Joint modelling of individual target lesions and survival to characterize the variability in the response to immunotherapy versus chemotherapy in advanced bladder cancer

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Genentech/Roche Clinical Pharmacology & Institut Roche, Boulogne-Billancourt, France

July 1^{st}, 2022

Université Paris Cité

iame UMR 1137 Infection • Antimicrobials • Modelling • Evolution

SPHERE methodS in Patient-centered outcomes & HEalth ResEarch

Inserm La science pour la santé From science to health

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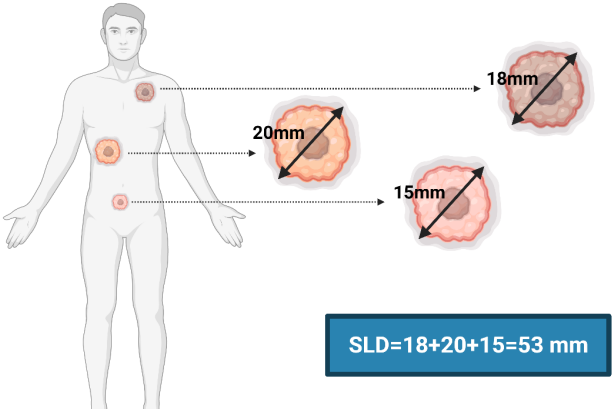
Treatment response evaluation

Tumor burden based on RECIST[1], relies on the Sum of the Longest Diameters (SLD) of the target lesions

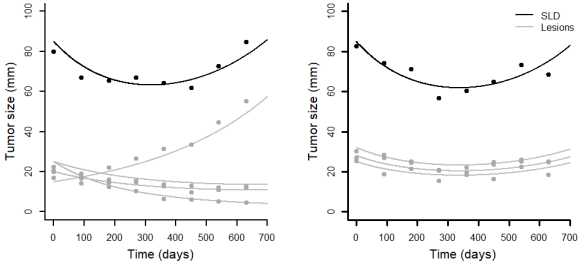


- Up to 5 target lesions within a patient
- Up to 2 target lesions per location

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

SLD limitations

➙ SLD aggregates the information at the patient level



- No distinction across target lesions,

[2] Mercier et al *J Pharmacokinet Pharmacodyn* (2020)
[3] Krishnan et al *CPT Pharmacometrics Syst Pharmacol* (2021)
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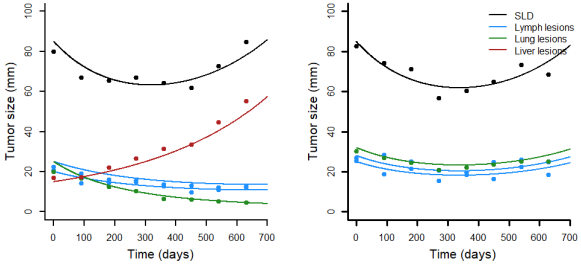

- No distinction across target lesions,
- Intra-patient variability might be partly explained by tumor location, that may impact lesion kinetics [2,3], and association with survival[4].

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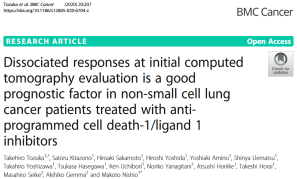
Increased variability in the response to immunotherapy treatments?

- Several studies reported the occurrence of Dissociated Responses (DR) to treatment[5,6,7,8,9]


Tozuka et al. BMC Cancer (2020) 20:207
https://doi.org/10.1186/s12885-020-6709-x

BMC Cancer

RESEARCH ARTICLE Open Access

Dissociated responses at initial computed tomography evaluation is a good prognostic factor in non-small cell lung cancer patients treated with anti-programmed cell death-1/ligand 1 inhibitors

Takehiro Tozuka[1,2], Satoru Kitazono[1], Hiroaki Sakamoto[1], Hiroshi Yoshida[1], Yoshiaki Amino[1], Shinya Uematsu[1], Takahiro Yoshizawa[1], Tsukasa Hasegawa[1], Ken Uchibori[1], Noriko Yanagitani[1], Atsushi Horiike[1], Takeshi Hora[2], Masahiro Seike[2], Akihiko Gemma[2] and Makoto Nishio[1*]


Drugs in R&D (2021) 21:399–406
https://doi.org/10.1007/s40268-021-00362-3

ORIGINAL RESEARCH ARTICLE

Dissociated Responses in Patients with Metastatic Solid Tumors Treated with Immunotherapy

Pauline Vaflard[1] · Xavier Paoletti[2,3] · Vincent Servois[4] · Patricia Tresca[1] · Elvire Pons-Tostivint[5] · Marie-Paule Sablin[1] · Francesco Ricci[1] · Delphine Loirat[1] · Ségolène Hescot[1] · Nouritza Torossian[1] · Diana Bello Roufai[1] · Maud Kamal[1] · Edith Borcoman[1] · Christophe Le Tourneau[1,3,4]


frontiers in Oncology

PERSPECTIVE
published: 16 September 2021
doi: 10.3389/fonc.2021.686297

Dissociated Response in Metastatic Cancer: An Atypical Pattern Brought Into the Spotlight With Immunotherapy

Olivier Humbert[1,2*] and David Chardin[1,2]

[1] Department of Nuclear Medicine, Centre Antoine-Lacassagne, Université Côte d'Azur, Nice, France, [2] IRCI-LIMPE EA 4320, Université Côte d'Azur, Nice, France

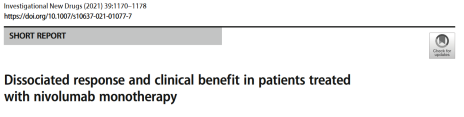

cancers

MDPI

Article

Organ-Specific and Mixed Responses to Pembrolizumab in Patients with Unresectable or Metastatic Urothelial Carcinoma: A Multicenter Retrospective Study

Takuto Shimizu [1], Makito Miyake [1,*], Nobutaka Nishimura [1], Kuniaki Inoue [1], Koyo Fujii [1], Yusuke Iemura [1], Kazuki Ichikawa [1], Chihiro Omori [1], Mitsuru Tomizawa [1], Fumisato Maesaka [1], Yuki Oda [1], Tatsuki Miyamoto [1], Koichi Sakamoto [1], Keisuke Kiba [1], Masahiro Tanaka [1], Nobuo Oyama [1], Eijiro Okajima [1], Ken Fujimoto [1], Shunta Hori [1], Yosuke Morizawa [1], Daisuke Gotoh [1], Yasushi Nakai [1], Kazumasa Torimoto [1], Nobumichi Tanaka [1] and Kiyohide Fujimoto [1] on behalf of the Nara Urological Research and Treatment Group [†]


Investigational New Drugs (2021) 39:1170–1178
https://doi.org/10.1007/s10637-021-01077-7

SHORT REPORT

Dissociated response and clinical benefit in patients treated with nivolumab monotherapy

Yuki Sato[1] · Takeshi Morimoto[2,3] · Shigeo Hara[4] · Kazuma Nagata[1] · Kazutaka Hosoya[1] · Atsushi Nakagawa[1] · Ryo Tachikawa[1] · Keisuke Tomii[1]

- This phenomenon remains controversial[10]

[5] Humbert et al *Front Oncol* (2020)
[6] Vaflard et al *Drugs R D* (2020)
[7] Shimizu et al *Cancers* (2022)
[8] Tozuka et al *BMC Cancer* (2020)
[9] Sato et al *Invest New Drugs* (2021)
[10] Litière et al *J Clin Oncol* (2019)

Objectives

- To quantify both inter-patient and intra-patient between lesions variability

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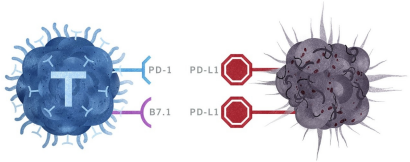
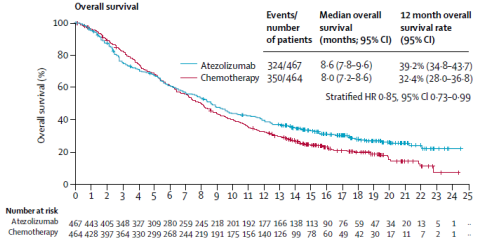
- To compare the intra-patient variability during immunotherapy versus during chemotherapy
- To assess the benefit of target lesions follow-up in predicting the individual treatment outcome

Clinical application

Phase 3 clinical trial IMvigor211[14]**:**

- 931 patients suffering from advanced or metastatic bladder cancer 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 in the intention-to-treat population





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

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

[15] Kerioui et al *ESMO Open* (2022)

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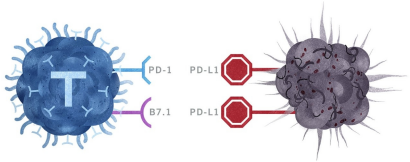

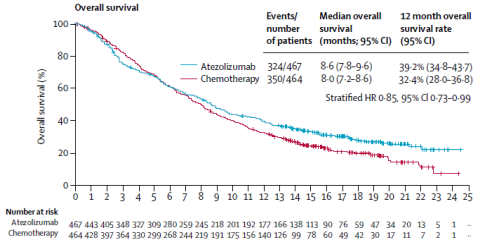

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- Focus on five locations: Lymph nodes, Lung, Liver, Bladder, Other
- Baseline covariates: alkaline phosphatase concentration, hemoglobin concentration, neutrophil-to-lymphocyte ratio and ECOG score[15]

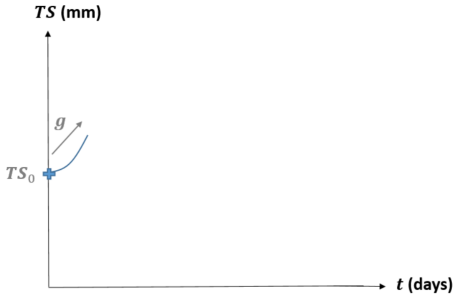
[14] Powles et al *The Lancet* (2018)

[15] Kerioui et al *ESMO Open* (2022)

Semi-mechanistic model for Tumor Size description

Claret simplified Tumor Growth Inhibition (sTGI) model[16]:

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



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- TS_0: baseline sum of longest diameters
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[16] Claret et al *J Clin Oncol* (2013)

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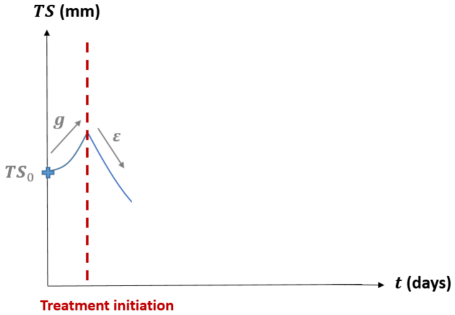

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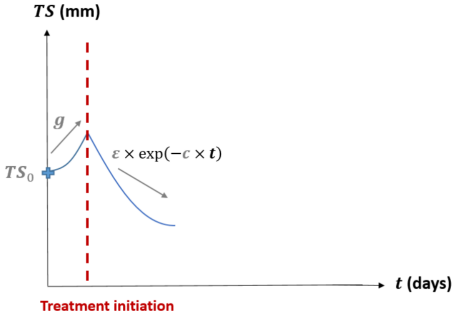

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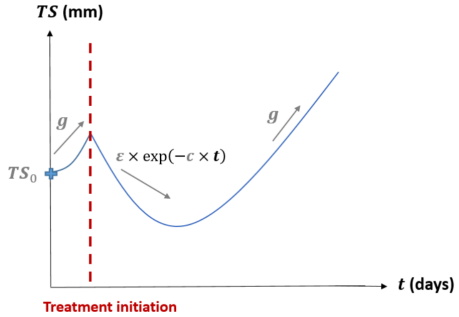

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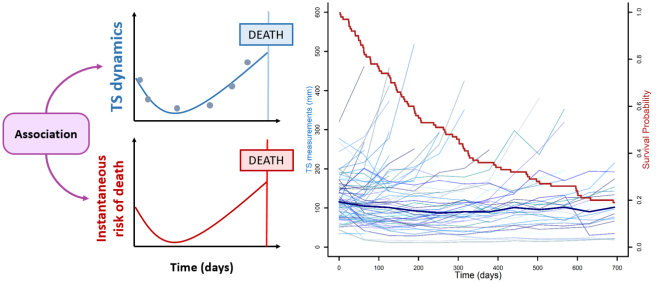
Modelling tumor size and survival

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)
- To account for the bias due to early end of longitudinal follow-up in the most-at-risk patients[17,18]



[17] Desmée et al *AAPS J* (2016)
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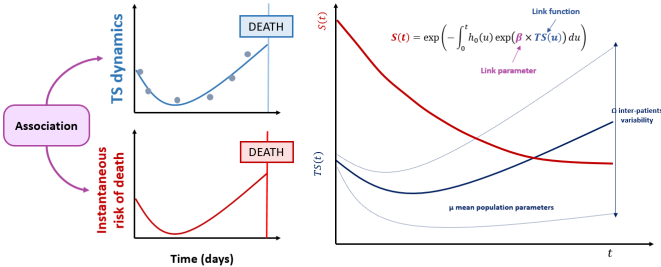
➙ **Nonlinear joint model of Tumor Size dynamics and survival**[19]



[17] Desmée et al *AAPS J* (2016)
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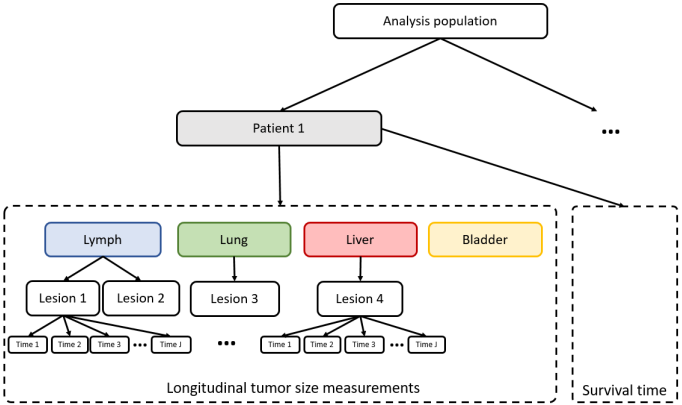
Modelling hierarchical data



[20] Kerioui et al *Stat in Med* (2020)

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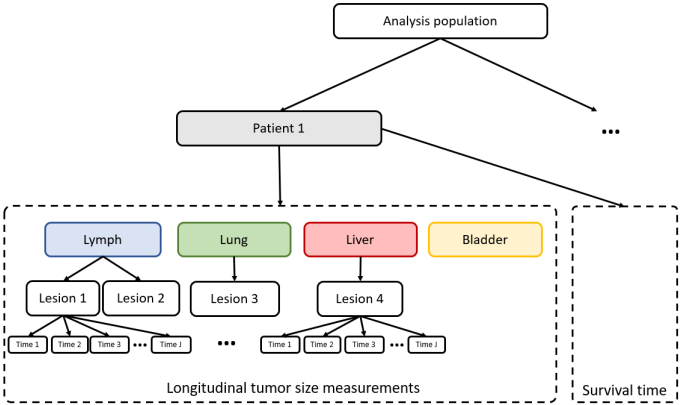


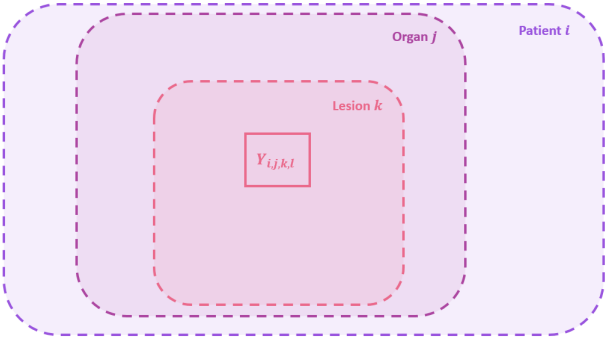
➙ **Bayesian inference** using Hamiltonian Monte-Carlo **(HMC) algorithm** in **Stan software**[20]

[20] Kerioui et al *Stat in Med* (2020)

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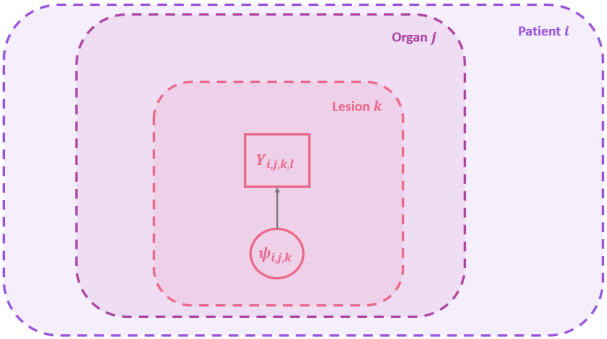
$$\psi_{i,j,k} = \mu \times \exp\left(\xi_j + \eta_i + \rho_{i,j,k}\right) \quad \text{with } \eta_i \sim \mathcal{N}(0, \omega_1^2) \text{ and } \rho_{i,j,k} \sim \mathcal{N}(0, \omega_2^2)$$



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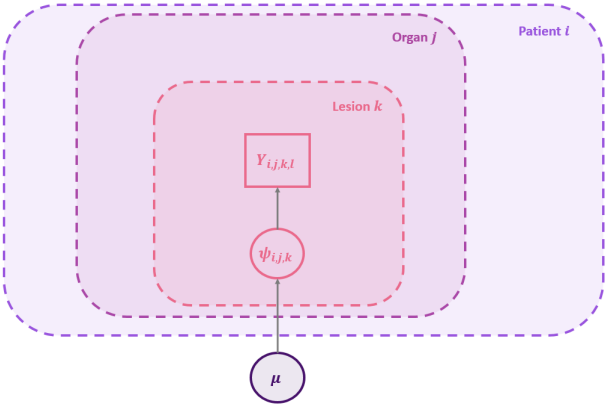

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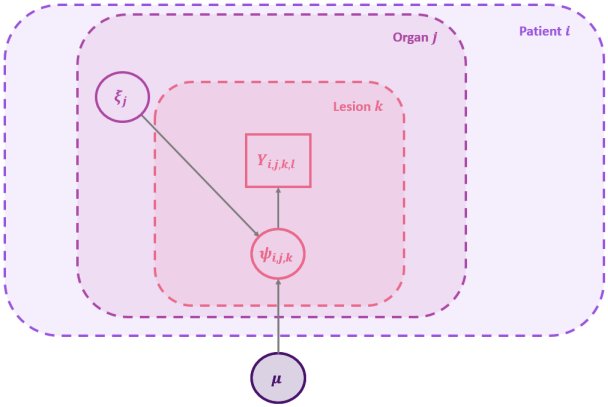

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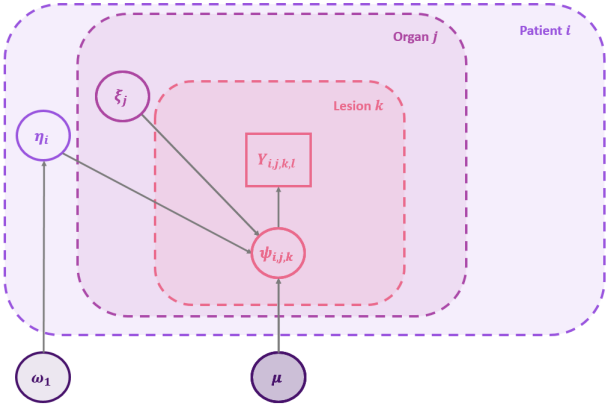

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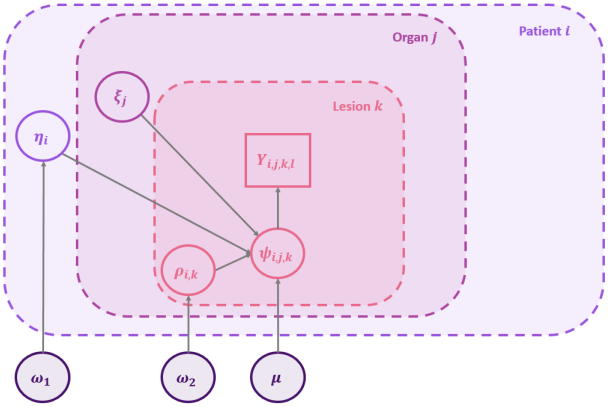

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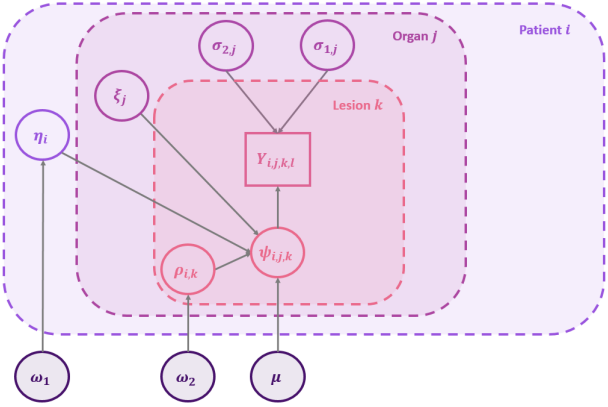

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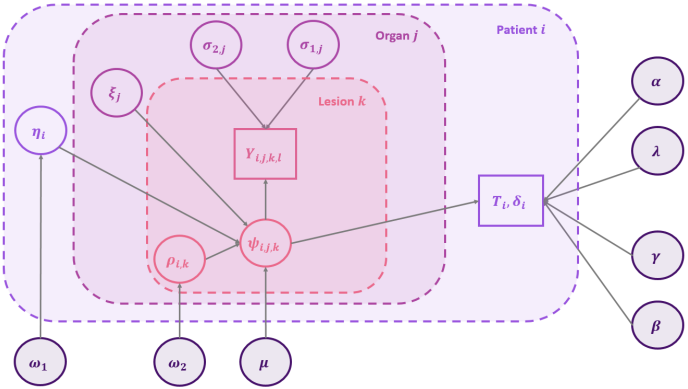
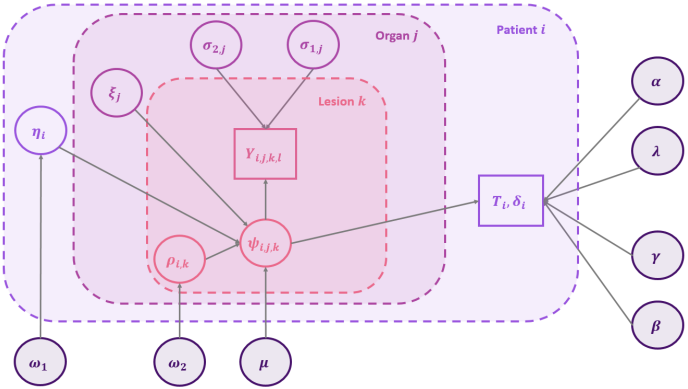
$$h(t, \psi_i) = h_0(t) \times \exp\left(\alpha \times z_i\right) \times \exp\left(\sum_{j=1}^{4} \beta_j \times \sum_{k=1}^{K_{i,j}} TS(t, \psi_{i,j,k})\right) \text{ with } h_0(t) = \frac{\gamma}{\lambda}\left(\frac{t}{\lambda}\right)^{\gamma-1}$$



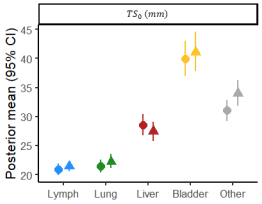
Multilevel joint model

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

➞ Inference in both treatment arms separately



Individual lesion kinetics



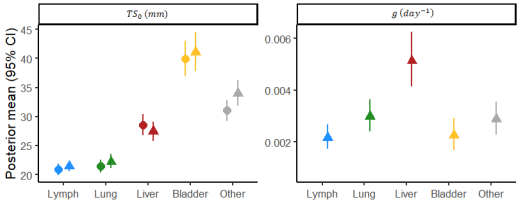
Treatment
- Chemotherapy
- Atezolizumab

Location
- Lymph
- Lung
- Liver
- Bladder
- Other

➙ Regardless of treatment, the lymph nodes and lung lesions were smaller at baseline than the liver and bladder lesions

[1] IPV=Inter-Patient Variability
[2] ILV=Inter-Lesion Variability

Individual lesion kinetics

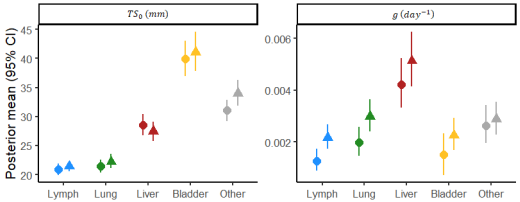


➙ In the atezolizumab arm, the liver lesions natural growth was much faster than in the other locations

[1] IPV=Inter-Patient Variability

[2] ILV=Inter-Lesion Variability

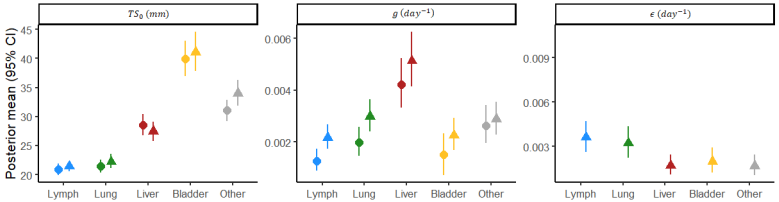
Individual lesion kinetics



→ Tumor regrowth was slightly larger in patients treated with atezolizumab as compared to chemotherapy

[1] IPV=Inter-Patient Variability
[2] ILV=Inter-Lesion Variability

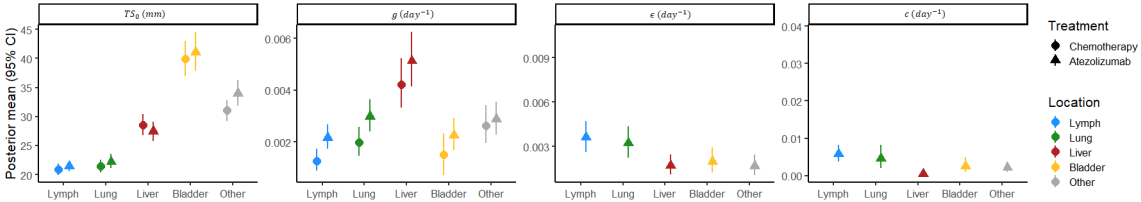
Individual lesion kinetics



➙ The shrinkage of the tumor size was larger in the lymph nodes and the lung lesions than in other location...

[1] IPV=Inter-Patient Variability
[2] ILV=Inter-Lesion Variability

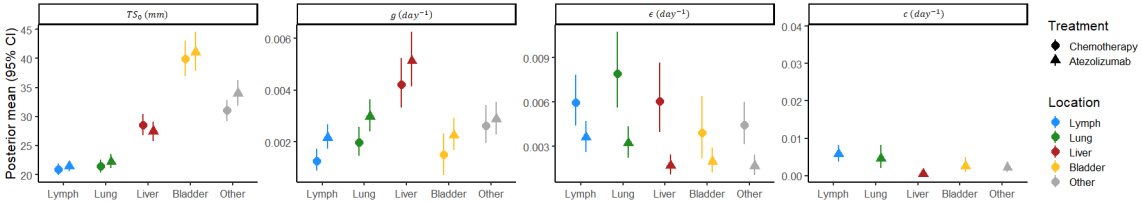
Individual lesion kinetics



→ ... but the durability of the treatment effect was smaller in these locations, as compared to the liver

[1] IPV=Inter-Patient Variability
[2] ILV=Inter-Lesion Variability

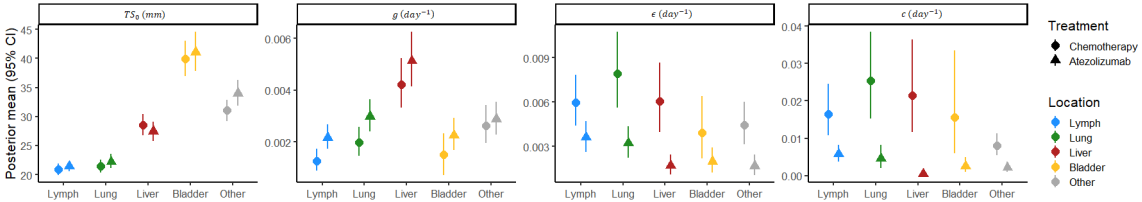
Individual lesion kinetics



➙ The shrinkage of the tumor size was lower in patients treated by atezolizumab than in the chemotherapy arm, especially in the liver lesions...

[1] IPV=Inter-Patient Variability
[2] ILV=Inter-Lesion Variability

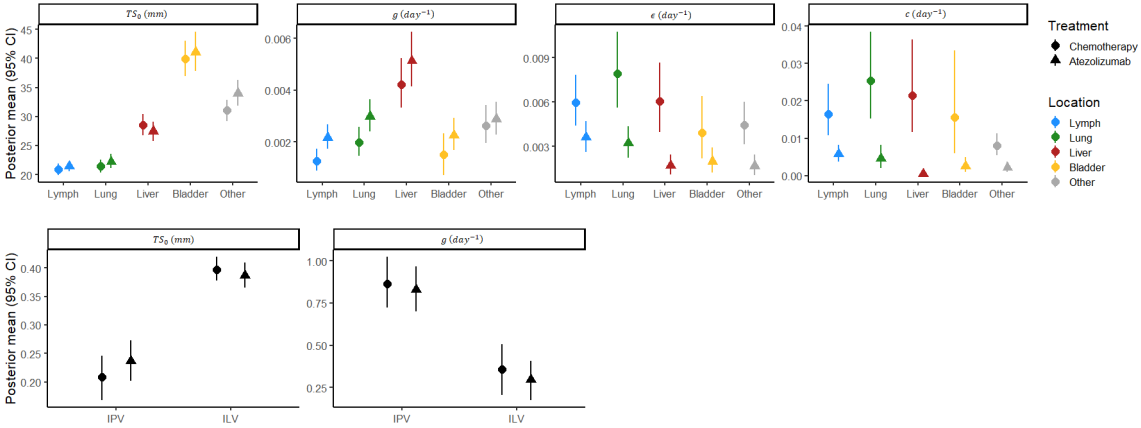
Individual lesion kinetics



→ ... but the duration of the response was longer in patients treated with atezolizumab regardless of tumor location

[1] IPV=Inter-Patient Variability
[2] ILV=Inter-Lesion Variability

Individual lesion kinetics

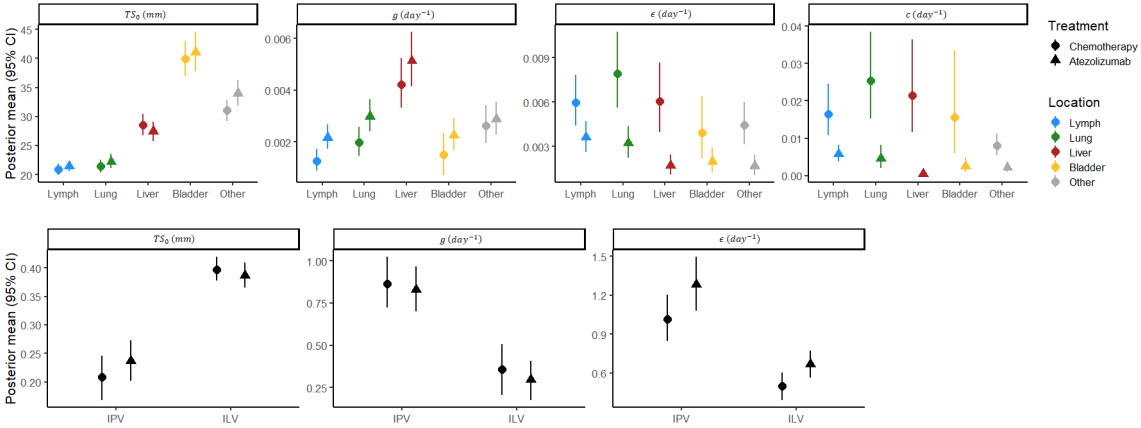


→ Both IPV[1] and ILV[2] were similar during atezolizumab and chemotherapy in the baseline tumor size and in the tumor growth

[1] IPV=Inter-Patient Variability

[2] ILV=Inter-Lesion Variability

Individual lesion kinetics



➙ Both IPV and ILV of the tumor shrinkage parameter were larger in patients treated with atezolizumab than in those receiving chemotherapy

[1] IPV=Inter-Patient Variability
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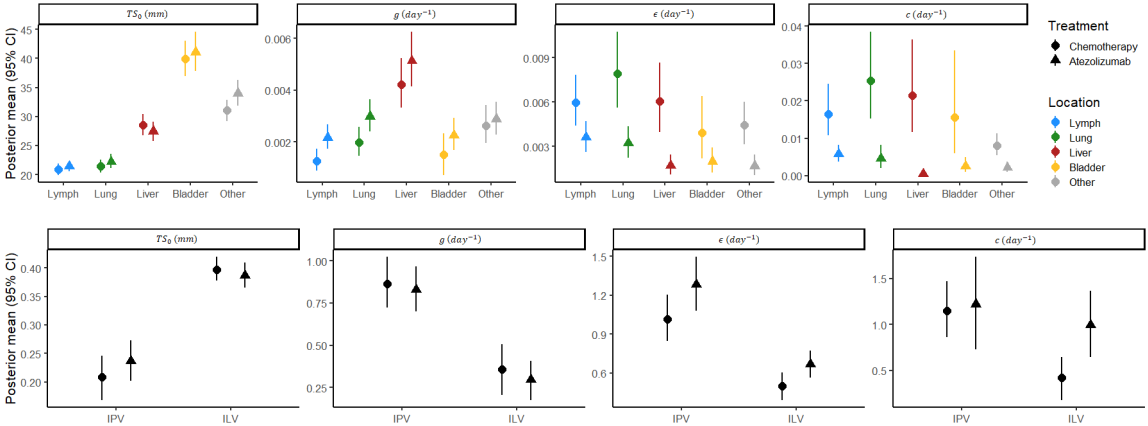
Individual lesion kinetics



→ In the response duration parameter, ILV was twice larger in patients treated with atezolizumab than in those treated with chemotherapy

[1] IPV=Inter-Patient Variability

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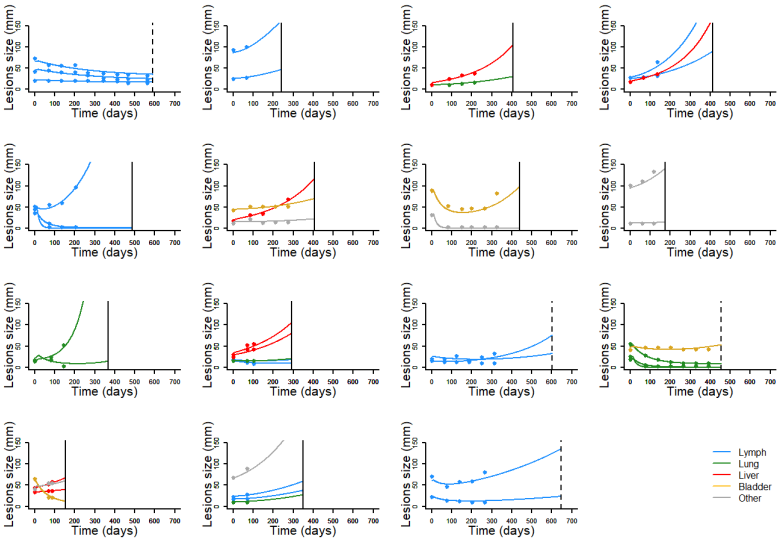
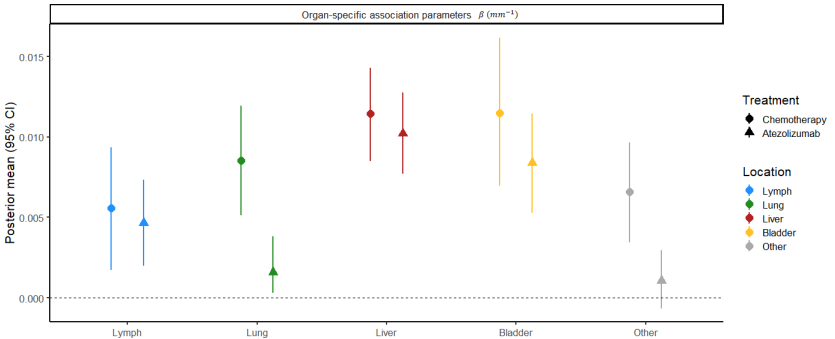
Individual fits of tumor size kinetics

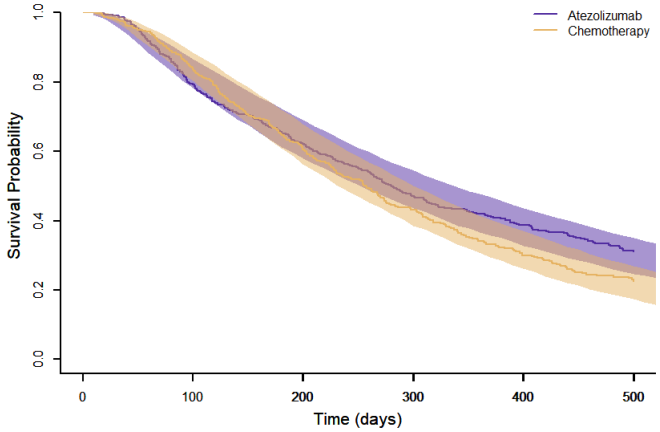


Association between organ tumor burden and survival



➞ The association between lesion dynamics and survival strongly depended on the tumor location, especially in patients treated with atezolizumab

Posterior Predictive Checks of survival curves (based on 1000 replicates)

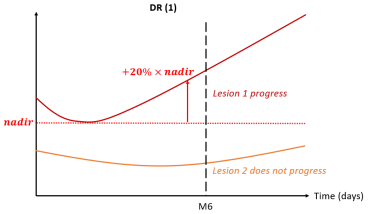


➞ The model was well able to replicate the observed survival curves in both treatment arms

Occurrence of Dissociated Responses (DR)

	6 months		12 months	
	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab
N total	279	294	144	187
>1 lesion	191	209	85	137
DR(1)	41 (21%)	39 (19%)	15 (18%)	27 (20%)

- DR(1) at least one target lesion progressing (+20% from NADIR) and one target lesion without progression



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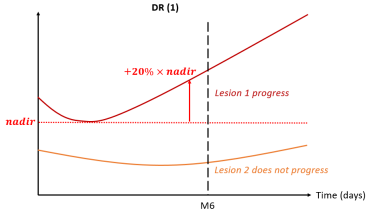
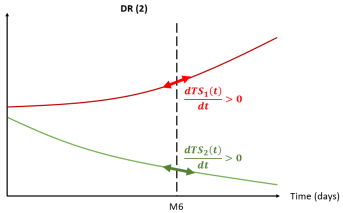
DR(2)	34 (18%)	35 (17%)	6 (7%)	25 (18%)

- DR(1) at least one target lesion progressing (+20% from NADIR) and one target lesion without progression
- DR(2) at least one target lesion with a positive slope ($\frac{dTS(t)}{dt} > 0$) and one target lesion with a negative slope ($\frac{dTS(t)}{dt} < 0$)





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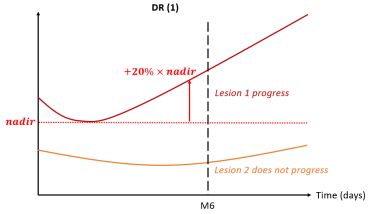
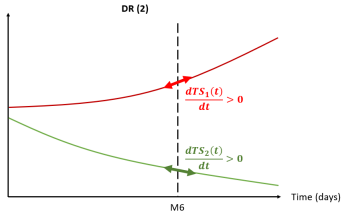
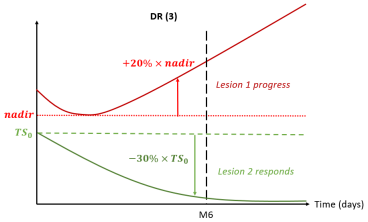
N total	279	294	144	187
>1 lesion	191	209	85	137
DR(1)	41 (21%)	39 (19%)	15 (18%)	27 (20%)
DR(2)	34 (18%)	35 (17%)	6 (7%)	25 (18%)
DR(3)	12 (6%)	15 (7%)	7 (8%)	23 (17%)

- DR(1) at least one target lesion progressing (+20% from NADIR) and one target lesion without progression
- DR(2) at least one target lesion with a positive slope ($\frac{dTS(t)}{dt} > 0$) and one target lesion with a negative slope ($\frac{dTS(t)}{dt} < 0$)
- DR(3) at least one target lesion progressing (+20% from NADIR) and one target lesion responding (-30% from baseline)

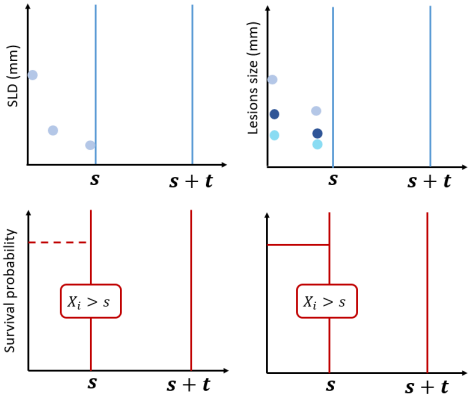






Dynamic predictions

➔ 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[21]



[21] Desmée et al, *BMC Med Res Methodol* (2017)

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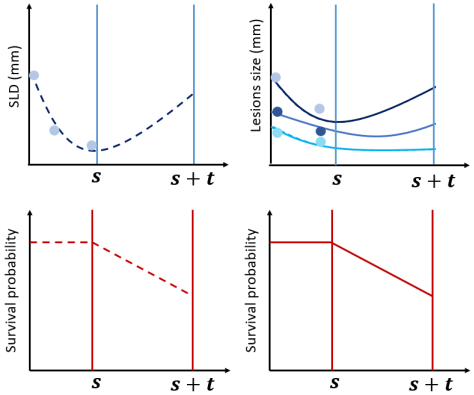

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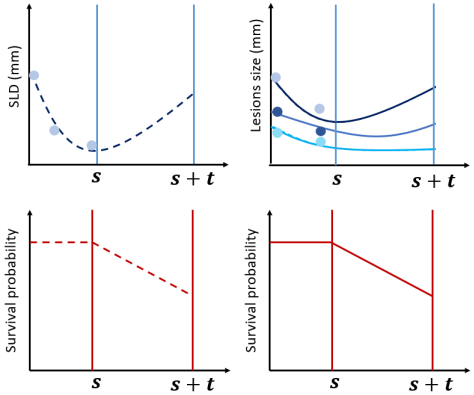

➔ **Area under the ROC curve**[22] to assess the model ability to discriminate between individuals

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

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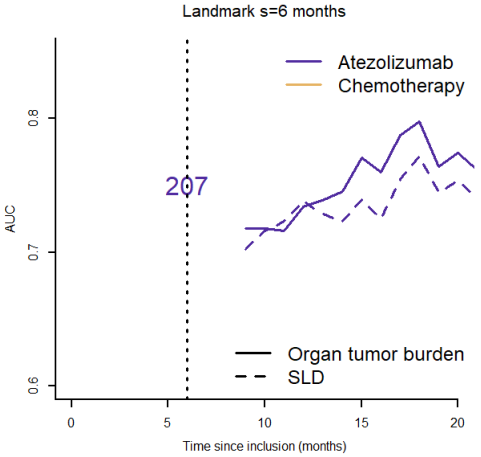
[22] Blanche et al *Stat Med* (2013)

Time-dependent AUC in the subpopulation of patients with more than one target lesion



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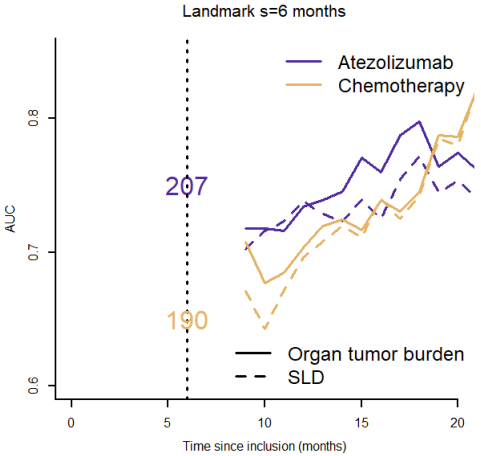

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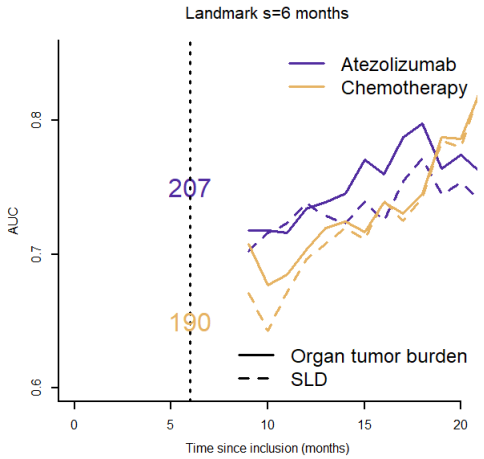

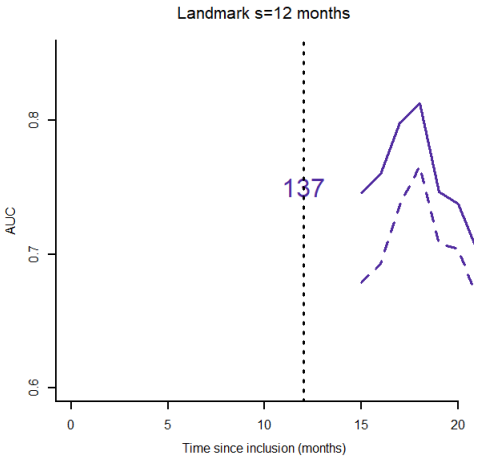

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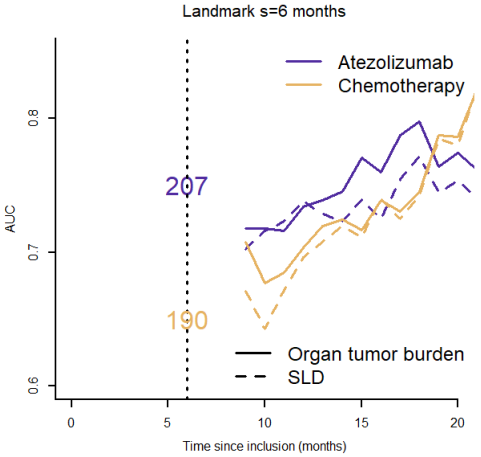
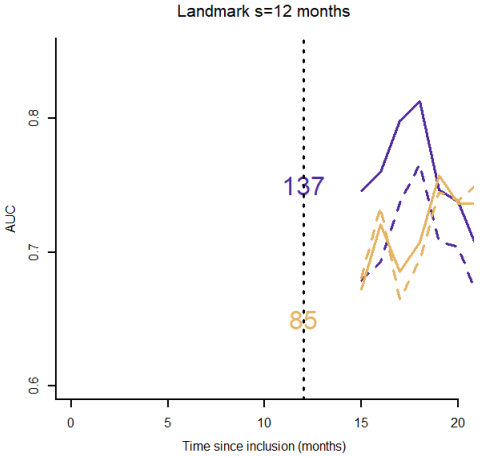
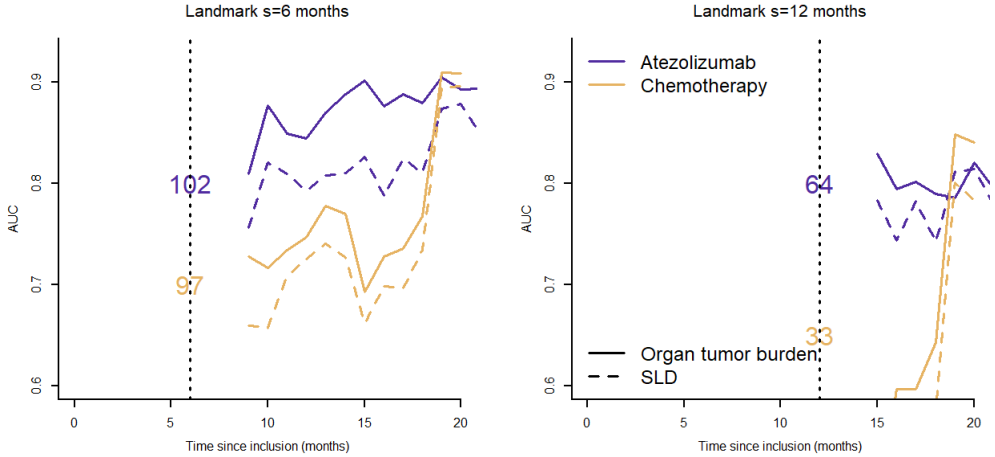




Time-dependent AUC in the subpopulation of patients with liver/bladder lesions



Conclusion

Main results:

- The intra-patient variability in the lesion kinetics parameters represented between 12 and 78% of the total variability
- The intra-patient variability in the durability of the treatment effect was markedly larger during atezolizumab than during chemotherapy (accounting for 40% vs 12% of the total variability respectively)
- Accounting for the intra-patient variability may improve the prediction of death and surpassed a model relying only on SLD, in both treatment arms

[23] Netterberg et al *Clin. Pharmacol. Ther.* (2018)
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Perspectives:

- Integrating immunological measurements[23] or markers to anticipate the durability of response to treatment
- Evaluating whether the occurrence of DR has an impact on the outcome of treatment[24,25]
- Apply this methodology in other cancer types and other treatments

[23] Netterberg et al *Clin. Pharmacol. Ther.* (2018)
[24] Sato et al *Invest New Drugs* (2021)
[25] Shimizu et al *Cancers* (2022)

Thank you for your attention !

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- Julie Bertrand and François Mercier
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