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Expect ADC dealmaking and investment to continue throughout 2024 and beyond.

CANCER-TARGETING ANTIBODY–DRUG CONJUGATES DRIVE DEALMAKING FRENZY

Improved linker technologies and broadening payload options mark a coming of age for these precision cancer therapies. **By Melanie Senior**

Antibody–drug conjugates (ADCs) are driving a multi-billion-dollar dealmaking frenzy. Big pharma is snapping up ADC assets and technologies amid accelerating approvals, broadening indications and advances in ADC design. Over 20 years since the first ADC was approved, the approach — using antibodies' specificity for targeted delivery of potent cytotoxic drugs — is coming of age.

Pfizer's $43-billion acquisition of Seagen and its four marketed ADCs, announced in March 2023, and AbbVie's $10.1-billion ImmunoGen purchase in November helped push the total value of ADC deals in 2023 to more than three times that seen in 2022. Both years eclipsed the 2021 deal tally, according to BioCentury. ADCs were also the subject of two of 2023's biggest partnerships: Merck & Co.'s licensing of three clinical-stage ADCs from Japan's Daiichi-Sankyo for $4 billion up front and up to $22 billion overall, and Bristol Myers Squibb's $800-million up-front deal for rights outside China to a bispecific ADC at SystImmune, in phase 1 trials for non-small-cell lung cancer (NSCLC).

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Table 1 | ADCs approved by regulators

Developer	Therapy	Target; payload	Indication	Year approved
ImmunoGen (AbbVie)	Elahere (mirvetuximab soravtansine)	FRα; microtubule disruptor maytansinoid DM4	Ovarian, fallopian tube and peritoneal cancer	2022
Seagen (Pfizer)	Tivdak (tisotumab vedotin)	Tissue factor (TF-011); microtubule disruptor MMAE	Cervical cancer	2021
ADC Therapeutics	Zynlonta (loncastuximab tesirine)	CD19; pyrrolobenzodiazepine dimer SCX	Large B cell precursor leukemia	2021
Gilead Sciences	Trodelvy (sacituzumab govitecan)	TROP2; topoisomerase inhibitor	Triple-negative breast cancer and urothelial cancer	2020
Daiichi Sankyo, AstraZeneca	Enhertu (fam-trastuzumab deruxtecan)	HER2; topoisomerase inhibitor	HER2-positive breast cancer, non-small-cell lung, gastric and gastroesophageal cancer	2019
Astellas, Seagen	Padcev (enfortumab vedotin)	Nectin-4; MMAE	Metastatic urothelial cancer	2019
Roche	Polivy (polatuzumab vedotin)	CD79b; MMAE	Diffuse large B cell lymphoma	2019
Pfizer	Besponsa (inotuzumab ozogamicin)	CD22; calicheamicin	CD22-positive B cell precursor acute lymphocytic lymphoma	2017
Roche	Kadcyla (ado-trastuzumab emtansine)	HER2; microtubule disruptor emtansine	HER2-positive metastatic breast cancer	2013
Takeda, Seagen	Adcetris (brentuximab vedotin)	CD30; MMAE	Hodgkin's lymphoma, anaplastic large cell lymphoma	2011
Pfizer	Mylotarg (gemtuzumab ozogamicin)	CD33; calicheamicin	Acute myelogenous leukemia	2000 (relaunched 2017)
AstraZeneca	Lumoxiti (moxetumomab pasudotox)	PE38; bacterial toxin *Pseudomonas* exotoxin A	Hairy cell leukemia	2018 (Withdrawn mid-2023)
GSK	Blenrep (belantamab mafodotin)	BCMA; MMAF	Multiple myeloma	2020 (Withdrawn 2022)
Rakuten Medical	Akalux (cetuximab sarotalocan)	EGFR; photosensitizer IR700	Head and neck cancer	2020 (in Japan)
RemeGen	Aidixi (disitamab vedotin)	HER2; MMAE	Urothelial and gastric cancer	2021 (in China)

Date of US FDA approval is shown, unless otherwise indicated. MMAE and MMAF, monomethyl auristatin E and F. Sources: FDA; company reports; F. Riccardi, M. Dal Bo, P. Macor & G. Toffoli, *Front. Pharmacol*. https://doi.org/10.3389/fphar.2023.1274088 (2023).

Momentum continues in 2024, with Johnson & Johnson's $2-billion cash deal for Ambrx Biopharma and a smaller licensing deal with Suzhou, China-based MediLink Therapeutics by Roche, whose management explicitly declared ADCs a "priority area" during the annual J.P. Morgan Healthcare Conference in San Francisco in early January.

The big money reflects a growing and increasingly valuable drug class that some proponents hope may eventually replace some forms of standard chemotherapy. There are now 11 marketed ADCs in the United States, over half of which gained FDA approval in or after 2019 (Table 1). Top-selling Enhertu (trastuzumab deruxtecan) brought in $1.6 billion last year to Daiichi Sankyo and partner AstraZeneca. By 2028, Enhertu, which links the antibody sold as Herceptin to a topoisomerase inhibitor, will generate sales of $9 billion, with the entire ADC category predicted to be worth more than three times that, according to Evaluate Pharma. Enhertu's approved indications have already expanded from human epidermal growth factor receptor (HER)-2-positive breast cancer into gastric cancer and NSCLC, and to breast cancers that express lower levels of HER2. ImmunoGen's Elahere (mirvetuximab soravtansine) is the newest approved ADC, gaining accelerated approved at the end of 2022 for folate receptor-α (FRα)-positive, platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. ImmunoGen filed for full approval in early December 2023 based on positive confirmatory survival data, a week after their acquisition by AbbVie was announced.

The ADC dealmaking splurge also features smaller acquisitions and licensing deals for assets and linker technologies promising better safety and efficacy, as well as an expanded range of antibody targets or toxic payloads. Eli Lilly bought Duisburg, Germany-based Emergence Therapeutics in June 2023, with its preclinical nectin-4-targeting ADC for bladder and triple-negative breast cancer. Weeks later the big pharma also snapped up the Lyon, France based company, Mablink Bioscience, that supplied the linker technology in Emergence's program – technology that may enable a more effective, safer and less resistance-prone ADC than Seagen and Astellas's approved urothelial cancer ADC Padcev (enfortumab vedotin), which also targets nectin-4. Mainz, Germany's BioNTech, of COVID-19 vaccine fame, paid $140 million up front for rights outside China to two topoisomerase-1 inhibitor-based ADCs from Shanghai-based DualityBio, including a HER2-targeting candidate in phase 2 trials. The biotech signed a second deal with MediLink for a HER3-targeting ADC.

Pharma and biotech interest has also drawn venture financing to ADC start-ups: Nijmegen, the Netherlands-based Tagworks Pharmaceuticals raised a $65-million series A in June 2023 to advance its 'click-to-release' conjugation approach, designed to drop toxic payloads just outside tumor cells, potentially enabling a more potent response across the tumor microenvironment. Copenhagen, Denmark-based Adcendo raised a $89-million extended series A in April to push an ADC based on a novel target antigen: uPARAP, an endocytic collagen receptor that may provide efficient entry for ADCs by targeting cells that overexpress uPARAP, including in soft-tissue sarcomas, osteosarcomas and mesotheliomas.

More deals and investment will likely follow, in part because ADCs offer triple innovation potential: across linker chemistry, cytotoxic payload and antibody. Buyers of ADC conjugation platforms hope to see multiple resulting products. Biotech investors like the high barriers to entry resulting from the need to master multiple skills, and ADCs' potential to shine as monotherapies. "To have an impact in oncology today, you need a product that can show anticancer activity on its own," thereby saving on the time, expense and complexity of combination trials, says Graziano Seghezzi, managing partner at Sofinnova, which co-led Mablink's $34-million series A in October 2022.

"We're evaluating a number of private and public ADC companies and think there are already five to ten [further] assets in the clinic that are likely to get approved," says Jake Simson, a partner at RA Capital, investors in ImmunoGen, Emergence and Adcendo. "We're closer to the beginning of the ADC story than to the end."

ADCs' bumpy ride

Like most new technologies, ADCs got off to a bumpy start. The idea of using antibodies for targeted toxic warhead delivery is compelling, with ADCs sometimes referred to as 'precision chemotherapy'. But in practice, finding the best combination of antibody, linker molecule and toxic payload is tricky. ADC designers seek to mimic as closely as possible the properties of a naked antibody, in terms of specificity, clearance profile and toxicity. Yet they also want to smuggle in a potent warhead that can easily spoil antibody pharmacokinetics. Most drugs are hydrophobic, making them prone to aggregation and poor at penetrating tissues.

The first ADC, Pfizer's Mylotarg (gemtuzumab ozogamicin), was approved in 2000 for acute myeloid leukemia. It was withdrawn ten years later due to off-target toxicity resulting from an unstable linker. The choice of linker determines how much payload the antibody can carry — the drug-to-antibody ratio (DAR) — and when and where it is released. Linkers influence the pharmacokinetics of an ADC and its therapeutic index — the range of doses that are effective yet also tolerable. Pfizer relaunched Mylotarg in 2017 with a new dosing schedule and narrowed patient population, but there have been many other ADC setbacks. AbbVie spent nearly $6 billion on Stemcentrx in 2016, only to find that lead ADC Rova-T (rovalpituzumab tesirine) was less effective at prolonging survival in relapsed or refractory small cell lung cancer than an older, standalone chemotherapy drug. The problem was likely Rova-T's design, rather than its target: delta-like ligand-3 (DLL3) remains the focus of several other clinical-stage programs, including Amgen's phase 2 bispecific T cell engager tarlatamab. In 2022, GlaxoSmithKline withdrew B cell maturation antigen (BCMA)-targeted Blenrep (belantamab mafodotin) from the US market after it failed to show superiority over pomalidomide-dexamethasone in a confirmatory trial.

The Enhertu effect

Linker chemistry accounts for much of the recent progress in ADC design. Linkers must be stable in plasma and drop their payload only once the target is reached. They must also be able to carry enough drug to be effective. Second-generation cleavable maleimide-based linkers (as used in Seagen's CD30-targeting Adcetris (brentuximab vedotin) and its Padcev, and in Roche's anti-CD79b Polivy (polatuzumab vedotin)) improved on Mylotarg and other first-generation approaches. But they are still prone to early deconjugation before they reach their target, leading to side effects such as neutropenia and neuropathy.

Enhertu's 2019 approval marked a breakthrough. Daiichi used a slightly less potent cytotoxic than the antitubulin agents used in Seagen's drugs or in Roche's HER2 targeting Kadcyla (ado-trastuzumab emtansine) and found a way to attach more of it to the antibody without increasing side effects. They modified the topoisomerase inhibitor exatecan to create a synthetic derivative called DXd. This was then conjugated to the antibody using tetrapeptide-based cleavable linkers, to create the deruxtecan drug–linker component of Enhertu. Critically, this setup masks the hydrophobicity of the payload, which would otherwise upset the ADC's pharmacokinetics.

DXd conjugation explains the multi-billion-dollar value gap between Enhertu and Kadcyla, which use the same antibody but different linkers and payloads. "Daiichi has identified something of a secret sauce," both with Enhertu and its other ADCs, says RA Capital's Simson.

That secret sauce is also why Merck was willing to pay $4 billion for three of Daiichi's other clinical-stage ADCs: HER3-targeted patritumab deruxtecan for epidermal growth factor receptor (EGFR)-mutated advanced NSCLC (slated for US regulatory submission in March 2024); B7-H3-directed ifinatamab deruxtecan (in phase 2 trials for previously treated small cell lung cancer); and phase 1 ovarian cancer candidate raludotatug deruxtecan, which targets cadherin-6. These candidates all use deruxtecan with its 'built-in' topoisomerase inhibitor payload.

Smaller competitors are vying to develop linkers with even more powerful hydrophobicity-masking properties. Mablink's conjugation platform features polysarcosine, a chain of the amino acid sarcosine. This enables higher payload capacity — a DAR of 8 — and a stronger 'bystander effect', whereby the toxic warhead also attacks nearby cells that do not express the target antigen. This effect is particularly important in solid tumors, where antigen expression profiles can vary widely. "Daiichi modifies exatecan to make it more hydrophilic, but this modification also reduces the bystander effect," explains Mablink co-founder Jean-Guillaume Lafay. Mablink's platform can handle unmodified exatecan and also reduces the risk of immunogenicity, Lafay adds, since sarcosine is naturally present in human cells.

Mablink's lead ADC targets FRα, the same target as ImmunoGen's (now AbbVie's) Elahere. The difference: Elahere carries the tubulin polymerization inhibitor soravtansine, which is more susceptible to resistance and has limited bystander activity. That's why it is approved only for patients with high levels of folate receptor expression, as determined by a diagnostic test. Mablink (now Lilly) hopes to overcome that restriction. In preclinical studies, its ADC showed similar stability and half-life to the unconjugated monoclonal antibody and potent antitumor activity across diverse FRα expression levels. "We had a mini-Daiichi," sums up Sofinnova's Seghezzi.

Seattle-based ProfoundBio also wants to improve upon the ADC technology used in Enhertu. Founded by ex-Seagen scientists Baiteng Zhao (CEO), Tae Han (chief strategy officer) and Xiao Shang (head of CMC), ProfoundBio's drug–linker combo sesutecan brings improved hydrophilicity, which can mask more hydrophobic and potent payloads than DXd, claims CMO Naomi Hunder. In early clinical data presented at the Society for Immunotherapy of Cancer meeting in November 2023, ProfoundBio's FRα-targeting ADC rinatabart sesutecan (Rina-S) generated antitumor responses from patients across the FRα expression spectrum.

Expanding payloads

Mablink and ProfoundBio both claim to have modular linkers that can be paired with other payloads. These payloads, experts say, will drive the next wave of ADC innovation.

Most approved and late-stage ADCs use only a handful of cytotoxics: those with proven potency and conjugation-friendly functional groups, such as amines or thiols. The main categories are microtubule inhibitors (such as the auristatin derivatives MMAE and MMAF) and DNA-damaging agents (topoisomerase inhibitors, calicheamicins and pyrrolobenzodiazepines).

Rapid advances in linker technology, including their ability to enhance stability and mask hydrophobicity, are expanding the range of payloads. This is good news, since having too many ADCs carrying the same payload could accelerate drug resistance. Scientists are still unpicking a range of possible mechanisms for ADC resistance, including payload resistance, downregulated antigen expression and changes to pathways that traffic therapies into cells.

"We want to unlock payloads that haven't previously been used," says Dominik Schumacher, CEO at Munich, Germany-based Tubulis. The company's P5 conjugation platform uses branched polyethylene glycol phosphonamidates to efficiently conjugate hydrophobic payloads in a stable, homogenous fashion across a range of DARs. It attracted $22.75 million up front in April 2023 from Bristol Myers Squibb, seeking to develop solid-tumor ADCs with topoisomerase inhibitors. Tubulis's second platform, Tub-tag, uses tubulin tyrosine ligase to tweak the antibody component while accommodating various payloads and DARs. The idea behind both technologies is to "enable flexible ADC design to suit the target and clinical profile in question," says Schumacher. He would not reveal which payloads Tubulis is testing in its own solid tumor-focused assets, but says the approach enables payloads to be conjugated in their native form and thereby maintain full potency. Chemically modifying payloads to facilitate conjugation, as occurs in many ADCs, can reduce their potency.

Elsewhere, protein degraders are attracting interest as ADC payloads. Bristol Myers Squibb in October 2023 paid $100 million up front to South Korea's Orum Therapeutics for a phase 1-ready CD33-targeting ADC carrying a small molecule designed to degrade the GSPT-1 (G1 to S phase transition-1) protein. The candidate will be tested in acute myeloid leukemia and myelodysplastic syndromes. Orum's lead in-house ADC is in phase 1 trials for breast cancer. Merck & Co. followed suit in December 2023 with a smaller, $10-million up-front payment to C4 Therapeutics for degrader payloads that it will conjugate to in-house antibodies. Merck will develop and commercialize the resulting 'degrader–antibody conjugates'.

Prague-based Sotio Biotech is working on an anthracycline-based payload using technology licensed from Boehringer Ingelheim-owned NBE Therapeutics in Basel, Switzerland. Phase 1/2 trials of a claudin18.2-targeting ADC using NBE's sortase-mediated conjugation platform are ongoing in gastric and pancreatic cancer. Sotio also promised up to $740 million to Lonza-owned Synaffix in October 2023 for rights to use its ADC technologies to develop three solid-tumor ADCs.

Other drug classes may also benefit from antibodies' targeting prowess. Oligonucleotide-conjugated antibodies, already used for protein diagnostics, offer another twist on ADCs, which may gain further traction as RNA-based therapies — including small interfering RNAs and antisense oligonucleotides — continue to grow. Preclinical work shows immune-stimulating antibody conjugates using payloads such as Toll-like receptors can trigger antitumor T cell responses; there are also efforts to tag radionuclides (radiation-emitting isotopes) onto antibodies to create precision radiation therapy.

First-generation radionuclide–antibody conjugates like GlaxoSmithKline's Bexxar (iodine-131 tositumomab) failed to get off the ground, in part because of toxicity concerns. Yet targeted radiotherapy — using peptides or other targeting agents to deliver precision radiation to tumors — is seeing a resurgence, as evidenced by Bristol Myers Squibb's $4.1-billion acquisition of RayzeBio in December 2023. RayzeBio's lead program builds on Novartis's Lutathera (lutetium-177 dotatate), which uses a somatostatin analog peptide to deliver a radionuclide to somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors and was approved in 2018.

Antibody alternatives

Further innovation may come from the antibody component of ADCs. Oncopeptides' melphalan flufenamide (approved in the European Union as Pepaxti for refractory multiple myeloma) combines alkylating agent melphalan with a peptide that enhances targeting and potency. That drug was withdrawn from the US in 2021 after failing to show better survival in a confirmatory trial, but peptide–drug conjugates continue to be investigated for their potential to deepen tumor penetration and expand target range, thanks to peptides' smaller size relative to full antibodies. Scientists are also finding ways to extend their otherwise short half-lives. Cambridge, UK-based Bicycle Therapeutics, for example, is designing looped peptides that are smaller than antibodies yet retain high target affinity and can be linked to cytotoxics, radioisotopes or immune cell agonists. Bicycle's nectin-4-targeting MMAE–peptide conjugate showed better tolerability than its nectin-4 ADC counterpart Padcev in preclinical and early clinical studies in metastatic urothelial cancer.

Few such alternatives have yet trumped full-size antibodies, whether conjugated or not. We have "no particular reason right now to fear that antibodies will be overshadowed," says RA Capital's Simson. Indeed, Pfizer in mid-December committed $37 million in up-front and near-term milestones to Nona Biosciences for its preclinical ADC containing a full-sized antibody designed to more effectively target mesothelin, overexpressed in a range of cancers. Bispecific antibodies, which saw four new FDA approvals in 2023, are also making their way into the ADC pipeline. These may target two different tumor-associated antigens, as does SystImmune's EGFR- and HER3-targeting ADC in phase 1 trials for NSCLC (the subject of December's licensing deal by Bristol Myers Squibb), or two epitopes on the same target, as does Zymeworks' phase 1 zanidatamab zovodotin, which hits non-overlapping HER2 epitopes.

Further to run

Despite ADCs' terrific year, there have been setbacks: Sanofi in December 2023 dropped phase 3 tusamitamab ravtansine, the product of a 2003 alliance with ImmunoGen, after it failed to improve progression-free survival relative to docetaxel in non-squamous NSCLC with high levels of carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), a novel target. Mersana Therapeutics' in-house STING-activating ADC was put on clinical hold in 2023 due to a serious adverse event; it is designed to activate the STING pathway in tumor cells and tumor-resident immune cells, potentially delivering enhanced antitumor activity. The hold has since lifted and the phase 1 trial resumed, but GSK, which paid $100 million in 2022 for the right to co-develop and sell the HER2 epitope-targeted ADC (then still preclinical), may feel less inclined to exercise its option. AbbVie dropped its anti-tumor necrosis factor (TNF)–steroid ADC in August 2023, a rare non-oncology candidate in development for polymyalgia rheumatica and Crohn's disease,

due to an unfavorable risk–benefit profile at higher doses. Better news followed for AbbVie in November, with positive top-line phase 2 trial data for c-Met-targeted telisotuzumab vedotin (Teliso-V) in previously treated NSCLC with c-Met overexpression, sparking hopes of an accelerated FDA approval. Early this year, Gilead Sciences announced that Trodelvy (sacituzumab govitecan) failed to improve survival in a phase 3 trial in metastatic NSCLC.

Still, the ADC pipeline is packed with over 150 next-generation hopefuls, including almost 40 in phase 2 trials and a dozen in phase 3 according to Citeline's Biomedtracker. Those with analyst sales forecasts attached — typically the most advanced — will be worth close to $6 billion by 2028, according to Evaluate Pharma.

Many development-stage ADCs chase validated targets like HER2, but indications and combinations are expanding. Padcev in late 2023 received full approval from the FDA in combination with Merck's checkpoint inhibitor Keytruda (pembrolizumab) as a first-line therapy for patients with advanced urothelial cancer. Other emerging modalities such as T cell engagers and radiopharmaceuticals, though behind ADCs in clinical validation and investment dollars, may offer future combination potential, entrenching ADCs deeper into clinical practice. "I'm excited about how well you can combine ADCs with other approaches, which will accelerate their move into earlier lines of treatment," says Tubulis's Schumacher. "I hope [ADCs] will replace, or be added to, chemotherapies, enabling prolonged responses with less toxicity."

ADCs also sit on the right side of the Inflation Reduction Act, a 2022 US law that imposes price curbs on small molecules much earlier in their life cycle than biologics (9 years versus 13 years after approval). ADCs' positioning under this law is a consideration for those, like Pfizer or AbbVie, buying late-stage or marketed assets. Although less of a driving force for venture capital investment in ADCs, according to Sofinnova's Seghezzi, "it certainly helps."

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