

Joint Modeling of Longitudinal and Time-to-Event Data for Earlier Estimation of the Primary Endpoint in Oncology Clinical Trials: A Retrospective Analysis of the ICARIA-MM Clinical Trial

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INTRODUCTION

- Earlier assessment of clinical trial outcomes would allow earlier decision making, especially for trials of long duration, where models developed in early phases may contribute to estimation of the primary endpoint at interim analyses
- Joint modeling has been increasingly used in therapeutic evaluation, especially in oncology,^{1,2} 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
- At the individual level, dynamic predictions obtained using nonlinear joint models can identify the most at-risk patients in oncology clinical trials³ and can improve patient follow-up. Evidence suggests a benefit of joint modeling at the population level to inform and support decision making; however, additional studies are needed
- The aim of this study was to assess the ability of a nonlinear joint model selected from Phase 1 and 2 data to earlier estimate the primary endpoint of a Phase 3 oncology clinical trial
- For this purpose, we performed a retrospective analysis of the ICARIA-MM Phase 3 clinical trial in the context of interim and final analyses and estimated the hazard ratio (HR) at study completion using both simulation- and observation-based approaches

METHODS

- Isatuximab (Isa), an IgG1-kappa monoclonal antibody that targets a specific epitope on CD38 and is approved in several countries in combination with pomalidomide and dexamethasone (Pd) or with carfilzomib and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM)⁴⁻⁶
- ICARIA-MM (NCT02990338) is a randomized, multicenter, open-label, pivotal Phase 3 study assessing the benefit of isatuximab plus pomalidomide and low-dose dexamethasone (Isa-Pd) versus Pd in patients with RRMM⁷
- A total of 256 (128, Isa-Pd; 128, Pd) of 307 patients in ICARIA-MM with >2 serum M-protein values, including 1 baseline value, and for whom responses could be evaluated by serum M-protein were included in the analysis
- Progression-free survival (PFS), the primary endpoint of the study, was defined as the time elapsed between patient date of randomization and the date of disease progression evaluation or death from any cause, whichever came first
- The PFS final analysis cutoff date was established *a priori* when 162 progression events occurred. Two retrospective interim analyses were performed when 33% (first interim analysis) and 65% (second interim analysis) of the expected total number of progression events occurred, with longitudinal data observed post PFS only until the respective interim analysis date

Primary endpoint estimation

- We used several alpha spending functions to avoid type 1 error inflation^{8,9}
 - Pocock
 - O'Brien-Fleming (OBF)
 - Haybittle-Peto (H-P)

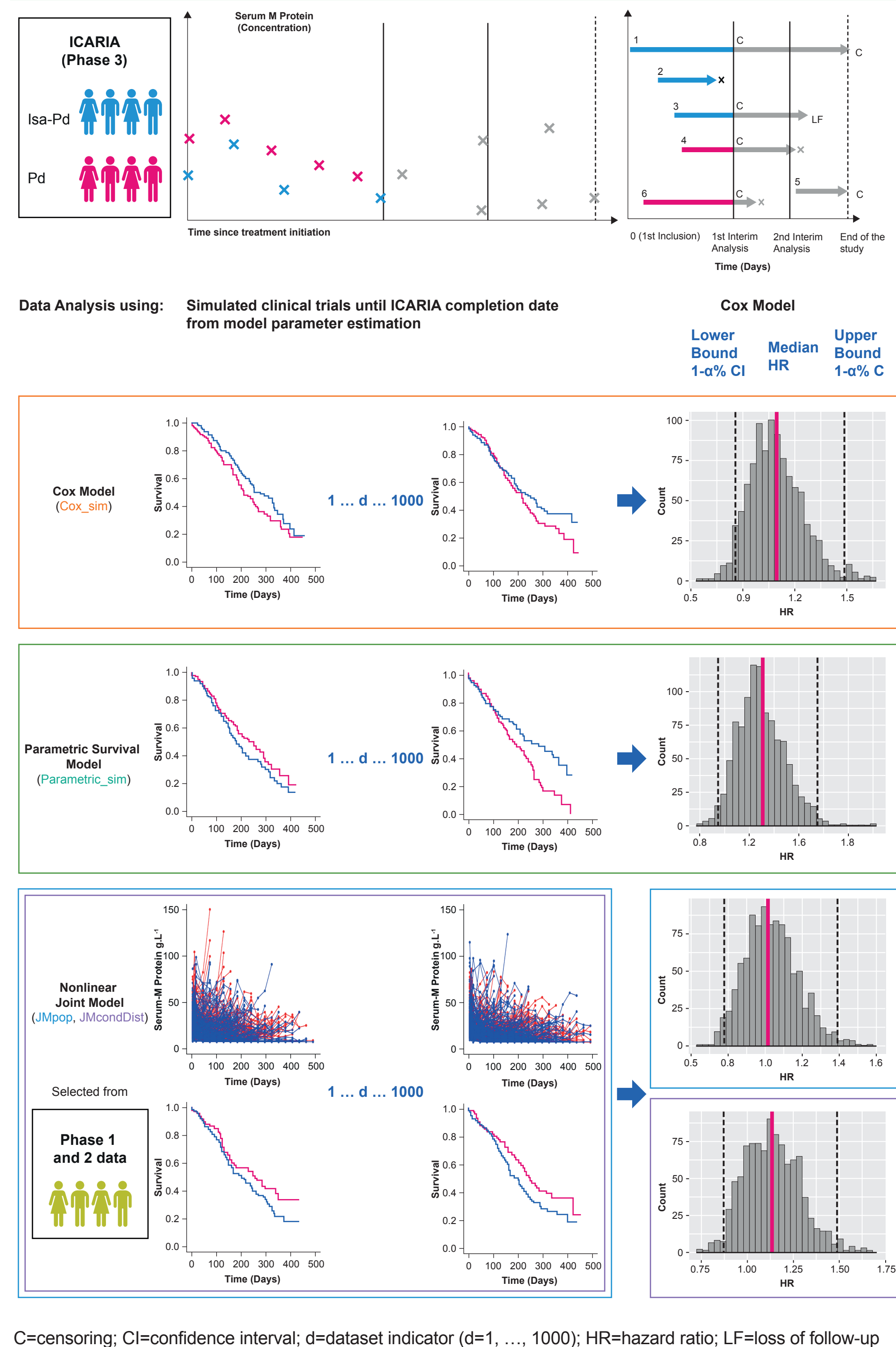
Table 1. Significance Levels According to Alpha Spending Functions

Analysis	First Interim Analysis	Second Interim Analysis	Final Analysis
t^* (%)	33	65	100
α_{Pocock}	1.1×10^{-2}	1.9×10^{-2}	2.5×10^{-2}
α_{OBF}	2.7×10^{-5}	3.9×10^{-3}	2.5×10^{-2}
$\alpha_{\text{H-P}}$	1.0×10^{-3}	1.0×10^{-3}	2.5×10^{-2}

t^* = fraction of progression events that has been observed

- HR estimation based on observed data only at each analysis were conducted using:
 - Cox model (Cox_obs)
 - Parametric proportional hazard model (Parametric_obs)
- HR estimation based on simulation of 1000 clinical trials until study completion, using model parameters estimated from observed data (Figure 1) at each analysis date, using:
 - Cox model (Cox_sim)
 - Parametric proportional hazard model (Parametric_sim)
 - Nonlinear joint model previously developed from Phase 1 and 2 data and simulating from the:
 - Population parameter distribution (JMpop)
 - Individual parameter conditional distribution (JMcondDist)

Figure 1. Schematic Representation of the Simulation-based Approach to Estimate the HR at the Study Completion for the Retrospective Analysis of the ICARIA-MM Trial at the Interim and Final Analysis Dates



C=censoring; CI=confidence interval; d=dataset indicator (d=1, ..., 1000); HR=hazard ratio; LF=loss of follow-up

Nonlinear joint models

- Developed by Riglet et al¹⁰ from Phase 1 and 2 data (for Isa-Pd) and by Thai et al² from ICARIA-MM data (for Pd)

$$M(t=0)=M_0$$

Before treatment initiation:

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

After treatment initiation:

$$\frac{dM}{dt} = Kg \times M(t) - Ks \times \left(\frac{I \times C_i}{EC_{50} \times (I + INT_{i-p} \times C_p) + C_i} + \beta_d \times C_d \right) \times e^{(-R \times t)} \times M(t)$$

$$\frac{dM}{dt} = Kg \times M(t) - Ks \times (C_p + C_d) \times e^{(-R \times t)} \times M(t)$$

$$h(t) = \frac{\alpha \times \left(\frac{t}{\lambda} \right)^{\alpha-1}}{1 + \left(\frac{t}{\lambda} \right)^{\alpha}} \times \exp(\beta_M \times \frac{dM}{dt})$$

With:

- M_0 Baseline serum M protein level (g.L⁻¹)
- Kg the natural tumor growth (day⁻¹)
- Ks tumor decrease rate due to the exposure (day⁻¹ in Isa-Pd versus L.day⁻¹.mol⁻¹ in Pd)
- R rate constant for resistance appearance to the treatment (day⁻¹)
- C_i molar concentration of isatuximab (mol.L⁻¹)
- C_p molar concentration of pomalidomide (mol.L⁻¹)
- C_d molar concentration of dexamethasone (mol.L⁻¹)
- β_M strength of the link between serum-M protein kinetics and survival (L.day.g⁻¹)
- α shape parameter of the log-logistic function
- λ scale parameter of the log-logistic function (day)
- $\frac{dM}{dt}$ Slope of serum M-protein (g.L⁻¹.day⁻¹)
- EC_{50} concentration of pomalidomide needed to reach 50% of isatuximab maximum effect on Ks (mol.L⁻¹)
- INT_{i-p} coefficient measuring the strength of the interaction between isatuximab and pomalidomide (L.mol⁻¹)
- β_d coefficient measuring the effect of dexamethasone on Ks (L.mol⁻¹)

Parametric proportional hazard model

- Baseline hazard defined by a log-logistic distribution

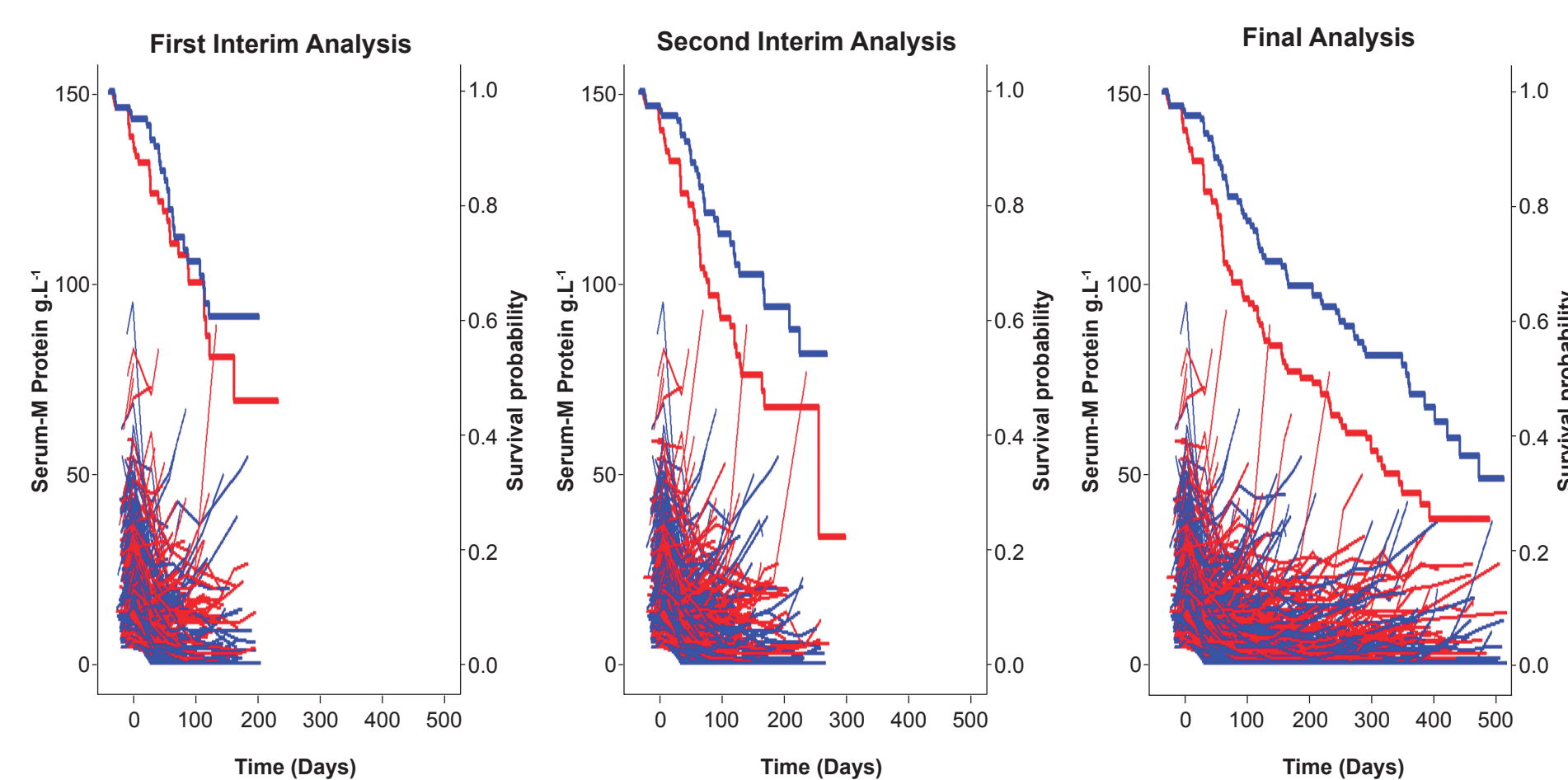
Implementation

- Nonlinear joint model and log-logistic model parameters were estimated by maximizing the joint likelihood with the Stochastic Approximation Expectation Maximization (SAEM) algorithm¹¹ in Monolix 2020R1
- Data simulation for parametric and joint modeling approaches was performed using RsSimulx in R software (version 3.6.1)
- Data simulation task for Cox_sim was performed using the coxed package in R

RESULTS

- Figure 2 displays serum M-protein levels and PFS available at the first interim analysis, second interim analysis, and final analysis

Figure 2. Spaghetti Plots of Serum M Protein Levels and Estimated Kaplan-Meier of PFS Curves for Patients Treated With Isa-Pd (Blue) and Pd (Red) for Each Analysis



Nonlinear joint model evaluation

- Parameters of the joint model were globally well estimated with relative standard error (RSE) $\leq 40\%$ (Tables 2–3).
- Differences were observed between estimates and values estimated by the Isa-Pd and Pd joint models due to differences between populations
- Good adequacy was observed between the predicted and observed dynamics of serum M-protein and PFS (Figure 3), except for Isa-Pd longitudinal visual predictive checks at the first interim analysis due to an under-prediction of the 90th percentile. Smaller prediction intervals were obtained at the final analysis compared with the interim analyses

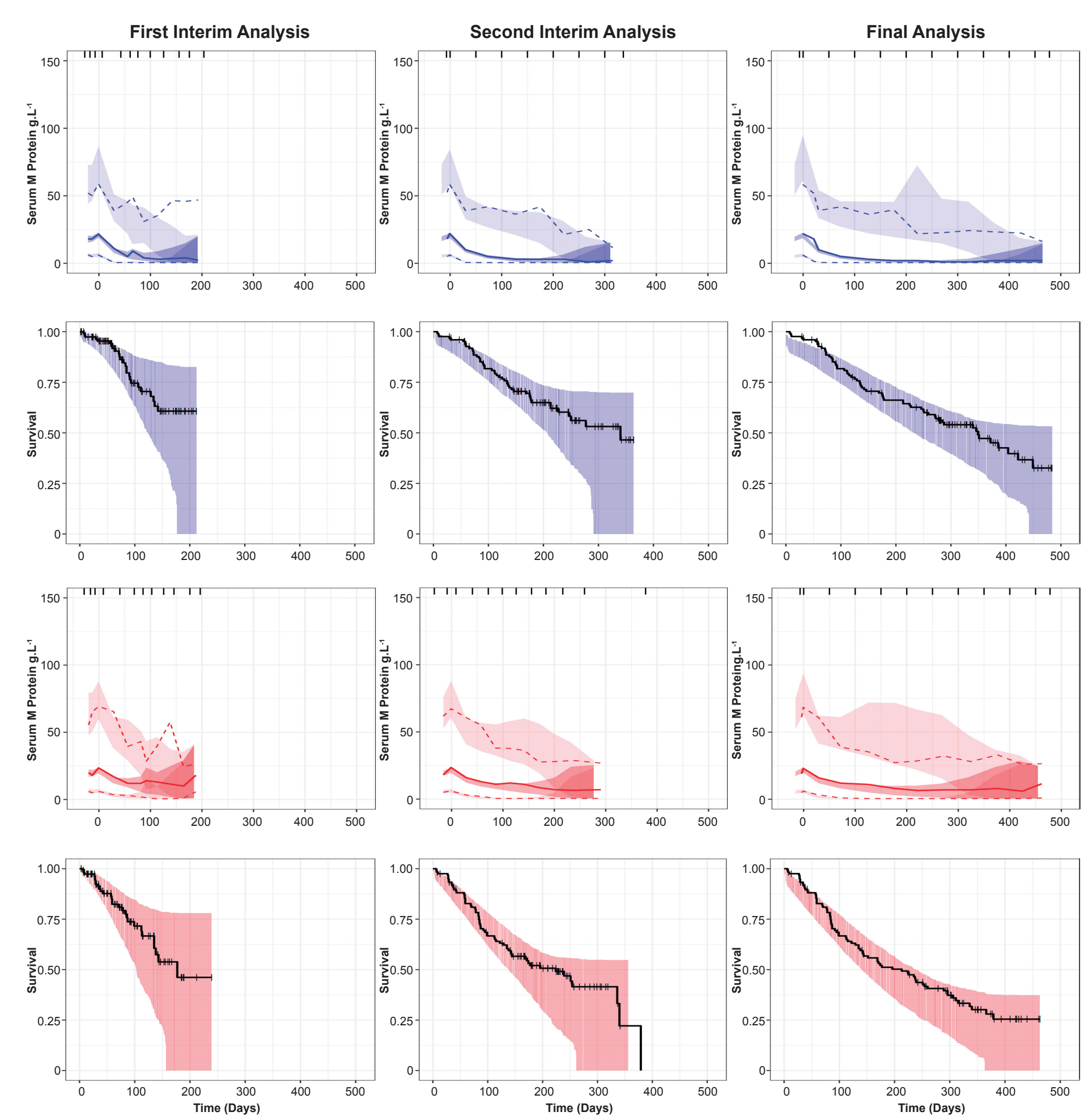
Table 2. Parameter Estimates (Relative Standard Error %) of the Nonlinear Joint Model Fitted to Data From the Isa-Pd Arm for Each Analysis and by Riglet et al¹⁰ From Phase 1 and 2 Data

	First Interim Analysis	Second Interim Analysis	Final Analysis	Riglet et al ¹⁰
Longitudinal model				
M_0 (g.L ⁻¹)	18 (6)	18 (6)	18 (6)	15 (17)
Ks (day ⁻¹)	0.04 (8)	0.04 (8)	0.04 (8)	0.04 (10)
Kg (day ⁻¹)	0.008 (12)	0.005 (13)	0.005 (13)	0.004 (10)
R (day ⁻¹)	0.016 (13)	0.011 (15)	0.010 (14)	0.01 (11)
ωM_0	0.62 (7)	0.62 (7)	0.62 (7)	0.5 (5)
ωKs	0.65 (10)	0.76 (9)	0.81 (8)	1.1 (7)
ωKg	0.62 (16)	0.77 (15)	1.06 (10)	1.1 (7)
ωR	0.76 (14)	1.33 (13)	1.29 (10)	1.1 (9)
a (g.L ⁻¹)	0.34 (19)	0.29 (12)	0.32 (9)	0.4 (5)
b	0.12 (8)	0.14 (6)	0.14 (5)	0.09 (4)
Survival model				
α	1.72 (9)	1.74 (16)	1.89 (13)	1.7 (1)
λ (day)	326 (21)	478 (24)	504 (18)	292 (5)
β_M (L.day ⁻¹ .g ⁻¹)	8 (16)	16 (42)	16 (9)	5 (1)

Table 3. Parameter Estimates (Relative Standard Error %) of the Nonlinear Joint Model Fitted to Data From the Pd Arm for Each Analysis and by Thai et al² on ICARIA Data From Both Arms

	First Interim Analysis	Second Interim Analysis	Final Analysis	Thai et al ²
Longitudinal model				
M_0 (g.L ⁻¹)	20 (6)	19 (6)	19 (6)	17 (3)
Ks (L.day ⁻¹ .mol ⁻¹)	0.32 (11)	0.28 (9)	0.27 (9)	0.19 (7)
Kg (day ⁻¹)	0.005 (18)	0.005 (14)	0.006 (12)	0.006 (8)
R (day ⁻¹)	0.015 (32)	0.011 (18)	0.009 (16)	0.01 (11)
ωM_0	0.61 (7)	0.61 (7)	0.61 (7)	0.51 (4)
ωKs	0.53 (17)	0.69 (10)	0.78 (9)	0.92 (7)
ωKg	0.72 (15)	0.85 (14)	0.98 (11)	0.89 (7)
ωR	1.55 (20)	1.11 (17)	1.20 (13)	1.1 (9)
a (g.L ⁻¹)	0.50 (23)	0.60 (14)	0.66 (10)	0.41 (7)
b	0.16 (7)	0.14 (6)	0.14 (5)	0.15 (4)
Survival model				
α	2.07 (11)	1.92 (15)	1.92 (20)	2.33 (10)
λ (day)	256 (17)	306 (13)	323 (11)	459 (12)
β_M (L.day ⁻¹ .g ⁻¹)	7 (13)	7 (8)	7 (13)	12 (8)

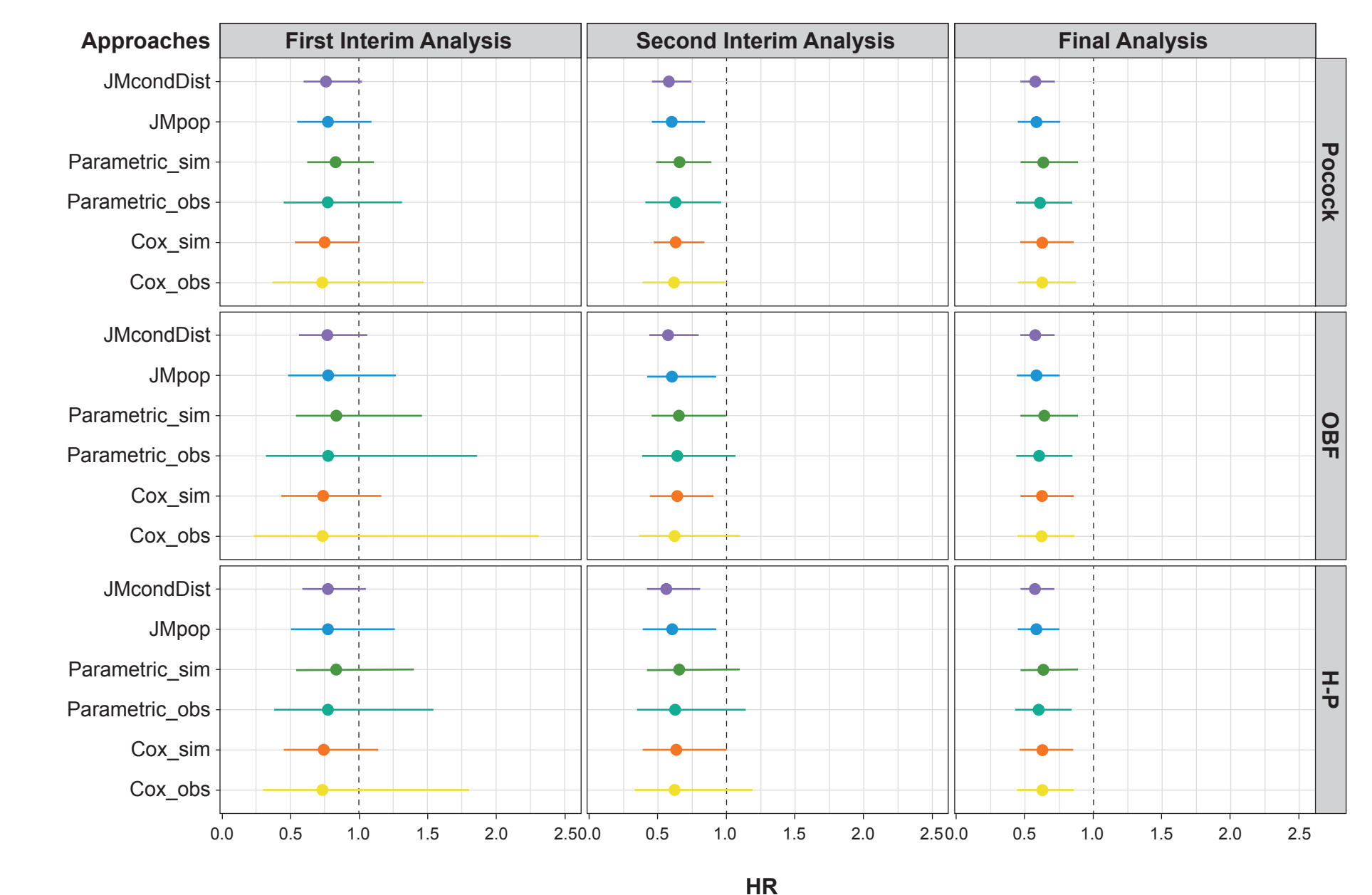
Figure 3. Longitudinal and Time-to-Event Visual Predictive Checks of the Nonlinear Joint Model Fitted to the Observed Data From Isa-Pd (Blue) and Pd (Red) for Each Analysis



Estimation of the ICARIA final HR

- At the first interim analysis, no approaches provided an HR significantly lower than 1, using all alpha spending functions (Figure 4)
- At the second interim analysis, only the JMcondDist and JMpop approaches provided HRs significantly lower than 1, using all alpha spending functions
- At the final analysis, all approaches allowed to conclude at Isa-Pd benefit on PFS prolongation, with HR estimations significantly lower than 1 using all alpha spending functions

Figure 4. ICARIA Final HR Estimations and Confidence Intervals at the Levels Established by the Alpha Spending Functions According to the Observation- and Simulation-based Approaches for Each Analysis



HR=hazard ratio

CONCLUSIONS

- Simulation-based approaches allow for earlier conclusion on the benefit of Isa-Pd versus Pd, but require a certain amount of information. The first interim analysis may be rather planned at 50% of the expected total number of progression events.
- A simulation study is now needed to evaluate the ability of nonlinear joint models developed from Phase 1 and 2 clinical trial data to contribute to earlier estimation of Phase 3 clinical trial outcomes

REFERENCES

- Desmée S, et al. *Biometrics*. 2017;73(1):305-12.
- Thai HT, et al. *Br J Clin Pharmacol*. 2022;86(5):2052-64.
- Tardivon C, et al. *Clin Pharmacol Ther*. 2019;106(4):810-20.
- Sarclisa® (isatuximab-irf) [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2021. Available from: <https://products.sanofi.us/Sarclisa/Sarclisa.pdf>. Accessed May 23, 2022.
- European Medicines Agency (EMA). Medicines. Sarclisa. Available from: <https://www.ema.europa.eu/en/medicines/human/summaries-opinion/sarclisa-0>. Accessed May 23, 2022.
- Sarclisa® (isatuximab) [package insert]. Nishi Shinjuku, Tokyo: Sanofi Co., Ltd.; 2021. Available from: <https://products.sanofi.us/Sarclisa/Sarclisa.pdf>. Accessed May 23, 2022.
- Attai M, et al. *Lancet*. 2019;394(10214):2096-2107.
- DoMets DL, et al. *Stat Med*. 1994;13(13-14):1341-52; discussion 1353-56.
- Peto R, et al. *Br J Cancer*. 1976;34(6):585-612.
- Riglet F TH, Veyrat-Follet C, Bertrand J. *CPT: Pharmacometrics & Systems Pharmacology*. Submitted.
- Delyon B LM, Moulines E. *The Annals of Statistics*. 1999;27:94-128.

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