METRUM
RESEARCH GROUP

Population pharmacokinetic and exposure-response modeling of patritumab deruxtecan (HER3-DXd)

Tim Waterhouse
March 20, 2025

Acknowledgments

Daiichi Sankyo, Inc.

Li Li
Yuan Xu
Rujuta Joshi
Mark Lee
Yang Chen
Shufang Liu
Toan Ngyuen

Metrum Research Group

Shelly Wang
Rena Byrne
Matthew Wiens
Hillary Husband
Ramon Garcia
Kyle Baron
Todd Yoder
Andrew Tredennick
Eric Anderson
Jonathan French
Bill Gillespie

Overview

01 Brief intro to ADCs and patritumab deruxtecan (HER3-DXd)

02 HER3-DXd population PK

03 HER3-DXd efficacy exposure-response

04 HER3-DXd safety exposure-response

05 Summary

Intro to ADCs

The ‘Magic Bullet’ Idea

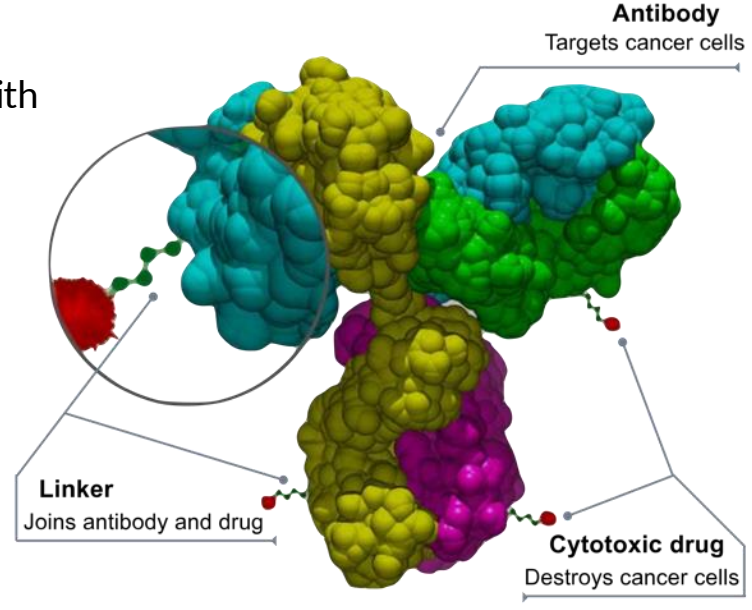
- Paul Ehrlich was born on March 14, 1854
- Nobel Prize in Physiology or Medicine in 1908 in recognition of his work on immunity.

Ever since [...] **chemotherapy**, science had sought to **increase the specificity** of such treatments by developing compounds with greater selectivity for killing cancer cells.
The notion of **combining specific binding to a diseased cell or organism with a toxic activity for that cell or organism was first articulated by Paul Ehrlich in 1907**. He referred to **“magic bullets”** to describe such molecules.
As the **specific binding properties and protein structure of antibodies** became known, there were early attempts to **conjugate cytotoxic drugs to serum immunoglobulins** to provide specificity to such agents.
However, it was not until the **invention of monoclonal antibodies in 1975** that the concept that antibodies could provide to a cell-killing agent the selective binding became the subject of a large research effort.
(~Lambert, 2015)

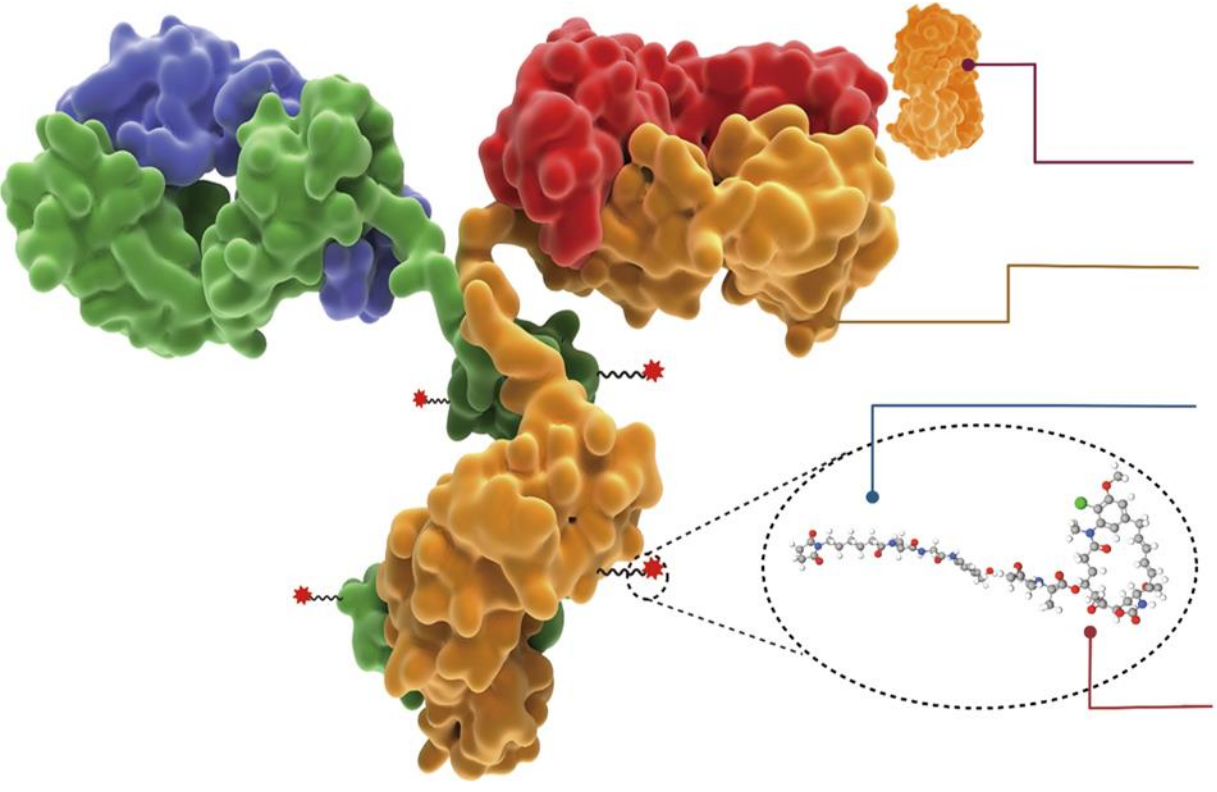
Slide courtesy of A. Katharina Wilkins

What are antibody-drug conjugates (ADCs)?

- ADCs are targeted cancer therapies that combine the specificity of monoclonal antibodies (mAbs) with the potency of cytotoxic drugs
- Goal: Deliver chemotherapy selectively to cancer cells, reducing off-target toxicity



What are antibody-drug conjugates (ADCs)?

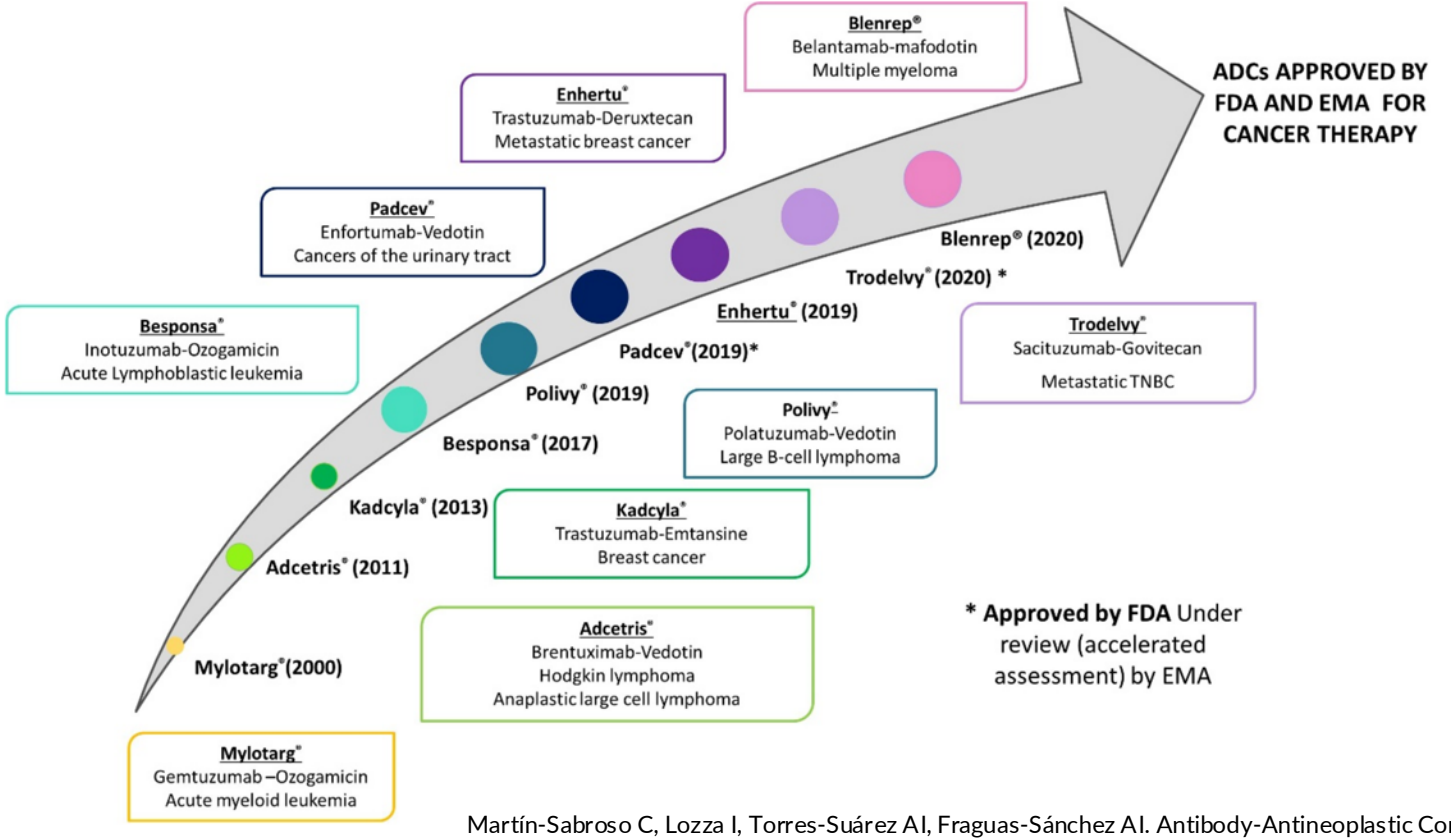


Key functions

Target antigen	Recognition of target cancer cells
Antibody	Guidance system for cytotoxic drugs
Linker	Bridge between antibody and drugs and to control the release of drugs inside cancer cells
Cytotoxic drug	Warhead for destroying cancer cells

Fu, Z., Li, S., Han, S. et al. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Sig Transduct Target Ther 7, 93 (2022). https://doi.org/10.1038/s41392-022-00947-7

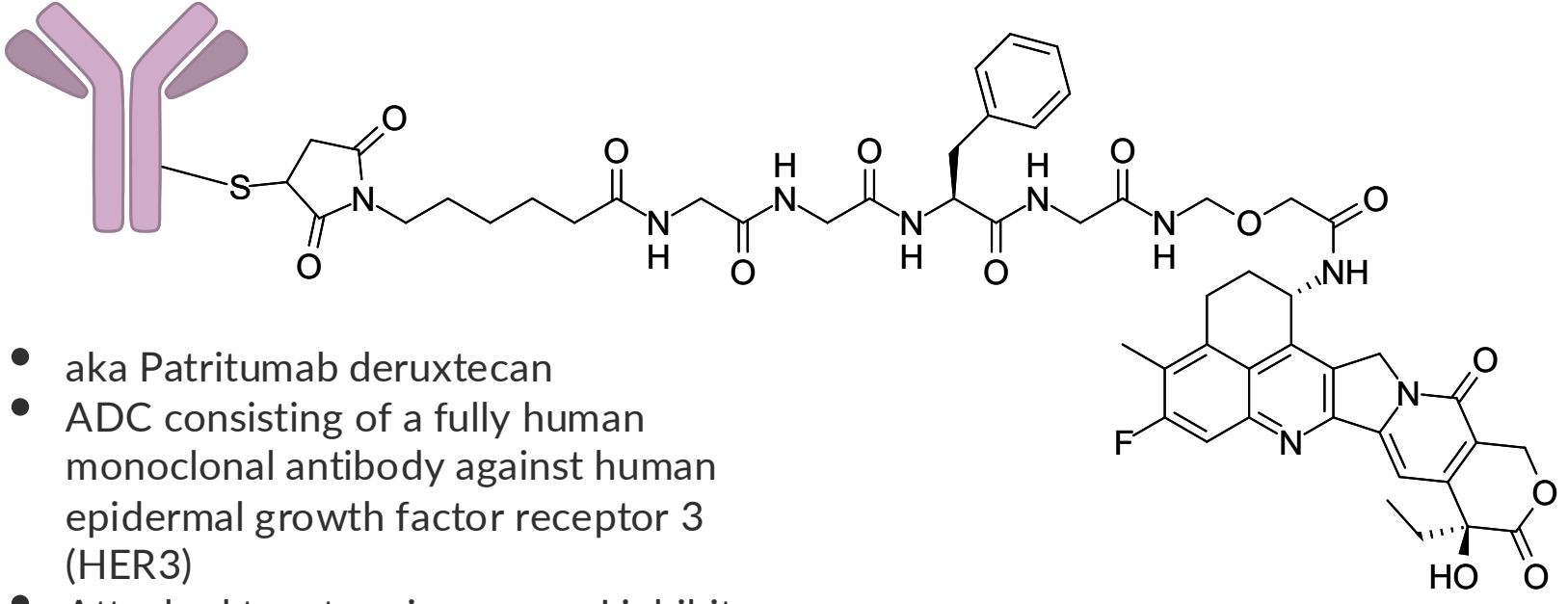
ADC approvals



Martín-Sabroso C, Lozza I, Torres-Suárez AI, Fraguas-Sánchez AI. Antibody-Antineoplastic Conjugates in Gynecological Malignancies: Current Status and Future Perspectives. Pharmaceutics. 2021; 13(10):1705.

METRUM RESEARCH GROUP

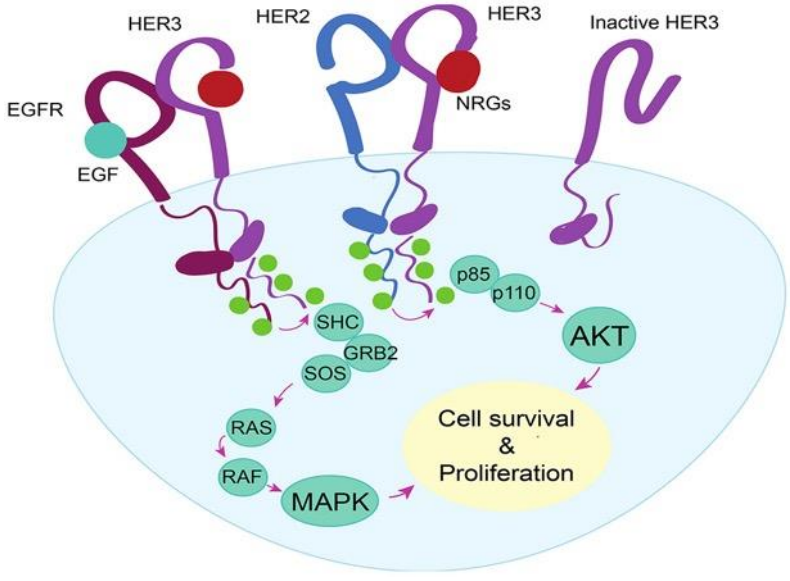
HER3-DXd



- aka Patritumab deruxtecan
- ADC consisting of a fully human monoclonal antibody against human epidermal growth factor receptor 3 (HER3)
- Attached to a topoisomerase I inhibitor payload (DXd) via a tetrapeptide-based cleavable linker

Why HER3?

- HER3 overexpression has been observed in several cancers, including breast (BC), colorectal, and non-small cell lung cancer (NSCLC)
- HER3 expression has been associated with shorter time to metastatic progression and shorter relapse-free survival



Haikala HM, Jänne PA. Thirty Years of HER3: From Basic Biology to Therapeutic Interventions. Clin Cancer Res. 2021 Jul 1;27(13):3528-3539.

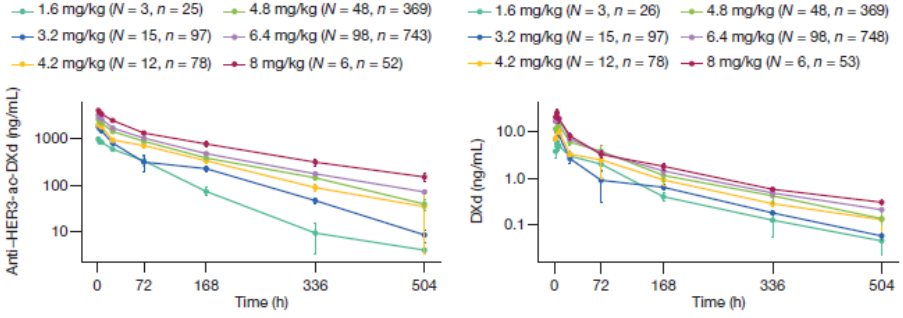
HER3-DXd Population PK

HER3-DXd studies

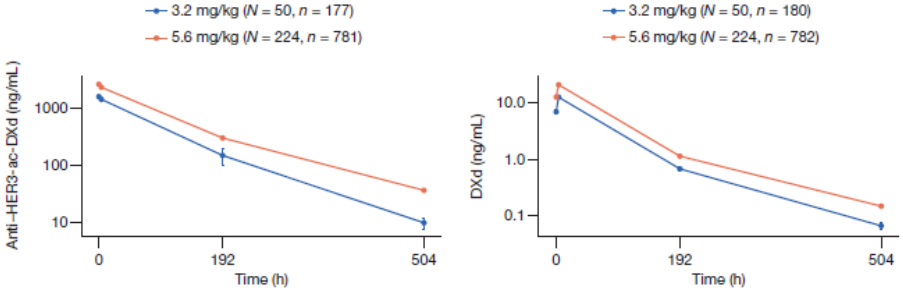
Study	Patients	# Subjects
U31402-A-J101	HER3-positive metastatic breast cancer	182
U31402-A-U102	NSCLC	237
U31402-A-U201	Metastatic or locally advanced NSCLC with an activating EGFRm	274
U31402-A-U202	Advanced or metastatic colorectal cancer who are resistant, refractory, or intolerant to ≥2 prior lines of therapy	40

21,750 PK samples from 733 subjects

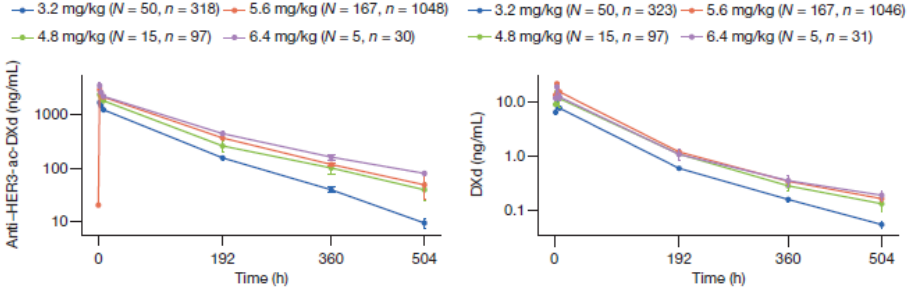
Study J101



Study U201



Study U102

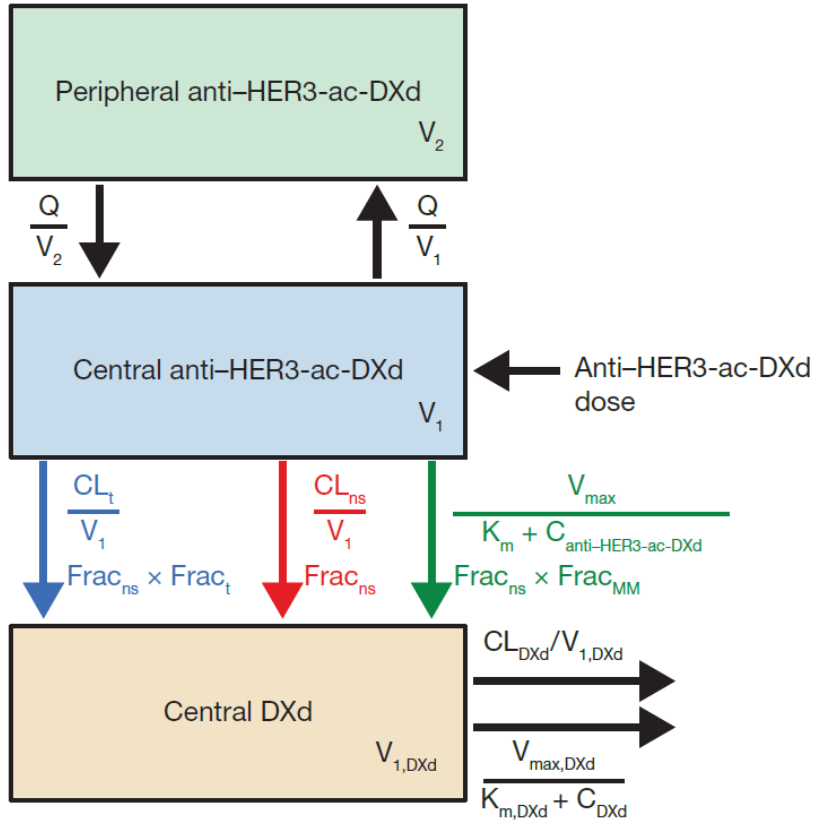


Study U202

- 5.6 mg/kg IV Q3W
- N = 40 subjects

PK model structure

- **Anti–HER3-ac-DXd PK**: two-compartment model with three elimination pathways:
  - linear transient clearance
  - nonspecific time-dependent clearance
  - nonlinear Michaelis-Menten clearance
- **DXd PK**: one-compartment model with two clearance pathways:
  - linear clearance
  - nonlinear Michaelis-Menten clearance
- **DXd formation** rate limited by all three clearance pathways of anti–HER3-ac-DXd



Clearance pathways: Nonspecific time-dependent linear clearance

$$CL_{ns} = CL_{inf} \cdot \left(1 + CL_{inf,Emax} \cdot \frac{T_{50}^{\gamma}}{T_{50}^{\gamma} + t^{\gamma}}\right)$$

- Clinf: nonspecific linear clearance at infinity after dosing Q3W
- CLinf,Emax: maximum effect of time on CLns
- T50: the time to half-maximal effect
- γ: Hill coefficient

Clearance pathways: Transient linear clearance

$$CL_t = CL_T \cdot \exp(-k_{des} \cdot t)$$

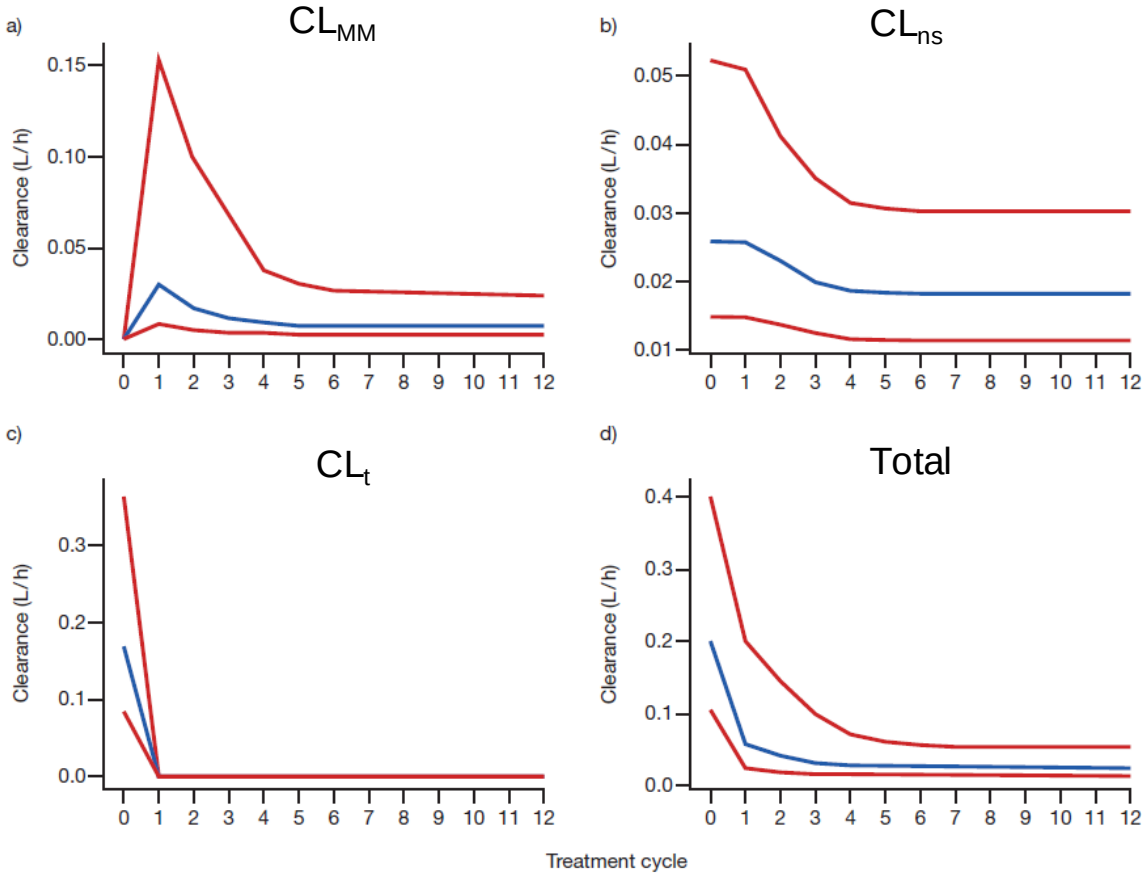
- CLT: clearance at baseline
- kdes: rate constant of exponential decline

Clearance pathways: Nonlinear clearance

$$\mathrm{CL_{MM}} = \frac{V_{\max}}{K_{\mathrm{m}} + C_{\mathrm{anti-HER3-ac-DXd}}}$$

- Vmax: maximal Michaelis-Menten elimination
- Km: exposure eliciting half of the maximum effect

Clearance components over time



Full covariate model

Anti–HER3-ac-DXd covariate effects

- CL_t: hepatic function, CRCL, prior therapies
- V1: sex, country
- CL_{inf}: country, sex, age, tumor type, prior chemo, prior immunotherapy, ECOG, prior therapies, hepatic function, CRCL, formulation
- $CL_{inf,Emax}$: albumin, tumor size

DXd covariate effects

- CL_{DXd}: country, sex, age, tumor type, prior chemo, prior immunotherapy, ECOG, prior therapies, hepatic function, CRCL, formulation
- V_{DXd}: sex, country

Reduced covariate model

Anti–HER3-ac-DXd covariate effects

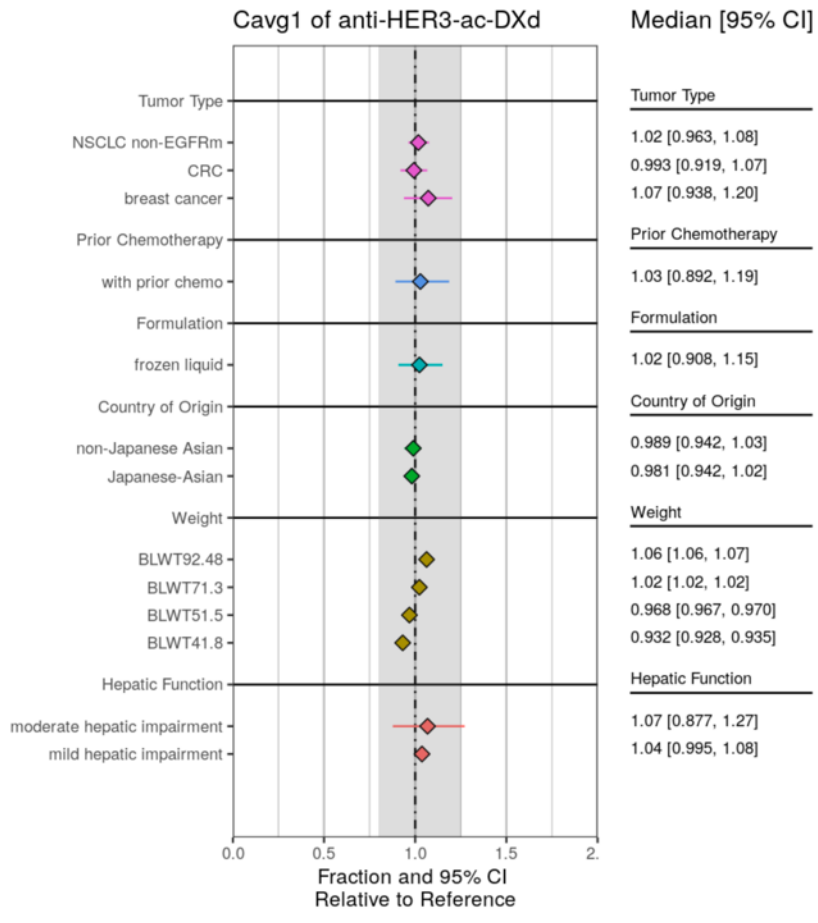
- CL_t: hepatic function, ~~CRCL, prior therapies~~
- V1: ~~sex~~, country
- CL_{inf}: country, ~~sex, age~~, tumor type, prior chemo, ~~prior immunotherapy, ECOG, prior therapies~~, hepatic function, ~~CRCL~~, formulation
- ~~$CL_{inf,Emax}$: albumin, tumor size~~

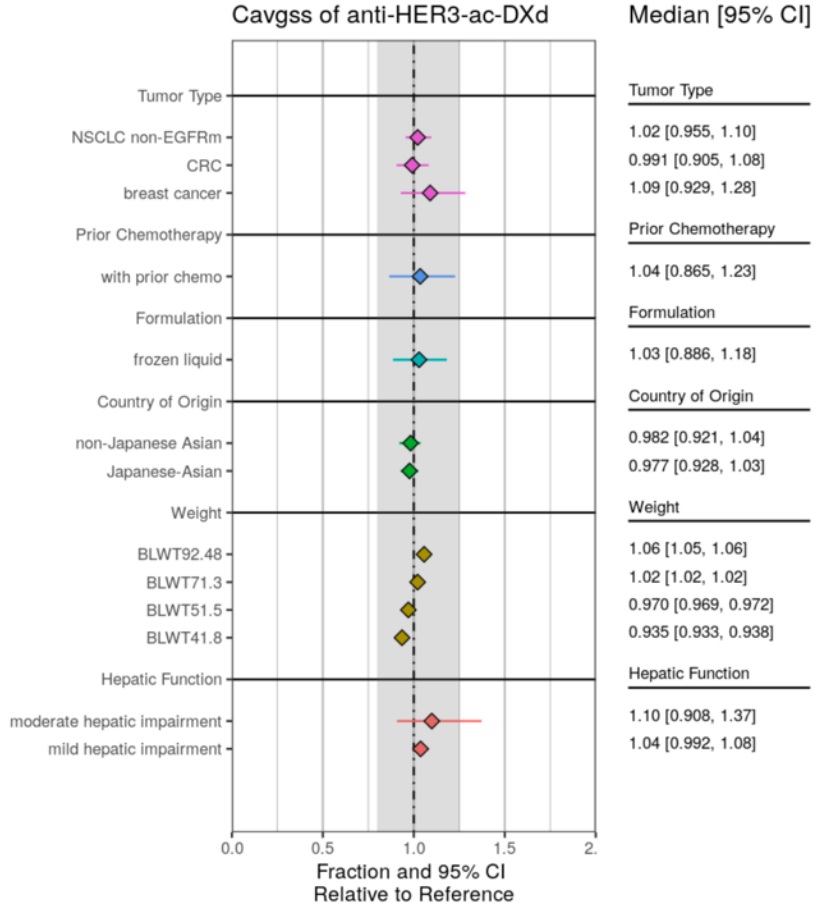
DXd covariate effects

- CL_{DXd}: country, ~~sex, age~~, tumor type, prior chemo, ~~prior immunotherapy, ECOG, prior therapies~~, hepatic function, ~~CRCL~~, formulation
- V_{DXd}: sex, ~~country~~

Covariates selected when relative exposures had 95% CI within 0.8 to 1.25, compared to reference subject

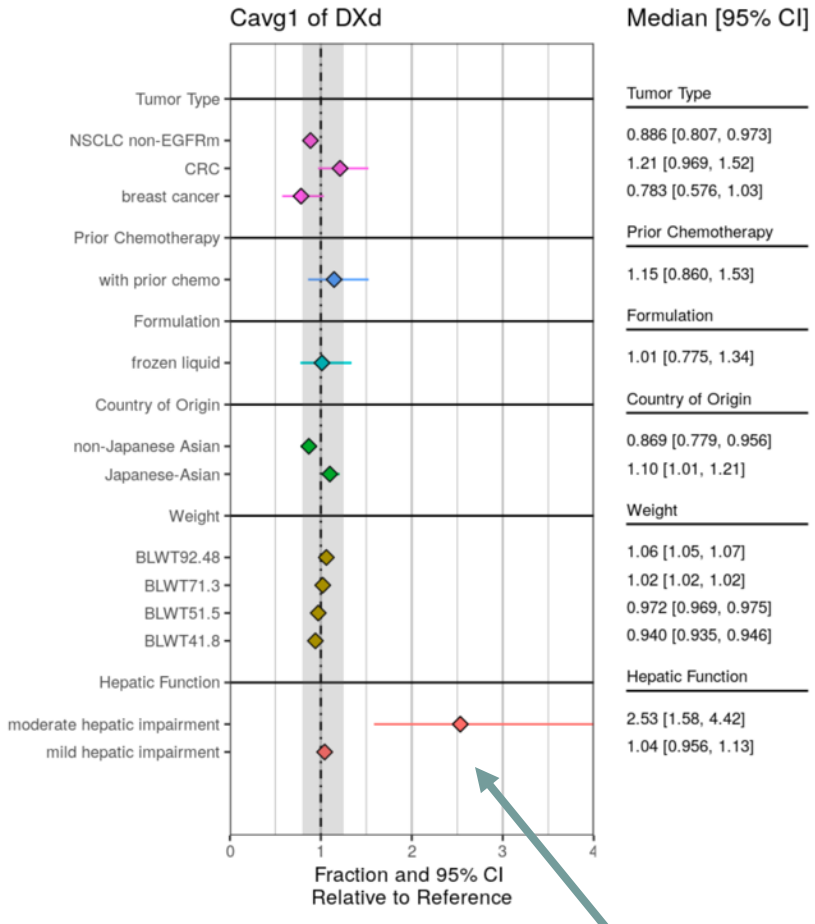
No clinically-relevant impact on anti-HER3-ac-DXd exposure

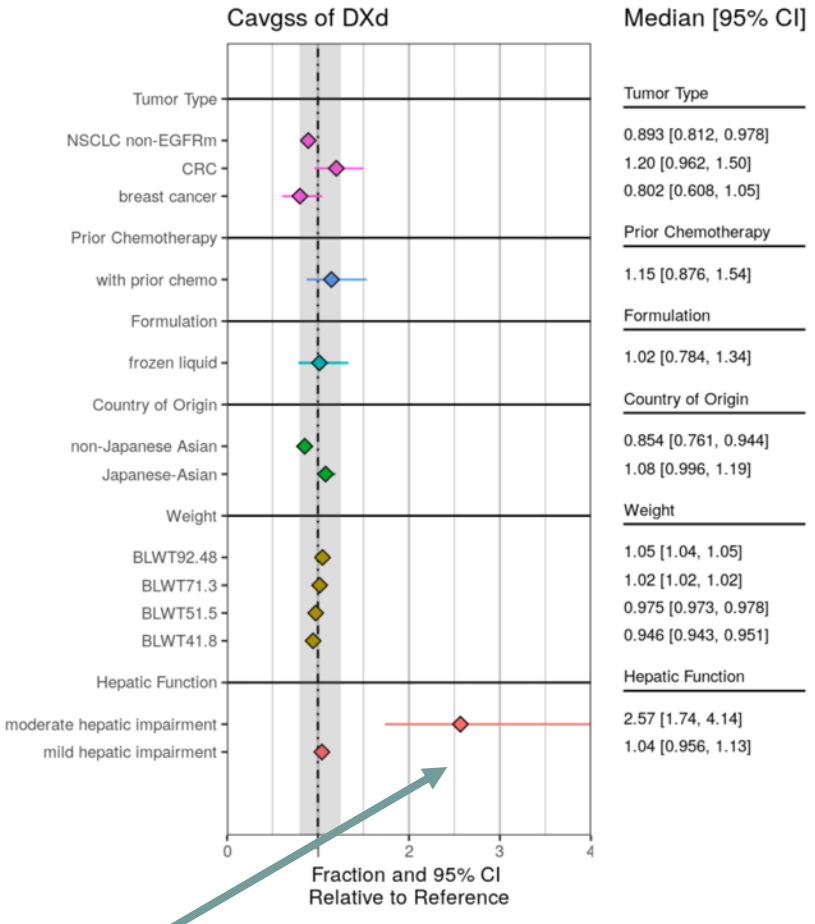




METRUM RESEARCH GROUP

Potential hepatic impairment effect on DXd exposure (N = 8)





Moderate hepatic function

HER3-DXd
Efficacy Exposure-Response

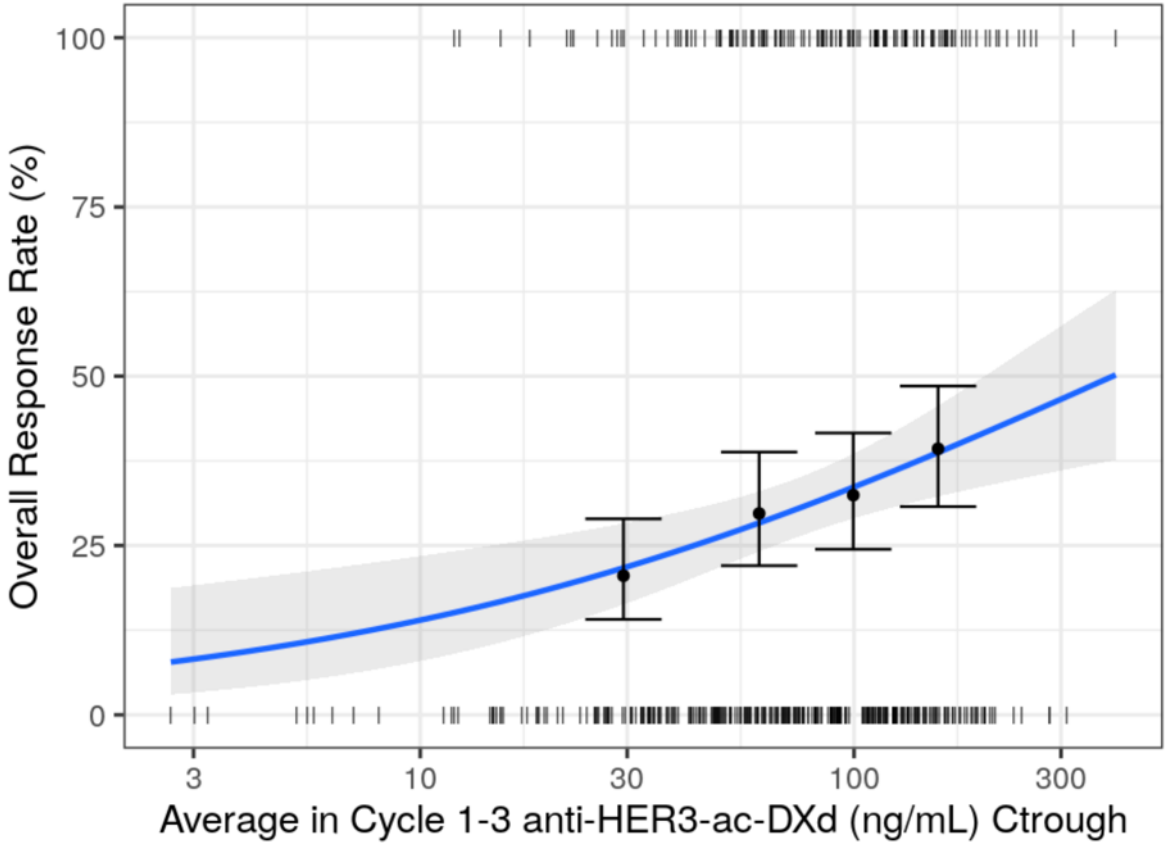
Efficacy data in patients with NSCLC

	Study		
	U31402-A-U102 n = 172	U31402-A-U201 n = 274	Summary n = 446
Dose Regimen			
3.2 mg/kg IV Q3W	4 (2.3)	0 (0.0)	4 (0.9)
4.8 mg/kg IV Q3W	15 (8.7)	0 (0.0)	15 (3.4)
5.6 mg/kg IV Q3W	102 (59.3)	224 (81.8)	326 (73.1)
6.4 mg/kg IV Q3W	5 (2.9)	0 (0.0)	5 (1.1)
Up-Titration	46 (26.7)	50 (18.2)	96 (21.5)

3.2 mg/kg, 4.8 mg/kg, followed by 6.4 mg/kg IV Q3W

METRUM RESEARCH GROUP

Overall Response Rate (ORR)



Logistic regression models fit in Stan/brms

Using weakly-informative priors

$$\text{logit}(\Pr(\text{ORR}_i = 1 | C_i)) = \alpha_0 + f(C_i, \theta) + X_i^T \gamma_1$$

C is either C_{max}, C_{trough}, or C_{avg}
in Cycle 1 or average of Cycles 1 to 3
for either anti-HER3-ac-DXd or DXd

$$f(C_i) = C_i \alpha_1 + C_i X_i^T \gamma_2 \quad \text{linear}$$

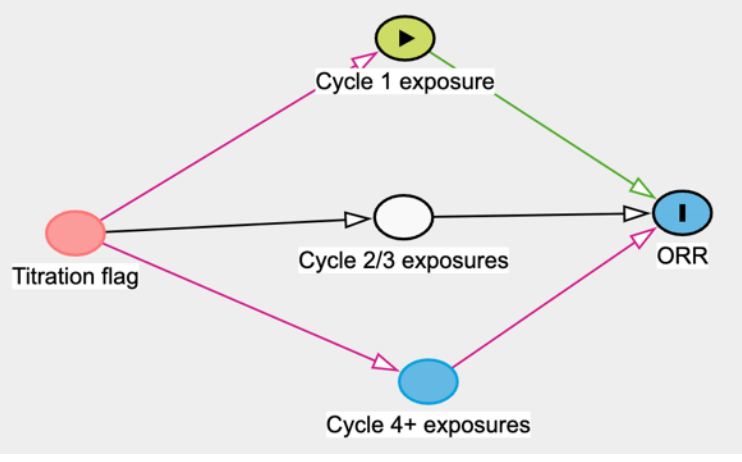
$$f(C_i) = \log(C_i)\alpha_1 + \log(C_i) X_i^T \gamma_2 \quad \text{log-linear}$$

$$f(C_i) = (\text{Emax} + X_i^T \gamma_2) \frac{C_i}{\text{EC50} + C_i} \quad \text{Emax}$$

$$f(C_i) = (\text{Emax} + X_i^T \gamma_2) \frac{C_i^h}{\text{EC50}^h + C_i^h} \quad \text{Sigmoidal Emax}$$

$3 \times 2 \times 2 \times 4 = 48$ possible base models!

ORR: Causal inference suggests including titration regimen flag



Causal effect identification

Adjustment (total effect)

Exposure: Cycle 1 exposure

Outcome: ORR

Adjusted: Cycle 2/3 exposures

Incorrectly adjusted.

Minimal sufficient adjustment sets containing Cycle 2/3 exposures for estimating the total effect of Cycle 1 exposure on ORR:

- Cycle 2/3 exposures, Cycle 4+ exposures
- Cycle 2/3 exposures, Titration flag

https://www.dagitty.net/dags.html

$3 \times 2 \times 2 \times 2 \times 4 = 96$ possible base models!

Exposure metric and ER function selected using ELPD & VPCs

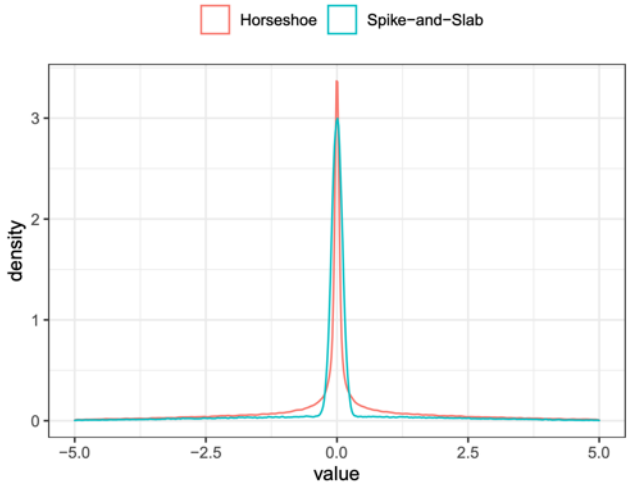
(Expected Log Pointwise Density: higher is better!)

Cycle	Titration Interaction	Analyte	Metric	Model	ELPD diff	SE diff
Average of Cycles 1 to 3	No	anti-HER3-ac-DXd	C_{trough}	Log-Linear	0.00	0.00
Average of Cycles 1 to 3	No	anti-HER3-ac-DXd	C_{trough}	Emax	−0.612	0.676
Average of Cycles 1 to 3	No	anti-HER3-ac-DXd	C_{trough}	Sigmoidal Emax	−0.690	0.737
Average of Cycles 1 to 3	No	anti-HER3-ac-DXd	C_{trough}	Linear	−0.843	1.24
Average of Cycles 1 to 3	Yes	anti-HER3-ac-DXd	C_{trough}	Log-Linear	−0.909	0.581
Cycle 1	No	anti-HER3-ac-DXd	C_{trough}	Log-Linear	−0.961	1.70
Average of Cycles 1 to 3	Yes	anti-HER3-ac-DXd	C_{trough}	Sigmoidal Emax	−0.992	0.787
Average of Cycles 1 to 3	Yes	anti-HER3-ac-DXd	C_{trough}	Emax	−1.06	0.734
Average of Cycles 1 to 3	No	anti-HER3-ac-DXd	C_{avg}	Linear	−1.35	1.24
Cycle 1	No	anti-HER3-ac-DXd	C_{avg}	Log-Linear	−1.55	1.74

Covariate “selection” using horseshoe priors

Main effects (intercept) and interactions (slope)

- age
- sex
- race
- country
- bodyweight
- tumor size
- ECOG
- prior chemotherapy
- prior immunotherapy
- number of prior lines of therapy
- prior third-generation TKI therapy
- HER3 membrane staining (2+/3+) ≥75%
- baseline bone/liver/brain metastasis
- *EGFR* mutations

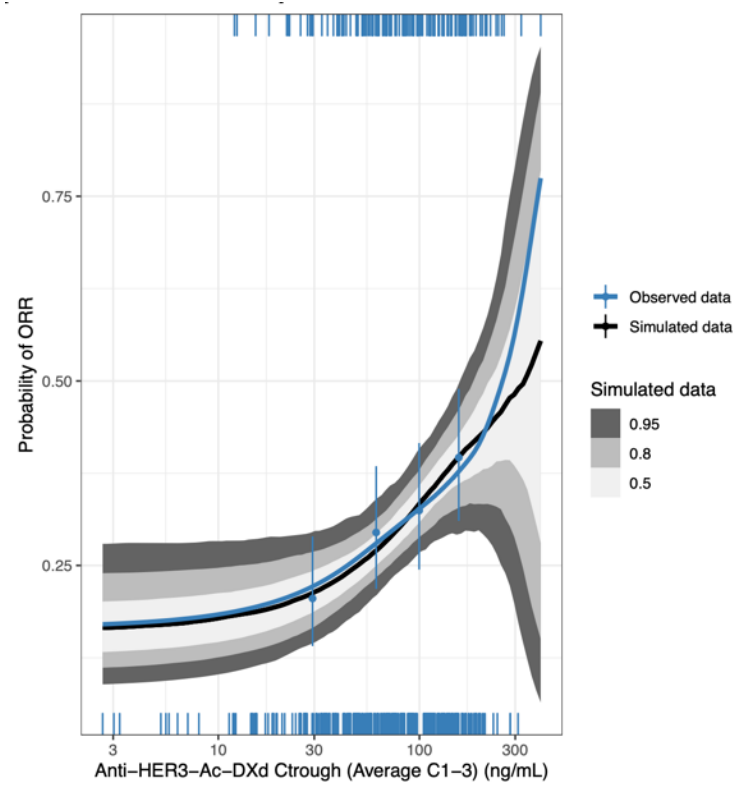


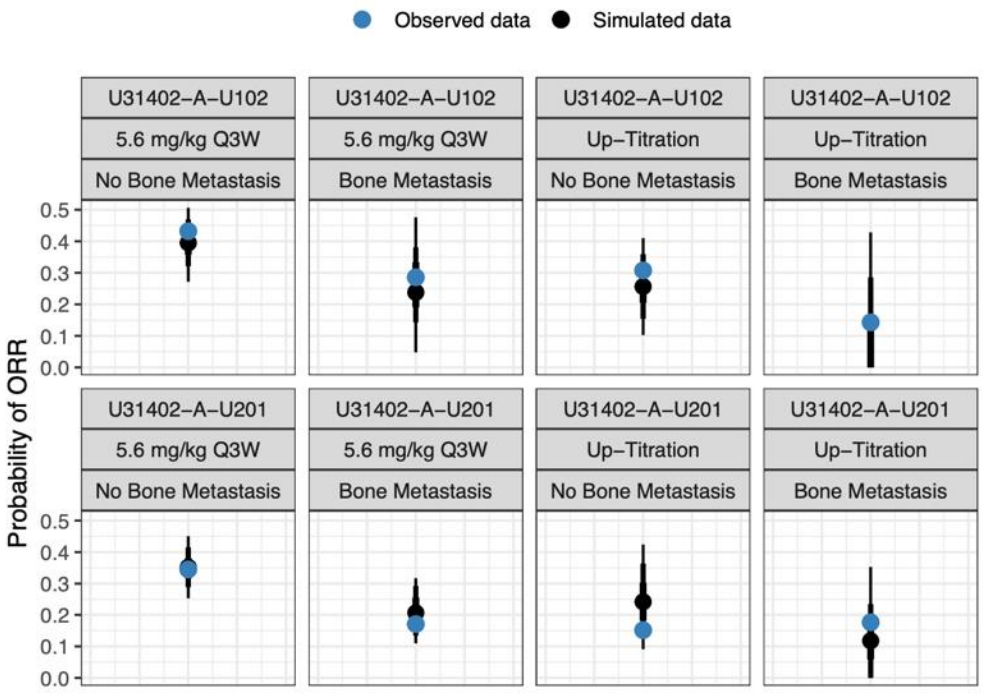
$$
\begin{aligned}
\gamma_{1,j}|\lambda_{1,j} &\sim N(0, \lambda_{1,j}\tau_1) \\
\gamma_{2,j}|\lambda_{2,j} &\sim N(0, \lambda_{2,j}\tau_2) \\
\lambda_{1,j} &\sim C^{+}(0,1) \\
\lambda_{2,j} &\sim C^{+}(0,1) \\
\tau_1 &\sim C^{+}(0, \hat{\tau}_1) \\
\tau_2 &\sim C^{+}(0, \hat{\tau}_2)
\end{aligned}
$$

Priors selected such that the proportion of non-negligible main effects and interaction effects were 1/2 and 1/4, respectively

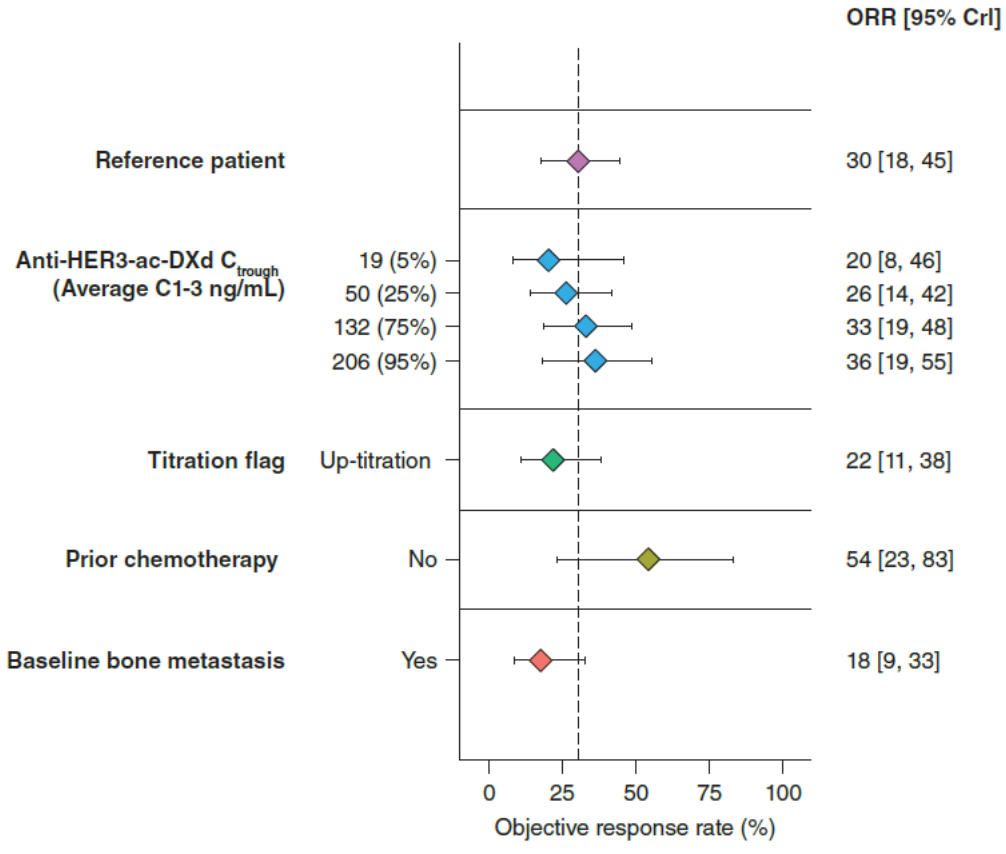
METRUM RESEARCH GROUP

Model describes the data well

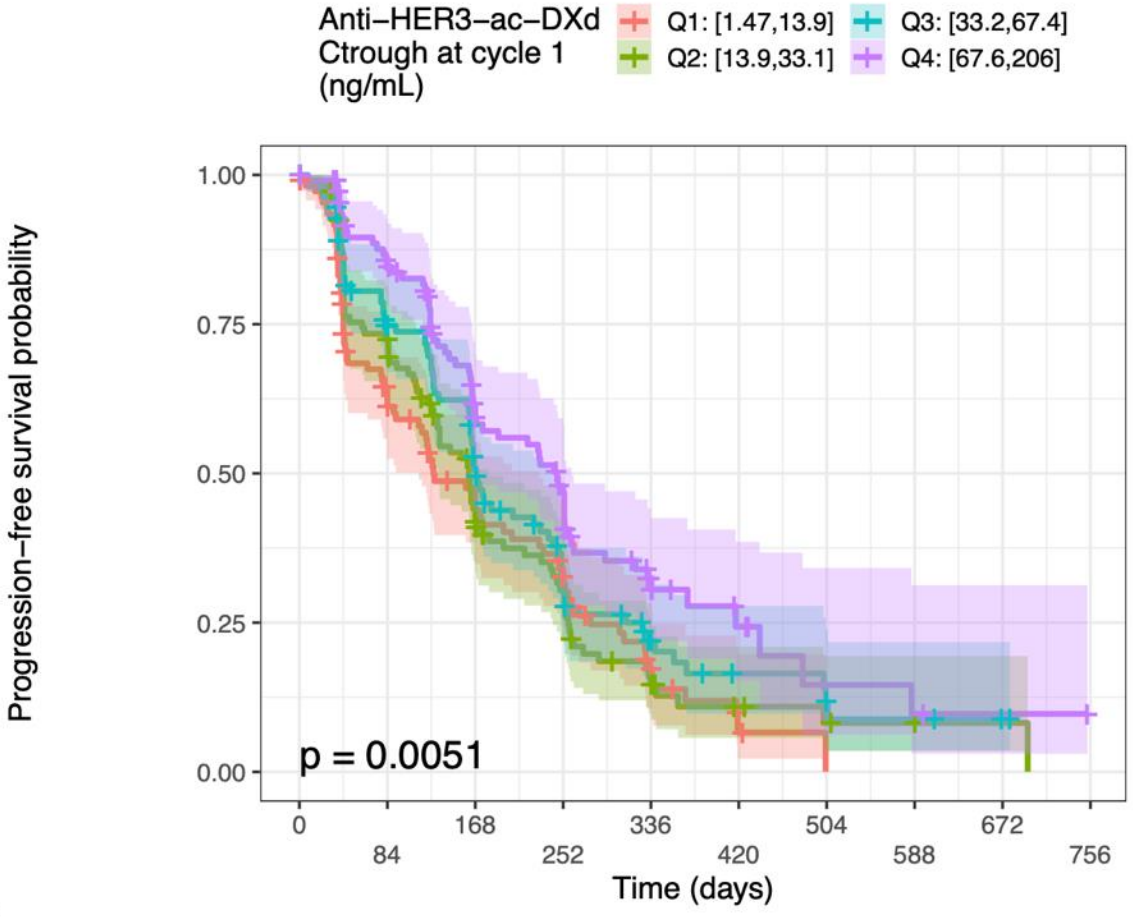




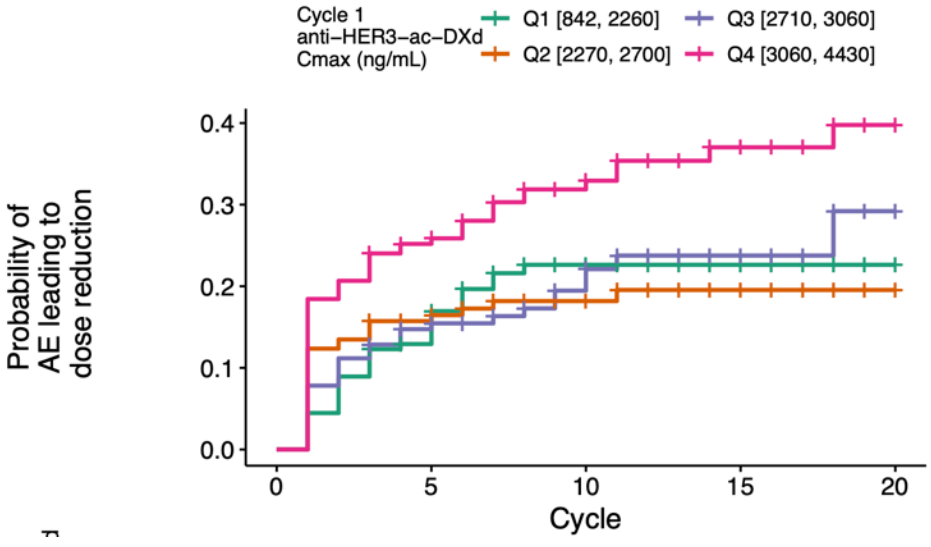
Most covariate effect estimates shrink to zero

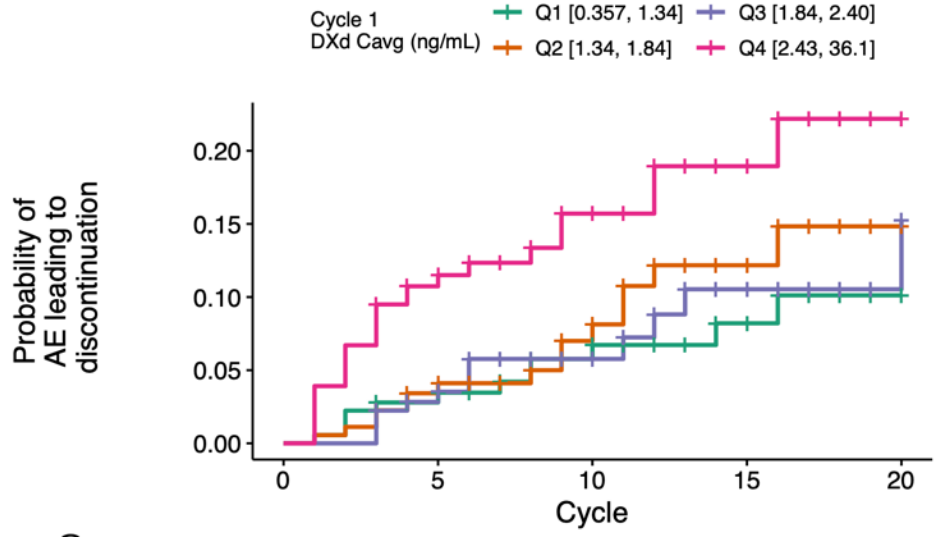


Progression-Free Survival (PFS)



Dose reductions and discontinuations were common



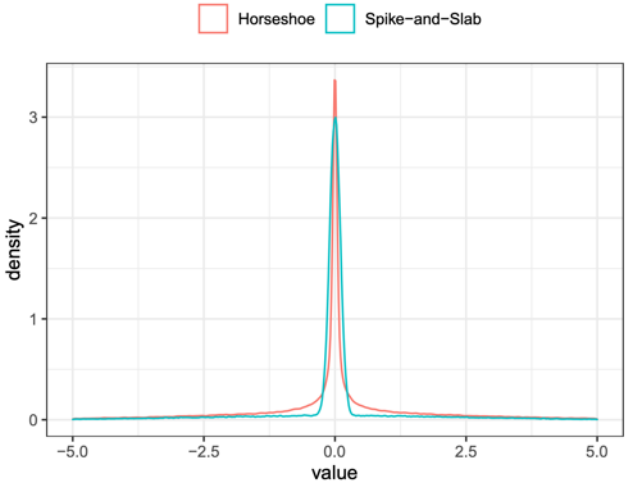


PFS modeled with time-varying exposure & hazard

Piecewise exponential time-to-event model

$$h(t_{ij}) = h_k 1_{t_{k-1},t_k}(t_{ij}) \exp(f(C_{ij},\theta) + X_i^T \gamma_1)$$

- Same exposure metrics as ORR
- Same ER functions as ORR
- Same covariates as ORR
- Spike & slab priors for covariates (shrinkage prior like horseshoe)
- Interval censoring and right censoring
- Parametric time-to-event models also considered



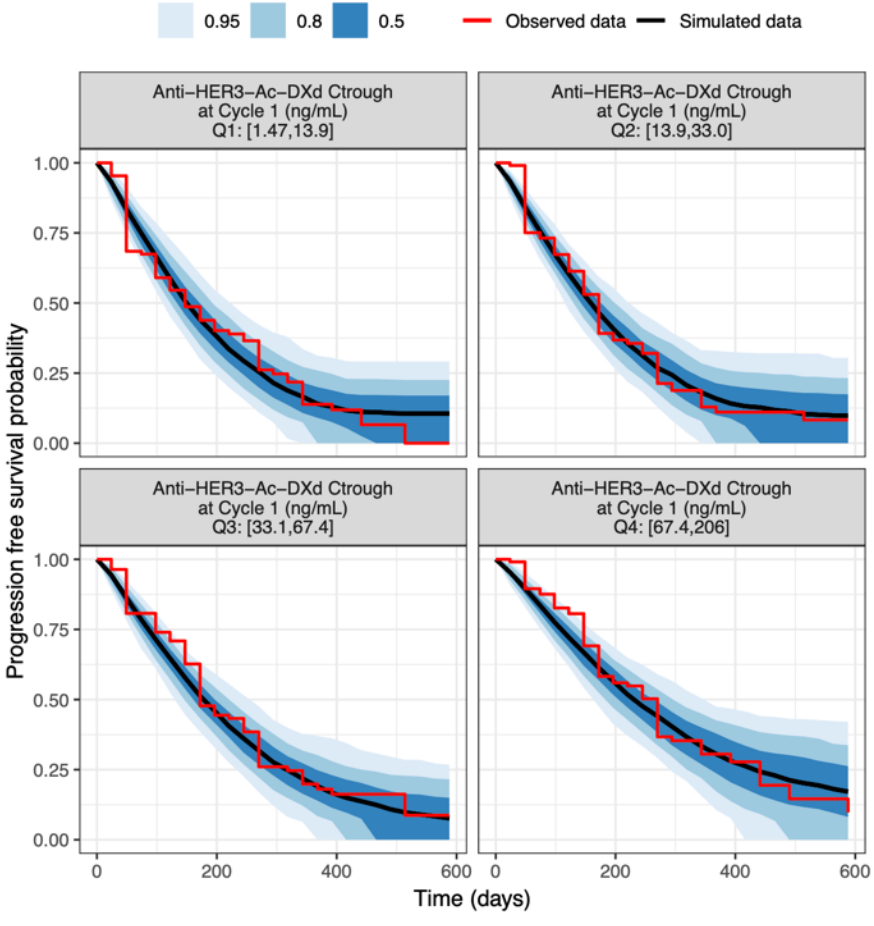
$$\begin{aligned}
h_k &\sim \text{Gamma}(\hat{h}_k/c, 1/c) \\
\alpha &\sim N_{\text{slab}} \\
\theta &\sim N_{\text{slab}} \\
\gamma_{1,j}|\lambda_1 &\sim \lambda_1 N_{1,\text{spike}} + (1-\lambda_1) N_{\text{slab}}, \\
\gamma_{2,j}|\lambda_2 &\sim \lambda_2 N_{2,\text{spike}} + (1-\lambda_2) N_{\text{slab}}, \\
\lambda_1 &\sim \text{Beta}(1,1) \\
\lambda_2 &\sim \text{Beta}(1/2, 1/4)
\end{aligned}$$

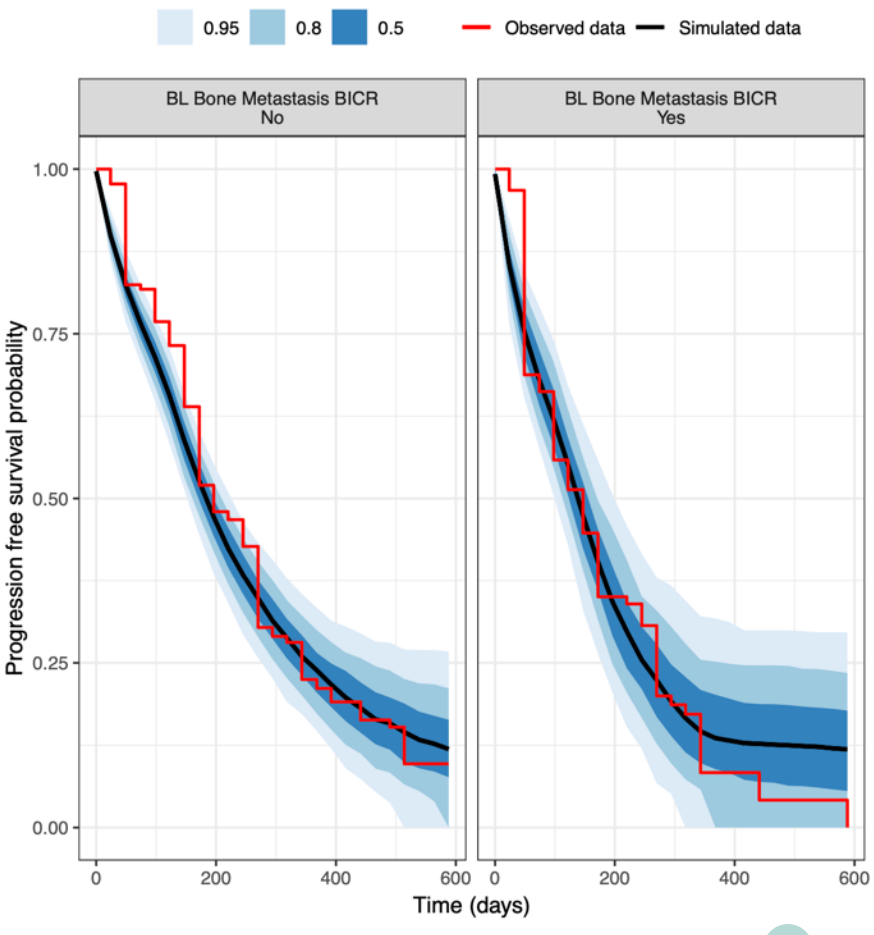
Same exposure & ER function as ORR comparable to “best” model

(Expected Log Pointwise Density: higher is better!)

Exposure metric	ER Relationship	ELPD	Δ_{ELPD}	$SE_{\Delta ELPD}$
DXd Cavg	Linear	-2239.15	0.00	0.00
DXd Cavg	Log Linear	-2242.78	-3.64	3.13
Anti-HER3-ac-DXd Ctrough	Emax	-2243.75	-4.60	6.07
Anti-HER3-ac-DXd Ctrough	Sigmoidal Emax	-2243.82	-4.67	6.06
Anti-HER3-ac-DXd Ctrough	Log Linear	-2244.54	-5.39	6.24
DXd Cmax	Linear	-2244.62	-5.48	2.73
Anti-HER3-ac-DXd Ctrough	Linear	-2244.71	-5.57	6.28
DXd Cmax	Log Linear	-2245.39	-6.24	4.09

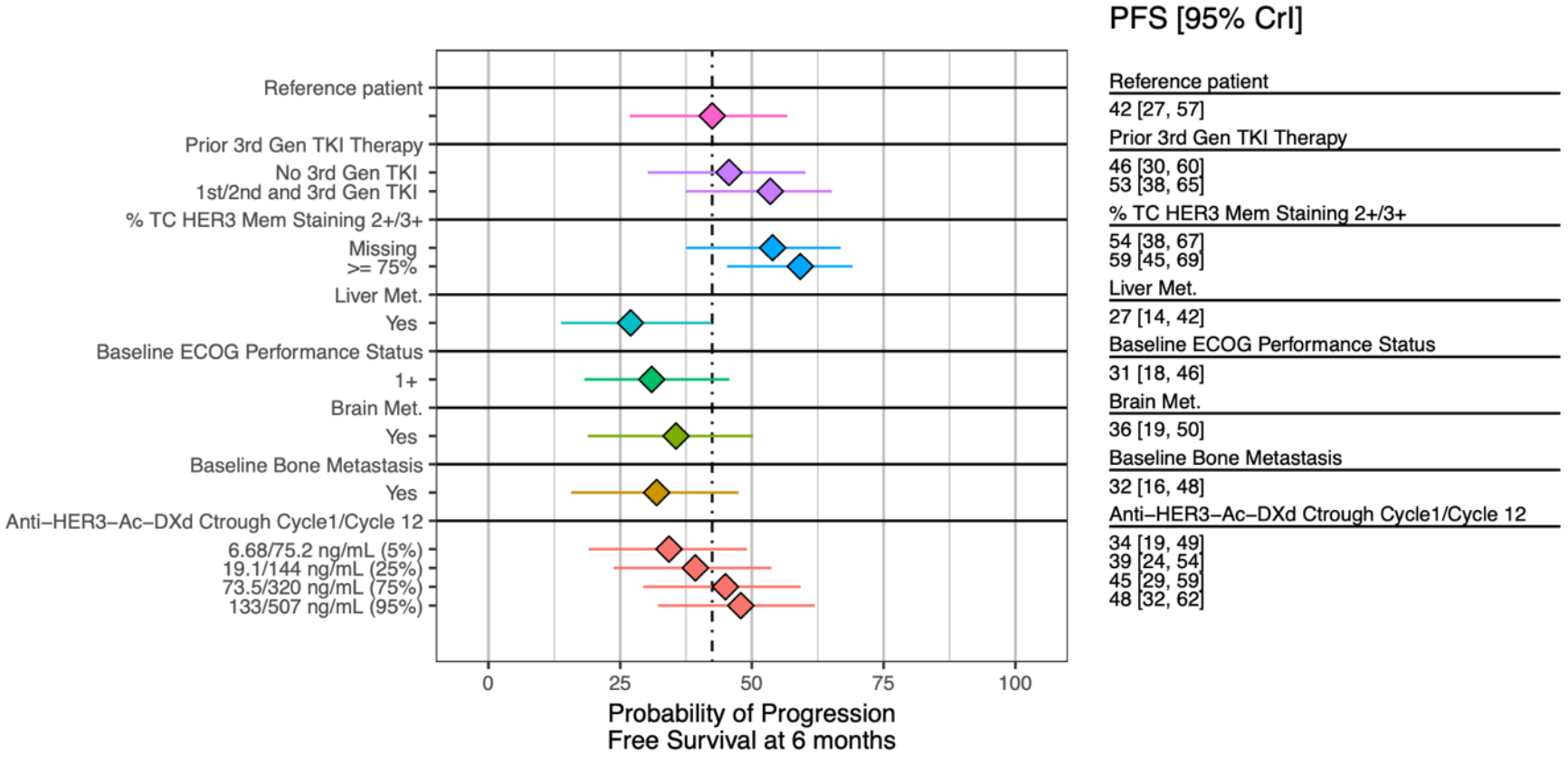
Model describes the data well



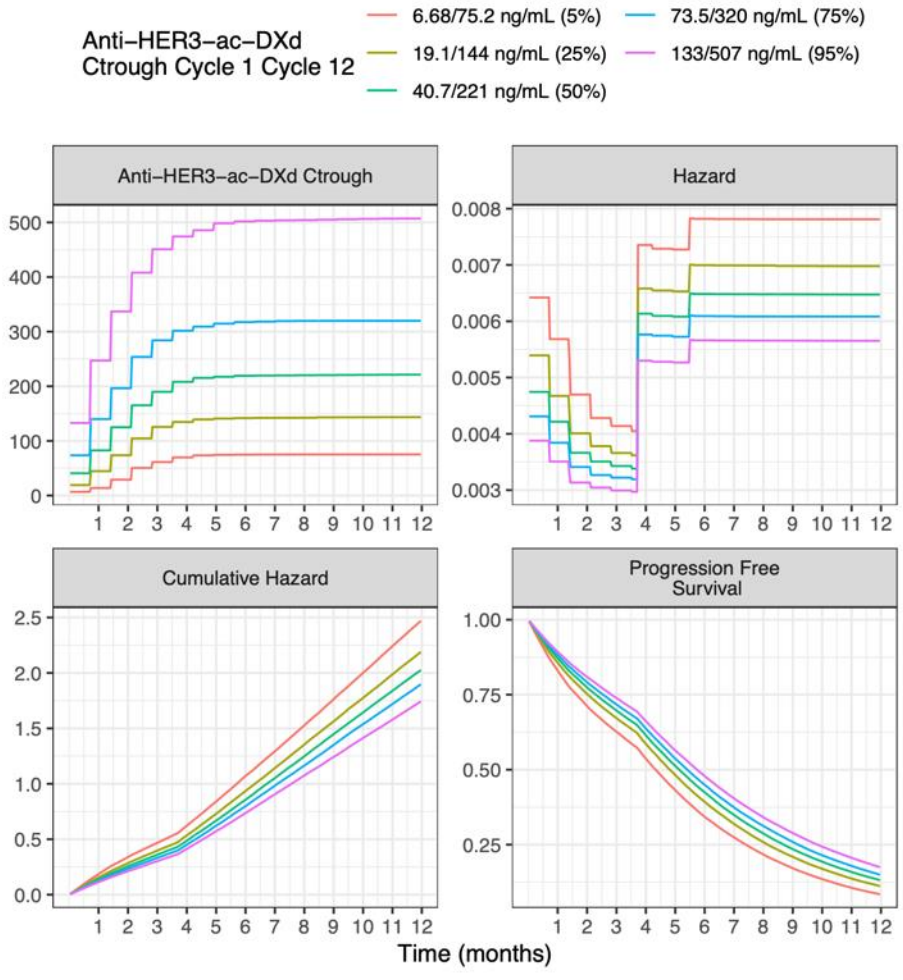


METRUM RESEARCH GROUP

Most covariate effect estimates shrink to zero



Piecewise exponential model allows for arbitrary changes in hazard

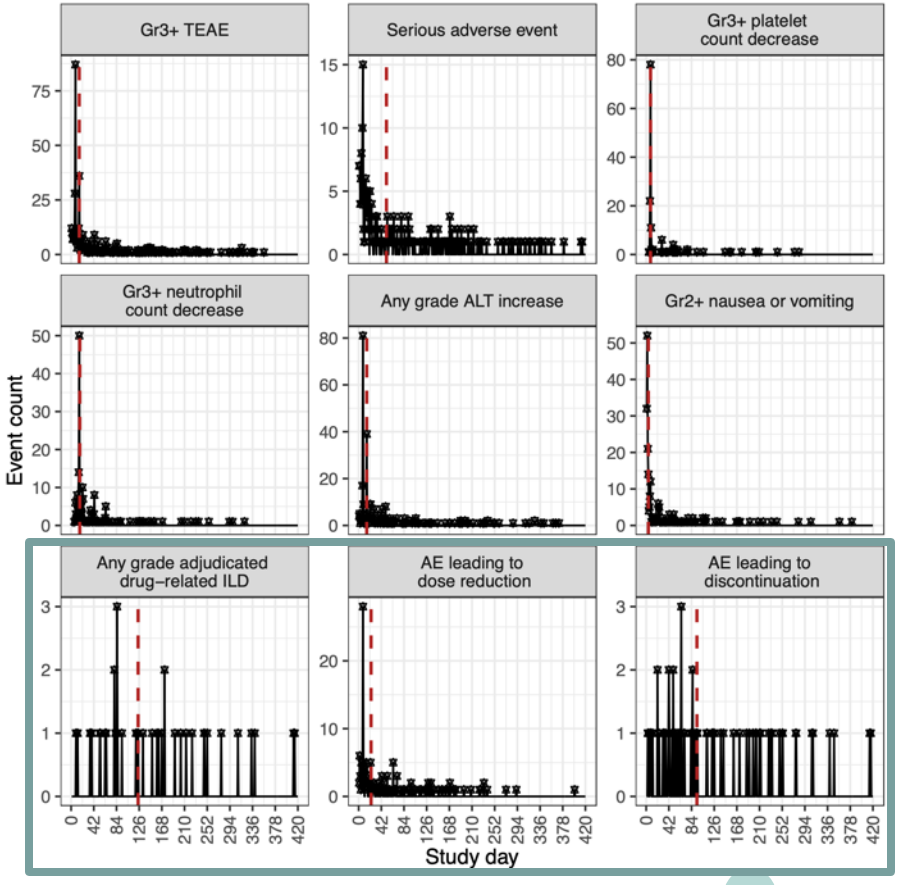


HER3-DXd
Safety Exposure-Response

Safety endpoints modeled as either binary or time-to-event

Depending on time of first event

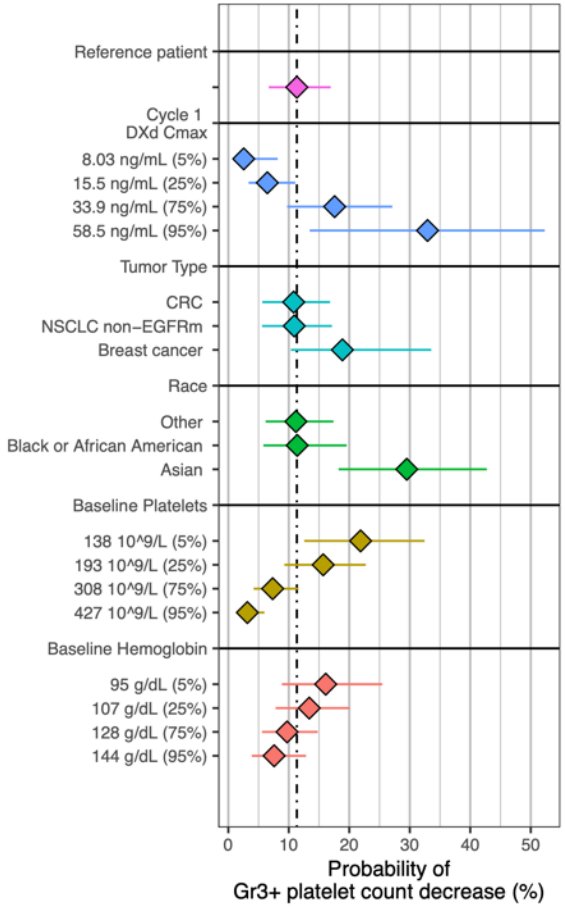
			Time to first event (days)				
Endpoint	Events	Subjects	Median	Mean	SD	Min	Max
Gr3+ TEAE	482	715	15	56.9	88.2	1	700
AE leading to dose interruption	314	715	64	99.6	104	1	723
AE leading to dose modification	421	715	43	83.8	110	1	723
AE leading to dose reduction	163	715	23	68.7	109	1	700
AE leading to discontinuation	69	715	94	141	123	3	584
Gr3+ platelet count decrease	162	714	8	28.8	50.6	5	283
Gr3+ neutrophil count decrease	196	698	16	41.6	56.9	6	321
Any grade adjudicated drug-related ILD	43	715	124	161	123	9	584
Serious adverse event	272	715	51.5	96.1	122	1	818
Any grade ALT increase	328	666	15	56.6	89.8	1	538
Any grade AST increase	408	630	19	54.6	77.4	1	575
Any grade bilirubin increase	156	707	46	103	130	1	735
Gr2+ nausea or vomiting	234	715	4	32.9	66.3	1	428
Fatigue	277	715	8	41.5	69.2	1	370
Reduced appetite	325	715	7	31.3	55.3	1	323

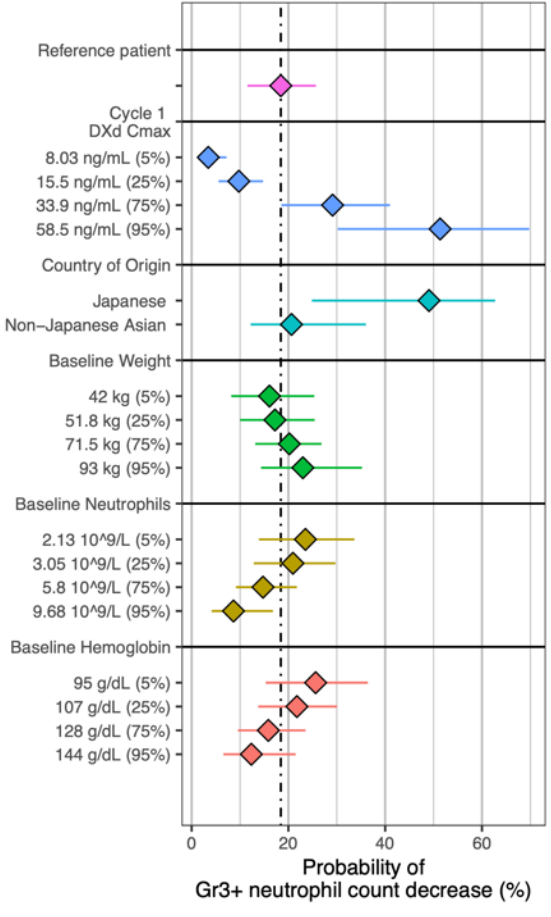


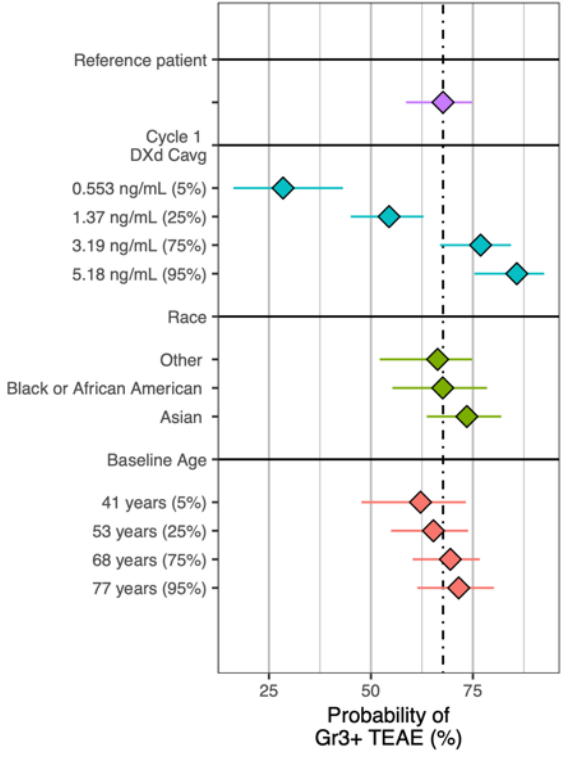
Most associations were with DXd exposure

Safety endpoint	Best-fitting analyte and PK exposure metric	Influential and significant covariates
Grade ≥3 TEAE	Cycle 1 DXd C_{avg}	Age
		Race: Asian
Serious AE	Cycle 1 DXd C_{avg}	Age
		Country of origin: Japan
Grade ≥3 platelet count decrease	Cycle 1 DXd C_{max}	**Baseline hemoglobin[a]**
		Baseline platelet count[a]
		Race: Asian[a]
		Tumor type: Breast cancer
Grade ≥3 neutrophil count decrease	Cycle 1 DXd C_{max}	Weight
		Baseline hemoglobin
		Baseline neutrophil count[a]
		Country of origin: Japan[a]
Grade ≥2 nausea or vomiting	Cycle 1 anti-HER3-ac-DXd C_{avg}	None
Any grade adjudicated drug-related ILD	Anti-HER3-ac-DXd C_{max}	None
AE leading to dose reduction	DXd C_{max}	Age
AE leading to discontinuation	DXd C_{avg}	None

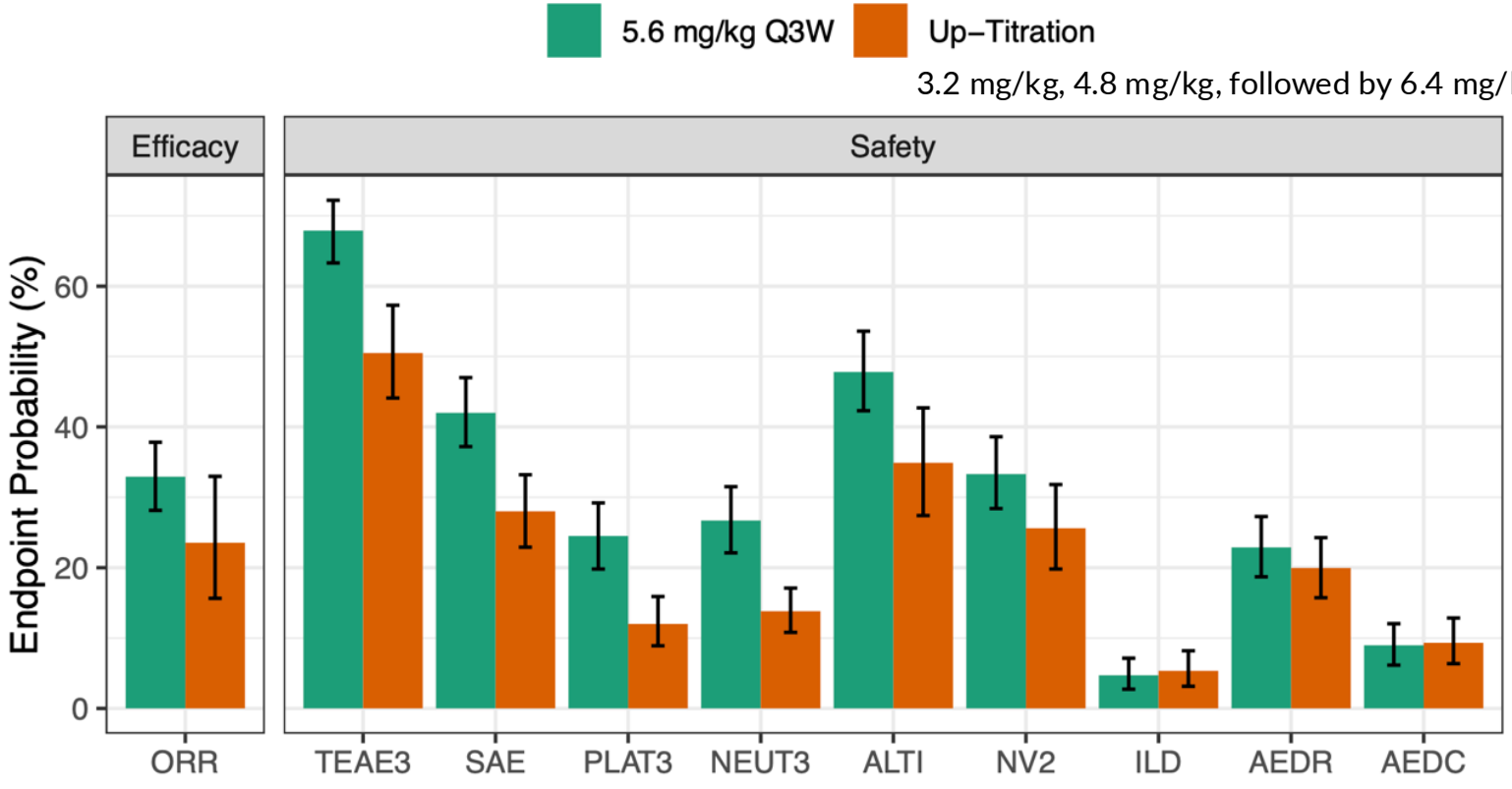
Only a handful of significant covariates on safety endpoints







Population simulations support 5.6 mg/kg over up-titration



AEDC, adverse events leading to discontinuation; AEDR, adverse events leading to dose interruption; DXd, deruxtecan; HER3, human epidermal growth factor receptor 3; ILD, interstitial lung disease; NEUT, neutrophil count decrease; NV, nausea or vomiting; PLAT, platelet count decrease; Q3W, every 3 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Summary

Summary

PK

- Anti–HER3-ac-DXd PK was described by a two-compartment model with three elimination pathways
- DXd PK was described by by a one-compartment model with linear and nonlinear clearance
- Most covariates did not have a clinically important impact on exposures
- Moderate hepatic impairment was associated with in DXd exposure
  - No dose reduction is proposed at this time since moderate hepatic impairment data was limited

Exposure-response

- Objective response rate and progression-free survival were positively associated with anti-HER3-ac-DXd exposure
  - bone metastasis identified as a predictive covariate for ORR
  - liver metastasis identified as a predictive covariate for PFS
- Grade ≥3 TEAEs, SAEs, and grade ≥3 platelet and neutrophil count decrease were positively correlated with increasing exposure to anti-HER3-ac-DXd or DXd
- Dose-response predictions showed that HER3-DXd 5.6 mg/kg Q3W had a positive benefit-risk profile with clinically meaningful efficacy for NSCLC and manageable safety

Thank you