Systematic Review

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A clinical systematic literature review of treatments among patients with advanced and/or metastatic human epidermal growth factor receptor 2 positive breast cancer

Kerigo Ndirangu*[,1], Rachel Goldgrub[2], Vanita Tongbram[3], Rajee Antony[4], Bagrat Lalayan[1], Joyce O'Shaughnessy[5] & Sarah E Schellhorn[6]

[1]Eisai, 200 Metro Blvd, Nutley, NJ 07110, USA
[2]ICON plc, 688 W Hastings St, Vancouver, BC V6B 1P1, Canada
[3]ICON plc, 475 Washington Ave, New York, NY 11238, USA
[4]Formerly of Eisai, 200 Metro Blvd, Nutley, NJ 07110, USA
[5]Texas Oncology-Baylor Charles A. Sammons Cancer Center, 3410 Worth St Suite 400, Dallas, TX 75246, USA
[6]Yale Cancer Center, Smilow Cancer Hospital, 35 Park St, New Haven, CT 06513, USA
*Author for correspondence: Kerigo_Ndirangu@eisai.com

Aim: This systematic literature review aims to summarize the efficacy/effectiveness of treatments, including eribulin (ERI)-based and anti-human epidermal growth factor receptor 2 (HER2) treatments in advanced/metastatic HER2+ breast cancer. **Methods:** Three databases from 2016 to September 2021 were searched for clinical trials and observational studies in patients receiving first-line (1L) standard of care (SOC), second-line (2L) SOC or third-line or subsequent lines (3L+). **Results:** 2692 citations were screened, and 38 studies were included. Eleven studies were randomized-controlled trials (RCTs; 5 in 1L, 6 in 3L+), 6 were single-arm trials (5 in 1L, 1 in 3L+) and 21 were observational studies (13 in 1L, 6 in 2L, 4 in 3L+ [note that studies with subgroups for 1L, 2L, 3L+ are double-counted]). Longer overall survival (OS) was associated with 1L and 2L treatment, and for 3L+ studies that included ERI, ERI or trastuzumab (Tmab) + ERI led to longer OS than treatments of physician's choice (median OS of 11, 10 and 8.9 months, respectively). Progression-free survival was 9 months in Tmab + pertuzumab (Pmab) + ERI, 4 months in Tmab + ERI and 3.3 months in ERI. **Conclusion:** Available treatments provide a wide range of efficacy. However, later lines lack standardization and conclusions on comparative effectiveness are limited by differing trial designs. Thus, the chance of prolonged survival with new agents warrants further research.

Plain language summary: Breast cancer (BC) is a leading type of cancer worldwide. Once BC has spread to nearby or distance parts of the body, survival rate decrease. A growing type of BC is caused when there is too much of a protein called 'HER2'. In this study, we looked at how well different treatments that target HER2 work for BC that has spread. We searched for studies published from 2016 to 2021 and found 38 studies to include. These studies looked at patients getting their first, second, or third or more rounds of treatment. Here are the key findings: treatment timing matters, people who got treatment earlier tended to live longer; in studies where people were on their third or more round of treatment and received eribulin (ERI) or the combination of ERI or trastuzumab (Tmab) tended to live longer compared with other treatments; and the time before the disease got worse varied with different treatments. For example, when people got Tmab + pertuzumab + ERI, it was 9 months before the disease got worse, with Tmab + ERI, it was 4 months, and with ERI alone, it was 3.3 months. In conclusion, there are many treatments available for this type of BC, but they vary in how well they work. Also, treatments in later rounds of therapy are not the same and there is no standard treatment that clinicians can provide. More research is needed to find out which treatments can help people live longer.

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Keywords: advanced breast cancer • chemotherapy • eribulin-based treatment • HER2+ breast cancer • metastatic breast cancer • systematic literature review

Breast cancer (BC) is the most prevalent cancer worldwide, and cases have continued to rise rapidly in the last 5 years [1]. In 2020 alone, 2.3 million women were diagnosed with BC, resulting in 685,000 deaths globally [1]. BC has several subtypes that lead to different treatment patterns and prognosis [2]. Human epidermal growth factor receptor 2 positive (HER2+) BC is a highly aggressive form of invasive BC, accounting for approximately 15–20% of all cases [3]. Over the years, advancements in research and diagnostic technologies have improved identification of this subgroup.

Traditionally, HER2+ status was determined through *in situ* hybridization (ISH) and fluorescent *in situ* hybridization (FISH) assays. However, with technological advancements and refined diagnostic criteria, such as dual-color *in situ* hybridization and updated scoring systems like the HER2 testing algorithm and the American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines, the landscape of HER2 testing has evolved significantly [4–6]. These updates have ultimately contributed to more tailored and effective treatment strategies for patients with HER2+ BC.

HER2 testing have paved the way for targeted therapies, such as trastuzumab [7], pertuzumab [8] and trastuzumab emtansine (T-DM1) [9]. Despite these improvements in overall prognosis, there is still a considerable risk of relapse for patients with HER2+ BC [10]. There are currently eight US FDA-approved therapies for HER2+ metastatic BC (mBC). The first approved therapy for first-line (1L) treatment in 1998 was chemotherapy + trastuzumab [11]. However, in 2012, based on the CLEOPATRA study, pertuzumab + trastuzumab ± taxane was established as a 1L standard of care (SOC) treatment [12]. For second-line (2L) treatments, options include lapatinib + capecitabine, ado-transtuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-Dxd) [13–15]. In the realm of third-line or subsequent lines (3L+), margetuximab + chemotherapy, neratinib + capecitabine, tucatinib + capecitabine + trastuzumab and T-Dxd have all received approval [15–18].

Eribulin mesylate (Halaven®) received approval in 2011 for treating patients with mBC following prior chemotherapy and has emerged as a pivotal option in the late-line setting [19]. The approval of eribulin was grounded in findings from the EMBRACE trial, revealing a significant enhancement in median overall survival (OS) when compared with the treatment chosen by physicians for patients with heavily pretreated a/mBC [20,21]. Its approval marked a crucial milestone, addressing the unmet need for effective treatments in advanced stages of a/mBC where limited therapeutic options exist.

This systematic literature review (SLR) comprehensively summarizes the efficacy and effectiveness of eribulin and other various treatment options for patients with HER2+ a/mBC receiving 1L, 2L or 3L+ care from observational studies and interventional trials.

Methods

A systematic search was performed in MEDLINE and MEDLINE In-Process, Embase and the Cochrane Central Register of Controlled Trials using the OVID SP® platform on 2 September 2021. The search was limited to 5 years (1 January 2016 to 2 September 2021). Keywords, synonyms and medical subject header terms for 'breast cancer', 'metastasis', 'longitudinal study' and 'randomized controlled trial' were used in the search strategy (see appendix). The SLR methodology adopted was consistent with recommendations published in the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement, the Centre for Reviews and Dissemination and the Cochrane Collaboration [22,23]. A congress abstract search of five conferences (2017-September 2021) was also performed. This included the ASCO Breast Cancer Symposium, European Society for Medical Oncology, San Antonio Breast Cancer Symposium, the American Association for Cancer Research and the Miami Breast Cancer Conference. Two reviewers independently assessed the eligibility of articles according to the predefined inclusion criteria as per the Patient, Intervention, Comparators, Outcomes and Study Design (PICOS) statement. Afterward, full-text screening and cross-referencing of previously published SLRs were performed. Any disagreements were resolved through discussion or a third reviewer when a consensus could not be reached.

The eligibility criteria included studies on adult patients (≥18 years) with HER2+ a/mBC receiving 1L, 2L or 3L+ treatments. Studies with mixed lines of treatment without separate outcomes were excluded such as studies with 1L/2L, or 2L+. Interventions eligible were SOC (at the time of protocol development; thus, T-Dxd not reported as SOC for 2L) for patients receiving 1L or 2L treatments with pertuzumab + trastuzumab ± taxane or T-DM1 defined by the ASCO and the National Comprehensive Cancer Network (NCCN) for patients with

HER2+ a/mBC [24,25]. However, patients receiving any 3L+ targeted therapy, immunotherapy, or chemotherapy of any kind were included as no SOC has been established. Observational studies (prospective and retrospective cohorts, case-control studies and cross-sectional studies) and interventional studies (randomized controlled trials [RCTs], single-arms studies and non-randomized intervention studies of any phase) that reported intervention-specific outcomes of interest (progression-free survival [PFS] and overall survival [OS]) were included based on 1L, 2L or 3L+. Studies with a sample size of <30 patients or published in any language other than English were excluded.

The following variables were extracted: study characteristics (year of publication, study name, study design, study country, study start/end year, inclusion/exclusion criteria, sample size, follow-up time and study conclusion), interventions (treatment regimen, line of therapy, dosage, route of administration, treatment schedule and duration), patient characteristics (age, disease status [locally advanced, metastatic, etc.], number and type of prior treatments and efficacy outcomes (OS and PFS). Safety data was extracted; however, the output is not reported here. One reviewer independently extracted data into a bespoke extraction sheet and a second reviewer was responsible for validation. Any discrepancies were resolved by discussion with a third reviewer. Supplementary data and errata were retrieved and reviewed as well.

A PRISMA flow diagram indicated the number of studies included and excluded at each review stage. Studies excluded at the full-text paper stage were tabulated alongside the reason for exclusion as per best practice guidelines [23].

All included full-text studies were assessed for internal validity using the appropriate quality assessment tool based on study design. A Newcastle Ottawa Scale was used to evaluate the risk of bias from observational studies and non-randomized controlled/open-label trials. The Cochrane risk of bias tool was used for RCTs [26,27]. Included conference abstracts and clinical study reports were not assessed.

Results

Literature search findings

A total of 3759 citations were found in the database search. Following de-duplication, 2692 abstracts were reviewed. A total of 2379 records were excluded during abstract screening resulting in 313 full publications assessed for inclusion. Of the 313 full-text, 278 articles were excluded: 59 for population (i.e., early breast cancer, non-HER2+ a/mBC), 99 for intervention/comparator, 54 for outcomes, 57 for study design, four duplicates, three conference abstracts (outside of conferences of interest) and two reviews (Figure 1). Furthermore, 683 conference abstracts from the five conferences of interest were screened, and eight were included in the SLR [16,18,28–68]. Two clinical study reports on patients receiving eribulin as 3L+ treatments were added [20,21], due to their reporting of HER2+ subgroups. Thus, 45 publications on 38 primary studies were included in the SLR [16,18,20,21,28–68]. The risk of bias assessment can be found in the Appendix.

Study & patient characteristics

First-line standard of care interventions

In total, 24 studies reported on 1L SOC for HER2+ a/mBC: five RCTs [28–34], five single-arm trials [35–41] and 14 observational studies [42–55]. Bahceci *et al.* included subgroups for patients receiving 1L, 2L and 3L+ is reported in each separate section [42]. Pizzuti 2020 reported subgroup populations for 1L and 2L [48]. The RCTs were either phase II (n = 2) or phase III trials (n = 3) and conducted in multinational settings with sample sizes ranging from 210 to 1092 patients (Table 1). The single-arm trials were either phase II (n = 2) or phase III trials (n = 3) and were conducted in multiple countries (n = 2), the USA (n = 2), or Australia (n = 1) with number of participants ranging from 50 to 1436. The observational studies were conducted in various countries (Italy [n = 6], one study each in Canada, Greece, Israel, Japan, Turkey, the UK and the USA, and only a single study did not report location). The sample sizes ranged from 35 to 414. All the studies included patient who received SOC, except for Puhalla 2016 [38] where patients received eribulin + trastuzumab (with or without prior trastuzumab). The median age of patients across the included studies ranged from 47 to 65 years.

Second-line standard of care interventions

Seven observational studies on patients with HER2+ a/mBC receiving 2L SOC were included in this SLR [42,48,56–60] and were conducted in different countries (Turkey [n = 1], Italy [n = 4], Japan [n = 1] and Spain [n = 1]). Fabi 2017b reported subgroups for patients receiving 2L and 3L+, thus the study is reported in both sections [57].

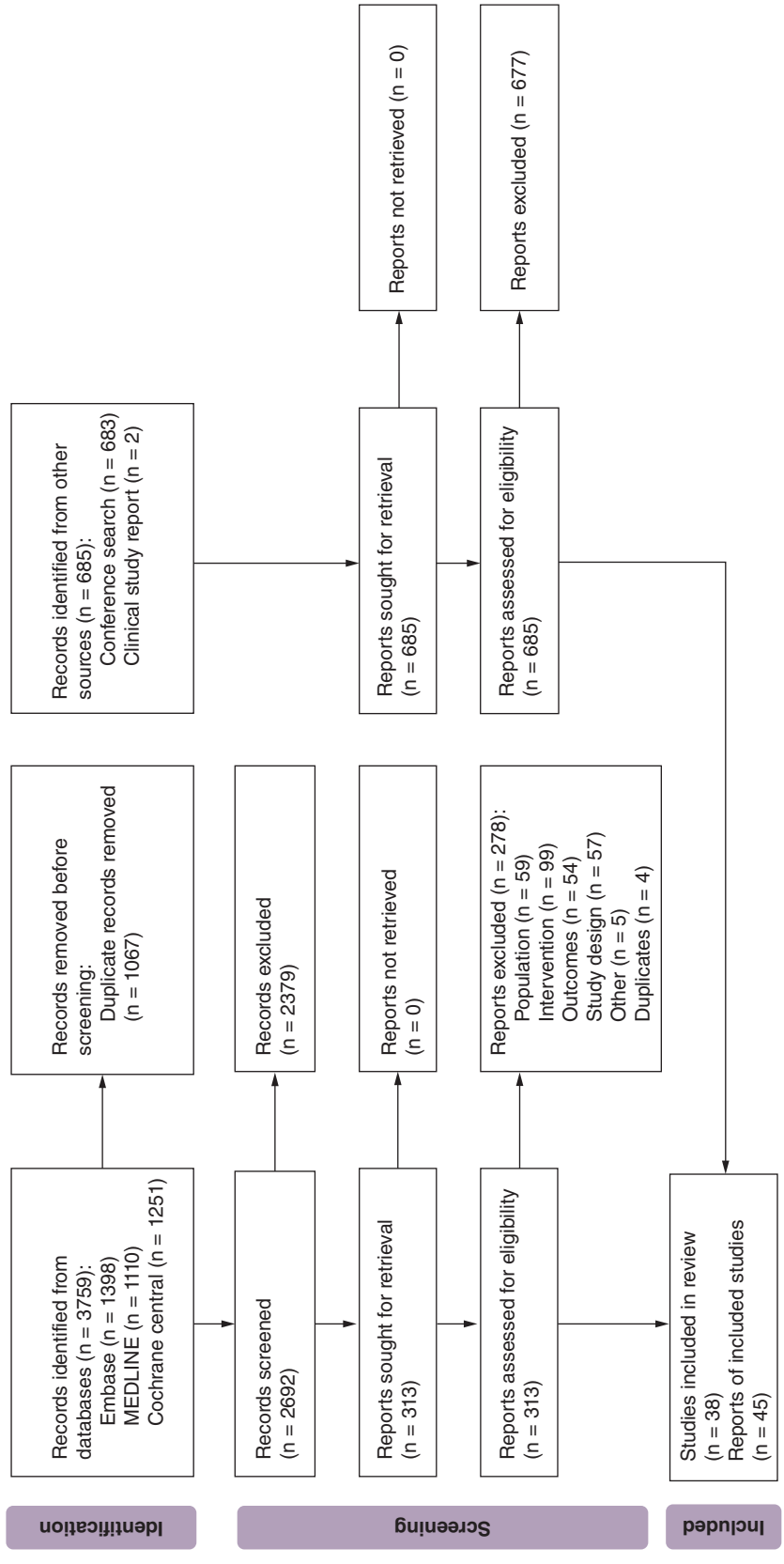

Figure 1. PRISMA flow diagram.

Table 1. Study and patient characteristics.

Study ID	Study design	Country	Intervention	Sample size	Median age (range)	HER2+ status	Prior treatments
First-line standard of care							
CLEOPATRA	RCT (phase III)	Multinational	Pertuzumab + trastuzumab + docetaxel	402	–	FISH+: 402 (100%)	–
MARIANNE	RCT (phase III)	Multinational	T-DM1	367	52 (27-82)	IHC 3+: 367 (100%)	–
PERNETTA	RCT (phase II)	–	Pertuzumab + trastuzumab ± weekly chemotherapy (paclitaxel or vinorelbine)	210	58 (-)	–	–
PERTAIN	RCT (phase II)	Multinational	Pertuzumab + trastuzumab + AI (anastrozole or letrozole) + docetaxel or paclitaxel	129	59 (35–87)	IHC 0: 0 (0%) IHC 1+: 0 (0%) IHC 2+: 15 (11.6%) IHC 3+: 108 (83.7%) Not performed: 6 (4.7%)	–
PUFFIN	RCT (phase III)	China	Pertuzumab + trastuzumab + docetaxel	122	51 (26–74)	IHC 1+: 1 (0.8%) IHC 2+: 34 (28.8%) IHC 3+: 83 (70.3%) FISH: 119 (97.5%)	–
MetaPHER	nRCT (single-arm)	Multinational	Pertuzumab + trastuzumab + docetaxel	412	Mean: 55.6 (SD 11.7)	412 (100%)	–
PERUSE	nRCT (single-arm)	Multinational	Pertuzumab + trastuzumab + taxane (docetaxel or paclitaxel or nab-paclitaxel)	1436	54 (23–87)	IHC 3+: 1436 (100%)	–
Puhalla 2016	nRCT (single-arm)	USA	Eribulin + trastuzumab (with prior trastuzumab)	21	65 (42–78)	IHC 3+: 21 (100%)	–
			Eribulin + trastuzumab (without prior trastuzumab)	31	56 (31–81)	IHC 3+: 31 (100%)	–
SAPPHIRE	nRCT (single-arm)	Australia	Pertuzumab + trastuzumab + taxane	50	Mean 52.9 (SD 12)	ISH+: 44 (88%) IHC 3+ (ISH not tested): 6 (12%)	–
Wang 2019	nRCT (single-arm)	USA	Pertuzumab + trastuzumab + paclitaxel	69	53 (26–84)	IHC 0/1+: 3 (4%) IHC 2+: 8 (12%) IHC 3+: 56 (81%) Unknown: 2 (3%)	–
Bahceci 2021	Observational study	Turkey	T-DM1	414	47 (24–80)	FISH+: 414 (100%)	–
De Placido 2018	Observational study	Italy	Pertuzumab + trastuzumab + taxane (docetaxel or paclitaxel)	155	52 (2979)	IHC 3+: 155 (100%)	–
Garrone 2020	Observational study	Italy	Pertuzumab + trastuzumab + taxane (docetaxel or paclitaxel)	180	55 (28–79)	180 (100%)	–
Lupichuk 2019	Observational study	Canada	Pertuzumab + trastuzumab + taxane	122	57 (24–86)	IHC 3+: 122 (100%)	–
Masuda 2019	Observational study	Japan	T-DM1	104	58 (30–89)	IHC 3+: 104 (100%)	–
Okines, 2018	Observational study	UK	Pertuzumab + trastuzumab + docetaxel	132	56.5 (-)	IHC 2+: 21 (15.9%) IHC 3+: 111 (84.1%)	–
Pizzuti 2020	Observational study	Italy	T-DM1	55	57 (26–82)	IHC 3+: 55 (100%)	–
Reinhorn 2021	Observational study	Israel	Pertuzumab + trastuzumab + taxane (docetaxel and/or paclitaxel)	87	58 (IQR 28–78)	IHC 3+: 87 (100%)	–

3L: Third-line; 4L: Fourth-line; 5L+: Fifth-line or more; AI: Aromatase inhibitor; FISH: Fluorescence *in situ* hybridization; HER2+: Human epidermal growth factor receptor 2-positive; IHC: Immunohistochemistry; IQR: Interquartile range; ISH: *In situ* hybridization; nRCT: Non-randomized controlled trial; RCT: Randomized controlled trial; SD: Standard deviation; T-DM1: Ado-trastuzumab emtansine; trastuzumab deruxtecan.

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Table 1. Study and patient characteristics (cont.).

Study ID	Study design	Country	Intervention	Sample size	Median age (range)	HER2+ status	Prior treatments
First-line standard of care							
RePer	Observational study	Italy	Pertuzumab + trastuzumab + vinorelbine	65	60 (IQR 27–82)	IHC 3+: 65 (100%)	–
Ricciardi 2017	Observational study	Italy	Pertuzumab + trastuzumab + taxane (docetaxel or paclitaxel)	264	53 (29–80)	IHC 2+ (ISH amplified): 57 (21.6%) IHC 3+ = 156 (59.1%) Positive, unknown = 51 (19.3%)	–
Robert 2017	Observational study	USA	Pertuzumab + trastuzumab + docetaxel	35	50 (20–71)	35 (100%)	–
Schettini 2021	Observational study	Italy	Pertuzumab + trastuzumab + taxane (docetaxel or paclitaxel)	266	57.3 (22.2–92.1)	266 (100%)	–
Stefanou 2018	Observational study	Greece	Pertuzumab + trastuzumab + docetaxel	40	62 (37–85)	40 (100%)	–
Studentova 2017	Observational study	–	Pertuzumab + trastuzumab + docetaxel	182	Mean: 56.5	182 (100%)	–
Second-line standard of care							
Bahceci 2021	Observational study	Turkey	T-DM1	149	–	–	–
Fabi 2017a	Observational study	Italy	T-DM1 with prior pertuzumab + trastuzumab	34	43 (29–77)	IHC 3+ or IHC 2+/FISH+: 34 (100%)	Prior paclitaxel combined to anti-HER2: 20 (58.9%) Prior docetaxel combined to anti-HER2: 14 (41.1%)
			T-DM1 with prior trastuzumab	73	51 (28–77)	IHC 3+ or IHC 2+/FISH+: 73 (100%)	Prior paclitaxel combined to anti-HER2: 49 (67.1%) Prior docetaxel combined to anti-HER2: 24 (32.9%)
Fabi 2017b	Observational study	Italy	T-DM1	300	51 (27–78)	300 (100%)	Immunotherapy: 300 (100%)
GIM14/BIOMETA	Observational study	Italy	T-DM1	77	50 (33–78)	77 (100%)	Pertuzumab + trastuzumab + taxane: 77 (100%)
Noda Narita, 2019	Observational study	Japan	Trastuzumab + Pertuzumab	18	53 (43–73)	18 (100%)	–
			Trastuzumab	24	60 (30–74)	24 (100%)	–
Pizzuti 2020	Observational study	Italy	Pertuzumab + trastuzumab + taxane and/or T-DM1	–	–	–	–
TDM1RM	Observational study	Spain	T-DM1	52	50 (29–75)	52 (100%)	Immunotherapy: 52 (100%) Chemotherapy: 52 (100%)
Third-line or more interventions							
EMBRACE	RCT (phase III)	Multinational	Eribulin	83	–	–	–
			Treatment of physician's choice	40	–	–	–
NALA	RCT (phase III)	Multinational	Neratinib + capecitabine	307	55 (IQR 47–63)	307 (100%)	Trastuzumab: 124 (40.4%) Trastuzumab + pertuzumab: 24 (7.8%) Trastuzumab + T-DM1: 58 (18.9%) Trastuzumab + pertuzumab + T-DM1: 101 (32.9%)
			Lapatinib + capecitabine	314	54 (IQR 47–62)	314 (100%)	Trastuzumab: 113 (36%) Trastuzumab + pertuzumab: 23 (7.3%) Trastuzumab + T-DM1: 64 (20.4%) Trastuzumab + pertuzumab + T-DM1: 114 (36.3%)

3L: Third-line; 4L: Fourth-line; 5L+: Fifth-line or more; AI: Aromatase inhibitor; FISH: Fluorescence *in situ* hybridization; HER2+: Human epidermal growth factor receptor 2-positive; IHC: Immunohistochemistry; IQR: Interquartile range; ISH: *In situ* hybridization; nRCT: Non-randomized controlled trial; RCT: Randomized controlled trial; SD: Standard deviation; T-DM1: Ado-trastuzumab emtansine; trastuzumab deruxtecan.

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Table 1. Study and patient characteristics (cont.).

Third-line or more interventions							
PATRICIA II	RCT (-)	Spain	Palbociclib + trastuzumab ± letrozole	71	Mean: 59.1 (34–89)	IHC 3+/FISH+: 71 (100%)	Immunotherapy: 71 (100%)
			ER- cohort: Palbociclib + trastuzumab	15	Mean: 61.7 (34–81)	IHC 3+/FISH+: 15 (100%)	Immunotherapy: 15 (100%)
			ER+ cohort: palbociclib + trastuzumab without letrozole	28	Mean: 60.1 (41–89)	IHC 3+/FISH+: 28 (100%)	Immunotherapy: 28 (100%)
			ER+ cohort: Palbociclib + Trastuzumab + letrozole	28	Mean: 56.6 (40–82)	IHC 3+/FISH+: 28 (100%)	Immunotherapy: 28 (100%)
Sim 2019	RCT (phase II)	South Korea	Vinorelbine + lapatinib	75	54 (28–80)	IHC 3+ or IHC 2+/FISH+: 75 (100%)	Chemotherapy: 75 (100%0
			Vinorelbine	74	52 (30–74)	IHC 3+ or IHC 2+/FISH+: 74 (100%)	Chemotherapy: 74 (100%)
SOPHIA	RCT (phase III)	Multinational	Margetuximab + chemotherapy	91	–	91 (100%)	Chemotherapy: 91 (100%)
			Trastuzumab + chemotherapy	90	–	90 (100%)	Chemotherapy: 90 (100%)
TH3RESA	RCT (phase III)	Multinational	Treatment of physician's choice	198	54 (28–85)	IHC 3+/FISH+: 198 (100%)	–
			T-DM1	404	53 (27–89)	IHC 3+/FISH+: 404 (100%)	–
DESTINY-Breast01	nRCT (single-arm)	Multinational	T-Dxd	184	55 (28–96)	IHC 3+/ISH+: 182 (98.9%)	Trastuzumab: 184 (100%) T-DM1: 184 (100%) Pertuzumab: 121 (65.8%) Other anti-HER2 therapy: 100 (54.3%) Hormone therapy: 90 (48.9%) Other systemic therapy: 183 (99.5%)
Araki 2017	Observational study	Japan	Eribulin + pertuzumab + trastuzumab	–	–	–	–
Bahceci 2021	Observational study	Turkey	T-DM1 (3L)	102	–	–	–
			T-DM1 (4L)	74	–	–	–
			T-DM1 (5L+)	44	–	–	–
Fabi 2017b	Observational study	Italy	T-DM1 (3L)	300	–	–	–
			T-DM1 (>3L)	300	–	–	–
Sarici 2021	Observational study	Turkey	Eribulin + trastuzumab	36	Mean: 43.3 (20–60)	IHC 3+ or IHC 2+/FISH+: 36 (100%)	–

3L: Third-line; 4L: Fourth-line; 5L+: Fifth-line or more; AI: Aromatase inhibitor; FISH: Fluorescence *in situ* hybridization; HER2+: Human epidermal growth factor receptor 2-positive; IHC: Immunohistochemistry; IQR: Interquartile range; ISH: *In situ* hybridization; nRCT: Non-randomized controlled trial; RCT: Randomized controlled trial; SD: Standard deviation; T-DM1: Ado-trastuzumab emtansine; trastuzumab deruxtecan.

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Sample sizes ranged from 42 to 300, and median ages of patients ranged from 43 to 60 years. Some studies also included information on prior treatments received (Table 1). Two observational studies did not report patient characteristics for patients receiving 2L treatments [42,48].

Third-line or greater interventions

Eleven studies reported on patients with HER2+ a/mBC receiving 3L+ treatments [16,18,20,21,42,57,61–68]. The SOPHIA trial included mixed 2L+ patients, however reported outcomes for a subgroup of 3L+ patients [16].

Six RCTs were conducted to investigate efficacy of different treatment options for 3L+ HER2+ BC [16,18,20,21,61–64]. Interventions included eribulin, neratinib + capecitabine, lapatinib + capecitabine, palbociclib + trastuzumab ± letrozole, vinorelbine + lapatinib, T-DM1, margetuximab + chemotherapy (capecitabine, eribulin, gemcitabine or vinorelbine) or trastuzumab + chemotherapy (capecitabine, eribulin, gemcitabine or vinorelbine). The sample sizes varied, ranging from 40 to 404 patients, and median age of the patients ranged from 53 to 55 years (Table 1). Four of the six RCTs were multinational, whereas PATRICIA II [62] was conducted in Spain and Sim 2019 [63] was carried out in South Korea. Prior treatments varied across trials.

One single-arm 3L+ trial was identified [65,66]. DESTINY-Breast01, a multinational study, investigated the efficacy of T-Dxd in 184 patients who are HER2+ and intolerant/refractory to T-DM1 [65,66].

Four observational studies reported on HER2+ a/mBC receiving 3L+ treatments [42,57,67,68]. Two studies were conducted in Turkey, one took place in Italy and the final observational study enrolled patients in Japan. T-DM1 was the most common intervention, which was studied in Bahceci 2021 [42] as 3L, fourth-line (4L), and fifth-line or subsequent lines (5L+) and in Fabi 2017b [57] as 3L and >3L. Two studies evaluated eribulin in combination with trastuzumab [67] or trastuzumab + pertuzumab [68]. Only one study reported patient characteristics [68]. However, the number of patients in the study ranged from 36 to 300. Araki 2017 [67] did not report sample size.

Efficacy outcomes

First-line standard of care interventions

Among RCTs, PERNETTA [32] reported the highest median PFS of 23.3 months (95% confidence interval [CI] 17.6–32.6 months) in patients receiving pertuzumab + trastuzumab ± weekly chemotherapy (paclitaxel or vinorelbine) (Table 2). None of the other RCTs that investigated pertuzumab + trastuzumab combinations included vinorelbine, and all reported slightly lower PFS. The median PFS in the other RCTs using pertuzumab + trastuzumab combinations ranged from 12.4 months (95% CI: 10–14 months) in pertuzumab + trastuzumab + docetaxel in CLEOPATRA [28,29] to 18.9 months (95% CI: 14.1–27.7 months) among patients receiving pertuzumab + trastuzumab + aromatase inhibitors (AI; anastrozole or letrozole) + docetaxel or paclitaxel in PERTAIN [33].

MARIANNE [30,31], the only RCT in our dataset to report median PFS on patients receiving T-DM1, achieved a result within the range observed for 1L patients at 14.1 months (95% CI not reported [NR]).

Regarding median OS, CLEOPATRA [28,29] reported 57.1 months (95% CI: 50–72) in patients receiving pertuzumab + trastuzumab + docetaxel. Patients receiving T-DM1 in MARIANNE [30,31] achieved median OS of 53.7 months (95% CI: NR). Median OS was not reached by patients receiving pertuzumab + trastuzumab + docetaxel in PERTAIN [33]. Other than median OS reported by these three RCTs, additional survival information was collected: 3-year OS rate was 73.1% in PERNETTA [32], and 5-year OS rate was 49% in CLEOPATRA [28,29].

In the single-arm trials, median PFS ranged from 11.5 months (95% CI: 6–13.9) in subgroup of patients receiving eribulin + trastuzumab with prior trastuzumab (Puhalla 2016 [38]) to 25.7 months (95% CI: 17-not reached) in Wang 2019 [40], a study evaluating pertuzumab + trastuzumab + paclitaxel. Both of these studies had small sample sizes (Puhalla 2016 [38] subgroup n = 21; Wang 2019 [40] n = 69).

Median OS was not reached in MetaPHER [36], SAPPHIRE [39] and Wang 2019 [40] and was not reported in the two remaining single-arm trials. The only reported median OS was 65.3 months (95% CI: 60.9–70.9) in patients receiving pertuzumab + trastuzumab + taxane (docetaxel, paclitaxel, or nab-paclitaxel) in PERUSE [35,37]. However, MetaPHER [36] reported 92.9% one-year and 81.1% two-year OS rate in patients receiving pertuzumab + trastuzumab + docetaxel.

Median PFS and OS ranged greatly between the same treatments in different observational studies. The combination of pertuzumab, trastuzumab and taxane was associated with a median PFS ranging from 12 months (95% CI: 2–38) (Ricciardi 2017 [51]) to 32.9 months (95% CI: NR) (Reinhorn 2021 [49]) and median OS ranging from 15.2 months (95% CI: 2–36) (Ricciardi 2017 [51]) to 74 months (95% CI: 62–87) (Pizzuti 2020 [48]). However,

Table 2. Progression-free survival and overall survival.

Study ID	Study design	Intervention	Analysis	Follow-up, median months	Assessor	Criteria used	Progression-free survival		Overall survival					
							Sample size	Median, months (95% CI)	Sample size	Median, months (95% CI)	1 year, OS (%)	2 year, OS (%)	3 year, OS (%)	5 years, OS (%)
First-line standard of care														
CLEOPATRA	RCT	Pertuzumab + trastuzumab + docetaxel	ITT	99.9	Investigator	RECIST v1.0	304	12.4 (10–14)	402	57.1 (50–72)	–	–	–	49%
MARIANNE	RCT	T-DM1	ITT	35	IRC	RECIST v1.1	367	14.1 (-)	–	–	–	–	–	–
				54	–			–	367	53.7 (-)				
PERNETTA	RCT	Pertuzumab + trastuzumab ± weekly chemotherapy (paclitaxel or vinorelbine)	–	24	–	–	210	23.3 (17.6–32.6)	105	–	–	–	73.1%	–
PERTAIN	RCT	Pertuzumab + trastuzumab + AI (anastrozole or letrozole) + docetaxel or paclitaxel	ITT	31	–	RECIST v1.1	129	18.9 (14.1–27.7)	129	Not reached	–	–	–	–
PUFFIN	RCT	Pertuzumab + trastuzumab + docetaxel	ITT	13.7	Investigator	RECIST v1.2	122	14.5 (12.5–18.6)	–	–	–	–	–	–
MetaPHER	Non-RCT	Pertuzumab + trastuzumab + docetaxel	–	27	Investigator	RECIST v1.1	412	18.7 (-)	412	Not reached	92.9%	81.1%	–	–
PERUSE	Non-RCT	Pertuzumab + trastuzumab + taxane (docetaxel or paclitaxel or nab-paclitaxel)	ITT	68.7	Investigator	RECIST v1.1	1436	20.7 (18.9–23.1)	1436	65.3 (60.9–70.9)	–	–	–	–
Puhalla 2016	Non-RCT	Eribulin + trastuzumab (with prior trastuzumab)	–	–	–	RECIST v1.1	21	11.5 (6–13.9)	–	–	–	–	–	–
		Eribulin + trastuzumab (without prior trastuzumab)	–	–	–	RECIST v1.1	31	12.2 (7.3–19.1)	–	–	–	–	–	–
SAPPHIRE	Non-RCT	Pertuzumab + trastuzumab + taxane	ITT	50	Investigator	RECIST v1.1	30	17 (12.5–31.2)	50	Not reached (31.3–not estimated)	–	–	–	–

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Table 2. Progression-free survival and overall survival (cont.).

Study ID	Study design	Intervention	Analysis	Follow-up, median months	Assessor	Criteria used	Progression-free survival		Overall survival					
							Sample size	Median, months (95% CI)	Sample size	Median, months (95% CI)	1 year, OS (%)	2 year, OS (%)	3 year, OS (%)	5 years, OS (%)
First-line standard of care														
Wang 2019	Non-RCT	Pertuzumab + trastuzumab + paclitaxel	–	59	–	RECIST v1.1	49	25.7 (17–not reached)	49	Not reached	–	–	–	–
Bahceci 2021	Observational	T-DM1	–	67.3	–	–	17	37	17	43	–	–	–	–
De Placido 2018	Observational	Pertuzumab + trastuzumab + taxane (docetaxel or paclitaxel)	–	–	–	RECIST v1.1	155	27.8	–	–	–	–	–	–
Garrone 2020	Observational	Pertuzumab + trastuzumab + taxane (docetaxel or paclitaxel)	–	–	–	–	180	14.9 (0.2–42)	–	–	–	–	–	–
Lupichuk 2019	Observational	Pertuzumab + trastuzumab + taxane	–	33.4	–	–	–	–	122	Not reached	–	–	–	–
		T-DM1	–	29.7	–	–	–	–	104	19 (12.5–25.5)	–	–	–	–
Masuda 2019	Observational	Pertuzumab + trastuzumab + docetaxel	–	–	–	–	132	22.8 (16.9–34.8)	–	–	–	–	–	–
Okines, 2018	Observational	T-DM1	–	20.5	–	–	–	–	55	17.8 (14.2–22)	–	–	–	–
Pizzuti 2020	Observational	Pertuzumab + trastuzumab + taxane	–	–	–	RECIST	371	16 (13–19)	371	–	–	–	–	–
		Pertuzumab + trastuzumab + taxane and/or T-DM1	–	–	–	RECIST	738	12 (11–13)	738	74 (62–87)	–	–	–	–
Reinhorn 2021	Observational	Pertuzumab + trastuzumab + taxane (docetaxel and/or paclitaxel)	–	46	–	RECIST	87	32.9	87	56 (-)	–	–	–	–
RePer	Observational	Pertuzumab + trastuzumab + docetaxel + paclitaxel	–	–	–	–	264	21 (17–25)	264	Not reached	–	80.5%	–	–
Ricciardi 2017	Observational	Pertuzumab + trastuzumab + docetaxel	–	55.6	–	RECIST v1.1	35	12 (2–38)	35	15.2 (2–36)	–	–	–	–
Robert 2017	Observational	Pertuzumab + trastuzumab + taxane	–	16.4	–	–	266	16.9 (14.2–19.7)	–	–	–	–	–	–

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Table 2. Progression-free survival and overall survival (cont.).

Study ID	Study design	Intervention	Analysis	Follow-up, median months	Assessor	Criteria used	Progression-free survival		Overall survival					
							Sample size	Median, months (95% CI)	Sample size	Median, months (95% CI)	1 year, OS (%)	2 year, OS (%)	3 year, OS (%)	5 years, OS (%)
First-line standard of care														
Schettini 2021	Observational	Pertuzumab + trastuzumab + taxane	–	–	–	–	44	16.8 (14–not available)	44	32.8 (14.8–not reached)	–	–	–	–
Schettini 2021	Observational	T-DM1	–	–	–	–	31	9.1 (6–16.3)	–	–	–	–	–	–
Stefanou 2018	Observational	Pertuzumab + trastuzumab + docetaxel	–	37	–	RECIST v1.1	40	24 (14.4–33.6)	40	35 (27.9–42.1)	–	–	–	–
Studentova 2017	Observational	Pertuzumab + trastuzumab + docetaxel	–	–	–	–	182	21.2 (12.2–not reached)	182	Not reached	–	–	–	–
Second-line standard of care														
Bahceci 2021	Observational	T-DM1	–	67.3	–	–	149	12 (-)	149	41	–	–	–	–
Fabi 2017a	Observational	T-DM1 with previous pertuzumab + trastuzumab	–	–	–	–	34	5 (4.3–5.7)	–	–	–	–	–	–
Fabi 2017b	Observational	T-DM1	–	–	–	–	300	9 (6.4–11.6)	–	–	–	–	–	–
GIM14/ BIOMETA	Observational	T-DM1	–	7	–	–	77	6.3 (4.8–7.7)	77	–	82%	–	–	–
Noda Narita 2019	Observational	Trastuzumab	–	7.5	–	RECIST v1.1	24	7.8 (5.5–15.9)	–	–	–	–	–	–
Pizzuti 2020	Observational	All regimens (pertuzumab + trastuzumab + taxane or trastuzumab + taxane or T-DM1)	–	–	–	RECIST	531	7 (6–8)	531	–	–	–	–	–
		T-DM1	–	–	–	RECIST	371	7 (5–9)	371	–	–	–	–	–
		T-DM1 (Pertuzumab as 1L)	–	–	–	RECIST	177	5.6 (4.5–6.6)	177	–	–	78.0%	62.7%	–
		T-DM1 (Pertuzumab not as 1L)	–	–	–	RECIST	194	8 (6.6–9.6)	194	–	–	92.1%	82.9%	–
		WIthout T-DM1 (Pertuzumab as 1L)	–	–	–	RECIST	109	6 (4.2–6.8)	109	–	–	89.1%	78.5%	–
		Pertuzumab + trastuzumab + taxane and/or T-DM1 regimen	–	–	–	RECIST	531	7 (6–8)	–	–	–	–	–	–
TDM1RM	Observational	T-DM1	–	33	–	–	52	8.4 (6.9–9.9)	52	23.6 (17.5–29.7)	–	–	–	–

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Table 2. Progression-free survival and overall survival (cont.).

Third-line or more interventions													
EMBRACE	RCT	Eribulin	ITT	–	IRC	RECIST	83	3.3 (2.1–4.1)	83	11.8 (10.2–14.7)	47.0%	19.6%	–	–
		Treatment of physician's choice	ITT	–	IRC	RECIST	40	3.4 (2.1–4.2)	40	8.9 (7.9–10.7)	30.0%	7.5%	–	–
		Eribulin	PP	–	–	RECIST	71	3.3 (-)	71	11.8 (10.7–15.7)	47.9%	20.1%	–	–
		Treatment of physician's choice	PP	–	–	RECIST	32	2.2 (-)	32	8.9 (6.2–10.7)	25.0%	3.1%	–	–
NALA	RCT	Neratinib + capecitabine	ITT	29.9	–	RECIST v1.1	307	8.8 (7.8–9.8)	307	Mean: 24 (22.1–25.9)	–	–	–	–
		lapatinib + capecitabine	ITT	29.9	–	RECIST v1.1	314	6.6 (5.9–7.4)	314	Mean: 22.2 (20.4–24)	–	–	–	–
PATRICIA II	RCT	Palbociclib + trastuzumab ± letrozole	mITT	–	Investigator	RECIST v1.1	71	5.1 (4.1–7)	–	–	–	–	–	–
		ER- cohort: Palbociclib + trastuzumab	mITT	–	Investigator	RECIST v1.1	15	4.2 (0.7–20.2)	–	–	–	–	–	–
		ER+ cohort: palbociclib + trastuzumab without letrozole	mITT	–	Investigator	RECIST v1.1	28	6 (4.1–27.1)	–	–	–	–	–	–
		ER+ cohort: Palbociclib + Trastuzumab + Letrozole	mITT	–	Investigator	RECIST v1.1	28	5.1 (3.7–9.1)	–	–	–	–	–	–
Sim 2019	RCT	Lapatinib + vinorelbine	ITT	–	–	–	75	3.7 (2.8–4.8)	75	15 (11.5–23.3)	–	–	–	–
		Vinorelbine	ITT	–	–	–	74	2.8 (2.5–4.2)	74	18.9 (13.3–29.1)	–	–	–	–

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Table 2. Progression-free survival and overall survival (cont.).

Third-line or more interventions														
SOPHIA	RCT	Margetuximab + chemotherapy	ITT	–	Investigator	RECIST v1.1	91	5.7 (5.4–6.9)	91	24.1 (16.2-NA)	–	–	–	–
		Trastuzumab + chemotherapy	ITT	–	Investigator	RECIST v1.1	90	4.8 (3.1–5.6)	90	17.5 (15.6–21.0)	–	–	–	–
TH3RESA	RCT	Treatment of physician's choice	ITT	30.5	Investigator	RECIST v1.1	–	–	198	15.8 (13.5–18.7)	–	–	–	–
		T-DM1	ITT	30.5	Investigator	RECIST v1.1	–	–	404	22.7 (19.4–27.5)	–	–	–	–
DESTINY-Breast01	Non-RCT	T-Dxd	–	29.2	–	–	–	–	184	28.4 (24.6–37.2)	–	–	–	–
		T-Dxd	–	11.1	Investigator	RECIST v1.1	184	16.4 (12.7–not reached)	184	–	86.2%	–	–	–
Araki 2017	Observational	Eribulin + pertuzumab + trastuzumab	–	13	Investigator	RECIST v1.1	–	9	–	–	–	–	–	–
Bahceci 2021	Observational	T-DM1 (3L)	–	67.3	–	–	102	8	102	46	–	–	–	–
		T-DM1 (4L)	–	67.3	–	–	74	8	74	23	–	–	–	–
		T-DM1 (5L+)	–	67.3	–	–	44	8	44	17	–	–	–	–
Fabi 2017b	Observational	T-DM1 (3L)	–	–	–	–	300	12 (9.7–16.3)	–	–	–	–	–	–
		T-DM1 (3L+)	–	–	–	–	300	5 (4–5.9)	–	–	–	–	–	–
Sarici 2021	Observational	Trastuzumab + Eribulin	–	–	–	–	36	4 (3.8–6.1)	36	10 (7.5–12.4)	–	–	–	–

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the higher end of the range was achieved in a study where patients received pertuzumab + trastuzumab + taxane and/or T-DM1 regimen [48]. The use of T-DM1 was also found to be effective, with a median PFS ranging from 9.1 (95% CI: 6–16.3) (Schettini 2021 [53]) to 37 months (95% CI: NR) (Bahceci 2021 [42]) and median OS from 17.8 months (95% CI: 14.2–22) (Okines 2018 [47]) to 43 months (95% CI: NR) in Bahceci 2021 [42]. Both longest PFS and OS were observed in Bahceci 2021 [42], however sample size in 1L was small (n = 17) and should be interpreted cautiously.

Second-line standard of care interventions

In the observational studies evaluating 2L SOC, the most common treatment was T-DM1. The median PFS in studies where patients received T-DM1 ranged from 5 months (95% CI: 4.3–5.7) (Fabi 2017a [56]) to 12 months (Bahceci 2021 [42]). In Noda-Narita 2019 [59], patients receiving trastuzumab monotherapy achieved median PFS of 7.8 months (95% CI: 5.5–15.9). In Pizzuti 2020 [48], in patients receiving pertuzumab + trastuzumab + taxane and/or T-DM1 regimen, the median PFS was 7 months (95% CI: 6–8), consistent with others in this group.

Median OS was reported by two T-DM1 studies [42,60], and ranged from 23.6 months (95% CI: 17.5–29.7) in Martinez-Garcia 2020 [60] to 41 months (95% CI: NR) in Bahceci 2021 [42]. Pizzuti 2020 [48] reported OS rates at 2- and 3 years for the cohorts reported (Table 2).

Third-line or greater interventions

In the 3L+ RCTs, patients receiving neratinib + capecitabine in NALA [61] had the longest median PFS of 8.8 months [95% CI: 7.8–9.8]) while patients receiving vinorelbine in Sim 2019 [63] had the shortest median PFS of 2.8 months (95% CI: 2.5–4.2). Patients receiving eribulin in the HER2+ subgroup of EMBRACE [21] had a median PFS of 3.3 months (95% CI: 2.1–4.1). Other 3L+ interventions included physician's choice of treatment (TPC), neratinib + capecitabine, palbociclib + trastuzumab ± letrozole, lapatinib + vinorelbine, margetuximab + chemotherapy, trastuzumab + chemotherapy had similar median PFS. TH3RESA [64] was the only study to evaluate T-DM1 in 3L+ patients, however, median PFS was not reported.

Median OS in the 3L+ RCTs ranged from 8.9 months (95% CI: 7.9–10.7) in the TPC arm of EMBRACE [20,21] to 24.1 months (95% CI: 16.2-not available) in patients receiving margetuximab + chemotherapy in SOPHIA [16]. NALA reported survival similar to the upper end of the range for patients receiving neratinib+ capecitabine or lapatinib + capecitabine (24 months [95% CI: 22.1–25.9] and. 22.2 months [95% CI: 20.4–24] respectively), although mean rather than median OS was reported. EMBRACE [20,21] reported 11.8 months (95% CI: 10.2–14.7) median OS in patients with HER2-positive disease receiving Eribulin.

DESTINY-Breast01 [65,66] was the only 3L+ single-arm trial. At the 11.1-month follow-up, median PFS was 16.4 months (95% CI: 12.7-not reached). At the 29.2-month follow-up, median OS was 28.4 months (95% CI: 24.6–37.2).

In the four observational studies on 3L+ treatments, Sarici 2021 [68] reported 4 months (95% CI: 3.8–6.1) median PFS in patients treated with trastuzumab + eribulin. Another trastuzumab + eribulin based study, Araki 2017 [67], investigated eribulin in combination with pertuzumab and trastuzumab, which resulted in 9 months (95% CI: NR) median PFS. Bahceci 2021 [42] evaluated the efficacy of T-DM1 as a 3L, 4L and fifth-line or greater (5L+) treatment, and interestingly PFS was 8 months in each line. Fabi 2017b [57] also provided patients with T-DM1. In 3L patients, the median PFS was 12 months (95% CI: 9.7–16.3); in 4L+ patients, the median PFS was 5 months (95% CI: 4–5.9).

Median OS was reported as 10 months (95% CI: 7.5–12.4) in patients receiving trastuzumab + eribulin in Sarici 2021 [68] and in Bahceci 2021 [42], the median OS decreased over the different lines of treatment (3L, 4L, 5L+). None of the other observational studies reported median OS.

Discussion

This study systematically reviewed published clinical trials and observational studies examining the efficacy and effectiveness of eribulin and various treatment options for patients with HER2+ a/mBC. The focus was on SOC in 1L and 2L, as well as any treatment 3L+. Our SLR at the time of protocol development, used the recommended 1L and 2L treatments of pertuzumab + trastuzumab ± taxane or T-DM1 as defined by the ASCO and the NCCN for patients with HER2+ a/mBC [24,25]. As 3L+ treatments do not have such recommendations, we included all treatments in the population group. The inclusion of 3L+ treatments was essential due to the limited therapeutic options available in advanced stages of a/mBC. In total, 45 publications on 38 primary studies were included in the

SLR [16,20,21,28–68]. Our SLR identified 24 studies (five RCTs, five single-arm trials and 14 observational studies) reporting on 1L SOC and 1L eribulin [28–40,42–55]. Additionally, seven studies (all observational) reported on 2L SOC [42,56–60], and 11 studies (six RCTs, one single-arm trial and four observational studies) presented data on 3L+ treatments [16,20,21,42,57,61–68].

Eribulin, alone or in combination, was evaluated as an intervention in one single-arm trial in 1L (Puhalla 2016 [38]; eribulin + trastuzumab) and in three studies in 3L+ (EMBRACE [21]; RCT; eribulin vs TPC; Araki 2017 [67]; observational study; eribulin + pertuzumab + trastuzumab; and Sarici 2021 [68]; observational study; eribulin + trastuzumab). The EMBRACE study was the only clinical trial that used eribulin monotherapy, and the study showed a numerical improvement in median OS with eribulin over TPC (11.8 months vs. 8.9 months in the HER2+ subgroup [20,21]. Overall, within the 3L+ studies, drawing conclusions proved challenging due to a lack of standardization within this group, characterized by variation in study design, sample size and treatments given.

Outcomes for 1L studies included in this analysis were as expected, as these regimens are the established standard of care. The observational studies had the greatest variation in median OS and PFS. In observational studies, OS ranged from 15.2 months with pertuzumab + trastuzumab + docetaxel [51] to 74 months in pertuzumab + trastuzumab + taxane and/or T-DM1 [48]. Similarly, median PFS in the observational studies examining T-DM1 ranged from 9.1 months to 37 months [42]. The RCTs in 1L SOC had less variation in PFS (ranging from 12.4 months with pertuzumab + trastuzumab + docetaxel in CLEOPATRA [28,29] to 23.3 months with pertuzumab + trastuzumab ± weekly chemotherapy (paclitaxel or vinorelbine) in PERNETTA [32].

Strikingly, we found limited studies on 2L SOC, primarily due to the exclusion of studies with mixed lines of treatment without separate outcomes such as studies that included a/mBC patients with HER2 positive breast cancer receiving 1L/2L, 2L/3L, or 2L+. Furthermore, we only included studies on treatment with our definitions of SOC. Thus, results from key trials like ALTERNATIVE [69], E-VITA [70], HER2CLIMB [71] and Study 301 [72] were not included in our SLR. However, in the seven observational studies included, median PFS was similar in the studies ranging from 5 months with T-DM1 with previous pertuzumab + trastuzumab [57] to 12 months with T-DM1 (without prior pertuzumab + trastuzumab? Or similar) [42]. The relatively short observed PFS highlights concerns about the consistency and efficacy of SOC treatment in the real-world evidence setting for this population group.

This SLR provides valuable insights in the current landscape of HER2+ a/mBC treatment. We observed considerable heterogeneity in the study designs and outcomes, specifically in the 3L+ studies, emphasizing the remaining gaps in therapeutic options for patients who have progressed after 1L and 2L treatment. Thus, continued research efforts are critical to understand effective treatment options for HER2+ a/mBC in the 3L+ setting and to establish clear and consistent guidelines for clinicians.

Comparing our findings with existing literature reveals both parallels and distinctions. Our research aligns with SLRs supporting the efficacy of pertuzumab + trastuzumab in improving outcomes for HER2+ BC patients [73–75]. One SLR evaluated HER2-targeted therapies in HER2+ BC and included 26 studies [73], in which trastuzumab or T-DM1 ± chemotherapy + pertuzumab was found to be effective treatment for patients with HER2+ breast cancer. The line of treatment was not reported, and this SLR included studies providing neoadjuvant, adjuvant and metastatic treatment. An additional SLR examined RCTs evaluating pertuzumab + trastuzumab versus trastuzumab in treating HER2+ BC [74], in which 14 trials in the neoadjuvant, adjuvant and metastatic (1L) settings were included; similar to the present study, this SLR demonstrated that pertuzumab + trastuzumab improves the outcomes of patients.

Lastly, an SLR conducted in 2015 evaluated HER2-targeted therapies for HER2+ mBC [75]. The review included 19 RCTs, of which 12 were in the 1L setting and the remaining seven were in 2L+. However, the review limited its inclusion criteria to only phase III RCTs, and found OS improved from 20.3 months with standard chemotherapy to 48 months with pertuzumab + trastuzumab + docetaxel. In 2L, OS improved from 15.3 months with capecitabine to 30.7 months with T-DM1. Lastly, in 3L, use of lapatinib + trastuzumab improved OS compared with lapatinib. A more recent SLR comprising 34 studies by Chabot *et al.*, 2020 [76] examined the real-world effectiveness of eribulin in 2L+ settings. The authors observed high variability in OS with eribulin use in the real-world setting in this SLR, aligning with our findings and accentuating the necessity for a more nuanced understanding the performance of eribulin across diverse clinical settings.

Our SLR included both clinical trials and observational studies to obtain a comprehensive understanding of all available evidence and minimize bias. Assessing read-world evidence provides insights on how treatments are being used in real-world clinical practice and adds additional long-term data for outcomes [77].

We limited our studies to primary (do you mean treatment for advanced HER2+ breast cancer? Primary is often synonymous with 'neoadjuvant') treatments rather than neoadjuvant or adjuvant treatments. We excluded studies that included a mixture of patients treated in the 1L+ and 2L+ settings. Thus, we excluded an important RCT in this patient population, DESTINY-Breast03 [15] and HER2CLIMB!, which limits our results for patients receiving treatment in the 2L. Lastly, our SLR search was conducted in September 2021, and more recent data on emerging anti-HER2 therapies, including tucatinib, fam-trastuzumab deruxtecan-nxki (DS-8201a), neratinib and margetuximab-cmkb, are not included.

This SLR focuses on efficacy and effectiveness of 1L SOC, 2L SOC and any treatments in 3L+. Although safety data from the 38 studies was extracted, it was notably lacking in all but three studies on 3L+ treatments (and all three studies reported AE rates ≥93%) [62,66,67]. It is imperative to highlight that safety, in addition to efficacy/effectiveness, is an essential consideration when choosing an appropriate treatment for patients with HER2+ a/mBC.

In summary, the present study provides a more nuanced understanding of eribulin in HER2+ a/mBC, placing its performance within the broader spectrum of HER2-targeted therapies. The landscape of therapies for HER2+ BC continues to evolve, with the development of novel systemic agents, other therapeutic modalities and more personalized and biomarker-driven treatment strategies, and understanding their effectiveness on the large cohorts of patients underscores the need for continued real-world research.

Conclusion

This SLR not only emphasizes the variability in outcomes (OS and PFS) between the clinical trials and the observational studies in 1L and 2L SOC for HER2+ a/mBC but also sheds light on the elevated level of heterogeneity observed in studies on 3L+ treatments. The diverse treatments and study design within the 3L+ subgroup pose a challenge in comparing the outcomes and determining the most effective treatment. The differences in the 3L+ group, characterized by the variations in study design, sample size and administered treatments, underscore the complexity in drawing definitive conclusions.

Furthermore, the potential for achieving prolonged survival with novel agents introduce a compelling argument for additional research. The observed variability in outcomes across different treatments in the 3L+ setting accentuates the need for more investigations into the efficacy and safety profiles of these interventions. This prompts a call for additional studies to determine the nuances of these new treatments, allowing for a more comprehensive understanding of their impact on patients with HER2+ a/mBC' survival outcomes.

Summary points

- Breast cancer (BC) is the most prevalent cancer worldwide and has continued to rise rapidly.
- This systematic literature review (SLR) comprehensively summarizes various treatment options for patients with HER2+ advanced/metastatic BC (a/mBC).
- We conducted a search for clinical trials and observational studies published from 2016 to September 2021.
- We included a/mBC patients receiving first-line (1L) standard of care (SOC), second-line (2L) SOC, or third-line or more (3L+) treatments.
- Of the 3,759 citations screened, we found 38 primary studies reported in 45 publications to include in this SLR.
- In total, there were 24 studies on 1L SOC, 8 studies on 2L SOC and 10 studies on 3L+.
- Overall survival and progression-free survival varied between treatments lines and study design, where patients in 1L tended to have better outcomes compared with patient in 3L+.
- We conducted a risk of bias assessment of the included studies, and many studies included had a minimal risk of bias.
- As we included different study design and that 3L+ treatments varied, this limited our ability to draw conclusions due to the lack of standardization.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://bpl-prod.literatumonline.com/doi/10.57264/cer-2023-0153

Author contributions

All authors were responsible for study conception and design. R Goldgrub and V Tongbram were responsible for data collection and analysis. Original draft was prepared by R Goldgrub and all the authors were responsible for review and editing. Supervision was provided by K Ndirangu, V Tongbram, R Antony and B Lalayan. All authors have read and approved the final manuscript. All authors have agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with anyorganization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt. The source of this data is from Eisai as they are two clinical study reports.

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