# HER2-Translation Inhibitor ADC: A Development Candidate ADC Featuring a Novel Translation Inhibitor Payload With Broad Efficacy and a Favorable Non Human Primate Safety Profile

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## Abstract

**Background**

Antibody drug conjugates (ADCs) have demonstrated clinical benefit across multiple cancers, yet resistance to existing payload classes, particularly topoisomerase and microtubule inhibitors, remains a major barrier to durable efficacy. To address this limitation, Hexagon Bio is leveraging its natural product discovery platform to identify new ADC payloads with mechanisms of action (MOAs) that are non-overlapping with currently approved payload classes.

**Results**

We identified a translation inhibitor as a highly potent ADC payload. We conjugated the payload to a diverse panel of antibodies recognizing tumor-associated antigens and observed consistent ADC-mediated cytotoxicity across cell lines, supporting broad applicability across tumor types. In vivo, ADCs generated using anti-TROP2 (sacituzumab) and anti-HER2 (trastuzumab) antibodies demonstrated deep and durable antitumor activity in bladder, gastric, breast and lung cancer models, including models with known resistance to topoisomerase inhibitor-based ADCs. Here, we provide updated efficacy data across multiple tumor models and report the non-human primate (NHP) safety profile of an ADC incorporating this payload.

Our new data include a comprehensive assessment of the HER2 translation inhibitor ADC in NHPs, evaluating multiple dose levels as well as repeat-dose regimens. These studies reveal an acceptable safety and tolerability profile. We will present the clinical observations, clinical pathology, histopathology and key findings from these studies.

**Conclusions**

In summary, we identified a novel translation inhibitor payload for ADCs that demonstrates strong efficacy, activity in resistance settings and a favorable NHP safety profile. These results support the potential of HER2-translation inhibitor ADC to address critical gaps in current ADC therapies and development activities for this candidate are now underway.

## Clinical Problem: New ADC Payloads are Needed For Cancer Cures

***1. Resistance to Existing ADC Payloads***

>100k patients/yr treated with ADCs, but most tumors relapse:

| ADC | mPFS |
|---|---|
| Enhertu (HER2) | 13-29 mo |
| Kadcyla (HER2) | 6-10 mo |
| Trodelvy (TROP2) | 5-11 mo |
| Datroway (TROP2) | 4-8 mo |

Tumor relapse is often due to **payload resistance** *(Destiny-Breast 02, Huppert et al. NPJ Breast Cancer 2025)*

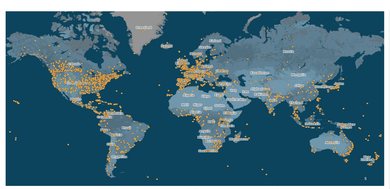
"The problem is, regardless of the antibody, there are sequencing issues when a tumor has already been exposed to a payload of similar class. **New payloads are desperately needed to advance ADCs forward.**"
- Patricia LoRusso, Yale School of Medicine, ASCO 2025

***2. Some tumor types don't respond to existing ADC payloads due to resistance against the same standard-of-care chemotherapy class***

- Chemo standard of care (SOC) often leads to resistance against many current ADCs due to existing payloads using the same class/mechanism of action (MOA)
- Novel payloads with non-overlapping MOAs present large opportunities where current topo-based ADCs cannot effectively compete today

Patients urgently need ADC payloads with **mechanistically distinct and novel MOAs**

## Hexagon's >100,000 Microbial Strains Are an Unparalleled Source for Novel Cytotoxic ADC Payloads



Strains were acquired from around the globe.
We have sequenced over 80,000 genomes.
Approximately 400 putative mechanisms of action predicted.

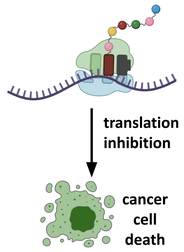
**Platform identifies mechanisms orthogonal to existing ADC payloads**

*~400 cytotoxic MoAs essential to cancer cell growth / survival:*

- **DNA/RNA-associated pathways**
  - Nucleotide biosynthesis
  - mRNA splicing
  - tRNA, rRNA modification
- **Protein-associated pathways**
  - Protein biosynthesis: Initiation, elongation, termination
  - Sumoylation
- **Energy production**
  - Electron transport
  - Citric acid cycle
  - Glutamine metabolism
- **Fat/lipid synthesis**
  - Cholesterol, sphingolipid, triglyceride biosynthesis
- **Plus many other mechanisms**
  - Cell cycle, vacuolar protein sorting, and dozens more

HER2-TI payload was not identified using platform

## Translation is a Key Vulnerability in Cancer

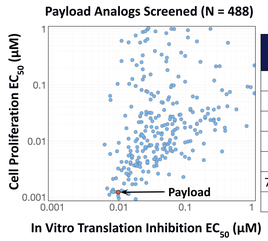



Tumor development and progression depends on continuous proteome remodeling and sustained production of oncogenic proteins.

Tumors likely to be most sensitive to translation inhibition are those that:

- Rely on continuous supply of oncogenic drivers
- Overexpress oncogenic proteins with short half-lives
- Express elevated levels of translational machinery

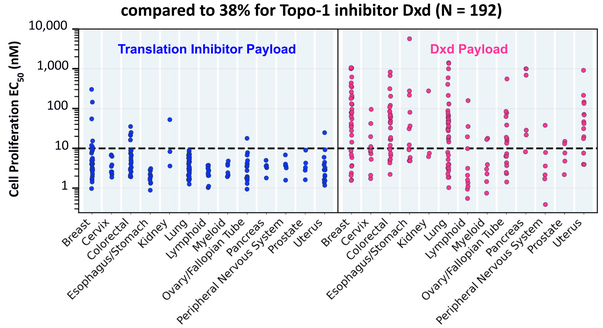
## Generation of Translation Inhibitor Payload



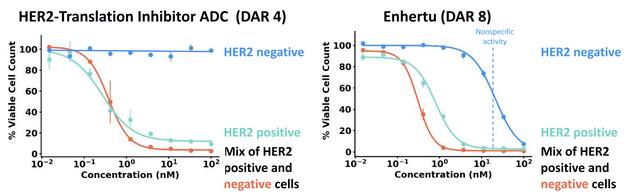

| Assessment | Translation Inhibitor Payload |
|---|---|
| ALogP \| ALogD(7.4) | 2.3 \| 2.2 |
| Topological polar surface area | 146 Å$^2$ |
| Calculated pKa (%ionized at pH 7.4) | 6.9 (24%) |
| Kinetic solubility (pH 7.4 PBS) | 290 µM |
| In vitro translation EC50 (span) | 14 nM (95%) |
| 72 hr in vitro cell killing EC50 (geo mean) | 1.4 nM |
| Permeability Caco-2 + elacridar | 6.5 µcm/s |

## Translation Inhibitor Payload Is Active Against Multiple Cancer Cell Types

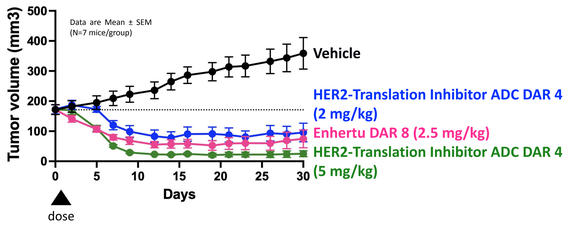
**Translation inhibitor payload inhibits 93% of cell lines with EC50 ≤ 10 nM compared to 38% for Topo-1 inhibitor Dxd (N = 192)**



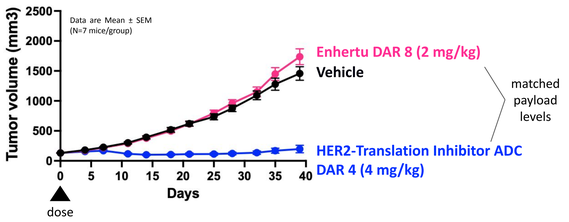

## HER2-Translation Inhibitor ADC Shows Antigen-Dependent Cancer Cell Killing and Bystander Killing



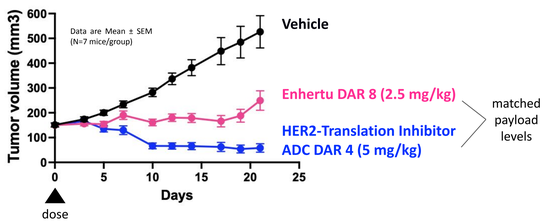

## A Single Dose of HER2-Translation Inhibitor ADC Is Effective in a Breast Cancer Model: MED <2 mg/kg (HCC1954: HER2 Medium ~250k receptors/cell)



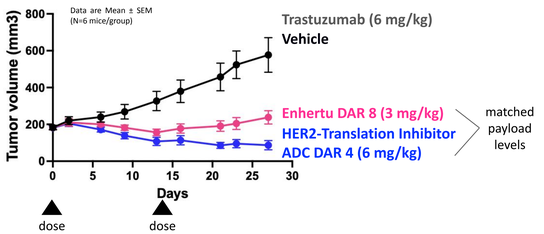

## A Single Dose of HER2-Translation Inhibitor ADC Is Effective in an Enhertu Acquired Resistance Gastric Cancer Model (NCI-N87-R: HER2 Medium ~200k receptors/cell)




## A Single Dose of HER2-Translation Inhibitor ADC Is Effective in an Enhertu Inherent Resistance Esophageal Cancer Model (KYSE410: HER2 High ~1000k receptors/cell)



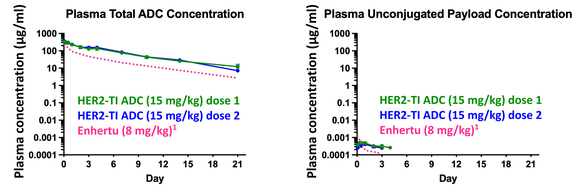

## HER2-Translation Inhibitor ADC Is Effective in Enhertu Resistant PDX CTG-0708




## HER2-Translation Inhibitor ADC Exhibits Favorable PK in Preclinical Species

| Assessment | HER2-Translation Inhibitor ADC Result |
|---|---|
| PK in Mouse | Total Antibody t1/2 = 264 h (matches Enhertu) |
| PK in Rat | Total Antibody t1/2 = 261 h (matches Enhertu) |
| PK in Cyno | Total Antibody t1/2 = 158 h (matches Enhertu) |

## The PK Profile for HER2-Translation Inhibitor ADC in NHP Is Similar to Enhertu




1. Habara, H.; Okamoto, H.; Nagai, Y.; Oitate, M.; Takakusa, H.; Watanabe, N. Transition of Average Drug-to-antibody Ratio of Trastuzumab Deruxtecan in Systemic Circulation in Monkeys Using a Hybrid Affinity Capture Liquid Chromatography-tandem Mass Spectrometry. Biopharm. Drug Dispos. 2023, 44 (5), 380–384.

## HER2-Translation Inhibitor ADC Is Tolerated Up to 15 mg/kg in NHPs and 40 mg/kg in Rats With No Body Weight Loss or Mortality

| | NHPs: 15 mg/kg (N=2) | Rats[1]: 40 mg/kg (N=3) |
|---|---|---|
| **Study design** | Two doses (d0, d21) with 21 days recovery | Single dose (d0) with 14 days recovery |
| **Mortality** | No mortality observed | No mortality observed |
| **Body weight** | Stable body weight (+/-5% of baseline) | Stable body weight (+/- 10% of baseline) |
| **Ophthalmic observations** | No findings | No findings |
| **Hematology & coagulation** | No thrombocytopenia and no neutropenia. Reversible increase in fibrinogen | Mild to moderate increases in WBC ≥20 mg/kg |
| **Clinical chemistry** | Reversible increase in ALT, AST, CK Stable bilirubin | Mild hypoalbuminemia, reduction in cholesterol ≥30 mg/kg and increase in LDH ≥30 mg/kg |
| **Necropsy observations** | N=1 Thyroid gland (increased size) N=1 Liver (adhesion) | Skin erythema, scabbing |
| **Histopathology** | No drug-related findings | Skin hyperplasia of the epidermis and dermal inflammation |

1: Anti-HER2 antibody is non-crossreactive with rat HER2

**Hallmark AEs of MMAE- and Topo1-based ADCs are not observed at tolerated dose levels of HER2-Translation Inhibitor ADC**

## Translation Inhibitor Payloads Enable Next Generation ADCs

| Payload Property | |
|---|---|
| Mechanism is not used in SoC chemotherapy (i.e., no prior exposure) | ✔ |
| Low vulnerability to resistance related to target mutation or expression | ✔ |
| Low vulnerability to resistance related to drug efflux by BCRP | ✔ |
| Highly potent across a broad range of cancer cell lines | ✔ |
| Induction of immunogenic cell death markers and T cell activation | ✔ |
| Reversible MOA contributing to favorable safety profile | ✔ |
| Absence of classical ADC toxicities: hematologic, ocular, pulmonary | ✔ |
| First-in-class potential across validated tumor targets | ✔ |