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REVIEW ARTICLE

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HER2-low — the new subtype of breast cancer?

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ABSTRACT

In the recent years, intensive research has been carried out on the use of targeted therapy against HER2 receptor in patients with the currently recognized HER2-negative breast cancer. The first results of studies with new generation conjugates are promising in the group of patients with HER2-low breast cancer (HER2 expression 1+ or 2+ in immunohistochemistry with negative FISH). This article summarizes the available data on this potentially new group of breast cancer that is now part of the luminal and triple-negative breast cancers. Data on clinical features of HER2-low cancer are discussed, as well as the results of clinical trials with anti-HER2 therapy in these patients are summarized. The efficacy of the new generation conjugates was recorded. The results of ongoing studies with these drugs may allow to use anti-HER2 therapy in a wider group of patients, including ones with HER2-low cancers. The new concept of "HER2-low" breast cancer will force a revision of the current division of breast cancer depending on HER2 expression into only two groups, introducing an intermediate group with low HER2 expression

Key words: HER2, HER2-low breast cancer, conjugate, breast cancer subtype

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Introduction

In breast cancers, 5 standard subtypes are distinguished: luminal A, luminal B, HER2-positive luminal, HER2-positive non-luminal, and triple-negative (TNBC). The original classification was created over 20 years ago and was based on the results of molecular analyses [1]. Subsequently, surrogates were elaborated, they are the results of immunohistochemical staining (IHC) evaluating the expression of estrogen receptor (ER), progesterone receptor (PgR), the receptor of the human epidermal growth factor 2 (HER2), and the Ki-67 proliferation index. Classification of breast cancer subtypes has been modified in recent years, especially in the group of luminal cancers. The changes were due, to a large extent, to increasing access to genetic tests evaluating the molecular subtype of breast cancers. However, in many countries (including Poland) it is standard practice to evaluate the subtype based on the expression of above-mentioned receptors, and this evaluation is the basis for therapeutic decisions [2].

The HER2 receptor

The discovery of the significance of HER2 protein expression in the 1980s was of great importance [3]. On a normal cell, there are about 20 000 HER2 receptors. However, when the expression is up-regulated or the HER2 gene amplified, the number of receptors on the cells increases considerably and is over 2 000 000 [4].

A poorer prognosis has been demonstrated for patients with HER2-positive cancer [5]. The introduction of anti-HER2 therapy, in subsequent years, was a breakthrough. The first pioneering drug was trastuzumab, and in the following years, lapatinib, pertuzumab, and ado-trastuzumab emtansine (T-DM1) were introduced. The achievements of the last years are trastuzumab deruxtecan (T-DXd) and tucatinib [6]. The results of treatment of HER2-positive breast cancer patients have been significantly increased by adding tucatinib to trastuzumab and capecitabine or the use of T-DXd [7–9]. The therapy with various anti-HER2 drugs, which leads to

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a constant blocking of the HER2 pathway, significantly improves the results of treatment.

New breast cancer classification depending on the intensity of HER2 expression

Standard anti-HER2 treatment is dedicated to patients in whom excessive expression 3+ of the HER2 receptor or amplification of the HER2 gene is observed by FISH [10]. HER2-positive cancers are estimated to be about 15% of all breast cancers [11]. The remaining cases are considered HER2-negative breast cancers. The commonly accepted group of HER2-negative breast cancers includes "true" cancers without HER2 expression (in IHC analysis — result 0) and cancers with low HER2 expression (HER2-low). Breast cancers with low HER2 expression are diagnosed in the case of HER2 expression evaluated by IHC of 1+ or 2+ without HER2 gene amplification. Tarantino et al. showed that true HER2-negative cancers constitute 30–40%, whereas cancers with low HER2 expression make up 45–55% of breast cancers [10]. Researchers have proposed a new diagnostic algorithm for breast cancers depending on the results of HER2 expression evaluated by IHC and FISH (Fig. 1). Thus triple-negative and luminal breast cancers are included in the group of cancers with low HER2 expression.

It is worth observing that many researchers point out the divergence in the results of evaluating HER2 expression. In one analysis performed centrally, in patients in whom no HER2 expression was noted (IHC was 0) in local assessment, in as many as 85% of cases the result was changed to 1+ or 2+ [12]. These data indicate the need for more precise HER2 evaluation, especially that in clinical practice there will be a necessity to distinguish a new group of cancers with low HER2 expression.

Prognostic value of HER2-low

Reports on the prognostic value of low HER2 expression are equivocal, and there is only a limited number of publications.

Schettini et al. presented a retrospective analysis of 3689 patients with HER2-negative breast cancer [13]. The percentage of breast cancers with a low HER2 expression was found to be statistically significantly higher in patients with luminal cancers (65.4%) in comparison with triple-negative cancers (36.6%) ($p < 0.001$). No difference was observed in the survival of patients with advanced breast cancer depending on the intensity of HER2 expression (no expression in comparison with low HER2 expression) in cancers commonly qualified as HER2-negative.

Denkert et al. [14] performed an analysis of 2310 patients with early HER2-negative breast cancer treated with preoperative chemotherapy in 4 clinical trials. Data concerning recurrences and survival were available for 1694 patients from 3 trials. In the case of 47.5% of cancers low HER2 expression was observed and in the remaining 52.5% no HER2 expression was detected. Very similar percentages of patients with particular

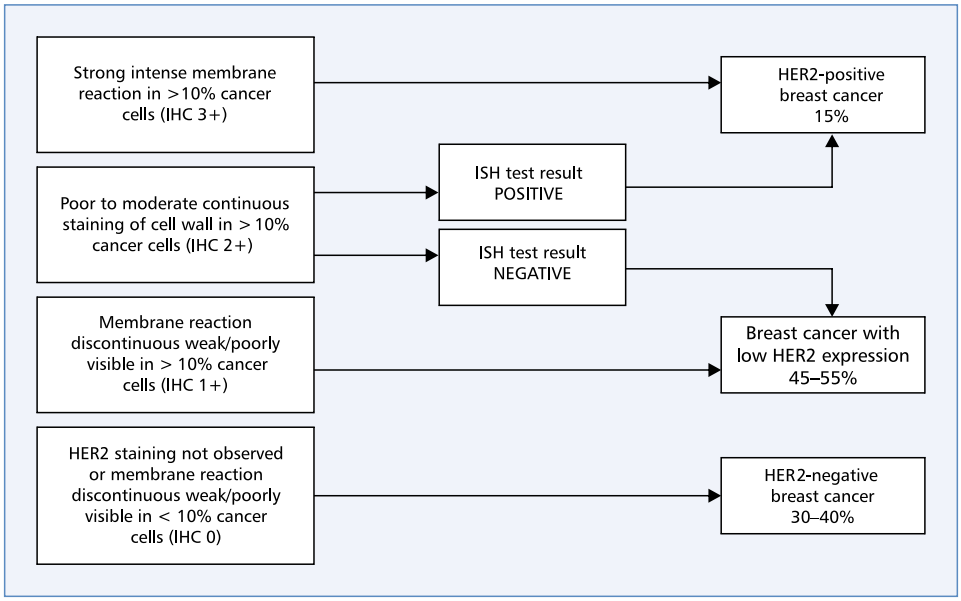

Figure 1. The proposed algorithm for breast cancer classification depending on the intensity of HER2 expression – elaborated on the basis of Tarantino et al. [11]

Table 1. Summary of data on breast cancer with low HER2 expression

Breast cancer HER2-low
Definition: HER2 expression evaluated by IHC as 1+ or 2+ without *HER2* amplification
Detected in 45–55% of breast cancers
Currently, this group includes triple-negative and luminal breast cancers
Found in 2/3 luminal and 1/3 TNBC
Retrospective analyses indicate an equivocal prognostic significance
Promising results of trials with new generation anti-HER2 conjugates

TNBC — triple-negative breast cancers

results of HER2 expression were observed as in the previous analysis [13]. Low HER2 expression was observed in 61.2% luminal cancers and in 34% triple-negative cancers ($p < 0.001$). A significantly lower percentage of pathological complete response (pCR) was observed in cancers with low HER2 expression (29.2% *vs.* 39.0%; $p = 0.0002$). The percentages of pCR in patients with luminal breast cancers were significantly lower in the case of low HER2 expression as compared to the group without HER2 expression (17.5% *vs.* 23.6%; $p = 0.024$). However, this was not observed in patients with TNBC (pCR was, respectively, 50.1% *vs.* 48.0%; $p = 0.21$). The authors of the analysis found a significantly better prognosis for patients with breast cancer with low HER2 expression in comparison with cancers without HER2 expression — 3-year disease-free survival (DFS) was 83.4% [95% confidence interval (CI): 80.5–85.9] *vs.* 76.1% (95% CI 72.9–79.0); respectively, $p = 0.0084$. Three-year overall survival (OS) was 91.6% (84.9–93.4) *vs.* 85.8% (83.0–88.1); $p = 0.0016$. The observation concerned patients with TNBC, for whom 3-year DFS were 84.5% (95% CI: 79.5–88.3) and 74.4% (70.2–78.0); $p = 0.0076$, respectively; and 3-year OS were 90.2% (86.0–93.2) *vs.* 84.3% (80.7–87.3); $p = 0.016$, but not in patients with luminal breast cancers (3-year DFS — 82.8% [79.1–85.9] *vs.* 79.3% [73.9–83.7]; $p = 0.39$; and 3-year OS — 92.3% [89.6–94.4] *vs.* 88.4% [83.8–91.8]; $p = 0.13$) [14].

The results of another interesting study evaluated the outcome of 608 patients with early ER-positive HER2-negative breast cancer were published. The effect of the strength of HER2 expression was analyzed (0 vs. low expression). In lobular cancers, the absence of HER2 (17% *vs.* 8%, $p = 0.005$) was significantly more common. In the whole analyzed population, no differences were observed in the prognoses of patients depending on the level of HER2 expression. However in the group with high recurrence risk in OncotypeDx, distant results were better in the case of low HER2 expression — a benefit was noted in the form of decreased risk in DFS by 60% (95% CI 0.20–0.82, $p = 0.01$), distant disease-free survival (DDFS) by 74% (95% CI: 0.11–0.63, $p = 0.002$), and OS by 69% (95% CI: 0.11–0.78, $p = 0.01$) compared to patients without HER2 [15].

In the next retrospective analysis evaluating the outcome of 2864 patients [16], a higher risk for brain metastases was observed for patients with low HER2 expression in comparison with cancers without the expression of this receptor ($p = 0.027$). This finding was particularly true for patients with hormone-dependent breast cancer. After a median time of follow-up of 95.4 months, the percentages of patients who had brain metastases depending on HER2 expression were 5.1% in patients without HER2 expression (IHC 0), 8.5% in the group with low HER2 expression, and 10.1% in patients with HER2-positive breast cancer [16].

Summing up, further research is necessary for evaluating the prognostic value of low HER2 expression.

In Table 1, the most important data on breast cancer with low HER2 expression are presented.

Classical anti-HER2 drugs in HER2-low breast cancer

The distinguishing of a new group of HER2-low breast cancers was due to the demands of the planned clinical trials. The interest in trastuzumab treatment in HER2-negative breast cancers was based on the results of additional analyses on trastuzumab used in adjuvant treatment. The benefits of its use were also demonstrated in the group of patients treated in clinical trials in whom, in a central analysis, HER2-negative breast cancer was diagnosed [17, 18]. Additional studies were planned to check the value of classical anti-HER2 drugs in HER2-negative breast cancers. Recently the results of clinical trial B-47 (National Surgical Adjuvant Breast and Bowel Project) were published, in which the experimental group, consisting of patients with HER2-negative breast cancer with a high recurrence risk, received additionally trastuzumab for 12 months besides chemotherapy. As many as 3270 patients with breast cancer with low HER2 expression (HER2-low) were included in the trial. After 46 months (median) of follow-up no difference was observed in the 5-year

invasive DFS (89.8% in the experimental arm and 89.2% in the control arm; p = 0.85). Similarly, trastuzumab therapy did not improve distant recurrences and OS [19].

A clinical trial was conducted using conjugates in breast cancer with low HER2 expression. Conjugates are composed of 3 parts: a monoclonal antibody directed against HER2, a load in the form of cytotoxic drug molecules, and linkers. The monoclonal antibody attaches to receptors on cancer cells, and the cytotoxic drug enters the cell. This form of targeted chemotherapy limits the effects of anti-cancer therapy on healthy tissues and, at the same time, increases the therapeutic index of the drug on breast cancer cells. This idea is very interesting. In recent years, many conjugates directed against various antigens have been tested.

The results of the first retrospective analyses suggested the limited effectiveness of T-DM1 in patients with low HER2 expression. Studies were performed in two phase II clinical trials (trial 4258g and 4374g) on the use of T-DM1 in HER2-positive breast cancer [20, 21]. As a result of the central evaluation of HER2, a cohort of patients with cancers with low HER2 expression was distinguished. The overall response rate (ORR) was significantly higher in HER2-positive cancers in comparison with cancers with low HER2 expression (respectively: 33.8% *vs.* 4.8% in trial 4258g and 41.3% *vs.* 20.0% in trial 4374g). Similar results with respect to progression-free survival (PFS) were better in the group of HER2-positive cancers (8.2 *vs.* 2.6 months in trial 4258g and 7.3 *vs.* 2.8 months in trial 4374g). The above data indicated the limited effectiveness of T-DM1 in cancers with low HER2 expression.

New anti-HER2 conjugates in HER2-low breast cancer

Further work with new anti-HER2 conjugates led to even more encouraging results. The effectiveness and toxicity profile for these drugs had been evaluated in HER2-positive cancers [8, 9, 22]. Two clinical phase I trials were performed with the new generation conjugates in the group of patients with low HER2 expression.

The first trial included 99 patients with breast cancer after many lines of treatment (including 47 patients with breast cancer with low HER2 expression). In that trial, trastuzumab duocarmazine (SYD-985) was used, which includes a cytotoxic alkylating drug. The response to treatment was similar in the groups, regardless of the intensity of HER2 expression. ORR in the group with low HER2 expression was 32% (exclusively partial responses) and, in the group with excessive HER2 expression, it was 33%. Additionally in the group with low HER2 expression, 2 subgroups were distinguished depending on the hormone receptor expression. ORR was 28% and 40% in the group with luminal breast cancer and in TNBC, respectively, and median PFS were 4.1 and 4.9 months, respectively. Adverse effects were observed (including frequent eye disorders: conjunctivitis, dry eye syndrome, increased tear production) [23].

In the second trial, the effectiveness of T-DXd in treating breast cancer with low HER2 expression was evaluated. Fifty-four patients with metastatic breast cancer after many lines of treatment were included in the trial. ORR was 37%, and the median time of response was 10.4 months. Median PFS was 11.1 months, and median OS attained 29.4 months. In the trial, there was no control arm with HER2-positive breast cancers, in contrast to the trial of Banerji et al. discussed above [23, 24].

The results of the most important studies with anti-HER2 drugs in breast cancer with low HER2 expression are summarized in Table 2.

Basic research on new generation conjugates indicates their innovative mechanism of action. HER2 receptors are the site of attachment of the monoclonal antibody (trastuzumab) which is part of the conjugate, and next the attached cytotoxic drug enters the cancer cell and destroys it. In the case of SYD-985, the drug to antibody ratio (DAR) is 2.8:1, and for T-DXd it is much larger and is 7.8:1. It is worth underlining that in the case of SYD-985 and T-DXd, basic research indicated there was a phenomenon based on the destruction of neighboring cancer cells regardless of the level of expression of the HER2 receptor on their surface (bystander effect). This is caused by the molecules of the charge, which is a cytotoxic drug, penetrating from destroyed cells showing HER2 expression to the neighboring cells. Thus, the pool of destroyed neoplastic cells is considerably larger [11].

The results of the trials discussed above and the idea of a unique mechanism of action of new generation conjugates contributed to the planning of large clinical trials evaluating the effectiveness of such a therapy for patients with breast cancers with low HER2 expression. Several clinical trials with patients with triple-negative or luminal breast cancer with low HER2 expression are ongoing. The effectiveness of T-DXd in monotherapy or combined with immune therapy is being studied. The results of the mentioned trials may affect the strategy of treating patients with breast cancer, as HER2 expression is found altogether in 60–70% of patients [11]. In the case of positive results of the conducted trials, a new category of HER2-low breast cancers will have to be distinguished.

Conflict of interest

KP: Honorarium for consultations/lectures/training/clinical trials and payment of conferences fees:

Table 2. Summary of results of trials with anti-HER2 drugs in breast cancer with low HER2 expression

Trial	Investigated drug	Population	Number of patients	Results
NSABP B-47 [19]	Trastuzumab	Early HER2-negative breast cancer with high recurrence risk	3270	5-year iDFS: 89.8% *vs.* 89.2%. HR = 0.98; 95% CI: 0.76–1.25; p = 0.85; 5-year OS: 94.8% *vs.* 96.3%. HR = 1.33; 95% CI: 0.90–1.95; p = 0.15
4258g [20]	Trastuzumab emtansine (T-DM1)	HER2-positive breast cancer (also with low HER2 expression in central evaluation)	112 (including 21 patients with breast cancer with low HER2 expression)	ORR: 4.8% (95% CI: 1.0–21.8%) *vs.* 33.8% (95% CI: 23.2–44.9%) Median PFS: 2.6 months (95% CI: 1.4–3.9 months) *vs.* 8.2 months (95% CI: 4.4 months–not reached)
4374g [21]	Trastuzumab emtansine (T-DM1)	HER2-positive breast cancer (also cancers with low HER2 expression after repeated evaluation)	110 (including 15 patients with breast cancer with low HER2 expression)	ORR: 20% (95% CI: 5.7–44.9) *vs.* 41.3% (95% CI: 30.4–52.8) Median PFS: 2.8 months (95% CI: 1.3–not reached) *vs.* 7.3 (95% CI: 4.6–12.3)
Banjeri et al. [23]	Trastuzumab duocarmazine (SYD-985)	Various advanced cancers with low HER2 expression	146 (including 47 patients with breast cancer with low HER2 expression)	ORR: cancers ER+ HER2-low: 28% (95% CI: 13.8–46.8%). cancers ER-HER2-low: 40% (95% CI: 16.3–67.6%); median PFS approx. 4 months
Modi et al. [24]	Trastuzumab deruxtecan (T-DXd)	Breast cancer with low HER2 expression after several lines of treatment	54	ORR: 37% (95% CI: 24.3–51.3%) Median DoR: 10.4 months (95% CI: 8.8 months–not reached); median PFS 11.1 months, median OS 29. 4 months

CI — confidence interval; DFS — disease-free survival; DoR — duration of response; HR — hazard ratio; ORR — overall response rate; OS — overall survival; PFS — progression-free survival

Roche, Novartis, Eli Lilly, Pfizer, MSD, AstraZeneca, Gilead, Teva, Egis, Vipharm.

AJG: Honorarium for consultations/lectures/training/clinical trials: AstraZeneca, Novartis, Roche, Gilead, Eli Lilly, Amgen, Pfizer, MSD.

ZN: Honorarium for consultations/lectures/training/clinical trials: Roche.

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