Review Article
Running Title: Management of HER2-Low mBC
Received: July 31, 2024; Accepted: December 21, 2024

Management of HER2-Low Metastatic Breast Cancer: A Comprehensive Statement by an Expert Group from the Middle East and Africa Region

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Abstract
Approximately 50 to 67% of breast cancers (BCs), traditionally categorized as human epidermal growth factor receptor 2 (HER2)-negative, but demonstrating low HER2 expression, are now being defined as a new HER2-low subset or HER2-low category of BC. For metastatic BC (mBC), standard therapy options include targeted approaches, such as cyclin-dependent kinase 4/6

inhibitors, phosphoinositide 3-kinase inhibitors, poly (adenosine diphosphate-ribose) polymerase inhibitors, and anti-programmed death-ligand 1 agents, depending on tumor type and its molecular profile. Recent clinical trials reported significant clinical benefits from novel anti-HER2 antibody-drug conjugates, such as trastuzumab deruxtecan in HER2-low mBC. Novel treatment options have increased the complexity of the clinical decision-making process, particularly for treatment sequencing for each clinical setting. A regional expert committee meeting was held to discuss the challenges, overcome limitations, and present recommendations to enhance HER2 reporting as well as treatment of patients with HER2-low mBC in the Middle East and Africa region.

Keywords: Breast Neoplasms, HER2-low, Immunoconjugates, Trastuzumab deruxtecan, Sacituzumab govitecan

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer among women affecting 2,261,419 women worldwide and accounting for 684,996 deaths in 2020.[1] In the Middle East and North Africa region, in 2020, there were an estimated 128,437 incident cases among women, which resulted in 44,590 deaths.[1] The American Cancer Society has approximated that 6% of women have metastatic disease at the time of diagnosis.[2]

Approximately 15 to 20% cases (up to 20%–30% in some Middle East and Africa (MEA) countries) of BC have reported human epidermal growth factor receptor 2 (HER2)-overexpression.[3,4] The other majority are traditionally categorized as HER2-negative.[4,5] Around 50% of BCs, categorized as HER2-negative have low expression of HER2,[5,6] which was defined as an immunohistochemistry (IHC) score of 1+ or 2+ with in situ hybridization (ISH)-negative.[7] A global, retrospective study has reported that 67.2% of BCs traditionally categorized as HER2-negative express low levels of HER2.[8]

HER2-low BC was previously treated as HER2-negative with patients being stratified according to HR status. In these patients with HR-positive status and metastatic disease, a combination of endocrine therapy (ET) and cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, such as palbociclib, ribociclib, or abemaciclib, demonstrated meaningful clinical benefits[9–11] and has remained a standard first-line treatment option; however, resistance often occurs after 2 years.[12] For patients with HR-negative, HER2-negative metastatic disease, available targeted agents include poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors for patients with BC gene (*BRCA*) mutations and immune checkpoint inhibitors for tumors with programmed death-ligand 1 (PD-L1) expression.[13] Overall, these patients have limited targeted treatment choices after progression, during primary therapy and mostly receive palliative chemotherapy.[12,14,15]

Novel HER2-targeting antibody-drug conjugates (ADCs), including trastuzumab deruxtecan (T-DXd)[16–18] and trastuzumab duocarmazine (SYD-985),[19,20] have demonstrated significant clinical benefits in HER2-low metastatic BC (mBC). In DESTINY-Breast04 trial, T-DXd significantly improved both progression free survival (PFS) and overall survival (OS) in patients with HER2-low mBC who had received prior 1 or 2 lines of chemotherapy, irrespective of the HR status.[21] Recently, the United States Food and Drug Administration approved T-DXd, as the first HER2-directed

therapy for adult patients with unresectable or metastatic HER2-low BC who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.[22] Novel treatment options have increased the complexity of the clinical decision-making process, especially regarding various treatment sequencing possibilities for each clinical setting. A regional expert committee meeting was held to discuss the challenges encountered by community oncologists in the management of HER2-low mBC in the MEA region. The experts reviewed the existing evidence and forthcoming data regarding the emerging treatments and proposed recommendations for improving HER2 testing and management of HER2-low mBC.

Methodology

An expert panel of 10 oncologists, specialized in BC from 7 different MEA countries (Egypt [n = 1], Saudi Arabia [n = 2], Lebanon [n = 1], Morocco [n = 1], Turkey [n = 2], South Africa [n = 1], and United Arab Emirates [UAE; n = 2]), congregated to discuss the challenges encountered by community oncologists for HER2 testing and management of HER2 low mBC in these countries. The literature on the burden of mBC, data on HER2 testing and existing evidence, and forthcoming data on the emerging treatments that have the potential to revolutionize the management of patients with HER2-low disease were presented. The experts provided recommendations for improving HER2 testing and the management of HER2-low mBC, based on their discretion and experience, and available literature. This consensus is based on the literature evidence, current recommendations from relevant international guidelines, and the clinical practice experience of the experts.

HER2 Testing and Its Interpretation in BC

HER2 testing is an enhanced diagnostic tool for mBC,[23] as it helps to determine the most effective treatment options. The HER2-low expression is found to be highly unstable during disease evolution.[24] Testing can be performed in some cases even after neoadjuvant treatment and/or in case of disease progression to understand change in the pathology in terms of HER2 status.[25] Miglietta et al. reported that approximately 30% of breast tumors can convert from, or to, HER2-low status, underscoring a possible need to retest for HER2 expression on relapse.[24] Retesting HER2 expression on tumor relapse may open new therapeutic opportunities.[24]

Currently, IHC, fluorescence in situ hybridization (FISH), silver ISH, and chromogenic ISH, to search for possible amplification of *HER2* gene on chromosome enumeration probe (CEP) 17, are considered standard approaches for the evaluation of HER2 status in BC.[26] The initial step of the HER2 testing workflow entails the performance of IHC (Figure 1).[23] In the instances where the IHC result is inconclusive (i.e., equivocal [score 2+]), ISH is employed as a reflex testing for confirmation.[23]

The American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) testing guidelines recommend the preferential use of dual-probe rather than single-probe ISH assays for HER2 ISH testing.[7,23] This approach includes the HER2/CEP17 ratio, along with the analysis of HER2, mean copy number when scoring ISH results.[7,23] An algorithm for assessing *HER2* gene amplification through ISH assay using a dual probe assay is explained in figure 2.[23]

Need for classification of HER2-low BC

The conventional binary classification of HER2 status in BC has been questioned by recent clinical trial evidence.[19,27,28] The use of novel HER2-directed ADCs, T-DXd, and SYD-985 in advanced BC with HER2-low expression has shown significant clinical benefit in clinical trials.[17–19,21]

Denkert et al. reported that HER2-low-positive tumors can be identified as a new subset of BC by standardized IHC, distinct from HER2-zero tumors.[29] Moreover, HER2-low-positive tumors have specific biology and distinctive molecular features and exhibit differences in response to treatment, which is particularly relevant in therapy-resistant HR-negative tumors.[29] All these novel findings reshaped the conventional categorization associated with HER2 status. The historically used classification was challenged to reclassify HER2-negative BC into 2 distinct categories: HER2-low BC, which includes cases with an IHC score of 1+ or 2+ without *HER2* gene amplification (ISH negative) and HER2-negative BC, which corresponds to an IHC score of zero.[15] This potential new nomenclature or classification is recently endorsed by 2023 ASCO/CAP guidelines[7] (Figure 3).

In the DESTINY-Breast04 trial,[21] HER2-low status was defined as an IHC score of 2+ or 1+ and a negative ISH score. Other published data and ongoing clinical trials have defined HER2-low BC the same as that in DESTINY-Breast04.[17,18,21] According to Won et al., patients with HR-positive disease are more likely to develop HER2-low BC compared with those with triple-negative BC. Among patients with HR-positive BC, HER2-low BC was observed more frequently in premenopausal patients and linked with higher histological grade, lower incidence of T4 tumors, and an absence of lymphatic invasion when compared with HER2 IHC zero BC.[30] In contrast, among patients with triple-negative BC, HER2-low disease was more frequent in elderly patients and was found to be associated with positive lymphatic invasion and a high lymph node ratio in comparison with HER2 IHC zero BC.[30]

Barriers for testing and distinguishing HER2-low from HER-2 negative and panel recommendations to improve current testing practices

Although there is a recognized need for IHC assays to accurately identify tumors that test HER2 IHC 1+ or 2+/ISH negative,[7] this clinical need is based on the inclusion criteria of the DESTINY-Breast04 clinical trial[21] rather than the establishment of a new predictive or prognostic threshold for HER2 IHC test results below overexpression (IHC 3+).[7] In this milieu, Fernandez et al. reported that the current standard assays used in the clinical setting do not efficiently differentiate between IHC zero and 1+ in patients with HER2 BC and only 65% of these cases had 90% concordance agreement.[31] Similarly, other clinical studies examining the consistency or reproducibility of HER2 testing involving central and local laboratories showed a significant interobserver, intraobserver, and temporal intratumoral disparateness in HER2-low status.[24,32,33] Schettini et al. evaluated the HER2 IHC scoring reproducibility and reported multirater overall kappa concordance score of 0.79 ($P < 0.001$), which is considered a substantial agreement; however, there were 35 cases that exhibited discordance.[32] Recently, Tarantino et al. reported that HER2-low expression was positively associated with estrogen receptor (ER) expression level and ER-low tumors were enriched among HER2 zero tumors and may confound prognostic analyses.[34]

In the MEA region, major challenges in different countries for HER2 testing and

reporting include: standardization and incorporation of new guidelines for HER2-reporting, delayed turnaround time (due to affordability, waiting for patient's approval, and outsourcing) and insurance approval delays. A detailed assessment of HER2-low cases is essential to harmonize all methodologies and establish comprehensive guidelines.[35] In this context, the role of the pathologist is crucial; Thus, specific training on HER2 testing, proper evaluation of HER2 scores, interpretation, and differentiation of ISH and special care during HER2 testing is crucial to avoid clinical errors. All pathologists need to adhere to the latest ASCO/CAP HER2 testing guidelines.[7] A clear communication between pathologists and clinicians is essential to improve patient outcomes. All hospitals should implement the HER2 scoring system into their local institution protocols.

Management of HER2-low mBC

Although treatment with curative intent may not be possible for mBC, improvements in survival outcomes have been noted with appropriate therapeutic strategies.[21,36,37] Treatment decisions of mBC are largely influenced by biological subtypes and patient characteristics. The heterogeneity seen in the clinicopathological and molecular profile of mBC also renders disease management challenging and complex.[38,39] Thus, a multidisciplinary team (MDT) is necessary for the optimal management of mBC.[12]

Current Treatments Practices for HER2-low mBC

HR-positive, HER2-low mBC (Previously included under HR-positive, HER2-negative mBC)

Currently, CDK4/6 inhibitors (ribociclib, palbociclib, and abemaciclib) in conjunction with ET are recommended for certain patients with no visceral crisis and HR-positive, HER2-negative mBC,[14,40] with improved survival outcomes and an acceptable toxicity profile.[9,41–43] In certain patients with no evidence of a visceral crisis, ET plus CDK4/6 inhibitors demonstrated similar or better PFS benefits along with higher objective response rates (ORRs) than chemotherapy, and is associated with lower toxicity.[44,45] In certain patients with visceral crisis, chemotherapy is recommended by current guidelines as a preferred first-line option.[14,44,45] Retrospective analysis of the real-world data demonstrates that ET plus CDK4/6 inhibitor combination is superior to chemotherapy with an improvement in OS, especially in patients experiencing a visceral crisis.[46] A recent phase 2 RIGHT Choice trial in pre- or perimenopausal patients with clinically aggressive HR-positive, HER2-negative advanced BC showed improved PFS with first-line ribociclib, letrozole/anastrozole, and goserelin when compared with combination chemotherapy.[47–49]

Other regimens for the management of certain HR-positive, HER2-negative mBC patients include tamoxifen, fulvestrant, exemestane, letrozole, anastrozole, and everolimus.[12,14,50] Fulvestrant reported superior efficacy and is a preferred treatment option in patients who have not previously received ET compared with a third-generation aromatase inhibitor, a standard of care (SOC) for first-line treatment in these patients.[51] Aromatase inhibitor in combination with CDK4/6 inhibitors and fulvestrant in combination with CDK4/6 inhibitors are the recommended first-line options for postmenopausal patients and premenopausal patients with ovarian ablation/suppression with HER2-negative, HR-positive BC.[14] In the second and subsequent lines, evidence-based available therapy options include fulvestrant–alpelisib for *PIK3CA*-mutated tumors, poly(adenosine diphosphate-ribose)

polymerase (PARP) inhibitors for tumors harboring germline *BRCA* mutation (*BRCA*m), exemestane–everolimus, tamoxifen–everolimus, fulvestrant–everolimus, aromatase inhibitors, tamoxifen, fulvestrant, and chemotherapy.[12] New options include ribociclib beyond progression after palbociclib,[52] AKT inhibitor capivasertib,[53] and oral selective ER degraders, elacestrant [54] and camizestrant.[55] After progression on CDK4/6 inhibitors, the optimal sequence of endocrine-based therapy remains uncertain.[12]

In the DESTINY-Breast04 trial, T-DXd exhibited clinically meaningful and superior efficacy in PFS and OS compared with standard chemotherapy (physician's choice) in patients with HER2-low unresectable disease or mBC those who received 1 or 2 prior lines of chemotherapy for mBC or those who received at least 1 line of ET (if HR-positive).[21] Results from updated analysis from DESTINY-Breast04 demonstrated sustained clinically meaningful improvement in survival outcomes with T-DXd compared with standard chemotherapy, irrespective of HR status.[56] Based on these findings, the latest NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for BC (version 2, 2024) recommended T-DXd as a NCCN category 1, preferred second-line option for patients with HR-positive and HER2 IHC 1+ or 2+/ISH negative recurrent unresectable (local or regional) or mBC with visceral crisis disease or endocrine refractory.[14] In the TROPiCS-02 trial, sacituzumab govitecan demonstrated significant PFS and OS benefit over chemotherapy in patients with pretreated, endocrine-resistant HR-positive, HER2-negative mBC.[57,58]

HR negative, HER-2 low mBC (Previously included under HR negative, HER-2 negative mBC)

Chemotherapy remains a standard therapeutic approach in the treatment of certain patients with HR-negative, HER2-negative mBC.[12,14] In these patients, to initiate the treatment, the establishment of PD-L1 and *BRCA*m status is paramount to enable appropriate sequencing. Chemotherapy combination therapies are generally reserved for select patients with high tumor burden, rapidly progressing disease, and visceral crisis. Most guidelines recommended a first-line anthracycline or taxane-based regimen as options for PD-L1 negative and germline *BRCA1*/*BRCA2* wild-type patients who have not received these agents in the neoadjuvant or adjuvant settings.[12,14] NCCN Guidelines® also list antimetabolites and microtubule inhibitors as preferred regimens for HER2-negative disease.[14] Patients with *BRCA1*/*BRCA2* mutant and other impairments in homologous recombination have shown remarkable effectiveness with platinum-based regimens.[59,60] In patients with PD-L1 expression, chemotherapy in combination with immunotherapy—either atezolizumab plus nab-paclitaxel[61] or pembrolizumab plus paclitaxel,[62] nab-paclitaxel, or carboplatin–gemcitabine is the preferred treatment option, as they have demonstrated a significant and clinically meaningful improvement in PFS.[12] If patients are PD-L1 negative and germline *BRCA*m, the preferred options include cisplatin, carboplatin, olaparib or talazoparib.[12,14] The PARP inhibitors have demonstrated PFS benefit in clinical studies but this did not translate into OS benefits.[63,64] In the first-line setting, bevacizumab plus either capecitabine or paclitaxel remain therapeutic options in nations where bevacizumab is accessible and approved.[12] Pooled analysis of multiple Phase 3 trials

revealed that the addition of bevacizumab to paclitaxel or capecitabine improved PFS in patients with HR-negative, HER2-negative mBC; however, there was no improvement in OS.[65] For the second-line, sacituzumab govitecan (if available) is a category 1 preferred treatment option[14] because it has demonstrated an impressive ORR[66] and significant PFS benefit in Phase 1/3 trials.[67] Subsequently, chemotherapy is the only available option once patients are treated with immunotherapy or sacituzumab govitecan.

The latest NCCN Guidelines recommended T-DXd as a category 1, preferred second-line option for patients with no germline *BRCA1/2* mutation and HR-negative and HER2 IHC 1+ or 2+/ISH negative recurrent unresectable (local or regional) or mBC.[14]

Current challenges, treatment gaps and practice recommendations in HER2-low mBC in the MEA

Despite all clinical practice guidelines recommending MDT for the optimal management of BC, limited centers in the MEA region practice the MDT approach for the management of mBC. Classic anti-HER2 drugs like trastuzumab, pertuzumab, trastuzumab emtansine, and lapatinib are readily available and used in the majority of the countries within the MEA region. However, the availability of new anti-HER2 drugs such as T-DXd, sacituzumab govitecan and neratinib are limited to some high-income countries in the region. Even in countries where novel anti-HER2 drugs are approved and cancer care is provided free of charge to all their citizens through health insurance, their cost is not always covered or reimbursed by the insurance companies due to cost- effectiveness of the medications. In countries like South Africa and Morocco, the treatment for mBC is defined mainly by the availability of insurance coverage. However, in some countries like Lebanon and Turkey, novel anti-HER drugs are available for compassionate use or if paid by on an out-of-pocket expense by the patients. The panel recommends avoiding delays in approvals, and reduced pricing of new anti-HER agents to improve patient accessibility. Another challenge is the lack of comprehensive experience among physicians in treating HER2-low mBC cases and incorporation of novel anti-HER2 agents effectively into the treatment algorithm. The panel recommends increasing awareness among physicians about the effective and safe use of novel anti-HER2 agents for the management of HER2-low mBC. Also, it is essential to keep physicians updated with the latest clinical practice guidelines and research findings to ensure optimal patient care.

Our panel suggests using the proposed recommendations and treatment sequencing algorithms based on the available evidence and existing NCCN Guidelines [14] and ESMO Guidelines[12] to help community oncologists provide a better and more standardized treatment approach (Box 1 and Figure 4). Clinical evidence supporting the treatment recommendations are presented in supplementary table S1,[9–11,21,41,43–45,56–58,63,64,68–88] and supplementary table S2.[21,59,62,65,67,89,90]

Future Perspectives in HER2-low mBC

In the past, outcomes of patients with HER2-low BC who received trastuzumab were not positive and the option of anti-HER2 agents was put on hold in this setting.[28] This treatment paradigm was rechallenged recently because of the encouraging efficacy outcomes observed with newer and more powerful anti-HER2 agents in the treatment of HER2-low mBC.[17,19,91] The new anti-HER2 agents suggest a potential predictive value of HER2-low tumors for novel compounds with unique mechanisms of action influencing clinical decision-

making.[15] Key efficacy data on anti-HER2 agents in HER2-low BC is presented in table 1.[19–21,28,17,18,56,91–98]

The ADC, T-DXd appeared as the most efficacious treatment in HER2-low mBC patients based on clinical trial data. A Phase 1B clinical study of T-DXd in patients with advanced HER2-low BC refractory to standard treatment reported an ORR of 37.0% and a duration of response of 10.4 months for T-DXd.[17] These results were reinforced by the DESTINY-Breast 04 Phase 3 trial, in which T-DXd decreased the disease progression risk by 50% and the mortality risk by 36% over chemotherapy in patients who had previously received treatment for HER2-low mBC.[21] Currently, the use of T-DXd in other scenarios such HER2-low, HR-positive mBC progressed on ET is being explored, as T-DXd in combination with chemotherapy, ET, and immunotherapy.[99]

With the success of the DESTINY-Breast04 clinical trial in HER2-low mBC, the current perceptive of mBC viewed as having a positive or negative expression of HER2 is transformed. The HER2-low is now recognized as a distinction for HER2-negative BC patients.[7] The T-DXd is a new SOC for HER2-low mBC patients who fulfill the inclusion criteria of DESTINY-Breast04.[21] ADCs, T-DXd, sacituzumab govitecan, other new agents such as SYD-985,[91,92] nelipepimut-S[95] combinations with checkpoint inhibitors[100] are promising and undergoing numerous ongoing clinical trials in HER2-low BC (Table 2).

A New Entity in BC: HER2 "Ultra-Low"

Although HER2-0 scored BC is typically seen as having insufficient responses to monoclonal antibodies, a subset has been identified as HER2-ultra-low, showing potential for targeted therapies such as ADCs.[101] This subtype is characterized by faint or barely perceptible and incomplete staining in less than 10% of tumor cells without amplification on FISH.[101] Results from NCCTG N9831 trial and NSABP B-31 trial showed that anti-HER2 therapy was beneficial for a subset of BC patients who tested negative for HER2 biomarker.[102] Recently, the preliminary findings of the DAISY trial revealed that about 30.6% patients with HER2 ultra-low expression benefited from T-DXd.[103] These findings indicate that the existing HER2 assessment may not entirely align with HER2 signaling impairment. Furthermore, HER2 targeting may hypothetically be possible even in tumors with score zero showing staining, although it may be faint and incomplete, in ≤10% of tumor cells.[25] Bose et al. demonstrated that HER2-activating mutations do not always result in protein overexpression. This finding suggests a complementary mechanism for stimulating HER2 pathway in BC.[104] Moreover, *HER2 V777L*-mutated BC cell lines exhibited sensitivity to tyrosine kinase inhibitors (lapatinib and neratinib), thereby indicating a plausible role for HER2 targeting in cases of BC with HER2 ultra-low expression.[104] A retrospective study has demonstrated that HER2 ultra-low patients exhibit distinct clinicopathological features compared with HER2-low patients in terms of N stage, HR status and Ki-67 expression.[105] Currently, there is sparse literature on HER2 ultra-low expression. Nevertheless, further prospective studies aimed at investigating the significance of HER2 ultra-low expression would contribute to advancing the application of precision medicine and unlocking its potential for these specific patients.

Conclusion

Targeted therapies and ADCs have exhibited remarkable benefits when used as

monotherapy or in combination for patients with HER2-low mBC. Recent data show that T-DXd has a significant role in the management of patients with HER2-overexpressed and HER2-low BC. Standardization and dissemination of new guidelines for reporting HER2 status, speedy approvals, and cost-control are important to improve equity and outcomes of patients with advanced BC in the MEA region and worldwide.

Funding
The present expert opinion statement was supported by AstraZeneca FZ LLC.

Acknowledgments
The authors would like to thank Dr. Sasikala Somara and Dr. Chinmayee Joshi of Fortrea Scientific Pvt Ltd (formerly Labcorp Scientific Services & Solutions Pvt Ltd) for medical writing support in accordance with Good Publication Practice 2022 guidelines.

Authors' Contribution
Shaheenah Dawood and Nagi S. El Saghir: Conceptualization, Writing, Reviewing, and Editing; Mohsen Mokhtar, Ahmed Alwbari, Bernardo Leon Rapoport, Ece Esin, Hassan Jaafar, Jamal Zekri, Narjiss Berrada and Ozgur Ozyilkan: Writing, Reviewing, and Editing

Conflict of Interest
Shaheenah Dawood received speaker honoraria from Roche, Pfizer, Eli Lilly, AstraZeneca, Biologics, and Bristol-Myers Squibb (BMS), and research funding from MSD and Jalila Foundation. Mohsen Mokhtar received honoraria from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Hospira, GlaxoSmithKline (GSK), Eli Lilly, Merck, Merck Sharp and Dohme (MSD), Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi Avantis, and Takeda. Ahmed Alwbari is the principal investigator for AstraZeneca-funded project DB006 and co-principal investigator for DB009; received speaker honoraria from AstraZeneca for advisory board meetings. Bernardo Leon Rapoport received speaker honoraria from Roche, MSD, Eli Lilly, Novartis, and AstraZeneca for advisory board meetings. Ece Esin received honoraria from AstraZeneca, GSK, and Novartis for advisory board meetings. Hassan Jaafar reports participation in advisory board meetings of AstraZeneca, Novartis, MSD, Eli Lilly, Pfizer, and Roche. Jamal Zekri was the speaker and engaged in advisory roles for AstraZeneca. Narjiss Berrada was the speaker for AstraZeneca and MSD. Ozgur Ozyilkan received grant/research support from Roche, MSD, Eli Lilly, Pfizer, BMS, Servier, speaker's bureau member for Roche, MSD, and AstraZeneca; consultant for Pfizer, Novartis, AstraZeneca, Eli Lilly, MSD, and Roche; received medical writing and editorial support from Eli Lilly. Nagi S. El Saghir received honoraria for lectures and advisory board meetings from AstraZeneca, Eli Lilly, MSD, Novartis, Pfizer, Pierre Fabre, and Roche.

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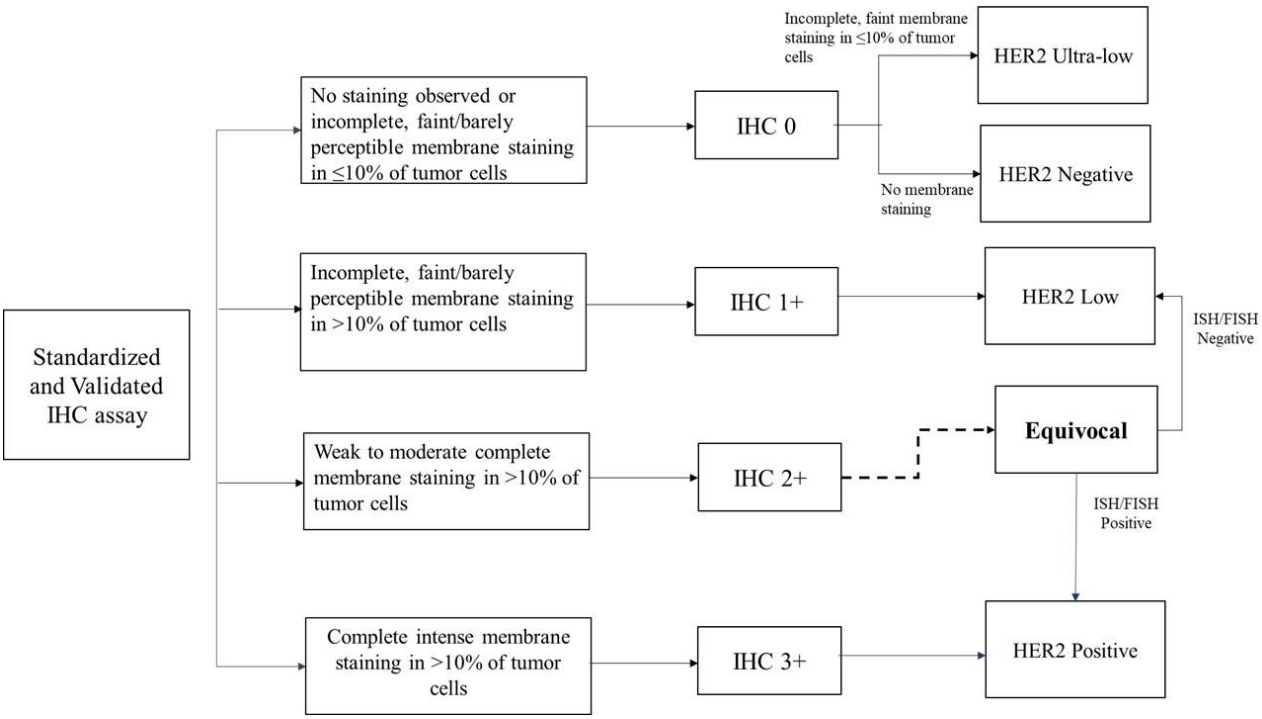

Figure 1. This figure depicts the algorithm for evaluation of HER2 gene amplification by IHC assay of the invasive component of a breast cancer specimen.

FISH: Fluorescence in situ hybridization; HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; ISH: In situ hybridization; +: Positive; –: Negative

Modified from Wolff AC, Hammond EH, 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 (*Arch Pathol Lab Med.* 2018;142(11):1364-82) with permission from Archives of Pathology & Laboratory Medicine. Copyright 2018. College of American Pathologists [23]

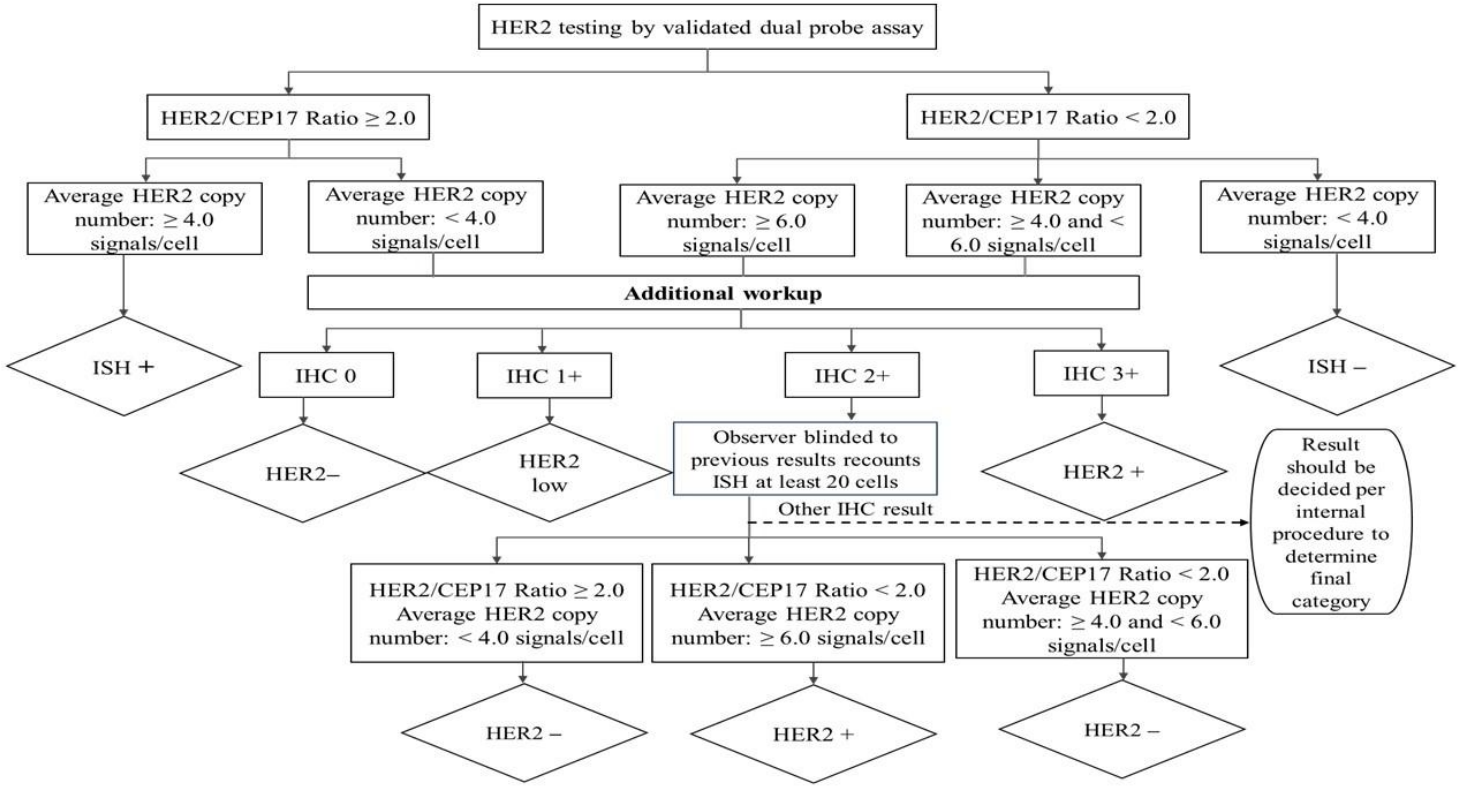

Figure 2. This figure depicts the algorithm for evaluation of HER2 gene amplification by ISH assay of the invasive component of a BC specimen using a dual-probe assay.

CEP: Chromosome enumeration probes; HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry positive; ISH: In situ hybridization; +: Positive; –: Negative
Modified from Wolff AC, Hammond EH, 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 (*Arch Pathol Lab Med.* 2018;142(11):1364-82) with permission from Archives of Pathology & Laboratory Medicine. Copyright 2018. College of American Pathologists [23]

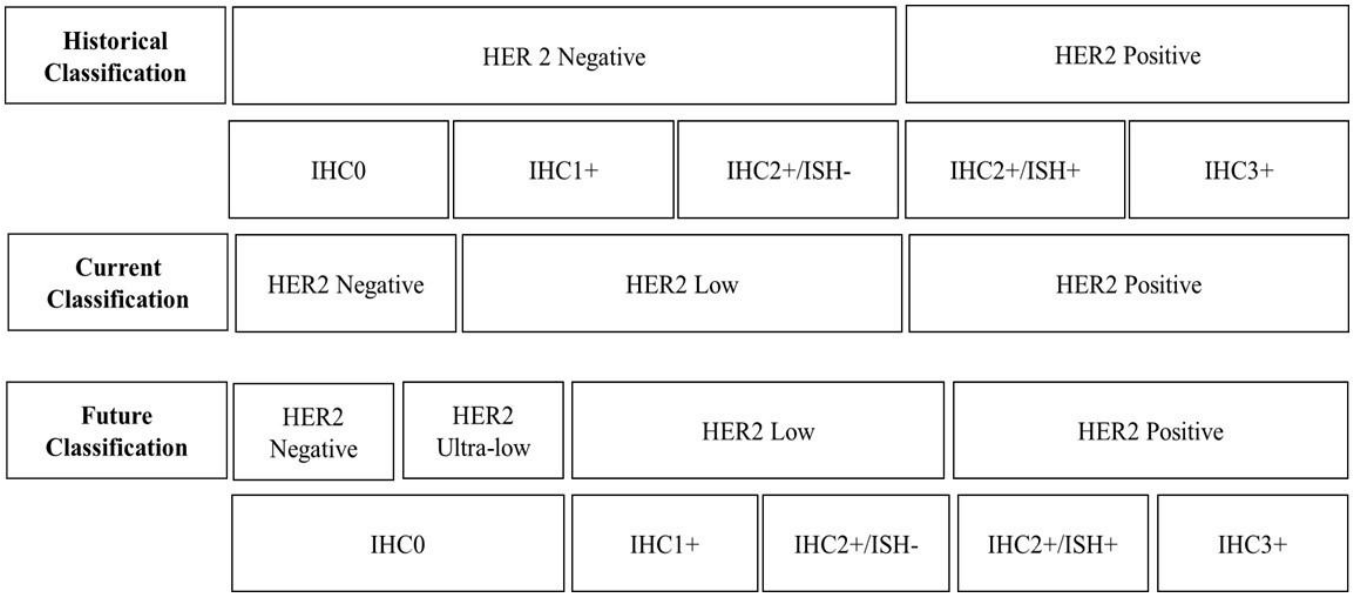

Figure 3. This figure depicts the historical, current and future HER 2 Classification.
HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; ISH: In situ hybridization; +: Positive; –: Negative

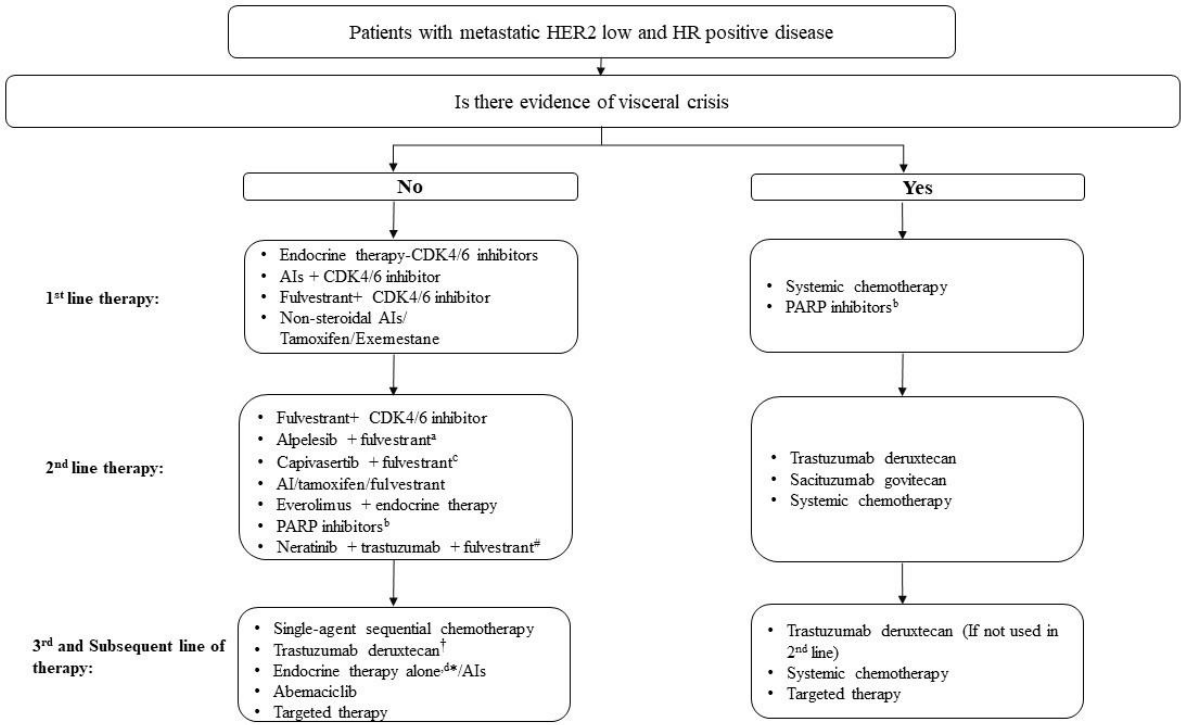

Figure 4. This figure shows the proposed treatment sequencing for the management of HR positive HER2 low metastatic breast cancer in the Middle East and Africa.

AI: Aromatase inhibitor; *BRCA*: Breast cancer; CDK4/6: Cyclin-dependent kinase 4 and 6; CDK4/6i: Cyclin-dependent kinase 4 and 6 inhibitors; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; PARP: Poly (adenosine diphosphate-ribose) polymerase; *PIK3CA*: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; [a]: if *PIK3CA*+; [b]: if *BRCA;* [c]: In patients with *PIK3CA* or *AKT1* activating mutations or *PTEN* alterations after disease progression or recurrence after ≥1 prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor; #: Patients who received CDK4/6 inhibitors; [d]: Agents not previously received in the metastatic setting may represent an option; [*]: For patients with endocrine-sensitive tumors; [†]: To the approved FDA indication

Box 1. Panel recommendations for management of HER2-low metastatic breast cancer in the Middle East and Africa

- For patients with HR-positive, HER2-low mBC, a CDK4/6 inhibitor in combination with ET can be used in the first-line therapy.
- The use of ET alone as a first-line option should be reserved for patients with existing comorbidities or a physical status that impedes the use of CDK4/6 inhibitor combinations.
- In the second-line treatment, the choice between CT or continuing with ET should be determined based on factors such as disease aggressiveness and organ function.
- For patients with *PIK3CA*-mutant tumors, who have not been exposed to AI with or without CDK4/6 inhibitors, alpelisib–fulvestrant is a viable treatment option.
- At second-line, the treatment options include fulvestrant–alpelisib for *PIK3CA*-mutated tumors, PARP inhibitors (olaparib or talazoparib) for tumors harboring g*BRCA*m, exemestane–everolimus, tamoxifen–everolimus, fulvestrant–everolimus, AIs, tamoxifen, fulvestrant, and chemotherapy.
- Neratinib–trastuzumab–fulvestrant (if feasible and available) is another available option in the second-line because this regimen had an encouraging response rate and was well-tolerated in predominantly heavily pretreated HER2-mutant, HR-positive breast cancers.
- In the third-line, T-DXd is recommended (if feasible and available) for the patients with HER2-low, HR-positive unresectable or mBC, who have received prior chemotherapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant chemotherapy.
- For patients with tumors sensitive to ET, continuing ET with agents that have not been previously given in the metastatic setting could be a viable option. Patients with tumors that are resistant to ET should be evaluated for CT treatment.
- For patients with HR-positive, HER2 low mBC with visceral crisis, T-DXd (if feasible and available) is preferred second-line option if disease has progressed after receiving chemotherapy for metastatic disease.
- In patients with HR-negative, HER2-low mBC with PD-L1 positive disease, the preferred approach is combining chemotherapy with an ICI. If the patient is PD-L1 negative and g*BRCA*m positive, the preferred options are olaparib or talazoparib, or chemotherapy with cisplatin or carboplatin.
- In the second-line, sacituzumab govitecan (if feasible and available) is the recommended treatment option for HR-negative, HER2-low mBC after chemotherapy. T-DXd is preferred option (if feasible and available) in the second line, if patients are PD-L1 positive, g*BRCA*m positive, or negative.
- In patients with HR-negative, HER2-low mBC, if PD-L1 is negative, T-DXd (if feasible and available) can be considered in the third-line (if not used in second-line) if the disease has progressed after receiving taxane or sacituzumab govitecan in the previous lines of treatment.

AI: Aromatase inhibitors; CDK: Cyclin-dependent kinase; CT: Chemotherapy; ET: Endocrine therapy; gBRCAm: Germline breast cancer gene mutated; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; ICI: Immune checkpoint inhibitors; mBC: Metastatic breast cancer; OS: Overall survival; PARP: Poly (adenosine diphosphate-ribose) polymerase; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; *PIK3CA*: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; T-DXd: Trastuzumab deruxtecan

Table 1. Overview of key clinical efficacy and safety data of anti-HER2 agents in HER2-low breast cancer

Name of study/author	Study design	Population characteristics	Number of patients	Treatment modality	Outcome
Modi et al, 2022, 2023[21,56]	Phase 3, RCT trial	• HER2-low mBC who had received 1 or 2 previous lines of CT	T-DXd Cohort: 373 Physician's choice Cohort: 184	• T-DXd • Physician's choice of CT	T-DXd vs. physician's choice in overall cohort • mPFS: 9.9 months vs. 5.1 months (HR: 0.50; 95% CI: 0.40 to 0.63; *P* < 0.001) • mOS: 23.4 months vs. 16.8 months (HR: 0.64; 95% CI: 0.49 to 0.84; *P* = 0.001) At median follow-up of 32 months: • Investigator assessed mPFS: 8.8 months vs. 4.2 months (HR: 0.36; 95% CI: 0.29 to 0.45; • mOS: 22.9 months vs. 16.8 months (HR: 0.69; 95% CI: 0.55 to 0.86) • OS rate at 36 months: 26.2% vs. 16.3%
Hamilton et al, 2021[93]	Phase 1b, 2-part, multiple-dose study	• HER2-positive disease that progressed on prior T-DM1 • HER2-low BC progressed on prior standard therapy	Total: 52 • Part 1: 7 • Part 2: 45	T-DXd + nivolumab • Part 1: T-DXd 3.2 mg/kg or 5.4 mg/kg and nivolumab 360 mg • Part 2: T-DXd 5.4 mg/kg and nivolumab 360 mg	Part 2 findings: In HER2-positive cohort • Confirmed ORR: 59.4% • mPFS: 8.6 months (95% CI: 5.4 to NE) In HER2-low cohort • Confirmed ORR: 37.5% • mPFS: 6.3 months (95% CI: 2.3 to NE)
Chick et al, 2021[95]	Randomized, single-blind, Phase 2b trial	• Node-positive and/or ER/PR-negative with HER2-low expression (1+ or 2+ by IHC)	275	• Nelipepimut-S + trastuzumab • Trastuzumab alone	Nelipepimut-S + trastuzumab vs. trastuzumab alone at 36 months: In patients with HER2 IHC 1+ expression • DFS rate: 91.6% vs. 77.5% (HR: 0.52; 95% CI: 0.22 to 1.25; *P* = 0.09) In TNBC patients with HER2 1+ expression • DFS rate: 94.1% vs. 66.9% (HR: 0.17; 95% CI: 0.04 to 0.79; *P* = 0.01) In patients with HER2 2+ expression • DFS rate: 77.9% vs. 86.0% (HR: 1.03; 95% CI: 0.33 to 3.21; *P* = 0.95) In TNBC patients with HER2 2+ expression • DFS rate: 60.6% vs. 76.0% (HR: 0.53; 95% CI: 0.09 to 2.93; *P* = 0.46)

Fehrenbacher et al, 2020[28]	Phase 3, multicenter, randomized adjuvant therapy trial	• High-risk primary invasive BC, HER2-negative IHC score of 1+ or 2+	3270	• CRx + trastuzumab • CRx alone	Trastuzumab + CRx vs. CRx alone • 5-year IDFS: 89.8% vs. 89.2% (HR: 0.98; 95% CI: 0.76 to 1.25; *P* = 0.85) • OS: 94.8% vs. 96.3% (HR: 1.33; 95% CI: 0.90 to 1.95; *P* = 0.15) • Distant recurrence-free interval: 92.7% vs. 93.6% (HR: 1.10; 95% CI: 0.81 to 1.50; *P* = 0.55) • AEs: 1625 vs. 1615
Pistilli et al, 2020[91]	Phase 2, open-label study	• hormone receptor -positive, HER2-low mBC refractory to ET or CDK4/6i	48	Zenocutuzumab (MCLA-128; 750 mg) + ET	• Disease control rate: 45% (90% CI: 32 to 59) • Common related AEs (all grades; grade 3-4) o Asthenia/fatigue (27%; 2%) o Diarrhoea (25%; 0) o Nausea (21%; 0)
Modi et al, 2020[17]	Phase 1, dose-expansio n study	• HER2-low BC refractory to standard therapies	54	T-DXd	• ORR: 37.0% (95% CI: 24.3 to 51.3) • mPFS: 11.1 (95% CI: 7.6 to NE) • Median duration of response: 10.4 months (95% CI: 8.8 months to NE) •
Hamilton et al, 2020[92]	Phase 2, open-label study	• HER2-positive mBC	28	MCLA-128 (zenocutuzumab)	• Disease control rate: 77% (90% CI: 60 to 89) • Common related AEs (all grades; grade 3-4) o Neutropenia/neutrophil count decrease (61%; 46%), o Diarrhoea (61%; 4%) o Asthenia/fatigue (46%; 0) o Nausea (29%; 0)
Banerji et al, 2019[19]	Phase 1, dose-escalatio n and dose-expansio n study	• Advanced BC, with at least HER2 IHC 1+	146	Trastuzumab duocarmazine	In patients with hormone receptor-positive, HER2-low BC • ORR: 28% (95% CI: 13.8 to 46.8) • mPFS: 4.1 months (95% CI: 2.4 to 5.4) In patients with hormone receptor -negative, HER2-low BC • ORR: 40% (95% CI: 16.3 to 67.6) • mPFS: 4.9 months (95% CI: 1.2 to NE)

Gianni et al, 2019[94]	Phase 2, multicohort trial	Patients with Ki67 >20% and HER2-low (1+/2+, no amplification) BC	49	Trastuzumab + pertuzumab + fulvestrant + palbociclib	• Mean Ki67 at baseline: 32.4% (range: 21.0 to 78.0) • Mean change in Ki67 at week 2: −29.5; $P < 0.001$ • Mean change in Ki67 at surgery: −19.3; $P < 0.001$ • ORR: 78.5%

Tamura et al, 2019[18]	Phase 1, dose-escalation and dose-expansion trial	HER2+ advanced BC with previous T-DM1 treatment	118	T-DXd: 5.4 mg/kg or 6.4 mg/kg	• Confirmed ORR: 59.5% (95% CI: 49.7 to 68.7)
					• Frequent grade 3 or worse treatment-emergent adverse events
					  ○ Anaemia (17%)
					  ○ Decreased neutrophil (14%), white blood cell (9%), and platelet (8%) counts
					• Investigator-reported AEs: 20 cases of ILD, pneumonitis, or organising pneumonia

Saura et al, 2018[20]	Phase 1 study	HER2-positive or HER2-low mBC	99	Trastuzumab duocarmazine	In patients with HER2-low, hormone receptor-positive mBC:
					• ORR: 27%
					In patients with HER2-low, hormone receptor-negative mBC:
					• ORR: 40%
					• Most common grade 3/4 adverse drug reactions:
					  ○ Neutropenia (6%)
					  ○ Conjunctivitis (4%)

Krop et al, 2012[96]	Phase 2, single-arm study	HER2-positive mBC (including HER2-low BC after retrospective re-evaluation)	110	T-DM1: 3.6 mg/kg, every 3 weeks	In overall population: • ORR: 34.5% (95% CI: 26.1 to 43.9) • Clinical benefit rate: 48.2% (95% CI: 38.8 to 57.9) • mPFS: 6.9 months (95% CI: 4.2 to 8.4) • Median duration of response: 7.2 months (95% CI: 4.6 to NE) • The most common grade ≥3 AEs were thrombocytopenia (9.1%), fatigue (4.5%), and cellulitis (3.6%) HER2-normal (HER2 FISH ratio less than 2.0 and IHC ≤2+) vs. HER2-positive

					• ORR: 20% (95% CI: 5.7 to 44.9) vs. 41.3% (95% CI: 30.4 to 52.8) • mPFS: 2.8 months (95% CI: 1.3 to NE) vs. 7.3 months (95% CI: 4.6 to 12.3)
Gianni L et al, 2010[97]	Phase 2 randomized trial	HER2-negative mBC (FISH-negative and IHC HER2 0, 1+, or 2+)	78	Pertuzumab • Arm A: loading dose of 840 mg, followed by 420 mg every 3 weeks • Arm B: No loading dose and 1050 mg every 3 weeks	Arm A vs. Arm B • Progressive disease: 51.2% vs. 59.5% • Clinical benefit: 9.8% vs. 5.4% • Median duration of clinical benefit: 36.5 (range: 22.1 to 74.9) vs. 33.6 (range: 31.0 to 36.3) • Median time to progression: 6.1 weeks (range: 2.0 to 37.0) vs. 6.1 (range: 2.7 to 36.3) • Both dose levels of pertuzumab were generally well tolerated with most frequent toxicities as grade 1 to 2 diarrhoea, fatigue/asthenia, nausea, and vomiting
Perez el al, 2010[98]	Phase 3 trial	HER2 overexpressing or amplified node positive or high-risk node-negative BC	1888	• CT + trastuzumab • CT alone	CT + trastuzumab vs. CT alone In patients with HER2/CEP17 ratio of ≥2.0 • DFS HR: 0.49; 95% CI: 0.36 to 0.68; $P < 0.0001$ In patients with normal HER2 protein expression (IHC score, 0 to 2) • DFS HR: 0.69; 95% CI: 0.36 to 1.32; $P = 0.26$ In patients with normal HER2 amplification (HER2/CEP17 ratio <2.0) • DFS HR: 0.54; 95% CI: 0.25 to 1.17; $P = 0.12$

AE: Adverse event; BC: Breast cancer; CDK4/6i: Cyclin-dependent kinase 4/6 inhibitors; CEP17: Chromosome enumeration probe ; CI: Confidence interval; CT: Chemotherapy; CRx: Adjuvant chemotherapy; DFS: Disease-free survival; ER: Estrogen receptor; ET: Endocrine therapy; FISH: Fluorescence in situ hybridization; HER2: Human epidermal growth factor receptor 2; HR: Hazard ratio; IDFS: Invasive disease-free survival; IHC: Immunohistochemistry; ILD: Interstitial lung disease; mBC: Metastatic breast cancer; mOS: Median overall survival; mPFS: Median progression-free survival; NE: Not evaluable; ORR: Overall response rate; OS: Overall survival; PR: Progesterone receptor; T-DM1: Trastuzumab-emtansine; T-DXd: Trastuzumab deruxtecan; TNBC: Triple-negative breast cancer; vs.: Versus

Table 2. Overview of ongoing clinical trials with anti-HER2 agents and immune checkpoint inhibitors in HER2-low breast cancer

ClinicalTrials.gov Identifier	Objective	Study design	Population characteristics	Treatment modality	Primary endpoint	Current status
NCT04042701	Evaluate efficacy, safety, and tolerability of T-DXd pus pembrolizumab	Phase 1b, open-label, 2-part, multicenter, nonrandomized, multiple-dose study	Advanced BC (HER2-positive and HER2-low)	T-DXd + pembrolizumab	Phase 1: DLTs, MTD, or recommended dose expansion Phase 2: ORR	Recruiting
NCT04556773	Investigate the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of T-DXd in combination with other therapies	Phase 1b, open-label, modular, dose-finding and dose-expansion study	Metastatic HER2-low advanced or metastatic BC	Module 1: T-DXd + capecitabine Module 2: T-DXd + durvalumab + paclitaxel Module 3: T-DXd + capivasertib Module 4: T-DXd + anastrozole Module 5: T-DXd + fulvestrant	Safety and tolerability: occurrence of AEs and SAEs	Active and not recruiting
NCT02576548	Evaluate safety, pharmacokinetics, immunogenicity, and antitumor activity of MEDI4276 in subjects with select HER2-negative disease	Phase 1/2 multicenter, open-label, dose-escalation, and dose-expansion study	HER2-negative expressing advanced solid tumors	MEDI4276	AEs, SAEs, DLTs	Completed
NCT03523572	Assess the effect of the combination of T-DXd with nivolumab in participants with HER2-expressing breast and urothelial cancer who had disease progression during or after prior therapies, did not respond to standard therapies, or	Phase 1b, multicenter, 2-part, open-label study	Advanced BC (HER2-positive and HER2-low) and urothelial cancer	T-DXd + nivolumab	Part 1: DLT Part 2: ORR	Ongoing

ClinicalTrials.gov Identifier	Objective	Study design	Population characteristics	Treatment modality	Primary endpoint	Current status
	for whom no standard therapy is available					
NCT03742102	Assess efficacy and safety of durvalumab in combination with novel oncology therapies with or without paclitaxel and durvalumab + paclitaxel for first-line metastatic triple-negative BC	Phase1B/2, 2-stage, open-label, multicenter	Patients with triple-negative breast neoplasms	Arm 1: Durvalumab + paclitaxel Arm 2: Durvalumab + paclitaxel + capivasertib Arm 5: Durvalumab + paclitaxel + oleclumab Arm 6: Durvalumab + T-DXd Arm 7: Durvalumab + datopotamab deruxtecan	Incidence of AEs Part 1: Safety and tolerability of each treatment arm Part 2: Endpoints based on investigator assessment according to RECIST 1.1 ORR: complete response or partial response Laboratory findings: Starting from informed consent until the safety follow-up after 3 months since the last dose of study drug	Ongoing
NCT05013554	Evaluate safety, pharmacokinetics, pharmacodynamics, and antitumor activity of SAR443216 in participants with relapsed/refractory HER2- expressing solid tumors	Phase 1/1b, open-label, first-in-human, single agent, dose-escalation and expansion study	Patients with relapsed/refractory HER2-expressing solid tumors	SAR443216	Part 1: MTD/ maximum administered dose, safety Part 2: preliminary clinical activity	Recruiting
NCT04494425	Study of T-DXd vs investigator's choice chemotherapy in	Phase 3, randomized, multicenter, open-label study	Patients with HR-positive, HER2-low BC expression who	T-DXd vs investigator’s choice, standard of care (capecitabine,	PFS	Recruiting

ClinicalTrials.gov Identifier	Objective	Study design	Population characteristics	Treatment modality	Primary endpoint	Current status
	HER2-low, HR-positive, metastatic BC		have had disease progression on at least 2 previous lines of ET or disease progression within 6 months of starting first-line with an ET combined with a CDK4/6 inhibitor	paclitaxel, nab-paclitaxel)		
NCT04553770	Evaluate the safety and efficacy of T-DXd with or without anastrozole for HER2-low, HR-positive BC in the neoadjuvant setting	Phase 2, multicenter, open-label study	Previously untreated operable invasive carcinoma >2.0 cm, clinical node negative disease or clinical node positive, deemed resectable, HER2-low BC	Arm A: T-DXd Arm B: T-DXd + anastrozole	pCR rate	Recruiting
NCT05113251	Evaluate efficacy and safety of T-DXd in a neoadjuvant setting, in high-risk, HER2-positive early nonmetastatic BC	Phase 3, open-label study	HER2-positive early BC T0-4, N1-3, M0 or ≥T3, N0, M0 as determined by the AJCC staging system, 8th edition	Arm A: T-DXd Arm B: T-DXd, followed by paclitaxel/ trastuzumab/ pertuzumab Arm C: doxorubicin and cyclophosphamide, followed by paclitaxel/ trastuzumab/ pertuzumab	pCR rate	Recruiting

AE: Adverse event; AJCC: American Joint Committee of Cancer; BC: Breast cancer; CDK4/6: Cyclin-dependent kinase 4 and 6; DLT: Dose-limiting toxicity; ET: Endocrine therapy; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; MTD: Maximum tolerated dose; ORR: Objective response rate; pCR: Pathologic complete response; PFS: Progression-free survival; RECIST: Response evaluation criteria in solid tumors; SAE: Serious adverse event; T-DXd: Trastuzumab deruxtecan

Supplementary Table S1. Summary of key studies for the treatment of women with hormone receptor-positive, HER2-negative advanced / metastatic breast cancer

Name of study	Treatment arms	Key outcomes
In first-line settings		
PALOMA-2 [9]	• Letrozole + Palbociclib[†] • Letrozole + Placebo[†]	Letrozole + Palbociclib vs. Letrozole + Placebo • mPFS: 24.8 months vs. 14.5 months; HR: 0.58; 95% CI: 0.46 to 0.72; *P* < 0.001
NCT04176354 [77]	• Palbociclib + Letrozole • Letrozole	Palbociclib + Letrozole vs. Letrozole • mrwPFS: 20.0 months vs. 11.9 months; HR: 0.58; 95% CI: 0.49 to 0.69; *P* < 0.0001 • mrwOS: not reached vs. 43.1 months; HR: 0.66; 95% CI: 0.53 to 0.82; *P* = 0.0002
MONALEESA-2 [41]	• Letrozole + Ribociclib[†] • Letrozole + Placebo[†]	Letrozole + Ribociclib vs. Letrozole + Placebo • mPFS: 25.3 months vs. 16.0 months; HR: 0.568; 95% CI: 0.457 to 0.704; *P* < 0.0001
MONARCH3 [69]	• Abemaciclib + NSAI • Placebo + NSAI	Abemaciclib + NSAI vs. Placebo + NSAI • mPFS: 28.18 months vs. 14.76 months; HR: 0.540; 95% CI: 0.418 to 0.698; *P* = 0.000002
MONALEESA-3 [70,71]	• Ribociclib + Fulvestrant • Fulvestrant + Placebo	Ribociclib + Fulvestrant vs. Fulvestrant + Placebo • mPFS: 20.5 months vs. 12.8 months; HR 0.59; 95% CI: 0.48 to 0.73 • mOS: not reached vs. 51.8 months; HR 0.64; 95% CI: 0.46 to 0.88
MONALEESA-7 [10,72]	• Ribociclib + ET (Goserelin + Tamoxifen or NSAI)[Ψ] • Placebo + ET (Goserelin + Tamoxifen or NSAI)[Ψ]	Ribociclib + ET vs. Placebo + ET • mPFS: 23.8 months vs. 13.0 months; HR: 0.55; 95% CI: 0.44 to 0.69; *P* < 0·0001 • mOS: 58.7 months vs. 48.0 months; HR: 0.76; 95% CI: 0.61 to 0.96 Ribociclib + Tamoxifen vs. Placebo + Tamoxifen • mPFS: 22.1 months vs. 11 months; HR: 0.59; 95% CI: 0.39 to 0.88 • mOS: not estimable vs. 49.3 months; HR: 0.71; 95% CI: 0.45 to 1.10 Ribociclib + NSAI vs. Placebo + NSAI • mPFS: 27.5 months vs. 13.8 months; HR 0.57; 95% CI: 0.44 to 0.74 • mOS: 58.7 months vs. 47.7 months; HR: 0.80; 95% CI: 0.62 to 1.04
TARGET [73]	• Anastrozole[§] • Tamoxifen[§]	Anastrozole vs. tamoxifen; *P* = non-significant for all • TTP: 8.2 months vs. 8.3 months • Clinical benefit: 56.2% vs. 55.5%
The North American trial [74]	• Anastrozole • Tamoxifen	Anastrozole vs. Tamoxifen • Median TTP: 11.1 months vs. 5.6 months; HR: 1.44; *P* = 0.005 • ORR: 21% vs. 17% • Clinical benefit: 59% vs. 46%; *P* = 0.0098
PEARL [44,68]	• Palbociclib + Exemestane or Fulvestrant[a] • Capecitabine[a]	Palbociclib + Fulvestrant vs. Capecitabine • mPFS: 7.5 months vs. 10.0 months; adjusted HR: 1.13; 95% CI: 0.85 to 1.50; *P* = 0.398 • mOS: 31.1 months vs. 32.8 months; adjusted HR: 1.10; 95% CI: 0.81 to 1.50; *P* = 0.550 Palbociclib + Exemestane vs. Capecitabine

Name of study	Treatment arms	Key outcomes
		• mPFS: 8.0 months vs. 10.6 months; adjusted HR: 1.11; 95% CI: 0.87 to 1.41; *P* = 0.404 • mOS: 32.6 months vs. 30.9 months; *P* = 0.995
KCSG-BR15-10 [45]	• Palbociclib + ET • Capecitabine	Palbociclib + ET vs. Capecitabine (at median follow-up of 17 months) • mPFS: 20.1 months vs. 14.4 months; HR: 0.659; 95% CI: 0.437 to 0.994; *P* = 0.0235
Gebhart et al, 2008 [75]	• Taxanes • Anthracyclines	Taxanes vs. anthracyclines In single-agent trials: • mPFS HR: 1.19; 95% CI: 1.04 to 1.36; *P* = 0.011 • mOS HR: 1.01; 95% CI: 0.88 to 1.16; *P* = 0.90 In combination trials • PFS HR: 0.92; 95% CI: 0.85 to 0.99; *P* = 0.031 • OS HR: 0.95; 95% CI: 0.88 to 1.03; *P* = 0.24
BOLERO-4 [76]	• Everolimus + Letrozole	• mPFS: 22 months • mOS: not reached • mOS rate: 78.7%
BOLERO-2 [78]	• Everolimus + Exemestane[$] • Exemestane + Placebo[$]	Everolimus + Exemestane vs Exemestane + Placebo (exploratory analysis) • PFS [according to central assessment]: 15.2 months vs. 4.2 months; HR: 0.32; 95% CI: 0.18 to 0.57
In second or third line setting		
PALOMA-3 [43,79]	• Fulvestrant + Palbociclib[$] • Placebo + Fulvestrant[$]	Fulvestrant + Palbociclib vs Placebo + Fulvestrant • mPFS: 9.5 months vs. 4.6 months; HR: 0.46; 95% CI: 0.36 to 0.59; *P* < 0.0001 • mOS: 39.7 months vs. 29.7 months; HR: 0.72; 95% CI: 0.55 to 0.94
SOLAR-1 [80]	• Alpelisib + Fulvestrant[#] • Fulvestrant + Placebo[#]	Alpelisib + Fulvestrant vs Placebo + Fulvestrant • mOS: 39.3 months vs. 31.4 months; HR: 0.86; 95% CI: 0.64 to 1.15; *P* = 0.15
NCT02000622 [63,81]	• Olaparib[¥] • Standard therapy[¥]	Olaparib vs Standard therapy • mPFS: 7.0 months vs. 4.2 months; HR: 0.58; 95% CI: 0.43 to 0.80; *P* < 0.001 • Response rate: 59.9% vs. 28.8% • mOS: 19.3 months vs. 17.1 months; HR: 0.90; 95% CI: 0.66 to 1.23; *P* = 0.513
EMBRACA [64,82]	• Talazoparib[¥] • Standard therapy[¥]	Talazoparib vs Standard therapy • mPFS: 8.6 months vs. 5.6 months; HR: 0.54; 95% CI: 0.41 to 0.71; *P* < 0.001 • mOS: 19.3 months vs. 19.5 months; HR: 0.848; 95% CI: 0.670 to 1.073; *P* = 0.17
NCT01231659 [83]	• Everolimus + Letrozole[$]	• Overall response rate: 23.3% • mPFS: 8.8 months; 95% CI: 6.6 to 11.0 months • mOS: 22.9 months; 95% CI, 18.5 to 28.9 months

Name of study	Treatment arms	Key outcomes
		• Disease-control rate: 85%
EVA study [84,85]	• Everolimus + Exemestane	• PFS: 5.6 months; 95% CI: 5.4 to 6.0 months • ORR: 31.6% • Disease control rate: 60.7%
BOLERO-4 [76]	• Everolimus + Exemestane	• mPFS: 3.7 months
BOLERO-6 [86]	• Everolimus + Exemestane[a] • Everolimus[a] • Capecitabine	Everolimus + Exemestane vs. Everolimus vs Capecitabine • mPFS: 8.4 months vs. 6.8 months vs 9.6 months; HR: 0.74; 90% CI: 0.57 to 0.97 • mOS: 23.1 months vs. 29.3 months; HR: 1.27; 90% CI: 0.95 to 1.70
MONALEESA-3 [70,71]	• Ribociclib + Fulvestrant • Fulvestrant + Placebo	Ribociclib + Fulvestrant vs. Placebo + Fulvestrant • mPFS: 14.6 months vs. 9.1 months; HR: 0.57; 95%CI: 0.43 to 0.74 • mOS: 39.7 months vs. 33.7 months; HR: 0.78; 95% CI: 0.59 to 1.04
MONARCH2 [11,88]	• Fulvestrant + Abemaciclib[$] • Fulvestrant + Placebo [$]	Fulvestrant + Abemaciclib vs. Fulvestrant + Placebo • mPFS: 16.4 months vs. 9.3 months; $P < 0.0001$ • mOS: 46.7 months vs. 37.3 months; $P = 0.01$
TROPiCS-02 [57,58]	• Sacituzumab govitecan[c] • Chemotherapy[c] (eribulin, vinorelbine, capecitabine, or gemcitabine)	Sacituzumab govitecan vs. Chemotherapy • mPFS: 5.5 months vs. 4.0 months; HR: 0.66, 95% CI, 0.53 to 0.83; $P = 0.0003$ • mOS: 14.4 months vs. 11.2 months; HR: 0.79, 95% CI, 0.65 to 0.96; $P = 0.020$ • ORR: 21% vs. 14%; odds ratio: 1.63, 95% CI 1.03 to 2.56; $P = 0.035$
DESTINY-Breast04 [21,56]	• T-DXd[b] • Physician's choice of chemotherapy[b]	T-DXd vs. Physician's choice of chemotherapy • mPFS: 10.1 months vs. 5.4 months; HR: 0.51; 95% CI: 0.40 to 0.64; $P < 0.001$ • mOS: 23.9 months vs. 17.5 months; HR: 0.64; 95% CI: 0.48 to 0.86; $P = 0.003$ At 32 months follow-up: • Investigator assessed mPFS: 9.6 months vs. 4.2 months; HR: 0.37; 95% CI: 0.30 to 0.46 • mOS: 23.9 months vs. 17.6 months; HR: 0.69; 95% CI: 0.55 to 0.87 • OS rate 36 months: 26.5% vs 16.9%
SUMMIT trial [87]	• Neratinib + Trastuzumab + Fulvestrant	• ORR: 38% • Median DOR: 14.4 months • mPFS: 8.2 months

BRCA: Breast cancer; CDK4/6: Cyclin-dependent kinase 4 and 6; CI: Confidence interval; DOR: Duration of response; ET: Endocrine therapy; HER2: Human epidermal growth factor receptor 2; HR: Hazard ratio; mOS: Median overall survival; mPFS: Progression-free survival; mrwOS: Median real-world overall survival; mrwPFS: Median real-world progression-free survival; NSAI: Nonsteroidal aromatase inhibitor; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression;

T-DXd: Trastuzumab deruxtecan; vs: Versus; † For the patient who has not received prior therapy for systemic therapy advanced disease; § HER2 status not reported; ᵠ For the patients who has not received previous treatment with CDK4/6 inhibitors; [a] In aromatase inhibitor-resistant patients; $ For patients whose disease had progressed on previous therapy; ¥ Patients with germline *BRCA* mutations; # Patients with *PIK3CA* mutations; [a] Patients whose disease had progressed during treatment with NSAIs; [b] Patients with HER2 low metastatic breast cancer; [c] Patients who received at least 1 previous ET, and a CDK4/6 inhibitor in any setting, and at least two lines of chemotherapy regimen, for metastatic disease.

Supplementary Table S2. Summary of key studies for the treatment of women with hormone receptor-negative, HER2-negative mBC

Name of study/author	Treatment arms	Outcome
Tutt et al, 2018 [59]	• Carboplatin • Docetaxel	Carboplatin vs. Docetaxel ***In unselected population*** • ORR: 31.4% vs. 34.0%; *P* = 0.66 ***BRCA-mutated population*** • ORR: 68% vs. 33%; *P* = 0.01 • mPFS: 6.8 months vs. 4.4 months; *P* = 0.40
Miles et al, 2013 [65]	• Bevacizumab + Chemotherapy • Chemotherapy	Bevacizumab + Chemotherapy vs. Chemotherapy • mPFS: 9.2 months vs. 6.7 months; HR: 0.64; 95% CI: 0.57 to 0.71 • mOS: 26.7 months vs. 26.4 months; HR: 0.97; 95% CI: 0.86 to 1.08
Cortes et al, 2020 [62]	• Pembrolizumab + Chemotherapy • Placebo + Chemotherapy	Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy ***In ITT population*** • mPFS: 7.5 months vs. 5.6 months; HR: 0.82; 95% CI: 0.69 to 0.97 ***In patients with CPS ≥10*** • mPFS: 9.7 months vs. 5.6 months; HR: 0.65; 95% CI: 0.49 to 0.86; *P* = 0.0012 ***In patients with CPS of ≥1*** • mPFS: 7.6 months vs. 5.6 months; HR: 0.74; 95% CI: 0.61 to 0.90; *P* = 0.0014
Schmid et al, 2019 [61]	• Atezolizumab + Paclitaxel • Placebo + Paclitaxel	Atezolizumab + Paclitaxel vs. Placebo + Paclitaxel ***In ITT population*** • mPFS: 7.2 months vs. 5.5 months; stratified HR: 0.80; 95% CI: 0.69 to 0.92; *P* = 0.0021 • mOS: 21.0 months vs. 18.7 months; stratified HR: 0.86; 95% CI: 0.72 to 1.02; *P* = 0.078 ***In patients with PD-L1 positive tumors*** • mOS: 25.0 months vs. 18.0 months; stratified HR: 0.71; 95% CI: 0.54 to 0.94 • mPFS: 7.5 months vs. 5.3 months; stratified HR: 0.63; 95% CI: 0.50 to 0.80; *P* < 0.0001 ***In patients with PD-L1 negative tumor*** • mOS: 19.7 months vs. 19.6 months; stratified HR: 0.97; 95% CI: 0.78 to 1.20 • mPFS: 5.6 months vs. 5.6 months; stratified HR: 0.93; 95% CI: 0.77 to 1.11
Miles et al, 2021 [89]	• Atezolizumab + Paclitaxel • Placebo + Paclitaxel	Atezolizumab + Paclitaxel vs. Placebo + Paclitaxel ***In the ITT population*** • mPFS: 5.7 months vs. 5.6 months; HR: 0.86; 95% CI: 0.70 to 1.05 • mOS: 19.2 months vs. 22.8 months; HR: 1.12; 95% CI: 0.88 to 1.43 ***In patients with PD-L1 positive tumor*** • mPFS: 6.0 months vs. 5.7 months; HR: 0.82; 95% CI: 0.60 to 1.12; log-rank *P* = 0.20 • mOS: 22.1 months vs. 28.3 months; HR: 1.11; 95% CI: 0.76 to 1.64

Name of study/author	Treatment arms	Outcome
Bardia et al, 2021 [67]	• Sacituzumab govitecan • Physician's choice chemotherapy	Sacituzumab govitecan vs. Chemotherapy • mPFS: 5.6 months vs. 1.7 months; HR: 0.41; 95% CI: 0.32 to 0.52; $P < 0.001$ • mOS: 12.1 months vs. 6.7 months; HR: 0.48; 95% CI: 0.38 to 0.59; $P < 0.001$
Winer et al, 2021 [90]	• Pembrolizumab • Chemotherapy	Pembrolizumab vs. Chemotherapy • mOS: 9.9 months vs. 10.8 months; HR: 0.97; 95% CI: 0.82 to 1.15
Modi et al, 2022 [21]	• T-DXd* • Physician's choice of chemotherapy*	T-DXd vs. Physician choice of chemotherapy • mPFS: 8.5 months vs. 2.9 months; HR: 0.46; 95% CI: 0.24 to 0.89 • mOS: 18.2 months vs. 8.3 months; HR: 0.48; 95% CI: 0.24 to 0.95

BRCA: Breast cancer gene; CI: Confidence interval; CPS: Combined positive score; HER2: Human epidermal growth factor receptor; HR: Hazard ratio; ITT: Intent to treat; mBC: Metastatic breast cancer; mOS: Median overall survival; mPFS: Median progression-free survival; ORR: Objective response rate; T-DXd: Trastuzumab deruxtecan; PDL-1: Programmed death-ligand 1; vs: Versus; *For patients with HER2 low mBC