Supplementary

TGI M-protein dynamic model

The tumor growth inhibition (TGI) model for M-protein (MP) dynamics is described by the following differential equation:

$$\frac{dMP_i(t)}{dt} = k_{prod,i}MP_i(t) - k_{dec,i}f(Drug_i)e^{-\lambda_i t}MP_i(t)$$

$$B_i = MP_i(0)$$

where B_i is the baseline MP at time 0 for the i^{th} subject; $k_{prod,i}$ is the first-order production rate of MP for the i^{th} subject; $k_{dec,i}$ is the MP decay rate induced by treatment (i.e., dug exposure) via tumor inhibition for the i^{th} subject; $e^{-\lambda_i t}$ is an exponentially function decreasing over time to account for the potential tumor resistance development over time; and $f(Drug_i)$ is a function of the treatment for the i^{th} subject. Treatment effect θ_{TRT} (daratumumab plus standards of care vs. standards of care) was incorporated into the model as follows:

$$f(Drug_i) = 1 + \theta_{TRT}$$

Interindividual variability were included in the model to account for the correlation among the individual longitudinal M-protein data, and the heterogeneous patterns of individual M-protein time profiles. Subject-specific parameter estimates were given by, for example, $k_{dec,i} = k_{dec} \bullet \exp(\eta_i)$, where k_{dec} is the population mean of the MP decay rate and η_i is the difference between the individual and population mean MP decay rate on a log scale that is assumed to follow a normal distribution with a mean of zero and variance of ω^2. All population mean parameters and associated variances were shared among patients with different disease types including serum, urine and FLC diseases, except for baseline M-protein Bi where different population mean and variances were estimated separately for different disease types. Log-transformed M-protein data were modeled due to wide ranges of M-protein concentrations. The residual error

for the log-transformed MP data, accounting for measurement error and all unexplained sources of variability, such as model misspecifications, followed a normal distribution with a mean of zero and variance of σ^2. The variances of residual error were estimated separately for different disease types. The M-protein longitudinal data from all patients were analyzed simultaneously by nonlinear mixed-effect analysis with NONMEM® Version 7.3.0 (Icon Development Solutions, Ellicott City, MD). The first-order conditional estimation with interaction (FOCEI) algorithm was used for parameter estimation.

Table S1. Comparison of PULLUX and CASTOR

	PULLUX (3003)	**CASTOR (3004)**
Treatment	• Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd)	• Daratumumab, Bortezomib, and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd)
Daratumumab regimen	• Daratumumab 16 mg/kg IV • QW for Cycles 1-2, Q2W for Cycles 3-6, then Q4W thereafter[a]	• Daratumumab 16 mg/kg IV • QW for Cycles 1-3, Q3W for Cycles 4-8, then Q4W thereafter[b]
Control dosing regimen	• Lenalidomide 25 mg orally (PO), on Days 1 through 21 of cycle[a] • Dexamethasone PO 40 mg weekly (or 20 mg weekly for subjects >75 years or BMI <18.5)	• Bortezomib 1.3 mg/m^2 subcutaneously (SC) on Days 1, 4, 8 and 11 of each cycle for 8 cycles[b] • Dexamethasone 20 mg PO on Days 1, 2, 4, 5, 8, 9, 11 and 12 of the first 8 bortezomib cycles
Eligibility Criteria	• Age ≥18 years with measurable, documented MM • ECOG performance status ≤2 • ≥1 prior line of therapy and a PR or better with a prior treatment • Disease progression on the last line of therapy • Not intolerant or refractory to lenalidomide	• Age ≥18 years with measurable, documented MM • ECOG performance status ≤2 • ≥1 prior line of therapy and a PR or better with a prior treatment • Disease progression on the last line of therapy • Not intolerant or refractory to lenalidomide
Follow-up	• Immediately following the End-of-Treatment Visit • Continue until death, loss to follow up, consent withdrawal for study participation, or study end, whichever occurs first	• Immediately following the End-of-Treatment Visit • Continue until death, loss to follow up, consent withdrawal for study participation, or study end, whichever occurs first

[a]28-day cycles.
[b]21-day cycles.

Table S2. Univariate analysis of M-protein dynamic features at different data cutoffs in the POLLUX (n = 569) study

M-protein data cutoff (month)	Variable	HR estimate	LLCI (2.5%)	ULCI (97.5%)	p-value
1	Maximum % reduction of M-protein (%)	1.07	1.03	1.11	0.0007
	Last observed M-protein change from baseline (%)	1.07	1.03	1.11	0.0004
	Rate of M-protein change (% per week)	4.15	0.64	26.80	0.136
2	Maximum % reduction of M-protein (%)	1.19	1.13	1.26	<0.0001
	Last observed M-protein change from baseline (%)	1.14	1.11	1.18	<0.0001
	Rate of M-protein change (% per week)	1.49	1.32	1.68	<0.0001
3	Maximum % reduction of M-protein (%)	1.25	1.18	1.32	<0.0001
	Last observed M-protein change from baseline (%)	1.15	1.12	1.18	<0.0001
	Rate of M-protein change (% per week)	1.42	1.24	1.62	<0.0001
6	Maximum % reduction of M-protein (%)	1.33	1.26	1.40	<0.0001
	Last observed M-protein change from baseline (%)	1.02	1.02	1.03	<0.0001
	Rate of M-protein change (% per week)	1.44	1.32	1.58	<0.0001
All Data	Maximum % reduction of M-protein (%)	1.40	1.33	1.48	<0.0001
	Last observed M-protein change from baseline (%)	1.02	1.02	1.03	<0.0001
	Rate of M-protein change (% per week)	1.46	1.33	1.59	<0.0001

Note: For the maximum reduction of M-protein (%) and last observed M-protein change from baseline (%), the hazard ratio is associated with each 10-unit increase. LLCI = the lower limit of the confidence interval, UPCL= the upper limit of the confidence interval

Table S3. Univariate analysis of M-protein dynamic features at different data cutoffs in the CASTOR (n = 498) study

M-protein data cutoff (month)	variable	HR estimate	LLCI (2.5%)	ULCI (97.5%)	p-value
1	Maximum % reduction of M-protein (%)	1.22	1.18	1.26	<0.0001
	Last observed M-protein change from baseline (%)	1.18	1.15	1.21	<0.0001
	Rate of M-protein change (% per week)	1.23	1.12	1.36	<0.0001
2	Maximum % reduction of M-protein (%)	1.23	1.20	1.27	<0.0001
	Last observed M-protein change from baseline (%)	1.11	1.10	1.13	<0.0001
	Rate of M-protein change (% per week)	1.16	1.10	1.22	<0.0001
3	Maximum % reduction of M-protein (%)	1.25	1.22	1.29	<0.0001
	Last observed M-protein change from baseline (%)	1.12	1.10	1.13	<0.0001
	Rate of M-protein change (% per week)	1.29	1.21	1.37	<0.0001
6	Maximum % reduction of M-protein (%)	1.27	1.23	1.32	<0.0001
	Last observed M-protein change from baseline (%)	1.02	1.02	1.03	<0.0001
	Rate of M-protein change (% per week)	1.33	1.24	1.42	<0.0001
All Data	Maximum % reduction of M-protein (%)	1.28	1.24	1.32	<0.0001
	Last observed M-protein change from baseline (%)	1.02	1.02	1.03	<0.0001
	Rate of M-protein change (% per week)	1.34	1.25	1.43	<0.0001

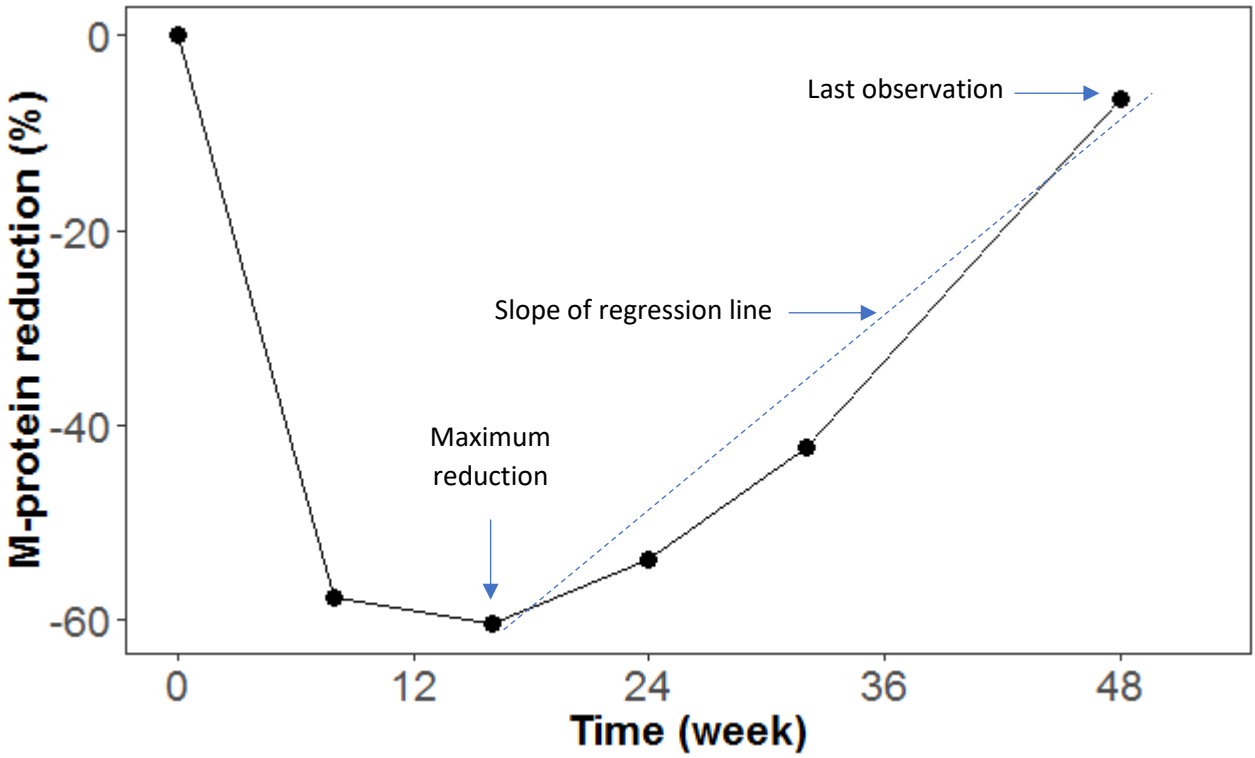
Note: For the maximum reduction of M-protein (%) and last observed M-protein change from baseline (%), the hazard ratio is associated with each 10-unit increase. LLCI = the lower limit of the confidence interval, UPCL= the upper limit of the confidence interval

Table S4. Parameter estimates of the TGI model for M-protein dynamics for POLLUX and CASTOR studies

Parameter (unit)	Description	Estimate (RSE%)	
		POLLUX	CASTOR
k_{prod} (1/week)	First-order production rate of M-protein	0.00969 (4.65)	0.0413 (10.9)
k_{kdec} (1/week)	First-order decay rate of M-protein	0.21 (4.3)	0.233 (4.65)
k_{λ} (1/week)	Rate constant of tumor resistance	0.108 (4.19)	0.12 (7.33)
B_{serum} (g/dL)	Baseline serum M-protein	20.4 (2.26)	22.2 (3.09)
B_{urine} (g/day)	Baseline urine M-protein	0.843 (10.9)	0.963 (13.6)
B_{FLC} (mg/L)	Baseline FLC	371 (12.9)	273 (24.5)
θ_{TRT}	Daratumumab treatment effect	0.546 (9.22)	0.526 (7.15)
ω_{kprod}	IIV on k_{prod}	1.78 (5.88)	0.845 (8.84)
ω_{kdec}	IIV on k_{dec}	0.677 (6.21)	0.647 (7.49)
ω_{λ}	IIV on λ	0.663 (7.39)	0.481 (12)
ω_{B_serum}	IIV on baseline serum M-protein	0.512 (4.05)	0.552 (3.97)
ω_{B_urine}	IIV on Baseline urine M-protein	0.831 (8.12)	0.942 (11.6)
ω_{B_FLC}	IIV on Baseline FLC	0.764 (14.6)	0.654 (23.1)
σ_{serum}	Residual error for serum M-protein	0.233 (5.9)	0.233 (6.7)
σ_{urine}	Residual error for urine M-protein	0.46 (5.93)	0.76 (25.6)
σ_{FLC}	Residual error for FLC	0.812 (10.2)	0.753 (15.6)

IIV: inter-individual variability; RSE: relative standard error
IIVs are expressed as coefficients of variation (%).

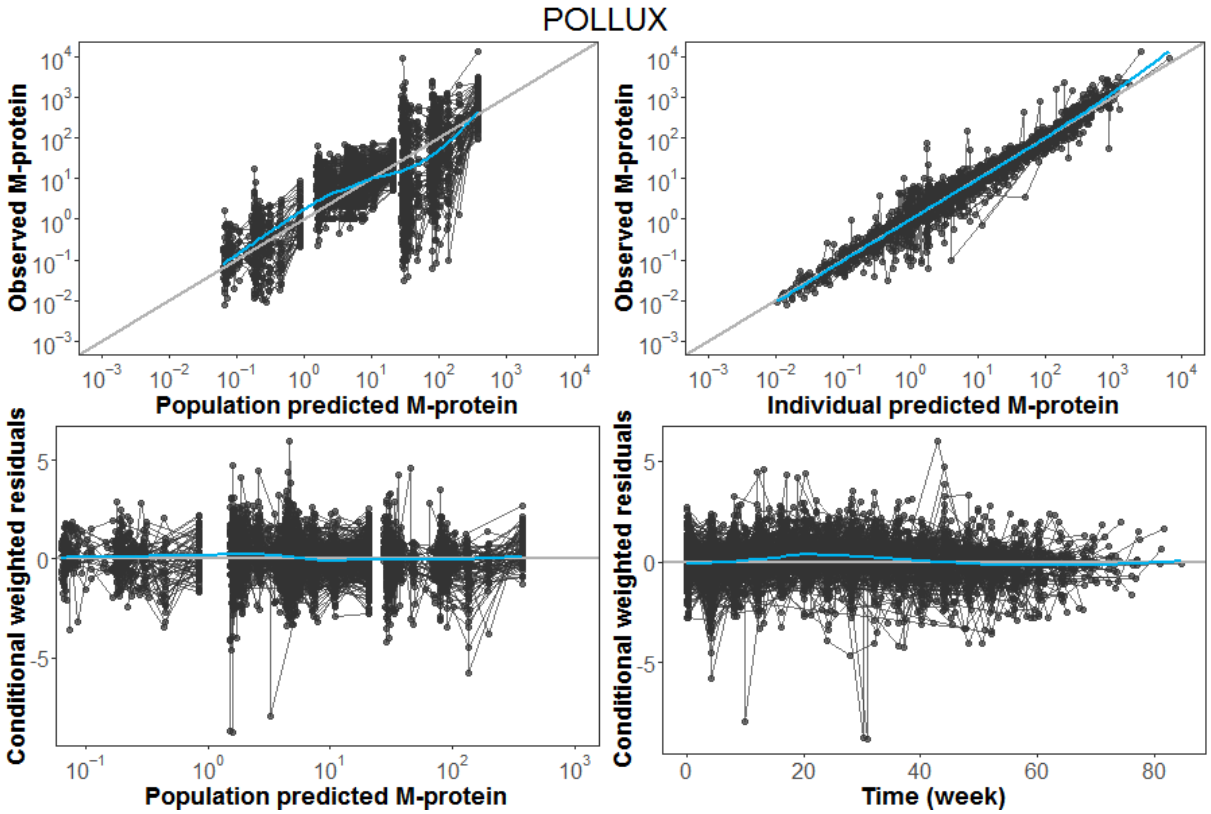
Figure S1. Graphical illustration of the M-protein dynamic features investigated in this study



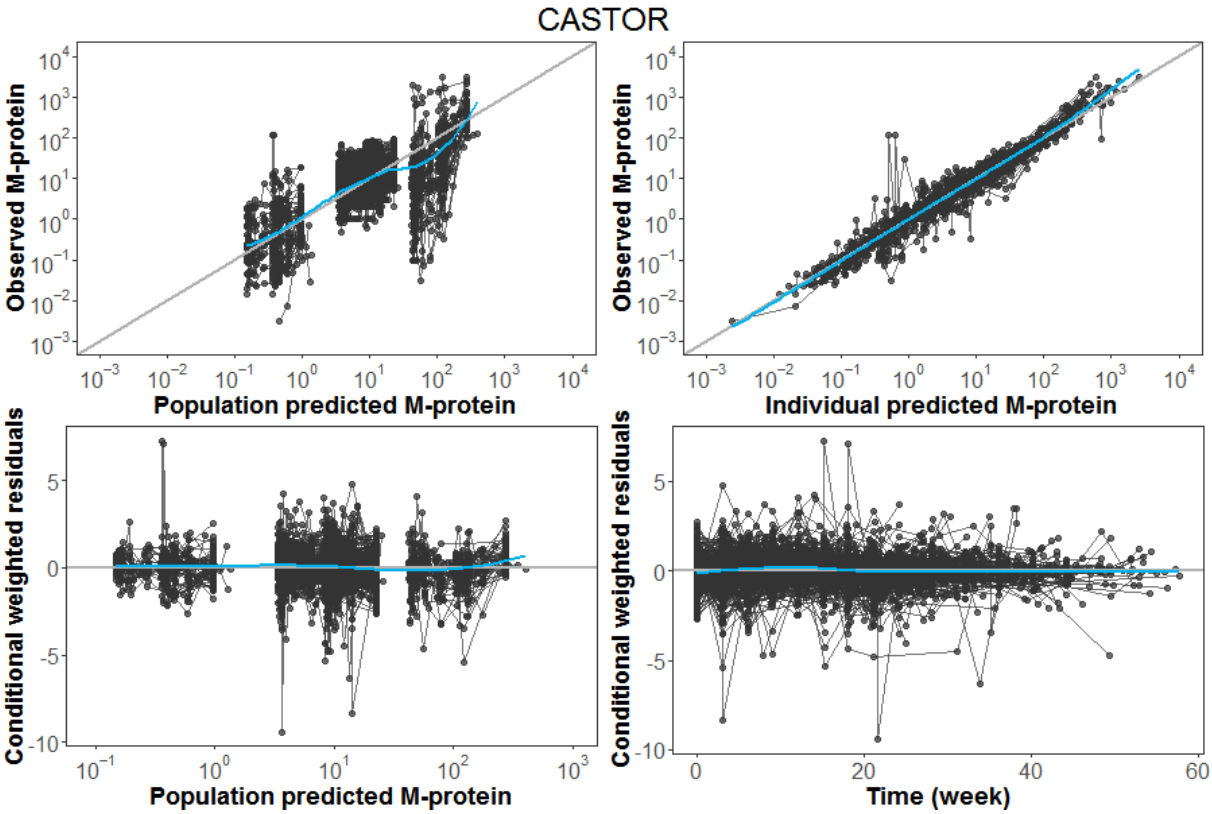
Note: All available data from nadir (the point of maximum reduction) to the last observation were used to calculate the slope.

Figure S2. Basic goodness-of-fit diagnostic plots for M-protein TGI modeling for A) POLLUX and B) CASTOR studies

A.



B



Note: The top panels present the observed data vs. population predictions and individual predictions, respectively. The bottom panels present the conditional weighted residuals (CWRES) vs. population predictions and time, respectively. Individual data points from the same subject are connected by black lines. The blue lines are loess smooth lines. The grey diagonal (top panels) and horizontal lines (bottom panels) are the lines of identity and zero lines, respectively.

Figure S3. Comparison of the predicted probability of progression-free survival with the observed probability (Kaplan–Meier survival curves) in a landmark analysis of the POLLUX and CASTOR studies

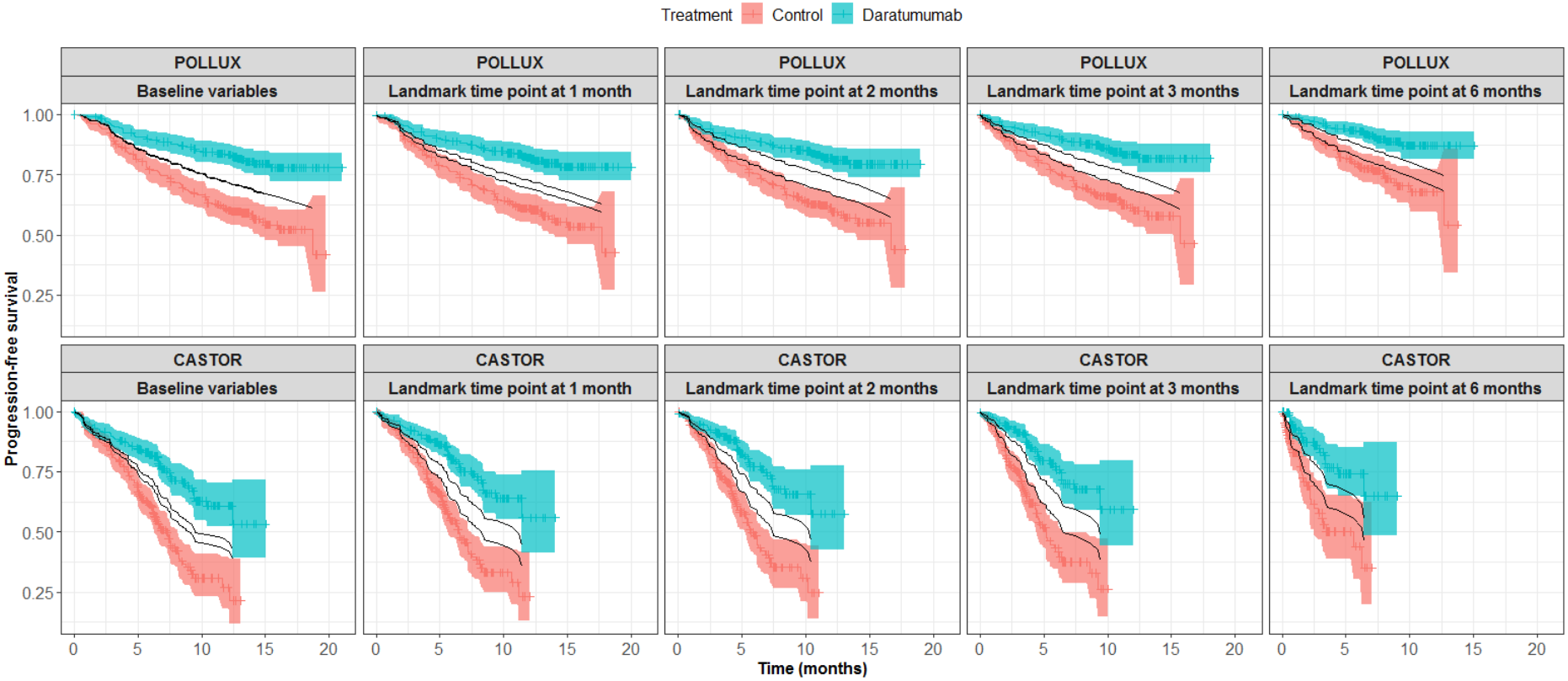
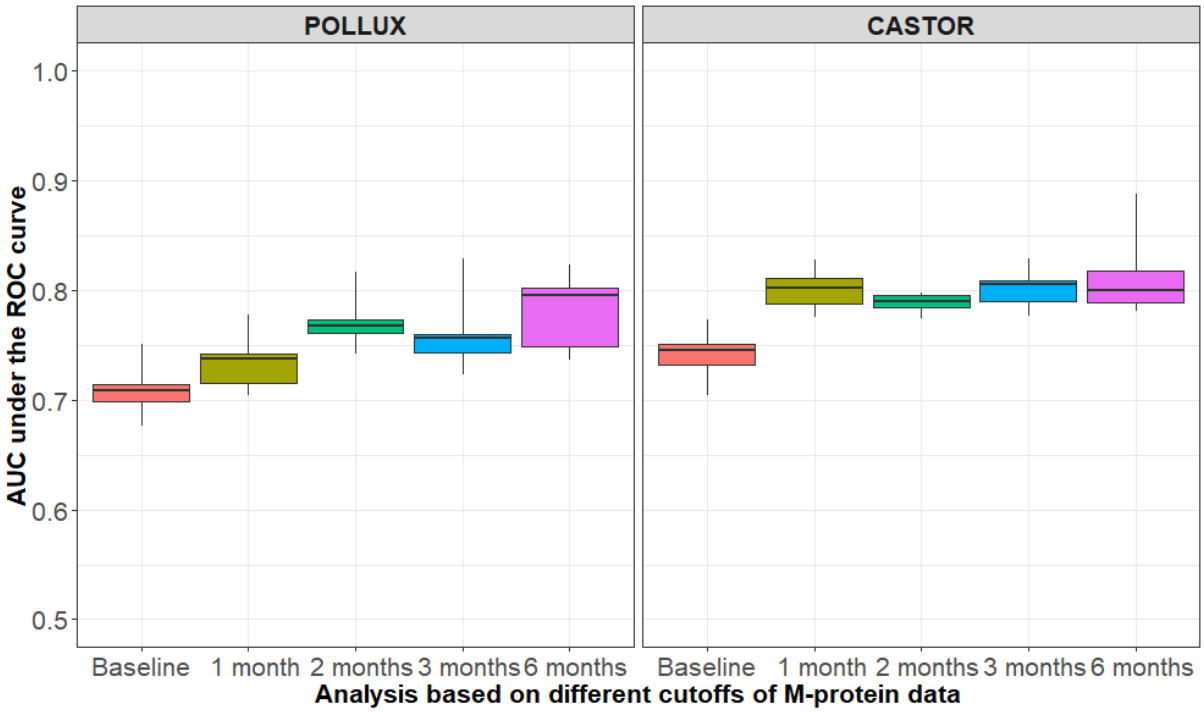
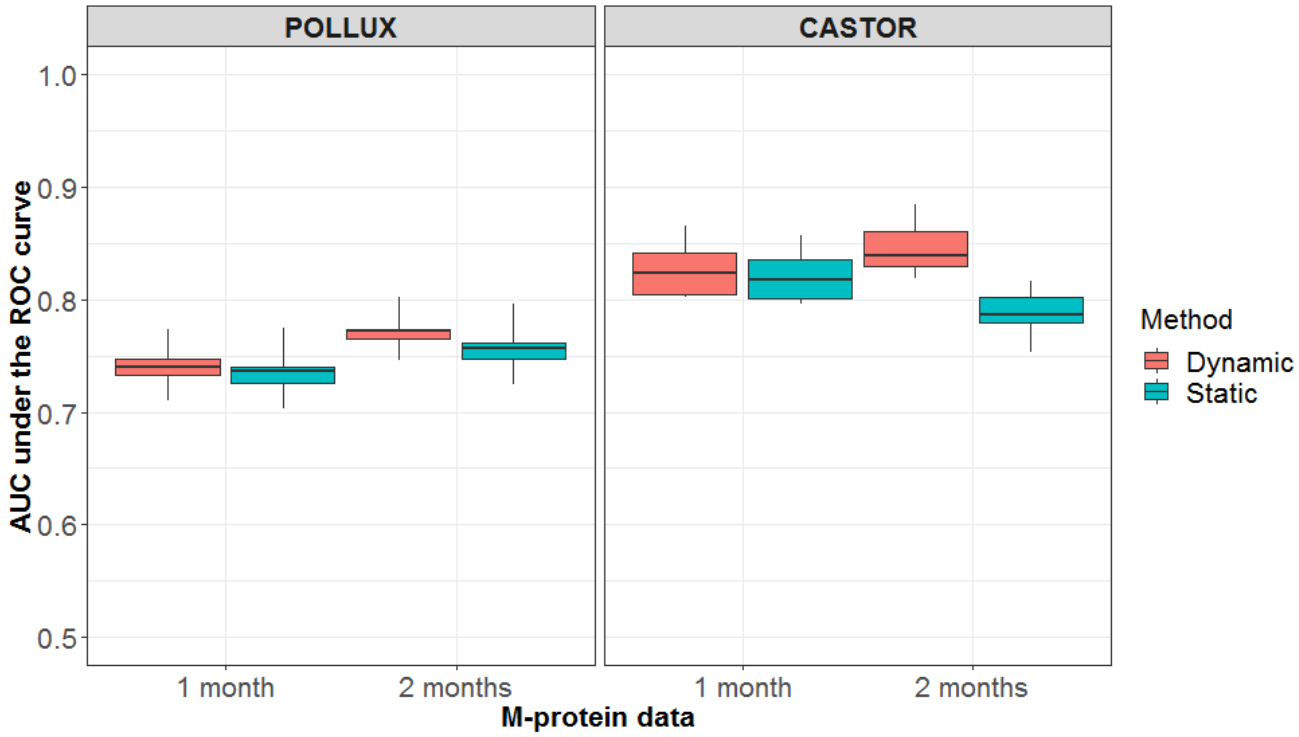


Figure S4. Distribution of AUCs from the time-varying ROC curves of each landmark multivariable survival model for POLLUX and CASTOR.



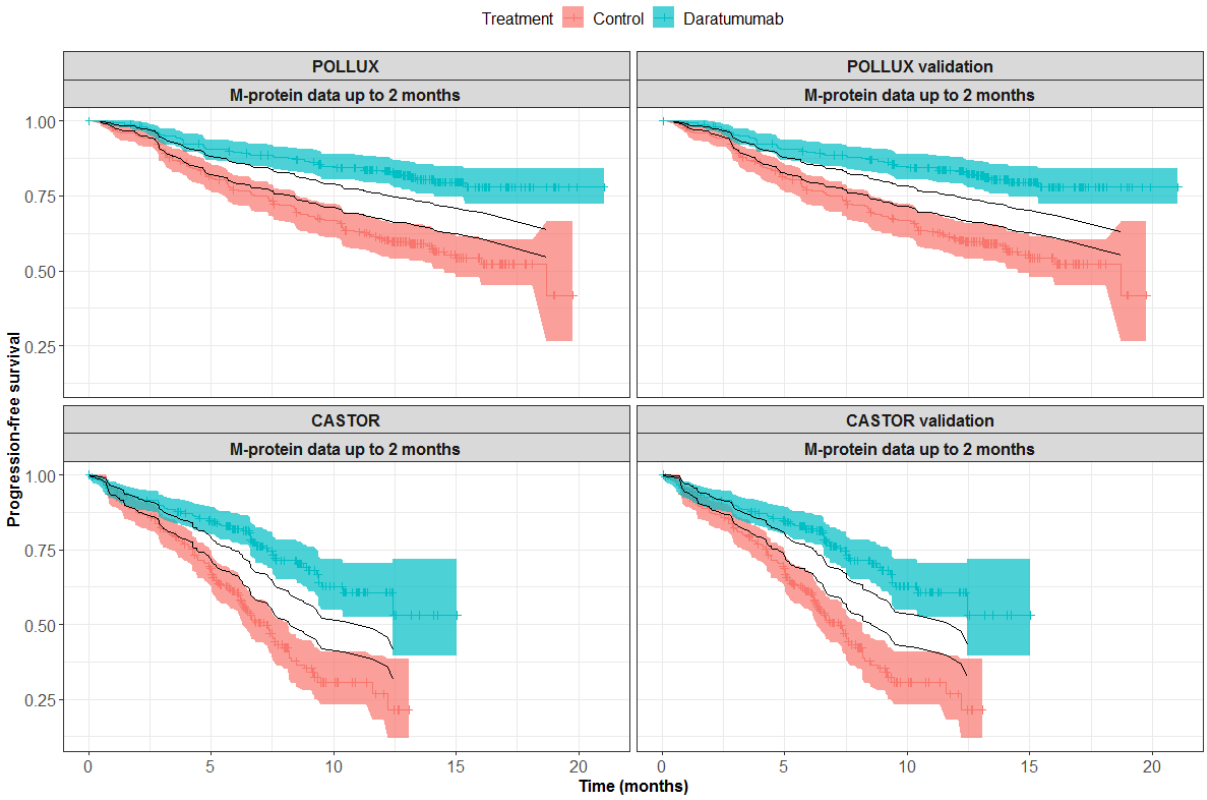
Note: AUC = area under the curve, ROC = receiver operating characteristic

Figure S5. Boxplot comparison of the AUCs under the time-varying ROC curves from different survival models based on dynamic and static M-protein data



Note: AUC = area under the curve, ROC = receiver operating characteristic

Figure S6. Cross-validation of predicted survival probability over time (Kaplan–Meier survival curves) in the POLLUX and CASTOR studies



Note: POLLUX: prediction based on the POLLUX model and POLLUX data; POLLUX validation: prediction based on the CASTOR model and POLLUX data; CASTOR: prediction based on the CASTOR model and CASTOR data; CASTOR validation: prediction based on the POLLUX model and CASTOR data. For POLLUX and CASTOR, the hazard ratio for PFS was in favor of daratumumab treated group with $P < 0.001$ (20,21). The predictive ability of M-protein data was evaluated together with the baseline variables.