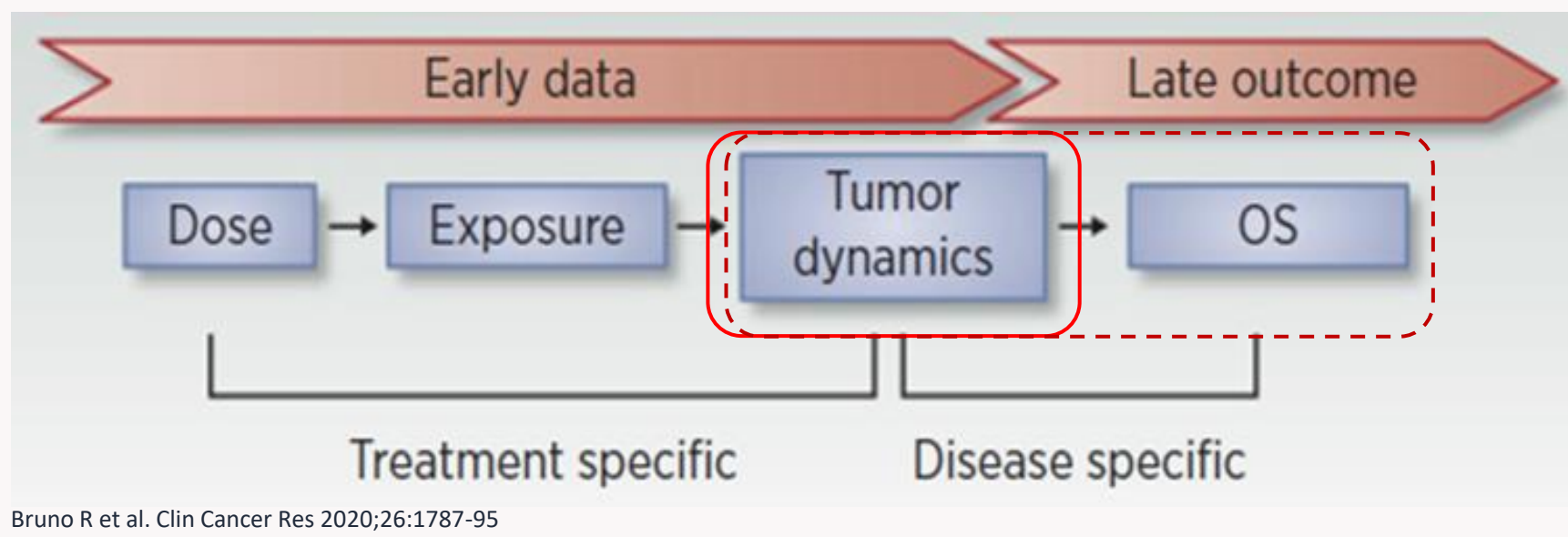


Operating Characteristics of M-protein Dynamic Metrics to Support Early Decisions in Multiple Myeloma

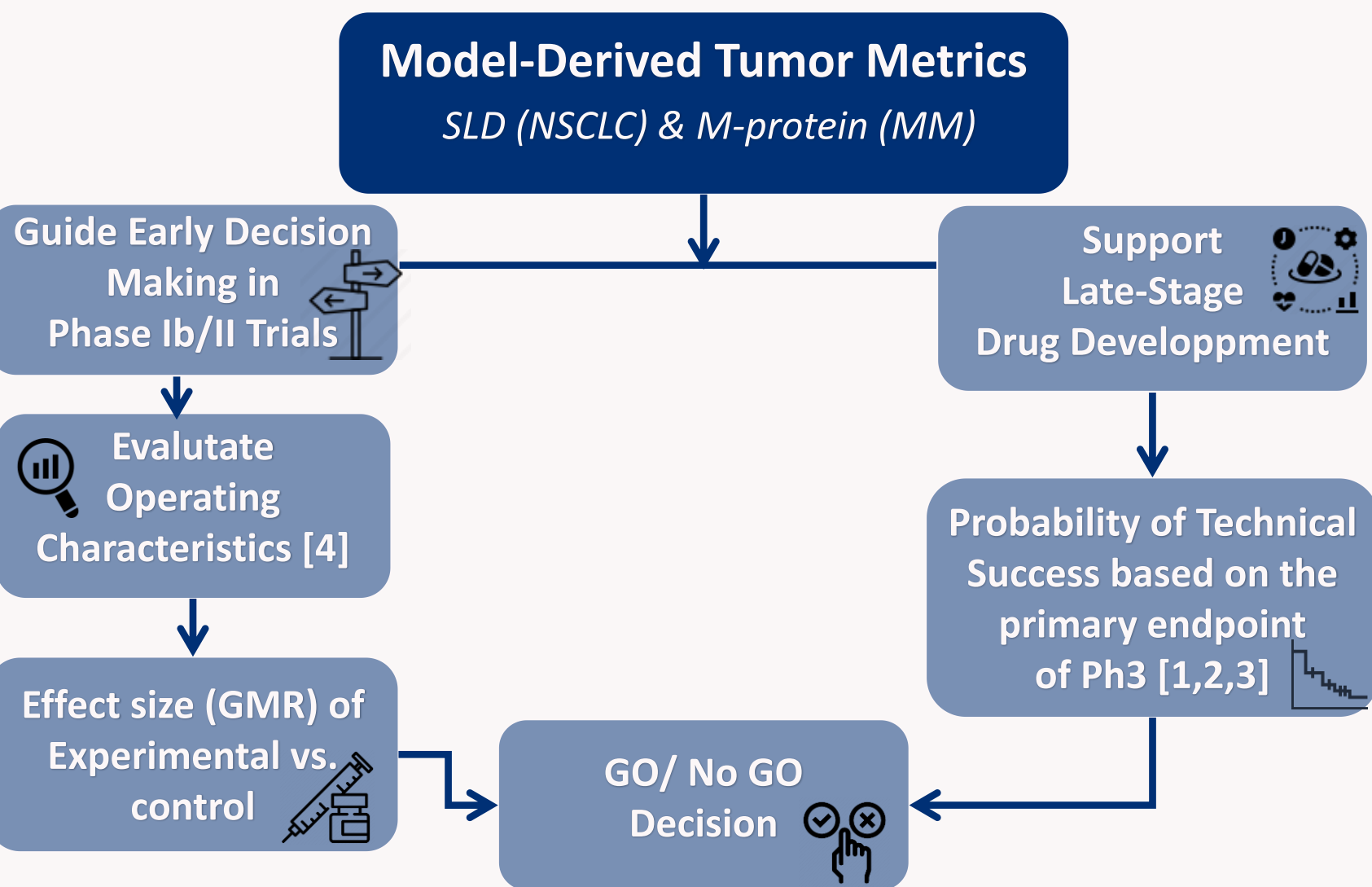
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Background and Objective



Bruno R et al. Clin Cancer Res 2020;26:1787-95



The objectives

- Assess operating characteristics (OC) of M-protein dynamics metrics in identifying effect size based on small Phase 1b/2 sample sizes with short follow-up (FU) by resampling a large positive Phase 3 study.
- Identify the right metric, target and gating criteria (probability of target achievement) to support GO/No GO decisions.
- Validation using the selected metric, target and gating criteria performed on CASTOR clinical trial
- Develop a PFS model to assess the probability of success of the ungated clinical trial.

Methods

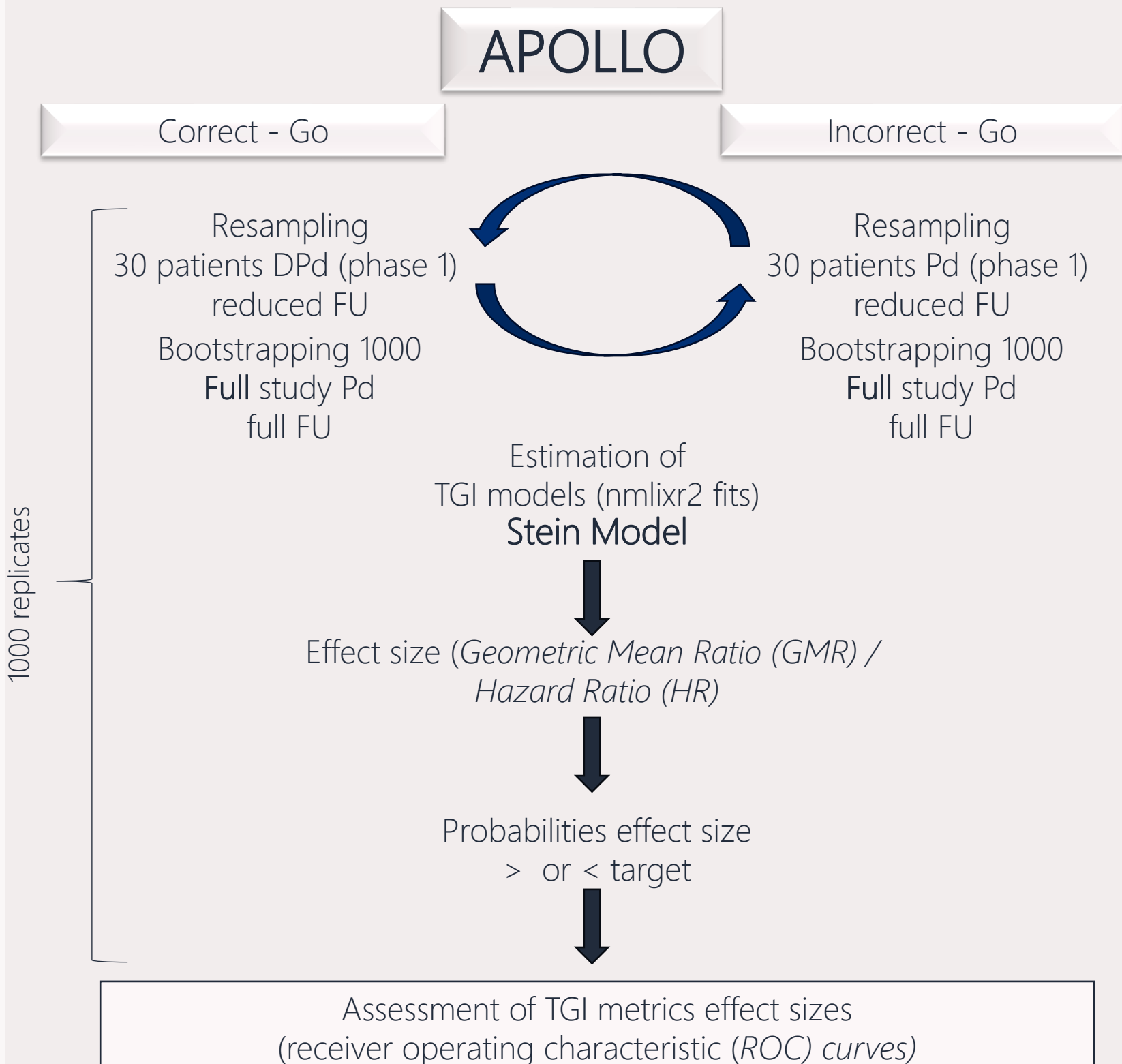
- Estimate TGI model on the whole APOLLO study
- Run the OC on APOLLO subsamples
- Validation on CASTOR subsamples
- TGI-PFS modeling on the whole APOLLO study
- Validation of PFS model (APOLLO and CASTOR)

Table 1. Description of the Clinical Data

Study	Experimental	Control	Disease
APOLLO [5] NCT02136134	Daratumumab, pomalidomide dexamethasone (DPd) N=151	Pomalidomide dexamethasone (Pd) N=153	Relapsed/Refractory Multiple Myeloma (RRMM)
CASTOR [9] NCT03180736	daratumumab bortezomib dexamethasone (DvD) N=251	bortezomib and dexamethasone (Vd) N=247	RRMM

The YODA project [6] allowed access to APOLLO and CASTOR clinical data.

Figure 1. Experimental Design for OCs



In each DPd subsample, the M-protein data were cut 24 weeks after treatment starts. For the Pd arm/control, the full FU was maintained.

Results

Table 2. Description of the TGI model used

Model	Equation	Description
Stein [7]	$t < 0 \text{ } Mprot(t) = Mprot_0 \cdot e^{KG_0 \cdot t}$ $t \geq 0 \text{ } Mprot(t) = Mprot_0 \cdot (e^{KG \cdot t} + e^{-KS \cdot t} - 1)$	t is the time (week) with time 0 at the start of treatment; $Mprot_0$ in (g/L) at the start of treatment KS , tumor shrinkage rate constant ([time] ⁻¹) KG_0 , tumor growth rate constant before treatment start ([time] ⁻¹) KG , tumor growth rate constant ([time] ⁻¹)

Stein: No assumption on treatment effect.
KS, KG on-treatment shrinkage and growth rates.
Note: pre-treatment KG_0 is known since pre-treatment M-protein measurement.

Table 3. Parameter estimates M-protein model
TGI model estimated on the whole APOLLO study

Parameter	Estimate	RSE (%)	Back-transformed (unit)	BSV%	Shrinkage%
log(KG_0)	-6.79	2.31	0.00112 (d ⁻¹)	165	48.5
log(KG_{exp})	-7.02	1.15	0.00090 (d ⁻¹)	82.2	61.3
log($KG_{control}$)	-6.36	1.34	0.00174 (d ⁻¹)	82.2	61.3
log(KS_{exp})	-4.23	2.91	0.0145 (d ⁻¹)	79.5	6.40
log($KS_{control}$)	-4.36	2.91	0.0129 (d ⁻¹)	79.5	6.40
log(BSL)	2.82	3.17	16.8 (g/L)	80.5	3.93
Residual (add)	2.93				

Figure 2. Examples of subsamples data by arm

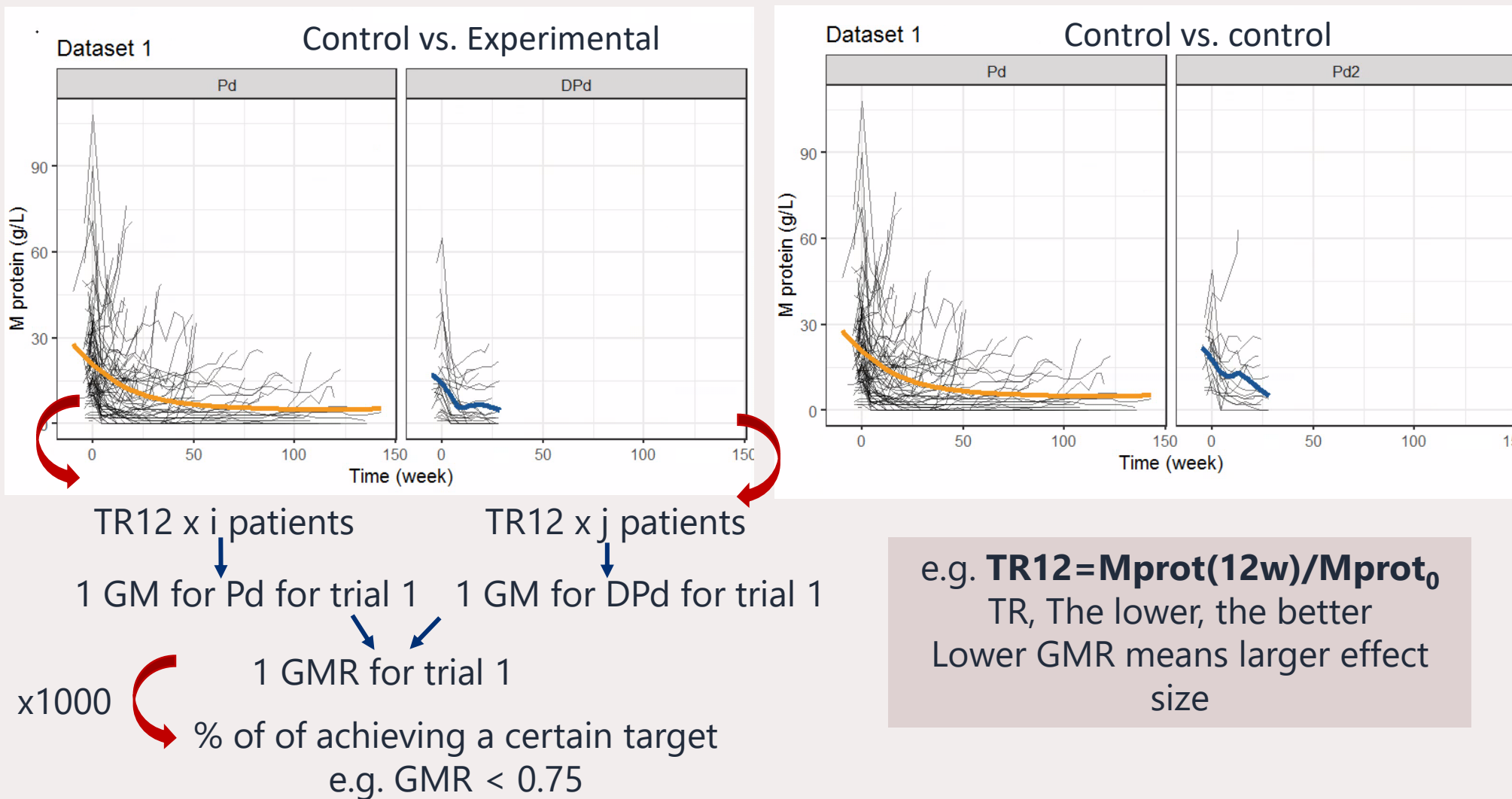
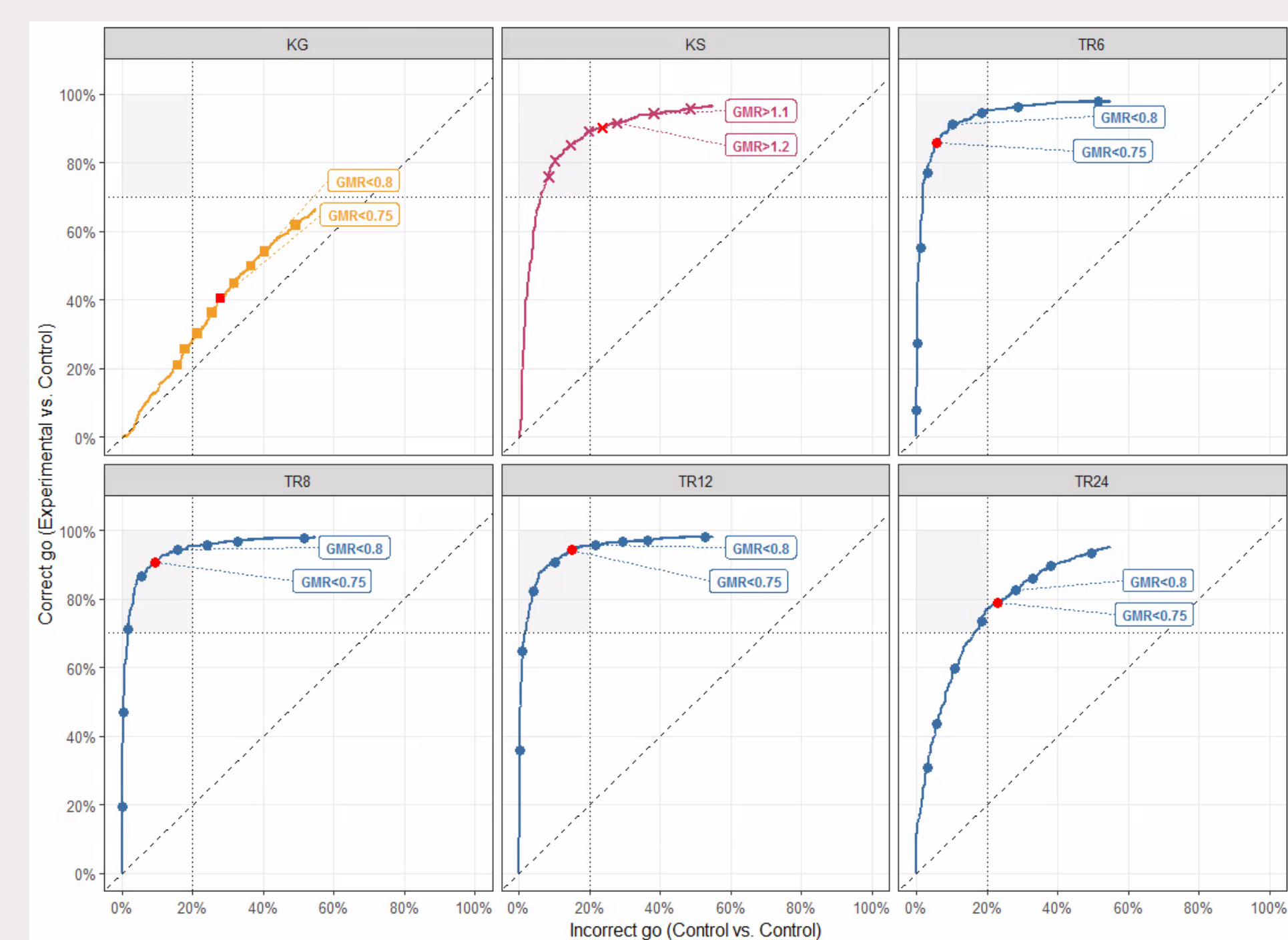


Figure 3. ROC curves for M-protein dynamic metrics



- Horizontal and vertical dotted lines sweet spot for a good decision by maximizing correct Go rate (70% or higher) and minimizing incorrect Go rate (20% or lower).
- TR6, TR8, TR12 (p(TR GMR < 0.75), p < 0.80) good
- KS: OCs with correct Go rate close to 80% but incorrect Go rate > 20%; p(KS GMR > 0.85)
- Chosen metric: TR8 and TR12, target < 0.75 GMR, target achievement > 70% on both metrics

Discussion / Conclusions

- Operating Characteristics of M-protein dynamic metrics were assessed on APOLLO trial (DPd vs Pd):
 - Metrics: TR8 and TR12
 - Target: GMR(experimental versus control) < 0.75
 - Gating criteria: 70% of target achievement
 - The approach was validated on the CASTOR trial
- LogKG was highly predictive of PFS, the PFS model well captured the treatment effects in APOLLO and CASTOR

This analysis suggests that model-derived M-protein dynamic metrics can support Go/No Go decision prior to Phase 3. Metrics may inform different aspects contributing to the decision: the M-protein ratio to baseline quantifies the effect size of an experimental arm versus a control based on limited Phase 1b/2 data, while logKG, requiring longer follow-up, is a strong predictor of PFS, the primary endpoint in Phase 3 studies.

Figure 4. Validation of Operating Characteristics

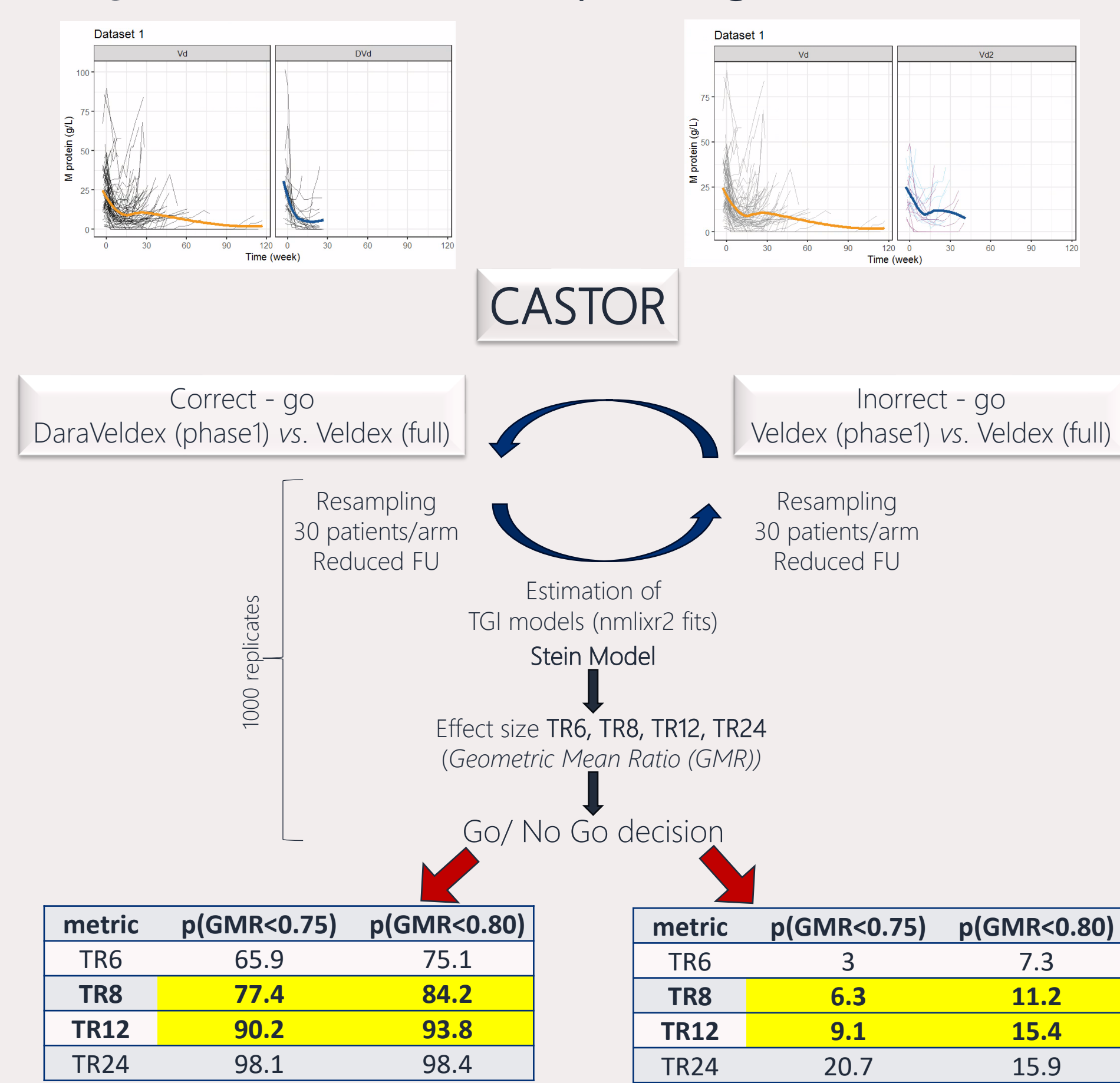
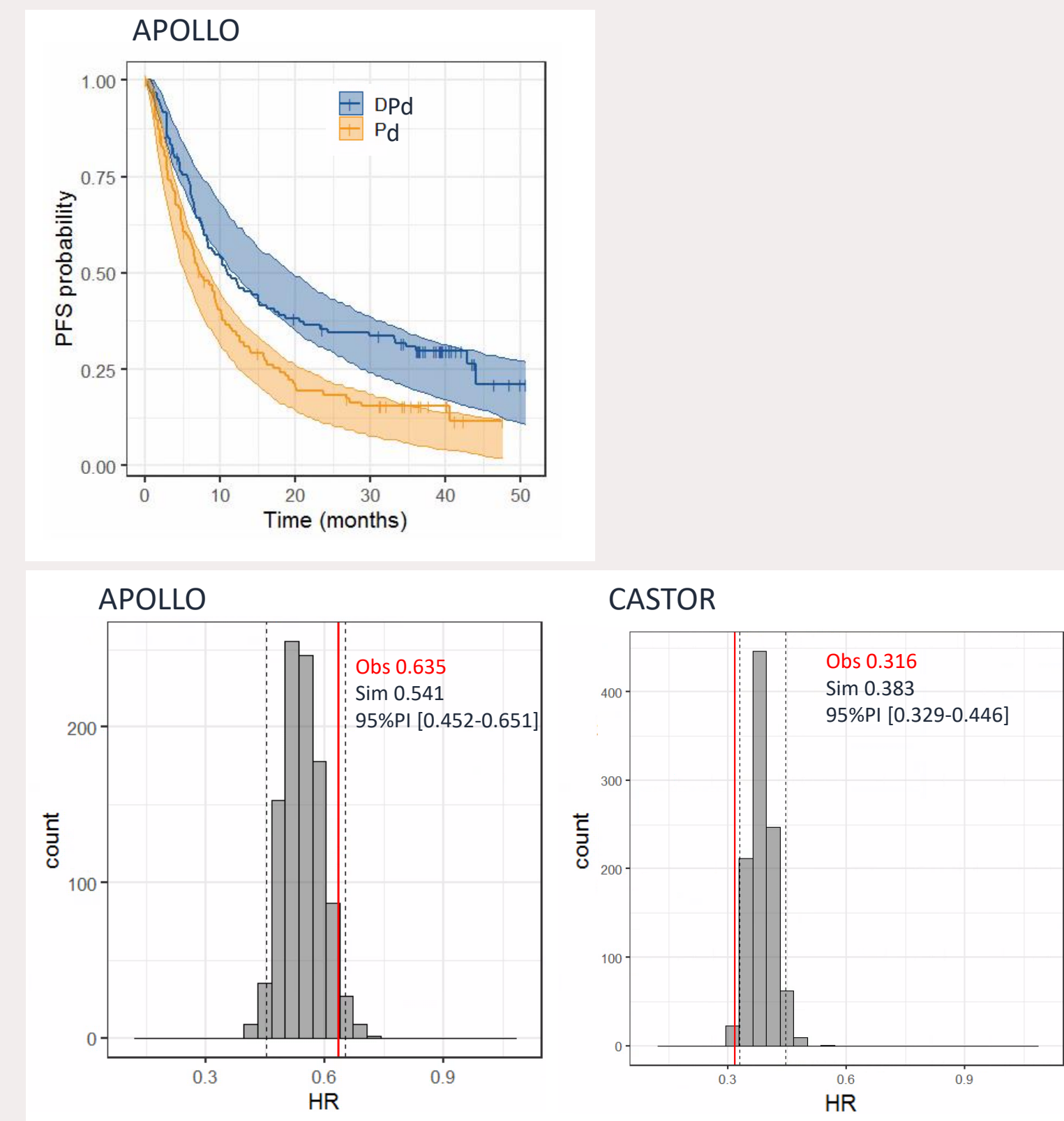


Table 4. Parametric PFS model from APOLLO

Term	Estimate	Std. Error	Z-value	p-value
(Intercept)	-5.563	0.482	-11.534	<2e-16
logKG	-0.861	0.045	-19.110	<2e-16
Hemoglobin	0.176	0.035	5.062	0
Log(scale)	-0.276	0.054	-5.093	0

Figure 5. PFS model validation



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*This study, carried out under YODA Project 2021-4660, used data obtained from the Yale University Open Data Access Project, which has an agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C.. The interpretation and reporting of research using this data are solely the responsibility of the authors and does not necessarily represent the official views of the Yale University Open Data Access Project or JANSSEN RESEARCH & DEVELOPMENT, L.L.C..



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