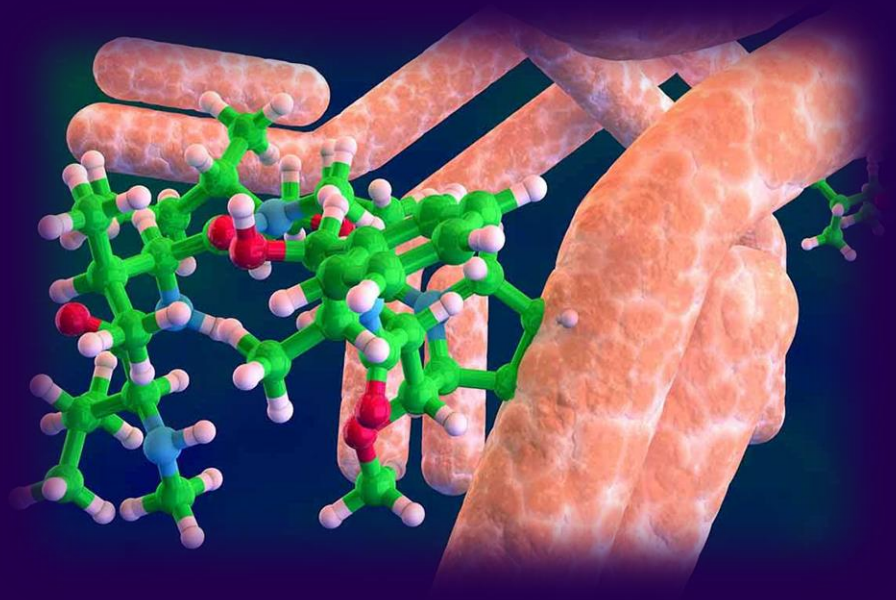
ADC:
Antibody-Drug-Conjugates



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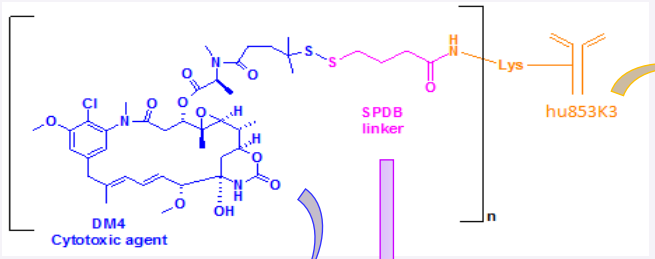
Clinical Pharmacology Challenges of ADCs in Early Drug Development

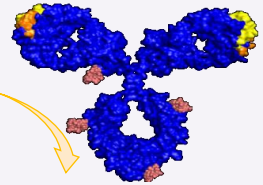
Case study: Tusamitamab Ravtansine

GPCO-Strasbourg October 2023

Laurent Nguyen

Tusamitamab Ravtansine (SAR408701)





IgG1

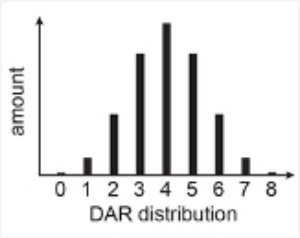
- Humanized IgG1, no ADCC
- Specific for CEACAM5 antigen

DM4: CYTOTOXIC AGENT

- Maytansinoid derivative
- tubulin binder

CEACAM5 TARGET

- Cell-surface glycoprotein *(cell adhesion & proliferation)*
- Highly expressed in several tumors of epithelial origin



SPDB LINKER

- Thiobutyramide linker
- Stable in plasma, cleavable inside cells
- Lysine conjugation with IgG1 and disulfide bound conjugation with DM4

- Number of payload per antibody: “drug to antibody ratio” = DAR
- DAR *(average)* = 4

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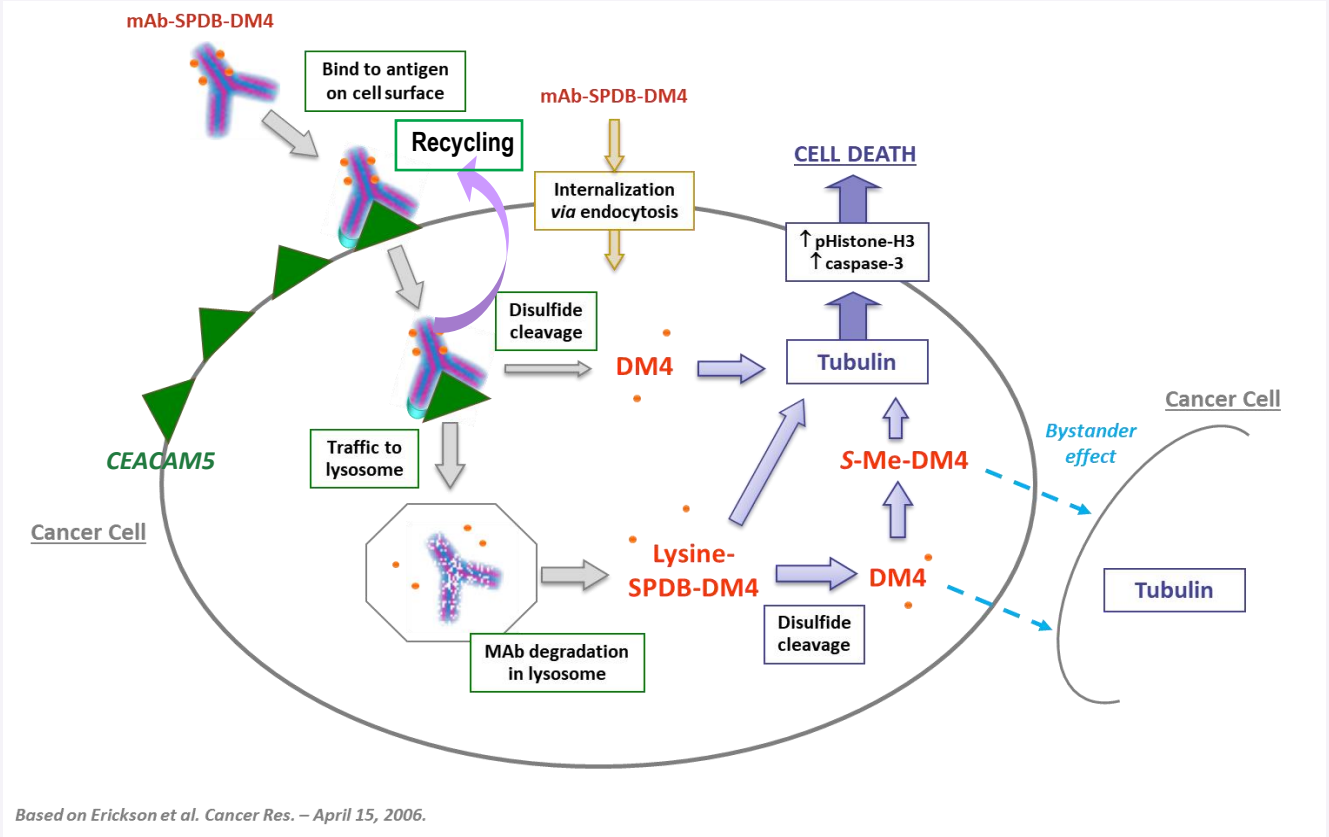
Tusamitamab Ravtansine: Mechanism of Action

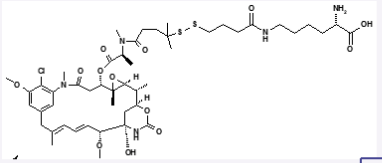


Based on Erickson et al. Cancer Res. – April 15, 2006.

- DM4
- S-Methyl-DM4 *(Me-DM4)*
- Lysine SPDB-DM4

} ***same potency***

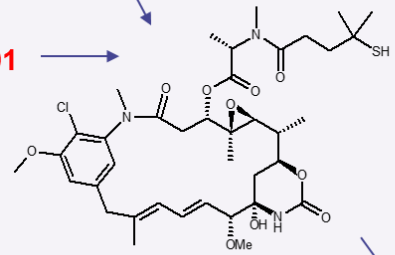
METABOLIC PATHWAYS OF PAYLOAD (DM4)



Lys-SPDB-DM4

Traces (<LOQ)

SAR408701

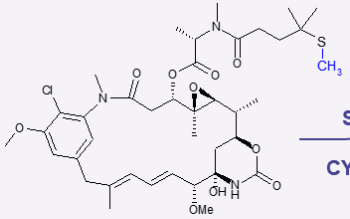


DM4

Active cytotoxic
<1% of SAR408701 AUC_{0-3d}

S-Methylation

Thiol Methyl Transferase (TMT)

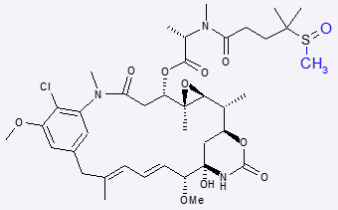


Methyl-DM4

Active circulating metabolite in patients
Approx. **6% of SAR408701** AUC_{0-3d}

S-Oxidation

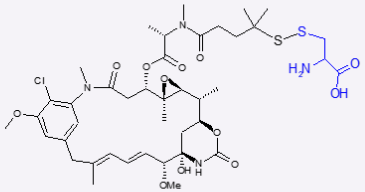
CYP3A (fm 0.9)



Sulfoxide-Methyl-DM4

<1% of SAR408701 AUC_{0-3d}

S-Cysteinyl Conjugation



S-Cysteinyl-DM4

Traces (<LOQ)

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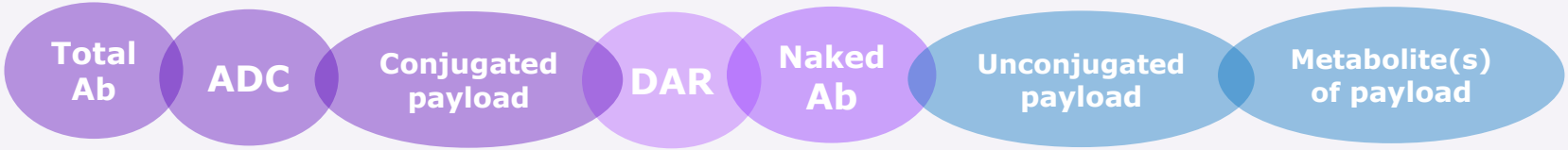
Clinical Pharmacology Challenges in Early Drug Development

❑ Bioanalytical consideration

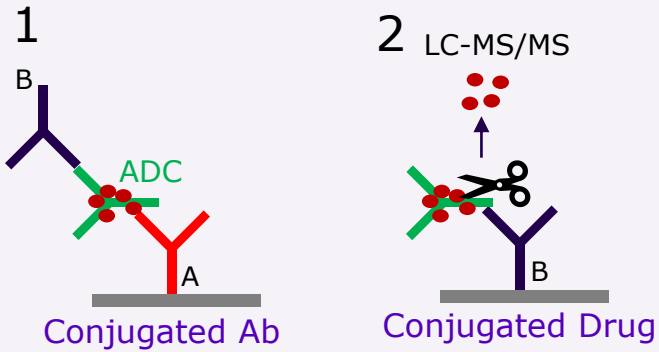
- Because of ADC structure: Large and small molecules to be characterized in plasma
- Payloads: low circulating levels
- IMP is a mixture of different DAR species (DAR 0 to 8)

What can be measured ?

Multiple analytes need different bioanalysis tools



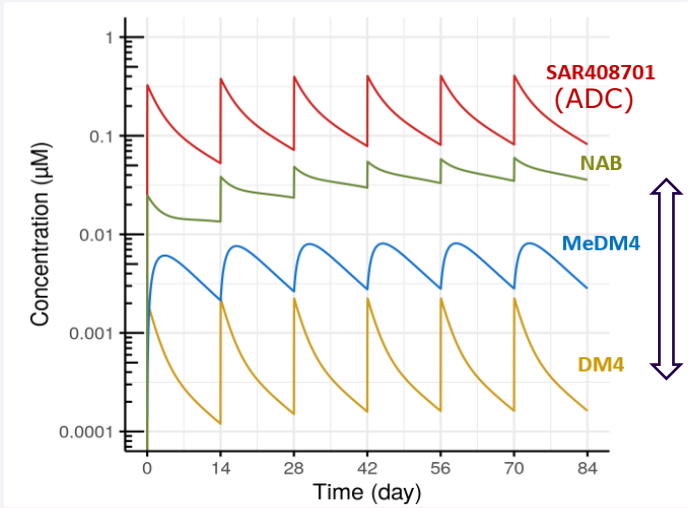
ADC measurement (ELISA based)



Concentration of Ab with at leat one payload (DAR≥1)

Concentrations of payloads conjugated to the Ab

Tusamitamab Ravtansine (100 mg/m²): **ADC, NAB, DM4 and MeDM4**



Low circulating payloads need sensitive LC/MS-MS

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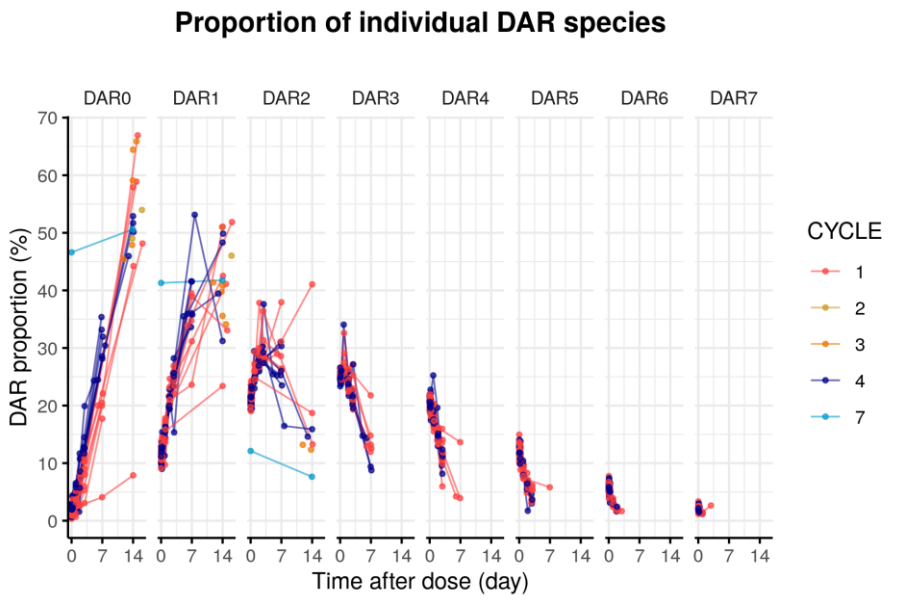
What can be measured ?

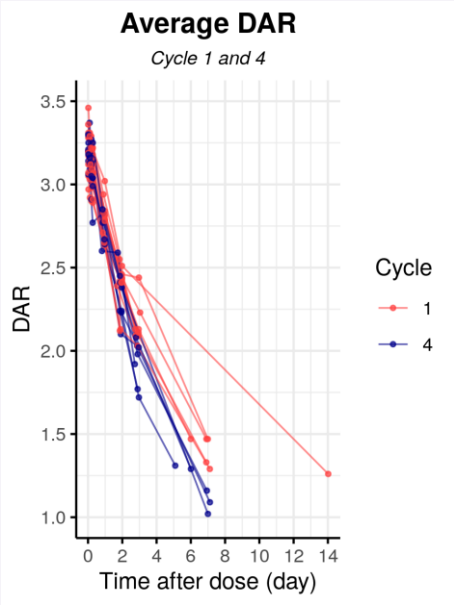
For Tusamitamab Ravtansine,

Proportion of individual DAR species in plasma were quantified by LC-MS/MS-high resolution

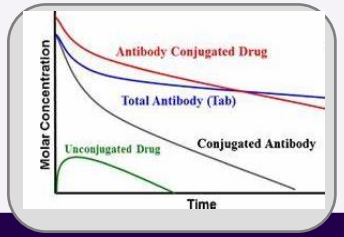
Individual DAR_i



$DAR_{average}$



Clinical Pharmacology Challenges During Drug Development



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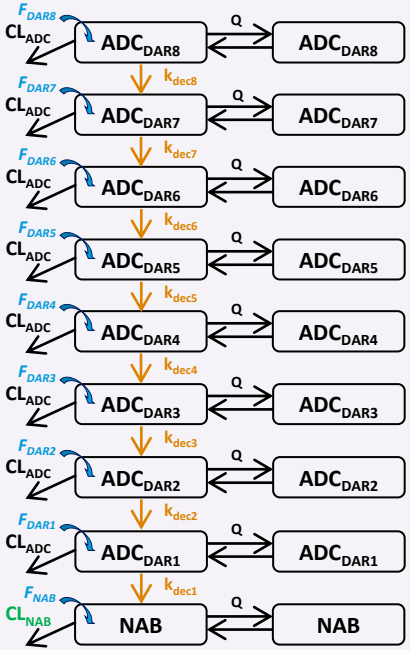
❑ PK characterization & modeling

- What are the PK characteristics of each component ?
- What are the PK variabilities ?
- How can we model all entities ?
- How to integrate mechanistic considerations ?

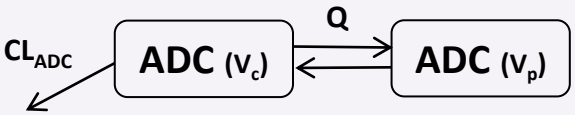
Integrated multiple analytes population PK model

FIH study: 250 pts IV doses: 5 to 190 mg/m² *Q2W, Q3W*



ADC (DARi) model

- 2 compartments distribution
- Linear clearance
- DAR1 to DAR8 species represented, same distribution (V_c and V_p) and clearance parameters (Q and CL_{ADC})
- $k_{dec,i}$: conversion of higher DAR to lower DAR successive deconjugations, modelled as an irreversible first-order process in central compartment
- $F_{DAR,i}$: fraction of each DAR species in the administered solution



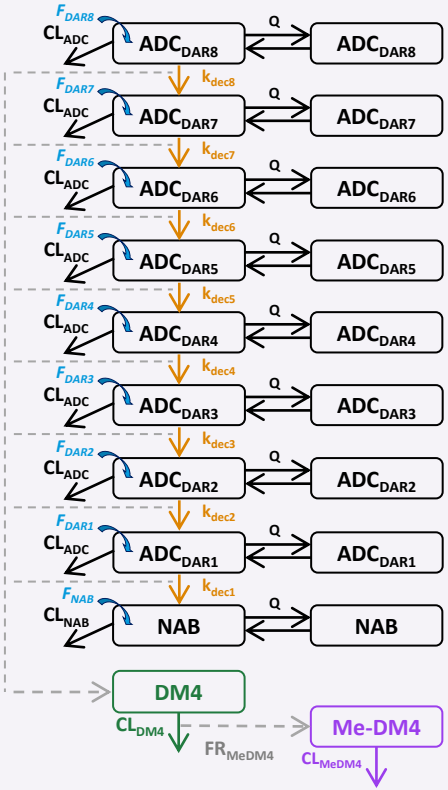
ADC is eliminated by two processes:

- **Deconjugation** releasing payload until NAB formation
- Global elimination reflecting systemic and/or **cellular proteolysis**

NAB *(naked antibody)*

- DAR0 species, same V_c, Q and V_p but **specific CL_{NAB} value**

Integrated multiple analytes population PK model



DM4

- 1 compartment distribution, linear elimination
- Each DAR≥1 deconjugation process was assumed to contribute to DM4 formation by releasing one DM4 molecule.

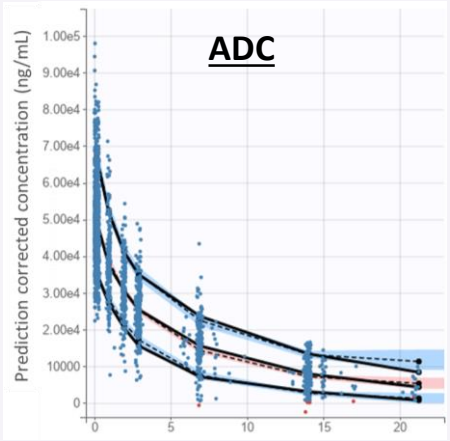
Me-DM4

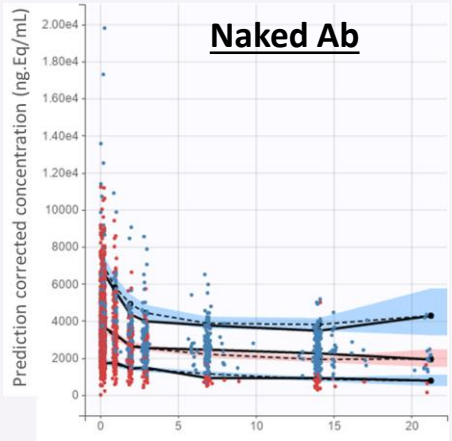
- 1 compartment distribution, linear elimination
- Me-DM4 formed from DM4 elimination

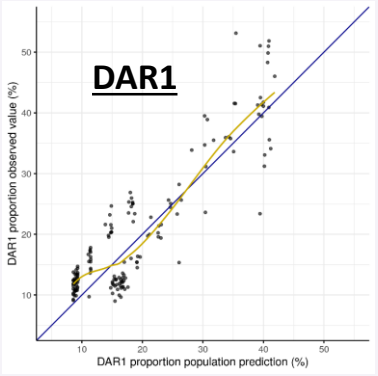
➢ **Fit simultaneoulsy of ADC, NAB, DM4, Me-DM4 PK data, proportion of individual DAR species and average DAR**

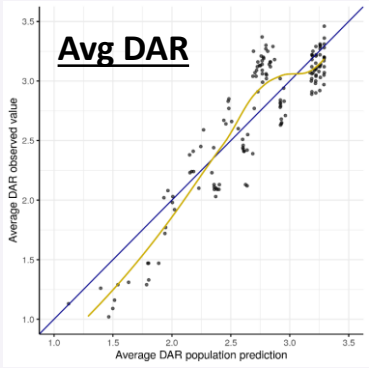
Model prediction vs. observed data

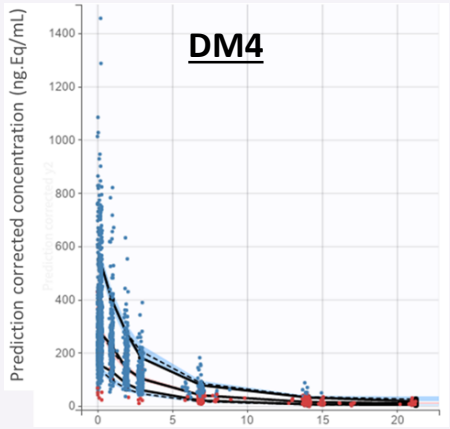
Cycle 1 data

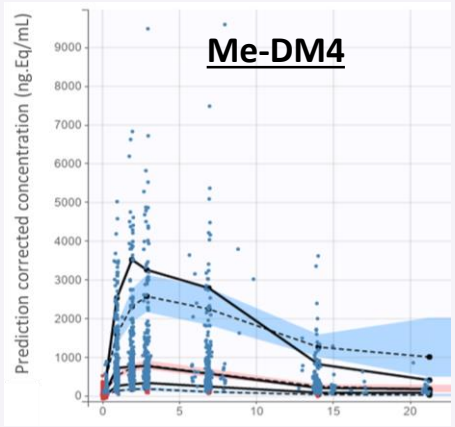


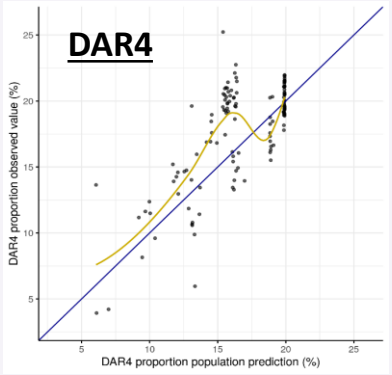












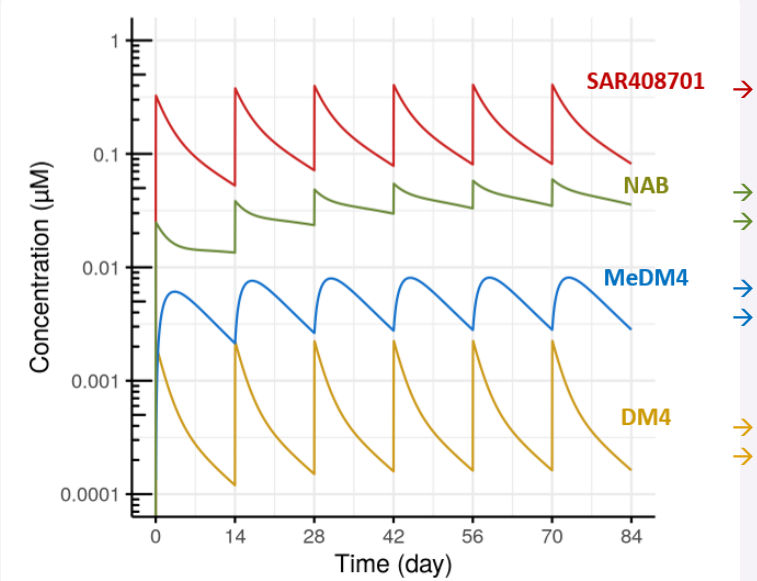
Integrated multiple analytes population PK model

Final structural model parameters:

Fixed effects		SD of the random effect, ω_p (RSE%)
Parameter	**Estimate (RSE%)**	
CL_{ADC} (L/day)	**0.392 (3)**	46.9% (5)
V_c (L)	3.37 (2)	24.5% (5)
Q (L/day)	0.543 (5)	52.9% (8)
V_p (L)	2.54 (5)	60.5% (8)
k_{dec8} (/day)		
k_{dec7} (/day)	0.938 (4)	
k_{dec6} (/day)		
k_{dec5} (/day)	0.751 (3)	20.2 (8)
k_{dec4} (/day)	0.525 (4)	
k_{dec3} (/day)	0.340 (4)	
k_{dec2} (/day)	0.181 (3)	
k_{dec1} (/day)	0.0565 (2)	
CL_{NAB} (L/day)	0.408 (3)	34.5 (6)
CL_{DM4} (L/day)	240 (3)	36.5 (6)
CL_{MeDM4} (L/day)	0.256 (5)	65.4 (6)
FR_{MeDM4}	0.0107 (5)	72.3 (5)

CL/F_{MeDM4}=24.8 L/h

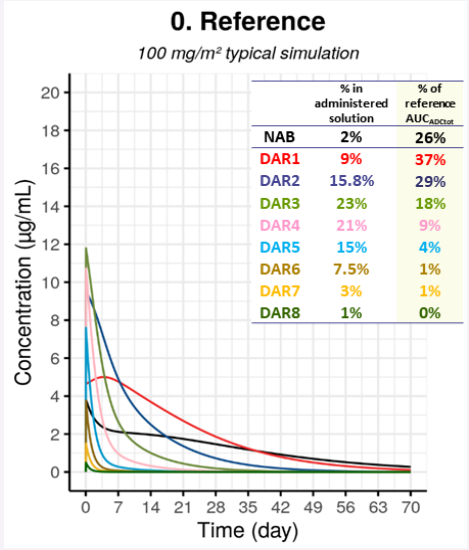
Typical SAR408701, NAB, DM4 and Me-DM4 PK profile after 100 mg/m² Q2W:

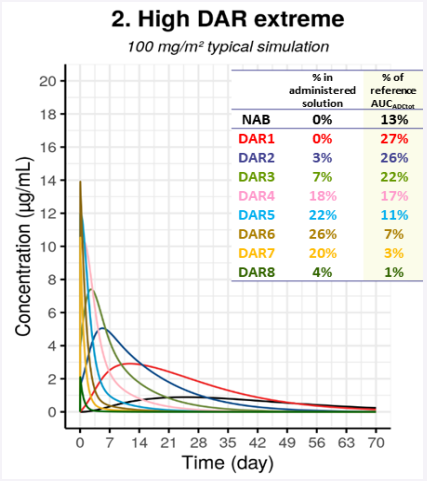


- ✓ Linear elimination (no TMDD)
- ✓ Stationnary clearance (no time-dependency)
- ✓ Low inter-occasion variability
  (CV = 12% for ADC to 22% for MeDM4)

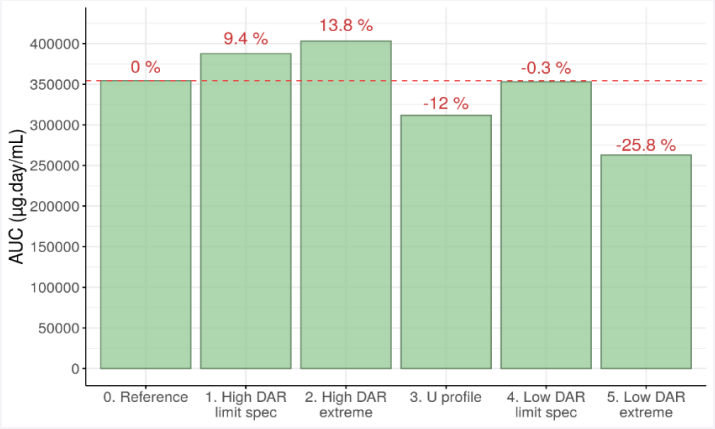
Individual DAR PK

DAR	Proteolytic clearance (L/d)	Deconjugation clearance (L/d)	Global clearance (L/d)
DAR≥6	0.392	3.16	**3.55**
DAR5	0.392	2.53	**2.92**
DAR4	0.392	1.77	**2.16**
DAR3	0.392	1.15	**1.54**
DAR2	0.392	0.611	**1.00**
DAR1	0.392	0.190	**0.582**
DAR0	0.408	-	**0.408**

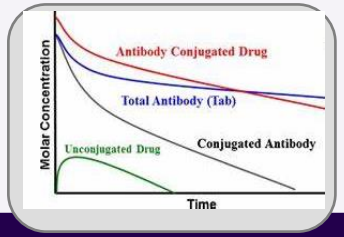




batch-to-batch variability on ADC



Clinical Pharmacology Challenges During Drug Development



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❑ PK characterization & modeling

- What are the PK characteristics of each component ?
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- How to integrate mechanistic considerations ?

❑ Intrinsic factors

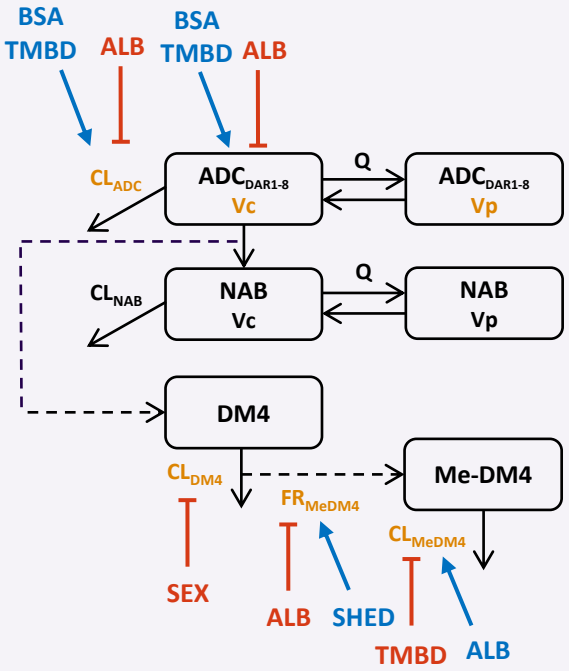
- Sources of PK variabilities ?
- subpopulations at risks ?
- Is BSA dose normalized justified ?

❑ Extrinsic factors: drug-drug interactions

- Payload released can modulate enzyme and transporters mediated **DDIs**
- Perpetrator or victim

Which intrinsic factors influence the PK ?

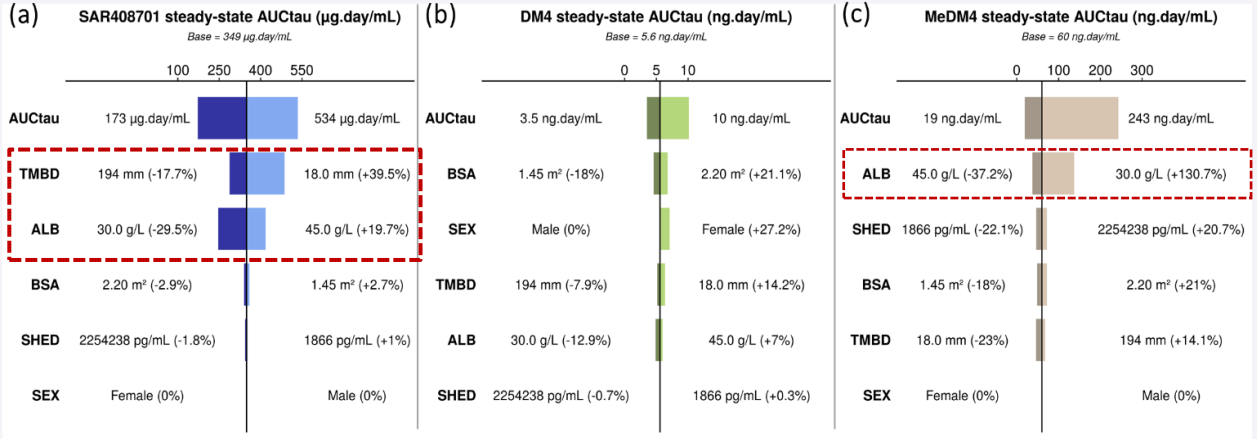
Covariate Population PK analysis from 248 pts (FIH study)



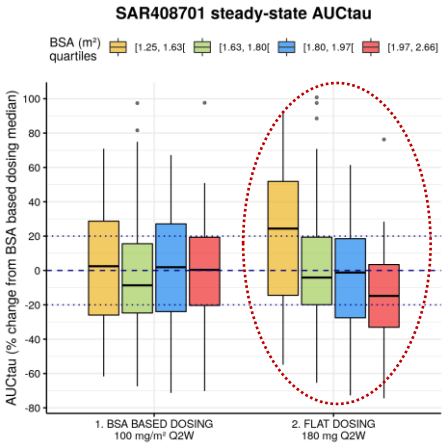
Five baseline covariates identified:

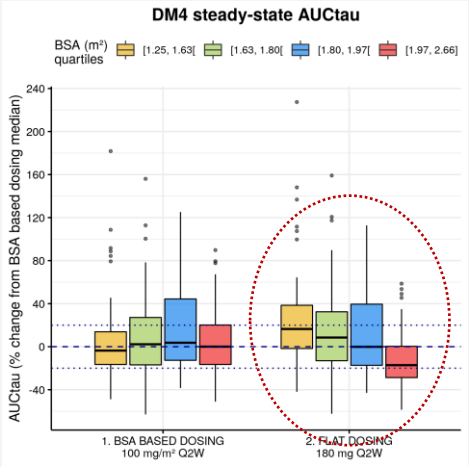
- BSA
- Albuminemia
- Tumor size (tumor burden:TMBD)
- Circulating CEA (SHED)
- Gender

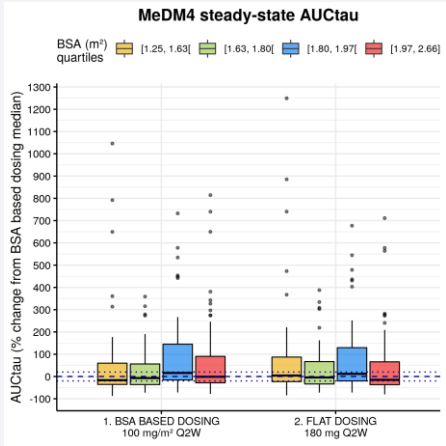
Influence of covariates (5th and 95th percentiles) on typical population drug exposure for ADC, DM4 and MeDM4



Is BSA based dosing justified for Tusa ?







- ✓ BSA: significant covariate of pop PK model (ADC CL and Vc)
- ✓ BSA-based dosing avoids over-exposure in low BSA group and under-exposure in high BSA group

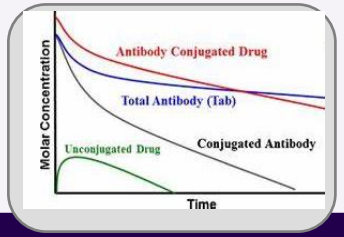
Covariates effect: comparison with other ADCs

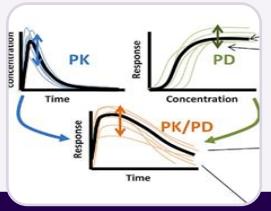
DRUG	STRUCTURAL MODEL	COVARIATES ON ADC	COVARIATES ON PAYLOAD	DAR	CLEARANCE
Gemtuzumab ozogamicin	2 comp (T-ADC); 2 comp (payload) separated	*CL: BW (fixed 0.75), DOSE, ALB Vc: BW (fixed 1), DOSE, ALB, SEX Vp: %Target_expression, blast_count, combination*	*None reported*	*Not included*	Combined linear + time-dependent CL *exp(-kdes) function*
Brentuximab vedotin	3 comp (ADC) + 2 comp (payload) combined	*CL, Q2, Q3: BW V1: BW, SEX V2, V3: BW*	*CL, Vc, Q, Vp: BW (fixed)*	DAR = DAR.[a+(1-a).EXP(-b.TIME)]	Linear CL
Trastuzumab emtansine	2 comp (ADC) *(payload < LOQ)*	*CL: BW, SHED, ALB, TMBD, Baseline_drug_concentration, ASAT Vc: BW*	*None reported*	*Semi-mechanistic model with interspecies first-order transfer rate constant*	Linear (if 2 comp model) or non-linear CL (if semi-mechanistic model)
Inotuzumab ozogamicin	2 comp (ADC) *(payload < LOQ)*	*CL: BSA, disease_ subtype, comedication, %blast Vc: BSA*	*None reported*	*Not included*	Combined linear + time-dependent CL
Polatuzumab vedotin-piiq	2 comp (ADC) + 2 comp (payload) combined	*CL: BW, SEX, ALB, combination, B_cell_count, TMBD, treatment_naive_status Vc: BW, SEX, RACE, treatment_naive_status Q: BW Vp: BW*	*Formation_fraction: BW, SEX, treatment_naive_status, combination, hepatic_imp, ECOG, ALB*	*Not included*	Combined non-specific linear time-dependent CL + linear time-dependent *exponentially declining CL* + non-linear CL
Enfortumab vedotin	3 comp (ADC); 2 comp (payload) separated	*CL: BW, AGE, Hb, SEX, TMBD Q2, Q3: BW V1: BW, SEX, TMBD V2: BW V3: BW, tumor_type*	*CL: BW, ALB, ECOG, Hb, BILI Vc: BW, ALB Q: BW Vp: BW, ALB, Hb, RACE, GENDER*	*Not included*	Linear CL
Trastuzumab deruxtecan	2 comp (ADC) + 1 comp (payload) combined	*CL: BW, ALB, country, SEX, TMBD Vc: BW, SEX Vp: country*	*CL: comedication, AST, BILI, BW Vc: AGE, formulation*	*Not included*	Linear CL
Belantamab mafodotin-blmf	2 comp (T-ADC) + 2 comp (ADC) + 1 comp (payload) combined	*CL: BW, ALB, SHED, IgG, DOSE, study Vc: BW, ALB, SEX, study Vp: DOSE*	*Vc: SHED, IgG*	DAR=DAR0*EXP(-RATE*TAD)	Combined linear + time-dependent CL *sigmoid function*
Tisotumab vedotin-tftv	2 comp (ADC) + 2 comp (payload) combined	*CL: BW, ALB, SEX Vc: BW, ALB, SEX Q: BW Vp: BW*	*CL: BW, ALB, eGFR, Tumor_type, ECOG, hepatic_imp, TMBD Vc: BW, ECOG, ALB ktr: BW, AGE*	DAR=1+3. EXP(-beta*TAD)	Combined linear + non-linear CL

- BSA or bodyweight are systematically relevant covariates
- Albumin, tumor burden and circulating target (sheding) are also relevant covariates for both ADC & payloads
- Covariates effects are of limited impact and do not require dose adjustment

from Liu SN and Li C. CCP (2021) 87:743-765

Clinical Pharmacology Challenges During Drug Development





❑ Bioanalytical consideration

- Because of ADC structure: Large and small molecules to be characterized in plasma
- Payloads: low circulating levels
- IMP is a mixture of different DAR species (DAR 0 to 8)

• PK characterization & modeling

- What are the PK characteristics of each component ?
- What are the PK variabilities ?
- How can we model all entities ?
- How to integrate mechanistic considerations ?

❑ Intrinsic factors

- Sources of PK variabilities ?
- subpopulations at risks ?
- Is BSA dose normalized justified ?

❑ Extrinsic factors: drug-drug interactions

- Payload released can modulate enzyme and transporters mediated **DDIs**
- Perpetrator or victim

❑ PK/PD

- Which entity best correlates with safety and efficacy endpoints?
- What are the relevant PK metrics ?
- How to model PK/PD relationships ?

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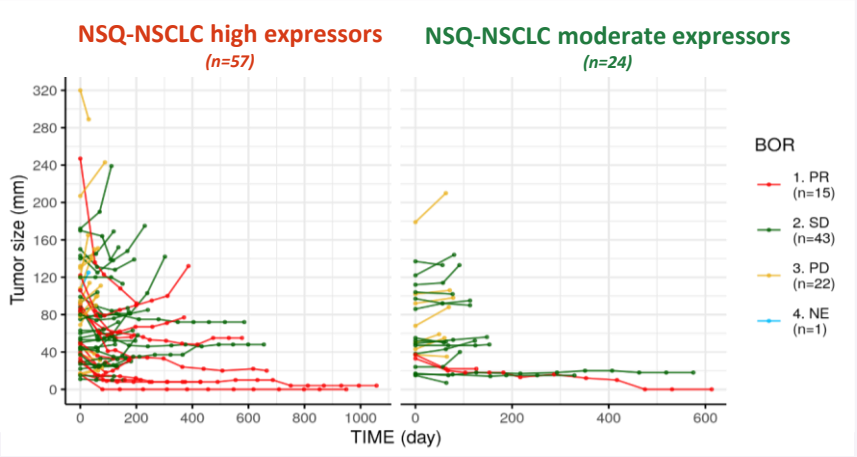
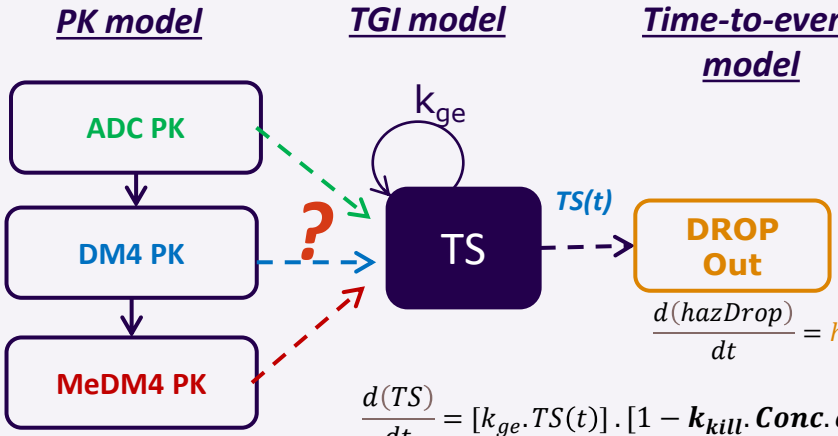
What is the driver(s) of efficacy (tumor size decrease) ?

Nsq NSCLC expansion cohorts from FIH



Tumor Growth Inhibition model

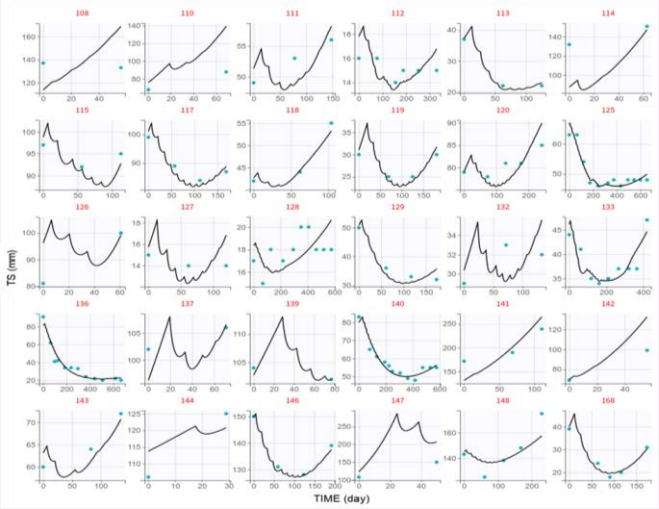


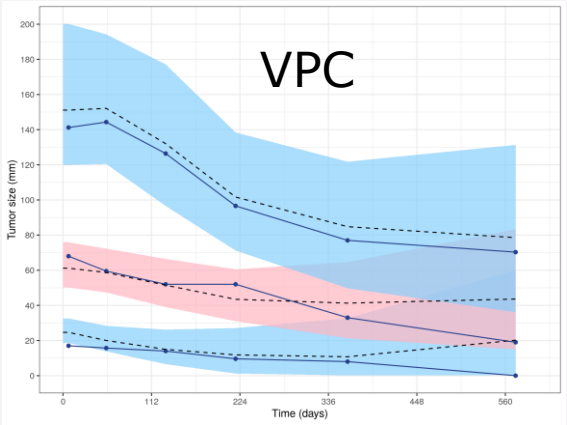
$$\frac{d(hazDrop)}{dt} = h_0(t) \cdot e^{g(TS(t))}$$

$$\frac{d(TS)}{dt} = [k_{ge}.TS(t)] \cdot [1 - \boldsymbol{k_{kill}}.\boldsymbol{Conc}.e^{-resistance(t)}]$$

Drug effect ? = $k_{kill\_ADC} \cdot C_{ADC}$ +/- $k_{kill\_DM4} \cdot C_{DM4}$ +/- $k_{kill-MeDM4} \cdot C_{MeDM4}$

ADC concentrations is the best driver of tumor Size dynamics

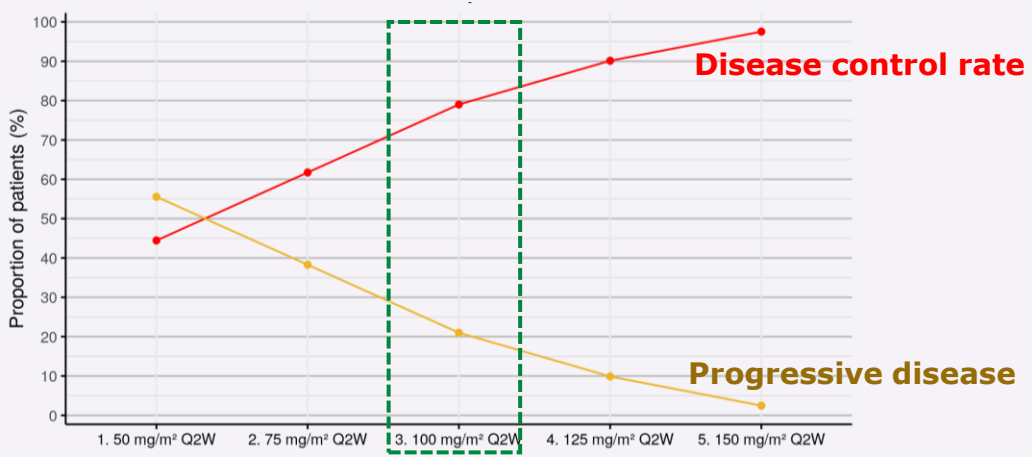




- ✓ No effect of DM4 or Me-DM4 PK

- $\frac{d(TS)}{dt} = [k_{ge}.TS(t)].[1 - k_{kill}.C_{SAR408701}(t).e^{-lambda(t)}]$

Simulations of best tumor shrinkage
(n=1000 simulated trials)

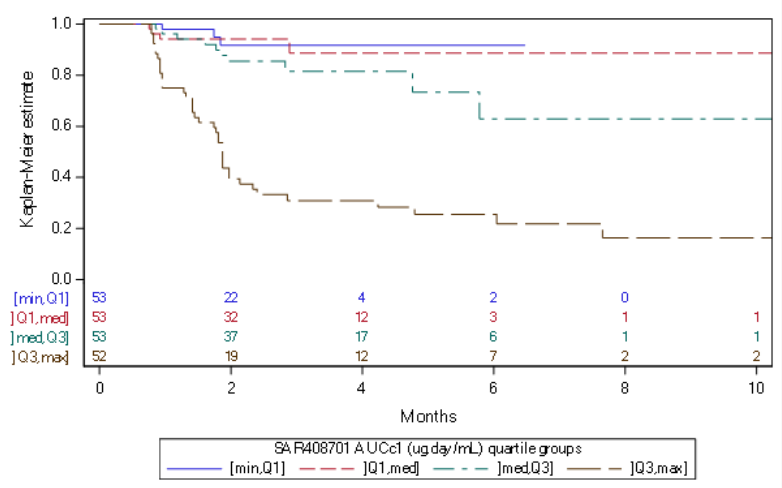


What is the driver(s) of toxicity ?

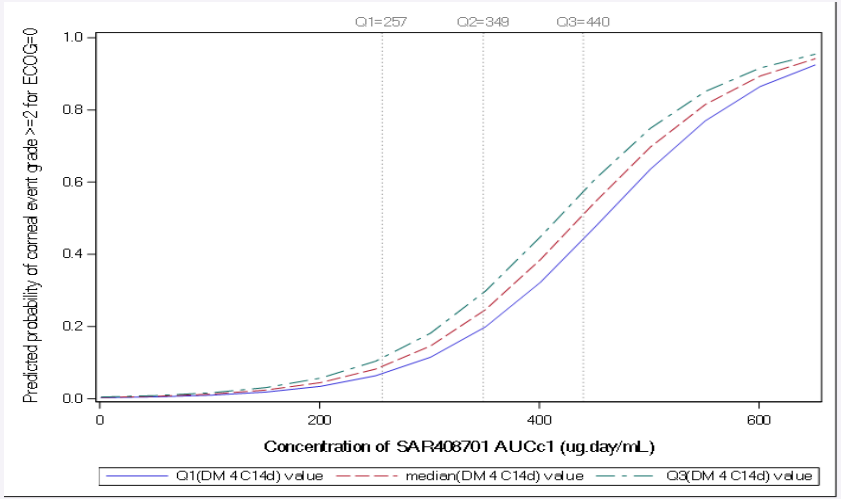
Exposure versus safety multivariate analyses (211 pts - 5 to 190 mg/m² Q2W – FIH study)

Corneal event main dose-limiting toxicity (26% of grade ≥ 2)

Time-to-event analysis
(1st event)



Logistic regression analysis



- Corneal event is mainly driven by <u>cycle 1 ADC exposure</u>
- No or limited Contribution of payload

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PK/PD: comparison with other ADCs

Cancer Chemotherapy and Pharmacology (2021) 87:743–765
https://doi.org/10.1007/s00280-021-04250-0

REVIEW ARTICLE

Clinical pharmacology strategies in supporting drug development and approval of antibody–drug conjugates in oncology

Stephanie N. Liu[1] · Chunze Li[1]

..”for most of the seven approved ADCs, the **efficacy endpoints** appear to **correlate best with ADC conjugate compared to that of unconjugated payload**.

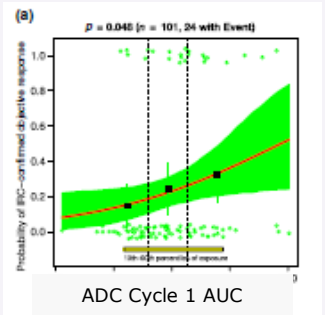
For **safety** outcomes, while ADC exposures were often correlated with AEs, **unconjugated payload exposures may also be important for certain AEs**”

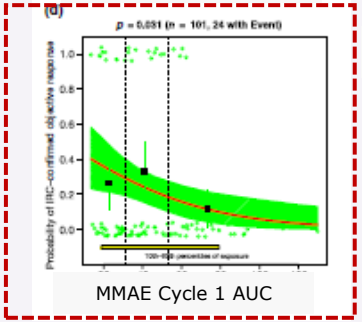
Exposure-safety and exposure-efficacy analyses for tisotumab vedotin for patients with locally advanced or metastatic solid tumors

Chaitali Passey[1] | Jenna Voellinger[2] | Leonid Gibiansky[3] | Rudy Gunawan[2] | Leonardo Nicacio[2] | Ibrahima Soumaoro[1] | William D. Hanley[2] | Helen Winter[4] | Manish Gupta[1]

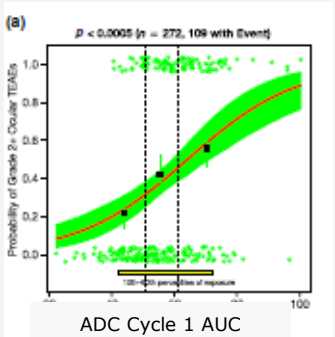
CPT PsP 2023:1-12

ORR

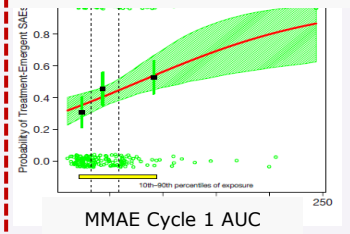




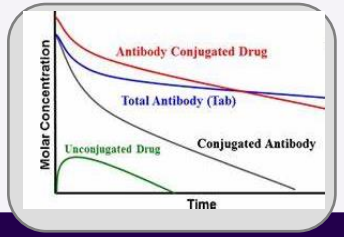
Occular Grade 2+

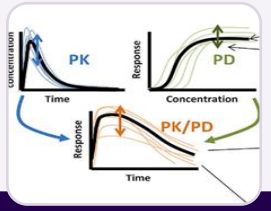


Treatment emergent SAE



Conclusions





❑ Bioanalytical consideration

- Need several bioanalytical tools to measure different components
- Low circulating payloads need sensitive assays

❑ PK characterization & modeling

- Population PK analysis enables multiple analytes integration with mechanistic considerations
- Useful to characterize the PK of all entities and to draw CMC specifications (e.g. DAR variability)

❑ Intrinsic factors

- Payload PK is much more variable than ADC PK
- Standard covariates (ALB, Tumor burden, circulating target) are commonly identified but of limited impact on ADC and paylaod exposure
- BSA or body weight are usually relevant covariates
- Impact of immunogenicity ?

❑ drug-drug interactions

- IVIVE or PBPK are useful to predict DDI mediated by payloads

❑ PK/PD

- Difficult to handle multiple analytes effects and to determine the best driver
- Combination of different approaches may help (E-R, longitudinal PK/PD modeling, PBPK, QSP)
- QSP modeling is likely meaningful (Scheuher B. et al. JPP, 2023)
- Impact of immunogenicity ?

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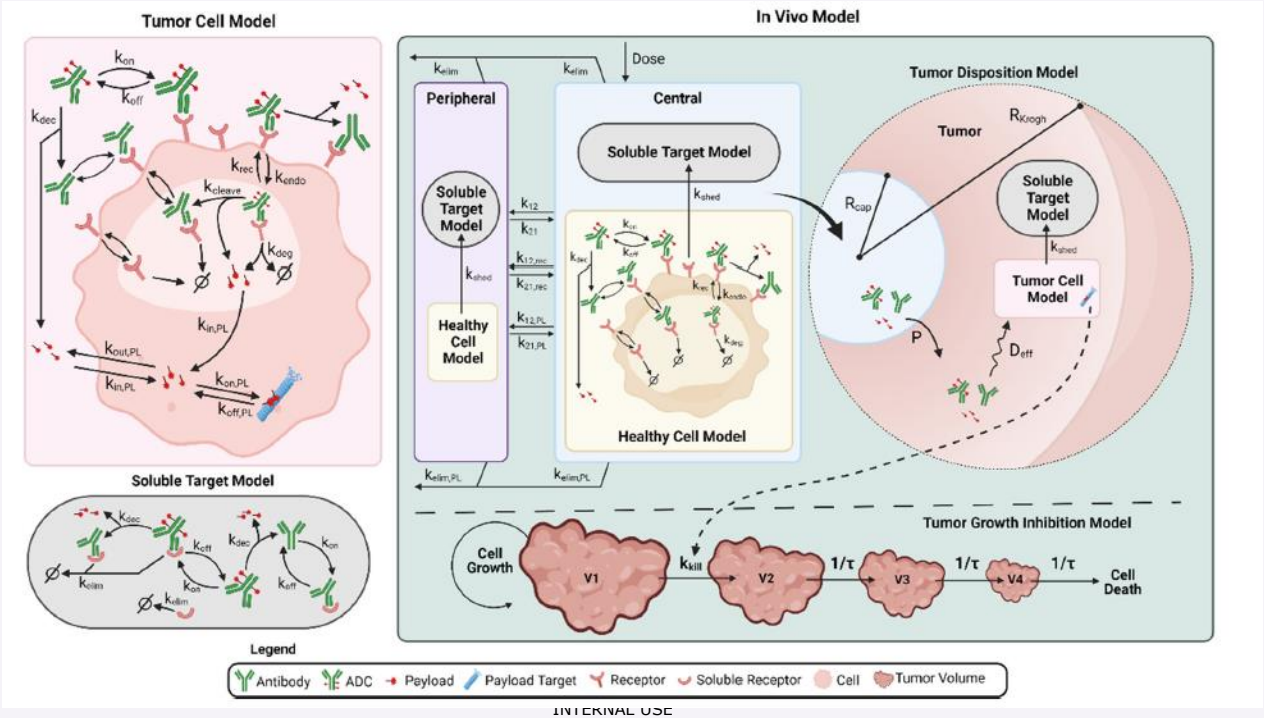
Journal of Pharmacokinetics and Pharmacodynamics
https://doi.org/10.1007/s10928-023-09884-6

ORIGINAL PAPER

Towards a platform quantitative systems pharmacology (QSP) model for preclinical to clinical translation of antibody drug conjugates (ADCs)

Bruna Scheuher[1,2] · Khem Raj Ghusinga[1] · Kimiko McGirr[1] · Maksymilian Nowak[1] · Sheetal Panday[1] · Joshua Apgar[1] · Kalyanasundaram Subramanian[1,3] · Alison Betts[1,2]



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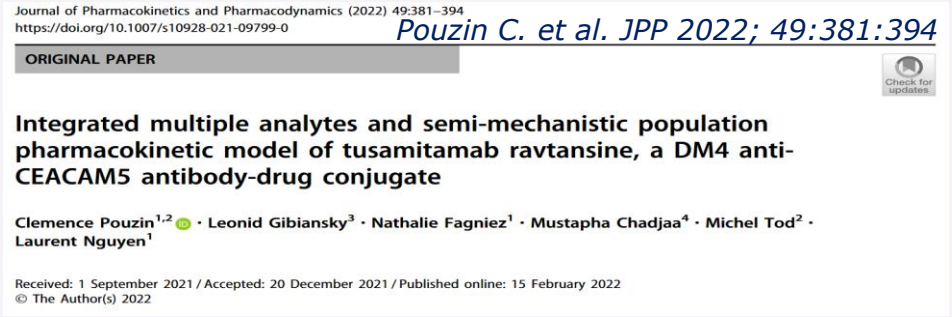
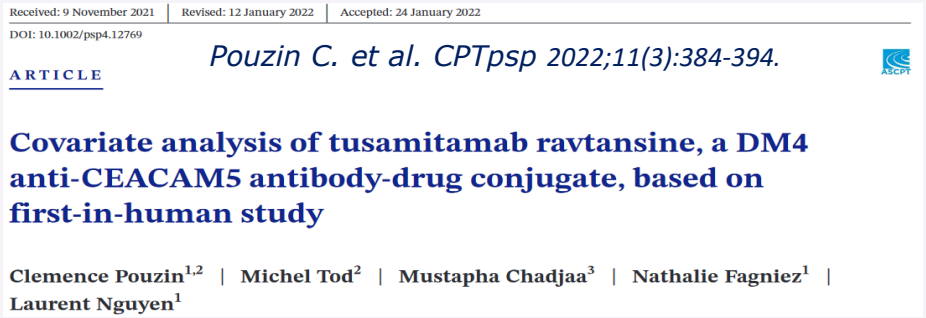
Samira Ziti-Ljajic (PK lead-Sanofi)
Mustapha Chadjaa (Clinical lead-Sanofi)
Michel Tod (Pr-University of Lyon)
Leonid Gibiansky (QuantPharm-USA)



Pouzin C. et al. JPP 2022; 49:381:394



Pouzin C. et al. CPTpsp 2022;11(3):384-394.

Prediction of CYP down regulation after tusamitamab ravtansine administration (a DM4-conjugate), based on an in-vitro-in-vivo extrapolation approach

CPT 2023 accepted

Clemence Pouzin[1], Donato Teutonico[1], Nathalie Fagniez[1], Samira Ziti-Ljajic[1], Anne Perreard-Dumaine[2], Magalie Pardon[3], Sylvie Klieber[4], Laurent Nguyen[1]

Thank you

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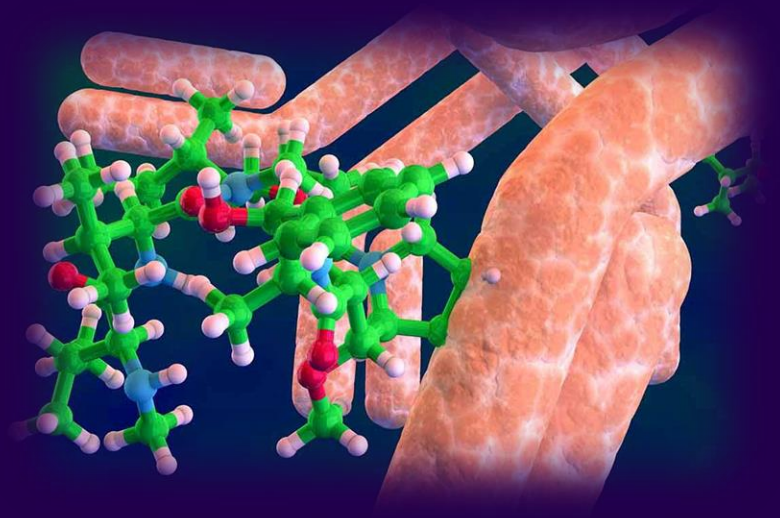
BACK UP



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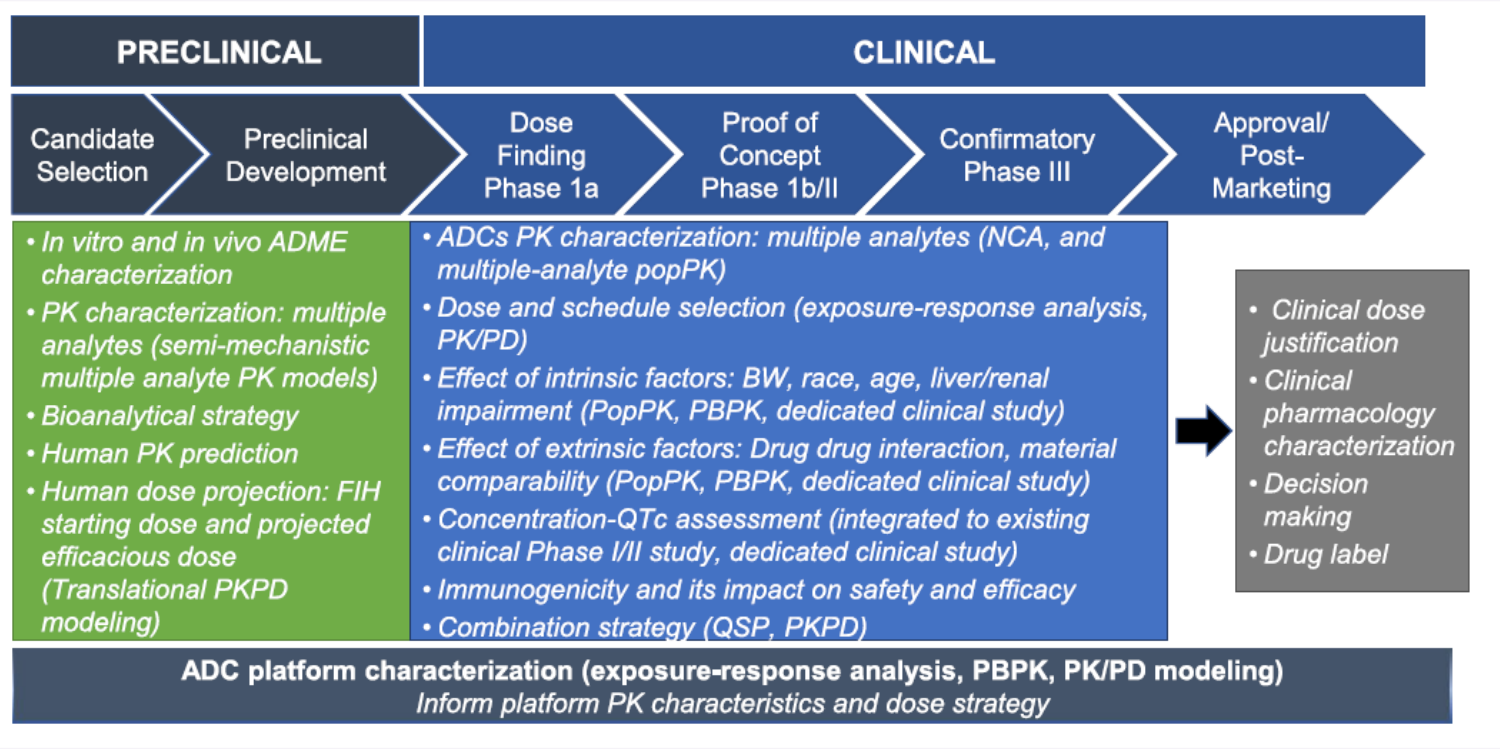
Clinical Pharmacology considerations for ADC development



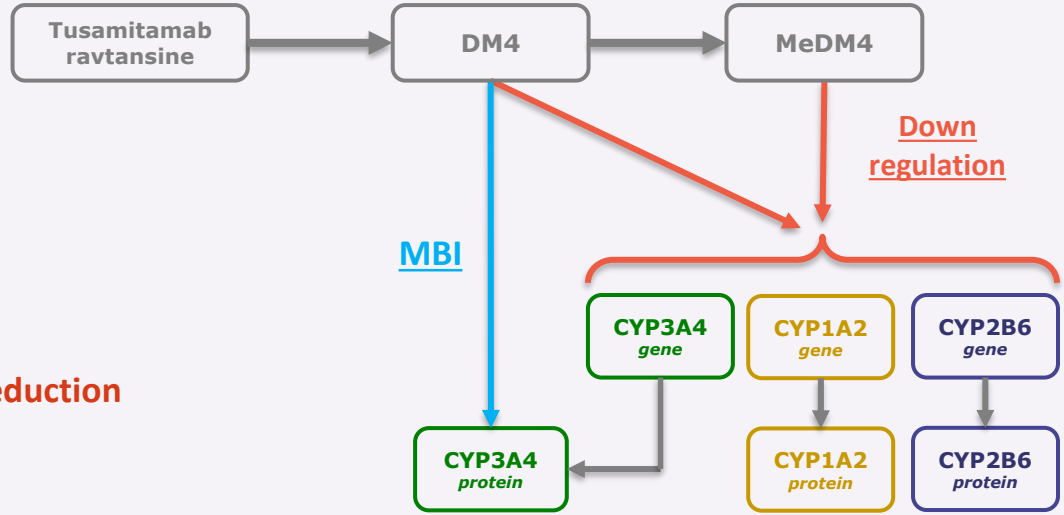
From Liu SN, CCP (2021)87:743-765

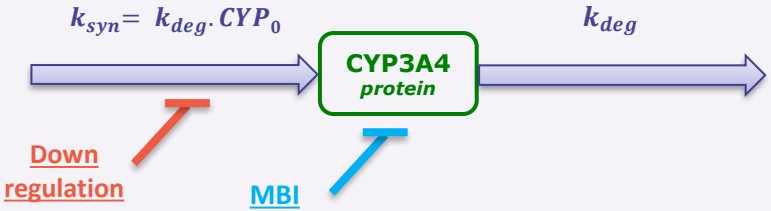
IVIVE-PK model to predict CYP down regulation

- In vitro data show
  - Down regulation of CYP3A4, 1A2 and 2B6 by Me-DM4 and DM4 observed in human hepatocytes
  - Mechanism based inhibition (MBI) of CYP3A4 by DM4 in human liver microsomes

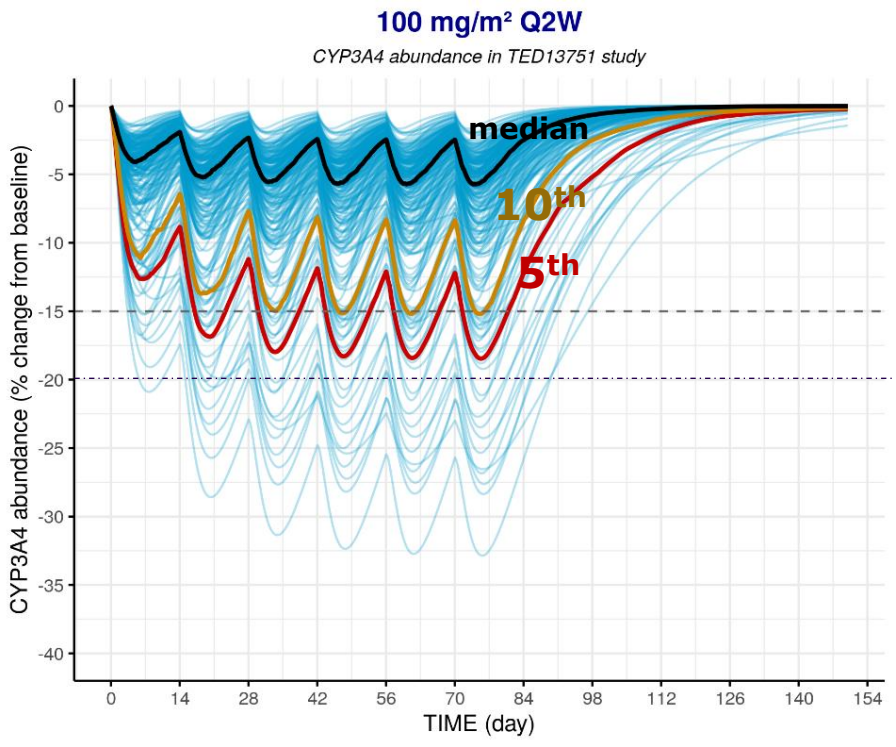
➢ **Simulation of CYP abundance time course reduction**

➢ **Prediction of MDZ AUC ratio** *(PBPK simulation)*



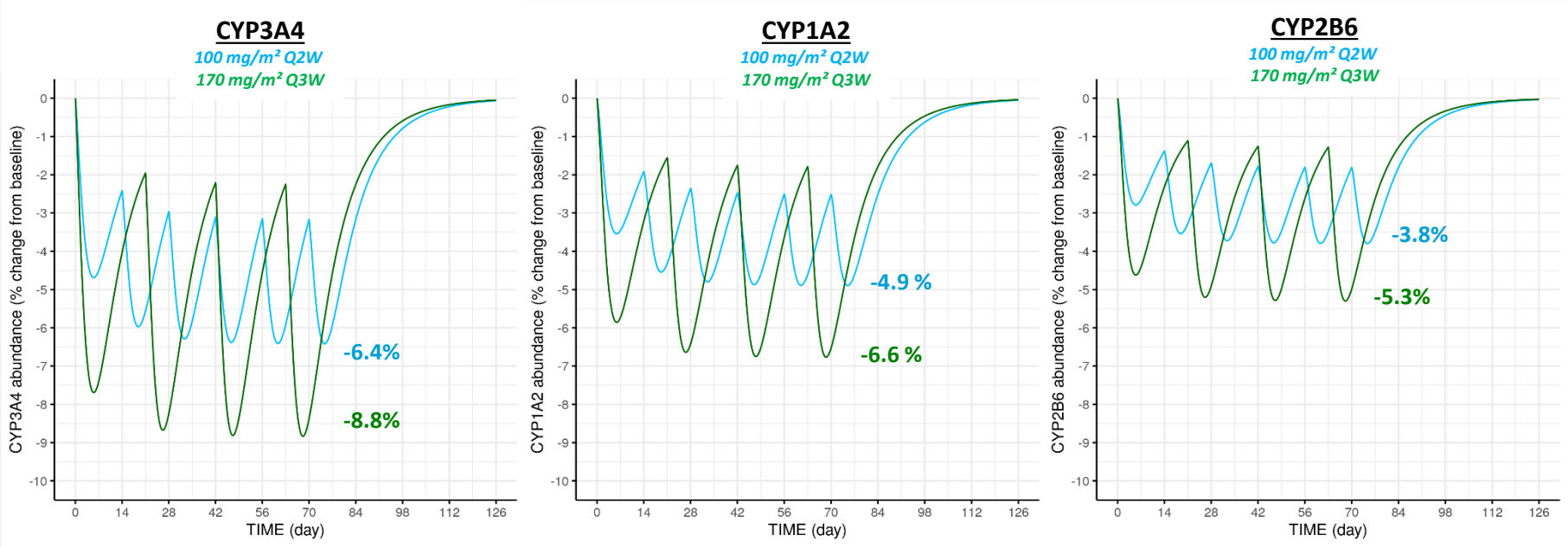


IVIVE PK simulations to predict CYP3A4 abundance decrease



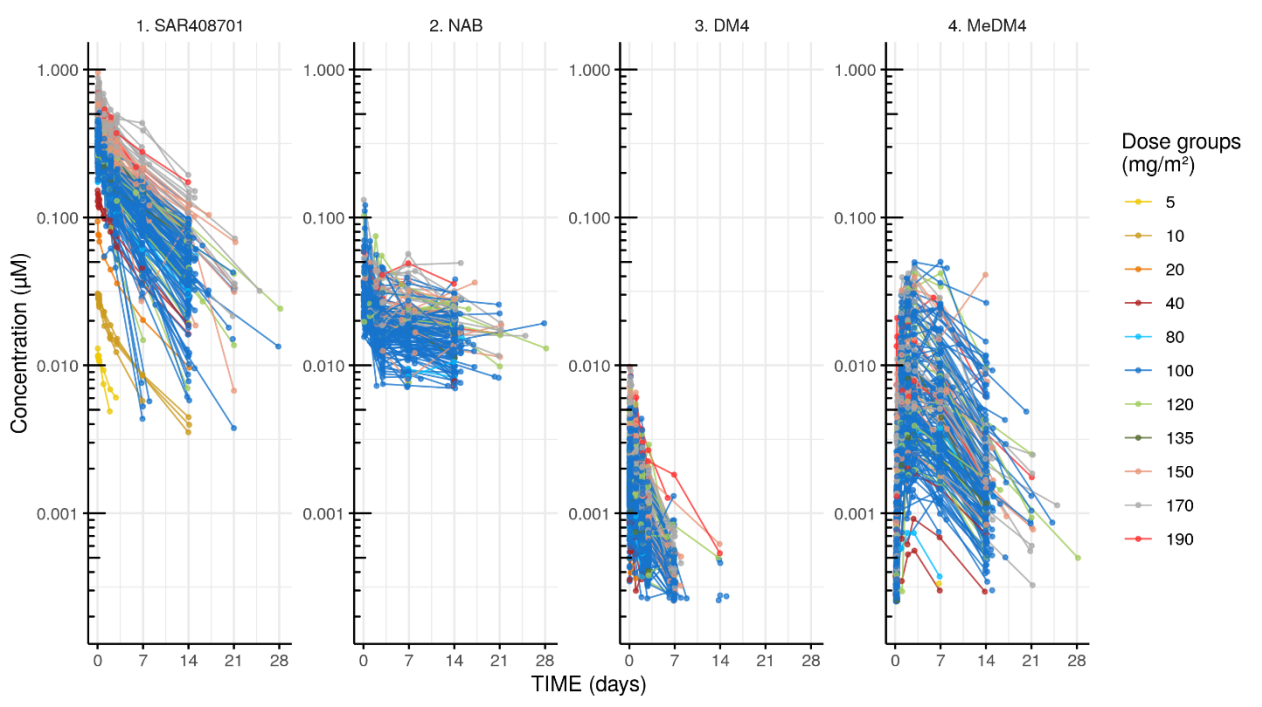
- Transient effect
- Less than 20% decrease in CYP3A4 abundance when considering extreme values *(5th percentile)*
- Expected AUC ratio for Midazolam CYP3A4 probe =1.14 (< 1.25) => no clinically relevant DDI effect on CYP3A4 substrate

IVIVE-PK model simulations to predict CYP down regulation



- Below 10% decrease of CYP abundance predicted by IVIVE modeling
- **Expected AUC ratio for Midazolam CYP3A4 probe =1.14 (< 1.25) => no clinically relevant (DDI guidelines)**

Cycle 1 TED


1. SAR408701
2. NAB
3. DM4
4. MeDM4
Concentration (µM)
1.000
0.100
0.010
0.001
0
7
14
21
28
TIME (days)
Dose groups
(mg/m²)
5
10
20
40
80
100
120
135
150
170
190

ADCs: Clinical use

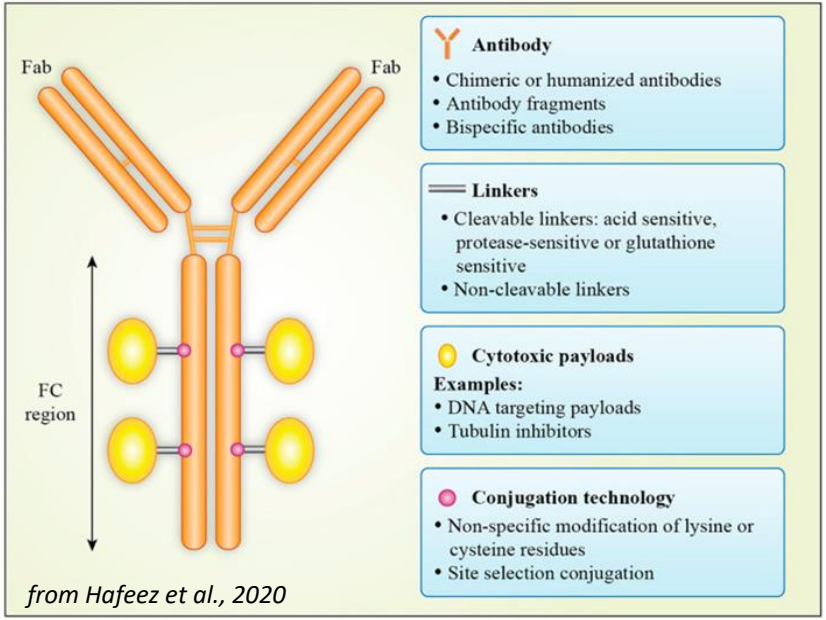
	Name | Trade Name, *Company*	Antibody Target	Payload	Payload Target	DAR	Approved Indication
HEMATOLOGICAL	**Gemtuzumab ozogamicin** | Mylotarg ® *Pfizer*	CD33	Calicheamicin	DNA	2-3	Acute Myeloid Leukemia
	Brentuximab vedotin | Adcetris ® *Seagen*	CD30	MMAE	Microtubule	4	HL and ALCL, PTCL, cHL
	Inotuzumab ozogamicin | Besponsa ® *Pfizer*	CD22	Calicheamicin	DNA	5-7	Acute Lymphocytic Leukemia
	Moxetumomab pasudotox | Lumoxiti ® *AstraZeneca*	CD22	PE38	-	NA	Hairy Leukemia
	Polatuzumab vedotin | Polivy ® *Roche*	CD79b	MMAE	Microtubule	3.5	Diffuse Lymphoma
	Belantamab mafodotin | Blenrep ® *GSK*	BCMA	MMAF	Microtubule	4	Multiple myeloma
	Loncastuximab tesirine | Zynlonta ® *ADC*	CD19	PBD dimer	DNA	2.3	Diffuse Lymphoma
SOLID TUMORS	**Trastuzumab emtansine** [1] | Kadcyla ® *Roche*	HER2	DM1	Microtubule	3.5	Breast
	Enfortumab vedotin | Padcev ® *Seagen*	Nectin4	MMAE	Microtubule	3.8	Urothelial
	Trastuzumab deruxtecan | Enhertu ® *Daiichi*	HER2	Dcd	DNA	7-8	Breast, Gastric, Lung [2]
	Sacituzumab govitecan | Trodelvy ® *Immunomedics*	TROP2	SN38	DNA	7.6	Triple Negative Breast Cancer
	Cetuximab saratolacan [3] | Akalux ® *Rakuten*	EGFR	IRdye700DX	Cell membrane	1.3-3.8	Head & Neck
	Tisotumab vedotin | Tivdak ® *Seagen*	TF	MMAE	Microtubule	4	Cervical
	Disitamab vedotin | Aldixi ® *Remegen*	HER2	MMAE	Microtubule	4	Gastric/ Gastroesophageal
	Mirvetuximab soravtansine | Elahere ® *ImmunoGen*	FRα	DM4	Microtubule	3.5	Ovarian, Fallopian, Peritoneal

Adapted from Zhiwen Fu et al. Nature 2023

ALCL= Anaplastic Large Cell Lymphoma; ALL = Acute Lymphocytic Leukemia; cHL= Classic Hodgkin Lymphoma; FR= Folate Receptor; HL = Hairy leukemia; PTCL = Peripheral T Cell Lymphoma; TF = Tissue Factor

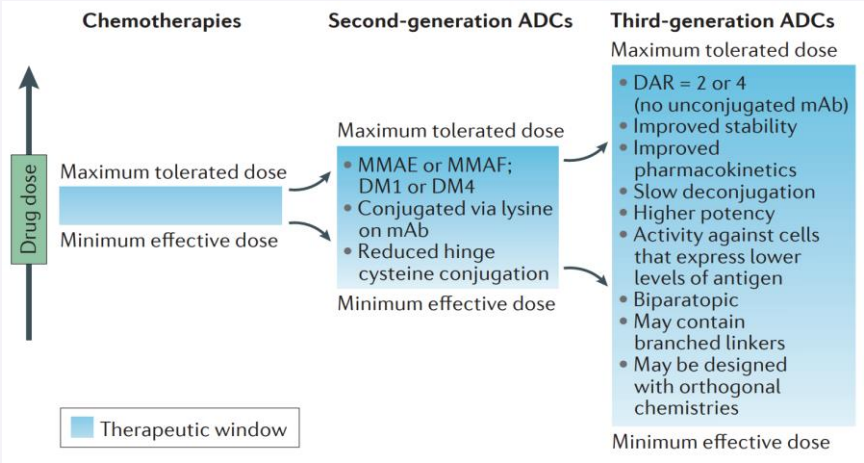
- 1st ADC approved in 2000 for AML *(Mylotarg®)*
- 15 Approved ADCs
- Pipeline is exponentially growing with more than 100 clinical studies

Key components of an ADC

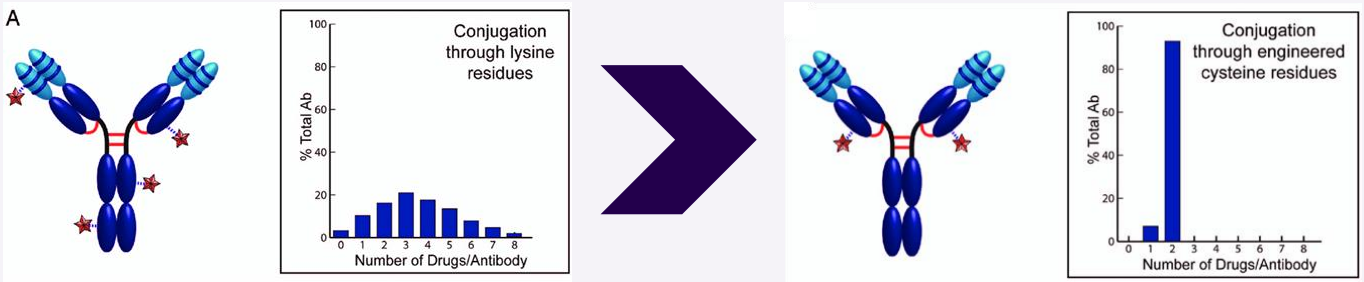


from Hafeez et al., 2020

ADC evolution *(from Beck et al. 2017)*



from Panowksi et al., 2014



Covariates

Baseline continuous covariates

	Min	Max	Median
Age (years)	31	91	**62**
Body weight (kg)	36.0	138.0	69.0
Body surface area (m^2)	1.25	2.66	1.80
Body mass index (kg/m^2)	14.6	40.8	24.1
Creatinine clearance (mL/min)	35.7	213.3	90.3
Albumin (g/L)	24.0	48.0	39.0
Bilirubin (µM)	1.70	51.3	7.83
Total Protein (g/L)	53.0	89.7	72.0
ASAT (IU/L)	10.0	208	25.0
ALAT (IU/L)	5.00	166.0	18.5
Tumoral CEACAM5 expression (%)	0	100	70.0
Tumor Burden (mm)	11.0	339	84.0
SHED: Circulating CEA (pg/mL)	500	41227000	56530
HSCORE	0	300	210

Baseline categorical covariates

	Subclass
SEX	**Male: N=156** **Female: N=98**
ETHNIC	Non Hispanic: N=224 Hispanic: N=30
RACE	Caucasians: N=209 Blacks: N=0 Oriental: N=45 Other: N=0
ECOG *(Eastern Cooperative Oncology Group status)*	PS 0: N= 87 PS 1: N=165 PS 2: N=1 PS 3: N=1
TUMOR TYPE	Breast: N=1 Colon/Rectum: N=93 Esophagus: N=1 Gastroesophageal: N=10 Lung: N=119 Pancreas: N=5 Stomach: N=25

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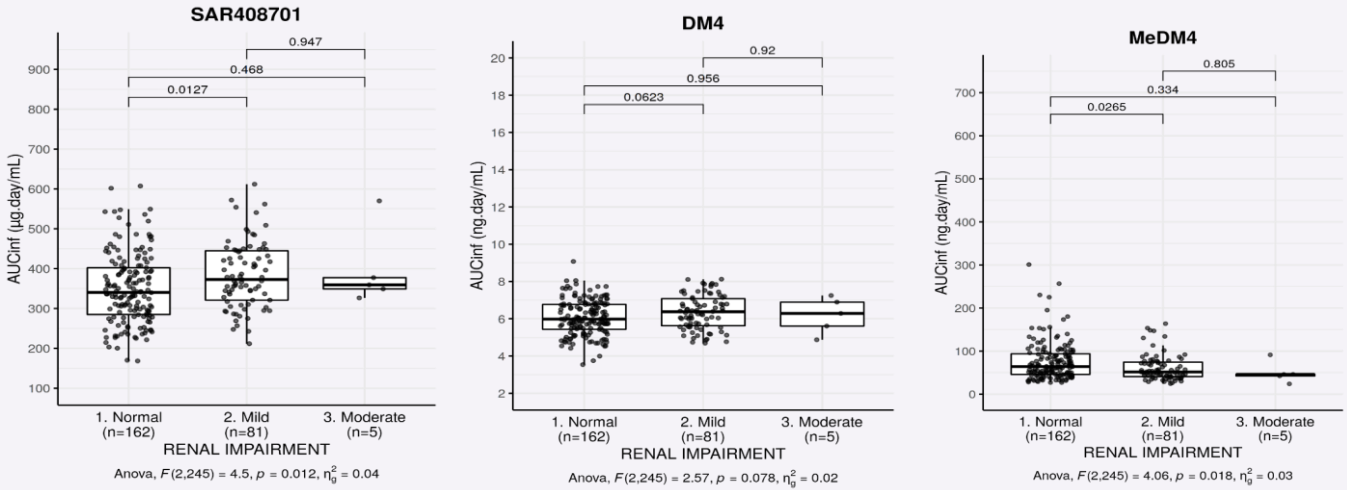
Impact of renal impairement on Tusa PK ?

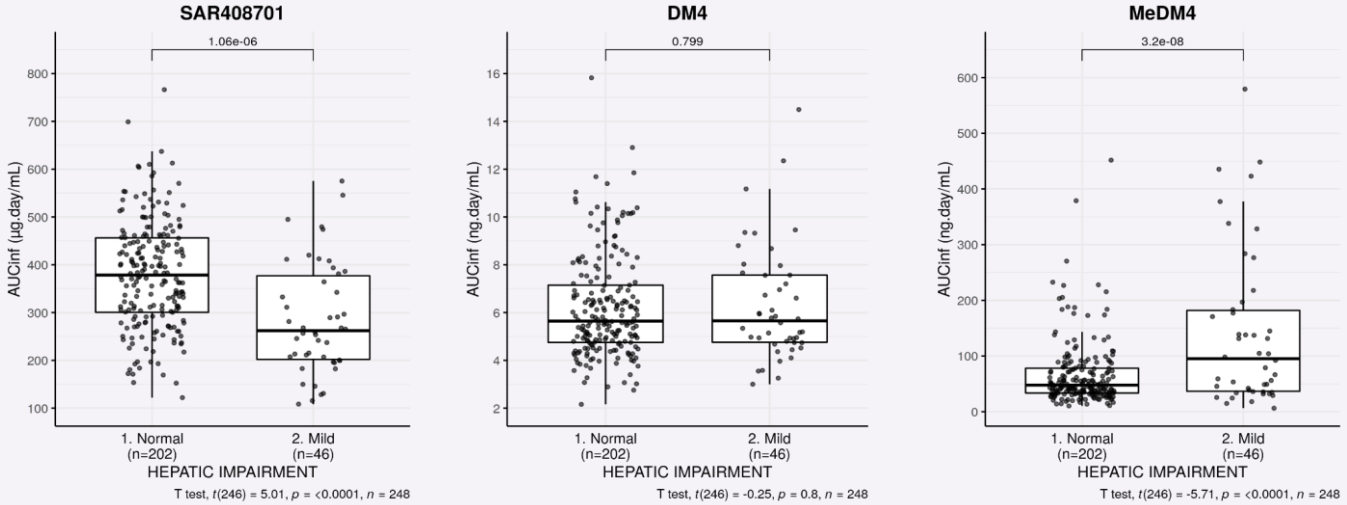


✓ Scr, CLcr (MDRD) are not significant covariates

Renal status based on eGFR (MDRD)

➢ No difference in ADC and payloads exposure between Mild/moderate RI vs normal renal function patients

Impact of liver impairement on Tusa PK ?

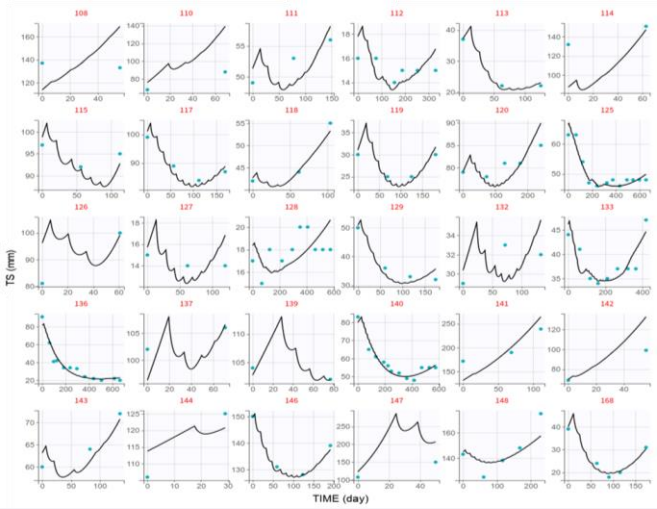


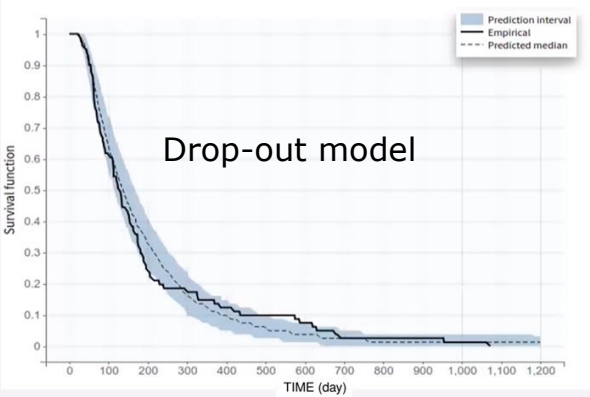
✓ Bilirubin, SGOT, SGPT are not significant covariates

Hepatic status was defined according to the National Cancer Institute

- Confounding effect of unbalanced covariates distribution between mild LI patients (higher tumor burden, lower albumin and higher circulating CEA) and normal patients. LI could be associated with disease severity or worsening.

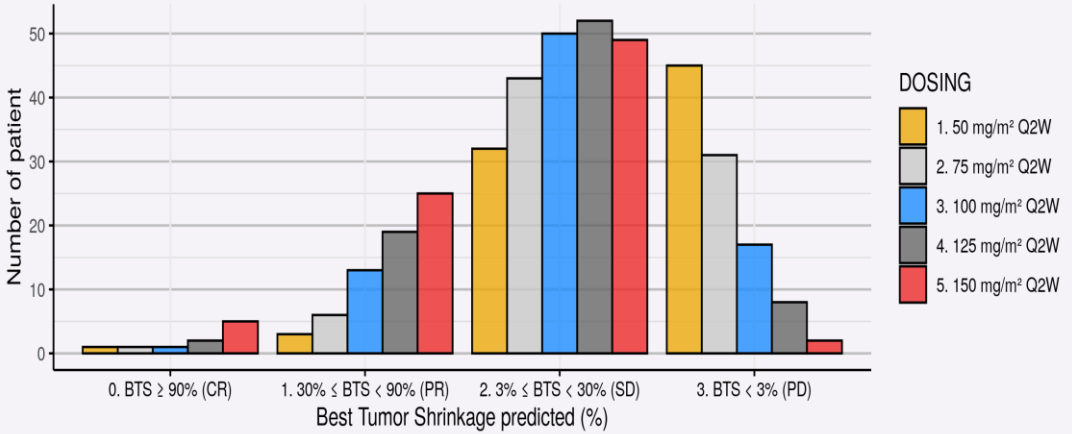
Tumor Size dynamics was accurately characterized by ADC concentrations





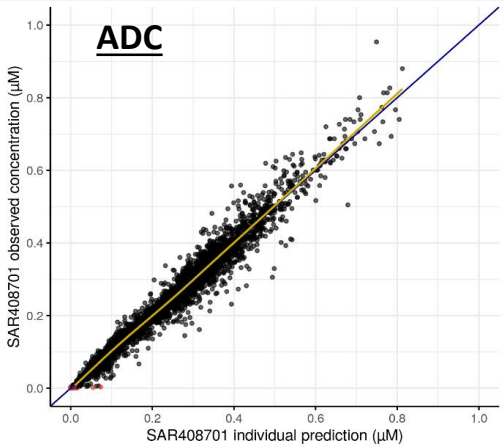
- ✓ No added value of DM4 or Me-DM4 PK concentrations.
  - $\frac{d(TS)}{dt} = [k_{ge}.TS(t)].[1 - k_{kill}.C_{SAR408701}(t).e^{-lambda(t)}]$
- ✓ Trend for better response for higher CEACAM5 expressors.

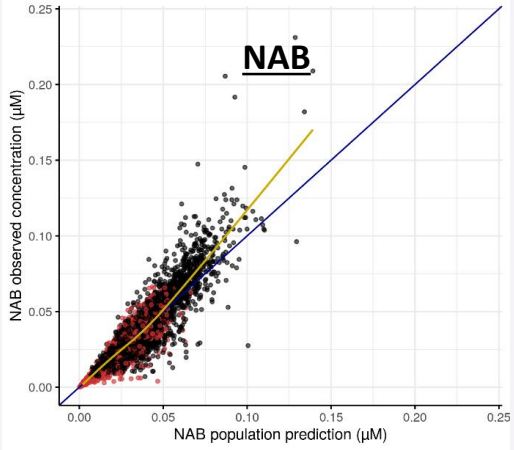
Simulations of best tumor shrinkage

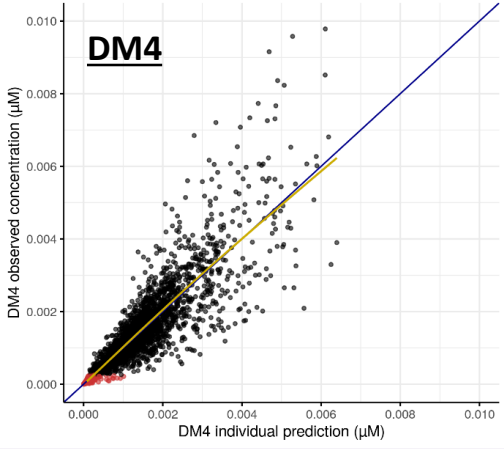


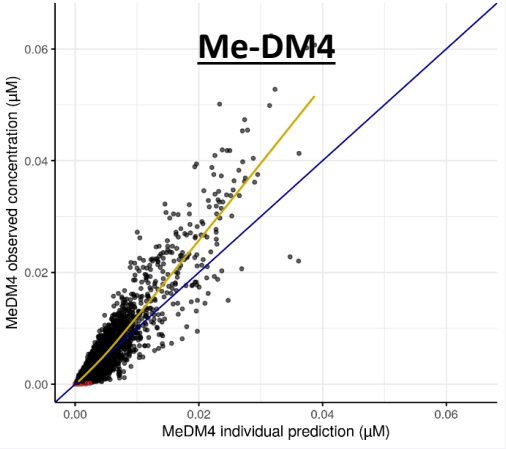
1. Tusamitamab ravtansine pop PK

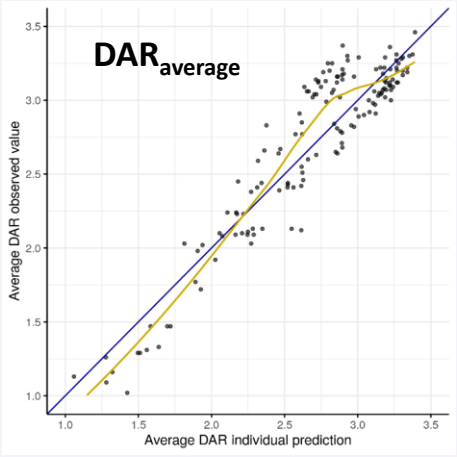
➢ **MODEL EVALUATION: OBSERVED DATA vs iPRED**







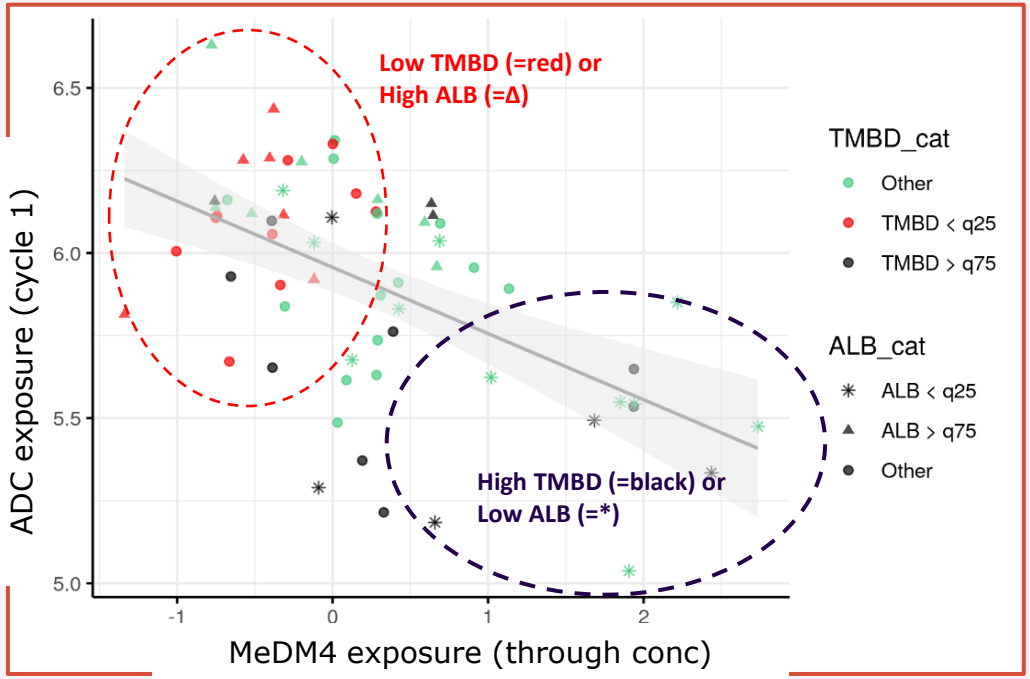




Observed data

Censored data

Impact of covariates (ALB and Tumor burden) on ADC and MeDM4 PK



Observed data from Nsq NSCL cancer pts (n=62 pts)

- ✓ Inverse correlation btw ADC and MeDM4 exposure
- ✓ High ALB and low tumor burden reflect lower ADC proteolysis and/or deconjugation
  - ↳Higher ADC exposure and lower MeDM4 exposure
- ✓ high tumor burden and low ALB reflect high proteolysis and/or deconjugation
  - ↳ Low ADC exposure and high MEDM4 exposure