Review article

UDC: 618.19-006.6-085
doi: 10.5633/amm.2025.0312

BREAST CANCER WITH LOW HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 EXPRESSION STATUS: A NEW THERAPEUTIC ENTITY

Ana Cvetanović[1,2], Kristina Janković[2]

Targeted human epidermal growth factor receptor 2 (HER2) therapies used in the treatment of HER2-positive early and metastatic breast cancer (mBC) include monoclonal antibodies such as trastuzumab, pertuzumab and margetuximab, as well as antibody-drug conjugates (ADC) trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), and tyrosine kinase inhibitors such as tucatinib, lapatinib, and neratinib. The introduction of these drugs into clinical practice has dramatically improved the course of treatment for HER2-positive breast cancer. However, the clinical evaluation of trastuzumab, pertuzumab, and T-DM1 in the HER2-low group of patients did not show significant benefits. Consequently, these patients were classified as HER2-negative cancers and treated in accordance with the expression of hormone receptors (HR) or other biomarkers. Trastuzumab deruxtecan, an ADC, which initially demonstrated its efficacy in the treatment of metastatic HER2-positive breast cancer, and subsequently in breast cancer with low HER2 expression, classified as immunohistochemistry IHC 1+ and IHC 2+ with a negative fluorescence *in situ* hybridization (FISH) introduced into clinical practice a new entity of HER2 breast cancers called HER2-low tumors. Following the publication of the DESTINY-Breast04 study results, it is clear that low HER2 positivity can be considered a rational target for the treatment of breast cancer. The results have changed clinical practice in both HR-positive and HR-negative HER2-low metastatic breast cancer. Further research is necessary in order to standardize HER2 testing, prevent T-DXd-related side effects and resistance to therapy, and identify the optimal sequence of available therapeutic options. Future research should also explore the role of these drugs in the treatment of early HER2-low breast cancer.

Acta Medica Medianae 2025;64(3): 90–99.

Key words: *breast cancer, human epidermal growth factor receptor 2-low, antibody-drug conjugate, trastuzumab deruxtecan, sacituzumab govitecan*

[1]University of Niš, Faculty of Medicine, Niš, Serbia
[2]University Clinical Center Niš, Clinic of Oncology, Niš, Serbia

Contact*:* Ana Cvetanović
48 Dr. Zorana Djindjića Blvd., 18000 Niš, Serbia
E-mail: ana.stankovic@yahoo.com

Introduction

Breast cancer (BC) expresses high levels of growth factors and their receptors. The HER2 receptor belongs to the HER 2/Neu receptor family, which includes four receptors: HER1-EGFR, HER2, HER3, and HER4. The natural ligand for the HER1 receptor is the EGFR—receptor for epidermal growth factor, while the natural ligand for the HER2 receptor is unknown. The natural ligands for HER3 and HER4 receptors are neuregulins. Receptors of the HER family belong to the transmembrane group of receptors, which consists of three subunits: the extracellular part, the transmembrane part, and the intracellular part of the receptor. A specific ligand binds to the receptor through its extracellular domain, which leads to receptor dimerization (either homo- or heterodimerization) and activates the intracellular tyrosine kinase domain. This is followed by a cascade of phosphorylation processes, ultimately resulting in the synthesis of proteins that influence cell growth, division, survival, motility, adhesion, and angiogenesis (1). The HER2 receptor is a glycoprotein the synthesis of which is encoded by the HER2 gene located on chromosome 17. In 20–30% of all breast cancers (15% in our country), a tumor disorder is present: increased synthesis of HER2 receptors on the cell surface and/or amplification of the HER2 gene in the nucleus. HER2-positive BC is characterized by a biologically aggressive clinical course, a shorter disease-free interval (DFI), as well as reduced overall survival (OS) compared to HER2-negative BC (2, 3). The presence of HER2 receptors on the surface of tumor cells is determined by the immunohistochemistry (IHC) and is expressed on a scale from 0 to 3+. A result labeled IHC 3+

(more than 10% of cells show intense and complete membrane staining) is considered HER2-positive BC. A HER2 result labeled IHC 2+ represents tumors with uncertain HER2 status, requiring retesting by means of chromogenic in situ hybridization (CISH) or fluorescence *in situ* hybridization (FISH). This determines whether gene amplification is present, which would confirm HER2-positive status (4).

The therapy, which has been in use for more than 15 years for the treatment of HER2-positive BC, such as trastuzumab or trastuzumab emtansine (T-DM1), has not shown benefits in HER2-low BC as shown in prospective randomized clinical studies (5, 6).

Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate (ADC), which initially demonstrated its efficacy in the treatment of metastatic HER2-positive BC, and subsequently in BC with low HER2 expression, classified as IHC +1 and IHC +2 with a negative FISH, introduced into clinical practice a new entity of HER2 breast cancers called HER2-low tumors (7, 8).

The Importance of the HER2 Signaling Pathway in Carcinogenesis and the Importance of HER2 Expression Levels

The HER2 receptor has been known to play a key role in the pathogenesis of BC since 1987 (9). In HER2-positive cancers, a specific ligand binds to the extracellular domain of the receptor, leading to homo- or heterodimerization of the receptor and subsequently the activation of the intracellular tyrosine kinase domain, followed by a cascade process of phosphorylation and the activation of signaling pathways via mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway. This results in the increased expression of certain cyclins, such as cyclin D1, E and CDK6, and the degradation of cell cycle inhibitors such as p27Kip1 (10, 11). The end result is the synthesis of proteins which affect cell proliferation, survival, motility, adhesion, as well as angiogenesis (12–15).

HER2-targeted therapies used in the treatment of HER2-positive early and metastatic breast cancer (mBC) include monoclonal antibodies such as trastuzumab, pertuzumab and margetuximab, as well as antibody-drug conjugates T-DM1 and T-DXd, and tyrosine kinase inhibitors such as tucatinib, lapatinib, and neratinib. The introduction of these drugs into clinical practice has dramatically improved the course of treatment for HER2-positive BC (2, 16–18). However, the clinical evaluation of trastuzumab, pertuzumab, and T-DM1 in the HER2-low group of patients did not show significant benefits. Consequently, these patients were classified as HER2-negative cancers and treated in accordance with the expression of hormone receptors (HR) or other biomarkers (5, 19–21).

HER2-Low as a Potential Target

For the past two decades, it has been believed that HER2 overexpression (IHC 3+ or IHC 2+/ISH positive) was necessary for the effectiveness of anti-HER2 therapies, but new data suggest that this has changed with the advent of newer and more potent agents, such as T-DXd, which is an antibody-drug conjugate. T-DXd consists of a humanized anti-HER2 monoclonal antibody (trastuzumab) linked to a topoisomerase I inhibitor (DX-895) via a cleavable linker. When T-DXd binds to the HER2 receptor, it enables the cytotoxic payload to act on both the tumor cell and the tumor microenvironment by means of a specific bystander effect, independent of the HER2 receptor expression level. This effect is the main difference between T-DXd and other HER2-targeted therapies, such as T-DM1 (22, 23).

The efficacy of as powerful a drug as T-DXd was first demonstrated in pretreated patients with HER2-positive mBC in phase 2 of the DESTINY-Breast01 study, and subsequently confirmed in phase 3 of the DESTINY-Breast02 study, in which the efficacy of T-DXd was statistically significantly better than conventional HER2 therapies in patients previously treated with multiple lines of anti-HER2 therapy and T-DM1. Another phase 3 of the DESTINY-Breast03 study, showed significantly longer survival with T-DXd versus T-DM1 in a patient population which was less heavily pretreated compared to those in DESTINY-Breast02 (24–26).

Efficacy of T-DXd in HER2-low mBC

Phase Ib and II studies initially demonstrated the activity of T-DXd in pretreated patients with HER2-low mBC, with an overall response rate (ORR) ranging from 33% to 38%, and progression-free survival (PFS) of 6.3–11.1 months (8, 27, 28). These results were the rationale behind the design of the phase 3 DESTINY-Breast04 study, which included 557 patients with HER2-low mBC (both hormone receptor positive HR+ and hormone receptor negative HR-) who had previously been treated for metastatic disease or had progressed during or within 6 months of adjuvant therapy completion. HR+ patients were required to have received ≥ 1 line of endocrine therapy. Patients were randomized 2:1 to receive T-DXd or the investigator's choice of therapy, including gemcitabine, capecitabine, paclitaxel, nab-paclitaxel, or eribulin. The primary aim was PFS in the HR+ patient population, while the secondary aims included PFS in the overall patient population and OS in the HR+ and overall population. The patient population had received an average of 3 lines of therapy for metastatic disease, with 88.7% of the patients being HR-positive and 11.3% HR-negative. The median follow-up time was 18.4 months. The ORR in the HR+ group of

patients treated with T-DXd was statistically significantly higher at 52.6%, compared to 16.3% in patients treated with chemotherapy. Moreover, the median PFS was almost doubled with T-DXd (10.1 vs. 5.4 months; HR: 0.51 [95% CI: 0.40–0.64]; p < 0.001), and OS was significantly longer (23.9 vs. 17.5 months; HR: 0.64 [95% CI: 0.48–0.86]; p = 0.003).

Similar results were observed in the HR-negative population, where ORR was 50% with T-DXd vs. 16.7% with chemotherapy, while PFS was 8.5 vs. 2.9 months (HR: 0.46 [95% CI: 0.24–0.89]). Overall survival was more than doubled, amounting to 18.2 months in the T-DXd group compared to 8.3 months in the investigator's choice chemotherapy group (HR: 0.48 [95% CI: 0.24–0.95]).

As for the adverse effects of the therapy, the most common ones in the T-DXd group were nausea (73.0%), fatigue (47.7%), and alopecia (37.7%). High-grade toxicity (grade 3 or higher) was significantly lower in the group of patients treated with T-DXd compared to those treated with chemotherapy (52.6% vs. 67.4%). The characteristic toxicity associated with T-DXd was pneumonitis or drug-related interstitial lung disease (ILD), which occurred in 12.1% of T-DXd-treated patients compared to only 0.6% of chemotherapy-treated patients. The majority of these events were grade 1 (3.5%) or grade 2 (6.5%) (7).

Based on all the aforementioned results, it can easily be concluded that low HER2 expression is indeed a good and reasonable target for ADC treatment. The results of the DESTINY-Breast04 study introduced HER2-low carcinoma into clinical practice as a completely new entity and changed the treatment paradigm for these patients.

New Treatment Algorithm for HER2-Low Patients

In the DESTINY-Breast04 study, the majority of patients with HR+ disease received ≥ 3 lines of systemic therapy and had endocrine-resistant mBC. Taking this into account, the use of T-DXd was considered rational in the fourth and subsequent lines of therapy (8). Another study, DESTINY-Breast06, the primary results of which were published at the latest ASCO conference, examines the efficacy of T-DXd versus the investigator's choice chemotherapy in HR-positive HER2-low and ultra-low mBC after progression on CDK4/6 inhibitors within 6 months or after the previous application of two lines of endocrine therapy, with or without targeted therapy, for metastatic disease. The primary aim of the study was PFS. A total of 866 patients were randomized, 90.4% of whom were previously treated with CDK4/6i. The control arm received capecitabine (59.8%), nab-paclitaxel (24.4%) or paclitaxel (15.8%). In HER2-low patients (HR, 0.62 [95% CI 0.51, 0.74], P < 0.0001), PFS was significantly longer in the T-DXd arm—13.2 months compared to 8.1 months in the chemotherapy arm, while the results were similar in the ultralow group. The median therapy duration was 11 months (T-DXd) versus 5.6 months (chemotherapy). Overall survival results are not yet mature, and a longer follow-up time is needed. Pneumonitis occurred in 11.3% of patients in the T-DXd-treated arm, but only in 1.4% was it grade 3 or higher. These results of the DESTINY-Breast06 study have established T-DXd as the standard treatment after one or more lines of endocrine therapy in patients with HER2-low and ultralow, HR+ mBC (29, 30).

The fact that ADC drugs are highly effective was confirmed by the results of another phase III study, TROPiCS-02, which examined the efficacy of sacituzumab govitecan (SG), an ADC targeting TROP2. The study enrolled pretreated patients with HR+ endocrine-resistant, locally recurrent, or mBC. Patients had previously been treated with CDK4/6 inhibitors and with 2–4 lines of chemotherapy. The experimental arm received SG, while the control arm received chemotherapy (CTX). After a median follow-up of 10.2 months, PFS in the SG arm was 5.5 months vs. 4.0 in the CTX arm (HR: 0.66 [95% CI: 0.53–0.83]; p = 0.0003). In these groups, OS was 14.4 and 11.2 months, respectively (HR: 0.79 [95% CI: 0.65–0.96]; p = 0.02), while ORR was 21% vs. 14%.

Subsequent subanalysis of the population of patients with HER2-low BC showed that the benefit of SG was comparable to that seen in the overall patient population. PFS interval was 6.4 months (SG) vs. 4.2 months with CTX (HR: 0.58 [95% CI: 0.42–0.79]; p < 0.001), and ORR was 26% with SG versus 12% with chemotherapy. The most common side effects of the therapy were neutropenia, which occurred in as many as 70% of patients, followed by diarrhea in 57% and nausea in 55%. Fatigue occurred in about one-third of patients (37%). There were no cases of pneumonitis in the group of patients treated with SG (31–33).

SG has been approved for the treatment of patients with metastatic triple-negative BC who have progressed on ≥ 2 previous lines of chemotherapy, including adjuvant therapy. It was approved after the results of the phase 3 ASCENT trial, which compared the effectiveness of SG to CTX of the investigator's choice. After a 17-month follow-up, the median PFS was 4.8 months with SG vs. 1.7 with CTX (HR: 0.43 [95% CI: 0.35–0.54]), and the median OS was 11.8 months with SG versus 6.9 months with CTX (HR: 0.51 [95% CI: 0.41–0.62]). A subanalysis of the study in HER2-low patients showed similar results to those in the overall patient population. The results were HR: 0.44 [p = 0.002] for PFS, HR: 0.43 [p < 0.001] for OS, and 32% vs. 8% for ORR. The safety profile of the drug was consistent with that in the TROPiCS-02 study (34, 35).

Optimal ADC Sequence

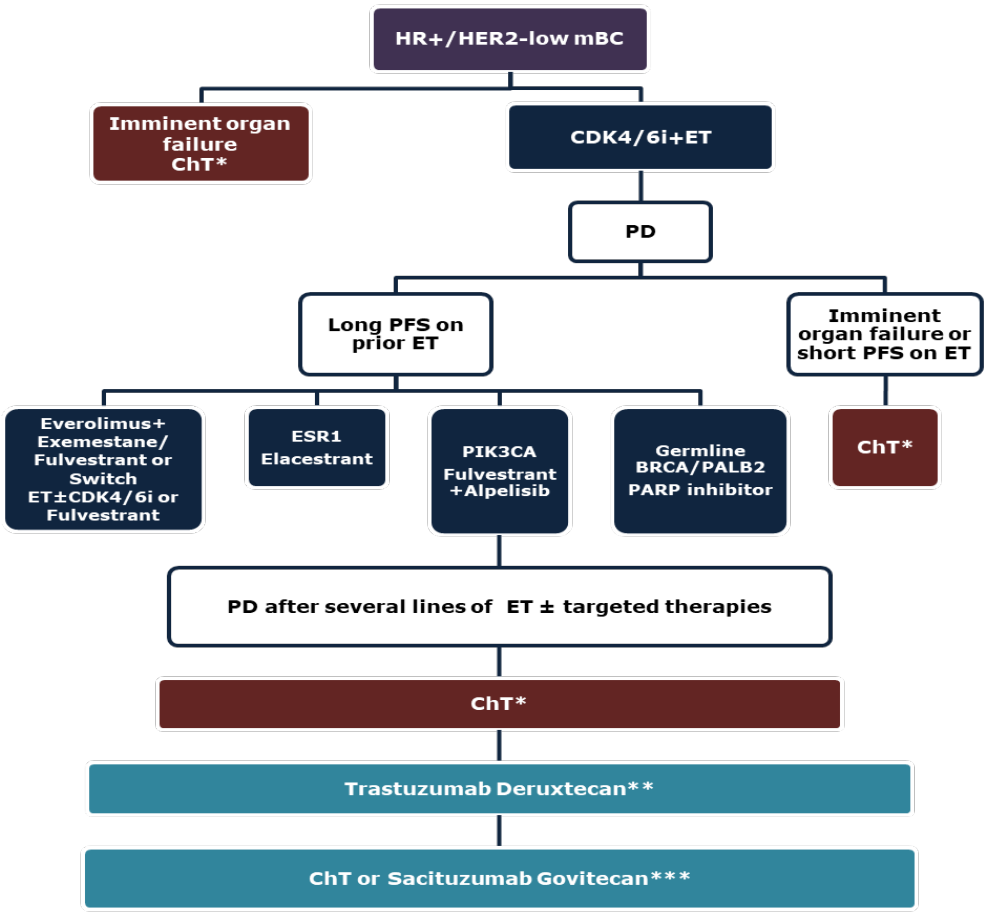
Based on the subanalysis of the ASCENT and TROPiCS-02 studies, it can be concluded that SG is another valid option for the population of

patients with low HER2 expression, although it is important to note that the optimal sequence of T-DXd and SG remains unknown.

In the aforementioned studies, the results showed HR for PFS of 0.51 and 0.46 with T-DXd in HR+ and HR- patients and HR for PFS of 0.58 and 0.44 for SG in HR+ and HR- patients, respectively. A direct comparison between the studies is not possible, given the differences in the study designs and patient populations. The studies examining the efficacy of SG involved more heavily pre-treated patients, with 71% having received 2 or more lines of therapy in the ASCENT study and 57% in TROPICS-02 more than 3 lines of therapy. In contrast, in DESTINY-Breast04, the majority of patients (60%) received only one line of therapy. Head-to-head randomized-controlled clinical trials are needed to determine the optimal sequence. In the absence of such studies, researchers currently favor T-DXd over SG for HR+/HER2-low patients who meet the inclusion criteria for the DESTINY-Breast04 and TROPiCS-02 trials. T-DXd is the preferred option due to the higher level of evidence in the HER2-low population, as the data for SG come from a post-hoc analysis, and because patients in DESTINY-Breast04 were treated with fewer lines of prior therapy. Needless to say, patient preferences, comorbidities and the risk the therapy carries based on adverse effects should also be taken into account (36–38).

The recommended algorithm in accordance with all valid clinical guidelines is shown in Figure 1 (16, 17, 39).

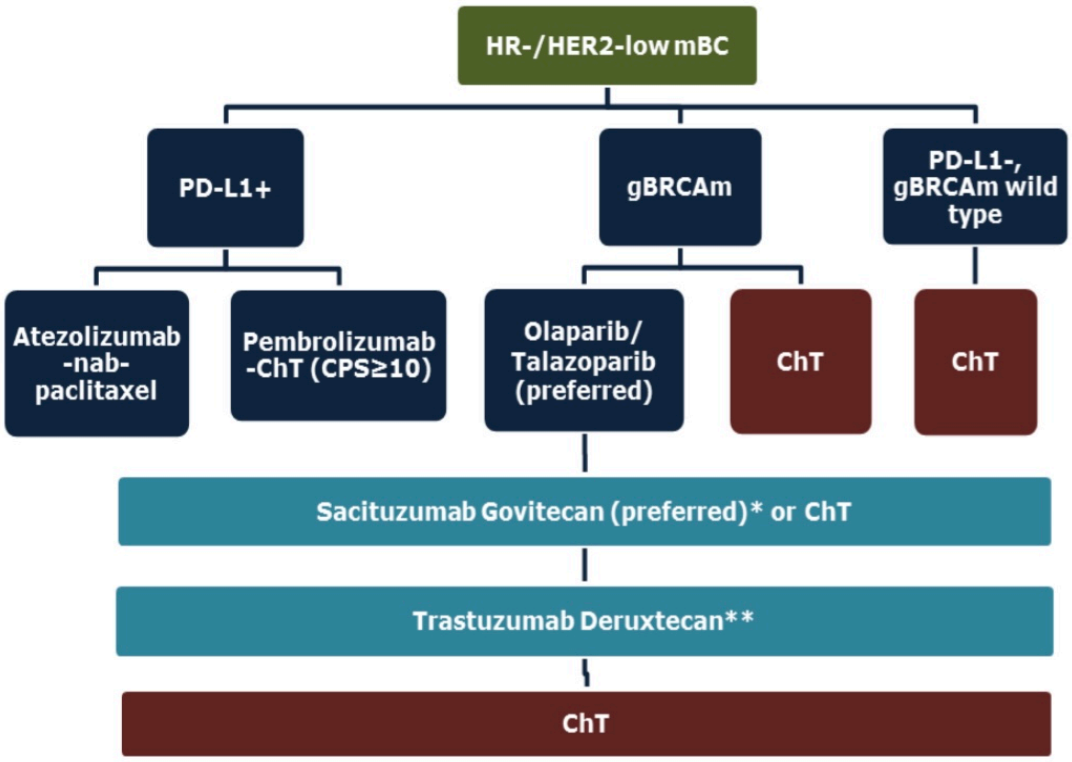
A) Recommended algorithm in treatment of HR+/HER2low mBC



MBC: metastatic breast cancer, HER2: human epidermal growth factor receptor 2; HR, hormone receptor, CDK4/6, cyclin-dependent kinase 4 and 6, ChT: chemotherapy; ESR1, estrogen receptor 1, m: mutation, PALB2: partner and localiser of BRCA2, PARP: poly (ADP-ribose) polymerase, PD: progressive disease, PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, T-DxT: Trastuzumab deruxtecan, ChT: chemotherapy, gBRCAm: germline BRCA1/2 mutation, PD-L1, programmed death-ligand 1

Figure 1. The recommended algorithm in treatment of A) HR+HER2-low advanced/mBC and B) HR-HER2-low advanced/mBC with all valid clinical guidelines (16, 17, 39)

B) Recommended algorithm in treatment of HR-/HER2low mBC



A) *In the absence of imminent organ failure, the standard first line is CDK4/6 inhibitors with ET. Chemotherapy is the second-line therapy for endocrine-resistant cancers, at least after two ETs. The choice of therapy depends on the previous therapy, disease aggressiveness, toxicity and the patient's condition. **Trastuzumab deruxtecan should be considered for patients with HER2-low mBC after at least one line of ChT according to DESTINY-Breast04 study. ***Sacituzumab govitecan should be considered after at least two lines of chemotherapy, according to the TROPiCS-02 trial. It is recommended after Trastuzumab Deruxtecan therapy.
B) *Sacituzumab govitecan is the preferred treatment option after previous ChT according to the ASCENT III trial. **Trastuzumab deruxtecan should be considered for patients with HER2-low MBC after at least one line of ChT, according to the DESTINY-Breast04 study.

Ongoing Studies for the Treatment of HER2-Low BC

A number of agents, either alone or in combination, such as ADCs, immunotherapy, and cytostatics, are currently being investigated for the treatment of HER2-low BC. Table 1 presents the most important phase 2 and 3 studies, the preliminary results of which are either already available or expected soon. One of the studies with an interesting design is the phase Ib DESTINY-Breast08 study, which has 5 cohorts that differ based on HR expression and prior therapy. Preliminary results suggest that T-DXd can be safely administered in combination with endocrine therapy (40–42). A major problem in real-world clinical practice is the treatment of patients with CNS metastases. The phase 2 DEBBRAH study is currently examining the effectiveness of T-DXd in HER2-positive and HER2-low patients with CNS metastases. The results have been published for 2 cohorts of HER2-low patients: the cohort with untreated asymptomatic CNS lesions, where an intracranial ORR of 67% was noted, and for the cohort with metastases which had progressed after prior therapy, where the expected ORR is lower and amounts to 33% (43–46). The DAISY study also examined this patient population and found the ORR of up to 33% and PFS of up to 6.7 months. Other agents worth mentioning include active studies with margetuximab and disitamab vedotin (47–49).

After observing the effectiveness of anti-HER2 therapies in the treatment of metastatic HER2-low BC, a large number of studies are now examining their effectiveness in earlier lines of BC therapy (50, 51).

Table 1. Ongoing clinical trials of T-DXd and other therapies in HER2-low advanced/mBC

Study drug	Study name	Phase	Pts population	N of HER2-low	Results for HER2-low
T-DXd	DEBBRAH[43-45]	2	HER2+ OR HER2-low with untreated BMs or LMC (5 cohorts)	41	ORR Cohort 2 66.7% ORR Cohort 4 33.3% PFS (both): 5.7 mo
T-DXd	DAISY[27]	2	HER2+ HER2-low HER2 0	72	OR: 33.3% mPFS:6.7 mo
T-DXd + nivolumab	NCT03523572[28]	Ib	HER2+ HER2-low	16	ORR: 37.5% mPFS: 6.3 mo
T-DXd + durvalumab (+ others)	BEGONIA[46]	Ib/2	HER2-low TNBC	11	ORR: 100% (4/4; 7 pts still on therapy)
Disitamab vedotin	NCT04400695[52]	3	HER2-low	Recruiting	
Disitamab vedotin	NCT05331326[53]	2	HER2 + HER2-low	Recruiting	
Margetuximab	NCT01828021[48]	2	HER2-low	25	Not published yet

T-DXd: trastuzumab deruxtecan, ORR: overall response rate, HER2: human epidermal growth factor 2, PFS: progression-free survival, LMC: leptomeningeal carcinomatosis

Conclusion

After the publication of the DESTINY-Breast04 study results, it is evident that low HER2 positivity can be considered a rational target for the treatment of BC. The results have changed clinical practice in both HR-positive and HR-negative HER2-low metastatic BC. Further research is necessary in order to standardize HER2 testing, prevent T-DXd-related side effects and resistance to therapy, and identify the optimal sequence of available therapeutic options. Future research should also explore the role of these drugs in the treatment of early HER2-low BC.

References

1. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ, et al. Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2011. Ann Oncol 2011;22(8):1736-47. [CrossRef] [PubMed]
2. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344(11):783-92. [CrossRef] [PubMed]
3. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA):end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol 2020;21(4):519-30. [CrossRef] [PubMed]
4. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018;36(20):2105-22. [CrossRef] [PubMed]
5. Fehrenbacher L, Cecchini RS, Geyer CE, Rastogi P, Costantino JP, Atkins JN, et al. NSABP B-47/NRG oncology Phase III randomized trial comparing adjuvant chemotherapy with or without trastuzumab in high-risk invasive breast cancer negative for HER2 by FISH and with IHC 1+ or 2+. J Clin Oncol 2020;38(5):444-53. [CrossRef] [PubMed]
6. Jacot W, Cottu P, Berger F, Dubot C, Venat-Bouvet L, Lortholary A, et al. Actionability of HER2-amplified circulating tumor cells in HER2-negative metastatic breast cancer: the CirCe T-DM1 trial. Breast Cancer Res 2019;21(1):1-9. [CrossRef] [PubMed]
7. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 2022;387(1):9-20. [CrossRef] [PubMed]
8. Modi S, Park H, Murthy RK, Iwata H, Tamura K, Tsurutani J, et al. 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 2020;38(17):1887-96. [CrossRef] [PubMed]
9. Tal M, King CR, Kraus MH, Ullrich A, Schlessinger J, Givol D. Human HER2 (neu) promoter: evidence for multiple mechanisms for transcriptional initiation. Mol Cell Biol 2023;7(7):2597-601. [CrossRef] [PubMed]
10. Belsches-Jablonski AP, Biscardi JS, Peavy DR, Tice DA, Romney DA, Parsons SJ. Src family kinases and HER2 interactions in human breast cancer cell growth and survival. Oncogene 2001;20(12):1465-75. [CrossRef] [PubMed]
11. Timms JF, White SL, O'Hare MJ, Waterfield MD. Effects of ErbB-2 overexpression on mitogenic signalling and cell cycle progression in human breast luminal epithelial cells. Oncogene 2002;21(43):6573-86. [CrossRef] [PubMed]
12. Graus-Porta D, Beerli RR, Daly JM, Hynes NE. ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling. EMBO J 1997;16(7):1647-55. [CrossRef] [PubMed]
13. Hynes NE, Stern DF. The biology of erbB-2/neu/HER-2 and its role in cancer. Biochim Biophys Acta 1994;1198(2-3):165-84. [CrossRef] [PubMed]
14. Ménard S, Tagliabue E, Campiglio M, Pupa SM. Role of HER2 gene overexpression in breast carcinoma. J Cell Physiol 2000;182(2):150-62. [CrossRef] [PubMed]
15. Olayioye MA. Update on HER-2 as a target for cancer therapy: intracellular signaling pathways of ErbB2/HER-2 and family members. Breast Cancer Res 2001;3(6):385-9. [CrossRef] [PubMed]
16. Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32(12):1475-95. [CrossRef] [PubMed]
17. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer. Version 4. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf [accessed Aug 29, 2024].
18. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015;372(8):724-34. [CrossRef] [PubMed]
19. Burris HA 3rd, Rugo HS, Vukelja SJ, Vogel CL, Borson RA, Limentani S, et al. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. J Clin Oncol 2011;29(4):398-405. [CrossRef] [PubMed]
20. Yazaki S, Hashimoto J, Ogita S, Nakano E, Yamauchi T, et al. Lower response to T-DM1 in metastatic breast cancer patients with HER2 IHC score of 2 and FISH positive compared with IHC score of 3. Ann Oncol 2017;28 Suppl 5:v102-3. [CrossRef]
21. Gianni L, Llado A, Bianchi G, Cortes J, Kellokumpu-Lehtinen PL, Cameron DA, et al. Open-label, phase II, multicenter, randomized study of the efficacy and safety of two dose levels of pertuzumab, a human epidermal growth factor receptor 2 dimerization inhibitor, in patients with human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2010;28(7):1131-7. [CrossRef] [PubMed]
22. Ogitani Y, Aida T, Hagihara K, Yamaguchi J, Ishii C, Harada N, et al. DS-8201a, a novel HER2-

targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. Clin Cancer Res 2016; 22(20):5097-108. [CrossRef] [PubMed]
23. Ogitani Y, Hagihara K, Oitate M, Naito H, Agatsuma T, et al. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. Cancer Sci 2016;107(7):1039-46. [CrossRef] [PubMed]
24. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 2020;382(7):610-21. [CrossRef] [PubMed]
25. Krop I, Park YH, Kim SB, Takano T, Im SA, Borges G, et al. Trastuzumab deruxtecan vs physician's choice in patients with HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine: primary results of the randomized, phase 3 study DESTINY-Breast02 (abstract GS2-01). In: Proceedings of the San Antonio Breast Cancer Symposium; 2022 Dec 6-10; San Antonio, Texas. [CrossRef]
26. Hurvitz S, Hegg R, Chung W, Im SA, Jacot W, Ganju V, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated survival results of the randomized, phase 3 study DESTINY-Breast03 (abstract GS2-02). In: Proceedings of the San Antonio Breast Cancer Symposium; 2022 Dec 6-10; San Antonio, Texas. [CrossRef]
27. Diéras V, Deluche E, Lusque A, et al. Trastuzumab deruxtecan (T-DXd) for advanced breast cancer patients (ABC), regardless HER2 status: a phase II study with biomarker analysis (DAISY) (abstract). Cancer Res 2022;82(4 Suppl):PD8-02. [CrossRef]
28. Hamilton E, Shapiro CL, Petrylak D, Boni V, Martin M, Del Conte C, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) with nivolumab in patients with HER2-expressing advanced breast cancer: a 2-part, phase 1b, multicenter, open-label study (abstract). Cancer Res 2021;81(4 Suppl):PD3-07. [CrossRef]
29. Bardia A, Barrios C, Dent R, Hu X, O'Shaughnessy J, Yonemori K, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) vs investigator's choice of chemotherapy in patients with hormone receptor-positive (HR+), HER2-low metastatic breast cancer whose disease has progressed on endocrine therapy in the metastatic setting: a randomized, global phase 3 trial (DESTINY-Breast06) (abstract). Cancer Res 2021;81(4 Suppl):OT-03-09. [CrossRef]
30. Curigliano G, Hu X, Rebecca A, Yonemori K, Barrios CH, O'Shaughnessy J, et al. Trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow metastatic breast cancer (mBC) with prior endocrine therapy (ET): Primary results from DESTINY-Breast 06 (abstract). J Clin Oncol. 2024;42(17 Suppl):LBA1000. [CrossRef]
31. Rugo HS, Bardia A, Marmé F, Cortes J, Schmid P, Loirat D, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor negative metastatic breast cancer. J Clin Oncol 2022;40(29):3365-76. [CrossRef] [PubMed]
32. Schmid P, Cortés J, Marmé F, Rugo HS, Tolaney SM, Oliveira M, et al. 214MO Sacituzumab govitecan (SG) efficacy in hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer (MBC) by HER2 immunohistochemistry (IHC) status in the phase III TROPiCS-02 study. Ann Oncol 2022;33(Suppl 7):S635-S636. [CrossRef]
33. Rugo HS, Bardia A, Marmé F, Cortés J, Schmid P, Loirat D, et al. LBA76 Overall survival (OS) results from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HR+/HER2- metastatic breast cancer (mBC) (abstract). Ann Oncol 2022;33(Suppl 7):S808-S869. [CrossRef]
34. Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. N Engl J Med 2021;384(16):1529-41. [CrossRef] [PubMed]
35. Hurvitz SA, Bardia A, Punie K, Kalinsky K, Cortés J, O'Shaughnessy J, et al. Sacituzumab govitecan (SG) efficacy in patients with metastatic triple-negative breast cancer (mTNBC) by HER2 immunohistochemistry (IHC) status: findings from the phase 3 ASCENT study. Ann Oncol 2022;33(Suppl 3):S194-S223. [CrossRef]
36. Rugo HS, Bianchini G, Cortés J, Henning JW, Untch M. Optimizing treatment management of trastuzumab deruxtecan in clinical practice of breast cancer. ESMO Open 2022;7(4):100553. [CrossRef] [PubMed]
37. Ocaña A, Amir E, Pandiella A. HER2 heterogeneity and resistance to anti-HER2 antibody-drug conjugates. Breast Cancer Res 2020;22(1):15. [CrossRef] [PubMed]
38. Collins DM, Bossenmaier B, Kollmorgen G, Niederfellner G. Acquired resistance to antibody-drug conjugates. Cancers (Basel) 2019;11(3):394. [CrossRef] [PubMed]
39. Curigliano G, Castelo-Branco L, Gennari A, Harbeck N, Criscitiello C, Trapani D, et al. ESMO metastatic breast cancer living guidelines, v1.1 May 2023. [Internet]. Available from: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline [Accessed Sep 10, 2024]. [CrossRef] [PubMed]
40. National Institutes of Health (NIH). A phase 1b study of T-DXd combinations in HER2-low advanced or metastatic breast cancer (DB-08) [Internet]. Identifier: NCT04556773. Available from: https://clinicaltrials.gov/study/NCT04556773 [Accessed Sep 10, 2024]. [CrossRef] [PubMed]
41. Jhaveri K, Hamilton E, Loi S, Schmid P, Darilay A, Gao C, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in combination with other anticancer agents in patients with HER2-low metastatic breast cancer: a phase 1b, open-label, multicenter, dose-finding and dose-expansion study (DESTINY-Breast08) (abstract). Cancer Res 2021;81(4 Suppl):OT-03-05. [CrossRef]
42. André F, Hamilton EP, Loi S, Im SA, Sohn J, Tseng LM, et al. Dose finding and expansion studies of trastuzumab deruxtecan in combination with other anticancer agents in patients with advanced/metastatic HER2+ (DESTINY-Breast07) and HER2-low (DESTINY-Breast08) breast cancer. J Clin Oncol 2022;40(16 Suppl):3025. [CrossRef]

43. Pérez-Garcia J, Vaz Batista M, Cortez P, Ruiz-Borrego M, Cejalvo JM, de la Haba-Rodriguez, et al. Trastuzumab deruxtecan in patients with active central nervous system involvement from HER2-low advanced breast cancer: the DEBBRAH trial (poster PD7-02). In: Proceedings of the San Antonio Breast Cancer Symposium; 2022 Dec 6-10; San Antonio, Texas. [CrossRef]
44. Perez-Garcia JM, Vaz Batista M, Cortez P, Ruiz-Borrego M, Cejalvo JM, de la Haba-Rodriguez J, et al. Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-positive breast cancer: the DEBBRAH trial. Neuro Oncol 2023;25(1):157-66. [CrossRef] [PubMed]
45. Vaz Batista M, Patricia C, Ruiz M, Cejalvo JM, de la Haba J, Garrigós L, et al. Trastuzumab deruxtecan in patients with HER2[+] or HER2-low-expressing advanced breast cancer and central nervous system involvement: preliminary results from the DEBBRAH phase 2 study (abstract). Cancer Res 2022;82(4 Suppl):PD4-06. [CrossRef]
46. Schmid P, Im SA, Armstrong A, Park YH, Chung WP, Nowecki Z, et al. BEGONIA: phase 1b/2 study of durvalumab (D) combinations in locally advanced/metastatic triple-negative breast cancer (TNBC)—Initial results from arm 1, d+paclitaxel (P), and arm 6, d+trastuzumab deruxtecan (T-DXd) (abstract). J Clin Oncol 2021;39(15 Suppl):1023. [CrossRef]
47. Pegram MD, Tan-Chiu E, Miller K, Rugo HS, Yardley DA, Liv S, et al. A single-arm, open-label, phase 2 study of MGAH22 (margetuximab) [fc-optimized chimeric anti-HER2 monoclonal antibody (mAb)] in patients with relapsed or refractory advanced breast cancer whose tumors express HER2 at the 2+ level by immunohistochemistry and lack evidence of HER2 gene amplification by FISH (abstract). J Clin Oncol 2014;32(15 Suppl):TPS671. [CrossRef]
48. NIH. Phase 2 study of the monoclonal antibody MGAH22 (margetuximab) in patients with relapsed or refractory advanced breast cancer [Internet]. ClinicalTrials.gov. Identifier NCT01828021. Available from: https://clinicaltrials.gov/ct2/show/NCT01828021 [Accessed Sep 07, 2024].
49. NIH. Disitamab vedotin (RC48) combined with penpulimab (AK105) for neoadjuvant treatment of HER2-low breast cancer [Internet]. ClinicalTrials.gov. Identifier NCT05726175. Available from: https://clinicaltrials.gov/ct2/show/NCT05726175 [Accessed Sep 07, 2024].
50. NIH. Trastuzumab deruxtecan alone or in combination with anastrozole for the treatment of early stage HER2 low, hormone receptor positive breast cancer [Internet]. ClinicalTrials.gov. Identifier NCT04553770. Available from: https://clinicaltrials.gov/ct2/show/NCT04553770 [Accessed Sep 08, 2024].
51. NIH. Phase II neoadjuvant pyrotinib combined with neoadjuvant chemotherapy in HER2-low-expressing and HR positive early or locally advanced breast cancer: a single- arm, non-randomized, single-center, open label trial [Internet]. ClinicalTrials.gov. NCT05165225. Available from: https://clinicaltrials.gov/ct2/show/NCT05165225 [Accessed Sep 08, 2024].
52. NIH. A study of RC48-ADC for the treatment of locally advanced or metastatic breast cancer with low expression of HER2 [Internet]. ClinicalTrials.gov. Identifier NCT04400695. Available from: https://clinicaltrials.gov/ct2/show/NCT04400695 [Accessed Sep 08, 2024].
53. NIH. A study of RC48-ADC for the treatment of HER2-expression metastatic breast cancer with abnormal activation of PAM pathway [Internet]. ClinicalTrials.gov. Identifier NCT05331326. Available from: https://clinicaltrials.gov/ct2/show/NCT05331326 [Accessed Sep 08, 2024].

Pregledni rad **UDC: 618.19-006.6-085**
doi: 10.5633/amm.2025.0312

KARCINOM DOJKE SA HER2 STATUSOM NISKE EKSPRESIJE: NOVA TERAPIJSKA POJAVA

Ana Cvetanović[1,2], Kristina Janković[2]

[1]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija
[2]Univerzitetski klinički centar Niš, Klinika za onkologiju, Niš, Srbija

Kontakt: Ana Cvetanović
Bulevar dr Zorana Đinđića 48, 18000 Niš, Srbija
E-mail: ana.stankovic@yahoo.com

Ciljane HER2 terapije koje se koriste u lečenju ranog karcinoma dojke pozitivnog na HER2 i metastatskog karcinoma dojke (engl. *metastatic breast cancer* – mBC) obuhvataju monoklonska antitela, kao što su trastuzumab, pertuzumab i margetuksimab, zatim konjugate antitela i leka (engl. *antibody–drug conjugate* – ADC), kao što su trastuzumab-emtazin (T-DM1) i trastuzumab-derukstekan (T-DXd) i inhibitore tirozin kinaze poput tukatiniba, lapatiniba i neratiniba. Uvođenje ovih lekova u kliničku praksu dramatično je popravilo tok lečenja karcinoma dojke pozitivnog na HER2. Uprkos tome, klinička evaluacija trastuzumaba, pertuzumaba i T-DM1 nije ukazala na njihove značajnije prednosti u grupi bolesnika sa slabo pozitivnim HER2, te su ovi bolesnici svrstani u grupu karcinoma negativnih na HER2 i lečeni na osnovu ekspresije hormonskih receptora (HR) ili drugih biomarkera. Trastuzumab derukstekan, konjugat antitela i leka, koji je najpre pokazao svoju efikasnost u lečenju metastatskog karcinoma dojke pozitivnog na HER2 a potom i u lečenju karcinoma dojke sa niskom HER2 ekspresijom, koji su prema imunohistohemijskom skoru klasifikovani kao IHC+1 i IHC+2 sa negativnom fluorescentnom *in situ* hibridizacijom (engl. *fluorescence in situ hybridization* – FISH), uveo je u kliničku praksu novi tip HER2 karcinoma dojke – tumore slabo pozitivnog HER2 statusa. Posle objavljenih rezultata studije DESTINY-Breast04 jasno je da se lečenje karcinoma dojke može usmeriti na nisku pozitivnost HER2. Rezultati su promenili kliničku praksu i u lečenju slabo pozitivnog HER2 metastatskog karcinoma dojke pozitivnog na HR i u lečenju slabo pozitivnog HER2 metastatskog karcinoma dojke negativnog na HR. Neophodna su dodatna istraživanja koja bi standardizovala HER2 testiranje, prevenirala neželjena dejstva koja ima T-DXd i rezistenciju na terapiju i odredila optimalnu dozu dostupnih terapijskih opcija. Takođe, potrebno je da buduća istraživanja pozicioniraju pomenute lekove i kada je reč o lečenju ranog karcinoma dojke slabo pozitivnog na HER2.

Acta Medica Medianae 2025; 64(3): 90–99.

***Ključne reči**: karcinom dojke, slabo pozitivni receptor humanog epidermalnog faktora rasta 2, konjugat antitela i leka, trastuzumab derukstekan, sacituzumab govitekan*