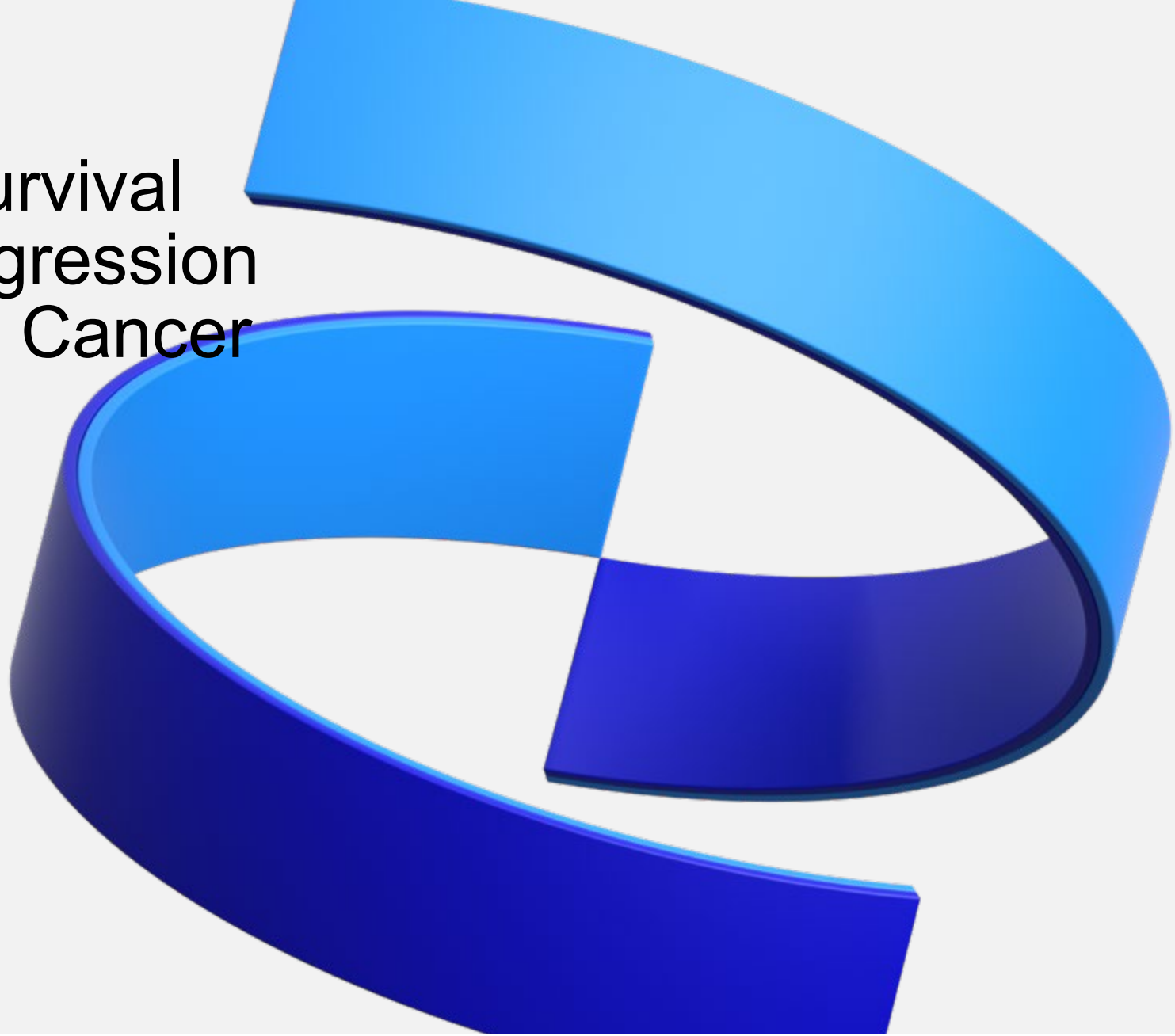
Prediction of Overall Survival (OS) from Disease Progression Dynamics in Metastatic Cancer Trials



Satrajit Roychoudhury

Statistical Research and Innovation

Pfizer Inc.

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Joint work with

- Sidi Wang, University of Michigan
- Kelley M Kidwell, University of Michigan
- Bo Huang, Pfizer Inc.

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Progression Free Survival as Endpoint in Metastatic Cancer Trials

- Approximately 80% of registration trials now use progression-free survival (PFS) as the primary endpoint
  - Defined as time from randomization until tumor progression or death due to any cause
- Provides proof of efficacy earlier than overall survival
  - Requires smaller sample size and shorter follow-up
  - A recent study showed that, on average PFS expedites the drug approval process by approximately a year
  - Regulatory discussion depends on the overall benefit-risk

Overall Survival (OS) Endpoint: the Ultimate Clinical Benefit

Overall survival (OS) is “the” gold standard to assess treatment efficacy

- Defined as time from randomization until death

OS data is often immature (i.e., a low number of deaths have been observed) at the time of the primary analysis of PFS

- Typically treated as an interim analysis of OS using group sequential set-up
- Regulatory agencies often require updated OS data
- **Prediction of time for mature OS analyses** is important for planning
- Understanding the probability of success in updated OS data

Extrapolating OS over time beyond the span of the available data is required for health-economic models

Proper evaluation incremental cost-effectiveness ratio

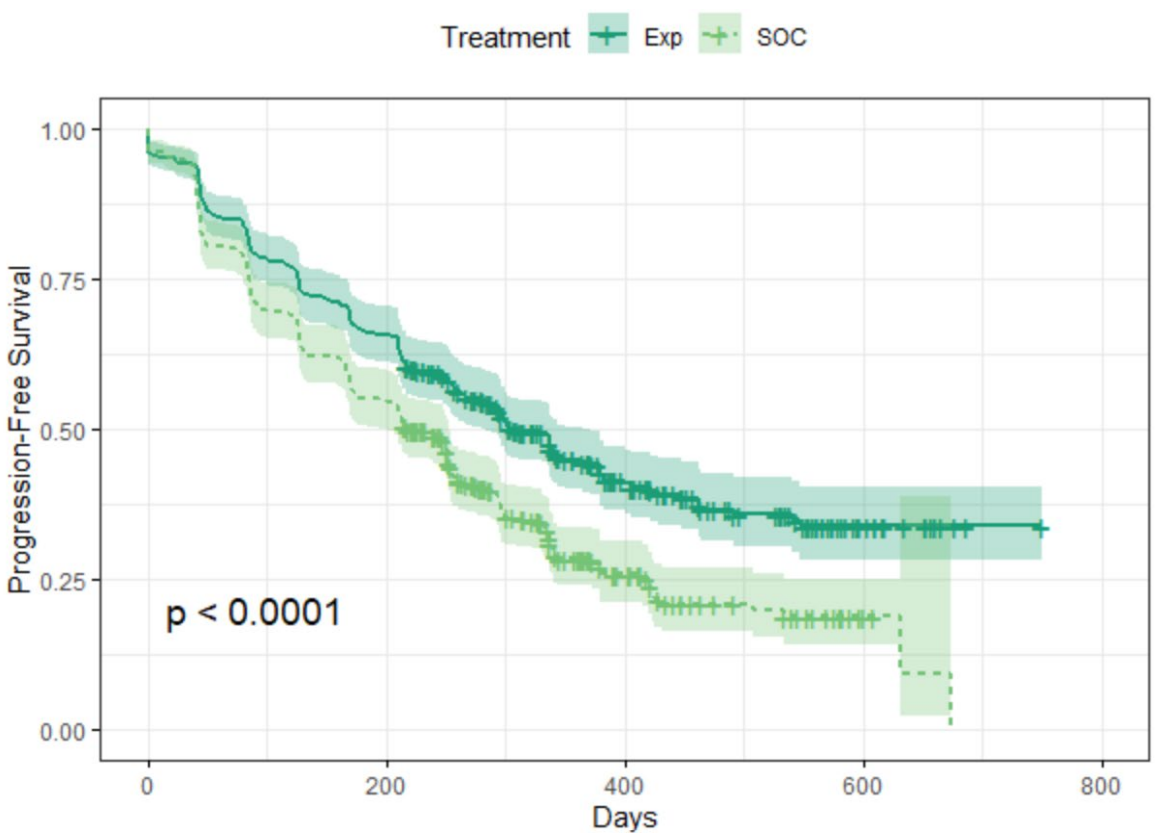
Prediction of OS

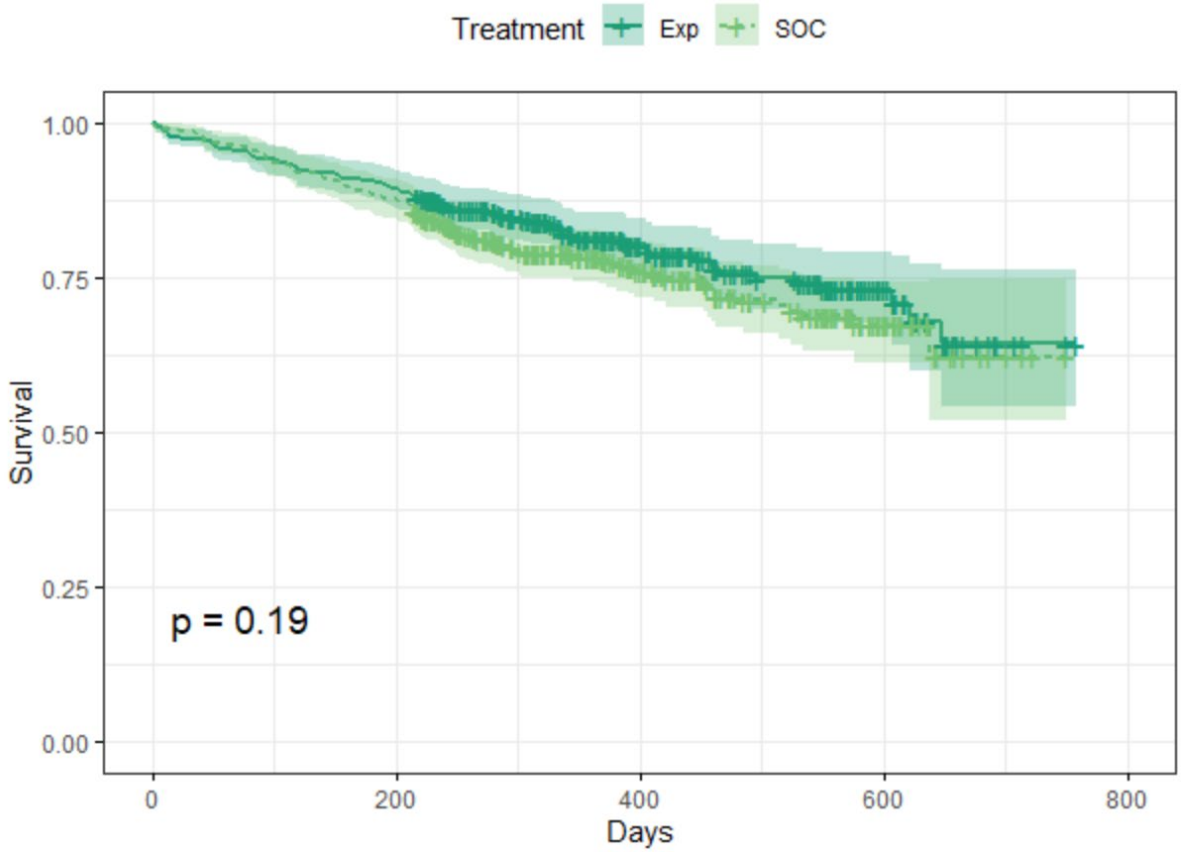
- Using available time to death data only
  - Using parametric or semi-parametric model e.g., single Weibull, piecewise exponential or Cox regression model
  - Often multiple models are used to fit the data: best fitted models are used for prediction
- Exploring relationship between progression and OS **for prediction**
  - Several research has been conducted to explore association between PFS and OS
  - Surrogacy or association between PFS and OS is not in scope for this project
  - **Interest is to enhance the prediction or extrapolation of OS using the tumor progression data**

Case Study: A Phase 3 Study on Renal Cell Carcinoma (RCC)

- Set-up is adopted from a real-life study comparing a novel treatment (T) with the standard of care (SOC)
- Study set-up
  - 800 patients were randomized 1:1 between T vs SOC
  - RECIST 1.1 was used for tumor assessment
  - Tumor assessment schedule: every six weeks for the first 18 months, and every 12 weeks afterwards
- Primary endpoint: PFS
  - Primary analysis was planned after **397** PFS events: first analysis of OS
  - An updated OS analysis is planned after **341 deaths**
  - Subjects are followed after primary PFS analysis to collect the OS data

Analysis of OS and PFS At Primary Analysis (After 146 Deaths)





- When will 341 deaths occur? Time for updated OS analysis
- How will survival effect emerge? Label update, pricing discussions

Prediction Models

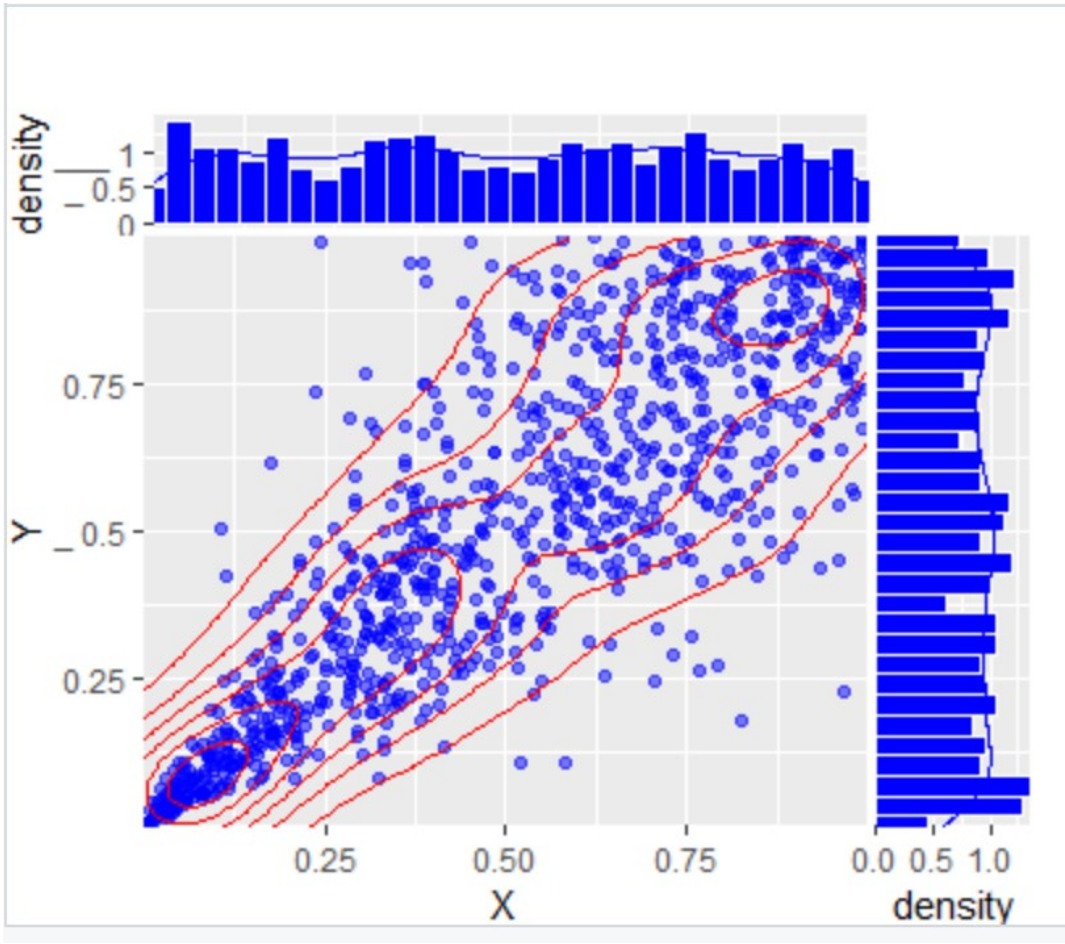
- Weibull model for OS data only
- Multivariate survival model for time to progression and OS
- Multi-state model
- **Multivariate joint modeling**

Copula Models for Time to Progression (TTP) and OS

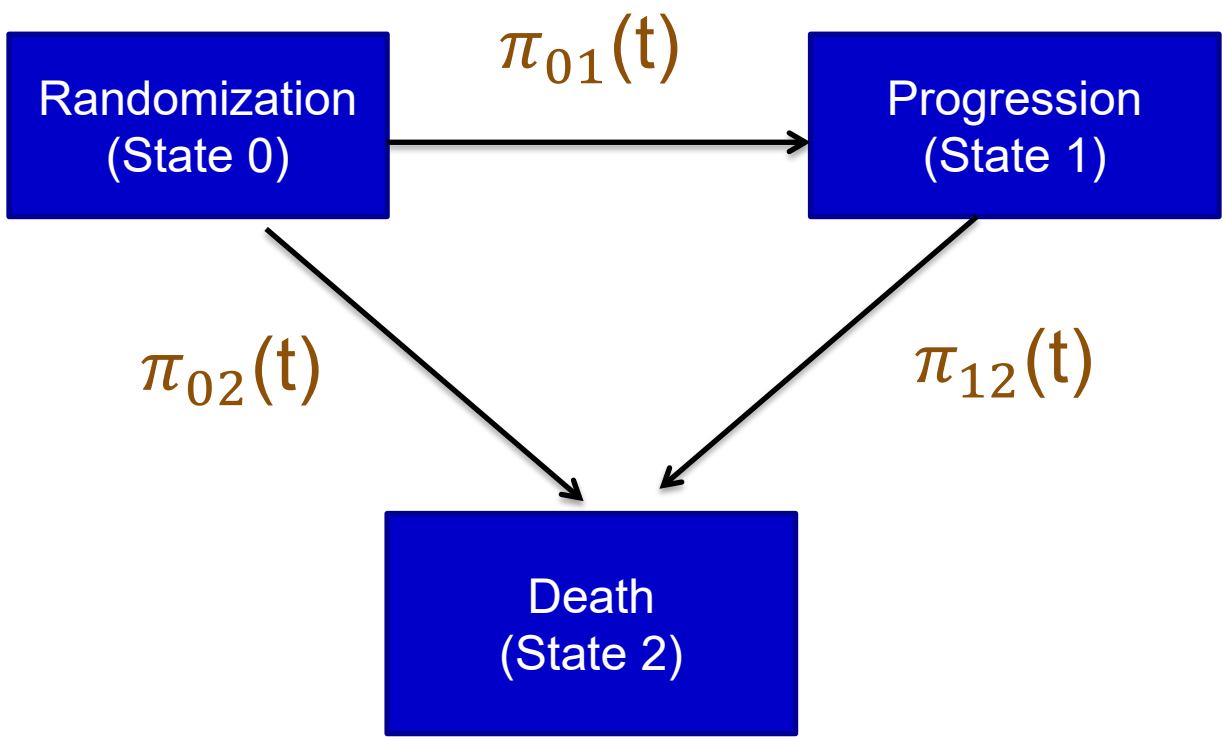
- Clayton copula model for bivariate survival data

$$C_\delta(u,v) = (u^{-\delta} + v^{-\delta} - 1)^{-\frac{1}{\delta}};\ \delta > 0$$

u and v are marginal survival functions modeled with Weibull distribution



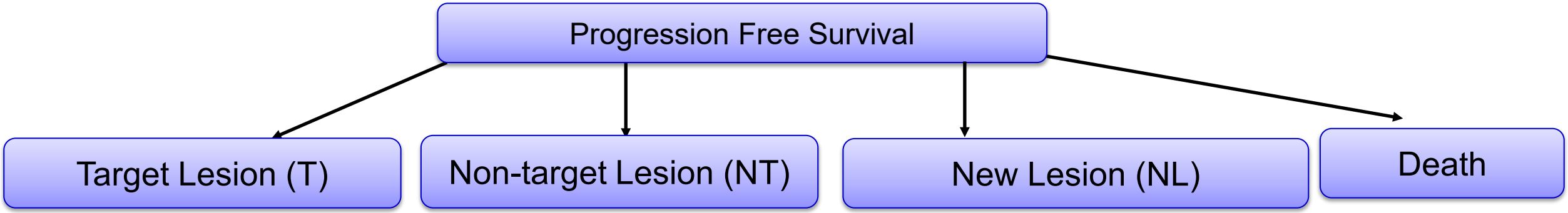
Multivariate Model: Semi-Markov Three-State Progression-Death Model



- $\pi_{lk}(t)$ = Hazard to state l at time t, conditionally on the present state k
- Homogeneous semi-Markov model
  - *Hazard of death after progression depends on time since progression*
- $\pi_{lk}(t)$ are modeled using Weibull distribution with common scale parameter

Progression Free Survival: Different Factors Measuring Disease Status

In an oncology study PFS is assessed by Response Evaluation Criteria in Solid Tumors, most known as RECIST 1.1



A. Measured at every visit
B. % change in the sum of LD (longest diameters) of target lesion.
C. 5mm absolute increase and > 20% increase from smallest sum of LD

A. Assessed at every visit
B. Enlargement/worsening of non-target lesions

A. Appearance of new lesions

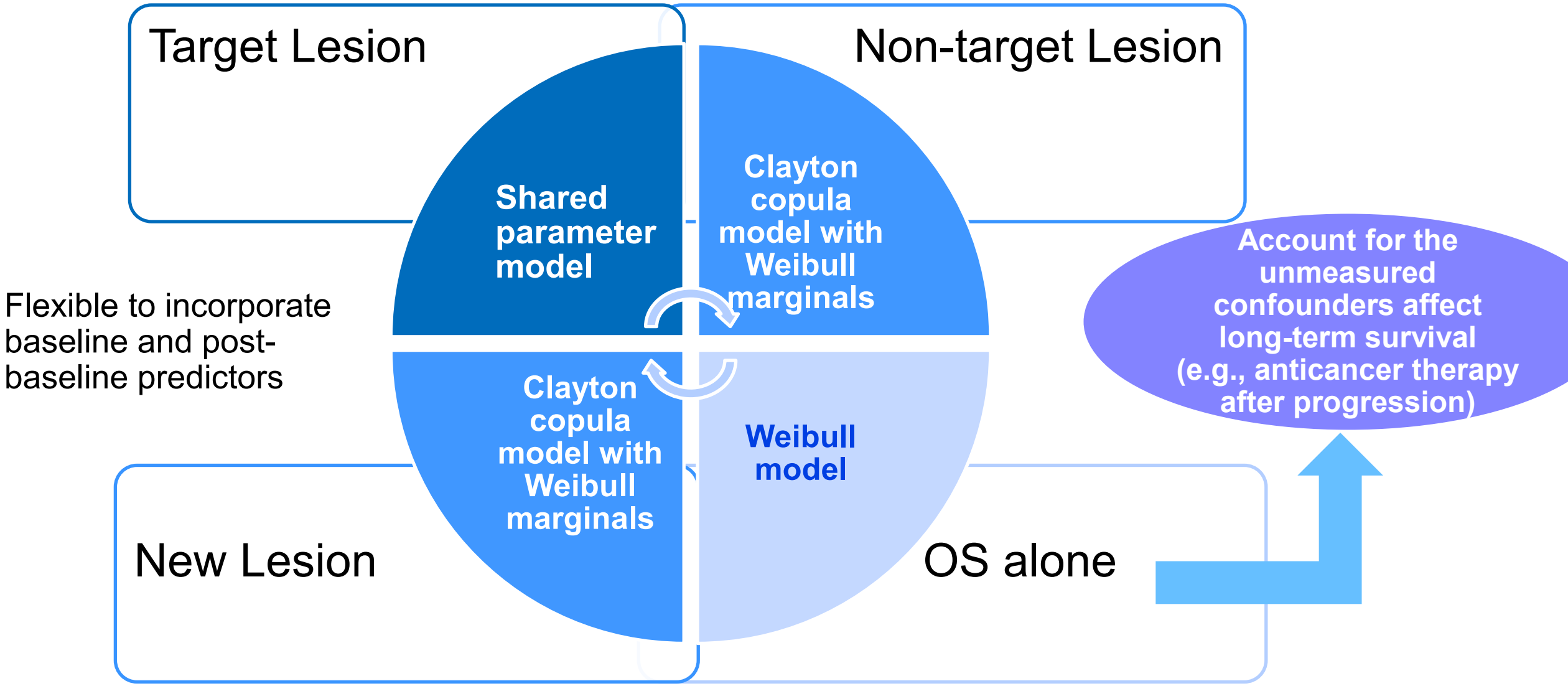
PFS is a composite endpoint: T, NT, and NL have differential effects on OS

Improving OS Prediction using Multivariate Joint Model (1/2)

- The idea is to improve prediction by harnessing four granular components
- Avoid “information loss”
- Fully capture the association between progression and death by considering random processes.

- **Joint model OS with:**
- **% change of sum of LD**
- **Time to NT lesion progression**
- **Time to appearance of NL**

Improving Prediction: Bridging Each Component with OS



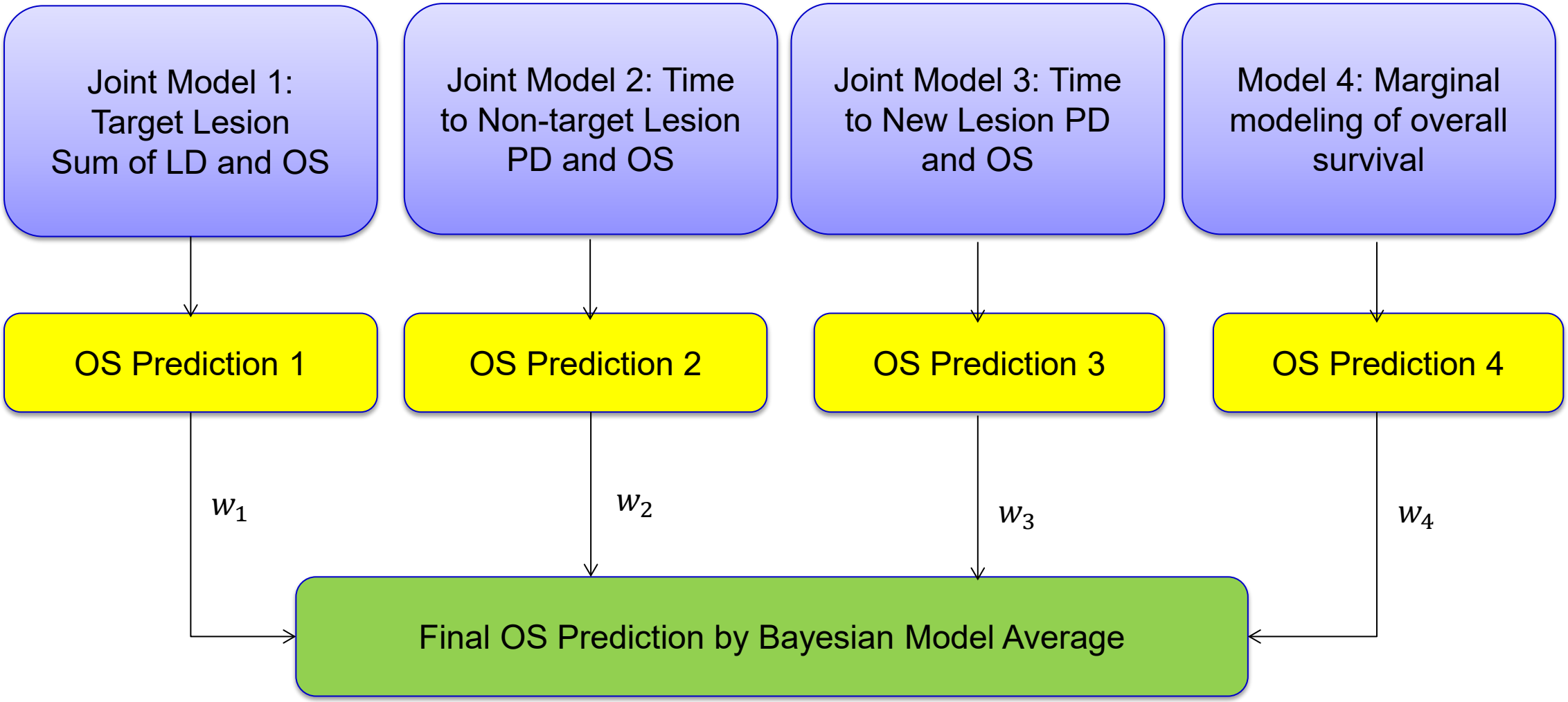
OS Prediction Under Different Models

- Uses posterior predictive distribution to extrapolate the “incremental survival” (δt) for patient with follow-up time t
  - Two sources of uncertainty
    - Sampling uncertainty: pr(Y*|**θ**) *uncertainty of unknown*
    - Parameter uncertainty: pr(**θ**| Y) *Uncertainty of known;* **θ** are model specific parameters
- Predictive distribution calculus

$$\mathbf{P(\delta t\,|Y) = \int P(\delta t,\ \theta|\ Y)d\theta = \int P(\delta t\,|\theta)\times P(\theta|Y)d\theta}$$

The predictive distributions under different models can be obtained by MCMC simulation using JAGS 4.0

Alternative Joint Modeling with Bayesian Model Average



Joint Bayesian Model Averaged (BMA) Prediction of OS

M_1 : Joint model 1 (Target lesion and OS − Linear mixed model + Weibull)
M_2 : Joint model 2 (Non−target lesion and OS − Weibull + copula)
M_3 : Joint model 3 (New lesion and OS − Weibull + copula)
M_4 : model 4 (Marginal modeling of OS − Weibull)

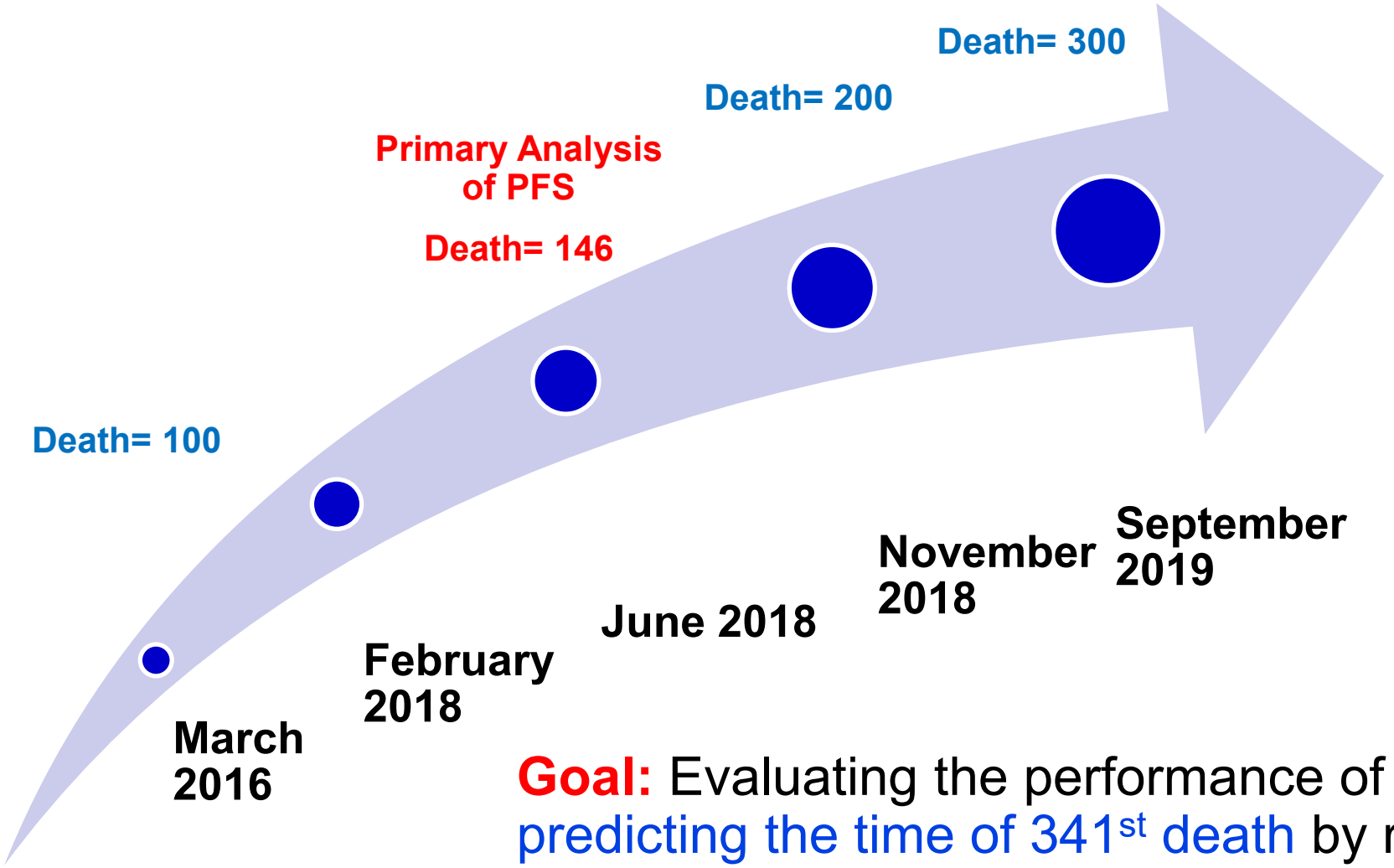
The predicted distribution of OS is a weighted average of predictions from M_1, M_2 M_3 and M_4:

$$Pr(\text{Predicted OS}|\text{Data}) = \sum_{i=1}^{4} Pr(\text{Predicted OS}_i|\text{Data}, M_i)w_i$$

$w_i = Pr(M_i|\text{Data})$ is the chance of selecting model M_i given data.

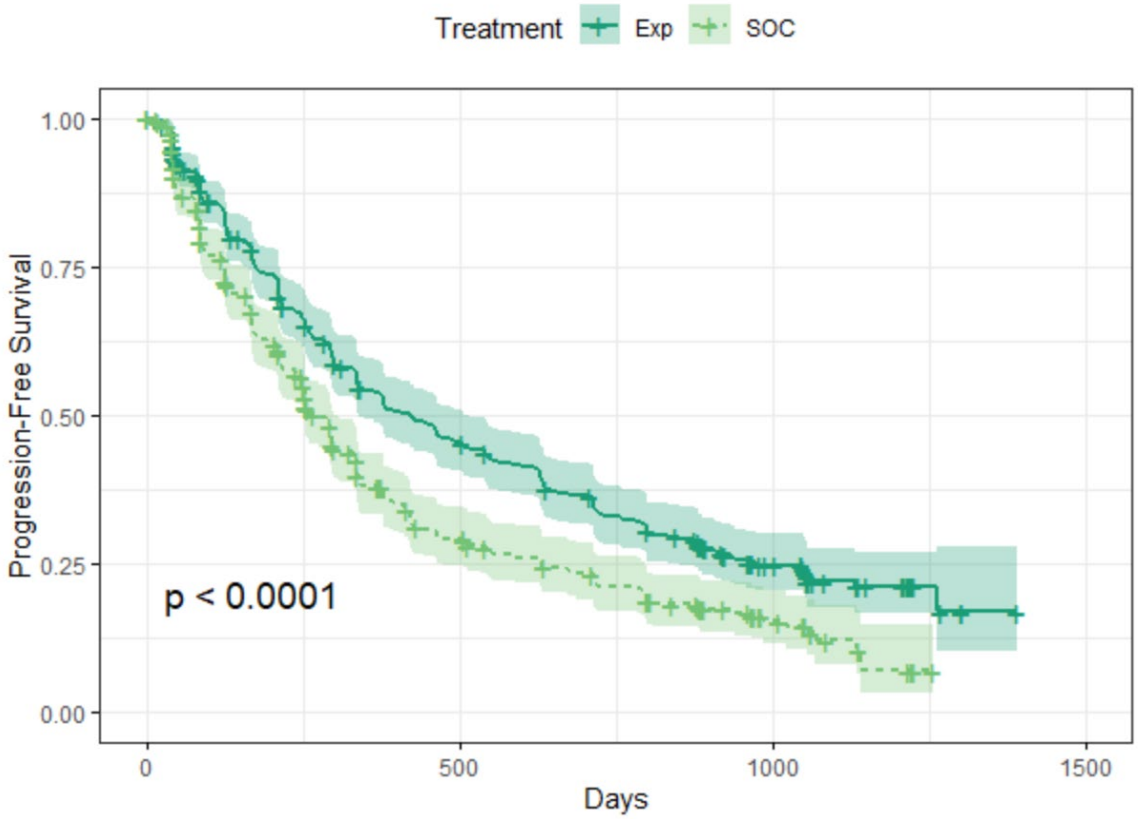
The marginal posterior distribution of overall survival across all 4 models equals to an average of all posterior distributions weighted by each posterior model probability.

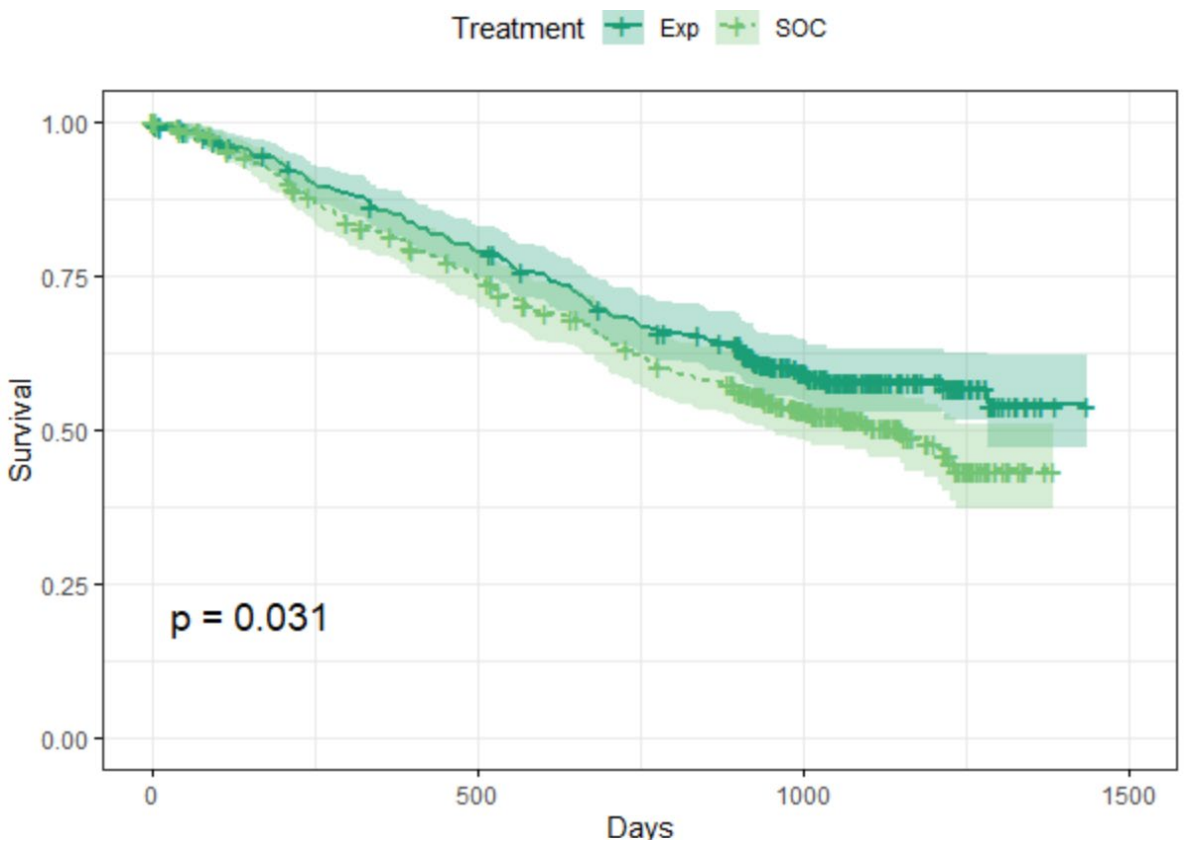
Case Study of RCC: Evolution of Progression and Death data in Trial



Goal: Evaluating the performance of the 4 models by predicting the time of 341st death by reconstructing the data set after 100, 146, 200, and 300 deaths

Analysis of OS and PFS After 341 Deaths





Model Implementation

Baseline covariates are included in the four models

- Age, Gender, ECOG Score, Baseline tumor burden, Nephrectomy at Baseline, Heng prognostic criteria at baseline
- Goodness of fit for model is assessed via DIC

No post-baseline information used: However, the models are flexible

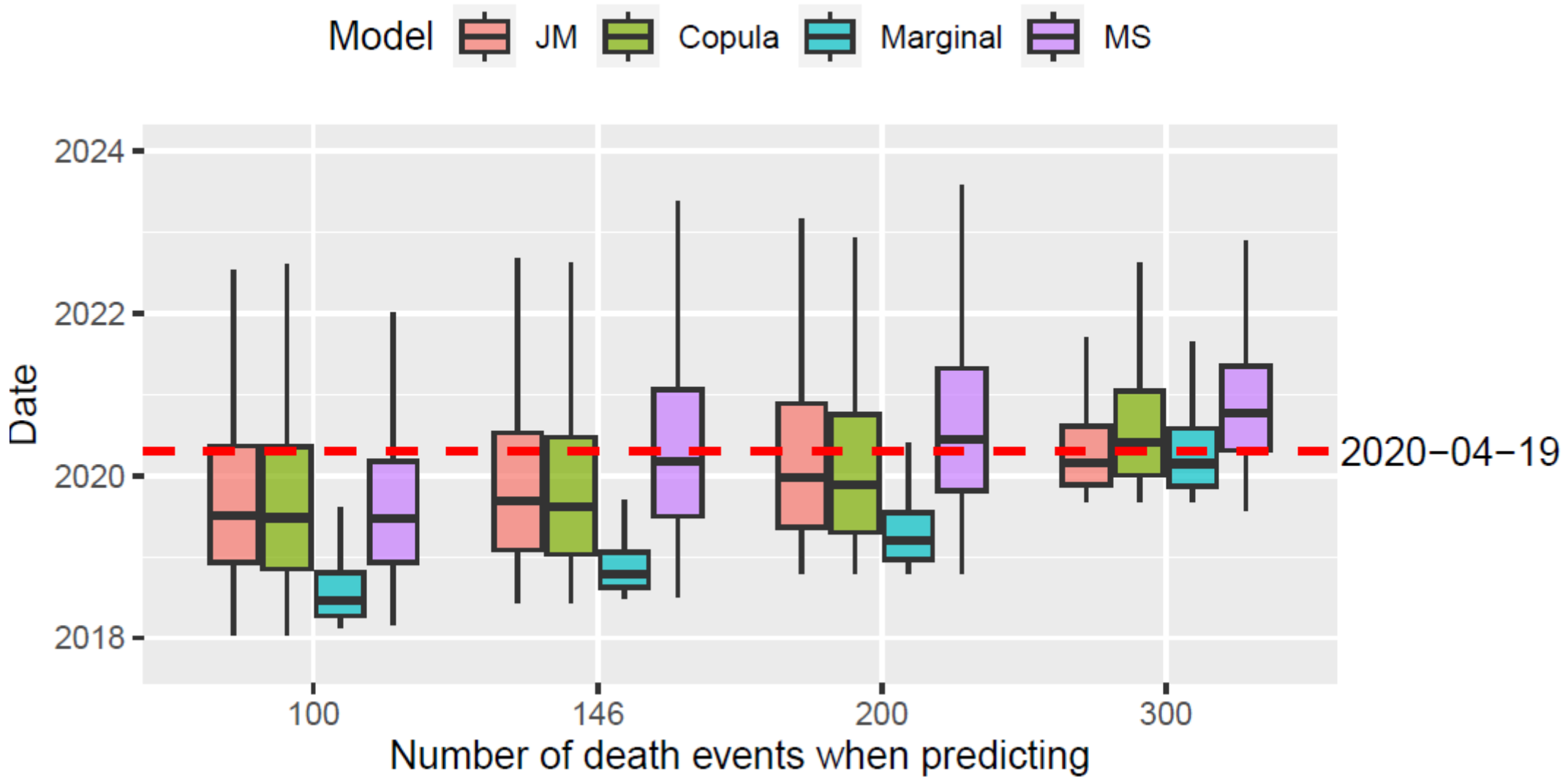
- Allows use of non-linear model

Weakly informative priors are used for model parameters

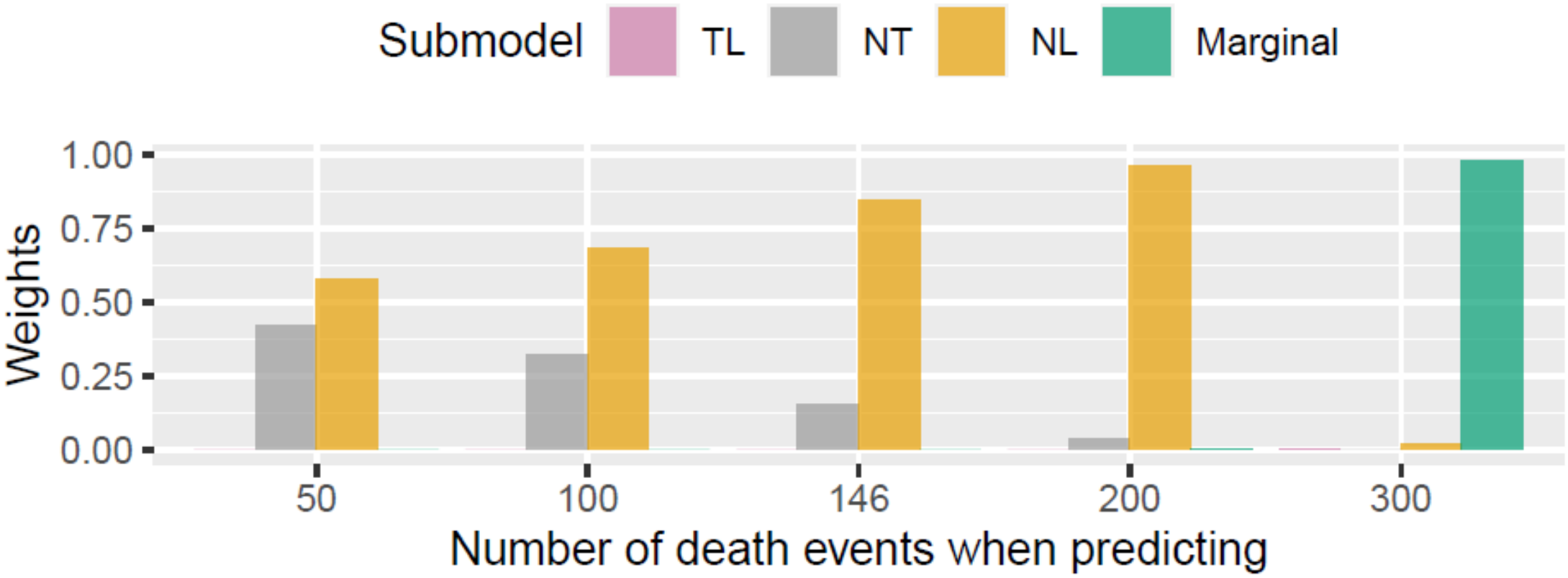
- Sensitivity analysis are often recommended to understand the impact

All Calculations are done using R and JAGS

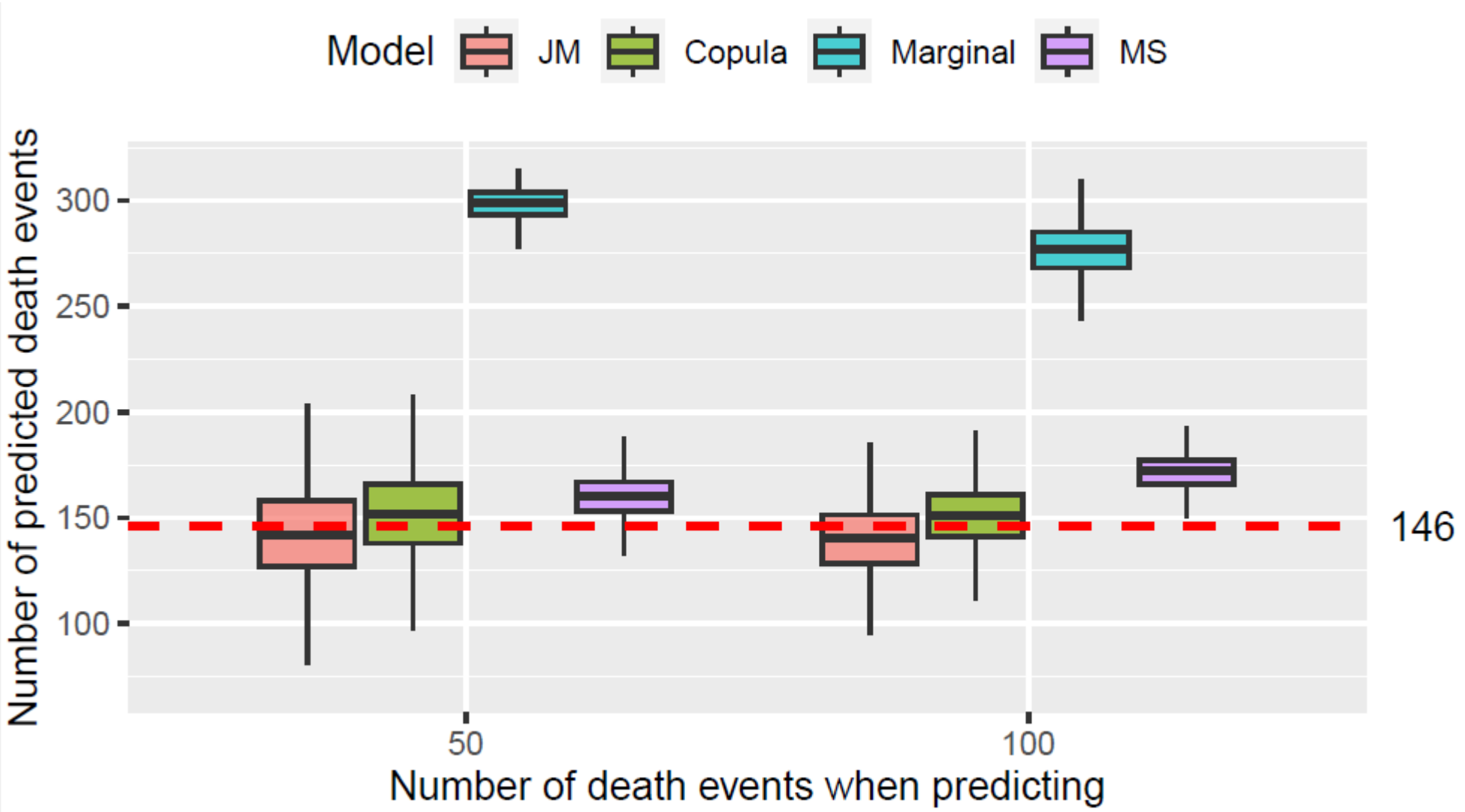
Prediction of Time of 341st Death by Different Models



Posterior Weight for Each Sub-model

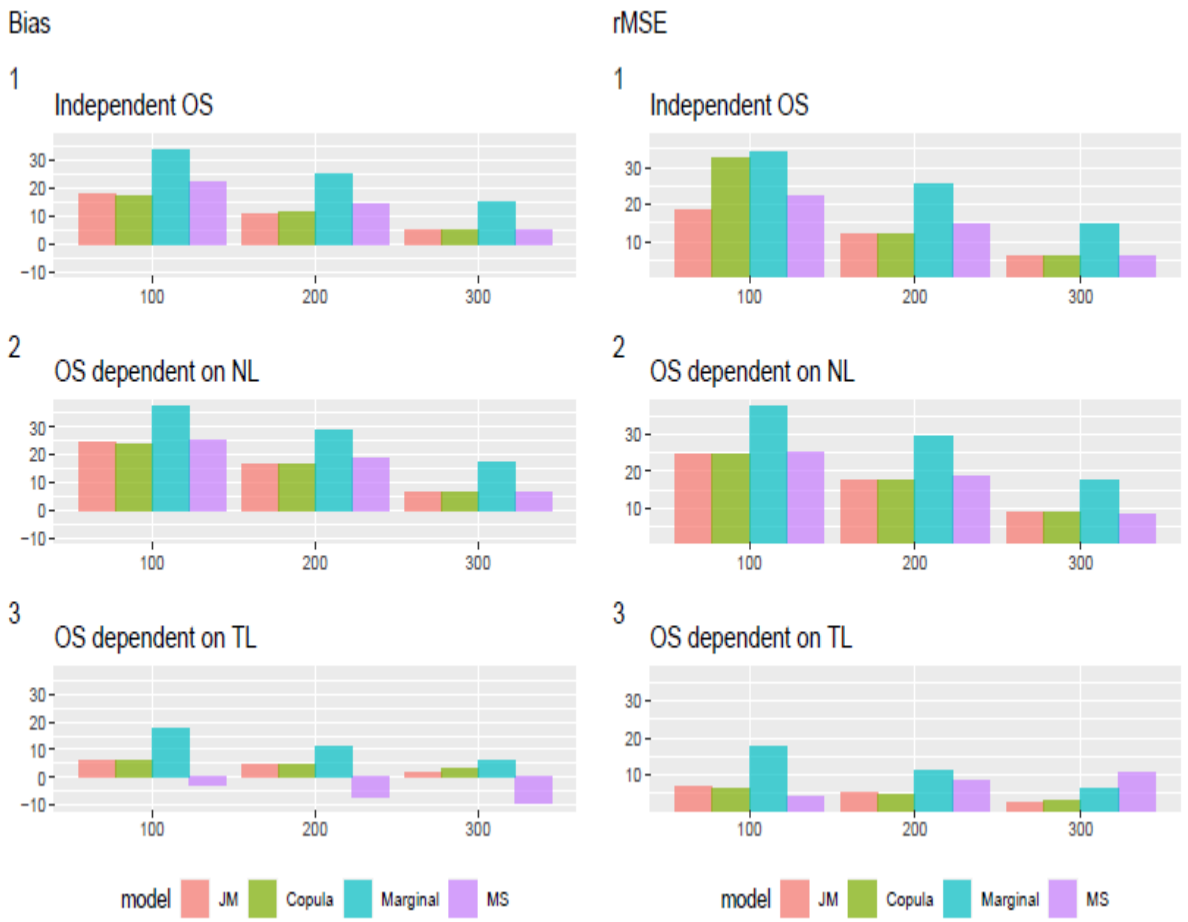


Predicted Number of Death at Primary Analysis by Different Models

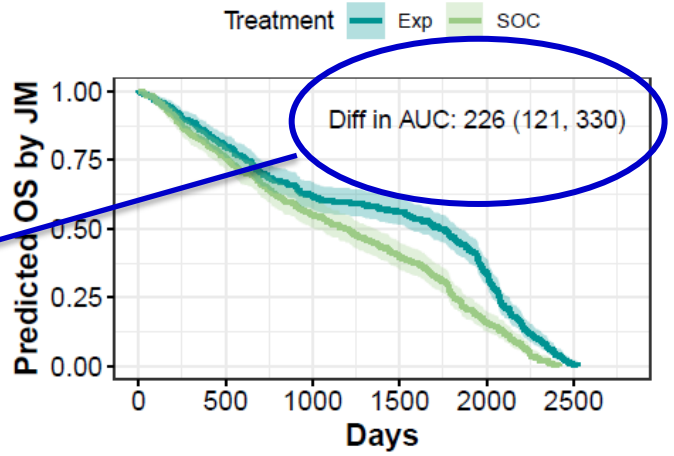


Further Evaluation: Simulation Studies

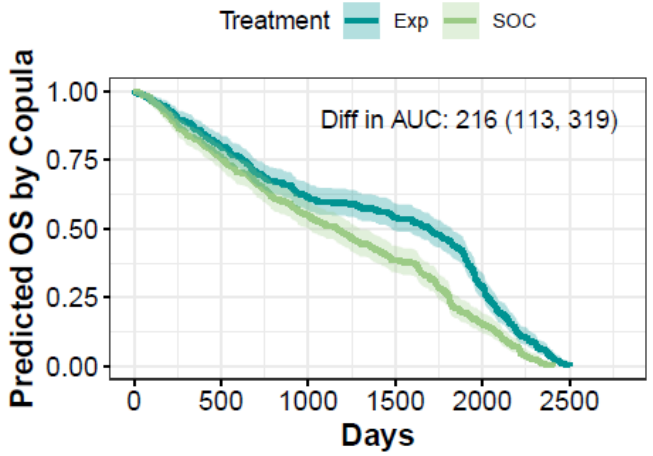
- Simulation studies are performed to assess the model performance
- Progression and death data were generated under different model assumptions
  - Risk of death is independent of any progression component
  - Risk of death depends on the burden of non-target lesion
  - Risk of death depends on the measurable tumor burden
- Date of death for last subject was predicted after observing 100, 200, and 300 deaths
- JM performs better than other three models in terms of prediction bias and MSE



Prediction of Expected Life Gain after All Subjects are Dead in the Case Study: Health Economic Modeling

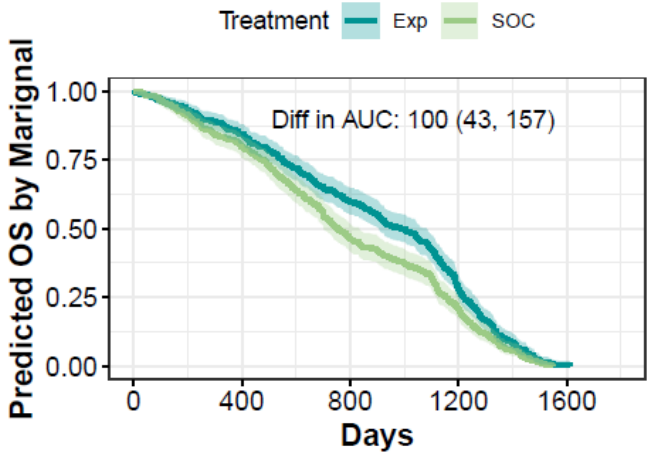


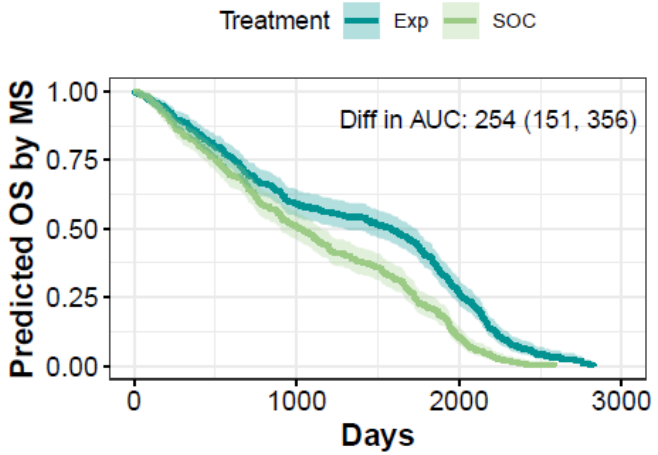
(a)



(b)

JM improves precision by using all relevant information

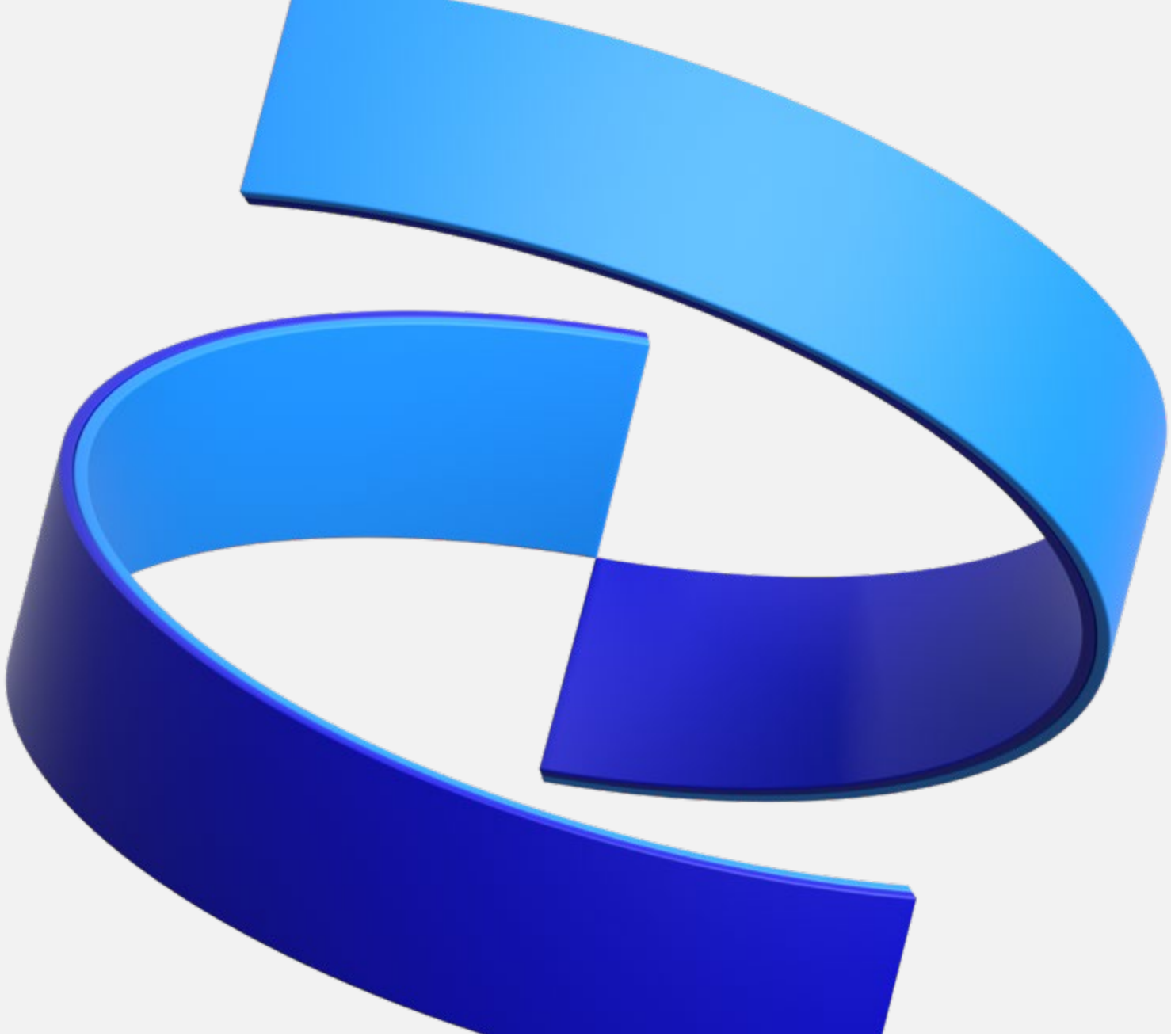


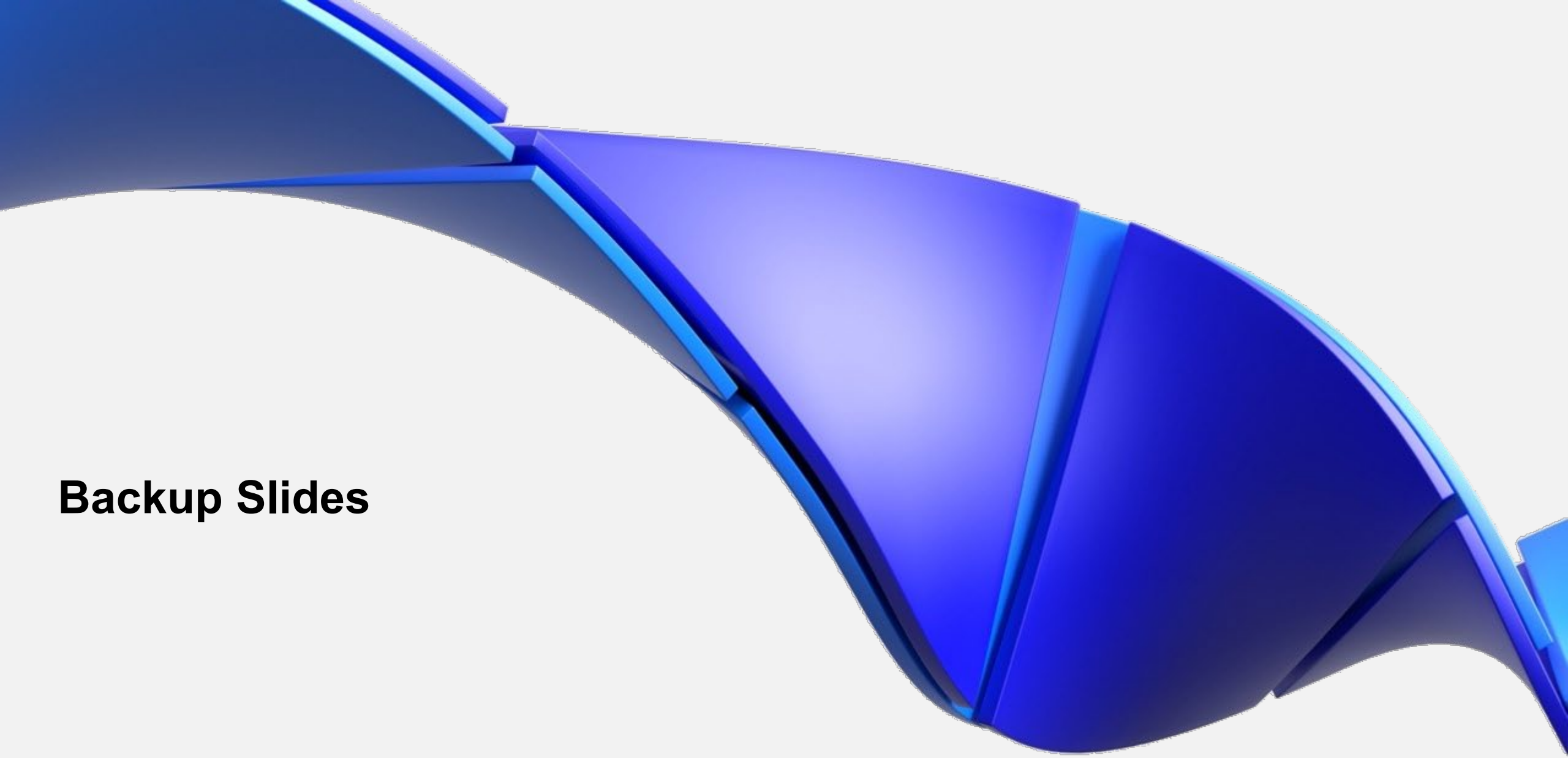


Concluding Remarks

- Model based prediction of death in metastatic cancer trial play an important role
  - Help planning for updated survival analysis required for regulatory purposes
  - Evaluating probability of survival benefit of a new drug
  - Facilitate economic evaluation of new cancer drug
- Exploring association between disease progression and death improves prediction
- Proposed joint model provides a flexible framework for prediction
  - Explore predictability of TL, TNL, and NL for OS
  - Considers the model uncertainties and unmeasured effects using BMA
  - Allows baseline and post-baseline variables (i.e., treatment d/c. cross-over)
- Joint model performs better than other multivariate models such as copula or multi-state model

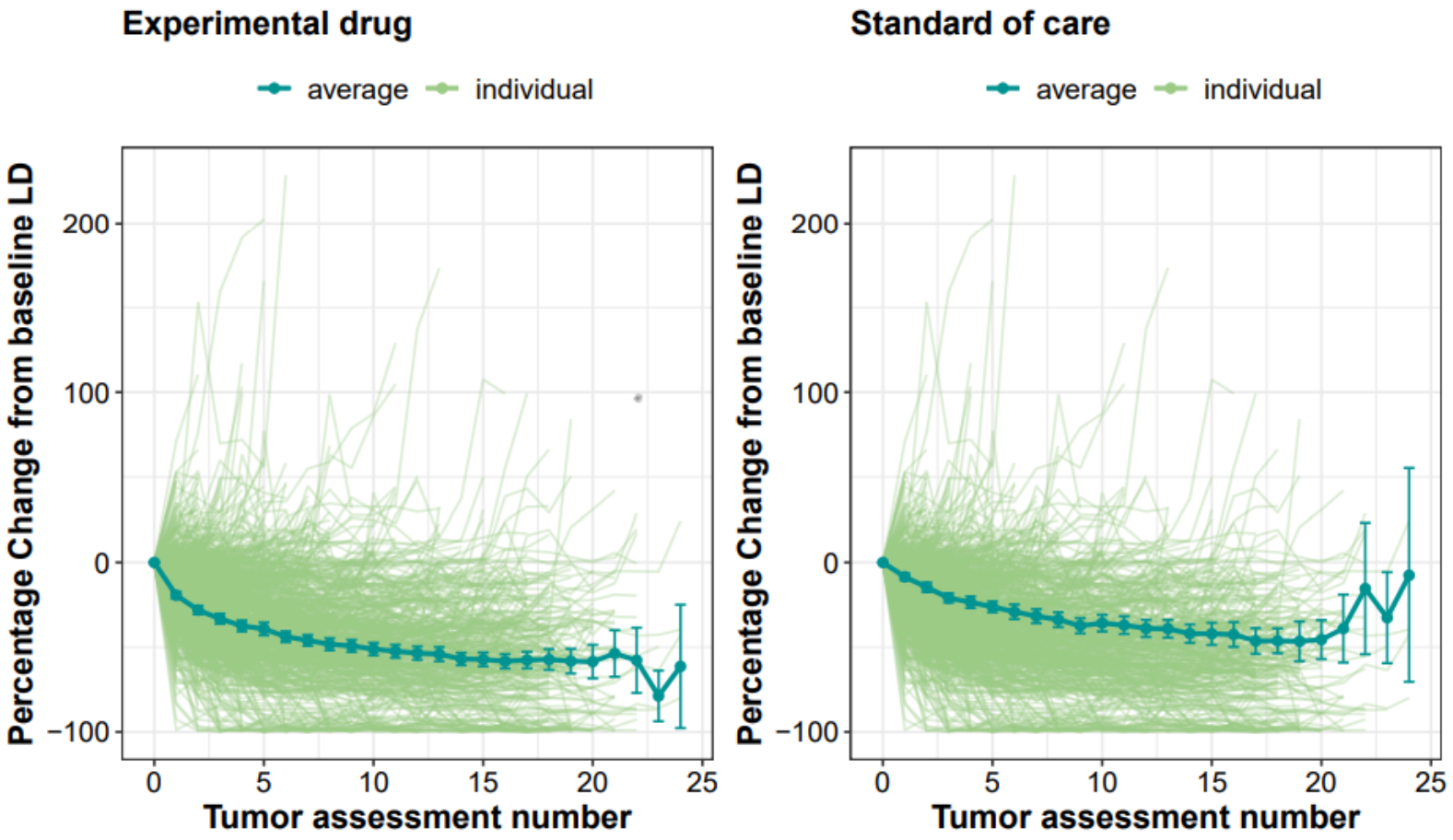
Thank You



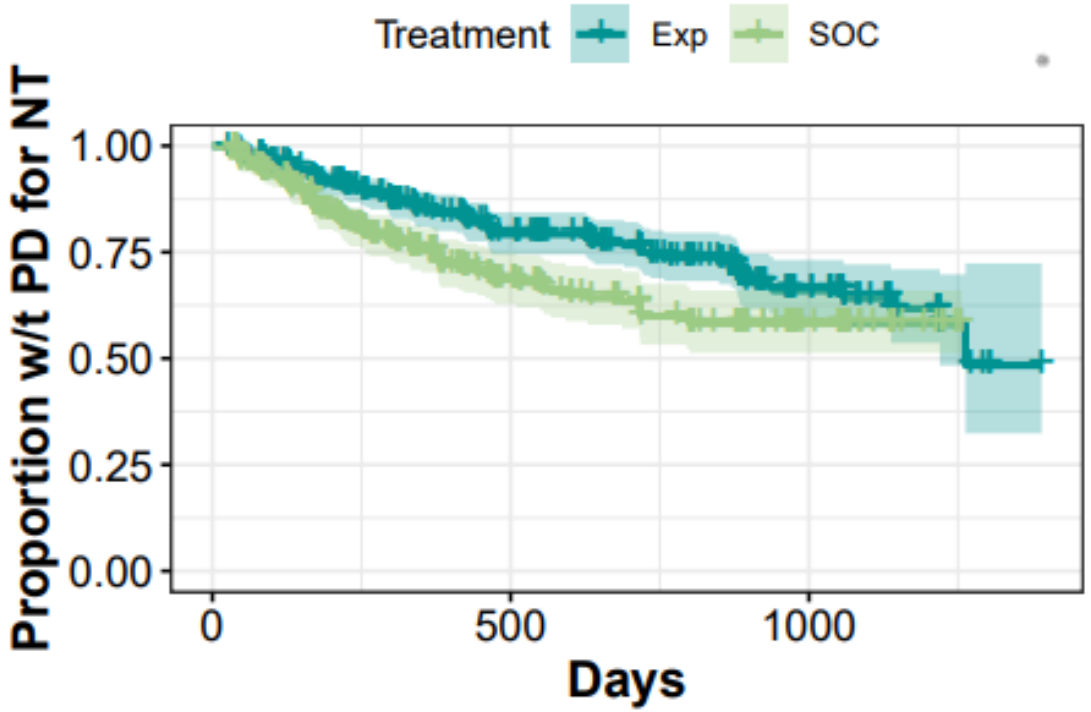


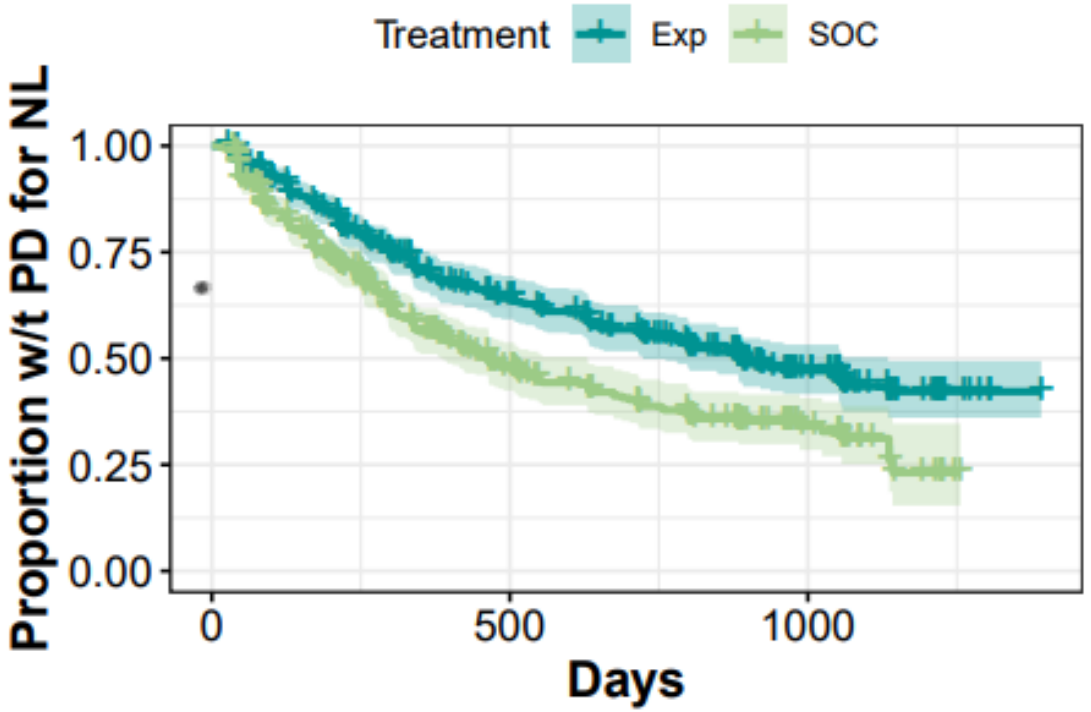
Backup Slides

Target Lesion – % Change in Sum of Longest Diameter (mm) After 341 Deaths



KM Plots of Non-target Lesion and New Lesion After 341 Deaths





Joint Model 1: Target Lesion and OS

- Target lesion measurement (tumor burden) is model by the linear mixed model:

$$\mu_i(t) = \mathbf{X}_i(t)'\boldsymbol{\beta}_\mu + b_{1i} + b_{2i} * t$$

- OS is model by the Weibull regression model:

$$\lambda(t) = \alpha_{\text{OS}}\gamma_{\text{OS}}t^{\alpha_{\text{OS}}-1}\exp(\mathbf{Z}_i'\boldsymbol{\beta}_{\text{OS}} + \lambda\mu_i(t) + b_{3i})$$

- Covariates used: gender, age, and other baseline characteristics

Joint Model 2 and 3: OS with Non-Target and New Lesion

- Joint survival function for time to NT/NL progression and OS is modeled by a Clayton copula:

$$S(t_{\mathrm{N}*}, t_{\mathrm{OS}}|Z) = \{S_{\mathrm{N}*}(t_{\mathrm{N}*}|Z)^{-\eta_{\mathrm{N}*}} + S_{\mathrm{OS}}(t_{\mathrm{OS}}|Z)^{-\eta_{\mathrm{N}*}} - 1\}^{-1/\eta_{\mathrm{N}*}}$$

- $\eta_{\mathrm{N}*}$ measures the correlation between NT/NL and OS.
- Marginal survival distributions for time to NT/NL progression and OS are modeled by using Weibull proportional hazard model.
- Covariates used: gender, age, and other baseline characteristics

$$S_{\mathrm{NT}}(t|Z) = \exp\{-\gamma_{\mathrm{NT}} t^{\alpha_{\mathrm{NT}}} \exp(Z'\beta_{\mathrm{NT}})\},$$

$$S_{\mathrm{OS}}(t|Z) = \exp\{-\gamma_{\mathrm{OS}} t^{\alpha_{\mathrm{OS}}} \exp(Z'\beta_{\mathrm{OS}})\}.$$

In probability theory and statistics, a copula is a multivariate cumulative distribution function for which the marginal probability distribution of each variable is uniform on the interval [0, 1]. Copulas are used to describe/model the dependence (inter-correlation) between random variables.

Marginal Model 4: OS

- OS is model by the Weibull regression model:

$$\lambda(t) = \alpha_{\mathrm{OS}}\gamma_{\mathrm{OS}}t^{\alpha_{\mathrm{OS}}-1}\exp(\mathbf{Z}_i'\boldsymbol{\beta}_{\mathrm{OS}})$$

- Covariates used: gender, age, and other baseline characteristics

Bayesian Model Average (BMA)

The model weight at t-th MCMC iteration is: $w^{(t)} = P(M_k|Data, \theta^{(t)}) = \frac{P(M_k, Data, \theta^{(t)})}{P(Data, \theta^{(t)})}$

$$= \frac{P(Data|M_k, \theta^{(t)})P(\theta^{(t)}|M_k)P(M_k)}{P(Data, \theta^{(t)})}$$

$\theta = (\theta_1, \theta_2, \theta_3, \theta_4)$ denotes the parameter set over all 4 models

$P(\theta^{(t)}|M_k)$ denotes prior distributions of θ under model k, $P(M_k)$ denotes the prior probability of M_k.
$P(Data|M_k, \theta^{(t)})$ denotes the joint likelihood of model k and its parameters

At each MCMC iteration, all 4 models are updated, and continuous measures of their relative performance are used to calculate the final w_i.