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Multistate model for pharmacometric analyses of overall survival in anticancer treatments

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Background

- The primary endpoint in late-stage oncology trials: Overall survival (OS)
  - Defined as the time from randomization to death from any cause
  - Requires long follow-up (~3-5years)
  - The results might be confounded by second line treatments

- The primary endpoint in early clinical development: Progression free survival (PFS)
  - Defined as the time from randomization to disease progression/death
  - PFS improvements do not always result in corresponding improvements in OS

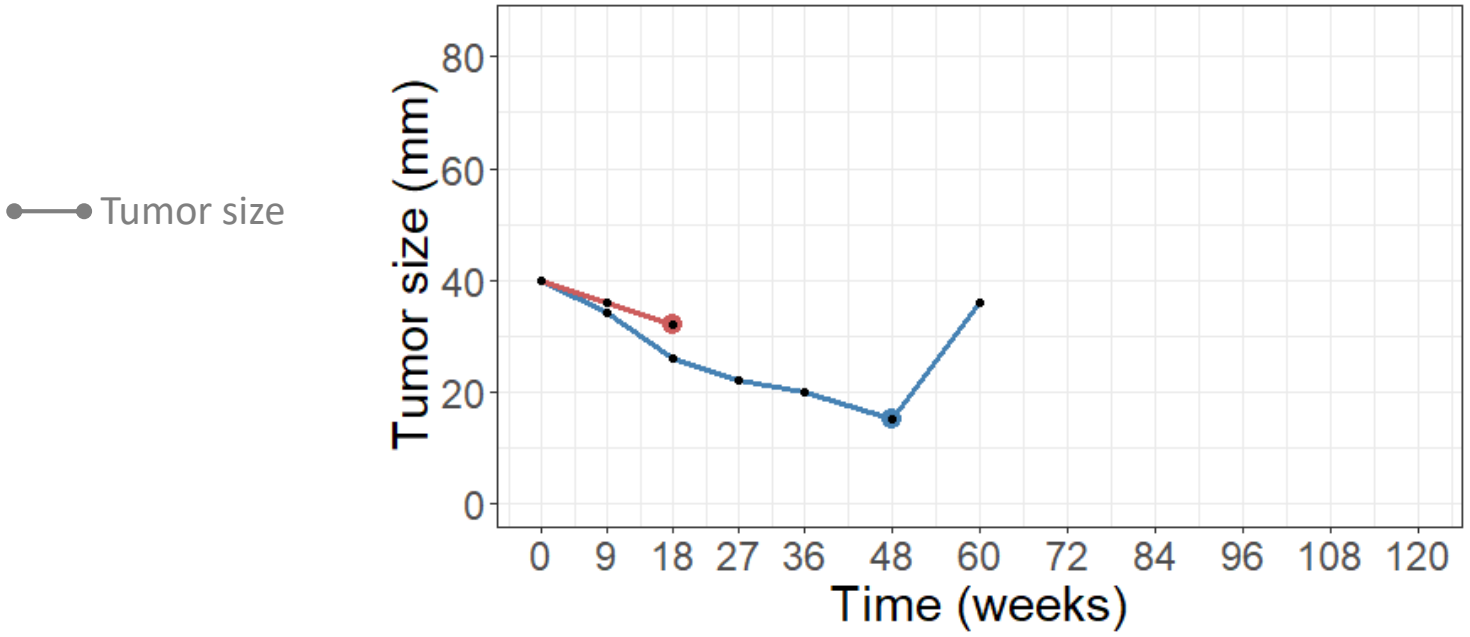
Survival analysis

Issues in handling time-dependent predictors

- Survival analysis

  Time to event model using a survival function

  - Hazard of death = $h_0(t) \cdot e^{(\beta 1 \cdot predictor1)}$
  - Ignoring immortal time bias can be a major issue
    - Example: “depth of tumor response” as a predictor of OS.



Patient 1 :

Depth of tumor response : ***62%***

Patient 2 :

Depth of tumor response : ***20%***

Survival analysis

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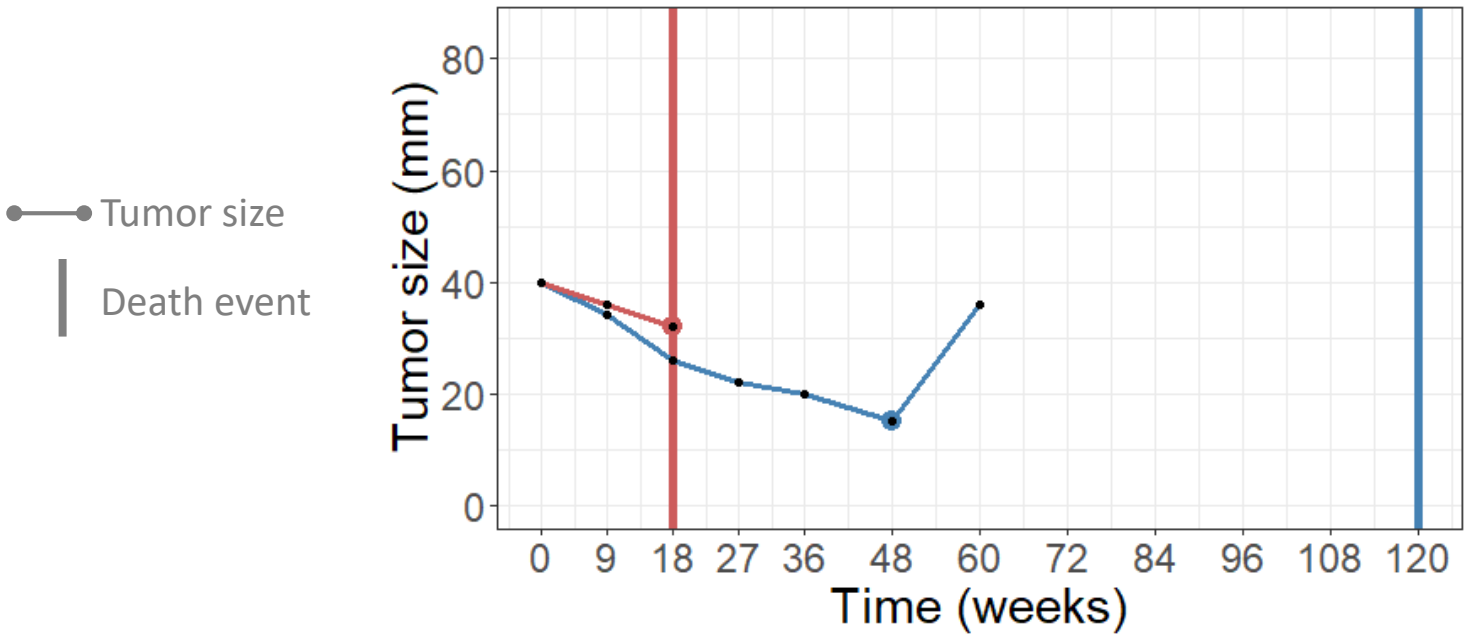

Patient 1 :

Depth of tumor response : ***62%***

Survival time : ***120 weeks***

Patient 2 :

Depth of tumor response : ***20%***

Survival time : ***18 weeks***

Survival analysis

Issues in handling time-dependent predictors

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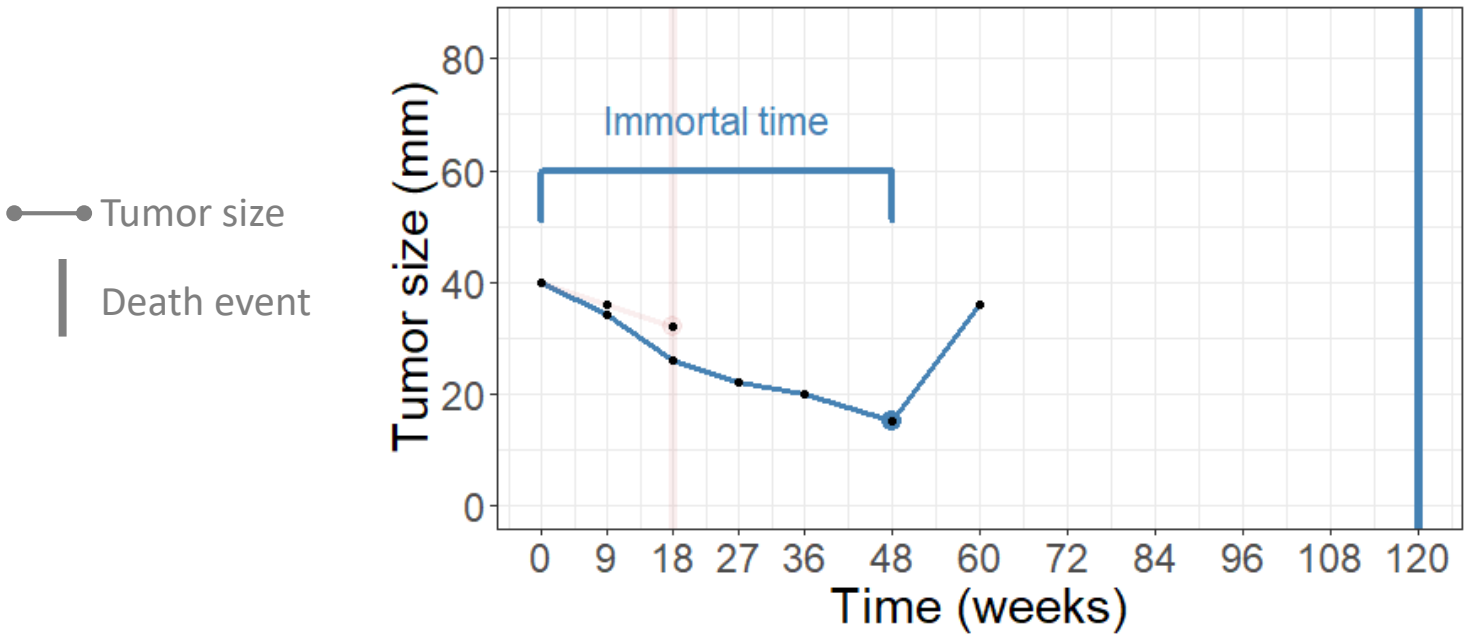


Patient 1 :

Depth of tumor response : ***62%***

Survival time : ***120 weeks***

Time to depth of tumor response: **48 weeks**

Patient 2 :

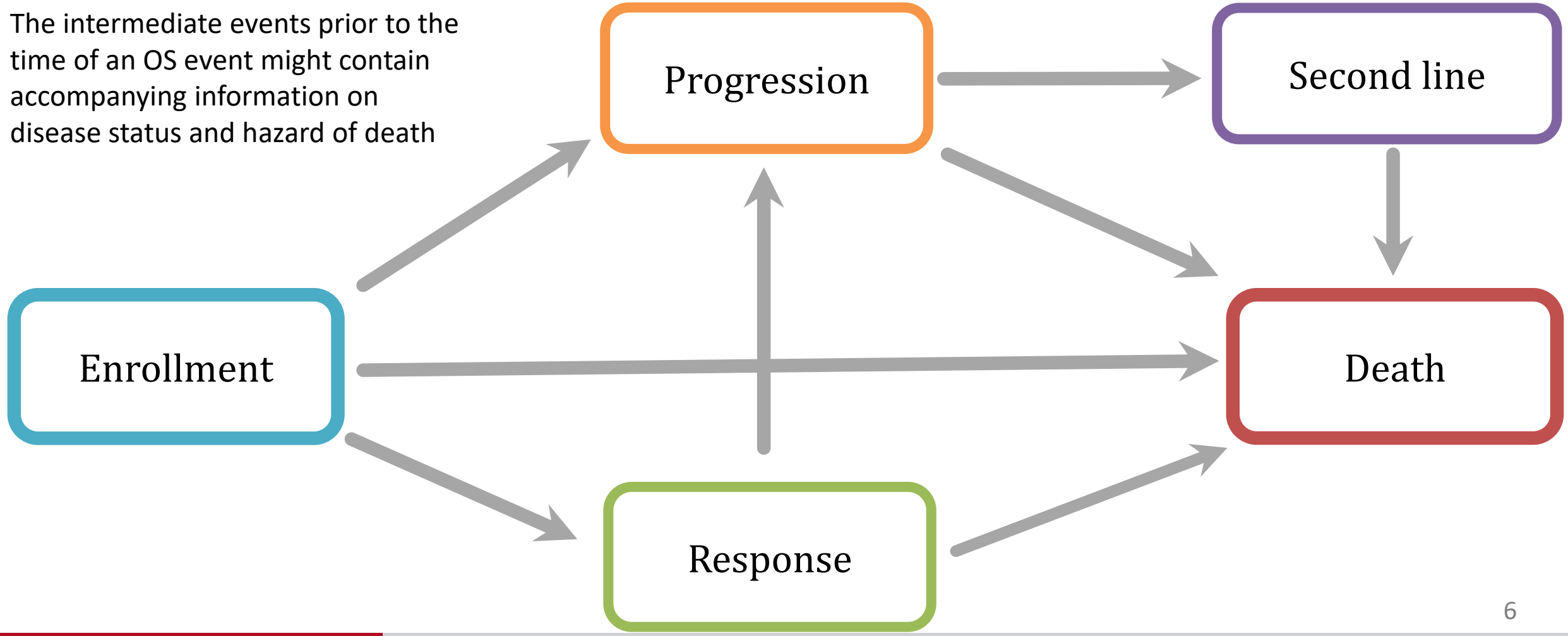
Depth of tumor response : ***20%***

Survival time : ***18 weeks***

Time to depth of tumor response: 18 weeks

Intermediate events

The intermediate events prior to the time of an OS event might contain accompanying information on disease status and hazard of death



Objectives

- Overall objective

To explore the potential of a multistate model, including its ability to predict OS using time-varying predictors while addressing the immortal time bias.

- Specific objectives
  - To develop a multistate model to characterize the transition probabilities between states
  - To investigate dynamic predictors on the transition hazards

Data

Simulation of data

- Longitudinal tumor size data (sum of longest diameters, SLD) and survival times for 1,000 subjects were simulated
  - Tumor size-OS joint model[1,2] for docetaxel treatment in HER2-negative metastatic breast cancer patients[3]
  - Tumor sizes at zero, and every 9 weeks during the first 36 weeks and thereafter every 12 weeks until disease progression (20% increase in SLD from tumor nadir[4])
  - Simulation duration: 3 years

[1] Bender et al., PAGE 26 (2017); [2] Krishnan et al., PAGE 28 (2019); [3] Miles et al., J Clin Oncol. (2010); [4] Eisenhauer et al., Eur J Cancer. (2009)

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Data

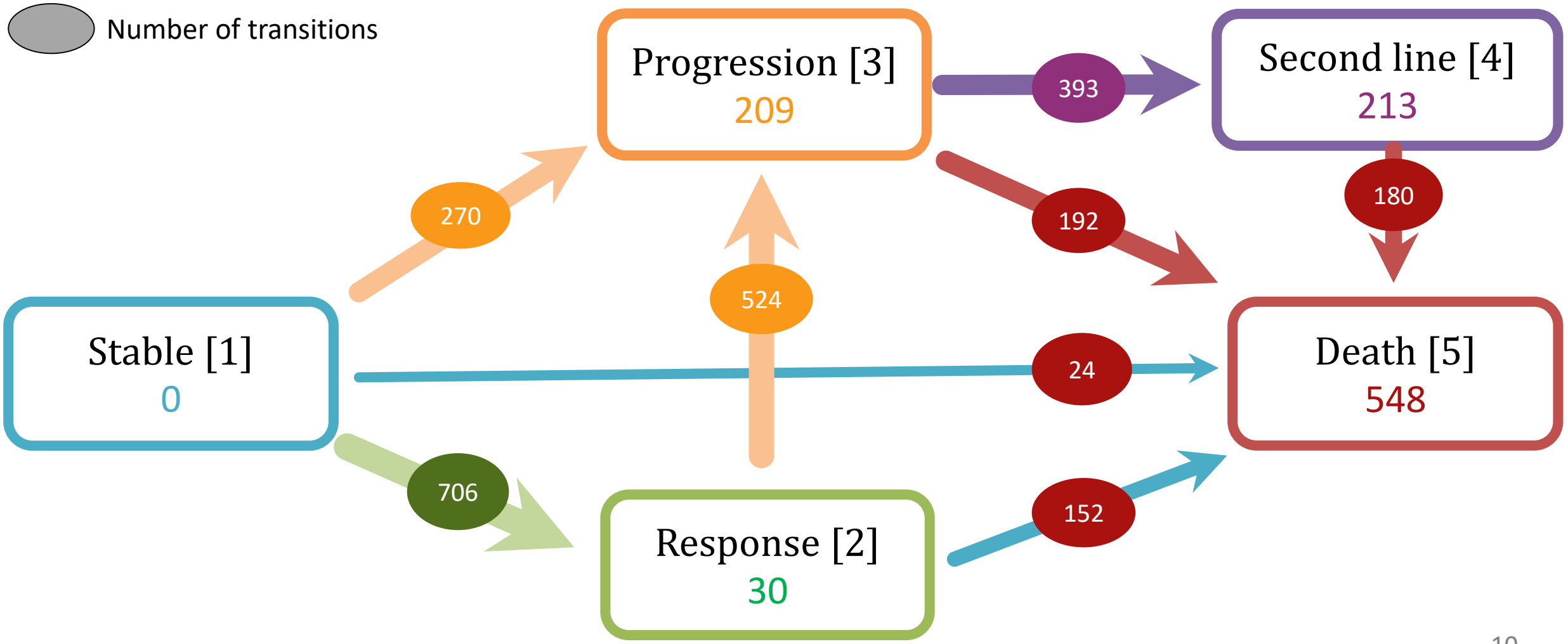
Definition of different states

State	Name	Description
1	Stable disease	Initial state for all subjects
2	Response	≥ 30% decrease in SLD from baseline SLD*
3	Progression	≥ 20% increase in SLD from tumor nadir*
4	Second-line	50% of the patients who had disease progression were switched to second line treatment within 6 [0.5-12] weeks after progression
5	Death	Death event

*Response evaluation criteria in solid tumours (RECIST v1.1) Eisenhauer et al., *Eur J Cancer*. (2009)

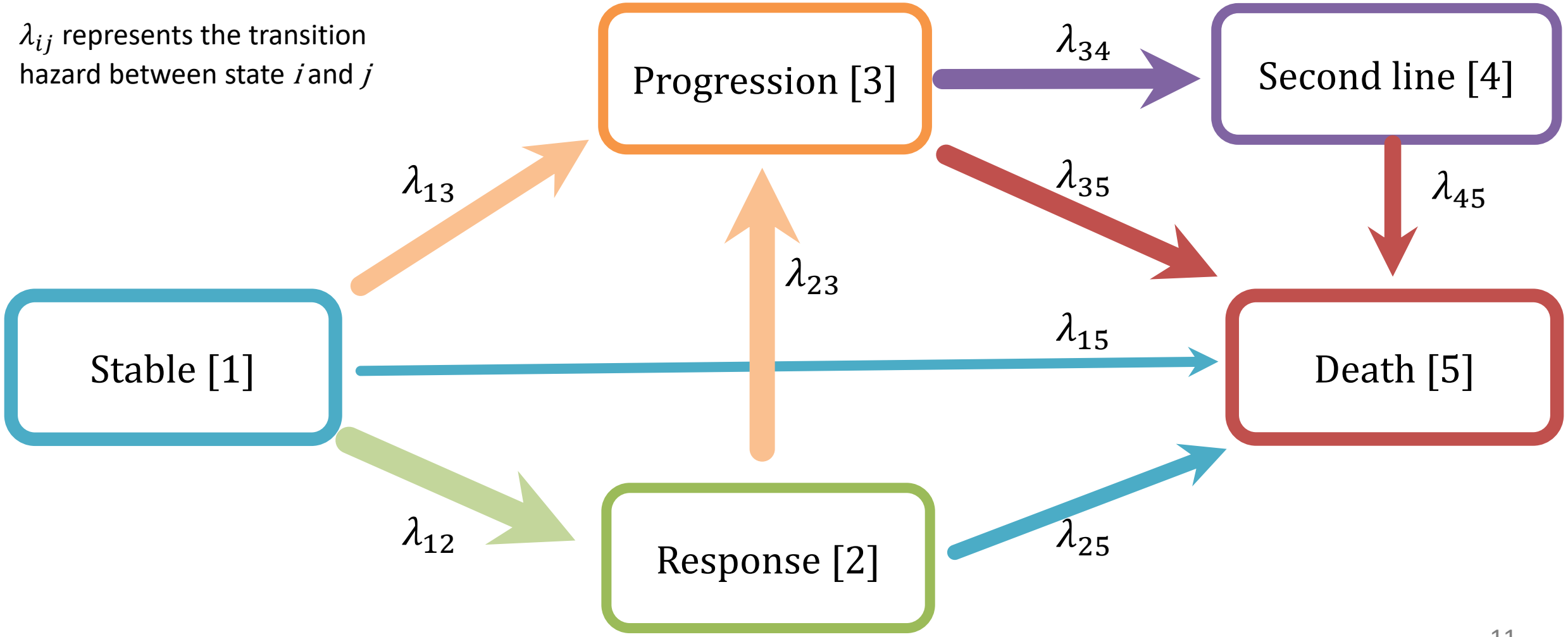
Multistate data

Number of transitions



Multistate model framework

λ_{ij} represents the transition hazard between state i and j



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Predictors of transition hazards

Baseline covariates	Time-varying predictors*	Investigated on
Tumor burden (SLD_0, mm) Age (years)	SLD change from baseline (%) SLD change between the two previous measurements (%) SLD change from tumor nadir (%)	λ_{12} λ_{13} λ_{24} λ_{35} λ_{45}

* *The time-varying predictors were investigated in a way that the future tumor observations would not influence the present predictions of transition rates.*
For example, SLD data until week 18 was used in the prediction of transition hazards at week 27.

Results

Structural model – combination of hazard functions

Transition	Hazard function	Interpretation
Stable to response (λ_{12})	Weibull	Hazard diminished with time
Stable to progression (λ_{13})	Weibull	Hazard increased with time
Progression to death (λ_{35})	Weibull	Hazard decreased with time
Second line to death (λ_{45})		Not statistically different from λ_{35}

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Response to progression(λ_{23})	Exponential	Constant hazard
Progression to second line* (λ_{34})	Exponential	Constant hazard

*A mixture model with two sub-populations, where pop-1 received second-line treatment and pop-2 did not receive second-line treatment.

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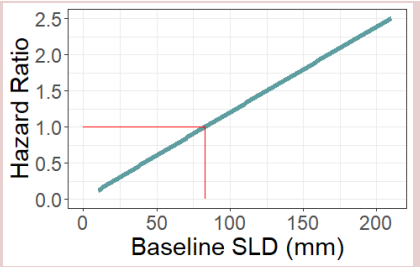
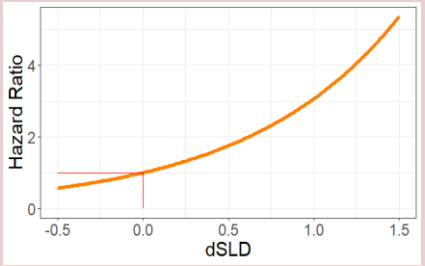
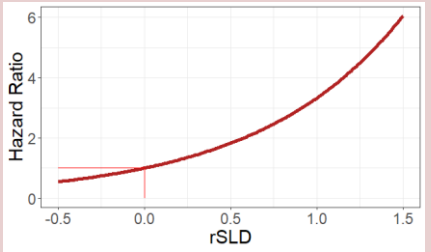
Progression to second line* (λ_{34})	Exponential	Constant hazard
Stable to death (λ_{15})	Gompertz-Makeham[#]	Age specific hazard
Response to death (λ_{25})		

*A mixture model with two sub-populations, where pop-1 received second-line treatment and pop-2 did not receive second-line treatment.

[#] Missove et al., Theor Popul Biol (2013).

Results

Predictors of transition hazard

Transition	Predictor	Hazard ratio	
Stable to response (λ_{12})	Baseline tumor size (SLD_0)	Hazard ratio = 1.10/every 10 mm increase from median SLD_0	
Response to progression (λ_{23})	Change in SLD between two previous measurements (dSLD)	Hazard ratio = 1.12/10% increase in SLD	
Progression to death (λ_{35})	Baseline tumor size SLD change from baseline at progression (rSLD)	Hazard ratio = 1.08/every 10 mm increase from median SLD_0 Hazard ratio = 1.12/10% increase in SLD from baseline	

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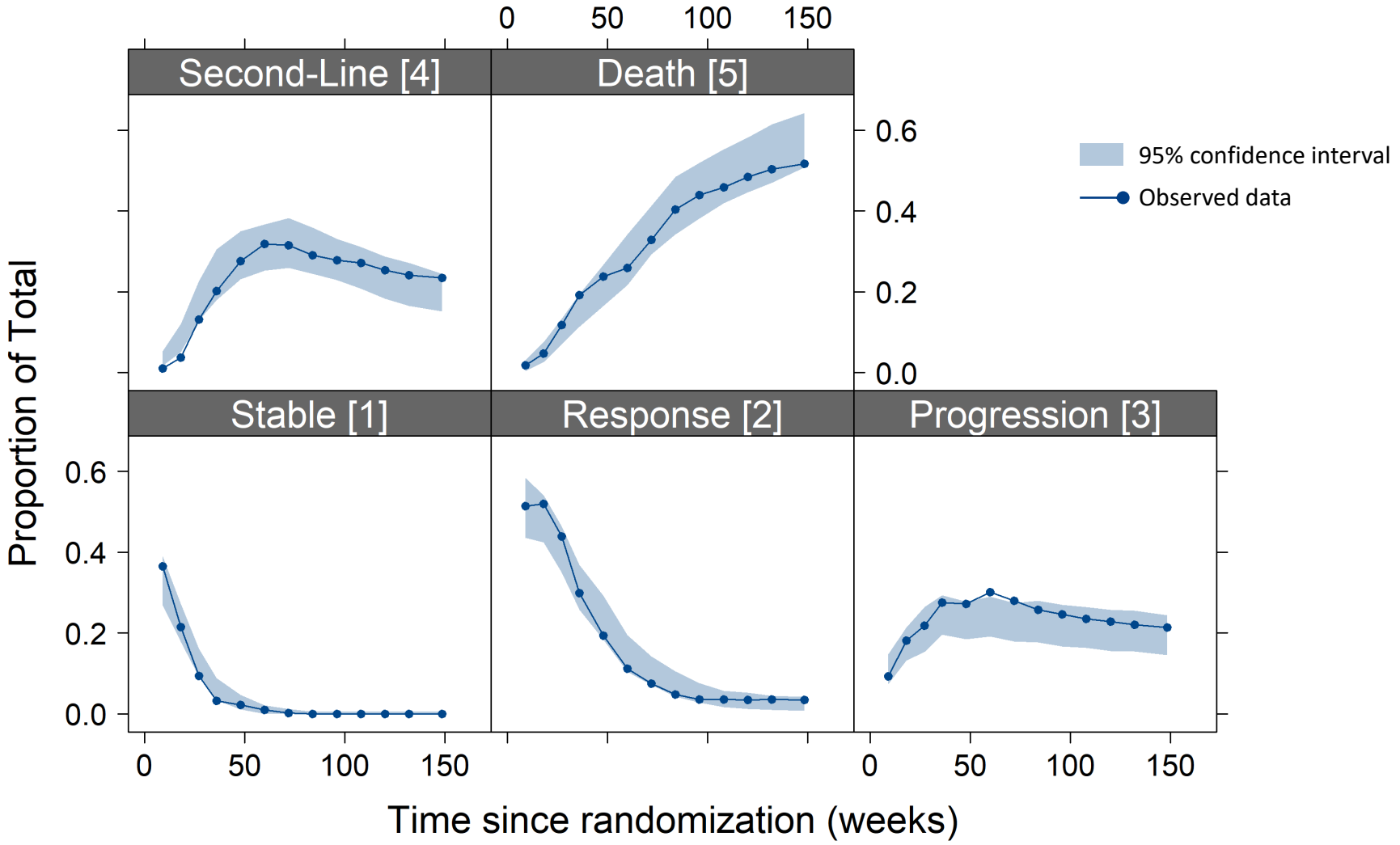
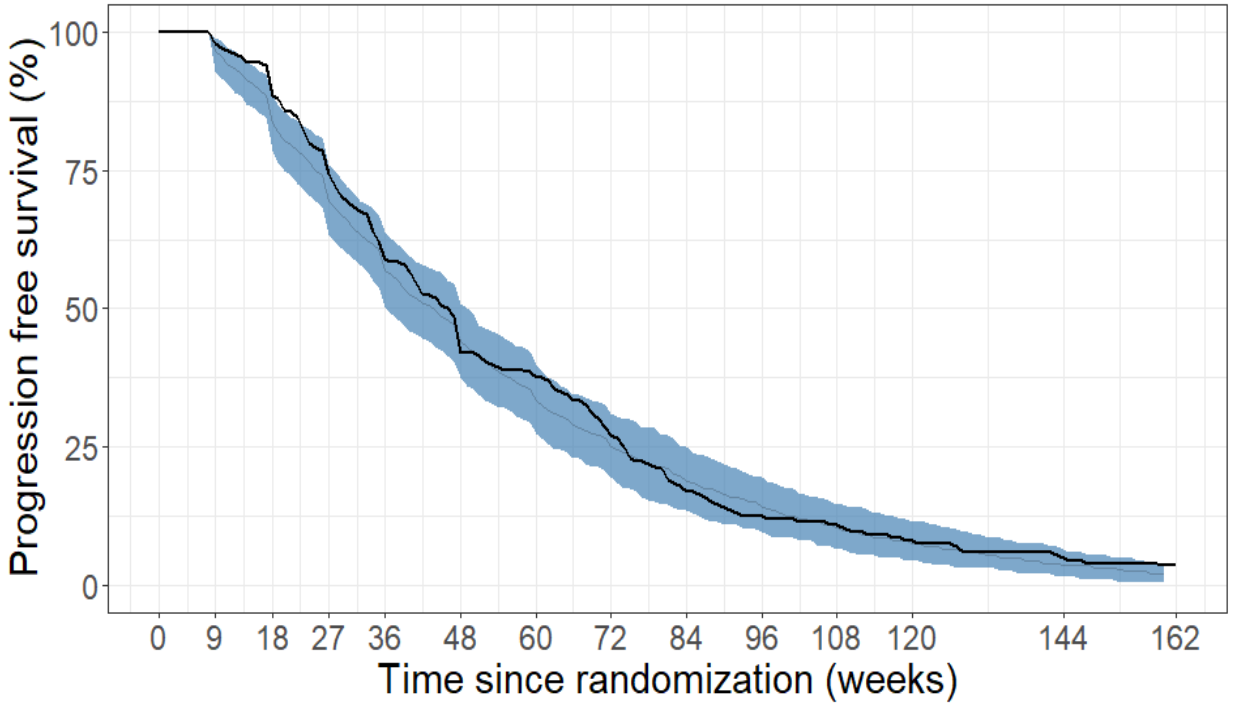
Visual predictive check



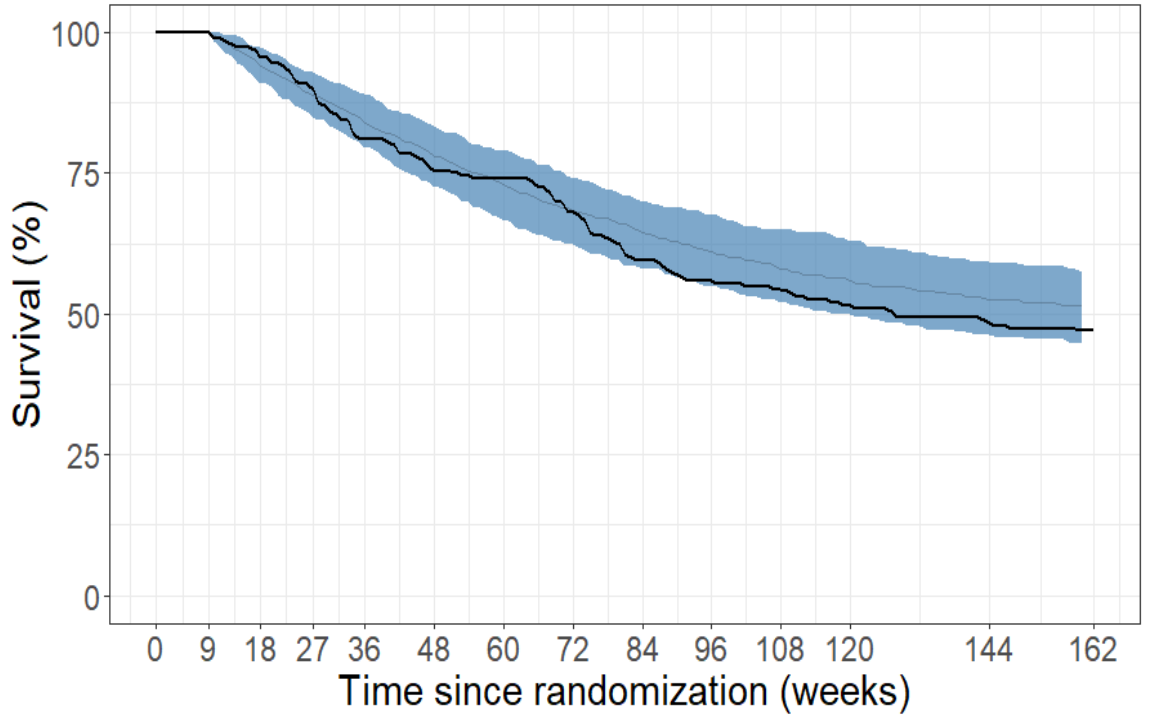
Clinical endpoints

95% confidence interval
Observed data

Progression free survival (PFS)



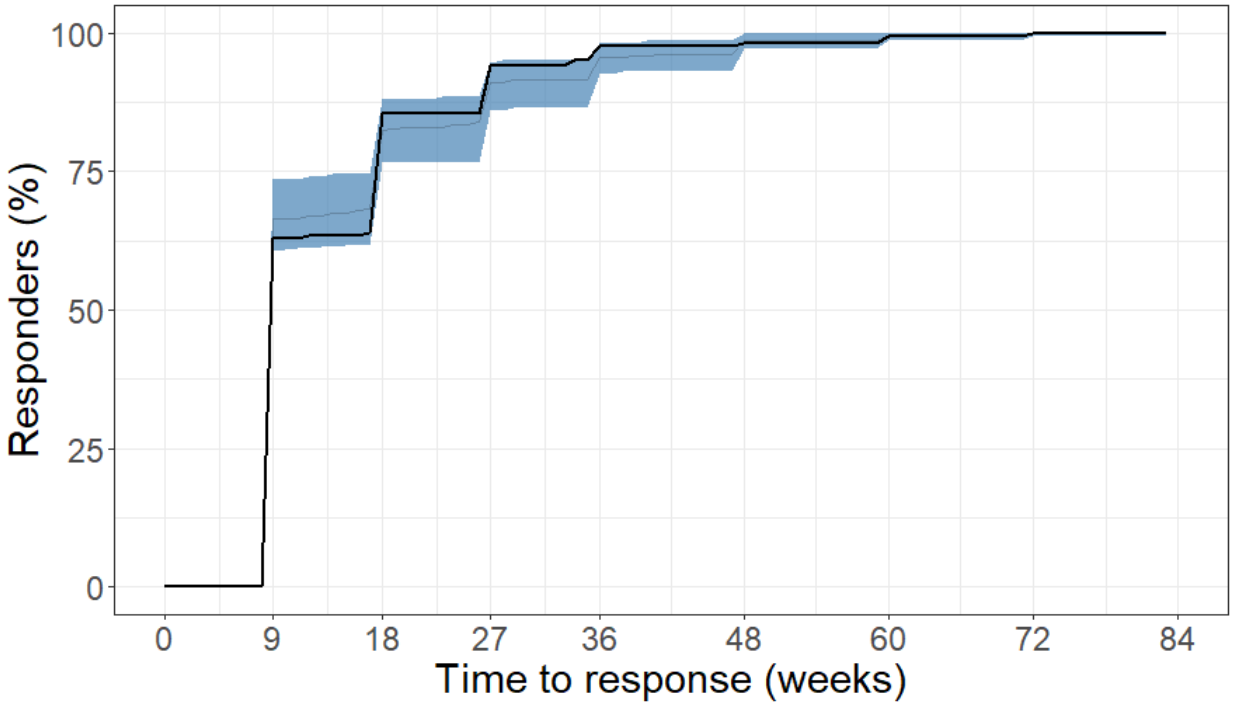
Overall survival (OS)



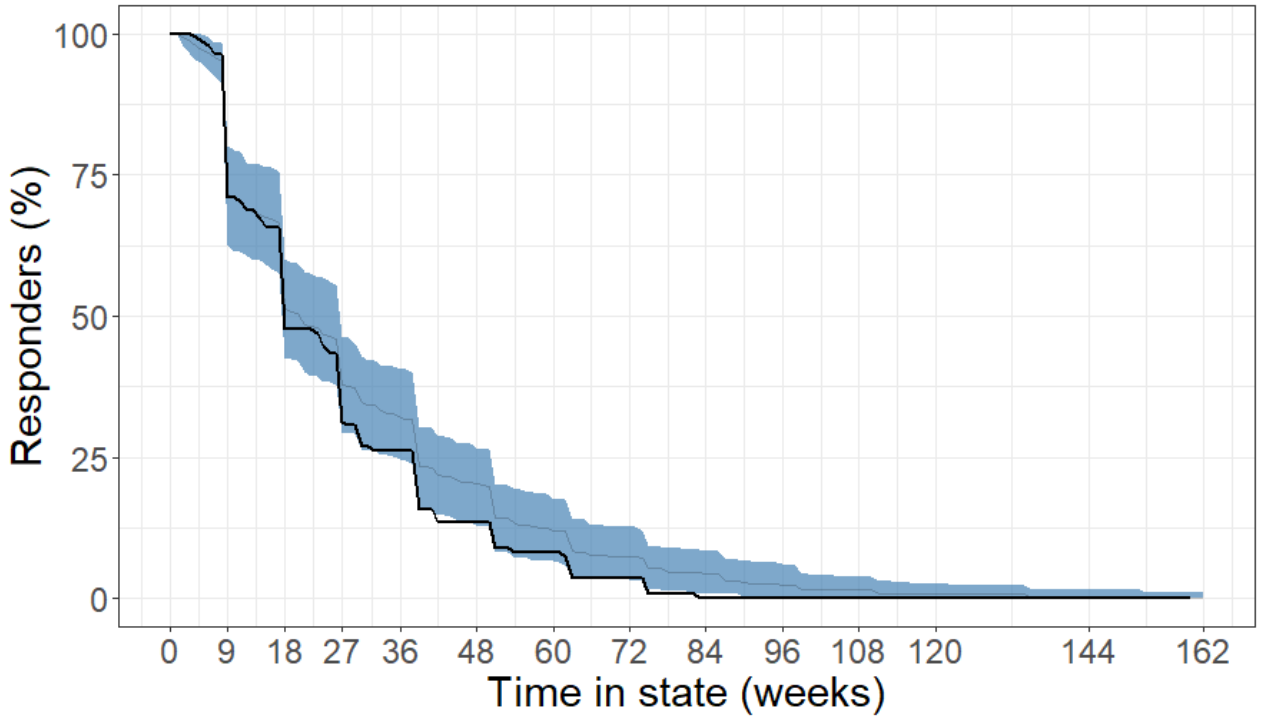
Docetaxel response

95% confidence interval
Observed data

Time to response



Duration of response



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Conclusion

- This novel approach for analyzing oncology data successfully characterized the intermediate events prior to survival time and jointly described the OS event.
- The predictors were evaluated in a prospective manner so not to cause immortal time bias.
- This multistate model framework allows for
  - extension (pseudo-progression, dropout, etc.)
  - simplification (absence of second line treatment)
- The investigation of predictors and the characterization of time to develop response, duration of response, and the overall outcome events PFS and OS can be performed in a single multistate modeling exercise.

Further reading

- Sreenath M. Krishnan, Lena E. Friberg, René Bruno, Ulrich Beyer, Jin Y. Jin, and Mats O. Karlsson. 2021. “Multistate Model for Pharmacometric Analyses of Overall Survival in HER2-Negative Breast Cancer Patients Treated with Docetaxel.” CPT: Pharmacometrics & Systems Pharmacology. https://doi.org/10.1002/PSP4.12693.

- Ulrich Beyer, David Dejardin, Matthias Meller, Kaspar Rufibach, and Hans Ulrich Burger. 2020. “A Multistate Model for Early Decision-Making in Oncology.” Biometrical Journal 62 (3): 550–67. https://doi.org/10.1002/bimj.201800250

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Thank you for your attention