REVIEW

Lib Oncol. 2022;50(2-3):118–125

doi: 10.20471/LO.2022.50.02-03.18

HER2-LOW ADVANCED BREAST CANCER TREATMENT

MARIJA BAN[1] and EDUARD VRDOLJAK[1,2]

[1]Department of Oncology and Radiotherapy, University Hospital Split, Split, Croatia;
[2]University of Split, School of Medicine, Split, Croatia

Summary

Breast cancer cells can express HER2 receptors on their membranes to varying degrees. HER2 signalling pathway is important for tumor growth and metastasis. Patients with HER2-positive disease had worse treatment outcomes until the implementation of trastuzumab started, followed by other anti-HER2 drugs. So far, they have been used exclusively for strong HER2 expression. The development of new drugs, primarily antibody-drug conjugates, has proven their efficacy on tumor cells that have lower levels of the HER2 receptors, today referred to as *HER2-low* tumors. Since the results of the DESTINY breast04 study showed a prolongation of progression free survival and overall survival in *HER2-low* pretreated patients, a new perspective opens up in the treatment, as well as in HER2 testing.

KEY WORDS: *breast cancer; advanced; HER2-low; treatment*

HER2-LOW BREAST CANCER

Drug development targeting HER2 receptors has led to significant progress in the treatment of HER2-positive breast cancer, either early-stage or advanced(1). The first researched drug, trastuzumab, had an effect exclusively in patients whose tumors were marked as HER2 3+ (determined by immunohistochemical methods - IHC) or 2+ with amplification of the HER2neu gene (≥2 copies) determined by fluorescent *in situ* hybridization (FISH) methods(2). Clinical studies and clinical guidelines aimed at the treatment of HER2-positive breast cancer have further developed on the basis of these results.

HER2-positive breast cancer accounts for about 20% of newly diagnosed breast cancers. However, in another 40-50% of breast tumors there is a certain level of HER2 receptor expression, lower than the one specified so far for it to be referred to as positive, and this group of tumors has recently been classified as so-called *HER2-low* breast cancer(3). *HER2-low* tumors represent a subgroup within nominally HER2 negative tumors (e.g. immunohistochemical 1+ or 2+, but negative on *in situ* methods). The group of *HER2-low* tumors includes very heterogeneous tumors, most of which are hormone receptor (HR)-positive (65-83%), and the rest are HR negative(4). Clearly, HR-positive *HER2-low* tumors have a different molecular profile compared to HR negative *HER2-low* tumors. The first group is dominated by luminal subtypes and the second by basal subtypes, which all delineates the genetic, clinical-pathological, and prognostic differences within the *HER2-low* group(4).

Although they are treated as HER2 negative tumors, according to current guidelines, *HER2-low* tumors may have a clinical behaviour more similar to HER2-positive tumors than to HER2 IHC 0+ tumors. In large prospective series of patients, it was shown that breast cancer presented with higher T stage, higher histological grade, higher expression of the proliferation marker Ki67 and more frequently affected axillary lymph no-

***Corresponding author**: Marija Ban, Department of Oncology and Radiotherapy, University Hospital Split, Spinčićeva 1, 21000 Split, Croatia. e-mail: marija.ban1979@gmail.com*

des in patients with HER2 IHC 2+, FISH negative breast cancer, compared to HER2 0+ breast cancer(5). Likewise, survival without disease recurrence was lower compared to the group of HER2 0+ tumors(5). Analysis of the trastuzumab effects shows that results for the so-called *HER2-low* tumors were worse than for those of HER2-positive patients. These results were confirmed, to a lesser or greater extent, in patient series in attempt to define patient subgroups and the level of HER2 receptor expression in the hitherto defined HER2 negative group that could potentially benefit from anti-HER2 therapy(6, 7).

Despite the progress made so far, the group of *HER2-low* tumors represents a grey zone between clearly positive and clearly negative tumors, and for now they are characterized as a potentially separate biological and clinical entity. However, potential problems include objectivity in testing, reproducibility, determination of the lower negative limit, selection of the test method and a new approach to the design of clinical studies.

For now, this group of patients is still mostly treated depending on the pathohistological features grouped into known immunophenotypes(8). Thus, patients with luminal advanced breast cancer will be treated with endocrine therapy (ET) (aromatase inhibitors, tamoxifen and fulvestrant) in combination with inhibitors of cyclin-dependent kinases (CDK4/6i), alpelisib and everolimus(8). Advanced triple-negative tumors are treated with immunotherapy if they are PD-L1-positive (*programmed death ligand 1*). Patients with a germline BRCA (*Breast cancer associated gene*) mutation are treated with PARP (*poly-ADP-ribose polymerase*) inhibitors. After progression to the mentioned treatment, patients are treated with sequential chemotherapy, taking into account all its limitations of dose-limited toxicity, profile of unwanted consequences, cumulative effect and, ultimately, a modest contribution to the outcome of treatment(8).

In an effort to improve treatment outcomes for advanced triple-negative cancer and hormone-resistant breast cancer with low expression of the HER2 receptor, the efficacy of newer drug treatment options targeting the HER2 receptor, but also the tumor microenvironment, is being researched, which has brought significant improvement in treatment outcomes for advanced HER2-positive cancer breast, potentially due to its different structure, pharmacodynamics and pharmacokinetics(7).

It is known that *HER2-low* breast cancer cell lines express a certain amount of HER2 receptor that can be targeted, which can potentially mean that anti-HER2 drugs can potentially work in patients beyond the limits of HER2 positivity established so far(9). In clinical research, regrettably, this effect was not achieved either with the use of trastuzumab or pertuzumab, as well as by use of the first antibody-drug conjugate trastuzumab-emtansine.

ANTIBODIES IN *HER2-LOW* BREAST CANCER TREATMENT

Trastuzumab

Trastuzumab was once considered to be effective in early-stage breast cancer even with minimal expression of the HER2 receptor, due to its property to activate antibody-dependent cytotoxicity(10). In the NSABP B-31 and NCCTG N9831 studies, in which adjuvant chemotherapy with trastuzumab and chemotherapy alone were compared, patients were included based on locally determined HER2 status(11). After central pathology reanalysis in study B31, 9.7% of patients were HER2 negative and still had some benefit from trastuzumab treatment (relative risk for survival without disease recurrence is 0.34, 95% CI 0.14-0.80), similar to HER2-positive patients(12). In N9831 study, the benefit of adding trastuzumab to chemotherapy was not demonstrated for 5.5% of patients who were determined to be HER2 negative by central reanalysis(13).

Following these early positive signals, a phase III study, NSABP B-47, was designed in which 3,270 patients with *HER2-low* early breast cancer were included(14). Patients were randomized to receive chemotherapy or a combination of trastuzumab and chemotherapy. Research has shown that the addition of trastuzumab does not contribute to survival without invasive recurrence of the disease (HR: 0.98, 95% CI 0.76-1.25)(14). Analysis of the subgroups, even those with a higher level of HER2 receptor expression, shows no benefit from the addition of trastuzumab.

Pertuzumab

In addition to its binding to the HER2 receptor, pertuzumab prevents its homodimerization and heterodimerization with other HER family

receptors. Unlike trastuzumab, pertuzumab can stop tumor growth in xenografts, even if the tumor cells do not overexpress the HER2 receptor(15). An attempt to prescribe pertuzumab as monotherapy in pretreated patients with HER2-negative or *HER2-low* breast cancer have been unsuccessful based on a phase II study, where patients were randomized to receive 2 doses of pertuzumab. The rate of clinical benefit was 9.8% and 5.4% respectively, and the median time to progression was 6.1 weeks in both groups(16).

Margetuximab

Margetuximab is an antibody whose Fab fragment has similar specificity and affinity for the HER2 receptor as trastuzumab. However, its Fc fragment was modified in such a way as to stimulate the effector function more intensely. It has a 4-5 times greater affinity than trastuzumab to bind to the activating Fc receptor of natural killer cells, but it has a 7-fold lower affinity to bind to the inhibitory Fc receptor found on antigen-presenting cells and thus significantly increases the immune response to the tumor cell by significantly increasing antibody-mediated cytotoxicity resulting in secretion of granenzymes and perforins and tumor cell death. In patients with *HER2-low* tumors, it was tested in phase 1, and no activity was demonstrated in the mentioned group(17).

ANTIBODY-DRUG CONJUGATES

Despite numerous studies of different drugs in *anti-HER2-low* tumors, antibody-drug conjugates are, for the time being, the only ones tested in randomized phase III studies. As the efficacy of the mentioned treatment is being confirmed, the overall approach to anti-HER2 therapy will potentially change. Aside from their blocking the HER2 receptors, the newer conjugates have a more pronounced antibody-dependent cytotoxicity, which is not necessarily related to the inhibition of the HER2 signalling pathway, but rather to the delivery of the cytotoxic substance to the cells. In addition, a higher drug-antibody ratio allows for greater cytotoxicity of the conjugate. The separable linker enables the killing of HER2-positive and surrounding HER2-negative cells, which can potentially overcome the diversity of HER2 receptor expression levels within the tumor itself. In addition, newer conjugates, unlike TDM1, which has a microtubule inhibitor as a cytostatic drug component, have cytotoxic that act directly on DNA, such as alkylating drugs and topoisomerase I inhibitors, which increases the cytostatic component. The aforementioned features explain the greater efficacy in *HER2-low* tumors, and to some extent justify greater toxicity. The side effect profile of T-Dxd and trastuzumab-duocarmazine from phase I and II clinical studies resembles that of their cytostatic moieties, which are partially released into the circulation due to the separable linker connecting the cytostatic to the antibody and the high drug-antibody ratio. Common side effects were myelosuppression, alopecia, stomatitis, and gastro-intestinal toxicity. Likewise, a potentially dangerous side effect is pneumonitis.

Trastuzumab- emtansine (T-DM1)

Trastuzumab-emtansine consists of trastuzumab to which a maytansine derivative is connected by an inseparable thioether bond. The drug-antibody ratio is 3.5:1. In addition to blocking the HER2 receptor and promoting antibody-dependent cytotoxicity, by internalizing cytostatics in HER2-positive cells the drug has a much stronger cytostatic effect on tumor cells than on healthy ones and a potentially more favourable therapeutic index compared to classic cytostatics. Unlike trastuzumab, there were no prospective studies of TDM1 in *HER2-low* tumors. In two phase II studies that studied the efficacy of TDM1 in pretreated HER2-positive patients, when after the central check of the HER status the patients who were defined as *HER2-low* status according to the results of the central check were analysed, a reduced efficacy of TDM1 compared to the HER2-positive patients was shown(18,19).

Trastuzumab-deruxtecan

Trastuzumab-deruxtecan (T-Dxd) is an antibody-drug conjugate that, like TDM1, binds to HER2 receptors; however, unlike TDM1, it has a separable linker that bonds trastuzumab with exatecan (a topoisomerase 1 inhibitor) and a significantly higher drug-antibody ratio (8:1)(20). As a result, a larger amount of cytostatic enters the target cell and has a greater cytotoxic effect. The second component is the so-called by-stander effect, which is described as the killing of neighbouring

antigen-negative cells after the cytostatic is released by free diffusion from antigen-positive cells that have died(20). The latter fact can potentially explain the effect in patients with *HER2-low* advanced breast cancer. However, it has been shown in xenograft models that T-Dxt is not only active in T-DM1-resistant HER2-positive breast cancer, but maintains its activity even at low expression of the HER2 receptor(21). Preclinical and early clinical studies have shown the effectiveness of T-Dxd in pretreated patients with *HER2-low* breast cancer(22,23) and the results of these studies led to the design and implementation of a phase III study. This year, the results of the DESTINY-Breast04 study were presented at the ASCO (American Society of Medical Oncology) meeting. It is a phase III clinical study involving 557 patients with advanced *HER2-low* breast cancer who received 1 or 2 lines of chemotherapy. Ninety percent of them had hormone-dependent breast cancer. They were randomized in a 2:1 ratio to receive T-Dxd or chemotherapy according to the researcher's choice. The primary outcome criterion was progression-free survival in hormone-dependent breast cancer. Secondary outcome criteria were progression-free survival in the total study population and overall survival in the hormone-dependent population and in the total population. In the hormone-sensitive group, the median survival without disease progression was 10.1 months in patients who received T-Dxd compared to 5.4 months for patients who received chemotherapy according to the researcher's choice (HR: 0.51, p<0.0001)(24). Overall survival in the mentioned group was 23.9 versus 17.5 months (HR: 0.64, p=0.0003). In the total population, the median survival without disease progression was 9.9 months in the group receiving T-Dxd, and 5.5 months in the chemotherapy group (HR:0.50, P<0.0001), and the overall survival was 23.4 months for T-Dxd and 16.8 months for chemotherapy (24). In subgroup analysis, it may be interesting to distinguish the stratification according to previous administration of CDK4/6 inhibitors. It has been shown that patients who were administered a CDK4/6 inhibitor and those who did not have a similar benefit in terms of survival without disease progression(24). The subgroup of patients with negative hormone receptors, whose share in the study was small, corresponds to the prevalence of this form of the disease in the *HER2-low* population. The side effect associated with T-Dxd described in the study is interstitial lung disease, which occurred in 12.1% of patients, and in 0.8% of patients it was grade V. The results of this study open a completely new and broader horizon for patients with *HER2-low* advanced breast cancer and will most likely lead to a change in clinical practice for several reasons. T-Dxd is the first drug with proven efficacy in the *HER2-low* environment, already commercially available and included in the US guidelines for the treatment of breast cancer. Patients with advanced disease defined as HER2 negative will potentially need to be retested in the future to receive T-Dxd as a useful therapeutic option.

Trastuzumab-duocarmazine (SYD985)

Trastuzumab-duocarmazine (SYD985) is a newer antibody-drug conjugate where trastuzumab serves as a carrier to which the alkylating agent duocarmazine is bonded by a soluble linker. Duocarmazine is a pro-drug (seco-duocarmycin-hydroxybenzamide-azaindole – seco-DUBA) that is released from the linker as the active DUBA toxin, which passes through the lysosomal system after internalization(25). When trastuzumab-duocarmazine is released by the breakdown of malignant cells into the interstitium, the secretion of cathepsin b is also activated. Although trastuzumab-duocarmazine also has a low drug-antibody ratio (2.8:1), in *HER2-low* xenograft models it proved to be significantly more effective than T-DM1(26).

Bi-specific Antibodies

By binding to two different epitopes, bi-specific antibodies can inhibit multiple oncogenic pathways, they lead to interaction between tumor cells and the immune system and/or deliver cytostatics to the tumor microenvironment. Several bi-specific antibodies are in development, and only a small part of them are being investigated in *HER2-low* disease(27, 28). In preclinical and early clinical trials, ZW25, which targets domains 2 and 4 of the HER2 receptor ZW49, ertumaxomab, GBR1302 and other bi-specific antibodies, are being tested for this population(28).

Bearing in mind the fact that most patients from the *HER2-low* group have expressed hormone receptors and the fact that the bidirectional connection of ER and HER2/HER3 receptors can promote endocrine resistance, the combination of the bi-specific antibody zenocutuzumab in combi-

nation with endocrine therapy was researched. Zenocutuzumab is a humanized monoclonal IgG1 antibody that binds to HER2 receptor domain 1 and blocks domain III of the HER3 receptor, leading to prevention of HER2/HER3 heterodimerization and consequent blockade of the signalling pathway(27). This feature is much more pronounced than in pertuzumab. A phase II clinical trial (N=50) in pretreated *HER2-low* ER-positive patients who had previously received CDK4/6i, the use of zenocutuzumab showed in 8 of them rates of clinical benefit after 24 weeks, while one patient had a partial long-term response(29).

Tumor Vaccines

Tumor vaccines, as is known, aim to prevent a tumor or treat it by enhancing the body's immune response. In the context of breast cancer, vaccines have been investigated mainly in early-stage breast cancer. Based on the fact that most breast cancer cells express a certain level of HER2 receptor, much higher than normal breast cells, HER2 vaccines were tested in HER2-positive and *HER2-low* patients (27). For now, we have the results of phase III clinical research in early-stage breast cancer, while research in metastatic *HER2-low* breast cancer is still in the preclinical and early clinical phase(27).

HER2-low Advanced Breast Cancer Treatment with Different Drug Combinations

In an attempt to achieve the best possible results in the treatment of *HER2-low* breast cancer, along with anti-HER2 drugs, checkpoint inhibitors, endocrine therapy and CDK4/6 inhibitors are combined in clinical research(28).

Immunotherapy

HER2-positive tumors are considered to have a higher number of tumor-infiltrating lymphocytes, a higher expression of PD-L1 (programmed cell death ligand 1), and a higher mutational load compared to luminal tumors. On the other hand, cytotoxicity mediated by antibodies is crucial in modulating the activity of trastuzumab(27). Preclinical studies have shown that the addition of drugs that target immune system checkpoints can overcome resistance to trastuzumab(30). Preclinical studies have shown that T-Dxd increases the expression of dendritic cells, increases the number of CD8+ T lymphocytes, and increases the expression of PD-L1 and MHC I on tumor cells. Furthermore, it was shown in mouse models that combination therapy of T-Dxd and anti-PD1 antibodies was more effective, probably due to increased T-cell activity and PD-L1 expression induced by T-Dxd(31).

T-Dxd was studied in combination with the anti-PD-1 drug nivolumab and with the anti-PD-L1 drug durvalumab in the clinical trial phase-Ib/II (BEGONIA), which consists of 2 parts and several study groups, and refers to the first-line treatment of triple-negative breast cancer with various combinations of durvalumab, paclitaxel and other newer drugs. In group VI the patients received durvalumab+T-Dxd; however, they could have had *HER2-low* status. At the time of data analysis (March 2021), 19 of the 21 patients included in the specified group of the study were receiving study treatment; median follow-up time was 3.6 months (0-9). The objective response rate was 66% (8/12). No dose-dependent toxicity was observed. The response rate did not depend on the level of PDL1 expression(31).

In the Phase Ib Study DS8201-A-U105, which consisted of 2 parts, patients with HER2-positive (N=32) and *HER2-low* (N=16) tumors were treated with a combination of nivolumab and T-Dxd. Median follow-up was 18.7 months for HER2-positive and 12.7 months for *HER2-low*. Overall response rate was 65.5% (95%CI:46.8-81.4) and 50% (95%CI: 24.7-75.3), median progression-free survival was 11.6 months (95%CI:6.9-NE) and 7 months (95%CI: 2.3-10.8) (32). Although the study showed a certain antitumor activity of the mentioned treatment, the data coming from the very small *HER2-low* subgroup are not sufficient to define the effect of PD-1/PD-L1 combination therapy in the mentioned group(32).

CONCLUSION

Up to 60% of advanced breast cancer includes a newer clinical-biological entity, *HER2-low* breast cancer, within which hormone-dependent tumors dominate quantitatively, while a group of triple-negative tumors, very different in clinical behaviour, treatment methods and outcomes, is rarer. Advanced *HER2-low* tumors are treated with sequential chemotherapy after exploration of relatively few targeted biological treatment options. Due to the need to improve treatment outcomes,

anti-HER2 therapy such as anti-HER2 antibodies, bispecific antibodies, combinations with checkpoint inhibitors and antibody-drug conjugates are also being investigated. The latter are the only ones so far tested in randomized phase III studies. The encouraging results of the DESTINY-breast04 study showed a significant prolongation of survival without disease progression and overall survival in pretreated patients with *HER2-low* hormone-dependent breast cancer and thus opened a completely new perspective in the treatment of this group of patients. It is also necessary to monitor patients carefully and in time for obvious unwanted consequences, primarily pneumonitis. It is extremely important to redefine HER2 positivity, because a binary classification in the sense of positive/negative will no longer be sufficient, but a clearer determination of the level of expression will be necessary.

REFERENCES

1. Mendes D, Alves C, Afonso N, Cardoso F, Passos-Coelho JL, Costa L, et al. The benefit of HER2-targeted therapies on overall survival of patients with metastatic HER2-positive breast cancer – a systematic review. Breast Cancer Res. 2015;17(1):140. doi: 10.1186/s13058-015-0648-2
2. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002;20(3):719-26. doi: 10.1200/JCO.2002.20.3.719
3. Giuliani S, Ciniselli CM, Leonardi E, Polla E, Decarli N, Luchini C, et al. In a cohort of breast cancer screened patients the proportion of HER2 positive cases is lower than that earlier reported and pathological characteristics differ between HER2 3+ and HER2 2+/Her2 amplified cases. Virchows Archiv. 2016;469(1):45-50. doi: 10.1007/s00428-016-1940-y
4. Schettini F, Chic N, Brasó-Maristany F, Paré L, Pascual T, Conte B, et al. Clinical, pathological, and PAM50 gene expression features of *HER2-low* breast cancer. NPJ Breast Cancer. 2021;7(1):1. doi: /10.1038/s41523-020-00208-2
5. 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. Arch Path Lab Med. 2018;142(11):1364-82. doi: 10.5858/arpa.2018-0902-SA
6. Gilcrease MZ, Woodward WA, Nicolas MM, Corley LJ, Fuller GN, Esteva FJ, et al. Even Low-level HER2 expression may be associated with worse outcome in node-positive breast cancer. Am J Surg Pathol. 2009;33(5):759-67. doi: 10.1097/PAS.0b013e31819437f9
7. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321(3):288-300. doi: 10.1001/jama.2018.19323
8. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-49. doi: 10.1016/j.annonc.2020.09.010
9. Ross JS, Fletcher JA, Linette GP, Stec J, Clark E, Ayers M, et al. The HER-2/neu gene and protein in breast cancer 2003: biomarker and target of therapy. Oncologist. 2003;8(4):307-25. doi:10.1634/theoncologist.8-4-307
10. Eggemann H, Ignatov T, Burger E, Kantelhardt EJ, Fettke F, Thomssen C, et al. Moderate HER2 expression as a prognostic factor in hormone receptor positive breast cancer. Endocr Relat Cancer. 2015;22(5):725-33. doi: 10.1530/ERC-15-0335
11. Perez EA, Romond EH, Suman VJ, Jeong J-H, Sledge G, Jr CEG, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2–positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744-52. doi: 10.1200/JCO.2014.55.5730
12. Paik S, Kim C, Wolmark N. HER2 status and benefit from adjuvant trastuzumab in breast cancer. N Engl J Med. 2008;358(13):1409-11. doi: 10.1056/NEJMc0801440
13. Perez EA, Reinholz MM, Hillman DW, Tenner KS, Schroeder MJ, Davidson NE, et al. HER2 and chromosome 17 effect on patient outcome in the n9831 adjuvant trastuzumab trial. J Clin Oncol. 2010;28(28):4307-15. doi 10.1200/JCO.2009.26.2154
14. Fehrenbacher L, Cecchini RS, Jr CEG, 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. doi: 10.1200/JCO.19.01455
15. Eiger D, Pondé NF, Azambuja Ed. Pertuzumab in HER2-positive early breast cancer: current use and perspectives. Future Oncol. 2019;15(16):1823-43. doi: 10.2217/fon-2018-0896
16. Gianni L, Lladó A, Bianchi G, Cortes J, Kellokumpu-Lehtinen P-L, 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. doi: 10.1200/JCO.2009.24.1661
17. Bang YJ, Giaccone G, Im SA, Oh DY, Bauer TM, Nordstrom JL, et al. First-in-human phase 1 study of margetuximab (MGAH22), an Fc-modified chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors. Ann Oncol. 2017;28(4):855-61. doi: 10.1093/annonc/mdx002

18. 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. doi: 10.1200/JCO.2010.29.5865
19. Krop IE, LoRusso P, Miller KD, Modi S, Yardley D, Rodriguez G, et al. A Phase II Study of Trastuzumab Emtansine in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer Who Were Previously Treated With Trastuzumab, Lapatinib, an Anthracycline, a Taxane, and Capecitabine. J Clin Oncol. 2012;30(26):3234-41. doi: 10.1200/JCO.2011.40.5902
20. Le Joncour V, Martins A, Puhka M, Isola J, Salmikangas M, Laakkonen P, et al. A novel anti-HER2 antibody–drug conjugate XMT-1522 for HER2-positive breast and gastric cancers resistant to trastuzumab emtansine. Mol Cancer Ther. 2019;18(10):1721-30. doi: 10.1158/1535-7163.MCT-19-0207
21. 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. doi: 10.1158/1078-0432.CCR-15-2822
22. 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. doi: 10.1200/JCO.19.02318
23. Modi S, Saura C, Yamashita T, Park YH, Kim S-B, Tamura K, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2019;382(7):610-21. doi: 10.1056/NEJMoa1914510
24. 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 doi: 10.1056/NEJMoa2203690
25. Staudacher AH, Brown MP. Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required? Br J Cancer. 2017;117(12):1736-42. doi: 10.1038/bjc.2017.367
26. van der Lee MMC, Groothuis PG, Ubink R, van der Vleuten MAJ, van Achterberg TA, Loosveld EM, et al. The preclinical profile of the duocarmycin-based HER2-targeting ADC SYD985 predicts for clinical benefit in low HER2-expressing breast cancers. Mol Cancer Ther. 2015;14(3):692-703. doi: 10.1158/1535-7163.MCT-14-0881-T
27. Tarantino P, Hamilton E, Tolaney SM, Cortes J, Morganti S, Ferraro E, et al. HER2-low breast cancer: pathological and clinical landscape. J Clin Oncol. 2020;38(17):1951-62. doi: 10.1200/JCO.19.02488
28. Eiger D, Agostinetto E, Saúde-Conde R, de Azambuja E. The exciting new field of HER2-low breast cancer treatment. Cancers (Basel). 2021;13(5). doi: 10.3390/cancers13051015
29. Pistilli B, Wildiers H, Hamilton EP, Ferreira AA, Dalenc F, Vidal M, et al. Clinical activity of MCLA-128 (zenocutuzumab) in combination with endocrine therapy (ET) in ER+/HER2-low, non-amplified metastatic breast cancer (MBC) patients (pts) with ET-resistant disease who had progressed on a CDK4/6 inhibitor (CDK4/6i). J Clin Oncol. 2020;38(15_suppl):1037-. doi: 10.1200/jco.2020.38.15_suppl.1037
30. Loi S, Giobbe-Hurder A, Gombos A, Bachelot T, Hui R, Curigliano G, et al. Abstract GS2-06: Phase Ib/II study evaluating safety and efficacy of pembrolizumab and trastuzumab in patients with trastuzumab-resistant HER2-positive metastatic breast cancer: Results from the PANACEA (IBCSG 45-13/BIG 4-13/KEYNOTE-014) study. Cancer Res. 2018;78(4_Suppl):GS2-06. doi: 10.1158/1538-7445.SABCS17-GS2-06
31. Iwata TN, Ishii C, Ishida S, Ogitani Y, Wada T, Agatsuma T. A HER2-targeting antibody–drug conjugate, trastuzumab deruxtecan (DS-8201a), enhances antitumor immunity in a mouse model. Mol Cancer Ther. 2018;17(7):1494-503. doi: 10.1158/1535-7163.MCT-17-0749
32. Hamilton EP, Shapiro CL, Boni V, Martin M, Del Conte G, Agrawal L, et al. 162O Primary analysis from DS8201-A-U105: A 2-part, open label, phase Ib trial assessing trastuzumab deruxtecan (T-DXd) with nivolumab (nivo) in patients (pts) with HER2-expressing advanced breast cancer. Ann Oncol. 2022;33:S196. doi: 10.1016/j.annonc.2022.03.181

Sažetak

HER2-LOW NAPREDNO LIJEČENJE RAKA DOJKE

M. Ban, E. Vrdoljak

Stanice karcinoma dojke na svojim membranama mogu imati različitu razinu ekspresije HER2 receptora. HER2 signalni put važan je za rast tumora i metastaze. Bolesnice s HER2 pozitivnom bolešću imale su lošije ishode liječenja sve dok nije uvedena upotreba trastuzumaba, a potom i drugih anti-HER2 lijekova. Do sada su se koristili isključivo za jaku ekspresiju HER2 receptora. Razvojem novih lijekova, prije svega konjugata protutijelo-citostatik, dokazana je učinkovitost djelovanja na tumorske stanice koje imaju niže razine HER2 receptora, danas poznatih kao *HER2-low* tumori. Budući da su rezultati studije DESTINY Breast04 pokazali produljenje preživljenja bez progresije bolesti i ukupnog preživljenja u prethodno liječenih pacijenatica s *HER-low* tumorima, otvaraju se nove mogućnosti, kako u liječenju, tako i u testiranju HER2 receptora.

KLJUČNE RIJEČI: *karcinom dojke; uznapredovali; HER2-low; liječenje*