Multilevel joint modelling of target lesions dynamics and survival: Application to the prediction of the response to immunotherapy in bladder cancer

Marion Kerioui

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June 10^{th}, 2022

Immunotherapy in metastatic Urothelial Carcinoma

Urothelial Carcinoma (UC):

- Represents 90% of bladder cancers[1]
- More than 550 000 cases and 200 000 deaths worldwide in 2020
- 5−year survival rate of 77% overall (all disease stages)[2] and 15% for the late stages[3]

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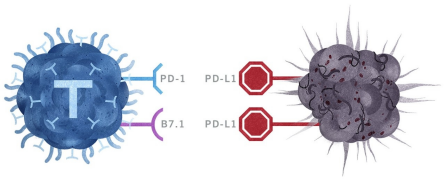

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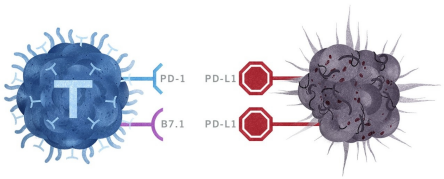
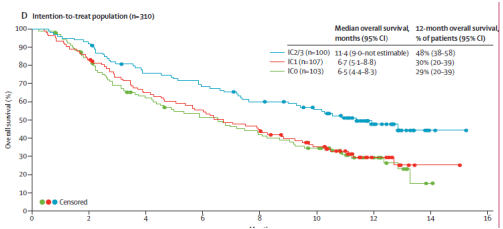


- Atezolizumab approved by FDA for second-line metastatic UC in 2016 based on IMvigor210 phase 2 trial results[5,6]



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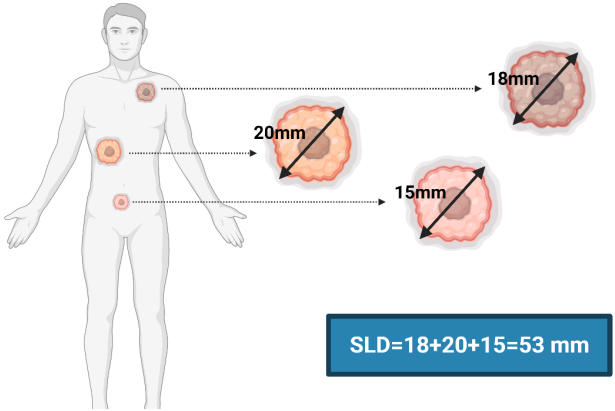
Treatment response

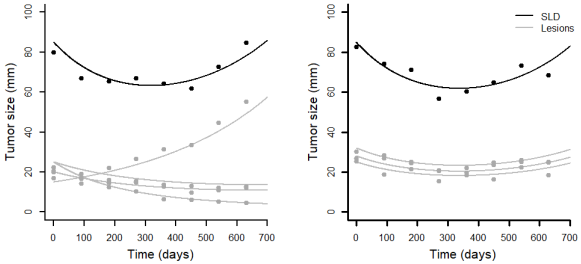
Tumor burden based on RECIST criteria[7], mainly relies on the Sum of the Longest Diameters (SLD) of the target lesions



[7] Eisenhauer et al *Eur. J. Cancer* (2009)

SLD limitations

➞ SLD aggregates the information at the patient level, without any distinction across target lesions



- Dissociated responses (DR) to treatment might occur[8,9] and could impact survival[10]

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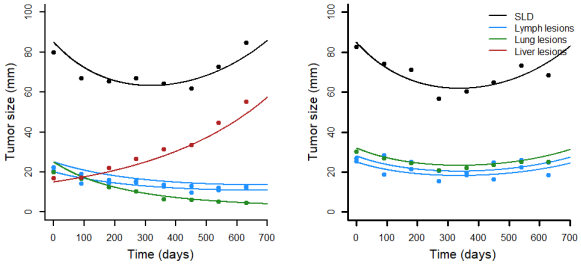

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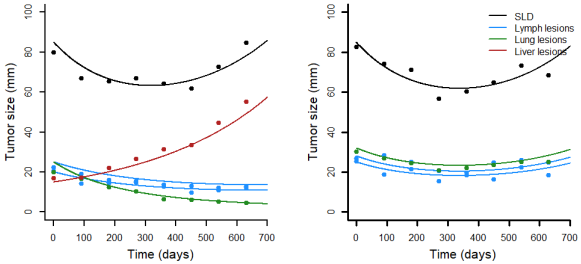

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- Might be partly explained by tumor location, that may impact lesion kinetics[11,12], and association with survival[13].
- Risk of DR exacerbated under immunotherapy[14,15].

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Semi-mechanistic model for Tumor Size description

- To describe the complex interaction between treatment exposure, treatment effect and disease evolution[16]
- Mostly rely on ODE system, might have analytical solution under some hypotheses

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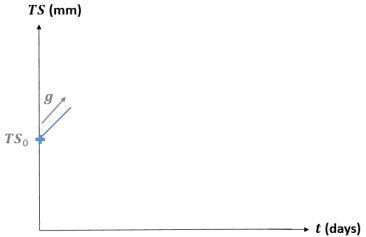
Claret simplified Tumor Growth Inhibition (sTGI) model[17]:

In absence of treatment: $\frac{d\text{TS}(t)}{dt} = g \times \text{TS}(t)$



Tumor parameters:

- TS_0: baseline sum of longest diameters,
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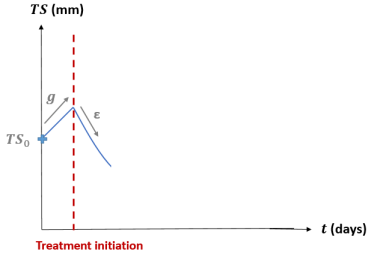

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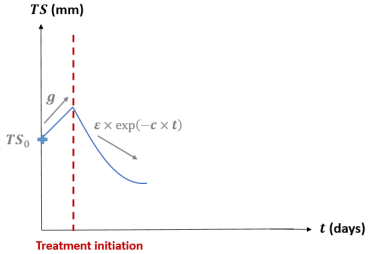

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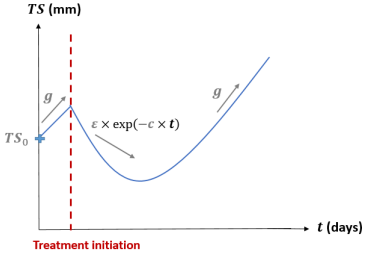

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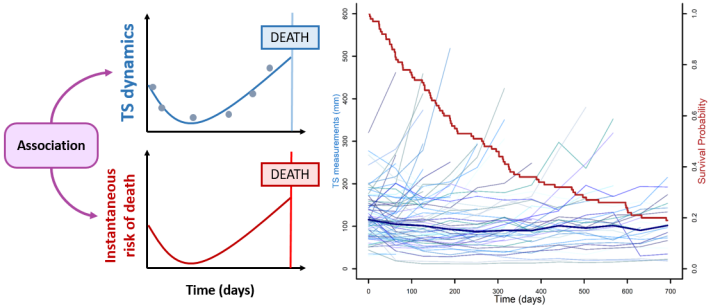
Modelling tumor size and survival

Motivations:

- To inform on the underlying mechanism of response to treatment
- To characterize the impact of the biomarker kinetics on the time-to-event process (and to improve prediction performances)
- To account for the bias due to early end of longitudinal follow-up in the most-at-risk patients[18,19]



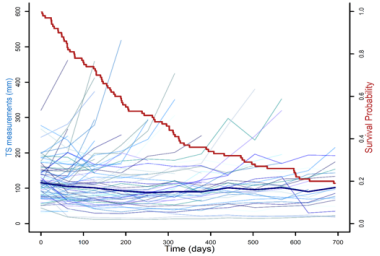
[18] Desmée et al *AAPS J* (2016)
[19] Bjornsson et al *AAPS J* (2016)

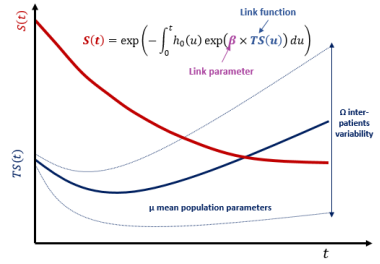
Nonlinear joint models

Longitudinal part - Nonlinear mixed-effect models (NLMEM)

$$y_{i,j} = TS(t_{i,j}, \psi_i) + (a + b \times TS(t_{i,j}, \psi_i))e_{i,j}$$

- $\tau(\psi_i) = \tau(\mu) + \eta_i$ with transformation function τ
  - μ fixed-effect parameters
  - $\eta_i \sim \mathcal{N}(0, \Omega)$ individual random effects





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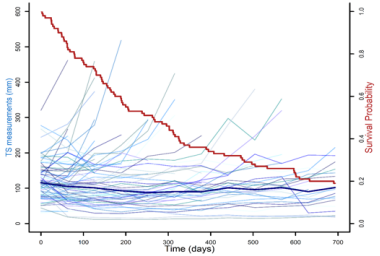
Survival part - Hazard function for patient i

$$h_i(t|\psi_i) = h_0(t) \exp(\beta \times f(t, \psi_i))$$

- h_0 baseline hazard function
- β link parameter and f link function ($f = TS$ for instance)



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Received: 13 February 2021 | Revised: 12 October 2021 | Accepted: 7 November 2021
DOI: 10.1111/bcp.15200

THEMED ISSUE REVIEW

Modelling the association between biomarkers and clinical outcome: An introduction to nonlinear joint models

Marion Kerioui[1,2,3,4] | Julie Bertrand[1] | René Bruno[5] | François Mercier[6] | Jérémie Guedj[1] | Solène Desmée[2]

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- Nonlinear joint models of tumor size and survival mainly rely on SLD[21,22]

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Inference

➞ Simultaneous estimation of both longitudinal and survival parameters, complex likelihood expression

- **Frequentist inference:** can be done by maximum likelihood using SAEM algorithm[23] ✓

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  - has been showed to provide satisfying estimates of the parameters of a nonlinear joint model [27] ✓

Received: 9 December 2019 | Revised: 31 August 2020 | Accepted: 4 September 2020
DOI: 10.1002/sim.8756

RESEARCH ARTICLE

Statistics in Medicine WILEY

Bayesian inference using Hamiltonian Monte-Carlo algorithm for nonlinear joint modeling in the context of cancer immunotherapy

Marion Kerioui[1,2,3] | Francois Mercier[4] | Julie Bertrand[1] | Coralie Tardivon[1] | René Bruno[5] | Jérémie Guedj[1] | Solène Desmée[2]

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Objectives

- To develop a Bayesian hierarchical nonlinear joint model to describe target lesions dynamics and their association with survival
- To assess the benefit of target lesions follow-up in predicting the individual survival probability as compared to SLD follow-up used in routine

Clinical application

Phase 3 clinical trial IMvigor211[28]**:**

- 931 patients suffering from advanced or metastatic UC who did not respond to chemotherapy,
- Randomized (1:1) between an Atezolizumab and a chemotherapy control arm
- Benefit of atezolizumab compared to chemotherapy on Overall Survival (OS) in the intention-to-treat population

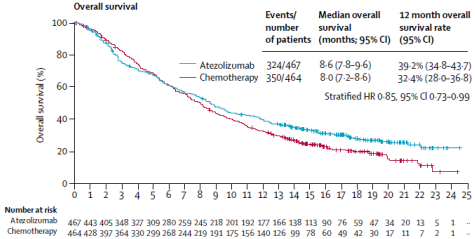
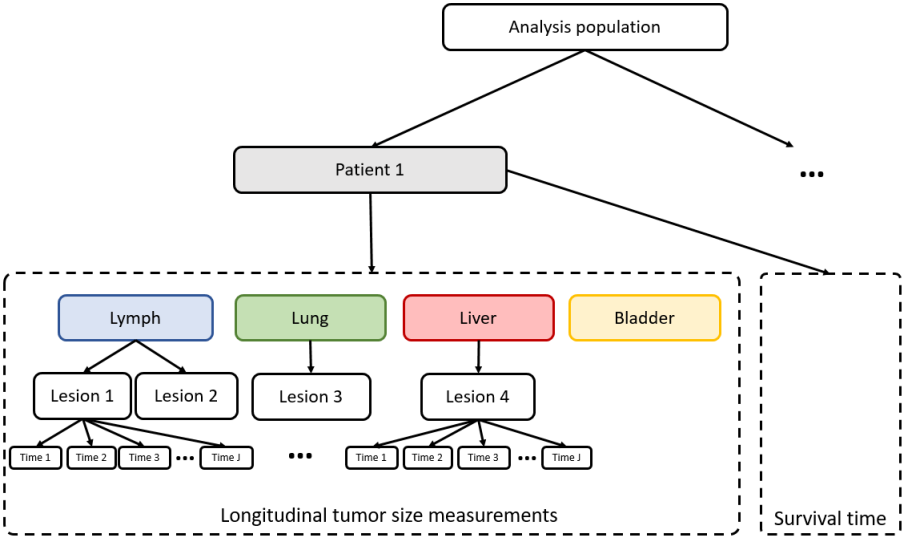


Figure: Survival curves of atezolizumab arm versus control chemotherapy arm in IMvigor211

	IMvigor211	
	Chemotherapy	**Atezolizumab**
Data description		
Analysis population (N)	443	457
Number of target lesions	1064	1069
Number of measurements	2981	3716

[28] Powles et al *The Lancet* (2018)

Modelling hierarchical data



Analysis population

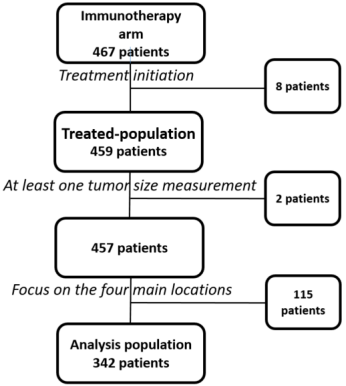


Figure: Flowchart of analysis population

Focus on four main locations:

- Lymph nodes,
- Lung,
- Liver,
- Bladder

Multilevel joint model

$y_{i,j,k,l}$ is the l^{th} measurement of the k^{th} target lesion in location j in patient i

$$y_{i,j,k,l} = TS(t_{i,l}, \psi_{i,j,k}) + \left(\sigma_{1,j} + \sigma_{2,j} \times TS(t_{i,l}, \psi_{i,j,k})\right) e_{i,j,k,l}$$

$$\psi_{i,j,k} = \mu \times \exp\left(\xi_j + \eta_i + \rho_{i,j,k}\right) \quad \text{with } \eta_i \sim \mathcal{N}(0, \omega_1^2) \text{ and } \rho_{i,j,k} \sim \mathcal{N}(0, \omega_2^2)$$

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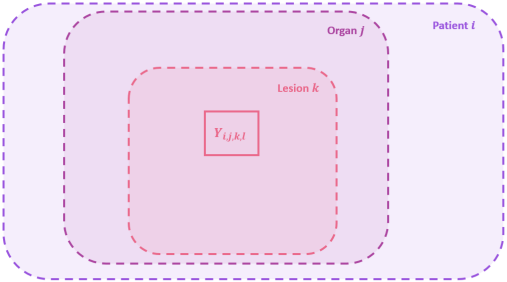

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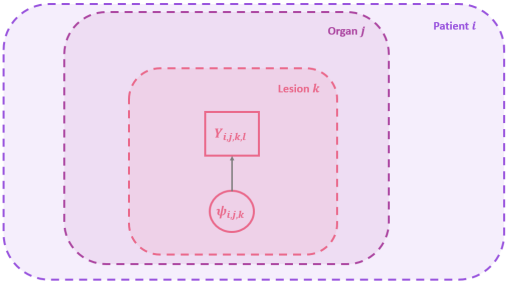

Multilevel joint model

$y_{i,j,k,l}$ is the l^{th} measurement of the k^{th} target lesion in location j in patient i

$$y_{i,j,k,l} = TS(t_{i,l}, \psi_{i,j,k}) + \left(\sigma_{1,j} + \sigma_{2,j} \times TS(t_{i,l}, \psi_{i,j,k})\right) e_{i,j,k,l}$$

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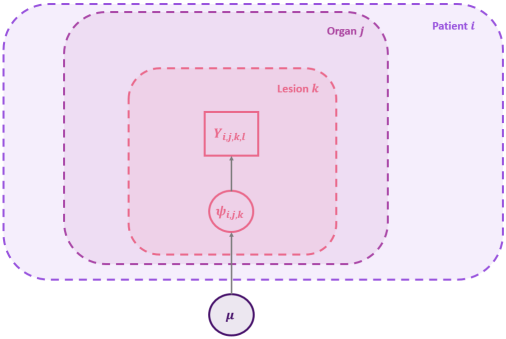

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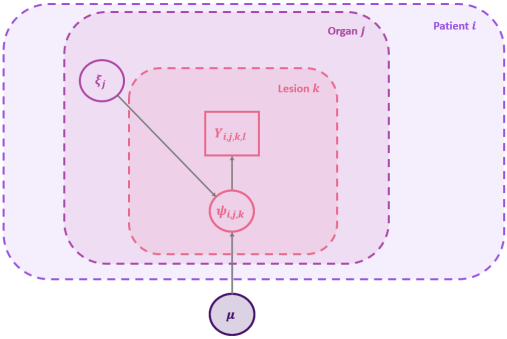

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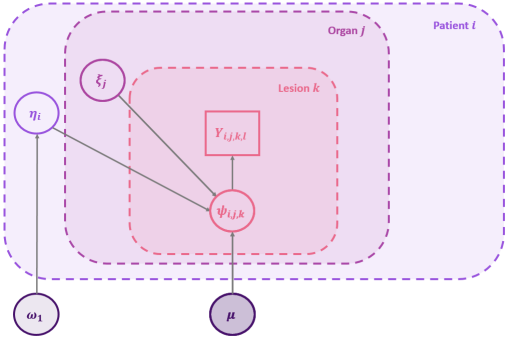

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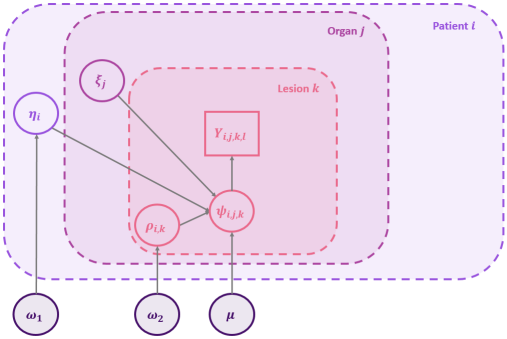

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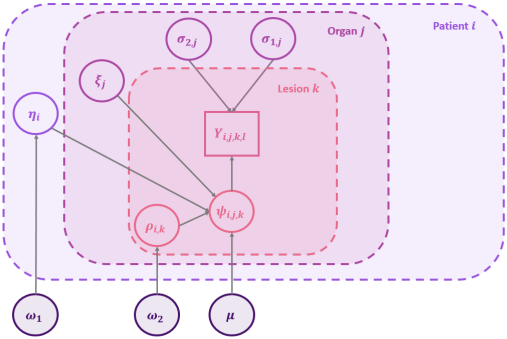

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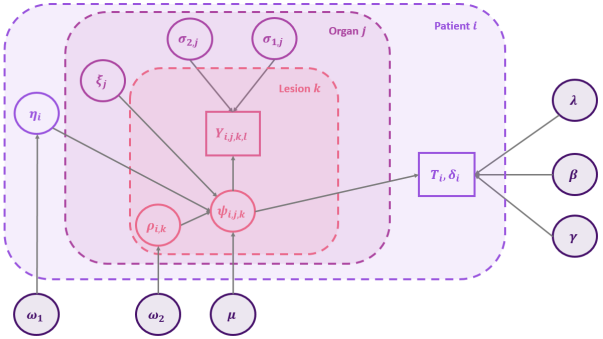
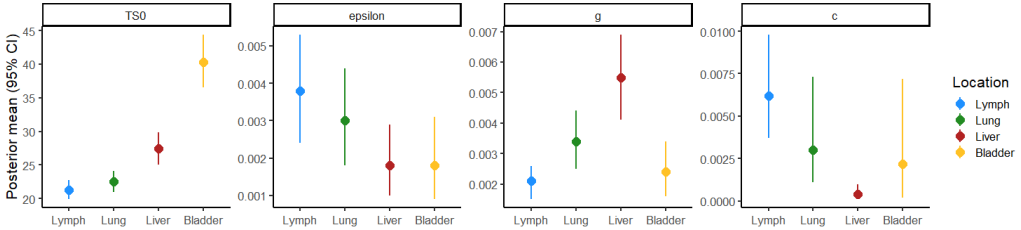


Population parameters estimates



	Variability	
	Inter-patient variability ω_1	Inter-lesion variability ω_2
TS_0 (mm)	0.25 [0.20;0.30]	0.36 [0.33;0.39]
ϵ (day^{-1})	1.29 [1.05;1.58]	0.67 [0.53;0.81]
g (day^{-1})	0.82 [0.63;1.02]	0.28 [0.09;0.47]
c (day^{-1})	1.29 [0.79;1.92]	0.81 [0.26;1.24]

Link functions

1. **Tumor burden model:** $\beta \times f(t, \psi_i) = \beta_{\text{lesion}} \times \sum_{j=1}^{4} \sum_{k=1}^{K_{i,j}} TS(t, \psi_{i,j,k})$
2. **Organ tumor burden model:** $\beta \times f(t, \psi_i) = \sum_{j=1}^{4} \beta_j \times \sum_{k=1}^{K_{i,j}} TS(t, \psi_{i,j,k})$

with:

- $K_{i,j}$ is the number of target lesions in organ j of patient i,
- β_{lesion} is the impact of each target lesion on the instantaneous risk of death,
- β_j is the impact of each target lesion on the instantaneous risk of death depending on its location.

Link functions

❶ **Tumor burden model:** $\beta \times f(t,\psi_i) = \beta_{\text{lesion}} \times \sum_{j=1}^{4} \sum_{k=1}^{K_{i,j}} TS(t,\psi_{i,j,k})$

❷ **Organ tumor burden model:** $\beta \times f(t,\psi_i) = \sum_{j=1}^{4} \beta_j \times \sum_{k=1}^{K_{i,j}} TS(t,\psi_{i,j,k})$

Model	Tumor burden ❶	Organ tumor burden ❷
Individual lesion impact β_{lesion} (mm^{-1})	0.011 [0.0090;0.013]	-
Organ-specific lesion impact β_j (mm^{-1})		
Lymph	-	0.0085 [0.0052;0.012]
Lung	-	0.0066 [0.0033;0.010]
Liver	-	0.013 [0.011;0.016]
Bladder	-	0.012 [0.0081;0.016]
WAIC	17810	17803

Table: WAIC criterion, posterior mean and 95% credibility intervals of the link parameters for each candidate models

Link functions

1. **Tumor burden model:** $\beta \times f(t,\psi_i) = \beta_{\text{lesion}} \times \sum_{j=1}^{4} \sum_{k=1}^{K_{i,j}} TS(t,\psi_{i,j,k})$
2. **Organ tumor burden model:** $\beta \times f(t,\psi_i) = \sum_{j=1}^{4} \beta_j \times \sum_{k=1}^{K_{i,j}} TS(t,\psi_{i,j,k})$
3. **Range model:** $\beta \times f(t,\psi_i) = \beta_{\text{range}} \times \left(\max_{j,k}\{TS(t,\psi_{i,j,k})\} - \min_{j,k}\{TS(t,\psi_{i,j,k})\}\right)$

with:

- $K_{i,j}$ is the number of target lesions in organ j of patient i,
- β_{lesion} is the impact of each target lesion on the instantaneous risk of death,
- β_j is the impact of each target lesion on the instantaneous risk of death depending on its location.
- β_{range} is the impact of the range between the maximum and the minimum of the lesions sizes

Link functions

1. **Tumor burden model:** $\beta \times f(t,\psi_i) = \beta_{\text{lesion}} \times \sum_{j=1}^{4} \sum_{k=1}^{K_{i,j}} TS(t,\psi_{i,j,k})$
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Lymph	-	0.0085 [0.0052;0.012]	-
Lung	-	0.0066 [0.0033;0.010]	-
Liver	-	0.013 [0.011;0.016]	-
Bladder	-	0.012 [0.0081;0.016]	-
Range of the lesions sizes β_{range} (mm^{-1})	-	-	-0.0067 [-0.013;-0.0013]
WAIC	17810	17803	17804

Table: WAIC criterion, posterior mean and 95% credibility intervals of the link parameters for each candidate models

Individual fits

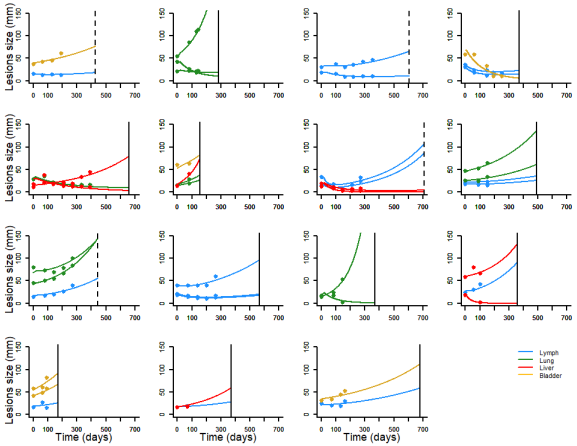
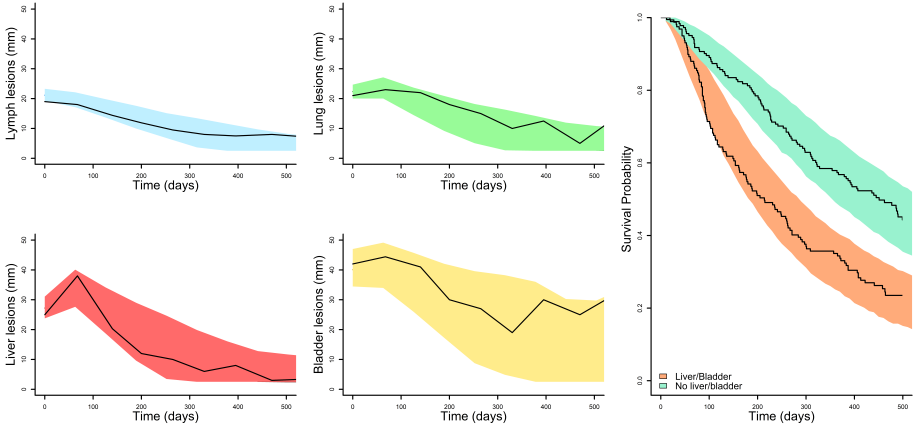


Figure: Individual fits: model prediction of lesions kinetics (solid lines) and observed longitudinal lesion size measurements (dots) in the lymph (blue), the lung (green), the liver (red) and the bladder (yellow) location, time of death (vertical solid black lines) or time of censor (vertical dashed black lines).

Posterior Predictive Checks

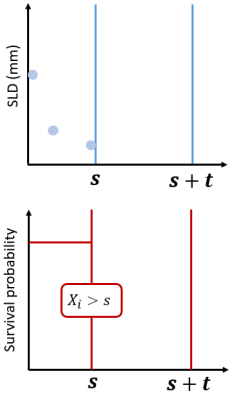


Based on 1000 replicated datasets of lesions sizes and time-to-death, keeping the same structure as the original data

Dynamic predictions

➔ We aim to predict the conditional survival probability $S_i(s+t|s) = \mathbb{P}(X_i > s+t | X_i > s, \mathscr{Y}_i(s))$ up to the prediction horizon $s+t$ following methodology by Desmée et al[29]

Assumption: *true* joint model and population parameters θ are known



[29] Desmée et al, *BMC Med Res Methodol* (2017)
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For $m = 1, ..., M$:

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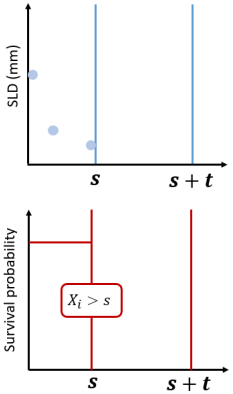

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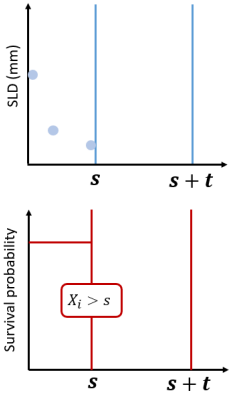

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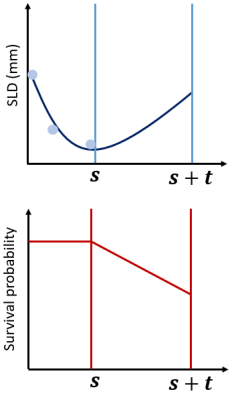
3. $\hat{S}_i(s+t|s) = \text{median}\left\{S_i^m(s+t|s)\right\}_{m=1,...,M}$



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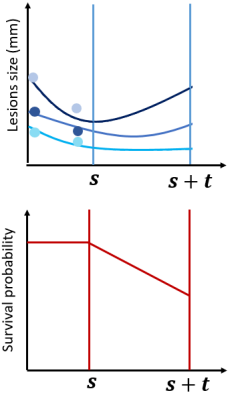

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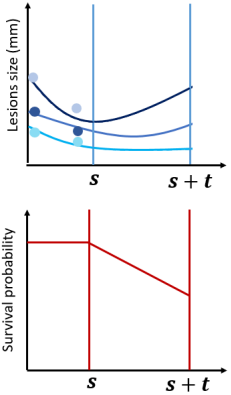
Area under the ROC curve[30]

$AUC(s,t) = \mathbb{P}(S_i(s+t|s) < S_j(s+t|s) | \mathbf{1}_{\{X_i < s+t\}} = 1, \mathbf{1}_{\{X_j < s+t\}} = 0, X_i > s, X_j > s)$

Brier score[31]

$BS(s,t) = \mathbb{E}[(\mathbf{1}_{\{X > s+t\}} - S(s+t|s))^2 | X > s]$



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Dynamic predictions - AUC

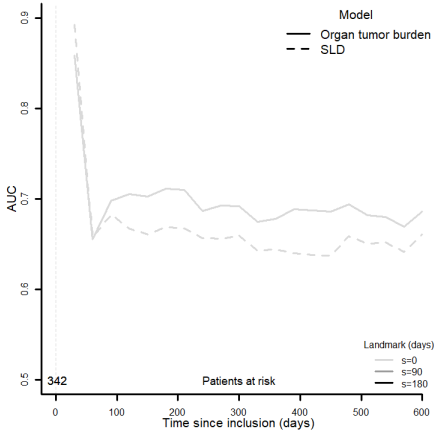
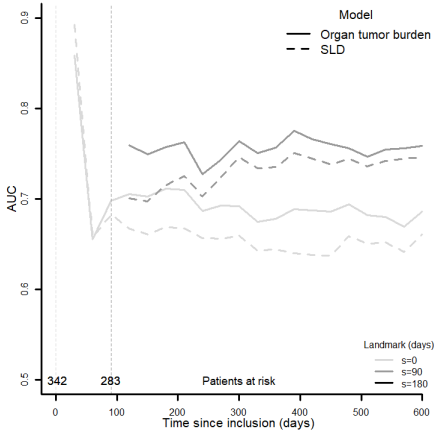


Figure: Time-dependent AUC for each landmark time; $s = 0$ months, $s = 3$ months, $s = 6$ months (from lightest to darkest respectively), depending on the joint model; organ tumor burden model (solid lines) or SLD model (dashed lines).

Dynamic predictions - AUC



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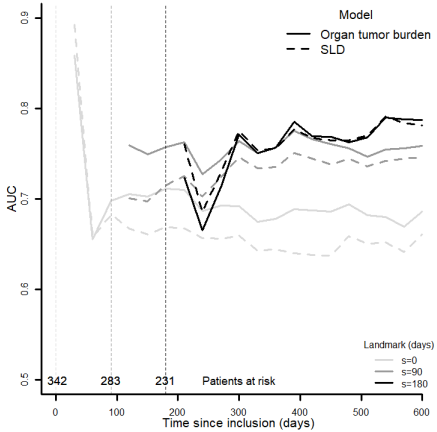

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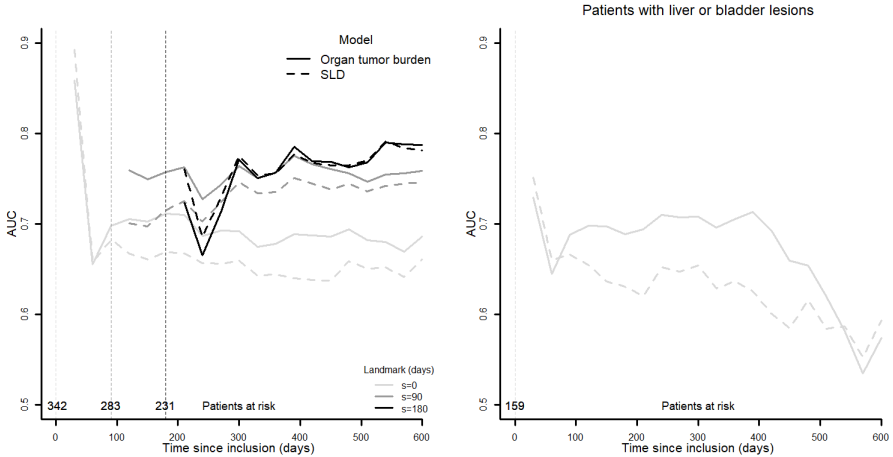

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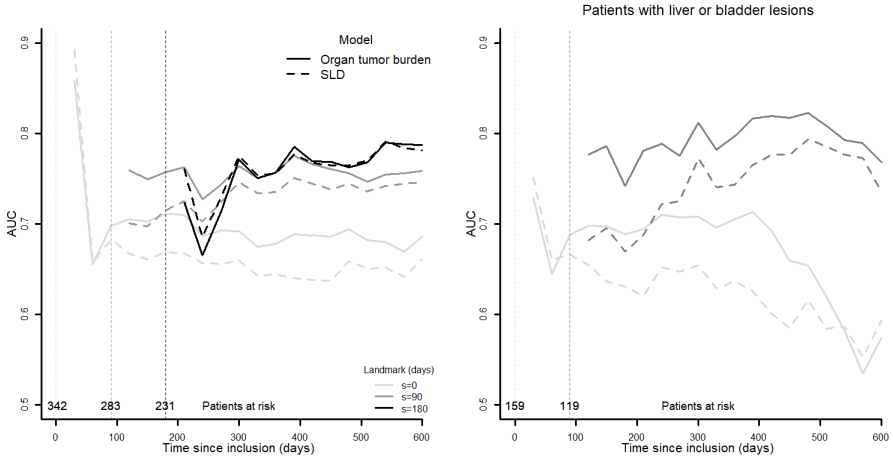

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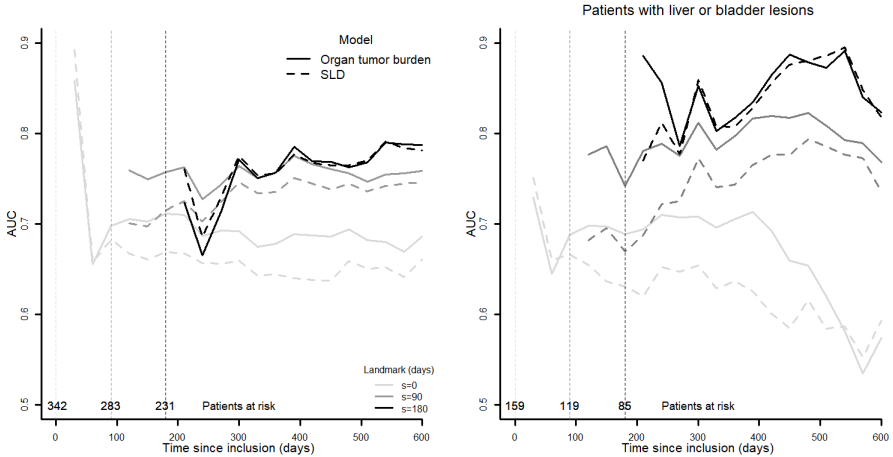

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Dynamic predictions - Brier Scores

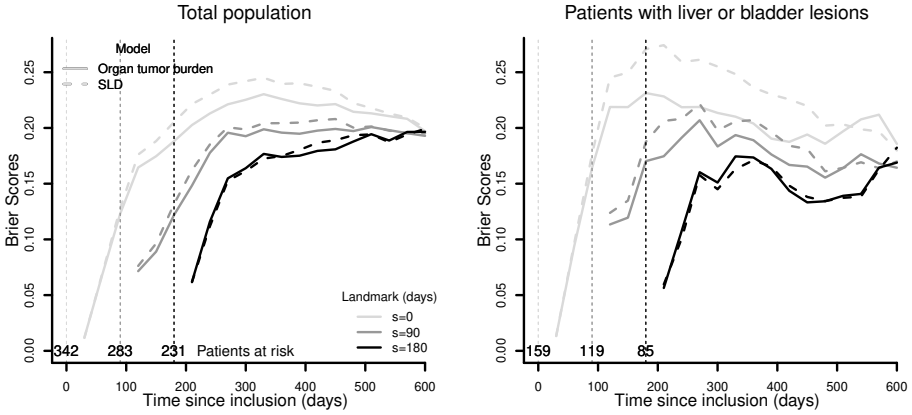

Figure: Time-dependent BS for each landmark time; $s = 0$ months, $s = 3$ months, $s = 6$ months (from lightest to darkest respectively), depending on the joint model; organ tumor burden model (solid lines) or SLD model (dashed lines).

Conclusion

Main results:

- We developed a nonlinear joint model of individual lesions and survival to quantify the intra-patient variability under immunotherapy
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→ Manuscript submitted in *Biometrics*

Perspectives

From a methodological point of view:

- Assess the quantity of information required for our new model to be identifiable in a simulation study (Maxime Beaulieu internship ongoing),
- Integrate other markers of disease progression such as the appearance of new lesions[32] or the non-target lesions kinetics.

[32] Król et al *Stat Med* (2018)
[33] Netterberg et al *Clin. Pharmacol. Ther.* (2018)
[34] Frelaut et al *BioDrugs* (2020)

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From a clinical point of view:

- This work paves the way for a better understanding of the variability in the response to immunotherapy treatments,
  - Compare the intra-patient variability under chemotherapy and under atezolizumab (manuscript to be submitted),
  - Integrating immunological measurements[33],
  - Develop a more mechanistic model, adapted to the specific tumor kinetics under immunotherapy (hyperprogression, pseudoprogression, oligoprogression[34]),
- Apply this methodology in other metastatic cancers.

[32] Król et al *Stat Med* (2018)
[33] Netterberg et al *Clin. Pharmacol. Ther.* (2018)
[34] Frelaut et al *BioDrugs* (2020)

Thank you for your attention !

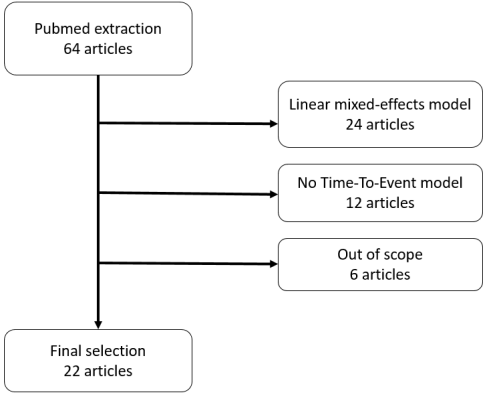
Thank you to:

- Jérémie Guedj, Solène Desmée and René Bruno
- The defense committee
- Julie Bertrand and François Mercier
- All members of IAME and SPHERE teams
- Jin Jin, Ben Wu, Genentech Clinical Pharmacology team, Nathalie Etienne, Magnus Fontes

This PhD was funded by Genentech, Roche and the Nationale Agency of Research and Technology (ANRT) through a CIFRE agreement.

PubMed research algorithm

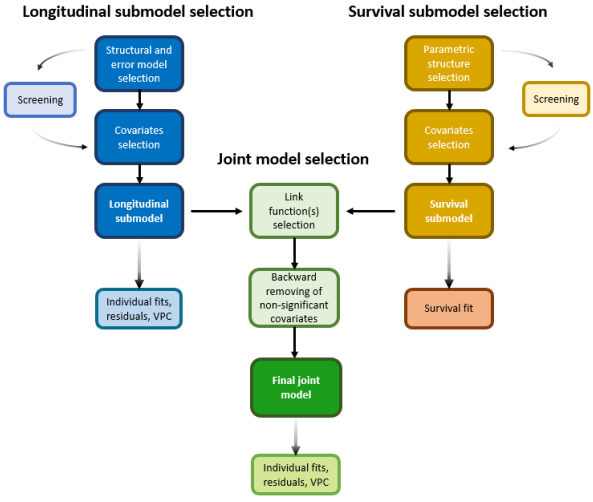
((model*) AND (("nonlinear*") OR ("non-linear*")OR (NLME*) OR (mechanistic*) OR ("non linear*") OR ("differential equation*"))AND (("mixed-effect*") OR (kinetics) OR (dynamics) OR (evolution) OR (longitudinal)) AND (("informative dropout") OR ("informative censoring") OR ("missing not at random")))
OR
(("joint model*" OR "joint analysis" OR "joint inference") AND ((nonlinear*) OR ("non linear") OR (mechanistic*) OR (NLME*) OR (kinetics)) AND ((longitudinal)OR (kinetics) OR (repeat* measure*) OR "mixed-effect*" OR (evolution) OR (dynamics)) AND ((survival) OR (event* time*) OR ("time-to-event") OR ("time to event") OR ("time to*")OR ("time-to*") OR (dropout) OR (risk) OR ("risk of*")))



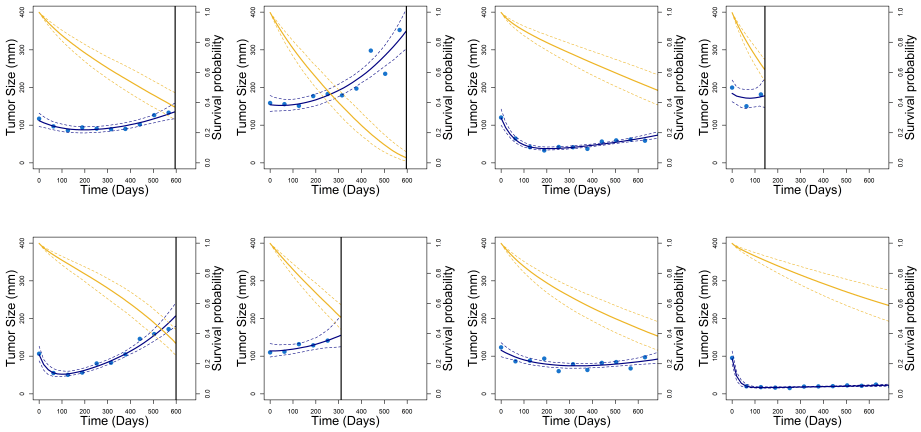
Review

	References	Count
Disease area		
Oncology	2,3,13,15–19	8
AIDS	20–25	6
Mental illness	4,5,24,27	4
Other	26–31	4
Journal		
Statistics	3,13,15,18–25	11
Pharmacology	2,4,5,16,17,26–31	11
Reasons for joint model use		
Characterize association between longitudinal and time-to-event data	2,3,13,17,19,20,22–24,26,27	12
Account for dropout in longitudinal data	4,5,18,20,22,25,28–31	10
Predictions purposes	2,15,16,18	4
Clustering	18,20	2
Publication year		
<2010	4,18,25,31	4
2010–2020	2,3,5,13,15–17,19–24,26–30	18
Structural model		
Analytical	2–5,15–23,25,27–29,31	19
Ordinary differential equation system	13,24,26,30	4
Baseline hazard function		
Parametric	2–5,13,15–17,24,26–31	15
Unspecified (Cox)	18,20–23,25	6
Splines	19	1
Link function		
Derived from biomarker current value	3,4,15–18,26–31	12
Random effects	19,20,22,23,25	5
Latent variables	2,5,13,21,24	5
Inference		
Frequentist	2,4,5,13,15–19,24–26,28,30,31	15
Bayesian	3,20–23	5
None	27,29	2
Software (algorithms)		
NONMEM (Laplace approximation)	4,5,24–31	8
Monolix (SAEM)	2,13,15–17	5
WinBUGS (Gibbs and Metropolis–Hastings)	20–23	4
Stan (NUTS HMC)	3	1
Other	18,19,24,25	4

Model selection strategy



Individual fits example



Model evaluation

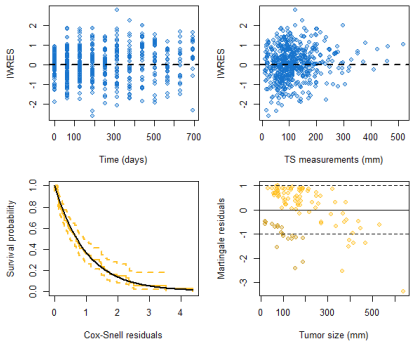
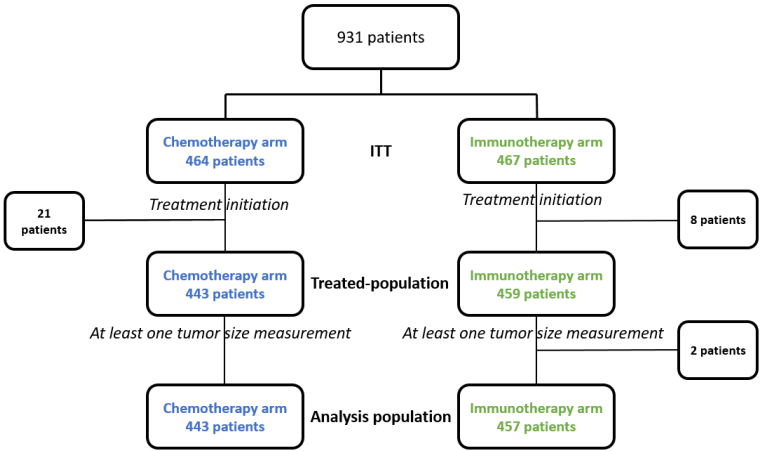


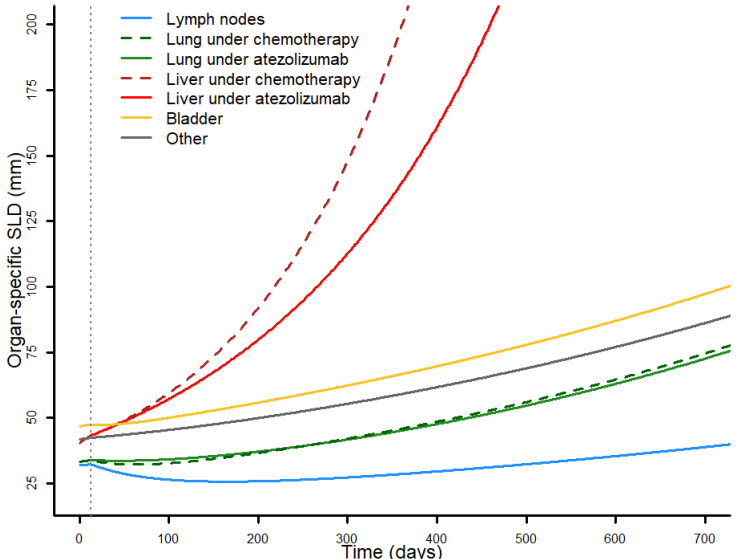
Figure: IWRES, Cox-Snells and Martingale residuals

- Longitudinal residuals $IWRES_{i,j} = \frac{y_{i,j} - m(t_{i,j}, \widehat{\psi_i})}{a + b \times m(t_{i,j}, \widehat{\psi_i})}$
- Survival residuals
  - Cox-Snells residuals $r_i^{CS} = \int_0^{T_i} h_i(u, \widehat{\psi_i}) du$
  - Martingale residuals $r_i^M = \delta_i - r_i^{CS}$
- Simulation-based tools
  - Visual Predictive Checks (VPC)
  - Normalized predictions distribution errors (npde)

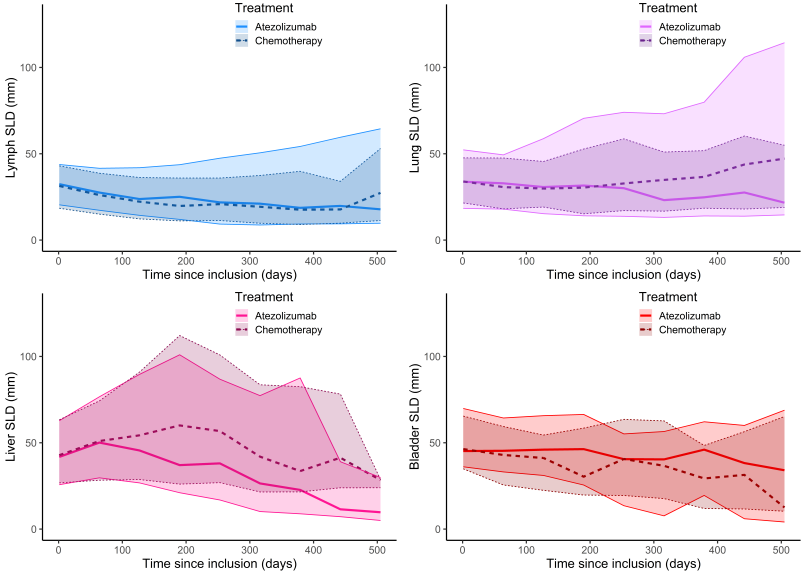
Population flowchart



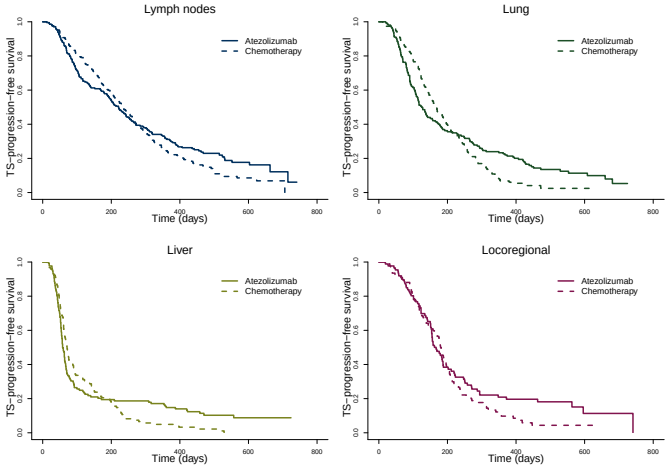
Median profiles for each location under treatment



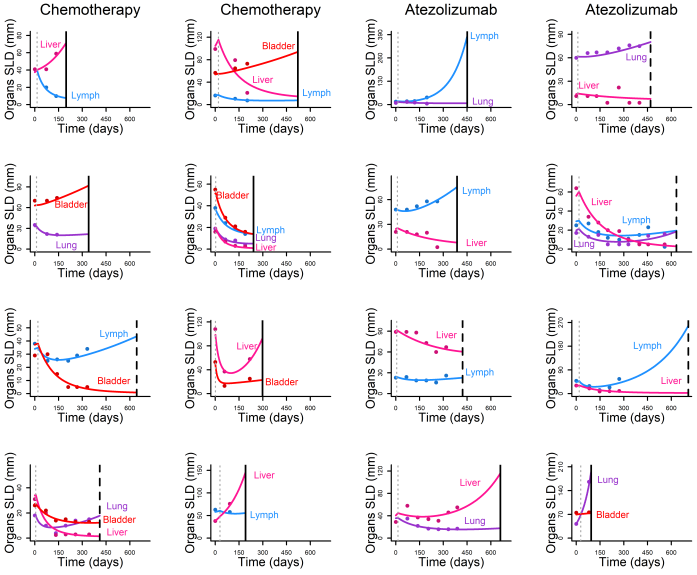
Inter-quantiles variability in organ-specific SLD



20% increase free survival



Individual fits



LRT association structure

$(H_0) : \forall m, m' \in \Lambda,\ \beta_m = \beta_{m'}$ versus the alternative hypothesis $(H_0) : \exists m, m' \in \Lambda,\ \beta_m \neq \beta_{m'}$.

Model	$-2 \times LL$	BIC
H_0	43514.92	43991.09
H_1	43444.56	43941.13

Table: -2 Log-Likelihood and BIC of the two nested joint models

Under the null hypothesis (H_0), the test statistics $\widehat{T} = -2LL(H_0) + 2LL(H_1)$ follows a chi-square distribution with 3 degrees of freedom $\chi^2(3)$. Therefore, we reject the null hypothesis (H_0) if the test statistic $\widehat{T}$ belongs to the following reject area: $[\chi^2; \infty]$, with χ^2 the chi-square value with three degrees of freedom. We computed $\widehat{T} = 70.36$ and rejected the null hypothesis with p-value$<10^{-14}$.

➙ The likelihood was significantly improved as compared to the model assuming no organ-specific association

Effective samples sizes and Rhat

		High informative		Weakly informative		Non informative	
	Parameter (Unit)	$\widehat{n}_{\text{eff}}^{\text{mean}}(\theta)$	$\widehat{R}_{\text{hat}}^{\text{mean}}(\theta)$	$\widehat{n}_{\text{eff}}^{\text{mean}}(\theta)$	$\widehat{R}_{\text{hat}}^{\text{mean}}(\theta)$	$\widehat{n}_{\text{eff}}^{\text{mean}}(\theta)$	$\widehat{R}_{\text{hat}}^{\text{mean}}(\theta)$
	Longitudinal						
	BSLD (mm)	41 (0.068)	1.07 (1.00-1.33)	50 (0.083)	1.07 (1.00-1.27)	46 (0.077)	1.07 (1.00-1.27)
Fixed	d (day^{-1})	143 (0.24)	1.02 (1.00-1.16)	92 (0.15)	1.03 (1.00-1.10)	78 (0.13)	1.04 (1.00-1.25)
Effects μ	g (day^{-1})	115 (0.19)	1.02 (1.00-1.11)	83 (0.14)	1.03 (1.00-1.08)	77 (0.13)	1.04 (1.00-1.22)
	ϕ	270 (0.45)	1.01 (1.00-1.16)	96 (0.16)	1.03 (0.99-1.05)	98 (0.16)	1.04 (1.00-1.23)
	BSLD (mm)	81 (0.13)	1.03 (1.00-1.17)	97 (0.16)	1.03 (1.00-1.18)	98 (0.16)	1.03 (1.00-1.15)
Standard	d (day^{-1})	144 (0.24)	1.02 (1.00-1.17)	115 (0.19)	1.03 (1.00-1.07)	108 (0.18)	1.03 (1.00-1.19)
deviations ω	g (day^{-1})	102 (0.17)	1.03 (1.00-1.16)	108 (0.18)	1.03 (1.00-1.18)	101 (0.17)	1.03 (1.00-1.36)
	ϕ	180 (0.3)	1.02 (1.00-1.10)	183 (0.3)	1.02 (1.00-1.08)	160 (0.27)	1.02 (1.00-1.11)
	σ	522 (0.87)	1.00 (1.00-1.02)	561 (0.93)	1.00 (1.00-1.03)	540 (0.9)	1.00 (1.00-1.02)
	Survival						
	λ (day)	573 (0.95)	1.00 (1.00-1.03)	575 (0.96)	1.00 (1.00-1.03)	587 (0.98)	1.00 (1.00-1.02)
	β(mm^{-1})	581 (0.97)	1.00 (1.00-1.03)	594 (0.99)	1.00 (1.00-1.03)	587 (0.98)	1.00 (1.00-1.01)

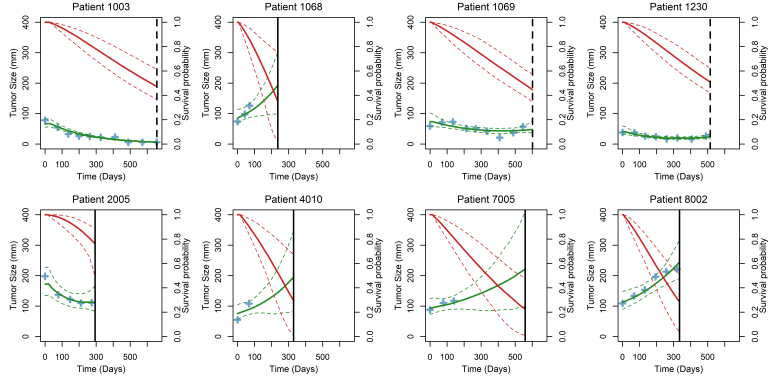
Table: Mean effective sample size (relative mean effective sample size) and mean (min-max) split-Rhat of the posterior distribution of population parameters estimated over the K simulated datasets under the three prior information scenarios.

Cross-validation scores on simulated datasets

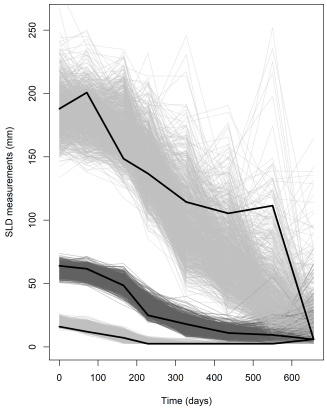
Models	No Link	Current SLD
$f(\text{SLD}(t,\psi))$	0	$\text{SLD}(t,\psi)$
Cross-Validation		
	-3000.23	-2963.08
	-3078.77	-3037.94
	-3217.72	-3170.47
	-3086.36	-3055.53
Score_{CV}	-2969.27	-2923.64
	-3101.03	-3070.01
	-3124.12	-3087.49
	-2978.94	-2936.50
	-2995.71	-2955.81
	-3098.08	-3061.32

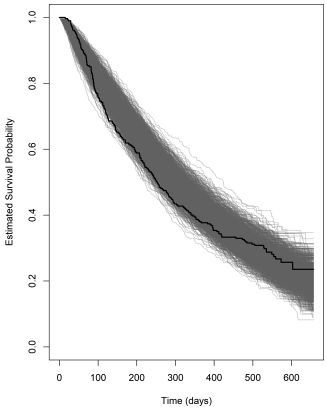
Table: Cross-validation scores of the no link model vs the current SLD link model on 10 randomly chosen datasets simulated under the current SLD link model.

Individual fits



Posterior Predictive Checks





Alternative association structures

Model	Maximum	Range	Maximum and range	Maximum and tumor burden
$\beta_{\max}$ (mm^{-1})	0.016 [0.012;0.020]	-	0.016 [0.012;0.021]	-0.00005 [-0.006;0.007]
β_{range} (mm^{-1})	-	0.014 [0.009;0.019]	-0.0006 [-0.0071;0.006]	-
β (mm^{-1})	-	-	-	0.010 [0.0065;0.015]
WAIC	17848	17898	17834	17831

Table: WAIC criterion, posterior mean and 95% credibility intervals of the link parameters for the alternative candidate models

Immunotherapy arm				
Parameters	TS_0 (mm)	ϵ (day^{-1})	g (day^{-1})	c (day^{-1})
Fixed-effect μ	27.0 [25.8;28.1]	0.0024 [0.0016;0.0034]	0.0031 [0.0025;0.0037]	0.0018 [0.0008;0.0031]
IPV ω_1	0.25 [0.21;0.29]	1.31 [1.04;1.63]	0.83 [0.63;1.02]	1.36 [0.80;2.14]
ILV ω_2	0.36 [0.33;0.39]	0.69 [0.55;0.86]	0.30 [0.06;0.48]	0.78 [0.24;1.27]
Location effect ξ				
Lymph	-0.24 [-0.28;-0.18]	0.43 [0.18;0.70]	-0.44 [-0.64;-0.23]	1.28 [0.72;2.04]
Lung	-0.18 [-0.24;-0.12]	0.15 [-0.15;0.44]	0.06 [-0.16;0.26]	0.41 [-0.46;1.39]
Liver	0.02 [-0.05;0.08]	-0.31 [-0.65;0.05]	0.62 [0.42;0.82]	-1.56 [-2.46;-0.71]
Bladder	0.40 [0.32;0.48]	-0.28 [-0.73;0.13]	-0.24 [-0.53;0.029]	-0.12 [-2.11;1.07]
Survival Parameters				
γ	1.05 [1.00;1.15]			
λ	1278 [1018;1602]			
β	0.011 [0.009;0.013]			

Chemotherapy arm				
Parameters	TS_0 (mm)	ϵ (day^{-1})	g (day^{-1})	c (day^{-1})
Fixed-effect μ	26.3 [25.1;27.5]	0.0051 [0.0036;0.0071]	0.0021 [0.0018;0.0029]	0.0085 [0.0030;0.016]
IPV ω_1	0.22 [0.17;0.27]	0.98 [0.77;1.22]	0.92 [0.74;1.13]	0.97 [0.66;1.31]
ILV ω_2	0.37 [0.34;0.41]	0.45 [0.30;0.59]	0.32 [0.09;0.51]	0.27 [0.010;0.65]
Location effect ξ				
Lymph	-0.24 [-0.30;-0.19]	0.11 [-0.20;0.41]	-0.42 [-0.76;-0.02]	0.62 [-0.22;1.60]
Lung	-0.22 [-0.28;-0.16]	0.41 [0.09;0.52]	0.10 [-0.19;0.46]	0.91 [0.003;1.98]
Liver	0.06 [-0.0005;0.13]	0.28 [-0.16;0.71]	0.86 [0.58;1.26]	0.99 [-0.19;2.38]
Bladder	0.40 [0.31;0.49]	-0.81 [-1.42;-0.13]	-0.54 [-1.52;-0.013]	-2.52 [-5.63;-0.17]
Survival Parameters				
γ	1.32 [1.15;1.50]			
λ	735 [612;899]			
β	0.012 [0.009;0.014]			