Development and application of a population PK-PD model quantifying trastuzumab induced changes in cardiac function

Optimizing monitoring strategies of trastuzumab induced cardiotoxicity

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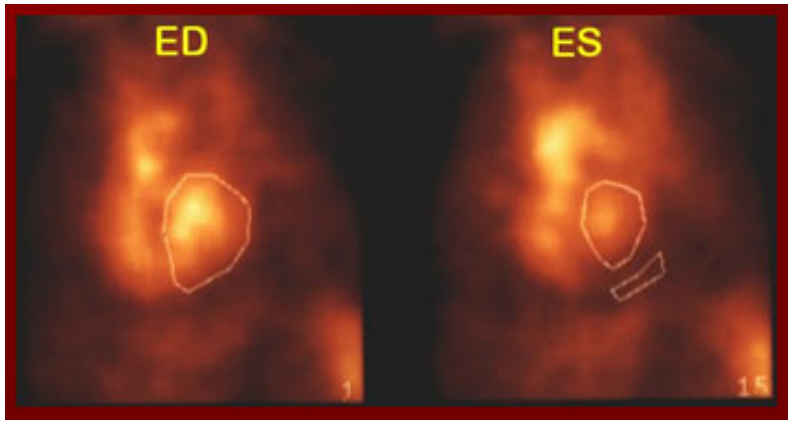
Trastuzumab treatment

- Trastuzumab is a mAB approved for early and metastasized HER2+ breast cancer.
- Treatment of early breast cancer consists of 1 year of trastuzumab every 1 or 3 weeks.
- Major side effect is cardiotoxicity, quantified as decrease in *left ventricular ejection fraction* (LVEF).
- Mechanism of trastuzumab cardiotoxicity still unclear.

Left ventricular ejection fraction

- The LVEF is a measure of cardiac output.
- Risk of heart failure.



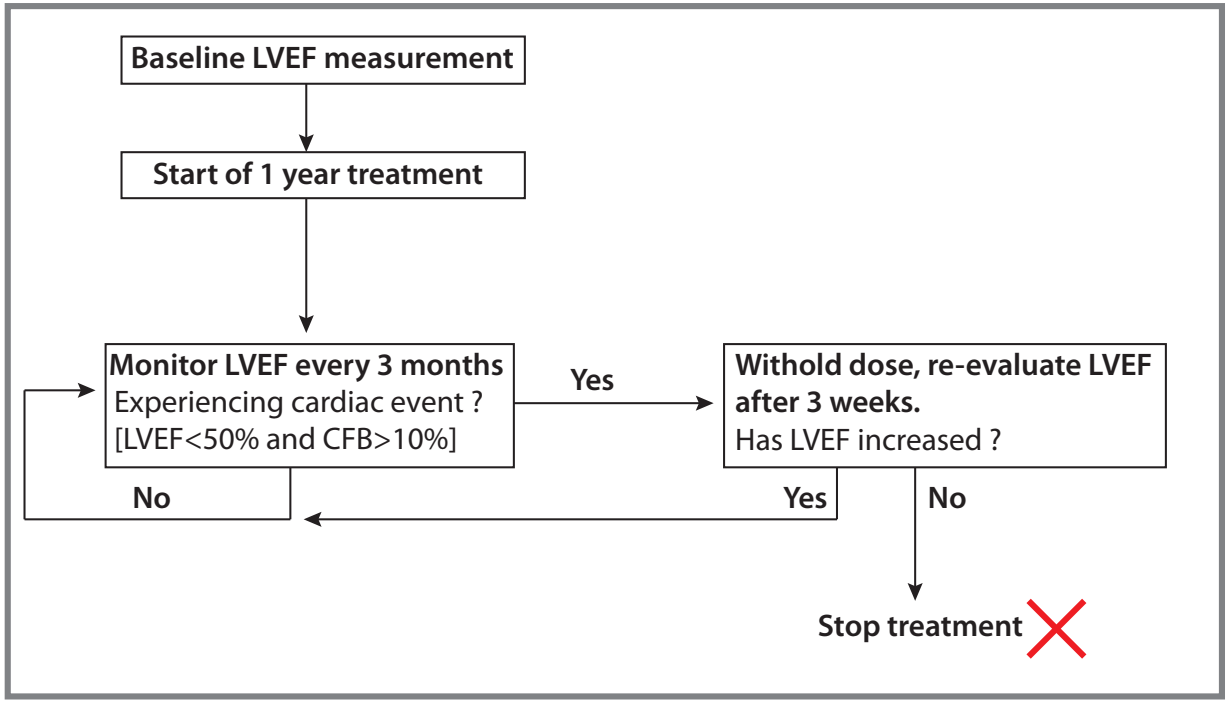
$$LVEF = \frac{EDV - ESV}{EDV}$$

- LVEF is monitored during treatment.
- Dose interruption or termination at occurence of a **cardiac event:**

Change from baseline LVEF > 0.10 ***AND*** *ABS(LVEF) < 0.50*

Cardiac management of cardiotoxicity

- The LVEF is monitored throughout trastuzumab treatment, as defined in the **Summary of Product Characteristics** (**SPC**) for trastuzumab.



- Clear **rationale** for monitoring strategy is missing.

Questions during routine patient care

1. Dynamics of the LVEF **recovery** ?
2. Effect of **prior anthracycline therapy** on LVEF dynamics ?
3. **Performance** of the cardiac monitoring protocols ?
4. Implications of changing **LVEF monitoring frequency/recovery time** ?
5. Feasibility of **adaptive monitoring** ?

Objectives

The objectives of this analysis were to:

1. Develop a **PK-PD model** for the relationship between trastuzumab exposure and associated changes in LVEF, and to identify **covariates** explaining between-subject variability.
2. Develop a **simulation framework** that can be used to address **clinical questions** regarding optimal cardiac management of trastuzumab associated cardiotoxicity.

Part I: Development of the PK-PD model

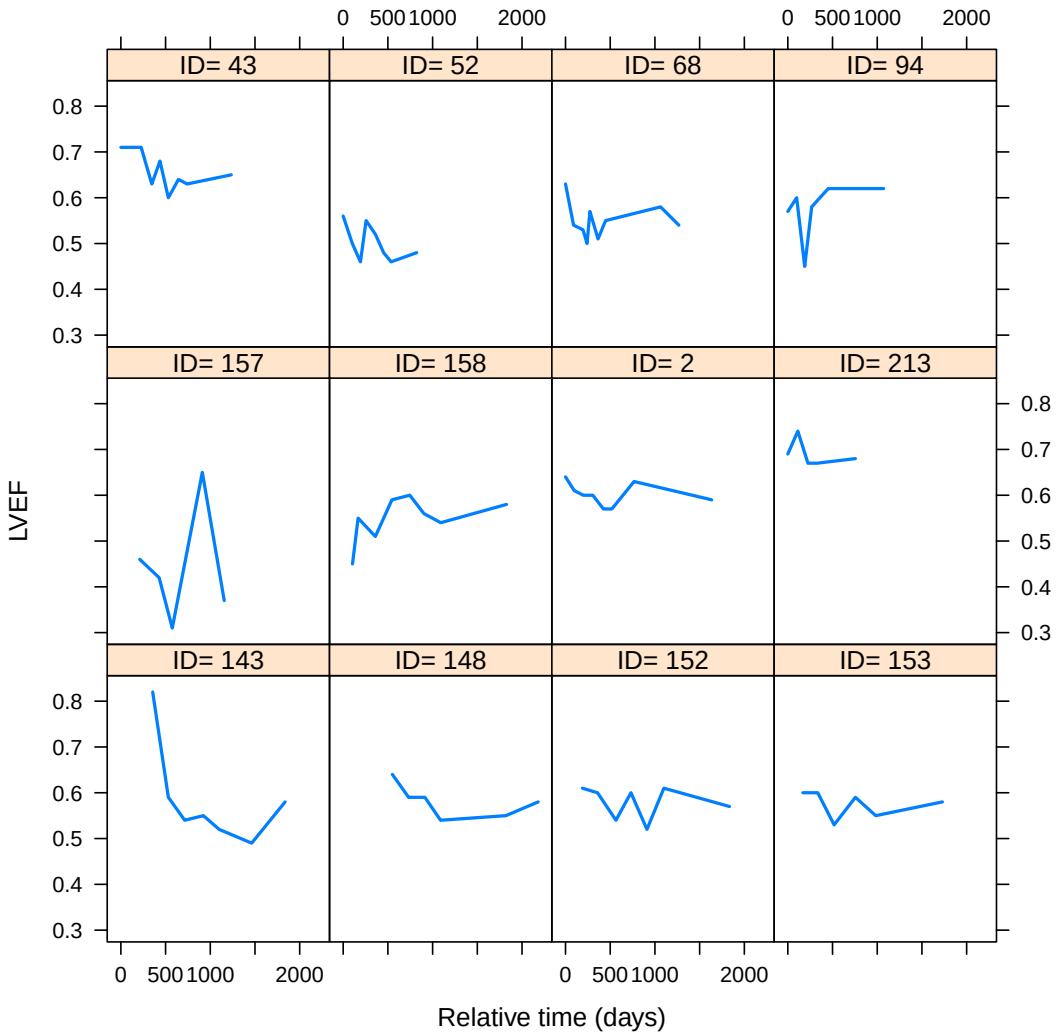
Dataset

- **Unselected** cohort of patients treated with trastuzumab.
- **Exposure**: Individual dosing histories.
- **Response**: LVEF measurements obtained from routine clinical practice.

Number of patients (early, metastatic)	240 (164/76)
Observations per subject (median)	6
Total nr of observations	1651
Age (median, IQR)	50 (43-59)
Cumulative dose anthracyclines (median, IQR)	0.43 (0.42-0.60)

Example LVEF profiles

- **Highly informative** but also **unbalanced and heterogeneous** data → *Population approach*!



Covariates

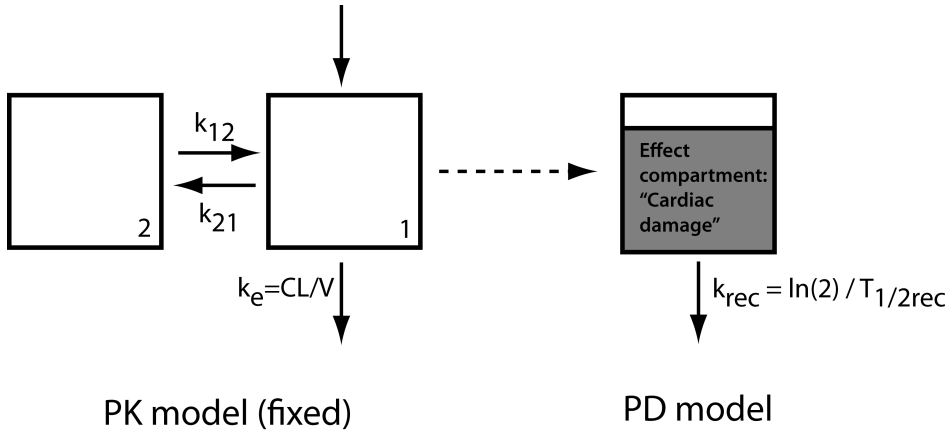
- Radiotherapy to the chest (left/right)
- Age
- Body mass index
- Adjuvant/metastasized
- Cumulative prior dose of cyclophosphamide
- Cumulative prior dose of **anthracyclines**

Anthracyclines

- Anthracycline chemotherapeutics: **doxorubicine** and **epirubicine.**
- Patients treated with prior anthracycline therapy are **more at risk** for trastuzumab associated cardiotoxicity.
- **Maximum cumulative anthracycline doses** have been defined.
- Relative anthracycline doses were calculated.
- Sum of the cumulative relative anthracycline dose was used as covariate.

Model building

- **PK** was described using a previously published model for trastuzumab PK[1] and individual dosing histories.
- **PD** was modelled using an effect compartment model and an Emax model.



$$LVEF = LVEF_0 \cdot \left(1 - \frac{C_{EF}}{EC_{50} + C_{EF}}\right)$$

[1] *Bruno R et al. Cancer chemotherapy and pharmacology 2005. 56(4), 361-369.*

Parameter estimates

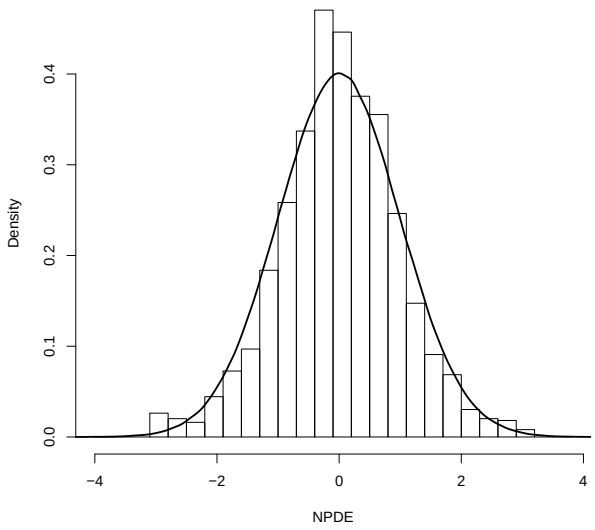
	Population mean (RSE)	**BSV (RSE)**
Recovery half-life (days)	49.7 (28.2)	79.4 (27.6)
EC50 (“Sensitivity”) (mg/ml)	4.82 (19.6)	103 (13.8)
Baseline LVEF(-)	0.636 (0.904)	30.0 (6.5)
	Prop. residual error (CV%)	
Method 1	7.35 (17.1)	
Method 2	9.11 (8.40)	

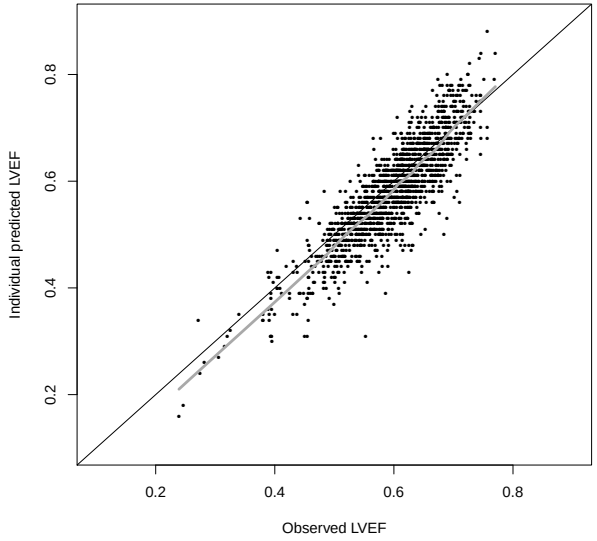
BSV=Between subject variability(CV%)

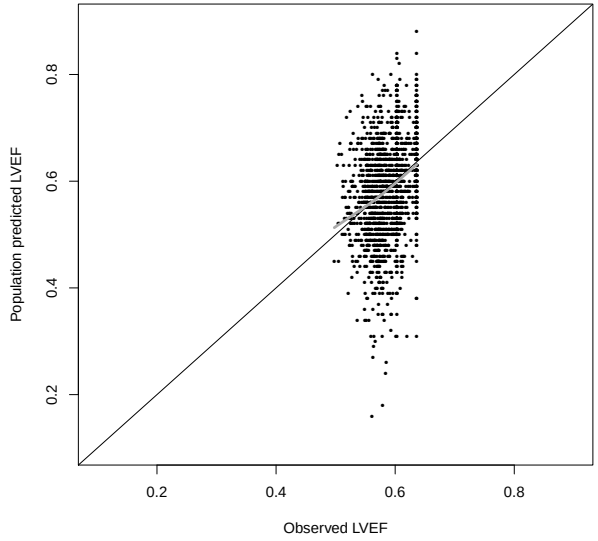
- Prior anthracycline dose was a covariate on EC50.
- A maximum prior cumulative **anthracycline** treatment causes a 45.9% decrease in EC50.

Model evaluation

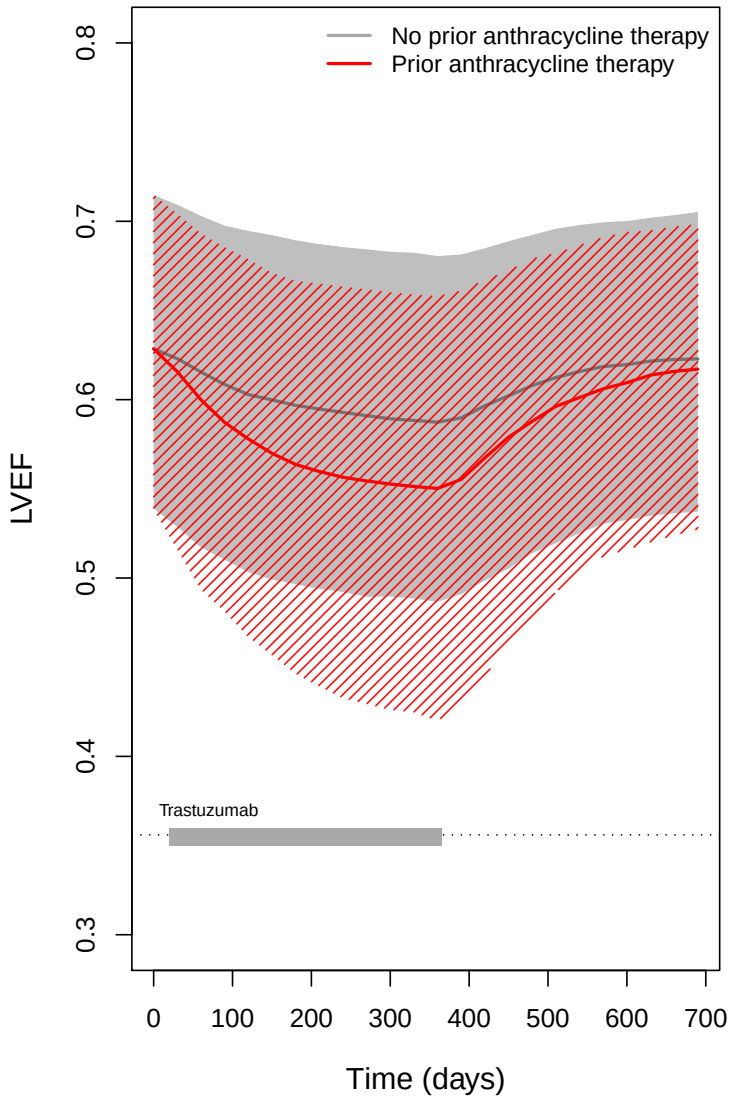
- Parameters were estimated with adequate precision and was confirmed with a bootstrap analysis.
- Goodness-of-fit and NPDE indicated adequate performance.







Anthracyline effect



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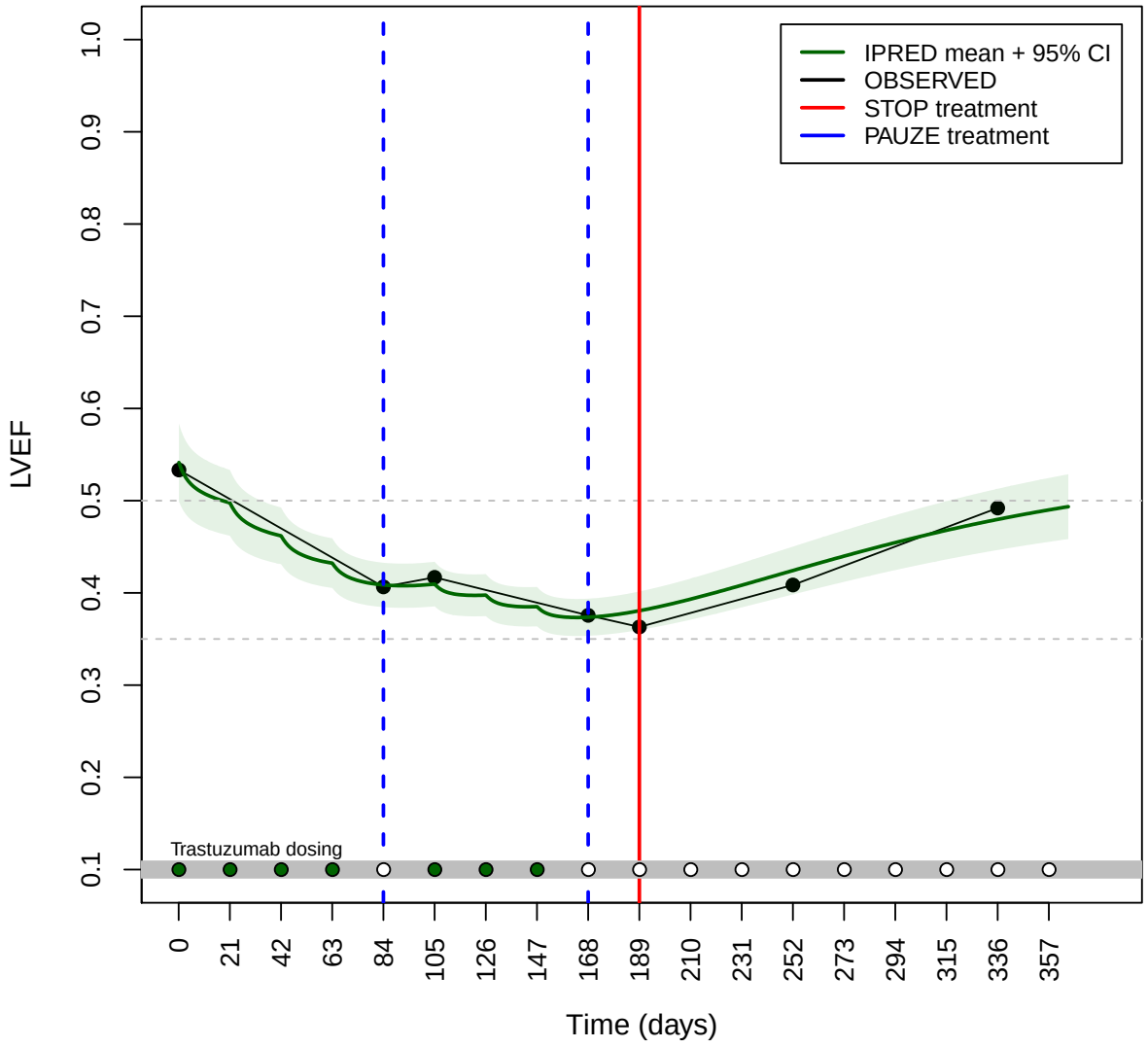
Part II: Development of a simulation framework

Simulation framework

- Aims:
  - Simulate **LVEF profiles** and related **dosing interruptions and terminations.**
  - SPC-defined cardiac monitoring protocol.
  - Early breast cancer treatment (1 year).

- Simulation framework steps:
  1. **Simulate** individual LVEF profiles (n=5000).
  2. **Apply** the SPC-defined cardiac **monitoring protocol.**
  3. **Re-calculate LVEF profiles** for patients with dose intervention.
  4. **Repeat step 2 & 3** until end or stop of of treatment.

Typical simulation profile



Outcome measures

- Outcome measures:
  - **Efficacy:** Dose intensity
  - **Diagnostic performance** of LVEF assessment protocols

SPC monitoring schedule performance

- **Efficacy**: prior anthracycline treatment has significant impact on **dosing intensity (DI).**
  - Anthracycline naive patients: 2.5th percentile of patients has a DI < 89%.
  - Maximum anthracycline pretreatment: 2.5th percentile of patients has a DI < 44%.
- **Diagnostic performance of the SPC:**
  - Sensitivity: 78%
  - Specificity: 97%
  - Substantial impact of residual error on performance of the SPC monitoring schedule.

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Discussion

- Framework can help to optimization of cardiac monitoring protocols, incorporating:
  - prior anthracycline use
  - recovery time
  - monitoring interval
- Future work will focus on development of optimized cardiac monitoring protocol, including prospective clinical validation.

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