ADCs:
Pharmacokinetics & dosing considerations

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Disclosures 2022-2023

Research:

- Institut Roche
- Merck Serono
- Astra Zeneca
- Pierre Fabre
- BMS

Fees:

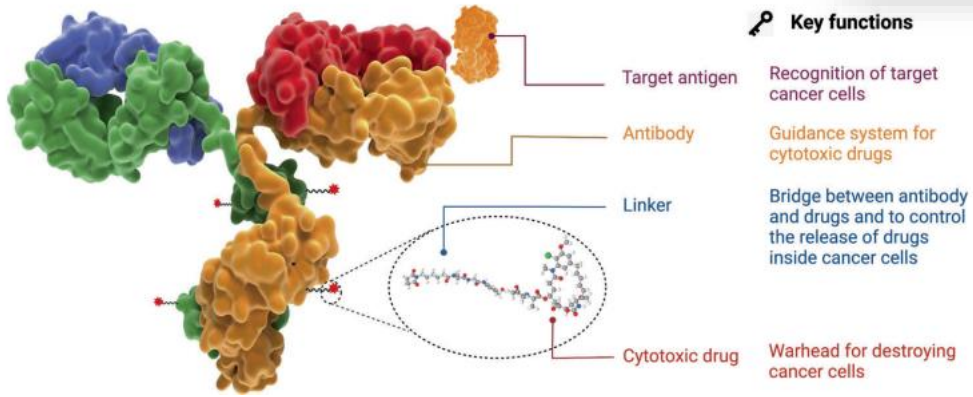
- Pierre Fabre
- Esai
- Daiichi Sankyo
- Pfizer
- Samsung Bioepis
- Pfizer
- Gilead
- Accord Healthcare
- GSK

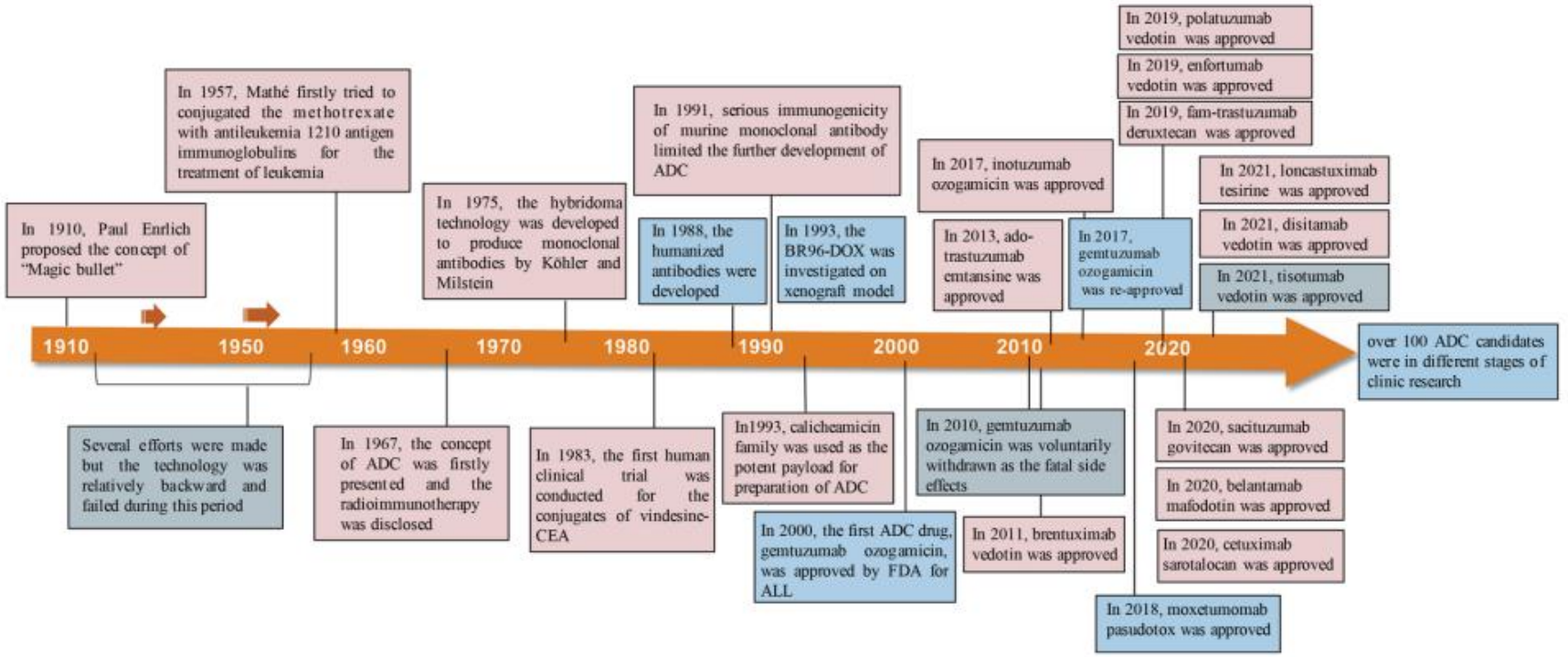
ADCs at a glance

REVIEW ARTICLE OPEN

Antibody drug conjugate: the "biological missile" for targeted cancer therapy

Zhiwen Fu[1,2], Shijun Li[1,2], Sifei Han[3,4], Chen Shi[1,2]✉ and Yu Zhang[1,2]✉





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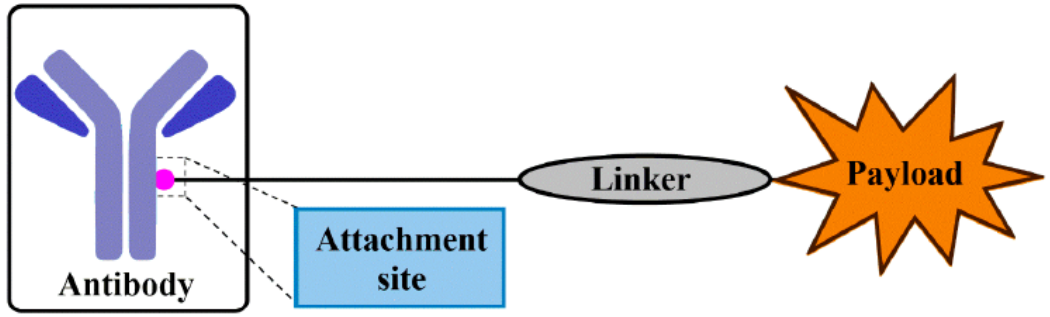
ADCs at a glance

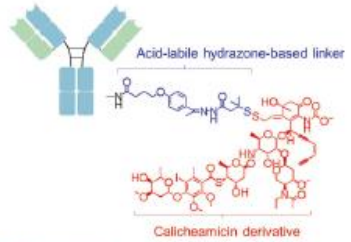


All ADC's are made of :

- ✓ A **delivery system** (mAb)
- ✓ A **Linker** (+ attachement site)
- ✓ A **highly cytotoxic drug** (« Payload » or « warhead »)

- ✓ Characterized by a **DAR** (Drug/Antibody Ratio)

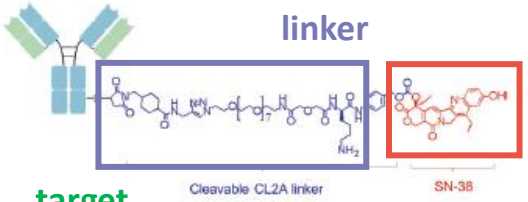
ADCs at a glance



Anti-CD33 Gemtuzumab ozogamicin (DAR~1.5)
Anti-CD22 Inotuzumab ozogamicin (DAR~6)

linker

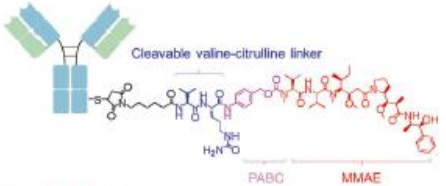
payload



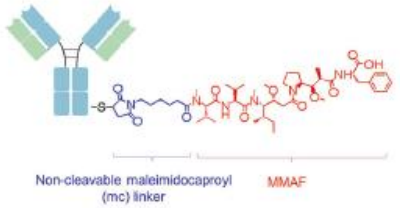
target

Anti-Trop2 Sacituzumab govitecan (DAR~7.6)

DAR

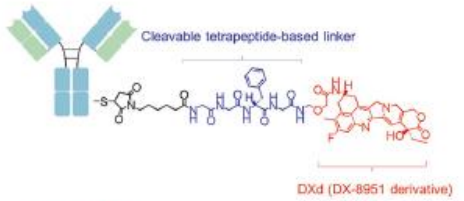


Anti-CD30 Brentuximab vedotin (DAR~4)
Anti-CD79b Polatuzumab vedotin-piiq (DAR~4)
Anti-Nectin-4 Enfortumab vedotin (DAR~4)



Anti-BCMA Belantamab mafodotin (DAR~4)

Anti-HER2 Ado-Trastuzumab emtansine (DAR~3.5)



Anti-HER2 Trastuzumab deruxtecan (DAR~8)

Anti-CD19 Loncastuximab tesirine-lpyl (DAR~2.3)

ADCs at a glance

Target Antigen

- ✓ Expression on tumor/target tissue *(i.e. tumor specific)*
- ✓ Expression on healthy proliferating tissue
- ✓ Homogenous or heterogeneous expression
- ✓ Internalization occurs upon receptor interaction

Antibody Selection

- ✓ Antibody format *(e.g. full, Fab fragment, etc.)*
- ✓ Higher specificity and affinity
- ✓ Low immunogenicity *(i.e. human vs. humanized vs. chimeric)*
- ✓ Fc-gamma receptor & FcRn binding

Linker

- ✓ Mechanism of drug release
- ✓ Stability in systemic circulation
- ✓ Cleavable versus non-cleavable within tumor cell
- ✓ Site of conjugation (to cytotoxic drug & antibody)

Cytotoxic Payload

- ✓ Capable of attaching to linker technology
- ✓ On/off target cytotoxicity (i.e. potency)
- ✓ Bystander effect
- ✓ PK/PD of free drug *(e.g. stable at physiological pH, metabolism)*
- ✓ Optimal DAR

It's all about chosing:

1. The right Target Antigen (tumor specific)
2. The right mAb (PK features, antiproliferative activity)
3. The right Linker (tumor specific release)
4. The right Payload (super-toxic)

ADCs at a glance

Name	Year(s) Approved	Indication	Target	Payload (Mechanism)
Gemtuzumab ozogamicin	2000 and 2017	Acute myeloid leukemia	CD33	Calicheamicin (DNA cleavage)
Brentuximab vedotin	2011	Hodgkin lymphoma, anaplastic large cell lymphoma	CD30	Auristatin (microtubule inhibitor)
Ado-trastuzumab emtansine	2013	HER2-positive breast cancer (after prior anti-HER2 therapy)	HER2	Maytansine (microtubule inhibitor)
Inotuzumab ozogamicin	2017	B-cell precursor acute lymphoblastic leukemia	CD22	Calicheamicin (DNA cleavage)
Moxetumomab pasudotox-tdfk	2018	Hairy cell leukemia	CD22	Pseudomonas exotoxin A (induction of apoptosis)
Polatuzumab vedotin-piiq	2019	Diffuse large B-cell lymphoma	CD79b	Auristatin (microtubule inhibitor)
Enfortumab vedotin-ejfv	2019	Urothelial cancer	Nectin-4	Auristatin (microtubule inhibitor)
Fam-trastuzumab deruxtecan-nxki	2019	HER2-positive breast cancer (after two or more lines of anti-HER2 therapy)	HER2	Deruxtecan (topoisomerase inhibitor)
Sacituzumab govitecan-hziy	2020	Triple-negative breast cancer	Trop-2	SN-38 (topoisomerase I inhibitor)

Abbreviation: FDA, U.S. Food and Drug Administration.

- Tumor-specific
- Little or no-expression in healthy cells
- Avoid off-site effects

- « super-toxic » (IC50 in pM)
- Diffusible & Stable
- Bystander Effect
- Off-target Effect?
- Off-site Effect ?

ADCs at a glance

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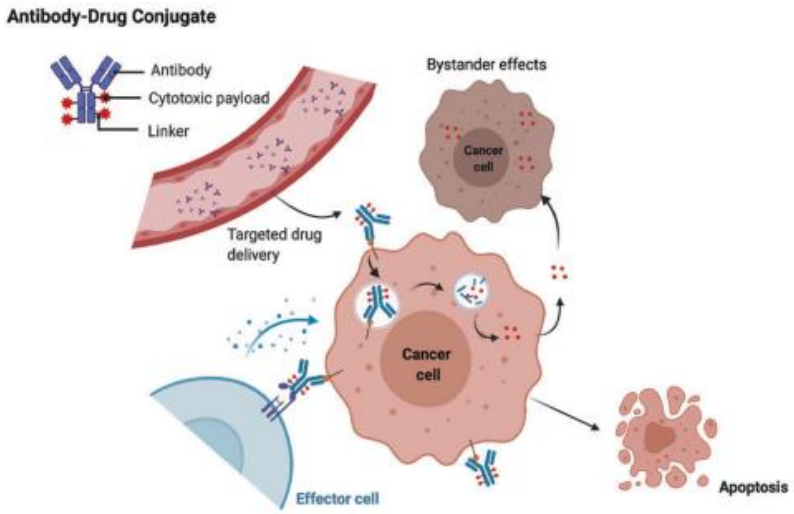
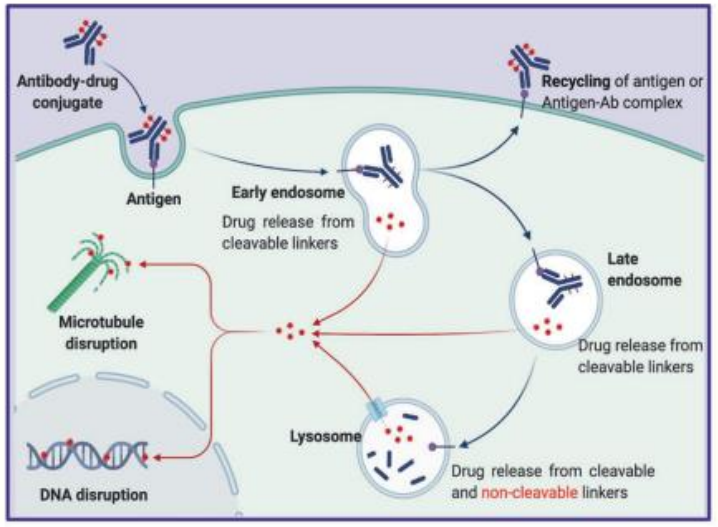
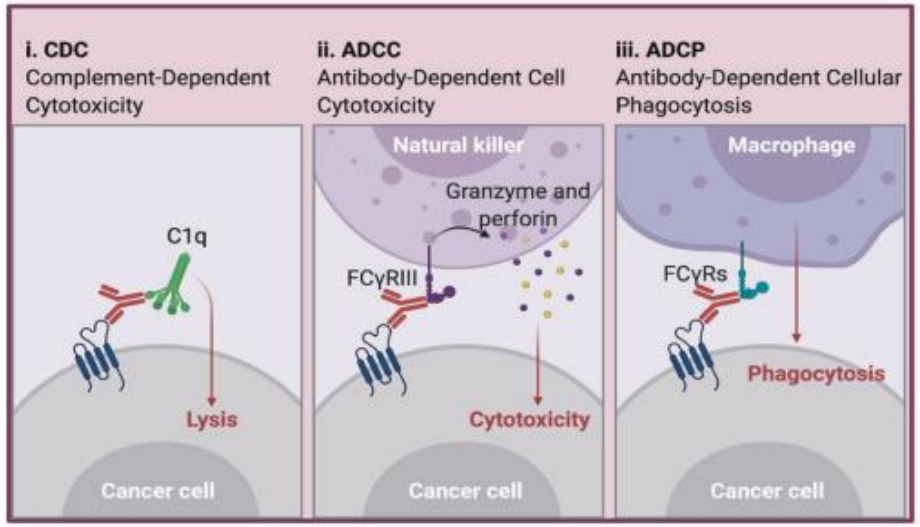


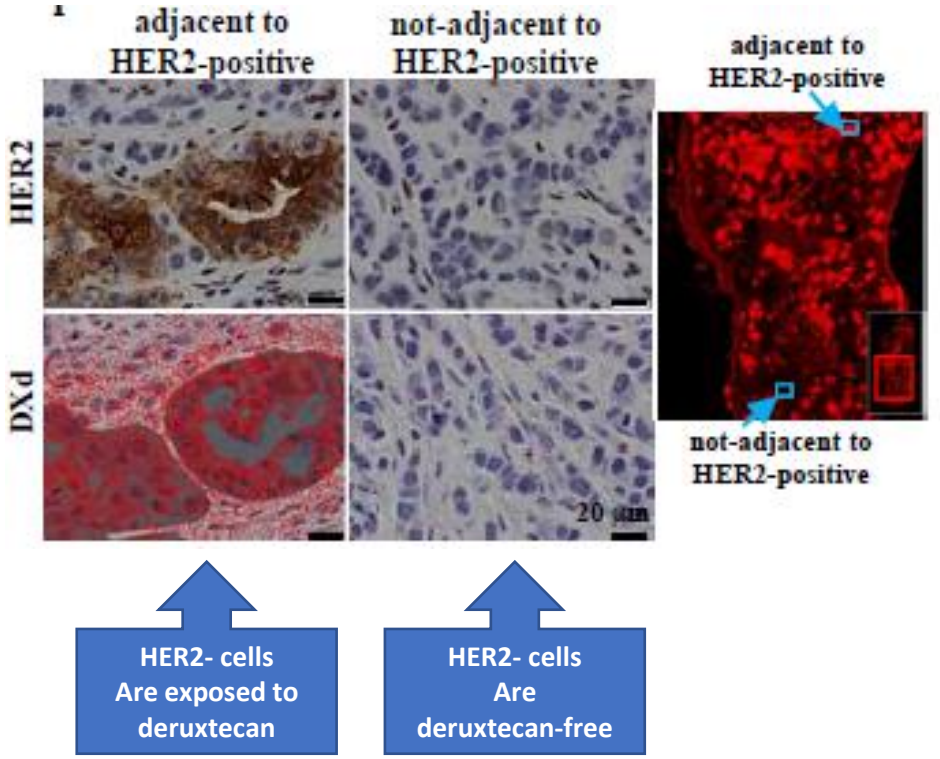


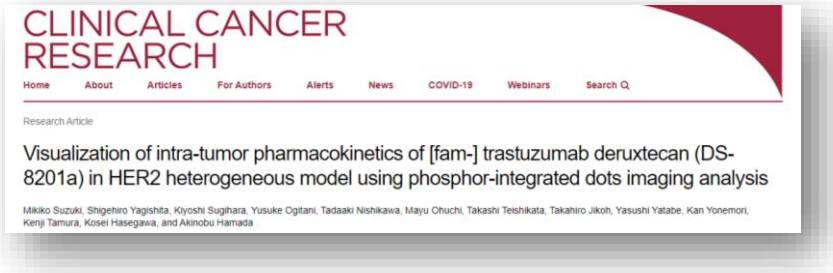


Log-In, Internalization, Payload Relase
(+ ADDCC/ADCP, + bystander effect)

ADCs at a glance

✓ **Bystander effect: ~~myth or~~ reality~~?~~**

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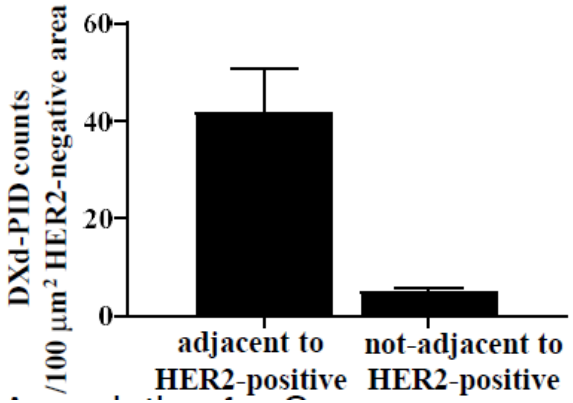
Research Article

Visualization of intra-tumor pharmacokinetics of [fam-] trastuzumab deruxtecan (DS-8201a) in HER2 heterogeneous model using phosphor-integrated dots imaging analysis

Mikiko Suzuki, Shigehiro Yagishita, Kiyoshi Sugihara, Yusuke Ogitani, Tadaaki Nishikawa, Mayu Ohuchi, Takashi Teishikata, Takahiro Jikoh, Yasushi Yatabe, Kan Yonemori, Kenji Tamura, Kosei Hasegawa, and Akinobu Hamada



HER2- cells Are exposed to deruxtecan

ADCs at a glance

✓ **Trastuzumab Deruxtecan…. works in HER2-low tumors too!**

BUZZ BUZZ OF THE YEAR

ASCO Daily News

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2022 ASCO ANNUAL MEETING

DESTINY-Breast04 Establishes Trastuzumab Deruxtecan As a New Standard of Care for HER2-Low Metastatic Breast Cancer

June 6, 2022

Science & Tech

ONCOLOGY >

The medication that is extending survival for patients with advanced cancer

An annual meeting of oncologists has unveiled new combinations of known drugs that are achieving remarkable results in prolonging life expectancy

The New York Times

Breast Cancer Drug Trial Results in 'Unheard-Of' Survival

For some patients with metastatic tumors not significantly affected by other forms of chemotherapy, the treatment halted their cancer's growth.

Perspective > Medscape Oncology > Miller on Oncology > ASCO 2022

COMMENTARY

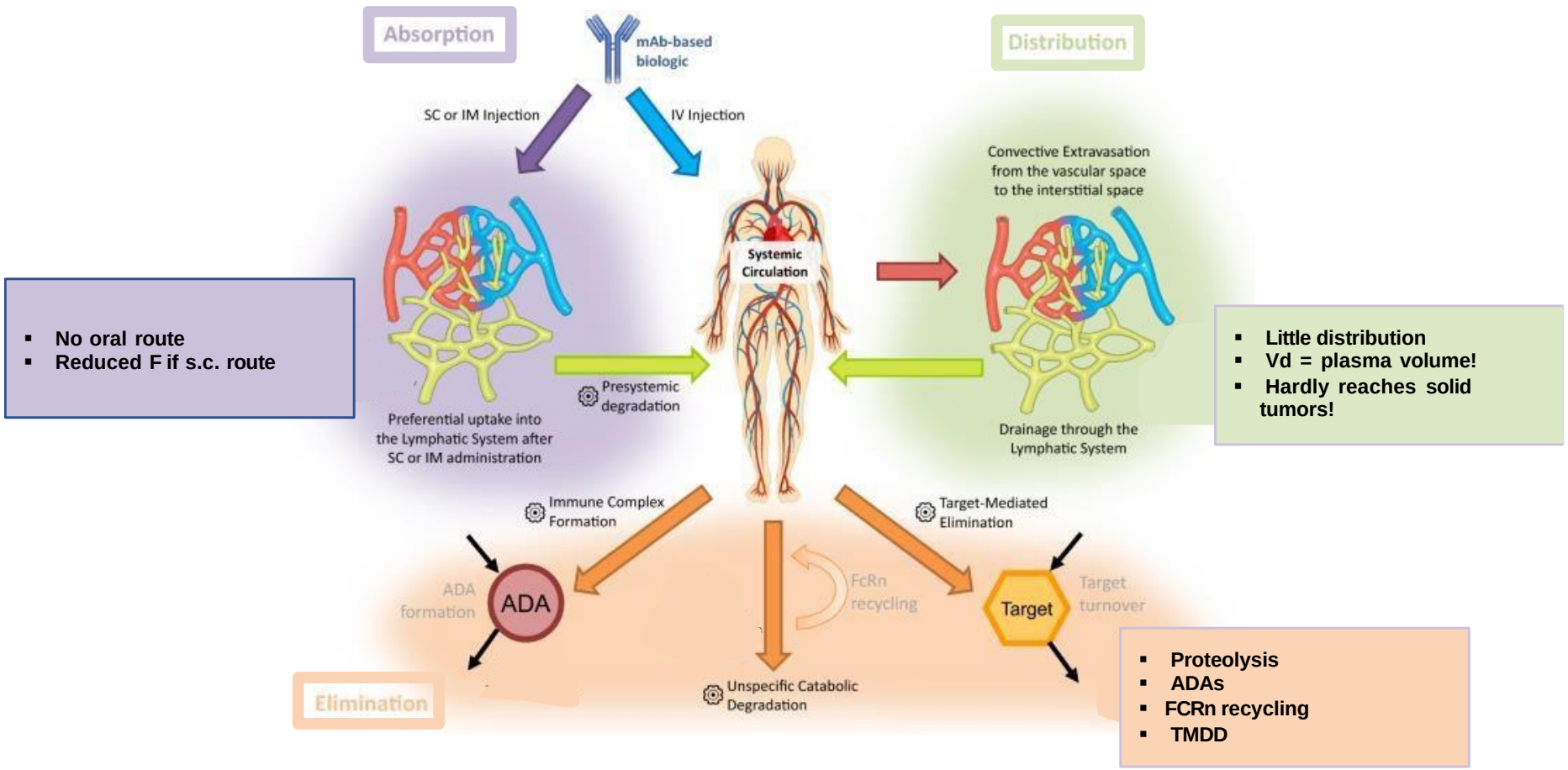
'It's an ADC World': New Breast Cancer Data From ASCO 2022

The Washington Post
Democracy Dies in Darkness

BUSINESS

This Drug Could Transform Breast Cancer Treatment

Biologics: PK characteristics



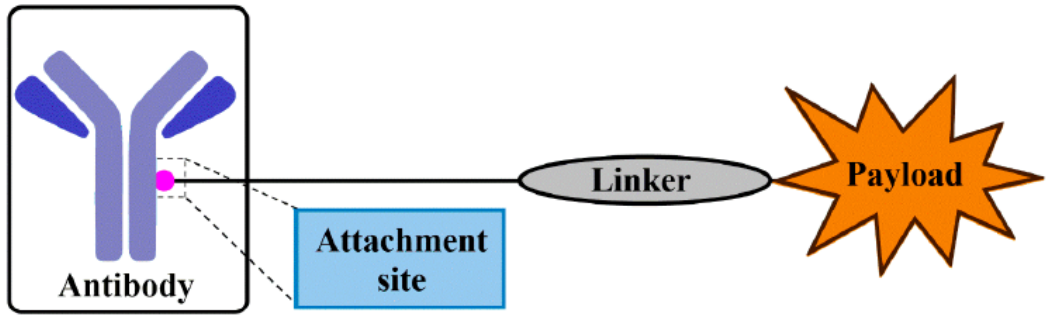
- No oral route
- Reduced F if s.c. route

- Little distribution
- Vd = plasma volume!
- Hardly reaches solid tumors!

- Proteolysis
- ADAs
- FCRn recycling
- TMDD

The PK of biologics is tricky to capture!

ADCs: which PK?



mAb PK
(with shortened half-life)

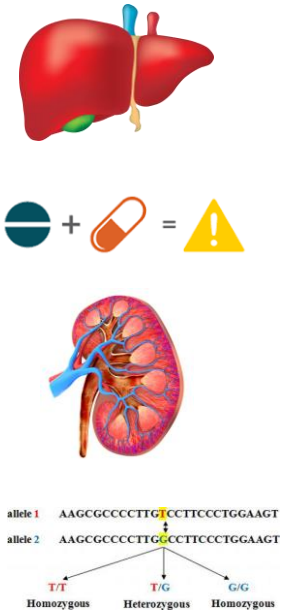
Intact scaffold

mAb PK

Blank mAb

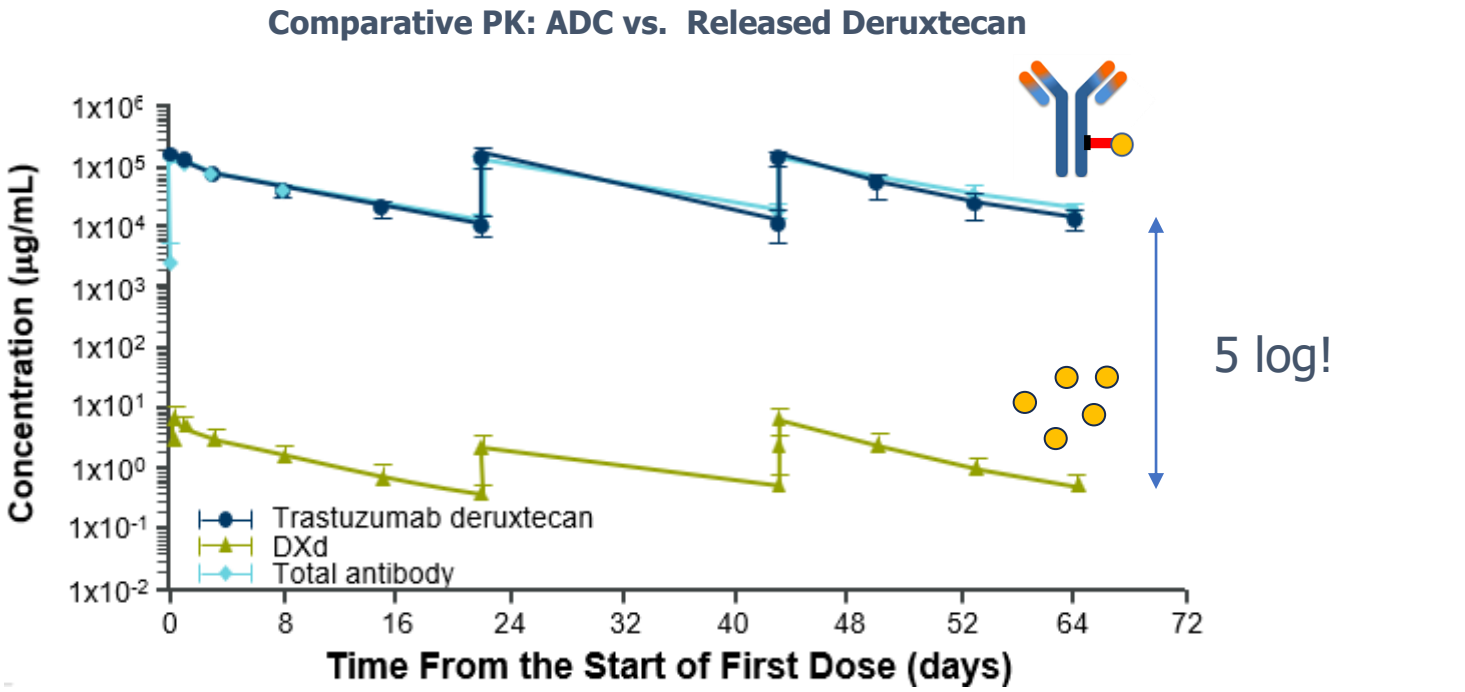
Released Payload

Small drug PK



Usually ADCs are expected to remain intact in the blood flow… but second generation linkers are less stable in plasma (+ bystanding effect)

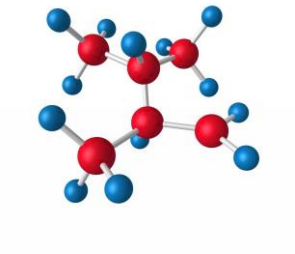
ADCs: which PK?



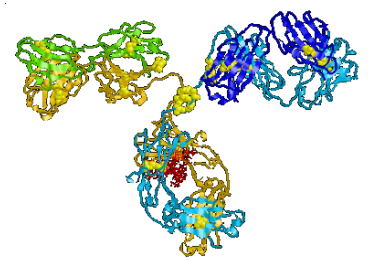
Doi T et al. the Lancet 2017

Released payload/ADC ratio: 1/100 000!
depends on the linker technology (2d generation: higher release)

ADCs: which PK?



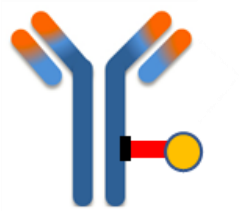
- Renal failure
- Liver failure
- age
- obesity
- gene polymorphisms
- sex
- DDI



- age?
- sex?
- albumin?
- cachexia?
- Body Weight? BSA ?
- gene polymorphism ?
- tumor burden?

Unlike payloads, sources for PK variability with ADCs remain largely unknown…..
but nobody has ever heard of most payloads before!

ADCs: which PK?



antibodies

MDPI

Review

Clinical Pharmacology of Antibody-Drug Conjugates

Iftekhar Mahmood

Table 2. Pharmacokinetic parameters of FDA approved ADCs (only the antibodies).

ADCs	Dose	CL (mL/h)	V_{ss} or V_c (L)	Half-Life (Days)
MYLOTARG	9 mg/m^2	350	21	2.6
ADCETRIS	0.1–3.4 mg/kg	65	6–10	4–6
BESPONSA	1.2–1.8 mg/m^2	33	12	12.3
POLIVY	1.8 mg/kg	900	3.2 *	12
KADCYLA	3.6 mg/kg	680	3.1 *	4
ENHERTU	3.2–8 mg/kg	420	2.8 *	5.7
PADCEV	1.25 mg/kg	100	11	3.4
TRODELVY	10 mg/kg	140	3.2	16 h
BLENREP	2.5 mg/kg	900	11	12

* Volume of distribution of the central compartment. Compiled from the FDA package inserts and references [12,13].

Dosing in mg/kg or mg/m²

Reduced Distribution (< 1L/Kg)

Shortened Half-Life compared with parent-mAb

ADCs: which PK?

✓ **Sources of variability?**

antibodies MDPI

Review

Clinical Pharmacology of Antibody-Drug Conjugates

Iftekhar Mahmood

Table 3. PK parameters (mean ± sd) of Gemtuzumab Ozogamicin in children following 9 mg/m^2 in period 1 as a function of age.

Age (Years)	CL (L/h)	V_{ss} (L)	Half-Life (h)
Infants (0–2), $n = 2$	0.03 ± NA	2.9 ± NA	113 ± NA
Children (3–11), $n = 5$	0.06 ± 0.03	3.9 ± 1.9	45.6 ± 30.8
Adolescents (12–16), $n = 7$	0.26 ± 0.30	9.4 ± 6.6	62.0 ± 16.5
Adults ($n = 59$)	0.27 ± 0.23	20.9 ± 21.5	72.4 ± 42.0

NA because $n = 2$.

Young age (i.e., below 11 years) can significantly change PK parameters

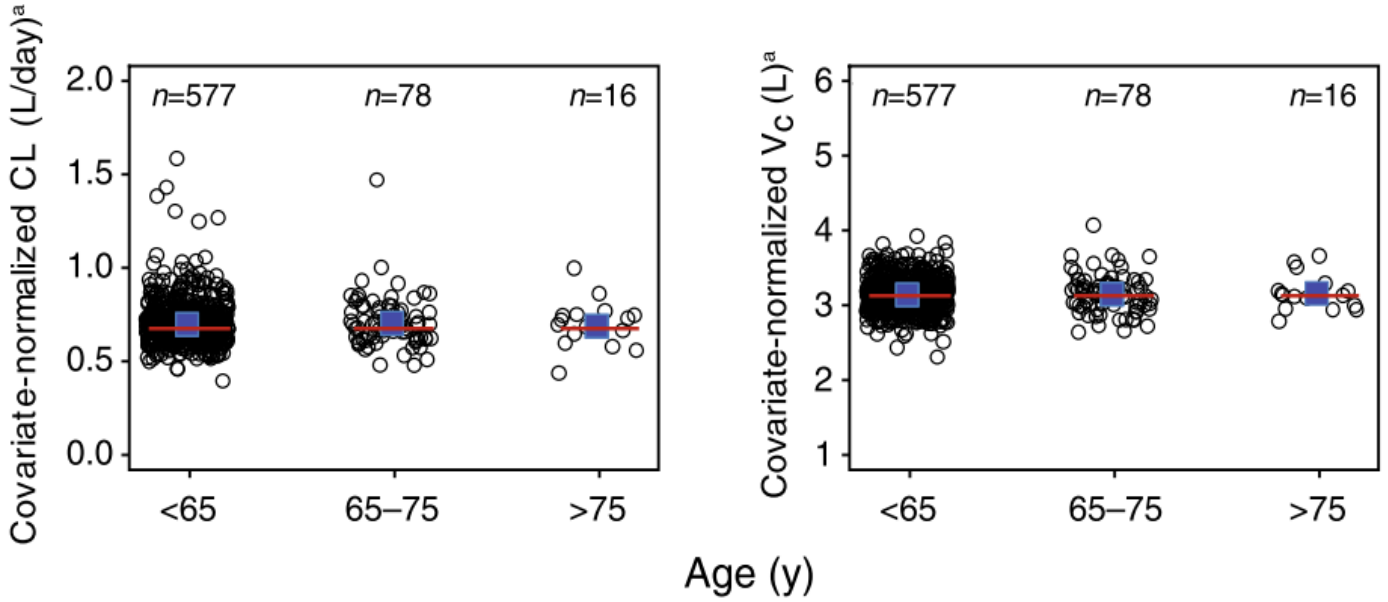
ADCs: which PK?

✓ **Sources of variability?**

Cancer Chemother Pharmacol (2014) 74:399–410
DOI 10.1007/s00280-014-2500-2

ORIGINAL ARTICLE

Population pharmacokinetics of trastuzumab emtansine (T-DM1), a HER2-targeted antibody–drug conjugate, in patients with HER2-positive metastatic breast cancer: clinical implications of the effect of covariates



In adults, differences in age do not influence PK parameters

ADCs: which PK?

✓ **Sources of variability?**

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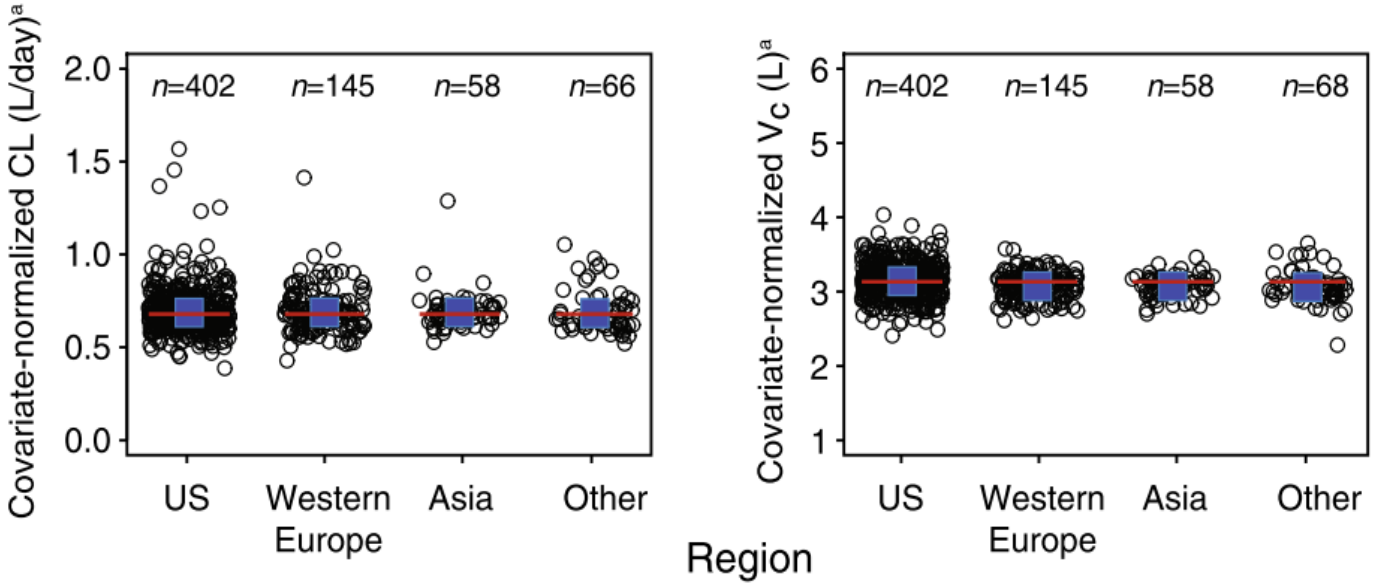

Nor Ethnicity

ADCs: which PK?

✓ **Sources of variability?**

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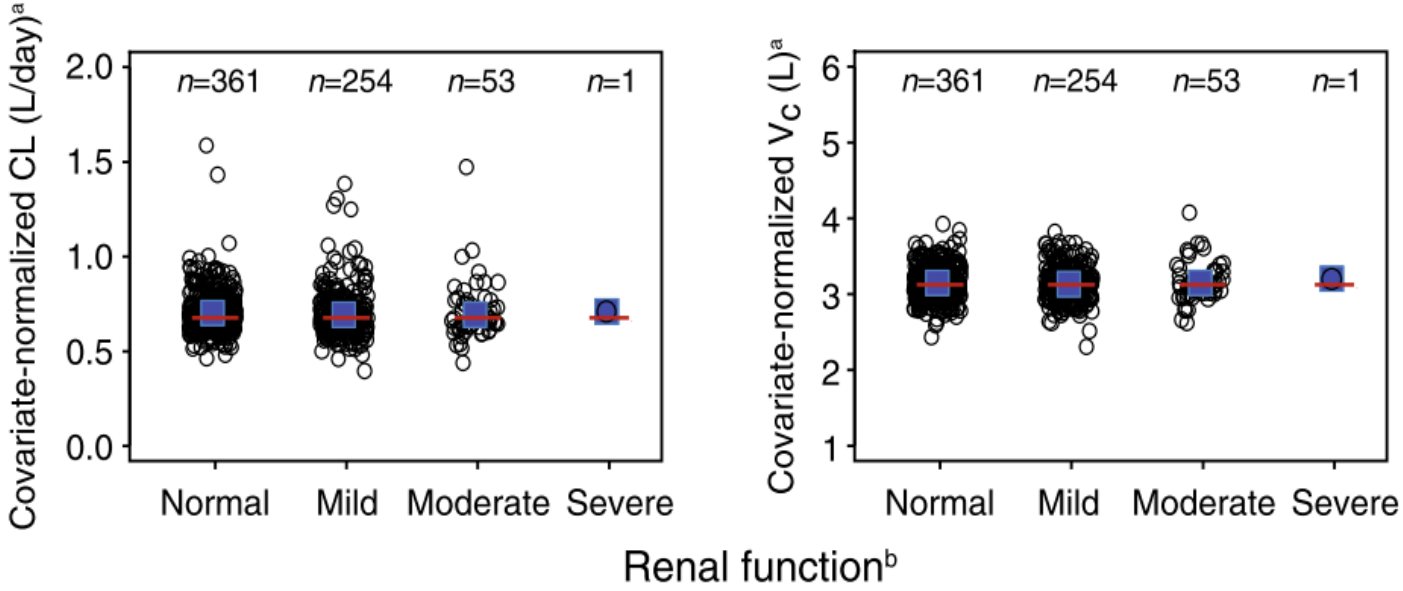

Nor Comorbidities

ADCs: which PK?

✓ **Sources of variability?**

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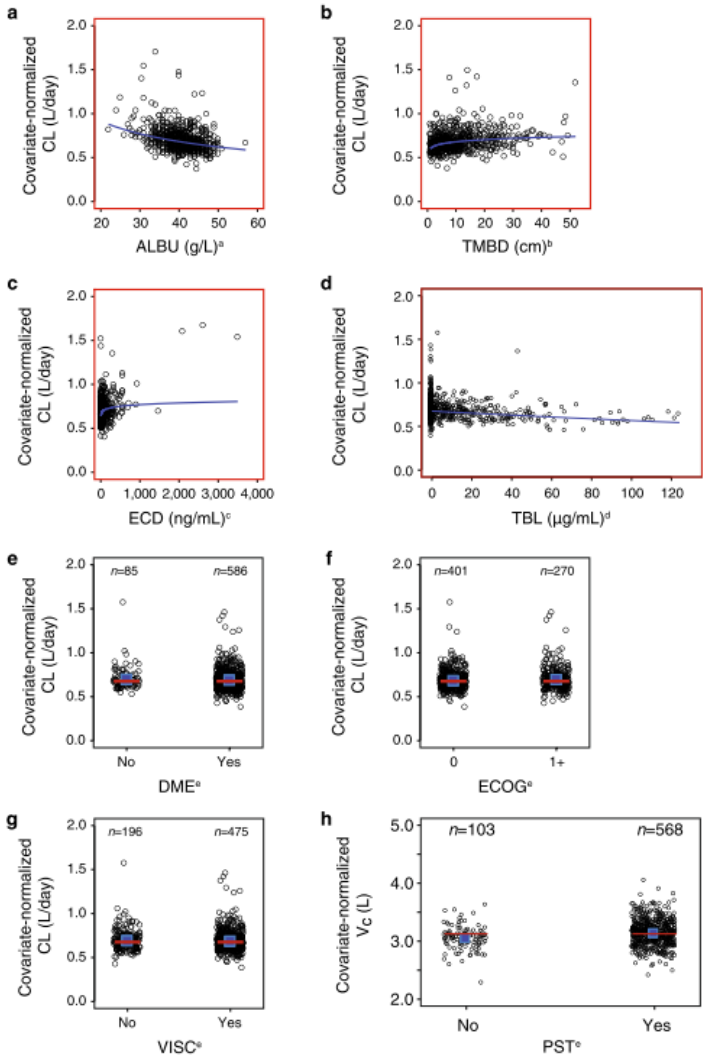

ALBU: albumin
TMBD: tumor mass
ECD: basal HER2 serum concentration
TBL: trastuzumab baseline concentration
DME: disease measurability
ECOG: general condition
VISC: visceral disease
PST: prior systemic therapy

ADCs: which PK?

✓ **Sources of variability?**

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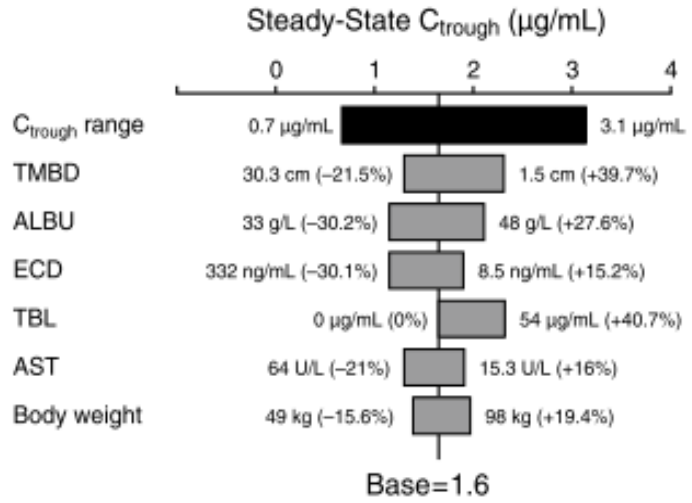
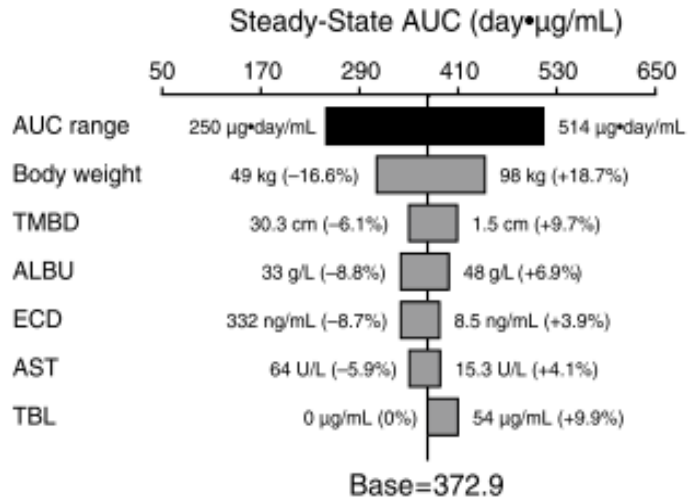
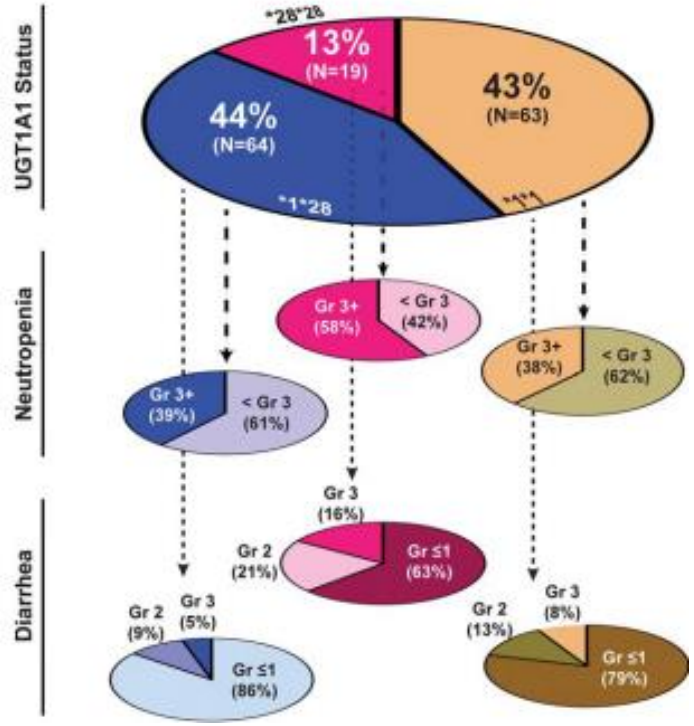


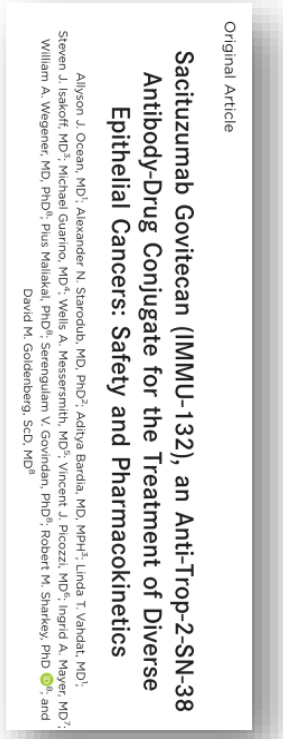


Tumor burden, albumin, Her2 serum levels partly impact
(N.B.: bioanalytical precision: 15%)

ADCs: which PK?

✓ **Sources of variability?**

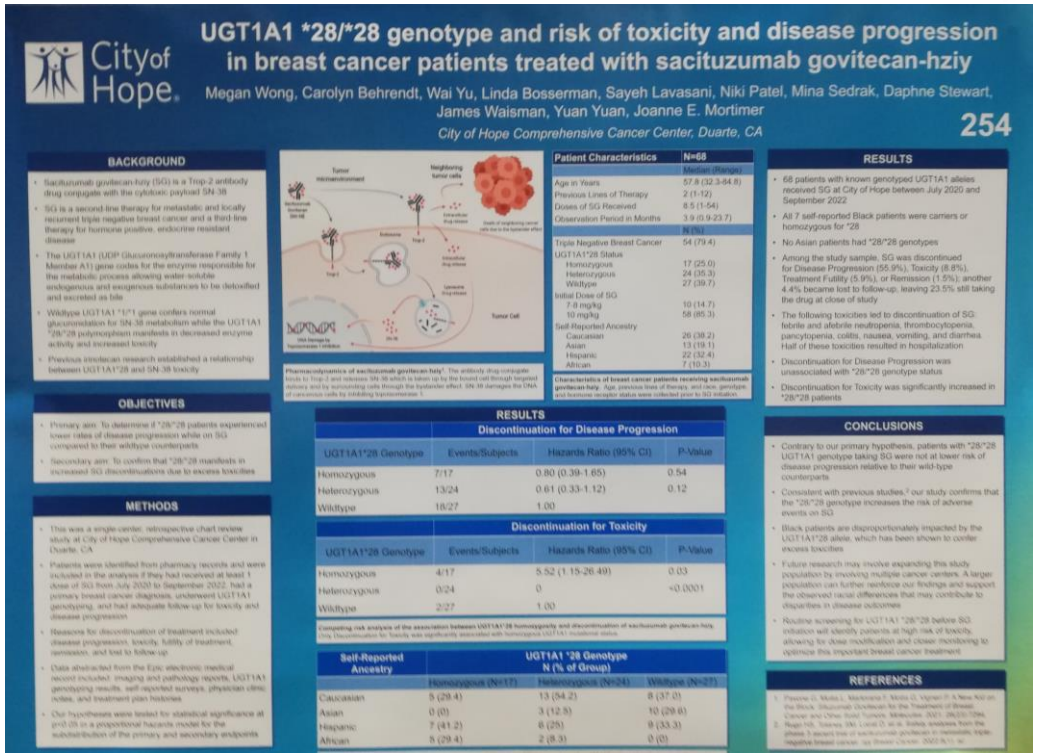



Original Article

Sacituzumab Govitecan (IMMU-132), an Anti-Trop-2-SN-38 Antibody-Drug Conjugate for the Treatment of Diverse Epithelial Cancers: Safety and Pharmacokinetics

Allyson J. Ocean, MD[1]; Alexander N. Starodub, MD, PhD[2]; Aditya Bardia, MD, MPH[3]; Linda T. Vahdat, MD[4]; Steven J. Isakoff, MD[5]; Michael Guarino, MD[6]; Wells A. Messersmith, MD[7]; Vincent J. Picozzi, MD[8]; Ingrid A. Mayer, MD[9]; William A. Wegener, MD, PhD[10]; Pius Maliakal, PhD[10]; Serengulam V. Govindan, PhD[10]; Robert M. Sharkey, PhD[10]; and David M. Goldenberg, ScD, MD[10]

2023 ASCO ANNUAL MEETING


City of Hope

UGT1A1 *28/*28 genotype and risk of toxicity and disease progression in breast cancer patients treated with sacituzumab govitecan-hziy

Megan Wong, Carolyn Behrendt, Wai Yu, Linda Bosserman, Sayeh Lavasani, Niki Patel, Mina Sedrak, Daphne Stewart, James Waisman, Yuan Yuan, Joanne E. Mortimer

City of Hope Comprehensive Cancer Center, Duarte, CA

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BACKGROUND

OBJECTIVES

METHODS

RESULTS

Discontinuation for Disease Progression

UGT1A1*28 Genotype	Events/Subjects	Hazards Ratio (95% CI)	P-Value
Homozygous	7/17	0.80 (0.39-1.65)	0.54
Heterozygous	13/24	0.61 (0.33-1.12)	0.12
Wildtype	18/27	1.00	

Discontinuation for Toxicity

UGT1A1*28 Genotype	Events/Subjects	Hazards Ratio (95% CI)	P-Value
Homozygous	4/17	5.52 (1.15-26.49)	0.03
Heterozygous	0/24	0	<0.0001
Wildtype	2/27	1.00	

Self-Reported Ancestry	UGT1A1 *28 Genotype N (% of Group)		
	Homozygous (N=17)	Heterozygous (N=24)	Wildtype (N=27)
Caucasian	5 (29.4)	13 (54.2)	8 (37.0)
Asian	0 (0)	3 (12.5)	10 (29.6)
Hispanic	7 (41.2)	6 (25)	9 (33.3)
African	5 (29.4)	2 (8.3)	0 (0)

Patient Characteristics N=68

	Median (Range)
Age in Years	57.8 (32.3-84.8)
Previous Lines of Therapy	2 (1-12)
Doses of SG Received	8.5 (1-54)
Observation Period in Months	3.9 (0.9-23.7)
	N (%)
Triple Negative Breast Cancer	54 (79.4)
UGT1A1*28 Status	
Homozygous	17 (25.0)
Heterozygous	24 (35.3)
Wildtype	27 (39.7)
Initial Dose of SG	
7-8 mg/kg	10 (14.7)
10 mg/kg	58 (85.3)
Self-Reported Ancestry	
Caucasian	26 (38.2)
Asian	13 (19.1)
Hispanic	22 (32.4)
African	7 (10.3)

RESULTS

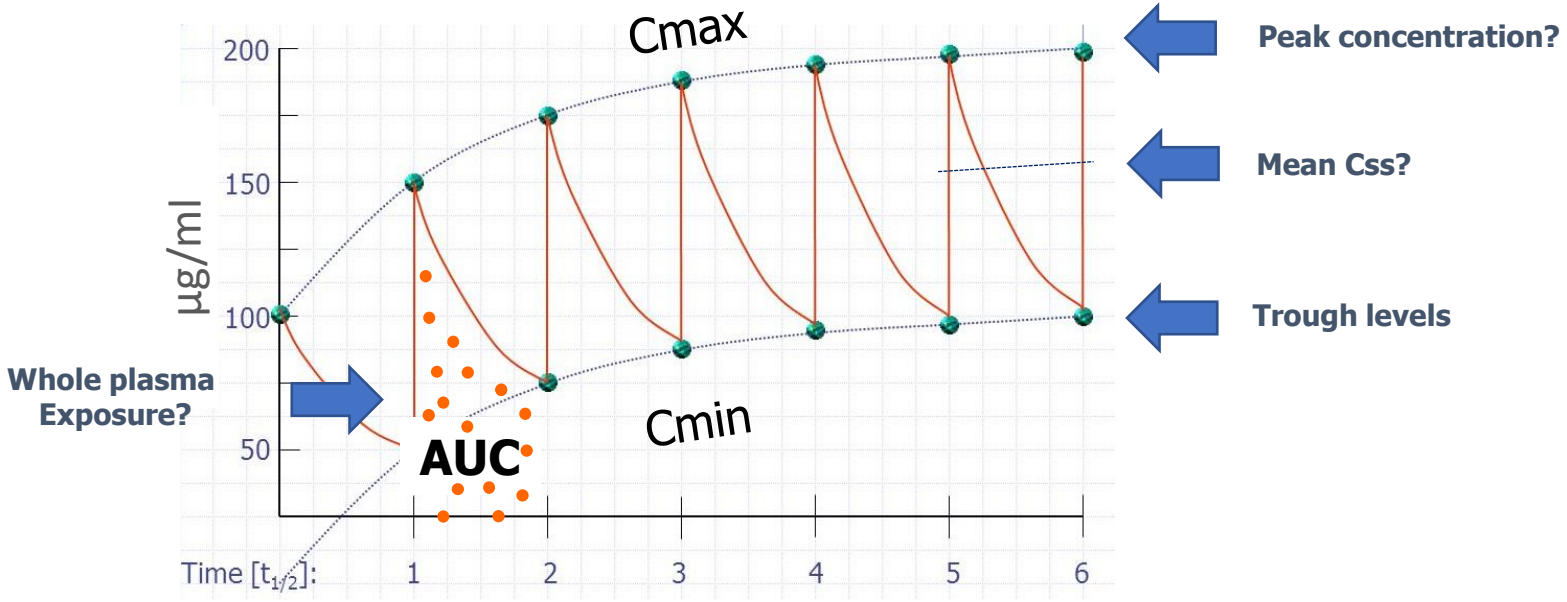
CONCLUSIONS

REFERENCES

UGT1A1 *28/*28 genotype associated with higher risk for toxicities!

ADC: PK/PD characteristics

✓ **PK/PD relationships are not fully elucidated**



What is the right metrics (if any relevant)?
What is the right entity (intact ADC vs. Payload)?

- Efficacy
- Toxicity

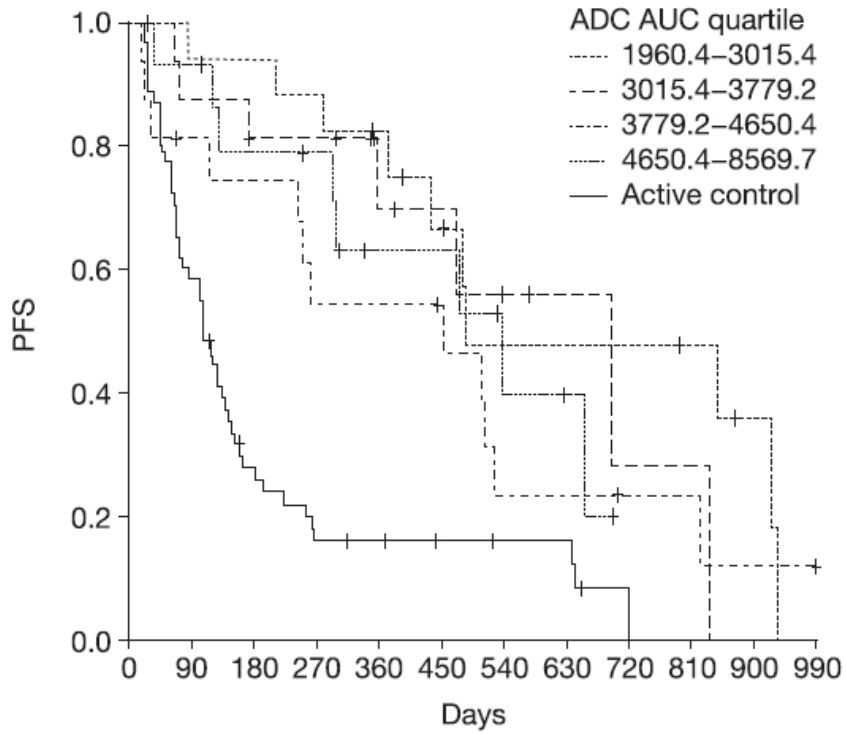
ADC: PK/PD characteristics

✓ **Brentuximab vedotin**

ARTICLE

Population Pharmacokinetic Modeling and Exposure–Response Assessment for the Antibody-Drug Conjugate Brentuximab Vedotin in Hodgkin's Lymphoma in the Phase III ECHELON-1 Study

Ajit Suri[1,*], Diane R. Mould[2], Gregory Song[1], Graham P. Collins[3], Christopher J. Endres[4], Jesús Gomez-Navarro[1] and Karthik Venkatakrishnan[1]



Suri A. et al. 2018

Survival can be associated with exposure (AUC)

ADC: PK/PD characteristics

✓ **Brentuximab vedotin**

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Population Pharmacokinetic Modeling and Exposure–Response Assessment for the Antibody-Drug Conjugate Brentuximab Vedotin in Hodgkin's Lymphoma in the Phase III ECHELON-1 Study

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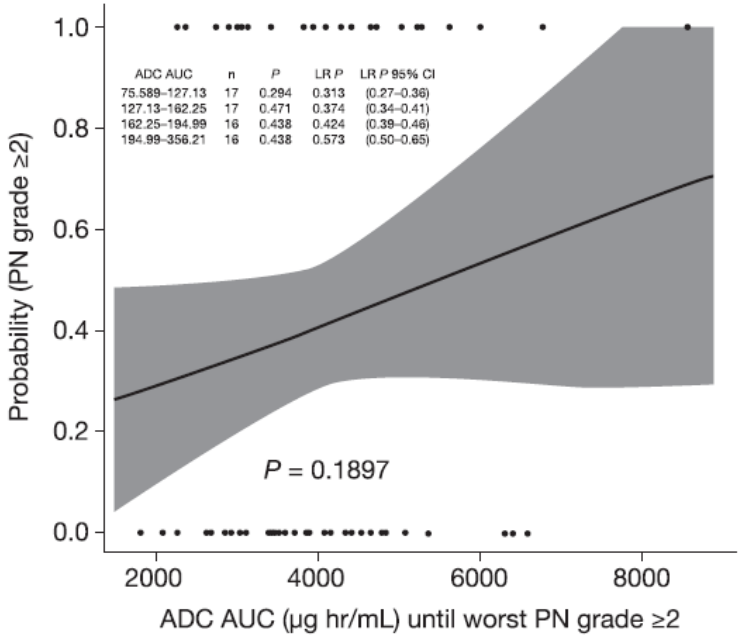
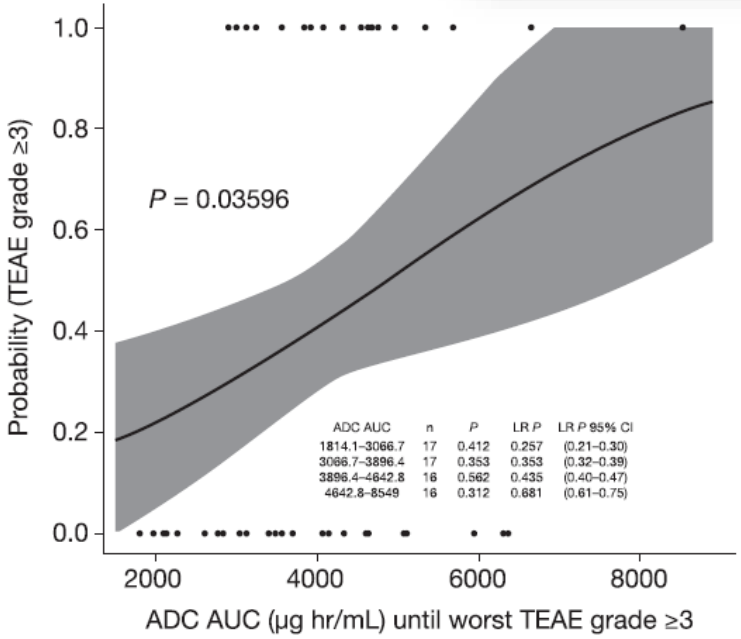


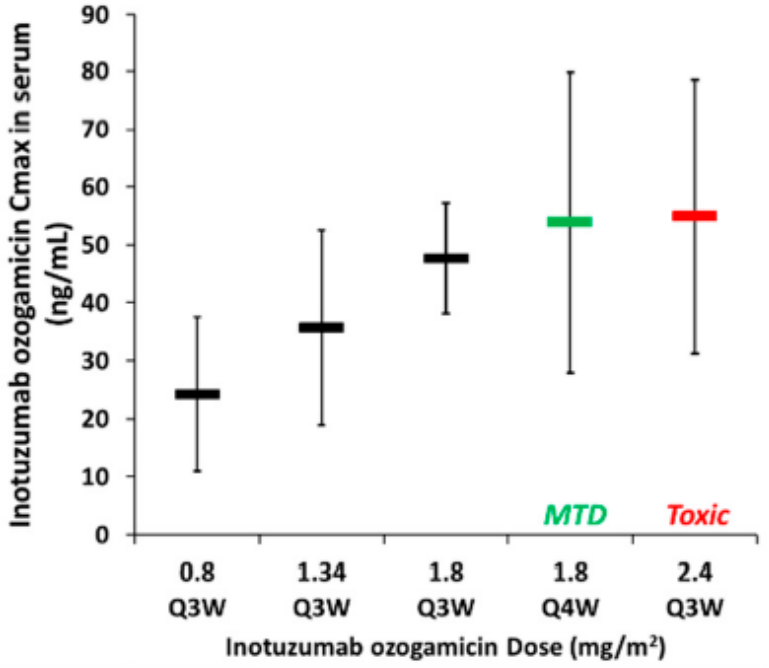


Suri A. et al. 2018

Safety can be associated with exposure (AUC)

ADC: PK/PD characteristics

✓ **Inotuzumab ozigamicin**



N	5	11	5	44	6
Mean ± SD	24.3 ± 13.3	35.7 ± 16.8	47.7 ± 9.5	53.9 ± 25.9	54.9 ± 23.6
CV%	55%	47%	20%	48%	43%

Lucas A. et al. 2019

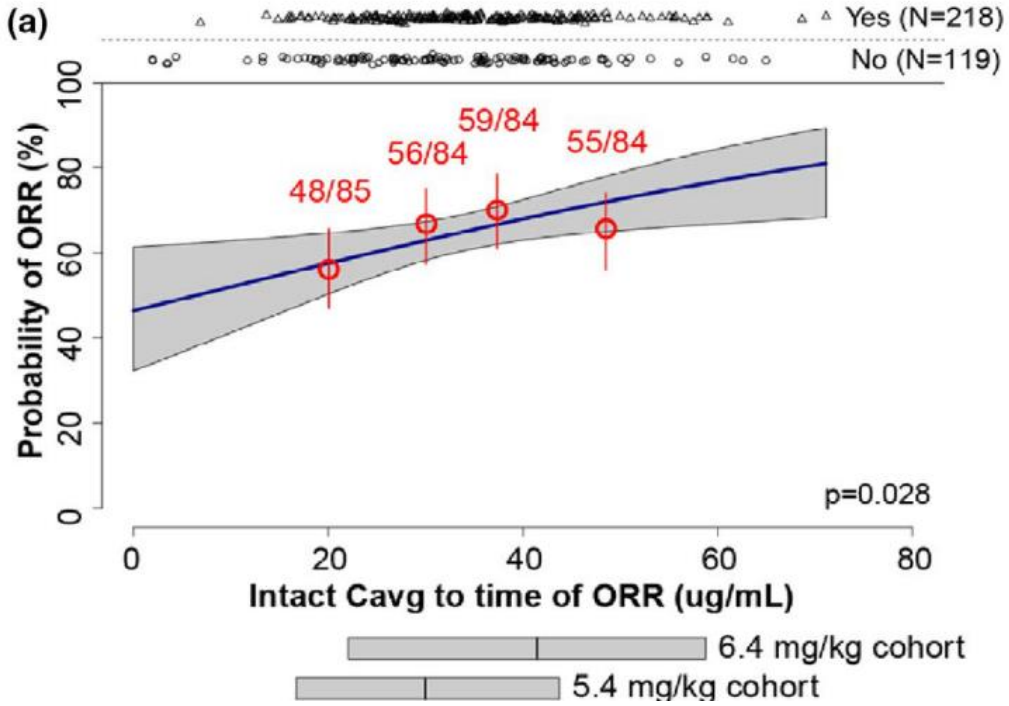
Safety is associated with exposure (Cmax)

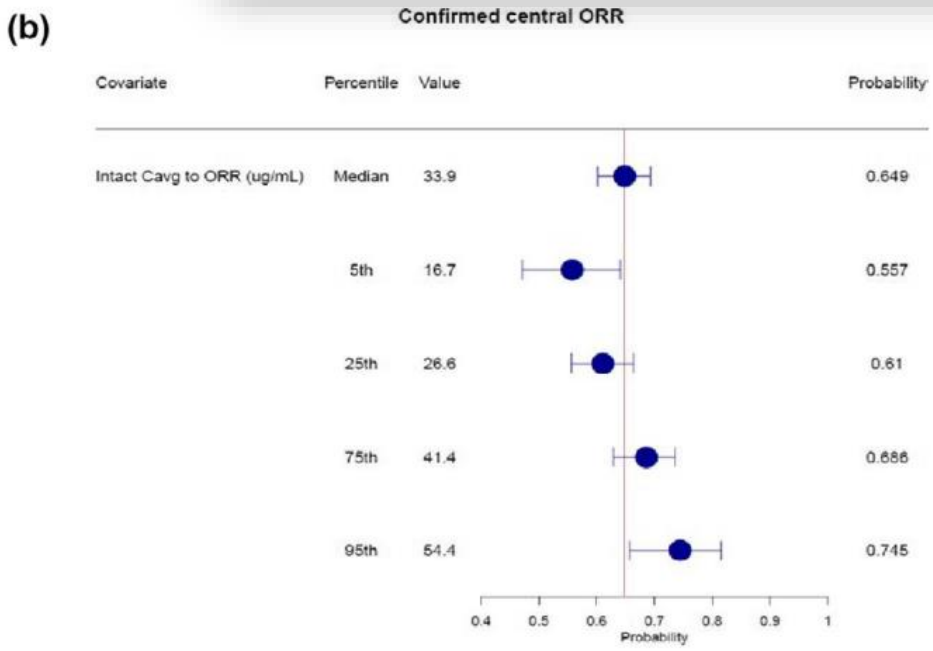
ADC: PK/PD characteristics

✓ **Trastuzumab deruxtecan**

Exposure-Response Relationships in Patients With HER2-Positive Metastatic Breast Cancer and Other Solid Tumors Treated With Trastuzumab Deruxtecan

Ophelia Yin[1,*], Hiroji Iwata[2], Chia-Chi Lin[3], Kenji Tamura[4], Junichiro Watanabe[5], Russ Wada[6], Helen Kastrissios[6], Malaz AbuTarif[1], Tushar Garimella[1], Caleb Lee[1], Lin Zhang[1], Javad Shahidi[1] and Frank LaCreta[1]





ORR is associated with exposure (Cavg)

From PK/PD characteristics to dosing

✓ **Approved dosing is expected to:**

- Ensure optimal toxicity/efficacy ratio
- Smooth inter-individual variability
- Maintain most patients in the therapeutic window
- Limit treatment discontinuations due to A.E.s

✓**ADCs are given as mg/m² or mg/kg**

- Unlike oral targeted therapies and immune checkpoint inhibitors (flat dosing)

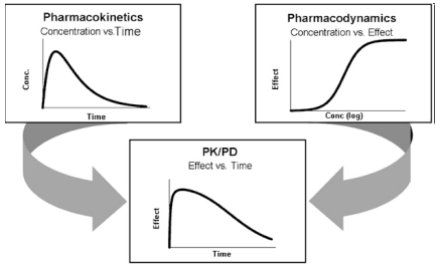
✓**Postulates a direct link between body mass and clearance (the bigger the patient, the more you put)**

✓Actually, only requires that **Cl=$f * BW^y$ with y>0,5** (i.e., no clear direct link is necessary)

From PK/PD characteristics to dosing

Identification Therapeutic Window

- Which metrics?
- Payload or ADC?
- Which PD endpoints?
- Single agent or combination?
- Which disease?



Deciphering PK/PD and relevant covariates

- m^2 or kg ?
- flat-dosing?
- univocal therapeutic window?

Determination of dosing and scheduling

- Which Dose?
- Which Frequency?
- Capping the dose?
- Capping the number of doses?

A variety of capping and adjustments

Inotuzumab Ozagamicin 

0,5 mg/m² D1/D8/D15 ⇨ 0,8 mg/m² D1 + 0,5 mg/m² D8/D15 if no CR

Enfortumab Vedotin 

1,25 mg/kg ⇨ 125 mg max

Brentuximab Vedotin 

1,8 mg/kg ⇨ 180 mg max as single agent

1,2 mg/kg ⇨ 120 mg max is associated to chemo

12 doses max if Hodgkin Lymphoma

6-8 doses max if peripheral T cells Lymphoma

Polatuzumab Vedotin 

1,8mg/kg ⇨ 6 cycles max

Trastuzumab Deruxtecan 

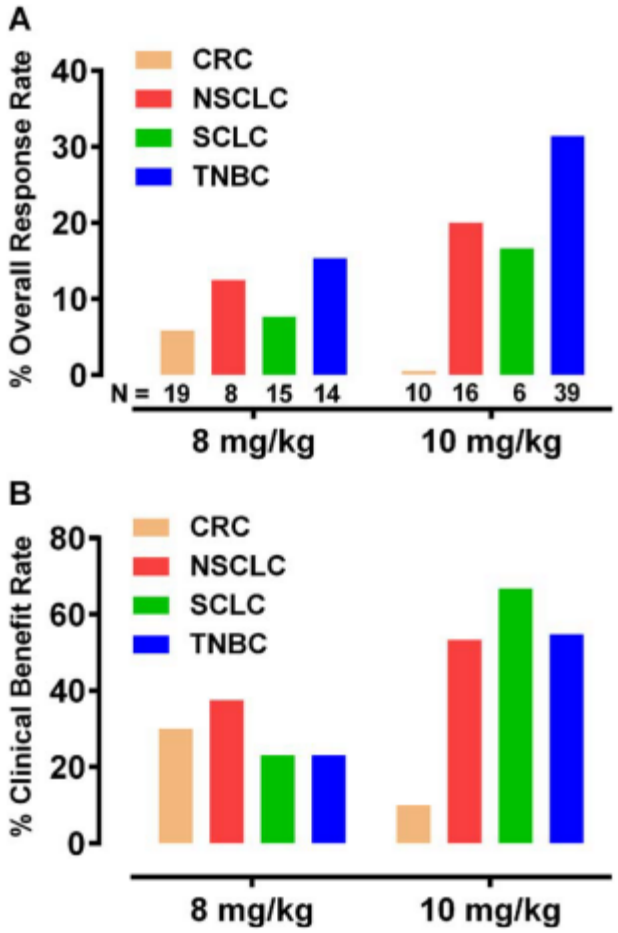
Breast: 5,4 mg/kg (no capping)
Gastric Cancer: 6,4 mg/kg (capping)

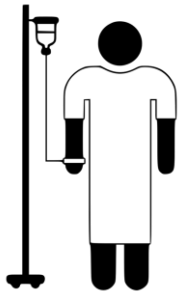
Same Payload
Different mAbs
Different Linker

Different Dosing
Different capping

Randomized dose-finding study (if PK/PD remains elusive)

Sacituzumab Govitecan



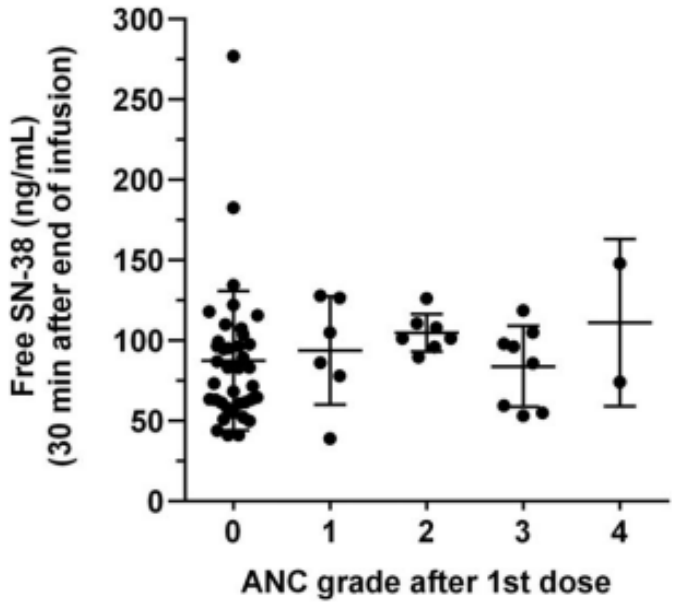


10 mg/kg performs better than 8 mg/kg

Original Article

Sacituzumab Govitecan (IMMU-132), an Anti-Trop-2-SN-38 Antibody-Drug Conjugate for the Treatment of Diverse Epithelial Cancers: Safety and Pharmacokinetics

Allyson J. Ocean, MD[1]; Alexander N. Starodub, MD, PhD[2]; Aditya Bardia, MD, MPH[3]; Linda T. Vahdat, MD[1]; Steven J. Isakoff, MD[3]; Michael Guarino, MD[4]; Wells A. Messersmith, MD[5]; Vincent J. Picozzi, MD[6]; Ingrid A. Mayer, MD[7]; William A. Wegener, MD, PhD[8]; Pius Maliakal, PhD[8]; Serengulam V. Govindan, PhD[8]; Robert M. Sharkey, PhD[8]; and David M. Goldenberg, ScD, MD[8]



Unclear PK/PD relationships
(i.e., SN38 levels hardly predict neutropenia)

The next frontier of ADCs

1. Combinatorial strategies

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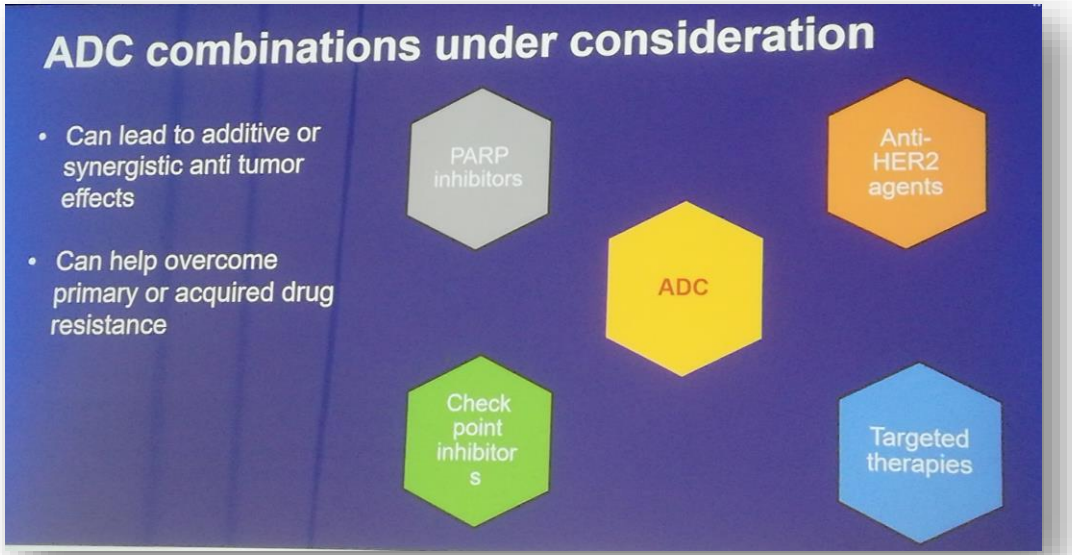

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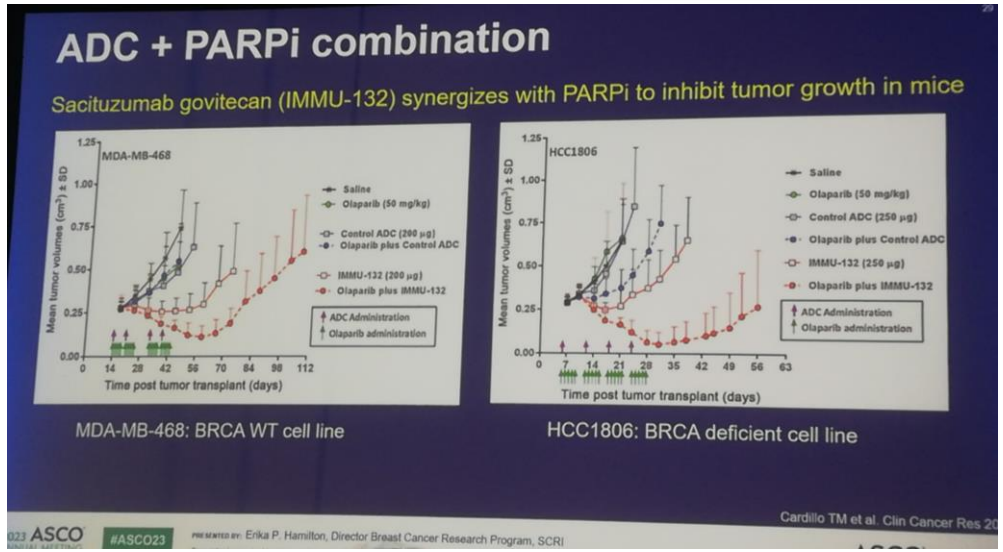


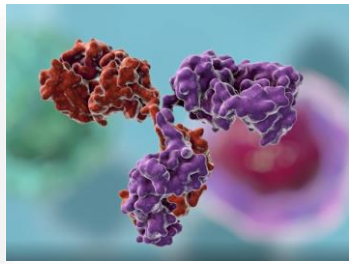
ADCs to be further associated with targeted therapies ?

The next frontier of ADCs

2. Next generation's ADCs

anti-EGFR/anti-HER3 antibody-drug conjugate BL-B01D1

A dual-targeted antibody-drug conjugate (ADC) consisting of a monoclonal antibody directed against the epidermal growth factor receptor (EGFR; HER1; ErbB1) and the epidermal growth factor receptor 3 (HER3; ErbB3) and conjugated to an as of yet not elucidated cytotoxic payload, with potential antineoplastic activity. Upon administration of anti-EGFR/anti-HER3 ADC BL-B01D1, the monoclonal antibody moieties simultaneously target and bind to EGFR and HER3 expressed on cancer cells. Following receptor internalization, the cytotoxic moiety is released and kills EGFR/HER3-expressing tumor cells through an as of yet unknown mechanism of action (MoA). EGFR and HER3, both upregulated and/or mutated in a variety of tumor cell types, play key roles in tumor cell proliferation. Simultaneously targeting both EGFR and HER3 may enhance the anti-tumor activity of BL-B01D1.



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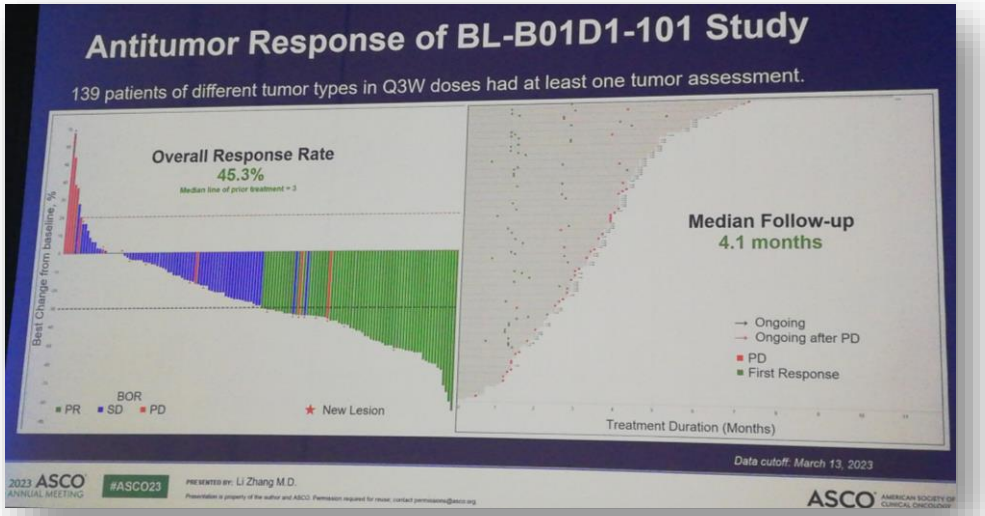

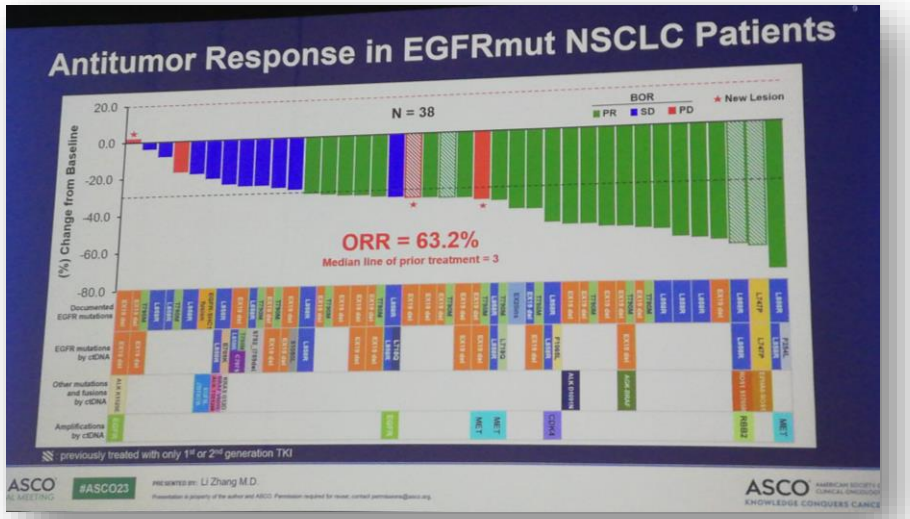

Bi-specific ADCs are coming!

Thanks for Listening