Model-based optimization of rituximab dosing regimen in follicular non-Hodgkin lymphoma

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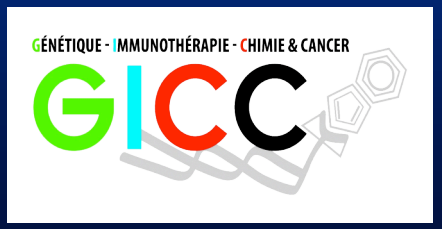


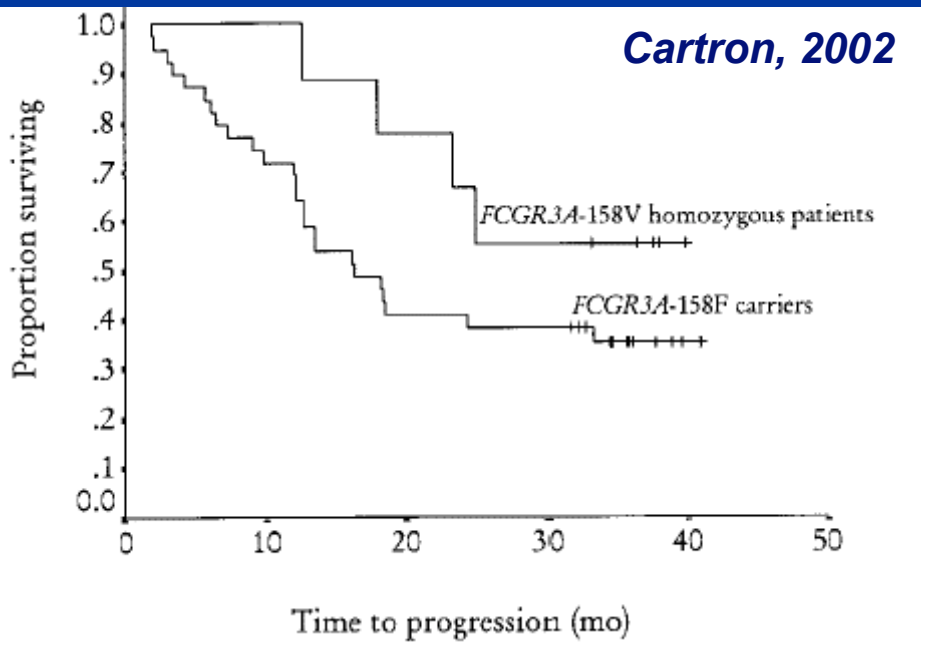
Introduction

- **Rituximab in follicular lymphoma**
  - Rituximab : Monoclonal antibody targeted against human CD20
  - Large variability of concentration-effect relationship due to:
    - Pharmacokinetic variability : efficacy ↗ for concentrations ↗
    - *FCGR3A* polymorphism: ***Progression-free survival (PFS) FCGR3A-VV > F carriers***

    (*Igarashi et al. 2002*)
    - Proportions VV (15%) – Fx (85%)

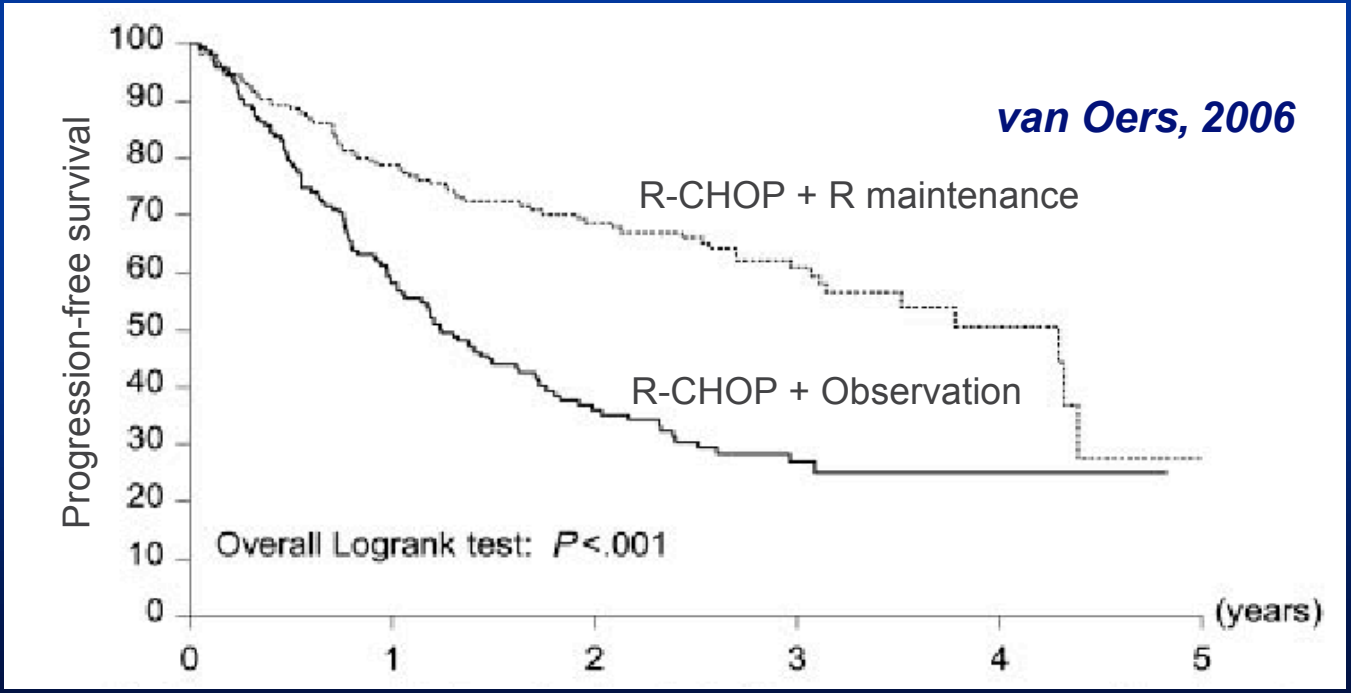
    (*Lejeune et al. 2009*)

Cartron, 2002



Introduction

- **Initial dosing regimen : induction treatment by 4 weekly 375 mg/m² injections**
- **↗ number of injections, maintenance treatment: ↗ PFS**



Introduction

- **The dosing regimen may be optimized:**
  - Increasing infusion dose
  - Adjusting dosing regimen according to *FCGR3A* genotype
  - But not confirmed by specific studies

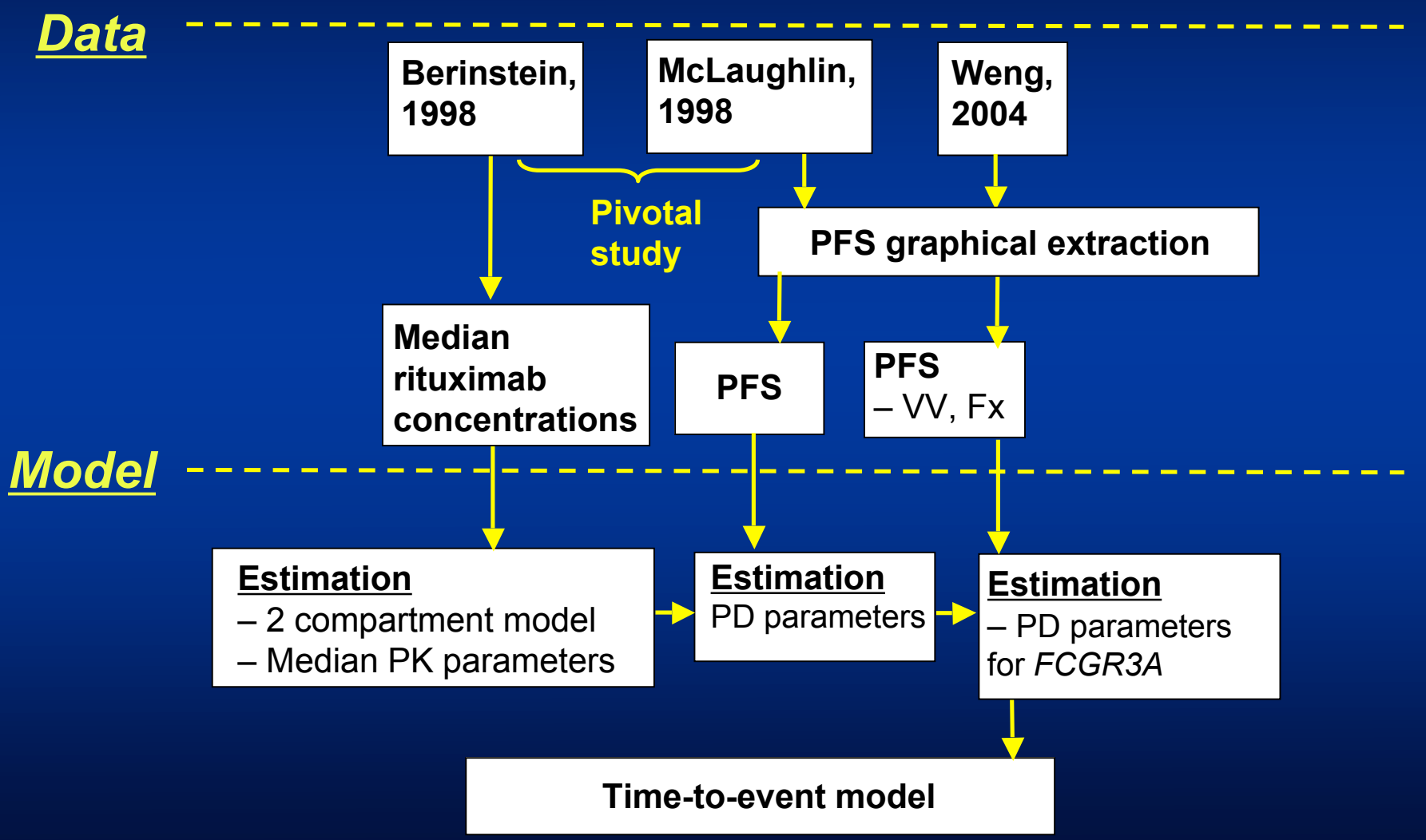
→ **Clinical trial simulation**

But… No PK-PD study of rituximab in FL

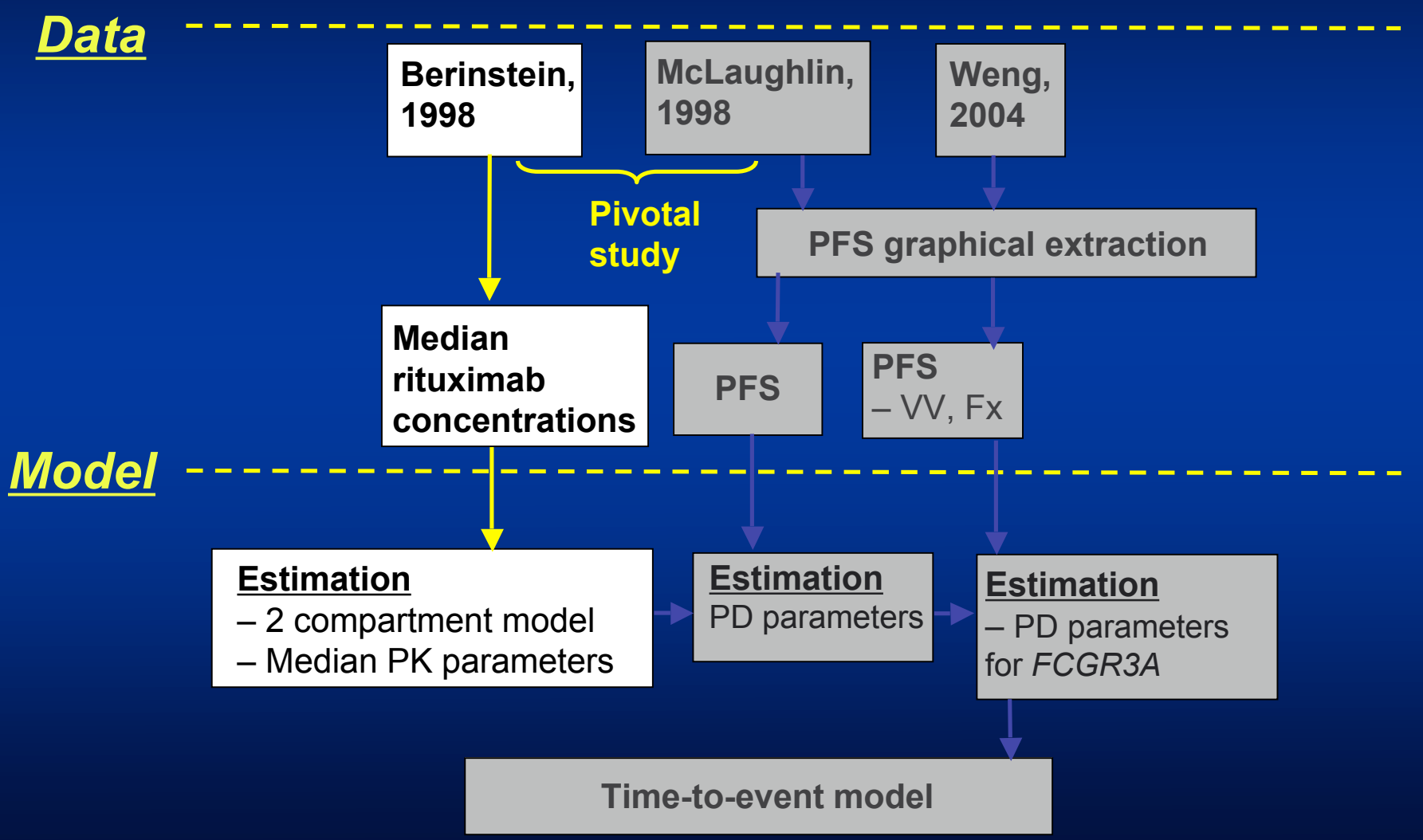
Objectives

- **Build and evaluate a dose – efficacy model of rituximab in follicular lymphoma**
  - Using data from literature
  - Considering *FCGR3A* genotype
- **Simulate dose – efficacy relationship for several dosing regimens**

Model building

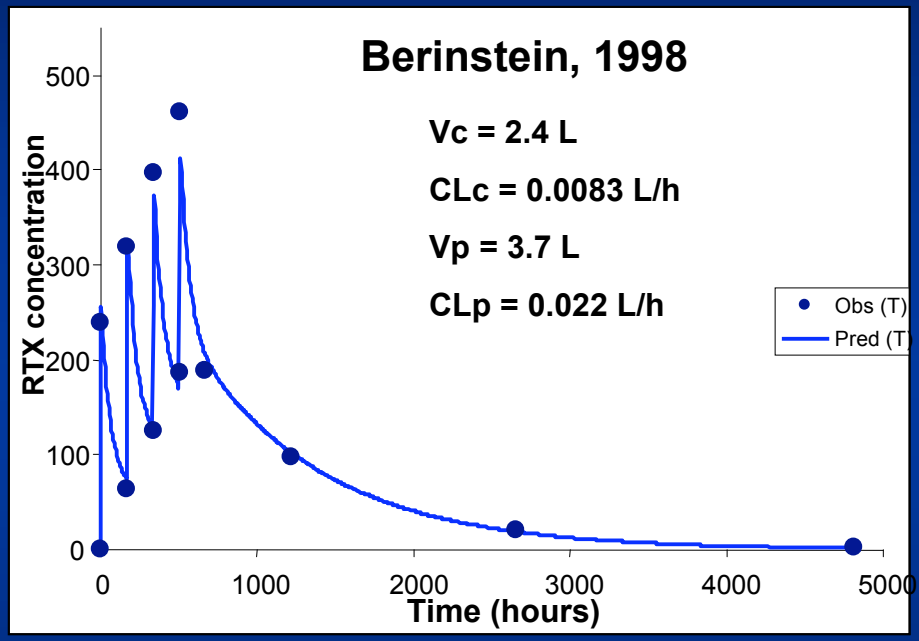


Model building

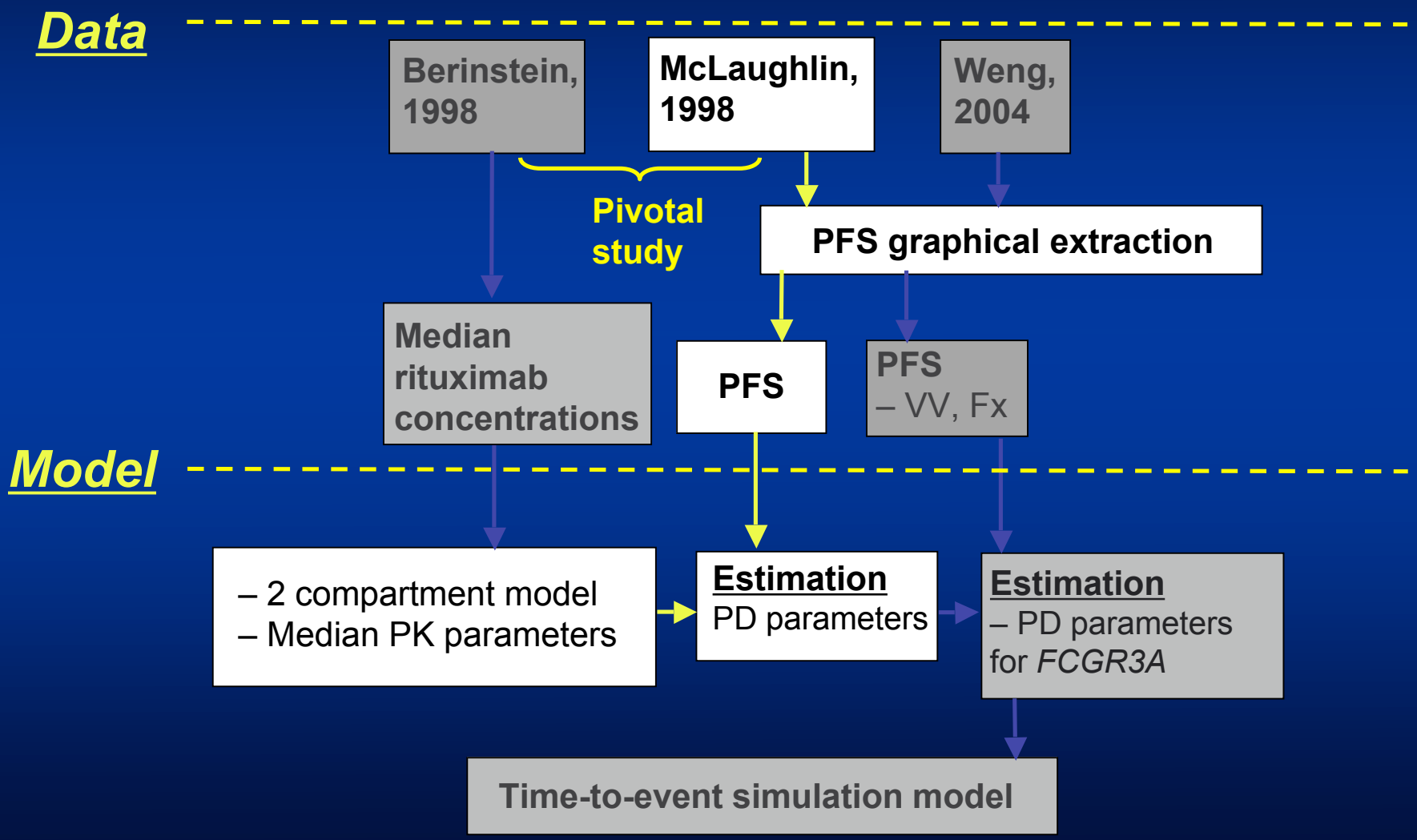


Pharmacokinetic model

- **Median concentrations of Berinstein et al.**
- **2-compartment model**
- **Median PK parameters**
- ***Winnonlin Professional 4.1***



Time-to-event model



Time-to-event model

$$PFS(t) = \exp(-\lambda \cdot t)$$

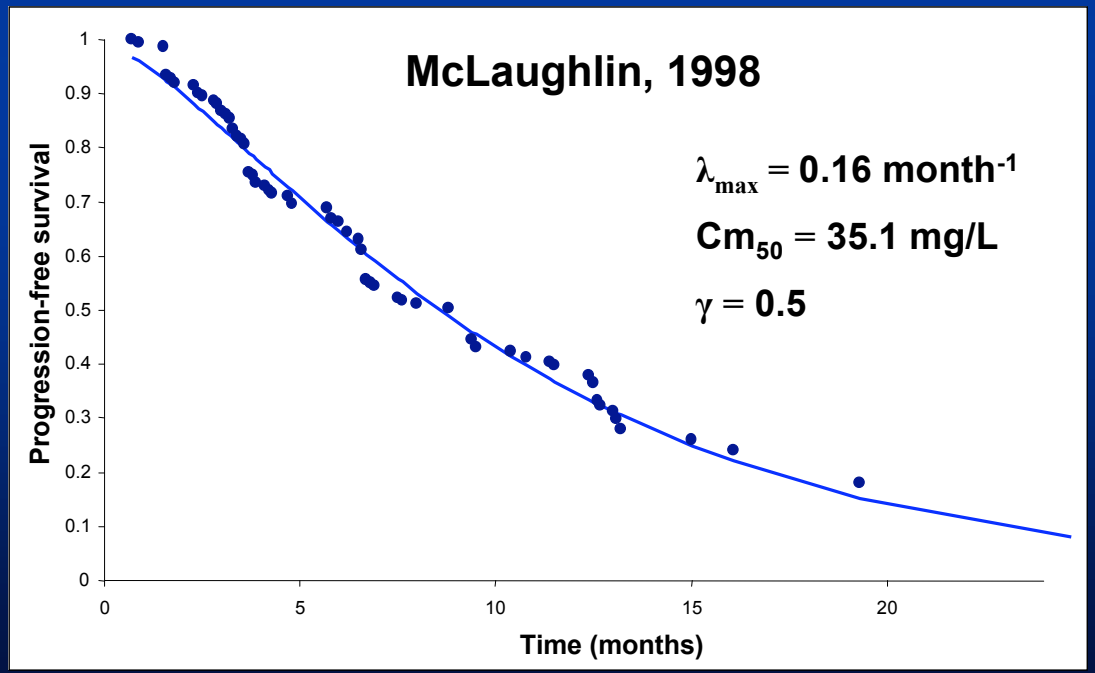
$$\lambda = \lambda_{max} \cdot \left(1 - \frac{Cm^{\gamma}}{Cm_{50}^{\gamma} + Cm^{\gamma}}\right)$$

$$Cm_{t_n - t} = \frac{AUC_{t_n - t}}{t_n - t} = \frac{\int_{t_n}^{t} C(\tau)\, d\tau}{t_n - t}$$

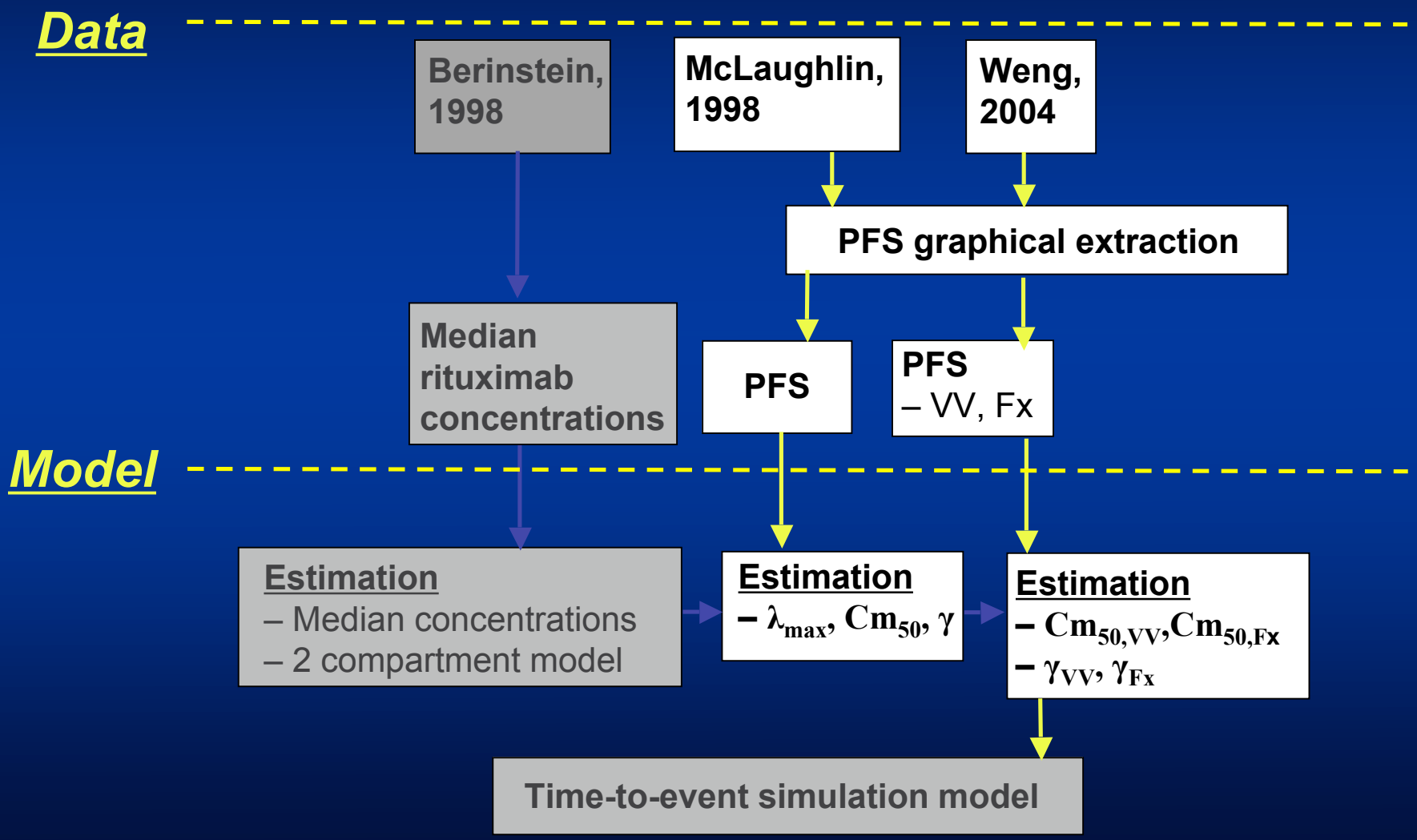
- λ : hazard function
- λ_{max} : maximum hazard (no rituximab efficacy)
- Cm : mean-time concentration
- Cm_{50} : Cm leading to 50% of λ_{max}
- γ : shape factor

Time-to-event model

- **Time-to-event model: parameter estimation**
  - Cm_{50}, γ: estimated
    - Median pharmacokinetics (Cm, *Berinstein, 1998*)
    - PFS (*McLaughlin, 1998*)



Influence of *FCGR3A*



Influence of *FCGR3A*

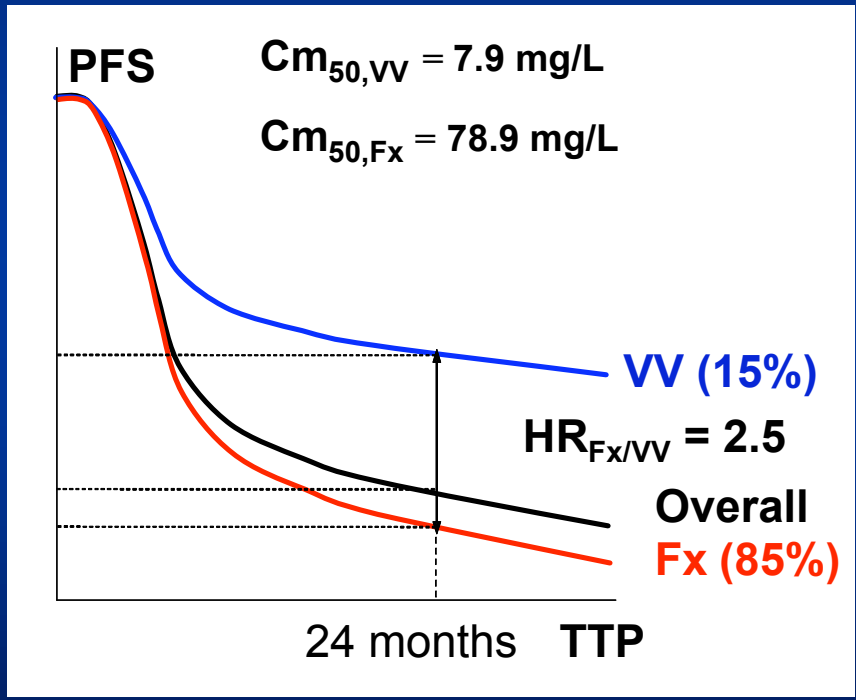
- γ values for VV and Fx were fixed:
  $\gamma_{Fx} = \gamma = 0.5.\ \ \gamma_{VV} = 2$
- Estimation of $Cm_{50,VV}$ and $Cm_{50,Fx}$
  - PFS_{VV} and PFS_{Fx} (24 months) *Weng, 2004.*
    $HR_{Fx/VV} = 2.5$
  - *McLaughlin, 1998:*

$$\lambda_{Fx,M24} = \hat{\lambda}_{M24} \times HR_{Fx/VV}^{\,1-0.85}$$

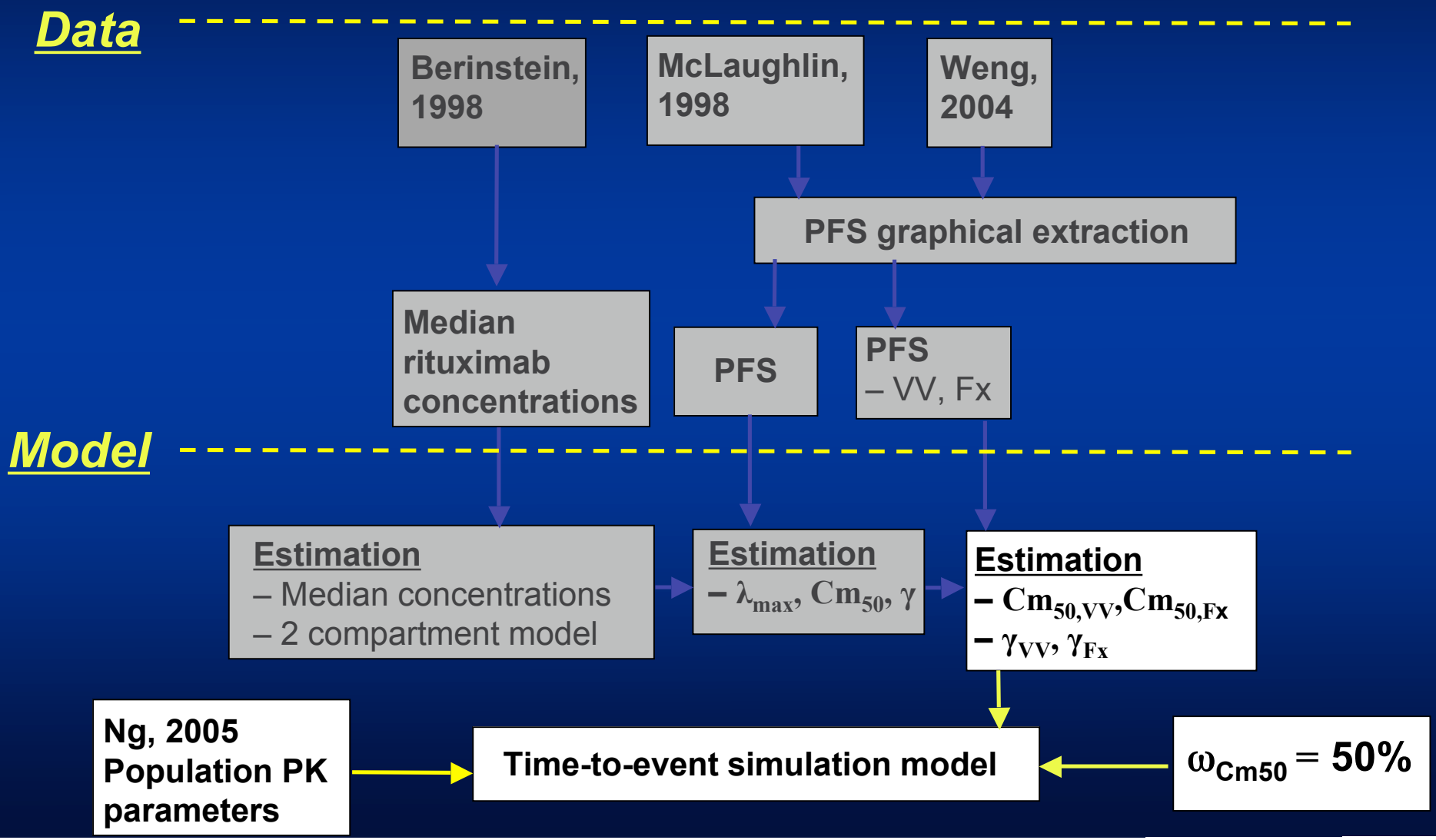
$$\lambda_{VV,M24} = \hat{\lambda}_{M24} / HR_{Fx/VV}^{\,1-0.15}$$

  - Then calculation of $Cm_{50,VV}$ and $Cm_{50,Fx}$ by solving the equations:

$$\boldsymbol{PFS_{genotype}(24M) = f(Cm_{50,genotype})}$$



Simulation model

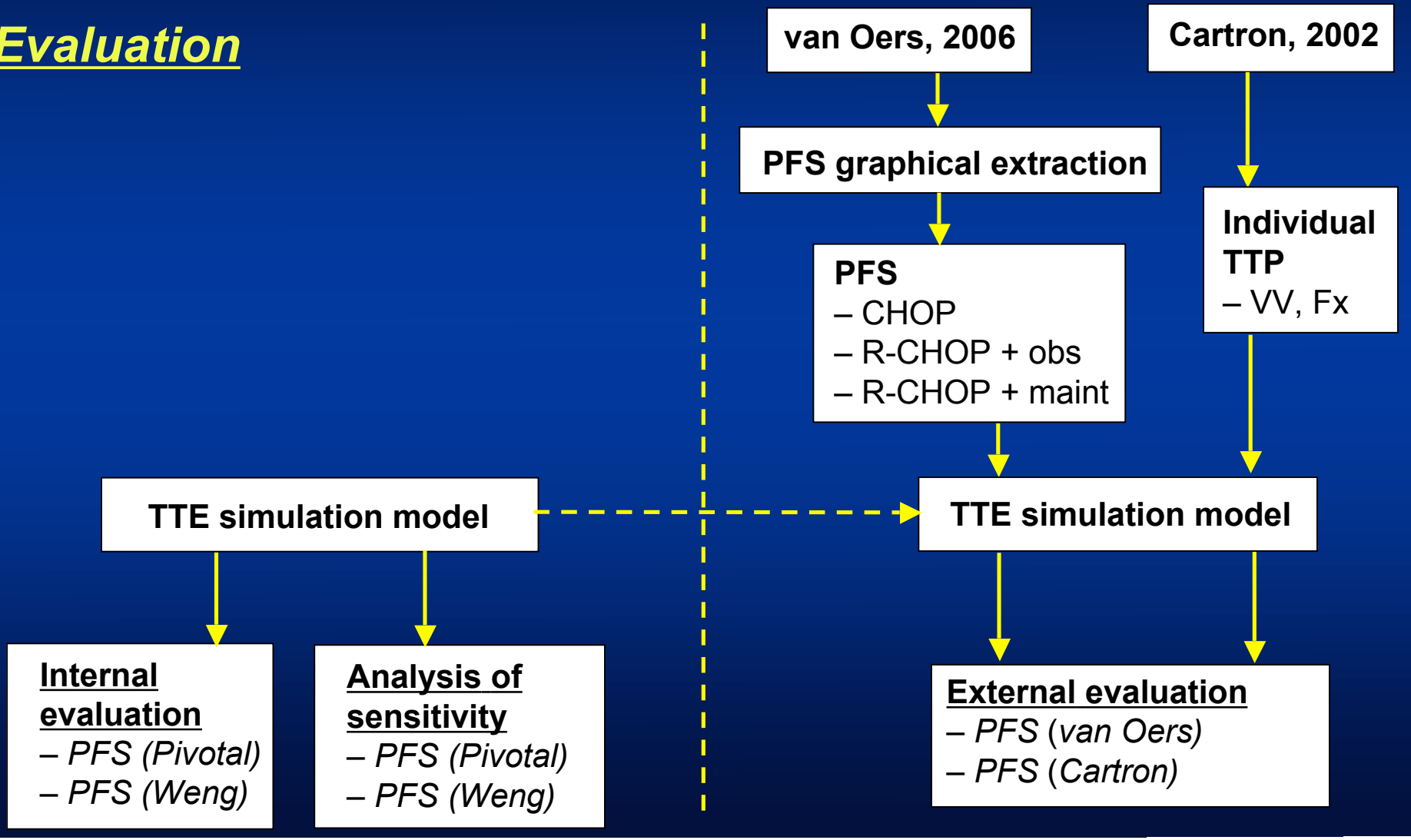


Simulation model

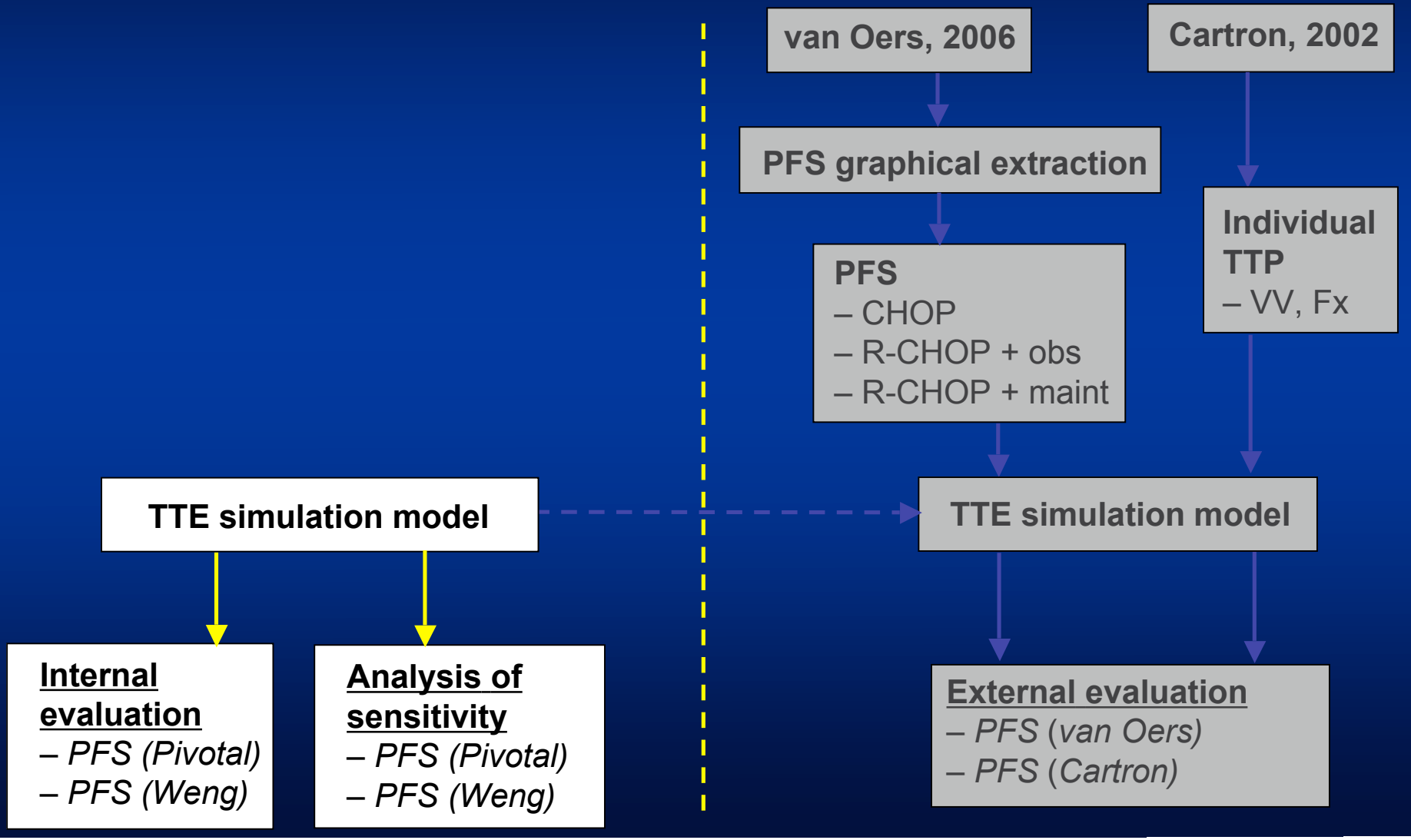
- **Simulation of published studies**
  - Number of patients = eligible patients of the study
  - Number of simulations = 500
  - Evaluation: visual predictive checks (VPC)
    - observed PFS
    - model-predicted PFS (90% confidence interval)
  - *Trial simulator II.2, S-Plus 6.2*

Model evaluation

Evaluation

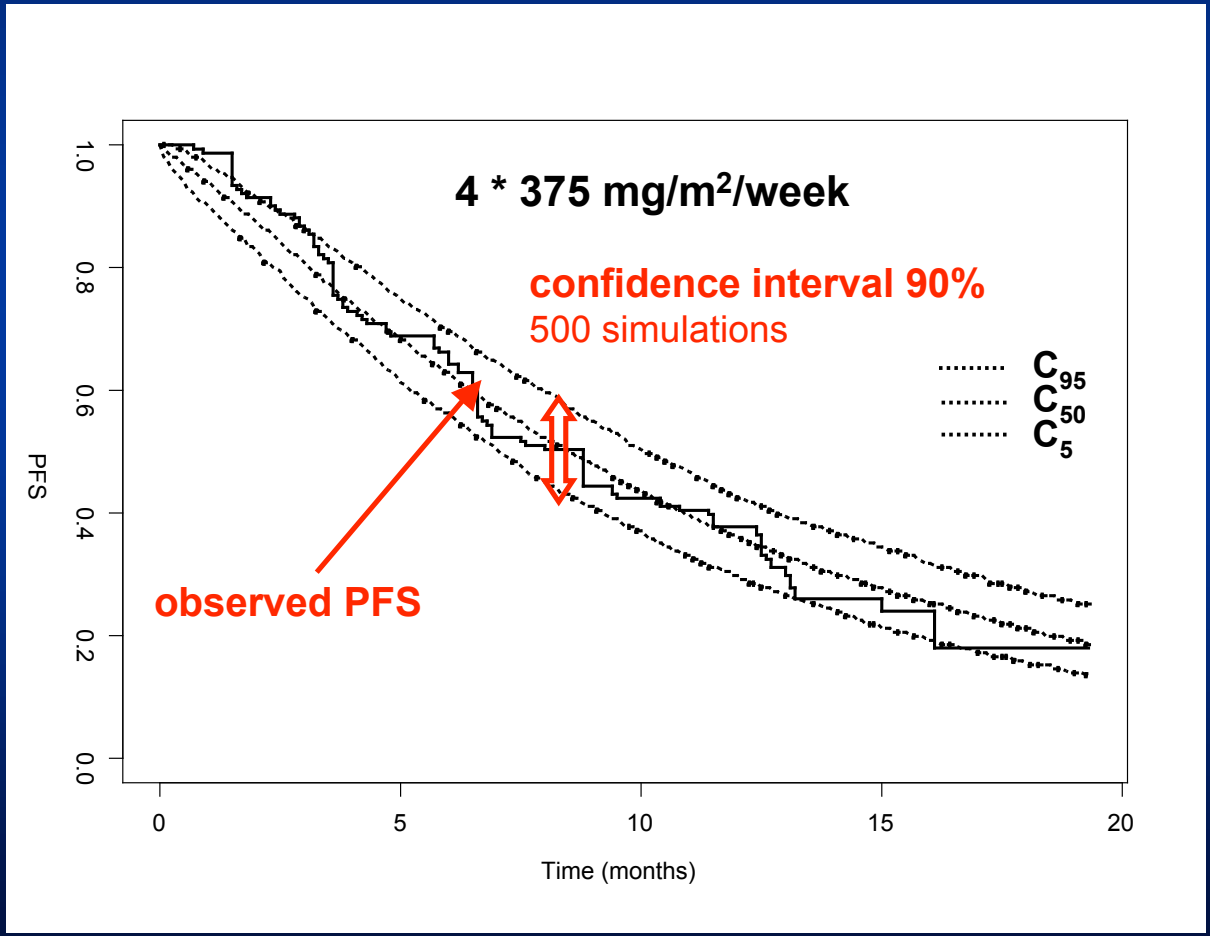


Internal evaluation



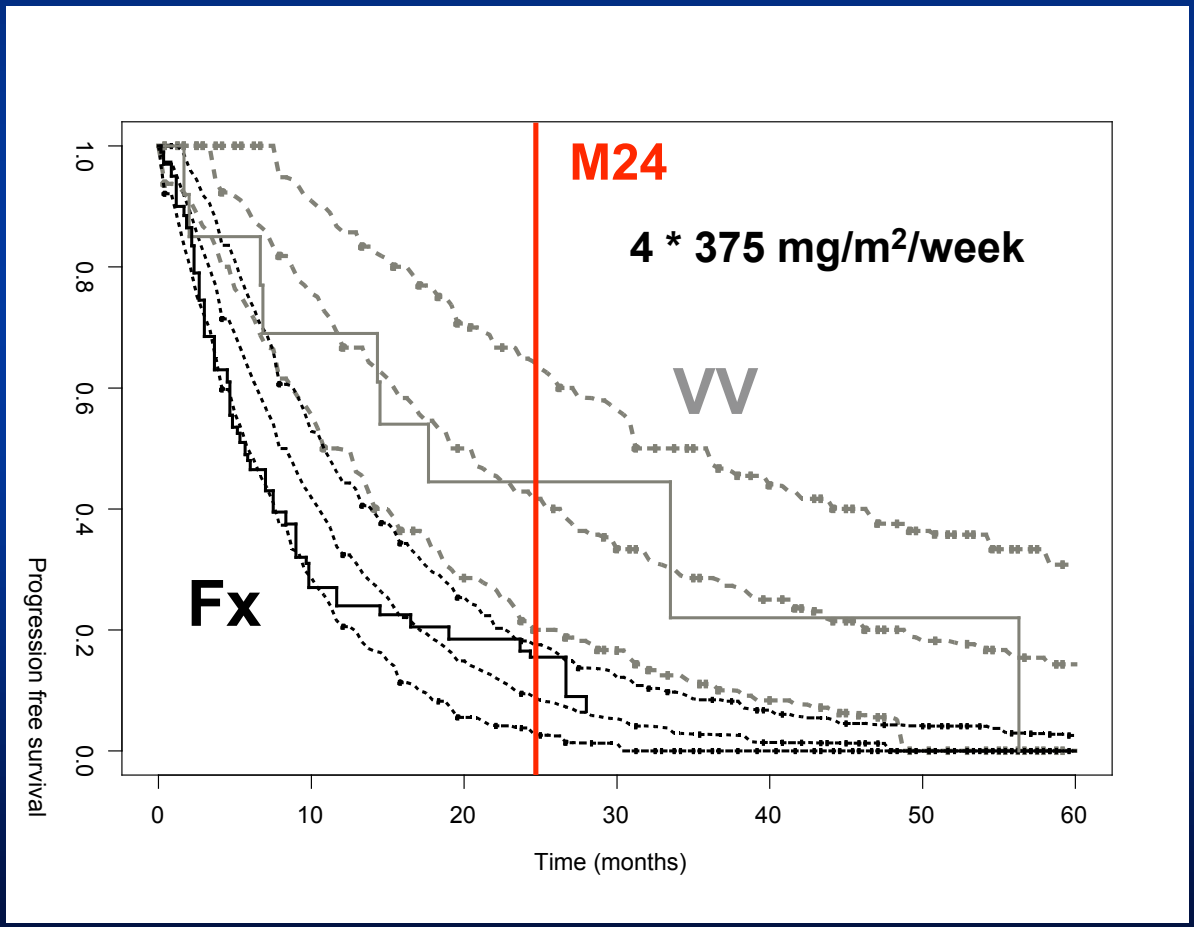
Internal evaluation

- **Pivotal study (*McLaughlin et al. 1998*)**

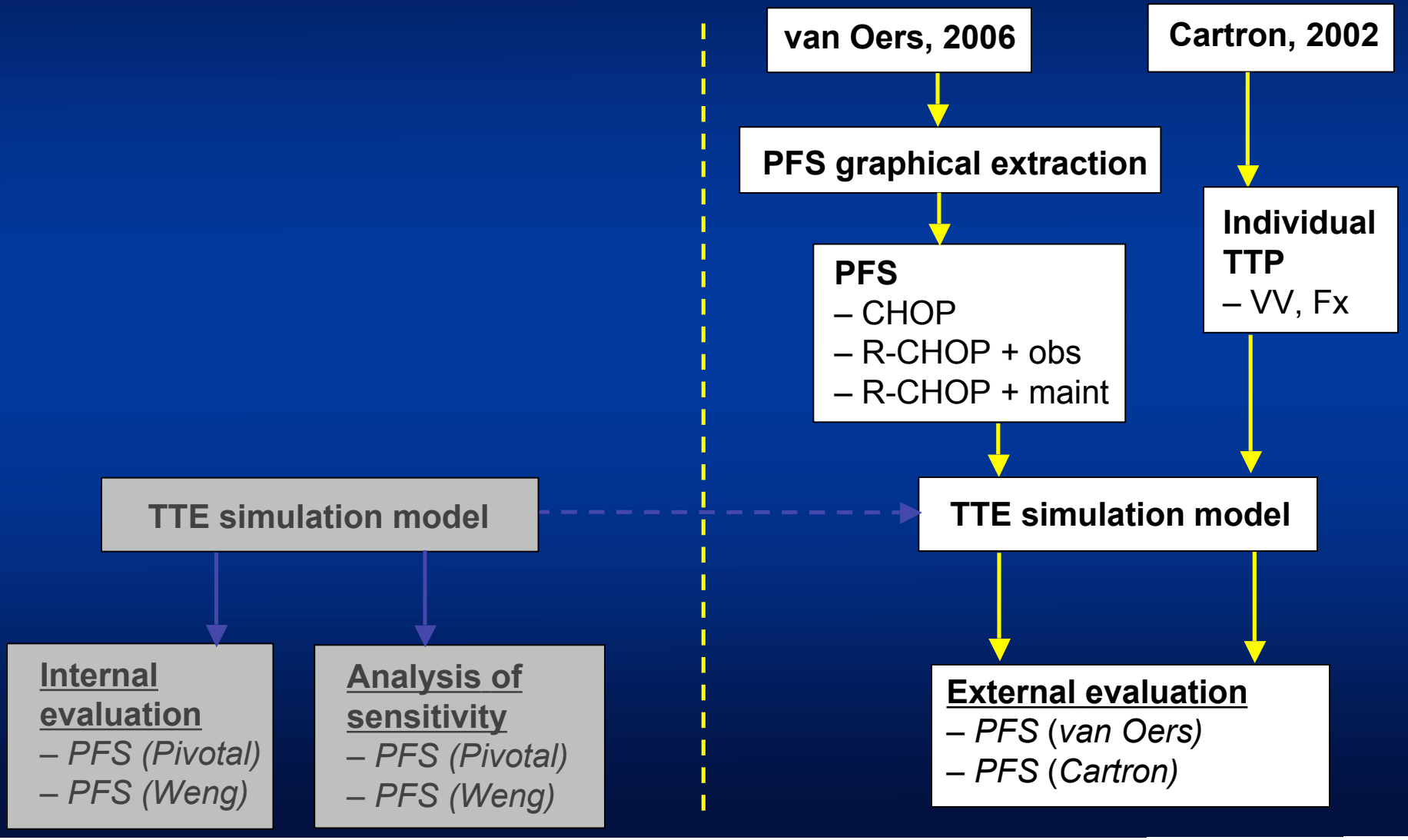


Internal evaluation

- **Influence of *FCGR3A* genotype : *Weng et al. 2004***



External evaluation



External evaluation

- **Studies**
  - *Van Oers et al.2006* :

    PFS of relapsed/resistent FL patients treated with:
    - R-CHOP
    - R-CHOP + rituximab maintenance (375 mg/m^2 every 3 months)
  - *Cartron et al., 2002* : PFS of first-line FL VV et Fx patients (rituximab 4 x 375 mg/m^2)

External evaluation

- *Van Oers et al.*

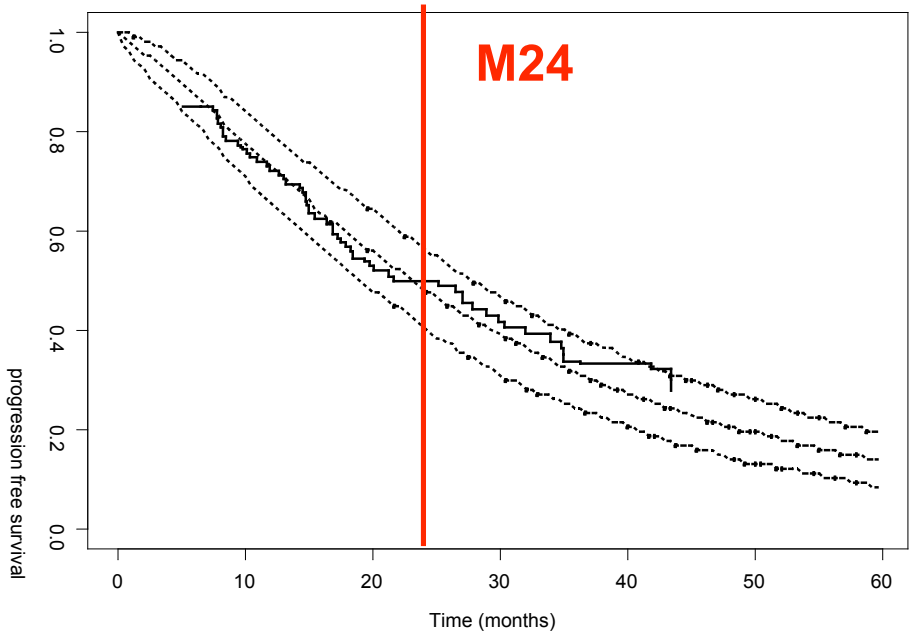
R-CHOP Without maintenance

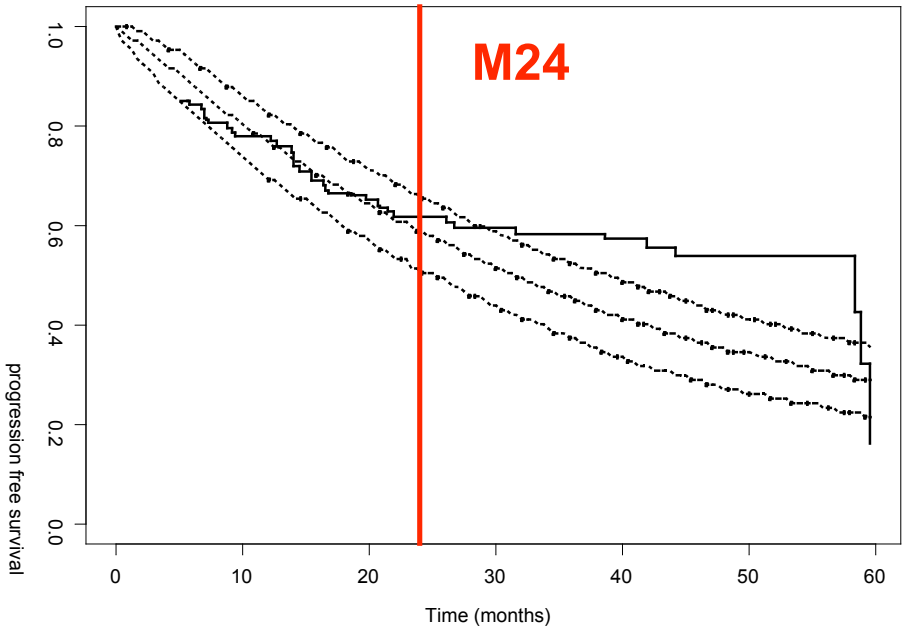
6 * 375 mg/m^2/21d

R-CHOP With maintenance

6 * 375 mg/m^2/21d

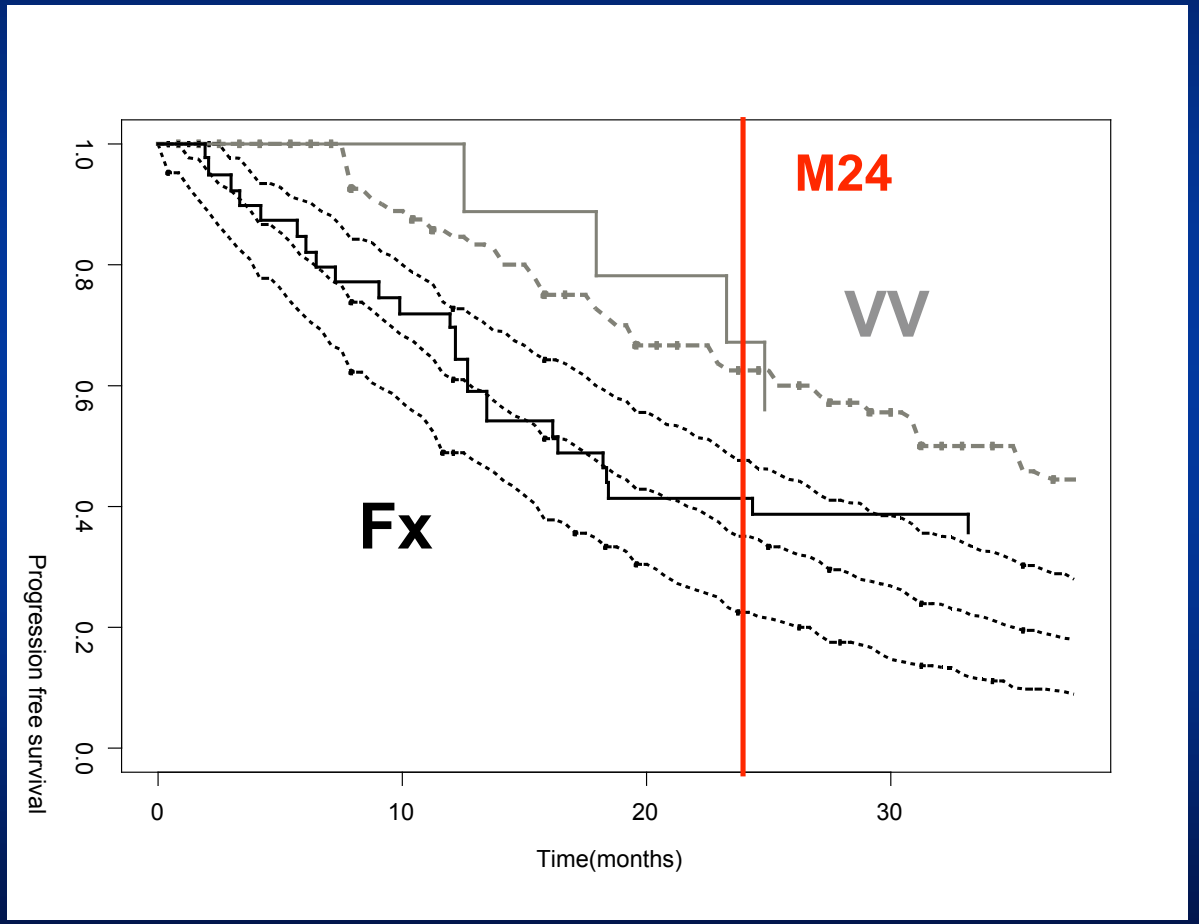
+ 375 mg/m^2/3months





Model evaluation

- *Cartron et al., 2002*
  - 4 x 375 mg/m^2/week.

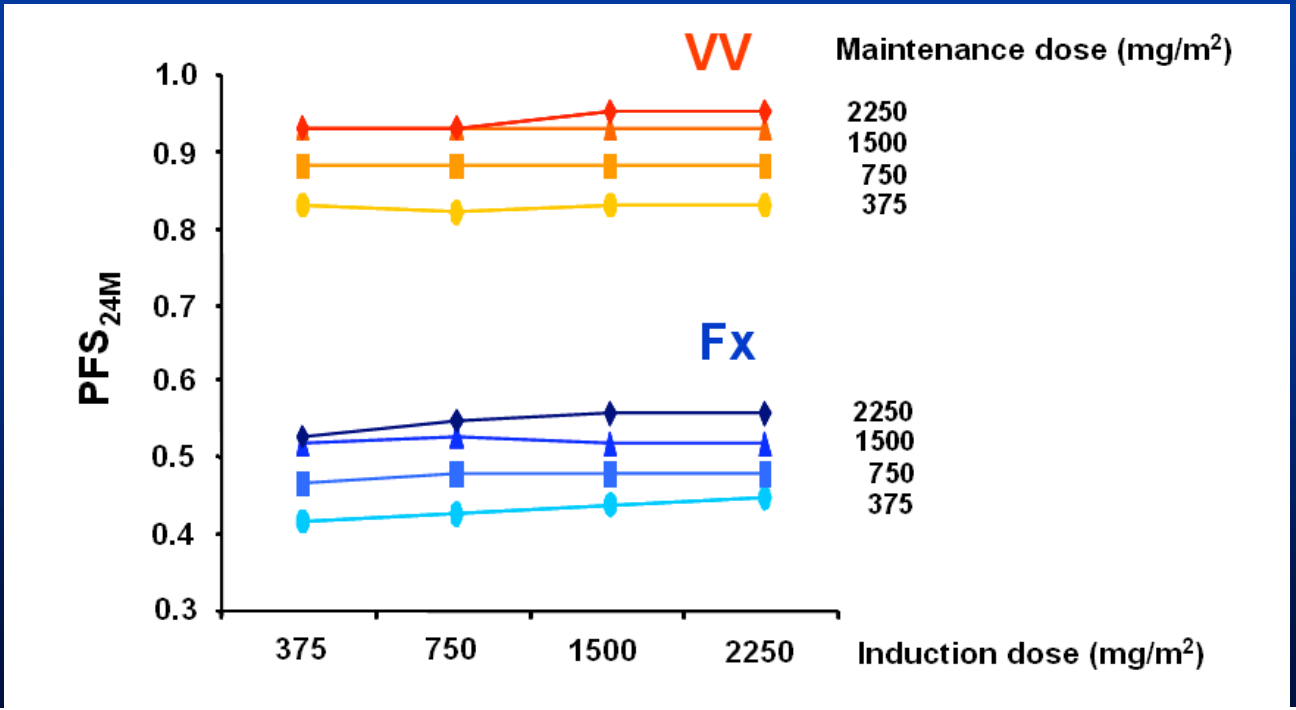


Conclusion: model

- **Satisfactory description of rituximab PFS within M24**
  - With and without rituximab maintenance
  - For both *FCGR3A* genotypes
- **PFS (M24) : metrics**

Dosing regimen alteration

- **Rituximab monotherapy (*Cartron et al. 2002*) : Fx vs. VV**
  - 4 weekly doses + maintenance every 2 months
  - Dose alteration
    - Induction : 375, 750, 1500, 2250 mg/m^2
    - Maintenance : 375, 750, 1500, 2250 mg/m^2



Conclusion and perspectives

- **Main benefit : increase of maintenance dose**
- **PFS of Fx never reach PFS of VV**
- **Perspectives**
  - Improvement of the model : Tumor burden, stage of disease
    → alteration of induction dose and schedule
  - Confirmation by clinical trials

References

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Time-to-event model

- **Parameter estimation**
  - λ_{max} : fixed
    - Rituximab (R) combined with chemotherapy (X)

$$\lambda_{max} = \lambda_X$$

    - R alone

Effects for R and X are assumed to be independent

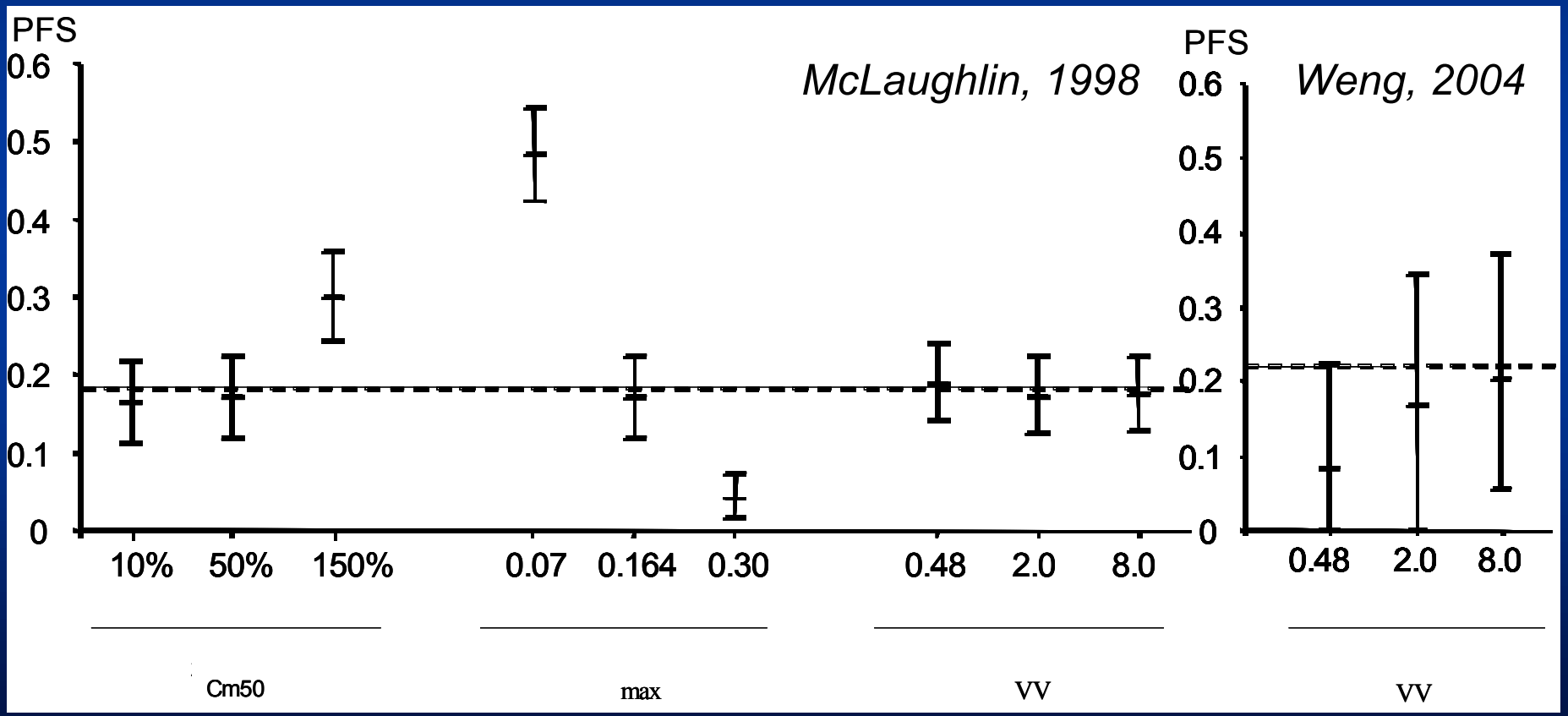
$$HR_{0/R} = HR_{X/R\text{-}X}$$

$$\lambda_{max} = \lambda_R \times HR_{X/R\text{-}X}$$

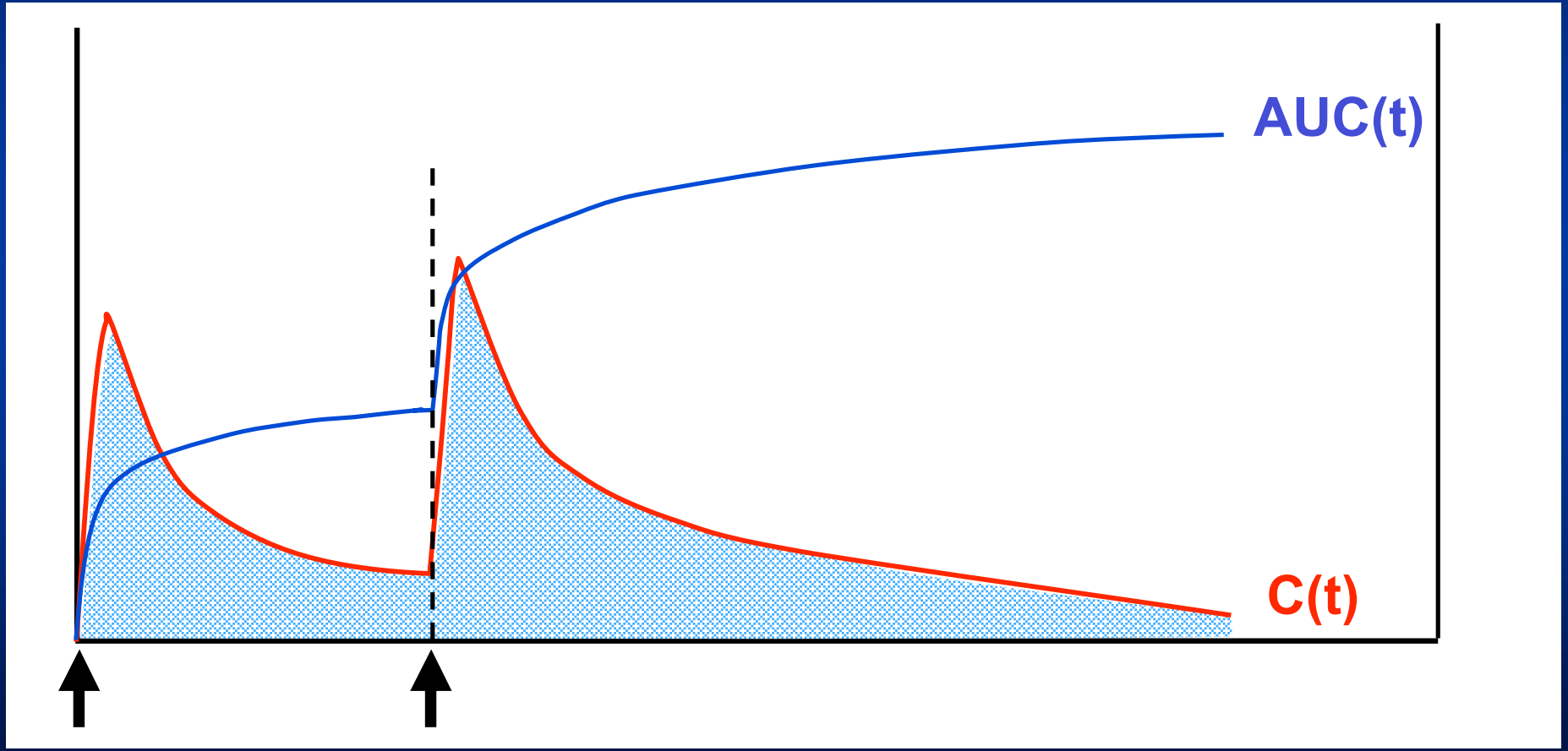
$HR_{X/R\text{-}X}$: *Marcus et al., 2008*

Internal evaluation

- **Sensitivity analysis (fixed parameters)**



Mean-time concentration



Model parameters