Contribution of Jointly Modeling Progression-Free Survival and Biomarker Longitudinal Data for Therapeutic Evaluation in Oncology: A Simulation Study

Antoine Pitoy[1–4], Solène Desmée[2], Hoai-Thu Thai[1], Marc Cerou[1], Dorothee Semiond[3], Christine Veyrat-Follet[1], Julie Bertrand[4]

[1]Translational Disease Modelling Oncology, Sanofi, Chilly-Mazarin, France; [2]Université de Tours, Université de Nantes, UMR 1246 SPHERE, INSERM, Tours, France; [3]Sanofi Translational Medicine & Early Development, Cambridge, MA, USA; [4]Université de Paris, UMR 1137 IAME, INSERM, Paris, France

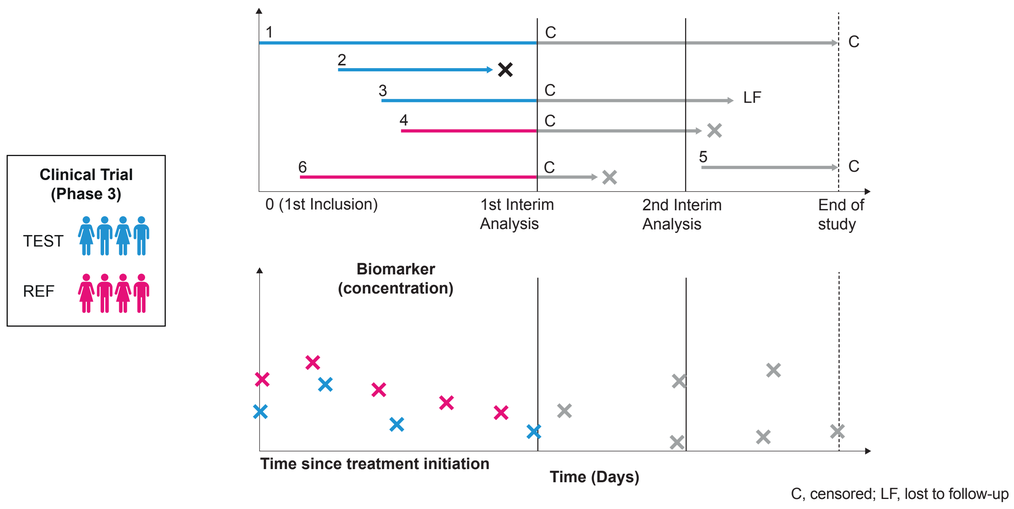
INTRODUCTION

- Joint modeling has been increasingly used in therapeutic evaluation, especially in oncology, as it allows for the simultaneous fit of longitudinal and time-to-event data to characterize and quantify the association between biomarker dynamics and risk of event[1,2]
- At the individual level, dynamic predictions obtained using nonlinear joint models can identify the most at-risk patients in oncology clinical trials and improve patient follow-up[3]
- At the population level, it remains to be demonstrated whether joint models developed in early phases could be used to inform and support earlier decision making
- The objective of this study was to assess the performance of a nonlinear joint model-based approach to estimate a Phase 3 oncology clinical trial primary endpoint at interim and final analyses, in comparison to traditional approaches

METHODS

Primary endpoint estimation

- The primary endpoint was PFS and the biomarker of interest was serum M-protein (MP)



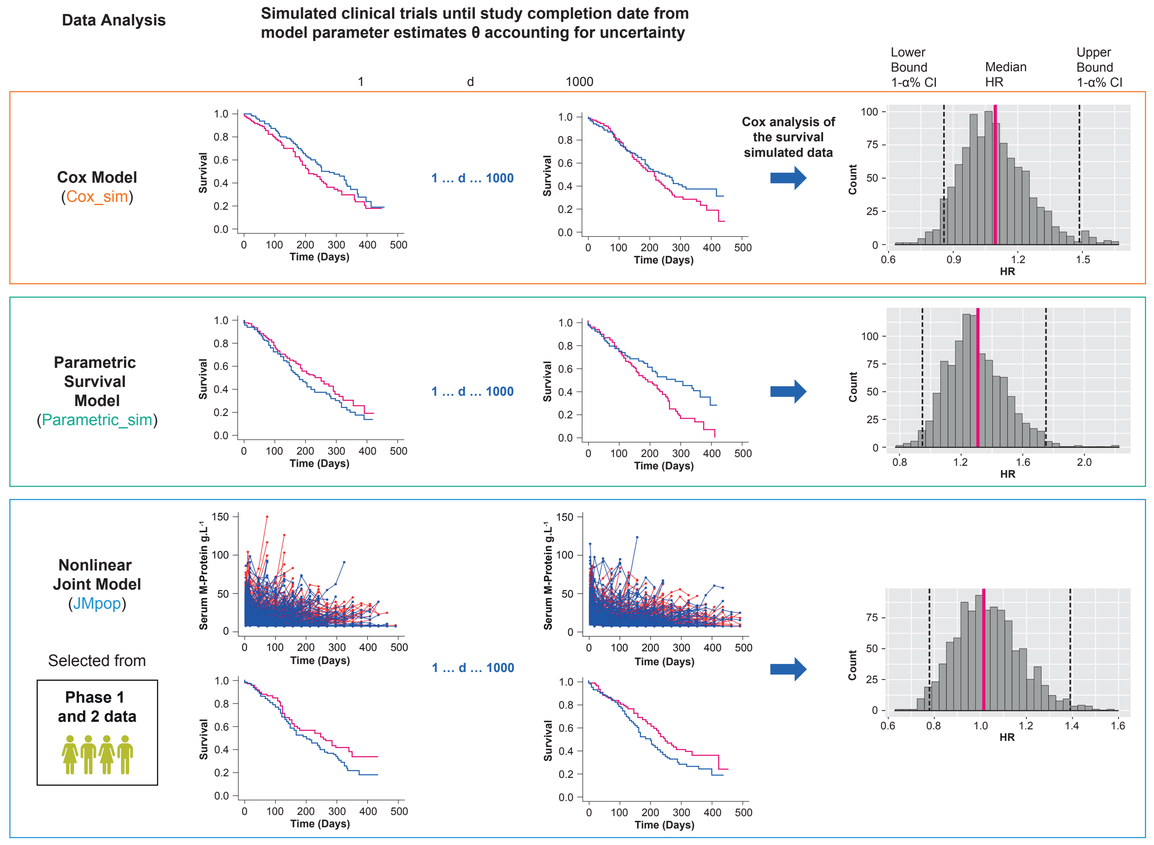
C, censored; LF, lost to follow-up

- Hazard ratio (HR) and confidence interval (CI) at the level α
  - Cox model (Cox_obs) and parametric proportional hazard model (Parametric_obs) of the observed data at each interim and final analyses
  - Median and percentiles of the HR obtained with a Cox model on 1000 datasets simulated until study completion, using population parameter estimates accounting for uncertainty of a Cox model (Cox_sim), a parametric proportional hazard model (Parametric_sim), and a nonlinear joint model (JMpop) of the observed data at each interim and final analyses (**Figure 1**)

Implementation

- Nonlinear joint model and parametric proportional hazard model maximum likelihood estimates (MLE) were obtained using the Stochastic Approximation Expectation Maximization (SAEM) algorithm in Monolix 2020R1[4]
- Data simulation for Parametric_sim and JMpop modeling approaches was performed using RsSimulx in R (version 3.6.1)
- Data simulation task for Cox_sim was performed using the coxed package in R
- All the other analysis (Cox_obs, Parametric_obs) and data management tasks were performed in R

Figure 1. Schematic representation of the simulation-based approaches to estimate oncology clinical trial HR at study completion, accounting for parameter estimate uncertainty at interim and final analyses



CI, confidence interval; d, dataset indicator (d=1,...., 1000); HR, hazard ratio

SIMULATION STUDY

Simulation framework

- Based on the randomized Phase 3 ICARIA-MM clinical trial (NCT02990338) that compared progression-free survival (PFS) with the anti-CD38 monoclonal antibody isatuximab in combination with pomalidomide-dexamethasone vs pomalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM), who had received ≥2 prior treatment lines[5-8]
- Simulation of K=100 clinical trials including N=300 patients randomized in a 1:1 ratio to a REF or a TEST treatment arm

Nonlinear joint model

MP kinetics is described by the function M(t) defined by the following differential equation:

$$M(0) = M_0$$

Before treatment initiation (t ≤ TSTART):

$$\frac{dM}{dt} = Kg \times M(t)$$

After treatment initiation (t > TSTART):

$$\frac{dM}{dt} = Kg \times M(t) - Ks \times e^{\wedge}(-R \times (t-TSTART)) \times M(t)$$

With:

- t: time elapsed since first serum MP measurement
- TSTART: treatment initiation time
- M_0: baseline serum MP level ($g.L^{-1}$)
- Kg: tumor growth rate (day^{-1})
- Ks: tumor shrinkage rate due to treatment exposure (day^{-1})
- R: rate constant for appearance of resistance to treatment (day^{-1})

Nonlinear mixed effect model (NLMEM):

$$y_{ij} = M(t_{ij}, \psi_i) \times (1+\varepsilon_{ij})$$

With:

- $M(t_{ij}, \psi_i)$: the true serum MP process of subject i at time t_{ij} described by the previous differential equation
- ψ_i: the individual parameter vector for subject i, decomposed into fixed (population) and random (individual) effects normally distributed with variance matrix $\Omega = diag(\omega_{M0}, \omega_{Ks}, \omega_{Kg}, \omega_R)^2$
- ε_{ij}: the residual errors, assumed to be independent and to follow a normal distribution $\mathcal{N}(0, b^2)$

PFS hazard is modeled by the following function:

Before treatment initiation (t ≤ TSTART):

$$h(t) = 0$$

After treatment initiation (t > TSTART):

$$h(t) = \frac{s}{\lambda} \times (\frac{t}{\lambda})^{s-1} \times exp(\beta_M \times \frac{dM}{dt})$$

With:

- s: shape parameter of the Weibull function
- λ: scale parameter of the Weibull function (day)
- β_M: strength of the link between the slope of MP kinetics $M(t)$ and survival ($L.day^{-1}.g^{-1}$)

Let $\theta = \{M_0, Ks, Kg, R, \omega_{M0}, \omega_{Ks}, \omega_{Kg}, \omega_R, b, s, \lambda, \beta_M\}$ the vector of nonlinear joint model-parameters to be estimated (ω, inter-individual variability standard deviation; b, residual variability parameter)

- Clinical trials simulations were performed under the null hypothesis of no improvement of the TEST treatment over the REF treatment, using the simulation values provided in **Table 1**

Table 1. Simulation values used for clinical trial simulations

	Fixed effects	Inter-individual variability standard deviation ω
Longitudinal model		
M_0 ($g.L^{-1}$)	19	0.6
Ks (day^{-1})	0.01	0.6
Kg (day^{-1})	0.005	0.6
R (day^{-1})	0.01	0.6
b (%)	0.25	
Survival model		
s	1.25	
λ (day)	430	
β_M ($L.day^{-1}.g^{-1}$)	12.5	

- The final analysis was planned after 162 PFS events occurred[8], plus 2 interim analyses after 50% (1st interim) and 65% (2nd interim) of the events, using the alpha spending functions described in **Table 2**

Table 2. Significance levels according to alpha spending functions with a nominal alpha of 0.025 at the final analysis[9,10]

	1st interim	2nd interim	Final
Pocock	1.5×10^{-2}	1.9×10^{-2}	2.5×10^{-2}
O'Brien and Fleming (OBF)	8.2×10^{-4}	3.9×10^{-3}	2.5×10^{-2}
Haybittle-Peto (H-P)	1.0×10^{-3}	1.0×10^{-3}	2.5×10^{-2}

Evaluation

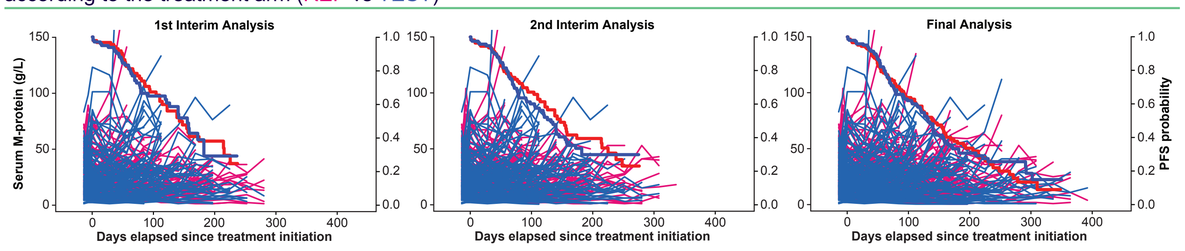
- Type I error was derived as the percentage of K simulated clinical trials reaching a PFS improvement in the TEST arm (i.e., CI upper bound <1) and compared to the target alpha level using a binomial exact test at 5%

RESULTS

Simulated data

- The median (min–max) 1st interim analysis date over the K=100 simulated clinical trials was 259 (220–289) days since first inclusion in the study, and 298 (262–331) and 379 (354–406) days since first inclusion for the 2nd interim and final analysis, respectively (**Figure 2**)

Figure 2. Spaghetti plot and Kaplan-Meier curves for simulated patients included in one simulated clinical trial, with longitudinal and survival data available at each interim and final analysis. Longitudinal and survival data are presented according to the treatment arm (REF vs TEST)



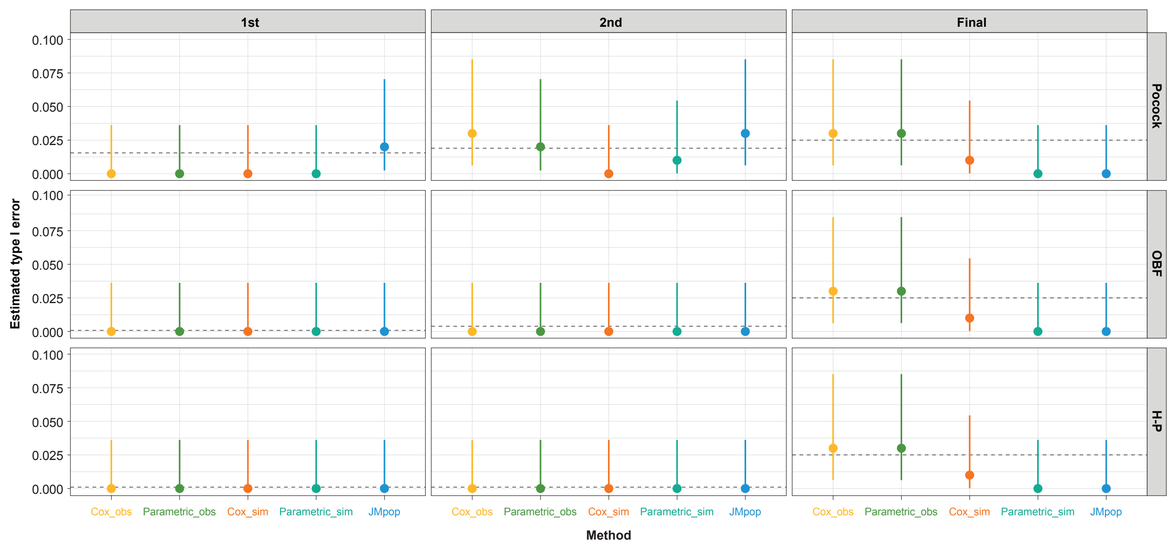
Nonlinear joint model population parameters

- At both interim analyses, the fixed effect and inter-individual standard deviation of the resistance parameter (R and ωR) were slightly overestimated and imprecise, with relative bias (Rbias) between 20% and 27% and relative root median square error (RRMSE) between 30% and 38%. All the other parameters were well estimated

Type I error estimation

- Observation-based and simulation-based approaches provided type I error estimates not significantly different from the significance levels defined by the alpha spending functions at each interim and final analyses (**Figure 3**)

Figure 3. Type I error estimates and 95% confidence intervals of all observation and simulation-based approaches at each interim and final analyses, compared to significance levels from the alpha spending functions (black dashed lines)



CONCLUSIONS

- All approaches control the type I error at each interim and final analyses whatever the alpha spending function
- JMpop suffers from inaccurate estimation of the resistance appearance parameter at interim analyses due to MP kinetic profiles being observed on a too short timeframe
- Simulation-based approaches not considering parameter estimate uncertainty led to inflated type I error (data not shown)
- Assessment of all the approach power is currently ongoing

REFERENCES:

1. Rizopoulos D. Joint models for longitudinal and time-to-event data: With applications in R. (1st ed.). 2022; Chapman and Hall/CRC.
2. Desmée S, et al. *Biometrics*. 2016;73(1):305–312.
3. Tardivon C, et al. *Clin Pharmacol Ther*. 2019;106(4):810–820.
4. Delyon B, et al. *Ann Statist*. 1999;27(1):94–128.
5. Sarclisa® (isatuximab-irfc) [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2021. https://products.sanofi.us/Sarclisa/Sarclisa.pdf. Accessed May 23, 2022.
6. European Medicines Agency (EMA). Medicines. Sarclisa. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/sarclisa-0. Accessed May 23, 2022.
7. Sarclisa® (isatuximab) [package insert]. Nishi Shinjuku, Tokyo: Sanofi Co., Ltd.; 2021. https://products.sanofi.us/Sarclisa/Sarclisa.pdf. Accessed May 23, 2022.
8. Attal M, et al. *Lancet*. 2019;394(10214):2096–2107.
9. DeMets DL, et al. *Stat Med*. 1994;13(13-14):1341–52; discussion 1353–1356.
10. Peto R, et al. *Br J Cancer*. 1976;34(6):585–612.

ACKNOWLEDGMENTS: This work was funded by Sanofi. Medical writing support was provided by S. Mariani, MD, PhD of Envision Pharma Group, funded by Sanofi.

DISCLOSURES: AP: research funding from the Association Nationale Recherche Technologie. SD and JB: nothing to disclose. H-TT, MC, DS, and CV-F are employees of Sanofi and may hold stock/stock options.

QUESTIONS: If you have questions about this poster, please email Antoine Pitoy; email: Antoine.Pitoy@sanofi.com

Presented at the Population Approach Group in Europe (PAGE) Meeting, June 27–30, 2023, A Coruña, Spain

GENCO1-18751-1 ISA PAGE23 joint modeling poster VP8.indd 1 16/06/2023 16:39