Modeling & Simulation
Decisions

Model-based survival meta-analysis

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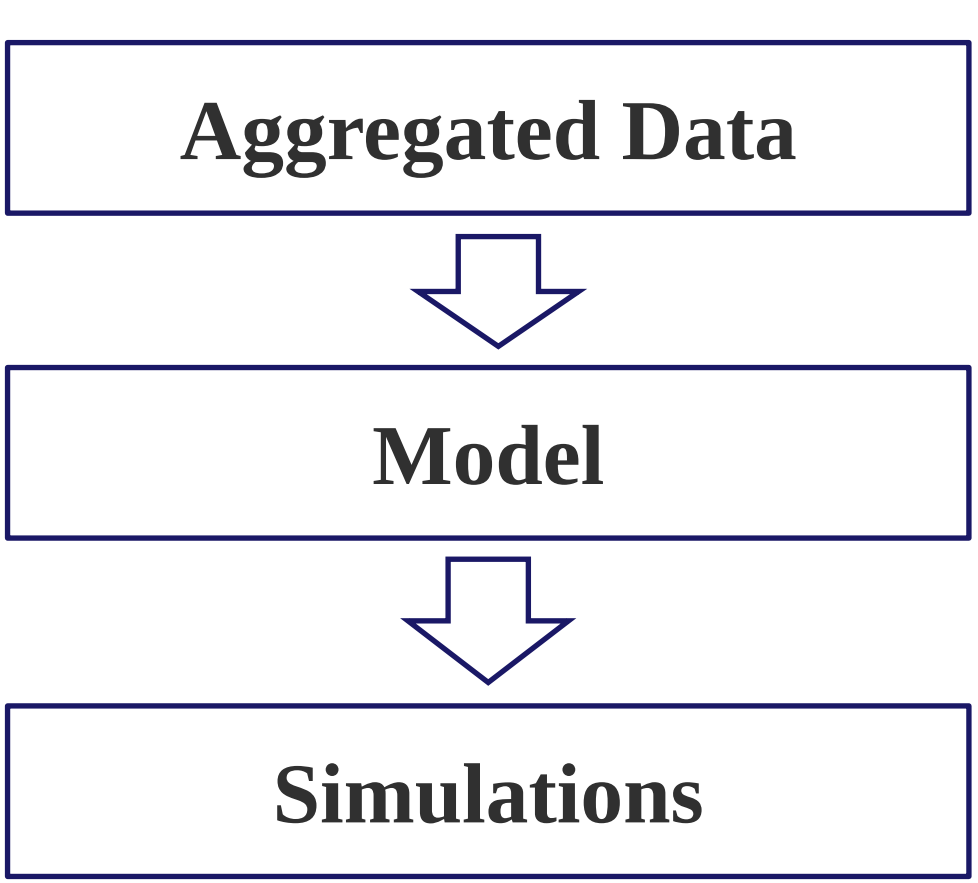
Model-based meta-analysis (MBMA)

Meta-analysis is a statistical procedure for combining numerical data from multiple separate studies



- Individual patient-level
- Trial summary-level

- Advanced scientific modeling
- Based on drug characteristics and the biology of the disease etc.
- Account for heterogeneity of trials

- Optimize trial design
- Inform go/no go, marketing decisions etc.
- **Indirect comparison**

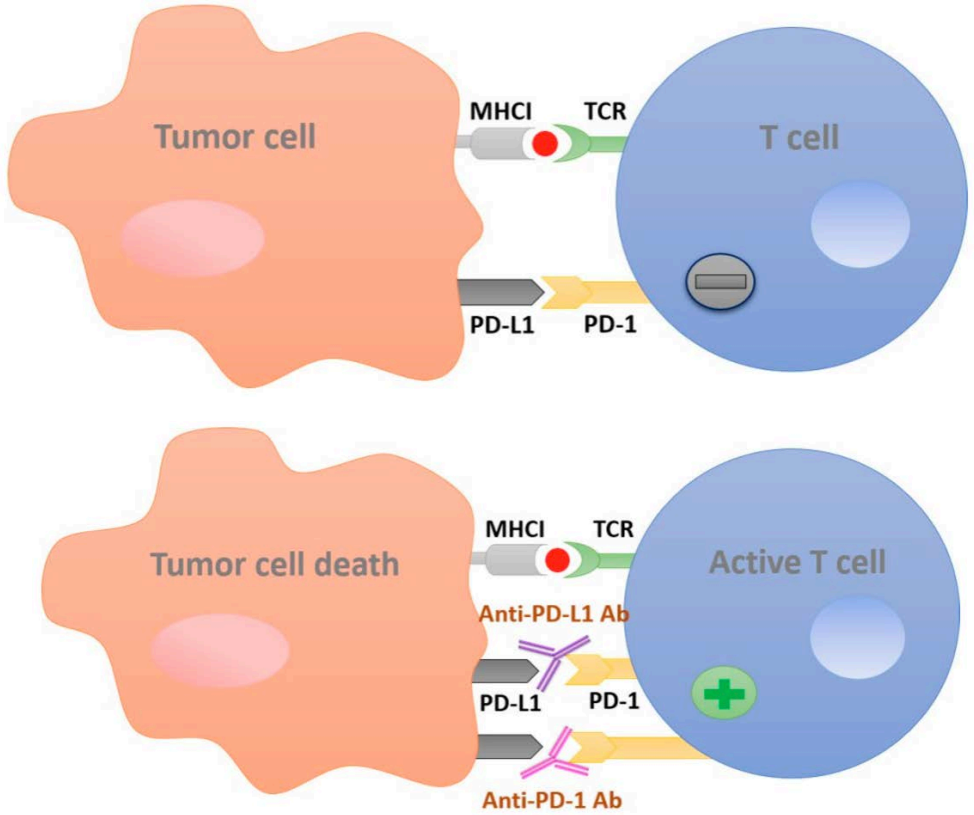
Upreti VV, Venkatakrishnan K. Model-based meta-analysis: optimizing research, development, and utilization of therapeutics using the totality Clin Pharmacol Ther. 2019;106:981-992.

Application to ICIs in treatment NSCLC

- Programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors are monoclonal antibodies called immune checkpoint inhibitors (ICIs)
- Don't kill cancer cells directly, instead, make the immune cells able to recognize and attack them
- Frontline treatments for patients with metastatic non-small cell lung cancer (NSCLC)
- Approved for clinical use based on comparison with chemotherapy as a standard of care
- **No head-to-head comparison (PD-1 vs PD-L1 inhibitors)**

MBMA can be used to conduct an indirect comparison

PD-1 and PD-L1 Checkpoint Signaling Inhibition:



Abdin, S.M.; Zaher, D.M.; Arafa, E.-S.A.; Omar, H.A. Tackling Cancer Resistance by Immunotherapy: Updated Clinical Impact and Safety of PD-1/PD-L1 Inhibitors. *Cancers* **2018**, *10*, 32.

Overall survival

- The ‘gold standard’ primary clinical endpoint to evaluate efficacy in oncology studies
- The time from randomization until death from any cause
- Right censored data

Survival Analysis. Basics

We can describe the distribution of T:

Survival function

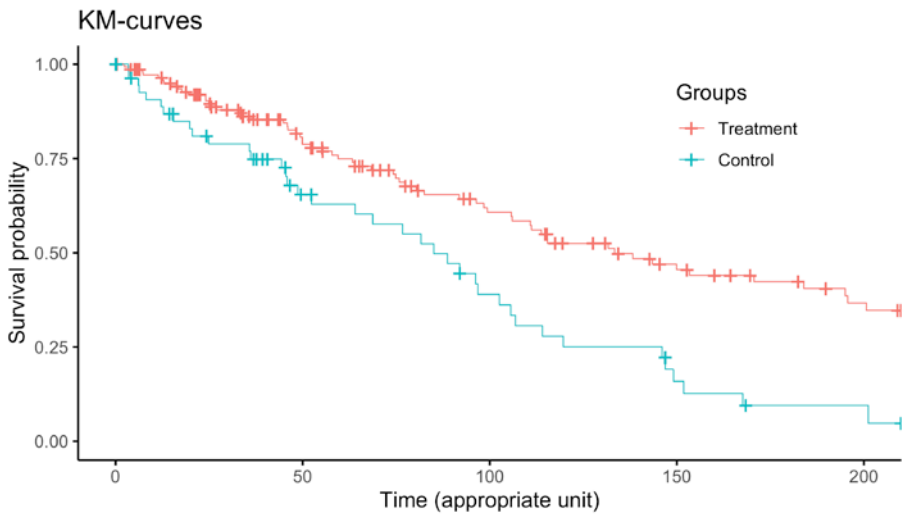
$$S(t) = P(T > t)$$

Kaplan-Meier estimator of $S(t)$:

$$\hat{S}(t) = \prod_{j:t_j \le t} \frac{r_j - d_j}{r_j}$$

d_j – is the number of event times at t_j,

r_j – is the number of individuals **at risk** right before the j-th failure time

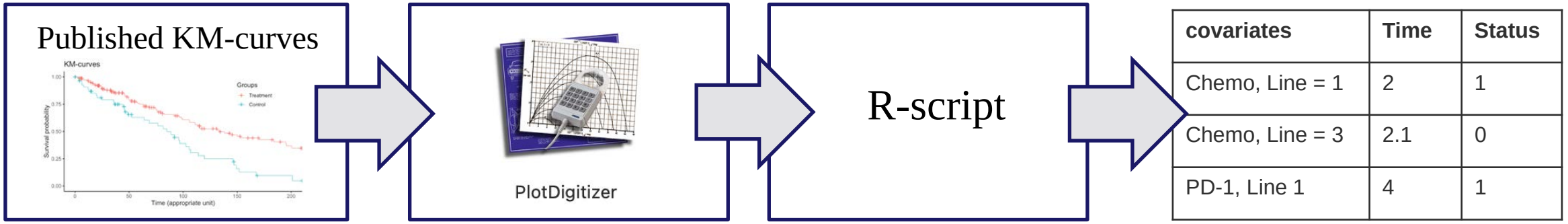


We account for censoring by suitably adjusting **the risk set**

Risk set: all observations that have not failed and have not been censored just prior to time t

Digitize survival data

- OS individual patient-level data are not publicly available for ICI trials
- KM OS curves and cohort covariates can be retrieved from published papers and then digitized into individual time-to-event data



covariates	Time	Status
Chemo, Line = 1	2	1
Chemo, Line = 3	2.1	0
PD-1, Line 1	4	1

[1] Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012 Feb 1;12:9.

[2] Wei Y, Royston P. Reconstructing time-to-event data from published Kaplan-Meier curves. Stata J. 2017;17(4):786-802.

Data

A dataset has been developed from 17 clinical trials (Arms = 45) reported from 2012 to 2022

ICI target	Drug	N observations
NONE	Chemotherapy	4425
PD-1	Pembrolizumab	1959
	Nivolumab	1014
PD-L1	Atezolizumab	1956
	Durvalumab	553
	Avelumab	264

ALL = 10171

Other covariate available from the cohorts:

- **PD-L1 expression level**

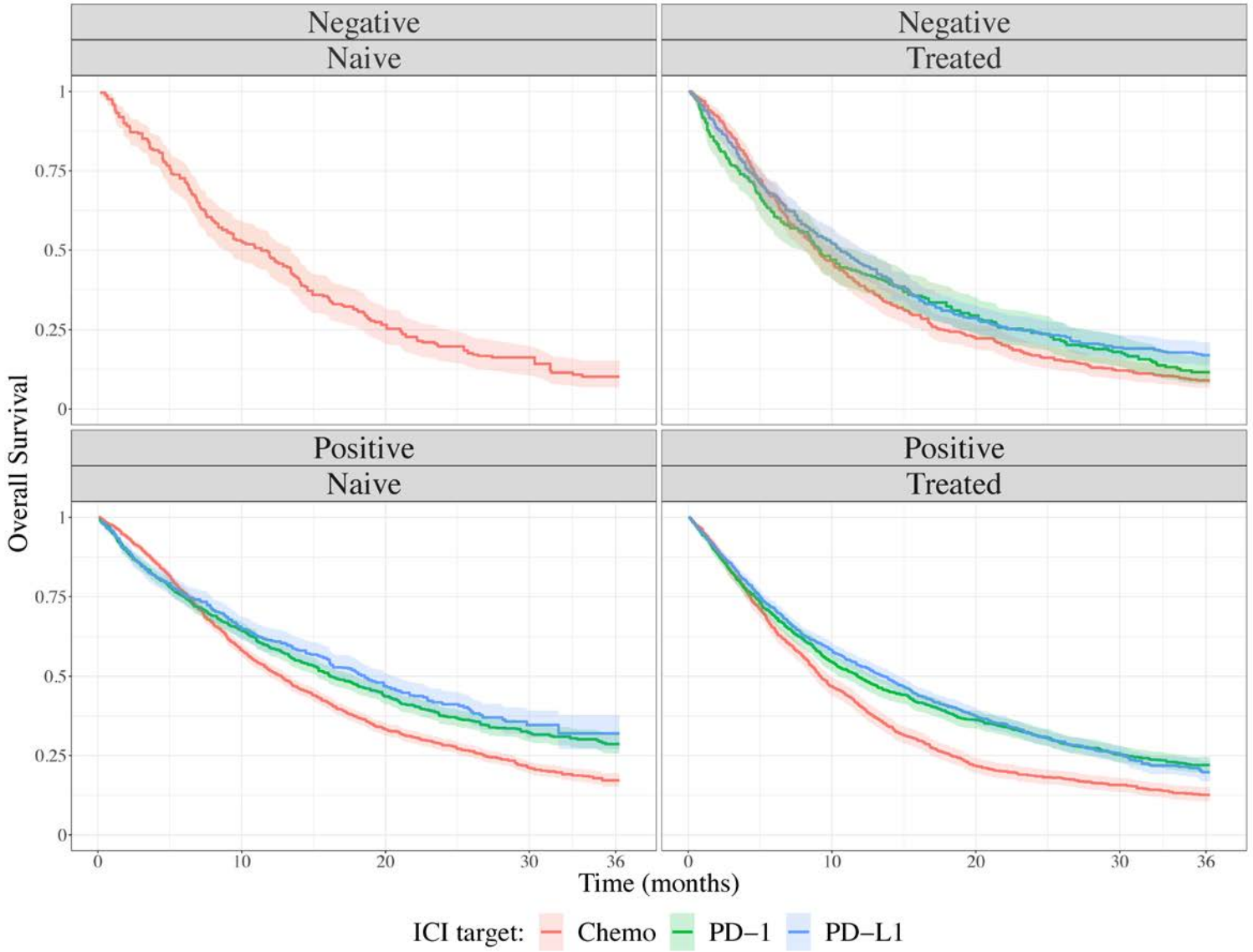
Measured by tumor proportion score (TPS)
TPS < 1% (Negative)
TPS ≥ 1% (Positive)

- **Line of Therapy**

Line = 1 (Naive)
Line > 1 (Treated)

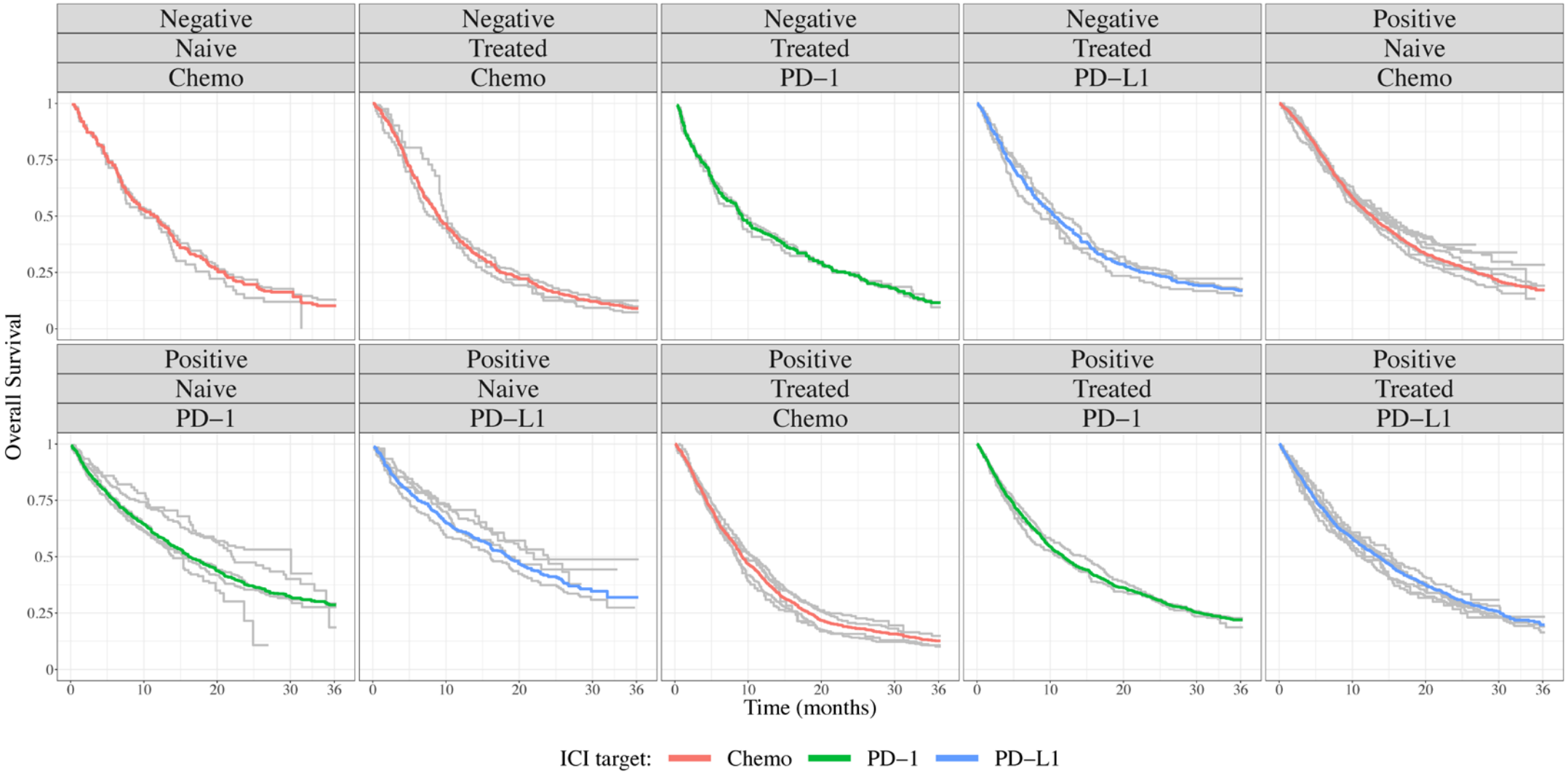
The Dataset was truncated at 36 months

Pooled KM-curves stratified by Line and PD-L1 status



- Curves for Immuno- and Chemo- therapies cross within 12 months (reverse effect)
- Higher survival for ICIs in Positive strata

KM-individual curves vs. pooled



- **Survival rate varies between the same strata depending on each particular study**

Hazard function

Distributions of survival times can be described by hazard function

Hazard function:

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t | T > t)}{\Delta t}$$

The **instantaneous risk** of an event at time t, given that the event has not occurred until time t

Can be interpretable as the expected number of events per individual per unit of time

$$h(t) = \frac{f(t)}{S(t)} \qquad H(t) = \int_0^t h(s)ds$$

$$H(t) = -\log \mathrm{S(t)} \qquad S(t) = \exp\{-H(t)\} = \exp\left\{-\int_0^t h(s)ds\right\}$$

Hazard regression models

The hazard function is the central focus for modelling variations in survival

multiplicative effect of Z_i

$$h(t|\mathrm{Z}) = h_0(t)\exp(Z_i\beta)$$

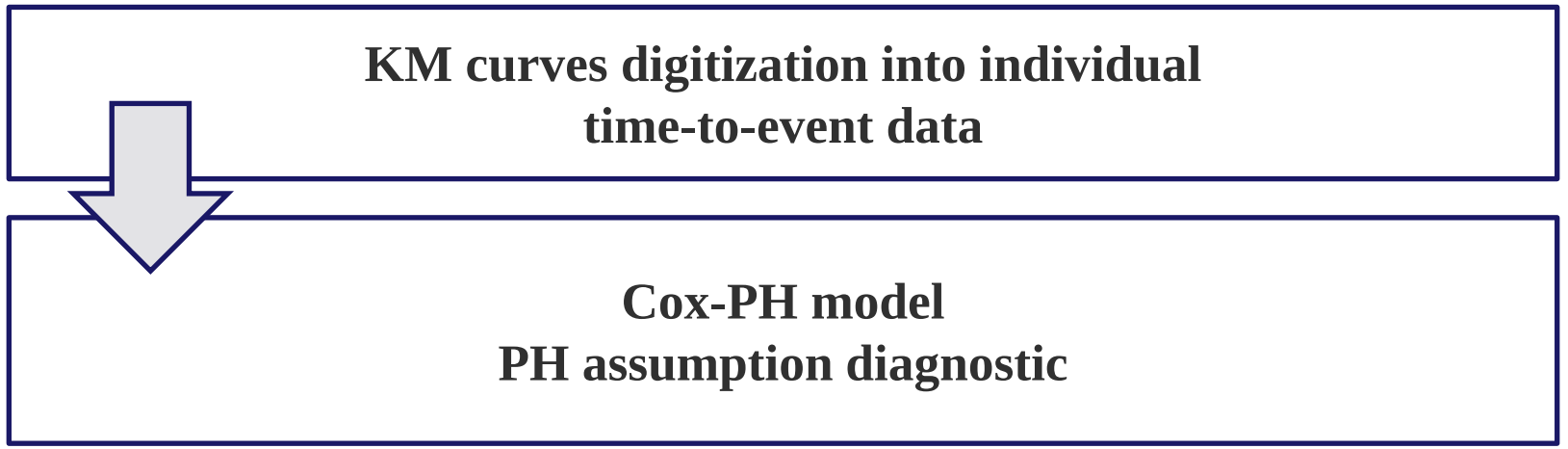
β is assumed to be constant (**Proportional Hazards models**)

baseline part

Can be omitted: semiparametric hazard regression models (CoxPH model)

Congdon, Peter. *Bayesian Hierarchical Models: With Applications Using R*. Second edition, CRC Press, taylor & Francis Group, 2021.

General Framework for Survival MBMA



Covariates

Patient Characteristics

PD-L1 status
- **Negative** *(TPS < 1%)*
- Positive *(TPS ≥ 1%)*

Line
- **Treated** *(Line > 1)*
- Naive *(Line = 1)*

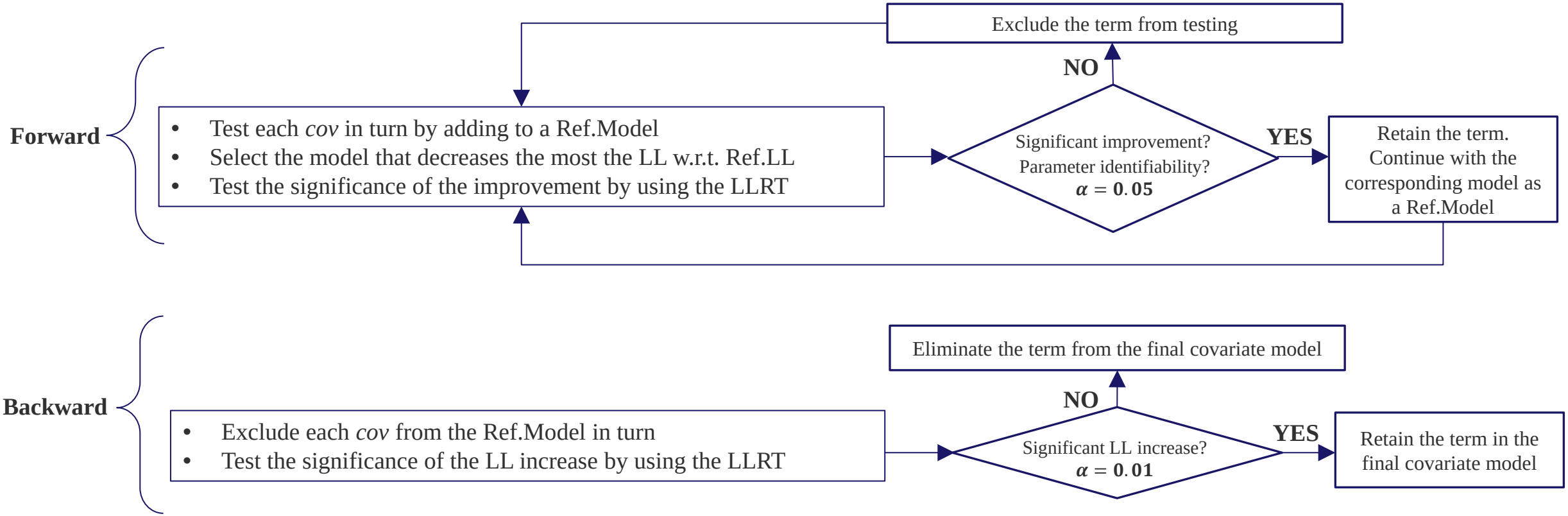
Treatment

ICI target
- **Chemo**
- PD-1 *(Pembro & Nivo)*
- PD-L1 *(Atezo & Ave & Durva)*

Possible interactions
- Atezo*PD-L1 status (Positive)
- Atezo*PD-L1 status (Negative)
- ICI target (Chemo)* Crossover (Yes)

The stepwise covariate model (SCM) building procedure for CoxPH models

Null model { **Null model → use it as a reference model (Ref.Model)** → retrieve LL (Ref.LL)



Ayral, Géraldine, et al. 'A Novel Method Based on Unbiased Correlations Tests for Covariate Selection in Nonlinear Mixed Effects Models: The COSSAC Approach'. *CPT: Pharmacometrics & Systems Pharmacology*, vol. 10, no. 4, Apr. 2021, pp. 318–29.

Cox-PH model. Stepwise Covariates Selection

Definition of the Cox-PH model:

$$HR = \frac{h_0(t)e^{\sum_{i=1}^{p}\beta_i Z_i^*}}{h_0(t)e^{\sum_{i=1}^{p}\beta_i Z_i}} = e^{\sum_{i=1}^{p}\beta_i(Z_i^* - Z_i)}$$

Results:

Covariates	Final Model	
	Est. (RSE%)	Hazard Ratio
ICIs_target(PD-1)	-0.25 (11.49)	0.78
ICIs_target(PD-L1)	-0.29 (10.38)	0.75
PDL1_status(Positive)	-0.16 (20.18)	0.85
Line(Naive)	-0.24 (10.55)	0.78
ICI_target(Chemo)*crossover(Yes)	–	–
Atezo*PDL1_status(Positive)	–	–
Atezo*PDL1_status(Negative)	–	–

Diagnostic of the PH assumption:

The Schoenfeld residuals (*Schoenfeld, 1982*):

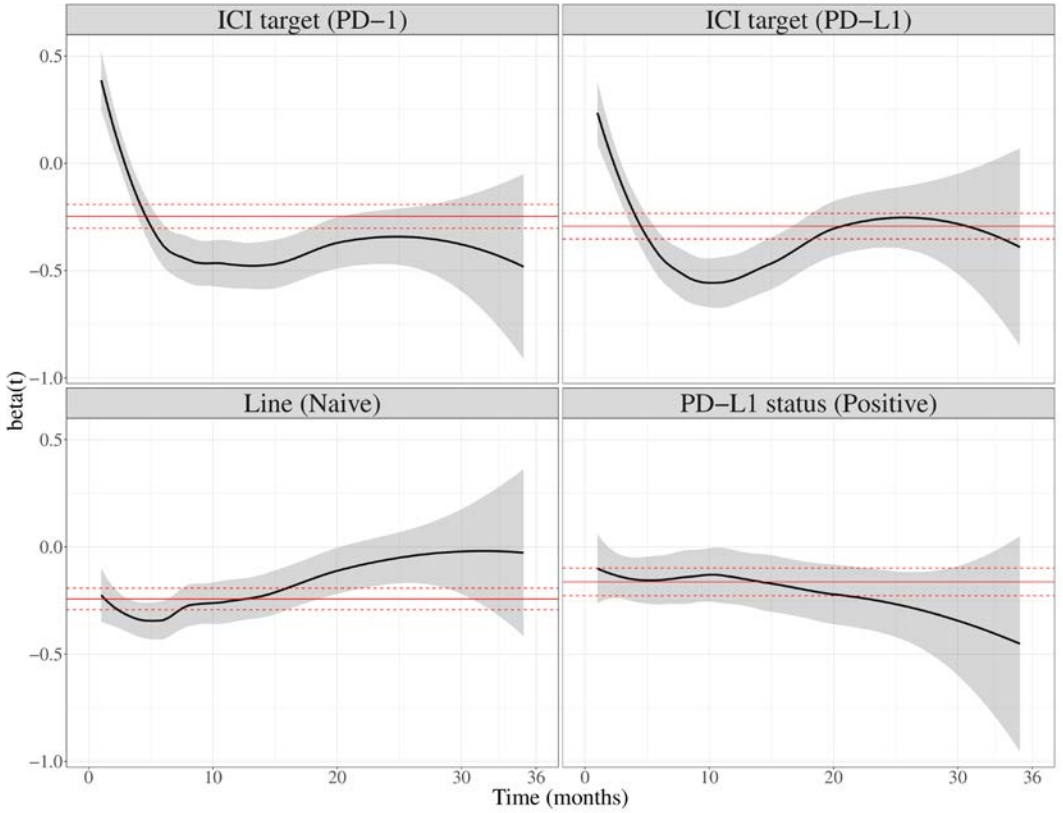
$$r_{ij} = Z_{ij}(X_i) - \bar{Z}_j(\hat{\beta}, X_i)$$

Scaled Schoenfeld residuals ***(****Grambsch & Therneau, 1993****)*****:**

$$r_{ij}^{w} = n\hat{V}r_{ij}$$

Covariates	p
ICI target	<0.001
PD-L1 status	>0.05
Line	<0.001
GLOBAL	<0.001

β(t) approximated with loess regression (span = 0.75)



small p-value indicates violation of hazard proportionality!

Grambsch, Patricia M., and Terry M. Therneau. 'Proportional Hazards Tests and Diagnostics Based on Weighted Residuals'. *Biometrika*, vol. 81, no. 3, 1994, pp. 515–26.

Hazard regression models

The hazard function is the central focus for modelling variations in survival

multiplicative effect of Z_i

$$h(t|\mathrm{Z}) = h_0(t)\exp(Z_i\beta)$$

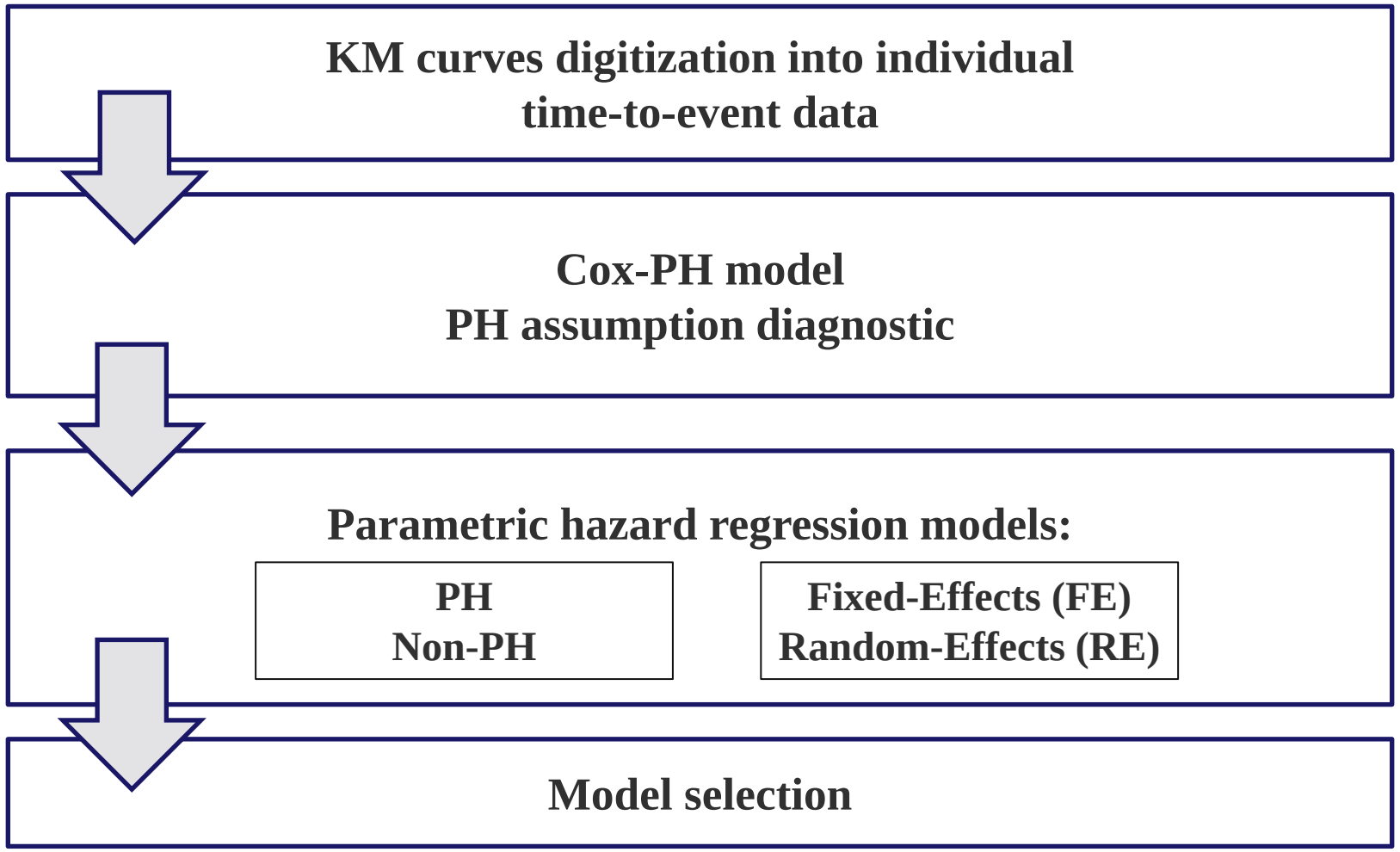
baseline part

β is assumed to vary with time
(**Non-Proportional Hazards models**)

Can be defined parametrically:
Parametric hazard regression models

Congdon, Peter. *Bayesian Hierarchical Models: With Applications Using R*. Second edition, CRC Press, taylor & Francis Group, 2021.

General Framework for Survival MBMA



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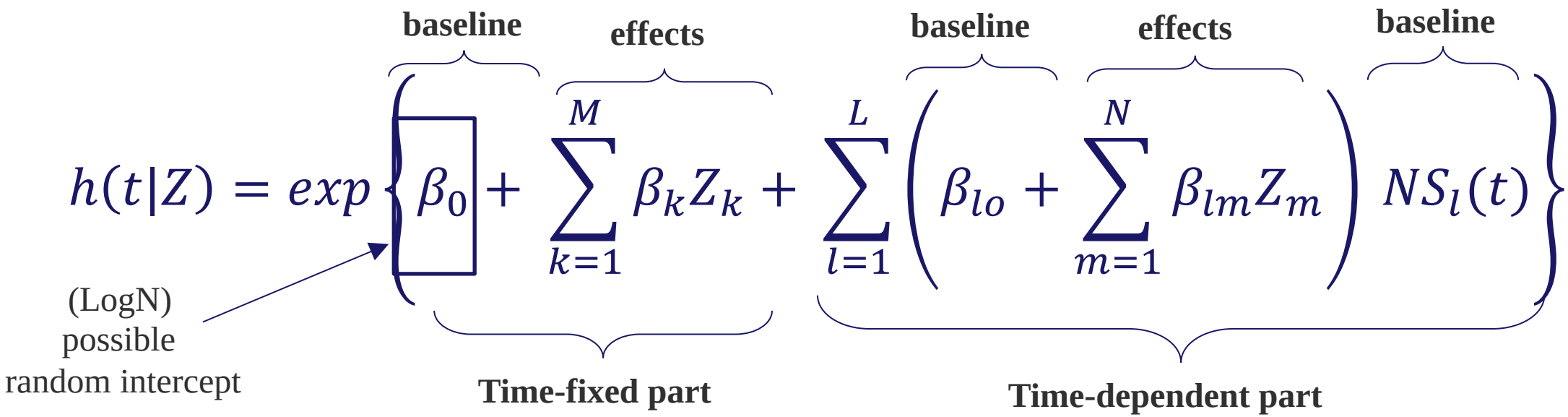
The general expression of the hazard to model with splines. Flexible Parametric Models



$NS_l(t)$ – the basis functions of time (defined as a Natural cubic spline)

Z – vector of covariates

β_k – the coefficients corresponding to the covariates modeled with time-fixed effect (TF)

β_{lo} – the coefficients for baseline hazard

β_{lm} – the coefficients corresponding to the covariates modeled with time-dependent effect (TD)

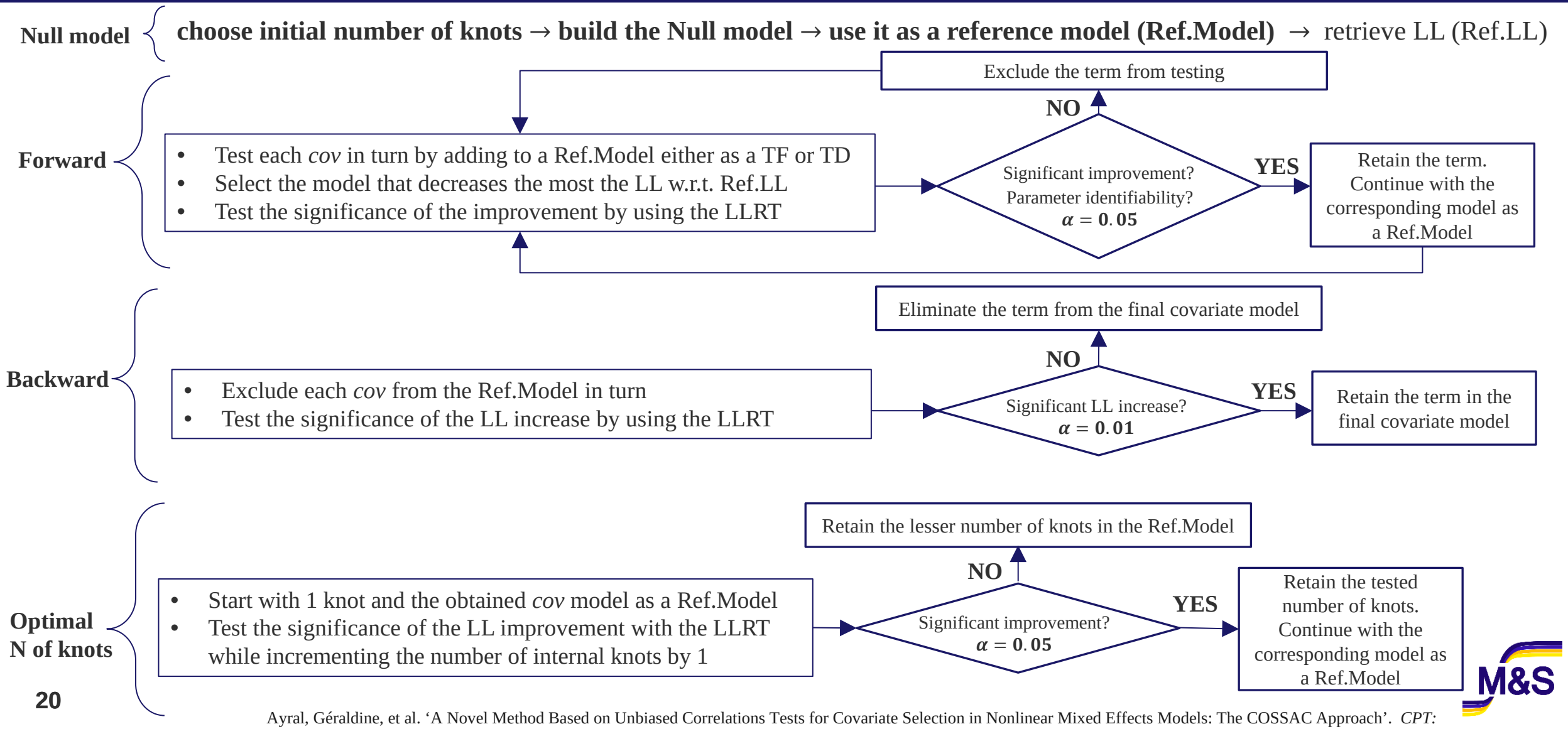
M – number of time-fixed effects

L – knot number + 1 (d.f.)

N – number of time-var effects

Charvat, H. and Belot, A. 2021. mexhaz: An R Package for Fitting Flexible Hazard-Based Regression Models for Overall and Excess Mortality with a Random Effect. *Journal of Statistical Software*. 98, 14 (Jul. 2021), 1–36.

The SCM procedure for flexible parametric models



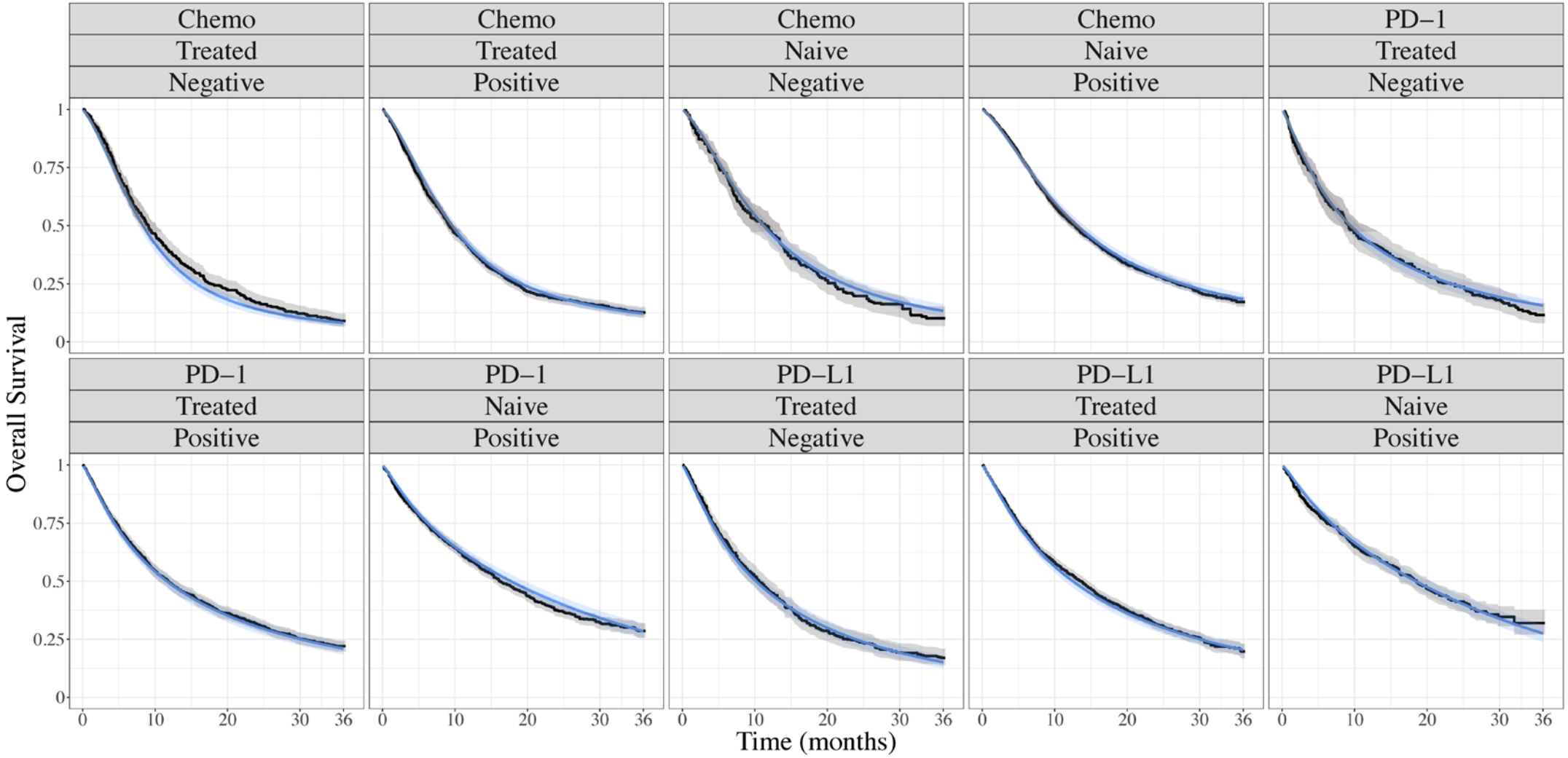
Ayral, Géraldine, et al. 'A Novel Method Based on Unbiased Correlations Tests for Covariate Selection in Nonlinear Mixed Effects Models: The COSSAC Approach'. *CPT: Pharmacometrics & Systems Pharmacology*, vol. 10, no. 4, Apr. 2021, pp. 318–29.

Summary table

	init.k	TF	TD	RE	opt.k	AIC
NPH, RE-model	1, 2	PD-L1 status	ICI target, Line	Study	2	26710.19
NPH, FE-model	1, 2	PD-L1 status	ICI target, Line	–	2	26719.58
	3, 4	Line, PD-L1 status	ICI target	Study	2	26720.87
	3, 4	Line, PD-L1 status	ICI target	–	2	26729.36
	5, 6	ICI target, Line, PD-L1 status		Study	1	26837.36
PH, FE-model	5, 6	ICI target, Line, PD-L1 status		–	1	26847.07

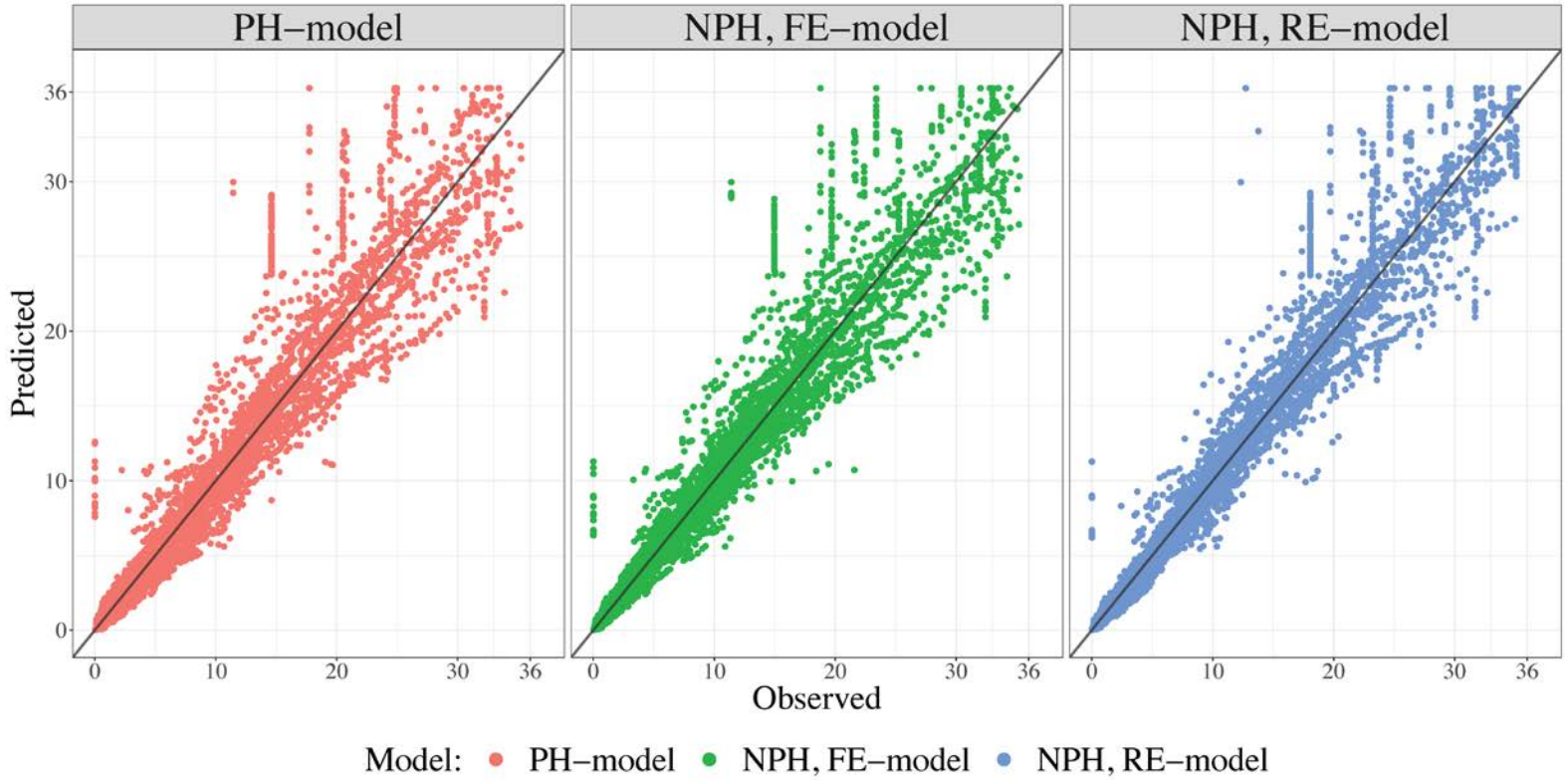
Models output are presented in the back-up section (slide 27)

Visual Predictive Check. NPH, RE-model. Pooled data



VPC for all models and estimated effects are in the back-up section (slides 29-33)

Observed vs Predicted. Individual studies

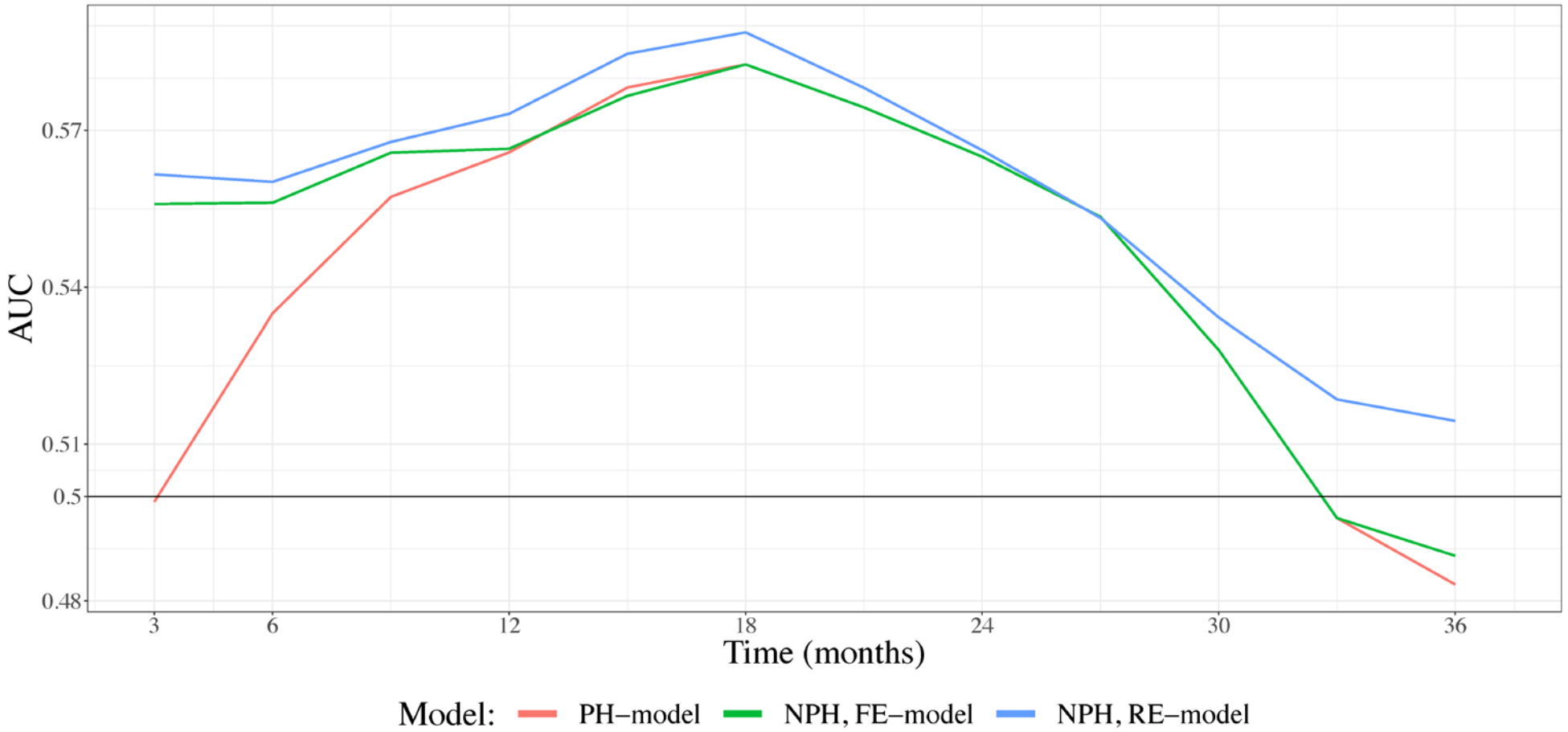


	MSE	RMSE
PH-model	8.245	2.871
NPH, FE model	7.595	2.756
NPH, RE model	5.29	2.3

Time-dependent AU(ROC)

Other calibration/discrimination metrics are in the back-up section (slide 35)

Cumulative-dynamic formulation



Heagerty PJ, Zheng Y. Survival model predictive accuracy and roc curves. Biometrics. 2005;61(1):92–105.

Summary

- The Platform for modeling aggregated time-to-event data has been developed and applied to the OS outcomes from various RCTs of ICIs in NSCLC treatment

- The spline based hazard model with incorporation time-dependent effects and random-effects results in better performance according to

    - Goodness-of-Fit
    - Parameter identifiability
    - Calibration/Discrimination metrics

- The model can be further exploited for simulations to conduct an indirect comparison of the efficacy of PD-1/PD-L1 inhibitors

Back-up

M&S Modeling & Simulation Decisions

Why mexhaz?

Package name *option*	**rstpm2**	**frailtypack*)** (currently removed form CRAN)	**mexhaz**
Parametric models	weibull, gen.gamma	exp, weibull	exp, weibull
Flexible modeling	Natural splines, B-splines	M-splines	Natural splines, B-splines)
Time-dependent effects	+	+	+
Random effect distribution	LogN Gamma	LogN Gamma	LogN
Empirical Bayes estimates	No	Yes (only for Gamma distribution, without uncertainty)	Yes (with uncertainty)

Charvat, Hadrien, and Aurélien Belot. "**Mexhaz** : An *R* Package for Fitting Flexible Hazard-Based Regression Models for Overall and Excess Mortality with a Random Effect." *Journal of Statistical Software*, vol. 98, no. 14, 2021

Model outputs

	PH, FE model		
	Est.	SE	RSE (%)
Intercept	-11.72	0.46	3.89
NS3.1	20.13	0.84	4.20
NS3.2	5.55	0.11	2.05
ICI_target (PD-1)	-0.25	0.03	11.46
ICI_target (PD-L1)	-0.29	0.03	10.45
Line (Naive)	-0.24	0.03	10.67
PDL1_status (Positive)	-0.16	0.03	20.36

Natural spline (NS) =
1 internal knot (8 months)

baseline

TF effects

TD effects

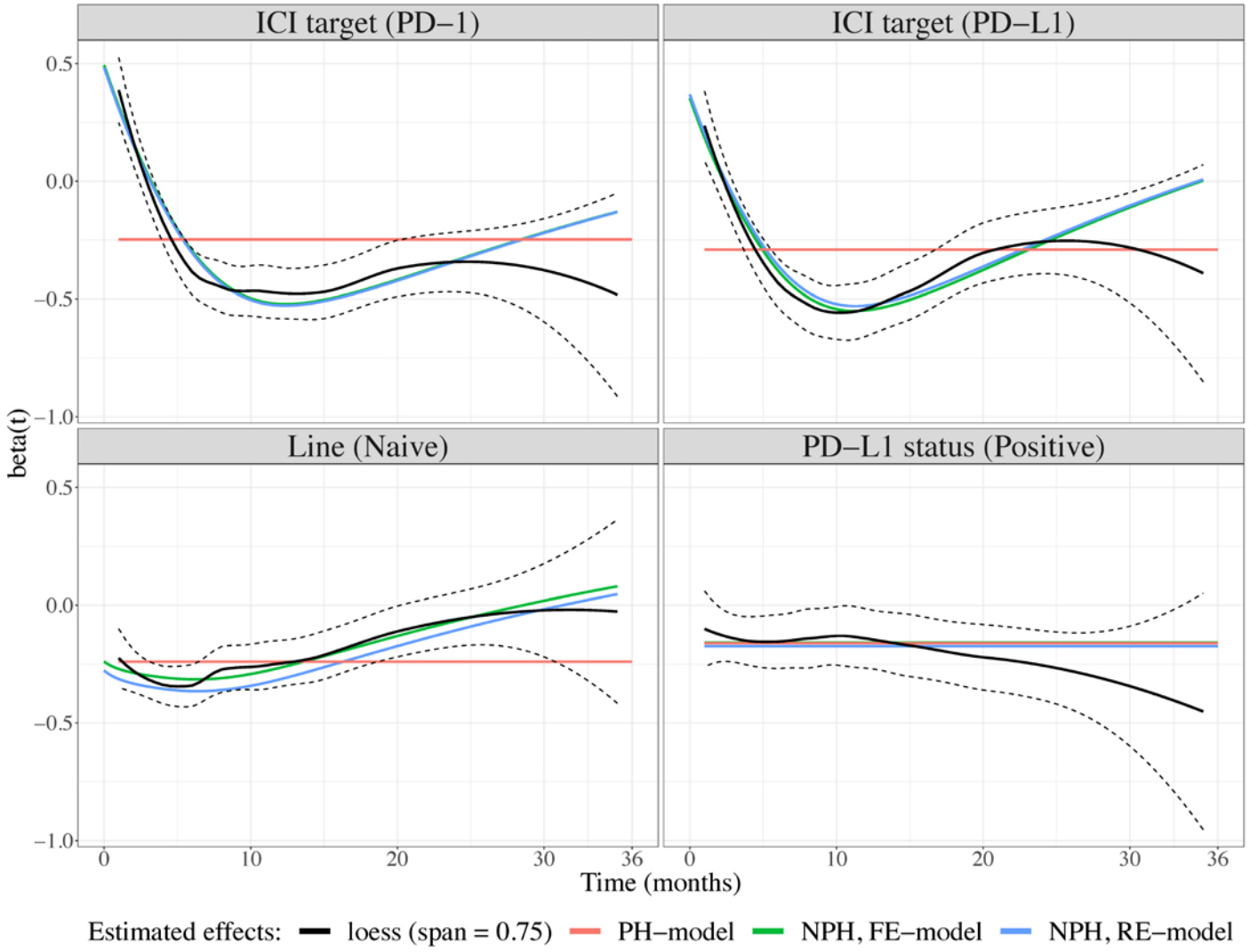
variance for RE

	NPH, RE model		
	Est.	SE	RSE(%)
Intercept	-11.90	0.88	7.39
NS3.1	9.44	0.55	5.85
NS3.2	20.31	1.75	8.63
NS3.3	7.08	0.35	4.90
PDL1_status(Positive)	-0.17	0.04	20.77
ICI_target(PD-1)*NS3.1	-1.09	0.11	9.86
ICI_target(PD-1)*NS3.2	0.61	0.15	24.24
ICI_target(PD-1)*NS3.3	-0.76	0.11	14.76
ICI_target(PD-L1)*NS3.1	-1.04	0.12	11.18
ICI_target(PD-L1)*NS3.2	0.53	0.16	30.70
ICI_target(PD-L1)*NS3.3	-0.51	0.12	23.83
Line(Naive)*NS3.1	-0.30	0.10	32.79
Line(Naive)*NS3.2	-0.38	0.15	39.78
Line(Naive)*NS3.3	0.21	0.10	47.05
Study [log(sd)]	-2.68	0.31	11.41

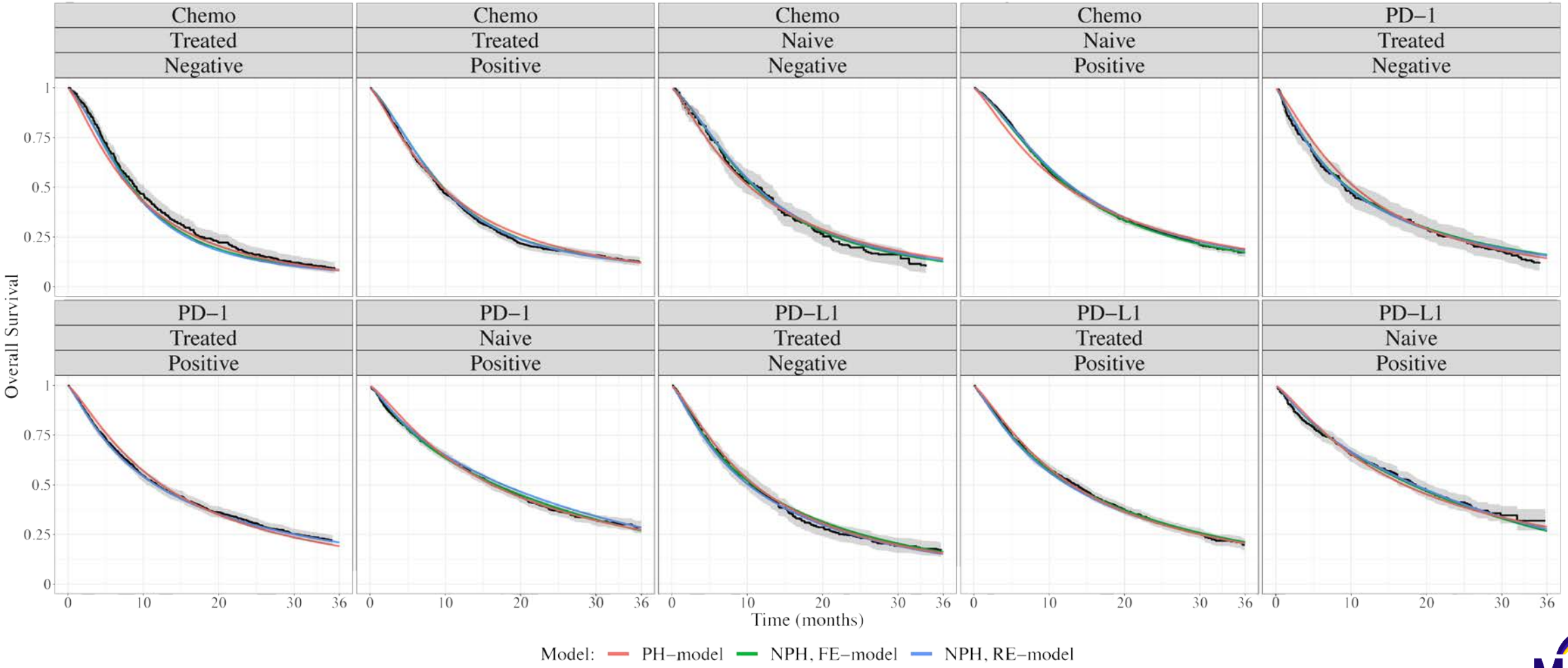
NPH, FE model		
Est.	SE	RSE(%)
-11.93	0.88	7.36
9.45	0.55	5.84
20.35	1.75	8.62
7.09	0.35	4.89
-0.16	0.03	20.69
-1.08	0.11	9.84
0.63	0.15	23.17
-0.76	0.11	14.58
-1.06	0.12	10.92
0.51	0.16	31.48
-0.51	0.12	24.02
-0.26	0.09	36.73
-0.30	0.13	43.53
0.22	0.10	44.30

NS = 2 internal knots (5.1 and 12 months)

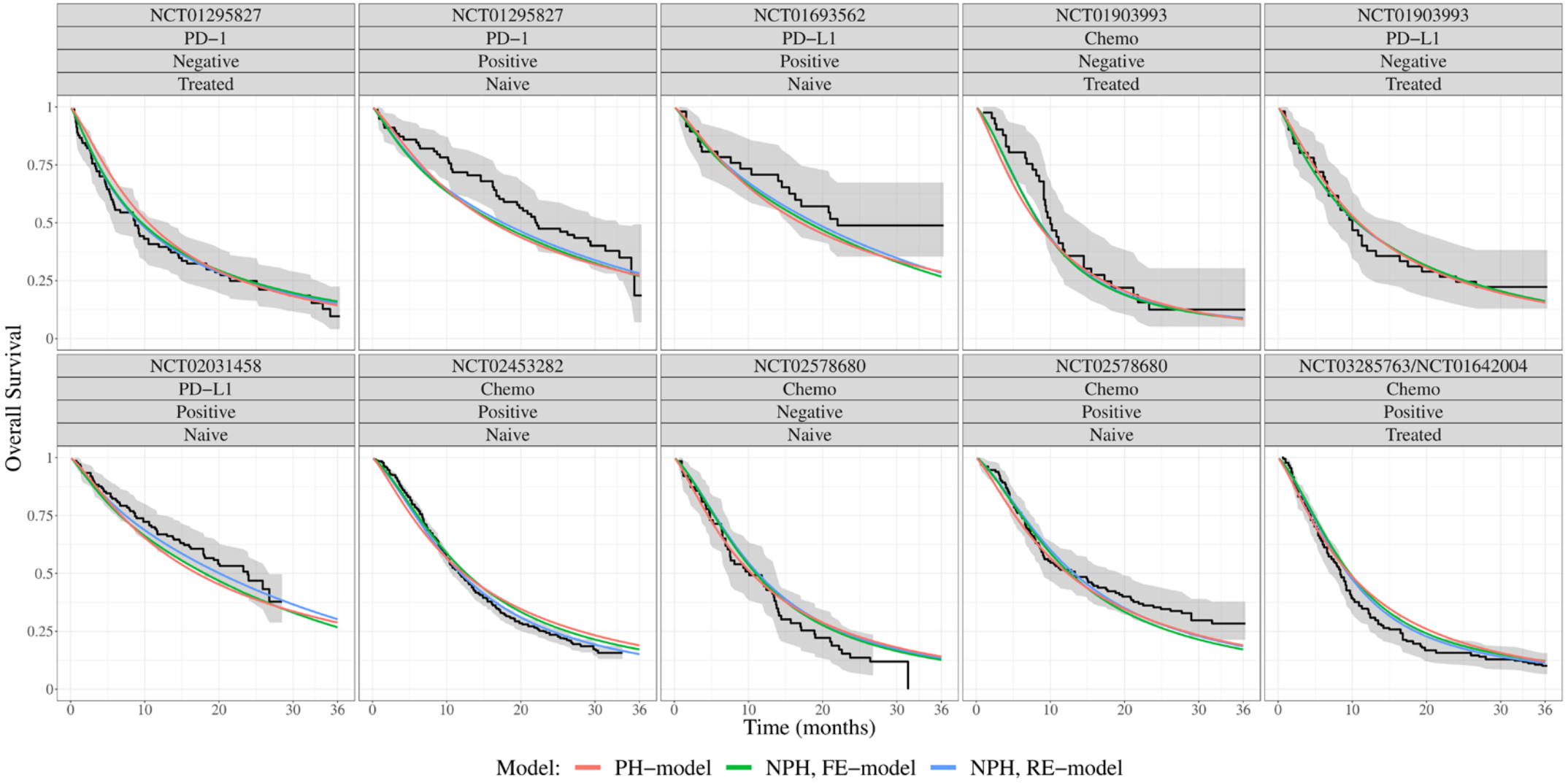
Estimated effects



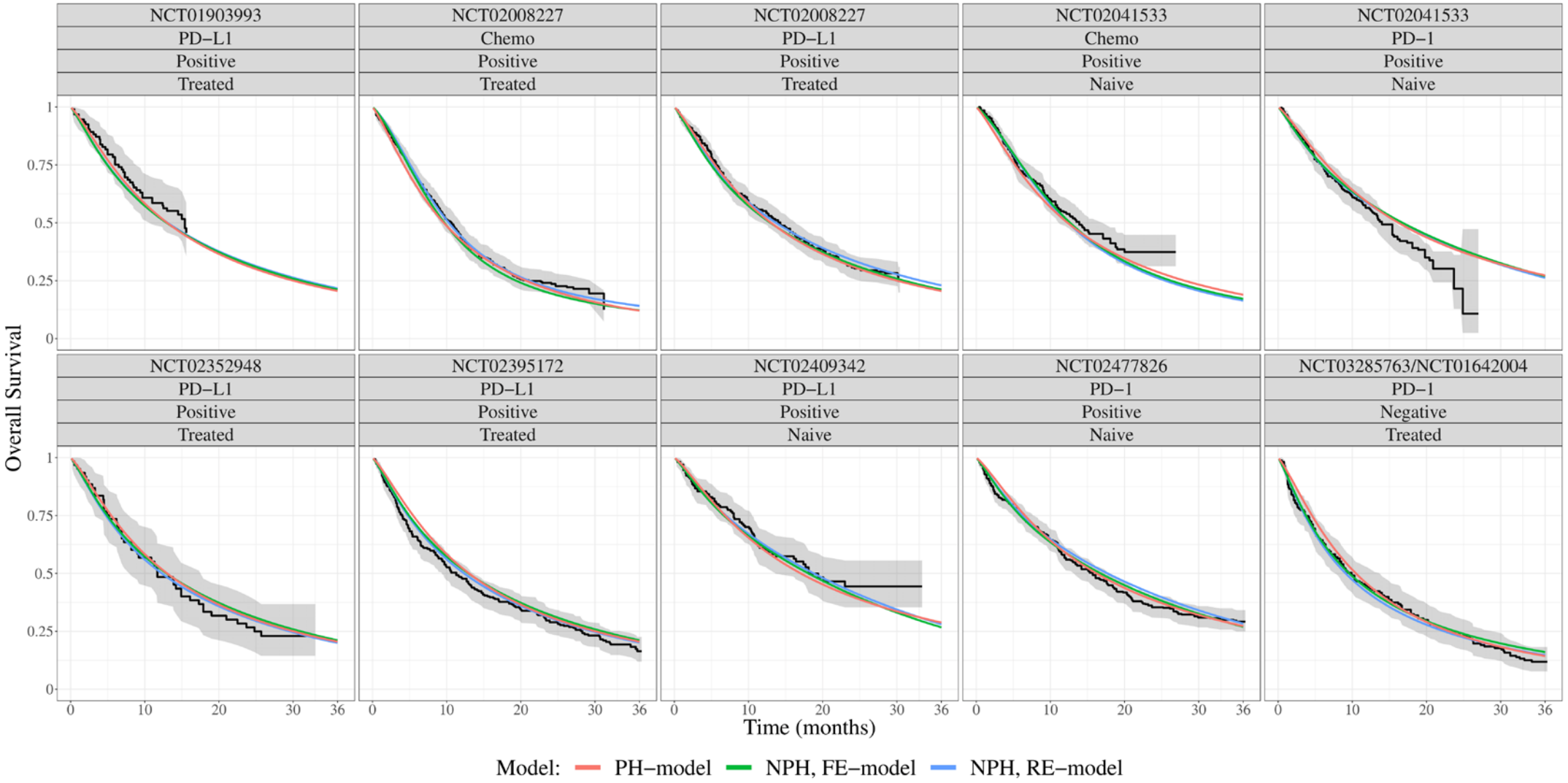
VPC. Pooled data



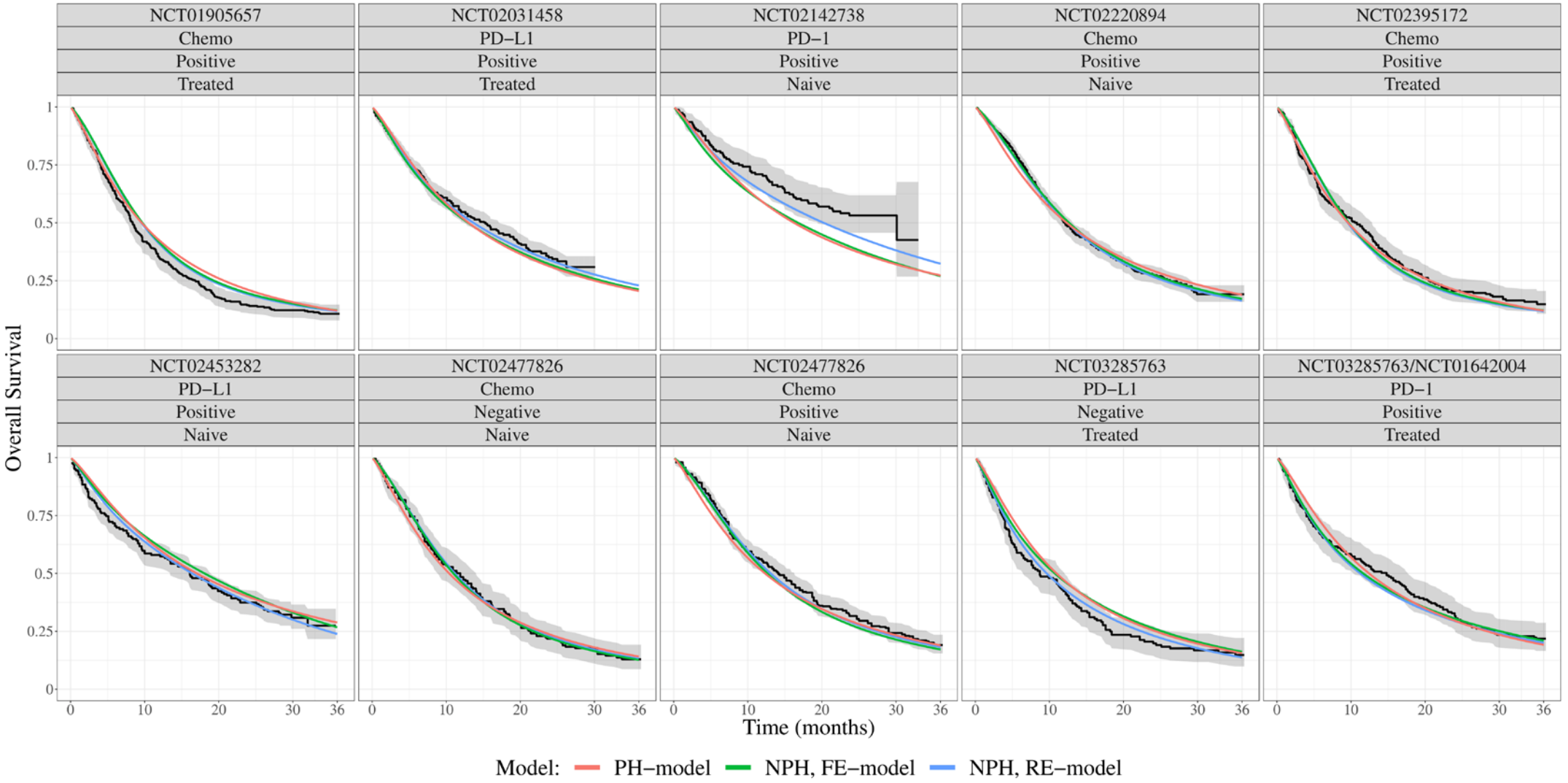
VPC. Individual



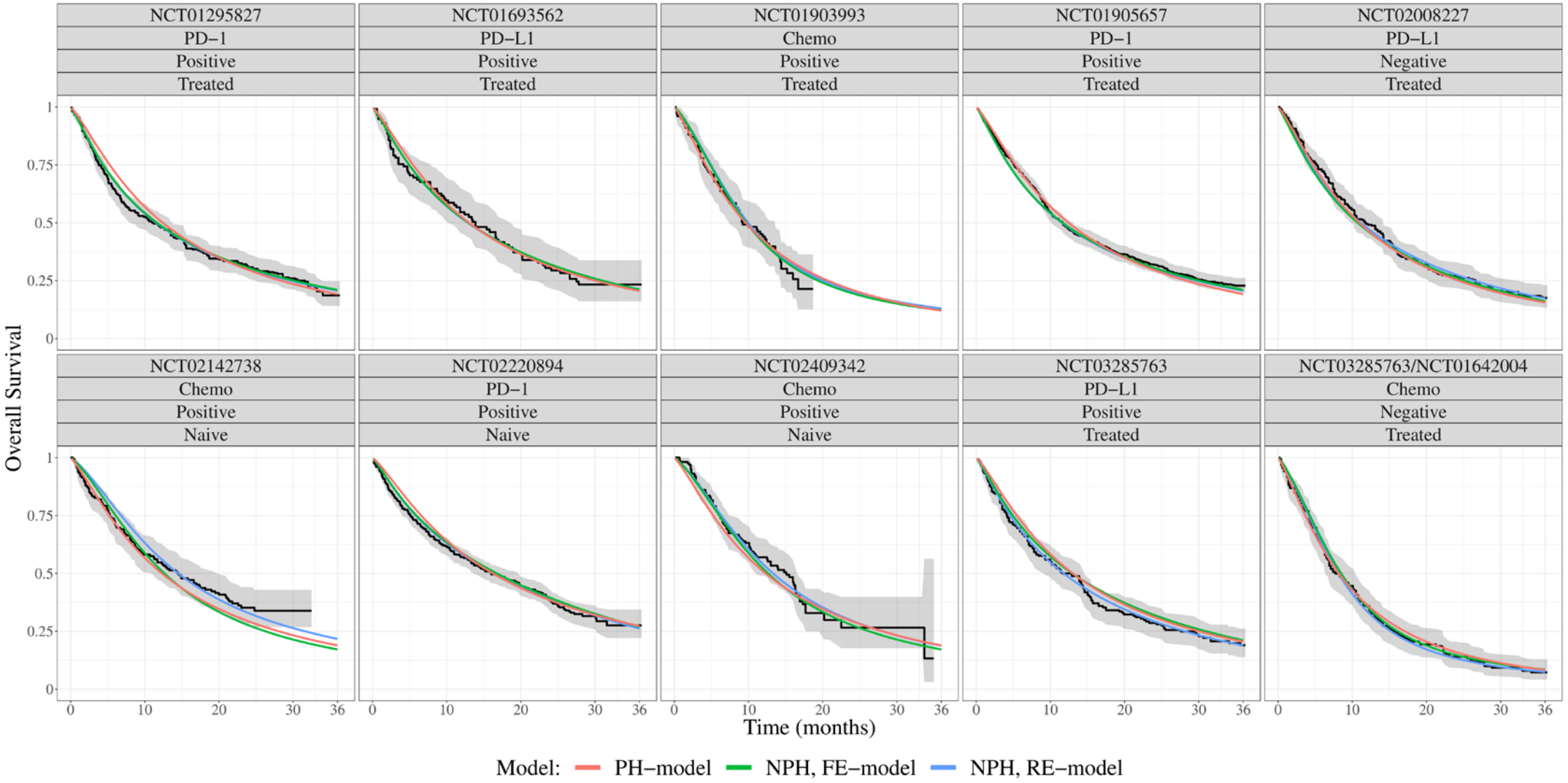
VPC. Individual



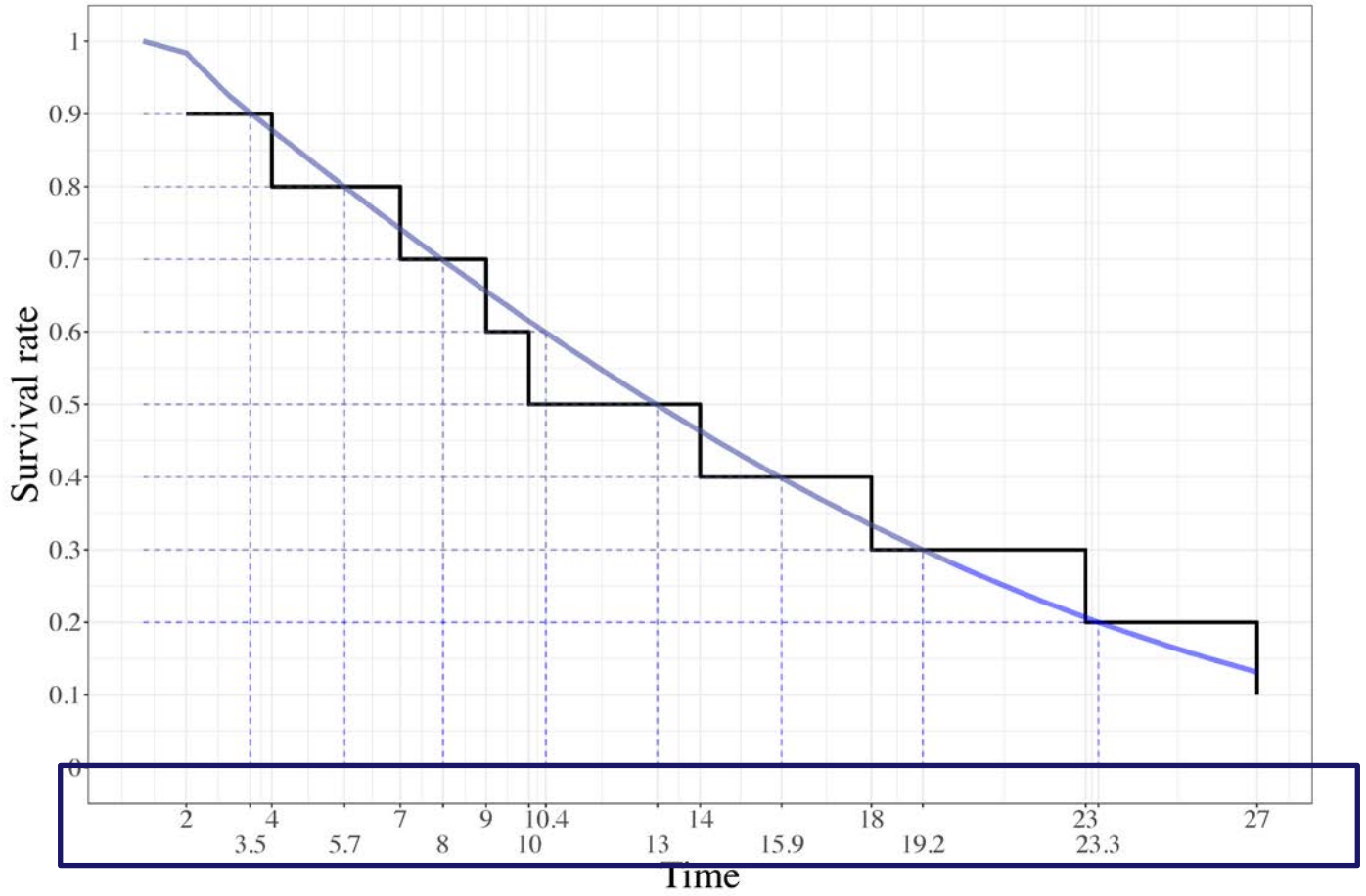
VPC. Individual



VPC. Individual



Summarize the agreement between estimated distribution and non-parametric distribution of event times

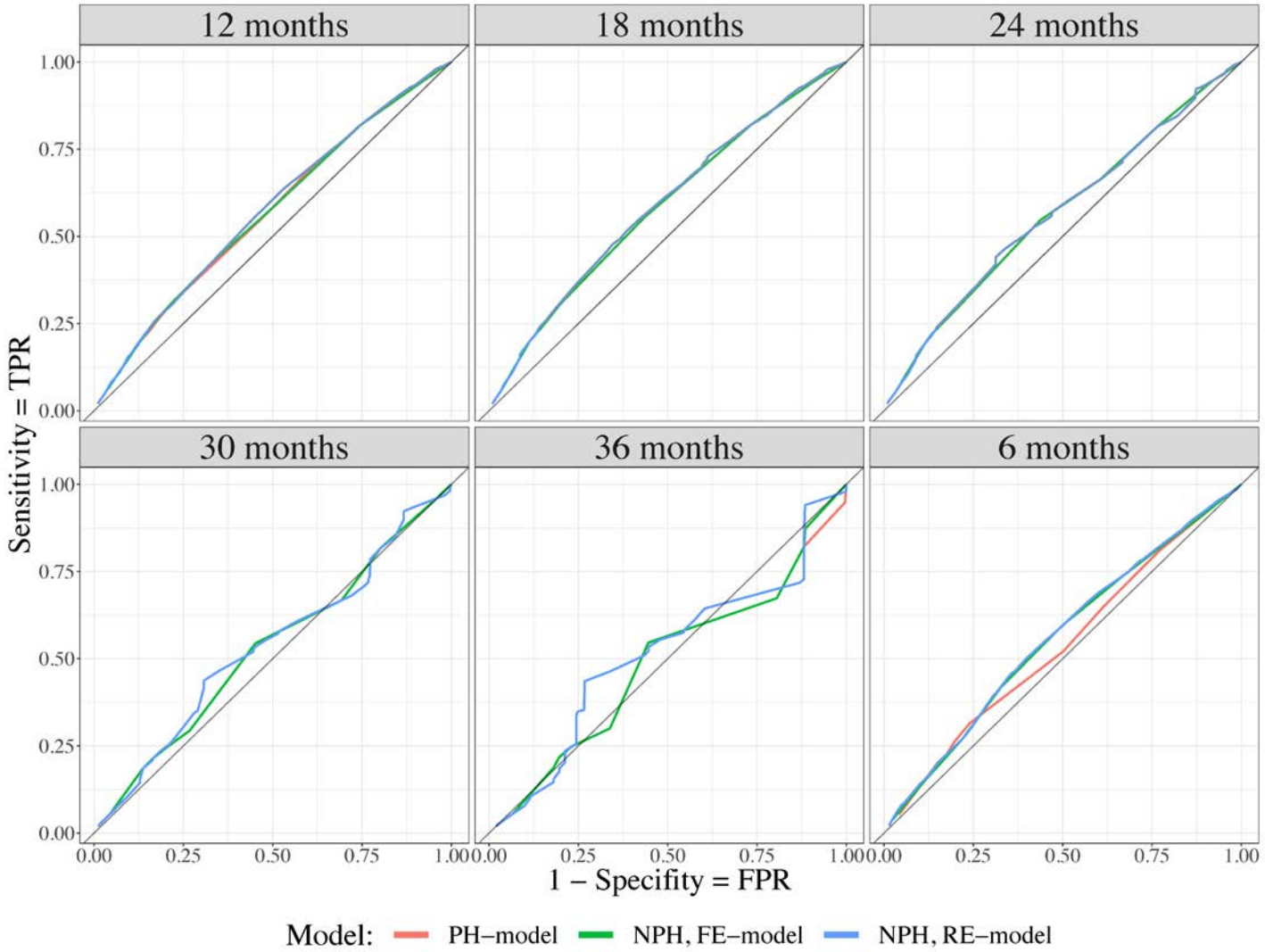


- Can visualize these times as observed vs predicted for all strata
- Can estimate residuals
- Can calculate MSE, RMSE:

$$MSE = \sum_{i=1}^{n} \frac{(\hat{y}_i - y_i)^2}{n}$$

$$RMSE = \sqrt{MSE}$$

Calibration/Discrimination metrics



Model	IBS	IPA	C-index
NPH, FE-model	0.187	-0.018	0.543
PH-model	0.188	-0.034	0.544
NPH, RE-model	0.187	-0.019	0.547