A PK-PD Modeling and Simulation Based Strategy for Clinical Translation of Antibody Drug Conjugates: A Case Study with T-DM1

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ROSA

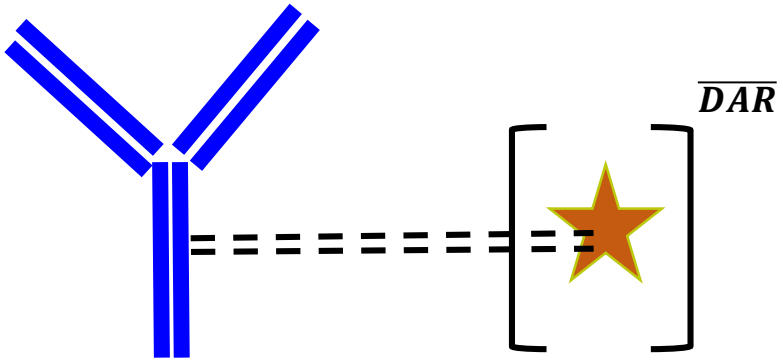
ROSA Impact Webinar
04/19/2017

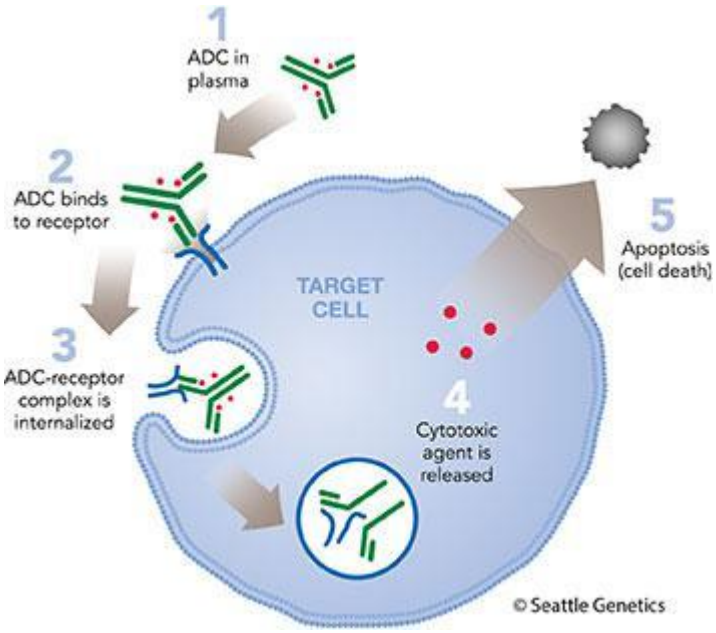
Buffalo Pharmaceutics

University at Buffalo The State University of New York
School of Pharmacy and Pharmaceutical Sciences

Background: ADCs

~60 Antibody Drug Conjugates are in clinical trial [1]

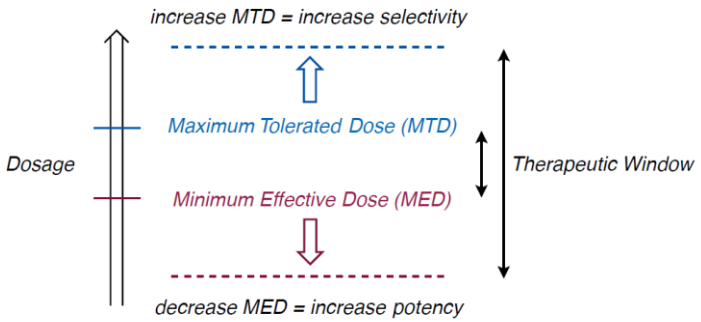




Humanized mAb construct (*IgG1, IgG2, IgG4)*
Selective for ***tumor antigens.***
Ab-Ag complexes *efficiently internalized*

Cleavable:
Cleaved based on differential extra- and intracellular properties.
e.g. *Enzymatic, Acid-labile, Disulphide*
Non-Cleavable:
Proteolytic Degradation inside a cell
e.g. *SMCC linker.*

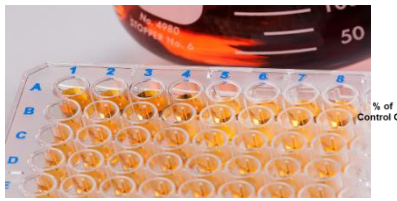
Microtubule Inhibitors:
e.g. *Maytansines (DM1)*
Auristatins (MMAE)
DNA Damaging Agents:
e.g. *Duocarmycins (DC1)*
Calcheamicin

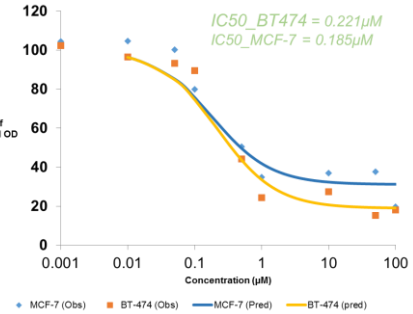


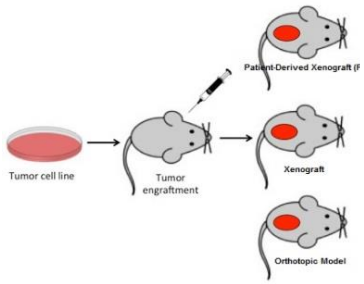
Angew. Chem. Int. Ed. **2014**, *53*, 3796.

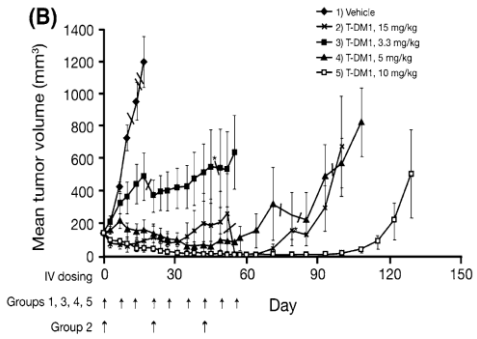
Rostami et al. **2014**

Motivation for Development of a Mechanistic Model









DISCOVERY PHASE

EARLY PRECLINICAL PHASE

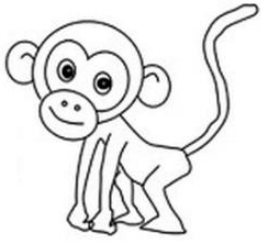
INFORM

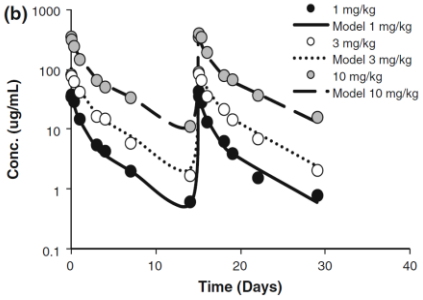
MULTI-SCALE MECHANISTIC PK-PD MODEL

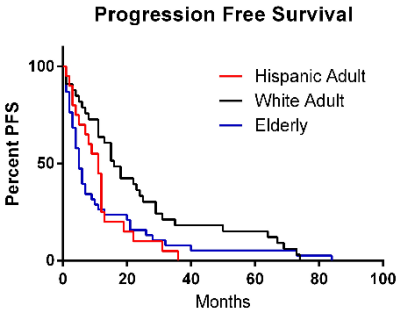
Learn → Predict → Confirm

LATE PRECLINICAL PHASE

CLINICAL PHASE







Motivation for Development of a Mechanistic Model

Bench to bedside translation of antibody drug conjugates using a multiscale mechanistic PK/PD model: a case study with brentuximab-vedotin

Valine-citrulline Linker
Microtubule Inhibitor

Dhaval K. Shah · Nahor Haddish-Berhane · Alison Betts

DISCOVERY

EARLY PRECLINICAL

Preclinical to Clinical Translation of Antibody-Drug Conjugates Using PK/PD Modeling: a Retrospective Analysis of Inotuzumab Ozogamicin

Acid-labile Linker
DNA Damaging Agent

Alison M. Betts,[1,9,10] Nahor Haddish-Berhane,[2] John Tolsma,[3] Paul Jasper,[3] Lindsay E. King,[1] Yongliang Sun,[4] Subramanyam Chakrapani,[5] Boris Shor,[6] Joseph Boni,[7] and Theodore R. Johnson[8]

PHASE

CLINICAL PHASE

Application of a PK-PD Modeling and Simulation-Based Strategy for Clinical Translation of Antibody-Drug Conjugates: a Case Study with Trastuzumab Emtansine (T-DM1)

Non-cleavable Linker
Microtubule Inhibitor

Aman P. Singh[1] and Dhaval K. Shah[1,2]

Time (Days)

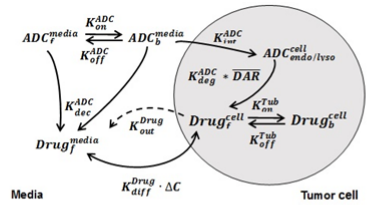
Months

General PK-PD Based Strategy for Clinical Translation of ADCs

Step 1

In Vitro Cellular Disposition Model

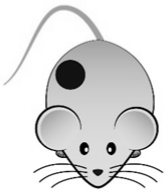
Characterize the internalization, degradation and payload release for ADCs in a tumor cell.

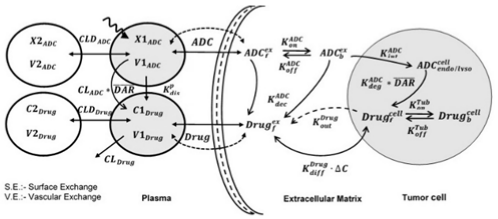


Step 2

In Vivo Tumor Distribution Model

A Priori predict plasma and tumor exposures of different analytes of ADC.

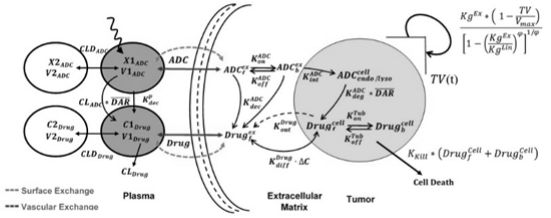




Step 3

In Vivo Tumor Growth Inhibition (PKPD) Model

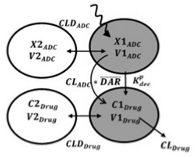
Use tumor concentrations to characterize TGI data and obtain PD parameters



Step 4

In Vivo Plasma PK Model in Monkey

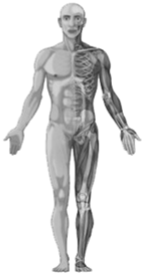
Characterize systemic concentrations of different analytes of ADCs in monkeys

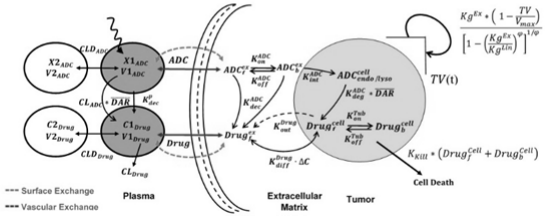


Step 5

Predict Clinical PK from monkey
Predict Clinical PD from mouse

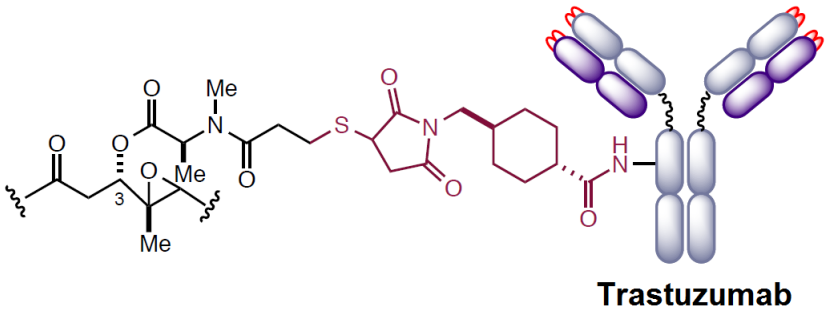
Scale up monkey PK parameters to predict human PK. Use mouse PD parameters to predict Progression Free Survival





Background- Trastuzumab Emtansine (Kadcylla®)

Average DAR of **3.5** molecules of **DM1** molecules per antibody.



Trastuzumab [Herceptin®]

- Humanized ***anti-HER2 mAb***
- Indicated for HER2-positive metastatic breast Cancer

Emtansine (DM1)

- Synthetic Derivative of Maytansine
- ***Microtubule Inhibitor***
- Highly potent: IC50 values of 10-100 pM

SMCC Thioether Linker

- Chemically non-labile **(uncleavable)** linker
- Proteolytic degradation of mAbs leads to formation of metabolites of Drug-linker-amino acid residue

Trastuzumab-smcc-DM1 (non-cleavable linker) (DAR4) → Proteolytic Degradation + Linker Cleavage → **Lysine-mcc-DM1 (charged)** → **Less Permeable** → **Minimal Bystander Killing**

Ogitani et al, *Cancer Sci* (2016)

Cellular Disposition Model for T-DM1

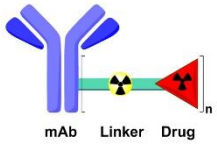
BT-474

SKBR3

MCF7/neo-HER2

30-40 nM

2-3 hrs



T-[H³]DM1

4°C

STOP

HER2-mediated Internalization

Washing

Media

Cell Pellet

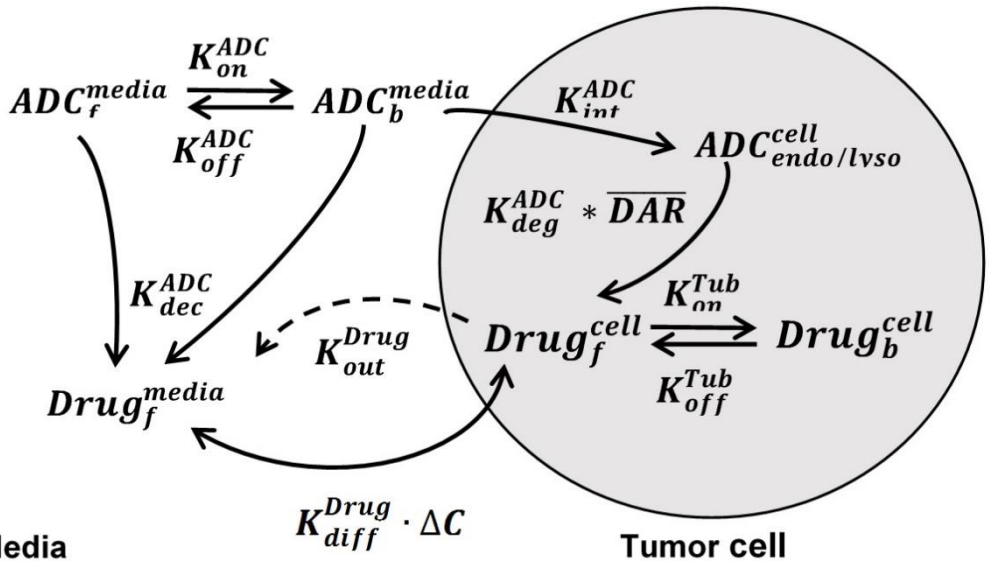
- Total DM1 Catabolites
- Unconjugated DM1
- Conjugated DM1

Sampling time= up to 24 hrs

In Vitro Cellular Disposition Model

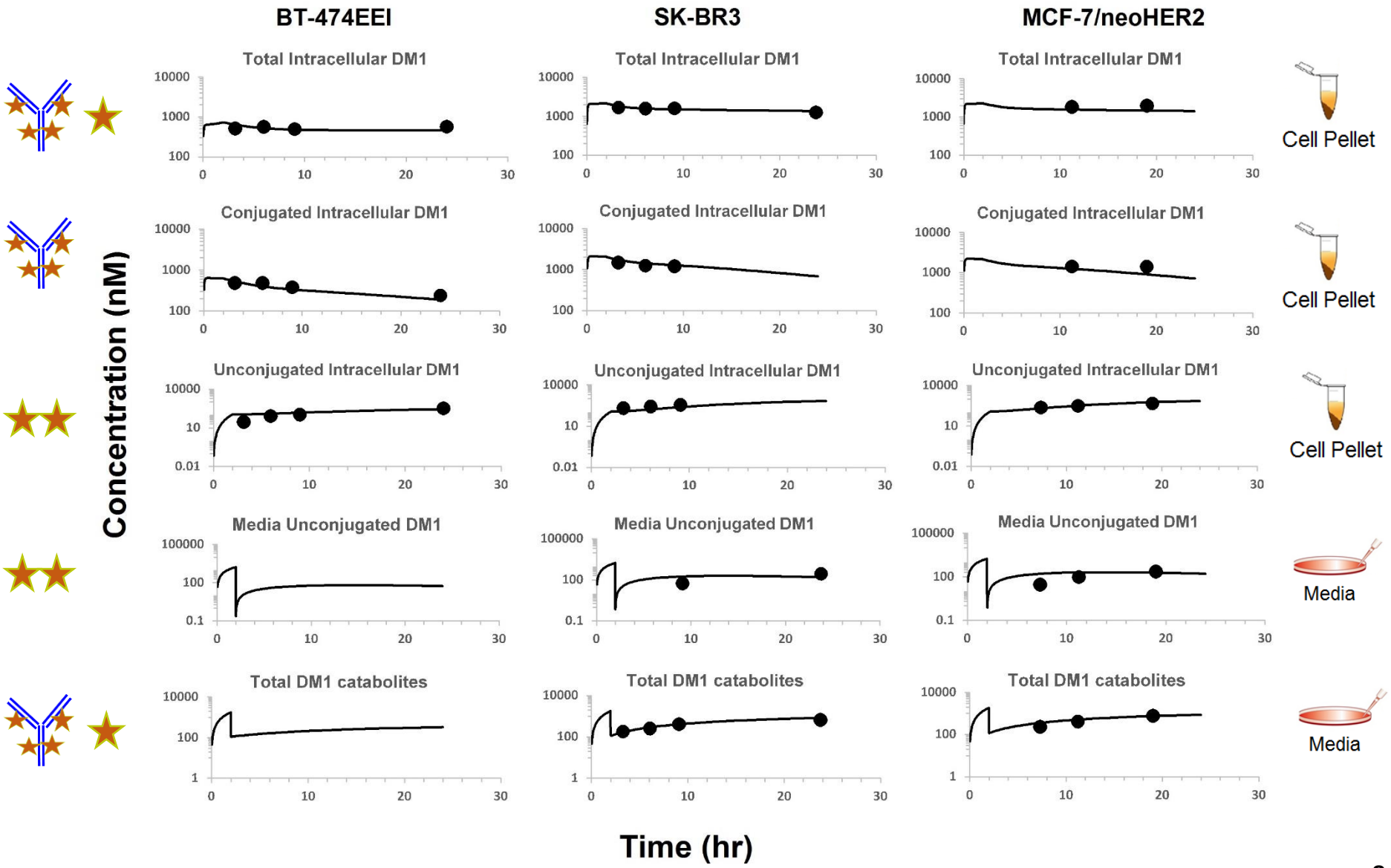
Characterize the internalization, degradation and payload release for ADCs in a tumor cell.

Step 1



Erickson HK et al, ***Mol Cancer Ther.*** (2012)

Cellular Disposition Model Fits-T-DM1



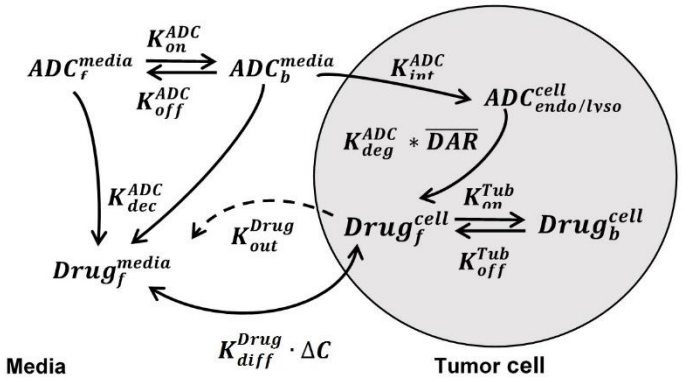
Cellular Disposition Model Parameters

Intracellular Model Parameters	Parameter Value	Units	Reference
K_{on}^{ADC}	0.37	1/nM/hr	Maass et al
K_{off}^{ADC}	0.014	1/hr	Maass et al
K_{int}^{ADC}	0.011	1/hr	Maass et al
K_{deg}^{ADC}	0.03	1/hr	Maass et al
K_{on}^{Tub}	0.03	1/nM/hr	Shah 2014
K_{off}^{Tub}	10.6	1/hr	Bhattacharyya (1977)
Tub_{total}	65	nM	Shah 2014
K_{dec}^{ADC}	0.0226	1/hr	Bender (2014)
K_{diff}^{Drug}	0.092 (17.4%)	1/hr	Estimated
K_{out}^{Drug}	0	1/hr	Fixed
$Ag_{total}^{BT-474EEI}$	0.594 (12.4%)	nM	Estimated
Ag_{total}^{SK-BR3}	1.6 (11.3%)	nM	Estimated
$Ag_{total}^{MCF-7/neoHER2}$	1.96 (11.8%)	nM	Estimated

In Vitro Cellular Disposition Model

Characterize the internalization, degradation and payload release for ADCs in a tumor cell.

Step 1



Maass KF et al, ***The AAPS Journal.*** (2016)

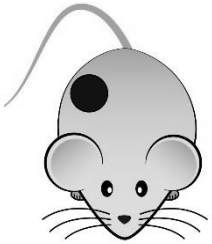
In Vivo Plasma Pharmacokinetics Model

Plasma PK Datasets

1) **Erickson et al (2007)** in normal mice at two dose levels (2 & 3 mpk) – TTmab and T-DM1
2) **Jumbe et al (2010)** in xenograft mice at 3 dose levels (0.3, 3 and 15 mpk) – T-DM1
3) **Shen et al (2012)** – single dose IV DM1 administration in rats.

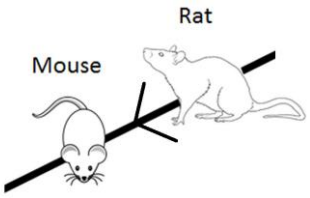
In Vivo Tumor Distribution Model

A Priori predict plasma and tumor exposures of different analytes of ADC.



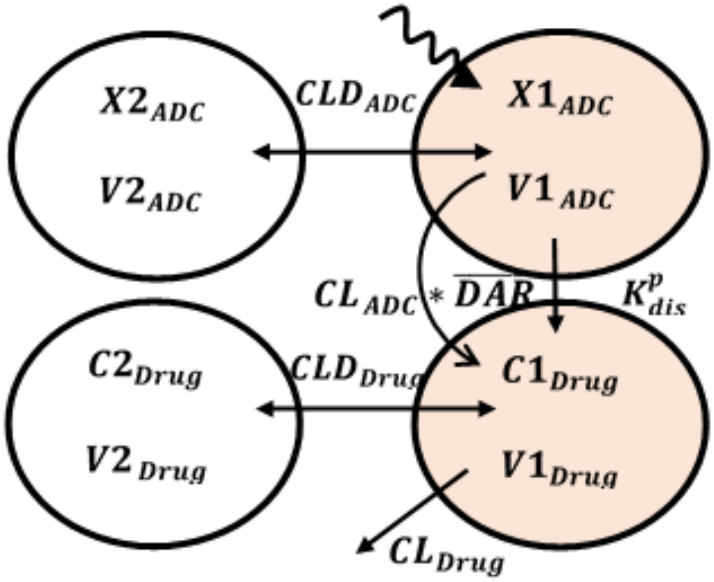
Step 2

Allometric Scale Down

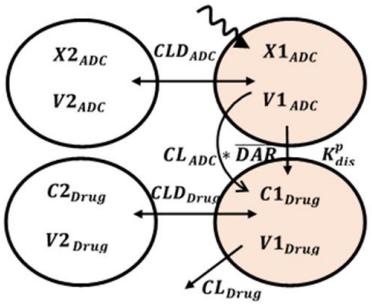


$$CL_{mice} = CL_{rats} \cdot \left[\frac{BW_{mice}}{BW_{rats}}\right]^{0.75}$$

$$V_{mice} = V_{rats} \cdot \left[\frac{BW_{mice}}{BW_{rats}}\right]^{1}$$

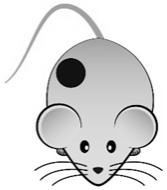


In Vivo Plasma Pharmacokinetics Model

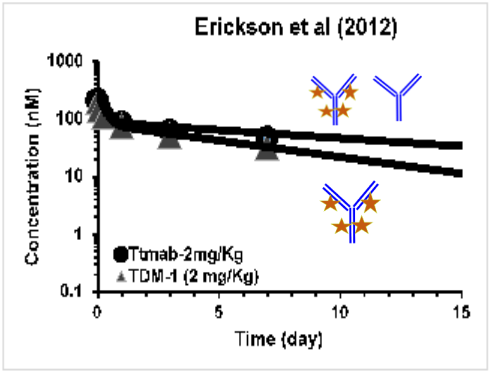


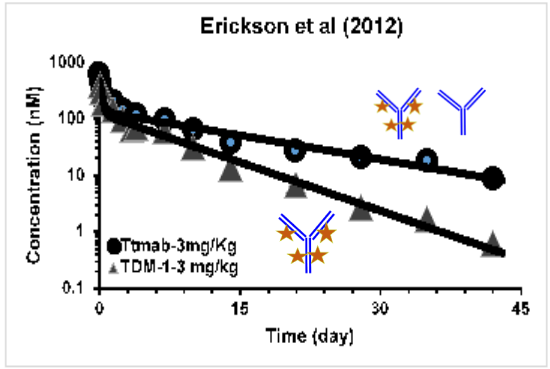
In Vivo Tumor Distribution Model

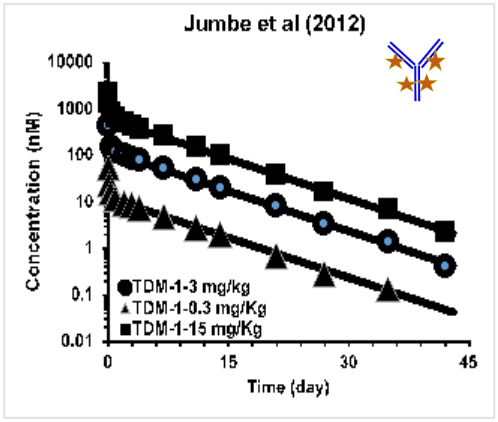
A Priori predict plasma and tumor exposures of different analytes of ADC.

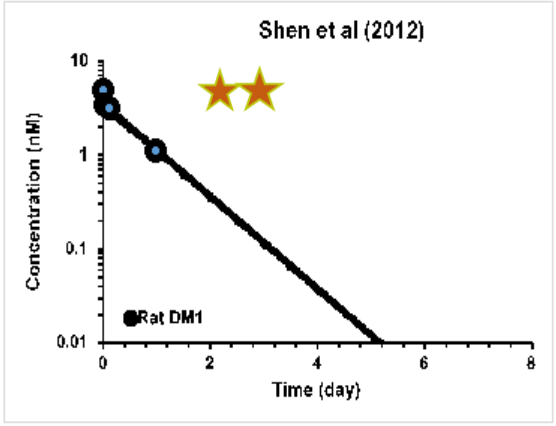


Step 2



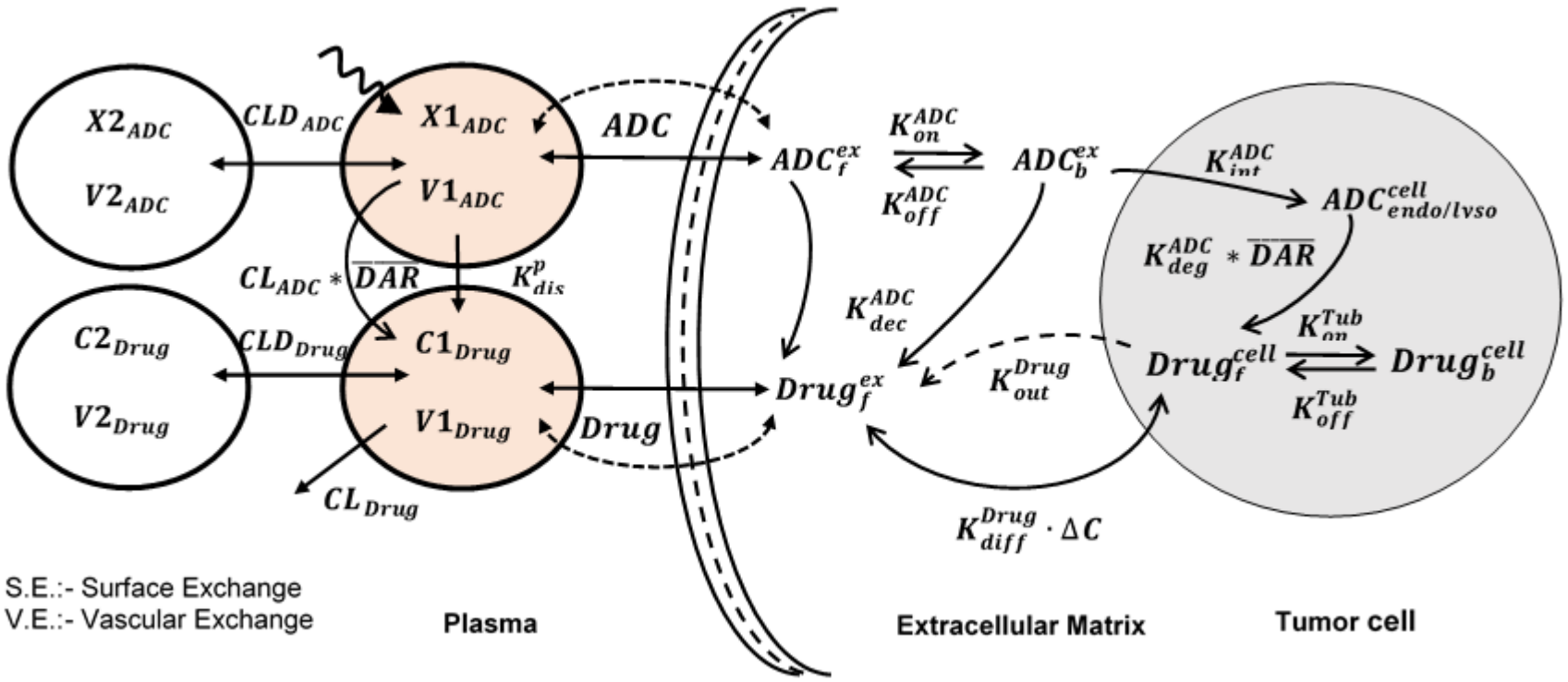






Systemic PK Parameters	Parameters	Units	Reference
CL_{ADC}	0.0093 (4.4 %)	L/day	Estimated
CLD_{ADC}	0.118 (12.6 %)	L/day	Estimated
$V1_{ADC}$	0.043 (7.3 %)	L	Estimated
$V2_{ADC}$	0.0948 (5.2 %)	L	Estimated
CL_{Drug}	11.29 (78.2%)	L/day	Estimated
CLD_{Drug}	155.4	L/day`	Fixed
$V1_{Drug}$	3.30 (48 %)	L	Estimated
$V2_{Drug}$	2.01	L	Fixed
K^P_{dec}	0.241 (8.8%)	1/day	Estimated

In Vivo Tumor Disposition Model for T-DM1



Parameters:-	Value	Unit	Reference
R_{Cap}	8	µm	Shah 2014
R_{Krogh}	75	µm	Shah 2014
P_{ADC}	334	µm/day	Shah 2014
P_{Drug}	21000	µm/day	Shah 2014
D_{ADC}	0.022	cm^2/day	Shah 2014
D_{Drug}	0.25	cm^2/day	Shah 2014
ε_{Drug}	0.44	Unitless	Shah 2014
ε_{ADC}	0.24	Unitless	Shah 2014

In Vivo Tumor Distribution Model

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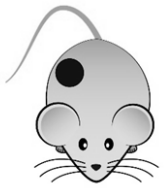
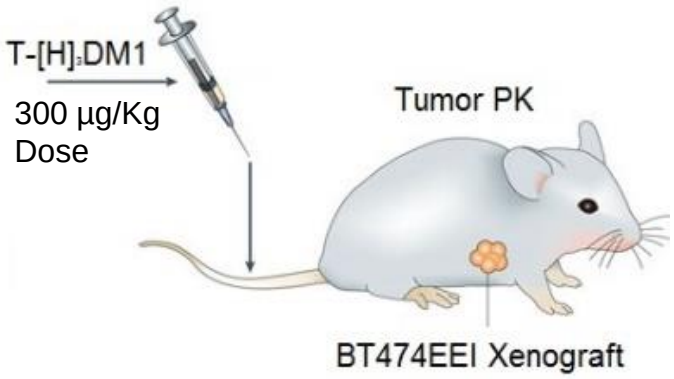


Step 2

Thurber GM et al, ***Adv. Drug. Deliv Rev.*** (2008)

Thurber GM et al, ***Trends Pharmacol Sci.*** (2008)

A Priori Predictions using our Tumor Disposition Model



Plasma and Tumor Homogenates

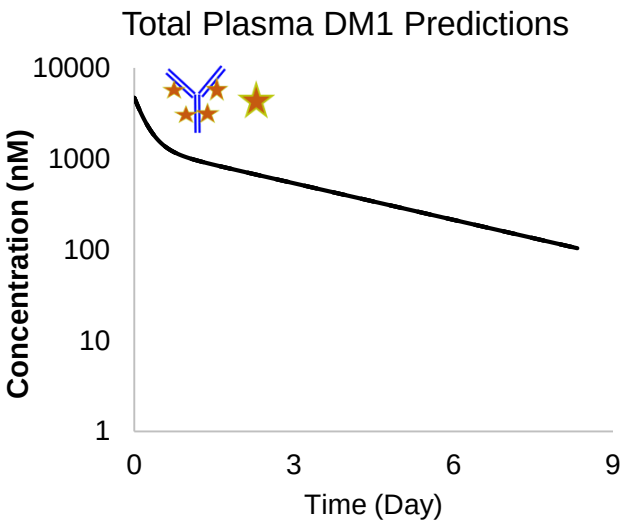
- Total DM1 Catabolites
- Unconjugated DM1

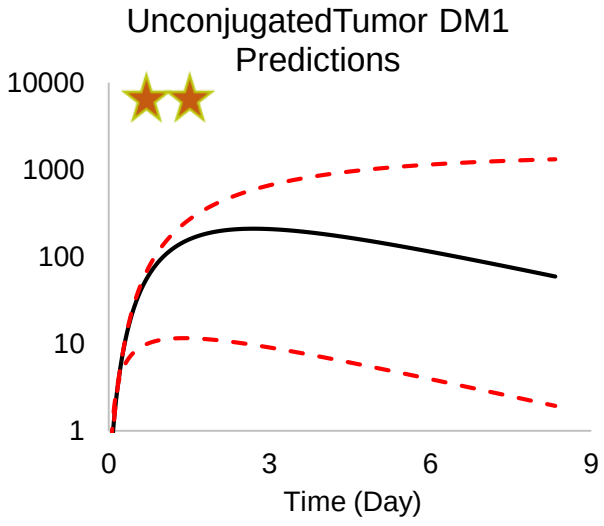
Sampling time= up to 7 Days

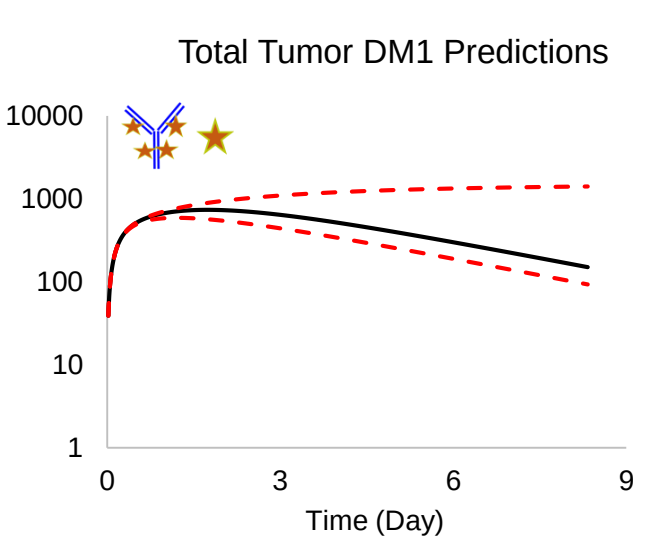
In Vivo Tumor Distribution Model

A Priori predict plasma and tumor exposures of different analytes of ADC.

Step 2



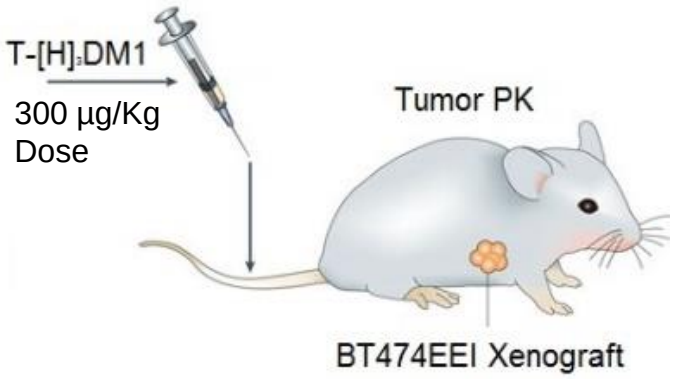




Monte-Carlo simulations were performed with ***IIV*** of **17.4 % on K_{diff} parameter.**

Erickson HK et al, ***Mol Cancer Ther.*** (2012)

Validation of our Predictions !



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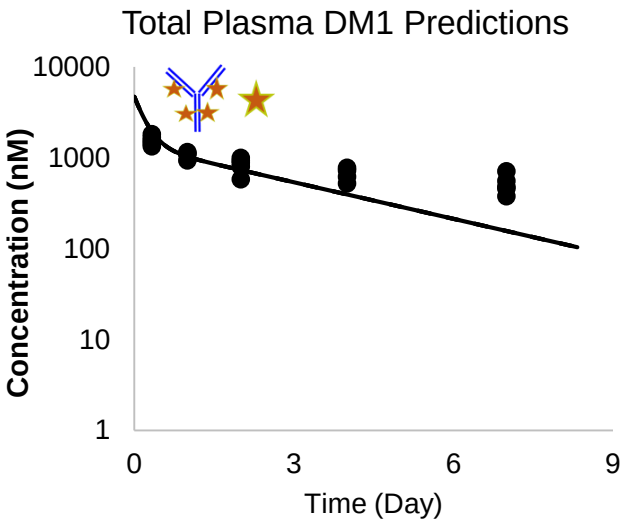
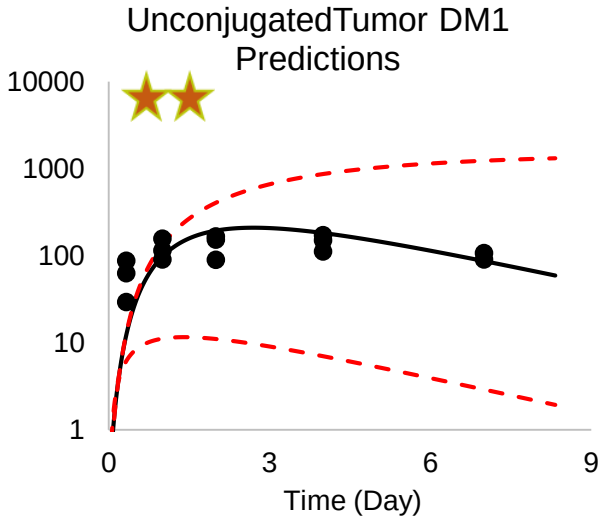
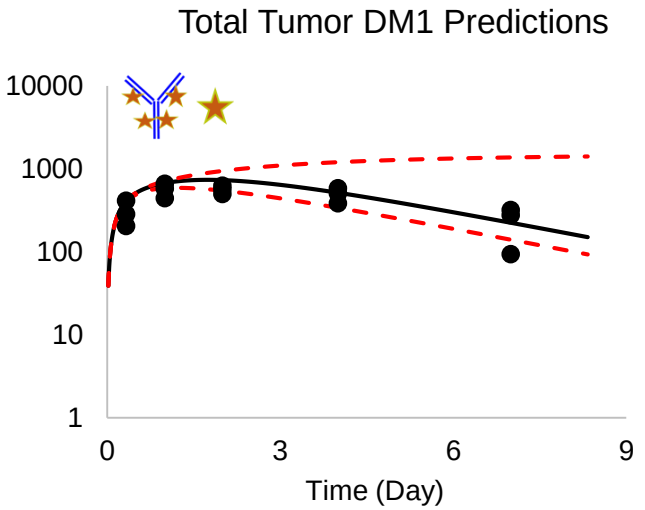
A Priori predict plasma and tumor exposures of different analytes of ADC.

Step 2

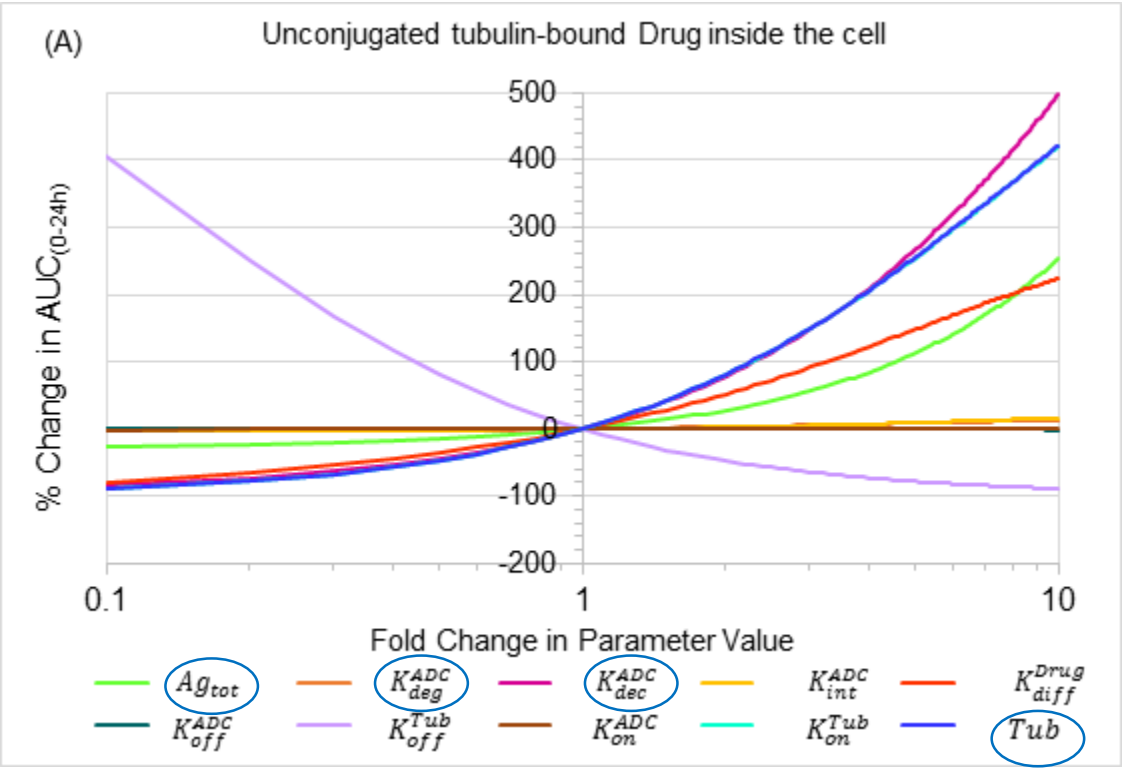


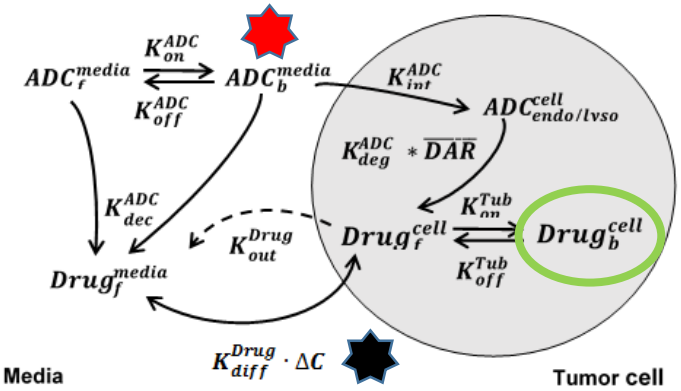


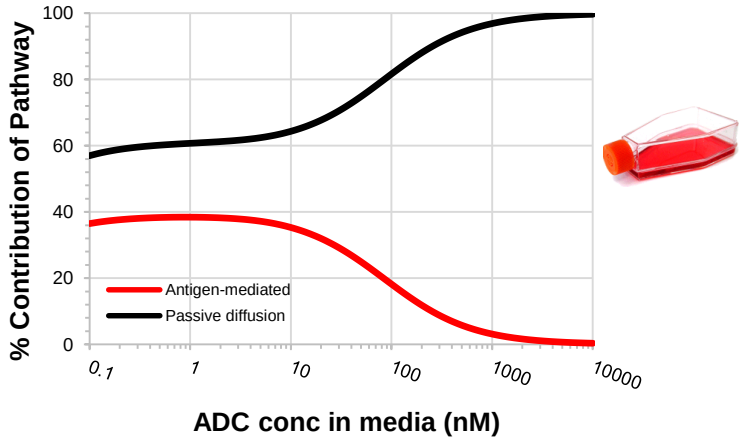


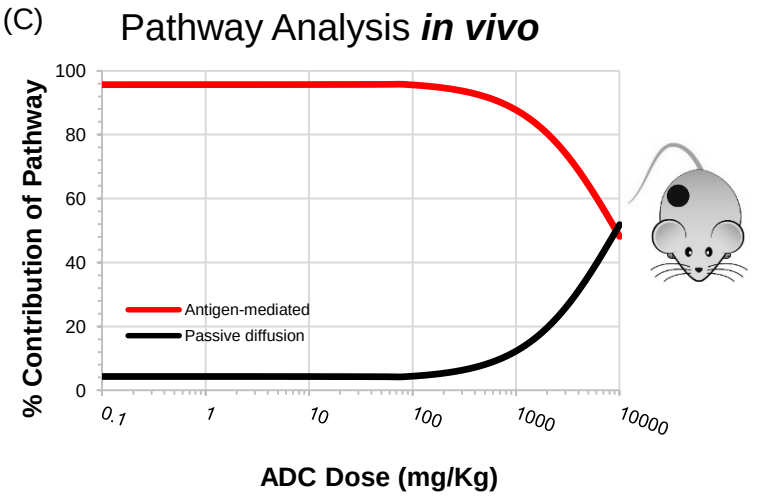
Monte-Carlo simulations were performed with ***IIV*** of **17.4 % on K_{diff} parameter.**

Pathway and Sensitivity Analysis







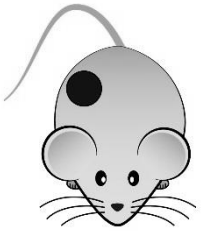


Integrated Tumor PK-PD model for T-DM1

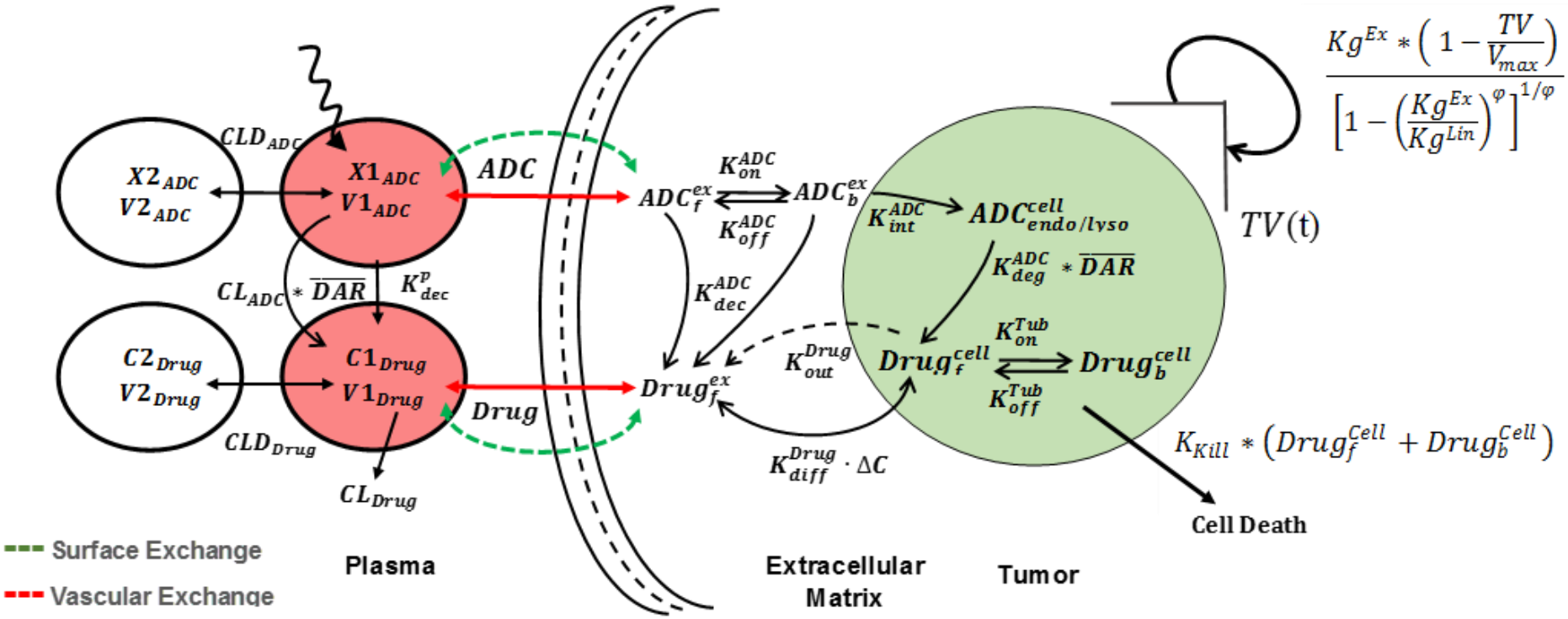
Use the Total DM1 Catabolite concentrations in the tumor to characterize the Tumor Growth Inhibition Data :

In Vivo Tumor Growth Inhibition (PKPD) Model

Use tumor concentrations to characterize TGI data and obtain PD parameters



Step 3



Meta-Analysis on Several HER2 + TGI Datasets

Preclinical Tumor Growth Inhibition (TGI) Studies of T-DM1

Mouse Models	Model Type	HER2 Status	Dosing Regimen	Reference
BT474EEI	Xenograft	3+	a) 0.3-15 mg/Kg Q3WX3 b) 3.3-18 mg/Kg Q1WX9 c) 6-18 mg/Kg Q2WX5	Jumbe et al (2010)
Fo5	Breast tissue-derived orthotropic and metastatic (BOM) model	3+	a) 1-30 mg/Kg Q3WX3 b) 3.3-10 mg/Kg Q1WX9	Jumbe et al (2010)
Calu-3	Xenograft	3+	a) 1-7 mg/Kg Single Dose b) 15 mg/Kg Q6DX3	a) Lewis Phillips et al (2013) b) Cretella et al (2014)
KPL4	Xenograft	3+	a) 0.3-3 mg/Kg Single Dose b) 15 mg/Kg Single Dose	a) Lewis Phillips et al (2013) b) Lambert et al (2014)
N87	Xenograft	3+	a) 1-10 mg/kg Single Dose b) 5 mg/Kg Single Dose	a) Haddish-Berhane et al (2013) b) Yamashita-Kashima et al (2013)
BT474	Xenograft	3+	0.2-5 mg/Kg Single Dose	Van der Lee et al (2015)
MAXF 1162	PDX	3+	1-10 mg/Kg Single Dose	Van der Lee et al (2015)
HBCx-34 HP	PDX	2+	3-30 mg/Kg Single Dose	Van der Lee et al (2015)
ST313 HP	PDX	2+	3-30 mg/Kg Single Dose	Van der Lee et al (2015)
HBCx-10	PDX	1+	3-30 mg/Kg Single Dose	Van der Lee et al (2015)
MAXF 449 TNBC	PDX	1+	3-30 mg/Kg Single Dose	Van der Lee et al (2015)

Assumptions for HER2 Receptor Numbers in different Mouse Models

HER2 Expression Level

Model	Type	HER2 FISH	HER2 IHC	ER/PR
BT474	CDX	+	3+	+
MAXF 1162	PDX	+	3+	-
ST313	PDX	-	2+	+
HBCx-34	PDX	-	2+	+
MAXF 449	PDX	-	1+	-
MAXF MX1	PDX	-	1+	-
HBCx-10	PDX	-	1+	-

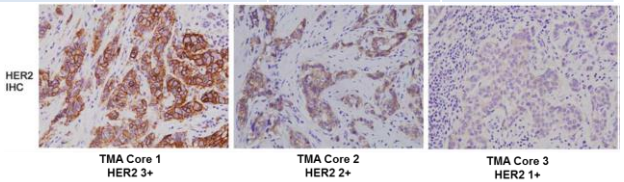
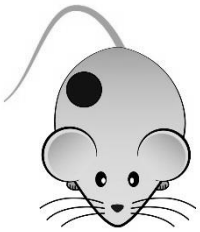
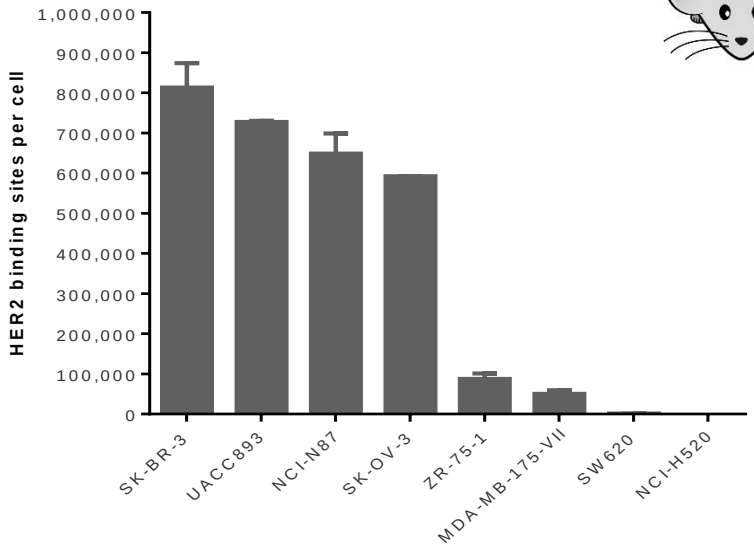


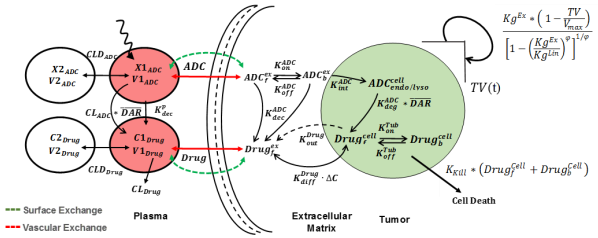
Figure S3.





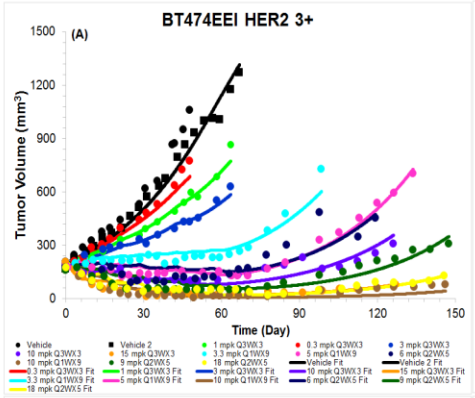
Assumptions:-

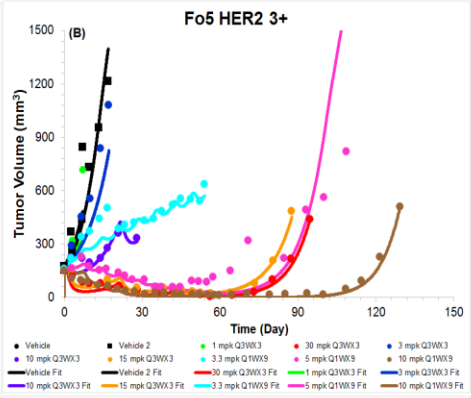
1. HER2 3+ ~ **1 million**, HER2 2+ ~ **0.5 million** and HER2 1+ ~**0.1 million Receptors**
2. Rest of all parameters were assumed the same

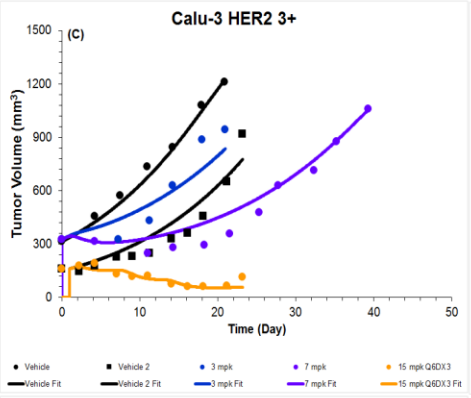


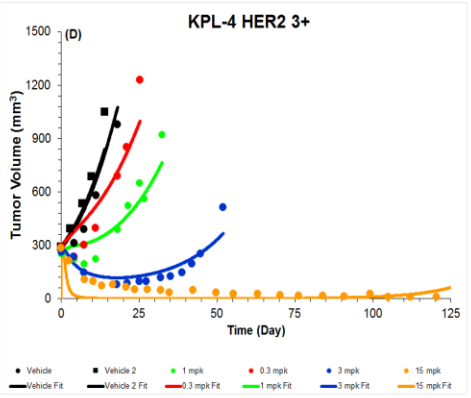
Van Der Lee et al, ***Mol Cancer Ther.*** (2015)

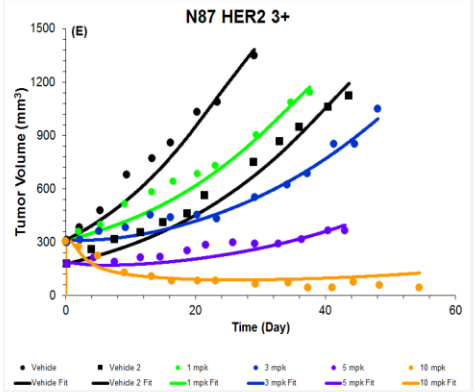
PK-PD Model Fittings to Different HER2 + TGI Datasets

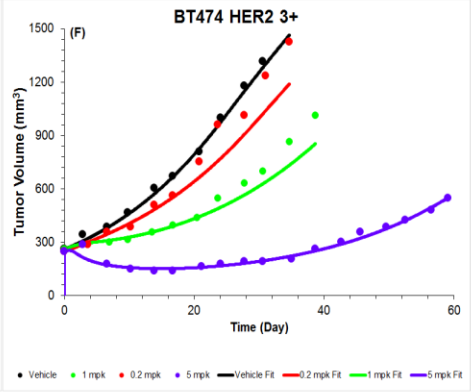


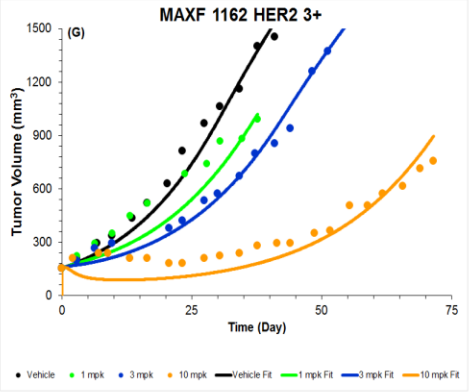


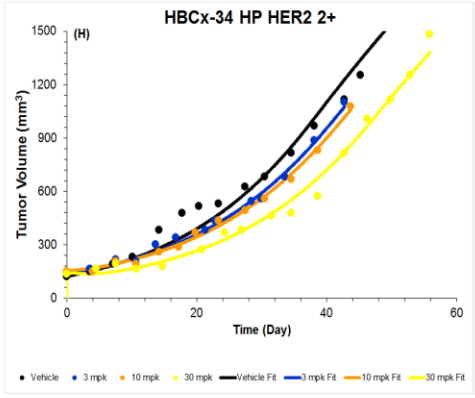


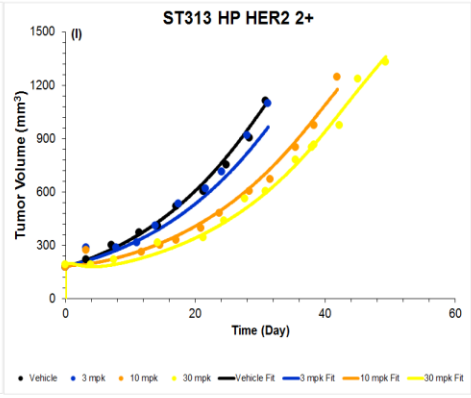


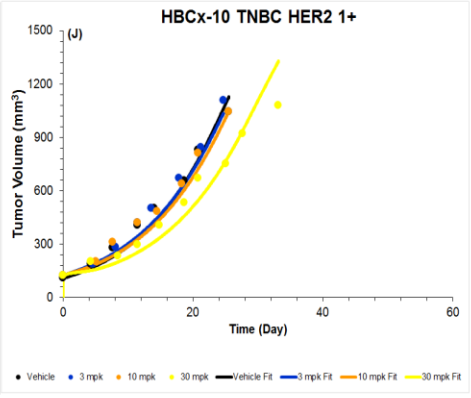


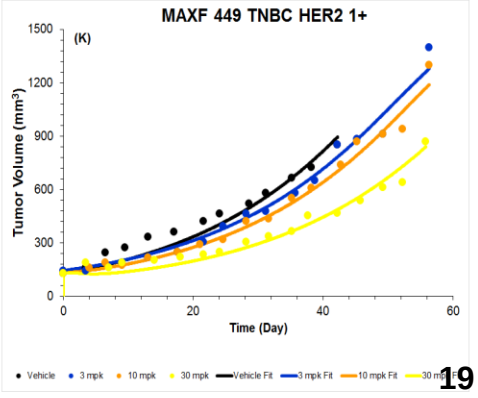




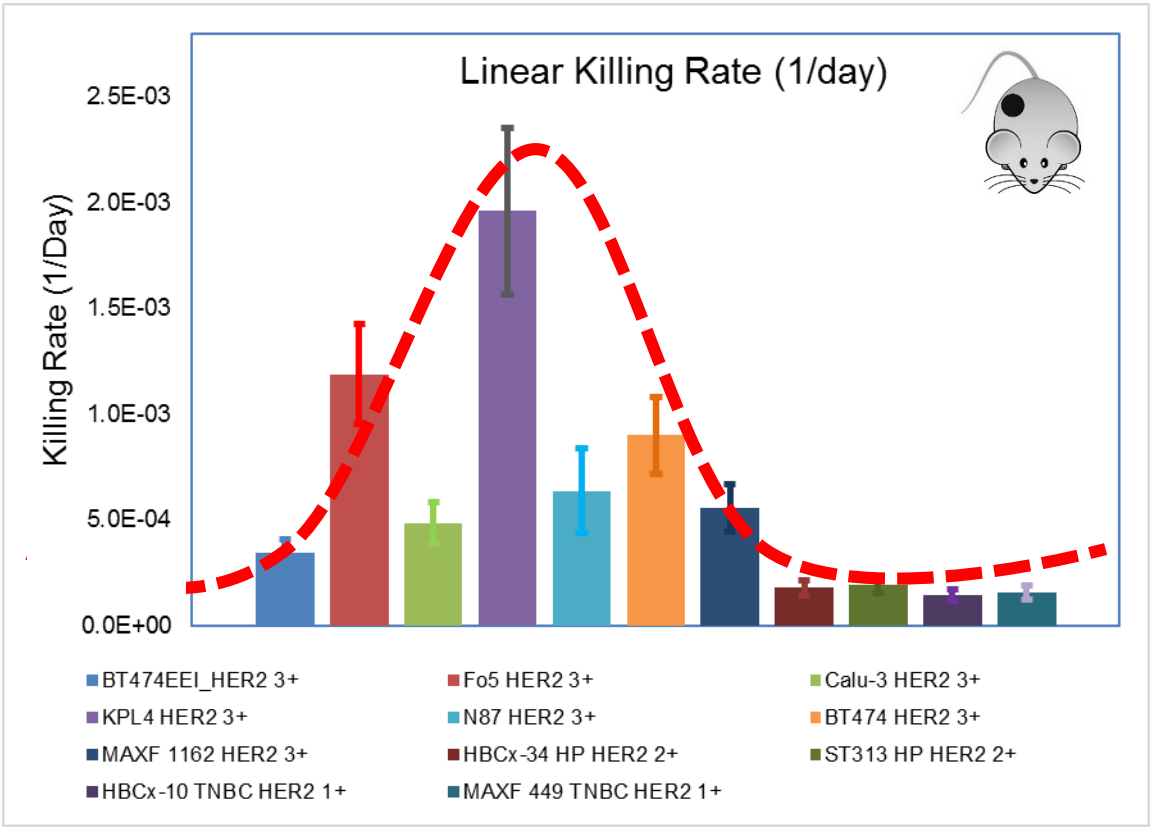


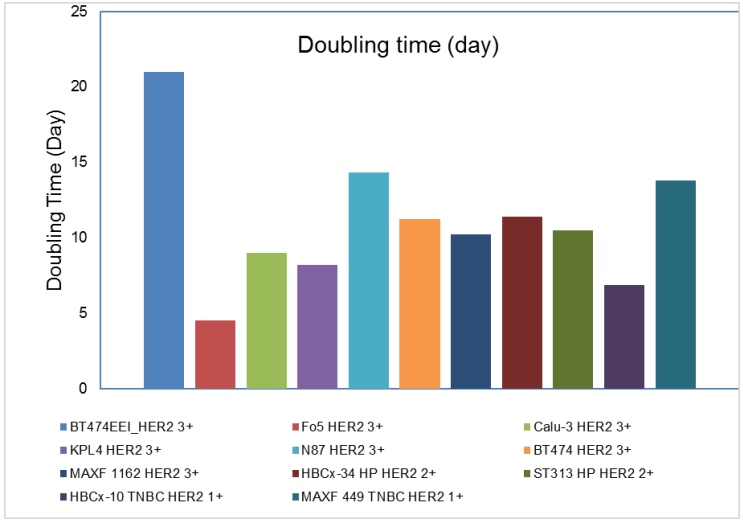






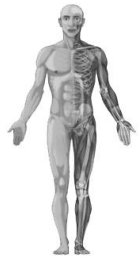
Distribution of Growth and Killing Parameters



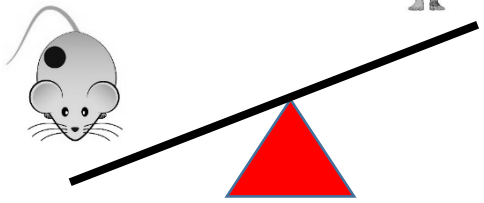


Tumor Growth

Slow



Fast

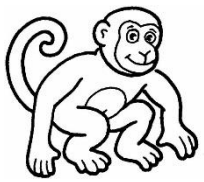


Resample from this Distribution to Predict Clinical Efficacy

Characterization of Plasma Pharmacokinetics in Monkeys

In Vivo Plasma PK Model in Monkey

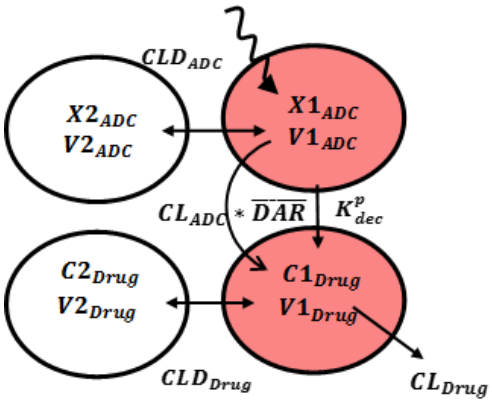
Characterize systemic concentrations of different analytes of ADCs in monkeys



Step 4

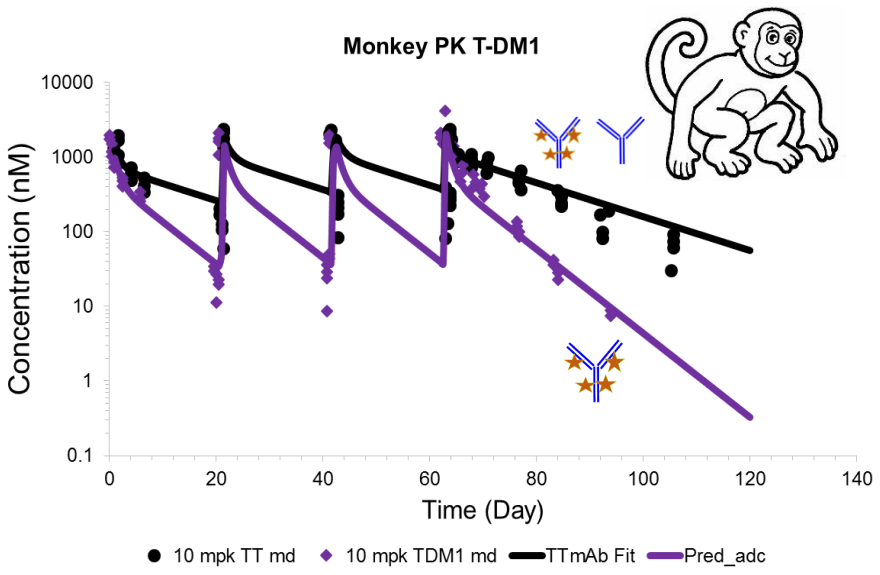
Pharmacokinetic Studies of T-DM1

Study	Species	Dosing Regimen	Reference
Preclinical (Toxicokinetic)	Cynomolgus Monkeys	10 mg/kg Q3WX4 (TTmab and T-DM1)	a) & b) Bender et al (2014)
		30 mg/Kg Single Dose (TTmAb and T-DM1)	c) Poon et al (2013)
		30 mg/Kg Q3WX4 (TTmab, T-DM1 and DM1)	

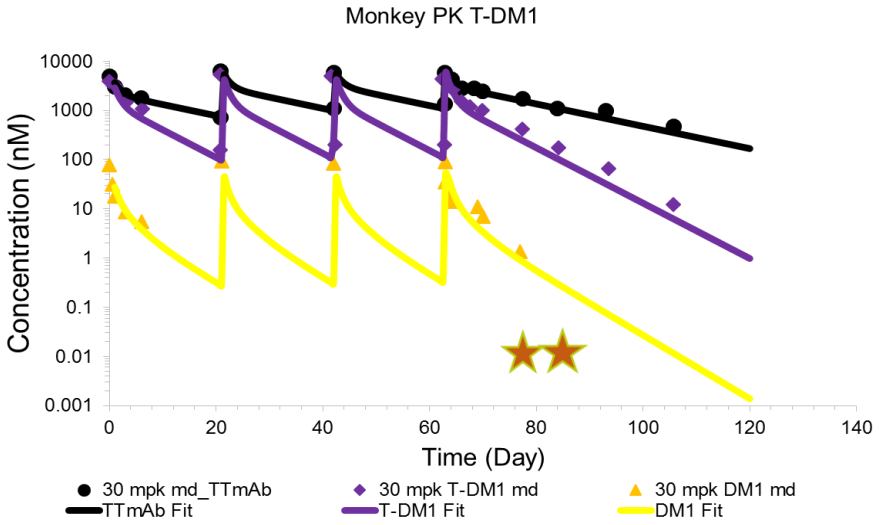


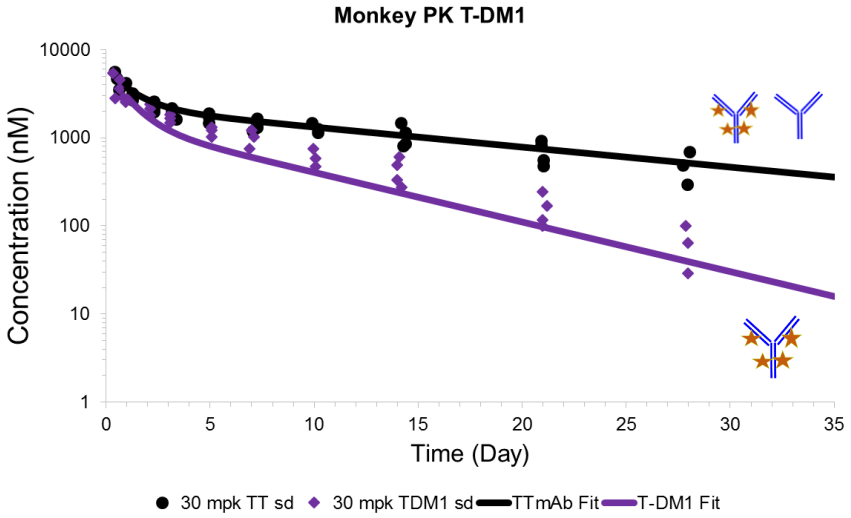
- Disposition of mAbs/ADCs is closer to Humans.
- Hence Non Human Primates (NHPs) are ideal species to predict human PK.

Plasma Pharmacokinetics Model Fits in Monkeys



Systemic PK Parameters	Parameters	Units	Reference
CL_{ADC}	0.0043 (8.2 %)	L/day/Kg	Estimated
CLD_{ADC}	0.014 (48 %)	L/day/Kg	Estimated
$V1_{ADC}$	0.034 (14 %)	L/Kg	Estimated
$V2_{ADC}$	0.04 (32 %)	L/Kg	Estimated
CL_{Drug}	2.92 (32%)	L/day/Kg	Estimated
CLD_{Drug}	1.0 (2.62%)	L/day/Kg	Estimated
$V1_{Drug}$	0.034	L/Kg	Fixed
$V2_{Drug}$	5.0 (7.9%)	L/Kg	Estimated
K_{dec}^{P}	0.241 (8.8%)	1/day	Estimated





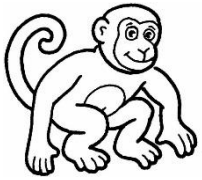
Allometric Scaling of Monkey PK parameters

$$CL^{human} = CL^{monkey} \times \left\{\frac{BW^{human}}{BW^{monkey}}\right\}^{e}$$

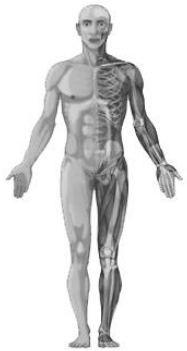
$$V^{human} = V^{monkey} \times \left\{\frac{BW^{human}}{BW^{monkey}}\right\}^{e}$$

Predict Clinical PK from monkey
Predict Clinical PD from mouse

Scale up monkey PK parameters to predict human PK. Use mouse PD parameters to predict Progression Free Survival



Step 5



For TTmAb and T-DM1:

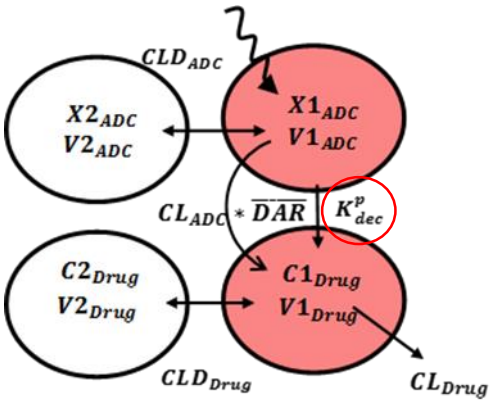
$e = 1$ *for* $CL, CLD, V1$ *and* $V2$

For DM1 Catabolites:

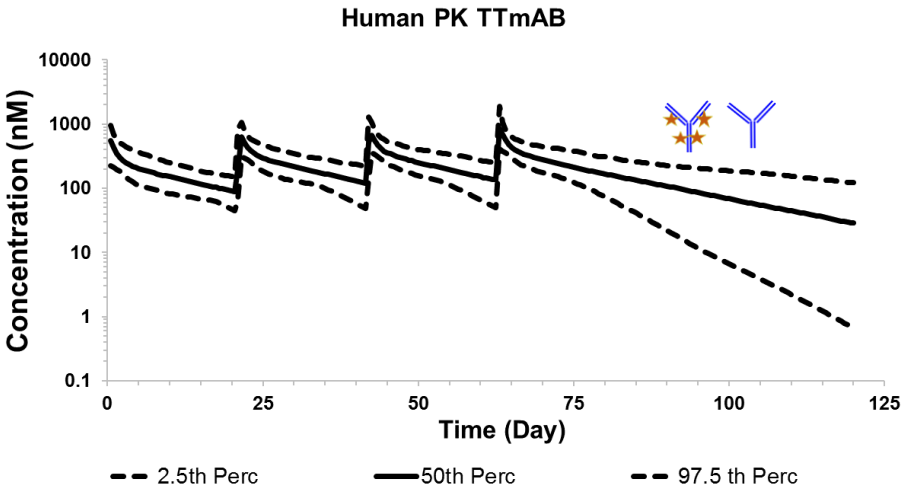
$e = 0.75$ *for* CL, CLD
1 *for* $V1$ *and* $V2$

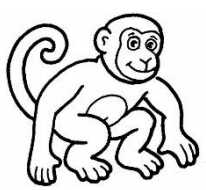
Pharmacokinetic Studies of T-DM1

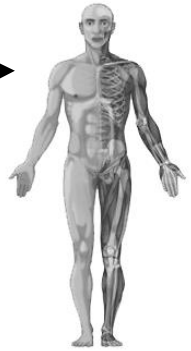
Study	Species	Dosing Regimen	Reference
Clinical (Phase-1&2)	HER2-positive Metastatic Breast Cancer Patients	3.6 mg/Kg Q3WX4 (TTmAb, T-DM1 and DM1)	a)Burris et al (2011)
		3.6 mg/Kg Single Dose (TTmAb, T-DM1 and DM1)	b)Agresta et al (2011)



A Priori Predicting Human Pharmacokinetics of T-DM1

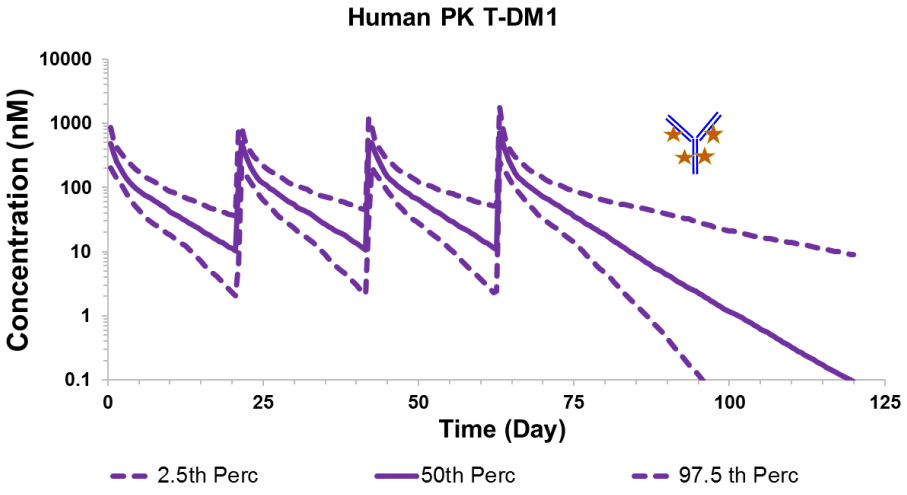


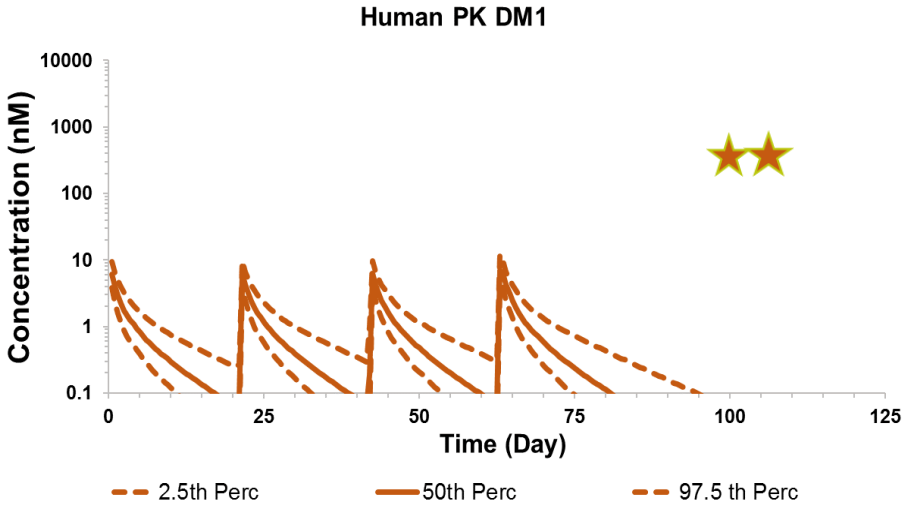




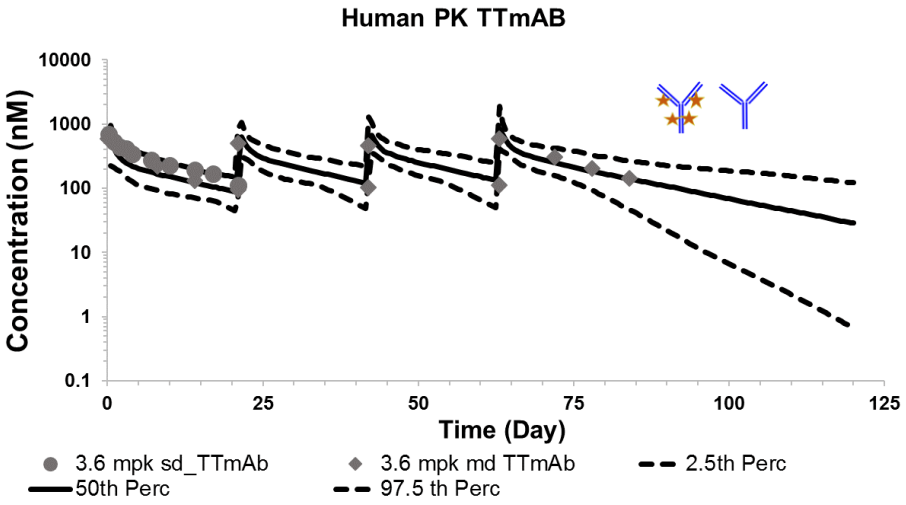
Predict Clinical PK from monkey
Predict Clinical PD from mouse

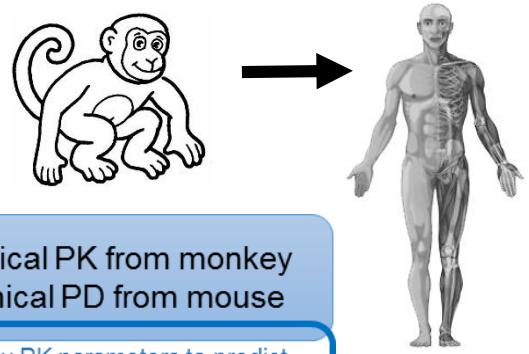
Scale up monkey PK parameters to predict human PK. Use mouse PD parameters to predict Progression Free Survival





Validation of Our Human PK Predictions for T-DM1





Predict Clinical PK from monkey
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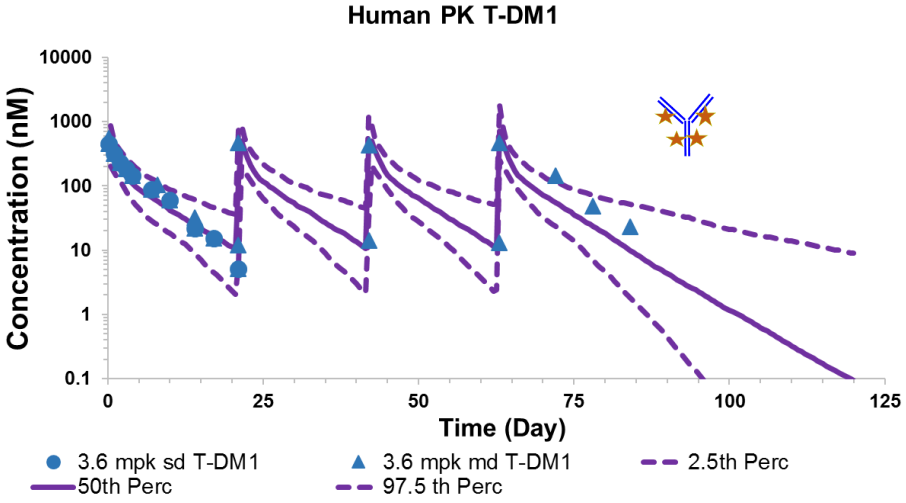
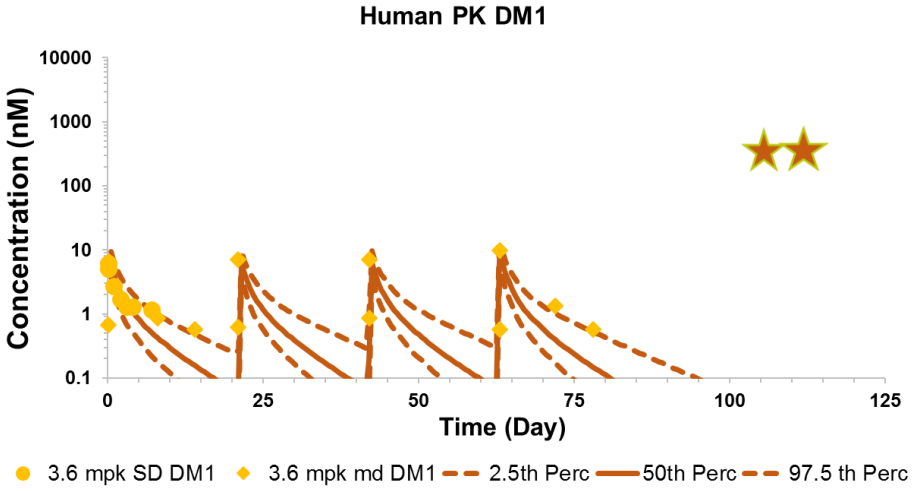
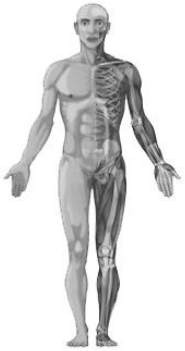
Scale up monkey PK parameters to predict human PK. Use mouse PD parameters to predict Progression Free Survival





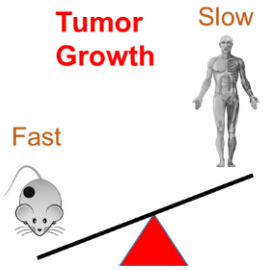
Preclinical to Clinical Translation:- *Clinical Growth Rate*



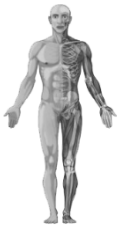
A list of clinically relevant tumor growth parameters for prediction of Progression Free Survival predictions.

Parameters	Definition	Value (CV %)	Units	Source
$TV(0)$	Initial tumor volume derived using the following expression $TV(0) = \frac{1}{2} * L * B^2$	Initial tumor lesion length = 19 mm (101%) Initial sum of Lengths and Breadth for tumor lesions = 35 mm (125%)	mm^3	Bernadou et al (2016)
DT^{Exp}	Doubling time associated with the exponential growth phase of the tumor	25 (200%)	Day	Pearlman et al (1976)
DT^{Lin}	Doubling time associated with the linear growth phase of the tumor	621 (85%)	Day	Weedon-Fekjær et al (2008)
φ	Switch between exponential growth and linear growth phases.	20	Unitless	Haddish-Berhane et al (2014)
V_{max}	Maximum achievable tumor volume	523.8	cm^3	Assumed based on maximum achievable tumor radius to be 5 cm

$$\frac{Kg^{Ex} * \left(1 - \frac{TV}{V_{max}}\right)}{\left[1 - \left(\frac{Kg^{Ex}}{Kg^{Lin}}\right)^{\varphi}\right]^{1/\varphi}}$$



Preclinical to Clinical Translation Strategy

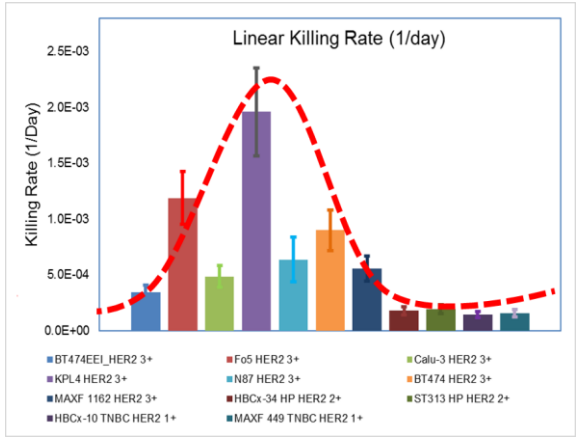


Clinical Growth

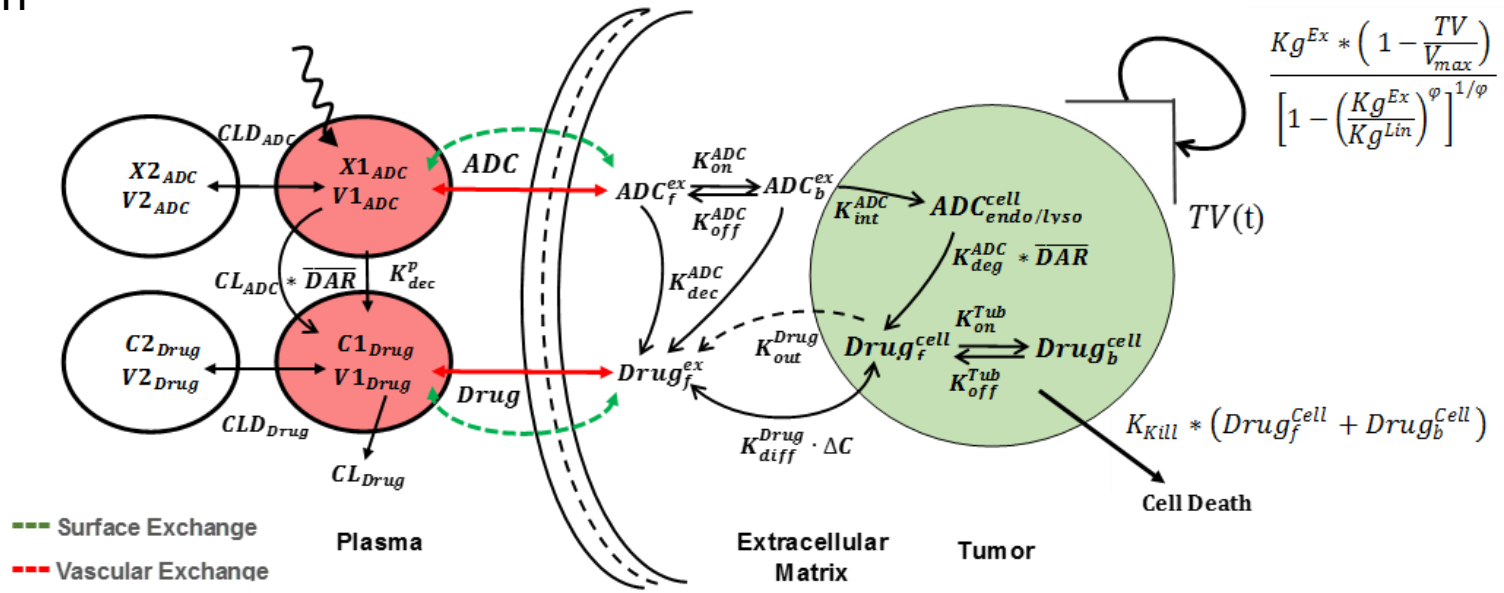
$$\frac{Kg^{Ex} * \left(1 - \frac{TV}{V_{max}}\right)}{\left[1 - \left(\frac{Kg^{Ex}}{Kg^{Lin}}\right)^{\varphi}\right]^{1/\varphi}}$$

Scaled Monkey PK

Mouse Efficacy



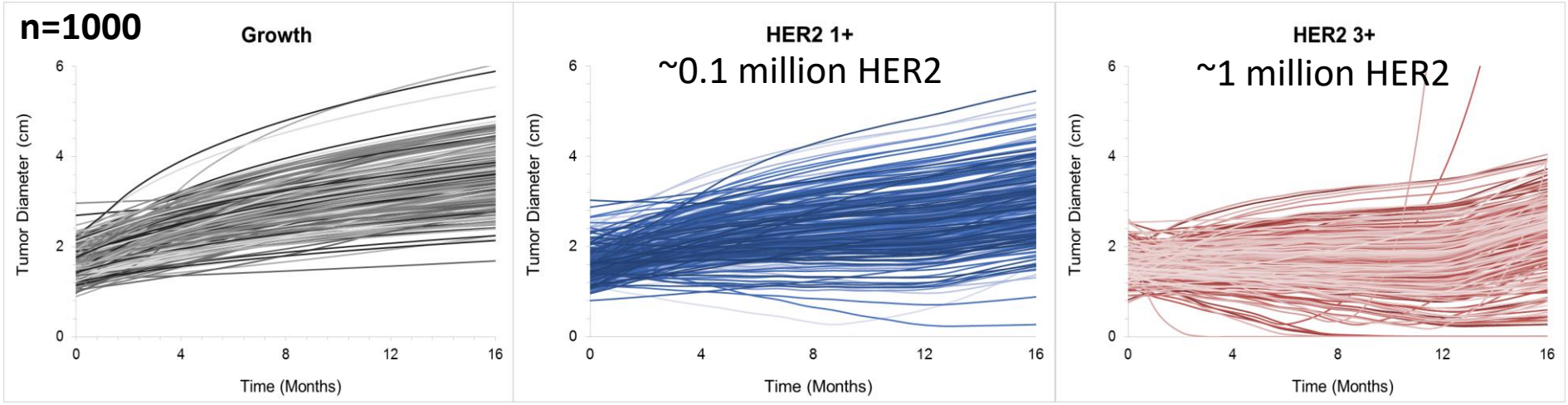
Cellular Disposition



Preclinical to Clinical Translation: *List of Clinical Trials*

Clinical Trials of T-DM1						
Study	**Patient Population**	**Phase**	**Number of Patients**	**Dosing Regimen**	**Treatment Arms**	**Reference**
TDM4450	First-Line HER2+ Metastatic Breast Cancer Patients	II	137	3.6 mg/Kg Q3W until Disease Progression	T-DM1 versus Trastuzumab+ docetaxel	Hurvitz et al
TDM4258g	HER2+ Metastatic Breast Cancer Patients with prior treatment with Trastuzumab	II	112	3.6 mg/Kg Q3W up to 12 months	Trastuzumab followed by T-DM1	Burris III et al Krop et al
EMILIA	HER2+ Metastatic Breast Cancer Patients with prior treatment with Trastuzumab and Taxane	III	991	3.6 mg/Kg Q3W until Disease Progression	T-DM1 versus capecitabine + lapatinib	Verma et al

Preclinical to Clinical Translation: *Clinical Trial Simulations*



- *T-DM1 administered at a Dosing regimen of Q3W for 1 Year (3.6 mg/Kg Dose)*

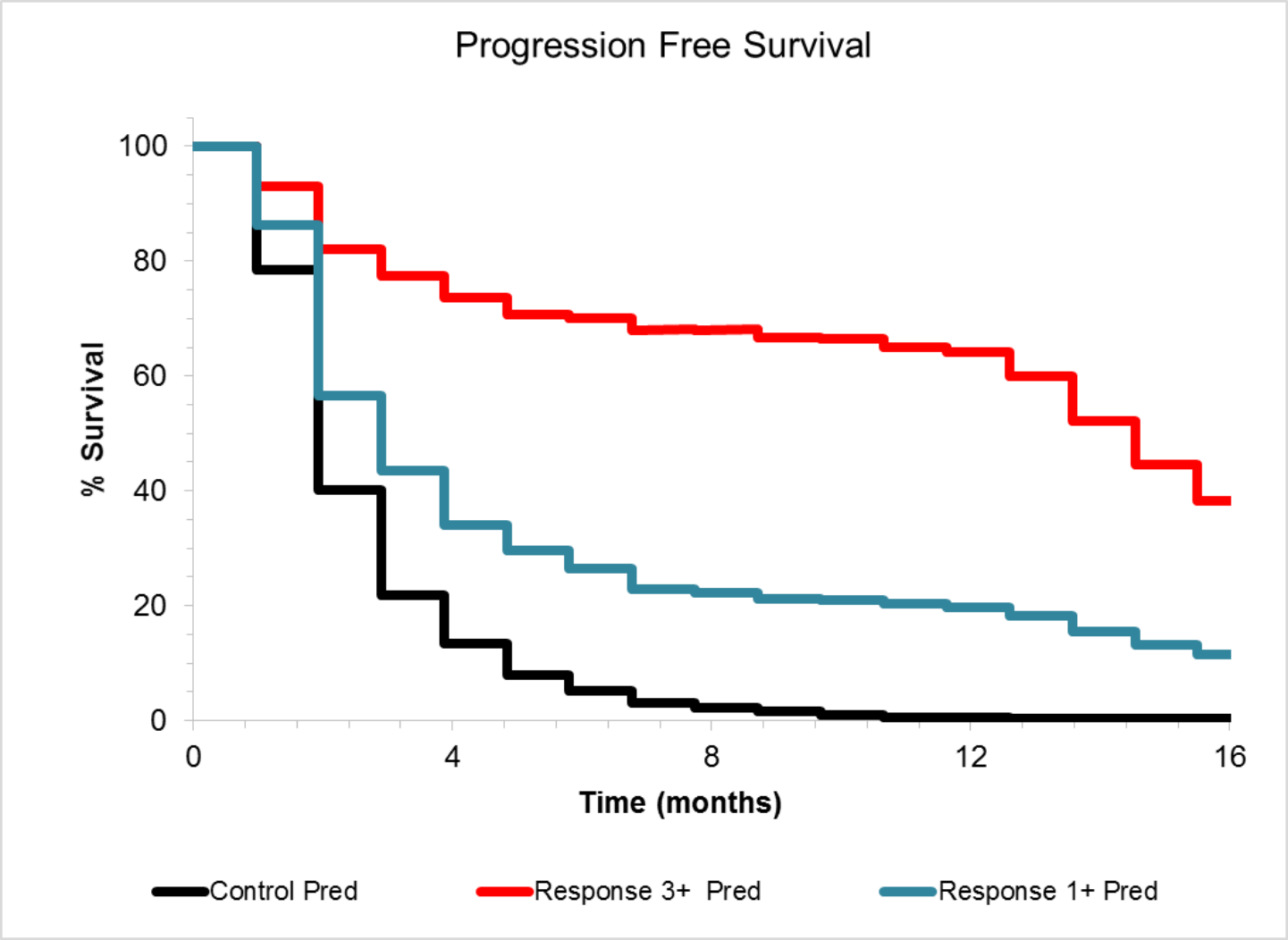
Calculation of PFS

Response Evaluation Criteria In Solid Tumors :- RECIST

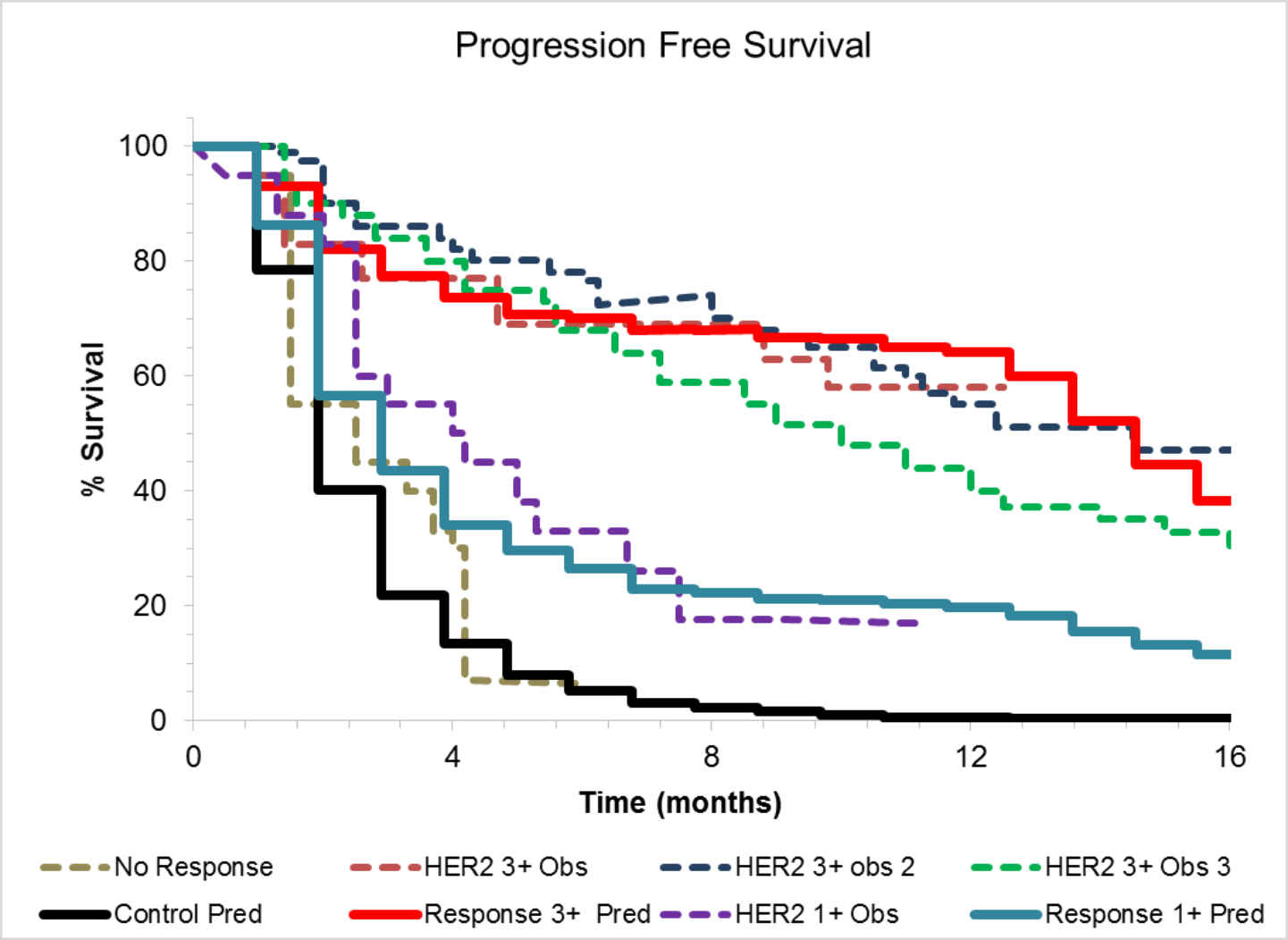
1) **Complete Response (CR):** Undetectable**<5-10 mm.** 2) **Partial Response (PR):** At least a **30% decrease** in the sum of diameters of target lesions. 3) **Progressive Disease (PD):** At least a **20% increase** in the sum of diameters of target lesions. 4) **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, **(<20% increase and <30% decrease)**.

Eisenhauer et al, ***E J C*** (2009)

Our Predicted Progression-Free Survival Rates



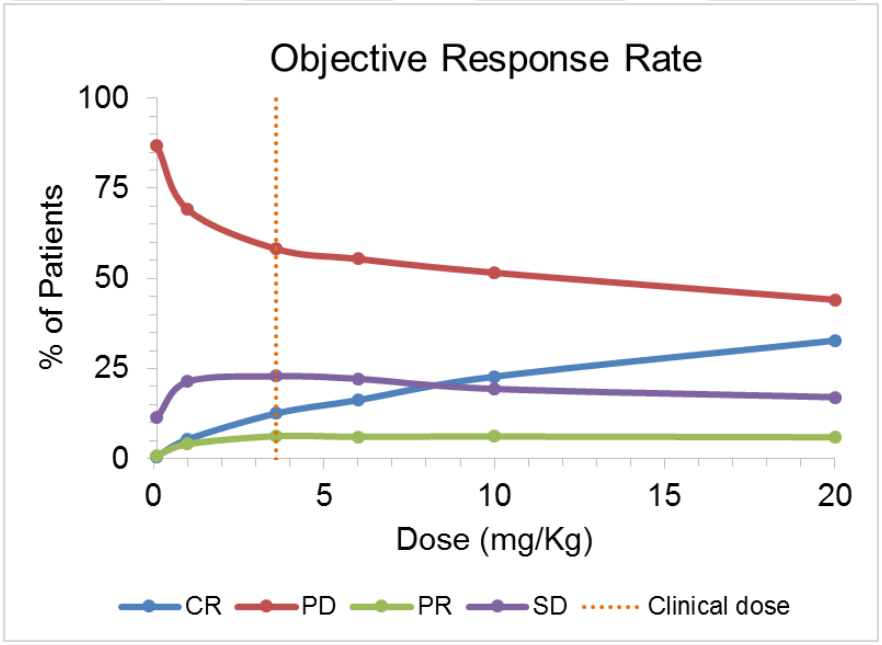
Our Predicted Progression-Free Survival Rates



- ***Control:-*** HER2 Normal Patients non responsive to T-DM1 and Trastuzumab
- ***HER2 1+:-*** Below Median HER2 Expressing Patients
- ***HER2 3+:-*** HER2 Over-expressing Patients

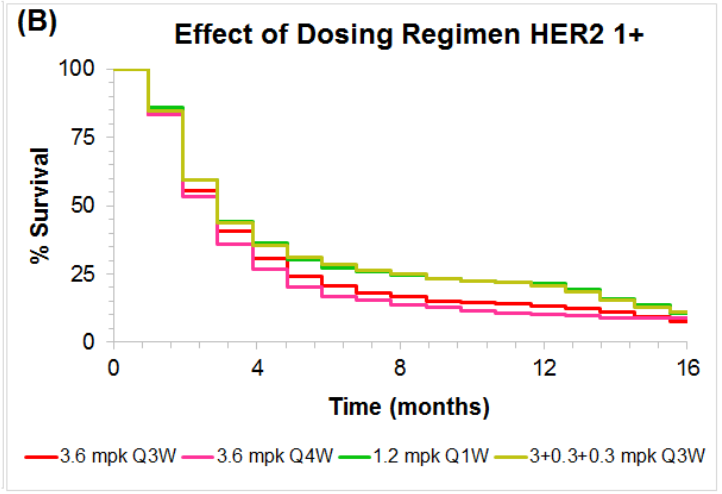
Simulating Objective Response Rates (ORRs) and Alternative Dosing Regimens

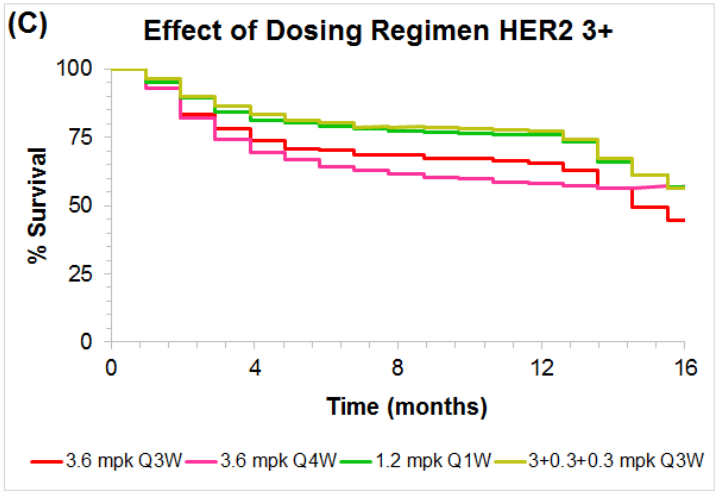
Learn → Predict → Confirm → Inform



ORRs Calculated at the end of 1 Year Therapy

- Not a Significant Improvement in Efficacy with a slight increase in Dose





- Fractionated Dosing Regimen e.g. Front Loading can be more beneficial

Overall Summary

- **A mechanistic Cellular Disposition Model** was developed with **more intracellular details** (i.e. ADC degradation, passive diffusion and tubulin binding) to characterize **Cellular PK of T-DM1.**
- When Combined with **Tumor Disposition Model**, we were able to ***a priori*** predict tumor pharmacokinetics of T-DM1
- Later the model was ***translated to clinic*** where mouse efficacy parameters, clinically observed growth parameters and scaled up human PK from NHPs was able to predict clinical efficacy in ***different sub-populations of HER2 + patients***
- Our multi-scale PK-PD Model has been validated on multiple ADC molecules (n=3) and can help ***inform*** about the **Dose-ORR relationships** as well as **alternative dosing regimens.**
- Presented Translation Strategy can serve as a **cornerstone for developing future ADCs.**

Acknowledgements

Center for Protein Therapeutics

Genentech IN BUSINESS FOR LIFE · Roche · Lilly · janssen · AMGEN · abbvie · ucb · SANOFI

- Roche
- NIGMS (NIH)

1R01GM114179-01

NATIONAL INSTITUTES OF HEALTH · NIGMS

Acknowledgements

Thanks to Our Collaborators !

1. Alison M. Betts (Pfizer®)
2. Lindsay E. King (Pfizer®)
3. Chethana Kulkarni (N E Biolabs®)
4. Professor K. Dane Wittrup (MIT)
5. Katie F. Maass (Genentech®)

Thanks to Krzyzanski Lab, UB

Buffalo Pharmaceutics

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