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The antibody–drug conjugate landscape

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Antibody–drug conjugates (ADCs) have become a key therapeutic modality in oncology, spurred by superior clinical profiles compared to standard-of-care chemotherapy across multiple indications. Consequently, revenue from approved ADCs and those in late phase III development is forecasted to reach $26 billion in 2028 (Supplementary Fig. 1).

Despite the success of ADCs, long-term growth in their application faces two main challenges. First, the few validated payloads are restricted to action (MoAs) restrict addressable indications. Approved ADC payloads cover three cytotoxic MoAs – anti-mitotic, DNA alkylation and topoisomerase I inhibition – that typically require tumour-specific overexpression of the target antigen to ensure sufficient and safe payload delivery. As such, these ADCs primarily target established tumour antigens such as HER2, CD20 and BCMA.

Second, non-specific and insufficient payload delivery narrows the therapeutic window of ADCs. Delivery components for approved ADCs typically include cleavable peptide linkers stochastically conjugated through cysteine reduction to monoclonal antibody carriers. Premature payload release, poor tumour penetration, variable drug-to-antibody ratios and aggregation are common issues.

To explore the impact of next-generation ADC technology on these challenges, we investigated innovation in the ADC clinical pipeline across five design levers – target, payload MoA, antibody, linker and conjugation method – and assessed the likelihood for expanding the addressable indications or widening the therapeutic window of ADCs.

Assessment of the clinical pipeline

ADC assets in development were categorized into two types based on the potential to overcome the two main challenges (Supplementary Fig. 2a). Type-1 assets have new targets and/or payload MoAs and have first-in-class potential. Type-2 assets leverage established target/payload MoA combinations with novel delivery components to achieve a best-in-class profile.

Daiichi Sankyo's patritumab deruxtecan, which targets HER3, is an example of a type-1 asset. Recent data from the phase II HERTHENA-Lung01 trial showed an overall response rate (ORR) of 30% in patients with an EGFR mutation and previously treated with an EGFR inhibitor and platinum-based chemotherapy, compared to an estimated real-world ORR of 14% in a similar patient population.

Merck and Kelun Biotech's SKB264, an example type-2 asset, has the same target and payload MoA as the approved ADC sacituzumab govitecan (Trodelvy; Gilead). SKB264's differentiated 2-methyladfonyl pyrimidine linker increases stability in circulation compared to sacituzumab govitecan. An ORR of 40%, with 56% of patients having adverse events (AEs) of grade 3 or higher, was reported for a phase II study of SKB264 in patients with pre-treated metastatic triple-negative breast cancer. This compares favourably to the 21% ORR and 74% AE rate reported for sacituzumab govitecan in a similar patient population.

We applied this framework to a database of 168 ADCs in clinical development (Supplementary Fig. 2b). Overall, ~85% of assets address solid tumour indications, with breast and lung cancer the most common (Supplementary Fig. 3). Of the phase III ADCs, ~60% are type-2 assets that leverage established targets and payload MoAs with improved delivery components, which may reflect the recency of the modality's success and a lower risk tolerance in late-stage development. Greater biological risk is evident in earlier-stage development: ~75% of phase I/II ADCs are type-1 assets with novel combinations of targets and payload mechanisms. Fig. 1 highlights specific components used by assets in development, with the highest concentration in components validated by approved products and a long tail of single-digit assets with novel components (Supplementary Fig. 4).

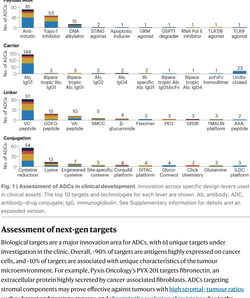

Fig. 1 | **Assessment of ADCs in clinical development.** Innovation across specific design levers used in clinical assets. The top 10 targets and technologies for each lever are shown. Ab, antibody; ADC, antibody–drug conjugate; IgG, immunoglobulin. See Supplementary information for details and an expanded version.

Assessment of next-gen targets

Biological targets are a major innovation area for ADCs, with 61 unique targets under investigation in the clinic. Overall, ~90% of targets are antigens highly expressed on cancer cells, and ~10% of targets are associated with unique characteristics of the tumour microenvironment. For example, Pyxis Oncology's PYX-201 targets fibronectin, an extracellular protein highly secreted by cancer-associated fibroblasts. ADCs targeting stromal components may prove effective against tumours with high stromal–tumour ratios such as breast and prostate cancers, and abrogate the evolution of resistance due to the genetic stability of stromal cells.

Assessment of next-gen technology

To gauge the potential impact of ADC innovation, we categorized next-gen technology according to our innovation framework and assessed the profile compared with marketed ADCs (Fig. 2). Here, we highlight a subset of next-gen designs levers that may be of interest given their novelty and/or promising preclinical and clinical data.

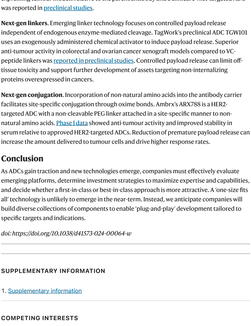

Fig. 2 | **Assessment of next-generation ADC technology.** Evaluation of next-gen ADC components on potential to either expand ADC applicability or optimize delivery components. Novel biological targets are not considered a technology and therefore not included in the assessment. ADC, antibody–drug conjugate. See Supplementary information for details and an expanded version.

Next-gen payloads. Small-molecule degraders are a promising payload class given their high specificity, picomolar potency and ability to target a broad set of intracellular proteins associated with cancer. Orum Therapeutic's ORM-5029 delivers a degrader payload selective for GSPT1, a GTPase overexpressed in multiple cancers including gastric, colorectal and breast cancer. Anticancer activity similar to trastuzumab deruxtecan (Enhertu; Daiichi Sankyo) was reported in breast cancer models in preclinical studies. The upcoming phase I data for ORM-5029 will be the first clinical data for antibody–degrader conjugates.

Next-gen carriers. Engineering antibodies with variable antigen binding affinity can reduce off-tissue toxicities and increase tumour-specific exposure. Strategies include shielding Fab domains with peptide masks susceptible to cleavage by proteases overexpressed in tumours, and engineering antibodies with optimized pH-sensitive binding characteristics. Despite past failures, antibody engineering has potential to expand the therapeutic window and treat patients with lower target expression levels. For example, Mythic Therapeutic's MYTX-011 is designed with lower antigen affinity at endosomal pH to enhance payload escape from endosomes. Increased internalization, cytotoxic activity and in vivo efficacy against c-Met expressing tumour models relative to the parent antibody and a clinical c-Met targeted ADC was reported in preclinical studies.

Next-gen linkers. Emerging linker technology focuses on controlled payload release independent of endogenous enzyme-mediated cleavage. TagWork's preclinical ADC TGW101 uses an exogenously administered chemical activator to induce payload release. Superior anti-tumour activity in colorectal and ovarian cancer xenograft models compared to VC-peptide linkers was reported in preclinical studies. Controlled payload release can limit off-tissue toxicity and support further development of assets targeting non-internalizing proteins overexpressed in cancers.

Next-gen conjugation. Incorporation of non-natural amino acids into the antibody carrier facilitates site-specific conjugation through oxime bonds. Ambrx's ARX788 is a HER2-targeted ADC with a non-cleavable PEG linker attached in a site-specific manner to non-natural amino acids. Phase I data showed anti-tumour activity and improved stability in serum relative to approved HER2-targeted ADCs. Reduction of premature payload release can increase the amount delivered to tumour cells and drive higher response rates.

Conclusion

As ADCs gain traction and new technologies emerge, companies must effectively evaluate emerging platforms, determine investment strategies to maximize expertise and capabilities, and decide whether a first-in-class or best-in-class approach is more attractive. A 'one-size fits all' technology is unlikely to emerge in the near term. Instead, we anticipate companies will build diverse collections of components to enable 'plug-and-play' development tailored to specific targets and indications.

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SUPPLEMENTARY INFORMATION

1. Supplementary information

COMPETING INTERESTS

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