Clinical Pharmacology Insights into Dosing Strategies of Approved Antibody-Drug Conjugates

B. Thalluri[1], P. Vajjah[3], K. Vishwanathan[2], and A. Sawant[2]
[1] The University of Tennessee Health Science Center;
[2]AstraZeneca, Waltham, MA, United States; [3]AstraZeneca, Cambridge, UK
Acknowledgement: Dr. Bernd Meibohm[1] & Dr. Shankar Lanke[2]

Statement of Purpose

Over the past decade, Antibody Drug Conjugates (ADCs) have quickly emerged, capitalizing upon the success of specificity of antibodies and to minimize drug toxicity of potent payloads/warheads without compromising efficacy. Currently there are 11 ADCs approved by US FDA of which 8 were approved between 2017 through 2023, reflecting upon the steady growth observed in this field. With continued interest in this modality, it is important to understand how the knowledge of current ADCs could be used to conduct dose selection of the future ADCs. Given the similarities across payloads and/or mechanism of actions, learnings from approved ADCs were extrapolated towards drug development of future ADCs.

Description of Methods

A dataset comprising all approved Antibody-Drug Conjugates (ADCs) was compiled using US FDA labels, on doses evaluated in First-in-Human (FIH) dose escalation and selection, Pharmacokinetic (PK) characteristics, Population PK analysis, Drug-Drug interactions, Exposure-Response analysis, Adverse Event, Immunogenicity, Post marketing requirement and Post marketing commitments. The primary source of data for doses evaluated was the *"Clinical Pharmacology Biopharmaceutics Review(s)"* or *"Multi-Discipline Reviews"*. However, in instances where accelerated approval was granted, with data from preliminary clinical trial data from smaller cohorts the clinical pharmacology updates available online, including published articles, abstracts, and relevant sources were also utilized.

Results

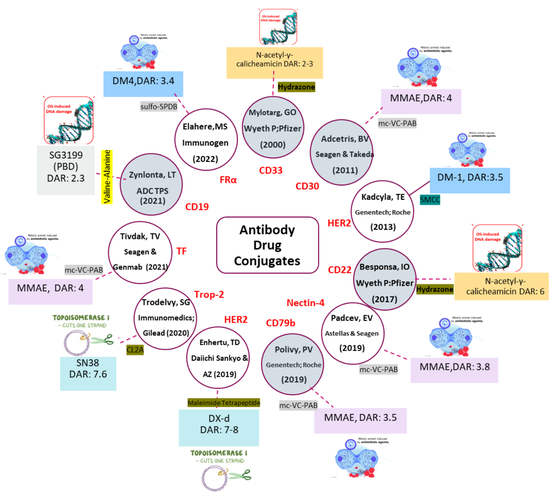

Fig.1 Characteristics of approved ADCs

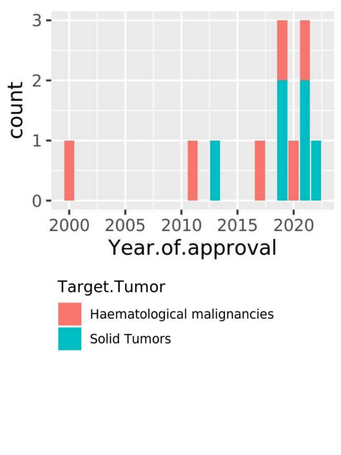

Fig.2 Trend of chronological Approval of ADCs

GO: Gemtuzumab ozogamicin, BV:Brentuximab vedotin, TE:Trastuzumab emtansine, IO: Inotuzumab Ozogamicin, EV: Enfortumab vedotin , PV: Polatuzumab vedotin , TD: trastuzumab deruxtecan, SG: sacituzumab govitecan-hziy, TV:Tisotumab vedotin , LT: Loncastuximab tesirine, MS:Mirvetuximab soravtansine-gynx, MMAE: Monomethyl auristatin E, DM1: Myotonic dystrophytype1, DXd: Deruxtecan, DAR: Drug to Antibody Ratio, AZ: Astrazeneca, GSK: GlaxoSmithKline, Filled circles: ADCs targeting Haems, Unfilled circles: ADCs targeting solid tumors

1.1 Dose escalation, Maximum tolerated dose & Approved dose

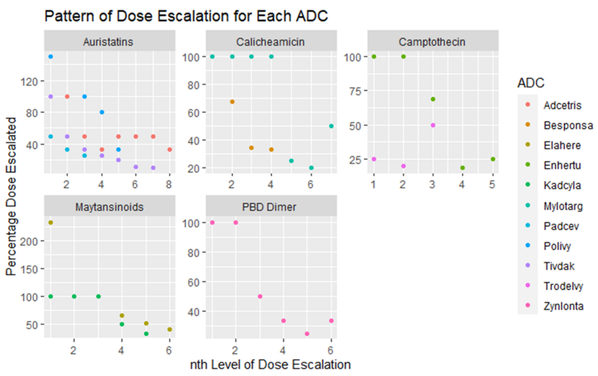

Fig.3 Dose escalation pattern for each ADC grouped on the payload category

Name of the ADC	HNSTD	Minimum dose in FIH	MTD	RP2D	Approved dose	Dosing regimen
Adcetris	3 mg/kg	0.1 mg/Kg	1.8 mg/Kg	1.8 mg/Kg	1.8 mg/Kg	Q3W
Besponsa	NA	0.4 mg/m^2	1.8 mg/m^2	1.8 mg/m$^{2\,\$}$	1.8 mg/m^{2} *	days 1,8,15
Elahere	NA	0.15 mg/Kg (total body weight)	6 mg/kg AIBW	6 mg/kg AIBW	6 mg/kg (AIBW)	Q3W
Enhertu	30 mg/Kg	0.8 mg/Kg	6.4 mg/kg (NBC/NGC)	5.4 mg/kg (BC, NSCLC), 6.4 mg/kg (NSCLC, GC)	5.4 mg/kg	Q3W
Kadcyla	10 mg/Kg	0.3 mg/Kg	3.6 mg/Kg	3.6 mg/Kg	3.6 mg/Kg	Q3W
Mylotarg	2.4 mg/m^2 (NOAEL)	0.25 mg/m^2	6 and 4 mg/m^2	9 mg/m2 or 6 mg/m$^{2\,\$}$	9 mg/m^{2}*	days 1,4, 7/ days 1 and day 8
Padcev	3 mg/kg	0.5 mg/Kg	Not reached	1.25 mg/kg	1.25 mg/kg	days 1, 8 & 15
Polivy	3 mg/kg	0.1 mg/Kg	Not reached	2.4 mg/Kg & 1.8 mg/Kg	1.8 mg/Kg	Q3W
Tivdak	3 mg/kg	0.3 mg/Kg	2 mg/Kg	2 mg/ Kg	2 mg/Kg	Q3W
Trodelvy	50 mg/Kg	8 mg/Kg	12 mg/Kg	8 & 10 mg/Kg	10 mg/kg	days 1 & 8
Zynlonta	NA	0.015 mg/Kg	Not reached	150 µg/kg, 75 µg/kg for subsequent cycles	150 µg/kg, 75 µg/kg for subsequent cycles	Q3W

Table.1. MTD vs RP2D vs Approved dose

HNSTD: Highest Non-severely Toxic Dose, FIH: First in Human Trials, MTD: Maximum Tolerated Dose, RP2D: Recommended Phase 2 Dose, Q3W: Once every three weeks, NBC: Non-Breast Cancer, Non-Gastric cancer, Breast cancer, LC: , NSCLC: non–small-cell lung cancer, AIBW: Adjusted Ideal Body Weight , NOAEL: No observed Adverse Effect Level, NA: Not found in the current literature search, $: Clinical Trials with fractionated dosing regimen were also conducted, *: Mylotrag and Besponsa has fractionated dosing regimen Mylotarg, Besponsa gives the details

1.2.1 Exposure response Analysis for Efficacy

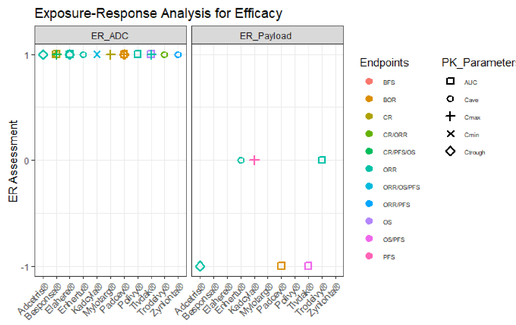

Fig.4 Values on the Y-axis shows the Positive correlation or meaningful or significant (value 1), Negative correlation or Not significant or non meaningful (value -1) and No correlation or flat relationship (value 0), for any of the exposure metrics (Cmax, Cave, Cmin, Ctrough, AUC) of the ADC or payload to 1 or more efficacy endpoints (CR, PFS, OS, ORR,BFS, PoR)

CR: Complete Response, PFS: progression-free survival, OS: overall survival, ORR: ORR (Overall response rate), BFS: attainment of Blast-free status, PoR: probability of response (PoR)

1.2.2 Exposure response Analysis for Safety

Name of the ADC	Safety End points Correlated with ADC	Safety End points Correlated with Payload	PK parameters used for the analysis	Exposure of ADC ~ AE	Exposure of Payload ~ AE
Adcetris	Grade ≥2 PN, Febrile Neutropenia	FN, grade ≥ 4 neutropenia, grade ≥ 3 TEAEs	AUC/time	Positive correlation	Positive correlation
Besponsa	VOD		AUC	Positive correlation	NA
Elahere	Ocular AEs of Grade ≥2 , Grade ≥ 2 PN		AUC, Cmax	Positive correlation	NA
Enhertu	Discontinuations associated with AEs (steady-state AUC), ILD (any grade (steady-state AUC) and grade ≥ 3 (steady-state Cmax)), and TEAEs decrease by ECHO/MUGA (grade ≥ 2 (steady-state Cmax)),	Anemia, neutropenia, and thrombocytopenia , dose reductions associated with AEs, drug interruptions associated with AEs, grade ≥ 3 AEs, and serious AEs	Cmax, Cmin, and AUC at cycle 1 and steady-state as well as average concentration (Cavg) during treatment or Cavg up to time of event	Positive correlation	Positive correlation
Kadcyla					No Correlation
Mylotrag	VOD, Grade ≥ 3 AE Hepatic AEs*		Cmax	Positive correlation	NA
Padcev	Grade 3 or higher treatment related adverse effects	Grade 3 or higher treatment related adverse effects	AUC, Cmax, Ctrough	Positive correlation	Positive correlation
Polivy	Grade ≥2 PN, time to first dose modification	Grade ≥3 anemia, Time to first dose modification	AUC, Cmax	Positive correlation	Positive correlation
Tivdak	Treatment-related AEs leading to dose interruption, reduction, or discontinuation, Grade 2+ ocular AEs	Treatment-related SAEs , all serious AEs	AUC, Cmax, CavgLast	Positive correlation	Positive correlation
Trodelvy	Grade ≥1 evaluated AEs, the risk of dose reductions and dose delays, Grade ≥3 Neutropenia	Nausea, Vomiting, diarrhea, Neutropenia (total SN38)	AUC, Cmax	Positive correlation	Positive correlation
Zynlonta	Grade ≥ 2 increased gamma-glutamyltransferase, liver function test abnormalities, pain, and skin/nail reactions		Cave, Cmin	Positive correlation	NA

Table.3 Brief overview on Exposure Response analysis for safety, AE: Adverse events, PN: Peripheral Neuropathy, VOD: Veno-occlusive Disorder, ILD: Interstitial Lung Disease, TEAEs : Treatment Emergent Averse Events, LVEF: Left Ventricular Ejection Fraction,

1.3 Adverse Events and toxicity profile

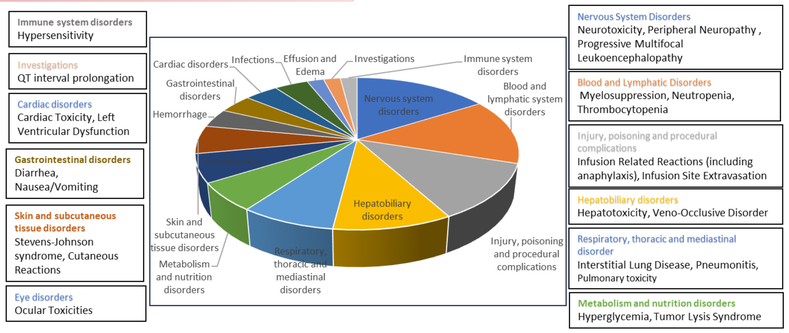

Fig.5 Distribution of adverse events across all the ADCs according to the label

1.4 Use of ADCs in specific populations

	Hepatic Impairment			Renal Impairment		
ADC	Mild	Mod	High	Mild	Mod	High
Adcetris						NE
Padcev						
Polivy						NE
Tivdak						NE
Mylotarg		NE	NE			NE
Besponsa		NE	NE			
Kadcyla	PMR					NE
Enhertu			NE			NE
Elahere						NE
Trodelvy		PMR		NE	NE	NE
Zynlonta		PMR				NE

Table.3 Impact of Hepatic and Renal Impairment on ADCs

Green: No dose modifications are required, Red : Avoid using , Orange : can be dosed with out any dose modifications but the patients should be monitored for the AEs, NE: not explored, PMR: Post marketing requirements

1.5 Drug-Drug interactions

Name of the ADC	Payload	In-Vitro	Clinical	PopPK	PBPK	Liability for DDI	FDA Label safety
Adcetris	MMAE	Yes	Yes			Yes	Concomitant use of strong inhibitors of CYP3A4 increase the exposure to monomethyl auristatin E (MMAE) and patients after coadministration should be monitored closely
Padcev	MMAE	Yes					
Polivy	MMAE	Yes		Yes	Yes		
Tivdak	MMAE						
Kadcyla	DM1	Yes				yes	Avoid use of strong CYP3A4 inhibitors or closely monitored if co-administered
Elahere	DM4	Yes				yes	Strong CYP3A4 Inhibitors: Closely monitor for adverse reactions.
Enhertu	DX-d		yes			No	
Trodelvy	SN38	NA				Yes	UGT1A1 inhibitors or inducers should not be administered
Mylotarg#	Calicheamicin	Yes	Drug-drug interactions between GO and AraC/DNR were also evaluated			Low	
Besponsa	Calicheamicin	Yes				Low	
Zynlonta	PBD	Yes				No	

Table.4 Drug-Drug Interactions for an ADC and FDA safety Label associated with it

#DDI b/w Mylotrag and Cytarabine /Daunorubicin were evaluated; NA : It was mentioned that BLA submission haven't included any DDI data Trodelvy

MMAE: Monomethyl auristatin E, PBD: Pyrrolobenzodiazepine, SN-38: 7-ethyl-10-hydroxy-camptothecin, DX-d: Deruxtecan

Interpretation

- Dose escalation of ADCs has utilized empirical and statistical methods, typically involving 3+3 or accelerated titration designs, with up to 6 dose levels tested for most ADCs, except Trodelvy which tested four levels
- Starting doses for ADCs in FIH studies range from 1/6th to 1/37th of the HNSTD. For Trastuzumab ADCs, a more conservative approach (>1/30th of the HNSTD) has been used. Except for Trodelvy, starting doses for ADCs ranged from 0.015 to 0.8 mg/kg, IV, Q3W
- For Padcev, Polivy, and Zynlonta, the maximum tolerated dose (MTD) was not established. For Zynlonta, the recommended phase 2 dose (RP2D) was determined based on accumulating toxicity at higher doses. Polivy's RP2D was decided based on the safety profile, using the maximum administered dose of 2.4 mg/kg
- For Adcetris, Besponsa, Elahere, Kadcyla, & Tivdak MTD is used as RP2D and eventually it is the approved dose
- Efficacy endpoints for ADCs often correlate with exposure levels, though exceptions and negative correlations exist for specific ADCs; safety endpoints are robustly predicted by ADC and UCPL exposures,
- Immunogenicity of ADCs varies, with generally low incidence of antidrug antibodies (ADAs) and inconsistent impact on pharmacokinetics, safety, or efficacy; ongoing research is needed to fully understand the clinical implications of ADA development.
- Most ADCs received Accelerated Approvals requiring further clinical trials to verify benefits, with specific post-marketing requirements issued for dosing regimens, safety in hepatic impairment, peripheral neuropathy, pediatric safety, and other evaluations, highlighting the ongoing need for comprehensive post-marketing studies.

Conclusion

This work summarizes approved ADCs and dosing strategies from end-to-end clinical development based on their clinical pharmacology characteristics. By conducting an analysis of US FDA labels of all approved ADCs w.r.t first-in-human, dose escalation, exposure-response relationships (efficacy and safety), and immunogenicity the review provides invaluable insights into dosing of ADCs during clinical development. Through synthesizing existing knowledge this work informs the key challenges and opportunities of ADC therapeutics.