INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Pharmacokinetic Characterization of Antibody-Drug Conjugates in Clinical Development: An IQ Consortium Perspective

Pharmacometrics & Pharmacokinetics (PMK) Community Webinar

11 September 2020

Presented by Rajeev Menon, PhD

(for the IQ ADC Working Group)

Disclosures

Rajeev Menon is an employee of and owns stock in Abbvie

This presentation was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader research and development community.

ADC WG: Mission and Composition

To gather existing data across pharma companies and develop a data-driven and risk-based framework for **pharmacokinetic characterization** and DDI assessment of ADCs

TALG	Dong Wei (Chair)	Takeda	CPLG	Chunze Li (Co-chair)	Genentech
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	Dominik Hainzl	Novartis		Chris Endres	Seattle Genetics
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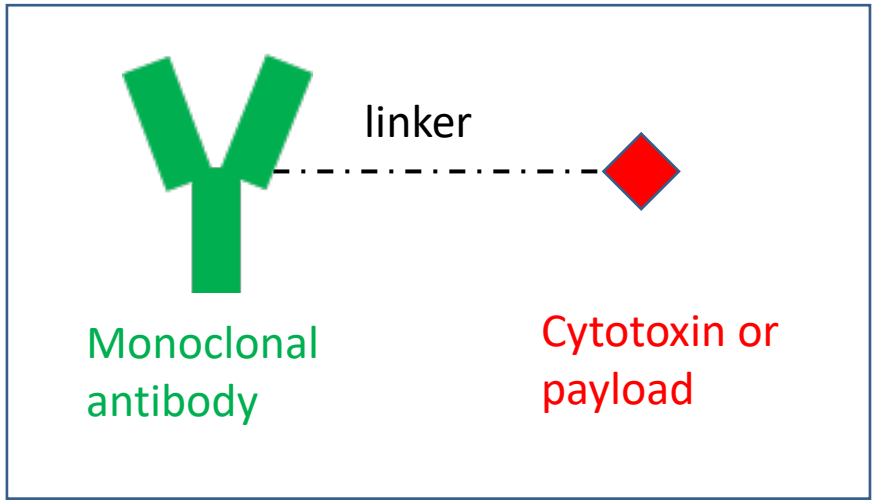
Sponsor	Jens Sydor	GSK			

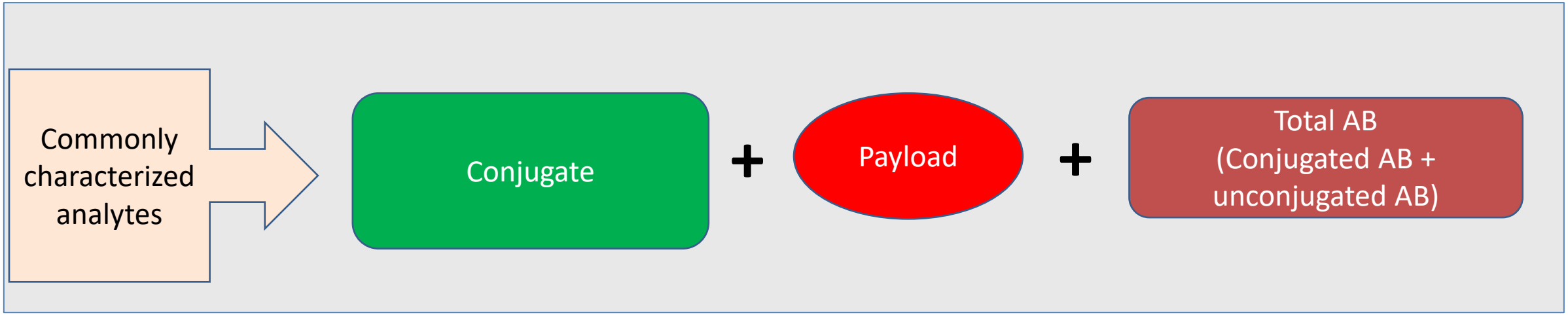
Antibody Drug Conjugates

- ADCs are tripartite drugs comprising a tumor-specific mAb conjugated to a potent cytotoxin via a stable linker.
- The three components of the ADC together give rise to a powerful oncolytic agent capable of delivering normally intolerable cytotoxins directly to cancer cells, which then internalize and release the cell-destroying drugs
- ADCs are now being explored using targeted payloads in oncology as well as in other therapeutic areas (e.g. immunology)



Ref: Christina Peters and Stuart Brown, Antibody–drug conjugates as novel anti-cancer chemotherapeutics Bioscience Reports (2015) 35, e00225, doi:10.1042/BSR20150089

Question: For Characterizing ADC Pharmacokinetics Which Analytes Should be Measured and When?

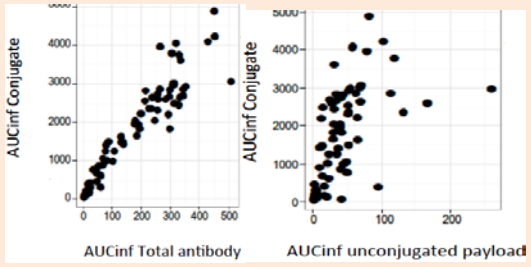


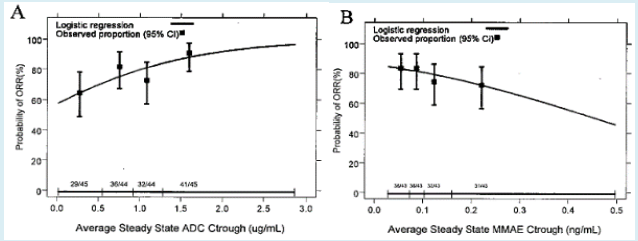
ADC: antibody drug conjugate
AB: antibody

Strategy to Develop a Data-Driven Stage Appropriate Pharmacokinetic Characterization Framework

The IQ ADC WG collected data to answer the following 2 questions to inform stage appropriate PK characterization

Exposure Correlation between analytes	Key Analyte(s) that correlate with efficacy and safety
Consideration: Monitoring one of the analytes may be sufficient at the late stage of ADC development if its exposure is highly correlated with other analytes or an integrated model can predict one analyte from the other	Consideration: Identify the pharmacologically relevant analyte(s) using exposure response (ER) analysis of clinical efficacy and safety

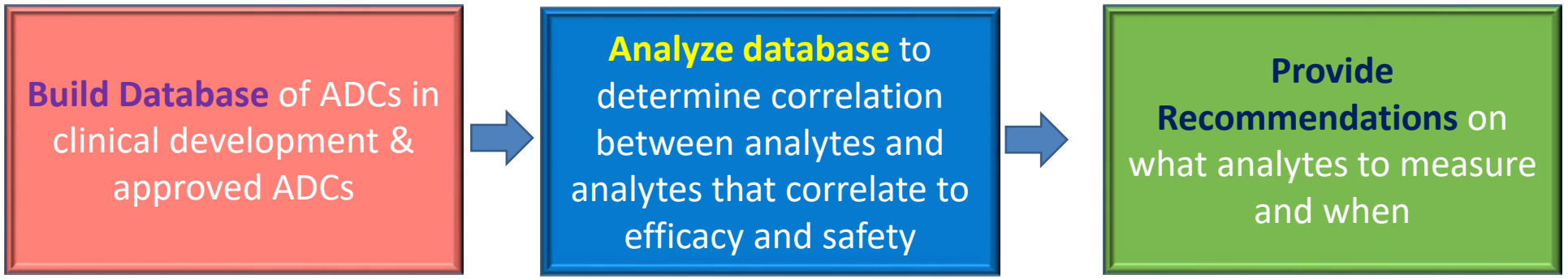




Leverage published data, mainly eight approved ADCs

ADC data from pharma industry pipeline

Workflow


Build Database of ADCs in clinical development & approved ADCs
Analyze database to determine correlation between analytes and analytes that correlate to efficacy and safety
Provide Recommendations on what analytes to measure and when

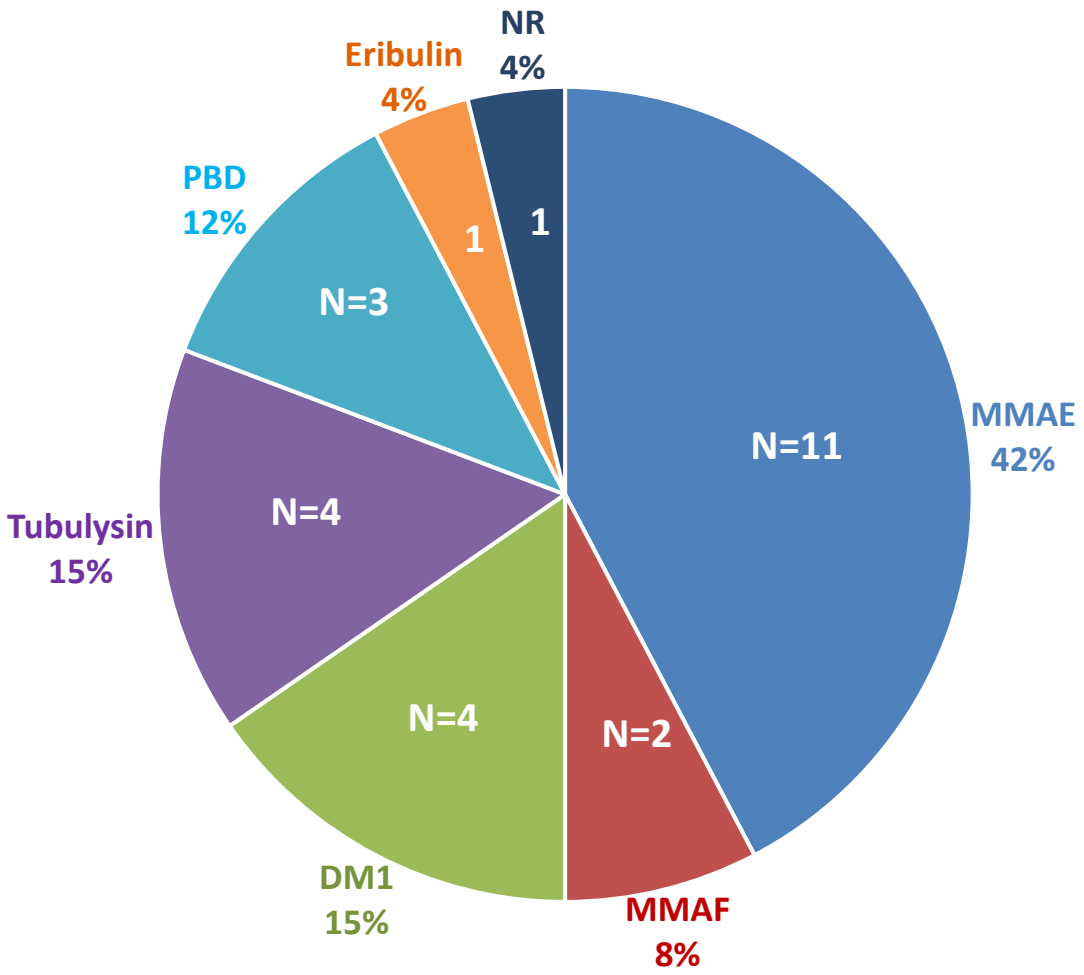
Building the Database

Each ADC WG member entered data in the database which was blinded to the working group

The following information was collected:

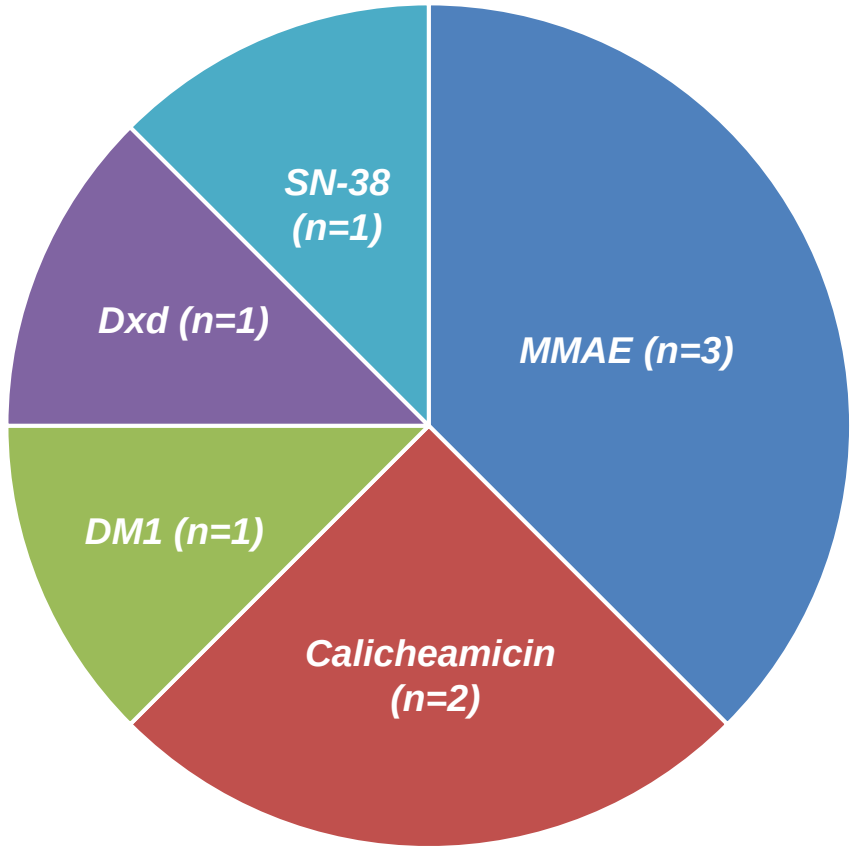
- Basic properties of ADC (e.g. payload, linker, type of conjugation, mAb activity)
- In vitro ADME properties (e.g. enzyme substrate/inhibitor, transporter substrate/inhibitor)
- Preclinical data (e.g. PK, efficacy and safety)
- Clinical Data (e.g. PK, efficacy and safety)

ADC Database
26 ADCs with 6 unique toxins



NR: not reported

Approved ADC
8 ADCs with 5 unique toxins



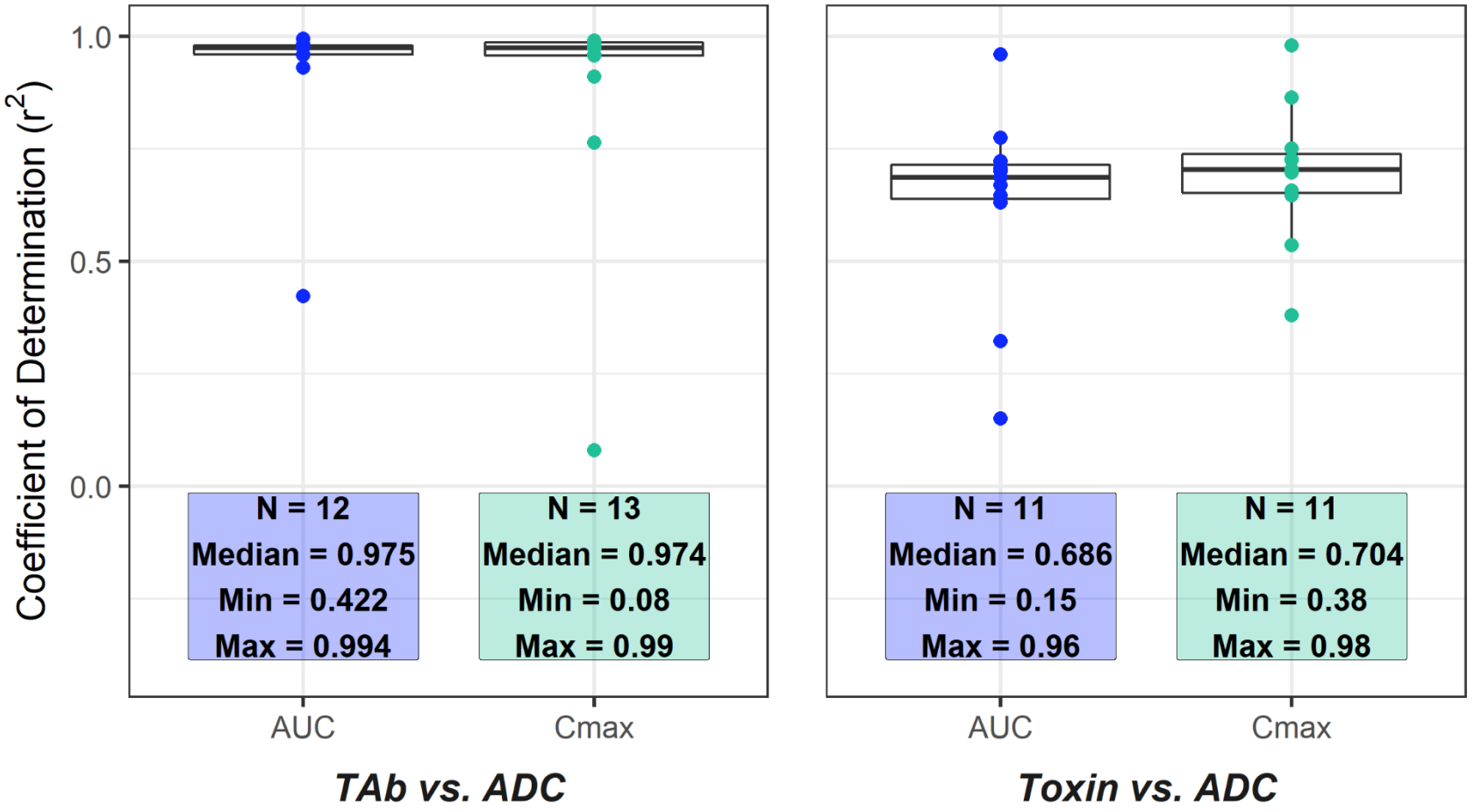
Analytes and PK correlation

All Three analytes Were Measured in Most Clinical Studies

- Data for 18 of 26 ADCs in the database were reported
- No data reported for Tubulysin (n=4) or erbulin (n=1).

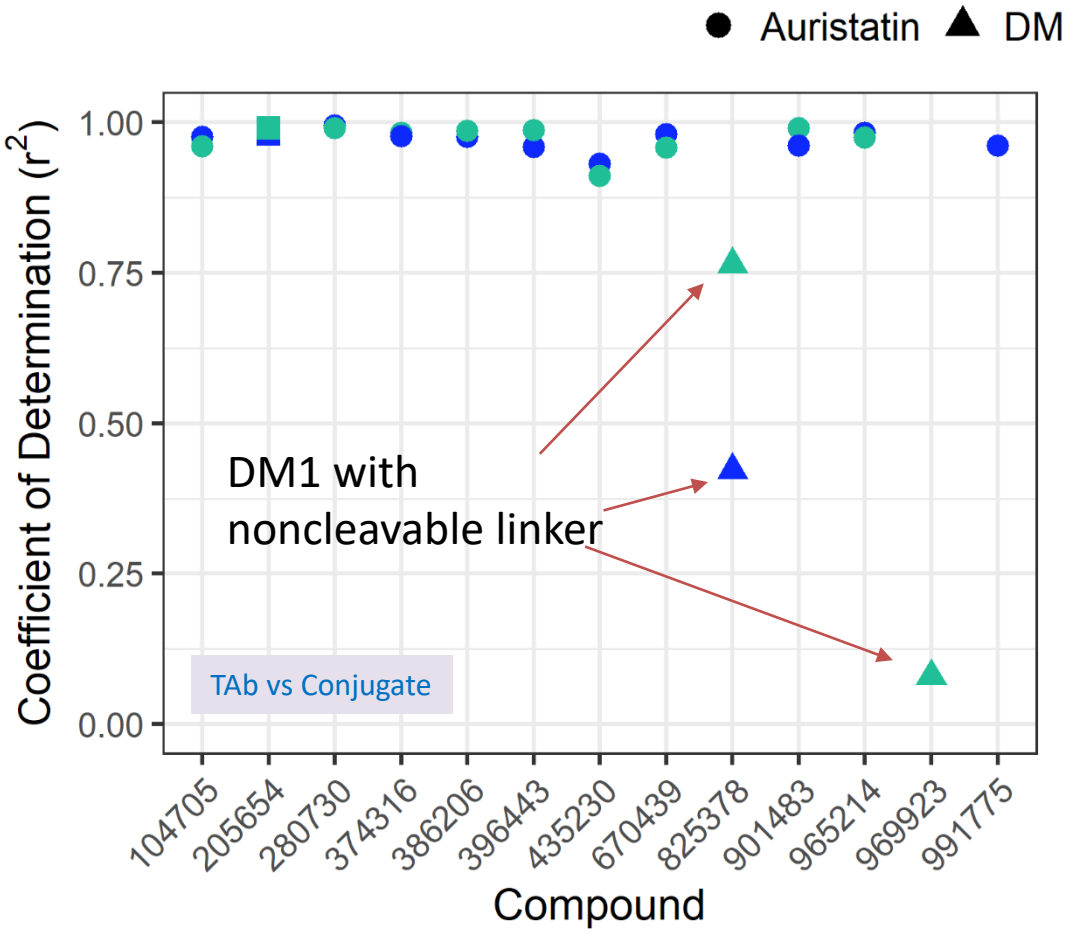
Analyte	Number of Times Tested		
	Phase 1	Phase 2	Phase 3
ADC + Toxin + Tab	18/18	5/7	1/1
ADC +Toxin	--	1/7	--
ADC + TAb	--	1/7	--

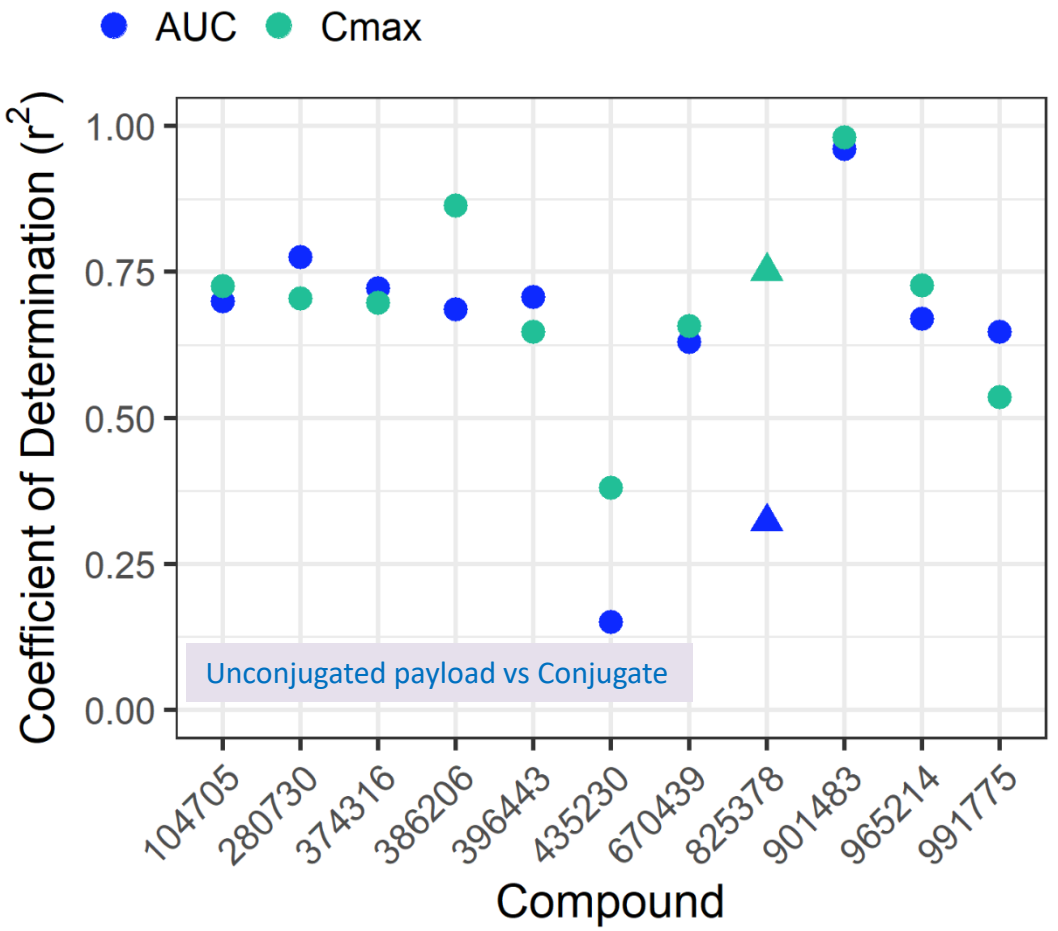
Total Antibody is Highly Correlated with Conjugate in Most Clinical Studies



Auristatin (n=10), DM-1 (n=2 for TAb and 1 for toxin), PDB (n=1 for TAb);

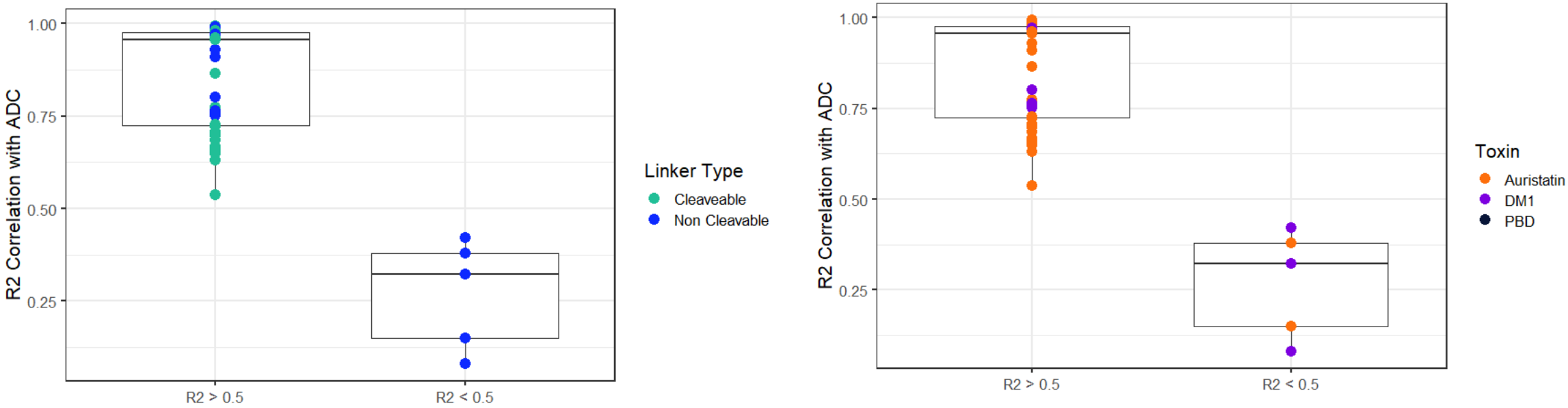
Total Antibody is Highly Correlated with Conjugate in Most Clinical Studies



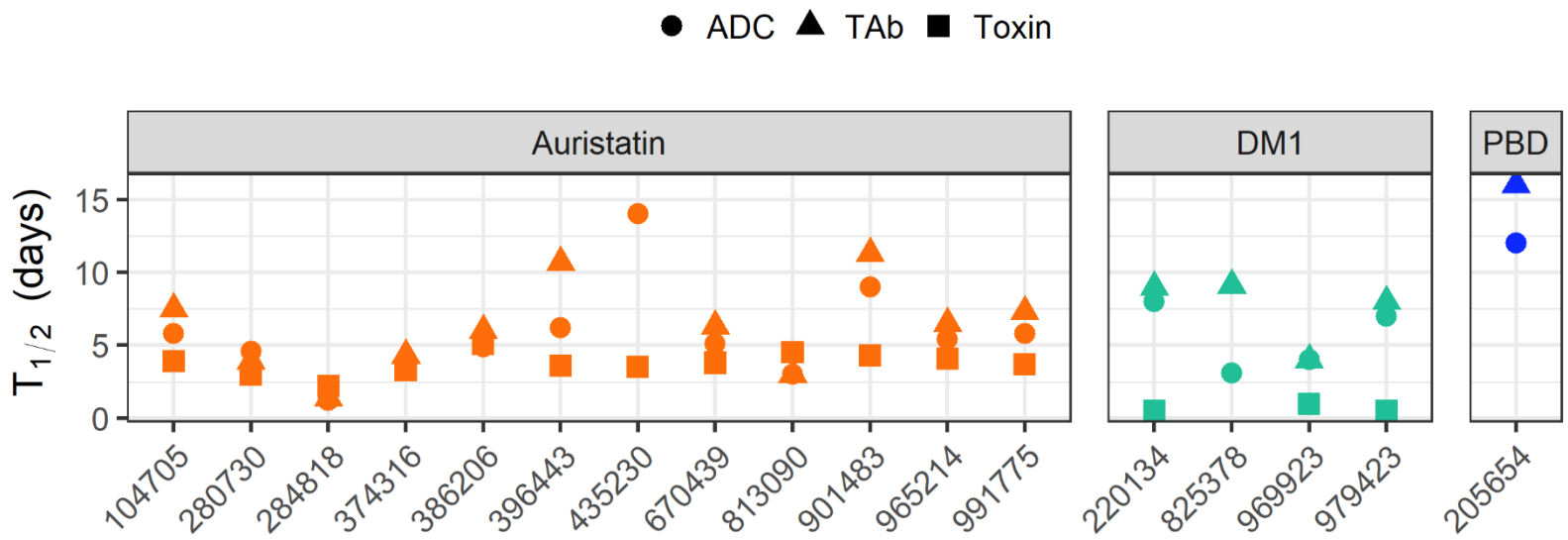


Compound #s are random #s assigned to the compounds in the database

Lower correlation with ADC PK may be due to linker type?



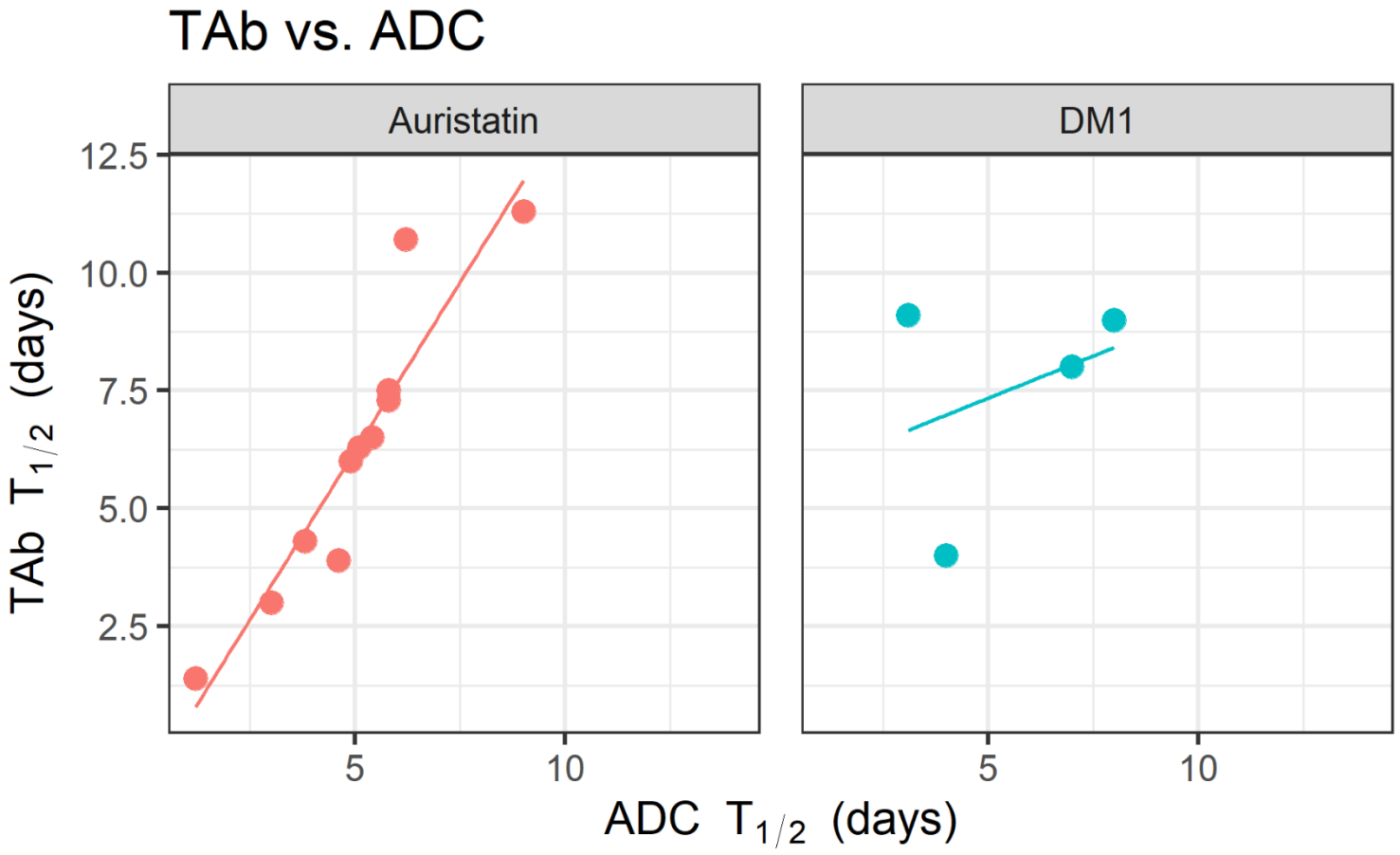
Half-life of Different ADC Analytes



Half-life in Days

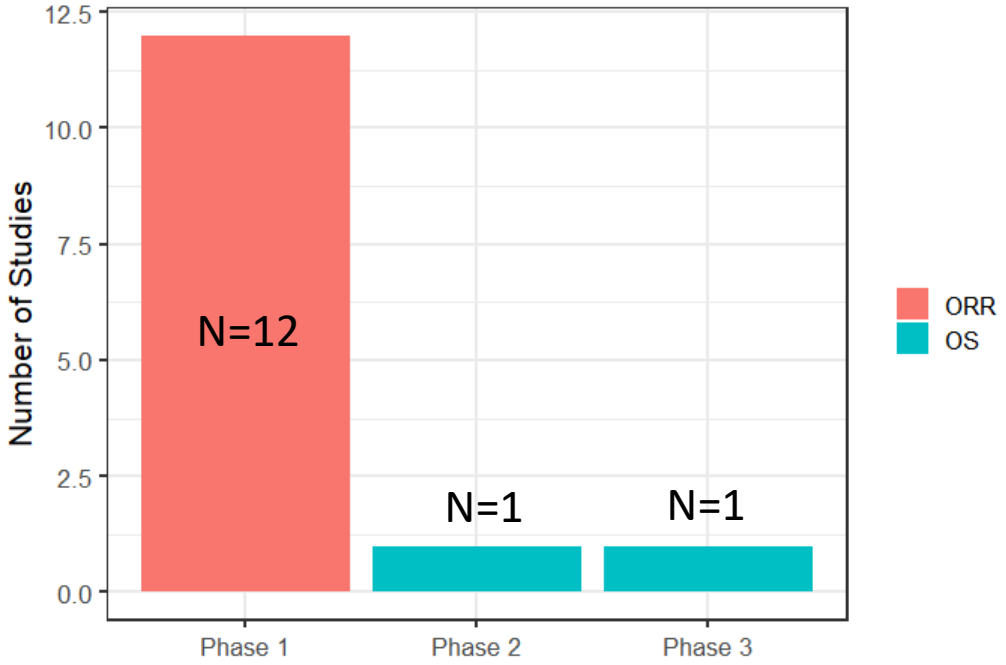
ADC	Total Antibody	Conjugate	Unconjugated Payload
Auristatin	6.2 (5.3)	5.7 (3.2)	3.8 (0.7)
DM1	7.5 (2.4)	5.4 (2.3)	0.67 (0.29)
PDB	16	12	--

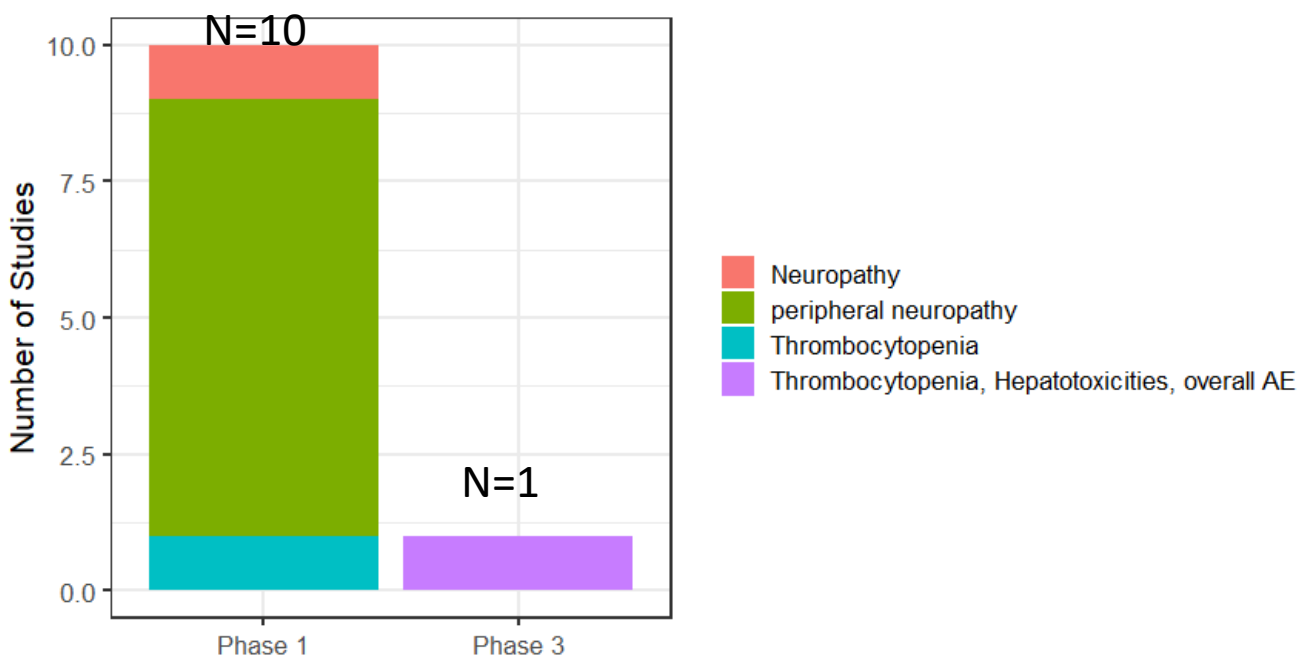
Half-life of Total Antibody and Conjugate are Highly Correlated



Exposure-Response Analyses

Efficacy & Safety Endpoints used for Exposure-Response Analyses in Clinical Studies





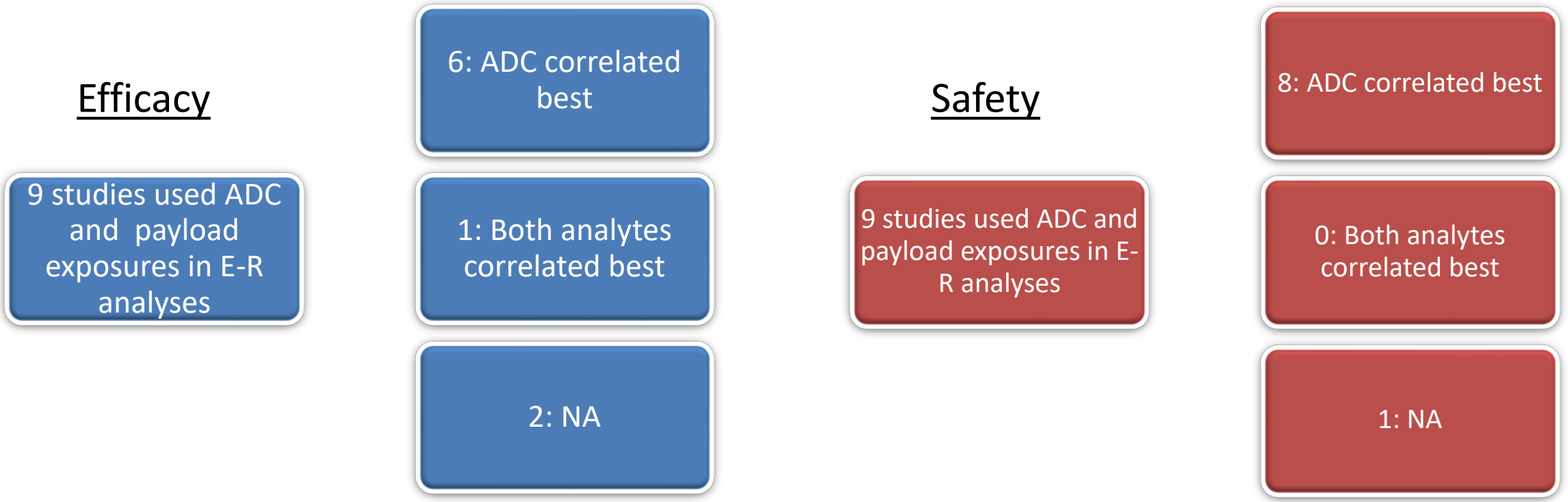
Conjugate Exposures Correlated Best with Safety and Efficacy Endpoints in Clinical Studies

Analyte	Number of Times Tested		Number of Times Analyte Correlated Best	
	Efficacy	Safety	Efficacy	Safety
Conjugate	12/12	11/11	9/9[a]	9/9[a]
Unconjugated Payload	9/12	9/11	1/7	0/8
Total Antibody	0/12	0/11	--	--

[a]For 2 studies (efficacy) and 1 study (safety), only conjugate was evaluated and found to be correlated

Efficacy: Auristatin (N=12), DM-1 (N=2)
Safety: Auristatin (N=11), DM-1 (N=2)

Which Analyte Correlates Better in E-R Analyses Clinically?



ADC = conjugate
Toxin = unconjugated payload

Conclusions

- Data from 26 ADCs with 6 toxin (payload) types were available for analysis
- Most ADCs collected all three analytes in all phases of clinical development
- Total antibody pharmacokinetics was highly correlated with conjugate pharmacokinetics, especially for Auristatin ADCs
- Conjugate and unconjugated payload (toxin) exposures were used for exposure-response analyses of clinical data.
  - No studies reported using total antibody for safety or efficacy analyses
  - Conjugate exposures correlated to safety and efficacy better compared to toxin exposures

Approved ADC Analyses

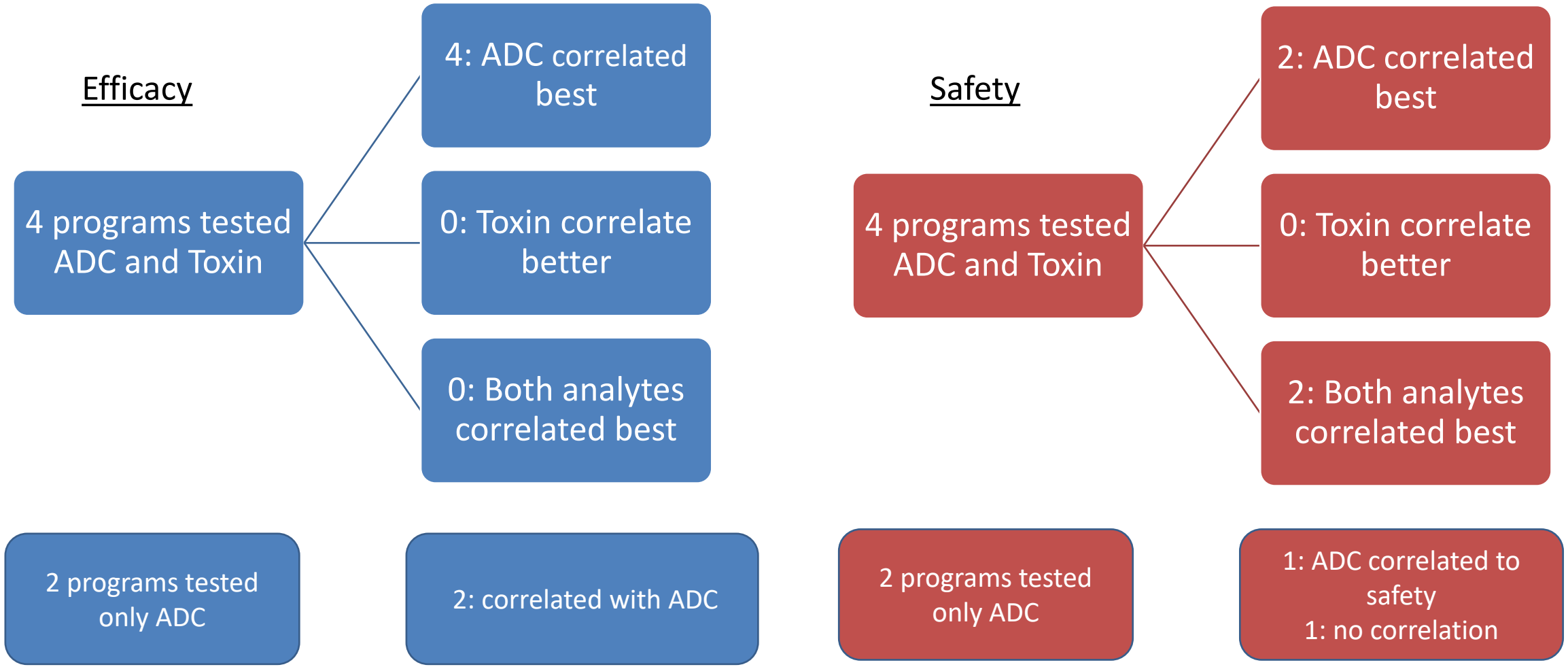
Data from approved ADCs from the US FDA summary basis of approval (SBA) were used for additional insights

As it was not possible to determine whether the approved ADCs were included in the database without unblinding, all approved ADCs were included in the analysis

Approved ADCs

ADC and submission date	Payload, Antibody	Efficacy Correlation	Best correlates to Safety
ADCETRIS brentuximab vedotin 2011 (AA)	MMAE; CD30-directed AB	ORR **Conjugate** **MMAE**	Neuropathy, neutropenia **Conjugate** **MMAE** TC: no relationship with Conjugate or MMAE
POLIVY polatuzumab vedotin - piiq 2019 (AA)	MMAE; CD79b-directed AB	ORR **Conjugate** **MMAE**	Anemia: **MMAE** Neuropathy: **Conjugate**
PADCEV enfortumab vedotin-ejfv 2019 (AA)	MMAE; Nectin-4 directed AB	ORR **Conjugate** **MMAE**	Grade 3 TEAEs) ≥ Grade 3 rash and hyperglycemia and ≥ Grade 2 peripheral neuropathy **Conjugate** **MMAE** (correlation was not considered meaningful)
KADCYLA ado - trastuzumab emtansine (T-DM1) 2012	Emtansine, anti-HER2 monoclonal antibody	OS, PFS, ORR **Conjugate**	Hepatotox, Thromocytopenia **Conjugate**
ENHERTU fam-trastuzumab deruxtecan-nxki, 2019 (AA)	topoisomerase inhibitor MAAA-1181a or DXd, HER2-directed antibody	ORR **Conjugate** **DXd**	For different end points: **Conjugate** **DXd**
Mylotarg gemtuzumab Ozogamicin 2016	N-acetyl-gammacalicheamicin, CD33-directed monoclonal antibody	CR **Total Antibody** (flat relationship)	Venoocclusive disease (VOD) **Total Antibody**
BESPONSA inotuzumab Ozogamicin 2016	N-acetyl-gammacalicheamicin CD22 targeted antibody	CR/CRi and OS **Conjugate**	VOD & Sinusoidal obstruction syndrome **Conjugate**
TRODELVY sacituzumab Govitecan - hziy 2020 (AA)	SN-38 (topoisomerase I inhibitor); Trop-2 targeted antibody	ORR, PFS, OS **Total SN-38** **Free SN-38** **TAb**	Nausea/Vomiting: **Free SN-38** Diarrhea/Neutropenia: **Total SN-38**

Which Analyte Correlates Better in E-R Analyses Clinically for Approved ADCs?



Recommendations

Based on evaluation of available clinical data from the database and approved ADCs

- For efficacy analyses quantifying conjugate appears to be sufficient
- For safety analyses both conjugate and unconjugated payload (toxin) exposures might be needed
- Total antibody was used for exposure-response analyses in limited number of cases

These findings are based on limited data set which is predominantly with auristatin payload and cleavable linker. However, despite this limitation, quantifying the total antibody in later studies does not appear to add value

Measure Total antibody in FIH study. If it correlates to conjugate, then measuring TAb in later Phase studies might not be needed

Other Points for Consideration

- Total antibody was not used for E-R analyses in most cases. Hence its difficult to comment on the value of conjugate vs total antibody in E-R analyses. This could be an important consideration if the antibody has antitumor activity. However, given the high PK correlation, both analytes should perform similarly.
- Of the approved ADCs, 5 of 8 were approved under accelerated approval pathway. E-R analyses were conducted with relatively small sample sizes, using clinical or surrogate endpoints and limited dose ranging. Data from confirmatory studies, and survival endpoints will help confirm these findings.
- The ADCs included in these analyses have cytotoxic payloads. ADCs with targeted payloads and immuno-oncology payloads may or may not show similar trends
- Safety and efficacy for ADCs can depend of multiple factors - target expression, tumor penetration, DAR, release of cytotoxin, bystander effect etc. Semi-mechanistic and QSP models are increasingly used to understand these factors. Quantifying all analytes will aid in developing these models and enhance understanding of ADC PK/PD. Data from clinical studies in early clinical development might be sufficient to develop these models.

Acknowledgements

- IQ ADC Working Group Members

TALG	Dong Wei (Chair)	Takeda	CPLG	Chunze Li (Co-chair)	Genentech
	Renu Singh	GSK		Rajeev Menon	Abbvie
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	Seema Kumar	EMD Serono		Ajit Suri	Takeda
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Sponsor	Jens Sydor	GSK			

- IQ Translational and ADME Sciences Leadership Group (TALG)
- IQ Clinical Pharmacology Leadership Group (CPLG)