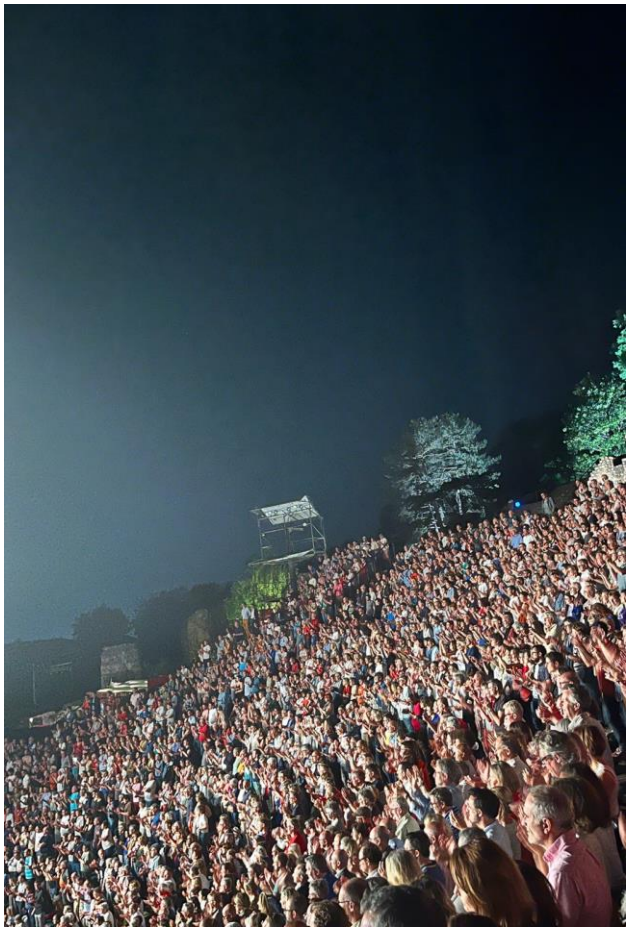
Lyon, France, 2 days ago…



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A disease model for Multiple Myeloma developed using Real World Data and validated on Phase 3 clinical trials

Pascal Chanu[1], Zao Li[2], Divya Samineni[2], Monica Susilo[2], Jin Y Jin[2], Chunze Li[2], René Bruno[1]

June 26, 2024, PAGE meeting, Roma, Italy

1 Clinical Pharmacology, Genentech/Roche, France
2 Clinical Pharmacology, Genentech Inc

OUTLINE

1 The use of RWD in Clinical Pharmacology, IQ consortium White Paper

2 Overall Survival (OS) model developed based on Flatiron RWD

3 External validations of OS model using YODA data

4 Progression Free Survival Modeling using CoMMpass data

MULTIPLE MYELOMA Research Foundation

CoMMpass℠ Study

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RWD in Clinical Pharmacology

Clinical Pharmacology Applications of Real-World Data and Real-World Evidence in Drug Development and Approval–An Industry Perspective

Rui Zhu[1,**,*], Bianca Vora[1], Sujatha Menon[2], Islam Younis[3], Gaurav Dwivedi[4], Zhaoling Meng[5], Amita Datta-Mannan[6], Pooja Manchandani[7], Satyaprakash Nayak[2], Brinda K. Tammara[2], Parag Garhyan[8], Shahed Iqbal[9], Simon Dagenais[10], Pascal Chanu[11], Arnab Mukherjee[2], Cyrus Ghobadi[6,*] and International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) Real-World Data Working Group

Collaboration with Pfizer, Gilead, Takeda, Sanofi, Eli Lilly, Astellas, Genentech

Zhu et al. Clin Pharmacol Ther. 2023 Oct;114(4):751-767.

Guide DDI assessments

Support regulatory decision mak-ing for label expansion

Inform dose recommen-dation for patients with organ impairment

Generate synthetic/ external control for rare diseases

Identify prognostic and predictive biomarker/ factors

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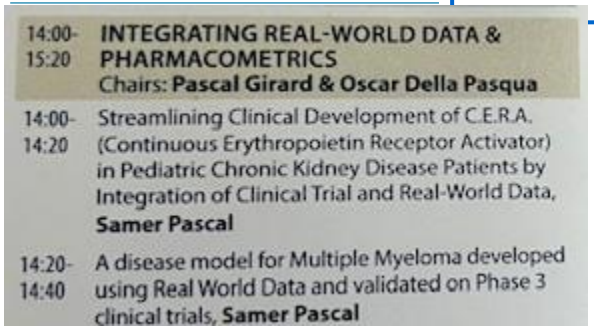
RWD in Clinical Pharmacology

Provide insights for pediatric plan development and study design	Chanu *et al.* (2020)[32]	Use RWD/RWE to supplement modeling work based on RCTs to optimize C.E.R.A. development in the confirmatory trial of the pediatric plan	IPDN database	Confirmed the model simulated treatment outcomes in pediatric patients receiving C.E.R.A. i.v. and s.c. and provided a strong rationale for applying the C.E.R.A. S.c. dosing regimen only in pediatric patients rather than both i.v. and s.c., leading to- a simplified confirmatory trial in pediatrics
	Zhang (2021)[33]	Evaluate t relationshi pediatric po RWD to su for etrolizum		
	Lukka *et al.* (2021)[34]	Support la the younge (< 4 year recommer		



14:00-15:20	**INTEGRATING REAL-WORLD DATA & PHARMACOMETRICS** Chairs: **Pascal Girard & Oscar Della Pasqua**	
14:00-14:20	Streamlining Clinical Development of C.E.R.A. (Continuous Erythropoietin Receptor Activator) in Pediatric Chronic Kidney Disease Patients by Integration of Clinical Trial and Real-World Data, **Samer Pascal**	
14:20-14:40	A disease model for Multiple Myeloma developed using Real World Data and validated on Phase 3 clinical trials, **Samer Pascal**	

14:00-15:20	**Integrating Real-World Data & Pharmacometrics**		*Pascal Girard & Oscar Della Pasqua*
14:00-14:20	*Pascal Chanu*	A disease model for Multiple Myeloma developed using Real World Data and validated on Phase 3 clinical trials	
14:20-14:40	*Samer Mouksassi*	Streamlining Clinical Development of C.E.R.A. (Continuous Erythropoietin Receptor Activator) in Pediatric Chronic Kidney Disease Patients by Integration of Clinical Trial and Real-World Data	
	Luca Marzano	Overcoming the discrepancies between clinical trials and real-world data of small cell lung cancer chemotherapy. A data-driven approach to learn across real-world evidence studies	
	Aole Zheng	A Novel Approach Using Pharmacometrics/Pharmacoeconomic (PMPE) Model for Cost-effectiveness Analysis of Tacrolimus-Diltiazem Combination in Liver Transplant Patients: Evidence from Real-world Clinical Data	

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RWD in Clinical Pharmacology

Category	Reference	Objective	RWD source	Insight/evidence generated
Enable and enrich MIDD notably disease progression modeling	Doler *et al.* (2013)[36] Jamalian *et al.* (2020)[37]	Develop a disease progression model to describe natural progression of Alzheimer's disease	ADNI database	Disease progression model was developed to quantitatively characterize the progression of the disease and can be used to predict natural disease progression in Alzheimer's disease patients
	Boucher *et al.* (2018)[38]	Investigate disease progression and treatment effect in patients diagnosed with hereditary transthyretin-mediated amyloid polyneuropathy, a rare disease	THAOS	Relevant and consistent disease progression and treatment effects (of tafamidis) were estimated in an independent clinical trial and in patients from RWD
	Wang *et al.* (2019)[39]	Model disease progression and identify risk factors for patients diagnosed with DMD, a rare disease	Cooperative International Neuromuscular Research Group DMD Natural History Study	Models adequately described disease progression for key end points in ambulatory and nonambulatory DMD boys
	Abrams *et al.* (2020)[40]	Develop a QSP model to predict response for patients diagnosed with GD1	ICGG Gaucher Registry	Generated virtual patients that captured the appropriate disease phenotypes of interest with more accurate representation of their variability, which enabled the QSP modeling that captured specific clinical attributes of the disease, incorporated markers of disease severity, and informed relevant treatment strategies
	Chanu *et al.* (2021)[42]	Use M-protein dynamics as an early time biomarker to predict OS for patients diagnosed with multiple myeloma	Flatiron Health EHR	Model built with RWD can inform drug development in multiple myeloma; e.g., predict survival outcomes of multiple independent Phase iii trials leveraging M-protein dynamics collected in a smaller early phase trial
	Kotani *et al.* (2021)[43]	Use RWD to check survival distribution from clinical trial used to develop a disease model for HER2–/HR+ mBC	Flatiron Health EHR	Survival data from RWD is consistent with the one from the clinical trial used to develop the disease model

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Leveraging multiple data sources

RWD

Daratumumab Clinical Trial data

Observational study

flatiron

YODA: Yale Open Data Access

MM RF MULTIPLE MYELOMA Research Foundation

CoMMpass℠ Study

OS model development

External validation

External validation

PFS model development

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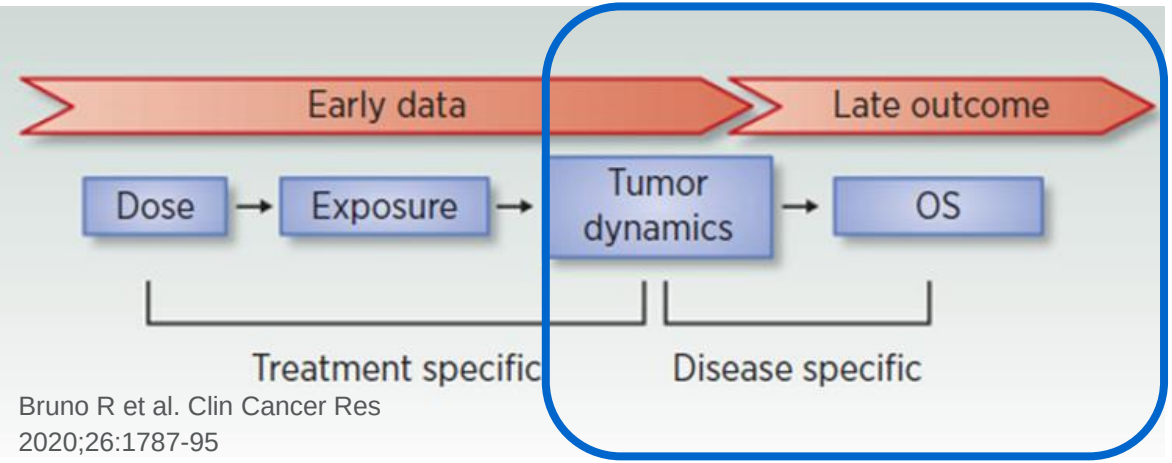
Drug-disease modeling framework in oncology



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

- Model-based tumor dynamic metrics are biomarkers capturing treatment effect and strong predictors of survival (OS or PFS) benefits
- Tumor dynamics-OS/PFS models are assumed to be drug-independent
- M-protein is the measure of tumor burden in Multiple Myeloma

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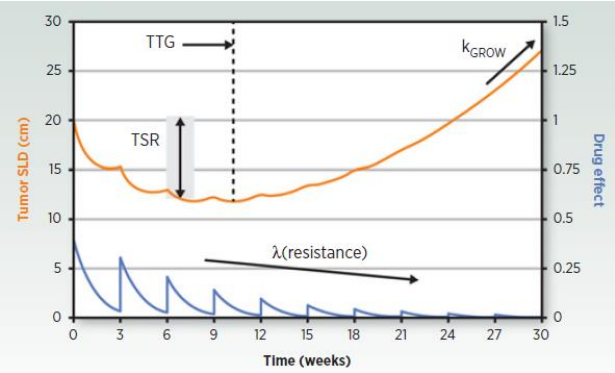
Application to Multiple Myeloma (MM)

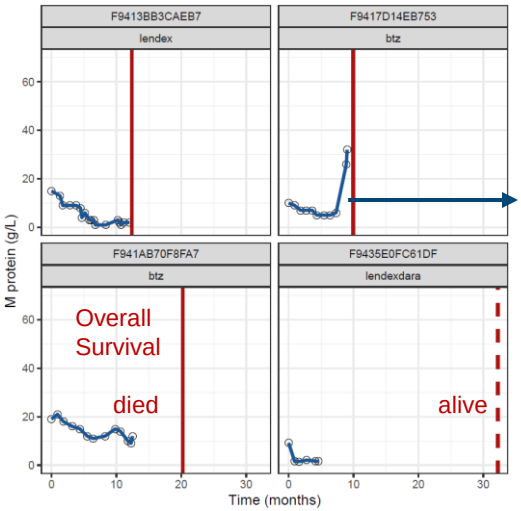
Model-based tumor dynamics metrics



SLD: sum of longest diameters
TSR: tumor size ratio from baseline
TTG: time to growth
K_{GROW} (or KG): growth rate constant

Application to Multiple Myeloma

- M-protein is a reliable marker of tumor burden in Bruno, et al. [abstr 1881]. Blood 118, 1881, 2011
- Link between M-protein dynamics and OS



M-protein dynamics metrics derived with empirical bi-exponential model

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

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

Stein et al. Clin Cancer Res, 17:907-17, 2011
Claret et al. Clin Cancer Res, 24:3292-8, 2018

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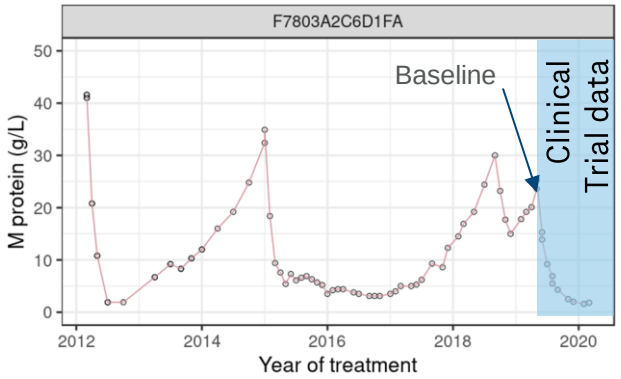
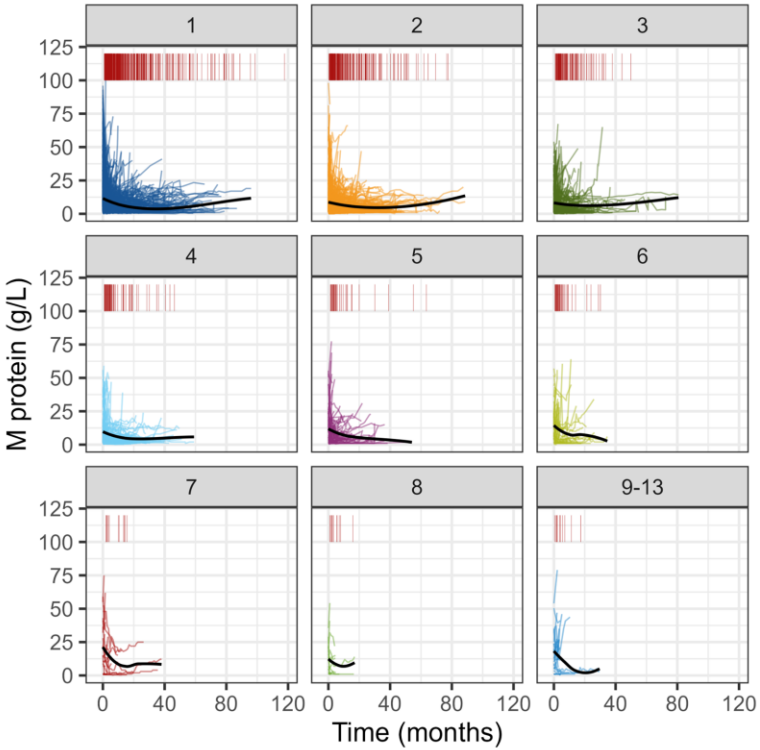
Using RWD for modeling: starting with 4108 MM patients





- Selecting the right line of therapy
  - Multiple Myeloma patients may have many lines of therapy
  - The definition of line of therapy may be different than the one used in clinical trials
- Latest line of therapy in each patient with at least 2 M-protein assessments
- Definition of “Baseline” in the context of use
- Data cleaning, erratic profiles
- IT challenges: cannot download data

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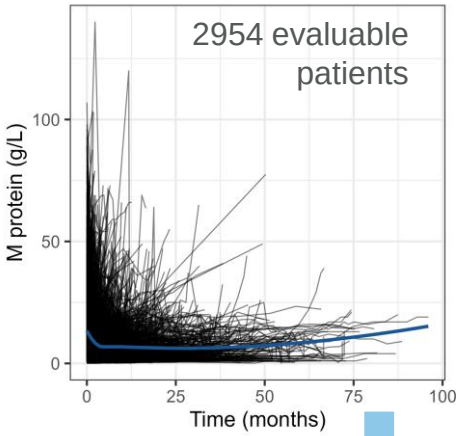
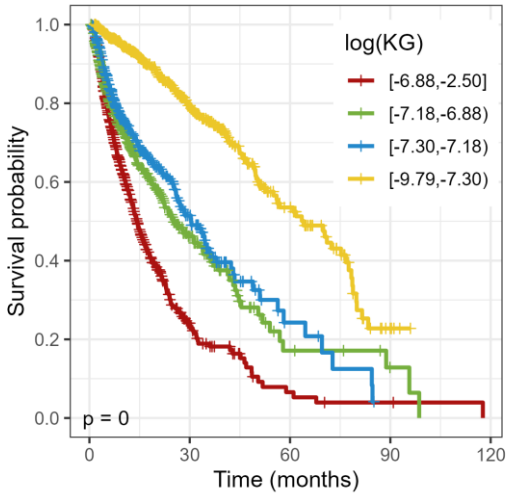
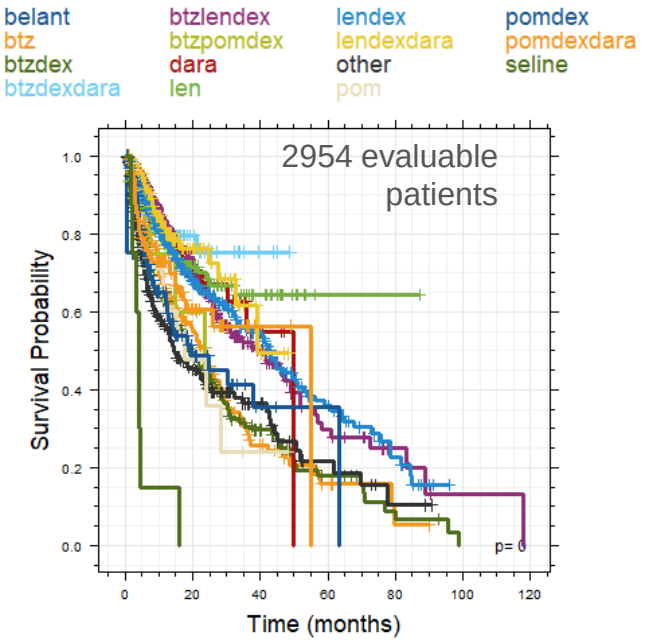
Analysis of M-protein and OS data from 2954 RWD patients



Model-based M-protein dynamics metrics, e.g. log(KG)



belant = belantamab
btz=bortezomib
dara=daratumumab
dex=dexamethasone
len=lenalidomide
pom=pomalidomide
seline = selinexor



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Parametric OS model

The model tested

- 10 M-protein dynamic metrics
- 33 baseline characteristics and prognostic factors

Survival data followed a log-normal distribution

The final model estimated on 1445 patients is consistent with a previously developed model: Bruno, et al. [abstr 1881]. Blood 118, 1881, 2011

	Value	Std. Error	p
(Intercept)	-3.243	0.4809	1.54E-11
log(KG)	**-0.585**	**0.04749**	**7.23E-35**
ECOG 0,1,2,≥3	-0.2936	0.05224	1.91E-08
Lactate dehydrogenase	-0.000821	0.0001429	9.14E-09
Albumin	0.04557	0.008543	9.59E-08
Hemoglobin	0.0963	0.02556	0.0001651
Creatinine clearance	0.0041	0.001301	0.00163
Sex	0.3113	0.08892	0.0004636
Line of therapy	-0.06603	0.02204	0.002739
Log(scale)	0.1637	0.03395	1.43E-06

Longer survival is predicted in patients with:

- Slower growth rate, lower values of ECOG status and LDH
- Higher values of albumin, hemoglobin and creatinine clearance
- Earlier line of therapy and in female

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External Validation on CASTOR trial: M- protein dynamic

The NEW ENGLAND JOURNAL of MEDICINE

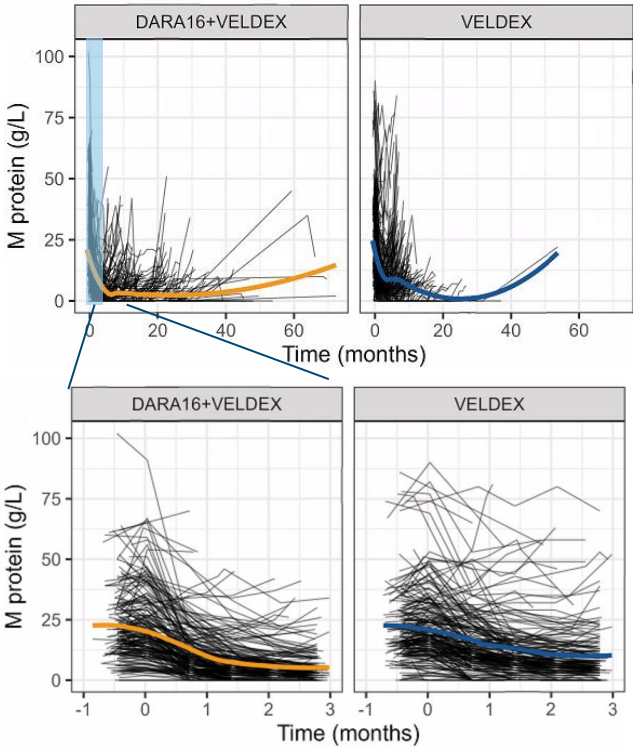
ORIGINAL ARTICLE

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*

Palumbo et al. N Engl J Med 2016;375:754-66.

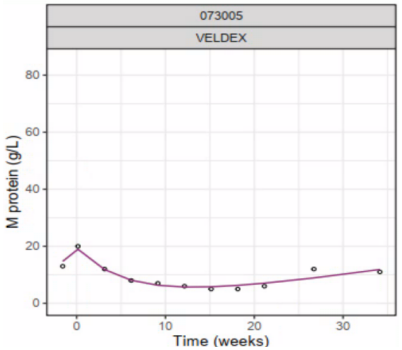
Patient level data available in YODA



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

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

Typical values:
KG_0=0.01131 /week
KG=0.00079 /week
See Marchand et al., poster III-09



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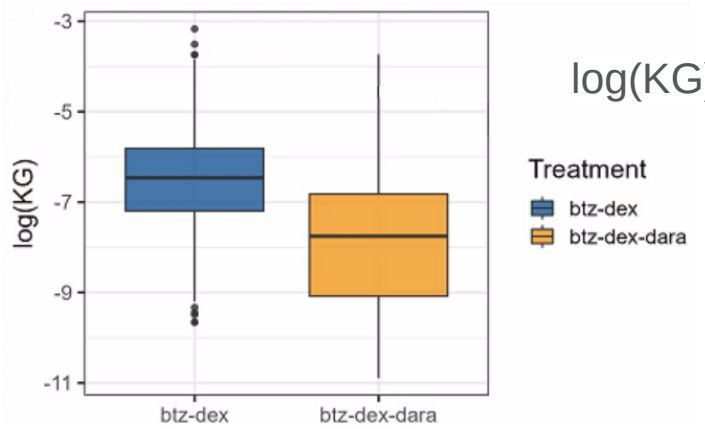
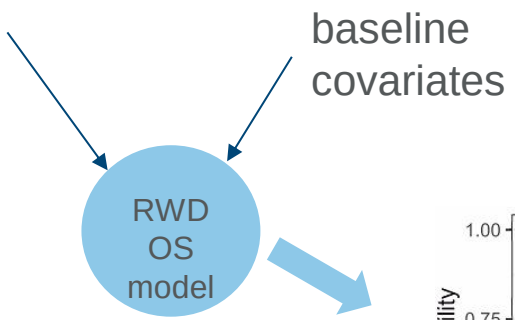
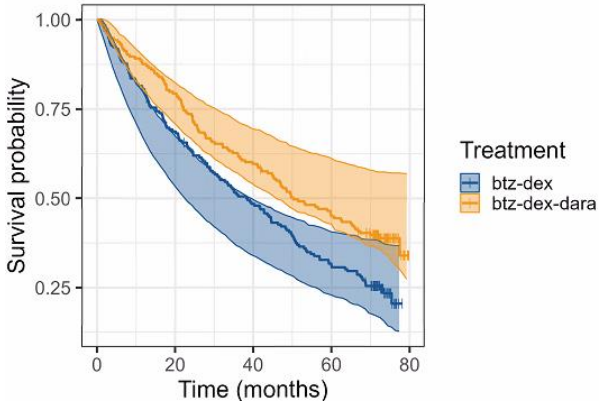
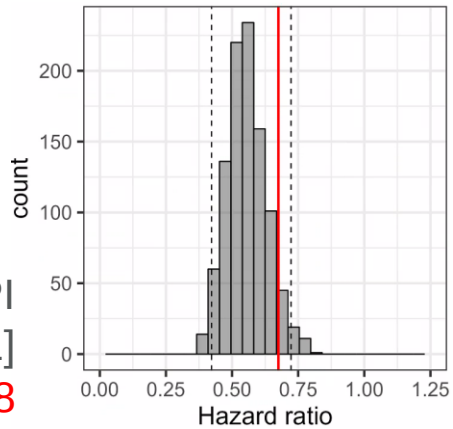
External Validation on CASTOR trial: OS









The RWD OS model well captured the daratumumab effect observed in CASTOR clinical trial

Simulated HR and 95% PI
0.55 [0.43;0.71]
Observed: 0.68

Simulations (95% prediction interval)

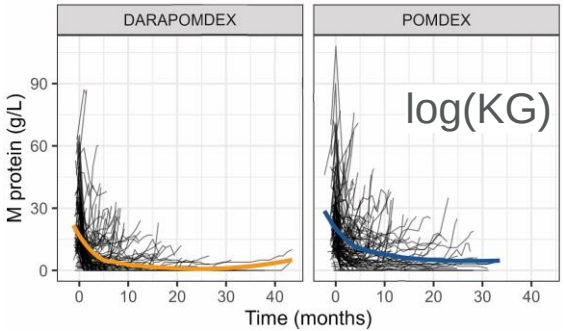
Observations and censored data – +

External Validation on APOLLO trial

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**

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

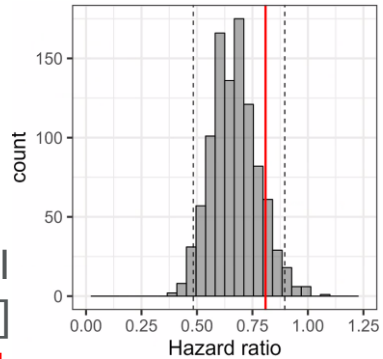


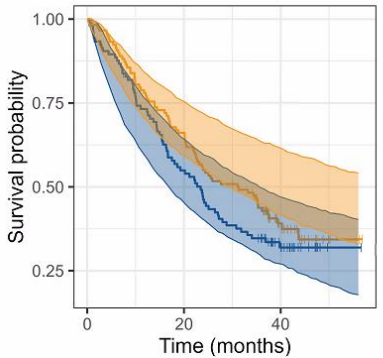
baseline covariates

RWD OS model

Patient level data available in YODA

The RWD OS model well captured well captured the daratumumab effect observed in APOLLO clinical trial





Treatment
pom-dex
pom-dex-dara

Simulations (95% prediction interval)

Observations and censored data – +

Simulated HR and 95% PI
0.66 [0.49;0.90]
Observed: 0.81

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PFS model developed on CoMMpass observational study

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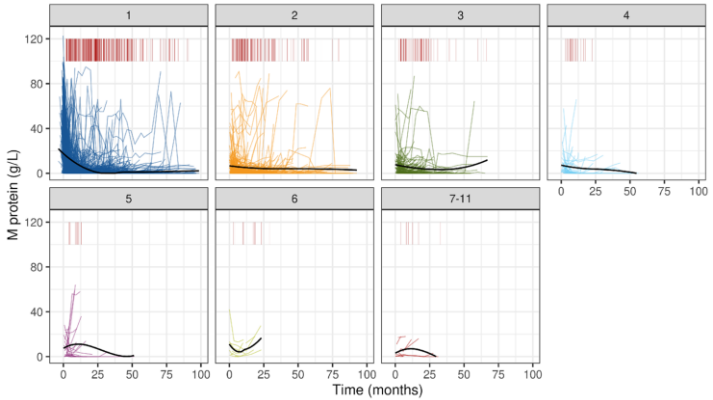
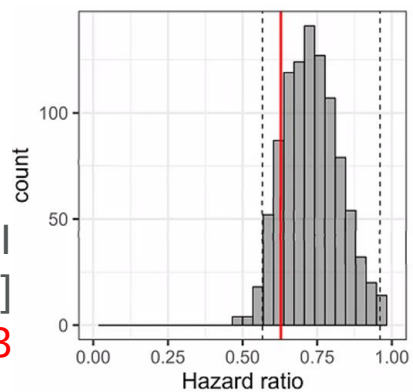
CoMMpass℠ Study



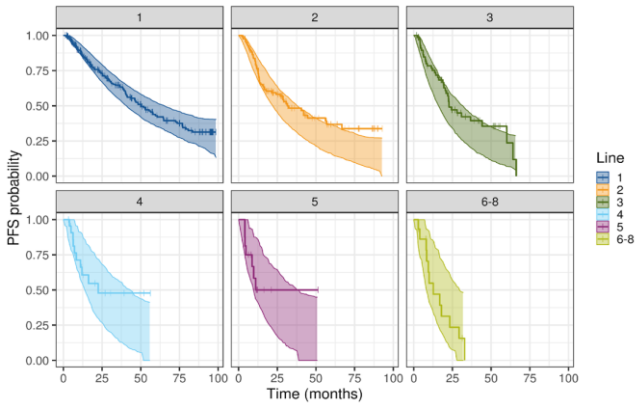
	Value	Std. Error	p-value
(Intercept)	0.06946	0.5609	0.9014
log(KG)	**-0.3383**	**0.02708**	**8.44E-36**
Hemoglobin (g/L)	0.01508	0.002859	1.33E-07
Lactate dehydrogenase (U/L)	-0.001586	0.00037	1.82E-05
Age (y)	-0.01219	0.004664	0.008942
ECOG status	-0.1808	0.06694	0.006917
Log(scale)	-0.1094	0.04659	0.01887

External validation on APOLLO

Simulated HR and 95% PI
0.73 [0.57;0.96]
Observed: 0.63



Simulations (posterior predictive checks) across lines of therapy



DISCUSSION

- A model linking M-protein dynamic to OS in Multiple Myeloma could be developed based on RWD across line of therapies and was qualified in predicting independent Phase 3 trials outcome : CASTOR, APOLLO
- An observational trial was used to develop a PFS model
- Similar and consistent predictors of survival outcomes: log(KG) ECOG, hemoglobin, albumin, lactate dehydrogenase…

Next steps:

- Use the OS model and the M-protein dynamic model to reconstruct a pseudo PFS
  - Methodological challenge by linking M-protein dynamics to predict PFS
- Joint models are getting easier to run: see Merlaud et al., poster III-022
- AI assistance!

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ACKNOWLEDGEMENTS

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