

# Identification of early longitudinal prognostic predictors of efficacy in lung cancer patients: A coupled tumour dynamics & C-reactive protein model

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**Tumour Growth Dynamics session  
31<sup>st</sup> PAGE meeting 2023, A Coruña, Spain  
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# C-reactive protein

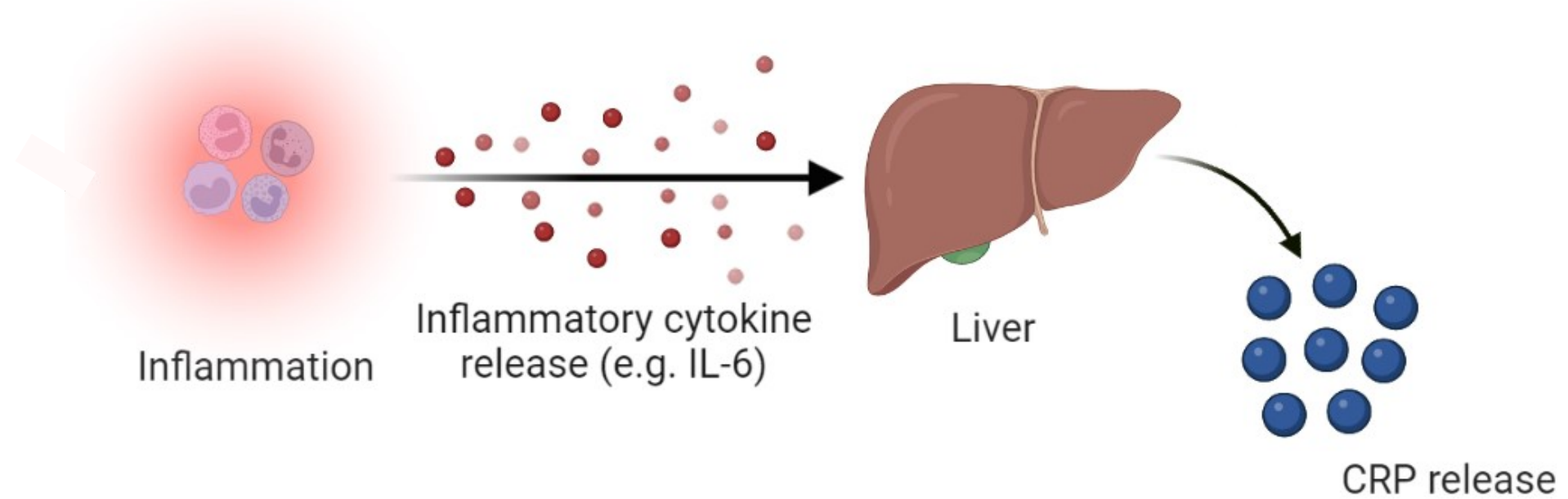


Figure created in Biorender.com

- Non-specific marker of inflammation, infection or tissue injury<sup>1,2</sup>
- Metric of inflammatory response<sup>1,2</sup>

<sup>1</sup> Ansar and Ghosh (2013)

CRP : C-reactive protein

<sup>2</sup> Pepys and Hirschfield (2003)

IL-6 : Interleukin 6

# C-reactive protein

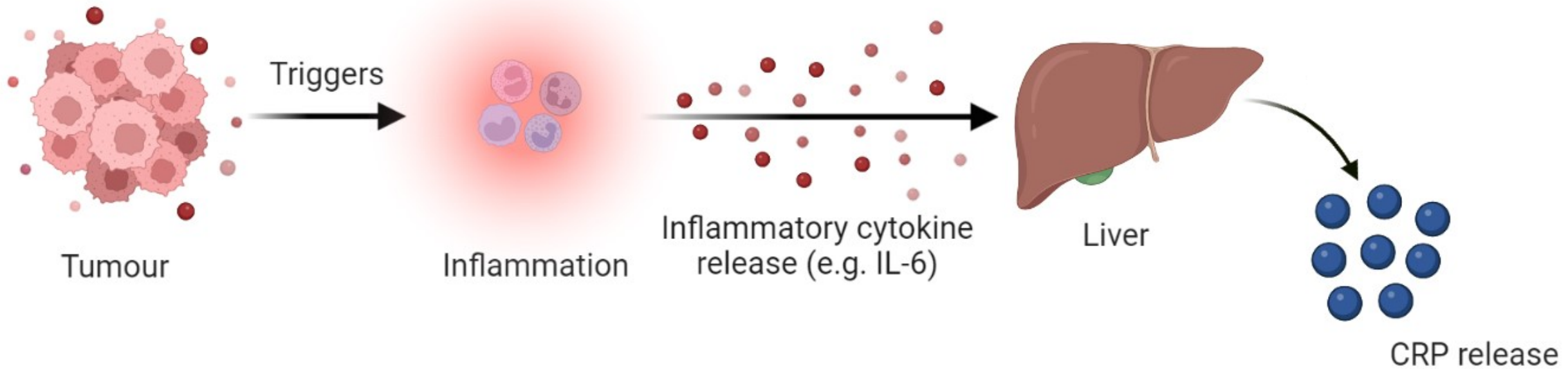


Figure created in Biorender.com

- Associated with advanced cancer stages, metastasis and poor prognosis<sup>1,2</sup>
  - CRP reflects severity of tissue damage associated with cancer growth and progression

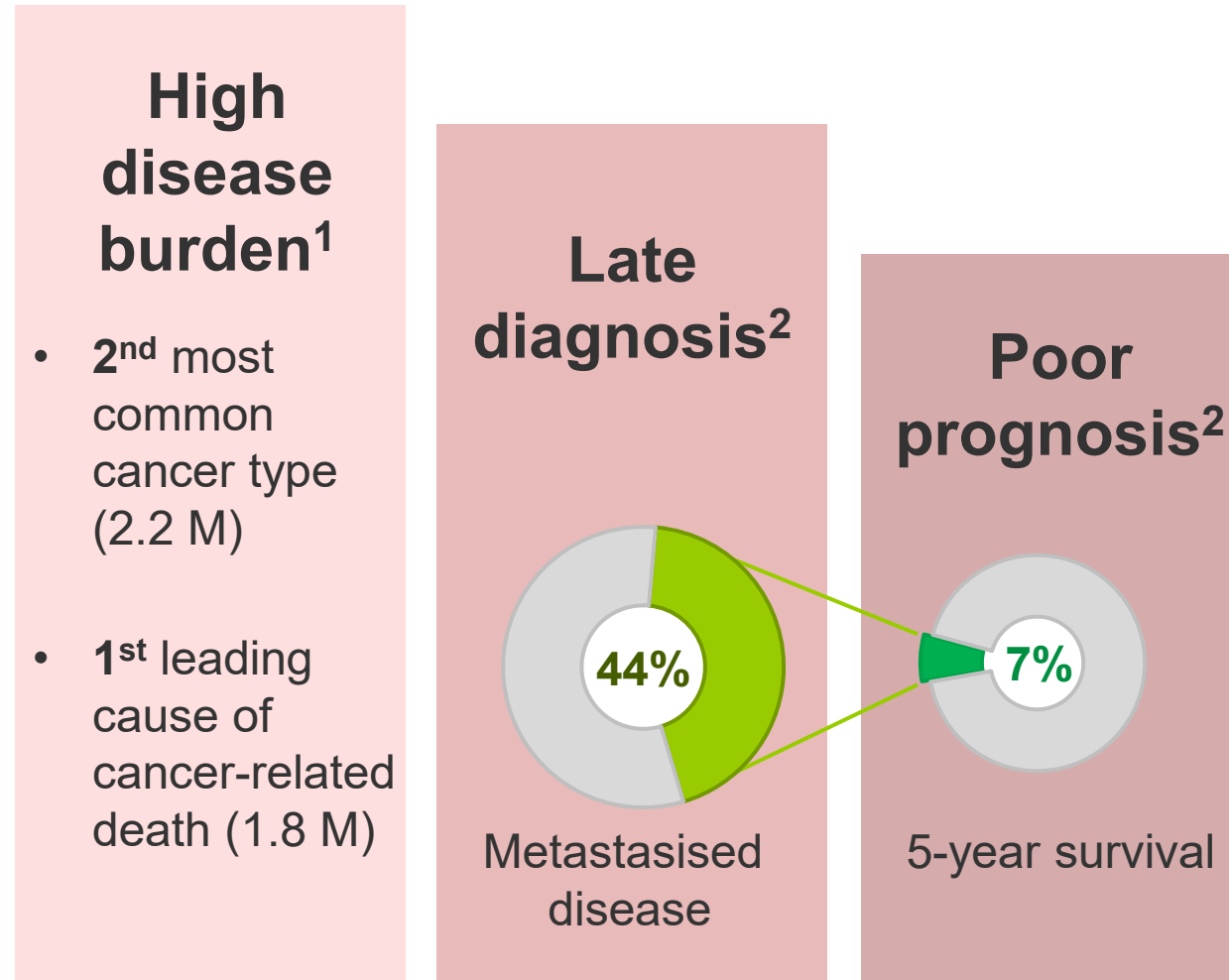
<sup>1</sup> Heikkilä *et al.* (2007)

CRP : C-reactive protein

<sup>2</sup> Hart *et al.* (2020)

IL-6 : Interleukin 6

# Lung cancer



<sup>1</sup> Data source: GLOBOCAN 2020 (<http://gco.iarc.fr/>) [Accessed 6 April 2023]

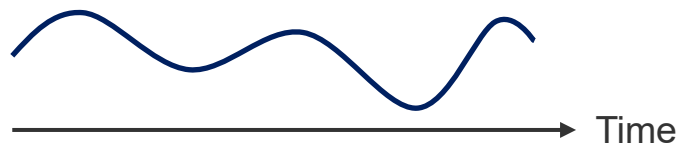
<sup>2</sup> State of lung cancer, American Lung Association 2022 report

## Motivation for our research

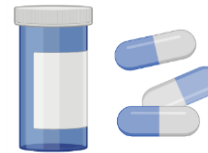
- Need prognostic markers to:
  - Predict response to NSCLC treatment
  - Identify patients at risk of poor prognosis

## Knowledge gap

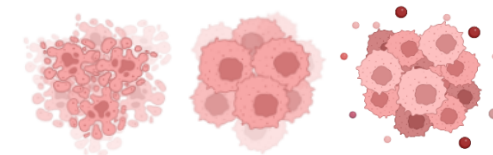
- Focus on baseline biomarker concentration rather than longitudinal concentration



*Biomarker kinetics*



*Influence of treatment*



*Tumour dynamics*

## Objective

- Identify **early** prognostic predictors of efficacy in lung cancer patients



- Focus on longitudinal data and CRP as inflammatory marker
- Would modulating inflammation be a good prognostic factor ?
- Would monitoring inflammation reflect disease outcome ?

CRP : C-reactive protein

# Data source: CEPAC-TDM study



Kantonsspital  
St.Gallen



Deutsches Herzzentrum München  
des Freistaates Bayern  
Klinik an der Technischen Universität München TUM

## Study population (n=365 patients)

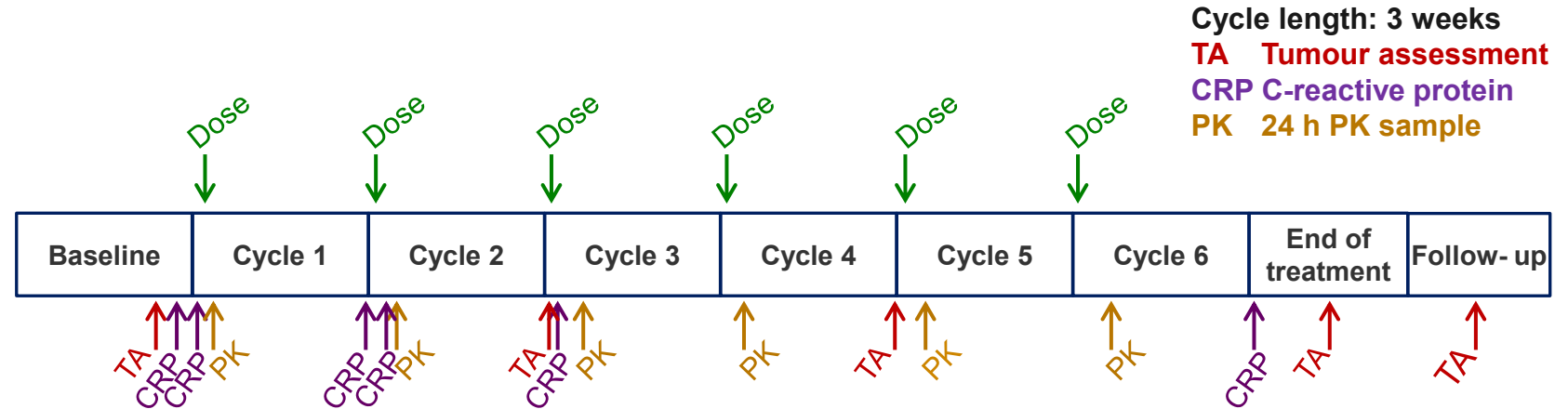


Lung cancer

Advanced NSCLC  
(Stage IIIB, IV)

**1<sup>st</sup>-line treatment**  
Paclitaxel +  
carboplatin/cisplatin

## Study design



Cycle length: 3 weeks  
TA Tumour assessment  
CRP C-reactive protein  
PK 24 h PK sample

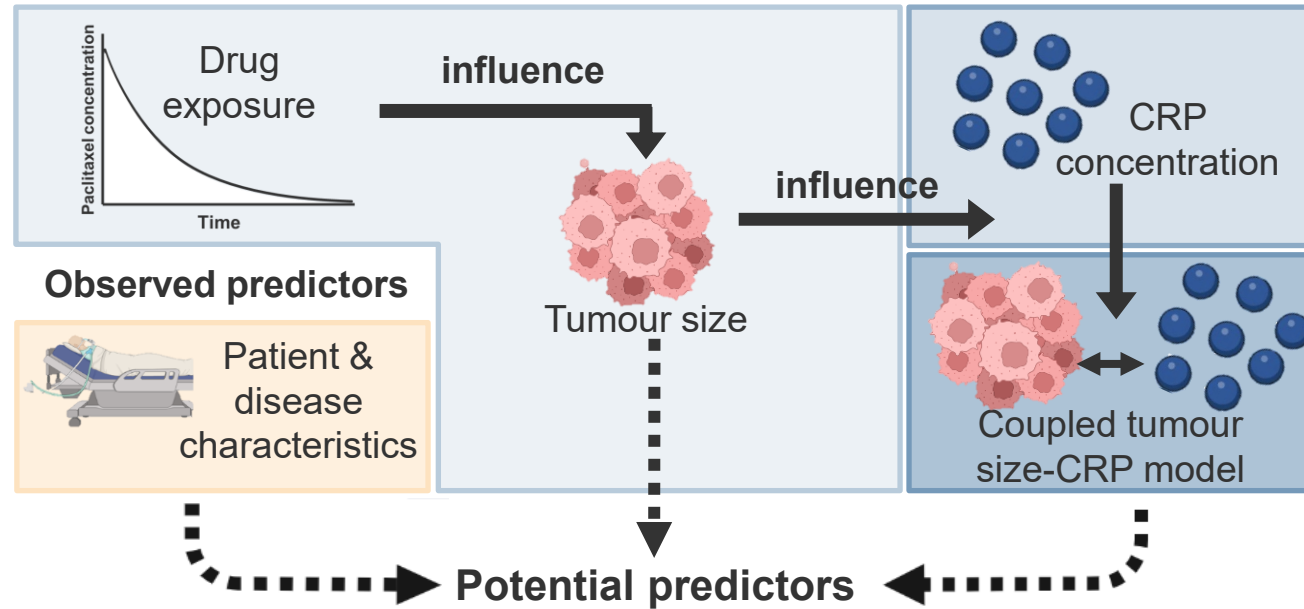
## Two paclitaxel treatment arms

Standard dosing (200 mg/m<sup>2</sup>)  
Individualised dosing (additional PK samples)



# Modelling framework

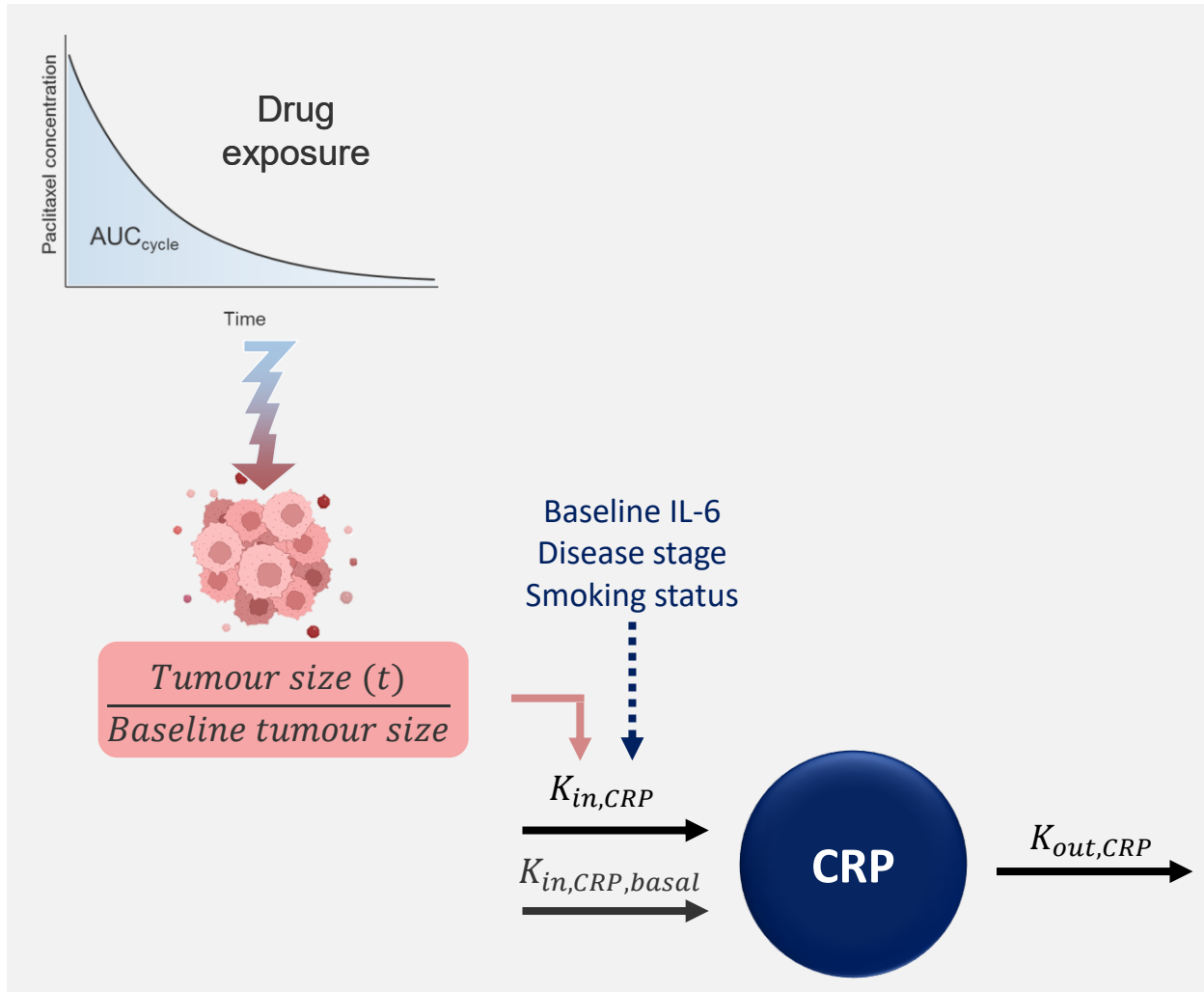
(A) Mechanistic understanding of relationship between drug exposure, tumour size and CRP concentrations, and model-derived predictors



(B) Impact on efficacy endpoints (Time-to-event modelling)

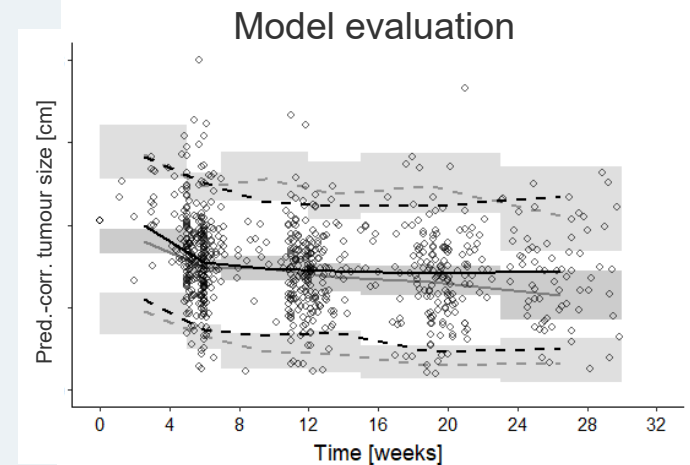


# Linking tumour dynamics to circulating CRP concentration



## Characterisation of tumour dynamics

- Previously developed tumour growth inhibition model<sup>1</sup> (n=365 patients)
- Chemotherapy-induced tumour dynamics model
  - Drug exposure
  - Resistance
- Derived individual tumour sizes

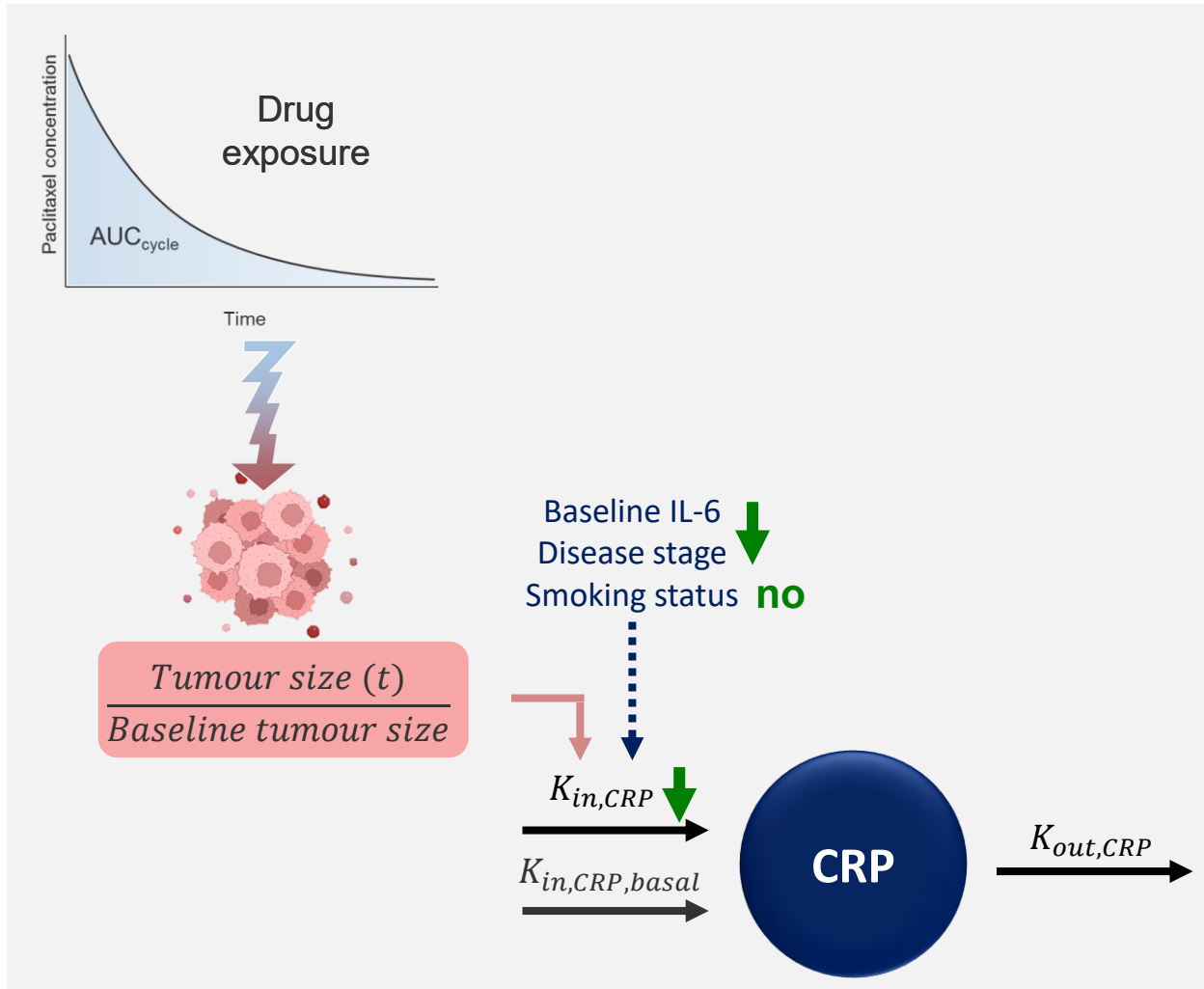


$K_{in,CRP}$  : Zero-order production rate constant  
 $K_{in,CRP,basal}$  : Zero-order basal production rate constant  
 $K_{out,CRP}$  : First-order degradation rate constant  
 CRP : C-reactive protein  
 IL-6 : Interleukin 6

<sup>1</sup> Ojara *et al.* (2023)



# Linking tumour dynamics to circulating CRP concentration



## Characterisation of tumour dynamics

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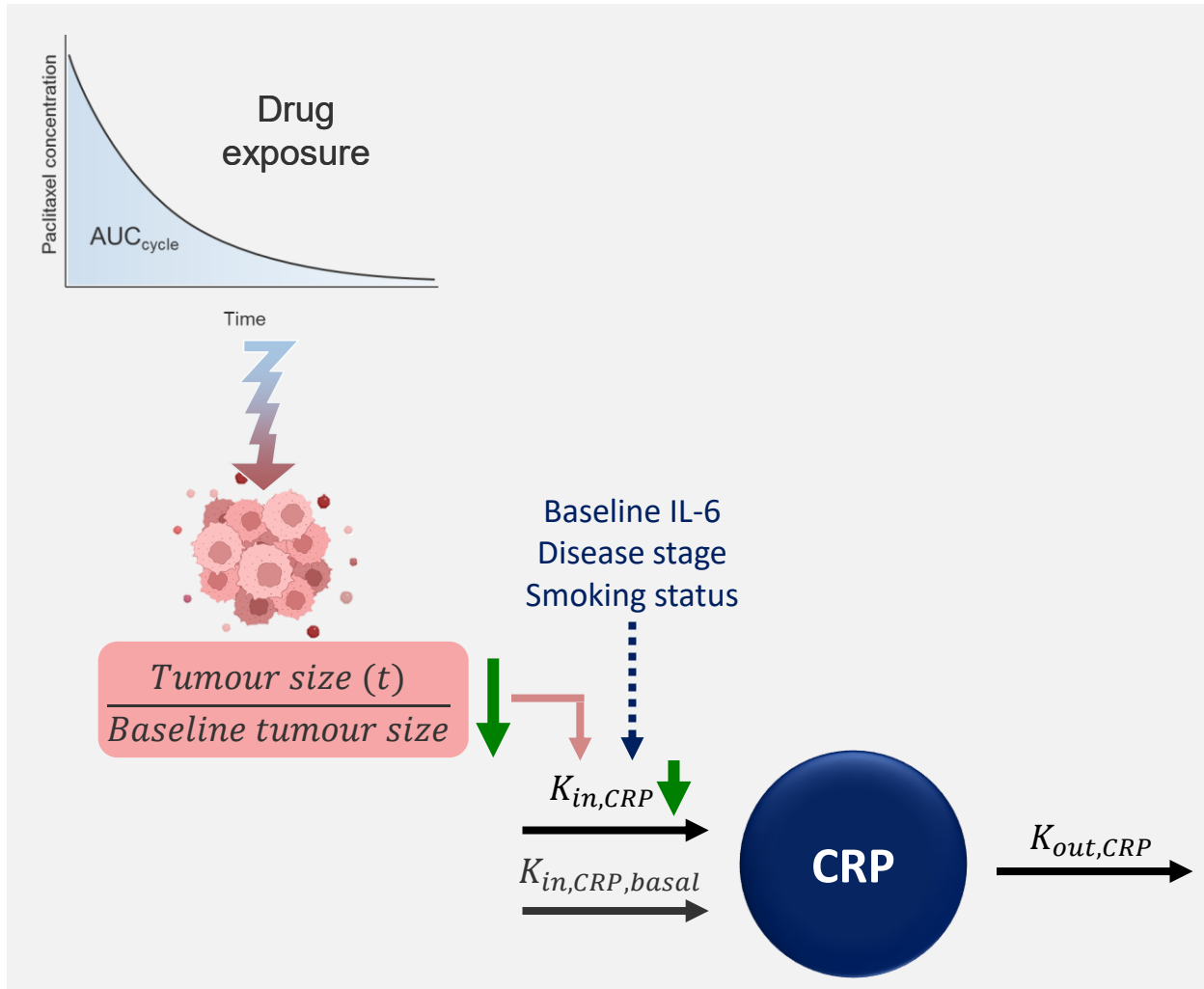
## Characterisation of CRP

- CRP turnover model (n=257 patients)
- Identify impacting factors on CRP synthesis

$K_{in,CRP}$  : Zero-order production rate constant  
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# Linking tumour dynamics to circulating CRP concentration



## Characterisation of tumour dynamics

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## Characterisation of CRP

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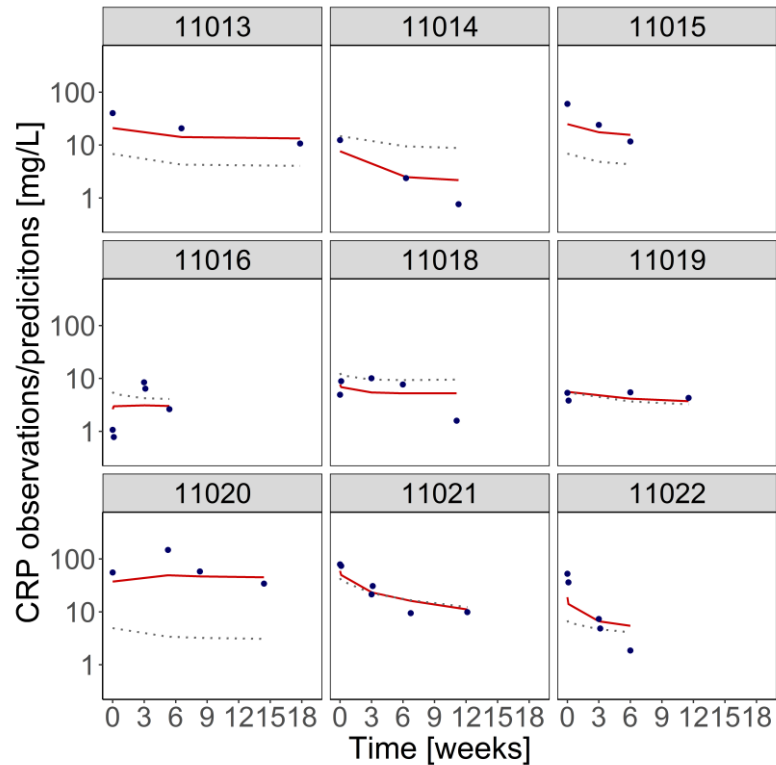
**Linear relationship between fold-change in tumour size relative to baseline and CRP synthesis**

$K_{in,CRP}$  : Zero-order production rate constant  
 $K_{in,CRP,basal}$  : Zero-order basal production rate constant  
 $K_{out,CRP}$  : First-order degradation rate constant  
 CRP : C-reactive protein  
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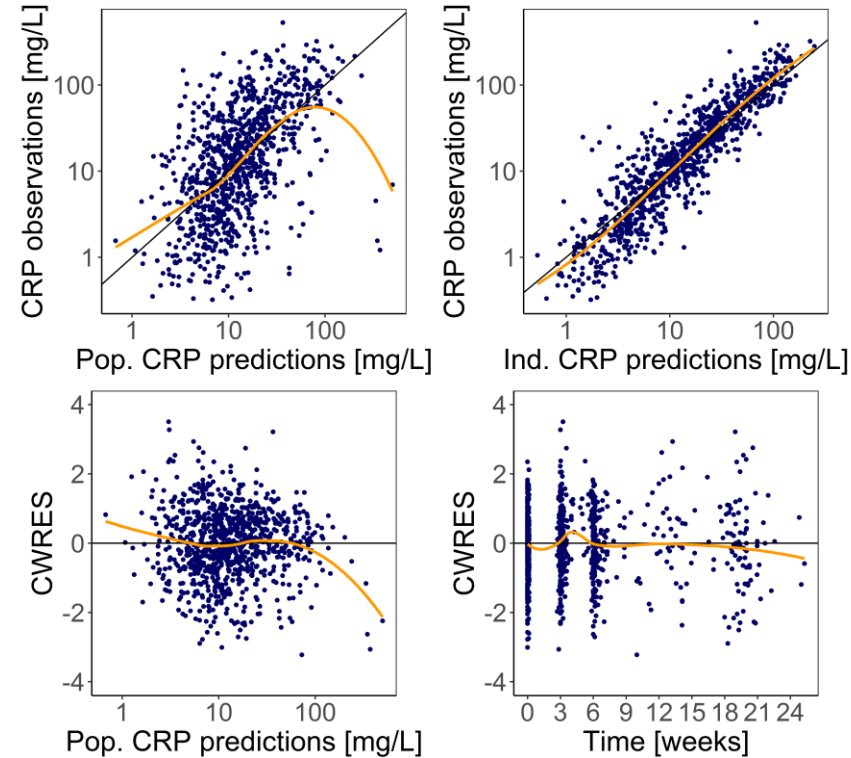
<sup>1</sup> Ojara *et al.* (2023)

# Linking tumour dynamics to circulating CRP concentration

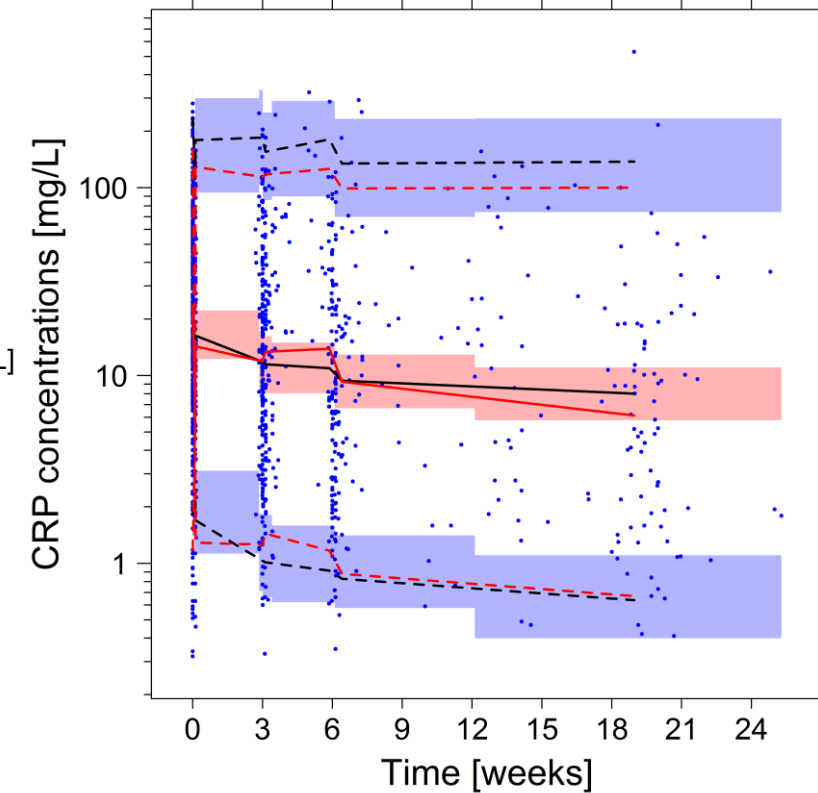
## Individual plots



## Goodness-of-fit plots



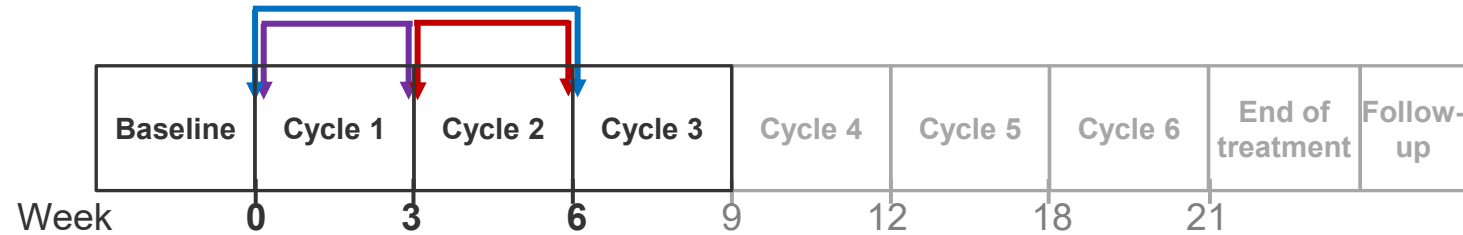
## Visual predictive check



CRP : C-reactive protein  
 CWRES : Conditional weighted residuals

# Selection of predictors

- Focus on **early** metrics (*first 3 cycles*)



- Selected predictors:
  - CRP-related metrics, neutrophil to lymphocyte ratio → *markers of inflammation*



## CRP-related metrics

- Observed baseline
  - Estimated: cycle 1,2,3
  - Relative change
  - Absolute change
  - Fold change
- } cycle 2 from 1  
 } cycle 3 from 1  
 } cycle 3 from 2

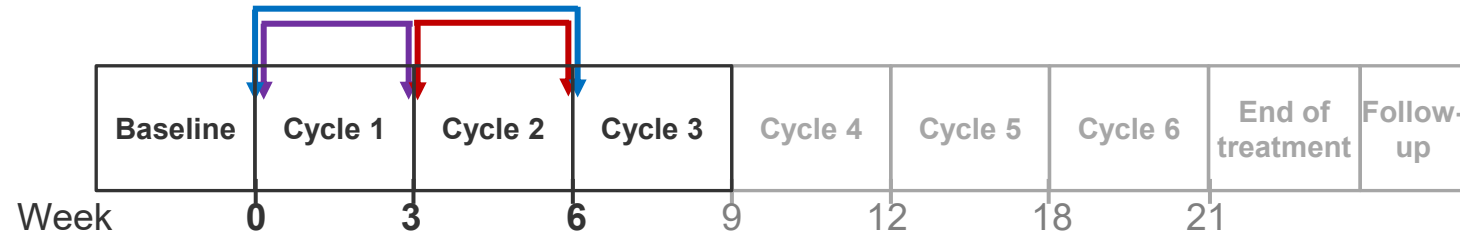


## Neutrophil to lymphocyte ratio

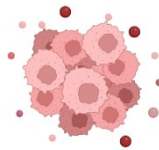
- Observed: cycle 1, 2
  - Relative change
  - Absolute change
  - Fold change
- } cycle 2 from 1

# Selection of predictors

- Focus on **early** metrics (*first 3 cycles*)



- Selected predictors:
  - CRP-related metrics, neutrophil to lymphocyte ratio → **markers of inflammation**
  - Tumour size-related metrics

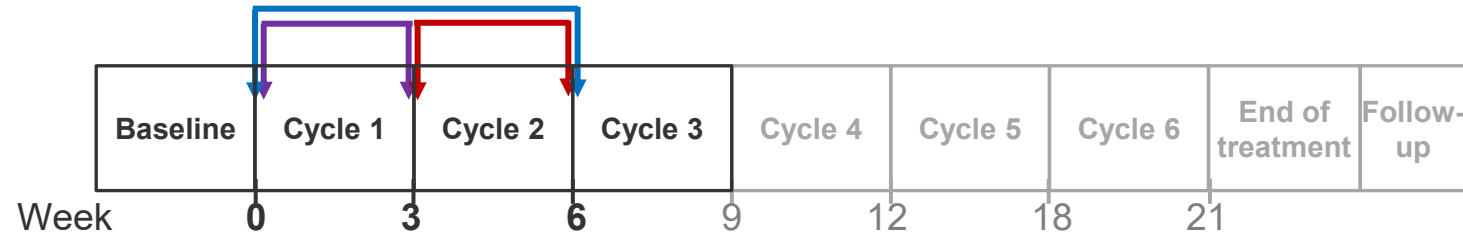


## Tumour size-related metrics

- Observed baseline
- Tumour growth rate
- Fold change in tumour size on  $K_{in,CRP}$
- Estimated tumour size relative to baseline tumour size:
  - Week 8
  - Week 7

# Selection of predictors

- Focus on **early** metrics (*first 3 cycles*)



- Selected predictors:
  - CRP-related metrics, neutrophil to lymphocyte ratio → **markers of inflammation**
  - Tumour size-related metrics
  - Patient/disease characteristics



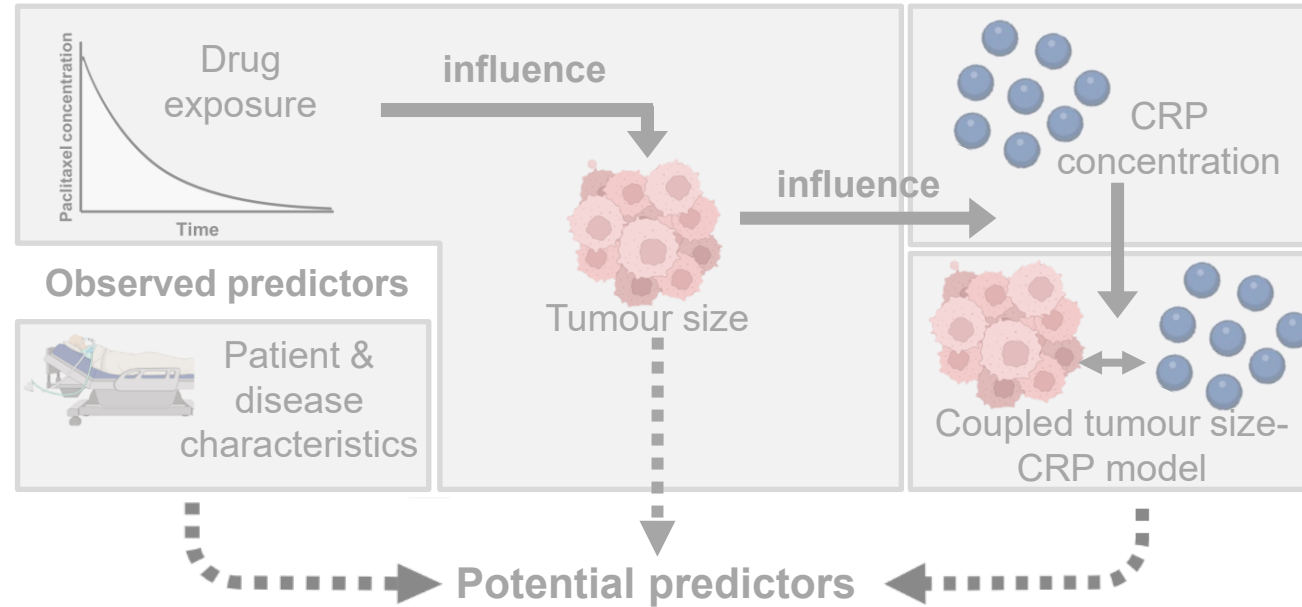
## Patient and disease characteristics

Baseline ECOG  
 Smoking status  
 Liver metastasis  
 Brain metastasis  
 Disease stage

CRP :C-reactive protein  
 ECOG :Eastern Cooperative Oncology Group

# Modelling framework

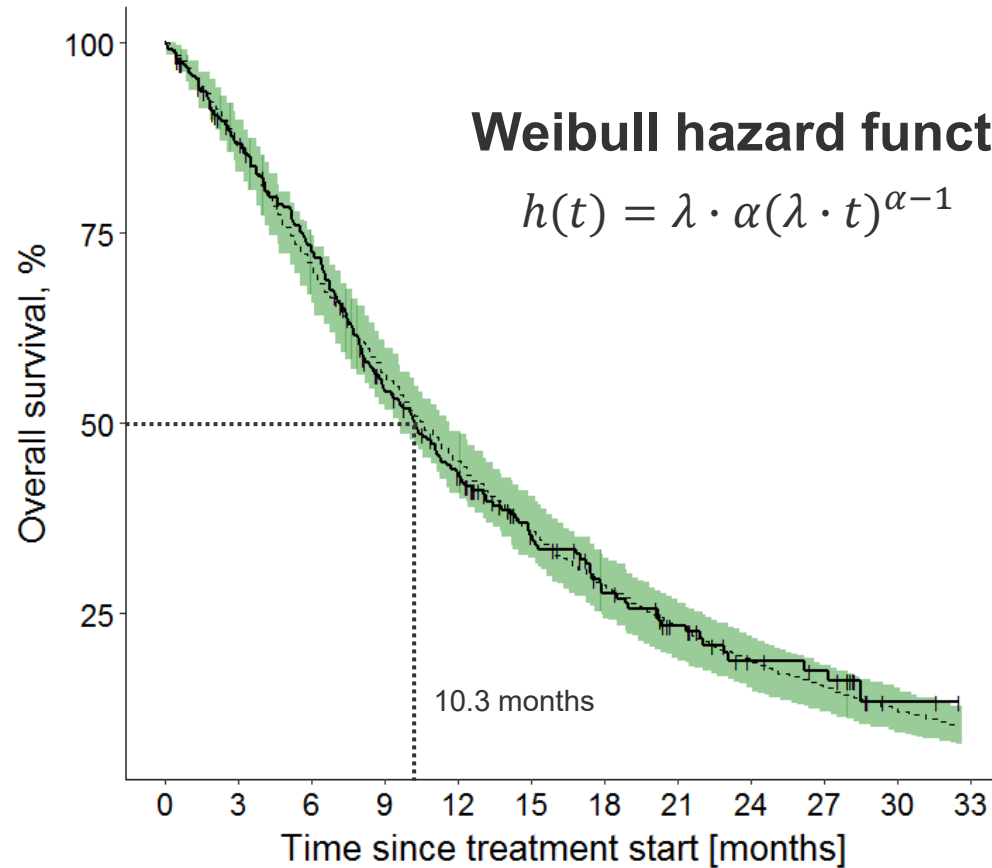
**(A) Mechanistic understanding of relationship between drug exposure, tumour size and CRP concentrations, and model-derived predictors**



**(B) Impact on efficacy endpoints (Time-to-event modelling)**



# Time-to-event modelling of overall survival and identification of significant predictors



## Identified significant predictors

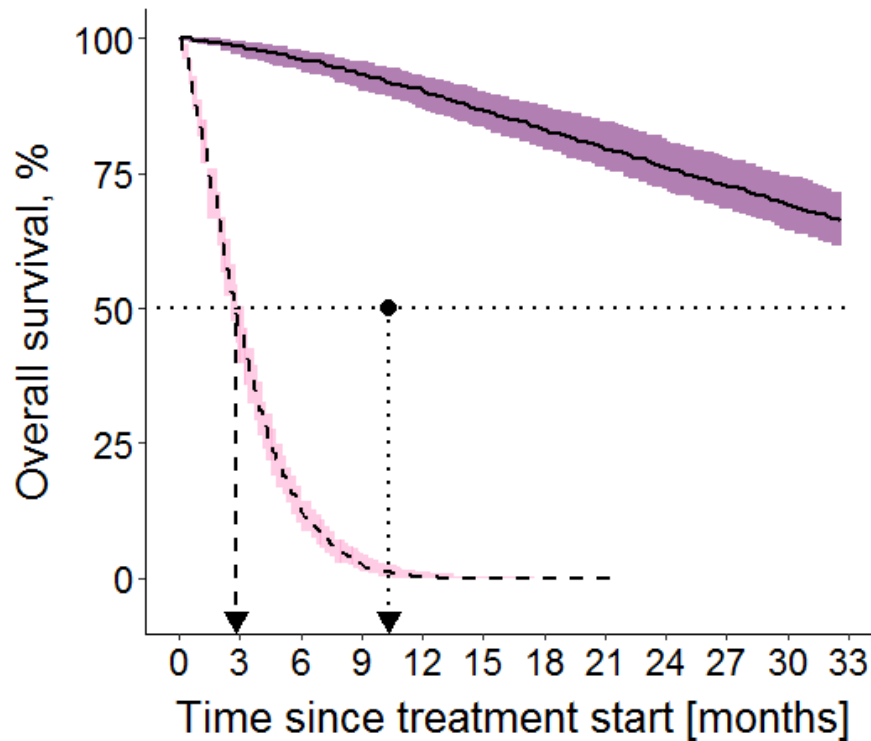
- *Inflammatory level at cycle 3* ( $CRP_{cycle3}$ )
- *Tumour load* (Baseline tumour size)
- *Tumour shrinkage* (RS8)
- *Liver lesions*

Solid line : Observed survival data  
 Dashed line : Median model predicted profile  
 Dotted line : Median overall survival  
 Vertical lines : Censoring  
 Green shade : 90% confidence interval

$\lambda$  : Scale parameter  
 $\alpha$  : Shape parameter  
 CRP : C-reactive protein  
 RS8 : Tumour size at week 8 relative to baseline tumour size



# Time-to-event modelling of overall survival and identification of significant predictors



## Identified significant predictors

- *Inflammatory level at cycle 3* ( $CRP_{cycle3}$ ) ↓↑
- *Tumour load* (Baseline tumour size) ↓↑
- *Tumour shrinkage* (RS8) ↓↑
- *Liver lesions* no yes

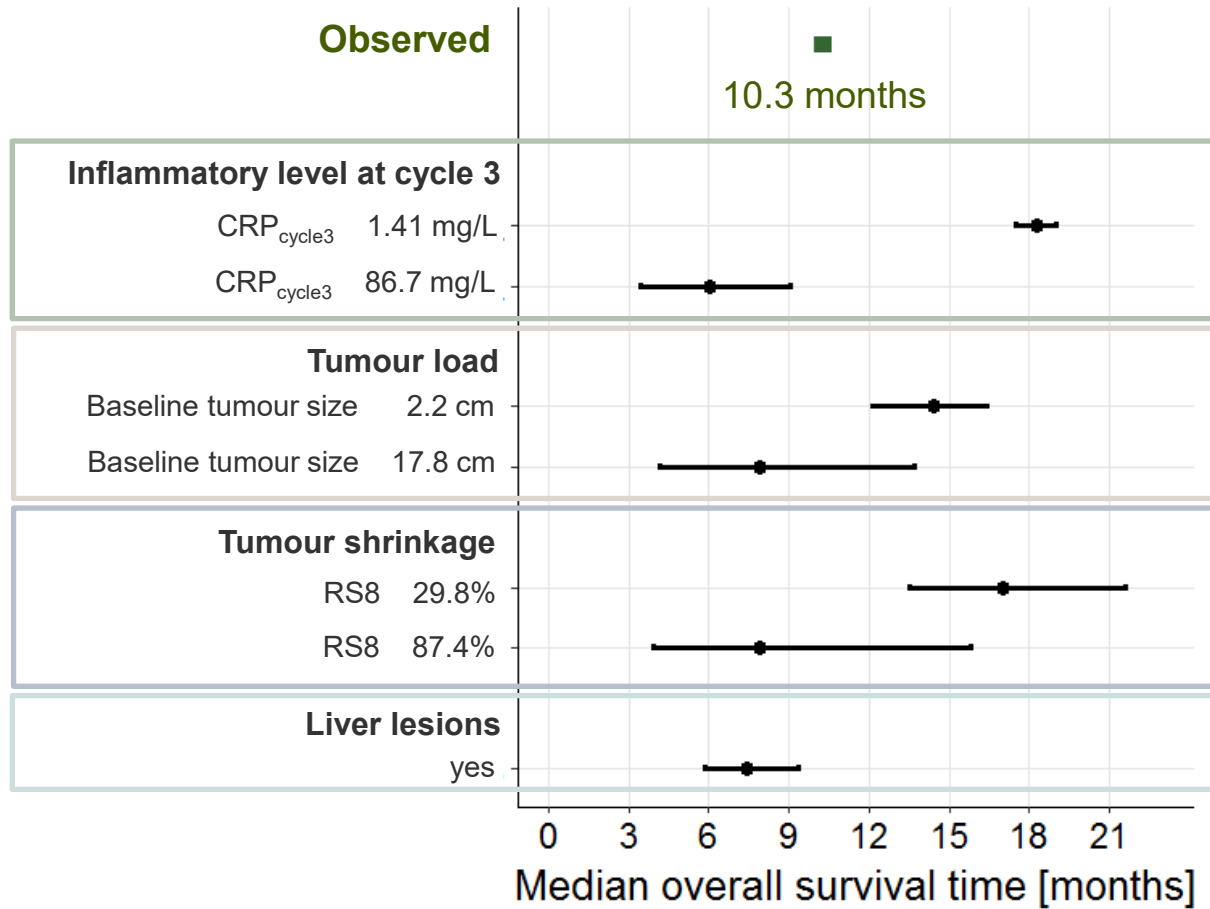
Solid line : Observed survival data  
 Dashed line : Median model predicted profile  
 Dotted line : Median overall survival  
 Vertical lines : Censoring  
 Green shade : 90% confidence interval

— Predictor: 5<sup>th</sup> percentile/no  
 - - - Predictor: 95<sup>th</sup> percentile/yes  
 .....●..... Observed median overall survival

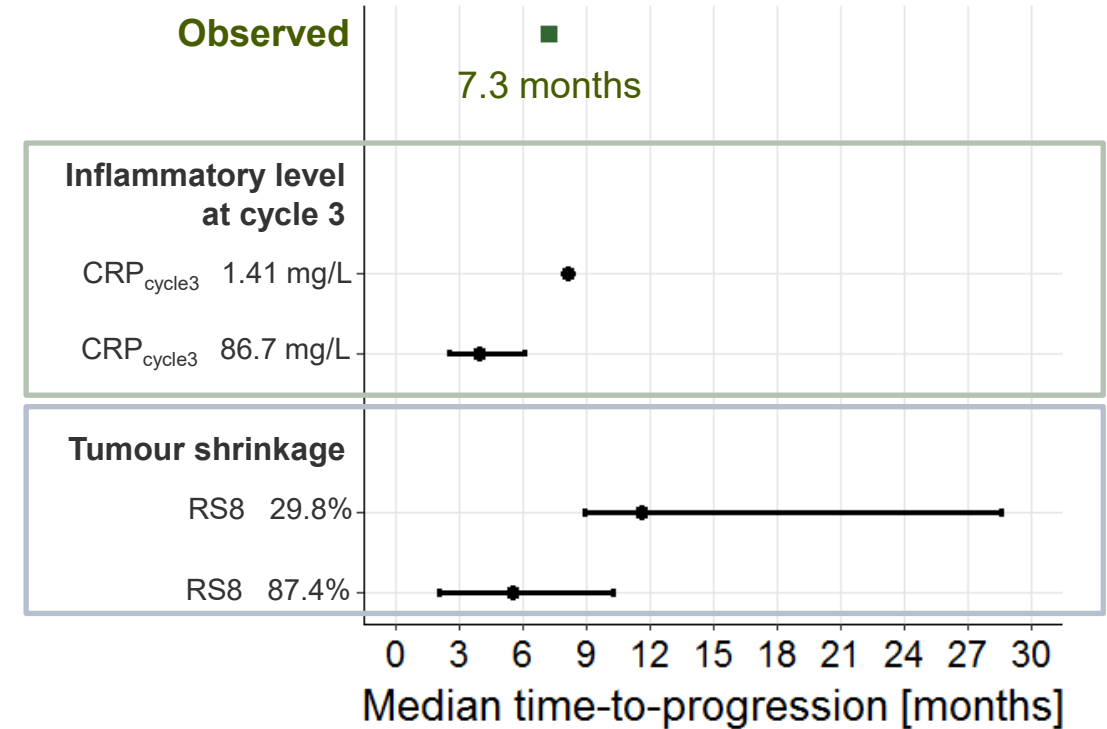
$\lambda$  : Scale parameter  
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# Impact of significant predictors

## Overall survival

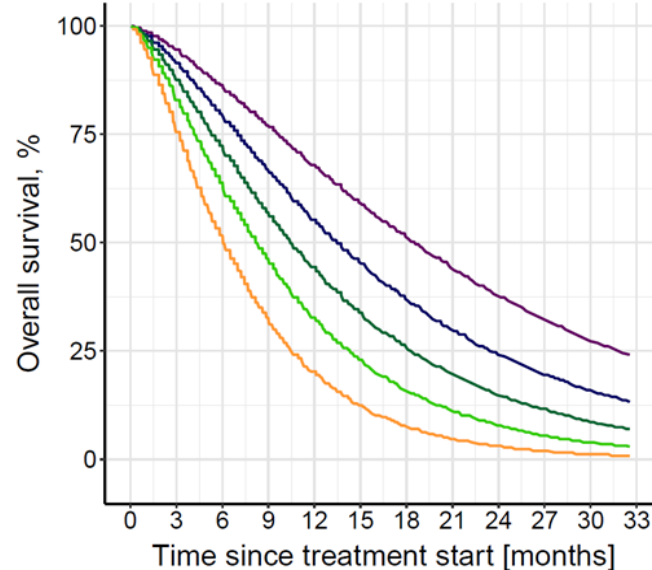
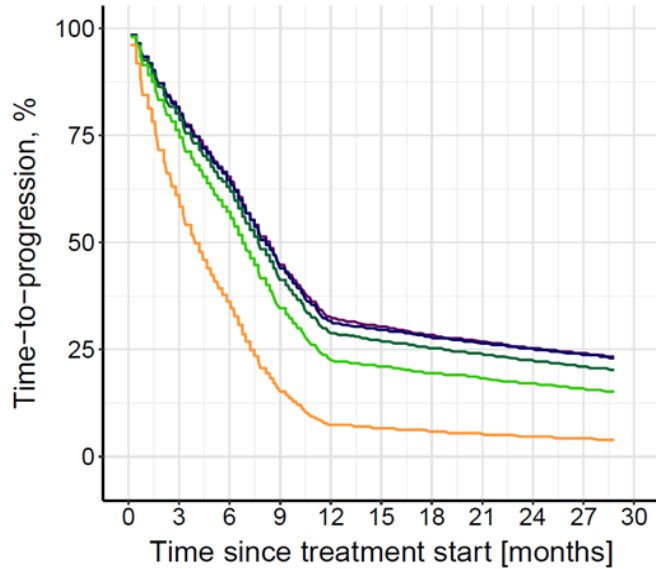


## Time-to-progression



CRP : C-reactive protein  
RS8 : Tumour size at week 8 relative to baseline tumour size

# Simulation-based impact of *inflammation* level ( $CRP_{cycle3}$ ) on time-to-progression and survival



## Model-based simulation

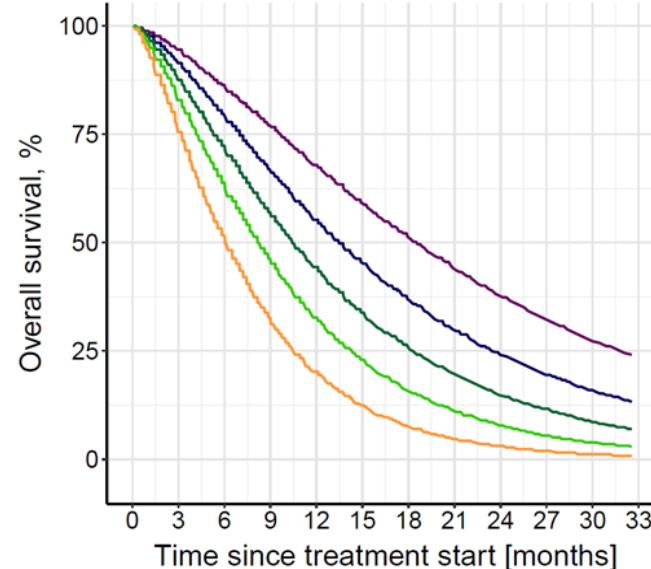
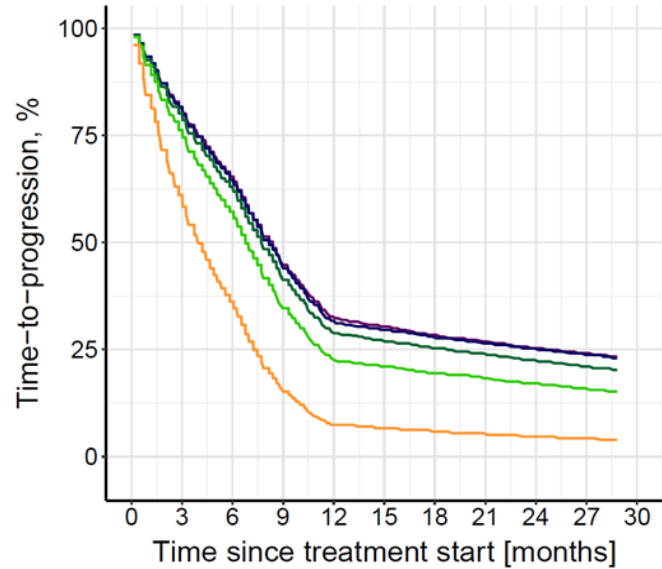
### $CRP_{cycle3}$ concentration (percentile)

<span style="color: purple;">—</span>	1.41 mg/L	( $P_{0.05}$ )
<span style="color: darkblue;">—</span>	4.37 mg/L	( $P_{0.25}$ )
<span style="color: green;">—</span>	11.1 mg/L	( $P_{0.50}$ )
<span style="color: lightgreen;">—</span>	28.8 mg/L	( $P_{0.75}$ )
<span style="color: orange;">—</span>	86.7 mg/L	( $P_{0.95}$ )

- At minimal inflammation level ~5 mg/L
    - No impact on risk of progression
  - At higher inflammation level ~ >30 mg/L
    - Worse outcome
  - Threshold: ~11 mg/L reached at cycle 3
- Regular pattern
  - No threshold

CRP: C-reactive protein

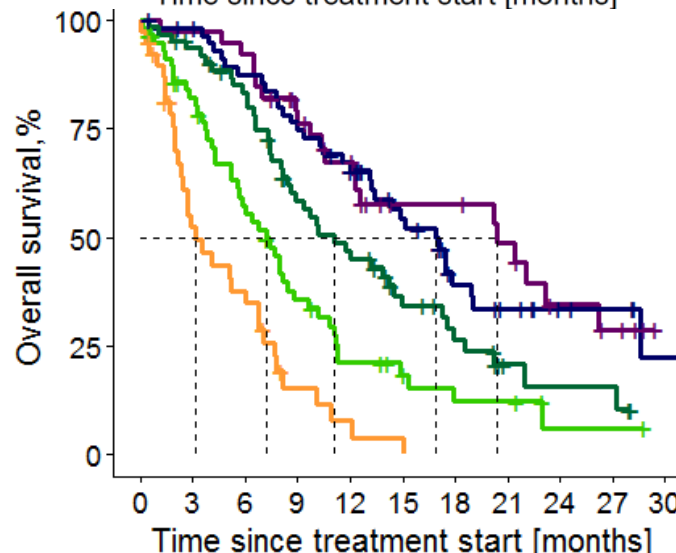
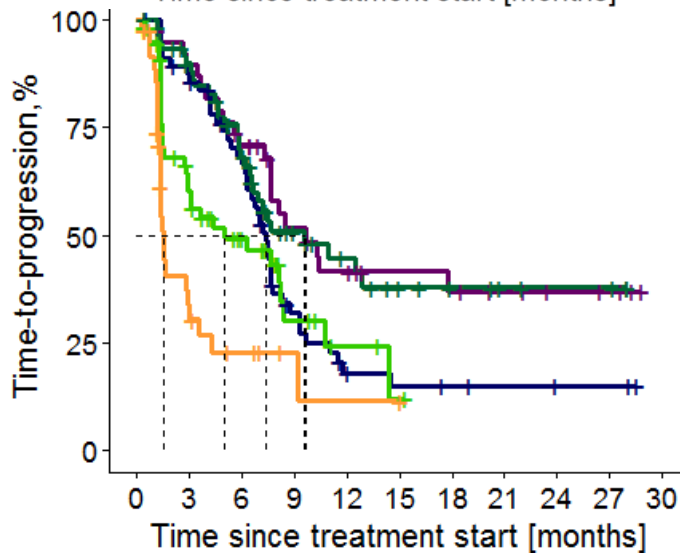
# Simulation-based impact of *inflammation* level ( $CRP_{cycle3}$ ) on time-to-progression and survival against observed events



## Model-based simulation

### $CRP_{cycle3}$ concentration (percentile)

- 1.41 mg/L ( $P_{0.05}$ )
- 4.37 mg/L ( $P_{0.25}$ )
- 11.1 mg/L ( $P_{0.50}$ )
- 28.8 mg/L ( $P_{0.75}$ )
- 86.7 mg/L ( $P_{0.95}$ )



## Observed events

### Model-estimated $CRP_{cycle3}$ concentration (percentile interval)

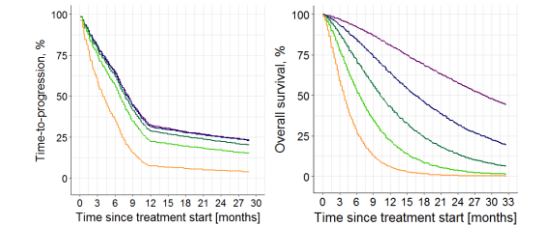
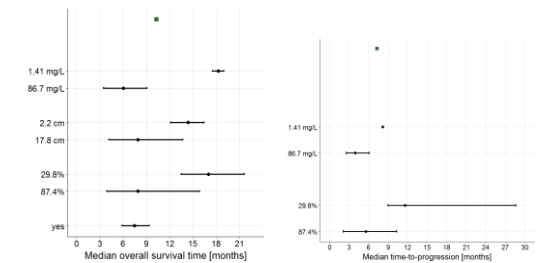
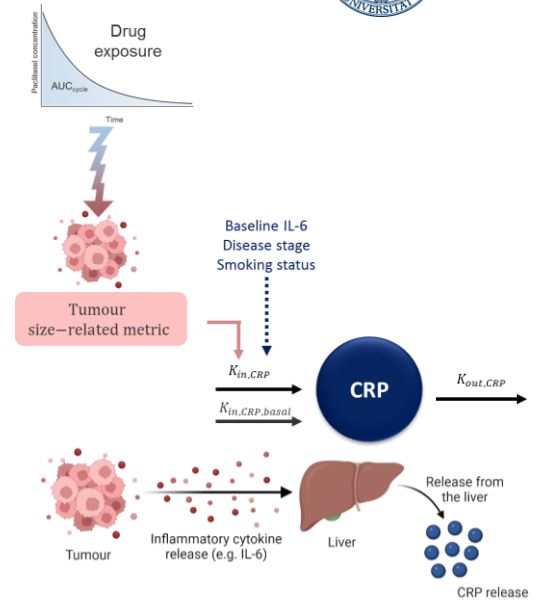
- $< 3.13$  mg/L ( $< P_{0.15}$ )
- $\ge 3.13 - < 6.86$  mg/L ( $\ge P_{0.15} - < P_{0.375}$ )
- $\ge 6.86 - < 16.5$  mg/L ( $\ge P_{0.375} - < P_{0.625}$ )
- $\ge 16.5 - < 47.1$  mg/L ( $\ge P_{0.625} - < P_{0.85}$ )
- $\ge 47.1$  mg/L ( $\ge P_{0.85}$ )

CRP: C-reactive protein



## Summary

- Developed **framework** incorporating relations between drug exposure, tumour dynamics and biomarker
  - Characterised **circulating CRP**
  - **Linked CRP** (*marker of inflammation*) and tumour size (*marker of disease aggressiveness*)
  - Allowed estimation of longitudinal predictors for *all* patients.
- **Early longitudinal prognostic variables identified:**
  - Progression and overall survival in NSCLC patients
  - Non-baseline CRP:
    - **more reflective** of patient status & disease status
    - **stronger predictor** compared with baseline concentration
  - Although CRP is a non-specific biomarker: holds a **strong** prognostic value as predictor of efficacy
  - Patient's **inflammatory status (CRP concentration)** reflects **risk** of progression and survival → **potential prognostic marker**



CRP :C-reactive protein  
NSCLC :Non-small cell lung cancer

## Conclusion & perspectives

- Identified patients at higher risk of early progression/short survival
  - Potential for early intervention
- Longitudinal biomarker data should be further exploited and chosen over baseline data for disease- and patient-related predictions

# Acknowledgements

## Supervisor/co-supervisor

**Prof. Charlotte Kloft**

Dept. of Clinical Pharmacy & Biochemistry,  
Freie Universität Berlin



**Prof. Wilhelm Huisinga**

Computational Physiology Group,  
Universität Potsdam



Universität Potsdam

## Senior scientists and former PhD students

**Dr. Francis Williams Ojara**

**Dr. Robin Michelet**

**Dr. Andrea Henrich**

Dept. of Clinical Pharmacy & Biochemistry,  
Freie Universität Berlin



## PharMetrx industry mentor

**Dr. Alejandro Pérez Pitarch**

Oncology Team lead  
Boehringer Ingelheim



## Collaboration Partners

**Prof. Markus Joerger (P.I.)**

CEPAC-TDM trial consortium



## Biomarker data

**Prof. Stefan Holdenrieder**

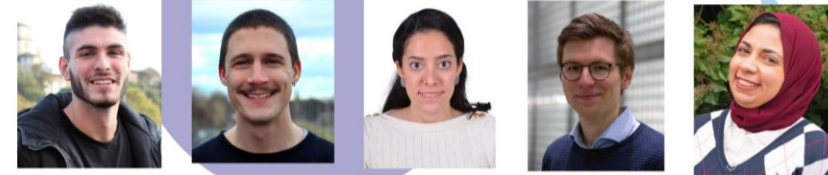
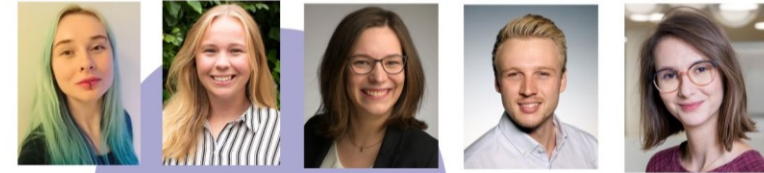
**Dr. Kimberly Geiger**

German Heart Centre Munich



## Graduate Research Training Program PharMetrx

Pharmacometrics & Computational Disease Modelling



Universität Potsdam    Universität Navarra    Humboldt Research Fellow    Universität Hamburg    Humboldt Research Fellow

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