

# Trastuzumab Deruxtecan: Novel Antibody-drug Conjugate Targeting HER2 in Patients with Gastric Adenocarcinoma

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## ABSTRACT

Gastric cancer (GC) is one of the main causes of death from a cancer with a multifactorial origin and is characterized by the expression of a gene known as HER2. This gene promotes cell proliferation and prevents apoptosis of cancer cells, facilitating uncontrolled cell growth. Trastuzumab Deruxtecan (T-DXd) is a drug for the treatment of tumors with a heterogeneous expression of HER2 that are resistant to conventional anti-HER2 therapy. It is believed that the positive results obtained from Trastuzumab Deruxtecan in the treatment of gastric cancer is related to its potent inhibitory effect of topoisomerase I, the stability of the linker in plasma, as well as its bystander effect. Furthermore, the drug is more efficiently delivered to its target (tumor cell), resulting in a higher concentration of the cytotoxic agent at the site of action. Another point to highlight is that trastuzumab deruxtecan has benefits in treating breast cancer compared to other anti-HER2 therapies, since more patients using this drug presented positive responses compared to trastuzumab emtansine (TDM1), in addition to presenting longer survival and fewer adverse effects. Thus, this literature review shows that T-DXd is a promising therapy of extreme importance and with great capability to respond to cancers with low expression of HER2 and to HER2-positive cancers that are insensitive to the trastuzumab emtansine drug.

**Keywords:** Gastric cancer, HER2-positive, Trastuzumab Deruxtecan.

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## INTRODUCTION

Gastric cancer can occur anywhere in the digestive system, where its pathology is configured by the growth of abnormal cells in the form of ulcerated and irregular lesions, which appear most often in the mucous layer, being the innermost layer of the stomach, and is that which enters in contact with food.<sup>1</sup> Epidemiologically, it is the fifth most common type of cancer, with approximately 1,030,000 new cases per year, and is the world's third leading cause of cancer-related deaths.<sup>2</sup>

It is estimated that about 15 to 20% of gastric cancers, specifically advanced adenocarcinomas of the gastric and gastroesophageal junction, have overexpression or amplification of human epidermal growth factor receptor 2 (HER2), which is an important biomarker and key factor in the formation process of gastric cancer.<sup>3</sup> This is associated with more aggressive cancers and worse expectations and is an important therapeutic target. Despite encountering obstacles, the production of drugs aimed at treating cancer has been undergoing advances. The antibody-drug conjugate (ADC) is one of the focuses of this challenge, being formed by three main components: the monoclonal antibody, the linker, and the payload.<sup>4</sup> Monoclonal antibodies have the ability to, through the ligand, bind to the specific antigen (HER 2), internalize its payload in the mutated cell and thus annihilate it.<sup>5</sup>

Trastuzumab deruxtecan (T-DXd) is an anti-HER2-drug conjugated antibody carrying a topoisomerase I inhibitor payload connected to trastuzumab via a cleavable tetrapeptide linker.<sup>6</sup> This ADC has the bystander effect, which consists of the diffusion of cytotoxic loads across membranes, killing neighboring tumor cells and preventing toxicity to normal cells.<sup>7</sup>

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Recently, T-DXd has been used as a biological therapy for treating unresectable or metastatic HER2-positive breast cancer. Studies have shown that trastuzumab deruxtecan has benefits in the treatment of breast cancer over other anti-HER2 therapies. When analyzed in patients with HER2 receptor-positive metastatic breast cancer, it obtained better results in the evolution of the neoplasm compared to patients who used trastuzumab emtansin.<sup>8,9</sup>

Trastuzumab demonstrated superior response levels and higher survival rates compared to conventional chemotherapy and was approved in September 2020 in Japan for the treatment of HER2-positive advanced gastric cancer (AGC)<sup>2</sup>, but it presented a relatively high incidence of lung toxicity (10%). In view of these points, Trastuzumab deruxtecan is expected to offer greater progression in the treatment of strong and weak HER2-positive gastric adenocarcinomas.<sup>10</sup>

Therefore, this literary review aims to elucidate the mechanism of action, pharmacokinetics and biotherapy of

trastuzumab deruxtecan against gastric cancer and highlight the differences in effectiveness between this new treatment and chemotherapy.

## MATERIALS AND METHODS

A literature review was carried out, searching the bibliographic databases PUBMED - NCBI (National Library of Medicine) and SciELO (Scientific Electronic Library Online), using as descriptors "Stomach Neoplasms", "Genes, erbB-2", "Trastuzumab Deruxtecan". Studies published between 2016 and 2022 (Table 1) were analyzed. Inclusion criteria (Flowchart 1) were studies containing Trastuzumab deruxtecan as a treatment for gastric cancer. Exclusion criteria were articles that addressed other types of trastuzumab or other treatment measures for gastric cancer. Of the 71 articles analyzed, 42 of those that did not meet the inclusion criteria or presented exclusion criteria were eliminated.

## DISCUSSION

### Gastric Cancer and the Relationship with HER2

Gastric cancer (GC) is one of the main causes of death from a cancer with a multifactorial origin and is characterized by the disorderly multiplication of cells in the wall of the affected organ.<sup>11</sup> The origin may be influenced by external matters that increase the risk of developing cancer, such as consumption of alcohol, eating habits, family history, smoking, and *Helicobacter pylori* and Epstein-Barr virus infections.<sup>12</sup>

This neoplasm is characterized by the expression of a gene known as HER2, which promotes cell proliferation and prevents the apoptosis of cancer cells, facilitating uncontrolled cell growth.<sup>7</sup> Thus, gastric tumors with positivity for the HER2 gene have a worse prognosis compared to tumors that are negative for the HER2 gene, since the positive ones result in tumors with greater capacity for invasion and proliferation.<sup>13</sup> Thus, the expression of this gene has a significant effect on prognosis of GC, in which it was analyzed that the tumor cells expressed HER2 in the basal membrane.<sup>14</sup>

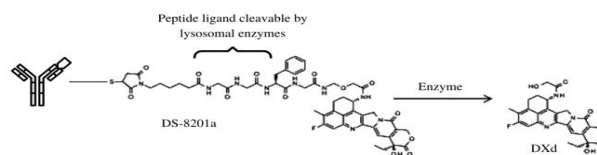


Figure 1: Author's own work

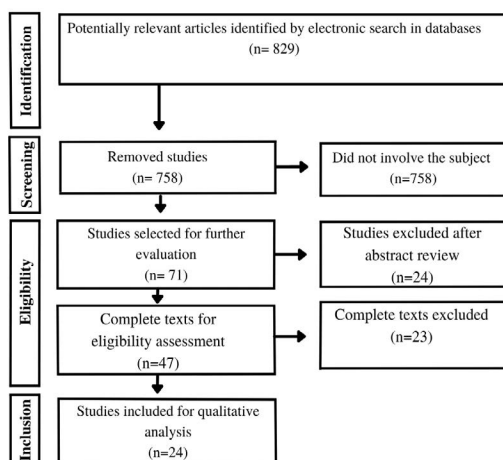
In addition, it was seen that the location of HER2 in the basal membrane presents different forms of manifestation of cancer in the patient, being therefore responsible for the prognosis of each neoplasm.<sup>15</sup> Thus, due to the different types of manifestation, the analysis of the presence of HER2 is used to ensure correct drug guidance, since it plays an important role in the growth and consequent spread of cancer.<sup>16</sup>

Trastuzumab Deruxtecan is an antibody-drug conjugate (ADC) directed to the human epidermal growth factor receptor 2 (HER2), as it has the anti-HER2 antibody a human monoclonal immunoglobulin G1, produced in a way that is corresponding to the primary amino acid sequence of trastuzumab. This ADC is a drug for the treatment of tumors with a heterogeneous expression of HER2 that are resistant to conventional anti-HER2 therapy. T-DXd (Figure 1) is prepared by conjugating humanized anti-HER2 antibody to a topoisomerase I inhibitor payload using a cysteine-conjugated peptide-based linker that is cleaved primarily by lysosomal enzymes.<sup>17</sup>

Studies by Suzuki *et al.* (2021)<sup>18</sup> evaluated the intratumoral through the analysis of mouse xenografts by phosphorus-integrated dot imaging (PID). Using three xenograft models that exhibited different HER2 expressions, it was possible to suggest that the tissue distribution of T-DXd is dependent on the level of HER2 expression. In HER2-negative tumors (which do not express the receptor), there was no such distribution, whereas in models that present heterogeneous expression (there are cells that express the receptor and cells that do not) there was a good response between the HER2-positive and HER2-negative areas adjacent cells, allowing one to conclude that the pharmacodynamics of trastuzumab deruxtecan exerts cytotoxic activity against such tumor cells and that the drug is also effective for heterogeneous models. This effect on neighboring cells is termed the "bystander effect," which is when a membrane-permeable payload leaks out of the cell and enters neighboring cells to facilitate death, regardless of their antigen expression.<sup>18</sup>

When it enters the cell, trastuzumab undergoes an initial cleavage by lysosomal enzymes, consequently releasing DXd. *In-vitro* studies of metabolism in liver microsomes indicate that CYP3A4 metabolizes DXd in oxidative pathways. Furthermore, it is believed that the drug fragment composed of the antibody is catabolized into peptides and amino acids in the same way as endogenous Ig Gs.<sup>17</sup>

Nagai *et al.* (2019)<sup>19</sup> analyzed the minimum systemic exposure



Flowchart 1: Author's own work.

Table 1: Research Papers for Trastuzumab Deruxtecan

Author/Date	Title	Methodology	Main results
AOKI <i>et al.</i> , 2021	Trastuzumab deruxtecan for the treatment of HER2-positive advanced gastric cancer: a clinical perspective	Phase 2 randomized trial	T-DXd was introduced into clinical practice as a rescue line chemotherapy for HER2-positive AGC, contributing to future advances.
CORTÉS, Javier <i>et al.</i> , 2022	Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer	Randomized trial	An overall response occurred in 79.7% of patients receiving trastuzumab deruxtecan and 34.2% of those receiving trastuzumab emtansine.
DOI <i>et al.</i> , 2017	Safety, pharmacokinetics, and antitumor activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumors: a phase 1 dose-escalation study	Phase 1 open study	Study shows disease control in 21 out of 23 patients, reporting the most common and serious adverse events.
ENHERTU, 2021	Enhertu®	Package leaflet	Demonstrates the efficacy and safety of Trastuzumab Deruxtecan in the treatment of HER2-positive cancer.
WATA <i>et al.</i> , 2018	Trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing solid tumors: Long-term results of a large phase 1 study with multiple expansion cohorts.	Phase 1 study	ORR confirmed by RECIST in the evaluated subject was 81/160 (50.6%) with the highest ORR in HER2+ BC (64.2%).
KOTANI <i>et al.</i> , 2021	Trastuzumab deruxtecan for the treatment of patients with HER2-positive gastric cancer	Literature review	T-DXd demonstrated a survival benefit over conventional chemotherapy.
MODI <i>et al.</i> , 2020	Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer	Literature review	Trastuzumab showed antitumor activity in pre-treated HER2-positive metastatic breast cancer.
NAGAI <i>et al.</i> , 2019	Comprehensive preclinical pharmacokinetic evaluations of trastuzumab deruxtecan (DS-8201a), a HER2-targeting antibody-drug conjugate, in cynomolgus monkeys	clinical trial	Presented low systemic exposure to DXd by the stable ligand and there were critical elements of the PK profile of DS-8201a.
NAKADA, 2019	The Latest Research and Development into the Antibody-Drug Conjugate, [fam-] Trastuzumab Deruxtecan (DS-8201a), for HER2 Cancer Therapy	Literature review	DS-8201a could provide a therapy with great potential against HER2-expressing cancers in clinical settings. In one study, DS-8201a showed acceptable safety profiles with potential therapeutic efficacy and a broad therapeutic index.
OGITANI <i>et al.</i> , 2019	DS-8201a, a new HER2-targeting antibody-drug conjugate incorporating a novel DNA topoisomerase I inhibitor, overcomes HER2-positive gastric cancer T-DM1 resistance	Clinical trial	T-DM1 resistant cells (N87-TDMR), established using the HER2-positive gastric cancer line NCI-N87 and continued exposure to T-DM1, were shown to be susceptible to DS-8201a. Tumor growth of the N87-TDMR xenograft was prevented by DS8201a.
SHITARA <i>et al.</i> , 2021	Discovery and development of trastuzumab deruxtecan and safety management for patients with HER2-positive gastric cancer	Literature review	T-DXd is the first HER2-targeted ADC that has demonstrated survival benefits over standard chemotherapy.
SHITARA <i>et al.</i> , 2019	Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study	Phase 1 open study	Study in 44 patients with HER2-positive cancer shows that all patients had at least one treatment-emergent adverse event.

SHITARA <i>et al.</i> , 2020	Trastuzumabe Deruxtecano em Câncer Gástrico HER2 Positivo Anteriormente Tratado	Phase 2 open study	Overall survival was longer with trastuzumab deruxtecan than with chemotherapy
SUZUKI <i>et al.</i> , 2021	Visualization of intratumor pharmacokinetics of [fam-] trastuzumab deruxtecan (DS-8201a) in HER2 heterogeneous model using phosphor-integrated dots imaging analysis	Experimental study	T-DXd in a heterogeneous model, HER2 expression tended to decrease in a time-dependent manner.
XU <i>et al.</i> , 2019	Novel HER2-Targeting Antibody-Drug Conjugates of Trastuzumab Beyond T-DM1 in Breast Cancer: Trastuzumab Deruxtecan(DS-8201a) and (Vic-) Trastuzumab Duocarmazine (SYD985).	Literature review	T-DM1 is a successful example of targeting HER2 as it improves efficacy in heterogeneous tumors.

when examining the comprehensive pharmacokinetics of T-DXd in monkeys and thus found its property of having a highly stable ligand in its receptor and of having a high capacity for the organism to eliminate it, preventing a residual effect. Furthermore, T-DX did not distribute extensively in the tissues and showed no retention.<sup>19</sup>

According to a study by IWATA *et al.* (2018)<sup>20</sup> T-DXd showed promising activity against HER2-positive cancer, this research was carried out in a group of people who had previously undergone some type of treatment against gastric cancer. However, in this study the highest dosage of the drug that would produce the desired effect and without unacceptable adverse effects was not found, as was the purpose of the research (currently, the standard dosage is 0.8–8.0 mg/kg).<sup>20</sup>

### Trastuzumab Deruxtecan in biotherapy against gastric cancer

In its mechanism of action in gastric cancer, T-DXd binds to the HER2 present in the tumor cell, thus managing to enter it. After its internalization, lysosomal enzymes are present in tumor cells that cleave the T-DXd, causing the compound to release its derivative, DXd, responsible for inhibiting Topoisomerase I in its complex with DNA, thus leading to cycle arrest of the mutated cell.<sup>21</sup> With the cell cycle stopped, damage to the cell DNA is induced, leading the cell to apoptosis - cytotoxic activity.<sup>22</sup> Added to this, the present compound is associated with the inhibition of cell growth in a dose-dependent manner in experimental models, in addition to not being amenable to metabolism by the enzyme UGT1A1 (UDP-glucuronosyltransferase 1-1).<sup>21</sup>

It is believed that the positive results obtained with trastuzumab deruxtecan in treating gastric cancer is related to the potent inhibitory effect of topoisomerase I and the stability of the linker in plasma, in addition to its bystander effect. What is more, the drug has a more efficient delivery to its target (tumor cell), resulting in a higher concentration of the cytotoxic agent at the site of action.<sup>23</sup> In regard to the bystander effect, the drug has the potential to combat gastric tumors because, unlike other trastuzumab, T-DXd does not act only on cells that show overexpression of HER2 receptors due to its bystander effect (Figure 2), and this allows it to be

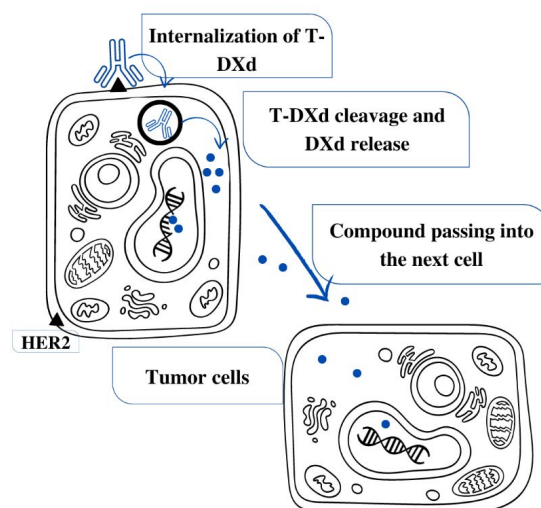


Figure 2: Author based on NAKADA, 2019 and KOTANI, 2022.

more effective against these tumors, which in turn present heterogeneity of expression.<sup>22</sup> It is estimated that less than 10% of gastric cancers express HER2, highlighting the need for the bystander effect in their treatment.<sup>23</sup>

The study by Shitara *et al.* (2020)<sup>24</sup> deals with the use of trastuzumab deruxtecan compared to conventional chemotherapy with irinotecan or paclitaxel in patients with HER2-positive advanced gastric cancer. This study demonstrates that of the 187 patients treated, 125 received trastuzumab deruxtecan and 62 underwent chemotherapy, 55 received irinotecan, and 7 received paclitaxel. When looking at the results, a significant response was obtained from 43% of patients in the trastuzumab deruxtecan group compared to 12% of those undergoing chemotherapy, and it became evident that the percentage of patients with an objective response was significantly higher in the group of patients treated with deruxtecan trastuzumab in relation to the group submitted to the chemotherapy of choice.<sup>24</sup>

The same study points out that more than 80% of patients who received trastuzumab deruxtecan achieved a reduction in tumor size, while only half of the group treated with chemotherapy achieved the same response. The study

also indicates that survival was higher in the group receiving trastuzumab deruxtecan compared to the group undergoing conventional chemotherapy.<sup>24</sup>

### Adverse effects of Transtuzumab Deruxtecan

According to research by Shitara *et al.* (2019)<sup>23</sup>, 44 patients with cancer at the gastroesophageal junction or with HER2-positive gastric cancer received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion. All patients, in general, had at least one treatment-emergent adverse event. Among the adverse effects, the most frequent was anemia corresponding to 30%, neutropenia with 20%, thrombocytopenia with 18%, and leukopenia with 16%. Furthermore, there were serious adversities (25%), with four cases of pneumonitis. However, there was no treatment-related mortality. Moreover, the same study reports that such adverse effects can be controlled by reducing or interrupting the appropriate dose, thus contributing to greater adherence to trastuzumab deruxtecan.<sup>9</sup>

Another point to highlight is in relation to the level of tumor expression of HER2 which, in the study in question, demonstrated an impact on the effectiveness of trastuzumab deruxtecan, that is, according to the collected data the response rates are higher in patients with tumors with higher expression of HER2 compared to patients with tumors with a low expression, observing an objective response percentage of 58% and 29%, respectively. Thus, according to the study, taking into account the results achieved, there is a need to develop more rigorous and sensitive HER2 tests in order to confirm the tumor expression level so that the antitumor efficacy of trastuzumab deruxtecan is achieved.<sup>7</sup>

## CONCLUSION

After detailed analysis of several studies, it is possible to state that T-DXd has a promising future for patients with HER2-positive and heterogeneous gastric cancer since the drug has shown an improvement in disease response and survival compared to conventional chemotherapy. Despite all these promising results, trastuzumab deruxtecan still needs further studies to prove its effectiveness against HER2-positive gastric cancer so that treatments can be more assertive and comprehensive.

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