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ARTICLE

Isatuximab–dexamethasone–pomalidomide combination effects on serum M protein and PFS in myeloma: Development of a joint model using phase I/II data

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Abstract

This study aimed at leveraging data from phase I/II clinical trials to build a non-linear joint model of serum M-protein kinetics and progression-free survival (PFS) accounting for the effects of isatuximab (Isa), pomalidomide (Pom), and dexamethasone (Dex) in patients with relapsed and/or refractory multiple myeloma. Serum M-protein levels and PFS data from 203 evaluable patients, included either in a phase I/II study ($n=173$) or in a phase I study ($n=30$), were used to build the model. First, we independently developed a longitudinal model and a PFS model. Then, we linked them in a nonlinear joint model by selecting the link function that best captured the association between serum M-protein kinetics and PFS. A Claret tumor growth-inhibition model accounting for the additive effects of Isa, with an E_{\max} function, Pom, and Dex on serum M-protein elimination was selected to describe serum M-protein kinetics. PFS was best described with a log-logistic model and associations with baseline beta-2 microglobulin level, age, and coadministration of Dex were identified. The instantaneous change in serum M-protein level was found to be associated with PFS in the final joint model. Using model simulations, we retrospectively supported the Isa 10 mg/kg weekly for 4 weeks, then biweekly (QW/Q2W) dosing regimen of the ICARIA-MM phase III pivotal study, and validated it using the same phase III pivotal study data.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Isatuximab, combined with pomalidomide–dexamethasone, is approved in several countries for relapsed/refractory multiple myeloma patients, based on the ICARIA-MM phase III study results. Serum M protein, an important biomarker in multiple myeloma, has been well studied for its association with PFS.

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WHAT QUESTION DID THIS STUDY ADDRESS?

Using phase I/II study data, we developed a model for serum M-protein kinetics and PFS, incorporating isatuximab, pomalidomide, and dexamethasone effects. Our objectives were to guide phase III dose selection and predict the ICARIA-MM trial experimental arm through simulation.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The nonlinear joint model, based on phase I/II trial data, successfully captured drug effects on serum M-protein kinetics. Model simulations support the approved isatuximab 10 mg/kg QW/Q2W dosing with pomalidomide–dexamethasone. External validation confirms the model's ability to predict serum M-protein kinetics and PFS in phase III ICARIA-MM trial patients.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This study supports using early clinical trial data for developing nonlinear joint models, highlighting their role in guiding decision making for future phase III studies.

INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disease responsible for 1.6% of all cancer cases and accounts for approximately 10% of the hematologic malignancies.^{1,2} For 2022, the Global Cancer Observatory estimated 187,952 new cases and 121,388 deaths caused by MM worldwide.³ Patients with MM can experience bone pain, bone fractures, infections, and deficiencies in organ functions.^{1,2,4} Conventional MM treatments comprise chemotherapies, proteasome inhibitors (e.g., bortezomib, carfilzomib), corticosteroids, and immunomodulatory drugs (e.g., lenalidomide, pomalidomide [Pom]).^{5–9} Despite therapeutic advances, relapse remains an inevitable feature of MM, resulting in a continued need for new active treatments.¹⁰ In the past few years, new treatment approaches using monoclonal antibodies improved outcomes in patients with relapsed/refractory MM (RRMM) as monotherapy or in combination with conventional treatments.^{11–14}

Isatuximab (Isa) is a monoclonal antibody that selectively binds to a specific epitope of CD38, which is expressed in almost all MM cells. Isa kills tumor cells via multiple mechanisms and can stimulate antitumor immune responses.^{15–17} Phase I/II studies highlighted good tolerability of single-agent Isa and greater antimyeloma activity in RRMM patients receiving at least Isa 10 mg/kg with an overall response rate (ORR) of 20–30%, compared with lower doses.^{18,19} Another phase Ib dose-escalation study of Isa in combination with Pom and low-dose dexamethasone (Dex) in RRMM patients showed clinical

activity with an ORR of 62% and a manageable safety profile.²⁰ Based on these phase I/II results, this combination was assessed in the randomized phase III ICARIA-MM study (NCT02990338), which showed that Isa 10 mg/kg weekly for 4 weeks, then every 2 weeks (QW/Q2W) plus Pom and low-dose Dex (Isa-Pd) significantly improved progression-free survival (PFS) in RRMM patients compared to Pom–Dex (Pd).²¹ Based on the ICARIA-MM study results, Isa–Pd was approved in many countries to treat RRMM patients with ≥ 2 prior lines, including lenalidomide and a proteasome inhibitor. Isa is also approved in combination with carfilzomib–Dex in the United States for RRMM patients with 1–3 prior treatment lines and in the European Union for RRMM patients with ≥ 1 prior therapy.^{12,22} More recently, Isa was approved in Japan as monotherapy or plus Dex for patients with heavily pretreated RRMM who have exhausted available options, including a proteasome inhibitor and an immunomodulatory drug.²³

In most patients, MM is characterized by the secretion of a monoclonal immunoglobulin from malignant plasma cells, called M protein. Changes from baseline in serum M-protein levels are used in the International Myeloma Working Group (IMWG) criteria to assess responses in MM patients.²² However, the whole serum M-protein trajectory could be used to predict long-term clinical benefit (eg, PFS, overall survival [OS]).²⁴ Nonlinear joint models are powerful tools to investigate disease progression through longitudinal biomarker kinetics and occurrence of clinical events (PFS, OS) simultaneously.^{25,26} A joint-modeling framework was successfully applied on early clinical trials data to select and support Isa dosing in

monotherapy or in combination with Dex in Japanese RRMM patients.²⁷ However, no joint model of the Isa–Pd combination was developed before the design, completion, and analysis of the ICARIA-MM study.

Therefore, the objectives of this study were (i) to build a nonlinear joint model of serum M-protein levels and PFS, accounting for Isa, Pom, and Dex effects on tumor response, using data from RRMM patients included in phase I/II studies, (ii) retrospectively support Isa dosing regimen for pivotal phase III studies from simulated virtual patients, and (iii) validate the model on observed ICARIA-MM data.

METHODS

Clinical trial data and study designs

We considered data from two clinical trials (NCT01084252, NCT02283775) conducted in RRMM patients. Study protocols were approved by the Institutional Ethics Committees or independent review boards for each center; the studies followed the Declaration of Helsinki and the ICH GCP guidelines. All patients provided informed consent.

The first phase I/II trial (NCT01084252) included four cohorts: a phase I, dose-escalation monotherapy study to determine the Isa maximum tolerated dose (I-P1); a phase II/stage 1 monotherapy study to explore several Isa dosing regimens (I-P2S1); and a phase II/stage 2 study to evaluate the recommended dose as monotherapy (I-P2S2) or in combination with Dex (Id-P2S2).

Patients in I-P1 received Isa intravenously at 1–20 mg/kg Q2W, or 10 and 20 mg/kg QW. I-P2S1 explored several dosing regimens: 3 mg/kg Q2W, 10 mg/kg Q2W, 10 mg/kg Q2W for 8 weeks, then every 4 weeks (Q2W/Q4W), and 20 mg/kg weekly for 4 weeks then biweekly (QW/Q2W). I-P2S2 patients received Isa 20 mg/kg QW/Q2W and so did patients from Id-P2S2, but in combination with Dex 40 mg (20 mg for ≥75-year-old patients) on days 1, 8, 15, and 22 of each 28-day cycle.

The second study, NCT02283775, was a phase I, dose-escalation study evaluating Isa safety, pharmacokinetics (PK), and efficacy in combination with standard doses of Pom and Dex (IPd-P1). Patients received Isa 5, 10, or 20 mg/kg QW/Q2W plus Dex (following the same dosing regimen as Id-P2S2) and Pom 4 mg, orally from day 1 to 21 of each 28-day cycle.

Disease progression was determined using the IMWG response criteria²² based on serum M-protein measurements and radiology review. Serum M-protein levels were measured at baseline, day 1 of each 28-day cycle, and at study end. As serum M-protein structure is patient specific, no lower limit of quantification (LLOQ) was defined

for serum M protein. Thus, LLOQ was set to the lowest observed level in the dataset.

PFS was defined as the time interval from first study treatment administration to disease progression or death due to any cause, whichever came first. In the absence of disease progression/death before the analysis cutoff date or new anticancer treatment initiation, the patient response was censored at the last valid assessment date.

For this study, we analyzed data from “serum M-protein” patients, for whom disease progression was determined by the serum M-protein-specific criteria. Patients with ≥2 serum M-protein measurements, including one baseline measurement (before treatment initiation), were included in the analysis.

Development of a nonlinear joint model of serum M-protein kinetics and PFS

We used the method described by Keroui et al.²⁸ and developed separately the longitudinal and the time-to-event model, and then we explored different link functions to build the joint model.

Longitudinal M-protein data analysis

We used a nonlinear mixed effect model (NLMEM) to analyze serum M-protein level evolution and characterize its kinetics in the population and interpatient variability (IIV). Let y_{ij} denote the serum M-protein level of individual i at measurement time t_{ij} , where $i \in \{1, \dots, N\}$ with N the total number of individuals, and $j \in \{1, \dots, n_i\}$ with n_i the number of serum M-protein measurements for patient i . Biomarker kinetic data can be described by the following model:

$$y_{ij} = M(t_{ij}, \psi_i, w_i) + g(t_{ij}, \psi_i, w_i, \xi) \varepsilon_{ij} \quad (1)$$

where the function M is the structural model describing the nonlinear trend of serum M-protein evolution. ψ_i is the vector of associated individual parameters, distributed from a log-normal distribution; $\psi_i = \mu \times e^{\eta_i + \beta^l \times w_i}$, with μ the vector of fixed effects, or mean population values, $\eta_i \sim \mathcal{N}(0, \Omega)$, the interindividual random effect vector for subject i with Ω variance–covariance matrix. IIV can be partly explained by some individual covariates w_i with β^l the vector of associated covariates effects. We used a combined error model; $g(t_{ij}, \psi_i, w_i, \xi) = \sigma_{\text{additive}} + \sigma_{\text{proportional}} \times M(t_{ij}, \psi_i, w_i)$, where $\xi = \{\sigma_{\text{additive}}, \sigma_{\text{proportional}}\}$ is the vector of model error parameters to be estimated. ε_{ij} is the residual error at time t_{ij} , assumed to be independently and identically distributed from a standard normal distribution ($\varepsilon_{ij} \sim \mathcal{N}(0, 1)$).

Serum M-protein kinetics

In line with previous studies,^{24,27} we used a Claret tumor growth inhibition (TGI) model²⁹ to describe serum M-protein kinetics with parameters that quantify the intrinsic tumor growth as well as the antitumor drug effect and resistance. The Claret structural model defines the serum M-protein kinetics $M(t)$, with t the time (in days) elapsed since the first serum M-protein measurement, by the following differential equations:

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

$$\frac{dM(t)}{dt} = kg \times M(t) - ks \times \text{Exposure}(t) \times \exp(-R \times (t - t_s)) \times M(t)$$

with t_s the time elapsed between the first serum M-protein measurement and treatment initiation, M_0 the baseline level of serum M protein (g.L^{-1}), kg the net tumor growth constant rate (days^{-1}), ks the drug-induced tumor shrinkage constant rate ($\text{L.mol}^{-1}.\text{days}^{-1}$), and R the drug resistance coefficient (days^{-1}). All drug exposures ($\text{Exposure}(t)$) were expressed in molar concentrations (mol.L^{-1}) to handle drug combinations. In this analysis, the mechanism-based TGI model was used to describe the serum M-protein kinetics in the presence of Isa, Dex, and Pom.

Isa and Dex effects on serum M-protein kinetics

In line with the Thai et al. study,²⁷ the Isa effect on serum M-protein time course was characterized by a maximum effect (E_{\max}) model ($\text{Exposure}_{\text{isa}}(t) = \frac{C_i(t)}{\text{EC50} + C_i(t)}$), where EC50 (mol.L^{-1}) denotes the Isa concentrations needed to reach 50% of its maximum effect and $C_i(t)$ the Isa molar concentration. The Isa PK was described using a two-compartment mammillary model and a target-mediated elimination with two parallel mechanisms: a nonspecific time-dependent clearance and a Michaelis–Menten elimination.³⁰ Given the complexity of the PK model, we used the individual PK parameter vector for subject i as regressors to derive $C_i(t)$.

A linear-effect model was already successfully implemented to capture Dex effect on serum M-protein kinetics.²⁷ Accordingly, we defined: $\text{Exposure}_{\text{dex}}(t) = k_{\text{Dex}} \times C_d(t)$ with k_{dex} the effect coefficient for Dex. Dex molar concentrations $C_d(t)$ were derived from a kinetic–pharmacokinetic (K-PD) model with an elimination rate constant at 0.10 h^{-1} .³¹

Pom effect on serum M-protein kinetics

To obtain the model accounting for all drug effects on ks , we considered the following models for the effect of Pom:

- Linear on ks

$$\text{Exposure}(t) = \text{Exposure}_{\text{isa}}(t) + \text{Exposure}_{\text{pom}}(t) + \text{Exposure}_{\text{dex}}(t)$$

$$\text{Exposure}(t) = \frac{C_i(t)}{\text{EC50} + C_i(t)} + k_{\text{Dex}} \times C_d(t) + k_{\text{Pom}} \times C_p(t)$$

- Interaction on ks

$$\text{Exposure}(t) = \left(\frac{C_i(t)}{\text{EC50} + C_i(t)} + k_{\text{Dex}} \times C_d(t) \right) \times (1 + \text{INT}_{i-p} \times C_p(t))$$

- Interaction on EC50

$$\text{Exposure}(t) = \frac{C_i(t)}{\text{EC50} \times (1 + \text{INT}_{i-p} \times C_p(t)) + C_i(t)} + k_{\text{Dex}} \times C_d(t)$$

with k_{Pom} and INT_{i-p} the linear and interaction effect coefficients for Pom, respectively. Pom molar concentrations $C_p(t)$ were derived from a K-PD model with an elimination rate constant at 0.15 h^{-1} .³²

We modeled serum M-protein levels from serum M-protein patients using the NLMEM model described in Equation (1). Assuming a TGI Claret model for the serum M-protein kinetics incorporating Isa E_{\max} and Dex linear-effect models, the best Pom effect model was selected on corrected version of Bayesian information criteria (BICc). Individual parameters were ensured to be positive following a log-normal distribution. It was assumed that $\eta_i \sim \mathcal{N}(0, \Omega)$ with $\Omega = \text{diag}(\omega_{M_0}, \omega_{kg}, \omega_{ks}, \omega_R, \omega_{\text{EC50}})$. We could estimate an IIV on EC50 given several patients had both Isa PK and serum M-protein data across a wide range of Isa doses.

Covariate effect on serum M-protein kinetics

Covariate associations were explored on M_0 , ks , kg , R , and EC50. We built the covariate model using COSSAC (COnditional Sampling use for Stepwise Approach).³³ We set the test significance threshold for the screening on the samples from the a posteriori conditional distribution $\text{top} = 0.05$. A total of 26 demographic and laboratory covariates were evaluated (listed in Supplementary Information). The continuous covariates were log transformed and centered on the median value. Missing continuous covariates were imputed to the median and missing categorical covariates were imputed to the most common value.

Time-to-event data analysis

We considered a parametric time-to-event model with $h_i(t)$ the individual hazard function as:

$$h_i(t) = \begin{cases} 0 & \text{before treatment initiation } (t \leq t_s) \\ h_0(t) \times \exp(\beta^s \times X_i) & \text{after treatment initiation } (t > t_s) \end{cases}$$

where $h_0(t)$ is the baseline hazard function and β^s is the vector of coefficients associated with the vector of baseline covariates X_i of individual i . To characterize $h_0(t)$, we selected a parametric function among the following: Weibull, log logistic, and Gompertz on BICc.

Covariate effects on time-to-event data were captured using the stepwise covariate modeling (SCM) method on BICc, with the same set of covariates as for the longitudinal data model plus concomitant treatment with Dex.

Joint analysis

The joint nonlinear model was defined as follows:

$$h_i(t | M_i(t), X_i) = \begin{cases} 0, & t \leq t_s \\ h_0(t) \times \exp(\beta^s \times X_i + \beta_M \times L(t, \psi_i, w_i)), & t > t_s \end{cases}$$

where $M_i(t) = \{M(u, \psi_i, w_i), 0 \leq u \leq t\}$ is the true underlying longitudinal biomarker process until time t ($t > 0$). β_M quantifies the effect on PFS of the link function $L(\cdot)$ depending on t , ψ_i , and w_i .

Several link functions $L(\cdot)$ were compared including:

- No link: $L(\cdot) = 0$
- Current serum M protein: $L(t, \psi_i, w_i) = M(t, \psi_i, w_i)$
- Serum M-protein slope: $L(t, \psi_i, w_i) = \frac{dM(t, \psi_i, w_i)}{dt}$

Link function selection was based on BICc.³⁴ Covariate associations selected in the longitudinal and TTE submodels were further evaluated in the joint model: a backward procedure based on Wald tests was performed to remove covariates no longer significant at the level $p = 0.05$.

Internal model evaluation

For the longitudinal submodel, we performed (i) standard goodness-of-fit (GOF) plots: individual fits, observations versus predictions, and individual weighted residuals (IWRES) versus predictions and (ii) simulation-based GOF plots: normalized prediction distribution errors (NPDE) and longitudinal visual predictive check (VPC)

plots. For the latter, we simulated 500 datasets accounting for the risk of progression and censoring using previously described methods³⁵ (more details on VPCs realization in Supplementary Information). The simulation accounted for the patient individual dosing history and censoring information. For the PFS submodel, we performed (i) Cox-Snell and Martingale residuals and (ii) TTE VPC using the 500 simulated datasets described earlier.

Model predictions

To compare the Isa dosing regimen 10 versus 20 mg/kg QW/Q2W in combination with Pom and Dex, we simulated the serum M-protein profiles and PFS of 1000 individuals for 80 weeks. We used the standard Dex and Pom dosing regimens in our population; 40 mg QW or 20 mg QW (for patients ≥ 75 years) for Dex and 4 mg on days 1–21 of each 28-day cycle for Pom. Patients' weight and age were set to the observed median value in our population. For each dosing regimen, we computed the change in serum M-protein level from baseline to weeks 8 and 12 as well as median PFS.

Of note, because our model could simulate individual time profiles of Isa clearance disconnected from serum M-protein individual kinetics, we used a different PK model for Isa exposure with parallel linear and nonlinear elimination, but without the nonspecific time dependence in the linear process (Supplementary Information).³⁶

External validation

External validation was performed using longitudinal and TTE VPC plots of data from the Isa-Pd treatment arm of the phase III ICARIA-MM trial.²¹ Here as well we used a PK model for Isa exposure without the nonspecific time dependence in the linear-elimination process.

To adjust for differences in baseline serum M protein in the phases I/II and III populations, we considered two approaches: (i) we used individual baseline serum M-protein (i.e., $y_i(t=0)$) levels observed in ICARIA-MM as regressors and (ii) we set μ_{M_0} and ω_{M_0} to the geometric mean of the observed baseline levels of serum M protein (i.e., $y_i(t=0)$) and the standard deviation of the logarithm of the observed baseline levels of serum M protein (i.e., $\log(y_i(t=0))$), respectively.

Implementation

Model parameters were estimated using the stochastic approximation of expectation-maximization (SAEM)

algorithm implemented in Monolix2021R2[®]. Estimation errors were calculated by asymptotic approximation and log likelihood by importance sampling. COSSAC and SCM covariate selection algorithms were ran using Monolix2021R2[®]. Model prediction simulations were performed using Simulx2021R2[®]. VPCs and other GOF plots were obtained with the R software (version 4.2.0).

RESULTS

Data

Of the 375 patients included in the NCT01084252 and NCT02283775 studies, a total of 203 serum M-protein patients with RRMM were included in this analysis (Table 1), with 1879 serum M-protein measurements (median [IQR], 8 [4–14] samples/patient). Median PFS was 33 weeks (95% CI: 27–45); 114 (56%) patients presented the event during the study and 89 (44%) were censored. Observed longitudinal data and PFS Kaplan–Meier curves for each cohort are shown in Figure 1.

In the studied population, median age was 65 years (range, 37–84) and the median weight (WT) was 72.4 kg (39.9–152.5) (Table 2). Baseline serum beta-2-microglobulin (B2MBL) and serum M-protein (MPROT) levels were 4.38 mg.L⁻¹ (1.4–19.5) and 27.10 mg.L⁻¹ (5.0–84.0), respectively. In IPd-P1, the median serum M-protein baseline level at 16.50 g.L⁻¹ (5.0–38.6) was lower compared with the other cohorts, and severe patients (ISS stage 3) were underrepresented. Of patients' MM included in the analysis,

68.5% were classified as immunoglobulin-G type. The rate of missing values at baseline was <20% for all covariates.

Longitudinal data model

Pom effect was better captured by an additive model on *ks* outperforming the model with Pom interaction on *ks* ($\Delta\text{BICc} = -6.79$) and the model with Pom interaction on EC50 ($\Delta\text{BICc} = -2.88$).

Applying the COSSAC procedure, normalized albumin level (ALBN), normalized alkaline level (ALKN), normalized aspartate aminotransferase level (ASTN), bone marrow plasma cells rate (BMPC), LINE, and the study (STUD) were found to have a significant influence on M_0 only; the main immunoglobulin type (IGGTYPE) was found to significantly influence M_0 , *kg*, and *ks*; and cytogenetic abnormality at initial diagnosis (CYTO) was significantly associated with treatment resistance apparition rate *R*.

Final serum M-protein model parameter estimates presented in Table S1 were precise (relative standard error [RSE] <50%). Individual predictive curves matched the observed biomarker measurements (Figure S1) and residuals were normally distributed around 0, indicating an absence of error model misspecification (Figure S2).

Time-to-event model

Log-logistic baseline hazard model best characterized the baseline hazard.

TABLE 1 Sample sizes and dosing regimen of the patient cohorts forming the NCT01084252 and NCT02283775 studies.

Study name	Phase	Cohort	Isa dosing regimen	Supplementary treatments	Study sample size	Serum M-protein patients
NCT01084252	Phase I	I-P1	1-20Q2W/10-20QW	–	73	0
	Phase II, stage 1	I-P2S1	3Q2W	–	23	13
			10Q2W	–	24	15
			20QW/Q2W	–	25	17
			10Q2W/Q4W	–	25	19
	Phase II, stage 2	I-P2S2	20QW/Q2W	–	107	71
	Phase II, stage 2	Id-P2S2	20QW/Q2W	Dex ^a	53	18
Total				330	173	
NCT02283775	Phase I	IPd-P1	5QW/Q2W	Dex ^a + Pom ^b	8	4
			10QW/Q2W	Dex ^a + Pom ^b	31	22
			20QW/Q2W	Dex ^a + Pom ^b	6	4
	Total				45	30

Abbreviations: Q2W, biweekly; Q2W/Q4W, biweekly for 8 weeks, then every 4 weeks; QW/Q2W, weekly for 4 weeks, then biweekly.

^aDexamethasone (Dex) administered at 40 mg/day (20 mg/day for patients ≥ 75 years) on days 1, 8, 15, and 22 of each treatment cycle.

^bPomalidomide (Pom) administered at 4 mg, orally from days 1 to 21 of each 28-day treatment cycle.

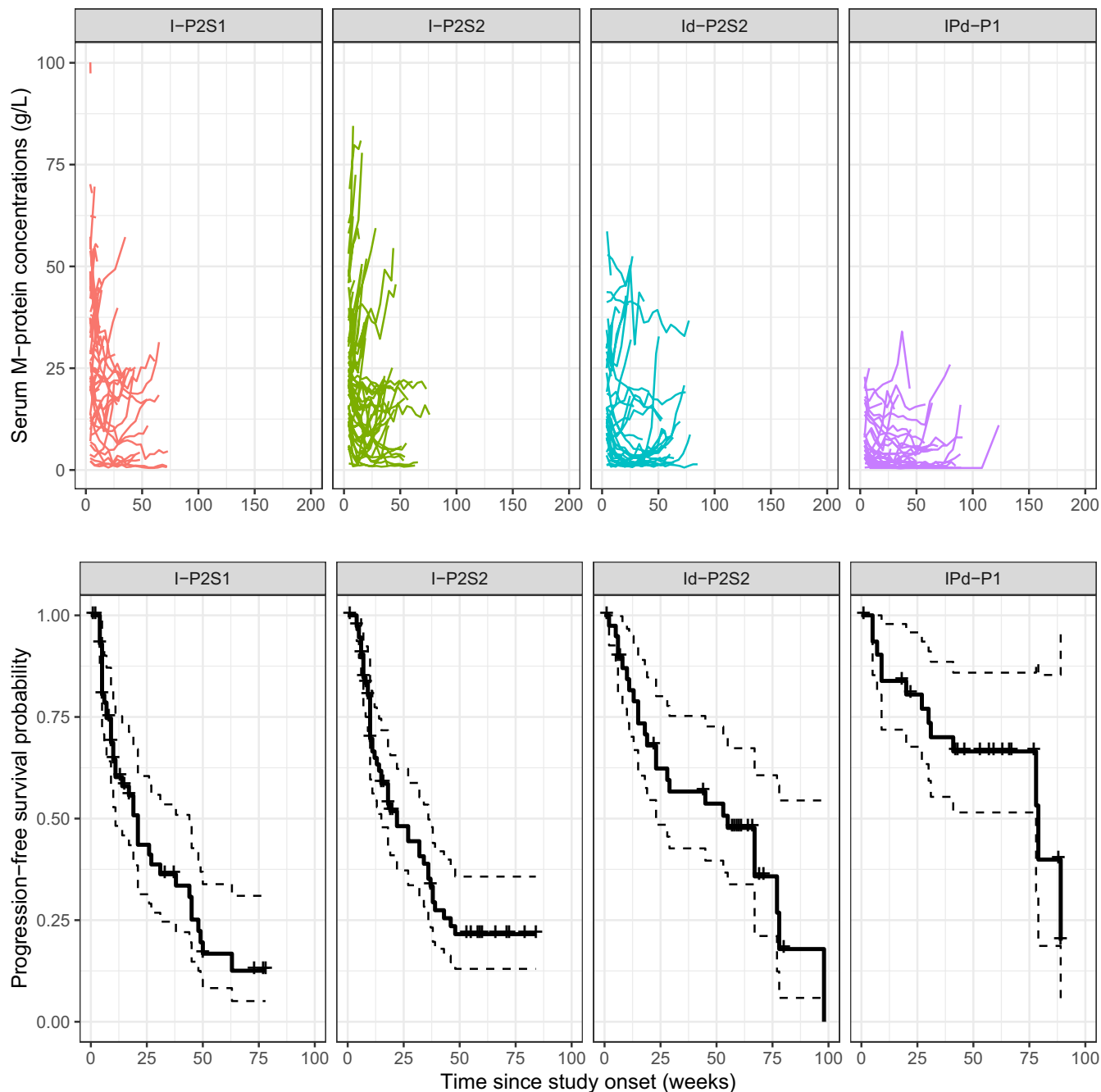


FIGURE 1 Spaghetti plots of individual serum M-protein profiles (top) and observed Kaplan–Meier curves with their 90% confidence interval (bottom) versus time since study onset per cohort.

$$h_0(t) = \frac{\frac{\alpha}{\lambda} \times \left(\frac{t}{\lambda}\right)^{\alpha-1}}{1 + \left(\frac{t}{\lambda}\right)^{\alpha}}$$

where α denotes the log-logistic shape parameter and λ the scale parameter corresponding to median PFS, which was estimated at 47.9 weeks (RSE = 7%).

SCM automatic covariate model selection procedure found a protective effect of age ($\beta_{AGE} = -1.82$) and Dex administration ($\beta_{DEX} = 0.69$), as well as a deleterious effect of B2MBL ($\beta_{B2MBL} = 1.13$) on PFS.

The final PFS covariate model parameter estimates presented in Table S2 were precise. GOF plots (Figures S3, S4) showed that the model predictions were in agreement with observed data.

Joint model

The link function that best captured the association of serum M-protein kinetics and PFS was the current M-protein slope. The effect of age on PFS was no longer

TABLE 2 Demographic and laboratory covariates at baseline in the population of serum M-protein patients from the NCT01084252 and NCT02283775 studies.

Study acronym	I-P2S1 n = 64	I-P2S2 n = 71	Id-P2S2 n = 38	IPd-P1 n = 30	All N = 203
Continuous covariates (unit), median [min-max]					
Age (years)	63.0 [38.0–84.0]	68.0 [37.0–84.0]	65.0 [47.0–79.0]	66.5 [42.0–82.0]	65.0 [37.0–84.0]
Wt (kg)	76.6 [42.5–152.5]	70.0 [39.9–100.0]	71.0 [42.0–129.8]	83.3 [49.6–118.8]	72.4 [39.9–152.5]
GFR (mL/1.73 m ² /min) ^a	72.30 [22.81–116.51]	71.21 [18.65–157.39]	72.33 [28.19–186.45]	72.34 [34.74–124.77]	72.12 [18.65–186.45]
B2MBL (mg.L ⁻¹) ^a	4.55 [1.64–16.10]	5.04 [1.32–19.50]	4.16 [2.05–14.80]	3.27 [1.84–7.30]	4.38 [1.32–19.50]
BMPC (%) ^a	26.7 [0–97.0]	30.0 [0–100]	30.0 [1.0–100]	28.5 [1.0–90.0]	30.0 [0–100]
MPROT (g.L ⁻¹)	27.35 [6.10–71.10]	31.20 [7.70–84.00]	26.35 [9.00–75.90]	16.50 [5.00–38.60]	27.10 [5.00–84.00]
LYM (giga.L ⁻¹) ^a	0.95 [0.30–3.60]	1.16 [0.30–2.58]	1.15 [0.52–3.59]	0.96 [0.34–1.69]	1.05 [0.30–3.60]
CCAL (mgdL ⁻¹) ^a	9.00 [7.60–14.30]	9.42 [4.81–13.83]	9.29 [8.02–12.93]	9.28 [8.72–10.53]	9.22 [4.81–14.30]
Duration (h)	68.27 [25.73–182.21]	62.72 [11.96–253.80]	64.94 [14.69–275.98]	60.22 [12.55–189.27]	65.68 [11.96–275.98]
Line	5 [2–12]	4 [2–10]	4 [2–10]	3 [1–10]	4 [1–12]
Categorical covariates, n (%)					
Sex					
Male	37 (57.8)	32 (45.1)	22 (57.9)	17 (56.7)	108 (53.2)
Female	27 (42.2)	39 (54.9)	16 (42.1)	13 (43.3)	95 (46.8)
Race					
White	53 (82.8)	58 (81.7)	33 (86.8)	28 (93.3)	172 (84.7)
Black	7 (10.9)	3 (4.2)	3 (7.9)	1 (3.3)	14 (6.9)
Asian	1 (1.6)	0	0	0	1 (0.5)
Other	3 (4.7)	10 (14.1)	2 (5.3)	1 (3.3)	16 (7.9)
ISS ^a					
1	21 (32.8)	16 (22.5)	10 (26.3)	15 (50.0)	62 (30.5)
2	20 (31.2)	27 (38.0)	15 (39.5)	13 (43.3)	75 (36.9)
3	23 (35.9)	28 (39.4)	13 (34.2)	2 (6.7)	66 (32.5)
PCYTOMA					
No	52 (81.2)	64 (90.1)	31 (81.6)	28 (93.3)	175 (86.2)
Yes	12 (18.8)	7 (9.9)	7 (18.4)	2 (6.7)	28 (13.8)
REF_LEN					
No	12 (18.8)	27 (38.0)	18 (47.4)	7 (23.3)	64 (31.5)
Yes	52 (81.2)	44 (62.0)	20 (52.6)	23 (76.7)	139 (68.5)
REF_POM					
No	6 (9.4)	19 (26.8)	6 (15.8)	6 (20.0)	37 (18.2)
Yes	58 (90.6)	52 (73.2)	32 (84.2)	24 (80.0)	166 (81.8)
CYTO ^a					
Standard risk	46 (71.9)	55 (77.5)	29 (76.3)	28 (93.5)	158 (77.8)
High risk	18 (28.1)	16 (22.5)	9 (23.7)	2 (6.7)	45 (22.2)

TABLE 2 (Continued)

Study acronym	I-P2S1	I-P2S2	Id-P2S2	IPd-P1	All
Sample size	n = 64	n = 71	n = 38	n = 30	N = 203
ECOG	0 10 (15.6)	33 (46.5)	21 (55.3)	15 (50.0)	79 (38.9)
	1 46 (71.9)	33 (46.5)	14 (36.8)	14 (46.7)	107 (52.7)
	2 8 (12.5)	5 (7.0)	3 (7.9)	1 (3.3)	17 (8.4)
DEX	No 64 (100)	71 (100)	0	0	135 (66.5)
	Yes 0	0	38 (100)	30 (100)	68 (33.5)
IGGTYPE	IgG 45 (70.3)	45 (63.4)	25 (65.8)	24 (80.0)	139 (68.5)
	Non-IgG 19 (29.7)	26 (36.6)	13 (34.2)	6 (20.0)	64 (31.5)

Abbreviations: B2MBL, beta-2 microglobulin; BMPC, bone marrow plasma cells; CCAL, corrected serum calcium; CYTO, cytogenetic abnormalities at initial diagnosis; DEX, patients treated with dexamethasone; Duration, time from diagnosis to first dose; ECOG, Eastern Cooperative Oncology Group performance status; GFR, estimated glomerular filtration rate; IGGTYPE, main immunoglobulin type; ISS, international staging system; Line, number of treatment lines; LYM, plasma lymphocyte number; MPROT, serum M-protein concentration; PCYTOMA, incidence of extramedullary disease or plasmacytoma; REF_LEN, patients refractory to lenalidomide (LEN); REF_POM, patients refractory to pomalidomide (POM); Wt, weight.

^aCovariates with missing values: GFR, 1.5% missing; B2MBL, 0.5% missing; BMPC, 13.3% missing; LYM, 0.5% missing; CCAL, 1.5% missing; ISS, 0.5% missing; CYTO, 18.2% missing. Missing continuous covariates were imputed to the median and missing categorical covariates were imputed to the most common value. The rate of missing values at baseline was >20% for all covariates.

significant in the final joint model ($p=0.22$). Final joint model parameter estimates and their RSEs are summarized in Table 3. Parameters were reasonably well estimated with RSE <50% for both fixed effects and IIV components. The final covariate model highlighted that patients included in TCD14079 or with lower baseline ALBN level, ALKN levels, or IgG patients tended to have higher M_0 . Similarly, patients with higher ASTN levels at baseline, BMPC, or higher number of previous treatment lines tended to have higher M_0 . In addition, non-IgG patients tended to have a higher kg and ks . The presence of cytogenetics abnormalities at diagnosis induced a faster R. Regarding PFS, the absence of Dex coadministration and higher baseline B2MBL level induced a higher instantaneous risk. Covariates effect on both serum M-protein kinetics and PFS probability is illustrated in Figure S5. The IGGTYPE and other longitudinal model-associated covariates impacted serum M-protein kinetics, but had limited impact on PFS probability. Only the presence of CYTO induced a faster R and led to a lower PFS probability over time compared with standard risk patients.

The model described reasonably well both serum M-protein and PFS data, as the observed percentiles from longitudinal data and the PFS Kaplan–Meier curve were within the corresponding model-predicted intervals. However, we observed an underestimation of PFS after 40 weeks in Id-P2S2 and IPd-P1 due to the small sample size and few patients remaining at end of study (Figure 2). Additional GOF plots are shown in Figures S7–S9.

Model predictions

No apparent differences in median change from baseline (90% PI) at 8 weeks (−55.8% [−98.0, 10.5] vs. −57.7% [−98.0, 9.2]) and at 12 weeks (−64.5% [−98.3, 15.1] vs. −66.2% [−98.4, 13.6]) between Isa 10 mg/kg versus 20 mg/kg in combination with Pom–Dex. Similarly, Isa 20 mg/kg did not improve median PFS with a simulation based estimate at 39.6 weeks (35.7–42.6) versus 38.9 weeks (35.6–41.7) for Isa 10 mg/kg.

External validation

Figure 3 displays the external validation of our final joint model, on data from the Isa-Pd arm of the ICARIA-MM trial, with individual estimates of baseline M-protein levels from ICARIA-MM as regressors. The longitudinal VPC demonstrates the model's ability to reproduce both the central trend and variability of the observed data. Regarding time-to-event VPC, the 90% prediction interval around the median Kaplan–Meier curve

Parameter	Estimates (RSE %)		<i>p</i> value (Wald test)
	Fixed effect	Interindividual coefficient of variation in %	
Longitudinal data model			
M_0 (g.L ⁻¹)	25.6 (4)	0.4 (4)	
$\beta_{M_0,ALBN}$	-1.8 (10)	-	$<2.2 \times 10^{-16}$
$\beta_{M_0,ALKN}$	-0.28 (27)	-	2.3×10^{-4}
$\beta_{M_0,ASTN}$	0.16 (41)	-	1.5×10^{-2}
$\beta_{M_0,BMPC}$	0.045 (45)	-	2.7×10^{-2}
$\beta_{M_0,LINE}$	0.21 (33)	-	2.2×10^{-3}
$\beta_{M_0,IGGTYPE_nonIgG}$	-0.26 (25)	-	4.5×10^{-5}
$\beta_{M_0,STUD_TED10893}$	-0.36 (25)	-	4.4×10^{-5}
<i>kg</i> (days ⁻¹)	0.003 (12)	1.11 (8)	
$\beta_{kg,IGGTYPE_nonIgG}$	0.58 (33)	-	2.5×10^{-3}
<i>ks</i> (L.mol ⁻¹ .days ⁻¹)	0.017 (11)	0.92 (8)	
$\beta_{ks,IGGTYPE_nonIgG}$	0.634 (29)	-	5.7×10^{-4}
<i>R</i> (days ⁻¹)	0.015 (12)	1.12 (8)	
$\beta_{R,CYTO_HighRisk}$	1.23 (24)	-	2.8×10^{-5}
EC50 (mol.L ⁻¹)	0.516 (41)	2.77 (37)	
<i>k_{Dex}</i>	9.35 (14)	-	
<i>k_{Pom}</i>	5.52 (23)	-	
$\sigma_{additive}$ (g.L ⁻¹)	0.46 (5)	-	
$\sigma_{proportional}$	0.08 (4)	-	
Time-to-event model			
α	1.86 (10)	-	
λ (days)	293.3 (27)	-	
β_M	14 (9)	-	
β_{B2MBL}	0.52 (20)	-	5.6×10^{-7}
β_{DEX}	-0.59 (20)	-	6.5×10^{-7}

Abbreviations: M_0 , baseline level of serum M protein; $\beta_{M_0,ALBN}$, effect of baseline serum albumin levels (ALBN) on M_0 with the later varying from 45.9 for the 5th percentile to 16.8 for the 95th percentile of ALBN in the population; $\beta_{M_0,ALKN}$, effect of baseline serum alkaline phosphatase levels (ALKN) on M_0 [30.4–21.5]; $\beta_{M_0,ASTN}$, effect of baseline aspartate amino transferase levels (ASTN) on M_0 [23.1–29.3]; $\beta_{M_0,BMPC}$, effect of bone marrow plasma cells (BMPC) on M_0 [22.9–26.8]; $\beta_{M_0,LINE}$, effect of number of lines (LINE) on M_0 [22.1–30.3]; $\beta_{M_0,IGGTYPE_nonIgG}$, effect of main immunoglobulin type (IGGTYPE) on M_0 [19.7 for non-IgG patients]; $\beta_{M_0,STUD_TED10893}$, effect of study (STUD) on M_0 [17.8 for patients included in TED10893]; *kg*, tumor net growth rate; $\beta_{kg,IGGTYPE_nonIgG}$, effect of IGGTYPE on *kg* [0.0052 for non-IgG patients]; *ks*, drug-induced cell-kill rate; $\beta_{ks,IGGTYPE_nonIgG}$, effect of IGGTYPE on *ks* [0.032 for non-IgG patients]; *R*, tumor resistance to the drug appearance rate; $\beta_{R,CYTO_HighRisk}$, effect of cytogenetic abnormalities at initial diagnosis (CYTO) on *R* [0.051 for high-risk patients]; EC50, isatuximab concentrations at which 50% of its tumor shrinkage activity is reached; *k_{Dex}*, additive effect coefficient of Dex; *k_{Pom}*, additive effect coefficient of Pom; $\sigma_{additive}$ and $\sigma_{proportional}$ additive and proportional residual error terms of serum M-protein kinetics; α and λ , shape and scale parameter of the log-logistic baseline hazard; β_M , β_{B2MBL} and β_{DEX} , effect coefficient of the model-predicted slope of serum M-protein at time *t*, baseline beta-2 microglobulin levels (B2MBL), and dexamethasone coadministration (DEX) on the baseline hazard.

TABLE 3 Estimates and relative standard errors (RSE %) of population parameters for the final joint covariate model of serum M-protein kinetics and progression-free survival in the serum M-protein patients of the NCT01084252 and NCT02283775 studies.

includes the Kaplan–Meier curve from the observed data. Additionally, the model predicted reasonably well the observed serum M-protein and PFS results, notably

with a median PFS (5th–95th percentiles) from simulation equal to 43.9 weeks (36.2–53.2), comparable to the median PFS of 49.6 weeks (38.1–63.9) observed in Isa-Pd

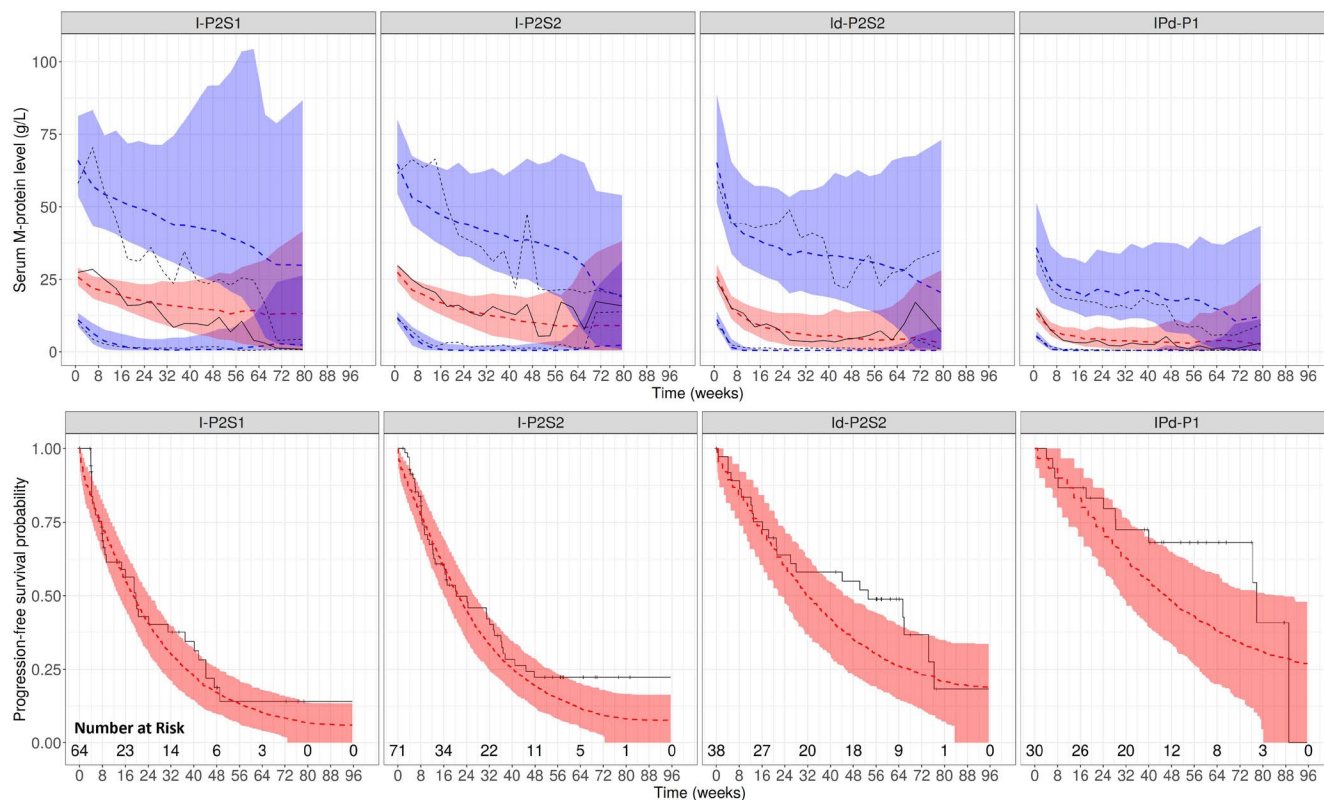


FIGURE 2 Visual predictive check plots for serum M-protein kinetics (top) and progression-free survival (bottom) of the final joint model stratified by cohort. Five hundred datasets were simulated. Top panel: The black solid and dashed lines represent the 50th, 5th, and 95th observed percentiles; the red and blue dashed lines represent the 50th, 5th, and 95th model-predicted percentiles; and the pink and blue areas represent the 90% prediction intervals around the 50th, 5th, and 95th model-predicted percentiles. Bottom panel: The black solid line represents the Kaplan–Meier curve of the observations and the red dotted line and pink area the 50th and the 90% prediction interval of the model-simulated Kaplan–Meier curves.

ICARIA-MM patients. VPCs fixing μ_{M0} at $17.66\text{g}\cdot\text{L}^{-1}$, the geometric mean of ICARIA-MM individual baseline M-protein levels, and ω_{M0} at 0.63 the standard deviation of the logarithms of ICARIA-MM individual baseline M-protein levels are represented in Figure S9. They show a similar ability to predict observed M-protein kinetics and PFS. Stratified VPCs (Figures S10, S11) demonstrate the ability of the final joint model to predict PFS according to ALBN, B2MBL, and IGGTYPE. However, the final joint model tended to overestimate the PFS probability for the 13 ICARIA-MM patients with extramedullary disease or plasmacytoma (PCYTOMA).

DISCUSSION

In this work, we developed a nonlinear joint model of serum M protein and PFS from 203 RRMM patients included in phase I/II studies. A joint modeling framework simultaneously analyzing Isa PK, serum M-protein, and PFS data was preferred to characterize the effect of Isa-Pd rather than exposure–response approaches not accounting

for longitudinal data or a two-stage approach that can lead to biased parameter estimates.³⁷ In addition, contrary to exposure–response analysis, joint modeling allows model-based simulations which were used to retrospectively support Isa dosing regimen of a pivotal phase III study and validate it on the data from the same pivotal phase III study.

In line with previous studies, we successfully used the Claret model to describe our serum M-protein data as a surrogate of tumor growth in RRMM patients.^{36,38} In addition to the effect of Isa and Dex on serum M-protein kinetics already described by Thai et al.,²⁷ we incorporated the additive effect of Pom. Also in agreement with previous analyses, we highlighted the slope of serum M-protein kinetics to best capture the association with PFS.^{24,27}

We also studied the impact of baseline covariates on both serum M-protein kinetics and risk of PFS. As missing covariates did not exceed 20%, we decided to proceed with a single imputation by the mode and the median value, as it was shown to efficiently capture the covariate–parameter relationship in NLMEM, when the rate of missing values does not exceed 50%.³⁹ The major baseline covariates

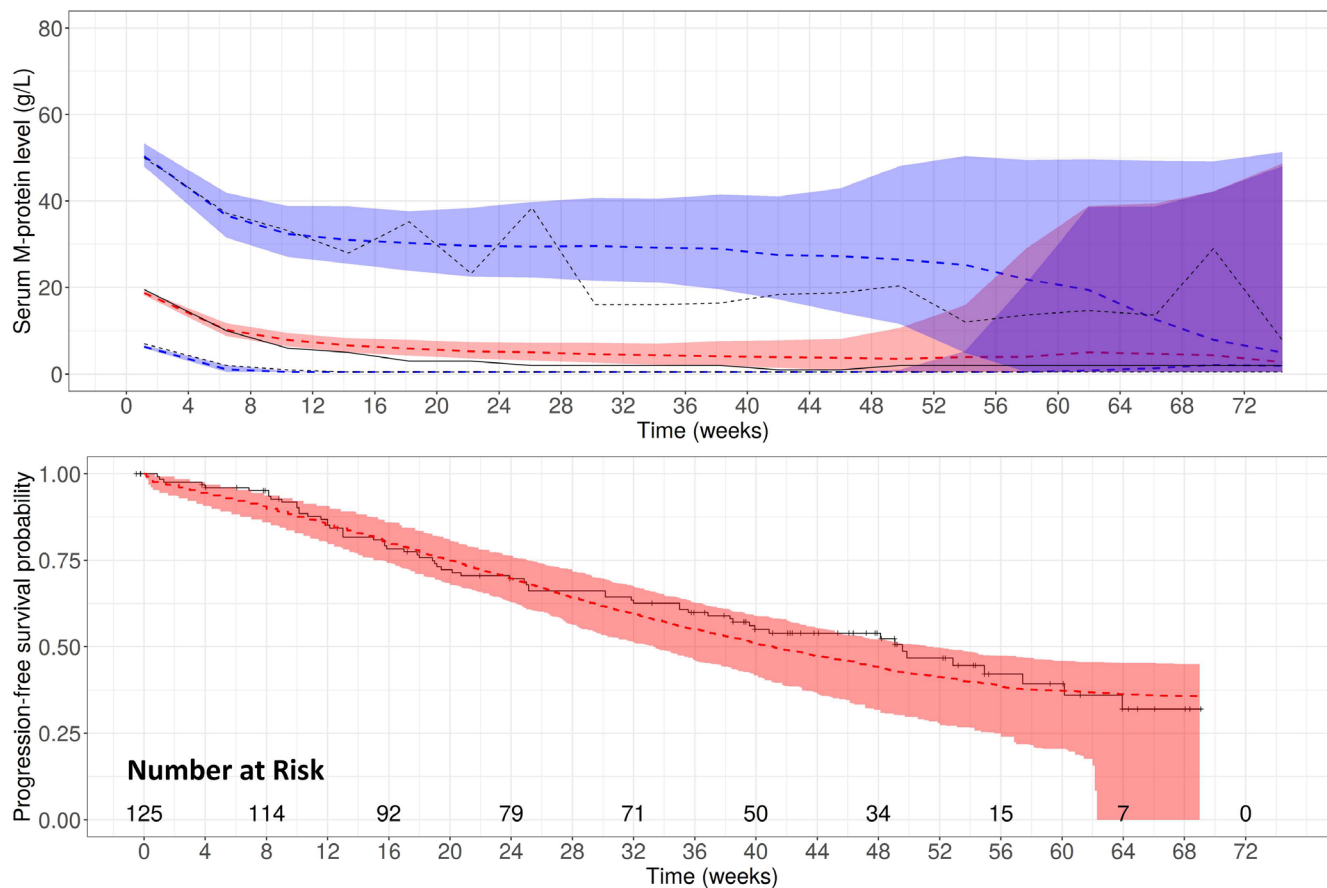


FIGURE 3 Visual predictive check plots for serum M-protein kinetics (top) and progression-free survival (bottom) of the final joint model. Five hundred datasets were simulated. Top panel: The black solid and dashed lines represent the 50th, 5th, and 95th ICARIA-MM observed percentiles; the red and blue dashed lines represent the 50th, 5th, and 95th model-predicted percentiles; and the pink and blue areas represent the 90% prediction intervals around the 50th, 5th, and 95th model-predicted percentiles. Bottom panel: The black solid line represents the Kaplan–Meier curve of the ICARIA-MM observations and the red dotted line and pink area the 50th and the 90% prediction interval of the model-simulated Kaplan–Meier curves.

identified were ALBN, IGGTYPE, CYTO, B2MBL, and DEX. ALBN and B2MBL are part of the ISS/Revised-ISS staging systems, which are relevant for prognosis, because patients with more advanced stage (ISS stage III) are less likely to respond to treatment. IGGTYPE was found to impact serum M-protein kinetics on M_0 , kg , and ks leading to slower and smaller decrease in serum M protein for IgG patients, but similar serum M-protein re-increase. This finding is in line with previous studies showing that IgG patients have a slower decrease in Isa clearance over time and therefore have a twofold lower drug exposure.³⁰ However, IGGTYPE tended to have a limited impact on PFS, in line with previous joint model²⁴ and exposure–response analysis.⁴⁰ The presence of cytogenetic risk at initial diagnosis was found associated for the first time with faster appearance of treatment resistance and increased risk of PFS events. Furthermore, Thai et al.²⁷ in a larger group including our patients plus 31 Japanese patients, also found a lower PFS probability over time for patients without Dex coadministration and higher baseline beta-2

microglobulin levels. However, they also found an effect of the presence of extramedullary disease or plasmacytoma which we did not identify in our model, though it was significantly associated with a higher risk of disease progression in a univariate survival model. Other genetic determinants such as FcGR3A polymorphism and factors such as HLA/KIR were observed, but not considered in our multivariate analysis.

Although using the biomarker slope as link function led to extreme values in survival model residuals in patients with atypical serum M-protein kinetics (Figure S8), GOF plots (Figures 2, S6, S7) did not show any model misspecification. Of note, the conditions were favorable as we used individual PK estimates for Isa exposure. However, to simulate virtual patients, we had to use a different PK model for Isa. The PK model we used to derive Isa exposure over time is a two-compartment mammillary model with a target-mediated elimination process via two parallel mechanisms: a nonspecific time-dependent clearance and a

Michaelis–Menten elimination.³⁰ Such models are commonly used for monoclonal antibodies^{30,41,42} where the time-dependent clearance is a proxy for the impact of an amelioration in disease status⁴³ in a virtuous cycle. However, simulating from these models can lead to disconnected serum M-protein kinetics and Isa clearance evolution in time since the impact of disease amelioration (eg, decrease in serum M protein) on Isa clearance could not be modeled. More mechanistic joint PK/TGI/PFS modeling would overcome this issue. Consequently, in our work, for the comparison of dosing regimen and the external validation, we used a simpler PK model without the time dependence in the linear elimination process.³⁶ Our simulations supported the choice of Isa 10 mg/kg QW/Q2W evaluated in the ICARIA-MM study. To take into account the difference between the population of predicted patients (phase III) and the population used to build the model (phase I/II), who generally have worse prognostic features with significantly greater baseline serum M-protein levels, two methods were implemented, which led to similarly realistic predictions for ICARIA-MM Isa-Pd arm patients. Both rely on baseline variables only obtained after the inclusion of all patients from the ICARIA data, which represents a major limitation. Using values from the literature for the baseline serum M-protein level population, model parameters could help mitigate this limitation. The latter option should be favored as more and more physiological models in different patient populations are built and published. However, we cannot adjust our model for any important prognostic factor not identified in the phase I/II study data. The PCYTOMA covariate is a good example. A higher risk of disease progression has been identified in patients with extramedullary disease or plasmacytoma among ICARIA-MM patients,^{24,27} but not in our model on phase I/II study data. Consequently, our predictions cannot well discriminate the risk of PFS events over time across PCYTOMA categories (Figure S11). This result points to a new methodology to calibrate the model for predicting phase III data.

No consensus exists on the optimal strategy for joint model selection. Using the Kerioui et al.²⁸ method, an alternative could be to systematically explore combinations of baseline hazards and link functions from a pre-defined panel. This could lead to the selection of a simpler baseline risk function (eg, exponential) so that change in risk evolution over time would only be driven by the biomarker kinetics.

In this work, we showed that PFS data in early clinical trials would be very useful to support dose selection and clinical study design of the investigated drug at a later stage. However, the availability of PFS data could be challenging, since PFS is generally not the primary endpoint

of phase I studies in oncology and more time is needed to collect PFS than ORR data. This is a fundamental challenge raised by the Optimus project promoted by the FDA to respond to novel problematics for dose optimization and selection in oncology drug development (Project Optimus/FDA). In case of nonavailability of PFS data, it was shown that modeling approaches aiming to characterize the relationship between drug exposure and tumor size kinetics can be recommended to optimize early dose-selection decisions.⁴⁴ In line with these recommendations, this study brings new evidence on the potential of modeling and simulation approaches to optimize the decision-making process. Joint models with PFS data could be used afterward to refine the prediction and inform the outcome of phase III trials.

To conclude, we presented here how nonlinear joint modeling of biomarker and clinical endpoint data from patients in phase I/II studies can effectively support the dosing decision for a phase III pivotal trial. This proof of concept was achieved from the retrospective analysis of data from studies at different phases of development for Isa combination therapy in RRMM patients. This work paves the way for a more systematic development of joint models based on early-phase data, to aid decision making in future trials. Joint modeling for efficacy could be extended to consider safety endpoints, for a better evaluation of the benefit–risk balance.

AUTHOR CONTRIBUTIONS

A.P., S.D., F.R., H-T.T., Z.K., D.S., C.V-F., and J.B. wrote the manuscript; S.D., H-T.T., C.V-F., and J.B. designed the research; A.P., S.D., H-T.T., C.V-F., and J.B. performed the research; A.P., S.D., H-T.T., D.S., C.V-F., and J.B. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

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employees of Sanofi and may hold stock/stock options in the company. All other authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: <https://www.vivli.org/>.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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