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White Paper

Antibody-drug Conjugates: ‘Magic Bullets’ Become Reality

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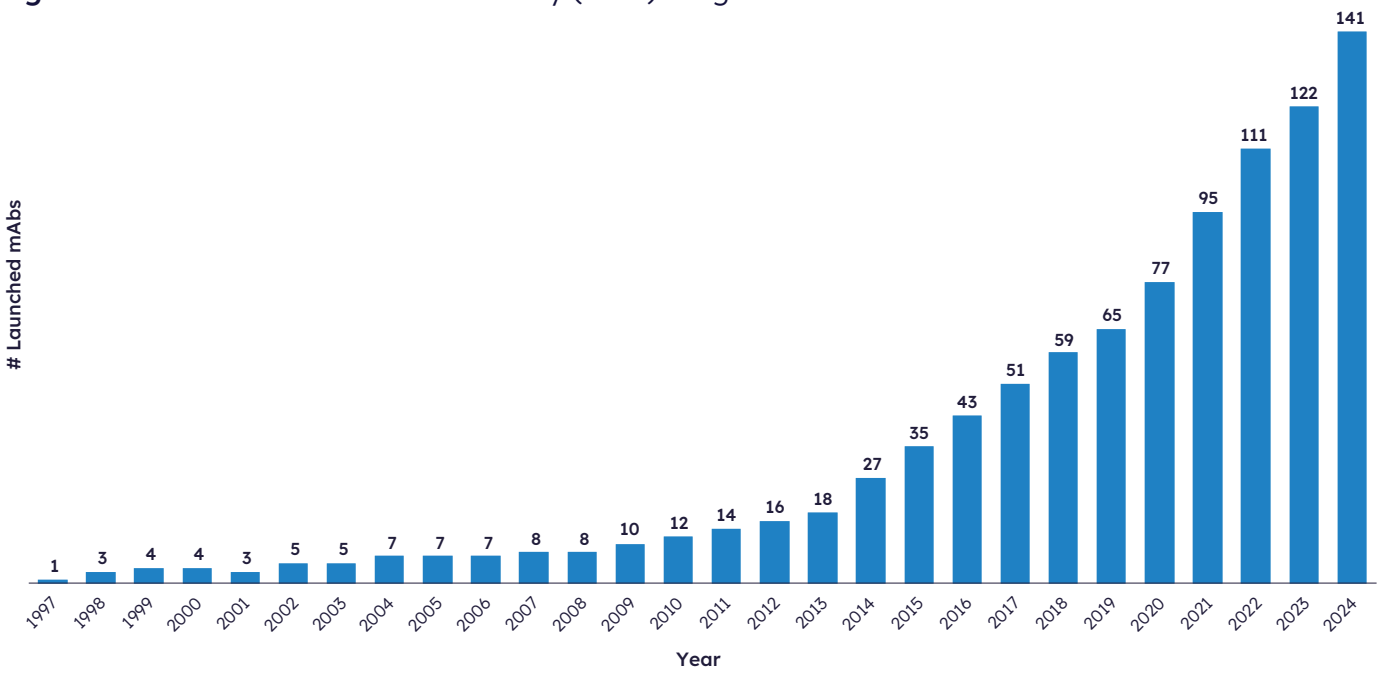
Cancer therapy goes monoclonal

Cancer is one of the leading causes of death globally, with a projected 16.3 million deaths by 2040.[1] Interventions for the treatment of cancer include surgical resection, radiotherapy, and drug therapy. While effective, the longstanding use of cytotoxic chemotherapy was a precarious balancing act of achieving sufficient antitumor efficacy while minimizing damage to healthy cells and debilitating side effects. Consequently, the 1990s saw a move away from traditional chemotherapy towards more targeted approaches, with tumor-specific antigens emerging as unique druggable targets. Targeted biologics such as monoclonal antibodies (mAbs) provided versatile new drug platforms, and in 1997 rituximab became the first mAb approved for cancer in the treatment-resistant B cell lymphoma setting. An explosion in mAb-driven cancer drug development followed, with 141 mAbs currently marketed for the treatment of various forms of cancer (Figure 1).

Figure 1: Launched monoclonal antibody (mAb) drugs for cancer 1997—2024



Source: Pharmaprojects, October 2024

Cancer therapy then was evolving from potent but somewhat indiscriminate chemotherapy to targeted biological therapy. Proposed by German physician Paul Ehrlich in 1907, the ideal would be a hybrid encompassing the cytotoxicity of chemotherapy with the tumor specificity of a biologic. Early development of chemotherapy had already yielded an array of cellular toxins too potent to administer systemically, but which could now potentially be linked to an antibody to become a form of “smart chemotherapy.” These antibody-drug conjugates (ADCs) thus had the potential to make Ehrlich’s “magic bullet” theory the new tool in the fight against cancer.[2]

The makeup of ADCs

ADCs consist of three components: an antibody, a linker, and a payload. An antibody against a tumor antigen acts as a targeted delivery system, guiding the ADC directly towards antigen-expressing tumor cells, avoiding toxicity to healthy cells and unwanted side effects. Target selection is crucial to the effectiveness of ADCs, and those preferentially or exclusively expressed at high levels on the surface of tumor cells make the best targets. In terms of antibody selection, current ADCs are widely based on immunoglobulin G (IgG) which combines a long half-life with strong antibody-mediated immune effects. Elsewhere, the problem of potential immunogenic side effects has been addressed through the use of chimeric and humanized antibodies.

The second component is the linker molecule. This links the antibody and payload moieties, and functions to ensure that the highly cytotoxic payload remains stably bound to the antibody and thus inert while in the systemic circulation. Cleavable linkers, most commonly used in development to date, are such that allow release of the payload in response to intracellular or extracellular environmental differences, such as changes in pH or redox potential, which cause a bond cleavage.[3] Conversely, non-cleavable linkers release the attached payload upon lysosomal degradation of the antibody. These bonds ensure greater stability in the circulation and tumor microenvironment and are associated with improved efficacy and reduced toxicity over cleavable linkers. As exemplified by

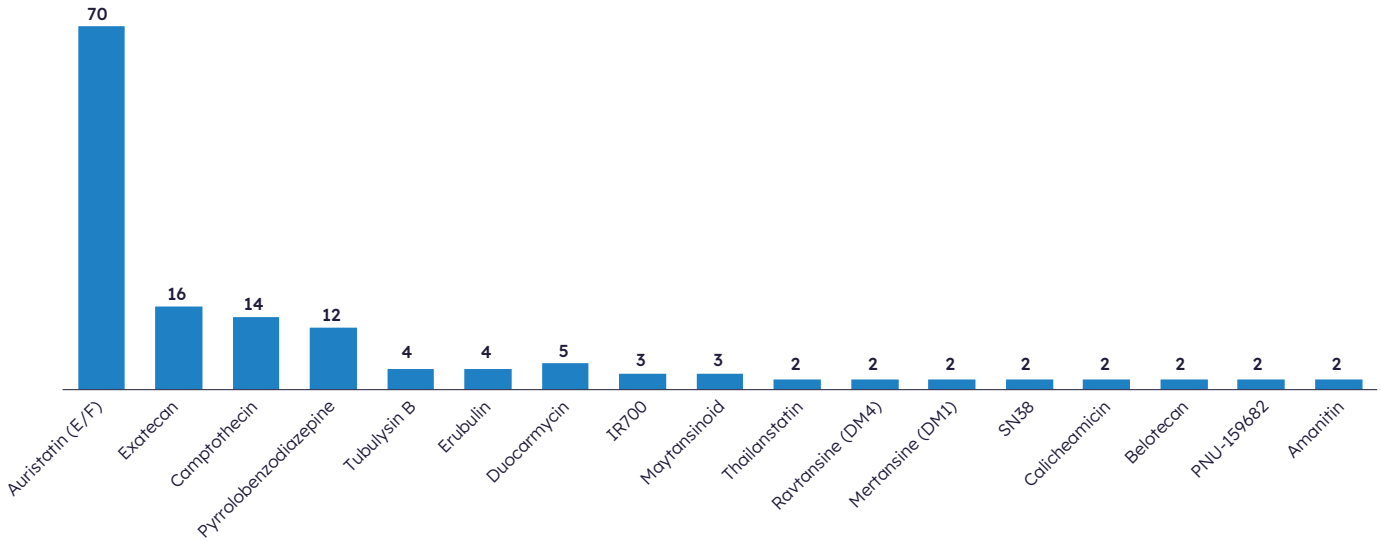
trastuzumab emtansine (Kadcyla), developed by Roche, composed of trastuzumab conjugated to a DM1 molecule via a non-reducible thioether linker,[4] which demonstrated greater activity when compared to conventional unconjugated trastuzumab and to trastuzumab conjugated via reducible disulfide linkers to other maytansinoids.[5]

The final and most important component of an ADC is the payload, the cytotoxic molecule responsible for its cancer-killing effect. While early ADCs utilized traditional chemotherapeutic agents as a cytotoxic payload, these lacked efficacy as such agents were not potent enough to produce sufficient anticancer effect.[4] However, structural conformation of an antibody also limits the amount of payload that can be carried by the ADC construct.

Currently, the most used payloads in ADC development are auristatins, specifically monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF), with 70 ADCs in active development as shown in Figure 2. A significant disparity between the most adopted and alternative payloads is observed, which can be attributed to the factors of payload properties, such as the stability and toxicity, that present challenges in clinical applications.

Accordingly, an ideal payload should be cytotoxic enough to achieve a therapeutic effect while reducing the requirement for higher doses that lead to harmful side effects.[6]

Figure 2: The most common payloads among ADCs in development



Source: Pharmaprojects, October 2024

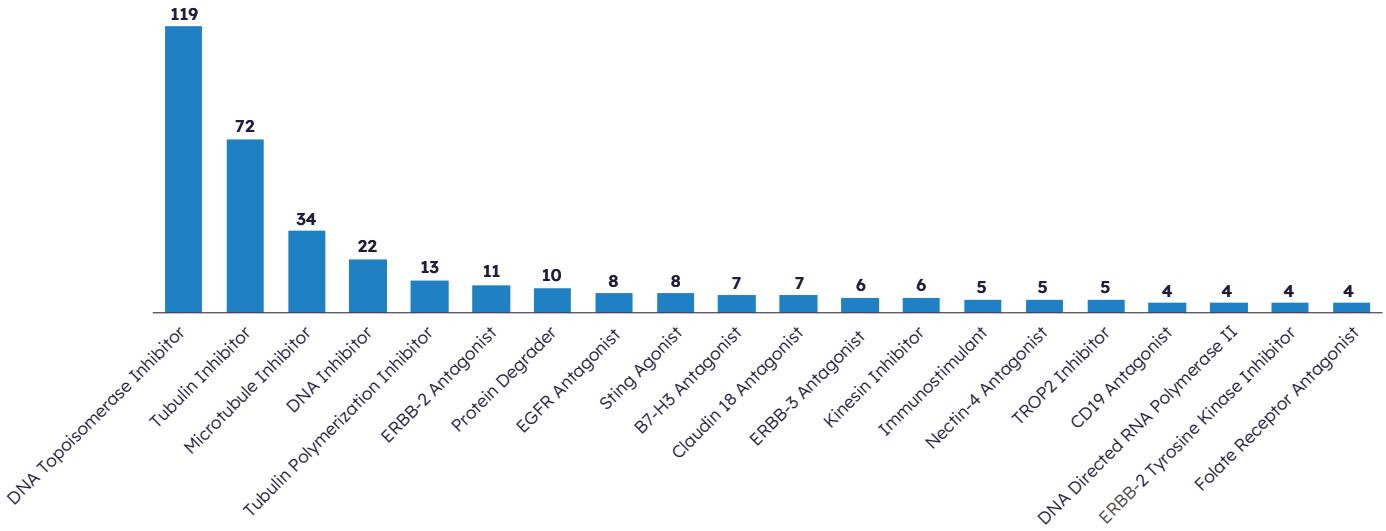
Mechanisms of ADCs

ADCs are administered intravenously into the bloodstream to avoid degradation of the mAb component. The attached antibody acts as a “biological missile,” guiding the ADC to the antigen expressing tumor cells where it binds, forming an ADC-antigen complex that is subsequently internalized via receptor-mediated endocytosis.[7] Upon internalization, the ADC is degraded, thereby releasing the cytotoxic payload and leading to death of cancer cells. The distinct mechanism of cell death depends on the payload agent, with DNA- and tubulin-binding agents being the most commonly employed[8] as shown in Figure 3.

Tubulin inhibitors such as auristatin and maytansinoid compounds work by interfering with mitosis. Brentuximab vedotin, launched in 2011 as Adcetris by Seagen, since acquired by Pfizer, is a CD30-directed mAb conjugated to monomethyl auristatin E (MMAE), for the treatment of relapsed or refractory Hodgkin’s lymphoma and systemic anaplastic large cell lymphoma. MMAE binds to tubulin dimers, inhibiting their polymerization, therefore interfering with the G2/M mitotic phase leading to cell death by apoptosis.[9]

While tubulin inhibitors are potent payloads that have demonstrated promising results in killing tumor cells, these compounds have found to be less effective against static cancer cells that are not actively dividing tumors.[10] On the other hand, DNA-damaging compounds, such as calicheamicins and duocarmycins, induce cell apoptosis by destroying the DNA structure, thus targeting the whole cell cycle. This mechanism has been exhibited in clinical practice by loncastuximab tesirine, launched as Zynlonta by ADC Therapeutics in 2021, as a CD19-directed mAb attached to pyrrolobenzodiazepine (PBD) payload. The PBD irreversibly binds to minor grooves on DNA, forming cross-links, which prevents DNA replication and thus cell division, causing cell death.[4]

Figure 3: Most common mechanisms for ADCs in active development



Source: Pharmaprojects, October 2024

A double-edged sword

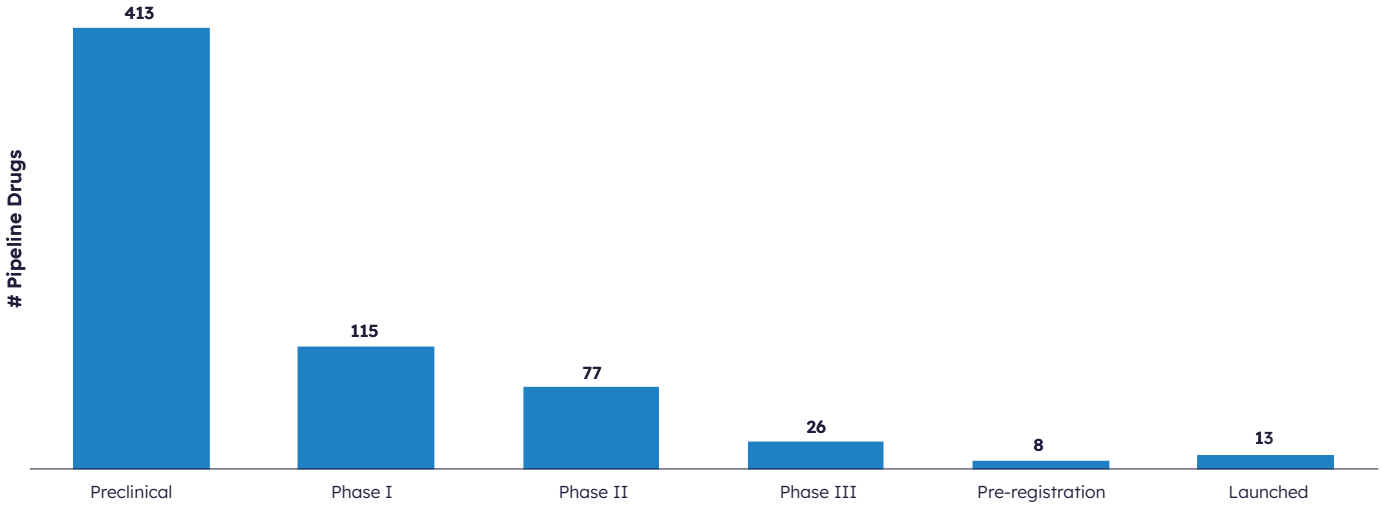
While there can be no doubt that ADCs present a promising alternative to traditional therapies by combining targeted drug delivery and cytotoxicity into a single agent, they are not without potential drawbacks. The highly cytotoxic payloads and potentially immunogenic antibody moieties mean that many ADCs will fail during clinical development due to unacceptable toxicity, adverse immune reactions, and adverse risk-benefit profiles. Even among the 13 currently approved ADCs, many patients will require dose reduction, delays in treatment, or treatment discontinuation due to intolerable side effects. In keeping with the pharmacokinetics and pharmacodynamics of mAb drugs, high affinity binding enables the conjugation of the payload to the mAb, increases the selectivity of the delivery of payload to target cells, and elevates its therapeutic index.[11] However, dose-limiting toxicity has been a persistent feature of ADC development, often necessitating a reduction of dose to sub-therapeutic levels, which limits the drug’s effectiveness.[7]

There are several mechanisms by which ADCs may produce toxic side effects. The initial generation of ADCs developed were unsuccessful in clinical settings due to aspects such as low-level toxicity, high immunogenicity, unstable payload-targeting linkages, and off-target drug toxicities. However, continued development has offered solutions to these potential problems, with second-generation ADCs ditching highly immunogenic murine antibodies in favor of humanized chimeric antibodies, which greatly reduced the risk of adverse immunological responses.[10]

Development landscape of ADCs

The current ADC development landscape features 654 drugs (Figure 4). As discussed later, this relatively large field features just 13 approved drugs, with well over half of the candidates still at preclinical development. A further 192 ADCs are currently in Phase I and II, with relatively few candidates reaching pivotal trials. This perhaps reflects a difficulty in balancing the potent disease-targeted effects with the potential to cause long-lasting serious side effects.[12]

Figure 4: Development landscape for ADCs



Source: Pharmaprojects, October 2024

The first ADC was approved by the FDA in 2000. Gemtuzumab ozogamicin, launched as Mylotarg by Pfizer, is a CD33-directed humanized mAb conjugated to an N-acetyl gamma calicheamicin cytotoxic payload. It is indicated for the treatment of CD33+ relapsed acute myeloid leukemia (AML). However, Pfizer discontinued commercial availability of Mylotarg in 2010, following fatalities due to premature release of the cytotoxic payload.[9] In 2017, Mylotarg was reapproved by the FDA for use at a lower dose with a different administration schedule and for a different patient population that lowered the maximum plasma concentration and enhanced safety.[13]

As shown by the approval journey of Mylotarg, the ADC development landscape is not without its pitfalls. GlaxoSmithKline’s (GSK) BCMA-targeting ADC belantamab mafodotin was given conditional EU and US approval in 2020 as Blenrep for the treatment of multiple myeloma. Utilizing a monomethyl auristatin F (MMAF) payload, Blenrep showed initial promise before being withdrawn after results of the Phase III DREAM-3 trial failed to meet its primary endpoint of progression-free survival. Despite this hurdle, GSK has continued to pursue approval, with a recent EU filing accepted for review in July 2024.[12,14]

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Following the approval of Mylotarg, a further 11 years passed before another ADC hit the market. Pfizer’s Adcetris (brentuximab vedotin) was approved in 2011 for the treatment of relapsed Hodgkin’s lymphoma (HL). The drug is targeted by a CD30 mAb and delivers a tubulin-targeting monomethyl auristatin E (MMAE) payload. Adcetris has seen further success in the non-Hodgkin’s lymphoma (NHL) setting and is now available in multiple markets worldwide. Other auristatin payload ADCs have followed, with Roche’s Polivy (polatuzumab vedotin) and Astellas’s Padcev (enfortumab vedotin) approved in 2019 for B cell lymphoma (BCL) and bladder cancer, respectively. MMAE is by far the most utilized payload, with RemeGen’s Aidexi (disitamab vedotin) and Genmab’s Tivdak (tisotumab vedotin) approved for further cancer indications in 2021, including bladder, cervical, and stomach malignancies. The most recent ADC approval came in 2022 when AbbVie’s Elahere (mirvetuximab soravtansine) was approved in the US for treatment-resistant ovarian, fallopian tube, and peritoneal cancer. An EU approval for the same indications followed in November 2024. This ADC targets folate receptor alpha (FRα) and uses the maytansinoid derivative ravtansine (DM4) as its cytotoxic payload. For the moment, auristatin leads the way in the payload table, and time will tell if continued development brings further innovations in payload technology.[12]

Table 1: Currently approved ADCs

Generic Name	Trade Names	Company	First Approval	Payload
gemtuzumab ozogamicin	Mylotarg	Pfizer	2000	N-acetyl-gamma calicheamicin
brentuximab vedotin	Adcetris	Seagen (Pfizer)/ Takeda	2011	MMAE
trastuzumab emtansine	Kadcyla	Roche	2013	DM1 mertansine
inotuzumab ozogamicin	Besponsa	Pfizer	2017	N-acetyl gamma calicheamicin dimethylhydrazide
polatuzumab vedotin	Polivy	Roche	2019	MMAE
enfortumab vedotin	Padcev	Astellas/Seagen (Pfizer)	2019	MMAE
trastuzumab deruxtecan	Enhertu	Daichii Sankyo/ Astrazeneca	2019	DXd (exatecan)
sacituzumab govitecan	Trodelvy	Gilead Sciences	2020	SN-38
cetuximab sarotalocan	Akalux	Rakuten Medical	2020	IR700
loncastuximab tesirine	Zynlonta	ADC Therapeutics/ SOBI	2021	PBD dimer
disitamab vedotin	Aidexi	RemeGen	2021	MMAE
tisotumab vedotin	Tivdak	Genmab/Pfizer	2021	MMAE
mirvetuximab soravtansine	Elahere	Abbvie	2022	DM4 Ravtansine

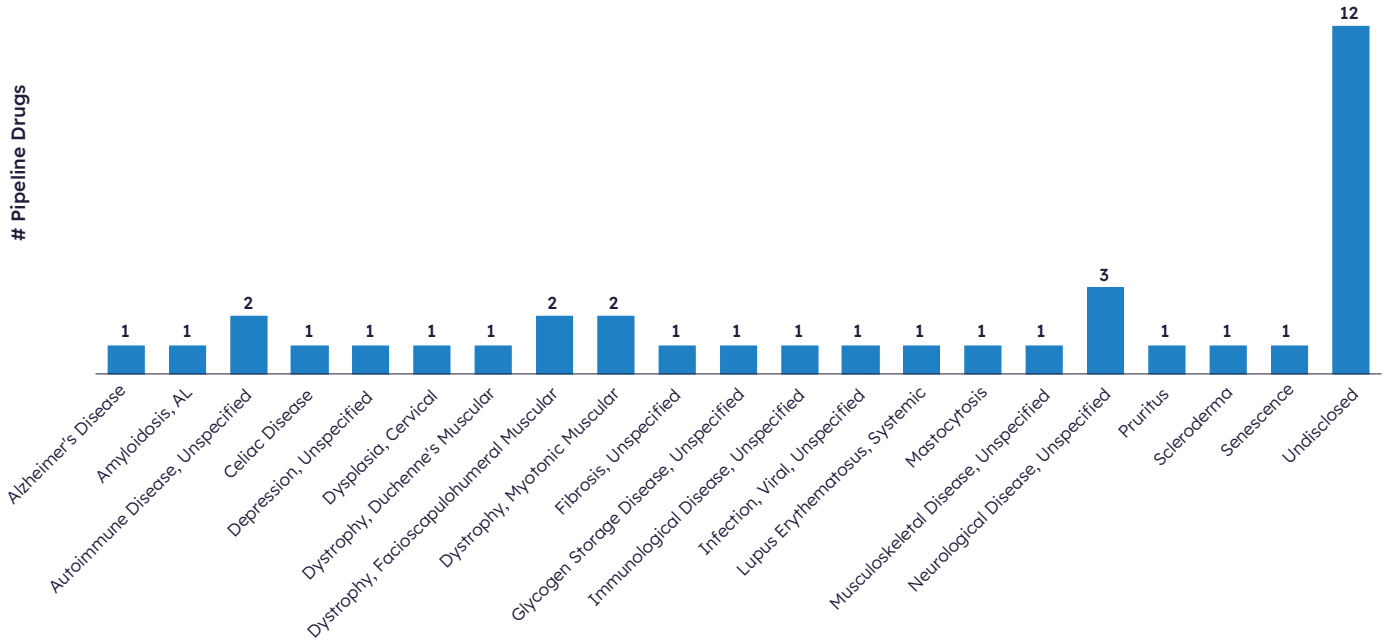
Source: Pharmaprojects, October 2024

A future beyond cancer

While the mainstay of ADC development has centered on the treatment of cancer, the potential of ADCs in treating non-cancer indications has attracted some attention. Currently the non-cancer ADC landscape features 37 drug candidates, with the majority of these in preclinical development. Pfizer’s Adcetris (brentuximab vedotin) has crossed the sphere into non-cancer use, having completed a Phase II trial in patients with diffuse scleroderma. Interim results showed the primary endpoint was met at 24 weeks, suggesting improvement in diffuse scleroderma symptoms.[12]

In a move away from conventional cytotoxic payloads, several antibody-oligonucleotide conjugates (AOC) are also in clinical development outside oncology. All three of these center on the treatment of forms of muscular dystrophy and feature delpacibart, a humanized anti-transferrin receptor antibody, as the targeting moiety. This is linked to a therapeutic oligonucleotide targeting expression of a disease-targeting protein. The most advanced of these is Avidity Biosciences’ delpacibart etedesiran. This promising candidate features an oligonucleotide moiety targeting expression of DM1 protein kinase (DMPK), a deficiency of which is implicated in the pathogenesis of myotonic muscular dystrophy.[15] The drug has successfully completed a Phase II trial and is currently in a Phase III trial (HARBOR) to evaluate safety and efficacy in patients with myotonic dystrophy. AOCs represent an exciting new facet in the antibody-conjugate landscape, potentially expanding this innovative field beyond the initial realm of cancer therapy.

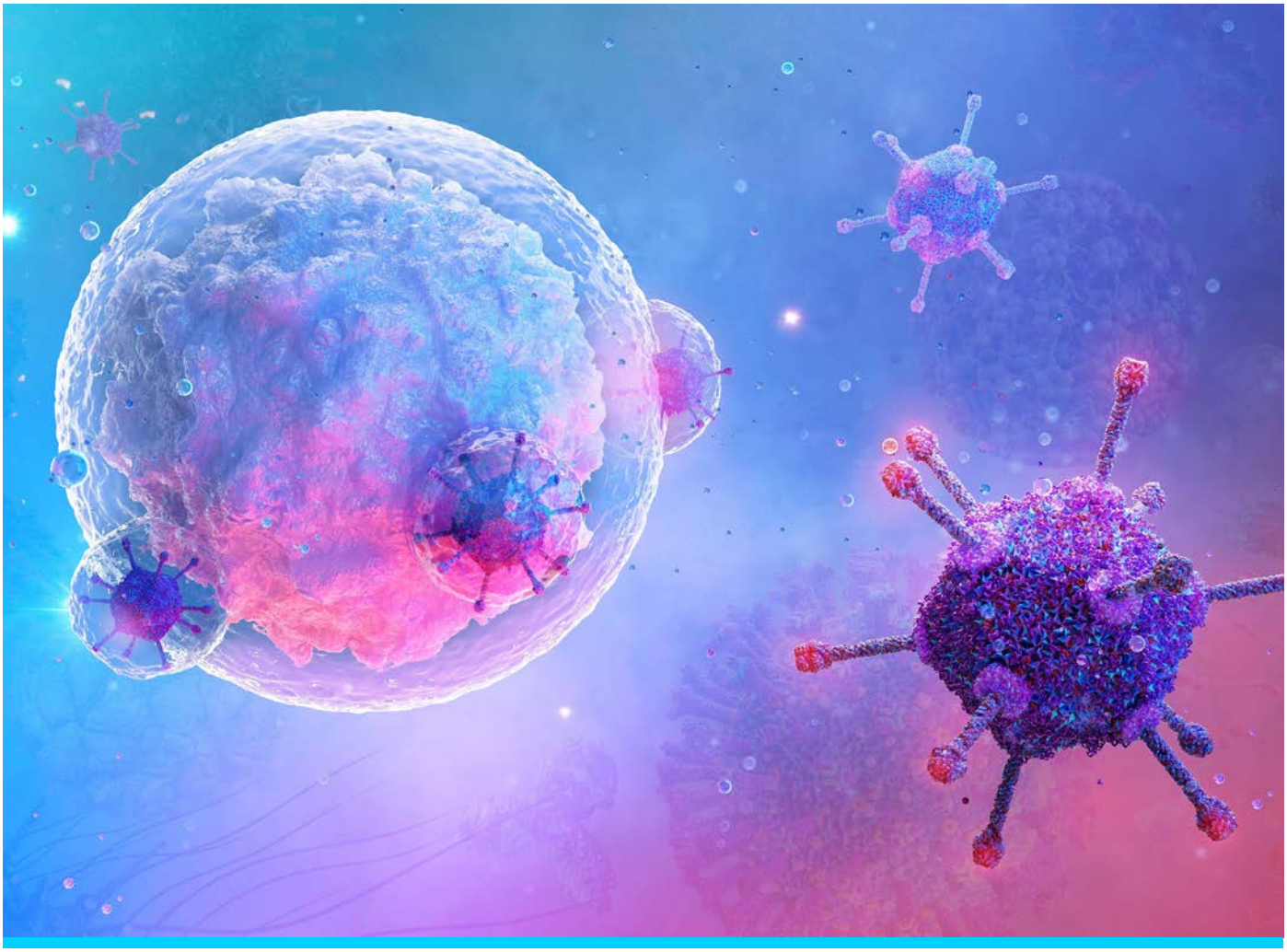
Figure 5: Non-cancer indications for ADCs in pipeline development



Source: Pharmaprojects, October 2024

Cytotoxic therapy comes full circle

From its emergence as the standard of care for cancer therapy in the 20th century, cytotoxic chemotherapy has brough promise and challenges in equal and conflicting parts, as physicians sought to balance the cancer-killing effects with the tendency to damage healthy tissues. While potent therapeutic agents were in plentiful supply, their effectiveness was blighted by the adverse side effects and dose-limiting toxicity. The advent of ADCs has addressed this problem head-on, pairing antibody targeting with cytotoxicity to create a new generation of potent therapeutic agents. This has already yielded several effective cancer treatments, with a large landscape of candidates set to follow. At the same time, conjugates utilizing oligonucleotides and immunotoxins offer opportunities for the field to expand outside oncology. ADCs have indeed made the once mythical “magic bullets” a reality, and the future of this therapeutic approach looks promising.



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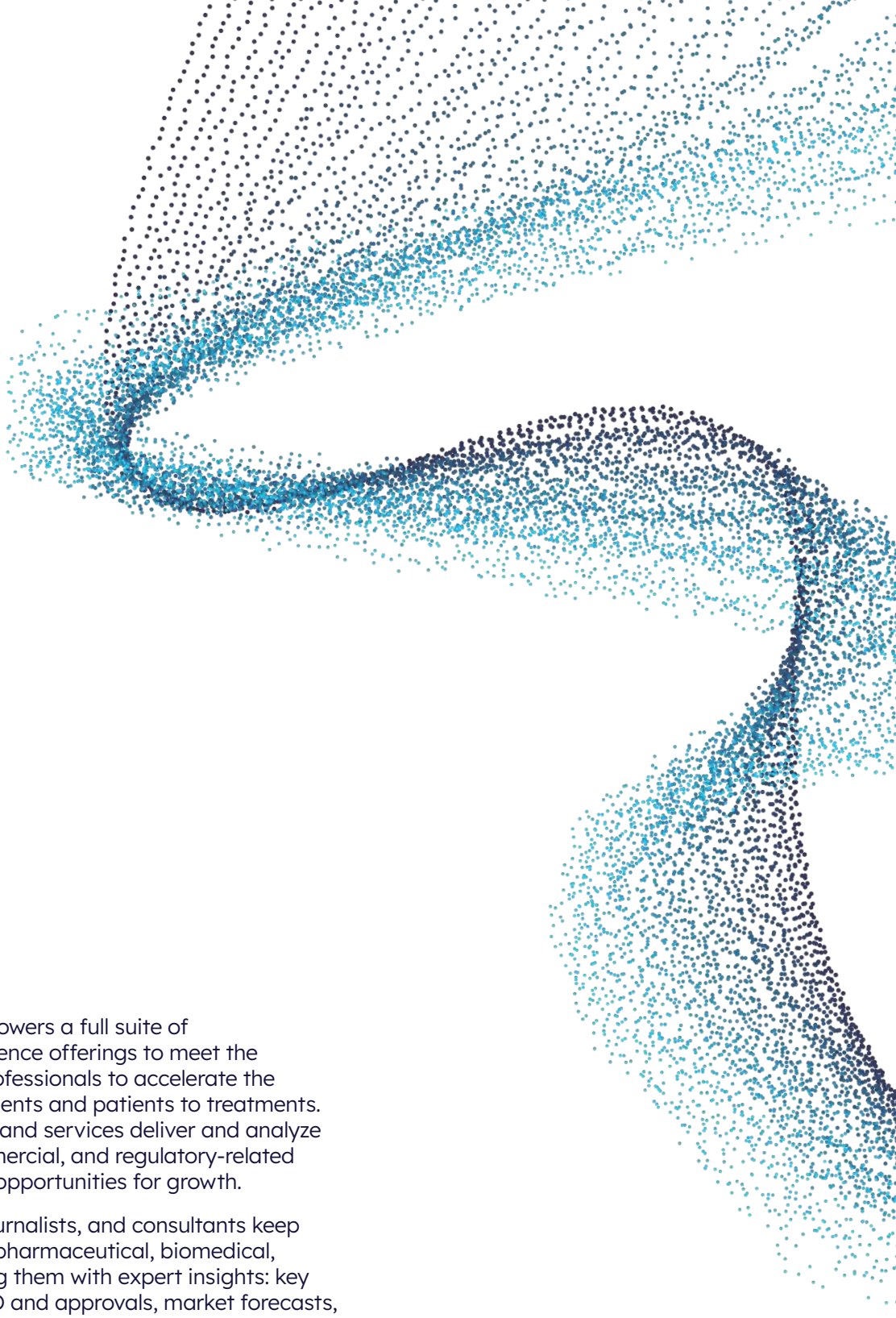

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