Impact of Target Expression on the Adverse Event Profile of Antibody-Drug Conjugates (ADCs): Implications for Target Safety Assessments

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Introduction

- Antibody-drug conjugates (ADCs) are an emerging class of drugs comprised of three main components: an antibody, a linker and a payload. Several antibody-drug conjugates (ADCs) are already approved for use in oncology indications.
- The antibody target should have high expression in diseased cells and no or low expression in normal tissues. However, expression of the antibody target in normal tissue may pose a potential safety risk where cytotoxic payloads are utilized.
- The aim of this study was to guide target safety assessments (TSAs) by determining if target expression data for ADCs correlates with reported clinical toxicity.
- TSAs use target biology, gene and protein expression data, genetic information from humans and animals and competitor compound intelligence to understand and mitigate the potential safety risks associated with modulating a biological target.

Methods

- Safety data were obtained from the US FDA drug labels of twelve approved oncology ADCs (see Figure 1). Clinical adverse events (AEs) were collated from the black box warnings, warnings and precautions and adverse reactions sections. The twelve oncology ADCs included in this study spanned ten individual targets.
- Data on target protein and/or mRNA expression levels in normal human tissues were obtained from publicly available datasets deposited by the Human Protein Atlas consortium, and categorized as high, medium, low or negligible expression across key organ systems.
- For organ systems with medium or high expression levels of the target, analysis was conducted to determine if any notable clinical toxicity was reported that aligned with expression in relevant cells/tissues within those organ systems.

Table 1. Overview of antibody-drug conjugates analyzed

Drug	Target	Indication
Mylotarg® Gemtuzumab ozogamicin	CD33	Relapsed acute myelogenous leukemia (AML)
Adcetris® Brentuximab vedotin	CD30	Relapsed HL and relapsed sALCL
Kadcyla® Trastuzumab emtansine	HER2	HER2-positive metastatic breast cancer (mBC) following treatment with trastuzumab and a maytansinoid
Besponsa® Inotuzumab ozogamicin	CD22	Relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia
Lumoxiti® Moxetumomab pasudotox	CD22	Adults with relapsed or refractory hairy cell leukemia (HCL)
Polivy® Polatuzumab vedotin-piiq	CD79b	Relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)
Padcev® Enfortumab vedotin	Nectin-4	Adult patients with locally advanced or metastatic urothelial cancer who have received a PD-1 or PD-L1 inhibitor, and a Pt-containing therapy
Enhertu® Trastuzumab deruxtecan	HER2	Adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens
Trodelvy® Sacituzumab govitecan	Trop-2	Adult patients with metastatic triple-negative breast cancer who have received at least two prior therapies for patients with relapsed or refractory metastatic disease
Blenrep® Belantamab mafodotin-blmf	BCMA	Adult patients with relapsed or refractory multiple myeloma
Zynlonta® Loncastuximab tesirine-lpyl	CD19	Large B-cell lymphoma
Tivdak® Tisotumab vedotin-tftv	Tissue factor	Recurrent or metastatic cervical cancer

Results

Target expression level and clinical toxicity

- Across all 12 ADCs, adverse events (AEs) occurred in 70 % of organ systems that had high expression of the target and in 43% of organ systems where there was medium target expression.
- The clinical AEs were only considered potentially related to target expression if the toxicity corresponded to the relevant tissue types showing medium or high expression.
- Half of the instances of high target expression occurred in the hematologic and immune organ system. However, all twelve ADCs had hematologic and immune AEs regardless of target expression level, suggesting a strong contribution of non-target related toxicity.

	Organ system											
Target expression/ Drug AEs	Cardiovascular	Endocrine	Gastrointestinal	Hematopoietic and immune	Hepatobiliary	Integumentary	Musculoskeletal	Nervous system	Reproductive	Respiratory	Sensory	Urinary
CD33	L	N	M Salivary	M Bone marrow; lymphatic tissue	N	N	N	N	H Testis	N	N	M Kidney
Mylotarg				Y Febrile neutropenia								
BCMA	L^{G}	L^{G}	M^{G} Stomach; intestines	H^{G} Lymphatic tissue	L^{G}	N^{G}	L^{G}	L^{G}	L^{G}	L^{G}	L^{G}	L^{G}
Blenrep			Y Nausea	Y Thrombocytopenia; ↓platelets, lymphocytes & neutrophils								
HER2	M Heart muscle	L	L	M Appendix	L	M Skin	M Skeletal muscle	N	M Testes; fallopian tube; endometrium; cervix; placenta	M Lung; nasopharynx	N	M Bladder
Kadcyla	Y ↓ LVEF						Y Musculoskeletal pain			Y ILD & pneumonitis		
Enhertu	Y ↓ LVEF					Y Alopecia	Y Musculoskeletal pain			Y ILD & pneumonitis		
CD22	N	N	N	H Lymphatic tissue	N	N	N	N	M Testes	N	N	N
Besponsa				Y Myelosuppression; thrombocytopenia; (febrile) neutropenia; lymphopenia; anemia								
Lumoxiti				Y Anemia								
CD79(b)	N	N	L	H Lymphatic tissue	N	N	N	N	N	N	N	N
Polivy				Y Myelosuppression; thrombocytopenia; neutropenia; lymphopenia; anemia								
Nectin-4	N	L	M Esophagus; oral mucosa	M Tonsil	N	M Skin	N	N	M Placenta	N	N	M Bladder
Padcev			Y Diarrhea; nausea; dysgeusia			Y Rash; alopecia; dry skin						
Trop-2	N	N	M Esophagus; oral mucosa	L	L	H Skin	L	N	M Seminal vesicle; cervix	M Nasopharynx; bronchus	N	M Kidney; bladder
Trodelvy			Y Diarrhea; nausea; vomiting			Y Alopecia						
Tissue Factor*	L^{G}	M^{G}	M^{G}	L^{G}	M^{G}	H^{G}	L^{G}	M^{G}	H^{G}	M^{G}	M^{G}	M^{G}
Tivdak			Y Diarrhea; nausea			Y Rash; alopecia		Y Peripheral neuropathy		Y Pneumonitis		Y ↑Creatinine
CD19	N	N	L	H Bone marrow; lymphatic tissue	N	N	N	N	N	N	N	N
Zynlonta				Y Myelosuppression; thrombocytopenia; neutropenia; anemia								
CD30	N	N	N	L	N	M^{G}	N	N	H Testis; fallopian tube	N	N	N
Adcetris												

*Tissues not listed for tissue factor as it has widespread expression. ISD, interstitial lung disease; LVEF, left ventricular ejection fraction

High expression; Medium expression; Low/negligible expression; Corresponding AEs for medium/ high target expression; No corresponding AEs for medium/ high target expression

Conclusions

- Overall, expression levels of the antibody target are associated with clinical AEs in that tissue.
- However, the likelihood of toxicity is dependent on many factors not yet assessed in this study including the distribution of the ADC, the expression level of the target in normal versus diseased tissue, the payload used and the proliferation rate of the target tissues. In addition, the analysis of publicly available expression data sets does not include all tissue/cells types.
- When considering TSAs for new ADCs, expression of the antibody target in normal tissues should be highlighted as a potential risk. However, careful experimental assessment will be required to determine if high levels of target expression translate into clinical and/or nonclinical adverse effects.