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ADCs Coming Of Age: Deals, Targets And Catalysts

by Lucie Ellis-Taitt

The antibody-drug conjugate field is beginning to reach its full potential and big pharma's attention has been caught.

Antibody-drug conjugate (ADC) technology is not new. The first ADC, *Pfizer Inc.*'s Mylotarg, reached the market two decades ago. The field has undergone slow but transformative enhancements.

"ADC development has historically not been without its setbacks," Datamonitor Healthcare analysts noted in a 2019 report. The concept of delivering a potent cytotoxic payload directly to tumor cells and causing minimum damage to non-tumor cells was viewed as a significant advance towards precision medicine, but it proved difficult to translate into the clinic. Now the field is coming of age, with more products on the market and a busy pipeline channeling new candidates into later stage trials. The number of big-name players in the ADC space is also on the rise.

"The resurgence in ADC development coincides with improvements in ADC platforms, linker technologies and new applications such as combination approaches with immunotherapy and chemotherapy to treat cancer," Datamonitor analysts said.

Next-generation ADCs are also entering the pipeline, even as the first generation of products are still securing global approvals. Mark Enyedy, CEO of *ImmunoGen, Inc.*, describes next generation ADCs as having "innovation to at least one and if not all of the components to the drug."

How They Work

ADCs are comprised of a monoclonal antibody (MAb) targeted to antigens on tumor cells conjugated to a cytotoxic payload. The unique feature of ADCs is that they use the MAb component to selectively deliver a highly potent cytotoxic to cancer cells, while at the same time leaving the surrounding normal tissue unaffected. An optimally designed ADC will have:

- a highly selective MAb targeted to a tumor-associated antigen with little or no expression on normal tissue cells;

- a potent cytotoxic agent designed to elicit cell death following internalization in tumor cells; and

- a linker that attaches the MAb to the cytotoxin, which is stable in circulation but releases the cytotoxic payload in target cells.

ADCs typically have less "off-target" action and less toxicity than conventional chemotherapy treatment. "As a result, patients are more likely to be able to tolerate an ADC therapy, potentially remaining on treatment for longer with better therapeutic outcomes and quality of life," highlighted Datamonitor analysts.

There has been less activity surrounding ADC development outside of oncology, though there is potential in other disease areas such as immune disorders and inflammation – where *AbbVie Inc.* is the leading developer.

ADCs In The Headlines

In March, Pfizer announced it would pay $43bn in cash to acquire ADC pioneer *Seagen Inc.* The US big pharma was attracted to Seagen's four approved products – three ADCs and a small-molecule cancer drug – plus candidates in its pipeline. Pfizer expects the purchase will generate $10bn in annual revenue by 2030. (Also see "*Pfizer Pays $43bn For Seagen With Goal Of Rapidly, Globally Advancing ADCs*" - Scrip, 13 Mar, 2023.)

Edward Tenthoff, a senior research analyst at Piper Sandler & Co, said in a 13 March note that while there was more to the acquisition than Seagen's ADC pipeline and technology, "we do believe this validates the coming of age of ADCs and frees up capital for next-gen ADC and conjugate plays."

Pfizer and Seagen's combined ADC pipelines will place the companies third in the list of top 20 companies active in ADC development (as it currently stands, before any potential consolidation of programs or divestments; the combined portfolios will have 18 ADC programs.)

ImmunoGen's Enyedy said the recent spotlight on the ADCs was positive for companies in the field. His company has seen more interest in recent years from developers looking to partner. "There are a number of companies that have what I call 'naked antibodies' that they think would make good ADCs," Enyedy told *In Vivo*. "We are regularly approached by companies with these antibodies looking to deploy our linker and payload technology to create an ADC that we can then co-develop."

He highlighted the company's partnership with *MacroGenics, Inc.* as one example. The two are co-developing IMGC936 as a first-in-class ADAM9-targeting ADC. ADAM9 is a cell surface protein that belongs to the ADAM (a disintegrin and metalloproteinase) family of proteases, which has been implicated in cytokine and growth factor shedding and cell migration. It has been shown that ADAM9 is overexpressed in multiple solid tumor types (eg, non-small cell lung cancer, gastric, pancreatic, triple-negative breast and colorectal) and minimally expressed on normal tissue. IMGC936 is being tested in Phase I studies.

BioNTech SE also announced a significant play into the ADC space in April. The German firm announced exclusive license and collaboration agreements with DualityBio for two antibody-drug conjugate assets to develop and commercialize globally (excluding some Asian markets). DualityBio will receive upfront payments of $170m, as well as potential development, regulatory and commercial milestone payments for both assets, totaling more than $1.5bn. Both products are targeting cancer indications.

Top 20 Players

There are a handful of blockbuster ADCs paving the way for more therapies to come to market. *Roche Holding AG*'s Kadcyla (trastuzumab emtansine), Seagen/*Takeda Pharmaceutical Co. Ltd.*'s Adcetris (brentuximab vedotin) and *AstraZeneca PLC* and *Daiichi Sankyo Co., Ltd.*'s Enhertu (trastuzumab deruxtecan) have seen great commercial success. For Enhertu, consensus analyst forecasts predict sales of more than $6bn by 2027.

Looking at the ADC pipeline from preclinical development to launched products, LegoChem is the most active company with 25 ADC programs. When narrowing the focus to big pharma only, AbbVie is the most active player with eight programs.

All of the top 10 big pharma companies (according to the most recent Scrip 100 league table) have at least one ADC program in their pipeline.

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New Targets

According to data from Pharmaprojects, there are 428 ADC drugs in the pipeline, with the majority of assets in preclinical development. This follows the idea that while a handful of launched products have been successful, industry is focused now on next-generation ADCs with improved efficacy and fewer side effects. HER2 is the most common target for ADC therapies, but other targets are growing in use. Claudin 18 has emerged as a fresh target for ADC developers.

In a 31 May 2022 paper on Claudin 18 as a novel biomarker, published by *BMC (part of Springer Nature)*, the authors noted, "The claudin18.2 (CLDN18.2) protein, an isoform of claudin18, a

member of the tight junction protein family, is a highly selective biomarker with limited expression in normal tissues and often abnormal expression during the occurrence and development of various primary malignant tumors, such as gastric cancer/gastroesophageal junction cancer, breast cancer, colon cancer, liver cancer, head and neck cancer, bronchial cancer and NSCLC."

The authors also said, "Global research and development have demonstrated that CLDN18.2 targeting candidates may become an important alternative for gastric cancer targeted treatment after HER-2-targeted agents."

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Beyond Cancer

Today, all approved ADC treatments target cancer indications. The three cancer indications with the most approved ADC treatments are: NSCLC (seven approved ADCs), bladder cancer (six) and breast cancer (six). The company with the most approved therapies is Seagen.

Still, the ADC field has some potential beyond the realm of oncology in immunological and musculoskeletal disorders. ADCs have also previously been studied in early trials for cancer pain and myelodysplastic syndrome.

While there are hundreds of pipeline candidates in development for cancer, there are just a handful in other disease areas. Musculoskeletal is leading the way, outside of oncology. There are five drug candidates in clinical development for musculoskeletal indications, all of which are in Phase II. These are being developed by AbbVie, *Avidity Biosciences, Inc.* and *Dyne Therapeutics*.

AbbVie also has Phase II programs active in Crohn's disease and rheumatoid arthritis.

Protection Against Biosimilars

Recent discussions, following Pfizer's bid for Seagen, have focused on the question of biosimilar competition for ADCs, and importantly whether these complex drugs are almost immune to biosimilar competition. "The existence of a biosimilar for ADCs is a very complicated issue," Pfizer's CEO Albert Bourla suggested on a company call after the Seagen deal was announced. (Also see "*Biosimilar Antibody-Drug Conjugates? Pfizer Isn't Banking On It*" - Pink Sheet, 16 Mar, 2023.)

"Large molecules are enjoying by regulation and *de facto* way larger exclusivity periods, particularly the ADCs, because they are very complex conjugates basically of three biologics in many cases, or two," Bourla pointed out.

Meanwhile, he opined that the regulatory pathway for biosimilars themselves was "very complicated and not well-defined. So, the durability of these assets is way beyond the normal durability of small molecules."

In the days before Pfizer's deal was announced, Seagen's CEO David Epstein had also laid bare the hurdles for biosimilar sponsors, both regulatory and development. "First, the regulatory path has to be determined. It doesn't exist today." He continued, "I don't think, for example, just injecting an ADC and then taking a blood level is going to tell you whether the drugs are the same or not."

Nevertheless, he suggested, "someday, I would imagine there's a biosimilar that can be made." But "it's not any time soon."

ImmunoGen CEO Enyedy agreed that biosimilars of ADC drugs are not in the immediate pipeline: "I certainly would not underestimate the ingenuity of innovators around the world to create biosimilars of antibody-drug conjugates. But among the molecules that one would seek to replicate ADCs are among the more difficult of the class of biologics."

Enyedy added that he expects to see "bio-better" competitors in the future for ADC therapies, rather than straight biosimilar products.

Ameet Mallik, CEO of *ADC Therapeutics SA* and former head of the biosimilars unit at Sandoz, told *In Vivo* that at one point people also thought biologics would be immune from copy products. However, he said the process to create an ADC was very complicated. "I would never say never... but the barriers to producing a generic ADC are much higher than what it takes to produce a biosimilar." He added that generic and biosimilar companies would need to develop their current capabilities to be able to produce ADC copy products.

Deal-Making Is On The Rise

According to data from Biomedtracker, between January 2018 and March 2023, there have been around 100 licensing deals publicly disclosed that include ADC assets. There were only a handful of licensing agreements identified in 2018, with dealmakers ramping up activity in the early 2020s. Eleven ADC-focused licensing deals were announced in the first three months of 2023 alone.

In March this year, ImmunoGen announced a global, multi-target license and option agreement granting Vertex Pharmaceuticals the rights to conduct research using ImmunoGen's ADC technology to discover novel targeted conditioning agents for use with gene editing. Following the research period for each target, Vertex will have the option to obtain a worldwide, exclusive license to research, develop, and commercialize conditioning agents employing ImmunoGen's technology for that target. ImmunoGen will retain full rights to the ADC technology for all

targets not covered by the Vertex license. ImmunoGen will receive an upfront payment of $15m and is eligible to receive up to $337m in option exercise fees and development and commercial milestone payments per target.

In January, Amgen signaled its determination to be a major ADC player by signing a huge preclinical deal with Synaffix. Amgen will gain access to Synaffix's ADC technologies for one program with the option to exercise exclusive research and commercial licenses for a further four programs at a later date. Announcing the deal on 5 January, Synaffix did not provide details of any upfront payment, but said a deal signing fee and milestones in the development of four candidates could reach up to $2bn, plus tiered royalties on potential future sales. (Also see "*Amgen And Synaffix Alliance Could Be Biggest Preclinical ADC Licensing Deal Yet*" - Scrip, 5 Jan, 2023.)

The new deal confirmed that ADCs are a priority for Amgen, coming just days after a very similar licensing agreement with LegoChem, announced on 27 December 2022. This was based on the South Korean company's ConjuAll ADC technology in up to five targets selected by Amgen, and worth up to $1.25bn including upfront, development and commercial milestone payments.

Also signing recent deals, in December 2022, were *Merck KGaA*, via a pact with *Mersana Therapeutics, Inc.* worth up to $830m, and Merck & Co. and Kelun-Biotech, in a deal which could hit a maximum value of $9.3bn, based on seven preclinical ADC candidates.

Despite "a flurry of activity," ADC Therapeutics' Mallik expects to see deals become more focused. He said there were two main types of collaborations: companies teaming up to access expertise or products, or deals to license linker, conjugation or toxin technology. "Those are the ones where it will be interesting to see them play out. Getting an ADC right is difficult. There will be a lot of learnings from those deals," Mallik said.

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Commercial Expectations

Of the newer ADC market entrants, those launching between 2019 and 2022, Daiichi Sankyo and AstraZeneca's Enhertu (trastuzumab deruxtecan) has been the best performer, with 2022 worldwide sales of $1.3bn, of which $863m came from US sales.

Enhertu is on the rise following a string of regulatory approvals for breast, lung and gastric cancers but new data suggest that the ADC could be an effective treatment for a wide range of other HER2-expressing tumors. AstraZeneca said in March 2023 that high-level results of a mid-stage trial of Enhertu met the prespecified target for objective response rate (ORR) and durable response across multiple HER2-expressing advanced solid tumors in heavily pre-treated patients.

The ongoing DESTINY-PanTumor02 Phase II study is evaluating the drug in patients not eligible for curative therapy, including biliary tract, bladder, cervical, endometrial, ovarian, pancreatic and rare cancers. (Also see "*AstraZeneca/Daiichi Sankyo Line Up More Enhertu Indications*" - Scrip, 6 Mar, 2023.)

No specific results from the 268-patient study were revealed but AstraZeneca said the data would be presented at an upcoming medical meeting. The safety profile in DESTINY-PanTumor02 was consistent with that seen in other trials of Enhertu with no new signals identified. Enhertu has become a major pillar of AstraZeneca's oncology franchise since the firm agreed to pay $1.35bn upfront and up to $6.90bn in total for the ADC.

Enhertu already enjoys blockbuster status. Analysts predict it could hit nearly $6bn in peak annual sales, especially if a label expansion is granted for earlier-stage breast cancer; AstraZeneca and Daiichi Sankyo are scheduled to report data from the Phase II DESTINY-Breast06 trial in second-line HER2-low breast cancer in the second half of 2023.

ImmunoGen's Elahere, which has only been on the market for one full quarter, is expected to report better-than-expected sales. "We will have revenue for the first quarter at the end of April and the launch is exceeding our expectations," Enyedy told *In Vivo*.

Elahere is ImmunoGen's first independently owned drug, although the company's ADC technology was used for the early development of Roche's Kadcyla and Sanofi's Sarclisa (isatuximab).

Enyedy, who previously held leadership roles at Genzyme and Shire before becoming CEO of ImmunoGen, said the volume of testing for patients eligible for treatment with Elahere was above the company's expectations for the first quarter of 2023. He noted that 1,500 patients had been tested in the first six weeks after launch and the volume of testing had "only accelerated since the beginning of the year."

The company had also been surprised by the "breadth and depth of adoption" of Elahere quickly after its launch. "Our initial view of this product was that it was likely to see early adoption, from a commercial perspective, in the large academic centers where the clinical studies have been run," Enyedy said. "In addition, what we're seeing is broad community use: 75% of our orders have come from community physicians." (Also see "*ImmunoGen's First ADC For Ovarian Cancer To Exceed Sales Expectations*" - Scrip, 3 Apr, 2023.)

As of March 2023, Biomedtracker analysts were forecasting total 2023 worldwide sales of $62m for Elahere.

ADC Therapeutics has a busy pipeline of ADC candidates, with several critical clinical trial

readouts coming up in 2024. This pipeline, as well as the company's one approved ADC Zynlonta (loncastuximab tesirine), were what attracted Mallik to the CEO position. He joined the company in 2022, having previously held leadership roles in Novartis and been CEO of Rafael Holdings, a cancer and immune metabolism therapeutics company.

Mallik highlighted that not many companies had been able to bring ADCs to market, so far. ADC Therapeutics' approved treatment "validated a lot of capabilities across the value chain," Mallik said. "Having a commercial product, also with the potential for expanding earlier lines of treatment, you could see a successful a path towards profitability, which is a rare thing in biotech."

Zynlonta, which is approved for diffuse large B-cell lymphoma, had worldwide sales of $75m in 2022.

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2023 ADC Catalysts

In early April 2023, *Merck & Co., Inc.*'s PD-1 inhibitor Keytruda won US approval for use in combination with Seagen Inc. 's ADC Padcev for the treatment of first-line urothelial carcinoma in an industry first. (Also see "*Merck's Keytruda And Seagen's Padcev Become First PD-1/ADC Combo To Win US Approval*" - Scrip, 4 Apr, 2023.)

The FDA approved Keytruda (pembrolizumab) with the nectin-4-directed antibody and microtubule inhibitor ADC Padcev (enfortumab vedotin) for first-line locally advanced or metastatic urothelial carcinoma patients ineligible for cisplatin-based therapy under an accelerated pathway several weeks in advance of the 21 April Prescription Drug User Fee Act date.

This marks the first time an anti-PD-1 has been approved in combination with an antibody-drug conjugate in the US, but continued approval will be contingent upon data from the ongoing confirmatory KEYNOTE-A39 trial.

Looking ahead through the year, there a number of regulatory decisions for ADC therapies expected in the US and Europe, as well as pivotal clinical trial readouts over the next one to two years.

In the US, Byondis has a PDUFA action date of 12 May 2023 for trastuzumab duocarmazine (SYD985) in patients with HER2-positive unresectable locally advanced or metastatic breast cancer. SYD985 has demonstrated an increase in PFS and OS when compared to physician's choice of treatment in heavily pretreated HER2-positive metastatic breast cancer patients. The

FDA granted fast track status to the ADC treatment after it demonstrated promising early efficacy results in a Phase I study in HER2+ metastatic breast cancer patients who had progressed during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease.

While Phase III results have been positive, and will likely result in approval in this setting, SYD985's commercial potential is limited by the increasingly crowded third-line market and Synthon's limited oncology marketing experience and resources in comparison to competitors, particularly Daiichi Sankyo and AstraZeneca. SYD985 is also in development for uterine cancer (Phase II) and solid tumors (Phase I). (Also see "*Byondis Seeks Partner For Lead ADC To Enter Crowded Breast Cancer Market*" - Scrip, 9 Jun, 2021.)

European marketing authorization for SYD985 for this indication is also expected between April 2023 and October 2023.

Further out, Mersana Therapeutics is preparing for US accelerated approval of upifitamab rilsodotin for ovarian cancer in 2024.

Other Important Upcoming ADC Pipeline Events

Elahere MIRASOL Data

Top-line data from the confirmatory Phase III MIRASOL study for ImmunoGen's Elahere in ovarian cancer are expected in the first half of 2023. Elahere received accelerated approval from the FDA on 14 November 2022 for the treatment of folate receptor alpha (FRα)-positive, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer in patients following three prior systemic treatment regimens and regardless of prior treatment with Avastin.

The accelerated approval, which came nearly two weeks ahead of the action date, was based on clinical trial data showing improvement in objective response rate (ORR) and duration of response (DOR) from the pivotal SORAYA trial.

The FDA's approval of Elahere under the accelerated approval pathway was likely smoothed by the fully enrolled MIRASOL clinical trial. (Also see "*Keeping Track: Early Thanks Given By ImmunoGen, Provention Bio; More PD-1/L1 Combo Approvals*" - Pink Sheet, 18 Nov, 2022.)

The MIRASOL trial will form the basis for a regulatory submission for Elahere in Europe, along with a contemporaneous submission to the MHRA for the UK. The company also has a collaboration in China with Huadong Medicine, where the drug is expected see a regulatory

submission later in 2023 – targeting approval in 2024.

TROPION-LUNG01 Study Of Datopotamab Deruxtecan

Daiichi Sankyo and AstraZeneca will release topline results from the Phase III TROPION-LUNG01 clinical trial in early 2023 for datopotamab deruxtecan in NSCLC with or without actionable genomic alterations.

Datopotamab, which targets TROP2, is also in late-stage development for use in breast cancer (both triple-negative and HR-positive/HER2-negative). TROP2 (trophoblast cell-surface antigen 2) is a transmembrane glycoprotein that is widely expressed in several types of solid tumors.

Tusamitamab Ravtansine In CARMEN-LC03

Sanofi's tusamitamab ravtansine (SAR408701) is the most advanced ADC to target CEACAM5. CEACAM5, or anti-carcinoembryonic antigen-related cell adhesion molecule 5, is a member of the CEA family of proteins which plays a key role in cell migration, cell invasion and cell adhesion, and is overexpressed by a variety of cancer cell types. Topline data from the Phase III CARMEN-LC03 study in CEACAM5-positive second- and third-line NSCLC patients are due in the first half of 2023. It has two primary endpoints: improvement of progression-free survival compared with docetaxel up to 15 months and improvement in overall survival compared with docetaxel up to two years.

DREAMM-7 Blenrep Trial

GlaxoSmithKline and Seagen are expected to produce data for Blenrep from the Phase III DREAMM-7 in 2023. GSK's blockbuster hopes for the BCMA-targeting Blenrep (belantamab mafodotin) took a hit when the product was taken off the US market late last year at the FDA's request after the drug failed to show significant PFS benefits in the Phase III DREAMM-3 confirmatory study. (Also see "*Blenrep US Withdrawal Is A Big Blow To GSK's Blockbuster Hopes*" - Scrip, 22 Nov, 2022.)

Blenrep was conditionally approved in the US in August 2020 for relapsed/refractory multiple myeloma, and later that same month by the European Medicines Agency, based on response rates in the DREAMM-2 study, for patients who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor and an immunomodulatory agent. The drug was the first BCMA-targeting agent to gain approval in myeloma, but eye toxicity concerns had already contributed to a modest launch trajectory – it only reached £36m ($42.8m) in revenues in the third quarter of 2022.

The product's future now rests largely on data from DREAMM-7 and DREAMM-8, both due in 2023, along with efficacy ocular, toxicity will be a key consideration.

Taking Next-Gen To The Next Level

The ADC field will not be short on headlines over the coming few years and the R&D space is very much in vogue. Despite products coming to market and late-stage clinical trials reading out critical data insights though, there is still more to uncover in ADC development.

ADC Therapeutics' Mallik said: "As an industry, we've been working with a small set of payloads up to this point and the number of potential payloads, both toxin and not toxin, such as immunostimulants, is just expanding."

Mallik added that he saw a world of potential for the future of ADCs. For example, the future could include bi-specific ADCs or ADCs with dual payloads.

The CEO wants to see continued improvement in ADC technology to expand the therapeutic index and reduce systemic toxicity when treating cancer.