Short Report
The ADCs of Next-Gen Cancer Treatment

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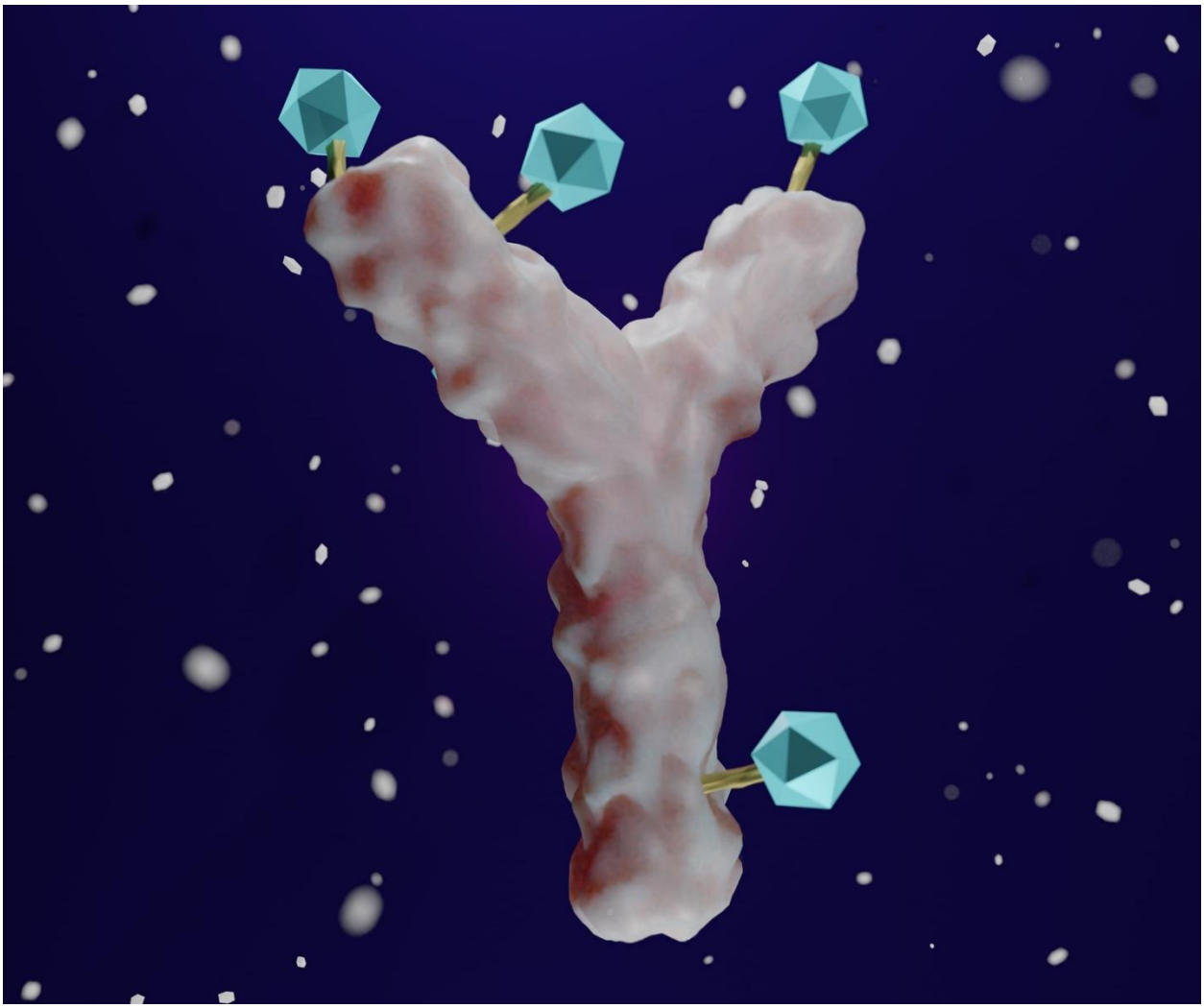
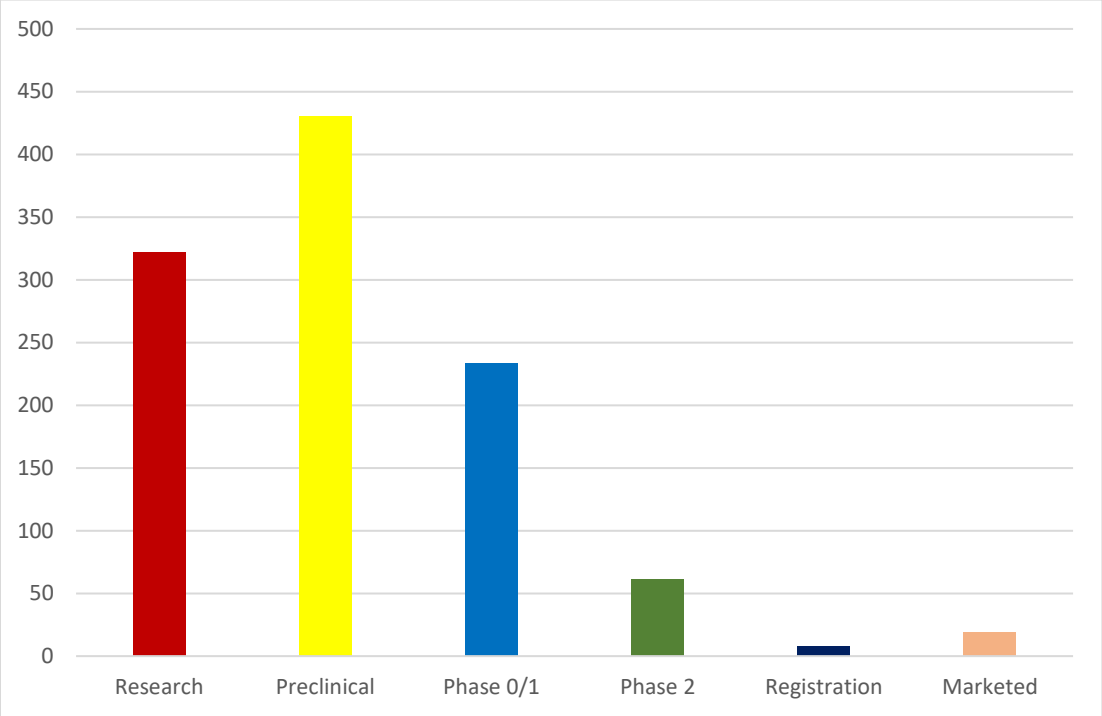


There are 11 antibody drug conjugants (ADCs) that have been approved by the FDA since 2000, more than half having received approval during or after 2019 (National Institutes of Health). To put this approval activity in some perspective, FDA approved 55 novel drugs in 2023 alone. Currently, there are more than 1,900 active ADC products in the pipeline; almost 750 of which are in research and pre-clinical development. The numbers significantly diminish as clinical trials progress with just 21 now in Phase 3 (**Figure 1**). The drop off can be attributed to the complexity of ADC development combined with excessive toxicities and unfavorable risk-benefit profiles, patients require dose reduction, treatment delays, or treatment discontinuation due to intolerable ADC-associated toxicity (*National Institutes of Health*).

Figure 1: Current ADC Active Development (Most Advanced Phase)



Source: PharmaCircle Pipeline & Products Intelligence

In the past year, we saw Sanofi suspend Phase 3 of its tusamitamab ravtasine for failing to indicate progression-free survival; Gilead Sciences failed to improve survival in a Phase 3 trial of its Trodelvy for metastatic NSCLC; and AbbVie dropped its anti-TNF steroid ADC (a non-oncology candidate for polymyalgia rheumatica and Chron's) due to an unfavorable risk-benefit profile at higher doses. Mersana Therapeutics' ADC was put on hold due to a serious adverse event, but the hold was eventually lifted for Phase 1 trials to continue.

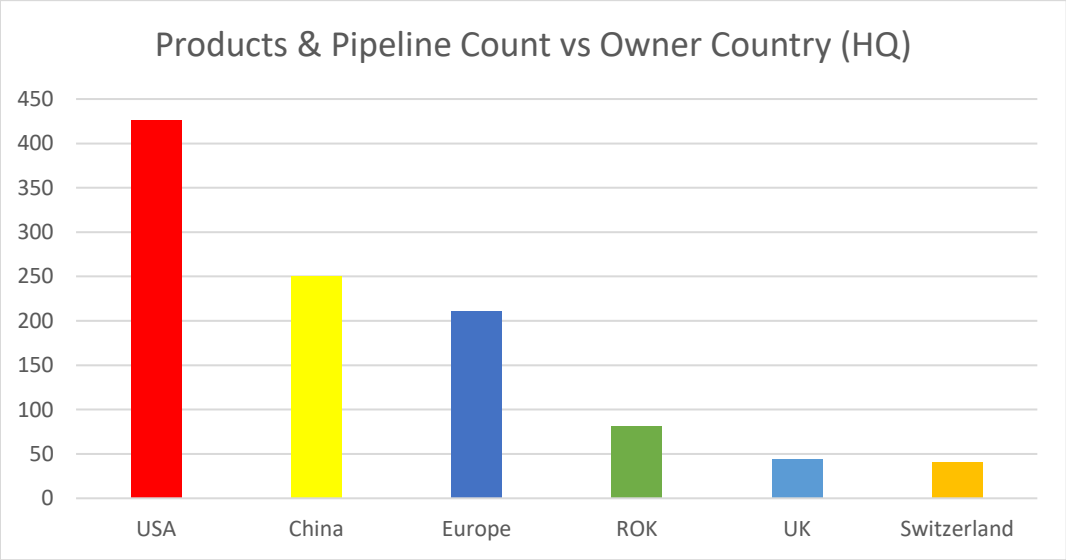
Adding to the complication of developing ADCs are the fact that they are a tri-pronged approach in the fight against cancer, armed with linker chemistry, cytotoxic payload, and antibody. The most recent approval came at the end of 2022 with the accelerated approval of ImmunoGen's Elahere (mirvetuximab soravtansine) for folate receptor α (FRα)-positive, platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. Full approval was filed in December 2023. Takeda's exclusive licensing agreement with ImmunoGen was to develop and commercialize Elahere, the first ADC developed for ovarian cancer, in Japan. ImmunoGen received $34 million in upfront payments and is eligible to receive milestone payments and double-digit royalties from the deal.

Daiichi Sankyo and partner AstraZeneca realized approximately $3 billion in sales last year for Enhertu (trastuzumab deruxtecan), a linker for the antibody Herceptin to a topoisomerase inhibitor. It is expected that Enhertu will generate sales of $10 billion by 2027/2028, as its indications have expanded from HER2-positive breast cancer into breast cancers that express lower levels of HER2 as well as gastric cancer and NSCLC.

In 2023, Pfizer announced its $43 billion acquisition of Seagen and its four marketed ADCs with he acquisiton nclosing in December. In November, AbbVie purchased ImmunoGen for $10.1 billion. Industry analysts say these two deals alone pushed the total value of ADC deals in 2023

to more than three times seen in 2022; and both of those years surpassed 2021 deals (*nature biotechnology*, *PharmaCircle Strategic Deals Analyzer, News and Insights*)
Two significant ADC partnerships were formed in 2023 as well. First is Merck's licensing of three clinical-stage ADCs from Daiichi-Sankyo, valued at up to $22 billion. Bristol Myers Squibb paid $800 million upfront for rights outside China to SystIummune for a bispecific ADS that is in Phase 1 trials for non-small-cell lung cancer. It appears 2024 is off to a similar start with Johnson & Johnson entering into a $2 billion cash deal for Ambrx Biopharma and a licensing deal with China-based MediLink Therapeutics by Roche.
These moves highlight the impact of China as an innovator in the ADC space (**Figure 2**). Many attribute this to the fact that the country is reporting high numbers of diagnosed cases for breast, bladder and gastric cancers.

Figure 2: ADC Development by Country

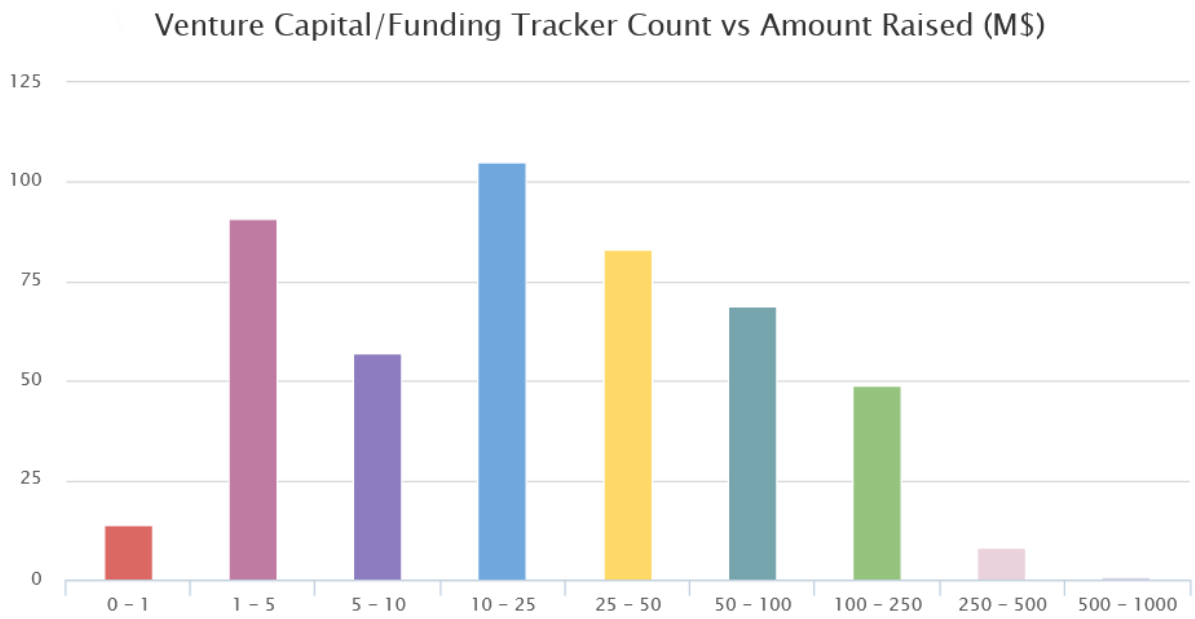


Source: PharmaCircle Pipeline & Products Intelligence

Smaller acquisitions and licensing deals are worth mentioning as they focus on linker technologies and the promise of safer and more efficacious medicines, as well as an expanded range of antibody targets and toxic payloads (*nature biotechnology*). For example, BioNTech paid $140 million upfront for rights outside China for two topoisomerase-1 inhibitor-based ADCs from Shanghai-based DualityBio, including a HER2-targeting candidate in Phase 2 trials. The biotech also deal with MediLink for a HER3-targeting ADC.
Beyond China, Eli Lilly bought Germany-based Emergence Therapeutics in June 2023, with its preclinical nectin-4-targeting ADC for bladder and triple-negative breast cancer. Lily also purchased France based Mablink Bioscience (which actually 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 (*nature biotechnology*).
The deal making hustle and bustle has industry insiders anticipating an ADC sales market value of $20-30 billion per year (*Foley & Lardner LLP*). This potential – combined with the innovation

potential of linker, payload and antibody – has VCs reaching into their pockets to fund ADC start-ups (**Figure 3**).

Figure 3: VC Investments in ADCs Since 2000



Source: PharmaCircle Venture Capital Capital/Funding Tracker

Of note is Netherlands-based Tagworks Pharmaceuticals raising a $65-million series A last June to advance its 'click-to-release' conjugation approach, designed to drop toxic payloads just outside tumor cells. Denmark-based Adcendo raised a $89 million extended series A for an ADC that targets cells that overexpress uPARAP, a collagen receptor.

The ADC pipeline is a promise in the making for next-generation cancer treatment. With close to 100 candidates currently in Phases 2 and 3 clinical trials (PharmaCircle), industry is optimistic about the future of a versatile and robust therapy.

ADC Short Report

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