after 2nd occurrence of G≥2 -50% after the 3rd 0% after the 4th	[50%, 100%]
Basic prediction-based	After the 1st occurrence of at least G1, if the risk of G≥2 exceeds the TR		Corresponding to predicted average risk of G≥2 over next 3 weeks ≤ **6**%	
Advanced prediction-based		If stable disease & no HFS (start after 4 cycles) or if ≥6 weeks in G1 and no G≥2	Corresponding to predicted average risk of G≥2 over next 3 weeks ≤ **4**%	Before G≥2: [50%, 150%] After G≥2: [50%, 100%]

RESULTS:
Performance of adaptation protocols

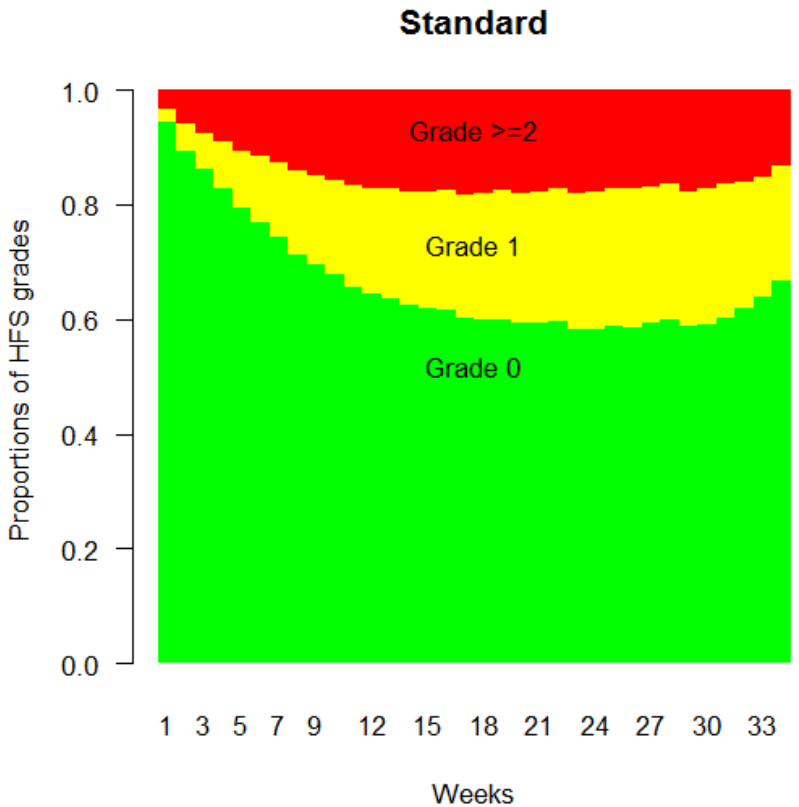
Results: impact on **toxicity**

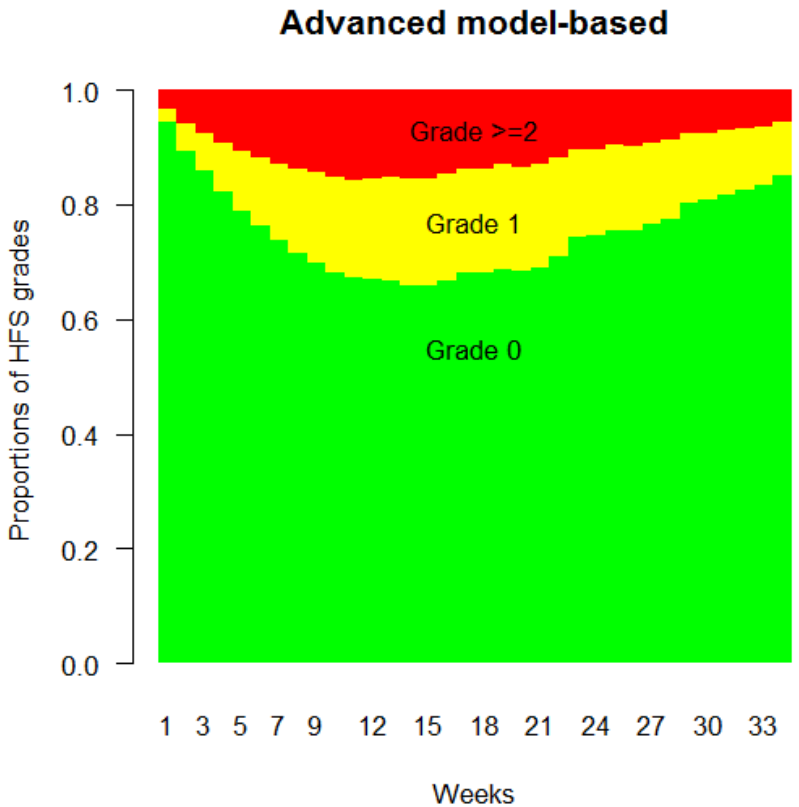
	Number of weeks with G≥2 (all patients / only those having G≥2)	% of patients having G≥2	% of patients having reoccurring events with G≥2	Duration of reoccurring events with G≥2 (weeks)	% of patients who dropout due to HFS
Standard	5.2 / 8.1	55.5%	13.6%	5.7	23.2%
Basic	3.9 / 6.9	55.6%	13.1%	5.4	22.4%
Advanced	3.8 / 6.8	55.2%	12.6%	5.0	21.6%

Results: impact on **efficacy**

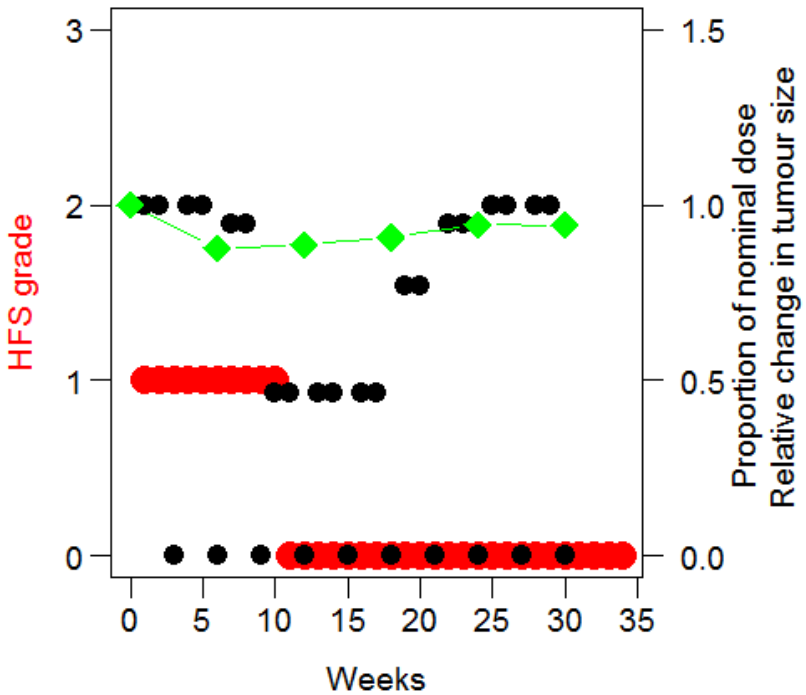
	% of responders	Relative change from baseline (median)	% of patients who have disease progression
Standard	49.2%	-23.3%	31.7%
Basic	49.4%	-23.3%	31.7%
Advanced	49.4%	-23.1%	31.9%

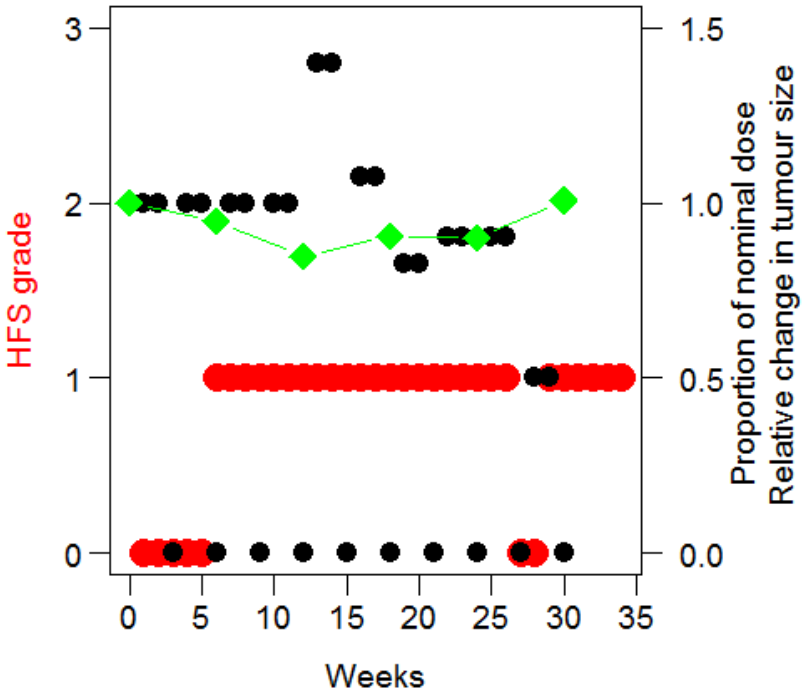
Dynamics of the distributions of the HFS grades





Examples of ”Advanced” method





Tested variations

of prediction-based dose adaptations

- Target risks: 4%, 5%, 6%
- Allowing dose reductions down to 25% of nominal dose
- Allowing dose increases up to 125% of nominal dose
- Time of starting dose increases: after 2 cycles
- Allowing dose increases only if no HFS was observed
- Lower target risk for increases than for reductions
- Lower target risk for reductions if patient has tumour response
  (only if 95th percentile of predicted tumour size at the next scan does not correspond to disease progression)

CONCLUSIONS

about capecitabine dose adaptation results

Individual prediction-based dose adaptation on the basis of **HFS grade** observations was developed and showed to be:

- slightly **superior** in terms of HFS toxicity and
- **equivalent** in terms of efficacy

The benefits on average could be:

- ↘ **10 days** for **duration** (by reducing the frequency and length of reoccurring events with G≥2)
- ↘ 7% for dropouts due to HFS

Obstacles & perspectives for dose adaptation based on **ordinal** variable

Estimates of individual random effects (EBEs) are **poor** due to:

- categorical data being poor in information,
- low identifiability of the dose-toxicity grade relationship (observed values of response-driving variable are too small to identify the toxic effect function well),
- uneven distribution of grades within-subject.

[*Paule et al. Empirical Bayes estimation of random effects of a mixed-effects proportional odds Markov model for ordinal data. Computer Methods and Programs in Biomedicine (in press)*]

However, for this model, poor EBEs did not have a significant impact on the results because the **probabilities** of HFS grades are highly **insensitive to dose changes**

Higher impact of prediction-based dose adaptation based on ordinal variable is expected for **reversible** toxicities with **faster dynamics** (e.g. gastrointestinal)

Acknowledgements

The colleagues from EMR3738 Therapeutic Targeting in Oncology:

Michel Tod, Emilie Hénin, Benoit You, Gilles Freyer, Pascal Girard





NOVARTIS for funding my PhD studies

Roche for providing the capecitabine toxicity data of two Phase III trials

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Thank you!


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Backups

Criteria for comparison of dose adaptation strategies

Concerning **HFS toxicity**:

- Number of weeks with HFS grade ≥2
- % of patients having reoccurring events with G≥2
- Duration of reoccurring events with G≥2
- % of patients who drop out due to HFS

Concerning **anticancer effect**:

- % of patient having tumour response
- % of patients who have progression of disease (→dropout due to lack of efficacy)
- Relative change from baseline of tumour sizes

Statistical power analysis

100 replications of trials with

- 300 patients per arm
- 350 patients per arm
- 600 patients per arm

Wilcoxon rank sum test used to test the difference in **severe toxicity duration**

CONCLUSION:
350 patients per arm would be needed for a clinical trial to achieve at least **90%** statistical power to demonstrate a difference in severe HFS duration at **α=0.05**.

Population dose-toxicity model

mixed-effects transitional proportional odds model for ordinal data

$$\frac{dQ}{dt} = Dose - K_i \cdot Q, \qquad K_i = K \cdot e^{\eta_{1i}}$$

$$\text{logit}[P(Y_{it} \le 0 \mid Y_{it-1} = G^*)] = B_0^* - \frac{E_{MAX}^* \cdot (Q_{it} \cdot K_i)}{ED_{50} + (Q_{it} \cdot K_i)} + (CLcr_i - 75.5) \cdot \theta_{CLcr} + \eta_{2i}$$

$$\text{logit}[P(Y_{it} \le 1 \mid Y_{it-1} = G^*)] = B_0^* + B_1^* - \frac{E_{MAX}^* \cdot (Q_{it} \cdot K_i)}{ED_{50} + (Q_{it} \cdot K_i)} + (CLcr_i - 75.5) \cdot \theta_{CLcr} + \eta_{2i}$$

$$P(Y_{it} \le C \mid Y_{it-1} = C^*) = \frac{\exp(\text{logit})}{1 + \exp(\text{logit})}$$

$$p_{it0} = P(Y_{it} = 0) = P(Y_{it} \le 0)$$

$$p_{it1} = P(Y_{it} = 1) = P(Y_{it} \le 1) - P(Y_{it} \le 0)$$

$$p_{it1} = P(Y_{it} = 2) = P(Y_{it} \le 2) - P(Y_{it} \le 1) = 1 - P(Y_{it} \le 1)$$

a priori **information:** $\Theta = (B_0^0, B_0^1, B_0^2, B_1^0, B_1^1, B_1^2, E_{MAX}^0, E_{MAX}^1, E_{MAX}^2, ED_{50}, K, \theta_{CLcr})$

$$\begin{pmatrix} \eta_1 \\ \eta_2 \end{pmatrix} \sim N(0, \Omega), \qquad \Omega = \begin{bmatrix} \omega_1^2 & \omega_{12} \\ \omega_{12} & \omega_2^2 \end{bmatrix}$$

[*Henin et al. Clin Pharmacol Ther. 2009 85(4):418-25*]

In silico clinical trial: doses

- Capecitabine is available in tablets of **150** mg and **500** mg
- Daily doses are **rounded** to values recommended in prescription guidelines (so that even amounts can be taken in the morning and in the evening) :

  3000, 3300, 3600, 4000, **…** , 5600 mg

  (+ reduced doses: 1000, 1300, …)
- Both models assume that dosing is **2500mg/BSA once a day** (the real dosing is 1250mg/BSA twice a day)

In silico clinical trial: simulation of Hand-and-foot syndrome

- **Basal creatinine clearance** simulated from a lognormal distribution, restricted to be in [27, 219]
  (logCLcr ~ N(mean = 4.34, SD = 0.349), CLcr = exp(logCLcr))
- **BSA** simulated from a normal distribution, restricted to be in [1.19, 2.5]
  (mean = 1.82, SD = 0.227)
- **Individual ETA** values are simulated from a bivariate normal distribution as reported for the HFS model
- **HFS grade observations** are obtained for **each week** by random sampling according to grade probabilities defined by the model

In silico clinical trial: simulation of tumour size and disease status

- **Baselines** simulated from a lognormal distribution, restr. to min 10 mm

  logbase ~ N(mean=4.25, SD=0.5), baseline = exp(logbase)

- **Observations every 6 weeks**,

  with an assumed proportional measurement error:
  observation = true value * exp (error),

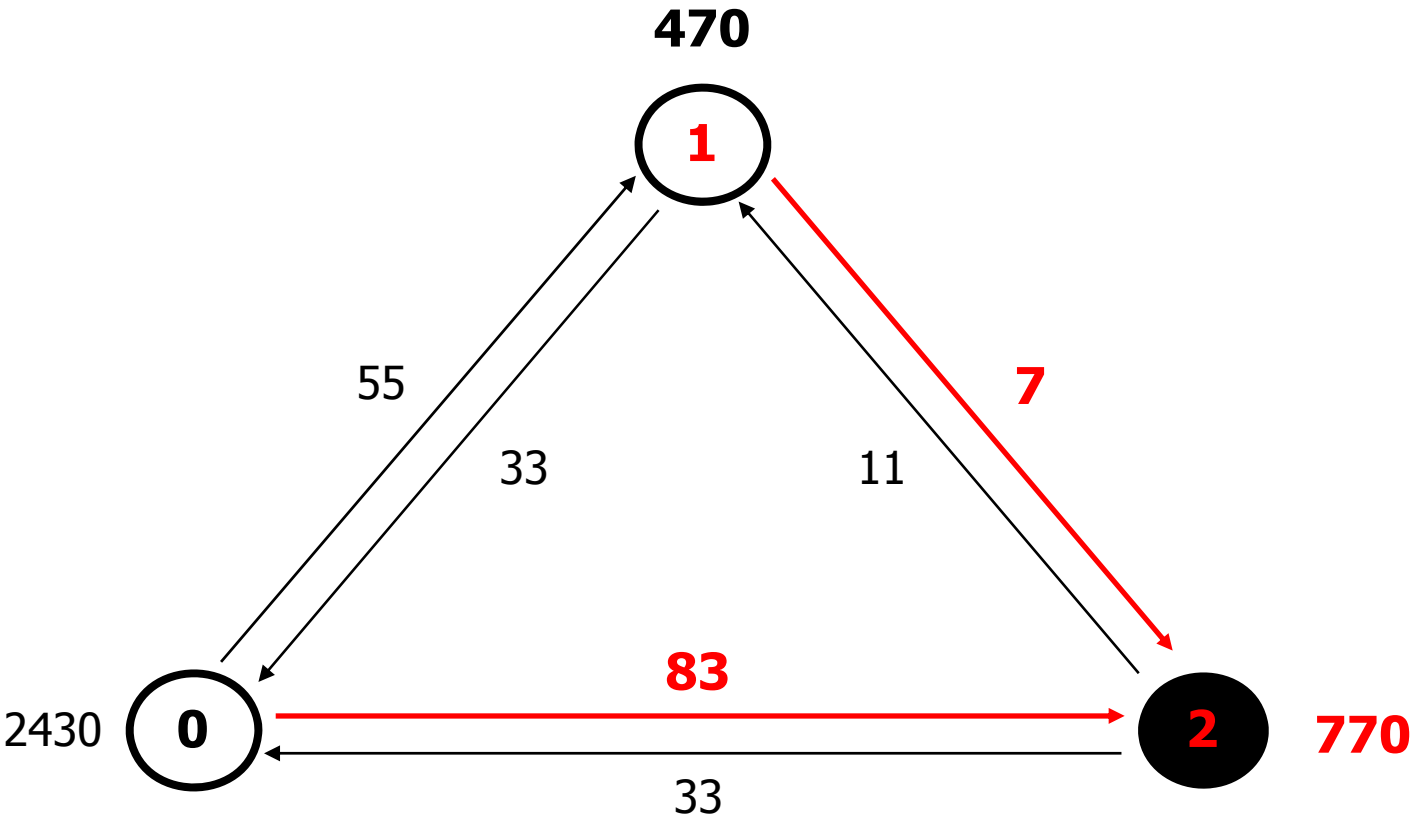
  error ~ N(mean=0, SD=0.025)

Disease status (similar to RECIST*)	**Criteria**
Partial response (PR)	>30% reduction from baseline
Complete response (CR)	<10 mm
Progressive disease (PD)	>20% and at least 5 mm increase above lowest observed value
Stable disease (SD)	all other cases

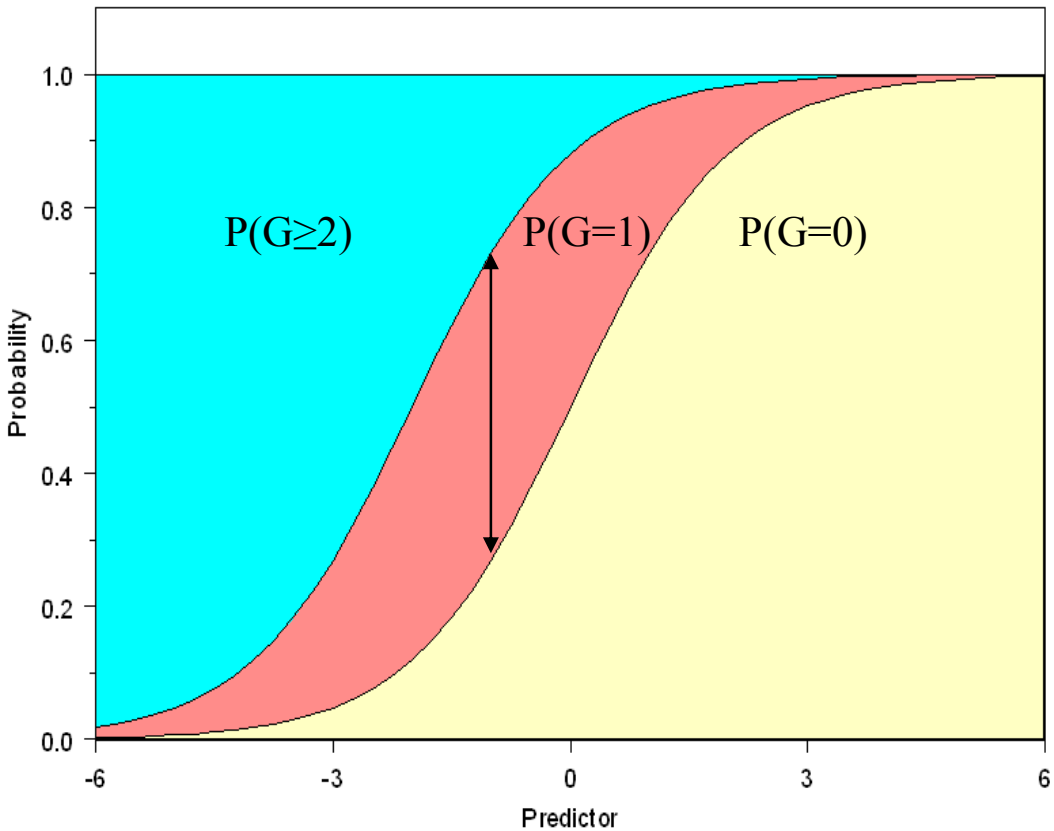
*RECIST: Response Evaluation Criteria In Solid Tumours

Transitions between grades (once a week)

(600 patients)

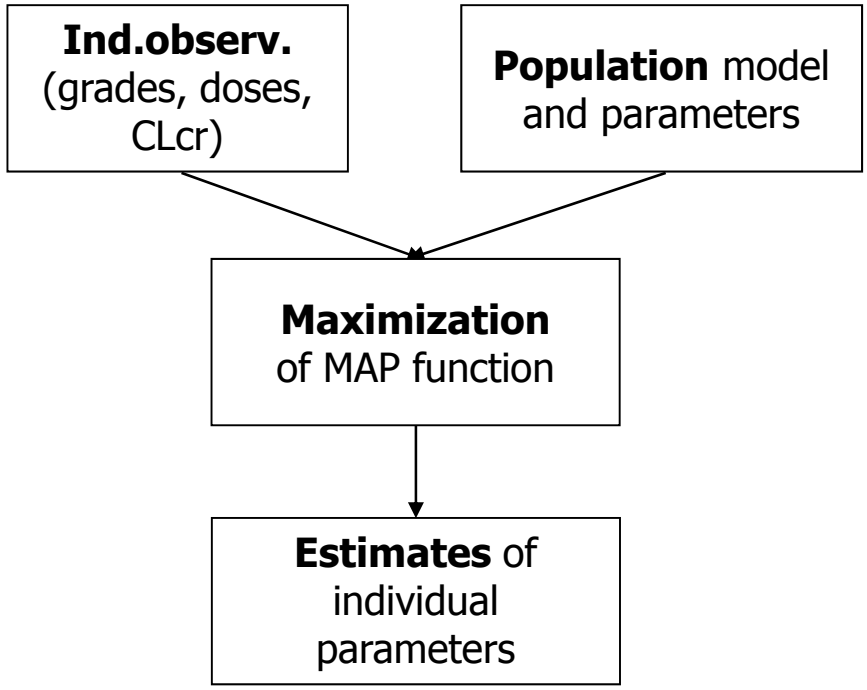


Grade probabilities



Estimation of individual random parameters

Bayesian estimation approach ***Maximum A Posteriori*** (MAP)
is used for estimation of individual parameters
on the basis of individual's observed data and population model



Estimation of individual random parameters

Implementation of the **MAP method**:

$$\hat{\eta}_{iMAP}(H_{it}) = Arg\left[\max_{\eta_i} \frac{p(\eta_i)\cdot p(H_{it}\left|D_{it}, H_{it-1}, CLcr_i, \Theta, \eta_i\right.)}{p(H_{it})}\right]$$

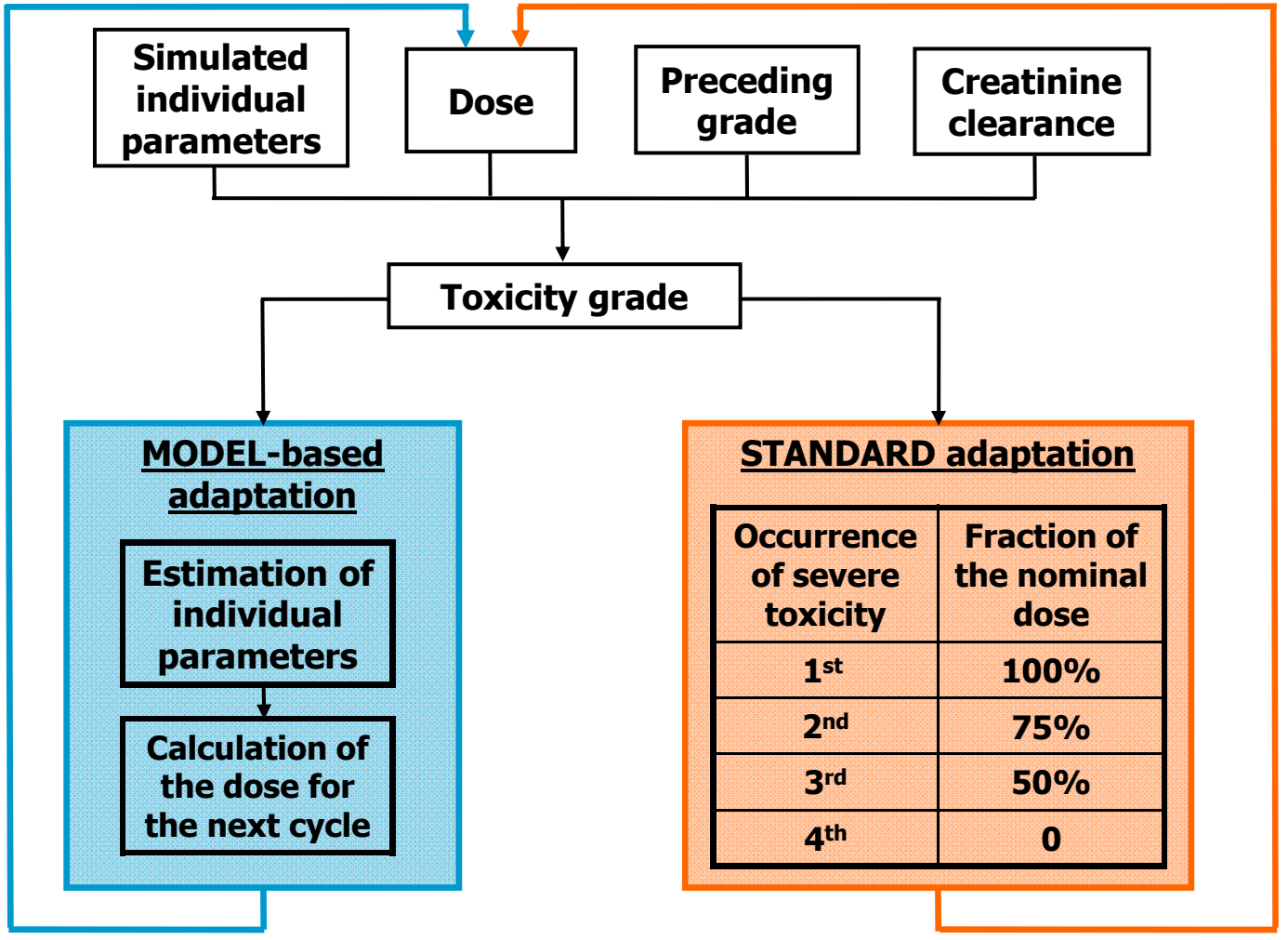
Likelihood (of **ordinal** observations):

$$p(H_{it}\left|D_{it}, H_{it-1}, CLcr_i, \Theta, \eta_i\right.) = \prod_{j=1}^{t}\prod_{g=0}^{2} p_{ijg}^{y_{ijg}}$$

$$y_{itg} = \begin{cases} 1, \text{ if } Y_{it} = G, \\ 0, \text{ otherwise;} \end{cases} \quad \text{where } G = \{0, 1, \geq 2\}$$

Maximization by Simplex

Simulation of the trial



Colorectal tumour inhibition model

$$\frac{dy(t)}{dt} = k_{growth} \cdot e^{\eta_1} \cdot y(t) - dose(t) \cdot k_{drugkill} \cdot e^{\eta_2} \cdot e^{-\lambda \cdot e^{\eta_3} \cdot t} \cdot y(t)$$

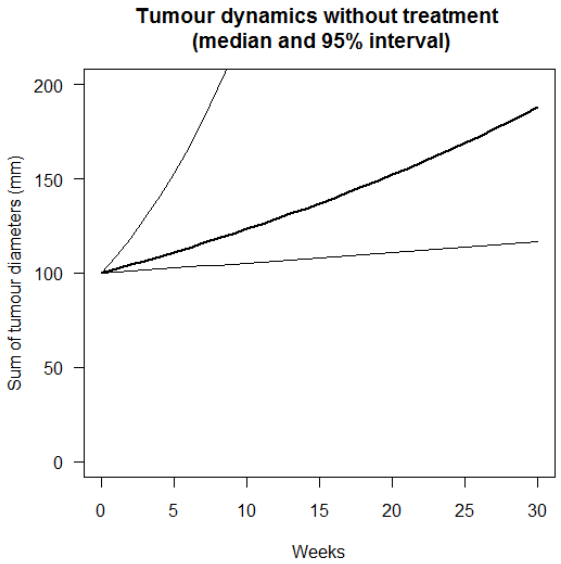
y(t) – sum of largest tumour diameters (mm), time is weeks

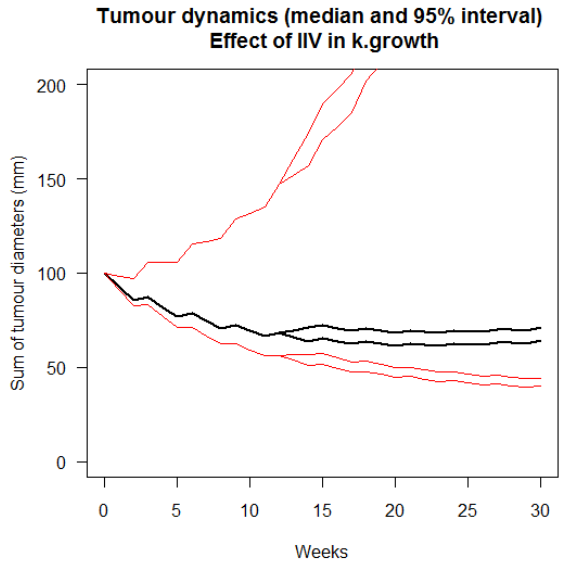
	TV	CV
k_{growth}	0.021	80%
$k_{drugkill}$	0.025	69%
λ	0.053	159%

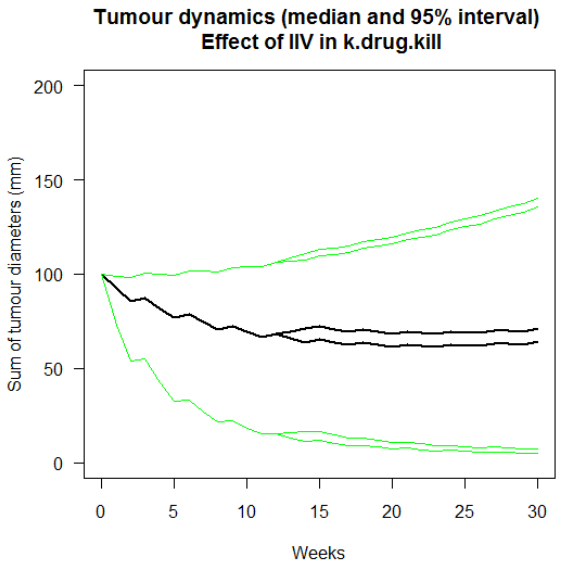
$$\sqrt{\sigma} = 11.83\ (mm)$$

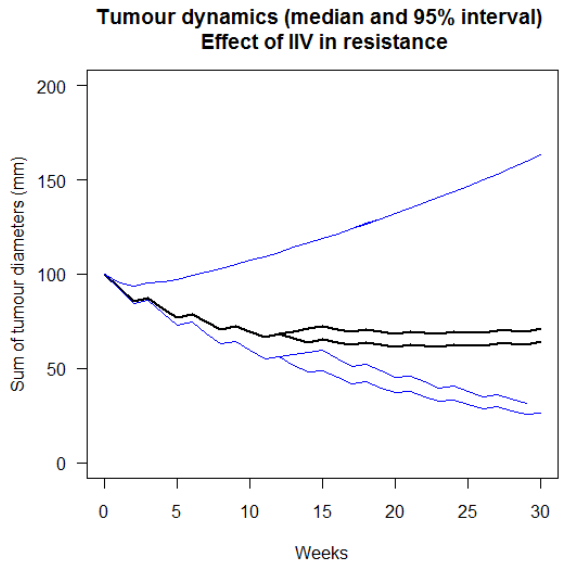
[*Claret et al. J Clin Oncol. 2009 27(25):4103-8*]

Simulated tumour dynamics









Results of ”Advanced” method if true ETAs or population values were used

	Number of weeks with G≥2 (all patients / only those having G≥2)	% of patients having G≥2	% of patients having reoccurring events with G≥2	Duration of reoccurring events with G≥2 (weeks)	% of patients who dropout due to HFS	% of responders	Relative change from baseline (median)	% of patients who have disease progression
Advanced EBE	3.8 / 6.8	55.2%	12.6%	5.0	21.6%	49.4%	-23.1%	31.9%
Advanced True ETAs	3.7 / 6.6	55.0%	12.5%	4.8	20.5%	49.1%	-22.1%	33.0%
Advanced No ETAs	3.8 / 6.8	55.1%	12.4%	5.2	22.0%	48.9%	-22.0%	33.3%

PPC for transitions