Genentech
A Member of the Roche Group

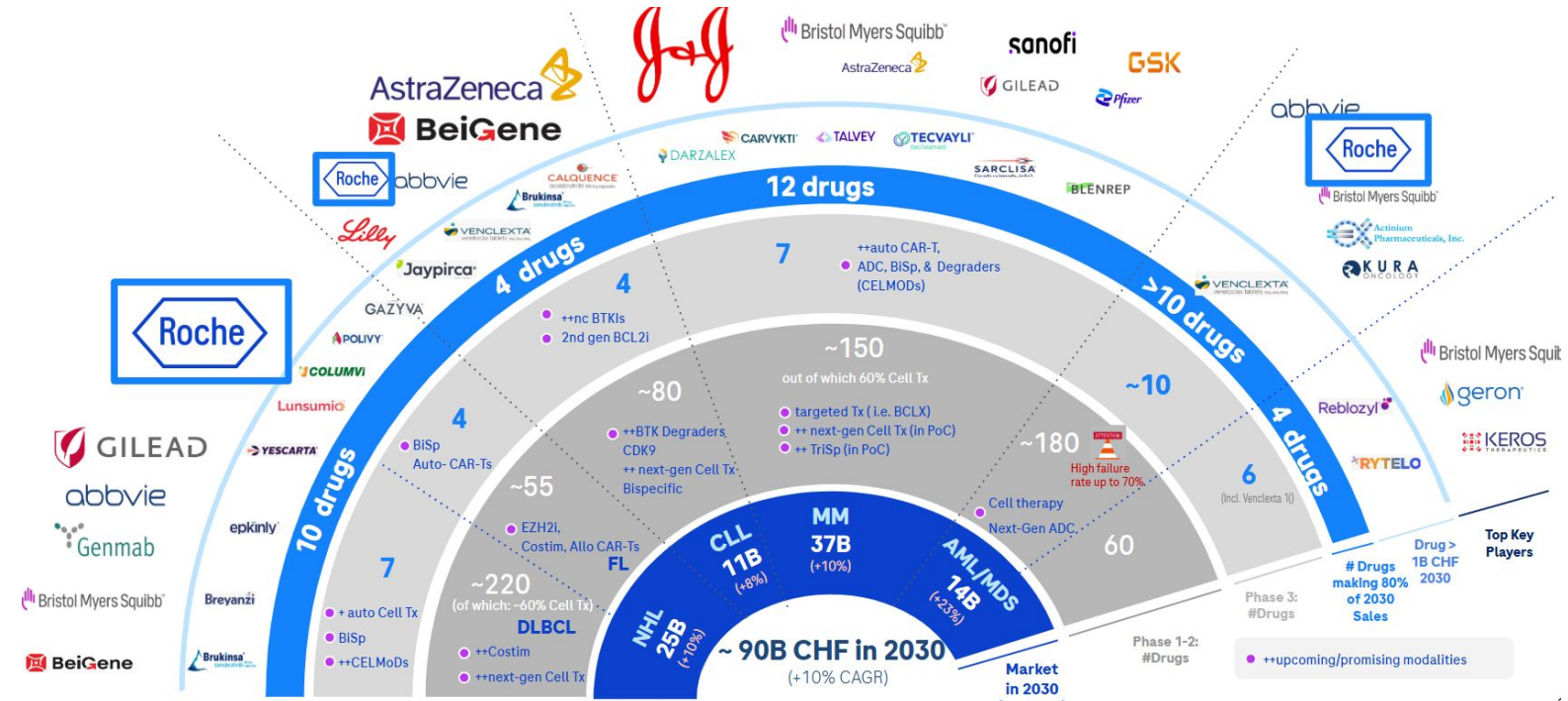
OPERATING CHARACTERISTICS OF M-PROTEIN DYNAMIC METRICS TO SUPPORT EARLY DECISIONS IN MULTIPLE MYELOMA

Pascal Chanu, **Mathilde Marchand (Certara)**, Federico Mattiello, Mark Yan, Tom Chambers, Felipe Castro, Monica Susilo, Divya Samineni, Dale Miles, Chunze Li, Jin Jin

Clinical Pharmacology - Modeling & Simulation

September 19, 2025, Pharmacometrics in France

MULTIPLE MYELOMA (MM) REMAINS AN APPEALING MARKET



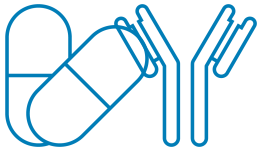
Sources: CI Heme Strategic Assessment based on EvaluatePharma (value CHF), Citeline PharmaProjects, (1) and details in the note - High level analysis not exhaustive - no vaccine included,

Sources used for the data

Oct 2024

Genentech
A Member of the Roche Group

EARLY DEVELOPMENT SITUATION IN MULTIPLE MYELOMA (MM)

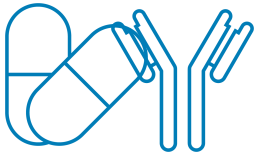


Combination therapy X in multiple myeloma
Phase 1b data, N=30,
2 dose levels, no control,
endpoint:
ORR i.e. VGPR rate

External data from YODA

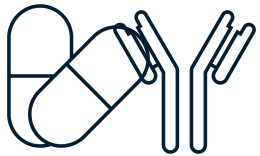
RWD flatiron

MM enabling decision framework



X

vs



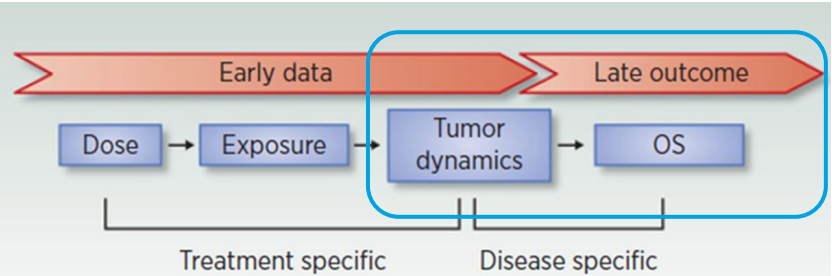
Standard of Care

Phase 3 study:
X
versus
Standard of Care:
daratumumab+polamidomide+
dexamethasone (DPd),
endpoint: PFS

Genentech
A Member of the Roche Group

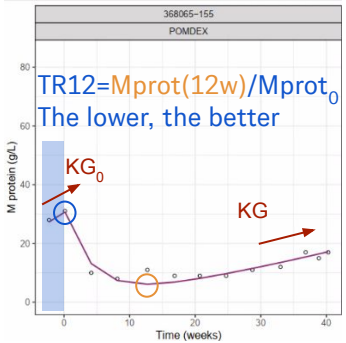
MODELING & SIMULATION FRAMEWORK IN MULTIPLE MYELOMA

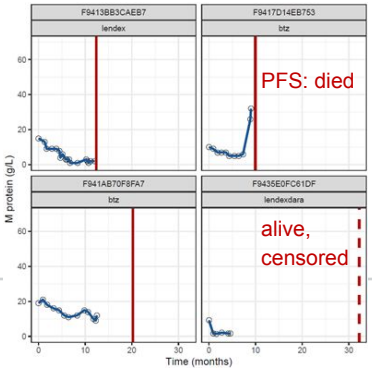
Model-based tumor dynamics metrics are biomarkers capturing treatment effect



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

Application to Multiple Myeloma





KG, TR12…
linked to PFS

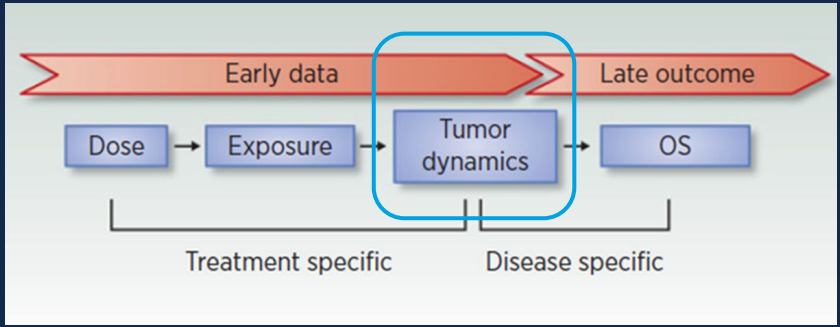
$$t < 0 \;\; Mprot(t) = Mprot_0 \cdot e^{KG_0 \cdot t}$$

$$t \geq 0 \;\; Mprot(t) = Mprot_0 \cdot (e^{KG \cdot t} + e^{-KS \cdot t} - 1)$$

Stein et al. Clin Cancer Res 2011;17:907-17

Genentech
A Member of the Roche Group

OPERATING CHARACTERISTICS OF M-PROTEIN DYNAMIC METRICS



OPERATING CHARACTERISTICS OF TGI METRICS

Tumor Dynamic Model-Based Decision Support for Phase Ib/II Combination Studies: A Retrospective Assessment Based on Resampling of the Phase III Study IMpower150

René Bruno[1], Mathilde Marchand[2], Kenta Yoshida[3], Phyllis Chan[3], Haocheng Li[4], Wei Zou[5], Francois Mercier[6], Pascal Chanu[7], Benjamin Wu[3], Anthony Lee[5], Chunze Li[3], Jin Y. Jin[3], Michael L. Maitland[8,9], Martin Reck[10], and Mark A. Socinski[11]

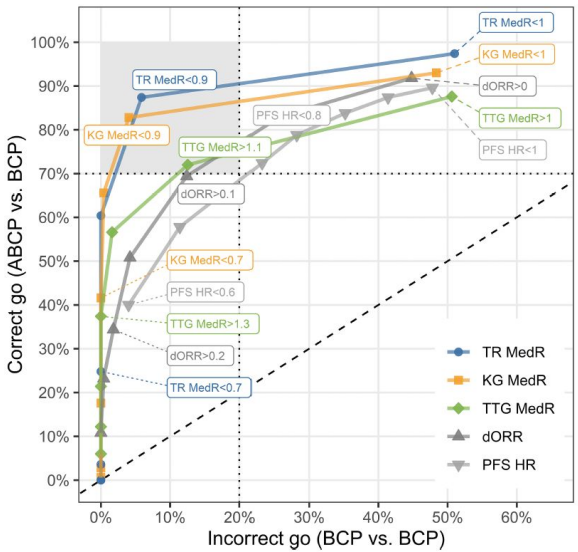
ABSTRACT

Purpose: Model-based tumor growth inhibition (TGI) metrics are increasingly incorporated into go/no-go decisions in early clinical studies. To apply this methodology to new investigational combinations requires independent evaluation of TGI metrics in recently completed Phase III trials of effective immunotherapy.

Patients and Methods: Data were extracted from IMpower150, a positive, randomized, Phase III study of first-line therapy in 1,202 patients with non–small cell lung cancer. We resampled baseline characteristics and longitudinal sum of longest diameters of tumor lesions of patients from both arms, atezolizumab+bevacizumab+chemotherapy (ABCP) versus BCP, to mimic Phase Ib/II studies of 15 to 40 patients/arm with 6 to 24 weeks follow-up. TGI metrics were estimated using a bi-exponential TGI model. Effect sizes were calculated as TGI metrics ratio of medians (MedR), objective response rate (ORR) difference (d), and progression-free survival (PFS), hazard ratio (HR) between arms. Correct and incorrect go decisions were evaluated as the probability to achieve desired effect sizes in ABCP versus BCP and BCP versus BCP, respectively, across 500 replicated subsamples for each design.

Results: For 40 patients/24 weeks follow-up, correct go decisions based on probability tumor growth rate (KG) MedR <0.90, dORR >0.10, and PFS HR <0.70 were 83%, 69%, and 58% with incorrect go decision rates of 4%, 12%, and 11%, respectively. For other designs, the ranking did not change with TGI metrics consistently over-performing RECIST endpoints. The predicted overall survival (OS) HR was around 0.80 in most of the scenarios investigated.

Conclusions: Model-based estimate of KG MedR is an exploratory endpoint that informs early clinical decisions for combination studies.



Genentech
A Member of the Roche Group

APOLLO PATIENT POPULATION IS REPRESENTATIVE

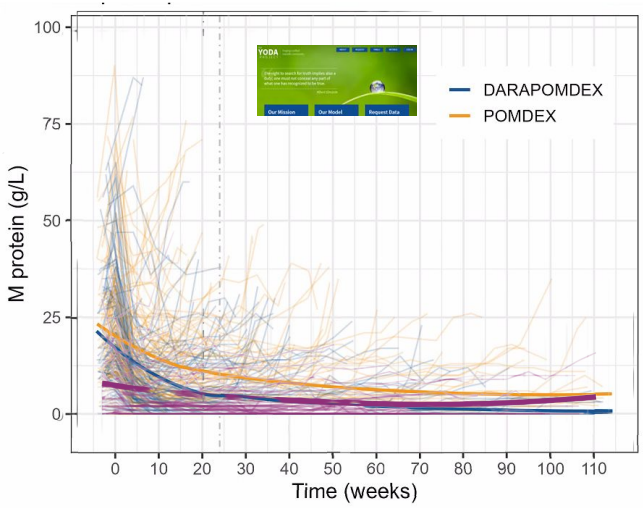
APOLLO: model development, DPd versus Pd

Dimopoulos et al. Lancet Oncol 2021;22:801-12

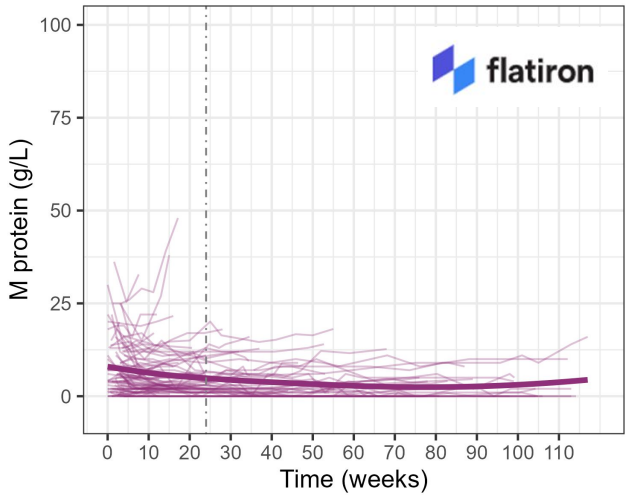
Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial

Meletios A Dimopoulos, Evangelos Terpos, Mario Boccadoro, Sosana Delimpasi, Meral Beksac, Eirini Katodritou, Philippe Moreau, Luca Baldini, Angiris Symeonidis, Jelena Bila, Albert Oriol, Maria-Victoria Mateos, Hermann Einsele, Ioannis Orfanidis, Tahamtan Ahmadi, Jon Ukropec, Tobias Kampfenkel, Jordan M Schecter, Yanping Qiu, Himal Amin, Jessica Vermeulen, Robin Carson, Pieter Sonneveld, for the APOLLO Trial Investigators*

RWD of the population of interest shows a good match with DPd arm from APOLLO



DPd in APOLLO considered as a relevant control for X assessment



RWD from Flatiron Health, an oncology-based electronic health record (EHR)-derived de-identified database

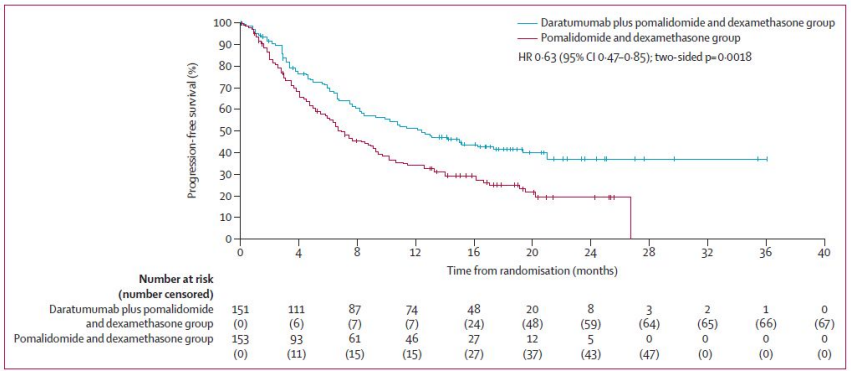
Genentech
A Member of the Roche Group

DATA: APOLLO & CASTOR CLINICAL TRIALS

APOLLO: model development, DPd versus Pd
Dimopoulos et al. Lancet Oncol 2021;22:801-12

Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial

Meletios A Dimopoulos, Evangelos Terpos, Mario Boccadoro, Sosana Delimpasi, Meral Beksac, Eirini Katodritou, Philippe Moreau, Luca Baldini, Argiris Symeonidis, Jelena Bila, Albert Oriol, Maria-Victoria Mateos, Hermann Einsele, Ioannis Orfanidis, Tahamtan Ahmadi, Jon Ukropec, Tobias Kampfenkel, Jordan M Schecter, Yanping Qiu, Himal Amin, Jessica Vermeulen, Robin Carson, Pieter Sonneveld, for the APOLLO Trial Investigators*



DPd in APOLLO considered as a relevant control for X assessment

For assessing operating characteristics of M-protein dynamics: DPd will be the experimental arm and Pd the control

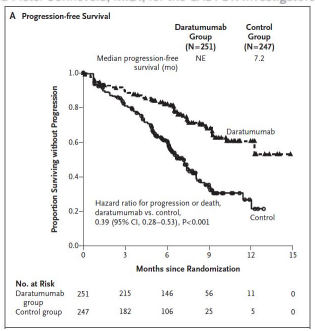
CASTOR: validation, DVd versus Vd
Palumbo et al. N Engl J Med 2016;375:754-66

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma

Antonio Palumbo, M.D., Asher Chanan-Khan, M.D., Katja Weisel, M.D., Ajay K. Nooka, M.D., Tamas Masszi, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Vania Hungria, M.D., Markus Munder, M.D., Maria V. Mateos, M.D., Tomer M. Mark, M.D., Ming Qi, M.D., Jordan Schecter, M.D., Himal Amin, B.S., Xiang Qin, M.S., William Deraedt, Ph.D., Tahamtan Ahmadi, M.D., Andrew Spencer, M.D., and Pieter Sonneveld, M.D., for the CASTOR Investigators*



Genentech
A Member of the Roche Group

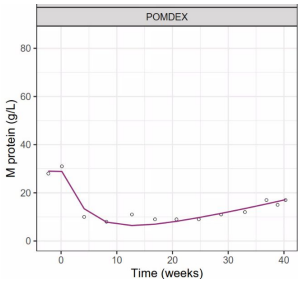
MODEL SELECTION TO ASSESS OPERATING CHARACTERISTICS (OC) ON APOLLO DATA

Model development performed in nlmixr²

$$t < 0 \;\; Mprot(t) = Mprot_0 \cdot e^{KG \cdot t}$$
$$t \geq 0 \;\; Mprot(t) = Mprot_0 \cdot (e^{KG \cdot t} + e^{-KS \cdot t} - 1)$$

Parameter	Estimate	SE	RSE (%)	Back-transformed	Unit	Shrinkage (%)
Fixed Effects						
ln(KG_DPd)	-7.50	0.0107	0.1	0.000553	day^{-1}	
ln(KG_Pd)	-6.49	0.0118	0.2	0.00152	day^{-1}	
ln(KS_DPd)	-3.78	0.0114	0.3	0.0228	day^{-1}	
ln(KS_Pd)	-4.33	0.0107	0.2	0.0132	day^{-1}	
TS0	2.80	0.00544	0.2	16.4	g/L	
Random Effects						
KG	82				%CV	66.8
KS	81				%CV	6.1
TS0	81				%CV	0.6
Residual variability						
Res add.	2.78				g/L	

Run: noKG0 objective function value: 13070.03

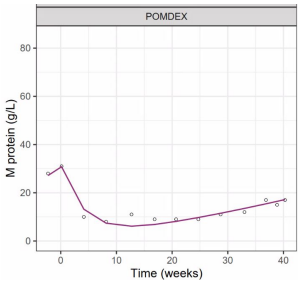


Estimating a different KG0 before treatment improves the model

$$t < 0 \;\; Mprot(t) = Mprot_0 \cdot e^{KG_0 \cdot t}$$
$$t \geq 0 \;\; Mprot(t) = Mprot_0 \cdot (e^{KG \cdot t} + e^{-KS \cdot t} - 1)$$

Parameter	Estimate	SE	RSE (%)	Back-transformed	Unit	Shrinkage (%)
Fixed Effects						
ln(KG0)	-6.79	0.157	2	0.00112	day^{-1}	
ln(KG_DPd)	-7.02	0.0808	1	0.000894	day^{-1}	
ln(KG_Pd)	-6.36	0.0852	1	0.00173	day^{-1}	
ln(KS_DPd)	-4.23	0.123	3	0.0146	day^{-1}	
ln(KS_Pd)	-4.36	0.127	3	0.0128	day^{-1}	
TS0	2.82	0.0893	3	16.8	g/L	
Random Effects						
KG0	165				%CV	48.5
KG	82				%CV	61.3
KS	80				%CV	6.4
TS0	81				%CV	3.9
Residual variability						
Res add.	2.93				g/L	

Run: KG0IIV objective function value: 13041.53



Genentech
A Member of the Roche Group

ASSESSMENT OF OPERATING CHARACTERISTICS (OC) APRIL 2025

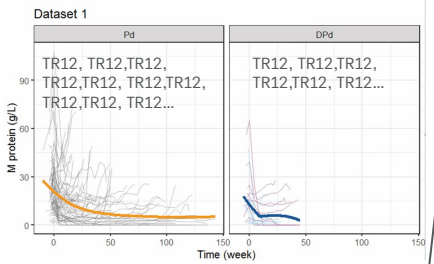
True GO: DPd *vs.* *Pd*

DPd: 15 (10mo mFU) + 15 pts (6mo mFU)

Bootstrapped ***Pd*** n=151, max FU

Fit models, derive metrics and compute GMR

Repeat 1000 times



1 GM of TR12

1 GM of TR12

1 GMR exp/control
The lower, the better

X 1000

% of achieving a certain target GMR
e.g. <0.75

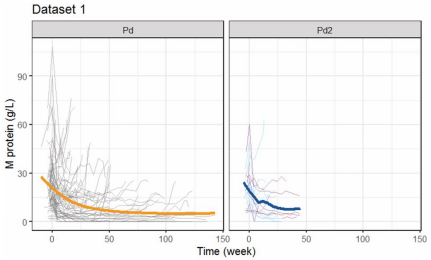
False GO: Pd *vs.* *Pd*

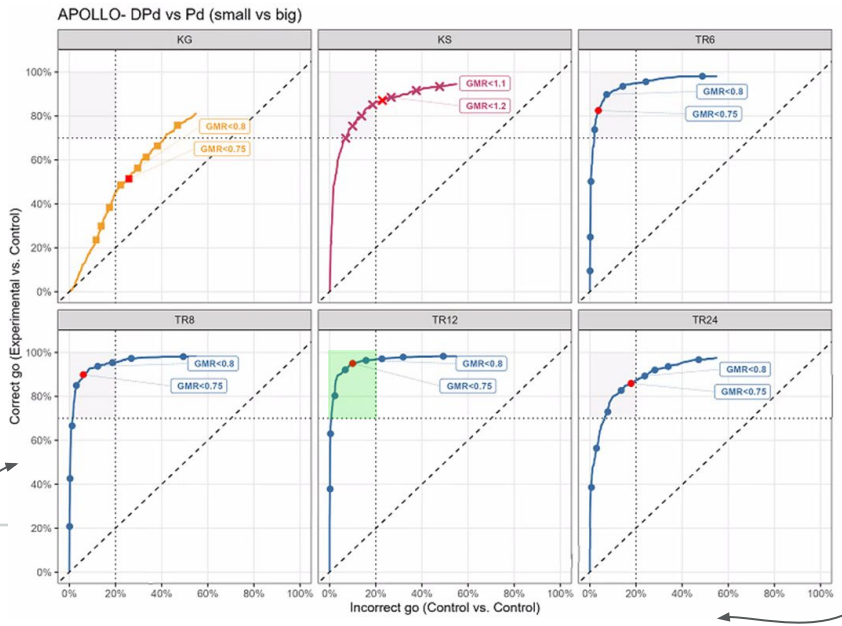
Pd: 15 (10mo mFU) + 15 pts (6mo mFU)

Bootstrapped **Pd** n=149, max FU

Fit models, derive metrics and compute GMR

Repeat 1000 times





- KG has poor OCs, **what's wrong?**
- TR8, TR12 are good metrics (better than TR6 and TR24
- p(TR GMR<0.75)) or p(TR GMR<0.80)) as gating criteria

Marchand et al. PAGE 2025

Genentech
A Member of the Roche Group

IMPORTANCE OF MODEL'S ROBUSTNESS WHEN ASSESSING OC

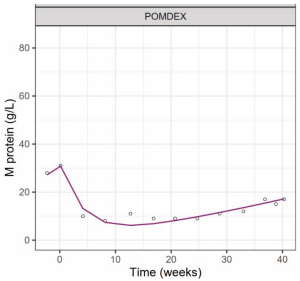
$$t < 0 \;\; Mprot(t) = Mprot_0 \cdot e^{KG_0 \cdot t}$$

$$t \geq 0 \;\; Mprot(t) = Mprot_0 \cdot (e^{KG \cdot t} + e^{-KS \cdot t} - 1)$$

Estimating a different KG0 before treatment improves the model

Parameter	Estimate	SE	RSE (%)	Back-transformed	Unit	Shrinkage (%)
Fixed Effects						
ln(KG0)	-6.79	0.157	2	0.00112	day^{-1}	
ln(KG_DPd)	-7.02	0.0808	1	0.000894	day^{-1}	
ln(KG_Pd)	-6.36	0.0852	1	0.00173	day^{-1}	
ln(KS_DPd)	-4.23	0.123	3	0.0146	day^{-1}	
ln(KS_Pd)	-4.36	0.127	3	0.0128	day^{-1}	
TS0	2.82	0.0893	3	16.8	g/L	
Random Effects						
KG0	165				%CV	48.5
KG	82				%CV	61.3
KS	80				%CV	6.4
TS0	81				%CV	3.9
Residual variability						
Res add.	2.93				g/L	

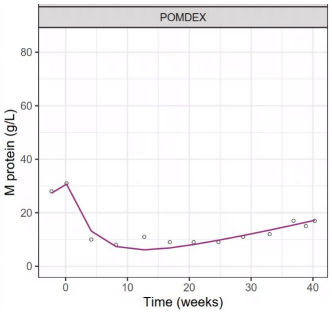
Run: KG0IIV objective function value: 13041.53



On small subsamples, the typical value of KG0 is identifiable but likely not its random effect

Parameter	Estimate	SE	RSE (%)	Back-transformed	Unit	Shrinkage (%)
Fixed Effects						
ln(KG0)	-5.96	0.127	2	0.00258	day^{-1}	
ln(KG_DPd)	-7.63	0.0792	1	0.000486	day^{-1}	
ln(KG_Pd)	-6.37	0.0966	2	0.00171	day^{-1}	
ln(KS_DPd)	-3.80	0.117	3	0.0224	day^{-1}	
ln(KS_Pd)	-4.32	0.129	3	0.0133	day^{-1}	
TS0	2.68	0.0769	3	14.6	g/L	
Random Effects						
KG0	NA				%CV	NA
KG	82				%CV	60.3
KS	76				%CV	5.3
TS0	70				%CV	7.9
Residual variability						
Res add.	3.27				g/L	

Run: KG0noIIV objective function value: 13326.31



This model makes more sense:

KG0 > KG_Pd > KG_DPd

[0.00201;0.00331] [0.00142;0.00207] [0.000416 ; 0.000567]

Let's redo OCs with this model

Genentech
A Member of the Roche Group

RE-ASSESSMENT OF OPERATING CHARACTERISTICS JULY 2025

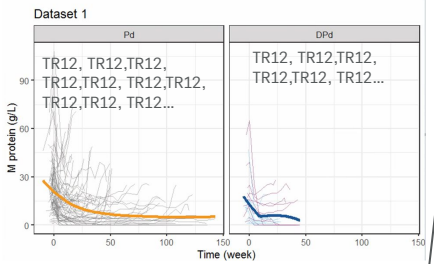
True GO: DPd *vs.* *Pd*

DPd: 15 (10mo mFU) + 15 pts (6mo mFU)

Bootstrapped ***Pd*** n=151, max FU

Fit models, derive metrics and compute GMR

Repeat 1000 times



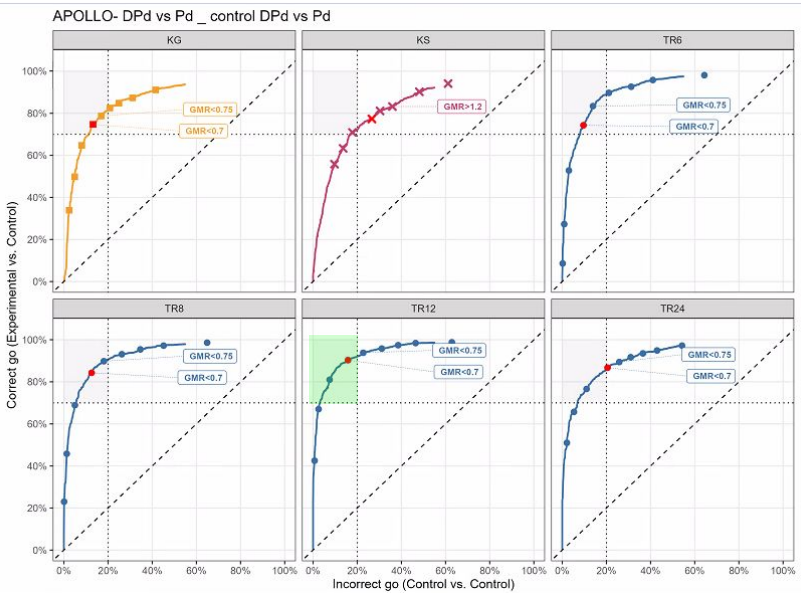
1 GM of TR12

1 GM of TR12

1 GMR exp/control
The lower, the better

X 1000

% of achieving a certain target GMR
e.g. <0.75



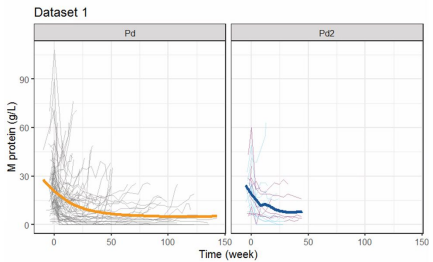
False GO: Pd *vs.* *Pd*

Pd: 15 (10mo mFU) + 15 pts (6mo mFU)

Bootstrapped **Pd** n=149, max FU

Fit models, derive metrics and compute GMR

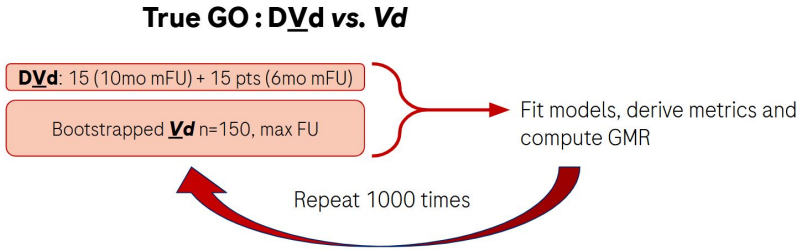
Repeat 1000 times

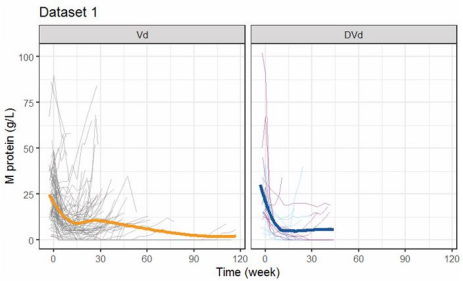


- Results make sense with a less parameterized model
- KG is now a decent metric
- TR8, TR12 are good metrics
- p(TR GMR<0.70) as gating criteria

Genentech
A Member of the Roche Group

LET'S TEST THE APPROACH ON THE CASTOR TRIAL





Would have DVd be a go based on this limited Phase 1b data and compared versus a large Vd control?
Yes!

GO

Probability of achieving the gating criteria

Experimental (DVd) versus Control (Vd): True GO

Metric	p(GMR<0.70)%	p(GMR<0.75)%
KG	94.1	96.9
TR8	74.3	77.4
TR12	87.5	90.2

Control (Vd) versus Control (Vd)/ False GO

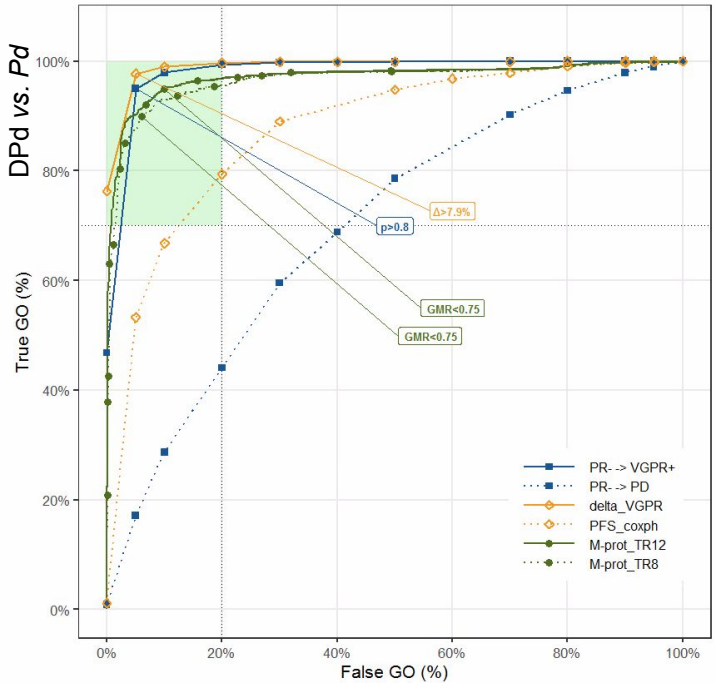
Metric	p(GMR<0.70)%	p(GMR<0.75)%
KG	11.8	16.3
TR8	3.8	8.2
TR12	7.6	12.1

The metric and the gating criteria are validated
We can use this approach to ungate a Phase 3 with treatment X in comparison to DPd

Genentech
A Member of the Roche Group

COMPARISON M-PROTEIN DYNAMICS VERSUS OTHER APPROACHES

Operating Characteristics (OCs) for the various metrics based on APOLLO



Method	Data	Assessment	Key assets
-VGPR+ (Bayesian approach) -ΔVGPR+	Observed	X	VGPR: Primary analysis - Association between ΔVGPR+ and PFS HR
Multistate model	Model-predicted	X vs control (DPd from APOLLO)	-Leverages longitudinal ORR -Transition PR→VGPR has good OCs
M-protein dynamic model	Model-predicted	X (M-protein evaluable) vs control (DPd from APOLLO)	-Leverages longitudinal continuous M-protein data -M-protein ratios to baseline at weeks 8 & 12 have good OCs

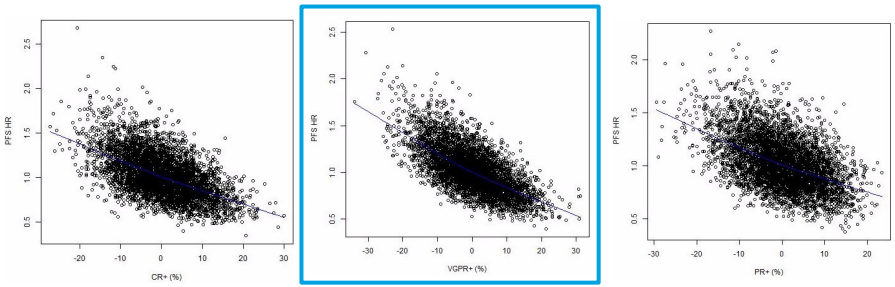
ΔVGPR+ and the 2 model-based approaches demonstrate very good OCs while PFS has relatively poor OCs in early development settings (few subjects, short follow-up)

Courtesy: Mark Yan, Federico Mattiello and MM decision enabling framework Multistate model and Bayesian analysis

Genentech
A Member of the Roche Group

LET'S PRESSURE TEST, WHAT IS THE ASSOCIATION WITH PFS?

- Meta-analysis based on 21 randomized Ph2/3 trials published after 2014
  - VGPR+ rate has the strongest association (among other response-based endpoints) with median PFS
  - No strong association found between delta in response rate and PFS HR probably due to heterogeneity in patient populations
- Patient-level data from APOLLO (DPd arm, N = 146)
  - Low to moderate correlation between response and PFS; VGPR+ is superior to PR+ and CR+
  - M-protein dynamic metric logKG shows similar association than delta in VGPR+



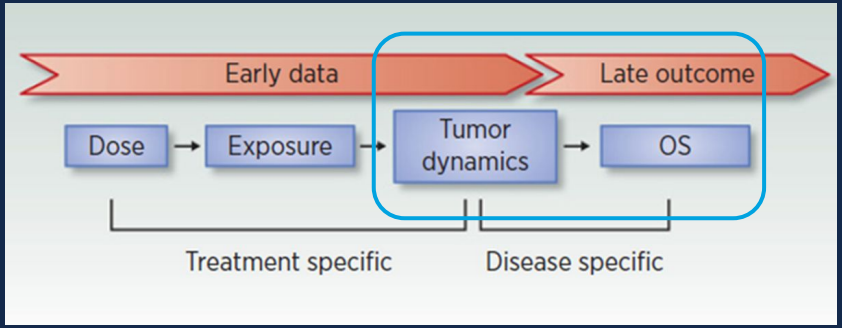
KG: growth constant, TR12: Tumor ratio to baseline at week 12, TTG: Time To Growth...

	APOLLO (DPd)	
Endpoint	**Correlation coef.**	**R-sq**
Delta in VGPR+	**-0.68**	**0.46**
logKG	**0.66**	**0.44**
KG	0.64	0.41
TR24	0.59	0.34
TR18	0.52	0.27
TTG	-0.49	0.24
TR12	0.40	0.16
TR8	0.31	0.10

Courtesy: Mark Yan and MM decision enabling framework

Genentech
A Member of the Roche Group

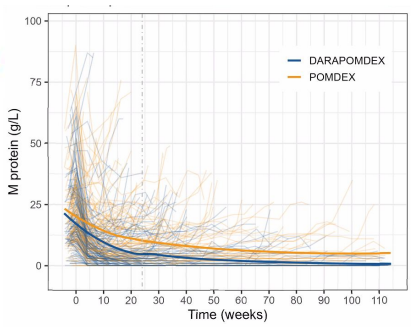
PROBABILITY OF TECHNICAL SUCCESS OF PHASE 3 BASED ON PFS SIMULATIONS



TGI-PFS MODEL DEVELOPMENT ON APPOLO

1. Derive M-protein dynamic metrics

nlmixr²



$$t < 0 \;\; Mprot(t) = Mprot_0 \cdot e^{KG_0 \cdot t}$$

$$t \geq 0 \;\; Mprot(t) = Mprot_0 \cdot (e^{KG \cdot t} + e^{-KS \cdot t} - 1)$$

Parameter	Estimate	SE	RSE (%)	Back-transformed	Unit	Shrinkage (%)
Fixed Effects						
ln(KG0)	-5.96	0.127	2	0.00258	day^{-1}	
ln(KG_DPd)	-7.63	0.0792	1	0.000486	day^{-1}	
ln(KG_Pd)	-6.37	0.0966	2	0.00171	day^{-1}	
ln(KS_DPd)	-3.80	0.117	3	0.0224	day^{-1}	
ln(KS_Pd)	-4.32	0.129	3	0.0133	day^{-1}	
TS0	2.68	0.0769	3	14.6	g/L	
Random Effects						
KG0	NA				%CV	NA
KG	82				%CV	60.3
KS	76				%CV	5.3
TS0	70				%CV	7.9
Residual variability						
Res add.	3.27				g/L	

Run: KG0nolIV objective function value: 13326.31

2. Univariate survival analysis

	Score	p.LRT	N	Sign
logKG	230.7	0.0000	239	+
TTG	89.7	0.0000	239	-
KG	77.2	0.0000	239	+
TR6	31.6	0.0000	239	+
pred_BSLD	25.3	0.0000	239	+
TR8	24.5	0.0000	239	+
ALBU	17.1	0.0000	239	-
HGB	15.3	0.0001	239	-
TR12	13.4	0.0003	239	+
iss	11.6	0.0006	239	+
iss1	10.9	0.0010	239	-
Obs_BSLD	10.9	0.0010	239	+
TR18	8.0	0.0047	239	+
cytrisk	7.2	0.0271	175	-
TR24	6.8	0.0090	239	+
iss3	5.9	0.0148	239	+
SECR	5.2	0.0230	239	+
logKS	3.6	0.0590	239	-
rengrpn	2.8	0.0948	239	-
LDH	2.4	0.1235	239	+
iss2	2.1	0.1502	239	+
BIL	1.7	0.1882	239	+
ALP	1.4	0.2330	239	+
CRCL	1.3	0.2577	239	-
TPRO	1.2	0.2670	239	+
KS	0.9	0.3479	239	-
ALT	0.7	0.4090	239	+
age	0.5	0.4940	239	-
BECOG0123	0.3	0.5928	239	+
BWT	0.2	0.6596	239	+
AST	0.1	0.7695	239	-
SEX	0.1	0.7386	239	-
racegr1n	0.1	0.7089	239	+

M-protein dynamic metrics

→ Tested in multivariate survival analysis

3. Multivariate parametric survival model

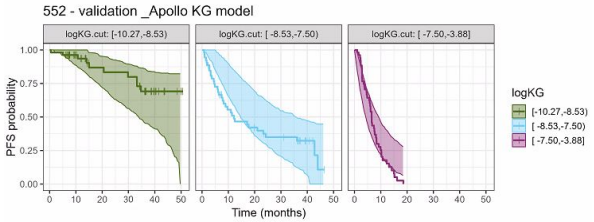
Term	Estimate	std.error	Z-value	p-value	Lower CI	Upper CI
(Intercept)	-5.210	0.563	-9.255	<2e-16	-6.313	-4.106
logKG	-0.770	0.051	-15.226	<2e-16	-0.869	-0.671
HGB	0.193	0.041	4.742	0	0.113	0.273
Log(scale)	-0.110	0.055	-2.010	0.0444		

PFS is longer with slower growth rate and higher baseline hemoglobin (HGB)

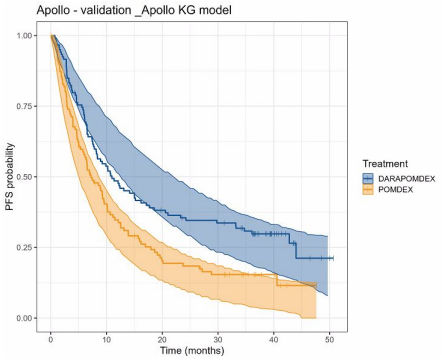
Genentech
A Member of the Roche Group

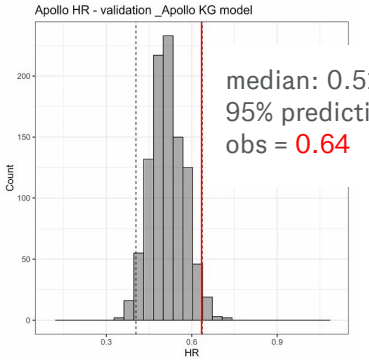
TGI-PFS MODEL VALIDATION ON APOLLO & CASTOR

PFS model qualification on APOLLO



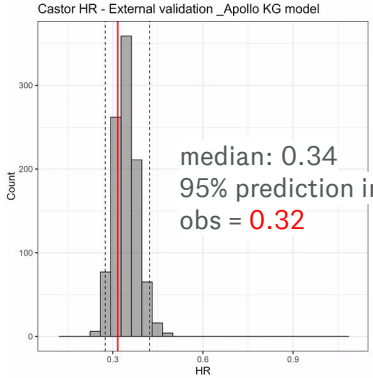
The model predicts quite well PFS in the different quartiles of log(KG)





median: 0.51
95% prediction interval[0.40;0.64]
obs = 0.64

External Validation on CASTOR



median: 0.34
95% prediction interval[0.28;0.42]
obs = 0.32

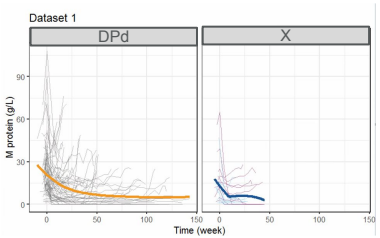
PFS model validated, it can be used to simulate Phase 3 trial with treatment X and assess its probability of technical success (PTS)

PROBABILITY OF TECHNICAL SUCCESS OF PHASE 3

Phase 3 study:
X
versus
Standard of Care:
daratumumab+polamidomide+
dexamethasone (DPd),
endpoint: PFS

X: 15 (10mo mFU) + 15 pts (6mo mFU)

DPd: complete arm n=120, max FU



Fit M-protein data,
get log(KG),
add HGB

PFS simulations of Phase 3 design
160 vs. 160 patients

1000 trials

1000 HR, 1000 Logrank tests

- 1 median HR and 95% prediction interval
- 1 probability of Logrank tests with p<0.05
- 1 probability of HR<target

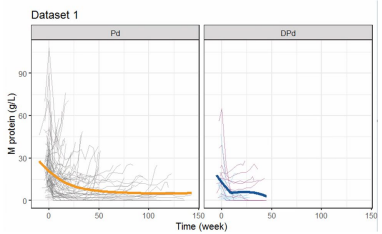
Genentech
A Member of the Roche Group

RISK ASSOCIATED WITH DECISION MAKING BASED ON LIMITED DATA

DPd: 15 (10mo mFU) + 15 pts (6mo mFU)

Pd: complete arm n=120, max FU

Fit M-protein data, get log(KG), add HGB



PFS simulations of APOLLO design
150 vs. 150 patients

200 trials

200 HR, 200 Logrank tests

- 1 median HR
- 1 probability of Logrank tests with p<0.05

X500
each with a different DPd arm

Distribution of median HR:
median 0.69 [0.25;1.09]
Observed HR: 0.63

Distribution of probability of success: median 71% [6;100]

PTS assessment highly depends on the small experimental arm data

In early development, we only have N=1 set of Phase 1b data to make the decision

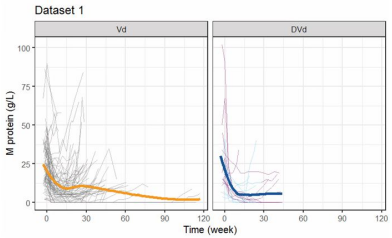
Genentech
A Member of the Roche Group

RISK ASSOCIATED WITH DECISION MAKING BASED ON LIMITED DATA

DVd: 15 (10mo mFU) + 15 pts (6mo mFU)

Vd: complete arm n=250, max FU

Fit M-protein data,
get log(KG),
add HGB



PFS simulations of CASTOR design
250 vs. 250 patients

200 trials

200 HR, 200 Logrank tests

- 1 median HR
- 1 probability of Logrank tests with p<0.05

X500
each with a different DPd arm

Distribution of median HR:
median 0.58 [0.20;0.91]
Observed HR: 0.39

Distribution of probability of success:
median 99.5% [19.0;100.0]

PTS assessment highly depends on the small experimental arm data

In early development, we only have N=1 set of Phase 1b data to make the decision

Genentech
A Member of the Roche Group

CONCLUSIONS

- Assessing Operating Characteristics is a valuable approach to identify what is the metric, the target and the gating criteria to rationalize early decision making in a quantitative manner
  - Importance of the robustness of the model used to analyze the 1000 subsamples
  - The metric selected should ideally be well associated to the primary endpoint used in the Phase 3 study we want to ungate

- The traditional TGI-PFS (OS) approach can also be used to simulate Phase 3 outcomes and assess its probability of technical success (PTS)
  - As expected, there is a very high weight on the small Phase 1b data on the decision, i.e. the variability of the PTS is huge which leads to risky decision, we should consider larger Phase 1b trials to de-risk Phase 3 Go/No Go decisions

THANK YOU

Genentech

A Member of the Roche Group