A step forward toward personalised medicine in oncology

Núria Buil-Bruna, José-María López-Picazo, Tarjinder Sahota,

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A step forward toward personalised medicine in oncology

Population modelling for the early prediction of disease progression using biomarkers

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A step forward toward personalised medicine in oncology

Population modelling for the early prediction of disease progression using biomarkers

Application to Small Cell Lung Cancer (SCLC)

Núria Buil-Bruna, José-María López-Picazo, Tarjinder Sahota,
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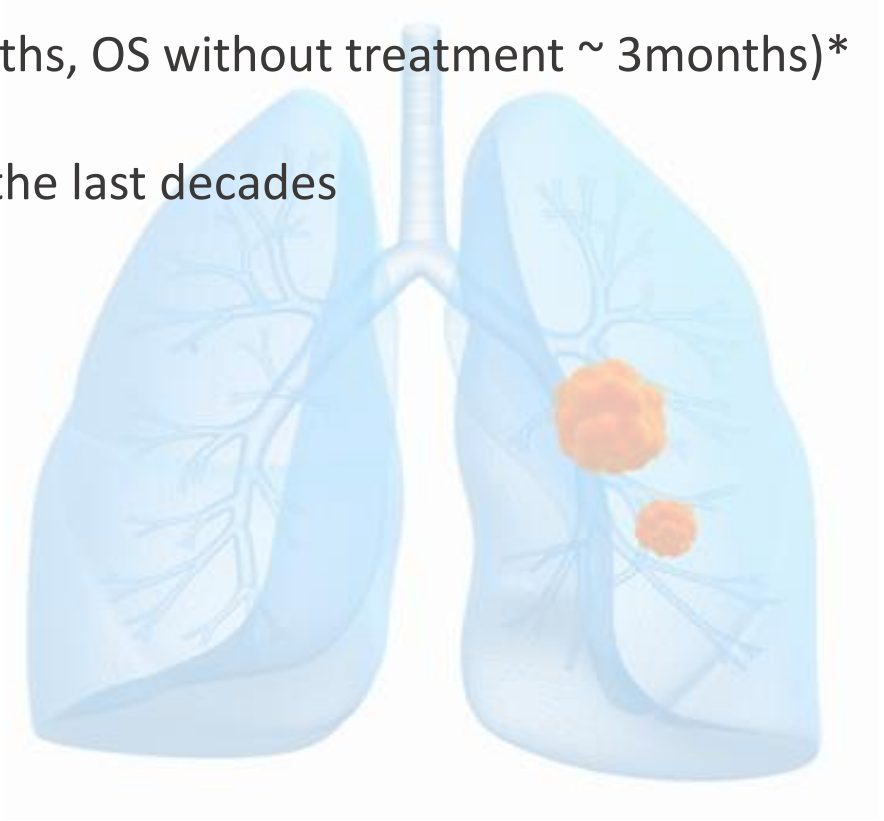
informatiques mathématiques
Inria

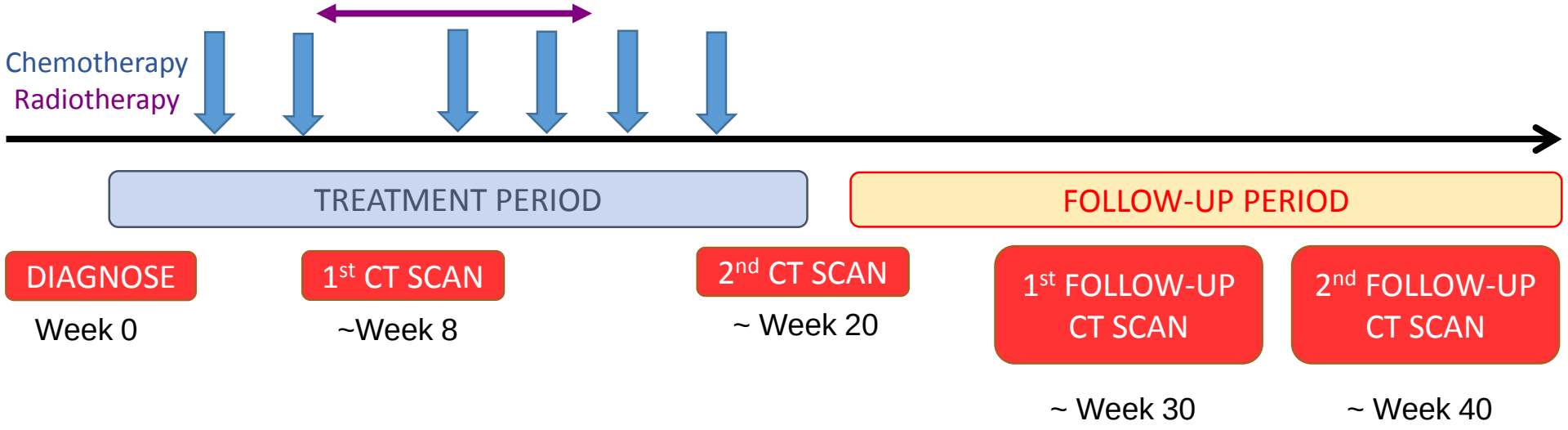
Background : Small Cell Lung Cancer (SCLC)

- Aggressive and fast growing neoplasm
- Highly sensitive to treatment (chemotherapy and radiation)
- Fast emergence of drug resistance
- Bad prognosis (OS with treatment ~ 10months, OS without treatment ~ 3months)*
- Treatment has not evolved significantly in the last decades



*http://lungcancer.about.com/

Background : Standard treatment in SCLC



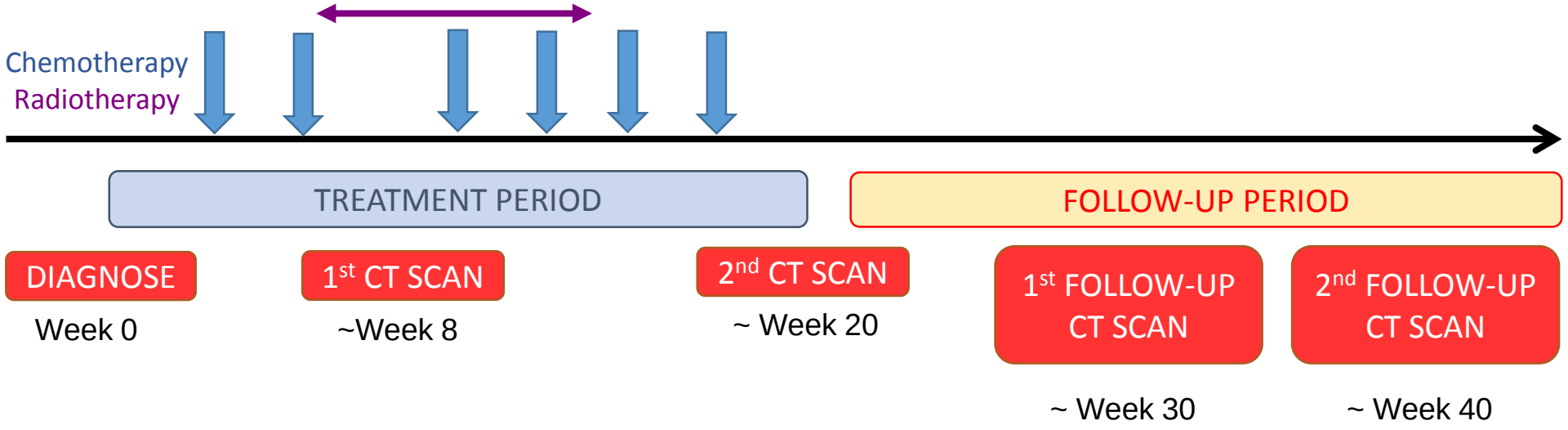
Tumour assessment

Response Evaluation Criteria In Solid Tumors (RECIST)

Categorise sum of tumour longest diameters (SLD) in target lesions:

- COMPLETE RESPONSE (CR): disappearance of all lesions
- PARTIAL RESPONSE (PR) : 30% decrease in SLD
- DISEASE PROGRESSION (DP): 20% increase in SLD or new lesions
- STABLE DISEASE (SD) : <20% increase or <30% decrease

Background : Standard treatment in SCLC



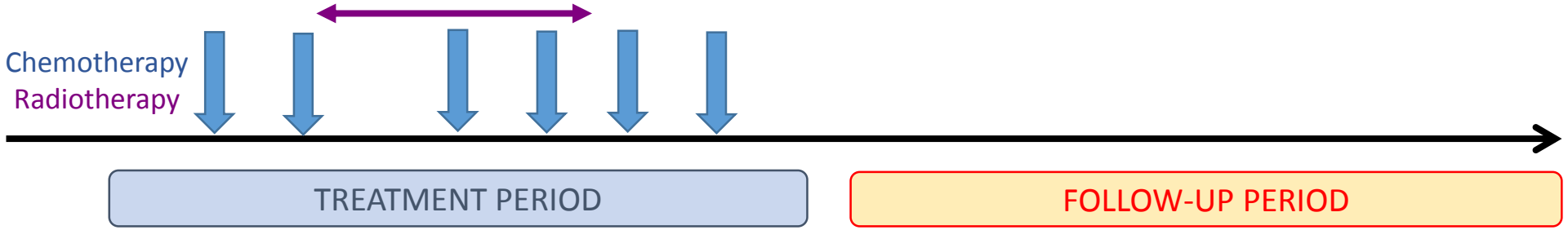
Biomarkers

Lactate dehydrogenase (LDH)

Neuron specific Enolase (NSE)

- Glycolytic enzymes easily measured in blood
- Known to be related to disease
- Collected clinical practice but not used to assess clinical efficacy
- Scepticism – low specificity and sensitivity
- Empirical analysis → Semi-mechanistic modelling

Aims



TREATMENT PERIOD

FOLLOW-UP PERIOD

1st FOLLOW-UP CT SCAN

2nd FOLLOW-UP CT SCAN

~ Week 30

~ Week 40

To develop a framework to early predict individual future disease progression

Aims

To investigate the feasibility of using circulating biomarkers as predictors of tumour progression in SCLC

To develop a framework to early predict individual future disease progression

Aims/workflow

To investigate the feasibility of using circulating biomarkers as predictors of tumour progression in SCLC

Biomarker model

(in absence of tumor size information)

To develop a framework to early predict individual future disease progression

Available data

SCLC patients (n=60): Diagnosed between **2005 – 2012** in University Clinic of Navarra

- 1ST LINE TREATMENT : Etoposide + cisplatin/carboplatin
- OBSERVATIONS
  - 369 LDH + 152 NSE
  - 218 CT scans
- 48% patients concomitant radiotherapy
- 50% patients concomitant GCSF

TRAINING DATASET

Available data

SCLC patients (n=60): Diagnosed between **2005 – 2012** in University Clinic of Navarra

- 1ST LINE TREATMENT : Etoposide + cisplatin/carboplatin
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  - 369 LDH + 152 NSE
  - 218 CT scans
- 48% patients concomitant radiotherapy
- 50% patients concomitant GCSF

TRAINING DATASET

SCLC patients (n=22): Diagnosed between **2012 – 2014** in University Clinic of Navarra

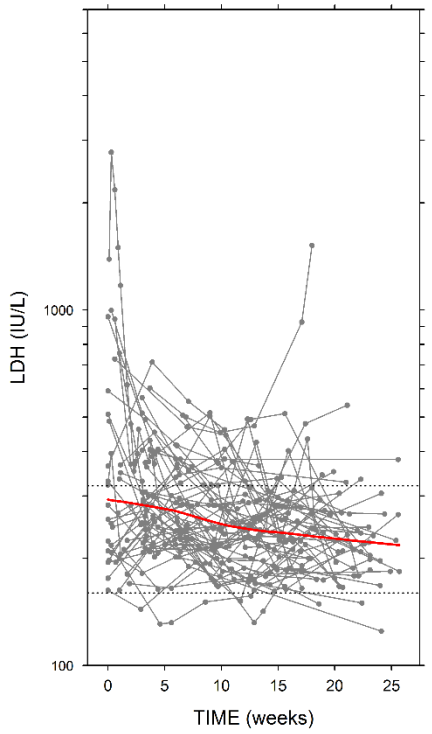
- 1ST LINE TREATMENT : Etoposide + cisplatin/carboplatin
- OBSERVATIONS
  - 138 LDH + 77 NSE
  - 78 CT scans
- 64% patients concomitant radiotherapy
- 47% patients concomitant GCSF

EXTERNAL DATASET

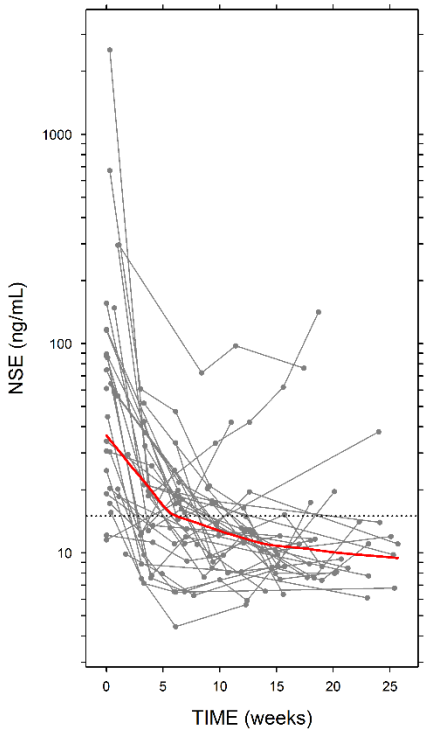
Available data

TRAINING DATASET (n=60)

LDH

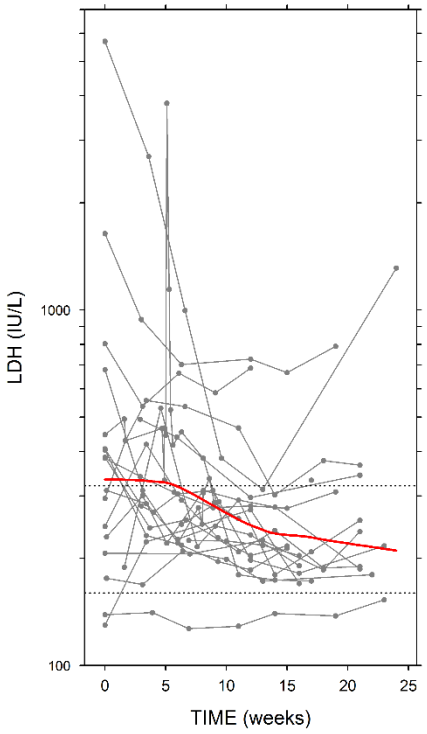


NSE

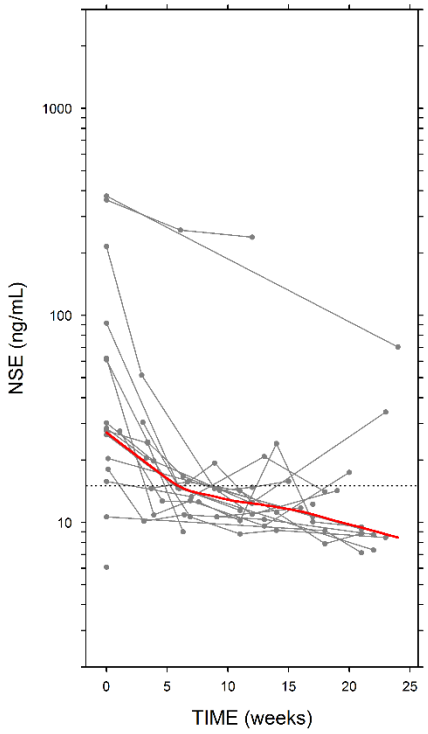


EXTERNAL DATASET (n=22)

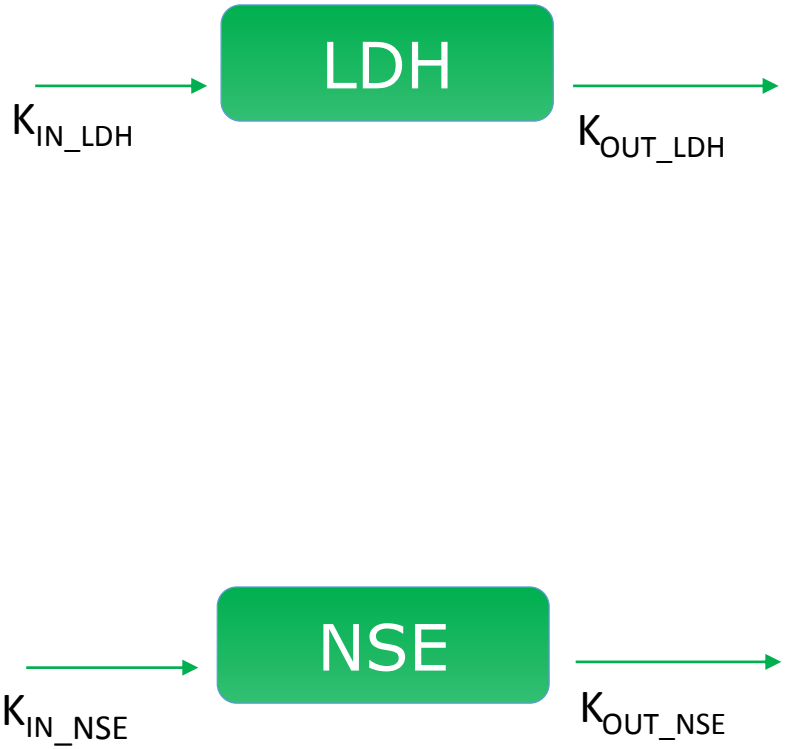
LDH



NSE



Biomarker model development



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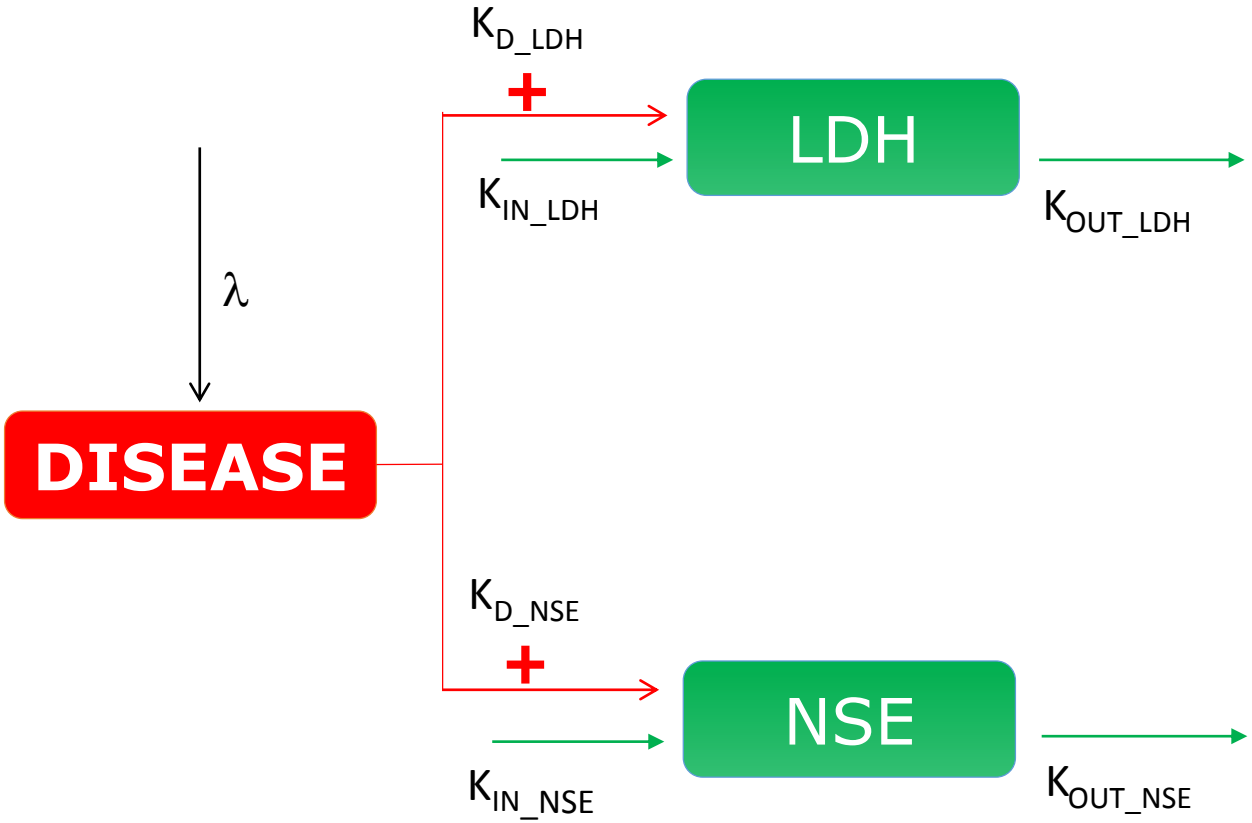
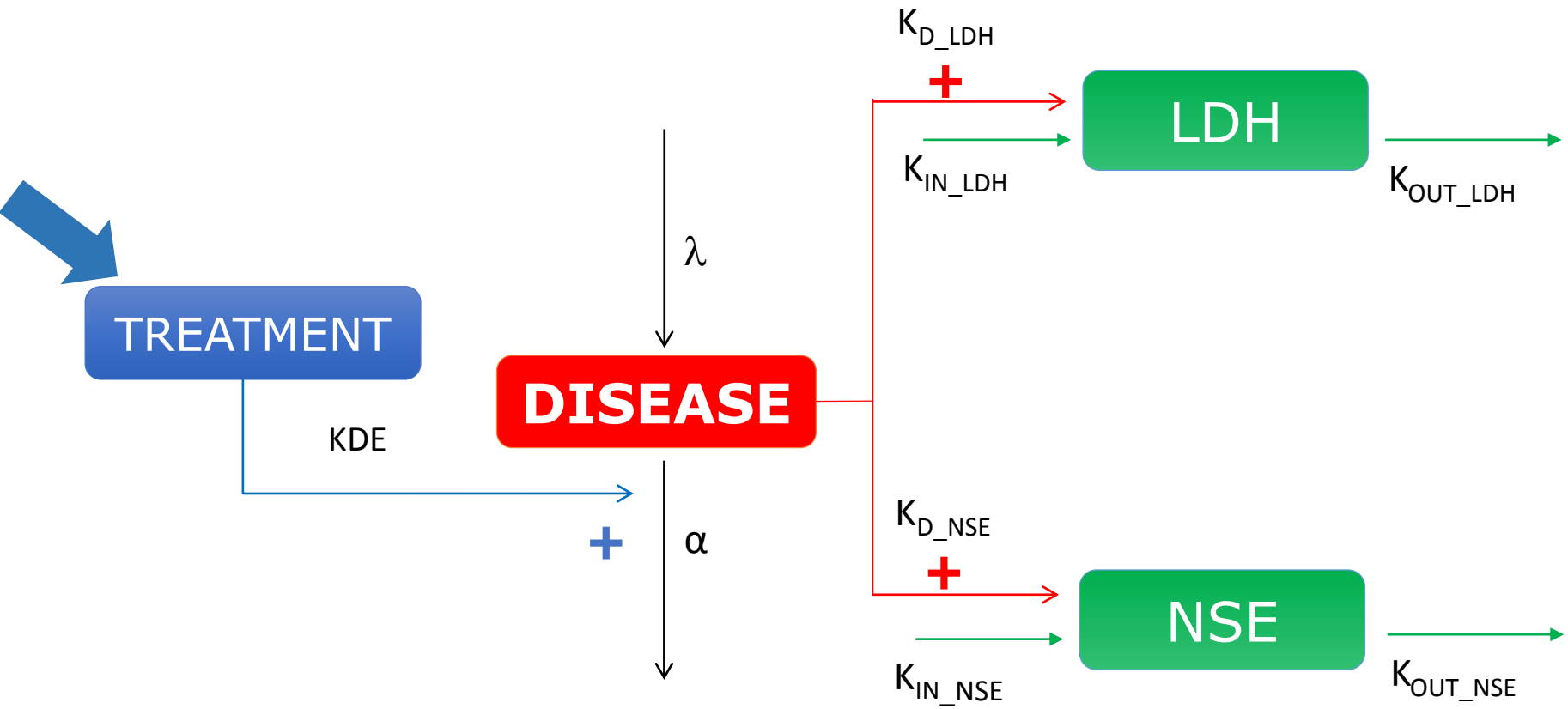


DISEASE represents tumour burden. However, tumour data (RECIST) were not included in the model

Biomarker model development



K-PD approach (PK data not available).

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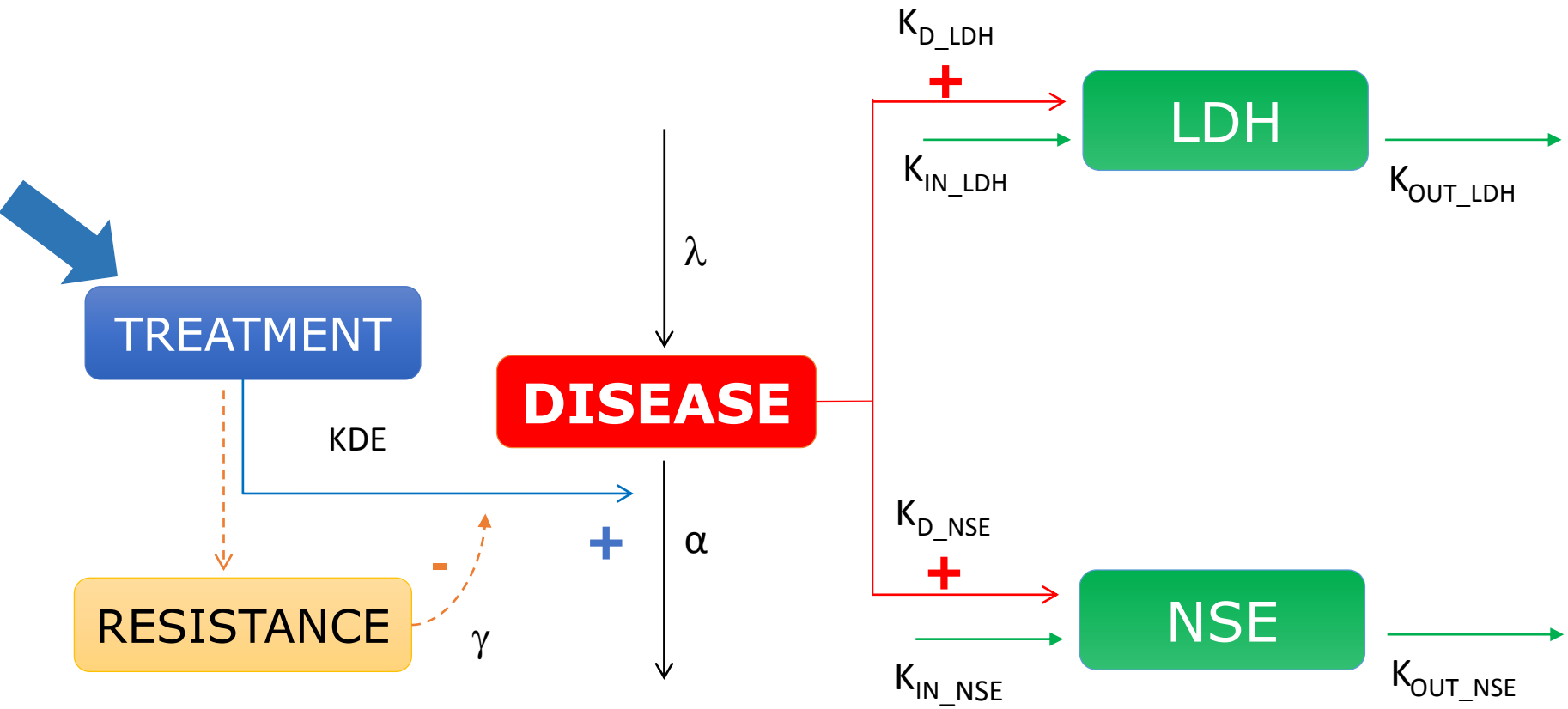
Biomarker model development



Resistance formed with cumulative chemotherapy doses

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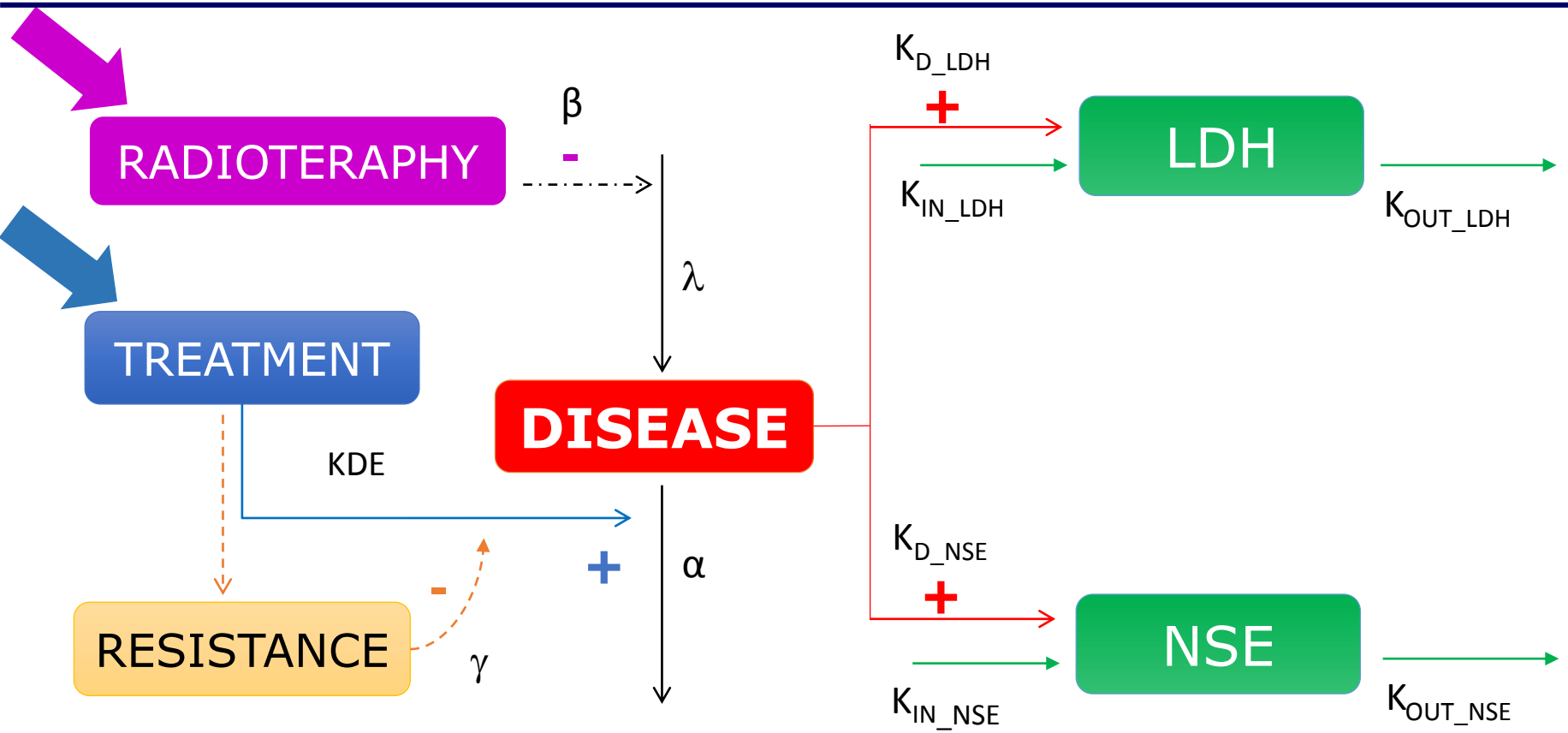

Radiotherapy included as in irreversible effect on the disease proliferation rate

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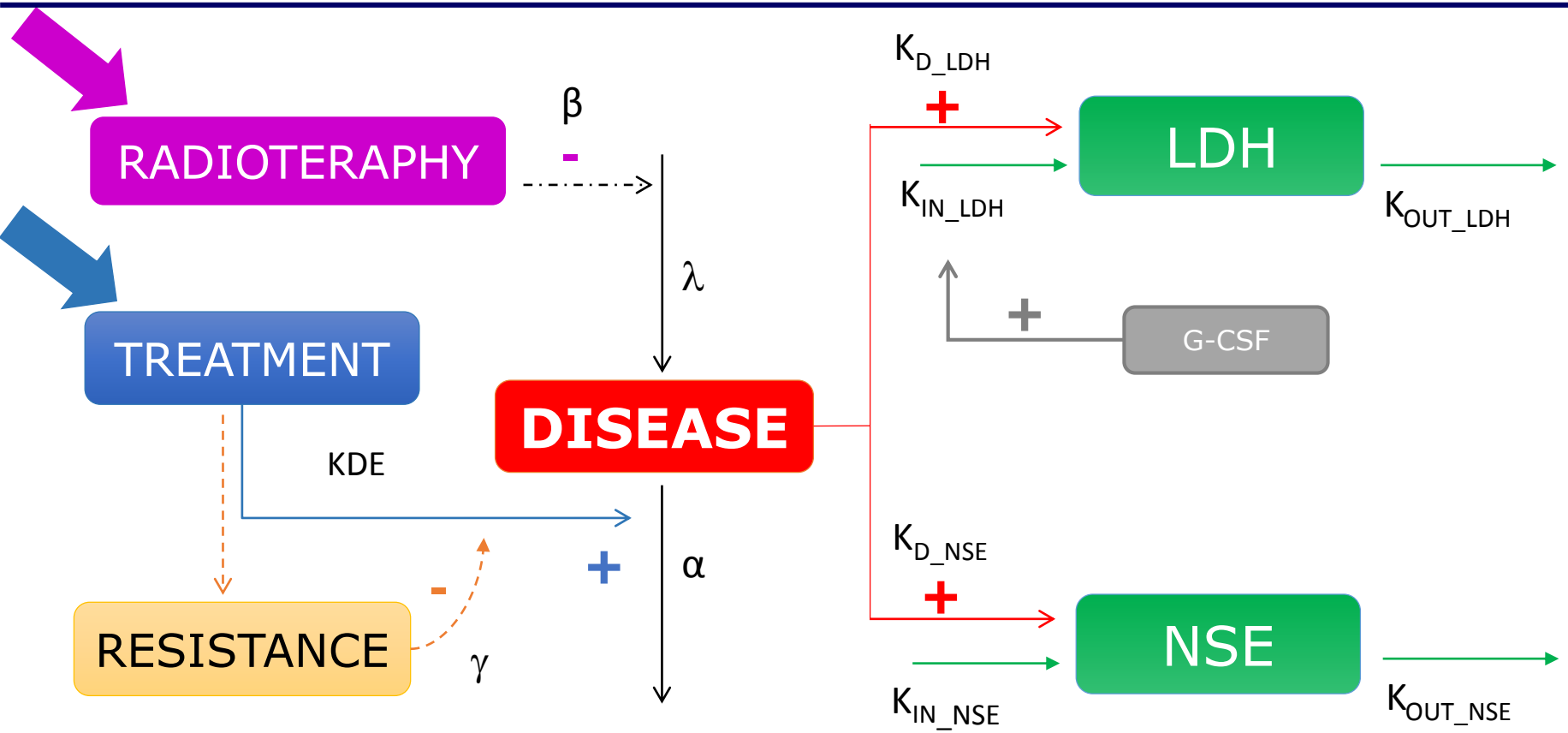

G-CSF (Granulocyte colony-stimulating factor), covariate increasing physiological LDH synthesis

Radiotherapy included as in irreversible effect on the disease proliferation rate

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Buil-Bruna et al, The AAPS Journal 2014

Biomarker model evaluation & validation

TRAINING DATASET (n=60)

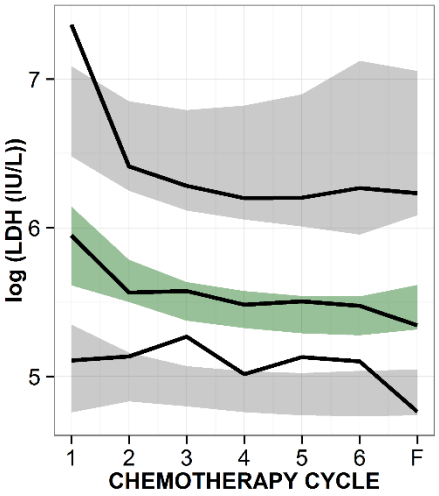
EXTERNAL DATASET (n=22)

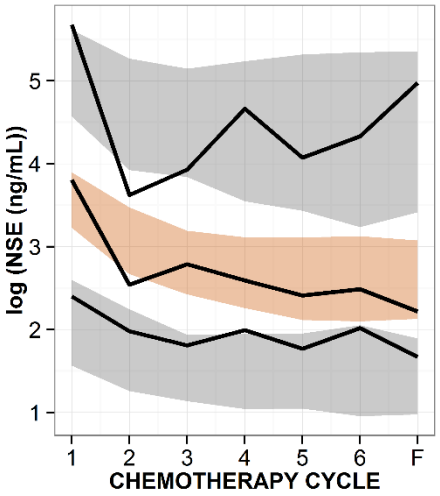
LDH

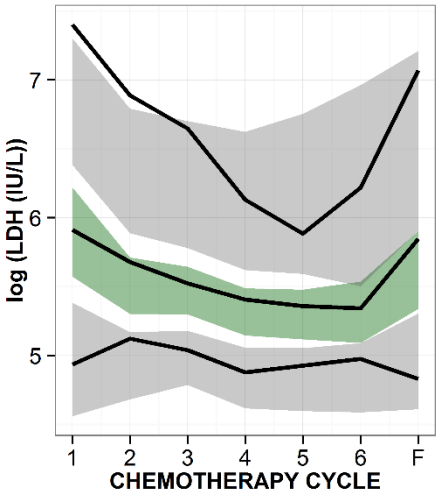
NSE

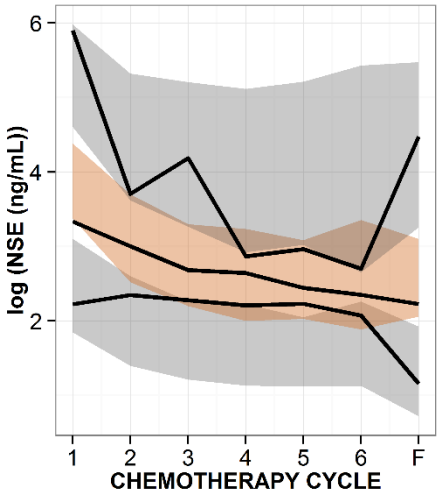
LDH

NSE









Aims/workflow

To investigate the feasibility of using circulating biomarkers as predictors of tumour progression in SCLC

Biomarker model

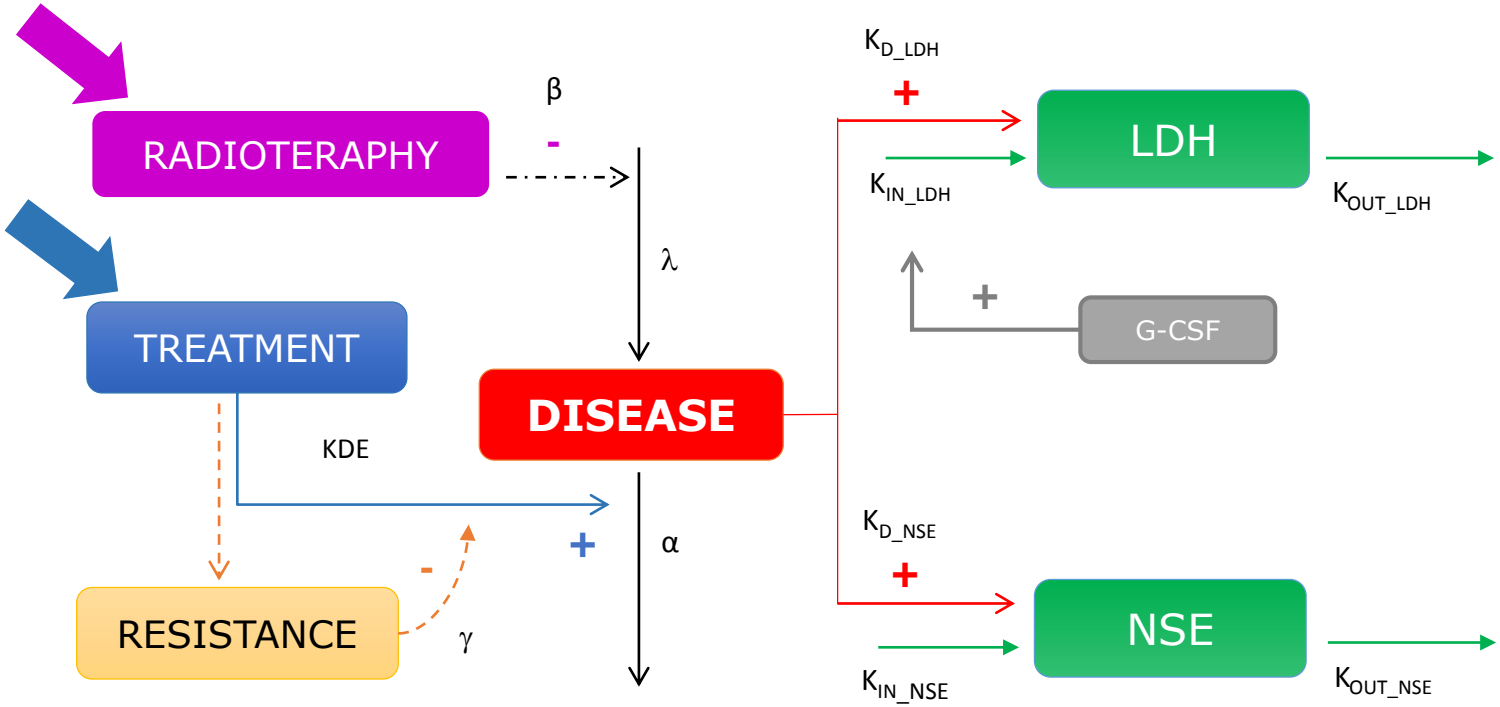
(in absence of tumor size information)

Is our model predictive of CT scan outcomes?

To develop a framework to early predict individual future disease progression

Is our model predictive of CT scan outcomes?

Patient's response was classified according to the change in total tumour size since the previous CT scan



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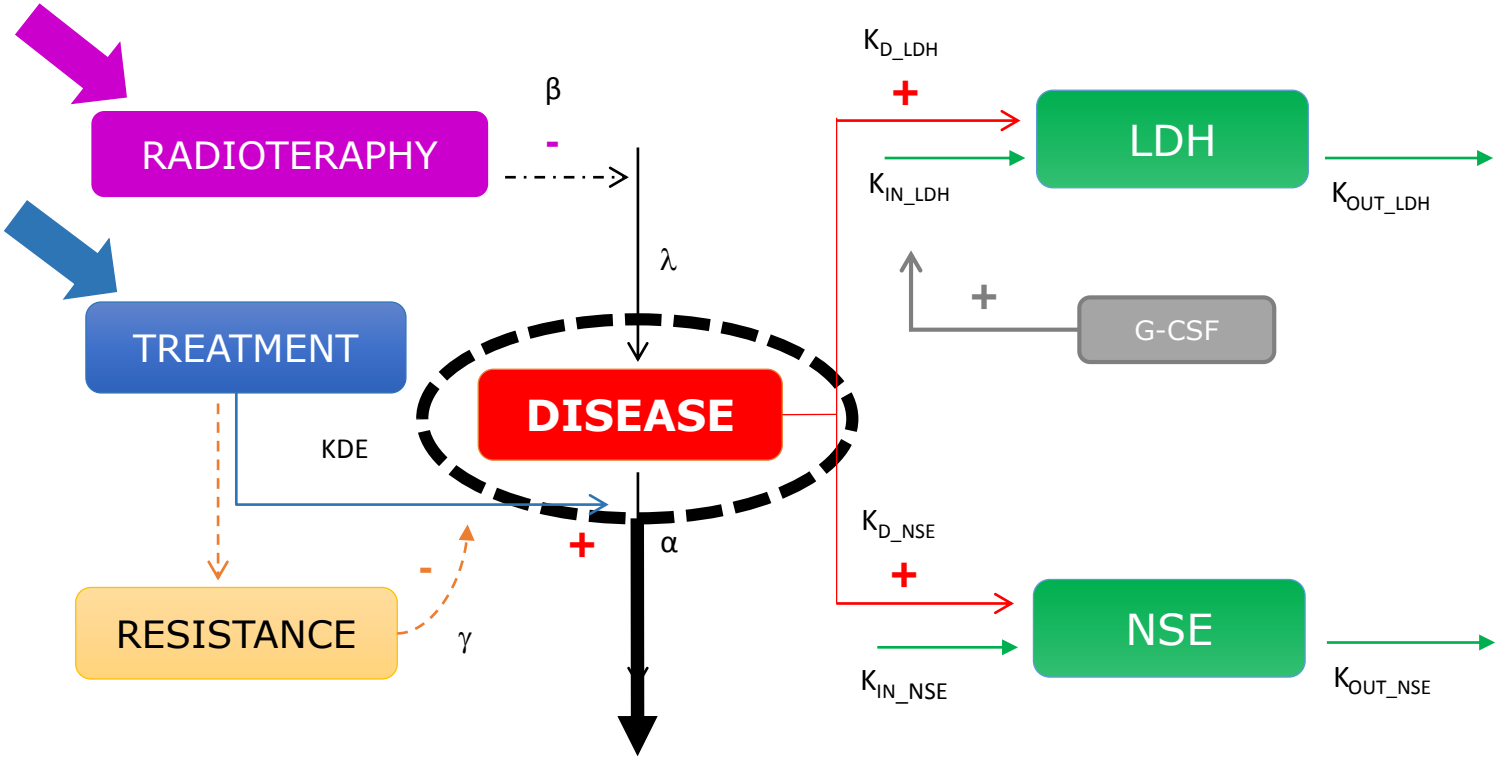
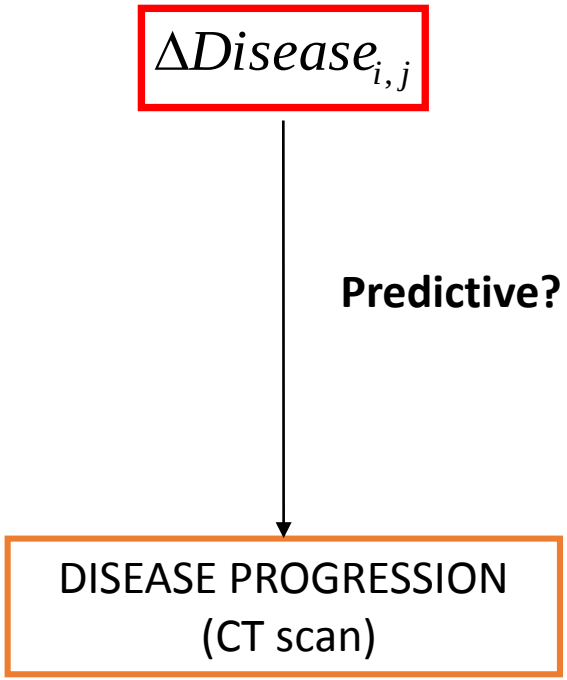


$$\Delta Disease_{i,j} = \frac{Disease_{i,j} - Disease_{i,j-1}}{Disease_{i,j}}$$

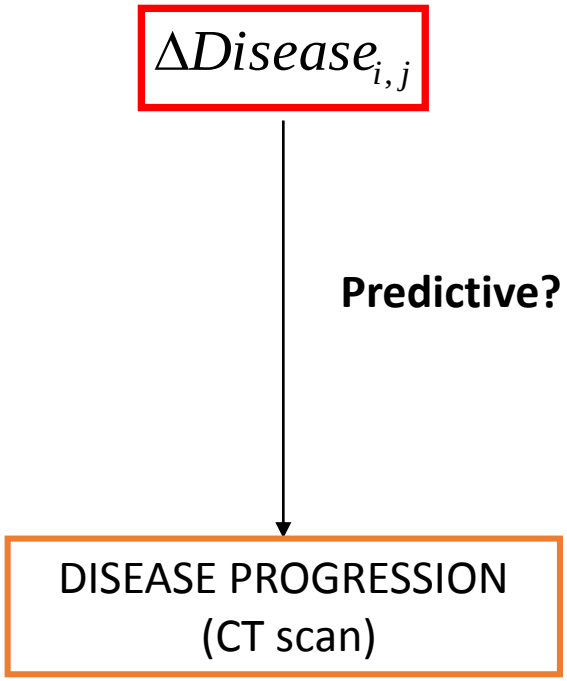
i = patient i
j = CT scan j

We can calculate the change in total underlying latent disease between a CT scan and its previous CT scan

Is our model predictive of CT scan outcomes?



Receiver operating characteristic (ROC)

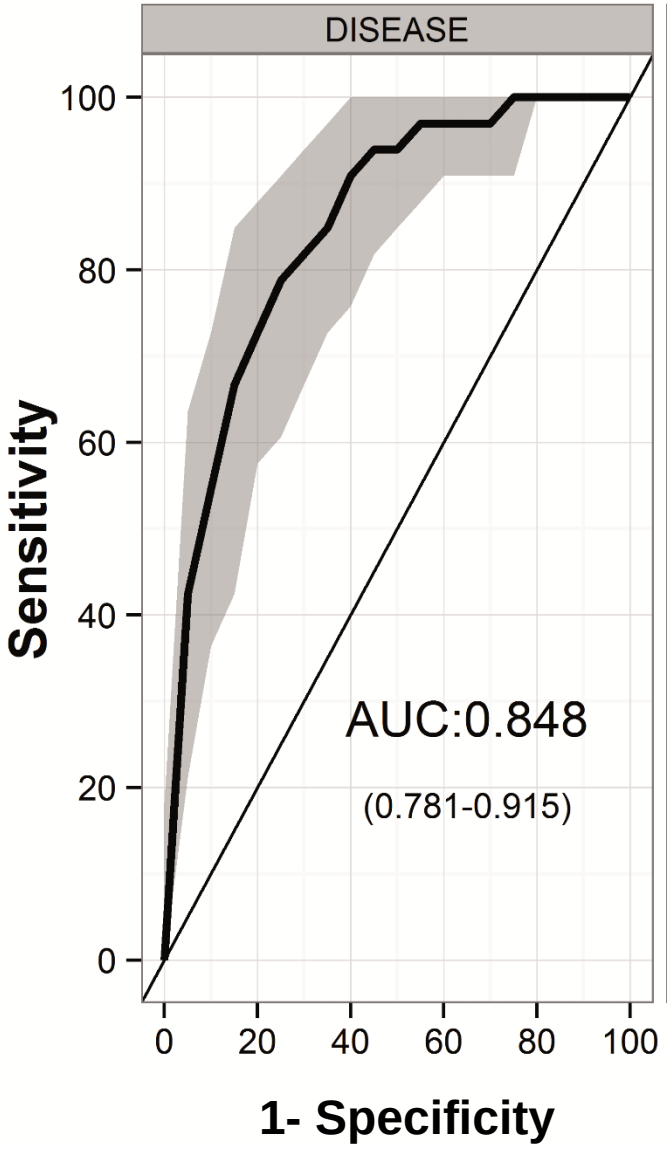


Receiver operating characteristic (ROC)

$\Delta Disease_{i,j}$

Predictive?

DISEASE PROGRESSION
(CT scan)



Buil-Bruna et al, The AAPS Journal 2014

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(in absence of tumor size information)

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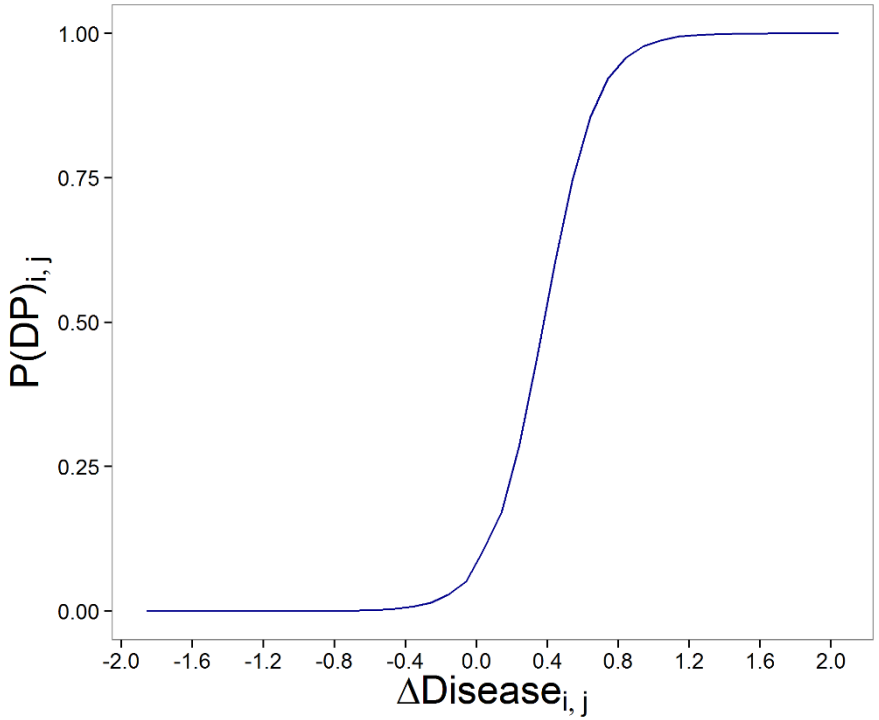
Combined biomarker/RECIST model

$$P(DP_{i,j} \mid \eta) = \frac{e^{L}}{e^{L}+1}, \quad L = \theta_1 + \theta_2 \times \Delta Disease_{i,j} + \eta$$



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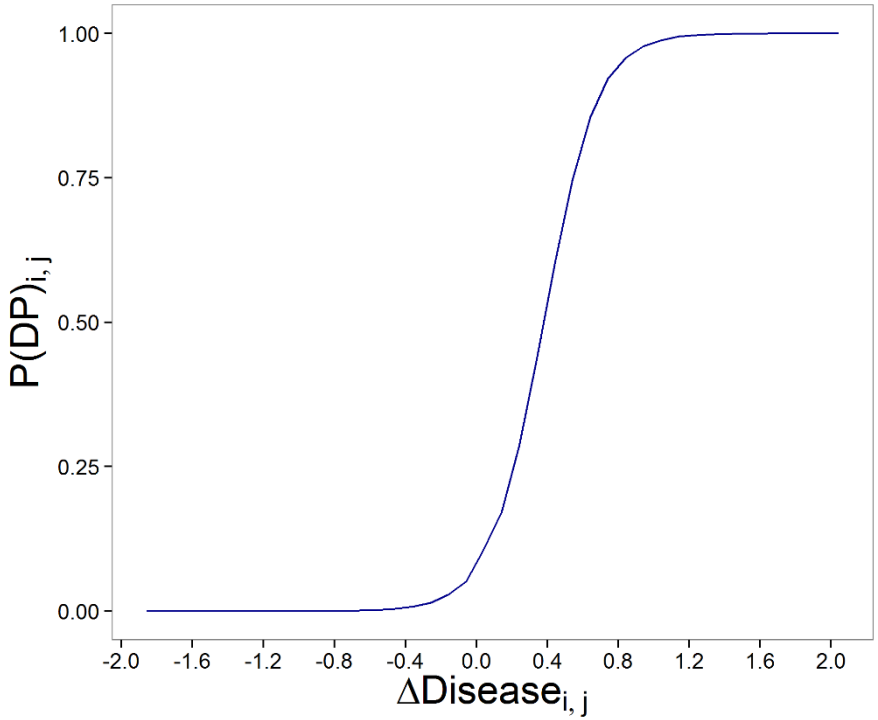
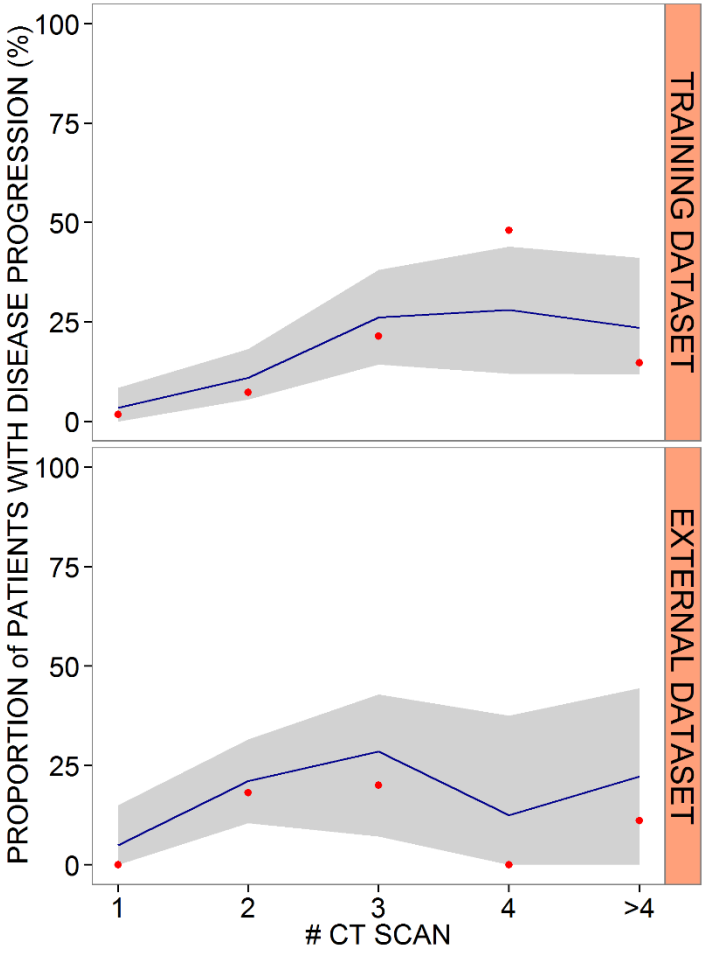
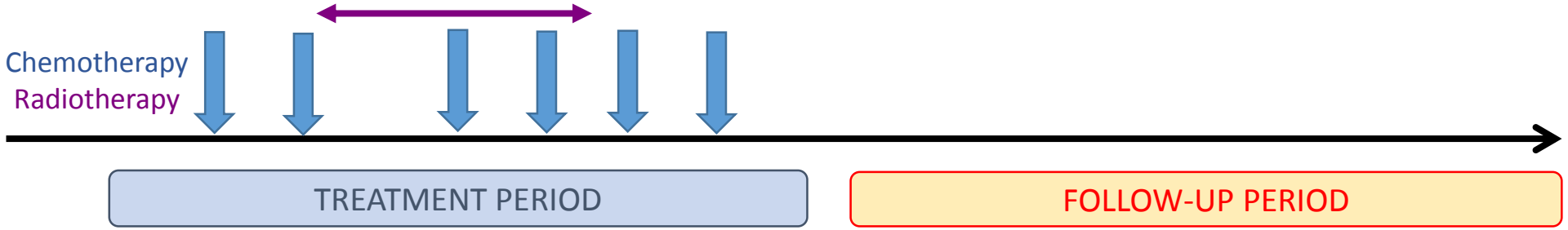


VISUAL PREDICTIVE CHECK



Aims



TREATMENT PERIOD

FOLLOW-UP PERIOD

1st FOLLOW-UP CT SCAN

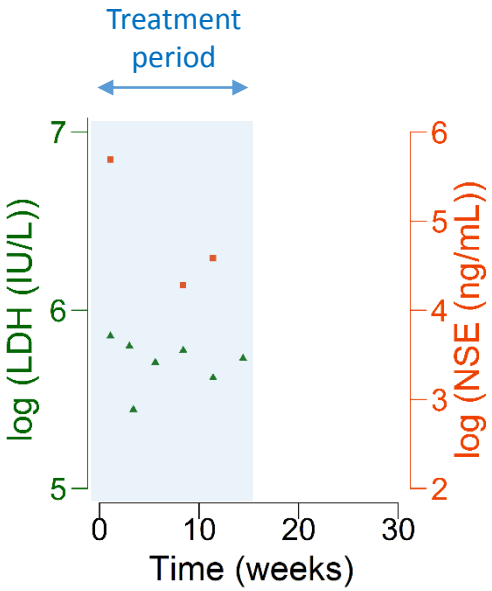
2nd FOLLOW-UP CT SCAN

~ Week 30

~ Week 40

To develop a framework to early predict individual future disease progression

Early prediction of P(DP): Example individual patient



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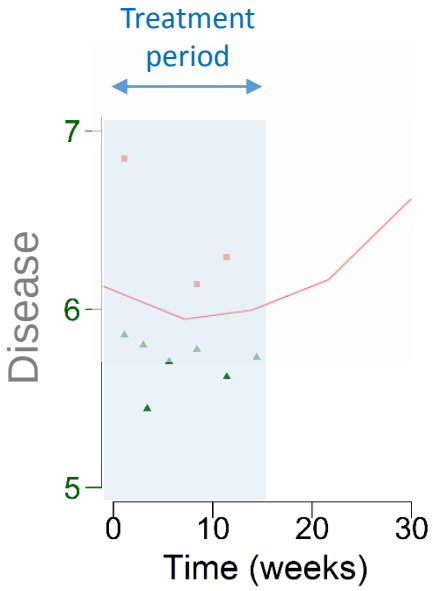
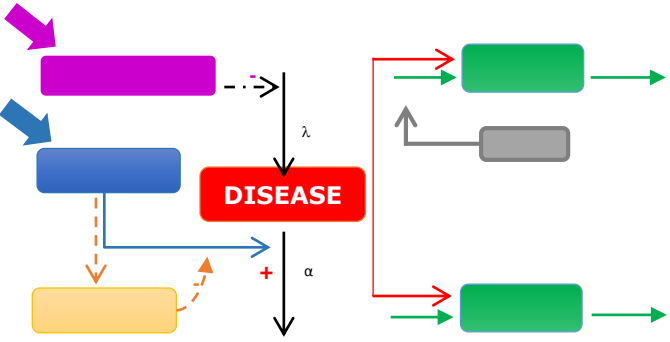
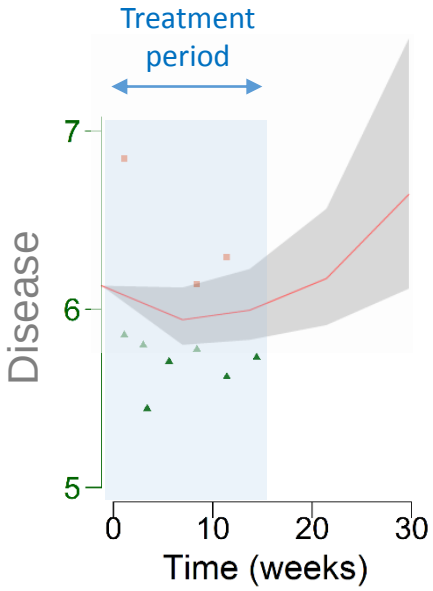


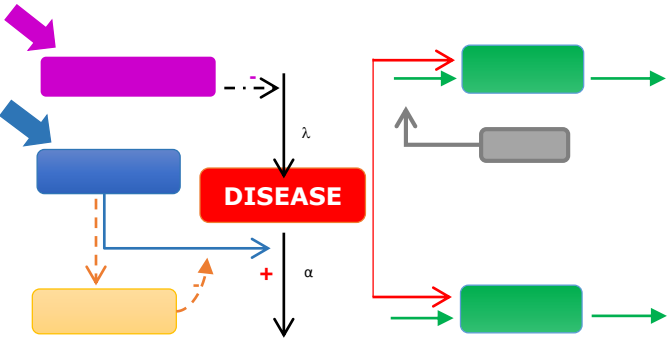


Early prediction of P(DP): Example individual patient

FULL BAYESIAN MCMC ANALYSIS:

- NONMEM 7.2 ($BAYES) + Verbatim code
- Retrieve last 1000 MCMC samples
  → individual posterior distribution





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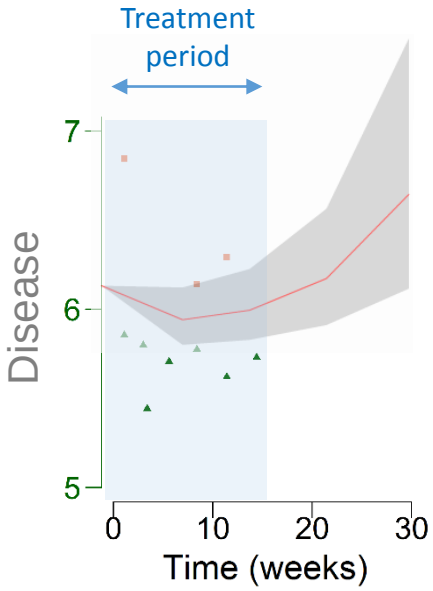

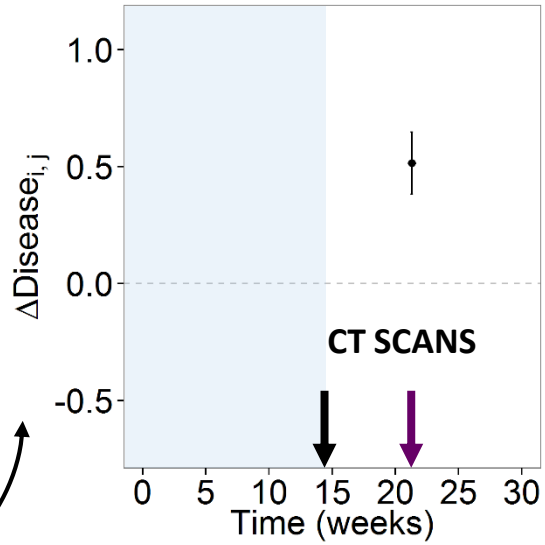

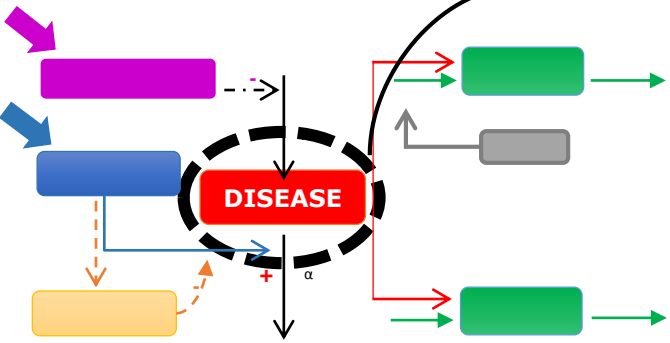

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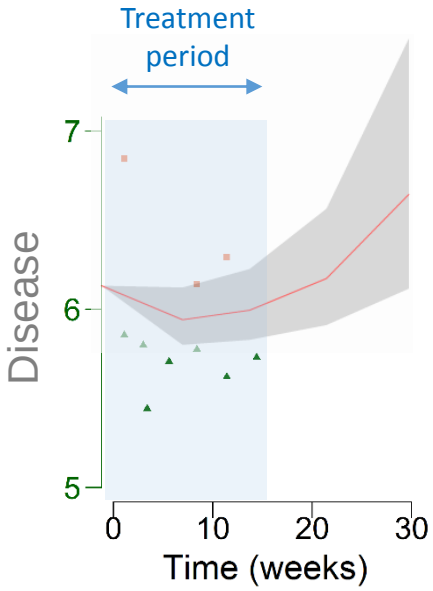
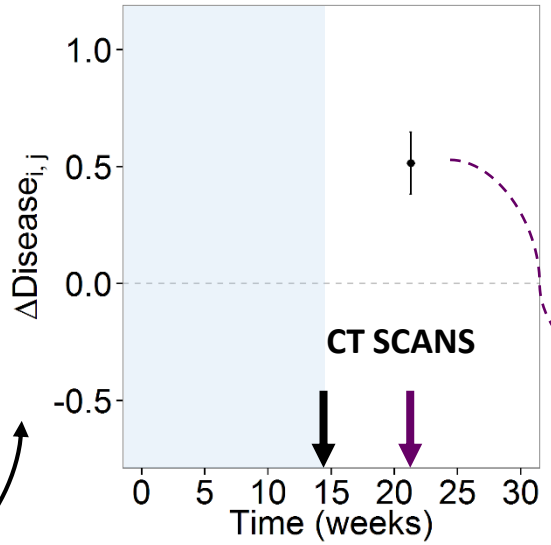
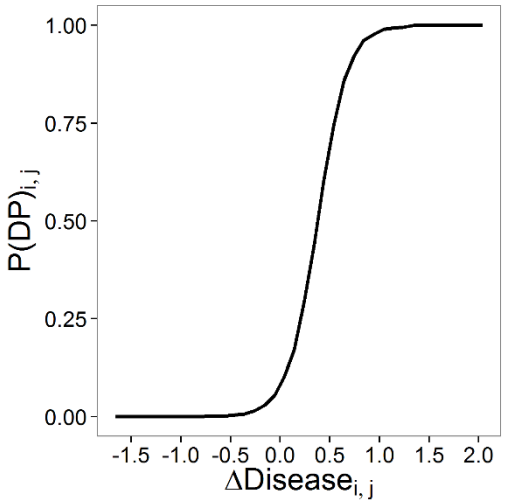
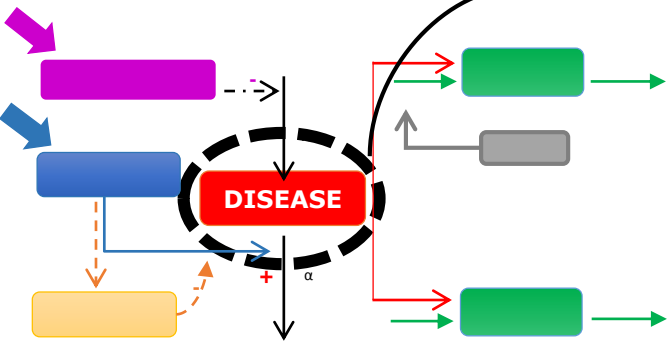




1st FOLLOW-UP SCAN





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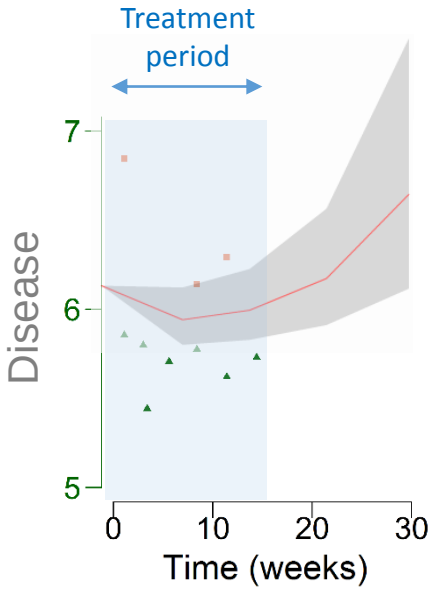

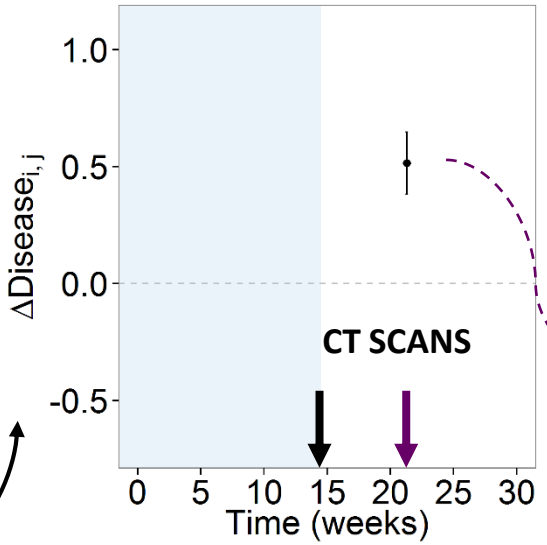

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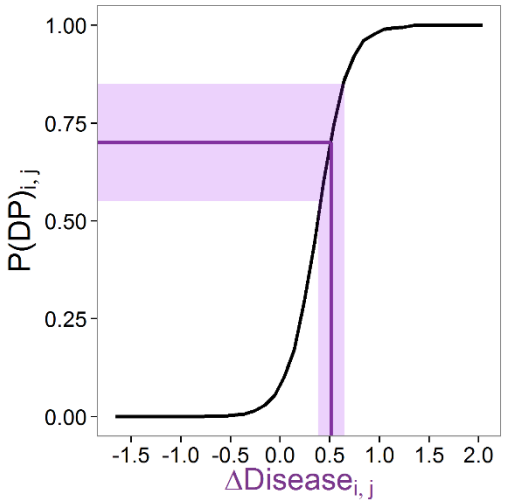

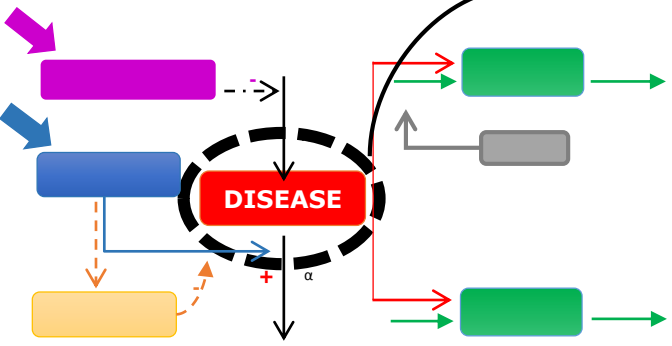

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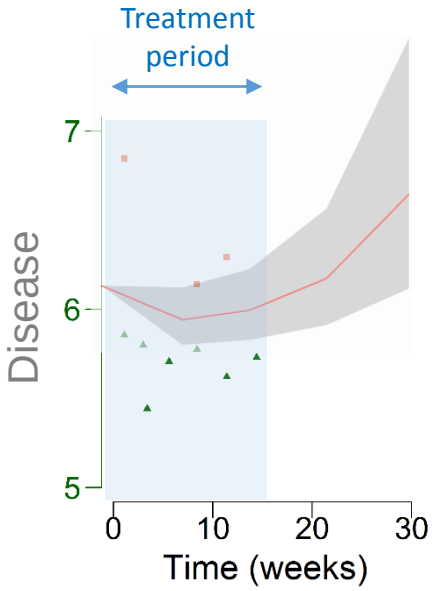
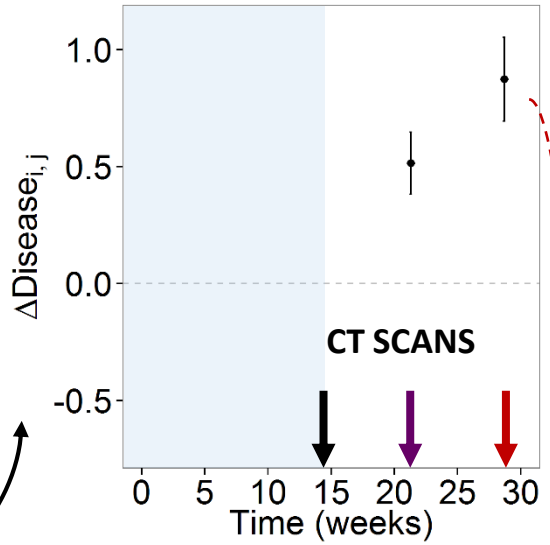
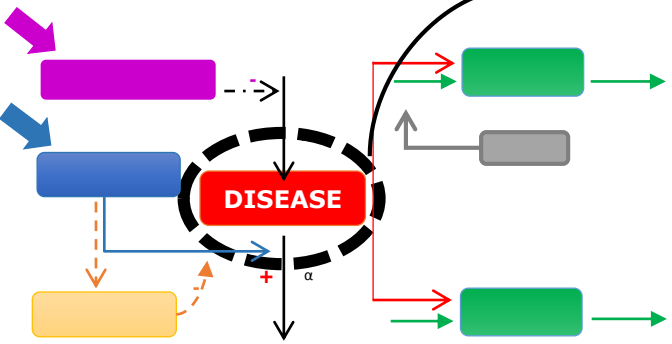
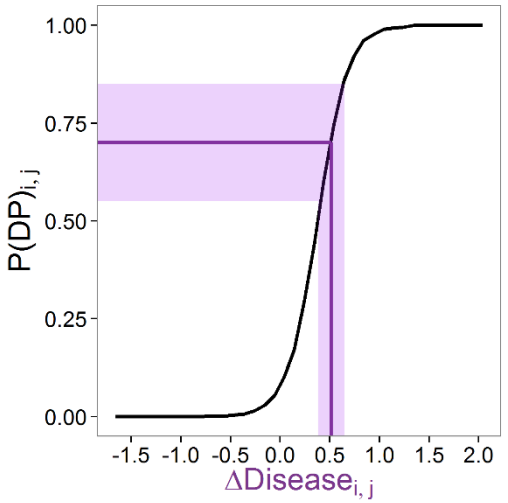
  → individual posterior distribution



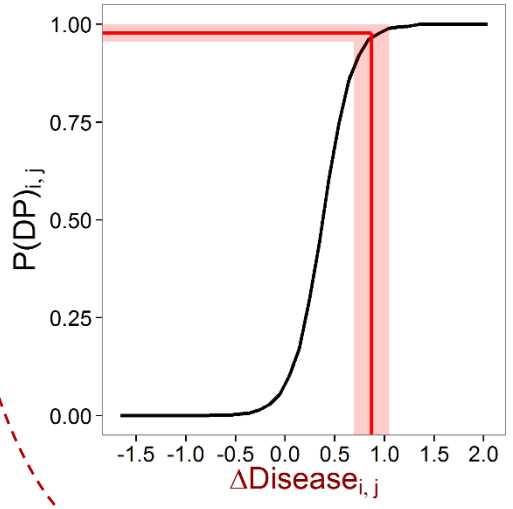




1st FOLLOW-UP SCAN



2nd FOLLOW-UP SCAN



Early prediction of P(DP): Decision making

- When P(DP) is high patients may be switched to 2nd line treatment early

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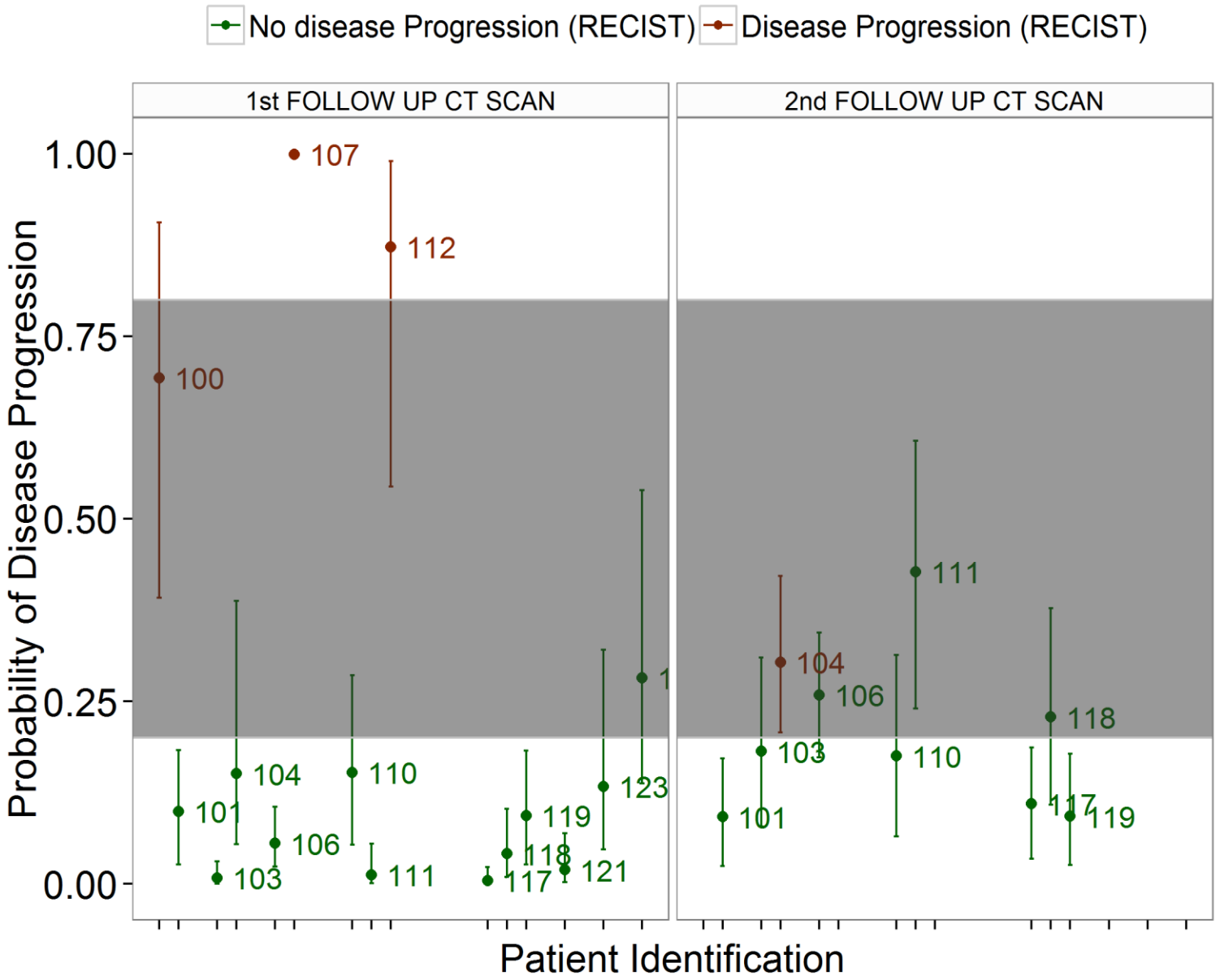
- Clinician's decision may depend on 2nd line treatment:
    - Expected efficacy and toxicity
    - Patient characteristics
    - Financial burden

Early prediction of P(DP): External dataset



Summary

- We have developed a model which allowed us to identify the relationship between biomarker dynamics and tumour size dynamics.

- We have predicted clinical outcome in an external data follow up CT scans for 75% of the patients using only their within treatment data.

- We propose a modelling framework which provides clinicians the possibility to improve disease monitoring in SCLC patients.

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