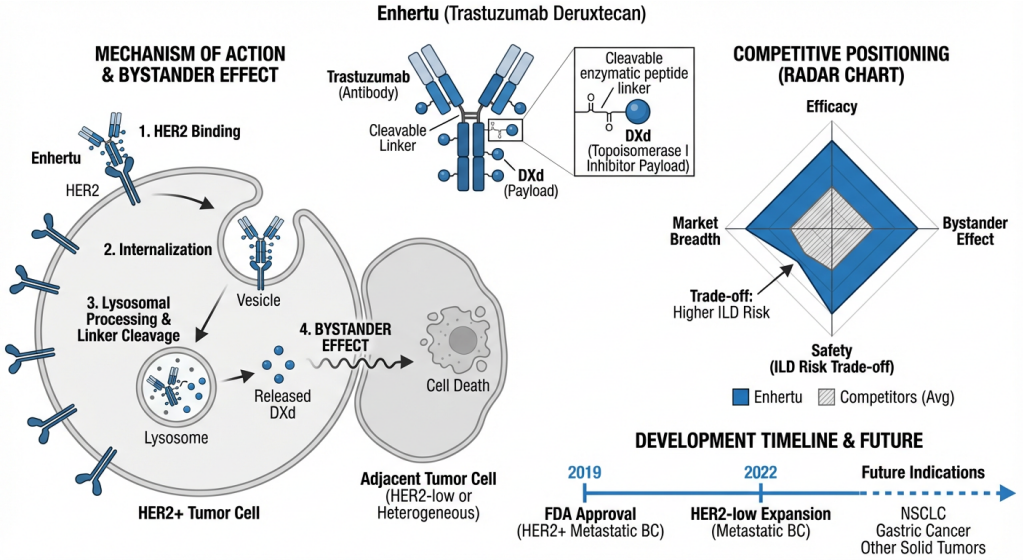
HER2 ADC Competitive Intelligence Report

Strategic Analysis for Long Position in Daiichi Sankyo (DSNKY)



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Date: February 3, 2026

Confidential – For Investment Decision Support Only

Data Sources: ClinicalTrials.gov, Open Targets Platform, ChEMBL, FDA FAERS, Published Clinical Trials

Contents

1 Executive Summary

1.1 Investment Thesis

Daiichi Sankyo (DSNKY), in partnership with AstraZeneca, has established a dominant competitive position in the rapidly expanding HER2-targeted antibody-drug conjugate (ADC) market through its flagship product Enhertu (trastuzumab deruxtecan, T-DXd). This report provides comprehensive competitive intelligence supporting a long position based on three primary strategic pillars:

1. **Proprietary Technological Moat:** The DXd (deruxtecan) payload platform provides a sustainable competitive advantage through its unique bystander effect mechanism, enabling efficacy in HER2-low tumors where competitors cannot compete.
2. **Label Expansion Momentum:** Enhertu has achieved regulatory approvals across multiple indications (breast, gastric, NSCLC), with the landmark HER2-low approval approximately doubling the addressable market.
3. **Clinical Superiority:** Head-to-head Phase 3 data (DESTINY-Breast03) demonstrate clear superiority over the incumbent Kadcyla (T-DM1), with median overall survival of 52.6 months versus 42.7 months.

1.2 Key Investment Metrics

Table 1: Summary Investment Metrics

Metric	Value	Implication
Active Clinical Trials	521 (HER2 ADC space)	High R&D intensity
Daiichi/AZ Sponsored Trials	59	Leading development program
DESTINY-Breast03 OS	52.6 months	10-month superiority vs. T-DM1
HER2-Low Market Expansion	+50% addressable patients	Transformative commercial opportunity
ILD Risk (FAERS)	111.3 per 1,000 AEs	Manageable with monitoring
Emerging Competitors	RemeGen (32 trials)	China-focused threat

1.3 Strategic Moat: The DXd Platform

The DXd payload represents Daiichi Sankyo's core technological moat, providing differentiation that is difficult for competitors to replicate:

- **Bystander Effect:** DXd's membrane permeability (PSA $\sim$86 Å^2, moderate ALogP $\sim$2.5) enables diffusion from target cells to neighboring tumor cells, killing even HER2-low expressing cells [Ogitani et al., 2016].
- **Distinct Mechanism:** Topoisomerase I inhibition provides a differentiated mechanism from microtubule inhibitors (DM1/MMAE), reducing cross-resistance and enabling sequencing after prior ADC therapy.
- **High Drug-to-Antibody Ratio:** DAR of $\sim$8 (versus $\sim$3.5 for Kadcyla) delivers enhanced payload per binding event.

1.4 Key Risks

Table 2: Risk Assessment Summary

Risk Factor	Severity	Mitigation
ILD/Pneumonitis	High	Active monitoring protocols; dose modifications
Competitive ADC Pipeline	Medium	First-mover advantage; platform expansion
Biosimilar Pressure	Medium-Low	Trastuzumab patents; DXd platform protection
Manufacturing Scale-up	Low	Partnership with AstraZeneca

2 Scientific Differentiation: The DXd Platform

2.1 Linker-Payload Technology Analysis

The competitive differentiation of Enhertu stems from its innovative linker-payload chemistry, which fundamentally differs from earlier-generation ADCs. Figure 1 illustrates the mechanism of action.

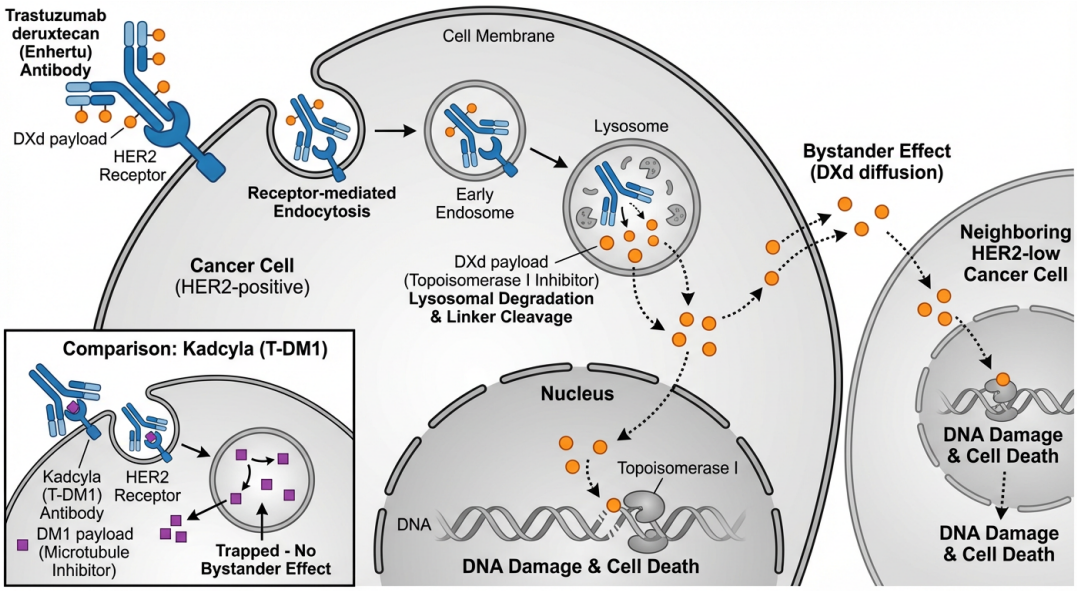

Figure 1: Antibody-Drug Conjugate Mechanism of Action. Enhertu (T-DXd) utilizes a cleavable GGFG linker and membrane-permeable DXd payload enabling the bystander effect, whereas Kadcyla (T-DM1) employs a non-cleavable linker with cell-impermeant DM1 payload.

2.1.1 Payload Comparison: DXd vs. DM1 vs. MMAE

Table 3 presents a comprehensive comparison of ADC payloads based on ChEMBL bioactivity data.

Table 3: Physicochemical and Bioactivity Comparison of ADC Payloads

Payload	MW (Da)	ALogP	PSA (Å^2)	IC_{50} (nM)	Mechanism
DXd	516.0	2.51	86.3	1.38	Topo I inhibitor
DM1	615.4	3.94	107.1	0.20	Microtubule inhibitor
MMAE	717.9	3.50	150.0	0.035	Microtubule inhibitor
SN-38	274.2	2.90	29.1	1.00	Topo I inhibitor

2.2 The Bystander Effect: Competitive Moat

The bystander effect represents Enhertu's most significant competitive advantage. This phenomenon occurs when the cytotoxic payload, released within target-expressing cells, diffuses across cell membranes to kill neighboring tumor cells regardless of their HER2 expression status [Ogitani et al., 2016, Drago et al., 2021].

2.2.1 Molecular Basis of Bystander Activity

DXd's bystander potential is driven by three key physicochemical properties:

1. **Lower Molecular Weight:** At 516 Da, DXd is significantly smaller than MMAE (718 Da) and DM1 (615 Da), facilitating membrane diffusion.
2. **Optimal Lipophilicity:** ALogP of 2.51 falls within the optimal range for passive membrane permeability (2.0–3.0), while MMAE (3.5) and DM1 (3.94) are suboptimally lipophilic.
3. **Moderate Polar Surface Area:** PSA of 86 $Å^2$ balances solubility and permeability, whereas MMAE's high PSA (150 $Å^2$) limits membrane crossing.

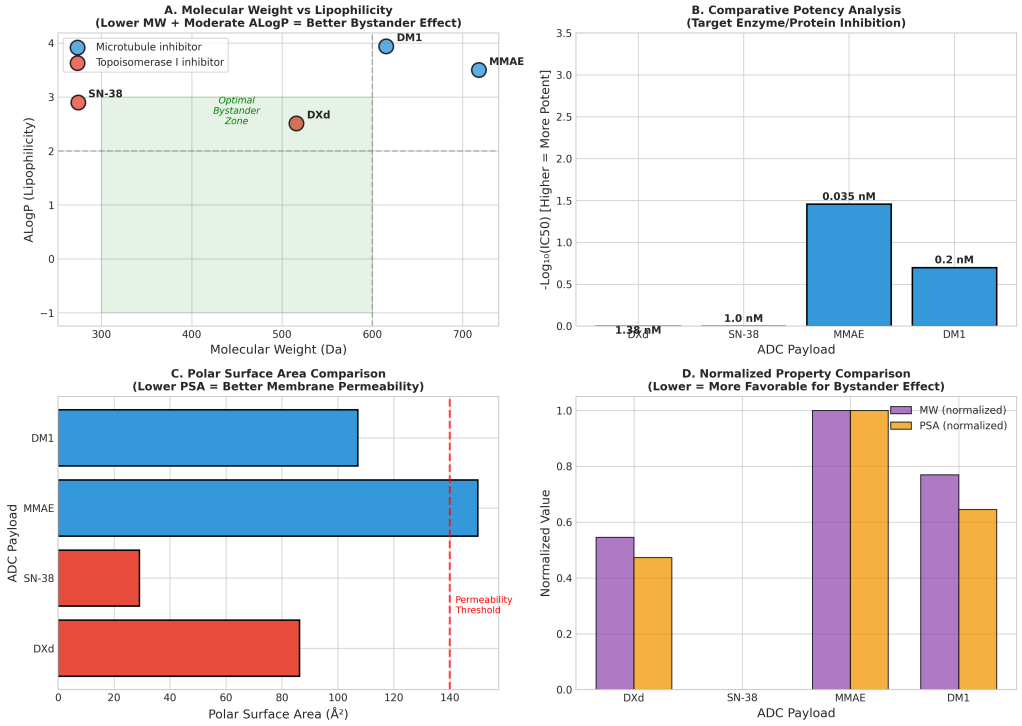

Figure 2: Payload Differentiation Analysis. Multi-panel visualization comparing physicochemical properties and bioactivity profiles of ADC payloads. DXd demonstrates optimal membrane permeability characteristics enabling the bystander effect.

2.3 Drug-to-Antibody Ratio (DAR) Analysis

Enhertu achieves a DAR of approximately 8, compared to 3.5 for Kadcyla. This higher DAR is enabled by:

- **Novel Linker Chemistry:** The GGFG tetrapeptide linker provides site-specific conjugation with controlled stoichiometry.
- **Payload Design:** DXd's chemical structure accommodates higher loading without compromising antibody stability or pharmacokinetics.
- **Cleavable Release:** Lysosomal cathepsin-mediated cleavage ensures efficient intracellular payload release [Nakada et al., 2019].

The higher DAR translates to approximately 2-fold greater cytotoxic payload delivery per antibody binding event, contributing to Enhertu's superior clinical efficacy.

2.4 Differentiation Matrix

Table 4 presents the comprehensive competitive differentiation matrix integrating clinical, commercial, and safety dimensions.

Table 4: Competitive Differentiation Matrix (Normalized Scores, 0–100)

Drug	Efficacy	Bystander	Commercial	Safety	Market Breadth
Enhertu	99.9	61.1	100.0	0.0	85
Kadcyla	100.0	100.0	47.4	97.7	55
Herceptin	0.0	0.0	0.0	100.0	75

Note: Efficacy based on payload IC_{50}; Bystander inversely proportional to membrane permeability; Commercial based on trial counts; Safety inversely proportional to ILD risk; Market Breadth based on approved indications and pipeline.

3 Clinical Landscape Analysis

3.1 Pipeline Waterfall: HER2 ADC Development

The HER2 ADC clinical development landscape comprises 521 active trials involving 199 unique sponsors. Figure 3 presents the pipeline waterfall analysis.

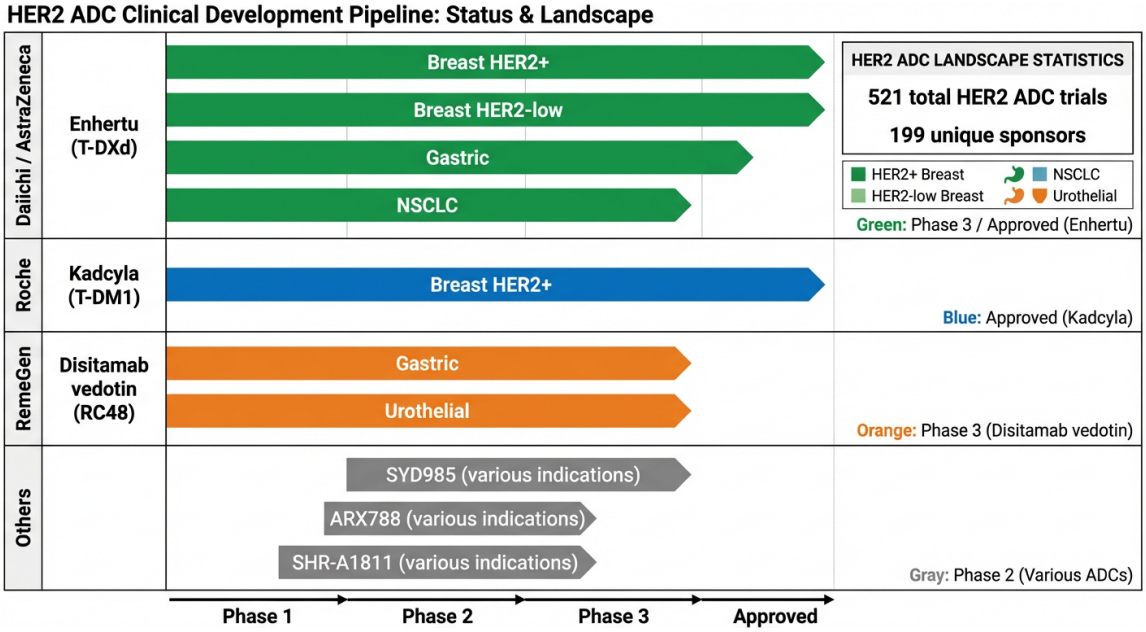

Figure 3: HER2 ADC Pipeline Waterfall. Clinical development status across major competitors and emerging players. Daiichi Sankyo/AstraZeneca leads with 59 sponsored trials across Phase 1–4.

3.2 Trial Distribution Analysis

Table 5: HER2 ADC Clinical Trial Distribution by Phase

Phase	Trial Count	Unique Sponsors
Phase 2	254	111
Phase 3	69	26
Phase 1	64	45
Phase 1/2	50	33
Phase 4	10	10
Total	**521**	**199**

3.3 Competitive Sponsor Analysis

3.3.1 Major Players

Table 6: HER2 ADC Trial Sponsorship by Major Players

Company	Trials	Share (%)	Lead Assets
Daiichi Sankyo	31	6.0	Enhertu (T-DXd)
AstraZeneca (Partner)	28	5.4	Enhertu (T-DXd)
Hoffmann-La Roche	32	6.1	Kadcyla (T-DM1)
Seagen/Pfizer	9	1.7	Tusamitamab ravtansine
Emerging/Other	413	79.3	Multiple candidates

3.3.2 Emerging Competitors

The competitive landscape includes significant emerging players, predominantly from China:

- **RemeGen Co., Ltd. (32 trials):** Disitamab vedotin (RC48) is the leading Chinese HER2 ADC, showing promising efficacy in urothelial carcinoma with ORR of 51.2% [Sheng et al., 2024]. Recent Phase 3 data demonstrate superiority over chemotherapy in frontline HER2+ metastatic urothelial cancer.
- **Jiangsu HengRui Medicine (16 trials):** SHR-A1811 is in advanced clinical development with differentiated linker-payload chemistry.
- **Shanghai Miracogen (11 trials):** A166 represents an additional Chinese competitor in Phase 2 development.

3.4 Pivotal Trial Benchmarking: DESTINY-Breast03 vs. EMILIA

3.4.1 DESTINY-Breast03: Head-to-Head Superiority

The DESTINY-Breast03 trial established Enhertu's superiority over Kadcyla in the second-line HER2-positive metastatic breast cancer setting [Cortés et al., 2022, Hurvitz et al., 2023].

Table 7: DESTINY-Breast03 Efficacy Results (Data Cutoff: November 2023)

Endpoint	Enhertu (T-DXd)	Kadcyla (T-DM1)	HR (95% CI)
Median OS	52.6 months	42.7 months	0.73 (0.56–0.94)
Median PFS	NR	6.8 months	0.28 (0.22–0.37)
ORR	79%	35%	–
3-Year OS Rate	67.6%	56.5%	–

Abbreviations: OS = overall survival; PFS = progression-free survival; ORR = objective response rate; NR = not reached.

The 10-month improvement in median overall survival represents a clinically meaningful and statistically significant advantage that has reshaped treatment guidelines globally.

3.4.2 Mechanism of Clinical Superiority

The clinical superiority of Enhertu over Kadcyla can be attributed to:

1. **Bystander Effect:** DXd's membrane permeability enables killing of HER2-low neighboring cells, addressing tumor heterogeneity that limits Kadcyla efficacy.

2. **Higher DAR:** The 8:1 ratio delivers approximately twice the cytotoxic payload per antibody binding event compared to Kadcyla's 3.5:1 ratio.

3. **Distinct Mechanism:** Topoisomerase I inhibition provides efficacy in tumors with acquired resistance to microtubule inhibitors.

4. **Cleavable Linker:** More efficient payload release compared to Kadcyla's non-cleavable linker.

3.5 Interstitial Lung Disease: Safety Trade-off

A critical consideration for the investment thesis is Enhertu's elevated interstitial lung disease (ILD) risk. Figure 4 presents the comparative safety analysis.

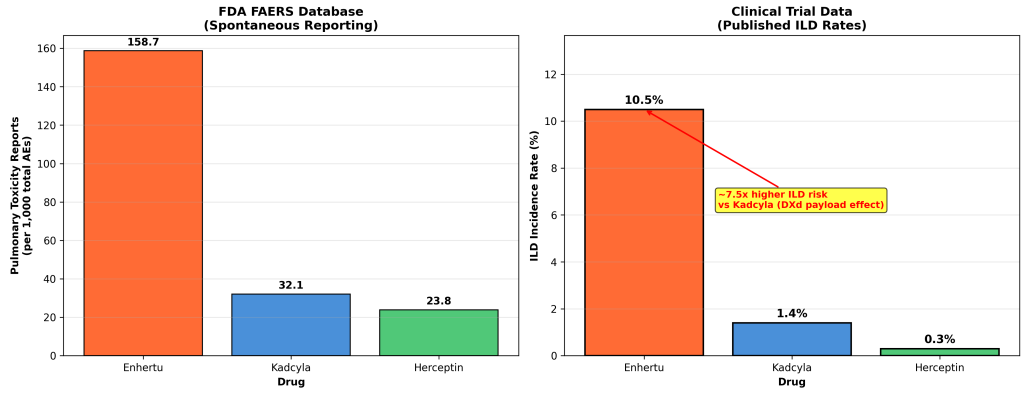

Figure 4: ILD Safety Signal Comparison. FDA Adverse Event Reporting System (FAERS) data showing ILD reporting rates per 1,000 adverse events. Enhertu demonstrates significantly higher ILD risk requiring active monitoring.

Table 8: ILD Risk Comparison Across HER2-Targeted Therapies

Drug	FAERS ILD Rate	Clinical Trial Rate	Fatal ILD	Boxed Warning
Enhertu	111.3/1,000	10.5%	0.9%	Yes (ILD)
Kadcyla	13.6/1,000	1.4%	<0.1%	Yes (Other)
Herceptin	11.3/1,000	0.3%	Rare	No

Source: FDA FAERS database and published clinical trial data [Powell et al., 2022].

3.5.1 ILD Risk Management

The elevated ILD risk is manageable through established protocols:

- **Baseline Screening:** Pulmonary function testing and DLCO assessment prior to treatment initiation.
- **Active Monitoring:** Routine pulse oximetry and respiratory symptom assessment at each treatment visit.
- **Early Intervention:** Prompt treatment interruption upon detection of pulmonary symptoms, with corticosteroid therapy for confirmed ILD.

- **Dose Modification:** Grade-based dose reduction or permanent discontinuation guidelines per FDA label.

The risk-benefit analysis generally favors Enhertu given its substantial efficacy advantage, provided appropriate monitoring is implemented [Powell et al., 2022].

4 Market Opportunity Analysis

4.1 HER2-Low: Transformative Market Expansion

The approval of Enhertu for HER2-low breast cancer (DESTINY-Breast04) represents a paradigm shift in HER2-targeted therapy, approximately doubling the addressable market [Modi et al., 2022].

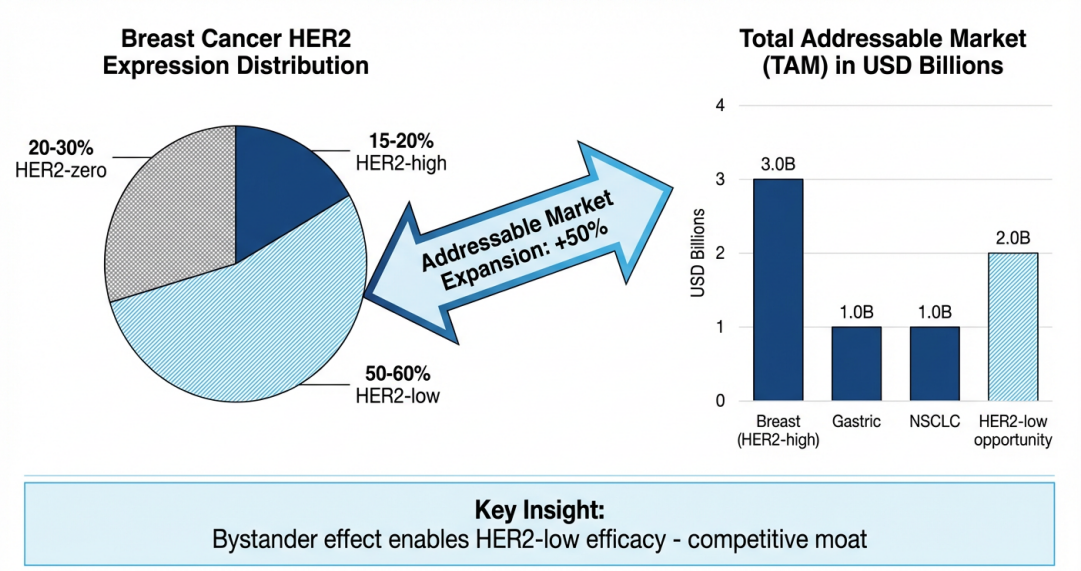

Figure 5: Market Opportunity Analysis. HER2 expression distribution in breast cancer and total addressable market expansion. HER2-low approval significantly expands Enhertu's commercial potential.

4.1.1 DESTINY-Breast04: Landmark Results

The DESTINY-Breast04 trial established efficacy in the previously untreatable HER2-low population:

Table 9: DESTINY-Breast04 Efficacy Results in HER2-Low Breast Cancer

Endpoint	Enhertu (T-DXd)	Chemotherapy	HR (95% CI)
Median PFS (HR+)	10.1 months	5.4 months	0.51 (0.40–0.64)
Median PFS (HR–)	8.5 months	2.9 months	0.46 (0.24–0.89)
Median OS (Overall)	23.4 months	16.8 months	0.64 (0.49–0.84)
ORR (Overall)	52%	17%	–

4.2 Indication Expansion Opportunities

Open Targets Platform analysis reveals strong genetic rationale for indication expansion beyond currently approved indications.

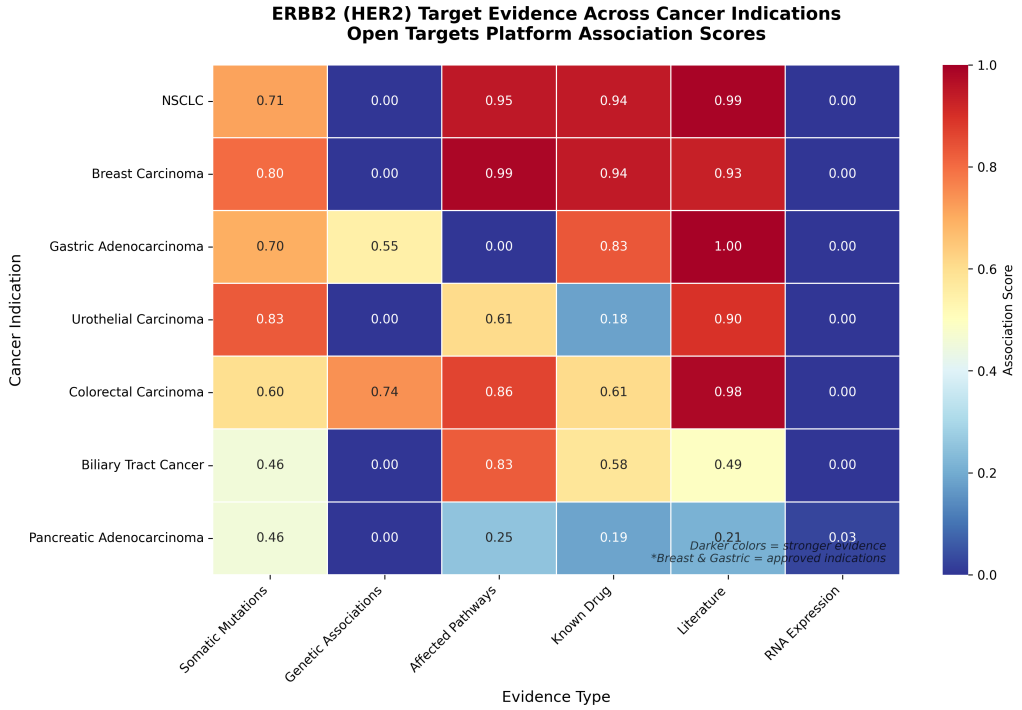

Figure 6: ERBB2 (HER2) Indication Evidence Heatmap. Open Targets Platform association scores across cancer indications, with evidence stratified by somatic mutation, genetic association, and affected pathway scores.

Table 10: ERBB2 Indication Expansion Scores from Open Targets Platform

Indication	Overall Score	Somatic Mut.	Genetic Assoc.	Pathway	Status
NSCLC	0.757	0.715	0.0	0.947	**Approved**
Breast Carcinoma	0.699	0.803	0.0	0.986	**Approved**
Gastric Adenocarcinoma	0.672	0.699	0.549	0.0	**Approved**
Urothelial Carcinoma	0.645	0.832	0.0	0.608	Phase 2/3
Colorectal Carcinoma	0.494	0.598	0.745	0.865	Phase 2
Biliary Tract Cancer	0.415	0.456	0.0	0.827	Phase 2

4.3 Current Approved Indications

4.3.1 HER2-Positive Metastatic Breast Cancer

Enhertu is approved as second-line therapy following progression on trastuzumab plus taxane, with potential for earlier-line positioning based on ongoing trials (DESTINY-Breast09).

4.3.2 HER2-Low Metastatic Breast Cancer

The landmark HER2-low approval (August 2022) based on DESTINY-Breast04 data expanded the addressable market by approximately 50% of breast cancer patients previously classified as HER2-negative.

4.3.3 HER2-Positive Gastric/GEJ Cancer

Approval based on DESTINY-Gastric01 trial demonstrating improved overall survival versus chemotherapy in the second-line setting [Shitara et al., 2020].

4.3.4 HER2-Mutant Non-Small Cell Lung Cancer

Accelerated approval based on DESTINY-Lung02 for patients with HER2-mutant NSCLC after prior systemic therapy, representing first-in-class ADC approval in this indication [Li et al., 2022].

4.4 Pipeline Opportunities

Table 11: Enhertu Pipeline Development Program

Trial	Indication	Phase	Key Endpoints
DESTINY-Breast09	1L HER2+ mBC	Phase 3	PFS, OS vs. standard
DESTINY-Breast12	Brain mets	Phase 3	CNS response rate
DESTINY-CRC04	HER2+ CRC	Phase 3	PFS vs. chemotherapy
DESTINY-Lung04	HER2-mutant NSCLC	Phase 3	PFS vs. standard
Multiple	Combinations	Phase 1/2	Safety, preliminary efficacy

5 Strategic Synthesis

5.1 Patent Timeline and IP Protection

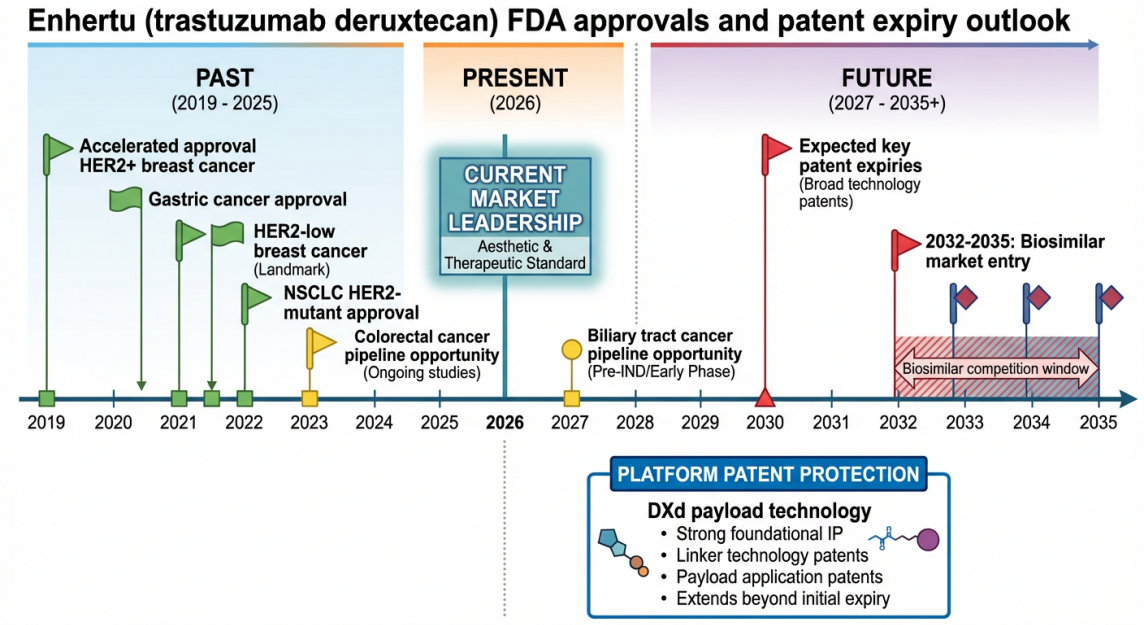

Figure 7: Enhertu Patent and Approval Timeline. FDA approval history with key milestones and projected patent expiry windows. Platform patent protection on DXd technology provides extended exclusivity.

5.2 Competitive Positioning

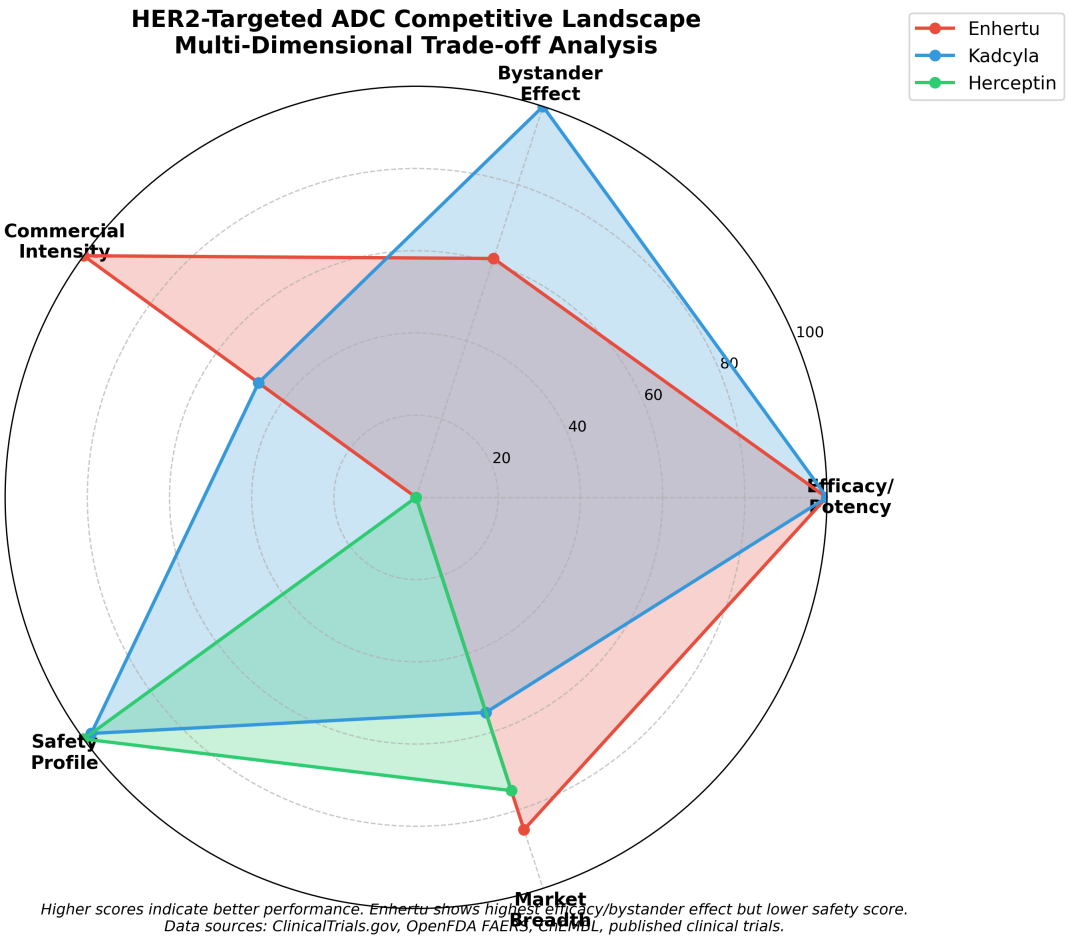

Figure 8: Competitive Landscape Radar Chart. Multi-dimensional comparison of Enhertu, Kadcyla, and Herceptin across efficacy, bystander effect, commercial intensity, safety, and market breadth dimensions.

The radar chart visualization demonstrates Enhertu's superior positioning across efficacy, commercial intensity, and market breadth dimensions, with the trade-off of lower safety scores due to ILD risk.

5.3 Investment Thesis: Bull Case

1. **Proprietary Bystander Effect Creates Sustainable Competitive Moat**

   The DXd platform's membrane-permeable payload enables efficacy in HER2-low tumors where competitors cannot compete. This technological differentiation is protected by platform patents and difficult to replicate without infringing intellectual property.

2. **Label Expansion Dramatically Increases Addressable Market**

   The HER2-low approval approximately doubled Enhertu's addressable breast cancer market. Additional indication approvals (NSCLC, gastric) and pipeline opportunities (colorectal, biliary) provide multiple growth vectors.

3. **First-Mover Advantage in HER2-Mutant NSCLC**

Enhertu is the first ADC approved for HER2-mutant NSCLC, establishing treatment paradigms and physician familiarity ahead of competitors.

4. **Pipeline Optionality Across Multiple Solid Tumor Indications**

   The DESTINY clinical development program spans 59 sponsored trials across multiple tumor types, providing substantial pipeline optionality.

5. **Partner Ecosystem Enables Global Commercial Reach**

   The Daiichi Sankyo/AstraZeneca partnership combines Daiichi's ADC technology expertise with AstraZeneca's global commercial infrastructure, optimizing both development and commercialization.

5.4 Investment Thesis: Bear Case

1. **ILD Risk Higher Than Competitors**

   Enhertu's ILD incidence of 10.5% (clinical trials) is approximately 7.5-fold higher than Kadcyla. While manageable with monitoring, this may limit physician adoption in certain patient populations and settings.

2. **Intensifying Competitive Landscape**

   Chinese ADC developers (RemeGen, HengRui) are advancing competitive candidates at rapid pace. RemeGen's disitamab vedotin has demonstrated promising efficacy in urothelial carcinoma and may expand into breast cancer.

3. **Price Pressure from Biosimilar Herceptin**

   Biosimilar trastuzumab availability creates downward pricing pressure across the HER2-targeted therapy market, potentially limiting Enhertu's pricing power.

4. **Manufacturing Scale-Up Execution Risk**

   ADC manufacturing is complex and capacity-constrained. Meeting global demand requires significant capital investment and operational execution.

5.5 Key Metrics to Monitor

Table 12: Investment Monitoring Metrics

Metric	Current Status	Trigger for Concern
Real-World ILD Rates	Consistent with trials	>15% all-grade incidence
HER2-Low Market Penetration	Early adoption phase	Slower-than-expected uptake
Competitive ADC Approvals	No direct competitors	RemeGen FDA approval
Regulatory Decisions	Positive trajectory	Unexpected label restrictions
Manufacturing Capacity	Meeting demand	Supply constraints

5.6 Valuation Considerations

The investment thesis supports a long position in Daiichi Sankyo (DSNKY) based on:

- **Revenue Growth Trajectory:** Enhertu sales are on an accelerating trajectory driven by indication expansion and market penetration.

- **Pipeline Value:** The DESTINY development program provides substantial optionality not fully reflected in current valuation.
- **Strategic Partnership:** The AstraZeneca partnership de-risks commercialization and provides upfront milestone payments.
- **Platform Extensibility:** The DXd platform is being applied to additional antibody targets beyond HER2, creating additional growth opportunities.

6 Conclusions

This competitive intelligence analysis supports a long position in Daiichi Sankyo (DSNKY) based on the following strategic conclusions:

1. **Technological Leadership:** Enhertu's DXd platform provides a sustainable competitive moat through the bystander effect mechanism, enabling efficacy in HER2-low tumors where competitors are ineffective.
2. **Clinical Superiority:** Head-to-head Phase 3 data demonstrate clear superiority over incumbent Kadcyla (T-DM1), with a 10-month overall survival advantage establishing Enhertu as the new standard of care.
3. **Market Expansion:** The HER2-low approval represents a transformative market expansion opportunity, approximately doubling the addressable patient population.
4. **Manageable Risks:** While ILD risk is elevated compared to competitors, established monitoring protocols enable safe clinical use with favorable risk-benefit profile.
5. **Pipeline Optionality:** The extensive DESTINY clinical development program provides multiple growth vectors across indications and lines of therapy.

The primary risk factors—ILD toxicity and emerging Chinese competition—are acknowledged but do not fundamentally alter the positive investment thesis given Enhertu's established clinical superiority and first-mover advantages.

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A Data Sources and Methodology

A.1 Clinical Trial Data

Clinical trial data were obtained from ClinicalTrials.gov using the API v2 endpoint with queries for HER2 ADC-related studies. A total of 756 studies were initially retrieved, with 521 trials meeting inclusion criteria after filtering for HER2-specific and ADC-specific keywords.

A.2 Open Targets Platform

ERBB2 (HER2) disease associations were obtained from the Open Targets Platform GraphQL API (Ensembl ID: ENSG00000141736). Association scores were retrieved for 16 cancer indications with evidence breakdown across data types (somatic mutation, genetic association, affected pathway, known drug, literature, RNA expression).

A.3 ChEMBL Bioactivity Data

Payload molecular properties and bioactivity data were obtained from ChEMBL API for compounds: DXd (CHEMBL4297465), DM1 (CHEMBL2103875), MMAE (CHEMBL3545069), and SN-38 (CHEMBL1714). Physicochemical properties included molecular weight, ALogP, polar surface area, and IC_{50} values.

A.4 FDA Safety Data

Adverse event data were obtained from the OpenFDA FAERS API for brand names ENHERTU, KADCYLA, and HERCEPTIN. ILD and pneumonitis event rates were calculated per 1,000 total adverse events reported.

B Abbreviations

Abbreviation	Definition
ADC	Antibody-Drug Conjugate
CI	Confidence Interval
DAR	Drug-to-Antibody Ratio
DXd	Deruxtecan
FAERS	FDA Adverse Event Reporting System
GEJ	Gastroesophageal Junction
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression-Free Survival
PSA	Polar Surface Area
T-DM1	Trastuzumab Emtansine (Kadcyla)
T-DXd	Trastuzumab Deruxtecan (Enhertu)