

MECHANISTIC JOINT MODELLING FOR LONGITUDINAL PSA AND SURVIVAL DATA IN ADVANCED METASTATIC PROSTATE CANCER

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INTRODUCTION

Context

- In phase III clinical trials, treatments for metastatic Castration-Resistant Prostate Cancer (mCRPC) are evaluated on their impact on time-to-death. Prostate-specific antigen (PSA) is frequently monitored as it is assumed to be linked to survival.
- Nonlinear joint modelling which consists in the simultaneous analysis of biomarker's evolution and survival [1,2] is particularly adapted to study this link.

Objectives

- To characterize the relationship between PSA kinetics and risk-of-death in mCRPC patients from the phase III study Proselica [3] who were previously non-responders to docetaxel and treated as second-line chemotherapy by Cabazitaxel
- To identify the impact of covariates on both processes

METHODS

Data (Fig. 1)

- 1174 mCRPC patients previously non-responders to docetaxel and treated as second-line chemotherapy by cabazitaxel
 - 580 at dose 20 mg/m² (CBZ 20)
 - 594 at dose 25 mg/m² (CBZ 25)
- 9443 PSA measurements
- 20 baseline covariates
- CBZ 20 dose demonstrated non-inferiority compared with CBZ 25 dose in term of overall survival
 - HR=0.96 [0.85-1.09] in CBZ 25 vs CBZ 20

Mechanistic PSA kinetics model

- PSA (ng.mL⁻¹) is assumed to be produced by 2 types of cells [4] (Fig. 2) :
 - Treatment-sensitive cells (S) (mL⁻¹)
 - Treatment-resistant cells (R) (mL⁻¹)
- The main mechanism of action of cabazitaxel would be the stimulation of the tumorous cells elimination.

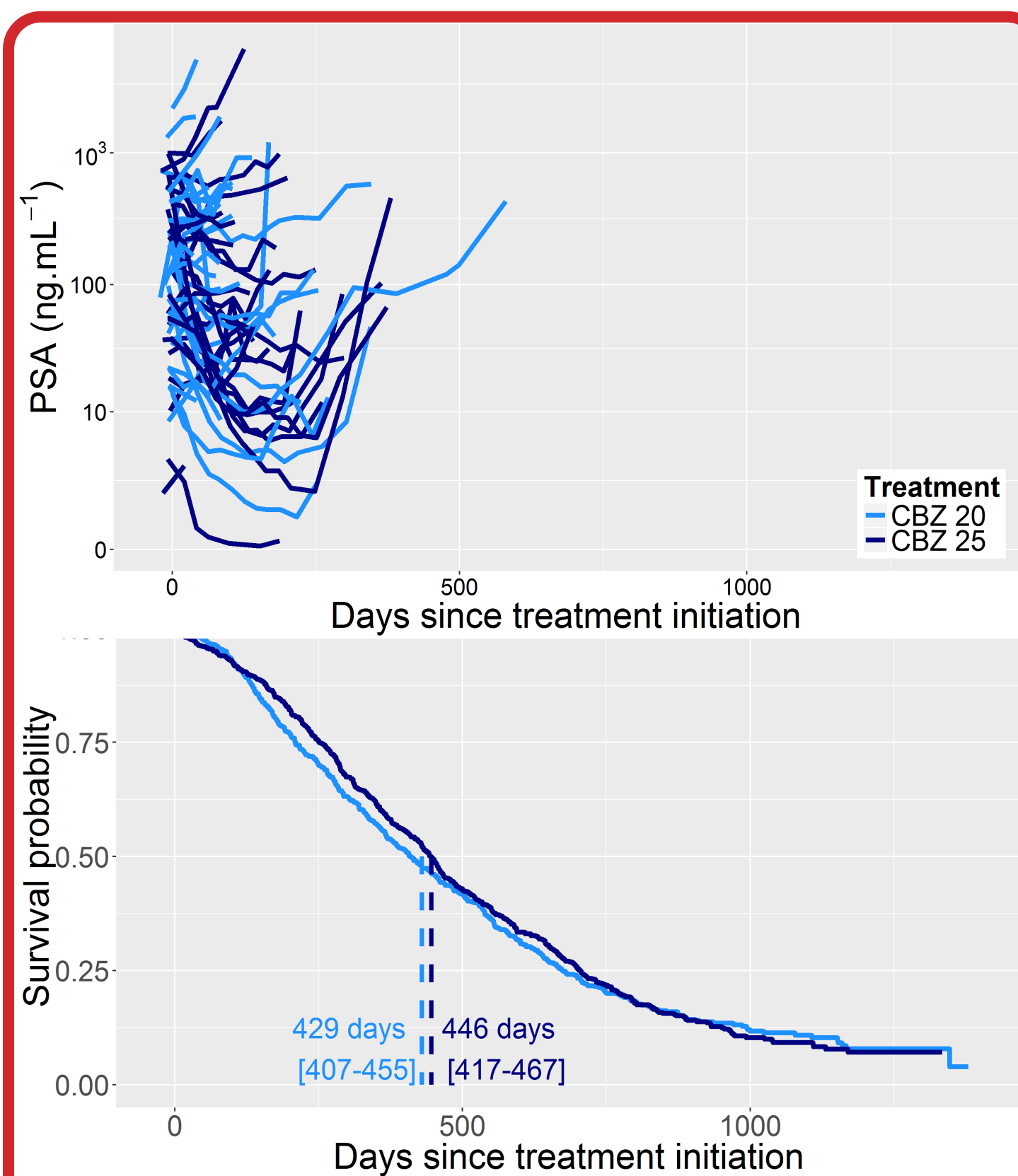
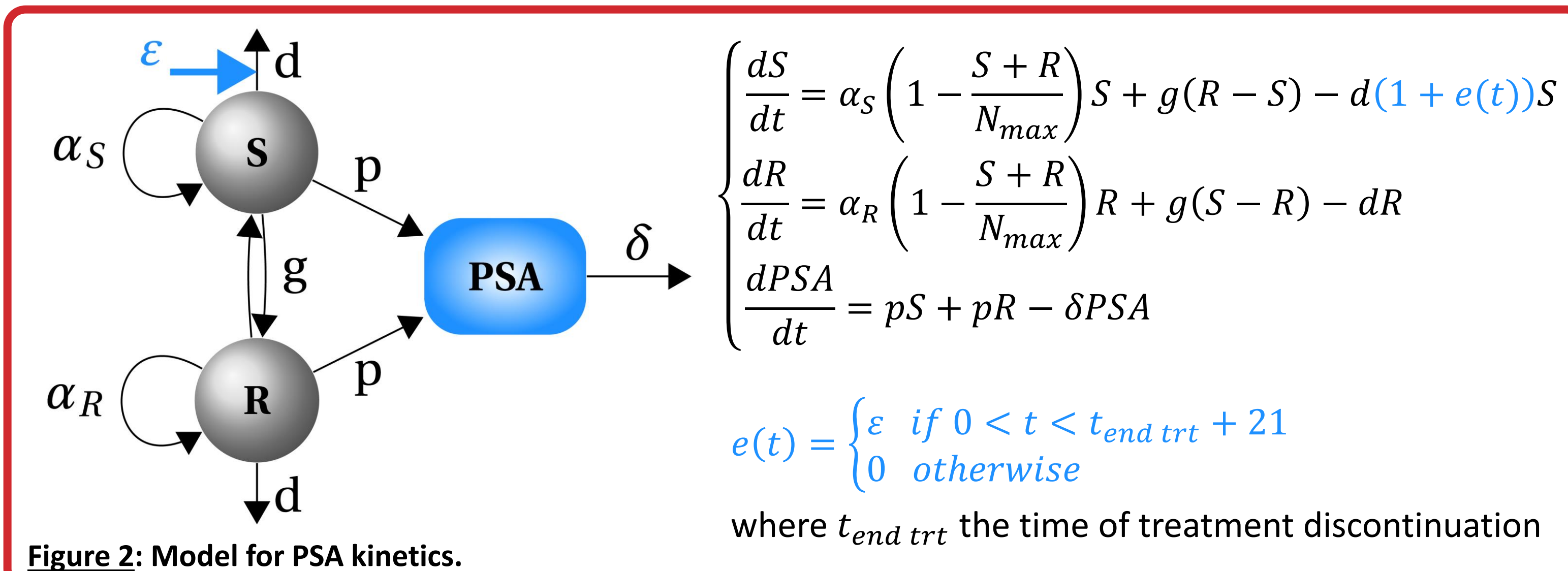


Figure 1: Top: PSA profiles of a random subset of 60 patients. Bottom: Kaplan-Meier curves of the 1174 patients, median survival [95% CI] by group of dose.



Joint model for longitudinal PSA and survival data

- Nonlinear mixed-effect model for longitudinal PSA data y_i

$$y_i(t) = \log(PSA(t, \psi_i) + 1) + e_i(t)$$
 - ψ_i : individual parameters
 - $e_i(t) \sim N(0, \sigma)$: residual error
 - Longitudinal model's parameters: $\alpha_S, RE = \frac{d}{\alpha_R}, PSA_b, RF = \frac{\alpha_R}{\alpha_S}, \varepsilon, N_{max}$
- Hazard function for patient i :

$$h_i(t|\psi_i) = h_0(t) \exp(\beta f(t, \psi_i) + \xi w_i)$$
 - $h_0(t) = \frac{k}{\lambda} \left(\frac{t}{\lambda}\right)^{k-1}$: Weibull baseline hazard function
 - ξ : vector of coefficients associated with the vector of baseline covariates w_i
 - β : vector of coefficients associated with the link function f
 - No link
 - Initial PSA
 - Current PSA
 - Current PSA slope
 - Area under PSA
 - Current S
 - Current R
 - Current S and R
- Joint parameter estimation using the SAEM algorithm [5] implemented in Monolix version 2016R1.

Model selection

- Selection of the link function f based on BIC, in absence of covariates, except dose effect on ε .
 - Computation of individual Empirical Bayes Estimates (EBEs)
- Baseline covariates selection:
 - From the joint model including all covariates having a significant correlation ($p < 0.10$) with a longitudinal PSA EBE, stepwise elimination based on Wald test
 - From this joint model including in addition all covariates having a significant effect ($p < 0.10$) in the univariate Weibull model, stepwise elimination based on Wald test
 - If necessary steps 1-2 were repeated until all covariates have p -value < 0.05 .
 - Lastly introduction of the dose as a binary covariate on survival and Wald test.

References

- [1] Tsiatis and Davidian. *Stat Sin.* 2004.
[2] Desmée, Mentré, Veyrat-Follet, Guedj. *AAPS J.*, 2015.
[3] Proselica study funded by Sanofi (NCT01308580)
[4] Desmée, Mentré, Veyrat-Follet, Sébastien, Guedj. *Biometrics*, 2016.
[5] Kuhn and Lavielle. *Comput Stat Data Anal.* 2005.

RESULTS

Link function selection

- The link function providing the smallest BIC was the one involving the current PSA and the risk of death: $f(t, \psi_i) = \log(PSA(t, \psi_i) + 1)$
- Treatment increased the stimulation of the S cells elimination by a factor 1.614 and 1.867 for CBZ 20 and 25 respectively, in absence of other covariates (Table 1).
- A decrease of one point in $\log(PSA+1)$ results in a decrease in hazard: HR=0.71 [0.68 - 0.74]

Table 1: Joint model selection

		Joint model without baseline covariate			Joint model with baseline covariates		
		parameter	r.s.e (%)	p-value	parameter	r.s.e (%)	p-value
Fixed effects	α_S	0.0303	3		0.0396	5	
	Presence of liver metastases				0.209	38	0.0082
	Prior steroid use				-0.188	33	0.0024
	RF	0.999	0		0.999	0	
	RE	0.612	1		0.555	8	
	Total protein				0.636	35	0.0047
	ε	0.614	4		0.0911	25	
	Dose 25	0.346	16	3.9×10^{-10}	0.326	16	7.5×10^{-10}
	Age (years)				0.0202	18	1.7×10^{-8}
	Bilirubin				0.423	33	0.0021
	Tumor progression				0.181	30	0.001
	PSA_b	145	5		203	15	
	Creatinine clearance (mL.min ⁻¹)				-0.0043	32	0.0016
	Lactate deshydrogenase				-0.0219	37	0.0073
	Presence of liver metastases				-0.243	49	0.041
Inter-individual standard deviation	Prior abiraterone treatment				0.558	19	2.4×10^{-7}
	Prior enzalutamide				0.932	31	0.0012
	Prior opioids use				0.297	32	0.0017
	Tumor progression				-0.252	40	0.012
	Lymph nodes only				-1.04	27	0.0002
	N_{max}	325	19		39.9	21	
	Lactate deshydrogenase				1.51	2	$< 10^{-10}$
	α_S	0.748	3		0.748	4	
Parameters related to survival	RF	2.29	4		2.38	4	
	RE	0.288	5		0.184	8	
	ε	0.735	4		0.675	4	
	PSA_b	1.62	2		1.56	2	
	N_{max}	2.7	5		2.56	6	
	σ	0.257	1		0.256	1	
	λ	3631	13		5123	16	
	k	1.16	2		1.25	2	
Parameters related to survival	β	0.342	6		0.37	7	
	Dose 25				0.0909	19	6.5×10^{-8}
	Lactate deshydrogenase				0.0186	17	2.9×10^{-9}
	Presence of liver metastases				0.628	26	0.00012
	Prior opioids use				0.38	22	5×10^{-6}
	Tumor progression				0.249	38	0.0078
	-2LL	27271			26919		
	BIC	27391			27180		

Impact of baseline covariates on PSA kinetics and risk of death

- Significant impact on PSA and/or survival of numerous baseline covariates (Table 1).
 - Impact of each covariate can be visualized in a "median" patient (Fig.3) but must be carefully interpreted because of large variability.

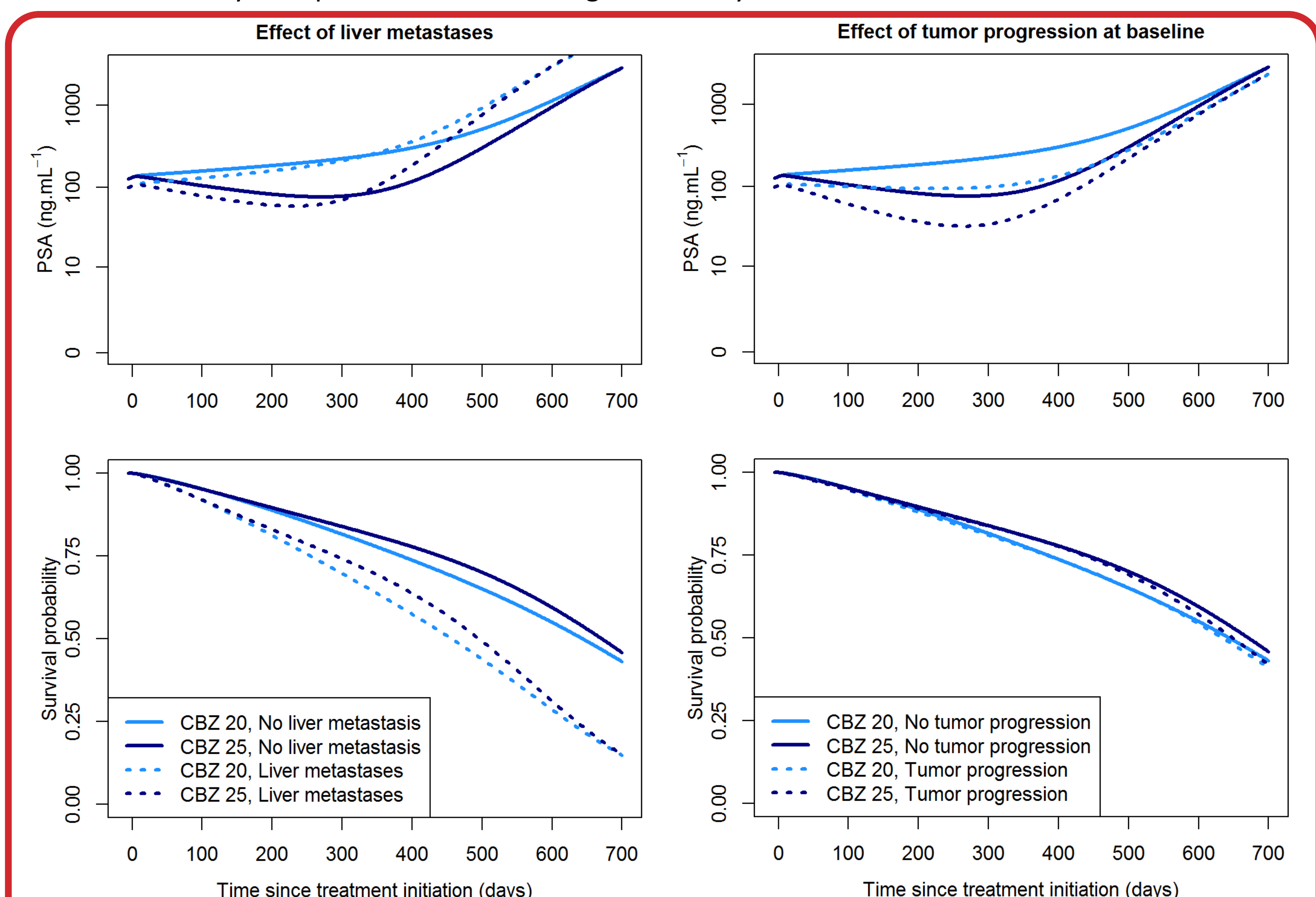


Figure 3: Impact of 2 baseline covariates on median profiles using population parameters (age=68.3 years, absence of liver metastasis, no prior abiraterone treatment, no prior enzalutamide, no prior opioids use, no prior steroid use, no tumor progression, no lymph nodes, CLCR=98mL.min⁻¹, LDH=1.6, bilirubin=0.4, total protein=0.8)

- Liver metastases $\nearrow$ tumorous cell proliferation
- Tumor progression $\nearrow$ treatment effect (ε) but (α_S) and risk of death (at the same PSA kinetics).
- $\nearrow$ risk of death (at the same PSA kinetics).

CONCLUSION

- In advanced metastatic prostate cancer, the development of a mechanistic joint model for PSA kinetics and survival allows to highlight:
 - The significant effect of numerous baseline covariates on PSA kinetics and/or survival
 - $\rightarrow$ Useful to identify subgroups of patients
 - A steeper PSA decline in CBZ 25 compared to CBZ 20 was observed.
 - However based on overall survival, CBZ 20 was shown to be non inferior to CBZ 25.
 - $\rightarrow$ PSA kinetics are not the only determinant of survival.