Calibrated predictions of survival based on tumor size dynamics and new lesions in lung cancer via Joint Modeling approach

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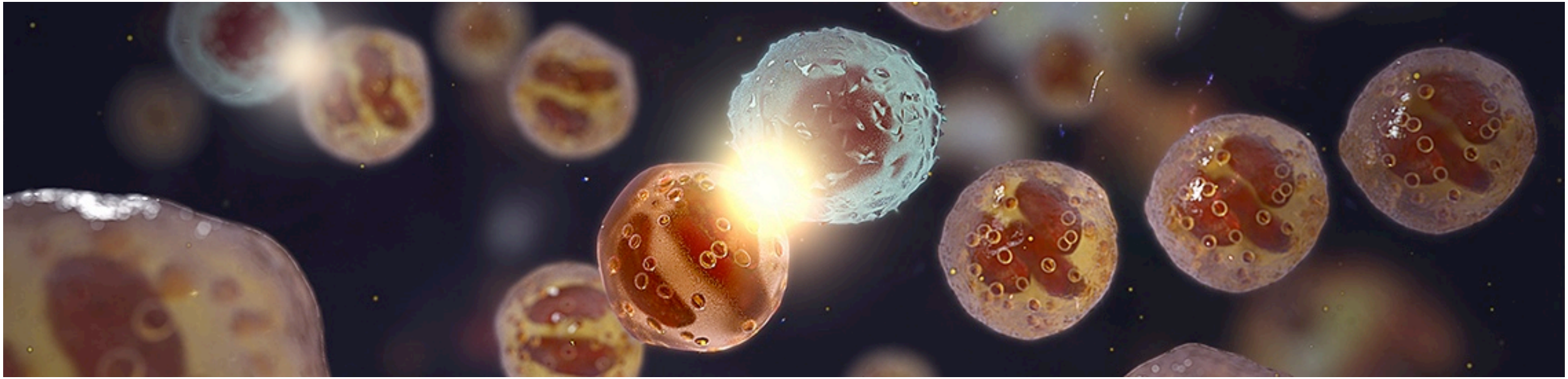


Executive Summary

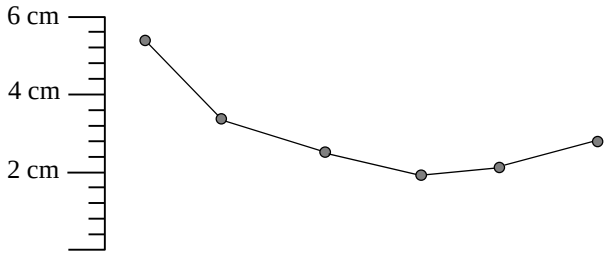
- In oncology, integration of multiple data sources can contribute to:
  - ✓ better prediction for important clinical outcomes
  - ✓ earlier decision making both on trial and individual level

- A statistical basis has been developed and validated to model:
  - ✓ longitudinal response dynamics (Tumor size)
  - ✓ time-to-event (Survival)

  (That is so called ”joint model”)

A problem with RECIST criteria

RECIST[1] data

Time (Month)	2	4	8	12
Target Lesion SLD[2](cm)				
Nontarget Lesion	SD[3]	SD	SD	SD
New Lesion	-	-	-	✗
Response	PR[4]	PR	PR	PD[5]

1. Response Evaluation Criteria In Solid Tumors
2. Sum of Longest Diameters of target lesions
3. Stable Disease
4. Partial Response
5. Progressive Disease

Reduction to Single Values

- Time to Progression : 12 months
- Best Overall Response : Partial Response
- Best Percent Change in SLD : 33.9%

Rich longitudinal tumor dynamic data are reduced to categorical endpoints with a subsequent loss of information

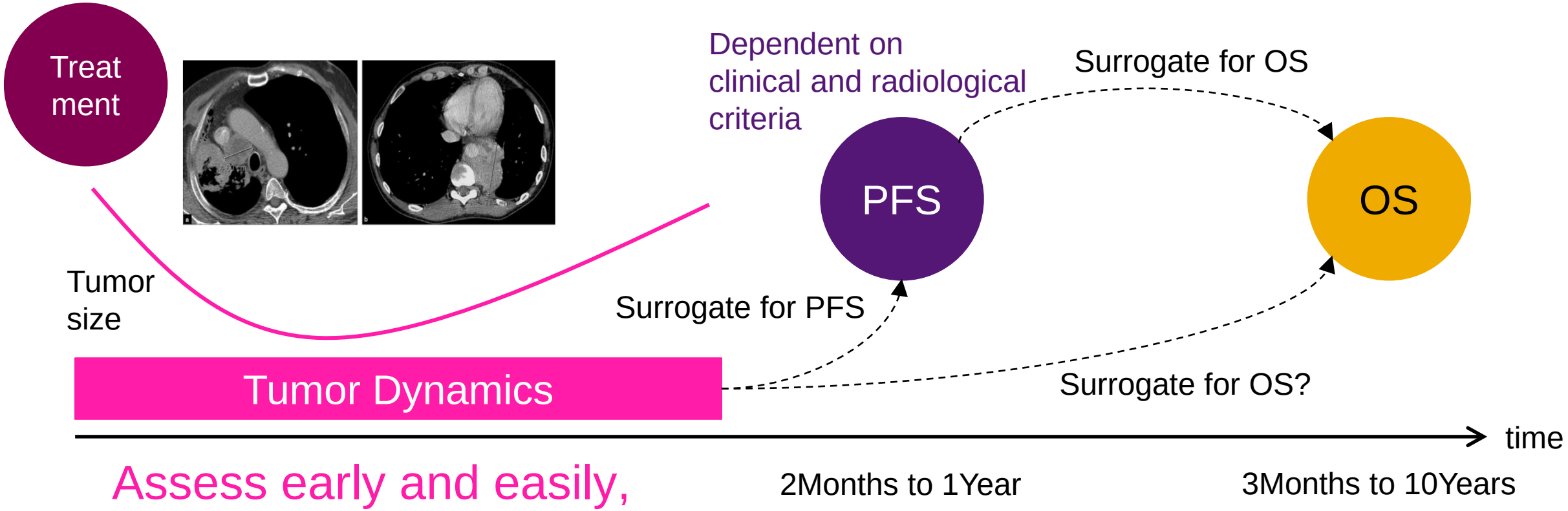
Research goal

This work develops a joint model of disease progression and survival (PFS/OS) that incorporates

- longitudinal tumor burden
- appearance of new lesions

in NSCLC patients, to interrogate the components of RECIST and to predict survival.

Why monitor tumor growth dynamics ?

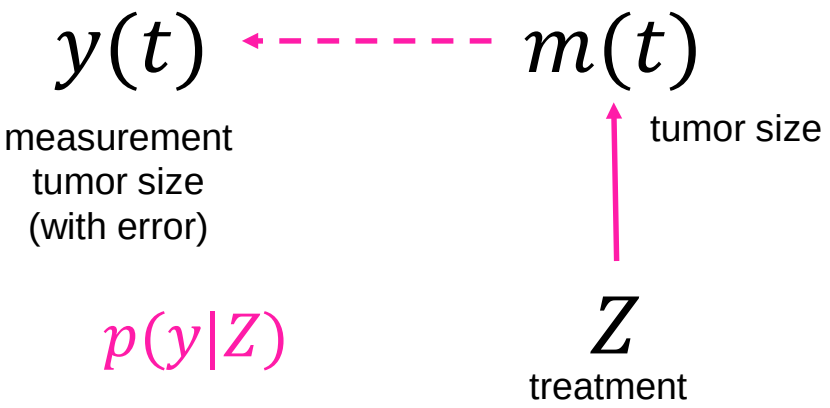


Assess early and easily,
for earlier decision making, e.g.

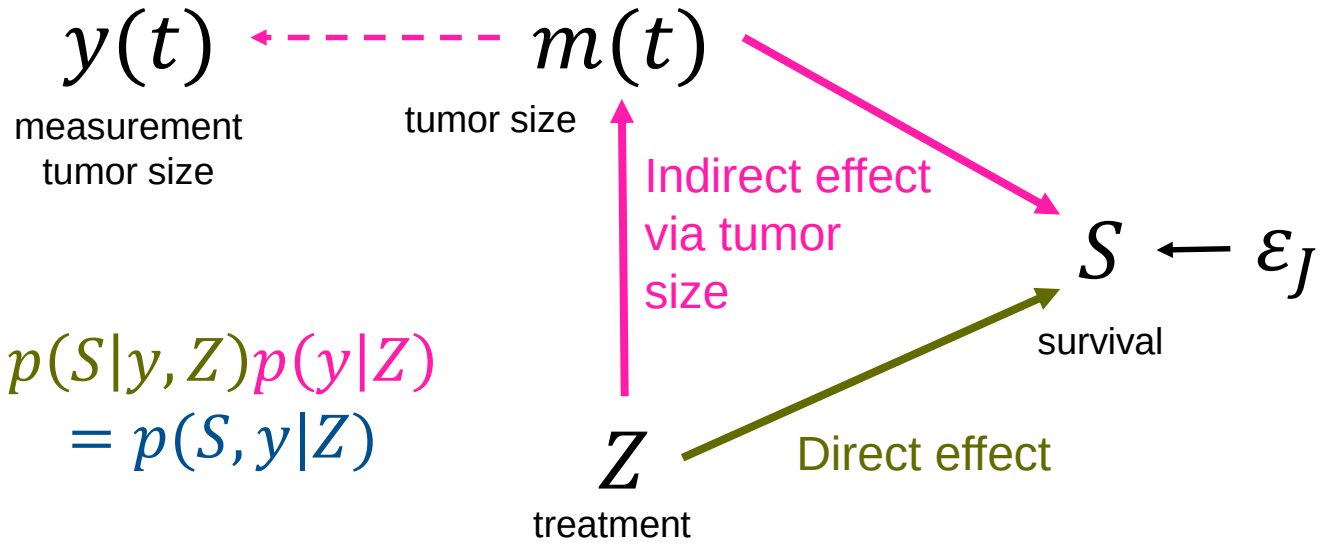
- Early clinical development stage: Decide which compound is better to go with?
- After market stage: Choose what treatment would be better for each patient?

What does Joint model look like?

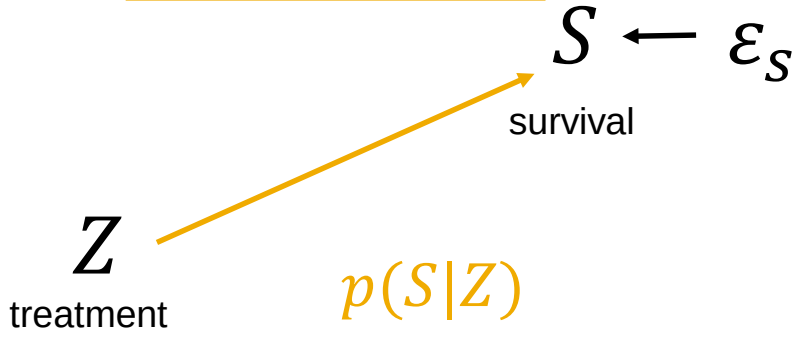
Tumor dynamics model



Joint modeling



Survival Model

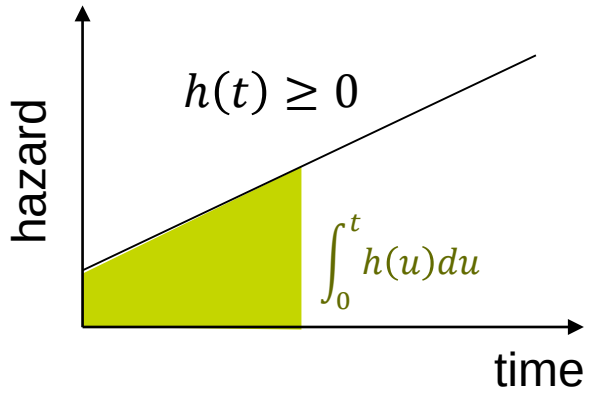


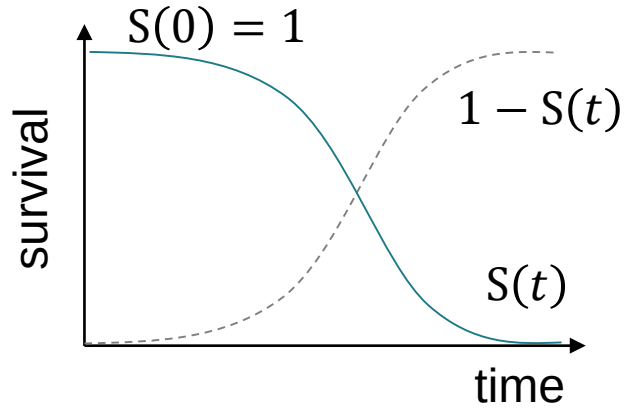
- Directly relate a quantity tumor dynamics to the outcomes OS or PFS (which determine product success).
- Reduce the uncertainty of survival rate.
  - $E[\varepsilon_S] > E[\varepsilon_J]$

How to get tumor size being involved?

Relation between survival and hazard:

$$S(t) = \exp\left(-\int_0^t h(u)du\right)$$





Proportional hazard model:

Tumor size — Treatment

$$h(t) = h_0(t) \cdot \exp[f(m(t), Z)]$$

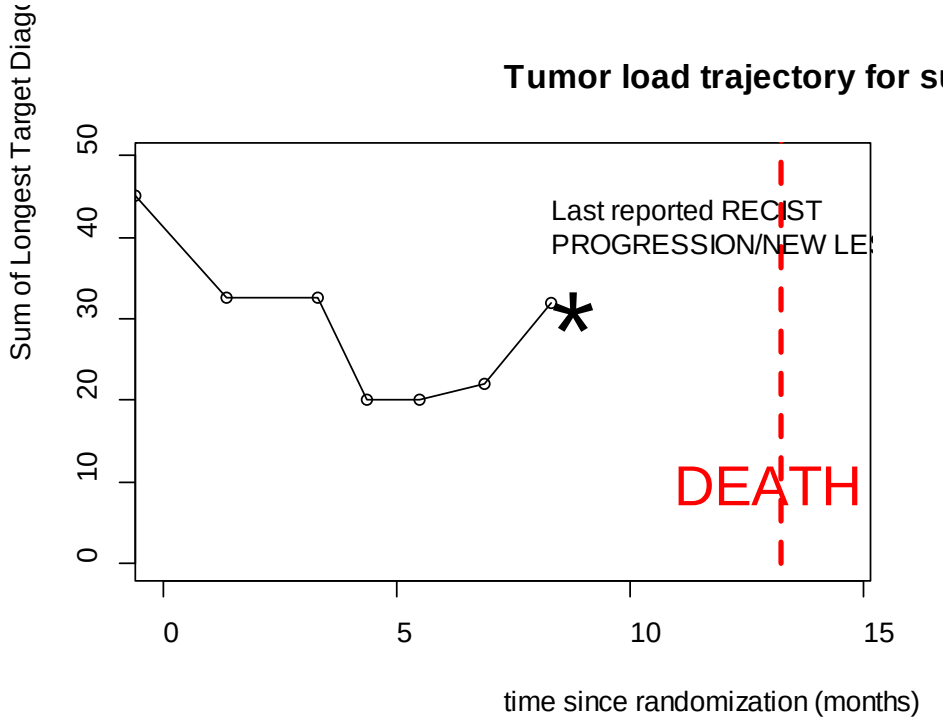
Baseline hazard

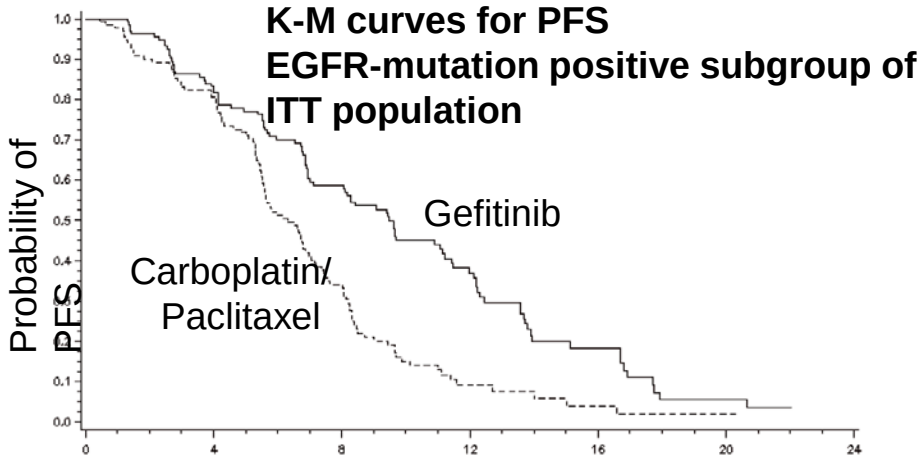
- Hazard is proportional to the baseline hazard
- The function f is a regressor function
- The tumor dynamics $m(t)$ and the treatment Z are included in the proportional part inside the function f

Data from Iressa IPASS Study

Gefitinib (N=609) or Carboplatin + Paclitaxel (N=608)
Hazard ratio for progression or death

- **Overall:** **0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001**
- **In EGFR-mutant (N=261):** **0.48; 95% CI, 0.36 to 0.64**
- **In EGFR-wild type (N=176):** **2.85; 95% CI, 2.05 to 3.98**
- **174 subjects progressed due to the appearance of new lesions**





Mok TS et al. **Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.** ***N Engl J Med. 2009 Sep 3;361(10):947-57***

Model

- **Tumor measurement model**

$$y_{ij} = m_i(t_{ij}) + \varepsilon_{ij}, \qquad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$$

- **Tumor dynamic model**

$$m_i(t) = \beta_i t + sld_{0,i} e^{-\alpha_i t}, \qquad \frac{dm_i(t)}{dt} = \beta_i - \alpha_i sld_{0,i} e^{-\alpha_i t}$$

- **Hazard for survival**

$$h_i(t|m_i) = h_0(t) \exp\left[\boldsymbol{\gamma}^{\mathrm{T}} \boldsymbol{\omega}_i + \alpha_l l(t) + \alpha_m m_i(t) + \alpha_{m'} \frac{dm_i(t)}{dt} \right]$$

Base line covariates

New lesion Appearance (0/1 value)

Tumor size

Change in tumor size

$$\boldsymbol{\omega}_i = [\omega_{i0} \quad \omega_{i1} \quad \omega_{i2} \quad \omega_{i3} \quad \omega_{i4} \quad \omega_{i5}]$$

Intercept

Normal Activity (0/1 value)

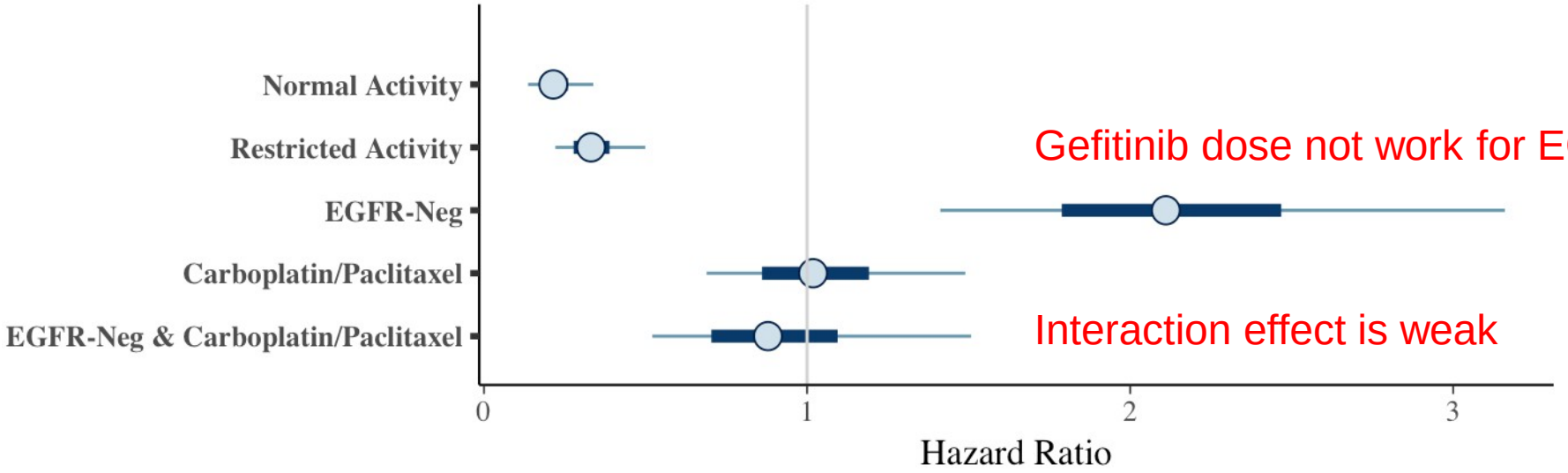
Restricted Activity (0/1 value)

EGFR Negative (0/1 value)

Chemotherapy (0/1 value)

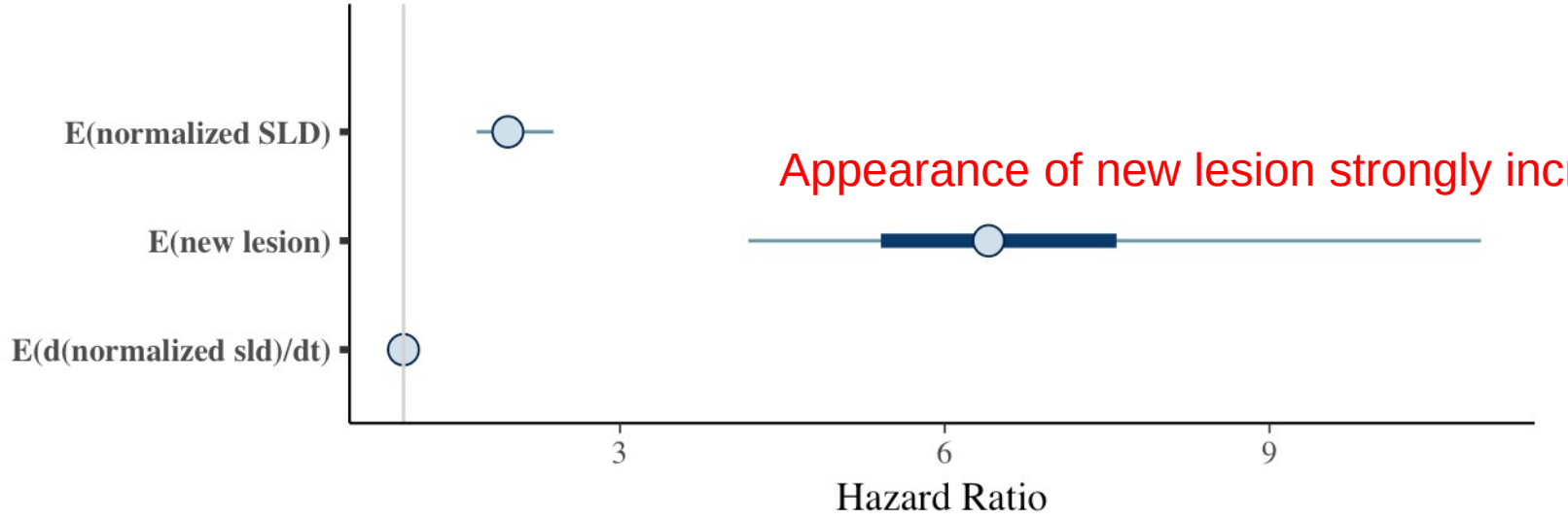
Interaction, ω_{i3} and ω_{i4} (0/1 value)

Selected result: Survival Model Coefficients



Gefitinib dose not work for EGFR-neg patients

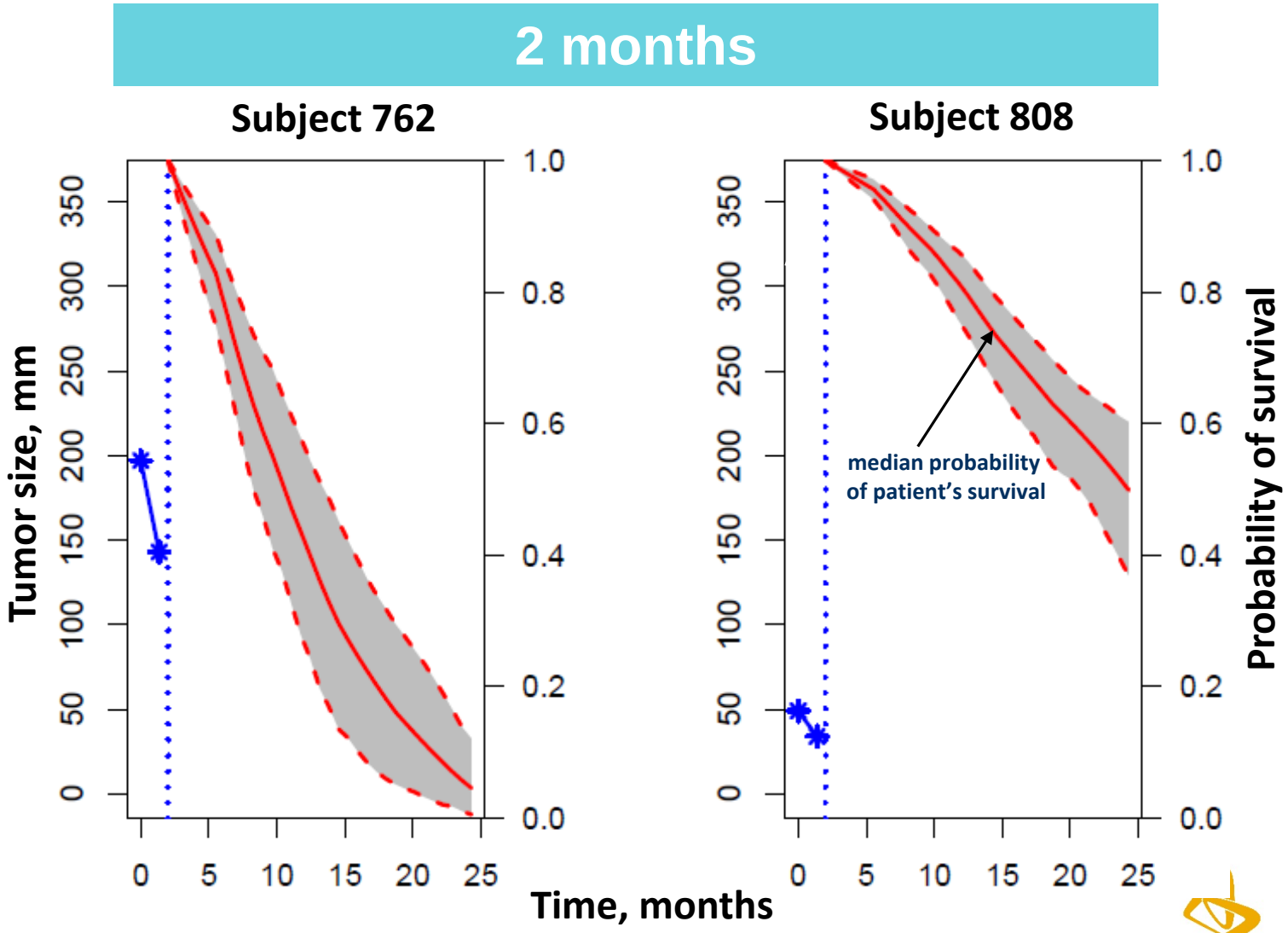
Interaction effect is weak



Appearance of new lesion strongly increases the hazard

Simulation example, Gefitinib

- Consider 2 patients with same baseline covariates (same dosing, EGFR status, WHO performance status)



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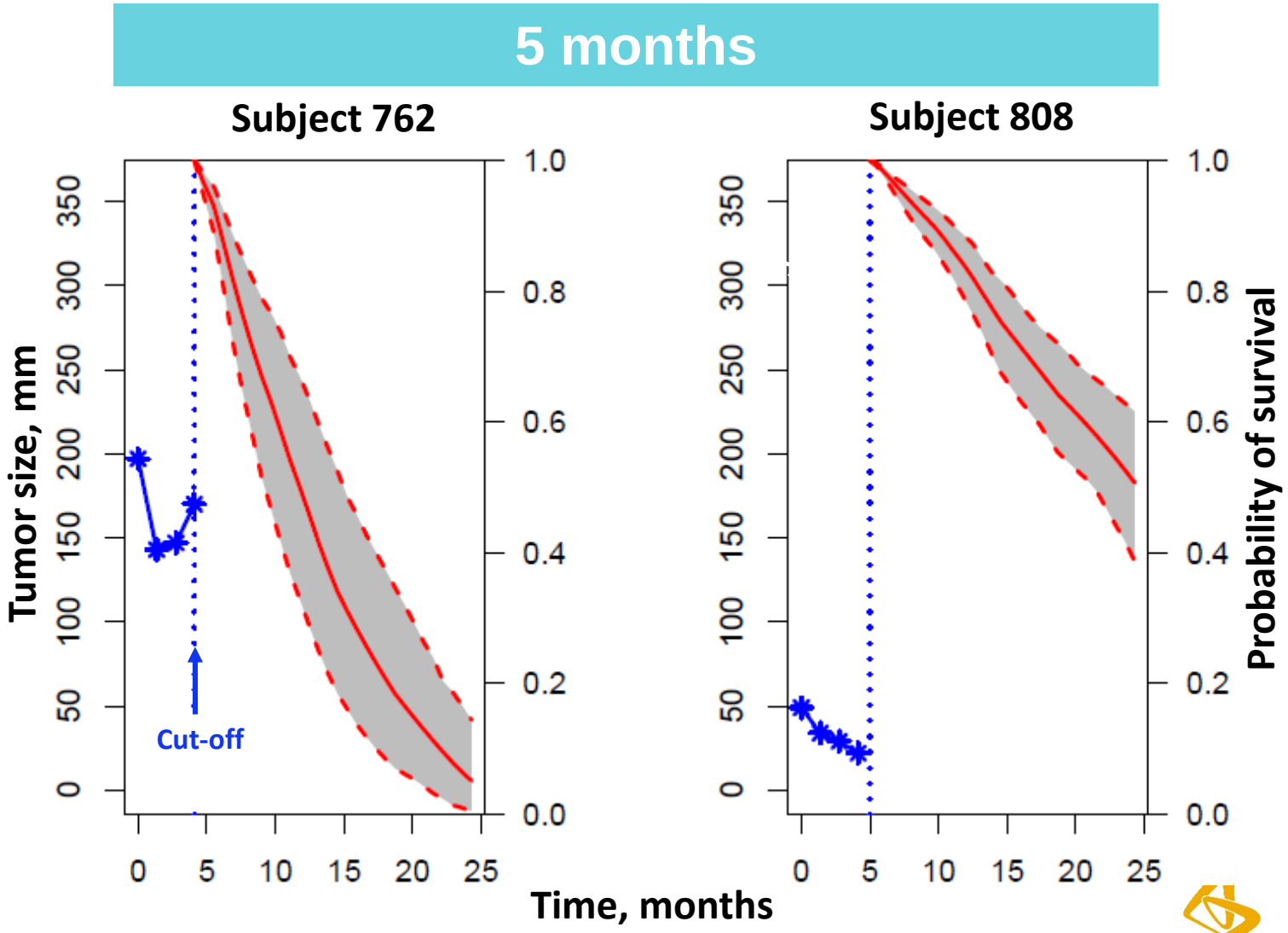
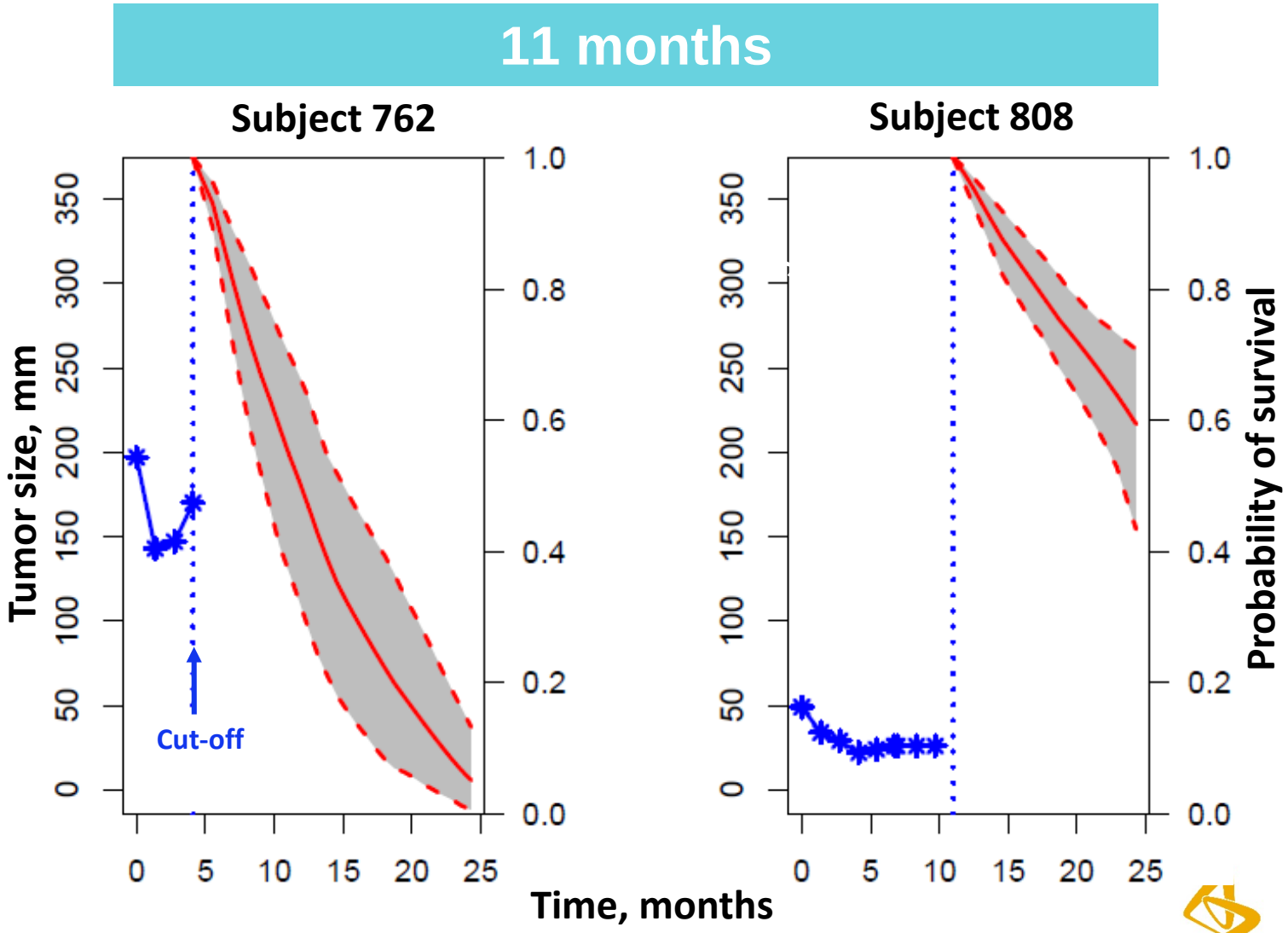


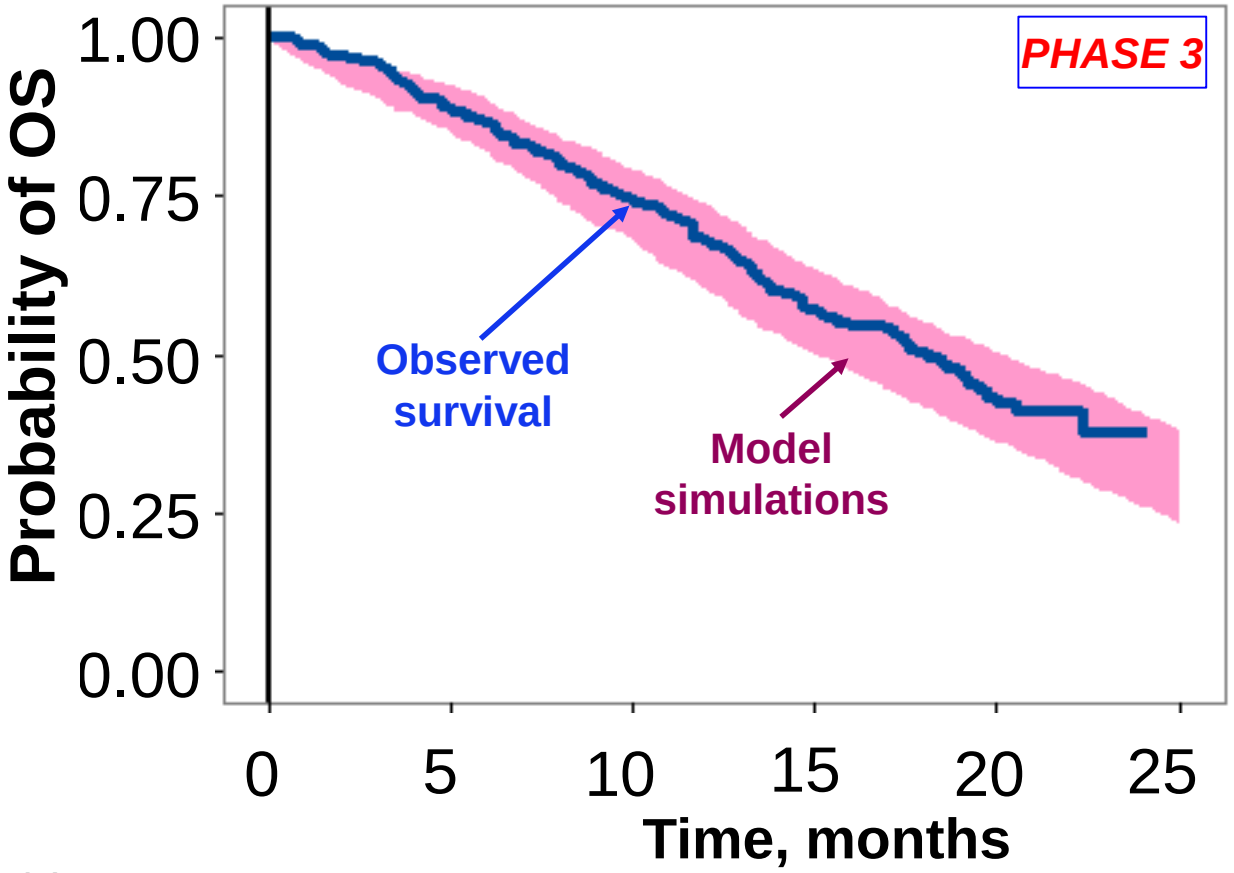
Simulation example, Gefitinib

- Consider 2 patients with same baseline covariates (same dosing, EGFR status, WHO performance status)
- Their therapeutic prognoses differ only because of differences in tumor dynamics (baseline & trajectory)

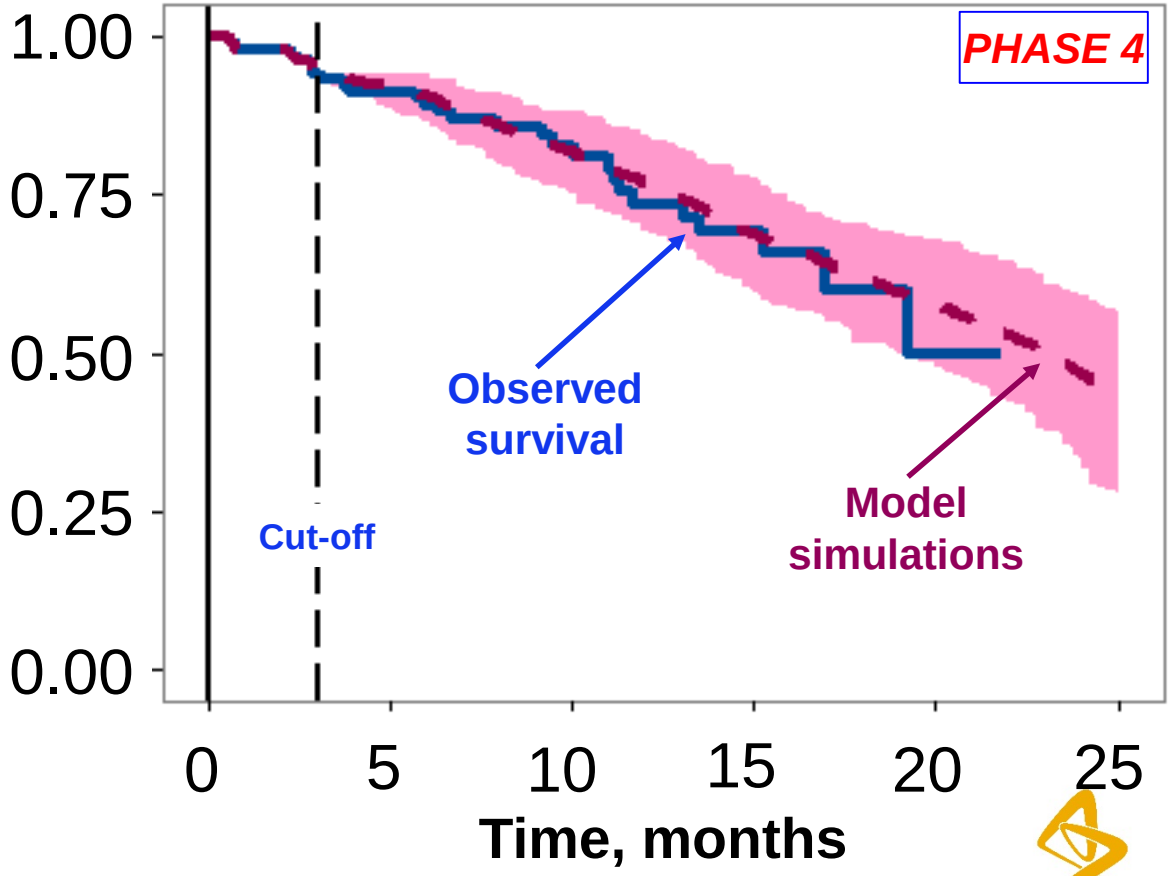


Simulation example, Gefitinib (2 studies)

Joint model validated on IPASS data

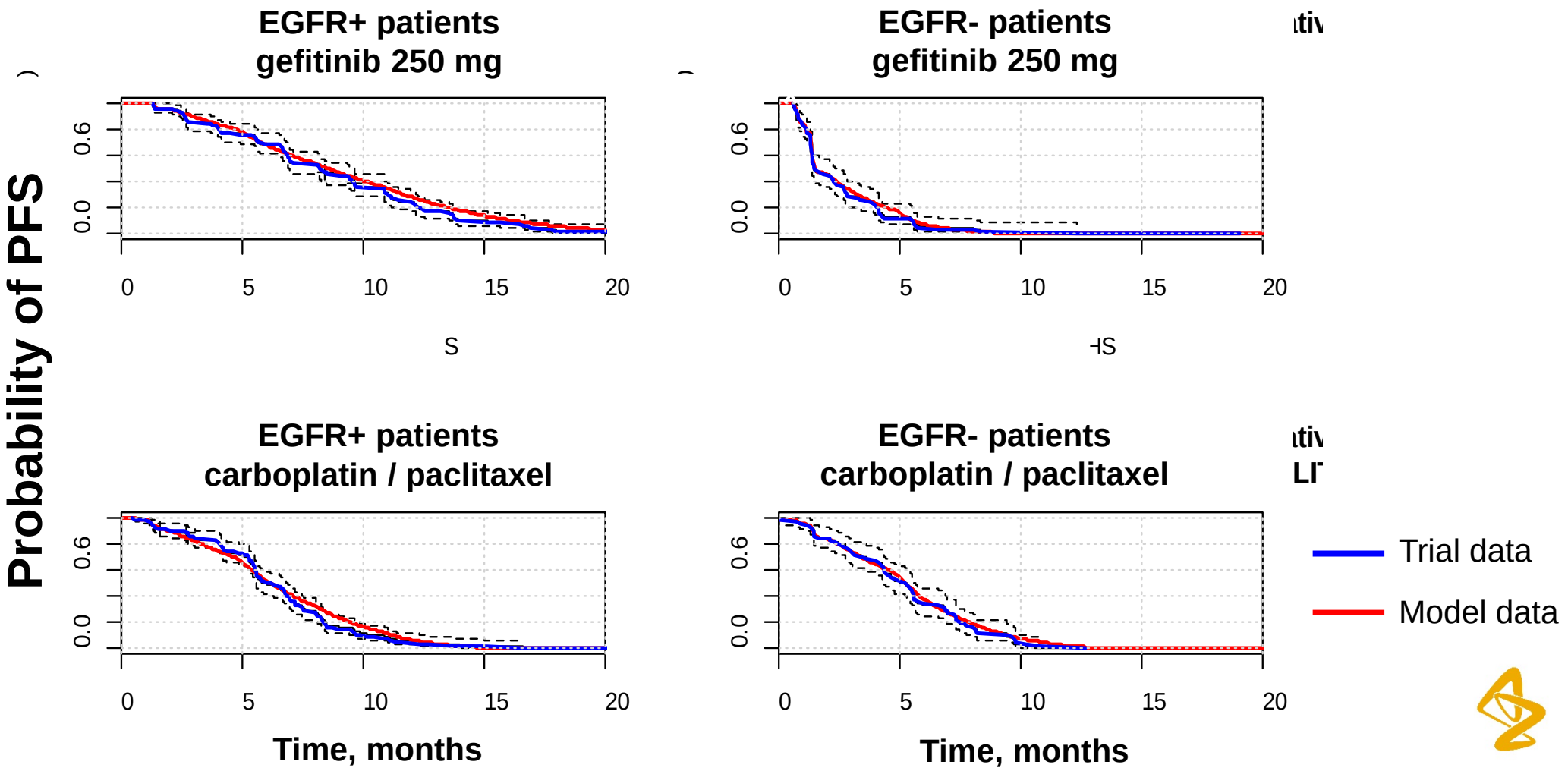


Model predicts IFUM OS using 3-month data cut-off



Simulation example, Gefitinib and chemo.

2-month tumor size data predict 2-year PFS outcome for both an EGF-R inhibitor & chemotherapy, in NSCLC patients



Conclusion

- Successfully validated a statistical method
  - ✓ Development of joint models of tumor dynamics and survival can be used to predict survival based upon tumor dynamics in a new trial
  - ✓ Magnitude of contribution of tumour size to survival varied across drugs and EGFR mutation status

- It can contribute to:
  - ✓ making better clinical development strategy (Go/No-go decision)
  - ✓ delivering better treatment tailored for each patient

- Next Step:
  - ✓ Evaluate how to broaden this approach across tumour types and drugs
  - ✓ Develop multivariate joint modeling (ctDNA, new lesions, individual lesion dynamics and other factors related to OS)

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Back-up

Likelihood function for joint model

Maximize the joint distribution of "Survival time(S_i)" and "Tumor size($\boldsymbol{y}_i$)", and it can be divided into 3 parts, given "the tumor size model (m_i)", for patient $\boldsymbol{i}$.

$$\prod_{i=1}^{n} p(S_i, \boldsymbol{y}_i) = \prod_{i=1}^{n} \int p(S_i, \boldsymbol{y}_i, m_i) dm_i = \prod_{i=1}^{n} \int p(S_i, \boldsymbol{y}_i | m_i) p(m_i)\, dm_i = \prod_{i=1}^{n} \int \overset{1}{p(S_i|m_i)} \overset{2}{p(\boldsymbol{y}_i|m_i)} \overset{3}{p(m_i)} dm_i$$

1.Survival model:
(Proportional hazard model)

$$p(S_i|m_i) = (h_0(S_i) \cdot \exp[f(m_i(S_i), Z)])^{\Delta_i} \exp\left(-\int_0^{S_i} h_0(u) \cdot \exp[f(m_i(u), Z)]\, du\right)$$

where Δ_i is indicator variables $\Delta_i = 0$ means censored and $\Delta_i = 1$ means occurrence of an event

2.Tumor size model: $p(\boldsymbol{y}_i|m_i) = \prod_{j=1}^{n_i} p(y_{ij}|m_i)$

3.Model variability: $p(m_i) = p(m_i|m)$

Numerical methods used

Part	Integrate out the inter individual tumor size model variability	Baseline hazard function	Integrate the hazard from 0 to survival time
	$\int * dm_i$	$h_0(t)$	$\int_0^{S_i} h(u)du$
Method	***MCMC sampling***	***Cubic spline with 6 nots***	***Gauss-Konrad quadrature with 13 quadrature points***
	• Using sampling instead of integration	• Divide interval into 6 parts • Approximate by 3rd order polynomial curve for each interval • Connect them smoothly, up to 2nd order derivative to be equal	• Standard numerical method for definite integral • Weighted sum of function value at a certain argument points • The argument points and weights are prespecified to be the most efficient for any functions