Evaluation of the treatment causal pathways between tumor growth kinetics and overall survival. A mediation analysis with Bayesian non linear joint models.

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Introduction

Motivation

Do patients survive longer because of the effect of the treatment on a biomarker? Do they survive longer due to a different reason?

- Create a framework to assess mediation for any biomarker in clinical development.
- Use tumor growth inhibition-overall survival (TGI-OS) joint modeling for application.

What is the proportion of treatment effect (PTE) mediated through TGI on OS?

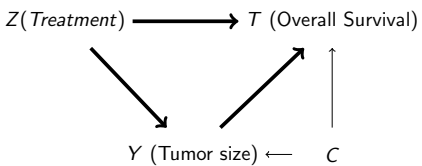
Benefits in drug development

- Improved Surrogate Endpoint Evaluation
- Comparison of therapies
- Trial Design Decision-Making

Introduction

Mediation analysis - Proportion of Treatment Effect

- A **Assessing** the impact of treatment (Z) on clinical outcome (T) with (**NIE**) or without (**NDE**) adjusting for the mediator (Y).
- Using potential outcomes framework.



- Natural Indirect Effect (NIE)
  - Measures the effect of the treatment on the outcome **through the mediator**.
- Natural Direct Effect (NDE)
  - Measures the direct effect of the treatment on the outcome, **not through the mediator**.
- Proportion of Treatment effect (PTE)
  - Measures the proportion of the treatment effect on the outcome, **through the mediator**.

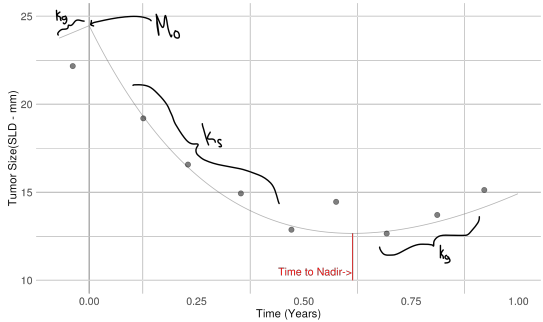
Methods

Longitudinal Sub-model: Tumor growth inhibition Stein-Fojo

$$y_{ij} = g_i(t_{ij})(1 + \epsilon_{ij})$$

$$g_i(t) = \underbrace{\mu_{M_0} e^{\xi_{M_{0_i}}}}_{M_0}\left[exp\{\underbrace{\mu_{k_g} e^{\xi_{k_{g_i}} + \beta_{k_g} Z_i}}_{k_g} t\} + exp\{-\underbrace{\mu_{k_s} e^{\xi_{k_{s_i}} + \beta_{k_s} Z_i}}_{k_s} t\} - 1\right]$$

- y_{ij} Observed SLD for subjet i at time j
- $g(t)$ Expected SLD (mm)
- k_g Tumor growth rate ($year^{-1}$)
- k_s Tumor shrinkage rate ($year^{-1}$) [a]
- M_0 Baseline expected SLD (mm)
- $\xi_{k_{s_i}}, \xi_{k_{g_i}}, \xi_{M_{0_i}}$ random effects
- $\mu_{k_s}, \mu_{k_g}, \mu_{M_0}$ population effects
- $\beta_{k_s}, \beta_{k_g}, Z_i$ Treatment effect and indicator



[a] Until treatment start at $t = 0$, the shrinkage parameter is considered to be $k_s = 0$

Methods

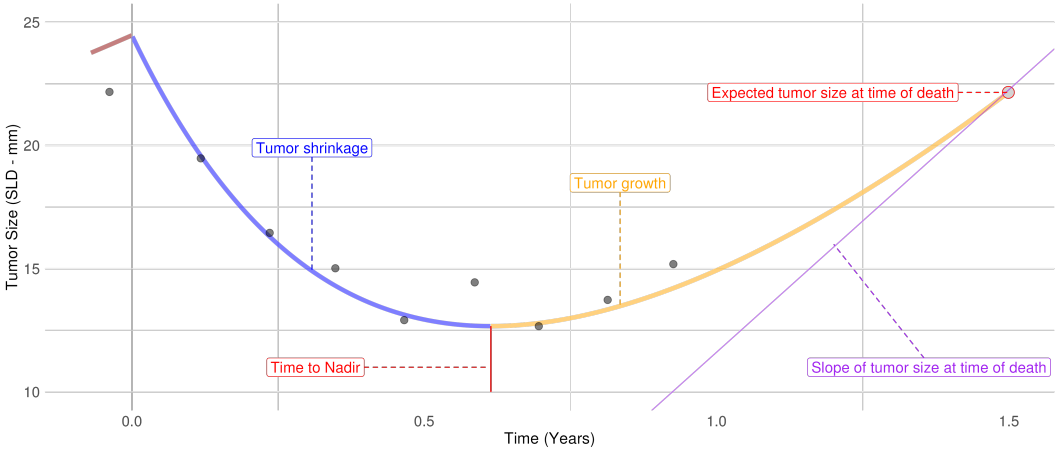
Survival Sub-model: Proportional hazard

$$\lambda_i(t|h(\cdot)) = \lambda_0(t)\exp\{\eta h(\cdot) + \beta_{os} Z_i\}$$

- $\lambda_i(t|h(\cdot))$: Hazard function linked to the TGI process.
- $\lambda_0(t)$: Baseline hazard function. Any parametric survival distribution.
- η: Parameter of association between TGI and survival process.
- β_{os}: Parameter of treatment (Z_i) effect on the survival process.
- $h(\cdot)$: Link function that captures the TGI process.

Methods

Link functions: capture the TGI process



Causal assumptions

Assumption	What it means	Why it holds here
SUTVA	Each patient's outcome depends only on *their* treatment.	Independent oncology patients in a randomized trial.
Consistency	The outcome we observe equals the outcome under the treatment actually received.	Well-defined regimens, consistent administration and RECIST measurements.
Positivity	Every covariate pattern has a non-zero chance for each arm.	Randomization $\Rightarrow$ both arms possible for all eligible patients.
Sequential Ignorability	No unmeasured confounding given baseline covariates / random effects.	Randomization removes Z-confounding; random effects capture heterogeneity; no time-varying confounders assumed.

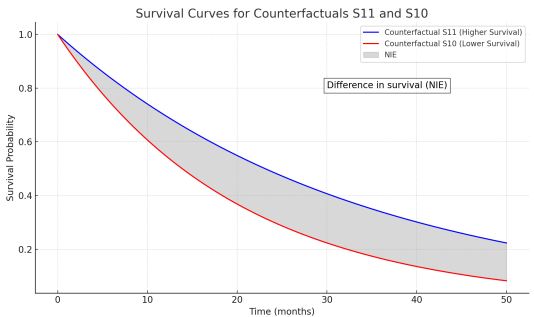
Methods

Proportion of Treatment Effect - Counterfactuals

- Natural Indirect Effect:
  $NIE(t) = \mathbb{S}_{11}(t) - \mathbb{S}_{10}(t)$
- Natural Direct Effect:
  $NDE(t) = \mathbb{S}_{10}(t) - \mathbb{S}_{00}(t)$
- Total Effect:
  $TE(t) = \mathbb{S}_{11}(t) - \mathbb{S}_{00}(t)$
- $PTE(t) = \frac{NIE(t)}{TE(t)}$

Counterfactuals over 2 years since start of treatment.

	Mediator path	
Survival path	$\beta_{tgi}(Z=0)$	$\beta_{tgi}(Z=1)$
$\beta_{os}(Z=0)$	$\mathbb{S}_{00}(t)$	$\mathbb{S}_{01}(t)$
$\beta_{os}(Z=1)$	$\mathbb{S}_{10}(t)$	$\mathbb{S}_{11}(t)$



Application

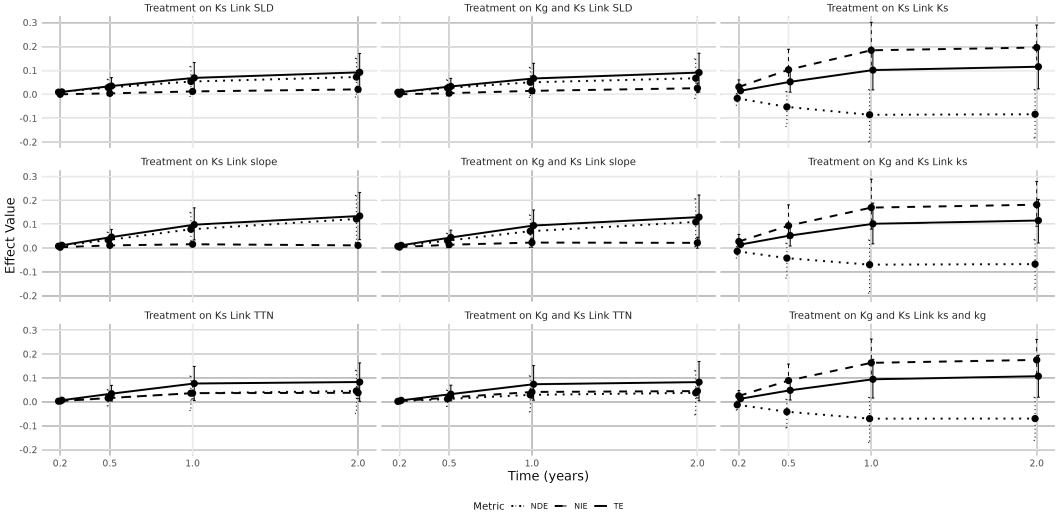
Data

- IMbrave150 trial [Cheng et al., 2022] for patients with unresectable hepatocellular carcinoma (HCC)
- Experimental treatment: Atezolizumab plus Bevacizumab
- Control arm: Sorafenib

Metric	**control**	**experimental**
Number of patients	159	326
Number of SLD observations	763	2676
SLD range (mm)	0-319	0-349
Median number of SLD observations per patient	4 (1-15)	8 (1-17)
Number of events (Overall survival)	113	228
Number of censored patients	46	98

Application

Natural Direct, Indirect and Total effect results



Application

Model selection

LOOIC model choice criterion [1] $\rightarrow$ sld slope as link function

Biological rationale $\rightarrow$ Joint model with treatment effect in k_s and k_g.

Treatment	Link	LOOIC	Δ_{LOOIC}	SE_{diff}	$Significant_{Diff}$
k_g **and** k_s	**Slope**	25681	0	0	No
k_s	**Slope**	25686	5	8	No
k_g and k_s	Sld	25754	73	15	Yes
k_s	Sld	25785	104	16	Yes
k_g and k_s	TTN	25809	128	14	Yes
k_g and k_s	ks and kg	25815	134	16	Yes
k_s	k_s	25826	145	17	Yes
k_g and k_s	k_s	25852	171	17	Yes
k_s	TTN	26544	863	55	Yes

[1] A significant improvement is indicated when the absolute value of the expected log predictive density (elpd) exceeds twice the standard error of the difference

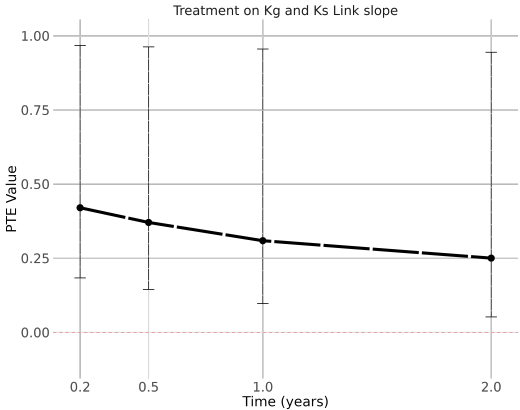
Application

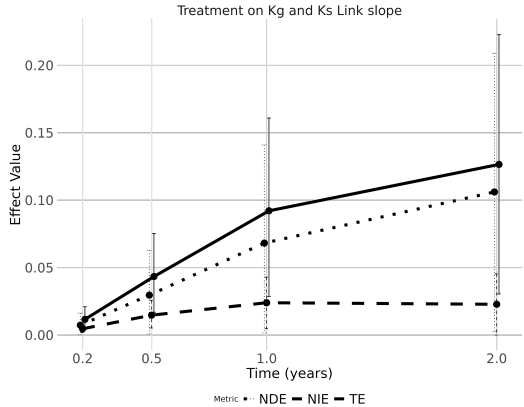
Joint model Results. Link function Slope. Treatment effect on tumor growth and tumor shrinkage.

Variable	Median	SD	5%	95%	$\hat{R}$	ESS
Survival Model						
Treatment (β_{os})	-0.318	0.147	-0.556	-0.070	1.004	1019
Association (η)	0.012	0.002	0.009	0.015	1.005	969
Shape (κ)	1.660	0.108	1.491	1.841	1.003	825
Scale (λ)	1.642	0.198	1.370	2.009	1.003	902
Longitudinal Model						
Treatment on k_s (β_{k_s})	1.093	0.283	0.652	1.573	1.005	332
Treatment on k_g (β_{k_g})	-0.182	0.242	-0.561	0.229	1.011	487
Tumor growth (μ_{k_g})	0.197	0.047	0.131	0.285	1.008	475
Tumor shrinkage (μ_{k_s})	0.163	0.050	0.096	0.255	1.009	342
Baseline tumor (μ_{M_0})	66.017	2.160	62.647	69.780	1.027	131
σ_{prop}	0.177	0.003	0.173	0.182	1.000	2038
Random effects						
ω_{M_0}	0.760	0.027	0.717	0.805	1.019	183
ω_{k_s}	1.434	0.122	1.252	1.655	1.011	308
ω_{k_g}	1.599	0.100	1.446	1.780	1.005	633

Application

PTE, Natural Direct, Indirect and Total effect results





Discussion

Conclusion

- Tumor size dynamics mediate a moderate portion of the treatment effect
  - Already used in practice surrogates mediate less of treatment portion
- Decomposition of the effects $\rightarrow$ mechanisms of treatment
- Investigations of potential surrogates
- Improves current mediation methods [Zhou et al., 2022, Zheng and Liu, 2022]
  - by dropping the linearity of tumor size assumption
- PTE is mostly driven from the selection of the link function (IMbrave150 trial)

Bibliography

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