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Supplementary information

The antibody–drug conjugate landscape

In the format provided by the authors

Database assembly
We assembled a comprehensive database of 182 antibody–drug conjugate (ADC) assets approved or in global clinical development as of December 2023. We limited our definition of ADCs to include antibody-based carriers and small-molecule payloads. Other drug-conjugated therapeutics using non-antibody carriers (such as peptides and small molecules) and non-chemotherapy payloads (such as radioisotopes and oligonucleotides) were not included.

We compiled our initial set of clinical assets using the CiteLine PharmaProjects database. To identify relevant products, we filtered the database based on keywords in the summary. For example, traditional ADCs were filtered with the keywords: “antibody” or “antibodies” or “mab” and “antibody drug conjugate” or “antibody-drug conjugate” or “antibody cytotoxin conjugate” or “antibody payload conjugate” or “antibody-calicheamicin conjugate” or “immunotoxin conjugate” or “trastuzumab conjugate”.

To verify that our list was comprehensive, we cross-checked it against multiple published databases on ADCs including ADCReview’s Drug Map and the recently published ADCdb database.

For each asset, we manually confirmed active clinical development using ClinicalTrials.gov and/or the company website. To determine components of ADCs, we first referred to the ADCdb database and ADC Drugmap. We then confirmed the accuracy of these components by referencing company websites, press releases, conference presentations, academic publications and SEC filings.

Application of two-class framework
We developed a two-class framework to categorize ADCs based on the potential to overcome the two main challenges in ADC development, as shown in Supplementary Figure 2. Of the 168 pre-launch ADC assets in clinical trials, 149 had sufficient publicly disclosed information for categorization. Products simultaneously pursuing novel payload MoAs/targets and optimized delivery components are considered type-1 assets, as their primary commercial differentiation will come from the new payload MoA/target. We assume that sponsors of clinical trials for assets with an identical target and payload mechanism of action (MoA) as on-market products believe their candidate can achieve best-in-class status through optimized delivery; therefore, we categorize these products as type-2 assets.

Assessment of next-gen technology
We evaluated a subset of next-gen ADC components used in clinical ADC assets. Three preclinical technologies with sufficient publicly disclosed information were included. Next-gen tech was categorized according to our framework to either expand ADC applicability or improve upon current ADCs through optimized design components (Supplementary Tables 1, 2 and 3). Evaluation of the potential impact of the different technologies is based on review of scientific literature.

Supplementary Table 1 | **ADC assets grouped by phase and asset type**

	Ph 1	Ph 2	Ph 3
Type-1 asset	72	32	5
Type-2 asset	18	15	7
Total	**90**	**47**	**12**

Supplementary Table 2 | **ADC assets grouped by phase and tumor type**

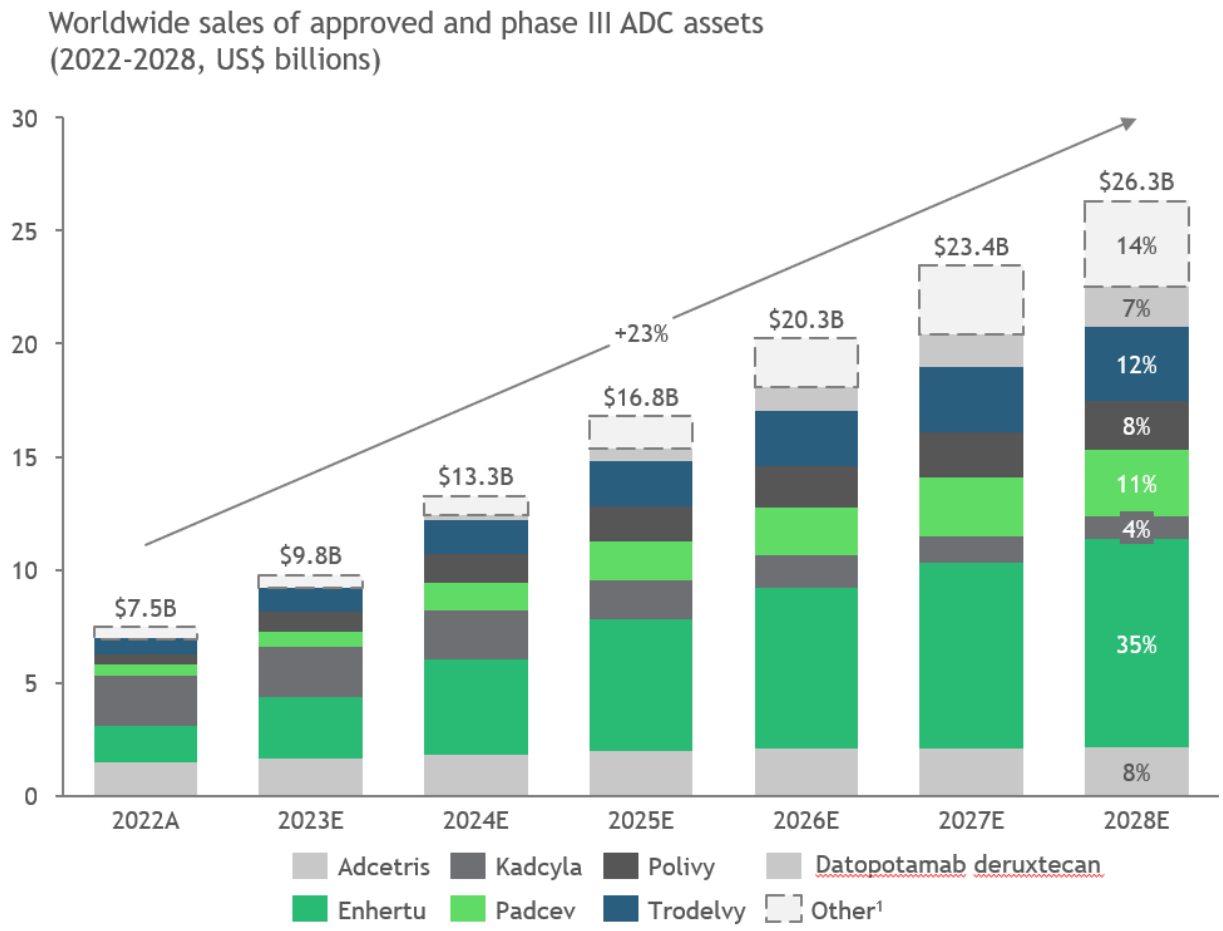
	Ph 1	Ph 2	Ph 3
Solid	88	43	12
Heme	51	7	0
Both	1	1	0
Total	**104**	**51**	**12**

Supplementary Table 3 | **Clinical ADC assets grouped by design levers**

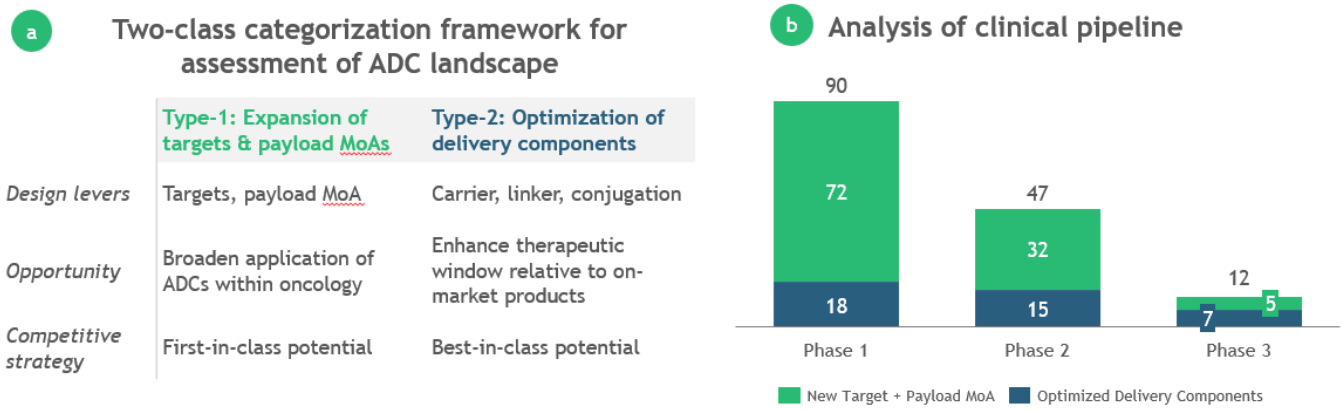
Payload MoAs	Ph 1	Ph 2	Ph 3
Degrader	1	-	-
Immunoactivator	3	1	-
Multi-drug payload	-	-	-
Apoptotic inducer	1	-	-
RNA Pol II inhibitor	1	-	-
Kinesin inhibitor	1	-	-
Undisclosed*	19	5	-
Carrier	**Ph 1**	**Ph 2**	**Ph 3**
Classic Ab	79	43	12
Bispecific	4	3	-
Conditionally activated	1	2	-
Ab fragment / nanbody	1	-	-
Undisclosed*	20	3	-

Linker	Ph 1	Ph 2	Ph 3
β-Glucuronidase cleavable	2	1	1
Legumain cleavable	1	-	-
Polysarcosine hydrophobic mask	-	-	-
Fleximer scaffolds	3	-	-
Click-Cleavable	-	-	-
Undisclosed*	59	14	-
Conjugation	**Ph 1**	**Ph 2**	**Ph 3**
Non-natural AAs	1	1	1
Glycan conjugation	4	1	-
Sortase-mediated transpeptidation	3	-	-
Undisclosed*	66	13	1

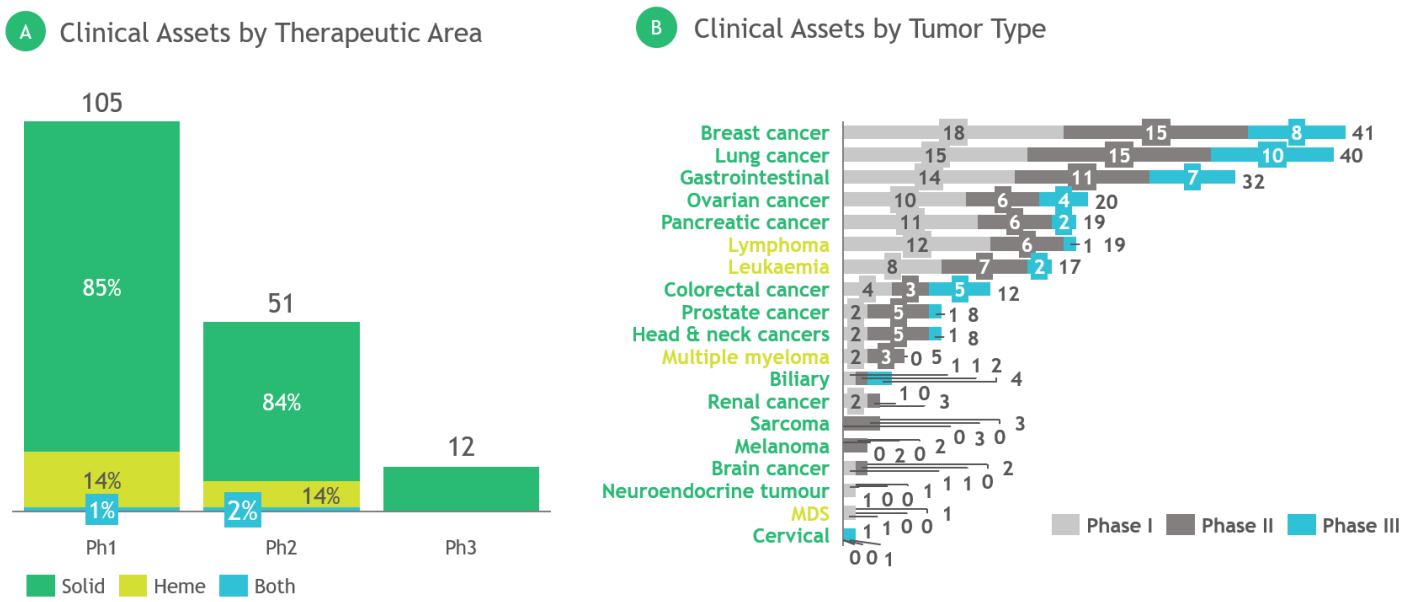
Categories reflect key innovation levers and are not exhaustive. *Undisclosed includes proprietary platforms with non-disclosed technology.



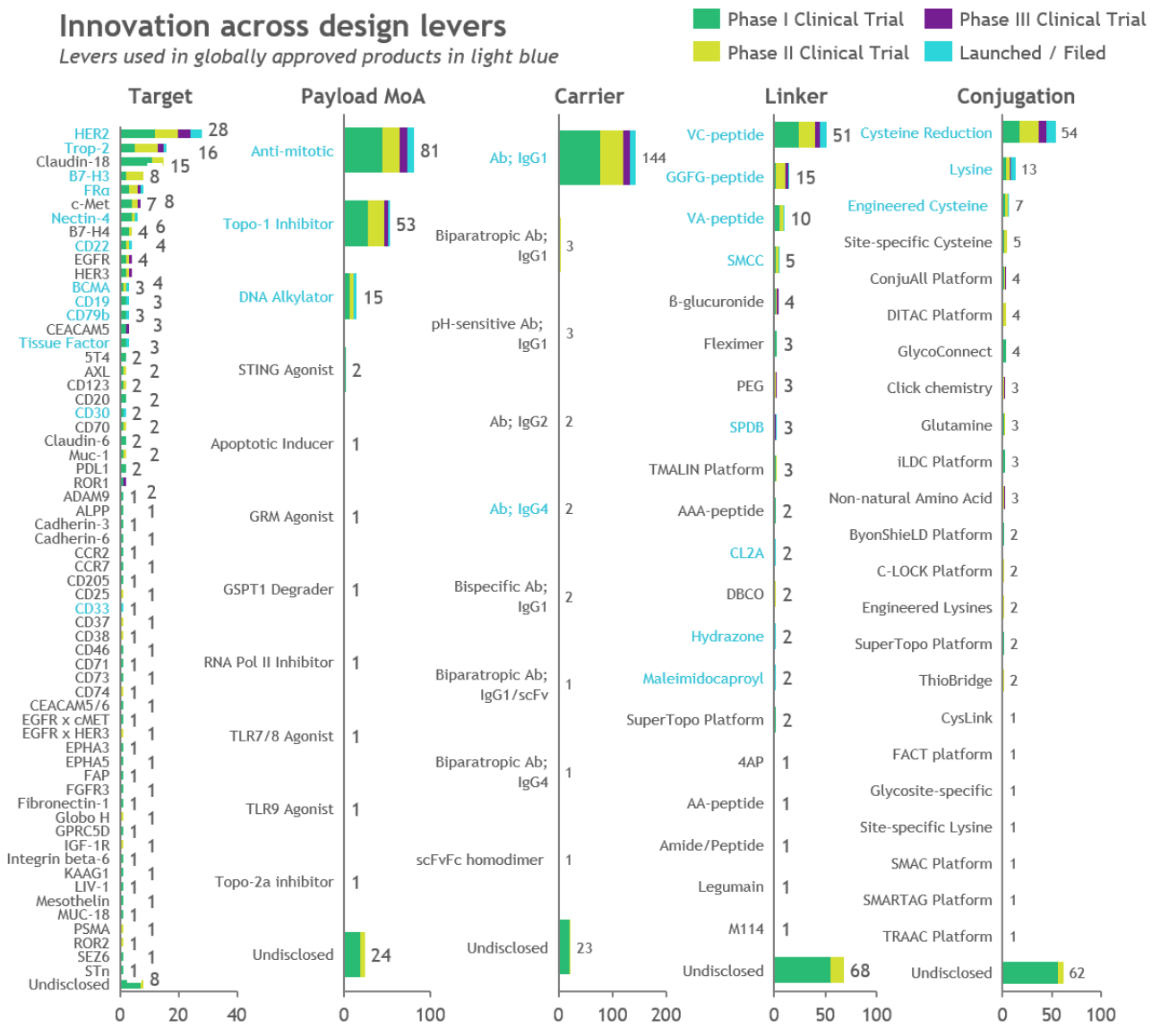
Supplementary Figure 1 | **Forecasted revenue for antibody–drug conjugates on the market or in phase III development.** [1]Other includes 10 approved and phase III ADCs with <$1 billion of forecasted sales between 2023–2028
Source: EvaluatePharma (October 2023); BCG analysis.



Supplementary Figure 2 | **Analysis of the antibody–drug conjugate landscape. a,** Categorization framework used for analysis of clinical-stage ADCs. **b**, Pipeline analysis using the framework; design levers for each clinical asset were compared with approved ADCs.



Supplementary Figure 3 | **Antibody–drug conjugates in clinical trials**. **A**, Tumour types. Both refers to assets studied in solid and haematological tumours. **B**, Indications. Assets studied for multiple tumour types are counted for each.



Supplementary Figure 4 | **Innovation across design levers**. Detailed and expanded view of the data shown in Figure 1.

Assessment of next-gen tech

Potential Profile Relative to Approved ADC Components

Improved profile | *Inferior profile* | *Similar*

		Next-gen Payloads	Tumor-cell killing	Acquired Tumor Resistance	Immune Activation	Toxicity	Combinability with SoC	Maturity	Likelihood to expand ADC applicability
Expansion of payload mechanisms	Payload Innovations	Degraders						Ph 1	• High
		Immunoactivators						Ph 2	• High
		Multi-drug payloads						PC	• Mid
		Apoptotic Inducer						Ph 1	• Low
		RNA Pol II Inhibitor						Ph 2	• Low
		Kinesin Inhibitor						Ph1	• Low

		Next-gen Delivery Components	Specific on-target binding	Cellular Uptake	Tumor Penetration	Stability in circulation	Payload Capacity	Mfr. Homogeneity	Ease of Mfr.	Maturity	Threat to current-gen ADCs
Optimization of delivery components	Carrier Innovations	Bispecific antibodies								Ph 2	• Mid
		Conditionally activated antibodies								Ph 2	• Mid
		Antibody fragments / nanobody								Ph 1	• Low
	Linker Innovations	β-Glucuronidase Cleavable								Ph 3	• Mid
		Legumain Cleavable								Ph 1	• Mid
		Polysarcosine Hydrophobic Mask								PC	• Mid
		Fleximer scaffolds								Ph 1	• Mid
		Click-Cleavable								PC	• Mid
	Conjugation Innovations	Non-natural AAs								Ph 3	• Mid
		Glycan Conjugation								Ph 2	• Mid
		Sortase-mediated Transpeptidation								Ph 1	• Low

Supplementary Figure 5 | **Assessment of next-gen tech**. Detailed and expanded view of the data shown in Figure 2.