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ADCs
The fuel for future growth

A deep dive into the fast-evolving landscape of Antibody Drug Conjugates (ADCs)

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The ADC market is red hot

The potential opportunity which ADC therapy offers for the treatment of multiple cancers has generated and continues to generate numerous deals and partnerships. Over the last five years, the number of ADC deals per month has almost tripled, with an average of two ADC deals closed per month in 2023, outpacing deals involving other emerging cancer therapies (see Figure 1). ADC deal values have also increased, over time, with most recent deals valued in the billion-or-more-dollar range.

Most partnerships occur early in the product development cycle, with the technology often owned by smaller companies, whilst the monoclonal antibody (mAb) and the commercial expertise lie with larger organisations.

Merck is one of the top companies actively licensing technologies for the development of ADCs. In December 2022, it generated one of the biggest licensing deals, valued at $9bn, by forming an alliance with Kelun-biotech for the exclusive rights to develop, manufacture and sell seven preclinical ADCs. In October 2023, Merck also announced an agreement to pay $4bn upfront to Daiichi Sankyo for the co-development and co-commercialisation of three of Daiichi's ADC candidates across multiple cancer types. If the three ADC candidates were to be successfully commercialized Merck is scheduled to pay up to $16.5bn in sales milestones. This will be an investment that could potentially bring in big returns for the two companies, based on the forecasted multi-billion-dollar commercial revenue.

One of the reasons Daiichi Sankyo is an attractive partner is because of their successful partnership with AstraZeneca in launching blockbuster ADC Enhertu. The Japanese company also has a well-established manufacturing capability – a key determinant of success with ADCs.

More recently (April 5, 2024), Merck announced its acquisition of biotech start-up Abceutic in hopes to leverage the biotech's new payload-binding selectivity enhancer (PBSE) technology to optimize ADC safety. The PBSE technology developed by Abceutic targets the neutralization of stray payload molecules resulting from off-target ADC delivery, addressing one of the most common undesirable effects of this therapy.

An alternative model for partnership deals is the acquisition of the ADC developer by big pharma.

In March 2023, Pfizer announced its purchase of Seagen for $43bn. This strategic acquisition makes Pfizer a powerful leader in the current and future ADC space as, together, they own almost half of the ADCs on the market, whilst continuing to invest in the clinical development of new candidates.

At the end of November 2023, AbbVie also announced its acquisition of Immunogen for $10.1bn – a deal in which they will gain FDA-approved ADC Elahere – and over 20 additional ADC assets that are under development. This agreement positions AbbVie in the ADC market – a territory they had not previously ventured into.

Notable deals and partnerships aim not only to bring technologies together, but also advance innovation and unlock new horizons whilst expanding the category's potential. For instance, Vertex Pharmaceuticals closed a deal with Immunogen to conduct research using its ADC technology to aid in the discovery of novel targeted conditioning agents for gene editing. In September 2023, Seagen also announced a deal with Nurix Therapeutics Inc to develop a new class of medicines called Degrader-Antibody Conjugates (DACs). The collaboration will focus on an innovative approach to combine antibody-drug combination and targeted protein degradation, to create new mechanisms of action as well as improve specificity for cancer treatment.

With big new players joining and disrupting the ADC market through major ADC deals and acquisitions, category leadership is evolving, with companies such as Daiichi Sankyo, AbbVie, Merck and Bicycle Therapeutics building out strong ADC pipelines. Certain category leaders appear on track to maintain their positions, with Pfizer notably solidifying its standing through the acquisition of Seagen, thereby expanding its pipeline to include 12 ADCs.

Figure 1

Pharma is expecting a second wave of ADC launches, following a rapid increase in the number of deals.

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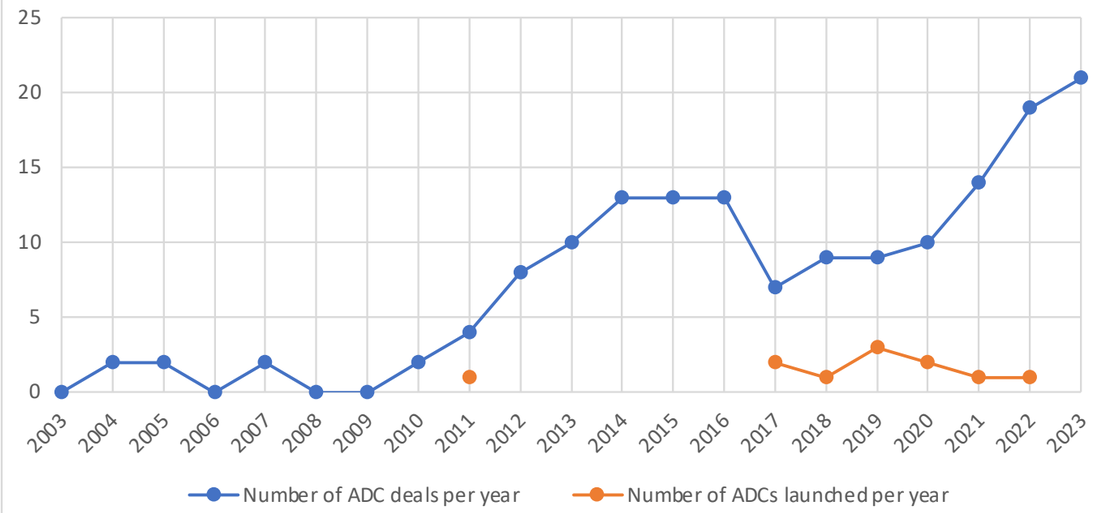
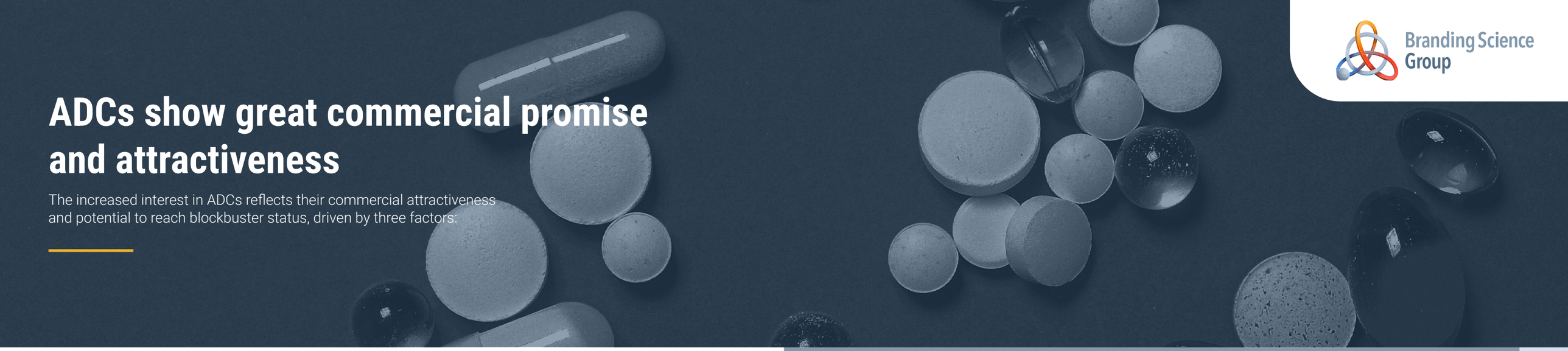
The trend in the number of ADC deals over the last 20 years is not one of continuous growth **(Figure 1)**. Following a rapidly growing wave of deals between 2009 and 2016, 10 out of the 13 approved ADCs were launched. Later, the number of ADC deals halved in 2017, taking a subsequent four years to climb back up. Since 2018, the number of deals has increased rapidly, which indicates the market is likely to enter a second wave of ADC approvals and launches.



Analysis based on BioMed Tracker data from January 2003 to December 2023. Data includes financing, acquisition, and alliance deals.



ADCs show great commercial promise and attractiveness

The increased interest in ADCs reflects their commercial attractiveness and potential to reach blockbuster status, driven by three factors:

1. Approval across different indications

One of the many benefits of ADCs' modes of action is that one mAb can show an affinity for biomarkers found on different tumor cells, and potentially even enable pan-tumor strategy. As such, approximately 70% of approved ADCs are undergoing further clinical trials to demonstrate their efficacy across a broad range of tumors that express its biomarker (1).

Kadcyla and Enhertu are leading the market in terms of revenue. Both target HER2- positive biomarkers with a trastuzumab mAb. Their success can be linked to the high prevalence of breast cancer, the presence of HER2 biomarkers on different cancerous tissues, and the high utilization of trastuzumab before the ADC entered the market.

The versatility of a mAb in targeting different biomarkers which may be found on different tumour cells increases the patient pool, which is a critical success factor for ADCs. For instance, as HER2 biomarker is also found on gastric solid tumors, and non-small-cell-lung cancer (NSCLC) tissue, Enhertu was further approved in these indications.

2. Reduced competitive intensity due to development and manufacturing complexity

The complex manufacturing processes in conjugating the antibody to the cytotoxic molecule makes the development of ADC biosimilars highly complex and costly. Developers undergo challenges in the manufacturing of ADCs due to their highly active cytotoxic component, requiring specialized assays, containment equipment and prolonged processes. These challenges, as well as strict regulatory guidelines, make biosimilar development challenging and expensive, thereby providing the original ADC with strong market share even after loss of exclusivity.

However, such an advantage doesn't apply in all cases. Zydus Cadila, an Indian biopharmaceutical company, has launched a biosimilar for Kadcyla in India. This marks a developmental breakthrough due to the complexity of achieving assay similarity. Whether an ADC biosimilar could demonstrate the data to gain approval from the US and EU drug regulatory entities remains to be seen.

3. Strong revenue potential and high return on investment (ROI)

ADCs generate stronger revenue and higher ROI than mAbs alone. Their novelty allows them to be marketed at a higher price because they target a wider and often more established patient population, and they gain a stand-alone Biologics License Application (BLA) regardless of the mAb they utilise. In fact, 3 out of 13 launched ADCs reached blockbuster status: Kadcyla, Adcetris and Enhertu.

To create a successful ADC, the developer needs to connect three complex components that carry distinct challenges:

1. The mAb and its affinity to targeted antigens

- Selecting a unique antigen is crucial to ensure the precision of the therapy and minimize off-target effects at the time of mAb binding.
- Investigating the mAb's affinity to other antigens in the microenvironment is crucial to minimize the risk of delivery to non-targeted cells.

2. The linker stability in circulation

- Existing linkers often release payloads off-target, leading to uncontrolled toxicity.
- Optimizing linker technology to increase circulation stability is at the forefront of ADC development.

3. The cytotoxic payload's balanced toxicity and safety

- Getting the right balance of payload potency, stability during conjugation and circulation, and overall safety is a significant challenge in ADC's development.

ADC development has its limitations

Whilst the commercial potential of ADCs is undeniable, they are not without limitations, much of which are driven by developmental challenges.

Toxicity and safety concerns

ADCs present with unique and sometimes unpredictable adverse effects profiles that are often not understood. Consequently, toxicity is front of mind throughout development and post-approval, as the potency of the cytotoxic molecule needs to be balanced with the requisite efficacy, without compromising safety.

Toxicity risk is a barrier to the approval of additional indications as it may vary in different cancerous tissues. For example, at ESMO 2023, Daiichi Sankyo and AstraZeneca presented positive results for two phase III trials (TROPION-Lung01 and TROPION-Breast01) testing ADC candidate Dato-DXd in two solid tumor types (2,3). While the clinical program results demonstrated significant improvements in progression-free survival compared to existing standards of care, significant safety concerns emerged because of several deaths (2,3). Daiichi Sankyo and Astra Zeneca addressed these concerns at ESMO 2023, saying the deaths were linked to existing lung damage prior to coming into the trial and overall disease progression, as more patients in the lung cancer study experienced adverse events compared to breast cancer (4).

However, some companies remain unconvinced by ADCs' safety profiles, specifically regarding interstitial lung disease side effects. In fact, at J.P. Morgan's Healthcare conference in January 2024, Novartis' CEO explained resisting the ADCs' temptation as he believes radiotherapies show a safety edge when compared to ADCs, whilst providing a similar targeted mode of action (5). Following years of unsuccessful ADC research, Novartis remains the only major cancer drug developer that doesn't have an ADC deal.

Safety issues are the cause of ADC Mylotarg's chequered past. It was removed from the market in 2010, ten years after its launch in the US (2000), after several early deaths were recorded, and due to a lack of ability to verify clinical benefits as part of clinical programs (6). Six years later (2017), Mylotarg was reintroduced in the US market, in a lower dosage. This is a reminder that a fine line exists between ADCs cytotoxic payloads' potency and safety.

Volume of complexity of manufacturing

One of the main barriers to ADCs is the reduced ability to produce large volumes due to challenging and costly manufacturing processes, which involve multiple steps, including antibody production, drug synthesis, and conjugation.

As most companies do not have these established, they need to build them, impacting both the profit margins and the ability of the company to guarantee supply. Drug developers are continuously thinking about ways to optimize ADC technology manufacturing, increase volume and reduce costs. Advances are made in the stable linker technology used to connect a chemotherapy payload to an antibody. With extensive heritage in ADC development, Daiichi Sankyo is leading the industry in terms of ADC design with its proprietary ADC technology composed of a tetrapeptide-based cleavable linker and an exatecan derivative (DXd) payload.

Consequently, the high production cost and the increased risk of achieving development success requires strong consideration to ensure expected profitability goals are achieved.

ADCs are here to stay, and innovation is key to their growth

The ADC landscape is ever evolving, with companies continuously forming new partnerships and closing new deals in pursuit of commencing ADC clinical programs in new indications and disease areas.

There has been explosive growth in the number of ADC clinical programs. In 2022, there was a 90% increase in the number of ADCs entering phase I clinical trials and an overall 35% increase in ADC clinical trials, compared to 2021. Most ongoing ADC programs are in early phases of development with 90% of ongoing ADC clinical trials being in phase I or phase II (7).

We have identified five key trends that will shape the ADC market in the next 5–10 years, in line with the increase in ADC deals over the years (see Figure 1).

1 Doubling down on versatile biomarkers

Although there are clinical programs evaluating the safety and efficacy of ADCs across various cancer indications, two cancer biomarkers stand out: HER2 and TROP2. Together, these two targets make up to 20% of all ADC programs in clinical development, as they are found in multiple types of cancerous cells.

2 Redefining the targeted patient pool

ADCs can also redefine the targeted patient pool. For example, the launch of Enhertu led to a renaissance in the field of pathology, transforming the traditional dichotomy HER2 definition to include descriptive and actionable HER2-low category. Promising results were recently reported at ESMO 2023 for Enhertu and Dato-DXd.

3 Pairing ADCs with immunotherapy

A hot topic at ESMO 2023 was the transformational clinical trial results (CheckMate-901; EV-302) of ADC Padcev (Seagen & Astellas) in combination with immune-oncology drug Keytruda (Merck). Data shows that the pairing demonstrated an increased overall survival rate when compared to chemotherapy (8). This is the first time an ADC and immunotherapy combination shows overall survival benefit, which is sure to spike the interest of others.

The field is likely to advance rapidly, with promising Phase Ib and Phase II data also presented at ESMO, for the combination of Dato-DXd and Imfinzi (AstraZeneca) for first-line advanced triple-negative breast cancer. Results demonstrate an impressive response rate of 79% (9).

4 Chasing tumour agnostic labels

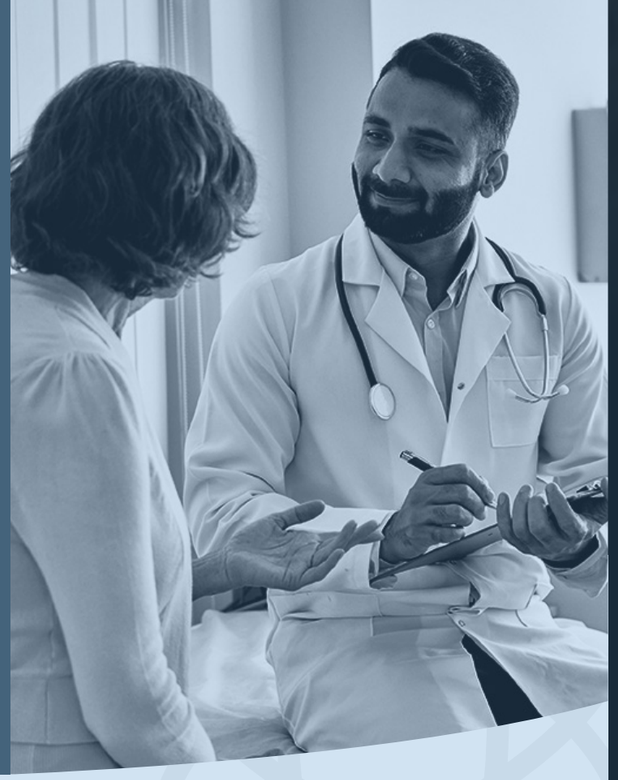
Research in breast cancer is leading the way to expand the application of ADCs to the treatment of a wide range of solid and blood cancer tumours, regardless of their location. In August 2023, the FDA granted Breakthrough Therapy Designation to Enhertu, for patients with previously treated HER2-expressing cancers (IHC 3+), after Enhertu demonstrated it can hit tumours regardless of their location and demonstrated progression-free survival and overall survival benefits (DESTINY-PanTumor02) (10). If approved, it will represent the largest patient population agnostic label, and the first ADC to achieve pan-tumour approval.

5 Indications beyond oncology

New ADC clinical programs are also testing ADCs for novel non-oncology indications, such as blood disorders (thalassemia and sickle cell anaemia), pseudomonas, HIV/ AIDs, bone marrow transplant and stem cell transplant. However, HIV/ AIDS is the only non-oncology indication being explored in clinical trials at this time. Insights on the future landscape suggest that oncology will remain the therapy area of focus, with greater emphasis on solid tumours.

The bottom line...

The increased interest in ADC technology and research carries a strong potential to advance patient care by offering better efficacy, superior tolerability, and new treatment options in categories with high unmet needs. Given their strong potential to achieve blockbuster status, ADCs appear to be a worthwhile investment. In fact, ADCs' improved efficiency and versatility draws increasingly more pharmaceutical companies to invest in the new therapy in hopes to strengthen their oncology pipelines and obtain higher profit margins.
However, the competitive landscape driven by the number of players, and the ability to launch biosimilars post loss of exclusivity, will dictate the overall revenue and profit gain of ADCs.



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