Annals of Case Reports
Damaj N, et al. Ann Case Rep: 9: 101931
www.doi.org/10.29011/2574-7754.101931
www.gavinpublishers.com

OPEN ACCESS

Case Report

GAVIN PUBLISHERS

# Life-Saving Reduced Dose of Trastuzumab-Deruxtecan in Metastatic HER2-Low Metastatic Breast Cancer with Major Hepatic Insufficiency: A Case Report

**Nahed Damaj[1*], Ghida Diab[1], Gilbert Freiha[1], Bryan Youssef[1], Joseph Amara[2], Celina Douaihy[2], Lina Menassa[3], Lynn Abdo[4], Serge Fenianos[5], Elie Haddad[6], Georges Dabar[7], Roland Eid[8], Hampig Raphaël Kourie[1]**

[1]Hematology and Oncology Department, Hôtel Dieu De France Hospital, Saint Joseph University, Beirut, Lebanon

[2]Gastroenterology Department, Hôtel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon

[3]Radiology Department, Hôtel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon

[4]Internal Medicine Department, Hôtel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon

[5]Nephrology Department, Hôtel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon

[6]Infectious Disease Department, Hôtel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon

[7]Pneumology and Intensive Care Department, Hôtel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon

[8]Gustave Roussy, Villejuif, Paris, France

***Corresponding author**: Nahed Damaj, Hematology and Oncology Department, Hôtel Dieu De France Hospital, Saint Joseph University, Beirut, Lebanon

Citation: Damaj N, Diab G, Freiha G, Youddef B, Amara J, et al (2024) Life-Saving Reduced Dose of Trastuzumab-Deruxtecan in Metastatic HER2-Low Metastatic Breast Cancer with Major Hepatic Insufficiency: A Case Report. Ann Case Report. 9: 1931. DOI:10.29011/2574-7754.101931

**Received:** 04 August 2024, **Accepted:** 09 August 2024, **Published:** 14 August 2024

**Abstract**

Trastuzumab Deruxtecan has recently shown a good response in patients with HER2-low metastatic breast cancer, resulting in longer progression-free and overall survival. The most common adverse reactions are bone marrow suppression, cardiac, pulmonary, dermatological, gastrointestinal and hepatic (increased serum alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase and bilirubin, Cholestatic jaundice) toxicities. In severe hepatic impairment (total bilirubin >3 times ULN and any AST), there are no dosage adjustments provided in the manufacturer's labelling (a recommended dose has not been established) [1,2]. The safety of this medication in liver failure is unknown. In the review of the literature, there is only one case report about a patient with metastatic HER2-positive breast cancer with liver failure and leptomeningeal metastases who was treated with dose-reduced trastuzumab -Deruxtecan. With treatment, the patient's hyperbilirubinemia resolved, and she demonstrated a response on imaging. She was dose-escalated to full dose with minimal adverse events [3]. We report here a rare case of a patient known to have HER2-low metastatic breast cancer with acute liver failure. She had received hormonal therapy and three lines of chemotherapy without improvement. Treatment with low dose Trastuzumab-Deruxtecan was started, and a significant improvement in liver function, liver metastases was observed after the first administration of Trastuzumab-Deruxtecan and normalization in 21 days after the second administration.

## Introduction

HER2-low metastatic breast cancer is a new entity in breast cancer. It is believed to represent about 45-55% of all breast cancer, it is more common in HR+ positive breast cancers (ranging from 43.5-67.6%) compared to TNBCs (ranging from 15.7-53.6%) [4,5]. Within HR-negative breast cancer, breast cancer with low HER2 expression exhibits a less aggressive profile when compared to HER2-zero tumors [6]. Her2 is an important target in the treatment of breast cancer. Clinical trials initially investigated Trastuzumab-Deruxtecan efficacy in HER2-positive advanced or metastatic breast, gastric, lung, and colorectal cancers. Moreover, in addition to Trastuzumab-Deruxtecan efficacy against brain metastasis, Trastuzumab-Deruxtecan is showing promising results in HER2-low and HER2-ultra-low metastatic breast cancer, indicating a broader population of patients who may benefit [7]. The DESTINY-Breast04 trial randomly assigned patients with HER2-low metastatic breast cancer who had received two or fewer lines of chemotherapy to Trastuzumab-Deruxtecan or physician choice of chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel). Among all patients, the median PFS was 9.9 months and median OS was 23.4 months with Trastuzumab-Deruxtecan compared with a median PFS of 5.1 months and median OS of 16.8 months with chemotherapy (PFS HR, 0.5; $P < .001$; OS HR, 0.64; $P = .001$). The patients with liver failure are not included in the trial [8]. Here we describe the case of a patient Her 2 low metastatic breast cancer with liver failure due to progressing liver metastases, who was treated with trastuzumab -Deruxtecan with an ongoing response to treatment, including normalization of her liver function test and an important decrease in liver metastasis on the abdominal CT scan.

## Case Presentation

A 56-year-old, premenopausal patient with no previous medical disease was first presented in September 2018 when a screening mammogram revealed dense, nodular-appearing breasts with multiple cysts. An MRI was recommended for six months later to provide a more detailed evaluation revealing a nodule with regular contours, interruption of the anterior wall, and central nodule enhancement, measuring 2 cm in diameter in the right breast. Consequently, a Tru-Cut biopsy was performed in March 2019 revealing a poorly differentiated infiltrating ductal adenocarcinoma, nuclear grade 2, SBR grade 2. The histological analysis indicated an invasive ductal carcinoma, hormone-dependent (ER+ strongly expressed in 90% of the tumor cells, PR-, HER2- (score 0)), with a proliferation index of 15%, as assessed by Ki-67 (MIB-1) immunostaining. PET scan conducted on March 21, 2019, showed no distant metastases and a few tiny right axillary lymph nodes with none to minimal FDG uptake, which were nonspecific. The patient, diagnosed with ductal adenocarcinoma in the lower inner quadrant of the right breast, stage IIA (cT2, cN0, cM0, ER+, PR-, HER2- (score 0)), underwent a right quadrantectomy and sentinel lymph node biopsy (SLNB). Histological analysis of the surgical specimen revealed a similar profile: ER+ in 70% of tumor cells, PR+ in 20% of tumor cells, HER2- (equivocal +2/3, FISH test negative), and a Ki-67 index of 30%. Nine sentinel lymph nodes are examined, and one is positive for carcinoma. Pathologic stage classification: pT2, pN1a. Predicted risk of recurrence without adjuvant systemic treatment based on Mamma Print was 29%. Thus, postoperatively, she received chemotherapy (4 cycles of Adriamycin and cyclophosphamide, 12 doses of Taxol weeekly) and 16 sessions of radiotherapy followed by a two-years course of tamoxifen (the patient had menstrual cycles in 2019). It should be noted that the complete hepatic profile is normal, with CA 15.3 at 17 U/ml, within normal limits post-surgery.

In August 2022, she reported lower back pain. Subsequent evaluation indicated a rise in CA 15.3 levels from 59.46 U/ml to 101.51 U/ml within 2 months. A PET/CT scan performed in October 2022 revealed findings consistent with left lower neck adenopathy, a solitary metastatic liver lesion, and multiple scattered metastatic bone lesions. Liver biopsy on October 2022 consistently showed hormone receptor positive metastatic breast cancer (ER+, PR-, HER2- (score 0)). The patient was treated with Letrozole and Ribociclib for six months (noted that she is menopausal in 2022). A follow-up PET scan in March 2023, conducted to evaluate disease progression, demonstrated an increase in hepatic metastases and a mixed response in osseous metastases. In April 2023, a repeat liver biopsy revealed a change in the histological profile. Estrogen receptors (ER) were not expressed in the tumor cells, while progesterone receptors (PR) and HER2 status remained unchanged (score 0). To optimize the patient's management, tumor profiling TTDx of the liver biopsy was performed, revealing: ERBB2-low status (variant frequency 1.35), no other reportable genomic alterations were detected, MSI stable, TMB low, no mutations in BRCA1, BRCA2, ESR1, ESR2, NTRK1, NTRK2, NTRK3, PIK3, PIK3CA. A PET CT scan conducted in May 2023 indicated progression of metastatic liver disease. The bones showed minimal improvement but remained within the limits of stable disease. Liver function tests in May revealed abnormalities (GGT 134 µg/dL, SGPT 68 U/L, SGOT 68 U/L, with normal bilirubin levels). A treatment regimen of Capecitabine and Vinorelbine was initiated in May for a duration of three months. A PET scan in August 2023 showed an excellent partial response to the treatment. However, a repeat PET scan in December 2023 indicated a relapse and progression of the disease, particularly in the liver. Subsequently, the patient was treated with Gemcitabine and Carboplatin until April 24. Despite this, the PET scan evaluation continued to show disease progression. On May 7, 2024, the patient presented with hepatic encephalopathy, hepatic insufficiency, abdominal ascites, jaundice, and abnormal liver function tests (SGOT 659 U/L, SGPT 145 U/L, GGT 1254

U/L, ALP 812 U/L, total bilirubin 121.2 µmol/L, direct bilirubin 58.6 µmol/L, indirect bilirubin 62.6 µmol/L, albumin 32 g/L, INR 1.32).Thoraco-abdominopelvic CT scan showed heterogeneous liver with lobulated contours, containing multiple diffuse heterogeneous lesions suggestive of secondary deposits. Lobulated hepatic contours, associated with a laminated appearance of the hepatic veins and branches of the portal vein. Esophageal and peri-gastric varices and homogeneous splenomegaly. Appearance indicative of portal hypertension, likely related to post-chemotherapy hepatic fibrosis. The patient subsequently initiated treatment with low dose Trastuzumab-Deruxtecan (300mg instead of 45mg:5.4mg*83kg)) with surveillance of liver function tests every 2 days. We noticed a significant improvement clinically, biologically and radiologically after the first dose of Trastuzumab- Deruxtecan. The patient was more conscious and cooperative with diminution of ascites and jaundice. We noticed an amelioration of liver function tests within 15 days (Curve1,2,3, Table 1, Figure4). On May 30, 2024: SGOT 93 U/L, SGPT 42 U/L, GGT 500 U/L, ALP 594 U/L, total bilirubin 69 µmol/L (direct 0 µmol/L, indirect 69 µmol/L), albumin 42 g/L, and INR 1.28. CA15-3 decreases from 450 to 320. On May 20, the TAP Scan of control showed a marked regression (50 to 60%) of multiple diffuse secondary heterogeneous lesions in both hepatic lobes, particularly in the left lobe and the posterior segment of the right lobe (Figure5). We noted also a normalization of liver function tests and a significant decrease of CA 15-3 to 89U/mL after the second dose of Trastuzumab-Deruxtecan on May 28. She also took the third dose in June 18.the Figures1,2,3 summarize the therapeutic approach of our patient.

***Figure 1:*** *A schematic representation summarizing the patient's therapeutic approach from 2019 (diagnosis of invasive breast cancer) to 2024 (initiation of Enhertu treatment).*

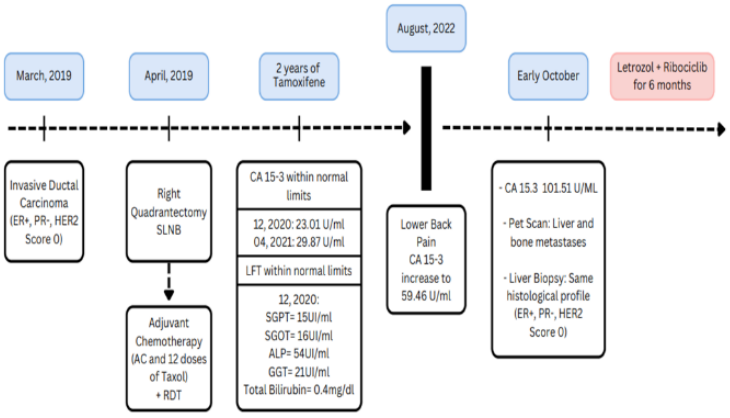


***Figure 2:*** *A schematic representation summarizing the patient's therapeutic approach from 2019 (diagnosis of invasive breast cancer) to 2024 (initiation of Enhertu treatment).*

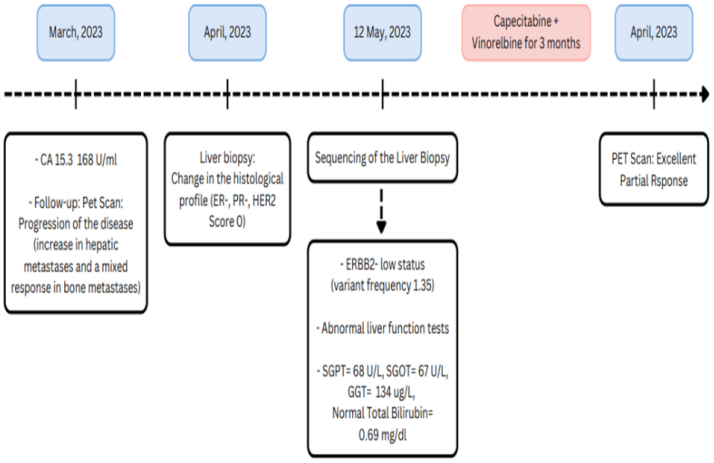
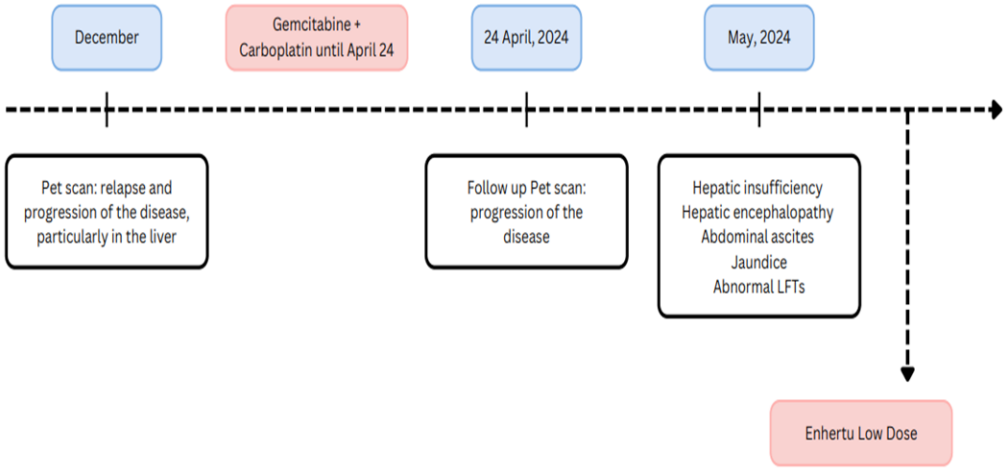
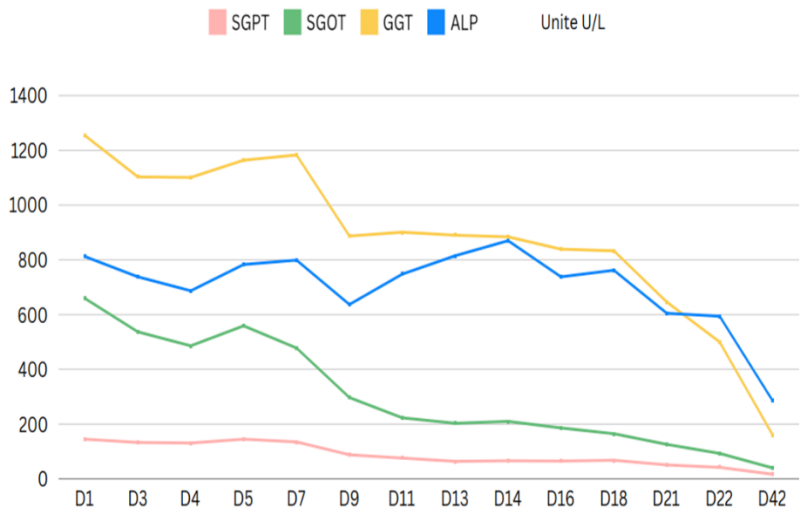



***Figure 3:*** *A schematic representation summarizing the patient's therapeutic approach from 2019 (diagnosis of invasive breast cancer) to 2024 (initiation of Enhertu treatment).*



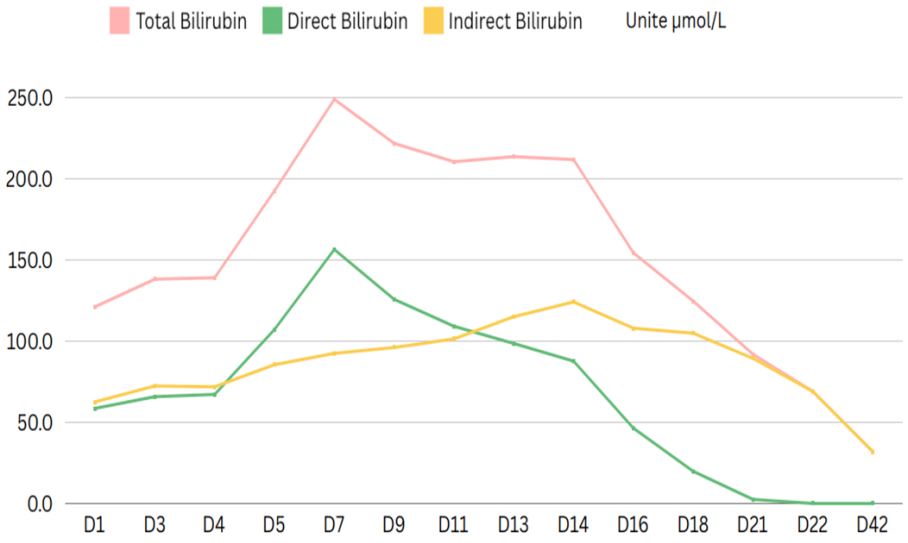
***Curve 1:*** *A chart depicting the progression of liver function tests (SGPT, SGOT, GGT, ALP) throughout the patient's hospitalisation*




*D1= 7-05-2024(first dose of Trastuzumab-Deruxtecan)

*D21=28-05-2024(second dose of Transtuzumab-Deruxtecan)

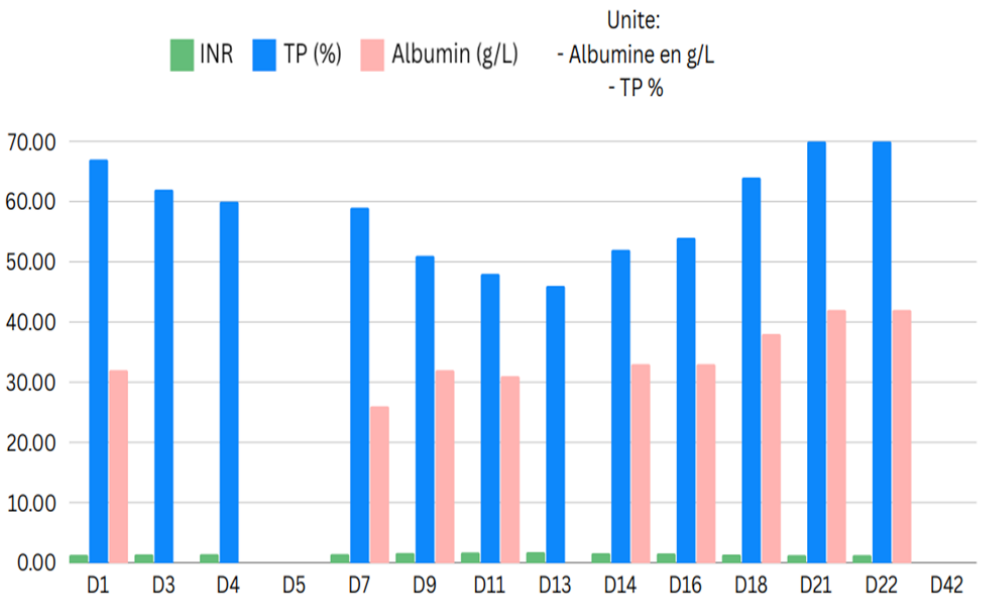
***Curve 2:*** *A chart depicting the progression of liver function tests (Total Bilirubin, Direct Bilirubin, Indirect Bilirubin) throughout the patient's hospitalisation*



*D1= 7-05-2024(first dose of Trastuzumab-Deruxtecan)

*D21=28-05-2024(second dose of Transtuzumab-Deruxtecan)

***Figure 4:*** *A chart depicting the progression of INR TP Albumin throughout the patient's hospitalisation*




*D1= 7-05-2024(first dose of Trastuzumab-Deruxtecan)

*D21=28-05-2024(second dose of Transtuzumab-Deruxtecan)

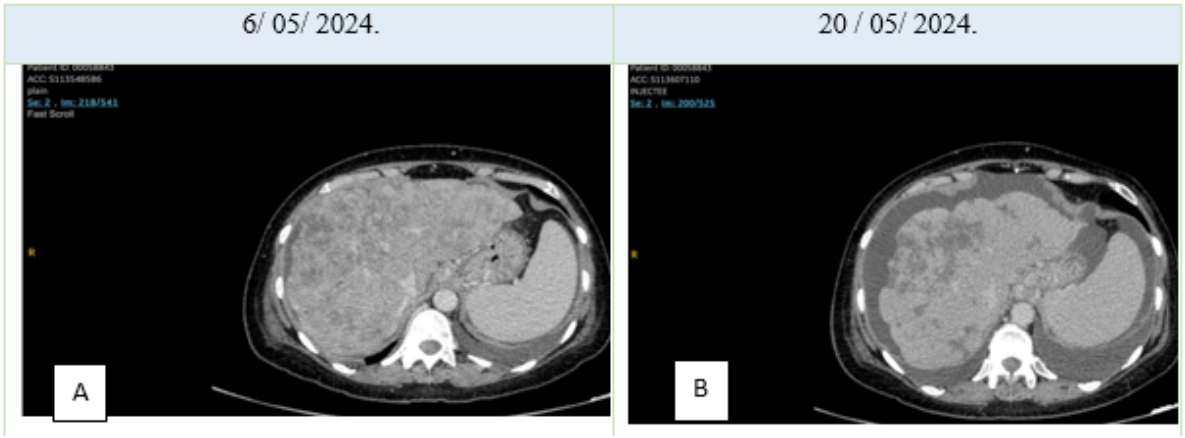



**Figure 5:** Comparative computed tomography abdominal scan of liver metastases before and after the initiation of Trastuzumab-Deruxtecan. A: Before the rechallenge with trastuzumab deruxtecan: Multiple metastatic lesions of both hepatic lobes predominantly in the right hepatic lobe with hepatomegaly and a perihepatic effusion. B: After one cycle of Trastuzumab-Deruxtecan: Important regression of the multiple diffuse secondary heterogeneous lesions of both hepatic lobes, with remaining sequelae hypo dense lesions and fibrotic changes deforming the liver contours. Changes indicative of a clear response evaluated to more than 50%.Dr Lina Menassa, Radiologist at Hotel Dieu De France Hospital.

| LFTs/ Day | SGOT U/L | SGPT U/L | GGT U/L | ALP U/L | Total Bilirubin | Direct Bilirubin µmol/L | Indirect Bilirubin µmol/L | INR | TP % | Albumin g/L |
|---|---|---|---|---|---|---|---|---|---|---|
| D1 | 659 | 145 | 1254 | 812 | 121.2 | 58.6 | 62.6 | 1.32 | 67 | 32 |
| D3 | 537 | 133 | 1103 | 738 | 138.2 | 65.8 | 72.4 | 1.4 | 62 | - |
| D4 | 486 | 131 | 1101 | 687 | 139.1 | 67.2 | 71.9 | 1.44 | 60 | - |
| D5 | 559 | 145 | 1164 | 783 | 192.7 | 107.2 | 85.5 | - | - | - |
| D7 | 478 | 135 | 1183 | 799 | 249 | 156.5 | 92.5 | 1.45 | 59 | 26 |
| D9 | 297 | 88 | 887 | 637 | 221.9 | 125.8 | 96.1 | 1.63 | 51 | 32 |
| D11 | 223 | 76 | 901 | 748 | 210.6 | 109.2 | 101.4 | 1.72 | 48 | 31 |
| D13 | 203 | 64 | 890 | 815 | 213.7 | 98.6 | 115.1 | 1.77 | 46 | - |
| D14 | 210 | 66 | 884 | 870 | 211.9 | 87.7 | 124.2 | 1.6 | 52 | 33 |
| D16 | 186 | 65 | 839 | 738 | 154.4 | 46.4 | 108 | 1.56 | 54 | 33 |
| D18 | 165 | 68 | 833 | 762 | 124.7 | 19.8 | 104.9 | 1.37 | 64 | 38 |
| D21 | 126 | 51 | 646 | 605 | 91.9 | 2.5 | 89.4 | 1.28 | 70 | 42 |
| D22 | 93 | 42 | 500 | 594 | 69 | 0 | 69 | 1.28 | 70 | 42 |
| D42 | 40 | 17 | 161 | 286 | 32 | 0 | 32 | - | - | - |

**Table1:** A table showing the progression of liver function tests throughout the patient's hospitalisation: *D1= 7-05-2024(first dose of Trastuzumab-Deruxtecan). *D21=28-05-2024(second dose of Transtuzumab-Deruxtecan).

## Discussion

In the review of the literature, there is only one case report of a patient with metastatic HER2-positive breast cancer with liver failure and leptomeningeal metastases who was treated with dose-reduced trastuzumab -Deruxtecan. With treatment, the patient's hyperbilirubinemia resolved, and she demonstrated a response on imaging. She was dose-escalated to full dose with minimal adverse events [3]. HER2-low breast cancer (BC) is a recently identified subgroup of HER2-negative BC, characterized by a HER2 immunohistochemical (IHC) score of 1+ or a score of 2+ with negative in situ hybridization (ISH). HER2-low breast cancer is estimated to constitute approximately 45-55% of all breast cancer [4,5-15]. Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate targeting human epidermal growth factor 2 (HER2). It is approved for use in HER2-expressing breast and gastric cancers, as well as in HER2-mutant non-small-cell lung cancer [16]. The mechanism of action of trastuzumab deruxtecan is based on the cleavage of the peptide that links the topoisomerase I inhibitor to the humanized anti-HER2 antibody. After cleavage, the portion consisting of the topoisomerase inhibitor is metabolized by CYP3A4, an enzyme found in the liver [17]. The DESTINY-Breast04 trial randomly assigned patients with HER2-low metastatic breast cancer (HER2 1+ or 2+ on immunohistochemistry, without fluorescence in situ hybridization amplification) who had received two or fewer lines of chemotherapy to Trastuzumab-Deruxtecan (5.4mg/kg intravenous infusion every three months for eight months) or physician choice of chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel). Most patients (88.7%) had hormone receptor–positive disease. Among patients with hormone receptor–positive cancer, the median PFS was 10.1 months and median OS was 23.9 months with Trastuzumab-Deruxtecan compared with a median PFS of 5.4 months and median OS of 17.5 months with chemotherapy (PFS HR, 0.51; P < .001; OS HR, 0.64; P = 003). Among all patients, the median PFS was 9.9 months and median OS was 23.4 months with Trastuzumab-Deruxtecan compared with a median PFS of 5.1 months and median OS of 16.8 months with chemotherapy (PFS HR, 0.5; P < .001; OS HR, 0.64; P = .001). The patients with liver failure are not included in the trial [16].

Trastuzumab deruxtecan is a medication that is generally well-tolerated with manageable side effects. The most common adverse reactions are bone marrow suppression, cardiotoxicity(edema), pulmonary toxicities (interstitial lung disease and pneumonitis), dermatological toxicities(alopecia,skin rash), gastrointestinal toxicities (nausea, vomiting, diarrhea, constipation and stomatitis) and hepatic toxicities (increased serum alanine aminotransferase (34% to 53%), increased serum alkaline phosphatase (22% to 54%), increased serum aspartate aminotransferase (35% to 67%), increased serum bilirubin (15% to 24%), Cholestatic jaundice (less than 10% can be severe) [17]. Dosing adjustment is not

necessary in mild hepatic impairment (total bilirubin ≤ ULN and any AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST). We should monitor closely for toxicities in patients with moderate hepatic impairment. In severe hepatic impairment (total bilirubin >3 times ULN and any AST), there are no dosage adjustments provided in the manufacturer's labeling (a recommended dose has not been established). Accordingly, the safety of this medication in patients with serious liver impairment remains uncertain [17]. Our patient, diagnosed with metastatic breast cancer with osseous and hepatic metastases, met the inclusion criteria of Destiny Breast 04 trial (ERBB2-low status and has undergone more than two lines of chemotherapy: capecitabine, gemcitabine and she is HR+ refractory to endocrine therapy) without achieving improvement in disease progression. In May 2024, she presented with hepatic insufficiency, manifesting as abdominal ascites, jaundice, and liver function test abnormalities. A low-dose regimen of Trastuzumab-Deruxtecan was initiated, despite the associated risk of hepatotoxicity and we noticed a significant improvement of liver function, decrease of more than 50% of liver metastasis and clinical improvement of the patient. The response to Traastuzumab-Deruxtecan is reported in few weeks after the infusion. In our case, the response initiate after the first week of infusion of Trastuzumab-Deruxtecan established by amelioration of liver enzymes and regression of liver metastasis by abdominal vct scan. It is noteworthy that no clinical studies have demonstrated the safety or efficacy of Trastuzumab-Deruxtecan in patients with hepatic insufficiency, rendering the therapeutic outcomes uncertain. We should mention the originality of our case, the rapidity of response rate to Trastuzumab-Deruxtecan in few weeks and changing the clinical outcomes of our patient. It's a life-saving medication. An important question to discuss we should continue the same dose of Trastuzumab-Deruxtecan or increase the dose to 5.4mg/kg.In conclusion, this medication could be adopted in the future in hepatic insufficiency patients. More studies are needed to demonstrate the safety and efficacy of Trastuzumab-Deruxtecan in patients with liver failure. Therefore, the use of dose-reduced trastuzumab -Deruxtecan in severe liver dysfunction should be investigated in prospective trials

## References

1. NDA/BLA multi-disciplinary review and evaluation (BLA 761139).cfm. Accessed 22 Sep 2020.
2. ENHERTU® (fam-trastuzumab deruxtecan-nxki) US prescribing information. Accessed 22 Sep 2020.
3. Nicole H, Julie N, Maryam NS, Nan C, Binu L M, et al (2020) Dose-reduced trastuzumab deruxtecan can be safely used in liver failure and active leptomeningeal metastases, Current Problems in Cancer: Case Reports, 2:100034.
4. Viale G, Basik M, Niikura N, Tokunaga E, Brucker S, et al (2023) Retrospective study to estimate the prevalence and describe the clinicopathological characteristics, treatments received, and outcomes of HER2-low breast cancer. ESMO Open. 8:101615.
5. Zhang H, Peng Y. (2022) Current Biological, Pathological and Clinical Landscape of HER2-Low Breast Cancer. Cancers (Basel). 15:126.
6. Khalil M, Habibian L, Martin C, Semaan K, Khaddage A, et al (2024). Landscape of HER2-low breast cancer: Insights from a six-year study on incidence and clinicopathological characteristics.. Journal of Clinical Oncology. 42. e13148-e13148.
7. Zouein, J, Karam, E, Strickler, J.H, Kourie HR (2024) Trastuzumab-Deruxtecan: Redefining HER2 as a Tumor Agnostic Biomarker. Targ Oncol.
8. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, et al (2020) DESTINY-Breast04 Trial Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 387:9-20.
9. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, et al (2022) DESTINY-Breast04 Trial Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 387:9-20.
10. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Trastuzumab Deruxtecan. [Updated 2024 Jan 30]. A
11. Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, et al(1999) Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol. 17:2639-48.
12. Horisawa N, Adachi Y, Takatsuka D, Nozawa K, Endo Y, et al (2022) The frequency of low HER2 expression in breast cancer and a comparison of prognosis between patients with HER2-low and HER2-negative breast cancer by HR status. Breast Cancer. 29:234-241.
13. Peiffer DS, Zhao F, Chen N, Hahn OM, Nanda R, et al (2023) Clinicopathologic Characteristics and Prognosis of ERBB2-Low Breast Cancer Among Patients in the National Cancer Database. JAMA Oncol. 9:500-510.
14. Schlam I, Tolaney SM, Tarantino P. (2023) How I treat HER2-low advanced breast cancer. Breast. 67:116-123.
15. T-DXd: New Standard for HER2-Low Breast Cancer. Cancer Discov. 12:1828.
16. Meric-Bernstam F, Makker V, Oaknin A, Oh DY, Banerjee S, et 2024) Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. J Clin Oncol. 42:47-58.
17. Modi S, Park H, Murthy RK, Iwata H, Tamura K, et al (2020) Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients with HER2-Low-Expressing Advanced Breast Cancer: Results from a Phase Ib Study. J Clin Oncol. 38:1887-1896.