Why Are ADCs So Hot Right Now?

HER2 AND TROP2 SUCCESS STORIES PROVIDE NECESSARY KINDLING TO SET THE WHOLE FIELD ABLAZE...AGAIN

An Ipsos Point of View

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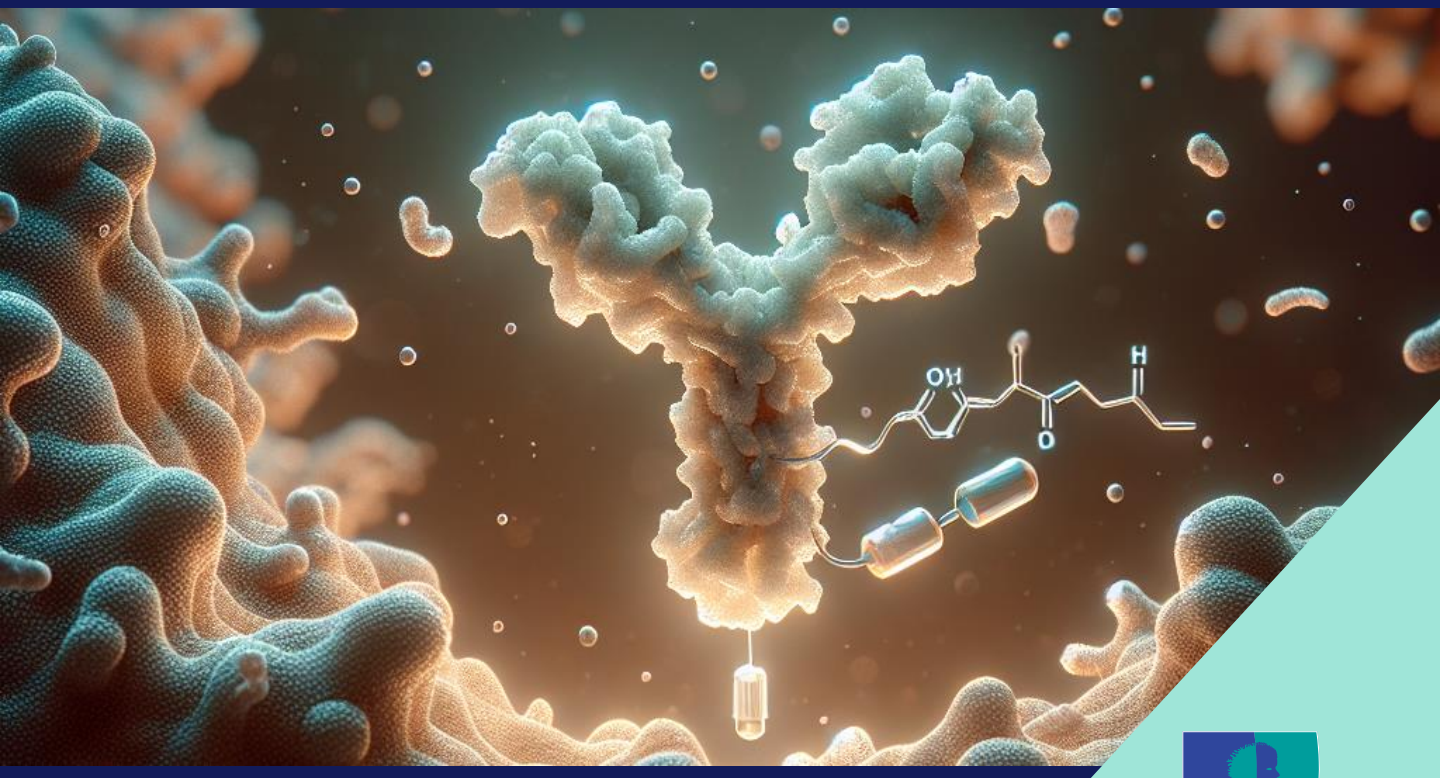
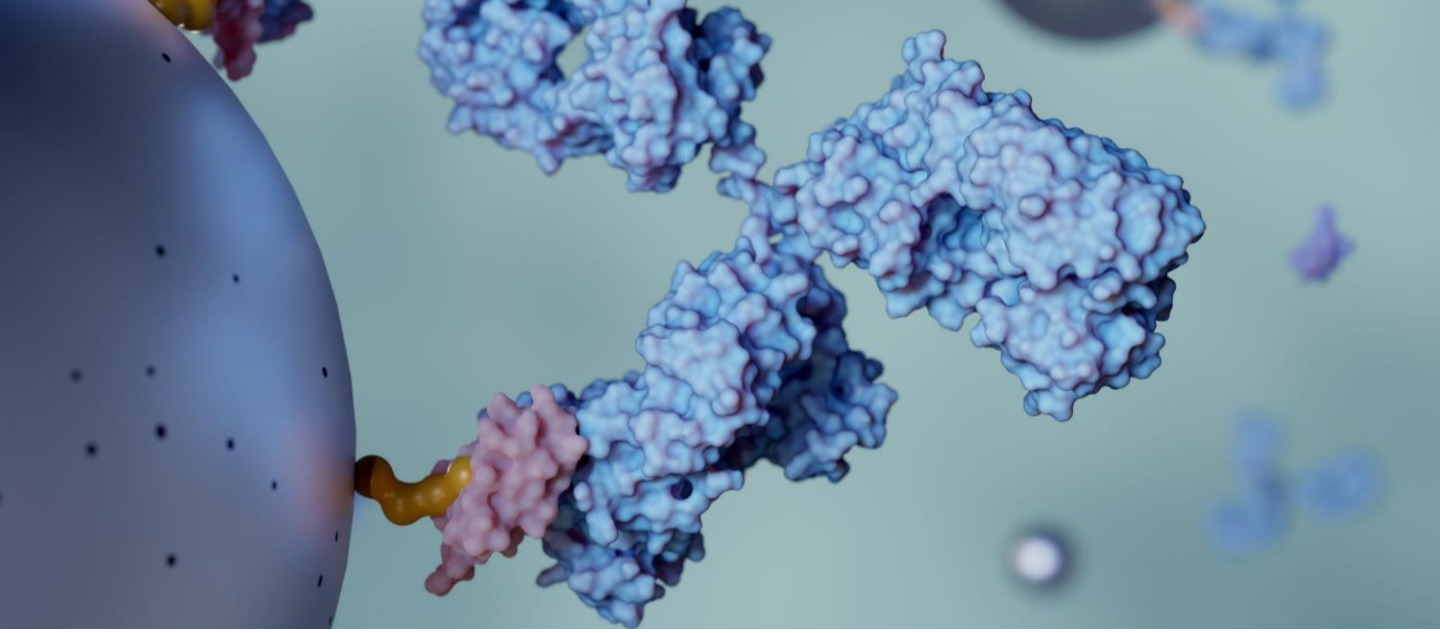


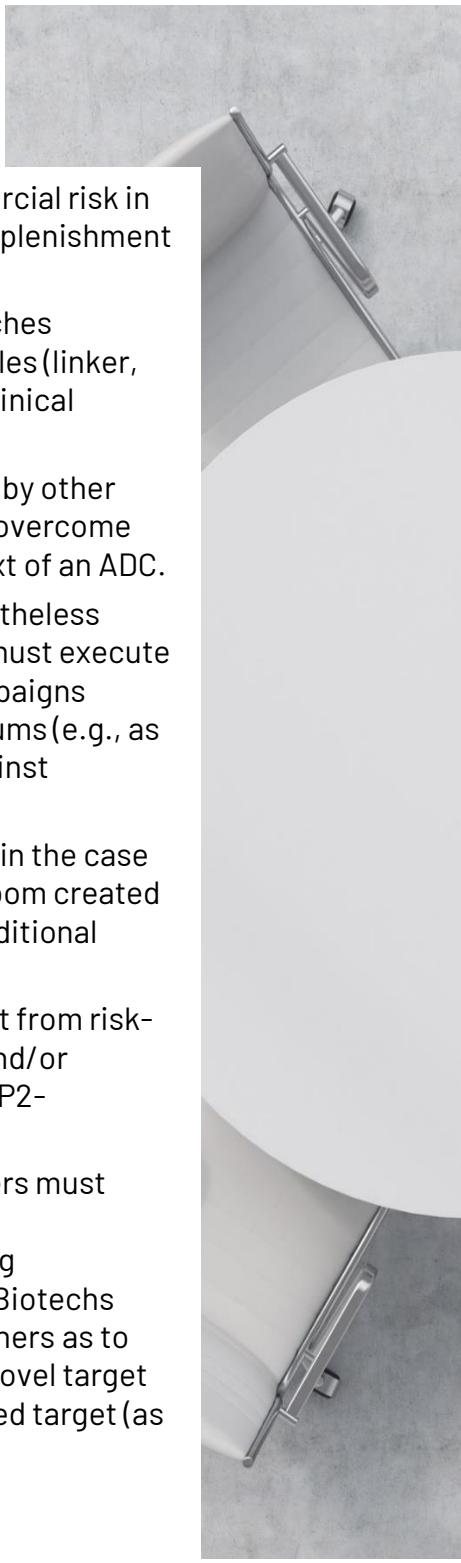


Introduction

As a modality which combines precision targeting of an antibody with the potency of a cytotoxic small molecule, antibody-drug conjugates (ADCs) allow developers to benefit from a unique combination of target-validation and optionality in the continual demand for novel anticancer medicines. In follow-up to our prior POV (check out Ipsos' 'The ADC Gold Rush Enters a New Chapter' here), which provides historical context and emerging trends in the ADC landscape, what follows is an assessment of competitive dynamics playing out across two prominent solid tumor ADC targets – HER2 and TROP2 – each of which have or will produce multiple blockbuster brands. While not unique to ADCs, these miniature case studies each underscore the interplay between scientific rationale and competitive positioning, key trade-offs between first- and late-mover status, and clues on how to achieve that ever-elusive optimal balance between clinical and commercial risk.

Pharma, which has always found the value proposition of ADCs to be compelling, is jumping back in to leverage technical improvements needed to maximize shots on goal, whether against novel targets (as first-mover) or validated/crowded targets (as late-mover/best-in-class).

Key Takeaways



- ADCs offer a favorable combination of clinical and commercial risk in an industry dependent on risk-mitigated paths towards replenishment of its blockbuster brands.
- Not all ADCs are created equal: antibody recognition enriches therapeutic concentrations at the tumor, but other variables (linker, payload, drug-antibody ratio [DAR]) create potential for clinical differentiation and commercial success.
- First-mover ADCs benefit from target validation achieved by other modalities (e.g., as Herceptin® did for Kadcyla®) but must overcome considerable risk in validating the target within the context of an ADC.
- First-movers enjoy competitive advantages but may nonetheless remain vulnerable to late-mover entrants. First-movers must execute on aggressive launch strategies and label-expansion campaigns needed to justify considerable risk and investment premiums (e.g., as paid by Gilead for Trodelvy®), and to establish barriers against competition from late-movers.
- Clinically-differentiated late-movers (or very late-movers in the case of Enhertu® vs. Kadcyla®) may capture commercial headroom created by shortcomings of first-movers, both in the same and additional indications (e.g., Enhertu® in HER2-low breast cancer).
- Thinly-differentiated late-movers can nonetheless benefit from risk-mitigation achieved by first-movers in sufficiently large and/or heterogeneous target markets (e.g., across different TROP2-expressing cancers for Trodelvy® and Dato-DXd).
- Regardless of respective positioning, first- and late-movers must execute on clinical-regulatory strategies aligned with an understanding of respective product features and evolving competitive dynamics. This is especially so for innovator Biotechs promoting an investment thesis to would-be Pharma partners as to why their product can achieve clinical success against a novel target (as a first-mover) or commercial success against a crowded target (as a late mover).

A Case Study: HER2

Target Overview:
Human epidermal growth factor receptor type 2 (HER2, synonyms: HER2/neu, ErbB-2) is a transmembrane tyrosine kinase receptor of the ErbB family (which includes HER1/EGFR, HER2, HER3, and HER4). HER2 overexpression has been observed in many tumor types, including up to 20% of gastric cancers and ~14% of breast cancers[1,2].

HER2 is arguably the most validated solid tumor target for biologics in general and ADCs in particular, with Roche/Immunogen's anti-HER2 ADC Kadcyla® among the few success stories from the early wave of innovation that was followed by Enhertu® as a late-mover.

	Kadcyla®[2,3]	Enhertu®[4,5]
Approval Year	2013	2019
Manufacturer	Roche/Genentech	Daiichi Sankyo/AstraZeneca
Initial Indication Approval	HER2+ unresectable or metastatic breast cancer (mBC) in the second line	HER2+ breast cancer (BC) patients with unresectable or metastatic disease who progressed on two prior lines of therapy
Subsequent Label Expansion(s)	➢ Adjuvant HER2+ early breast cancer with residual invasive disease after neoadjuvant taxane and trastuzumab - based treatment (2019)	➢ Locally advanced/metastatic, HER2+ gastric cancer who have received prior trastuzumab-based therapy (2021) ➢ HER2+ mBC who had progressed on one prior HER2-based regimen (2022) ➢ Unresectable/metastatic HER2-low BC who received a prior chemotherapy (2022) ➢ Unresectable/metastatic NSCLC with activating HER2 mutations and who have received a prior systemic therapy (2022) ➢ Unresectable/metastatic HER2+ solid tumors who have received prior systemic therapy and have no satisfactory alternative treatment options (2024)
Antibody	Trastuzumab	Trastuzumab
Linker	Non-cleavable Thioether	Cleavable Maleimide tetrapeptide
Payload	DM1 (Microtubule inhibitor)	DXd (exatecan derivate; TOP1 inhibitor)
Drug-Antibody Ratio (DAR)	3.5	~8

A Case Study: HER2

First-Mover: Kadcyla®

Roche's Genentech unit licensed the ADC technology for Kadcyla® (ado-trastuzumab emtansine) from ImmunoGen in 2000 to bolster its HER2 franchise established by monoclonal antibody therapies Herceptin® (trastuzumab) and Perjeta® (pertuzumab). In addition to its HER2-targeting ability, Kadcyla's® cytotoxic payload (DM1) was chosen because breast cancer is known to be sensitive to spindle microtubule inhibitors based on efficacy of taxanes like Taxol. Kadcyla® was initially approved for metastatic second-line (or later) HER2+ breast cancer patients who previously received Herceptin® and a taxane[6]. Kadcyla® was successfully positioned to cannibalize Herceptin® sales in advance of the latter's 2019 loss-of-exclusivity but failed to supplant Herceptin® plus a taxane as frontline treatment for locally advanced or metastatic, HER2-positive breast cancer. Kadcyla® was therefore never quite able to unlock the full commercial promise of a HER2-targeting ADC. Roche reported 2023 sales of $2.2B for Kadcyla®[7], likely representing peak revenues with biosimilar entry anticipated in 2025 (for comparison, Herceptin® generated $7B in 2018, and Perjeta® generated $4.3B in 2022).

Late-Mover: Enhertu®

Daiichi Sankyo granted AstraZeneca worldwide commercialization and development rights (excluding Japan), to Enhertu® (fam-trastuzumab deruxtecan-nxki) in 2019 for $1.35B upfront[8]. The FDA granted accelerated approval to Enhertu® in 2019 based on impressive efficacy (ORR: 60.9%; mPFS: 16.4 months) in heavily pretreated HER2-positive breast cancer patients. Notably, patients in the Enhertu® trial were all Kadcyla®-experienced, and Daiichi took the rare step of testing Enhertu® head-to-head against Kadcyla®, resulting in its subsequent expansion into second-line and supplanting of Kadcyla®[9]. The label for Enhertu® has since been expanded to include patients with 'HER2-low' breast cancer, HER2-positive lung cancer, and HER2-positive gastric cancer, all indications that have proven inaccessible to Kadcyla®. The topoisomerase inhibitor payload of Enhertu® is purported to be more effective than Kadcyla's® tubulin inhibitor payload in relapsed/refractory patients that had already been exposed to a taxane in the front line. It was also demonstrated that Enhertu's® payload more easily crosses the cell membrane to generate a cytotoxic effect independent of target expression (the so-called "bystander effect"), which may help explain Enhertu's® efficacy in the heterogeneous group of HER2-low breast cancer patients. Combined sales of the drug for the two companies amounted to $2.57B in 2023, more than doubling from $1.25B the year before[10].

A Case Study: HER2

Commercial Dynamics

With Kadcyla®, ImmunoGen scored an early success story that helped ratchet up demand and upfront payments for its subsequent deal-making efforts. While Roche never achieved outsized commercial success with Kadcyla®, its regulatory approval and incorporation in treatment guidelines did help to bolster the Pharma giant's already-formidable position as the leader in HER2-targeted medicines. Daiichi/AstraZeneca's Enhertu® only recently emerged as a blockbuster after Roche's market share had already begun to erode with the entry of Herceptin/trastuzumab biosimilars. Enhertu's® success, in turn, illustrates the ability to leverage a first-mover both to validate the clinical/commercial rationale and underscore headroom for improvement with a differentiated late-mover challenger.

Enhertu's success illustrates the ability to leverage a first-mover both to validate the clinical/commercial rationale and underscore headroom for improvement

Depending on the level and nature of differentiation, late-mover products can be positioned to capture later-line patients on the path towards upward movement (in this case, with Enhertu® directly displacing Kadcyla® in second-line breast cancer) and outward movement (in this case, with Enhertu® capturing labels in HER2-low breast cancer, gastric cancer, and NSCLC). What gave Daiichi the confidence to develop yet another HER2-targeting biologic at a time when many believed Roche had this market locked up tight? Differences in payload, DAR, and membrane permeability have all been cited as differentiators between Enhertu® and Kadcyla®.

To be fair, Enhertu® is far from perfect. It has a blackbox warning for interstitial lung disease (ILD) and embryo-fetal harm in pregnant women (for which Kadcyla® also has a blackbox warning). But its success (and perhaps shortcomings) supports the notion that innovation is on a continual upward trajectory, and we can only hope there'll be more to come.

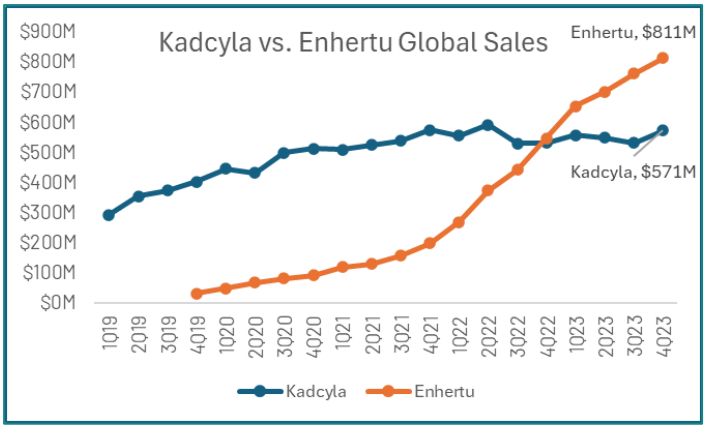


Figure 1: Kadcyla® vs. Enhertu® Quarterly Global Sales (1Q19 – 4Q23)

Source: Company websites

A Case Study: TROP2

Target Overview:
Trophoblast cell surface antigen 2 (TROP2, synonyms: GA733-1, EGP-1, TACSTD2, paralog: EpCAM/Trop-1) is a transmembrane glycoprotein and intracellular calcium signal transducer. TROP2 protein is upregulated in nearly all cancers, including up to 90% of TNBC, 64% of adenocarcinoma and 75% of squamous cell carcinoma NSCLC[11].

Trodelvy® is currently the only approved TROP-2 agent to-date yet faces fierce competition in the pipeline with impending late-mover approvals, such as Datopotamab deruxtecan (Dato-DXd).

	Trodelvy®[12, 13]	Dato-DXd[14]
Approval Year	2020	Not Yet Approved (BLA Accepted)
Manufacturer	Immunomedics/Gilead	Daiichi Sankyo/AstraZeneca
Initial Indication Approval	Metastatic triple-negative breast cancer who received at least two prior therapies for metastatic disease	Locally advanced/metastatic non-squamous non-small cell lung cancer (NSCLC) who have received prior systemic therapy
Subsequent Label Expansion(s)	➢ Unresectable locally advanced/ metastatic HR+, HER2-, breast cancer who have received endocrine-based therapy and at least two additional systemic therapies for metastatic disease ➢ Locally advanced/metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and PD-1/L1 inhibitor (Accelerated approval)	➢ N/A
Antibody	Humanized anti-TROP2 Antibody	Humanized anti-TROP2 Antibody
Linker	A hydrolyzable linker, with a short PEGylated unit	Cleavable Maleimide tetrapeptide (only with lysosomal proteases)
Payload	SN-38 (irinotecan metabolite; TOP1 inhibitor)	DXd (exatecan derivate; TOP1 inhibitor)
Drug-Antibody Ratio (DAR)	7.6	~4

A Case Study: TROP2

First-Mover: Trodelvy®

Gilead acquired Immunomedics for approximately $21B in September 2020 to access Trodelvy® (sacituzumab govitecan-hziy), a first-in-class TROP2-targeting ADC developed with a potent irinotecan analog as its payload, a cleavable linker to drive a bystander effect, and high DAR[15]. The product was first launched in mTNBC after its accelerated April 2020 approval based on a single-arm study (ORR: 33%; mDOR: 7.7mos), with subsequent full approval in 2021 following demonstration of an OS benefit over chemotherapy (mOS: 11.8 vs. 6.9 months; HR: 0.51)[16]. The bladder cancer label was also under accelerated approval based on surrogate endpoints (ORR: 28%; mDOR: 7.2 months), with full approval still pending[17]. Trodelvy® is also being tested in NSCLC (though the program recently suffered a Phase 3 set-back[18]) and in a tumor-agnostic basket trial for solid tumor patients overexpressing TROP2. Trodelvy® revenues reached $1.1B in 2024 and are anticipated to reach $2.3B in 2026[19]. Drug resistance and safety concerns (myelosuppression, diarrhea) remain major obstacles to its broader success.

Late-Mover: Dato-DXd

Daiichi/AstraZeneca's Dato-DXd (datopotamab deruxtecan) is a novel, investigational TROP2-directed ADC. In July 2020, Daiichi granted AstraZeneca rights to co-develop and commercialize Dato-DXd (excluding Japan), which was in Phase 1 at the time, for an upfront payment of $1B[20]. Relative to Trodelvy®, Dato-DXd has a lower DAR (4:1), a linker selectively cleaved by tumor cell–enriched lysosomal enzymes[21], and a more convenient dosing schedule (q21 vs. once weekly on days 1 and 8 of a continuous 21-day treatment cycle). The partners are pursuing development of Dato-DXd in similar indications as Trodelvy®, including NSCLC, TNBC, HR+/HER2- breast cancer, and a tumor-agnostic 'basket' trial. Projected peak revenue forecasts range anywhere from $2B to $10B, with commercial performance largely hinging on BLAs submitted for advanced, previously treated, non-squamous NSCLC (PDUFA 4Q2024) and pretreated HR+/HER2- metastatic breast cancer (PDUFA 1Q2025)[22].

A Case Study: TROP2

Commercial Dynamics

Did Gilead overpay for Immunomedics? $21B was indeed a handsome reward for the Biotech and its investors, helping rotate funds back to earlier-stage innovators willing to take on similar levels of risk to solve additional unmet medical needs. Gilead paid roughly half that amount for its other large oncology acquisition, Kite Pharma[23], revenues from which generated $487 million in the third quarter of 2023[24]. While Gilead's share price did not drop when the Immunomedics acquisition was announced, it has since been argued that Trodelvy® sales would need to reach at least $4B for Gilead to recover the cost of the acquisition[25]. Dato-DXd, for which AstraZeneca paid $1B, may well hit this target (its well within analysts' range of $2-10B[19]), but Trodelvy® likely will not.

To be fair, one cannot judge Gilead against AstraZeneca based solely on the price each paid for access to their respective TROP2-targeting ADCs (see Box 1). Regardless, Gilead has far more to lose than its competitors given the premium paid for first-mover status. Merck is also in this space, having paid just $47M for ex-China rights to a TROP2 ADC that is in phase 3 development at Kelun-Biotech[27]. Though clearly positioning Merck as third-in-class in the TROP2 race, the deal provided Merck with access to additional ADC candidates from Kelun, which along with the company's more high-profile collaboration announced with Daiichi more recently, provide a foundation upon which it hopes to build a modern-day ADC arsenal needed to compete in this white-hot market landscape.

The $1B price commanded by Daiichi had to account for several counterbalancing factors:

(1) Gilead acquired an entire company, whereas AstraZeneca paid for co-commercialization rights to be shared with a Pharma partner,

(2) The prior success with Enhertu®, which at the time of deal-making was already well on its way to becoming a blockbuster,

(3) AstraZeneca entered into the agreement already knowing that Dato-DXD would not have first-mover advantage since Trodelvy® had already been approved by the time the partnership was announced in July 2020,

(4) While Trodelvy® provided Gilead with a cornerstone asset for its transition into solid tumors, Enhertu® and Dato-DXd provided AstraZeneca with cornerstones in its journey towards becoming an ADC powerhouse[26].

Box 1: Insights into rationale for Dato-DXd deal garnering a $1B price tag

Concluding Thoughts

Ours is an industry built on the promise of exit opportunities for Biotech investors to rotate funds back towards earlier risky ventures that address additional unmet medical needs. Biotechs should be aspiring towards exit opportunities created by target product profiles (TPPs) that resonate with would-be Pharma partners and the markets they sell into. Pharma, in turn, will always be attracted to an investment thesis if the scientific rationale and evidence generation align with a clear path to blockbuster-level revenues.

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As a modality, ADCs provide a favorable combination of risk-mitigation (target validation) and optionality (linker technology, payload, DAR) needed to win, whether it be as a first- or late-mover in the lucrative oncology landscape. This unique combination of target-validation and optionality has driven many oncology leaders, including Roche, AstraZeneca, Daiichi, Merck, Pfizer, AbbVie, and Astellas, into this space. Pharma, which has always found the value proposition of ADCs to be compelling, is jumping back in to leverage technical improvements needed to maximize shots on goal, whether against novel targets (as first-mover) or validated/crowded targets (as late-mover/best-in-class). While subsequent clinical and commercial performance may fall short of expectations set at the time of an acquisition or partnership (a risk Pharma partners must be willing to take), competitive dynamics playing out across the ADC landscape underscore opportunities for win-win opportunities at the heart of incremental or even groundbreaking clinical achievements, returns on investments, and meaningful success stories for patients that need them most.

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