Esteva *et al. J Cancer Metastasis Treat* 2023;9:39
DOI: 10.20517/2394-4722.2023.124

Journal of Cancer Metastasis and Treatment

Perspective

Open Access

Check for updates

HER2-low metastatic breast cancer: molecular insights and therapeutic strategies

Francisco J. Esteva[1], **Shabnam Jaffer**[2]

[1]Division of Hematology and Medical Oncology, Lenox Hill Hospital, New York, NY 10065, USA.
[2]Department of Pathology, Lenox Hill Hospital, New York, NY 10065, USA.

Correspondence to: Dr. Francisco J. Esteva, Division of Hematology and Medical Oncology, Lenox Hill Hospital, 210 East 64th Street, New York, NY 10065, USA. E-mail: festeva@northwell.edu

How to cite this article: Esteva FJ, Jaffer S. HER2-low metastatic breast cancer: molecular insights and therapeutic strategies. *J Cancer Metastasis Treat* 2023;9:39. https://dx.doi.org/10.20517/2394-4722.2023.124

Received: 7 Oct 2023 **First Decision:** 18 Oct 2023 **Revised:** 5 Nov 2023 **Accepted:** 29 Nov 2023 **Published:** 30 Nov 2023

Academic Editors: Christos Papadimitriou, Andrea Nicolini **Copy Editor:** Fangyuan Liu **Production Editor:** Fangyuan Liu

Abstract

The identification of HER2-low metastatic breast cancer as a novel subgroup with therapeutic implications underscores the intricacies in breast cancer classification. This subset, comprising 45%-60% of breast cancer cases, presents a challenge due to its heterogeneous nature, characterized by varying HER2 protein expression levels. This heterogeneity complicates diagnosis and treatment decisions. The advent of trastuzumab deruxtecan (T-DXd), a second-generation antibody-drug conjugate (ADC), instills renewed hope for HER2-low breast cancer patients, having demonstrated effectiveness in clinical trials. The article also explores the evolution of HER2 testing guidelines, notably the 2023 ASCO/CAP guidelines that acknowledge the potential benefits of HER2-targeted therapies for this subgroup. In summary, this article emphasizes the significance of collaborative efforts between Pathologists and Oncologists in the era of precision medicine. It also highlights the potential for innovative, tailored therapies for HER2-low breast cancer, promising enhanced treatment outcomes and a broader range of therapeutic options.

Keywords: HER2-low breast cancer, heterogeneity, trastuzumab deruxtecan (T-DXd), HER2 testing guidelines, precision medicine, therapeutic strategies, immunohistochemistry, *in situ* hybridization.

INTRODUCTION

Human Epidermal Growth Factor Receptor 2 (HER2) is a tyrosine kinase encoded by the *Erb*B2 gene

located on chromosome 17q12[1,2]. HER2 plays a pivotal role in cellular signaling pathways that regulate key processes such as proliferation, differentiation, and survival[3]. HER2 is amplified or overexpressed in 15%-20% of invasive breast cancers, leading to the promotion of angiogenesis, enhanced invasion capabilities, and an increased propensity for metastasis[4-6].

The development of trastuzumab monoclonal antibody therapy represented a paradigm shift from non-specific chemotherapy to an era of targeted therapeutic interventions in breast cancer[7-9]. Since the original approval of trastuzumab in 1998 we have witnessed the successful development of additional HER2-targeted therapies, including monoclonal antibodies, tyrosine kinase inhibitors, and antibody-drug conjugates (ADCs)[10-18]. The emergence of trastuzumab deruxtecan (T-DXd) has sparked renewed hope for treating not only patients with HER2-positive breast cancer but also patients whose tumors express low levels of HER2[19].

HER2-Low breast cancer is defined by HER2 immunohistochemistry (IHC) score of 1+ or 2+ and negative *in situ* hybridization (ISH)[20,21]. This category accounts for approximately 45%-60%, of all invasive breast cancer cases[22,23]. HER2-low tumors comprise a heterogeneous group of tumors at a clinical, morphological, immunohistochemical, and molecular level. Thus, it is to be expected that studies examining the prognostic significance of HER2-low in breast cancer patients show conflicting results. Discrepancies in these studies maybe due to heterogeneity in patient populations, therapies, and HER2 assessments. Nevertheless, most studies show that in both early and advanced stages of breast cancer, HER2-low was associated with better disease-free survival, overall survival, and lower Oncotype DX recurrence scores, regardless of hormone status[24]. However, HER2-low tumors exhibited lower rates of pCR in the ER+ group but not in the triple negative tumors, compared to HER2 0.

CLINICAL DEVELOPMENT OF ANTI-HER2 THERAPIES

From the early clinical development of trastuzumab, the once-explored possibility of using trastuzumab in early-stage HER2-low breast cancer was abandoned after the discouraging results of the NSABP B-47 trial[25]. This study evaluated the effectiveness of trastuzumab in patients with HER2-low breast cancer, which at the time was considered HER2-negative. The trial enrolled over 3,000 patients with high-risk early breast cancer, who were randomized to one of two groups: the control group received standard taxane-based chemotherapy and the experimental group received the same chemotherapy with a one-year trastuzumab regimen. Eligibility criteria were based on IHC scores of 1+ or 2+ with a FISH ratio less than 2.0, or, if FISH ratio data were unavailable, a HER2 gene copy number less than 4.0. After a median follow-up of 46 months, the study did not show improvement in invasive disease-free survival (IDFS) by adding trastuzumab to chemotherapy in the adjuvant setting to this population. The 5-year IDFS rates were 89.8% for the chemotherapy plus trastuzumab group and 89.2% for the chemotherapy-only group, with a hazard ratio (HR) of 0.98 (95%CI, 0.76 to 1.25; $P = 0.85$). These findings were consistent across different HER2 IHC expression levels, lymph node involvement, and hormone-receptor status. Moreover, distant disease-free survival (DFS) and overall survival (OS) rates were similar in both groups. The NSABP-B47 trial results raised questions about the universality of targeted therapies directed against HER2 across all HER2 expression levels.

CirCe T-DM1 was a phase 2 trial that failed to demonstrate T-DM1 effectiveness in HER2-negative metastatic breast cancer patients who had evidence of HER2-positive circulating tumor cells (CTC) based on HER2/CEP17 ratio of ≥ 2.2 using FISH. Out of the 11 patients who underwent T-DM1 treatment, only one experienced a confirmed partial response. Four patients exhibited disease stability. Median progression-free survival was 4.8 months, with a median OS of 9.5 months.

The introduction of trastuzumab deruxtecan (T-DXd), a second-generation anti-HER2 antibody-drug conjugate (ADC), marked a significant turning point. T-DXd incorporates trastuzumab, a cleavable peptide linker and a topoisomerase I inhibitor payload called deruxtecan[26]. In the DESTINY-Breast01 study, T-DXd demonstrated remarkable efficacy in heavily pretreated patients with HER2-positive metastatic breast cancer[27]. Retrospective studies and preclinical data suggested that T-DXd could also work in the HER2-low breast cancer setting. In an early clinical trial, Modi *et al.* reported an overall response rate of 37.0% in patients with HER2-low breast cancer, further underlining its effectiveness in this population[28].

The DAISY trial evaluated the efficacy of T-DXd in metastatic breast cancer whose tumors expressed different HER2 levels[29]. Three cohorts were selected according to HER2 score by IH: HER2 overexpressing (3+), HER2-low (1+/2+ FISH negative) and HER2 non-expressing (0) cancers, with respective response rates of 70.6%, 37.5% and 29.7%. While T-Dxd was most effective in tumors with high HER2 expression, some meaningful response was seen in tumors with low to no HER2 expression that may be explained by several hypotheses. First, HER2 0 is defined by the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) guidelines as either no staining or incomplete membrane staining that is faint/barely perceptible in ≤ 10% of tumor cells. The latter has been termed as "ultralow" by some authors[30,31] and may represent a small enough target to allow T-Dxd uptake and thus response. Second, the payload effect of T-Dxd could explain the positive response of tumors with low to no HER2 expression. Third, the HER2 value by IHC may be falsely negative for various reasons. IHC may not be sensitive enough to detect low levels of HER2 expression that require more sophisticated quantitative methods. Pre-analytic factors influence HER2 IHC results, and lack of compliance can lead to false negative results. Tumors may have intra tumoral spatial and temporal heterogeneity that can cause discrepancies and falsely negative values. The high interobserver variability amongst pathologists in discriminating between HER2 0 and 1+ can be yet another cause. Like the DAISY trial patient population, the DESTINY-Breast06 is currently investigating the role of the T-DXd ADC in patients with hormone receptor positive metastatic breast cancer that is either HER2 low or HER2 0. The results of this trial will shed light on whether we should interpret HER2 values either as a dynamic range or in a simplistic dichotomous fashion.

Moreover, T-DXd has not been the sole focus of research in this arena. Other second-generation ADCs, such as RC48, SYD985, ARX788, BL-M0701, and MRG002 have demonstrated bystander efficacy in preclinical and clinical studies, expanding the range of future therapeutic options potentially available in a variety of solid tumors with low HER2 expression. Other HER2-targeted therapies under investigation include novel monoclonal antibodies (e.g., margetuximab), bispecific antibodies (e.g., zenocutuzumab (MCLA-128), vaccines and tyrosine kinase inhibitors (e.g., tucatinib)[18]. Therapeutic agents providing clinical benefit in HER2-positive breast cancer are being explored in patients with HER2-low tumors [Table 1].

EVOLUTION OF HER2 TESTING AND CURRENT GUIDELINES

The first national guidelines for HER2 testing published by ASCO/CAP included three categories: Negative (0 and 1+), Equivocal (2+, reflex ISH testing) and positive (3+)[21]. These guidelines have been updated at regular intervals over the last two decades. In 2023, the ASCO/CAP guidelines incorporated a more granular definition of HER2-negative breast cancer, specifying whether the IHC was 0 or 1+; tumors with IHC score 2+ and ISH not-amplified remained HER2 negative. Furthermore, it was acknowledged that even tumors with low HER2 expression might be candidates for HER2-targeted therapies (e.g., T-DXd). Best practice updates assist pathologists in distinguishing HER2 0 from 1+, by paying attention to ischemic and fixation times in primary and metastatic sites, viewing IHC slides at high power, using a range of controls, and seeking consensus when necessary.

Table 1. Ongoing Studies in HER2-low locally advanced and metastatic breast cancer

Study ID	Type of study	Population	Intervention	Primary endpoint	Secondary endpoints
NCT04400695	Phase III randomized with parallel assignment	• Hormone receptor-positive subjects need to progress after receiving endocrine therapy for metastatic disease • Patients who are not suitable for endocrine therapy can be included in this study after undergoing chemotherapy (first-line or second-line) • No history of HER2 positive breast cancer, defined as IHC 3+ or FISH amplification • No history of HER2 targeted therapy	Experimental group: Disitamab vedotin (RC48-ADC) 2.0 mg/kg, intravenous drip, once every 2 weeks Control group: Physician's choice, including Paclitaxel (IV), Docetaxel (IV), Vinorelbine (IV), or Capecitabine (Oral)	PFS evaluated by an independent committee	PFS, evaluated by the investigator, ORR, DoR, DCR, TTP
NCT04742153	Phase II	• Received at least first-line standard treatment for recurrent or metastatic breast cancer	MRG002 will be administrated via intravenous infusion of 2.6 mg/kg once on Day 1 of every 3 weeks (21-day cycle)	ORR	PFSR, TTR, DoR, DCR, OS, Safety, PK, PKCS, Immunogenicity, ADA analysis
NCT05633979	Phase 1b	• HER2 low/ultra-low/null metastatic breast cancer	Valemetostat (EZH1/2 Inhibitor) in combination with Trastuzumab Deruxtecan	MTD, RDE	ORR, DoR, PFS, OS, CBR, Safety, PK, immunogenicity
NCT05814354	Randomized, open, parallel-controlled, multicenter phase III trial	• Hormone receptor positive breast cancer • At least one endocrine therapy and disease progression judged by the investigator to no longer benefit from endocrine therapy • Up to one prior line of chemotherapy in the metastatic setting; documented radiologic progression (during or after most recent treatment)	SHR-A1811 *vs.* investigator's chemotherapy (Capecitabine/Eribulin/Gemcitabine/Paclitaxel/Nab-paclitaxel)	PFS	OS, ORR, DoR, CBR
NCT05831878	Phase II	• No history of antibody-drug conjugate use • Up to one previous chemotherapy for advanced disease	Disitamab vedotin (RC48-ADC) 2.0 mg/kg, intravenous drip, once every 2 weeks	ORR	Safety and toxicity
NCT05904964	Phase II	• Measurable disease • Confirmed that ER and/or PR were positive, and HER-2 was low expression • Prior endocrine therapy	Disitamab vedotin (RC48-ADC) 2.0 mg/kg, intravenous drip, once every 2 weeks	PFS	OS, ORR, DCR, CBR, QOL, safety, biomarker analysis

ORR: Overall response rate; IRC: Independent Review Committee; CR: complete response; PR: partial response; TTP: tumor progression time; RFS: recurrence-free survival; PFS: progression-free survival; PFSR: progression free survival rate; TTR: time to response; DoR: duration of response; DCR: disease control rate; PK: pharmacokinetics; PKCS: pharmacokinetics concentration set; ADA: anti-drug antibody (ADA) analysis; MTD: maximum tolerated dose (MTD); RDE: recommended dose for expansion; CBR: clinical benefit rate; QOL: quality of life.

A challenge highlighted by practice guidelines is the discrimination between IHC 1+ and 0 results. The concordance among pathologists for distinguishing these categories is low. A study involving 18 pathologists from 15 institutions with expertise in breast cancer assessed the agreement and reliability of HER2 IHC scoring in 170 breast cancer biopsies. The results showed significant inter-observer variability, particularly in the intermediate zones (1+ and 2+), and even within the IHC 0 category[31]. Using a 3-category system improved agreement, but challenges persisted in accurately categorizing HER2-low or HER2-

negative cases[32]. This created a demand for novel sensitive quantitative assays such as, antibody bound fluorescent tags, reverse transcription polymerase chain reaction, targeted mass spectrometry, and HER2 automated image analysis, all of which are being developed and tested. In 2023, Paige received approval in the U.K. for using artificial intelligence to measure HER2 expression in cases that are negative (0) by IHC or HER2-low (IHC 1+, or IHC 2+ with ISH negative)[33].

Prior to the Destiny B04 trial, pathologists could lump all 0 and 1+ cases as negative with no incentive to separate them. Consequently, pathologists now must provide a more detailed HER2 IHC report by assigning granularity to a negative result as being either 0 or 1+. Historic reports and slides may need to be re-reviewed if this information is lacking.

IMPLICATIONS FOR THE FUTURE

The DESTINY Breast-04 study brought to recognition the concept of HER2-low tumors, a unique group within the realm of breast malignancies initiating a significant shift in clinical approaches. The 2023 ASCO/CAP guidelines for assessment of HER2 testing aim to reduce the false negative rate by decreasing inter-observer variability and artifacts from pre analytical conditions. Consequently, changes in assay validations, proficiency testing, and education of pathologists and oncologists needs to be validated and updated.

IHC and ISH are the only approved current methods for measuring HER2 expression. Admittedly IHC is limited in sensitivity prompting the discovery of innovative methods to measure the low expression of HER2 by using artificial intelligence or other testing methods (e.g., RT-PCR). This is timely as more novel ADCs for customized therapeutic approaches for previously treated metastatic HER2-low breast cancer emerge. HER2 expression is also prevalent in various other metastatic solid tumors, potentially paving the way for new treatment possibilities for patients who have few alternatives[34].

The intricate nature of HER2-low breast cancer mandates a multidisciplinary approach to patient care[13]. Efficient communication between pathologists and oncologists is indispensable for precise diagnosis, judicious selection of therapeutic modalities, and the seamless orchestration of comprehensive patient care, accounting for the nuanced attributes of the disease. The emergence of HER2-low breast cancer has brought to light the need for a patient-centric approach to diagnosis and treatment. Informed decision-making, transparent and open communication between healthcare providers and patients, along with shared decision-making, constitute integral components in navigating the complexities of HER2-low disease. Patients are encouraged to actively engage in their therapeutic regimens, comprehending the scientific rationale underpinning therapeutic choices, as well as the prospective advantages and drawbacks entailed. The definition of HER2 low will continue to evolve as the results of future clinical trials such as Destiny Breast-06 mature. The preliminary results of DAISY question the potential role for T-DXd therapy in HER2-null (0) tumors. If proven true, we may need to revert to a binary classification of HER2 (positive or negative).

The development and implementation of more sensitive and reliable testing methodology will lead to improved diagnoses, treatments, and patient outcomes for HER2-low breast cancer, emphasizing the need to integrate ongoing scientific collaboration and innovation within the fields of pathology and oncology.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception of the article: Esteva FJ, Jaffer S

Availability of data and materials
Not applicable.

Financial support and sponsorship
None.

Conflicts of interest
Esteva FJ is a consultant for AstraZeneca. Jaffer S is a consultant for AstraZeneca and Daiichi-Sankyo.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

REFERENCES
1. Schechter AL, Hung MC, Vaidyanathan L, et al. The *neu* gene: an *erb*B-homologous gene distinct from and unlinked to the gene encoding the EGF receptor. *Science* 1985;229:976-8. DOI
2. Coussens L, Yang-Feng TL, Liao YC, et al. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. *Science* 1985;230:1132-9. DOI
3. Holmes WE, Sliwkowski MX, Akita RW, et al. Identification of heregulin, a specific activator of $p185^{erbB2}$. *Science* 1992;256:1205-10. DOI
4. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/*neu* oncogene. *Science* 1987;235:177-82. DOI PubMed
5. Pritchard KI, Shepherd LE, O'Malley FP, et al; National Cancer Institute of Canada Clinical Trials Group. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J Med* 2006;354:2103-11. DOI
6. King CR, Kraus MH, Aaronson SA. Amplification of a novel v-*erb*B-related gene in a human mammary carcinoma. *Science* 1985;229:974-6. DOI
7. Baselga J, Tripathy D, Mendelsohn J, et al. Phase II study of weekly intravenous trastuzumab (Herceptin) in patients with HER2/neu-overexpressing metastatic breast cancer. *Semin Oncol* 1999;26:78-83. PubMed
8. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783-92. DOI
9. Nahta R, Esteva FJ. Herceptin: mechanisms of action and resistance. *Cancer Lett* 2006;232:123-38. DOI PubMed
10. Emens LA, Esteva FJ, Beresford M, et al. Trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo in previously treated, HER2-positive advanced breast cancer (KATE2): a phase 2, multicentre, randomised, double-blind trial. *Lancet Oncol* 2020;21:1283-95. DOI
11. Esteva FJ, Franco SX, Hagan MK, et al. An open-label safety study of lapatinib plus trastuzumab plus paclitaxel in first-line HER2-positive metastatic breast cancer. *Oncologist* 2013;18:661-6. DOI PubMed PMC
12. Morrow PK, Wulf GM, Ensor J, et al. Phase I/II study of trastuzumab in combination with everolimus (RAD001) in patients with HER2-overexpressing metastatic breast cancer who progressed on trastuzumab-based therapy. *J Clin Oncol* 2011;29:3126-32. DOI PubMed PMC
13. Nahta R, Yuan LX, Du Y, Esteva FJ. Lapatinib induces apoptosis in trastuzumab-resistant breast cancer cells: effects on insulin-like growth factor I signaling. *Mol Cancer Ther* 2007;6:667-74. DOI PubMed
14. Stebbing J, Baranau Y, Baryash V, et al. CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial. *Lancet Oncol* 2017;18:917-28. DOI
15. Esteva FJ, Hubbard-Lucey VM, Tang J, Pusztai L. Immunotherapy and targeted therapy combinations in metastatic breast cancer. *Lancet Oncol* 2019;20:e175-86. DOI PubMed
16. He X, Yeung SJ, Esteva FJ. A new paradigm for classifying and treating HER2-positive breast cancer. *Cancer Rep* 2023;6:e1841. DOI PubMed PMC
17. Hess KR, Esteva FJ. Effect of HER2 status on distant recurrence in early stage breast cancer. *Breast Cancer Res Treat* 2013;137:449-55. DOI PubMed PMC
18. Ye F, Dewanjee S, Li Y, et al. Advancements in clinical aspects of targeted therapy and immunotherapy in breast cancer. *Mol Cancer*

2023;22:105. DOI PubMed PMC

19. Modi S, Jacot W, Yamashita T, et al; DESTINY-Breast04 Trial Investigators. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med* 2022;387:9-20. DOI
20. Wolff AC, Hammond ME, Hicks DG, et al; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol* 2013;31:3997-4013. DOI
21. Wolff AC, Hammond MEH, Allison KH, 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;36:2105-22. DOI
22. Check DK, Jackson BE, Reeder-Hayes KE, et al. Characteristics, healthcare utilization, and outcomes of patients with HER2-low breast cancer. *Breast Cancer Res Treat* 2023. DOI
23. Gaudio M, Jacobs F, Benvenuti C, et al. Unveiling the HER2-low phenomenon: exploring immunohistochemistry and gene expression to characterise HR-positive HER2-negative early breast cancer. *Breast Cancer Res Treat* 2023. DOI
24. Molinelli C, Jacobs F, Agostinetto E, et al. Prognostic value of HER2-low status in breast cancer: a systematic review and meta-analysis. *ESMO Open* 2023;8:101592. DOI PubMed PMC
25. Fehrenbacher L, Cecchini RS, Geyer CE Jr, 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;38:444-53. DOI
26. Doi T, Shitara K, Naito Y, et al. Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. *Lancet Oncol* 2017;18:1512-22. DOI
27. Modi S, Saura C, Yamashita T, et al; DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med* 2020;382:610-21. DOI
28. Modi S, Park H, Murthy RK, 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;38:1887-96. DOI PubMed PMC
29. Mosele F, Deluche E, Lusque A, et al. Trastuzumab deruxtecan in metastatic breast cancer with variable HER2 expression: the phase 2 DAISY trial. *Nat Med* 2023;29:2110-20. DOI PubMed PMC
30. Venetis K, Crimini E, Sajjadi E, et al. HER2 low, ultra-low, and novel complementary biomarkers: expanding the spectrum of HER2 positivity in breast cancer. *Front Mol Biosci* 2022;9:834651. DOI PubMed PMC
31. Fernandez AI, Liu M, Bellizzi A, et al. Examination of low ERBB2 protein expression in breast cancer tissue. *JAMA Oncol* 2022;8:1-4. DOI PubMed PMC
32. Mantrala S, Ginter PS, Mitkari A, et al. Concordance in breast cancer grading by artificial intelligence on whole slide images compares with a multi-institutional cohort of breast pathologists. *Arch Pathol Lab Med* 2022;146:1369-77. DOI
33. Paige answers call to better identify breast cancer patients with low expression of HER2. 2022. Avaliable from: https://www.businesswire.com/news/home/20220623005253/en/Paige-Answers-Call-to-Better-Identify-Breast-Cancer-Patients-with-Low-Expression-of-HER2 [Last accessed on 1 Dec 2023].
34. Uzunparmak B, Haymaker C, Raso G, et al. HER2-low expression in patients with advanced or metastatic solid tumors. *Ann Oncol* 2023;34:1035-46. DOI