Web-based Supplementary Materials for "Joint Model for Left-Censored Longitudinal Data, Recurrent Events and Terminal Event: Predictive Abilities of Tumor Burden for Cancer Evolution with Application to the FFCD 2000-05 Trial"

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A Bivariate joint models

In the following we adopt the notation and assumptions from the Section 2 of the main manuscript.

Bivariate joint model for recurrent events and a terminal event
In a joint model for recurrent events and a terminal event, for subject i at each rank j we

observe $\{T_{ij}, \delta_{ij}, \delta_i\}$. The model is expressed by [7]:

$$\begin{cases} r_{ij}(t|v_i) = r_0(t)\ \mathrm{e}^{v_i + \boldsymbol{X}_{rij}{}^\top \boldsymbol{\beta}_r} = \mathrm{e}^{v_i} r_{ij}(t) \\ \lambda_i(t|v_i) = \lambda_0(t)\ \mathrm{e}^{\alpha v_i + \boldsymbol{X}_{ti}{}^\top \boldsymbol{\beta}_t} = \mathrm{e}^{\alpha v_i} \lambda_i(t) \end{cases}, \tag{A.1}$$

Shared frailty terms v_i are assumed to be independent of each other. Gamma and normal distributions are the most common distributions adapted for v_i. In order to compare the results of this model to the results of our proposed trivariate model (see Section 2 of the main manuscript), we choose normal distribution, $v_i \sim \mathcal{N}(0, \sigma_v^2)$.

The variance σ_v^2 reflects the population heterogeneity, the intensity of the association between the recurrent events and the terminal event as well as the correlation between the recurrent events of the same subject. Finally, the parameter of association α determines the intensity and the sign of influence of the recurrent events on the terminal event.

In the application (Section 6 of the main manuscript) a recurrent events represents either a tumor progression or an occurrence of new lesions.

Bivariate joint model for recurrent events and a terminal event
Here, for subject i we observe a triplet $\{T_i, \delta_i, \boldsymbol{y}_i\}$ with $\boldsymbol{y}_i = \{y_i(t_{ik}), k = 1, \ldots, n_i\}$, the n_i repeated measurements of a biomarker Y (tumor size metric). The joint model consists of two submodels: a linear mixed-effects model for the longitudinal outcome Y and a proportional hazards model for the terminal event T_i^*, linked via shared random effects [9, 5]:

$$\begin{cases} Y_i(t) = m_i(t) + \epsilon_i(t) = \boldsymbol{X}_{li}(t)^\top \boldsymbol{\beta}_l + \boldsymbol{Z}_i(t)^\top \boldsymbol{b}_i + \epsilon_i(t) \\ \lambda_i(t|\boldsymbol{b}_i) = \lambda_0(t)\ \mathrm{e}^{\boldsymbol{X}_{ti}{}^\top \boldsymbol{\beta}_t + h(\boldsymbol{b}_i, \boldsymbol{\beta}_l, \boldsymbol{Z}_i(t), \boldsymbol{X}_{li}(t))^\top \boldsymbol{\eta}_t} \end{cases} \tag{A.2}$$

The covariates $\boldsymbol{Z}_i(t)$ are associated with the q_1-vector of the random effects parameters $\boldsymbol{b}_i = (b_0, \ldots, b_{q-1})^\top$, and $\epsilon_i(t) \sim \mathcal{N}(0, \sigma_\epsilon^2)$ independent of each other. The random effects $\boldsymbol{b}_i$ are assumed to be normally distributed, $\boldsymbol{b}_i \sim \mathcal{N}(\boldsymbol{0}, \mathbf{B})$ and independent of $\epsilon_i(t)$.

To consider the left-censoring we introduce a threshold s identifying the censored outcomes $\boldsymbol{y}_i^c$ of length n_i^c and the observed ones $\boldsymbol{y}_i^o$ ($n_i = n_i^o + n_i^c$). In the likelihood inference, the individual contribution is the product of the observed outcomes and of the conditional distribution function of the censored outcomes [3].

B Developpement of the likelihood function of the trivariate model

Given the assumption that the submodels of Equation (1) (Section 2.1 of the main manuscript) are independent of each other given $\boldsymbol{u}_i = (\boldsymbol{b}_i, v_i)$, the joint distribution of the

outcomes $\boldsymbol{\xi}_i = \{\boldsymbol{y}_i^o, \boldsymbol{y}_i^c, \boldsymbol{T}_i^r, \boldsymbol{\delta}_i^r, T_i, \delta_i\} = \{\boldsymbol{y}_i, \boldsymbol{T}_i^r, \boldsymbol{\delta}_i^r, T_i, \delta_i\}$ with $\boldsymbol{T}_i^r = \{T_{ij}, j = 1, \ldots, r_i\}$ and $\boldsymbol{\delta}_i^r = \{\delta_{ij}, j = 1, \ldots, r_i\}$ and parameters $\boldsymbol{\theta}$ in calendar timescale, is

$$\begin{aligned} f(\boldsymbol{\xi}_i|\boldsymbol{u}_i;\boldsymbol{\theta}) &= f_{Y|\boldsymbol{u}_i}(\boldsymbol{y}_i|\boldsymbol{b}_i;\boldsymbol{\theta}) f_{T^r|\boldsymbol{u}_i}(\boldsymbol{T}_i^r, \boldsymbol{\delta}_i^r|\boldsymbol{u}_i;\boldsymbol{\theta}) f_{T^t|\boldsymbol{u}_i}(T_i, \delta_i|\boldsymbol{u}_i;\boldsymbol{\theta}) \\ &= \prod_{k=1}^{n_i} \left[f_{Y|\boldsymbol{u}_i}(y_i(t_{ik})|\boldsymbol{b}_i;\boldsymbol{\theta})\right] \prod_{j=1}^{r_i} \left[f_{T^r|u_i}(T_{ij}, \delta_{ij}|\boldsymbol{u}_i;\boldsymbol{\theta})\right] f_{T^t|\boldsymbol{u}_i}(T_i, \delta_i|\boldsymbol{u}_i;\boldsymbol{\theta}), \end{aligned}$$

Let $f_v(\cdot)$ and $f_b(\cdot)$ be density functions of the random effects v_i and $\boldsymbol{b}_i$. The joint marginal likelihood is then

$$\begin{aligned} L_i(\boldsymbol{\theta}) = \int_{v_i} \int_{\boldsymbol{b}_i} \prod_{k=1}^{n_i} f_{Y|\boldsymbol{b}_i}(y_i(t_{ik})|\boldsymbol{b}_i;\boldsymbol{\theta}) \prod_{j=1}^{r_i} f_{T^r|v_i,\boldsymbol{b}_i}(T_{ij}, \delta_{ij}|v_i, \boldsymbol{b}_i;\boldsymbol{\theta}) \\ \times f_{T^t|v_i,\boldsymbol{b}_i}(T_i, \delta_i|v_i, \boldsymbol{b}_i;\boldsymbol{\theta}) f_v(v_i;\boldsymbol{\theta}) f_b(\boldsymbol{b}_i;\boldsymbol{\theta}) \mathrm{d}\boldsymbol{b}_i \mathrm{d}v_i. \end{aligned}$$

The part of the likelihood related to the survival of terminal event, given that $S_i(\cdot)$ is the survival function for subject i, is

$$\begin{aligned} f_{T^t|v_i,\boldsymbol{b}_i}(T_i, \delta_i|v_i, \boldsymbol{b}_i;\boldsymbol{\theta}) &= \left(\lambda_i(T_i|v_i, \boldsymbol{b}_i;\boldsymbol{\theta})\right)^{\delta_i} S_i(T_i|v_i, \boldsymbol{b}_i;\boldsymbol{\theta}) \\ &= \left(\lambda_i(T_i|v_i, \boldsymbol{b}_i;\boldsymbol{\theta})\right)^{\delta_i} \exp(-\int_0^{T_i} \lambda_i(t|v_i, \boldsymbol{b}_i;\boldsymbol{\theta}) \mathrm{d}t). \end{aligned}$$

Similarly, the contribution from the recurrent events to the likelihood, given that $S_{ij}(\cdot)$ is the survival function of the jth event for patient i, is as follows

$$\begin{aligned} f_{T^r|v_i,\boldsymbol{b}_i}(T_{ij}, \delta_{ij}|v_i, \boldsymbol{b}_i;\boldsymbol{\theta}) &= \left(r_{ij}(T_{ij}|v_i, \boldsymbol{b}_i;\boldsymbol{\theta})\right)^{\delta_{ij}} S_{ij}(T_{ij}|v_i, \boldsymbol{b}_i;\boldsymbol{\theta}) \\ &= \left(r_{ij}(T_{ij}|v_i, \boldsymbol{b}_i;\boldsymbol{\theta})\right)^{\delta_{ij}} \exp(-\int_{T_{i(j-1)}}^{T_{ij}} r_{ij}(t|v_i, \boldsymbol{b}_i;\boldsymbol{\theta}) \mathrm{d}t), \end{aligned}$$

with $T_{i0} = 0$.

The conditional distributions of the observed $\boldsymbol{y}_i^o$ and censored $\boldsymbol{y}_i^c$ longitudinal biomarker given the random effects are $\boldsymbol{y}_i^o|\boldsymbol{b}_i \sim \mathcal{N}(\boldsymbol{m}_i^o = \boldsymbol{X}_{li}^{o\top}\boldsymbol{\beta}_l + \boldsymbol{Z}_i^{o\top}\boldsymbol{b}_i, \sigma_\epsilon^2 I_{n_i^o})$ and $\boldsymbol{y}_i^c|\boldsymbol{b}_i \sim \mathcal{N}(\boldsymbol{m}_i^c = \boldsymbol{X}_{li}^{c\top}\boldsymbol{\beta}_1 + \boldsymbol{Z}_i^{c\top}\boldsymbol{b}_i, \sigma_\epsilon^2 I_{n_i^c})$. Therefore, the probability density function of the longitudinal outcome is

$$\begin{aligned} f_{Y|b}(\boldsymbol{y}_i|\boldsymbol{b}_i;\boldsymbol{\theta}) = f_{Y^o|b}(\boldsymbol{y}_i^o|\boldsymbol{b}_i;\boldsymbol{\theta}) \cdot \mathbb{P}(\boldsymbol{y}_i^c \leq s|\boldsymbol{b}_i;\boldsymbol{\theta}) &= \frac{1}{(\sqrt{2\pi\sigma_\epsilon^2})^{n_i^o}} \mathrm{e}^{-\frac{||\boldsymbol{y}_i^o - \boldsymbol{m}_i^o||^2}{2\sigma_\epsilon^2}} \prod_{k=1}^{n_i^c} F_{Y^c|b}(s|\boldsymbol{b}_i;\boldsymbol{\theta}) \\ &= \frac{1}{(\sqrt{2\pi\sigma_\epsilon^2})^{n_i^o}} \mathrm{e}^{-\frac{||\boldsymbol{y}_i^o - \boldsymbol{m}_i^o||^2}{2\sigma_\epsilon^2}} \prod_{k=1}^{n_i^c} \Phi\left(\frac{s - m_i(t_{ik})^c}{\sigma_\epsilon}\right) \end{aligned}$$

where $||\boldsymbol{x}|| = \sqrt{\sum_i x_i^2}$ denotes the Euclidean vector norm and $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution.

Given that $\boldsymbol{u}_i$ follows the multivariate normal distribution $\mathcal{N}(\mathbf{0}, \mathbf{B})$, the individual contribution to the likelihood is

$$\begin{aligned} L_i(\boldsymbol{\theta}) = & \int_{\boldsymbol{u}_i} \frac{1}{(\sqrt{2\pi\sigma_\epsilon^2})^{n_i^o}} \exp\left(-\frac{||\boldsymbol{y}_i^o - \boldsymbol{m}_i^o||^2}{2\sigma_\epsilon^2}\right) \prod_{k=i}^{n_i^c} \Phi\left(\frac{s - m_i(t_{ik})^c}{\sigma_\epsilon}\right) \\ & \times \prod_{j=1}^{r_i} \left[\left(r_{ij}(T_{ij}|v_i, \boldsymbol{b}_i; \boldsymbol{\theta})\right)^{\delta_{ij}} \cdot \exp\left(-\int_{T_{i(j-1)}}^{T_{ij}} r_{ij}(t|v_i, \boldsymbol{b}_i; \boldsymbol{\theta}) \mathrm{d}t\right)\right] \\ & \times \left(\lambda_i(T_i|v_i, \boldsymbol{b}_i; \boldsymbol{\theta})\right)^{\delta_i} \exp\left(-\int_0^{T_i} \lambda_i(t|v_i, \boldsymbol{b}_i; \boldsymbol{\theta}) \mathrm{d}t\right) \\ & \times \frac{1}{(2\pi)^{q/2}} |\mathbf{B}|^{-1/2} \exp\left(-\frac{\boldsymbol{u}_i{}^\top \mathbf{B}^{-1} \boldsymbol{u}_i}{2}\right) \mathrm{d}\boldsymbol{u}_i. \end{aligned}$$

We note that $r_{ij}(t|v_i, \boldsymbol{b}_i) = r_{ij}(t)\mathrm{e}^{v_i + g(\boldsymbol{b}_i, \boldsymbol{\beta}_l, \boldsymbol{Z}_i(t), \boldsymbol{X}_{li}(t)^\top \boldsymbol{\eta}_r}$ and $\lambda_i(t|v_i, \boldsymbol{b}_i) = \lambda_i(t)\mathrm{e}^{\alpha v_i + h(\boldsymbol{b}_i, \boldsymbol{\beta}_l, \boldsymbol{Z}_i(t), \boldsymbol{X}_{li}(t))^\top \boldsymbol{\eta}_t}$. For simplicity, let $g(t) = g(\boldsymbol{b}_i, \boldsymbol{\beta}_l, \boldsymbol{Z}_i(t), \boldsymbol{X}_{li}(t))$ and $h(t) = h(\boldsymbol{b}_i, \boldsymbol{\beta}_l, \boldsymbol{Z}_i(t), \boldsymbol{X}_{li}(t))$. Then, the likelihood can be written as

$$\begin{aligned} L_i(\boldsymbol{\theta}) = & \frac{1}{(\sqrt{2\pi\sigma_\epsilon^2})^{n_i^o}} \left(\lambda_i(T_i)\right)^{\delta_i} \prod_{j=1}^{r_i} \left[\left(r_{ij}(T_{ij})\right)^{\delta_{ij}}\right] \times \int_{\boldsymbol{u}_i} \prod_{k=i}^{n_i^c} \Phi\left(\frac{s - m_i(t_{ik})^c}{\sigma_\epsilon}\right) \exp\left[-\frac{||\boldsymbol{y}_i^o - \boldsymbol{m}_i^o||^2}{2\sigma_\epsilon^2}\right. \\ & \left. -\mathrm{e}^{\alpha v_i} \int_0^{T_i} \lambda_i(t) \mathrm{e}^{h(t)^\top \boldsymbol{\eta}_t} \mathrm{d}t + \delta_i h(T_i)^\top \boldsymbol{\eta}_t\right] \times \prod_{j=1}^{r_i} \exp\left[-\mathrm{e}^{v_i} \int_{T_{i(j-1)}}^{T_{ij}} r_{ij}(t) \mathrm{e}^{g(t)^\top \boldsymbol{\eta}_r} \mathrm{d}t + \delta_{ij} g(T_{ij})^\top \boldsymbol{\eta}_r\right] \\ & \times \mathrm{e}^{(N_i^r(T_i) + \delta_i \alpha) v_i} \frac{1}{(2\pi)^{q/2}} |\mathbf{B}|^{-1/2} \mathrm{e}^{-\frac{\boldsymbol{u}_i{}^\top \mathbf{B}^{-1} \boldsymbol{u}_i}{2}} \mathrm{d}\boldsymbol{u}_i. \end{aligned}$$

where $N_i^r(t)$ is the observed number of recurrent events until time t. The full likelihood is the product of the individual contributions, $L(\boldsymbol{\theta}) = \prod_{i=1}^N L_i(\boldsymbol{\theta})$. The derived formulation of the log-likelihood considers a calendar timescale. However, the trivariate model can be applied using a gap timescale as well. Such a possibility is available using the **R** package **frailtypack** (since version 2.8)[8].

C Results of the simulation study

The results of the simulation study are shown in Table C.1. We compared the standard models (two first columns from the left) with the trivariate model (the 3rd column) that assumes the left-censoring for the outcomes below the threshold s and the trivariate "naïve" model that assigns the limit of detection s for all the longitudinal measurements below it (the last column). For all the models we used the same generated datasets.

Table C.1: Results of the simulation study, 500 simulations, comparison of the trivariate joint model with the standard bivariate joint models and the trivariate "naïve" joint model.

	Standard model Recurrent events & Terminal event			**Standard model** Left-censored biomarker & Terminal event			**Trivariate model** Left-censored biomarker & Recurrent events & Terminal event			**Trivariate model** Biomarker (LOD) & Recurrent events & Terminal event		
	Mean (SE)	ESE	CP	Mean (SE)	ESE	CP	Mean (SE)	ESE	CP	Mean (SE)	ESE	CP
Fixed regression coefficients												
$\beta_0 = 3.0$	-	-	-	2.963 (0.15)	0.13	91.4%	2.993 (0.13)	0.13	96.0%	3.032 (0.12)	0.12	94.2%
$\beta_1 = 0.5$	-	-	-	0.821 (0.79)	0.18	24.0%	0.495 (0.20)	0.18	92.2%	0.472 (0.19)	0.17	92.2%
$\beta_2 = 0.5$	-	-	-	0.528 (0.16)	0.17	96.0%	0.510 (0.16)	0.17	96.6%	0.492 (0.15)	0.16	96.0%
$\beta_3 = 0.5$	0.503 (0.10)	0.09	94.2%	-	-	-	0.504 (0.10)	0.10	94.2%	0.504 (0.10)	0.10	94.2%
$\beta_4 = 0.1$	0.109 (0.20)	0.20	94.8%	0.055 (0.17)	0.14	90.0%	0.111 (0.20)	0.20	95.0%	0.111 (0.20)	0.20	94.8%
Association parameters												
Covariance matrix $\boldsymbol{B}$ *parameters*												
$\sigma_0 = 1.5$	-	-	-	1.496 (0.08)	0.08	94.2%	1.493 (0.08)	0.08	95.0%	1.439 (0.08)	0.08	87.2%
$\sigma_{01} = -0.5$	-	-	-	−0.378 (0.27)	0.10	42.4%	−0.496 (0.14)	0.09	76.6%	−0.452 (0.13)	0.09	78.2%
$\sigma_1 = 0.8$	-	-	-	1.045 (0.16)	0.10	38.0%	0.808 (0.07)	0.06	94.8%	0.771 (0.06)	0.07	89.8%
$\sigma_v = 0.8$	0.827 (0.09)	0.09	91.2%	-	-	-	0.761 (0.09)	0.09	90.8%	0.762 (0.09)	0.09	90.6%
Measurement error parameter												
$\sigma_\epsilon = 1.5$	-	-	-	1.503 (0.02)	0.02	95.0%	1.500 (0.02)	0.02	95.2%	1.454 (0.02)	0.02	45.8%
Link parameters												
$\eta_{r1} = 0.2$	-	-	-	-	-	-	0.191 (0.06)	0.06	94.0%	0.196 (0.07)	0.06	94.4%
$\eta_{r2} = 0.2$	-	-	-	-	-	-	0.185 (0.20)	0.18	88.2%	0.172 (0.21)	0.19	89.2%
$\eta_{t1} = 0.5$	-	-	-	0.272 (0.21)	0.08	41.6%	0.485 (0.17)	0.17	93.6%	0.493 (0.17)	0.17	94.4%
$\eta_{t2} = 0.5$	-	-	-	0.555 (0.98)	0.21	19.6%	0.464 (0.65)	0.57	87.4%	0.410 (0.68)	0.60	88.8%
$\alpha = 2.6$	2.679 (0.39)	0.37	93.0%	-	-	-	2.689 (0.43)	0.41	95.6%	2.695 (0.43)	0.41	95.4%

SE - mean empirical standard error, ESE - mean estimated standard error, CP - coverage probability, LOD - limit of detection
Baseline hazard and survival functions approximated by splines, $Q = 6$, $\kappa_1 = 1.00$, $\kappa_2 = 1.00$

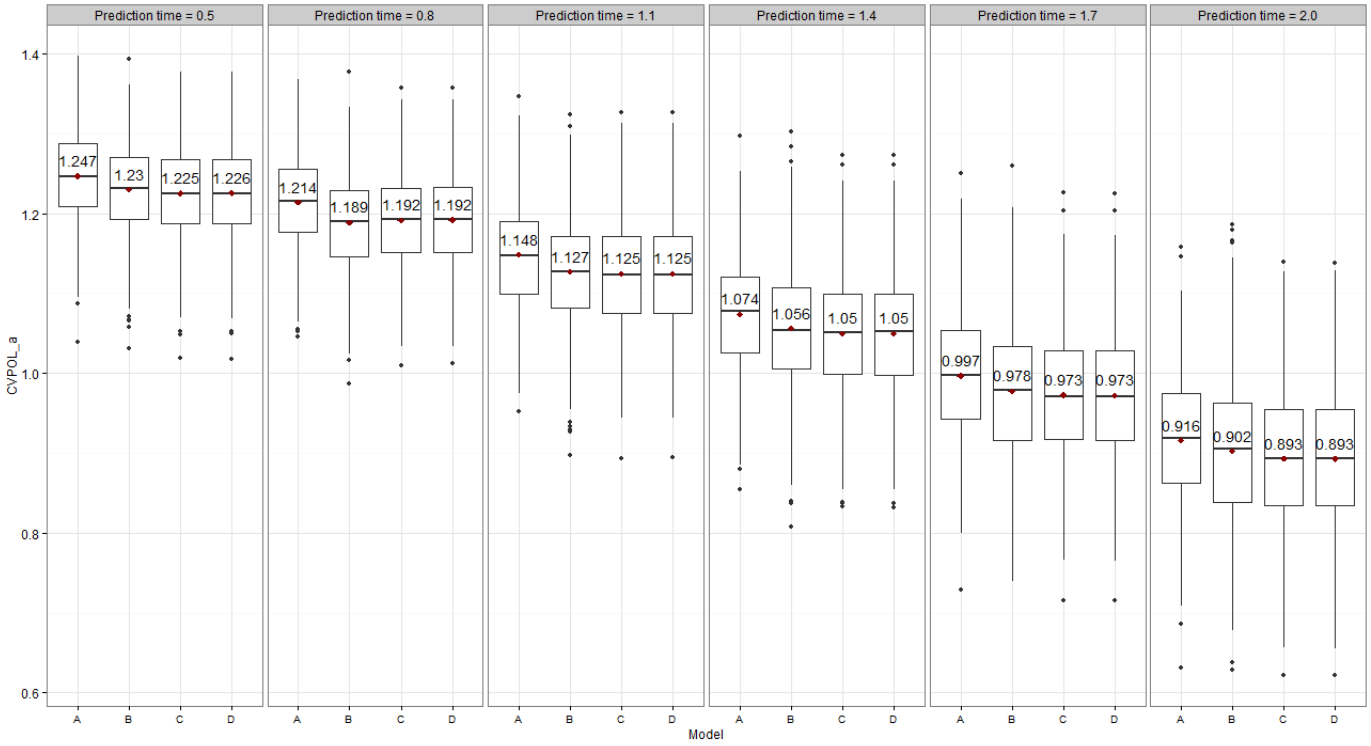

Figure C.1: Boxplots of CVPOL_a for the standard joint models for recurrent events and survival (Model A), for the left-censored biomarker and survival (Model B) and trivariate models with the left-censored biomarker (Model C) and the biomarker with the "limit-of-detection" approach (Model D). The prediction times vary from 0.5 to 2.0.

D FFCD 2000-05 clinical trial supplementary information

D.1 Data characteristics

In the FFCD 2000-05 trial the primary analysis showed better progression-free survival (PFS) after the first-line treatment in the combination (C) arm than in the sequential (S) arm (HR=0.7, 95% CI: $[0.6; 0.9]$), but no significant difference in PFS after introducing the second-line treatment which was the primary endpoint of the trial (HR=1.0, 95%CI: $[0.8; 1.2]$), nor in the OS (HR=1.0, 95% CI: $[0.8; 1.3]$) [2]. In an additional analysis it was found that the risk of repeated progression was not significantly different between the arms (HR=0.9, 95% CI: $[0.8; 1.1]$). Early during the follow-up, the prognostic effect

on survival of progression under the first-line therapy was greater in C arm (HR = 18.0, 95% CI: [7.9; 41.2]) than in S arm (HR = 7.7, 95% CI: [3.9; 17.4]). This difference was significant, but it decreased over time [4]. The risk of toxicities was greater in C arm.

Among 410 patients, 407 started their treatment (204 in S and 203 in C arm), 310 (76%) received the second-line chemotherapy (160 in S and 150 in C arm), and 188 (46%) - the third-line chemotherapy (111 in S and 77 in C arm). However, 402 patients were included in our analysis as 5 patients did not have their measurements of baseline coavariates. Patients enrolled to the trial had to have measurable disease and WHO performance status of 0-2. Previous adjuvant chemotherapy without oxaliplatin was allowed provided that the last administration was given at least 6 months before the randomization.

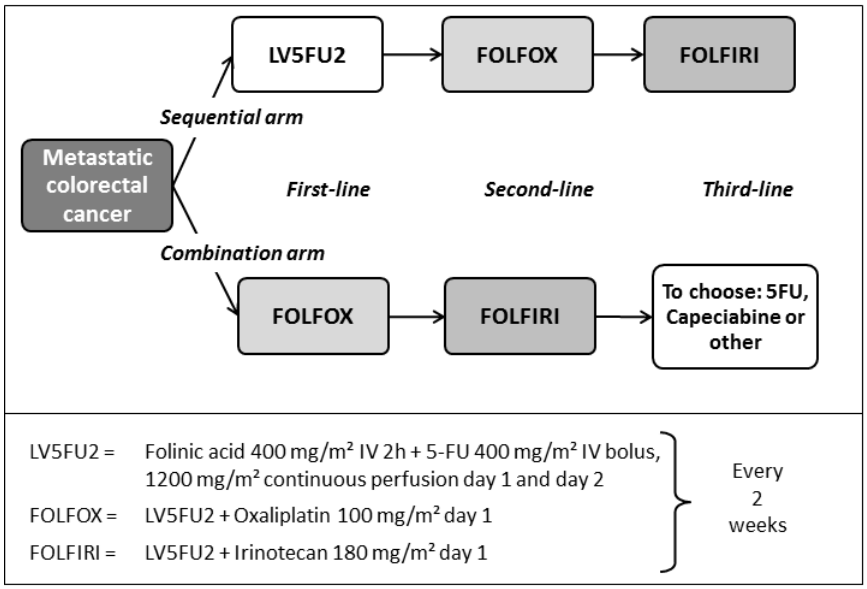

Figure D.1: Therapeutic lines of the clinical trial FFCD 2000-05; the sequential arm for the control group and the combination arm for the experimental group.

Table D.1: Summary of the database FFCD 2000-05 for the sequential and the combination treatment arms.

	Sequential arm	Combination arm	Total
Number of patients	204	203	407
Number of deaths	160	161	321
Av. number of visits per patient	6.14	6.23	6.18
SLD* metric			
Number of all SLD measurements	1253	1264	2517
Number of 'zero' SLD measurements	25	81	106
Av. SLD per patient (cm)	10.33	9.22	9.78
Appearance of new lesions			
Number of observed events	215	211	426
Av. number of new lesions per patient	1.05	1.04	1.05
Tumor progressions according to WHO criteria			
Number of observed events	594	554	1148
Av. number of progressions per patient	1.91	1.73	1.82

* Sum of the longest diameters.

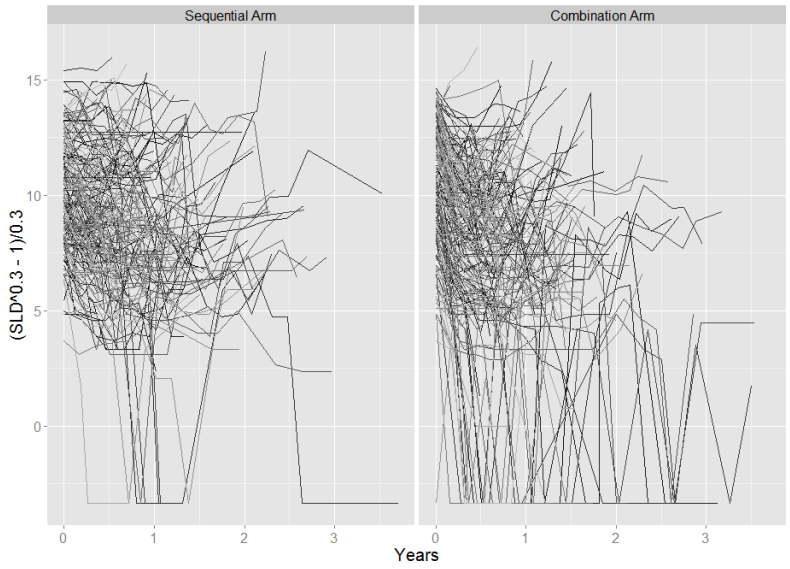

Figure D.2: Subject-specific longitudinal trajectories of the transformed sum of the longest diameters $(\text{SLD}^{0.3} - 1)/0.3$ for the sequential and the combination arm.

Table D.2: Characteristics of baseline covariates used in the joint models for 402 patients included in the models.

		Sequential arm	Combination arm	Total
Age	<60 years	68	64	132
	60-69 years	68	55	123
	≥70 years	65	82	147
Sex	Women	81	74	155
Center size	≥30 patients	55	53	108
	10-30 patients	73	72	146
	<10 patients	73	76	149
WHO PS	Status 0	94	89	183
	Status 1	75	79	154
	Status 2	32	33	65
Previous resection	Yes	131	120	251
Number of metastatic sites	≥ 2 sites	96	97	193
*Tumor localization**	Liver	176	186	362
	Peritoneum	23	39	62
	Abdominal lymph.	36	46	82

* A given patient might have none or several different localizations.

D.2 Sensitivity analysis

To investigate the sensitivity of the trivariate model (Model 4) to the choice of link functions $g(\cdot)$ and $h(\cdot)$ we compared its results with a model in which the link functions were assumed to be the current level of the biomarker $m_i(t)$ (Model 4A). The results of the Model 4A are presented in Table D.3. The estimates of the effects of the covariates are close to the estimates from Model 4 (Table 4 in the main manuscript) with few differences that modified the interpretation. The effect of time on the biomarker was significant in the model with the random effects link functions (-0.35, $p = 0.006$) and only close to the significance level in the model with the current level link functions (-0.20, $p = 0.055$). The effect of metastases localized in peritoneum was found smaller in Model 4A so that it was no longer significant (-0.30, $p = 0.13$). The estimates of the covariance effects $\boldsymbol{B}$ were also comparable, with only the covariance of the random intercept and slope being more accentuated in Model 4. Given values of LCV criterion [1], the models fit the data similarly with LCV for Model 4 equal to 1.315 and for Model 4A equal to 1.318.

This sensitivity analysis implies that the choice of the link functions indeed influence the effects on the estimates of the parameters but only moderately. The estimates related

Table D.3: Parameter estimates for Model 4A: the trivariate joint random effects model with current level of the biomarker as the link functions fitted to the FFCD 2000-05 dataset.

	Biomarker: SLD		Recurrent events		Terminal event	
Covariate	Est. (SE)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Intercept	3.06 (0.30)	<0.001	-	-	-	-
Time	−0.20 (0.11)	0.055	-	-	-	-
Treatment Arm (C/S)	−0.25 (0.14)	0.08	0.93 (0.73-1.19)	0.57	0.95 (0.56-1.62)	0.91
Treatment Arm (C/S)×Time	−0.46 (0.15)	0.002	-	-	-	-
Age (60-69/<60 years)	0.18 (0.17)	0.30	0.73 (0.54-0.99)	0.043	0.88 (0.46-1.71)	0.71
Age (≥70/<60 years)	−0.02 (0.16)	0.90	0.79 (0.59-1.05)	0.11	1.28 (0.69-2.38)	0.44
Sex (Female/Male)	0.23 (0.14)	0.10	0.85 (0.66-1.09)	0.20	0.95 (0.55-1.64)	0.86
Center (10-29/≥ 30 patients)	−0.17 (0.17)	0.32	1.02 (0.74-1.39)	0.92	1.01 (0.51-2.01)	0.98
Center (<10/≥ 30 patients)	−0.10 (0.16)	0.55	1.08 (0.81-1.43)	0.60	1.15 (0.63-2.11)	0.66
Baseline WHO PS (1/0)	−0.19 (0.15)	0.20	1.12 (0.86-1.46)	0.39	1.35 (0.75-2.42)	0.32
Baseline WHO PS (2/0)	0.41 (0.21)	0.054	2.14 (1.42-3.22)	<0.001	11.31 (4.57-28.00)	<0.001
Previous resection (Yes/No)	−0.73 (0.14)	<0.001	-	-	0.52 (0.33-0.83)	0.006
Number of metastatic sites (≥2/1)	−0.42 (0.14)	0.003	-	-	-	-
Metastases localization (Yes/No):						
Liver	0.75 (0.24)	0.001	-	-	-	-
Peritoneum	−0.30 (0.20)	0.13	-	-	-	-
Abdominal lymphad.	0.38 (0.17)	0.028	1.61 (1.19-2.17)	0.002	2.51 (1.27-4.98)	0.008
Association Parameters*	Est. (SE)	p-value	Matrix **B** components		Est. (SE)	p-value
η_{r1}	0.04 (0.04)	0.34	Var(Intercept)		1.53 (0.06)	<0.001
η_{t1}	0.46 (0.10)	<0.001	Var(Slope)		0.88 (0.07)	<0.001
α	3.10 (0.46)	<0.001	cov(Intercept, Slope)		−0.18 (0.08)	0.07
σ^2_ϵ	0.96 (0.02)	<0.001	σ^2_v		0.47 (0.09)	<0.001

* η_{r1} - link parameters (biomarker and recurrences), η_{t1} - link parameters (biomarker and death)
σ^2_v - variance of the frailty term, α - link parameter between the processes, σ^2_ϵ - variance of the measurement error
HR - hazard ratio, CI - confidence interval, SE - standard error, PS - performance status

to the explanatory variables were not much different between two models with different link functions. However, the choice of the link functions should be done with caution.

D.3 Prediction error

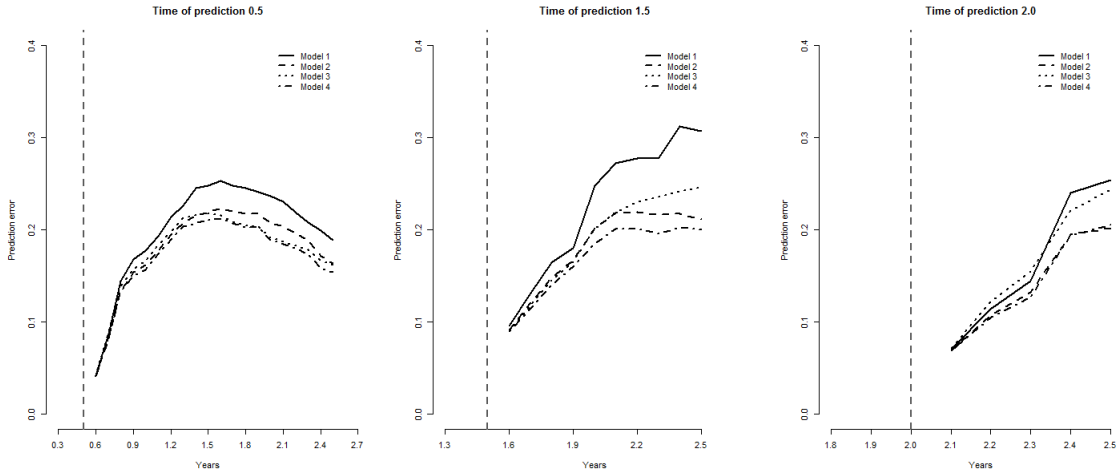

Figure D.3: 10-fold cross-validated error of prediction at $t = 1$ year and varying window w from 0.1 to 1.5. Model 1 - tumor progressions and death, Model 2 - occurrence of new lesions and death, Model 3 - SLD measure and death, Model 4 - SLD measure, occurrence of new lesions and death.

E Data and R code

All the analyses from this work were performed using R package **frailtypack** [6]. The package enables estimations of joint frailty models in the context of recurrent events and a terminal event. Since version 2.7.7 (2015), the bivariate model for longitudinal data and a terminal event and the trivariate model for longitudinal data, recurrent events and a terminal event are available for estimation in the package.

Here, we provide an example on how to apply function `trivPenal` for the trivariate model that corresponds to Model 4 in the main manuscript. Firstly, two datasets are required for the estimation, a dataset with longitudinal measurements and covariates (`colorectlLongi`) and a dataset with information on recurrent and terminal events and covariates (`colorectal`). Tables E.1 and E.2 present extracts of the dataset FFCD 2000-05. In Table E.1, variable "year" represents visit times in years and "tumor.size" is the longitudinal biomarker. In table E.2, a calendar timescale is used with a counting process formulation. Variable "time1" represents the time in years since randomization.

Table E.1: Extract from dataset `colorectalLongi` for the longitudinal measurements and covariates.

id	year	tumor.size	treatment	age	who.PS	prev.resection
1	0.00	3.153	1	0	1	1
1	0.14	2.792	1	0	1	1
1	0.25	2.226	1	0	1	1
1	0.42	2.643	1	0	1	1
1	0.65	3.620	1	0	1	1
1	0.84	2.620	1	0	1	1
1	1.01	3.912	1	0	1	1
1	1.20	4.102	1	0	1	1
2	0.00	3.416	1	0	1	0
2	0.20	3.602	1	0	1	0
2	0.45	3.216	1	0	1	0
2	0.71	2.069	1	0	1	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮

Table E.2: Extract from dataset `colorectal` for recurrent and terminal events and covariates.

id	time0	time1	new.lesions	state	treatment	age	who.PS	prev.resection
1	0.00	1.20	1	0	1	0	1	1
1	1.20	1.33	0	1	1	0	1	1
2	0.00	0.71	1	0	1	0	1	0
2	0.71	1.02	0	1	1	0	1	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

Here is how to perform the estimation of the trivariate model on an extract of 150 patients from the trial (datasets included in the package):

```
R> library("frailtypack")
R> data("colorectalLongi")  #data for longitudinal measurements
R> data("colorectal")       #data for recurrent and terminal events

R> modTrivariate <- trivPenal(Surv(time0, time1, new.lesions) ~ cluster(id) +
+    age + treatment + who.PS + prev.resection +  terminal(state),
+    formula.terminalEvent = ~ age + treatment + who.PS + prev.resection,
```

```
+    tumor.size ~ year * treatment + who.PS, data = colorectal,
+    data.Longi = colorectalLongi, random = c("1", "year"),
+    id = "id", link = "random-effects", left.censoring = -3.33,
+    recurrentAG = TRUE,  n.knots = 5, kappa = c(0.03, 2.12))
```

The above function fits the trivariate model with cubic M-splines with 5 knots (`n.knots`) approximation for the baseline hazard functions using smoothing parameters `kappa` 0.03 for recurrent events and 2.12 for the terminal event in the penalized likelihood. Argument `recurrentAG = TRUE` represents the Andersen-Gill counting process approach for recurrent event times. For the biomarker, a random intercept and slope are chosen using argument `random`. By default, the link between the longitudinal biomarker and survival and between the biomarker and recurrent events uses random effects (`link = "random-effects"`), otherwise `"current-level"` for the current level of the biomarker can be used as the link functions. Argument `left-censoring` is equal to a threshold for the left-censored biomarker. If this argument is set to logical value `FALSE`, the left-censoring is not considered.

The results can be obtained using methods `print` and `summary`. Estimated baseline survival and hazard functions can be plotted with method `plot`. Finally, dynamic predictions can be calculated using function `prediction` and the predictive ability of a model can be evaluated using function `epoce`.

References

[1] Daniel Commenges, Pierre Joly, Anne Gégout-Petit, and Benoît Liquet. Choice between Semi-parametric Estimators of Markov and Non-Markov Multi-state Models from Coarsened Observations. *Scandinavian Journal of Statistics*, 34(1):33–52, March 2007.

[2] Michel Ducreux, David Malka, Jean Mendiboure, Pierre-Luc Etienne, Patrick Texereau, Dominique Auby, Philippe Rougier, Mohamed Gasmi, Marine Castaing, Moncef Abbas, Pierre Michel, Dany Gargot, Ahmed Azzedine, Catherine Lombard-Bohas, Patrick Geoffroy, Bernard Denis, Jean-Pierre Pignon, Laurent Bedenne, and Olivier Bouché. Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-05): an open-label, randomised, phase 3 trial. *The Lancet Oncology*, 12(11):1032–44, October 2011.

[3] Robert H Lyles, Cynthia M Lyles, and Douglas J Taylor. Random regression models for human immunodeficiency virus ribonucleic acid data subject to left censoring and

informative drop-outs. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 49(4):485–497, 2000.

[4] Juliette Pénichoux, Stefan Michiels, Olivier Bouché, Pierre-Luc Etienne, Patrick Texereau, Dominique Auby, Philippe Rougier, Michel Ducreux, and Jean-Pierre Pignon. Taking into account successive treatment lines in the analysis of a colorectal cancer randomised trial. *European Journal of Cancer*, 49(8):1882–8, May 2013.

[5] Dimitris Rizopoulos. Dynamic predictions and prospective accuracy in joint models for longitudinal and time-to-event data. *Biometrics*, 67(3):819–29, September 2011.

[6] Virginie Rondeau, Juan R. Gonzalez, Yassin Mazroui, Audrey Mauguen, Agnieszka Krol-Listwon, Amadou Diakite, and Alexandre Laurent. *frailtypack: General Frailty Models: Shared, Joint and Nested Frailty Models with Prediction*, 2015. R package http://CRAN.R-project.org/package=frailtypack.

[7] Virginie Rondeau, Simone Mathoulin-Pelissier, Hélène Jacqmin-Gadda, Véronique Brouste, and Pierre Soubeyran. Joint frailty models for recurring events and death using maximum penalized likelihood estimation : application on cancer events. *Biometrics*, 8(4):708–721, 2007.

[8] Virginie Rondeau, Yassin Mazroui, and Juan R Gonzalez. frailtypack : An r package for the analysis of correlated survival data with frailty models using penalized likelihood estimation or parametrical estimation. *Journal of Statistical Software*, 47(4), 2012.

[9] Michael S Wulfsohn and Anastasios A Tsiatis. A joint model for survival and longitudinal data measured with error. *Biometrics*, 53(1):330–9, March 1997.