Association between tumor size kinetics and survival in urothelial carcinoma patients treated with atezolizumab: implication for patient's follow-up

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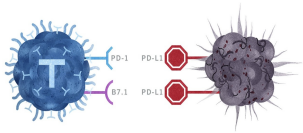
Context

Atezolizumab in metastatic urothelial carcinoma (mUC)

- mUC is the 10^{th} most common form of cancer worldwide [1]
- platinum-based chemotherapy is the standard of care [2]
- poor prognosis for patients progressing after a first line of chemotherapy [3]
- immune-oncology opens a new way in cancer : "Immune checkpoint inhibitors" → **atezolizumab** approved by FDA in 2016 for mUC patients not responding to chemotherapy



Treatment evaluation usually relies on the analysis of both

- overall survival
- response to treatment → guided by the longitudinal evolution of a biomarker (e.g. tumor size with RECIST)

Analyzing a biomarker kinetics can provide a better understanding of survival

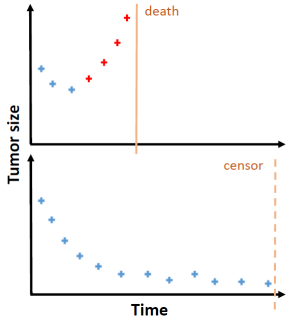
The association between the tumor size dynamics and the survival is particularly complex and remains poorly characterized [4, 5]

1. Bray et al. (2018) CA Cancer J Clin
2. Von der Maase (2005) J Clin Oncol
3. Bellmunt et al. (2009) J Clin Oncol
4. Bellmunt et al. (2017) N Engl J Med
5. Powles et al. (2018) Lancet

Joint models in analyzing the association between tumor size dynamics and overall survival

Introducing a biomarker kinetics as a time-dependent covariate in a survival model can lead to methodological issues

- bias generated by the inclusion of an endogenous covariate → subject to informative censoring [1, 2]
- measurements made with error, and variation over time considered piecewise constant [3]



A proper way to overcome these issues is to use a JOINT MODELING approach

- longitudinal estimation
- survival estimation
- account for the correlation between those two processes

1. Rizopoulos (2012) Joint Models for Longitudinal and Time-to-Event Data
2. Hu and Sale (2003) J Pharmacokinet Pharmacodyn
3. Tsiatis, DeGruttola and Wulfsohn (1995) J Am Stat Assoc

Study Objectives

1. To characterize the association between tumor size kinetics, baseline covariates and overall survival using a nonlinear joint model

2. To evaluate the possibility to characterize "in real time" patient's profile of response and early detect patients most-at-risk of death or progression

Strategy for model building and model validation

PHASE 2 - Learning dataset (N=309)

Nonlinear mixed-effects model to describe tumor size kinetics

- structural model selection
- covariate selection

Parametric model for survival

- covariate selection

↳ **JOINT MODELING**

- link function selection
- Goodness-of-fit assessment

Lancet. 2016 May 7;387(10031):1909-20. doi: 10.1016/S0140-6736(16)00561-4. Epub 2016 Mar 4.

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial.

Rosenberg JE[1], Hoffman-Censits J[2], Powles T[3], van der Heijden MS[4], Balar AV[5], Necchi A[6], Dawson N[7], O'Donnell PH[8], Balmanoukian A[9], Loriot Y[10], Srinivas S[11], Retz MM[12], Grivas P[13], Joseph RW[14], Galsky MD[15], Fleming MT[16], Petrylak DP[17], Perez-Gracia JL[18], Burris HA[19], Castellano D[20], Canil C[21], Bellmunt J[22], Bajorin D[23], Nickles D[24], Bourgon R[24], Frampton GM[25], Cui N[24], Mariathasan S[24], Abidoye O[24], Fine GD[24], Dreicer R[26].

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PHASE 3 - Validation dataset (N=457)

Prediction of overall survival using the joint model selected with the learning dataset

Prediction of survival at individual level

- Dynamic individual predictions

Lancet. 2018 Feb 24;391(10122):748-757. doi: 10.1016/S0140-6736(17)33297-X. Epub 2017 Dec 18.

Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial.

Powles T[1], Durán I[2], van der Heijden MS[3], Loriot Y[4], Vogelzang NJ[5], De Giorgi U[6], Oudard S[7], Retz MM[8], Castellano D[9], Bamias A[10], Fléchon A[11], Gravis G[12], Hussain S[13], Takano T[14], Leng N[15], Kadel EE 3rd[15], Banchereau R[15], Hegde PS[15], Mariathasan S[15], Cui N[15], Shen X[15], Derleth CL[15], Green MC[15], Ravaud A[16].

Baseline characteristics

	Learning dataset PHASE 2	Validation dataset PHASE 3
Number of patients	309	457
Categorical covariates	**% (N)**	
Presence of baseline liver metastasis	31 (95)	30 (136)
Female sex	22 (69)	23 (107)
Baseline ECOG score = 1	62 (192)	53 (242)
≥ 5% of PD-L1 positive immune cells	32 (100)	25 (113)
>1 prior line of systemic therapies in the metastatic setting	52 (162)	29 (133)
>1 metastatic sites at baseline	67 (208)	62 (283)
Previous therapy with platinum-based regimen		
Cisplatin-based	73 (226)	56 (255)
Carboplatin-based	26 (80)	42 (192)
Other platinum combination	1 (3)	2 (9)
≥ 1% of PD-L1 positive tumour cells	20 (61)	27 (123)
Continuous covariates	**Median (min - max)**	
Age	66 (32 - 91)	67 (33 - 88)
Baseline albumin concentration ($g.L^{-1}$)	37 (27 - 49)	39 (20 - 54)
Baseline alkaline phosphatase value ($U.L^{-1}$)	96 (34 - 612)	96 (36 - 1409)
Baseline lactate dehydrogenase value ($U.L^{-1}$)	216.5 (107 - 1642)	221.5 (0.8 - 1603)
Baseline neutrophil-to-lymphocyte ratio	5.6 (1.5 - 69)	3.5 (0.6 - 60)
Baseline C-reactive protein concentration ($mg.L^{-1}$)	26.7 (0.83 - 288)	15.2 (0.21 - 318)
Baseline hemoglobin concentration ($g.L^{-1}$)	109 (85 - 150)	82 (79 - 162)
Baseline sum of target lesions diameters (mm)	64 (10 - 329)	53 (10 - 301)
Median overall survival (days)	243	272

Nonlinear joint models

➔ 2 sub-models

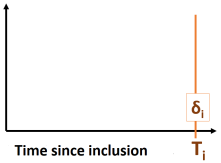
Longitudinal part - Nonlinear mixed-effects model (NLMEM)

$$y_{ij} = b(t_{ij}, \psi_i) + \left(\sigma_{inter} + \sigma_{slope}\, b(t_{ij}, \psi_i)\right) \epsilon_{ij}$$

- b : process of interest (tumor size) **possibly non-linear**
- ψ_i : individual longitudinal parameters as a function of fixed effects μ, random effects $\eta_i \sim \mathcal{N}(0, \Omega)$ and covariates z_i
  $\hookrightarrow$ e.g. log-normal distribution for $\psi_i \Rightarrow \psi_i = \mu \times e^{\eta_i + c \cdot z_i}$
- ϵ_{ij} : residual error with $\epsilon_{ij} \sim \mathcal{N}(0, 1)$

Survival part

- T_i : observed event time
- δ_i : event indicator $= \begin{cases} 1 & \text{if event observed} \\ 0 & \text{if event not observed} \end{cases}$



Hazard function for patient i : $\quad h_i(t|\psi_i) = h_0(t) \exp(\beta \times \boldsymbol{f}(t, \psi_i)) \quad$ for $t \geq 0$

$$\hookrightarrow S_i(t|\psi_i) = P(T_i \geq t) = \exp\left[-\int_0^t h_i(u|\psi_i)\, du\right]$$

- Link function $\boldsymbol{f}$ depends on $\boldsymbol{\psi_i}$

Longitudinal sub-model

Longitudinal part

- **Structural model selection by BIC**

Wang model [1]

$$SLD(t) = \begin{cases} BSLD\, e^{g\, t} & \text{if } t < tx \\ BSLD\, e^{g\, tx} \cdot (e^{-d(t-tx)+g \cdot tx} + g(t-tx)) & \text{if } t \geq tx \end{cases}$$

Stein-Fojo model [2]

$$SLD(t) = \begin{cases} BSLD\, e^{g\, t} & \text{if } t < tx \\ BSLD\, e^{g\, tx} \cdot (e^{-d(t-tx)} + e^{g(t-tx)} - 1) & \text{if } t \geq tx \end{cases}$$

Tumor size model with parameter ϕ for proportion of cells sensitive to treatment [3]

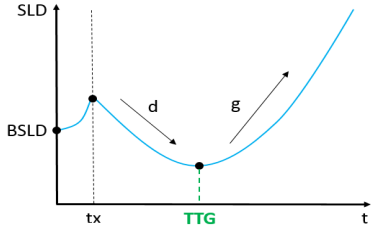
$$SLD(t) = \begin{cases} BSLD\, e^{g\, t} & \text{if } t < tx \\ BSLD\, e^{g\, tx} \times (\phi e^{-d(t-tx)} + (1-\phi) e^{g(t-tx)}) & \text{if } t \geq tx \end{cases}$$

1. Wang et al. (2009) Clin Pharmacol Ther
2. Stein et al. (2008) Oncologist
3. Chatterjee et al. (2017) CPT Pharmacomet Syst Pharmacol

Longitudinal sub-model

Longitudinal part

- **Structural model selection by BIC**



t : time since inclusion (days)
tx : time elapsed between inclusion and treatment onset

SLD : Sum of target lesions diameters (mm)
BSLD : SLD at inclusion time (mm)
d : tumor shrinkage parameter
g : tumor growth parameter

Tumor size model with parameter ϕ for proportion of cells sensitive to treatment [1]

$$SLD(t) = \begin{cases} BSLD\, e^{g\, t} & \text{if } t < tx \\ BSLD\, e^{g\, tx} \times (\phi e^{-d(t-tx)} + (1-\phi) e^{g(t-tx)}) & \text{if } t \geq tx \end{cases}$$

$$\Rightarrow \textbf{TTG} = \frac{\log\left(\frac{d\phi}{g(1-\phi)}\right)}{g+d} + tx$$

- **Forward covariate selection by BIC**

1. Chatterjee et al. (2017) CPT Pharmacomet Syst Pharmacol

Survival sub-model and link function selection

Survival part

$$h_i(t|\psi_i) = h_0(t)\exp(\gamma^T z_i + \beta^T f(t,\psi_i))$$

Weibull baseline hazard function $h_0(t) = \frac{k}{\lambda}\left(\frac{t}{\lambda}\right)^{k-1}$

Forward covariate selection by BIC : z_i

Link function f depends on SLD kinetics of patient i through the true longitudinal process

$\Rightarrow$ Forward selection by BIC :

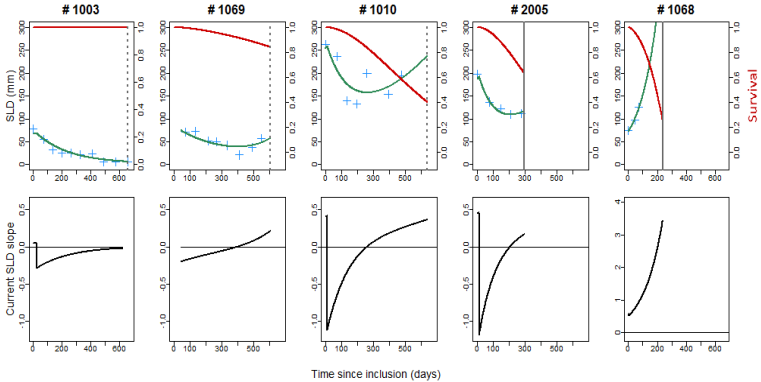
- Baseline covariates : $f(t,\psi_i) = 0$
- Current SLD : $f(t,\psi_i) = SLD(t,\psi_i)$
- Current SLD slope : $f(t,\psi_i) = \frac{d\,SLD(t,\psi_i)}{dt}, t \geq tx_i$
- Time-to-growth (TTG) : $f(t,\psi_i) = \frac{\log\left(\frac{d_i\phi_i}{g_i(1-\phi_i)}\right)}{g_i+d_i} + tx_i$

Joint model results

BIC and parameters estimates (R.S.E. (%)) of tumor size kinetics and survival

MODELS	Baseline covariates	Current SLD	Current SLD slope	TTG	TTG and current SLD slope
BIC	**12525**	12463	12456	12442	**12416**
LONGITUDINAL SUB-MODEL					
BSLD (mm)	53.7 (4)	53.6 (4)	53.4 (4)	53.8 (4)	53.5 (4)
Presence of baseline liver metastasis	0.47 (16)	0.47 (16)	0.47 (16)	0.47 (16)	0.47 (16)
Hemoglobin at baseline ($g.L^{-1}$)	-0.01 (20)	-0.01 (29)	-0.01 (20)	-0.01 (20)	-0.01 (20)
d (day^{-1})	0.00667 (18)	0.00675 (17)	0.00669 (17)	0.00923 (13)	0.00881 (14)
g (day^{-1})	0.0012 (17)	0.0013 (17)	0.0015 (17)	0.0011 (16)	0.0013 (17)
Presence of baseline liver metastasis	0.917 (23)	0.965 (23)	0.873 (23)	0.936 (22)	0.901 (23)
ϕ	0.104 (53)	0.089 (53)	0.104 (49)	0.0352 (53)	0.0421 (59)
Alkaline phosphatase at baseline ($U.L^{-1}$)	-0.0283 (28)	-0.0285 (27)	-0.0281 (26)	-0.0273 (23)	-0.0268 (29)
SURVIVAL SUB-MODEL					
λ (day^{-1})	546 (15)	922 (18)	733 (16)	288 (14)	368 (15)
$\geq$ 5% of PD-L1-positive immune cells	-0.59 (26)	-0.51 (32)	-0.57 (31)	-0.32 (53)	-0.34 (53)
Baseline ECOG score = 1	0.604 (26)	0.57 (30)	0.72 (25)	0.36 (46)	0.453 (40)
Alkaline phosphatase at baseline ($U.L^{-1}$)	0.0038 (17)	0.0027 (26)	0.0039 (19)	0.0034 (20)	0.0036 (21)
Baseline neutrophil-to-lymphocyte ratio	0.0503 (17)	0.055 (17)	0.053 (20)	0.0496 (20)	0.0509 (21)
Hemoglobin at baseline ($g.L^{-1}$)	-0.0131 (34)	-0.0105 (47)	-0.0124 (41)	-0.0152 (31)	-0.0145 (35)
$>$ 1 metastatic sites at baseline	0.41 (39)	0.22 (81)	0.38 (49)	0.35 (50)	0.30 (62)
k	1.2 (5)	1.19 (4)	1.31 (4)	1.45 (6)	1.5 (5)
$\beta_{\text{current SLD}}$ (mm^{-1})	-	0.00732 (15)	-	-	-
β_{TTG} (day^{-1})	-	-	-	-0.00758 (17)	**-0.0064** (20)
$\beta_{\text{current SLD slope}}$ (mm^{-1}.day)	-	-	1.1 (10)	-	**0.697** (13)

Model illustration



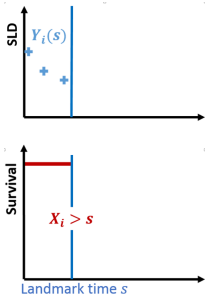
- $\beta_{\text{TTG}} < 0 \Rightarrow$ durable response associated with extended OS
- $\beta_{\text{current SLD slope}} > 0 \Rightarrow$ instantaneous response to treatment (i.e. pace of tumor growth during relapse) directly related to OS

$\Rightarrow$ need to rapidly identify the time of tumor relapse in order to minimize the time window where the tumor will grow

Dynamic predictions of a new individual [1, 2, 3]

- Landmark time s
- Horizon time window t

Assumption : *true* joint model is known
➔ *Population parameters used as priors*



1. Rizopoulos (2011) Biometrics
2. Rizopoulos (2012) Joint Models for Longitudinal and Time-to-Event Data
3. Desmée et al. (2017) BMC Med Res Methodol

Dynamic predictions of a new individual [1, 2, 3]

➔ Predict $S_i(s+t|s) = \mathbb{P}(X_i > s+t | X_i > s, \mathscr{Y}_i(s))$ the conditional survival probability up to the prediction horizon $s+t$ with $t>0$

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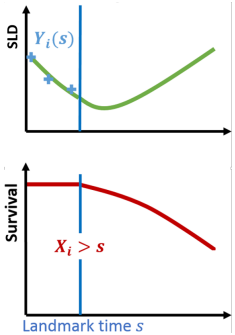

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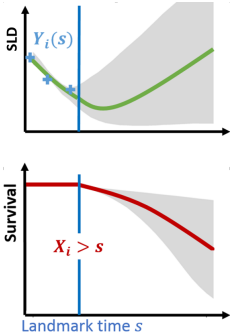
- Landmark time s
- Horizon time window t

Assumption : *true* joint model is known
➔ *Population parameters used as priors*

For $\ell = 1, ..., L$:

1. Draw in the *a posteriori* distribution of the individual parameters $\psi_i^{(\ell)}$
2. Compute $S_i^{\ell}(s+t|s)$ + 90% credibility interval



1. Rizopoulos (2011) Biometrics
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3. Desmée et al. (2017) BMC Med Res Methodol

Discrimination and calibration metrics [1, 2]

Discrimination - ability of the model to distinguish patients of low and high risk of death

➟ **Area under the ROC curve** (AUC)

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

The higher the better

Discrimination

+

Calibration - ability of the model to predict future events

➟ **Brier score** (BS)

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

The lower the better

1. Blanche et al. (2015) Biometrics
2. Desmée et al. (2017) BMC Med Res Methodol

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2. Desmée et al. (2017) BMC Med Res Methodol

AUC for various landmark and horizon times

95% CI based on the bootstrap percentile method [3]

AUC		Models	Horizon windows (months) t = 3	t = 6	t = 9	t = 12
Landmark times (months)	s = 0	Baseline covariates	0.73 (0.66 - 0.79)	0.76 (0.71 - 0.81)	0.75 (0.71 - 0.80)	0.73 (0.68 - 0.77)
		Current SLD	0.75 (0.69 - 0.81)	0.79 (0.74 - 0.83)	0.78 (0.73 - 0.82)	0.74 (0.69 - 0.79)
		Current SLD slope	0.74 (0.68 - 0.80)	0.79 (0.74 - 0.83)	0.77 (0.73 - 0.81)	0.74 (0.69 - 0.78)
		TTG	0.75 (0.69 - 0.81)	0.78 (0.73 - 0.82)	0.76 (0.71 - 0.80)	0.74 (0.69 - 0.78)
		TTG + Current SLD slope	**0.76 (0.71 - 0.82)**	**0.79 (0.74 - 0.83)**	**0.77 (0.73 - 0.81)**	**0.74 (0.70 - 0.79)**
	s = 3	Baseline covariates	0.75 (0.70 - 0.81)	0.73 (0.67 - 0.78)	0.69 (0.64 - 0.74)	0.70 (0.64 - 0.76)
		Current SLD	0.84 (0.78 - 0.88)	0.80 (0.75 - 0.84)	0.79 (0.74 - 0.83)	0.80 (0.75 - 0.84)
		Current SLD slope	0.84 (0.79 - 0.89)	0.78 (0.73 - 0.83)	0.76 (0.71 - 0.81)	0.78 (0.73 - 0.83)
		TTG	0.79 (0.75 - 0.84)	0.79 (0.74 - 0.83)	0.78 (0.74 - 0.83)	0.78 (0.72 - 0.83)
		TTG + Current SLD slope	**0.84 (0.79 - 0.89)**	**0.81 (0.77 - 0.85)**	**0.81 (0.77 - 0.85)**	**0.82 (0.77 - 0.86)**
	s = 6	Baseline covariates	0.65 (0.58 - 0.72)	0.62 (0.56 - 0.69)	0.64 (0.57 - 0.71)	0.65 (0.58 - 0.73)
		Current SLD	0.72 (0.65 - 0.79)	0.74 (0.68 - 0.79)	0.78 (0.72 - 0.83)	0.81 (0.75 - 0.87)
		Current SLD slope	0.69 (0.61 - 0.76)	0.70 (0.64 - 0.76)	0.74 (0.68 - 0.80)	0.76 (0.69 - 0.82)
		TTG	0.75 (0.69 - 0.81)	0.78 (0.72 - 0.83)	0.78 (0.72 - 0.84)	0.83 (0.77 - 0.89)
		TTG + Current SLD slope	**0.75 (0.69 - 0.82)**	**0.79 (0.73 - 0.84)**	**0.80 (0.75 - 0.85)**	**0.84 (0.79 - 0.89)**
	s = 9	Baseline covariates	0.55 (0.45 - 0.65)	0.60 (0.52 - 0.68)	0.63 (0.54 - 0.72)	-
		Current SLD	0.71 (0.62 - 0.79)	0.73 (0.65 - 0.80)	0.79 (0.72 - 0.86)	-
		Current SLD slope	0.67 (0.57 - 0.77)	0.70 (0.61 - 0.77)	0.75 (0.66 - 0.82)	-
		TTG	0.74 (0.67 - 0.81)	0.75 (0.68 - 0.81)	0.82 (0.75 - 0.88)	-
		TTG + Current SLD slope	**0.76 (0.69 - 0.84)**	**0.76 (0.69 - 0.82)**	**0.82 (0.75 - 0.88)**	**-**
	s = 12	Baseline covariates	0.65 (0.53 - 0.75)	0.68 (0.58 - 0.77)	-	-
		Current SLD	0.73 (0.64 - 0.82)	0.82 (0.74 - 0.89)	-	-
		Current SLD slope	0.71 (0.61 - 0.81)	0.76 (0.68 - 0.85)	-	-
		TTG	0.72 (0.62 - 0.82)	0.82 (0.75 - 0.90)	-	-
		TTG + Current SLD slope	**0.73 (0.63 - 0.82)**	**0.82 (0.75 - 0.89)**	**-**	**-**

3. Qin and Hotilovac (2008) Stat Methods Med Res

AUC for various landmark and horizon times

95% CI based on the bootstrap percentile method [3]

AUC		Models	Horizon windows (months) t = 3	t = 6	t = 9	t = 12
Landmark times (months)	s = 0	Baseline covariates	0.73 (0.66 - 0.79)	0.76 (0.71 - 0.81)	0.75 (0.71 - 0.80)	0.73 (0.68 - 0.77)
		Current SLD	0.75 (0.69 - 0.81)	0.79 (0.74 - 0.83)	0.78 (0.73 - 0.82)	0.74 (0.69 - 0.79)
		Current SLD slope	0.74 (0.68 - 0.80)	0.79 (0.74 - 0.83)	0.77 (0.73 - 0.81)	0.74 (0.69 - 0.78)
		TTG	0.75 (0.69 - 0.81)	0.78 (0.73 - 0.82)	0.76 (0.71 - 0.80)	0.74 (0.69 - 0.78)
		TTG + Current SLD slope	**0.76 (0.71 - 0.82)**	**0.79 (0.74 - 0.83)**	**0.77 (0.73 - 0.81)**	**0.74 (0.70 - 0.79)**
	s = 3	Baseline covariates	0.75 (0.70 - 0.81)	0.73 (0.67 - 0.78)	0.69 (0.64 - 0.74)	0.70 (0.64 - 0.76)
		Current SLD	0.84 (0.78 - 0.88)	0.80 (0.75 - 0.84)	0.79 (0.74 - 0.83)	0.80 (0.75 - 0.84)
		Current SLD slope	0.84 (0.79 - 0.89)	0.78 (0.73 - 0.83)	0.76 (0.71 - 0.81)	0.78 (0.73 - 0.83)
		TTG	0.79 (0.75 - 0.84)	0.79 (0.74 - 0.83)	0.78 (0.74 - 0.83)	0.78 (0.72 - 0.83)
		TTG + Current SLD slope	**0.84 (0.79 - 0.89)**	**0.81 (0.77 - 0.85)**	**0.81 (0.77 - 0.85)**	**0.82 (0.77 - 0.86)**
	s = 6	Baseline covariates	0.65 (0.58 - 0.72)	0.62 (0.56 - 0.69)	0.64 (0.57 - 0.71)	0.65 (0.58 - 0.73)
		Current SLD	0.72 (0.65 - 0.79)	0.74 (0.68 - 0.79)	0.78 (0.72 - 0.83)	0.81 (0.75 - 0.87)
		Current SLD slope	0.69 (0.61 - 0.76)	0.70 (0.64 - 0.76)	0.74 (0.68 - 0.80)	0.76 (0.69 - 0.82)
		TTG	0.75 (0.69 - 0.81)	0.78 (0.72 - 0.83)	0.78 (0.72 - 0.84)	0.83 (0.77 - 0.89)
		TTG + Current SLD slope	**0.75 (0.69 - 0.82)**	**0.79 (0.73 - 0.84)**	**0.80 (0.75 - 0.85)**	**0.84 (0.79 - 0.89)**
	s = 9	Baseline covariates	0.55 (0.45 - 0.65)	0.60 (0.52 - 0.68)	0.63 (0.54 - 0.72)	-
		Current SLD	0.71 (0.62 - 0.79)	0.73 (0.65 - 0.80)	0.79 (0.72 - 0.86)	-
		Current SLD slope	0.67 (0.57 - 0.77)	0.70 (0.61 - 0.77)	0.75 (0.66 - 0.82)	-
		TTG	0.74 (0.67 - 0.81)	0.75 (0.68 - 0.81)	0.82 (0.75 - 0.88)	-
		TTG + Current SLD slope	**0.76 (0.69 - 0.84)**	**0.76 (0.69 - 0.82)**	**0.82 (0.75 - 0.88)**	**-**
	s = 12	Baseline covariates	0.65 (0.53 - 0.75)	0.68 (0.58 - 0.77)	-	-
		Current SLD	0.73 (0.64 - 0.82)	0.82 (0.74 - 0.89)	-	-
		Current SLD slope	0.71 (0.61 - 0.81)	0.76 (0.68 - 0.85)	-	-
		TTG	0.72 (0.62 - 0.82)	0.82 (0.75 - 0.90)	-	-
		TTG + Current SLD slope	**0.73 (0.63 - 0.82)**	**0.82 (0.75 - 0.89)**	**-**	**-**

3. Qin and Hotilovac (2008) Stat Methods Med Res

AUC for various landmark and horizon times

95% CI based on the bootstrap percentile method [3]

AUC		Models	Horizon windows (months) t = 3	t = 6	t = 9	t = 12
Landmark times (months)	s = 0	Baseline covariates	0.73 (0.66 - 0.79)	0.76 (0.71 - 0.81)	0.75 (0.71 - 0.80)	0.73 (0.68 - 0.77)
		Current SLD	0.75 (0.69 - 0.81)	0.79 (0.74 - 0.83)	0.78 (0.73 - 0.82)	0.74 (0.69 - 0.79)
		Current SLD slope	0.74 (0.68 - 0.80)	0.79 (0.74 - 0.83)	0.77 (0.73 - 0.81)	0.74 (0.69 - 0.78)
		TTG	0.75 (0.69 - 0.81)	0.78 (0.73 - 0.82)	0.76 (0.71 - 0.80)	0.74 (0.69 - 0.78)
		TTG + Current SLD slope	**0.76 (0.71 - 0.82)**	**0.79 (0.74 - 0.83)**	**0.77 (0.73 - 0.81)**	**0.74 (0.70 - 0.79)**
	s = 3	Baseline covariates	0.75 (0.70 - 0.81)	0.73 (0.67 - 0.78)	0.69 (0.64 - 0.74)	0.70 (0.64 - 0.76)
		Current SLD	0.84 (0.78 - 0.88)	0.80 (0.75 - 0.84)	0.79 (0.74 - 0.83)	0.80 (0.75 - 0.84)
		Current SLD slope	0.84 (0.79 - 0.89)	0.78 (0.73 - 0.83)	0.76 (0.71 - 0.81)	0.78 (0.73 - 0.83)
		TTG	0.79 (0.75 - 0.84)	0.79 (0.74 - 0.83)	0.78 (0.74 - 0.83)	0.78 (0.72 - 0.83)
		TTG + Current SLD slope	**0.84 (0.79 - 0.89)**	**0.81 (0.77 - 0.85)**	**0.81 (0.77 - 0.85)**	**0.82 (0.77 - 0.86)**
	s = 6	Baseline covariates	0.65 (0.58 - 0.72)	0.62 (0.56 - 0.69)	0.64 (0.57 - 0.71)	0.65 (0.58 - 0.73)
		Current SLD	0.72 (0.65 - 0.79)	0.74 (0.68 - 0.79)	0.78 (0.72 - 0.83)	0.81 (0.75 - 0.87)
		Current SLD slope	0.69 (0.61 - 0.76)	0.70 (0.64 - 0.76)	0.74 (0.68 - 0.80)	0.76 (0.69 - 0.82)
		TTG	0.75 (0.69 - 0.81)	0.78 (0.72 - 0.83)	0.78 (0.72 - 0.84)	0.83 (0.77 - 0.89)
		TTG + Current SLD slope	**0.75 (0.69 - 0.82)**	**0.79 (0.73 - 0.84)**	**0.80 (0.75 - 0.85)**	**0.84 (0.79 - 0.89)**
	s = 9	Baseline covariates	0.55 (0.45 - 0.65)	0.60 (0.52 - 0.68)	0.63 (0.54 - 0.72)	-
		Current SLD	0.71 (0.62 - 0.79)	0.73 (0.65 - 0.80)	0.79 (0.72 - 0.86)	-
		Current SLD slope	0.67 (0.57 - 0.77)	0.70 (0.61 - 0.77)	0.75 (0.66 - 0.82)	-
		TTG	0.74 (0.67 - 0.81)	0.75 (0.68 - 0.81)	0.82 (0.75 - 0.88)	-
		TTG + Current SLD slope	**0.76 (0.69 - 0.84)**	**0.76 (0.69 - 0.82)**	**0.82 (0.75 - 0.88)**	**-**
	s = 12	Baseline covariates	0.65 (0.53 - 0.75)	0.68 (0.58 - 0.77)	-	-
		Current SLD	0.73 (0.64 - 0.82)	0.82 (0.74 - 0.89)	-	-
		Current SLD slope	0.71 (0.61 - 0.81)	0.76 (0.68 - 0.85)	-	-
		TTG	0.72 (0.62 - 0.82)	0.82 (0.75 - 0.90)	-	-
		TTG + Current SLD slope	**0.73 (0.63 - 0.82)**	**0.82 (0.75 - 0.89)**	**-**	**-**

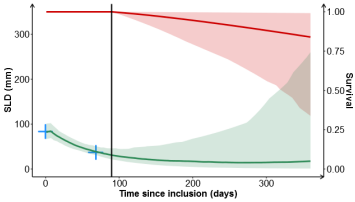
3. Qin and Hotilovac (2008) Stat Methods Med Res

Dynamic individual predictions

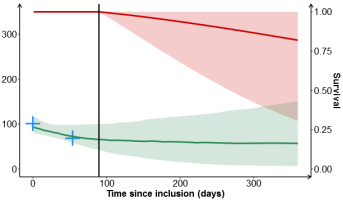
Example on 3 patients alive at 12 months

Landmark s=3 months

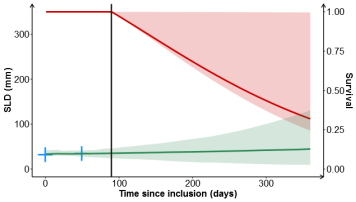
Patient 1305



Patient 3710



Patient 3873

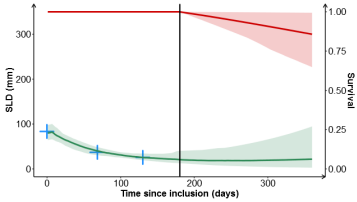


Dynamic individual predictions

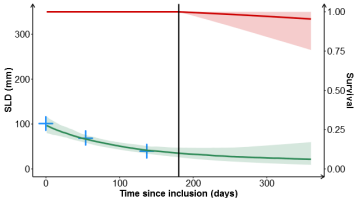
Example on 3 patients alive at 12 months

Landmark s=6 months

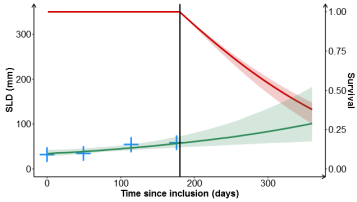
Patient 1305



Patient 3710



Patient 3873

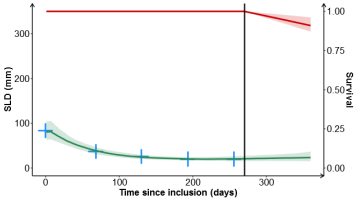


Dynamic individual predictions

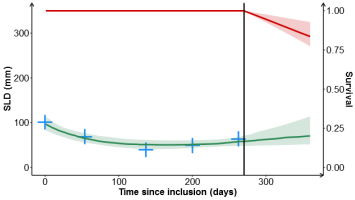
Example on 3 patients alive at 12 months

Landmark s=9 months

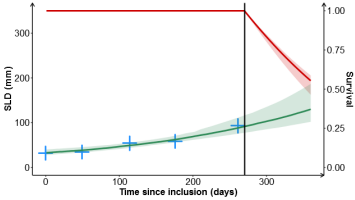
Patient 1305



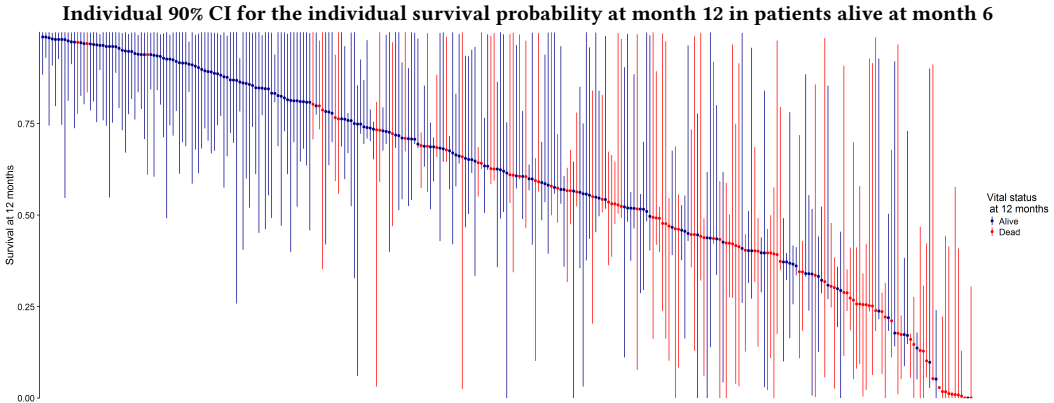
Patient 3710



Patient 3873



Model predictions at the individual level



- Landmark s=6 months
- Horizon s+t=12 months

Conclusion

- We used a **joint modeling approach** to characterize the relationship between
  - tumor size kinetics
  - overall survival
  - baseline covariates

  in mUC patients treated with atezolizumab.

- **Time-to-growth (TTG)** and the **current SLD slope** were identified as the **best kinetic predictors of OS**, in addition to baseline covariates.

- **On-treatment tumor dynamic data** included in a relevant statistical framework may be useful to **identify most-at-risk patients in "real time"**.

- Nonlinear joint models pave the way to **improve prediction** at a **population and individual level**.

Limits / Perspectives

Our approach could be extended to **increase the predictive ability of such models** by including

- clinical events (e.g. our model did not account for other events associated to disease progression, like the apparition of new lesions)
- more frequent data, other longitudinal markers
- PK data to measure the impact of drug exposure on longitudinal kinetics and OS

⇒ This will need the use of more complex and/or more mechanistic models

Acknowledgements

Clin Pharmacol Ther. 2019 Apr 15. doi: 10.1002/cpt.1450. [Epub ahead of print]

Association between tumor size kinetics and survival in urothelial carcinoma patients treated with atezolizumab: implication for patient's follow-up.

Tardivon C[1], Desmée S[2], Kerioui M[1,2], Bruno R[3], Wu B[4], Mentré F[1], Mercier F[5], Guedj J[1].

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Thank you for your attention!