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The role of chemotherapy in treatment of advanced breast cancer: an overview for clinical practice

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ABSTRACT

This review aims to evaluate the role of chemotherapy-containing regimens in the treatment of advanced breast cancer (ABC), with the purpose to optimize selection, sequencing and duration of treatment with the currently available agents for clinical practice. Data from observational as well as randomized phase II and III studies were included. Chemotherapy yielded a median overall survival (OS) of 2 years in registration studies, with comparable efficacy of different agents. Combining chemotherapy agents did not yield OS improvement and caused greater toxicity compared with single-agent chemotherapy. Continuing chemotherapy till progression or unacceptable toxicity generated greater efficacy without detrimental impact on quality of life compared with a limited amount of cycles. In real-world studies, benefits after third-line chemotherapy were modest compared with first- and second-line. Furthermore, effects of previous chemotherapy predicted effects of next-line therapy in real-world. Physicians increasingly prescribed capecitabine or taxanes as first- or second-line chemotherapy over time.

1. Introduction

Breast cancer is the most prevalent malignancy among women worldwide, resulting in a significant global disease burden [1]. Fortunately, the prognosis of early stages of this disease has improved considerably due to improved screening and introduction of more effective systemic treatment options [2]. However, about 5-10% of patients with a new diagnose of breast cancer present with metastatic disease [3]. Additionally, 20-30% of patients who initially present with early breast cancer will acquire a metastatic relapse over time [4].

Whenever the disease reaches a metastatic stage, it remains largely incurable with a median overall survival (OS) of 2-3 years depending on the tumor subtype. Real-world data indicated that patients with tumors with a hormone receptor (HR) and HER-2-neu receptor (HER2) positive status have the most favorable prognosis, followed in descending order by the HR + /HER2- subtype, the HR-/HER2 + subtype, and lastly the triple-negative (TN) subtype [5]. Although in the past decennia numerous new targeted therapies like CDK 4/6 inhibitors [6–8], PARP-inhibitors [9,10], a PI3K inhibitor [11], immunotherapy [12], and HER2-targeted therapies [13–15] have been implemented, the absolute improvement in the prognosis of patients with advanced breast cancer (ABC) was relatively small [16].

More and more we begin to understand that molecular characteristics play a crucial role in the prognosis and optimal treatment of ABC. The expectation for the future is that the indicated treatment will no longer solely depend on the four tumor subtypes, but will be based on the underlying genetic profile and signaling pathways, which can be important targets for so-called precision medicine [17].

Considering the ample arsenal of available treatment options and the growing knowledge on genomic profiles and signaling pathways, the question rises whether chemotherapy still has a place in the treatment of ABC or if future treatment will comprise of targeted therapies such as CDK4/6 inhibitors combined with endocrine- or HER2-directed therapies. However, as chemotherapy remains a competent treatment option also in cases where targeted therapies are (no longer) effective, and we only just begin to understand the genomic profiles that divide the heterogeneous breast cancer population into clinically relevant subgroups, the expectation is that for the near-future, chemotherapy

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will remain integrated as a backbone in the treatment of ABC. Thus, optimization of chemotherapy use with the currently available agents is vital. The goal is to use the most effective agents, without pursuing treatment of the disease at the cost of quality of life or social activities.

This review aims to evaluate the role of chemotherapy-containing regimens in the treatment of ABC, with the purpose to optimize selection, sequencing and duration of treatment with the currently available agents for clinical practice.

2. Methods

2.1. Study design and selection criteria

This review was based on published full-text data of observational as well as randomized phase II and III studies that included patients receiving chemotherapy for ABC. The aim was to assess which evidence the FDA/EMA used to approve modern chemotherapy regimens, if we should use single-agent or a combination of multiple cytostatic agents, how long chemotherapy should be continued, how many lines of chemotherapy are actually given in clinical practice, what outcomes can be expected of these lines and which sequence of agents is used, and what the effects are of the addition of targeted therapy to a chemotherapy backbone versus chemotherapy alone.

Studies on the following topics were included: 1) studies underlying FDA and/or EMA-approval of chemotherapy-containing regimens for advanced breast cancer between January 1994 and December 2019, 2) randomized controlled trials (RCTs) investigating single-agent vs. multiple-agent chemotherapy, 3) studies investigating durations of chemotherapy-containing regimens, 4) studies investigating the total number of chemotherapy-containing treatment lines, 5) studies investigating outcomes of specific chemotherapy-containing treatment line(s), 6) studies investigating the use of chemotherapy-agents over different treatment lines, 7) RCTs investigating chemotherapy in combination with targeted therapy vs. chemotherapy alone (single- or multiple agents). There were no exclusions based on the agents used, the number of participants, the use of concomitant endocrine or targeted therapies, or the timing of randomization. Studies reporting one or more of the following outcome measures were included: 1) Overall response rate (ORR), 2) Progression-free survival (PFS) or time to progression (TTP), 3) Overall survival (OS), 4) Quality of life (QoL), or 5) Treatment duration or time to treatment failure (TTF). Outcomes were collected as reported in the included studies.

2.2. Search methods

Studies were identified by electronically searching PubMed and the Cochrane Library. Details of these searches can be found in the online Appendix A. Additionally, reference lists of included studies were checked for additional studies.

2.3. Data collection and statistical analysis

Two reviewers (A.C. and K.I.) screened titles and abstracts of the items yielded by the search for eligibility. Full text was obtained when articles seemed fit. Neither of the reviewers was blinded to the journal titles or study authors. Data was extracted by the two reviewers, which included the primary author, year of publication, study design, patient characteristics, number of evaluated patients, and primary and secondary endpoints. Based on previous reports we expected the studies to be insufficiently homogeneous in terms of design and outcome parameters to conduct a meta-analysis. Thus, we aimed to provide a narrative, qualitative synthesis with information presented in text, figures, and tables to summarize the characteristics and outcomes of the included studies.

3. Results

3.1. Chemotherapy regimens approved in 1994 - 2019

Of the 22 chemotherapy-including regimens for ABC approved by the FDA and/or EMA, five [18–22] were based on results from trials investigating the approved drug without comparison to other agents (Supplementary Table 1). In the comparative trials underlying the 17 remaining authorizations, the approved regimens yielded superior PFS or TTP in 15 trials, [12–14,23–35], with an improvement in medians ranging from 1.2 [26] up to 6.3 months [13] in favour of the 'new' regimen. Superior OS, ranging from an increase in medians of 2.2 [24] up to 8.5 months [32], was found for the approved regimen in 10 trials [12–14,23–25,27,28,31,32], compared with the control treatments (Supplementary Table 1). Nine trials also reported QoL outcomes, with four trials using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [23,24,26,27], four trials using the Functional Assessment of Cancer Therapy - Breast Cancer (FACT-B) questionnaire [14,29,35,36], and one trial using other methods [37]. All of them found the approved regimens to generate comparable [23,24,26,27,29,35,36] or better overall / global QoL [14,37] (data not shown). No new cytotoxic agent has been approved since the registration of eribulin mesylate in 2010.

3.2. Single agent chemotherapy vs. combination chemotherapy

Based on PFS and/or OS results of registration studies, it seems outcomes of combination chemotherapy might be beneficial to single-agent chemotherapy within the approval studies (Supplementary Table 1). Single-agent chemotherapy yielded a median PFS or TTP in the range of 3.1–6.9 months, and median OS in the range of 8.6–21.0 months in the eight reported trials [18–21,23–25,38]. Outcomes were relatively favorable for the study that was done in first-line [38]. Doublet chemotherapy resulted in a median PFS or TTP in the range of 5.1-8.6 and median OS in the range of 14.5-20.4 months in six trials [26–30,39]. The ORRs were in the range of 12-75% for single-agent chemotherapy, and 41-65% for doublet chemotherapy.

Other RCTs reporting on ORR showed increased rates for combination chemotherapy compared with single-agent chemotherapy, although these benefits were statistically significant in only 6 out 22 trials (Supplementary Table 2). Two meta-analyses also indicated a significant improvement in ORR for combination chemotherapy in pooled analyses (RR 1.29; 95%CI 1.14-1.45 and RR 1.32; 95%CI 1.06-1.65) (Supplementary Table 3). Similar results were observed for PFS, for which individual trials showed inconsistent results (Supplementary Table 2) and 4 out of 5 systematic reviews reported an improved pooled PFS for combination chemotherapy compared with single-agent chemotherapy [40–43]. For OS, improvements were of little clinical relevance and were not significant in all but three [27,44,45] of the individual clinical trials, although in pooled analyses this improvement was statistically significant in 3 meta-analyses [40,41,46]. Lastly, the majority of the individual clinical trials (15 out of 22) [28,45,47–58] and all reviews found significantly more toxicity with combination chemotherapy, especially more hematological and gastro-intestinal toxic effects.

The 4th ESO-ESMO international consensus guideline for advanced breast cancer (ABC4) recommends the use of single-agent chemotherapy [59]. Combination chemotherapy is advised to be reserved for patients with high tumor burden where rapid disease control is needed [59]. Concordantly, observational studies showed that in clinical practice single-agent-regiments were employed more common than combination regimens, especially as first-line chemotherapy [60–62].

3.3. Duration of chemotherapy: clinical trials and clinical practice

Over the years the optimal duration of chemotherapy for the

Table 1
Randomized trials on shorter versus longer durations of first-line chemotherapy for advanced breast cancer.

Study	N = short vs. long	Short vs. Long	Median nr. of received cycles: short vs. long	Re-introduction in short arm at PD	Median PFS or TTP short vs. long (mo.)	PFS / TTP short vs. long HR (95% CI) or *P*-value	Median OS short vs. long (mo.)	OS short vs. long HR (95% CI) or *P*-value	QoL
Randomization at start of first-line chemotherapy, same therapy in long arm									
Coates, 1987 [64]/ 1988 [77] *Australia & New-Zealand*	151 vs. 154	AC or CMF x3 vs. until PD	n.r.	Yes	4.0 vs. 6.0	*1.84 (1.41-2.39)*	9.4 vs. 10.7	*1.40 (1.10-1.79)*	Long better
Ejlertsen, 1993 [71] *Denmark*	161 vs. 157	FEC x8 vs. × 24	n.r.	Yes	10.0 vs.14.0	*P < 0.001*	18 vs. 23	*P = 0.03*	n.r.
French Epirubicin Study Group, 2000 [65] *France*	129 vs. 273	FEC x4 vs. × 11 or 12	3.7 vs. 8.2	Yes	6.2 vs. 9.6	*P < 0.001*	16.3 vs. 18.4	P = 0.47	n.r.
Claessens, 2018 [75] *Netherlands*	210 vs. 210	P + Bev x4 vs. × 8 both followed by Bev until PD	4 vs. 8	Yes	7.4 vs. 9.7*	1.17 (0.88-1.57) *	17.5 vs. 20.9	1.38 (1.00- 1.91)	Similar
Randomization after completion of short arm, same therapy in long arm									
Harris, 1990 [72] *UK*	21 vs. 22	M x4 vs. until PD	4 vs. 7	Yes	6.0 vs. 5.1	P > 0.1	12.0 vs. 11.3	P > 0.1	n.r.
Becher, 1996 [66] *Germany*	60 vs. 63	EI x6-8 vs. × 14-16	n.r.	Yes	3.2 vs. 5.4	*P < 0.01*	13.2 vs. 13.5	P = n.s.	Long worse
Gregory, 1997 [68] *UK*	52 vs. 48	VEC or VAC or MMM x6 vs. x 12	6 vs. 10	No	7 vs.10	*P = 0.01*	10.5 vs. 13.0	P = 0.3	n.r.
Nooij, 2003 [73] *European*	100 vs. 96	CMF x6 vs. until PD	n.r.	Yes	3.5 vs. 5.2	*P = 0.011*	14.5 vs. 14.2	P = 0.64	Similar
Park, 2013 [67,111] *Korea*	115 vs. 116	PG x6 vs. until PD	6 vs. 12	No	3.8 vs. 7.5	*1.37 (1.03-1.81)*	23.5 vs. 32.3	*1.54 (1.01-2.38)*	Similar
Randomization after completion of short arm, different therapy in long arm									
Muss, 1991 [76] *USA*	74 vs. 71	FAC x6 followed by observation vs. followed by CMF (max x12 or 1 yr.)	3.0 vs. 8.1 months	Yes	3.2 vs. 9.4 6.7 vs. 9.4*	*P < 0.001* P = 0.41*	19.6 vs. 21.1	P = 0.68	n.r.
Falkson, 1998 [74] *USA*	73 vs. 68	A-containing ≥6 mo. (DAVTH/ CAF/ CAFT/ CAF alt. TsAVbH) followed by observation vs. followed by CMF until PD	n.r.	n.r.	7.8 vs. 18.0	*P < 0.001*	28.7 vs. 32.2	P = 0.74	n.r.
Gennari, 2006 [69] *Italy*	106 vs. 109	E/AP x6-8 followed by observation vs. followed by P x8	6 vs. 12	n.r.	9.0 vs.8.0	P = 0.817	29 vs. 28	P = 0.547	n.r.
Alba, 2010 [70] *Spain*	77 vs. 78	A x3 followed by D x3 followed by observation vs. followed by PLD x6	6 vs. 12	n.r.	5.1 vs. 8.4	*1.85 (1.32-2.56)*	22.0 vs. 24.8	1.12 (0.79-1.72)	n.r.

NOTE *italic* HR's and/or P-values are statistically significant. Studies by Becher et al. [66], Park et al. [67], Claessens et al [75] were not included in the meta-analysis by Gennari et al. [63] PFS was defined as the period between randomization and first progression of disease in the studies by Coates, the French Epirubicin Study Group, Becher, Gregory, Park, Gennari, and Alba. PFS was defined as the period between randomization and the final progression of disease after reintroduction of therapy in the ''short'' treatment arm (marked by and asterisk *) in the study by Claessens. In the study by Muss et al. both definitions for PFS were used in separate analysis. Other studies did not specify their definitions of PFS. Abbreviations: CT = chemotherapy; PD = progressive disease; PFS = progression-free survival; TTP = time to progression; HR = Hazard Ratio; 95%CI = 95% confidence interval; OS = overall survival; QoL = quality of life; n.r. = not reported; n.s. = not significant; A = doxorubicin; AC = doxorubicin plus cyclophosphamide; Bev = Bevacizumab; CAF = cyclophosphamide plus doxorubicin plus fluorouracil; CAFTH = CAF plus tamoxifen plus floxymesterone; CAF alt. CAF alt. TAVTH = CAF alternating with thiothepa plus doxorubicin plus vinblastine plus fluoxymesterone; CMF = cyclophosphamide plus methotrexate plus fluorouracil; D = docetaxel; DAV = dibromodulcitol plus doxorubicin plus vincristine plus tamoxifen plus fluoxymesterone; E = epirubicin; EI = epirubicin + iphosphamide; ; FAC = fluorouracil plus doxoribicin plus cyclophosphamide; FEC = fluorouracil plus epirubicin plus cyclophosphamide; M = mitozantrone; MMM = mitoxantrone plus methotrexate plus mytomicin; nPLD = non-pegylated liposomal doxorubicin; P = paclitaxel; PG = paclitaxel plus gemcitabine; PLD = pegylated liposomal doxorubicin; VAC = vincristine plus doxorubicin plus cyclophosphamide; VEC = vincristine plus epirubicin plus cyclophosphamide; X = capecitabine.

treatment of ABC has been discussed extensively. Especially when disease control is achieved without significant toxicity, consensus is lacking in clinical practice. Generally, there are two approaches; either patients are treated with a pre-specified number of cycles followed by a chemotherapy-free period, or chemotherapy is continued until progression of disease during treatment or unacceptable toxicity occurs.

RCTs on pre-specified durations versus continued chemotherapy for ABC are summarized in Table 1. All studies evaluated first-line chemotherapy, but with different moments of randomization and different types of continued therapy. The median number of cycles ranged from 4-6 in the 'short' versus 8-12 in 'long' treatment arms respectively. Ten trials reported in Table 1 were also included in a meta-analysis published by Gennari et al. in 2011, which indicated a substantially prolonged PFS for continued chemotherapy compared with pre-specified shorter durations in the pooled analyses [63]. Of note, heterogeneity in definitions of PFS makes it hard to draw solid conclusions. Seven studies evaluated PFS as the interval between randomization and the first occurrence of progression of disease [64–70]. Other studies either did not specify how PFS was defined [71–74], or evaluated the period from randomization until progression of disease including a possible re-introduction of chemotherapy in the 'short' treatment arm [75].

Overall, 10 out of 13 individual trials indicated a relevant and significant improvement in PFS with longer durations of chemotherapy [64–68,70,71,73,74,76]. Muss et al evaluated both definitions of PFS and found results were only statistically significantly better for the long arm when looking at the first occurrence of disease progression, not including PFS duration of re-introduction of chemotherapy in the 'short' treatment arm [76].

Regarding OS, 3 individual trials reported a significant benefit with longer compared with shorter durations of first-line chemotherapy [67,71,77]. In the previously mentioned meta-analysis the pooled median OS gain of 3 months was statistically significant (HR 0.91; 95%CI 0.84-0.99) [63]. However, most of the trials included in this pooled analysis comprised outdated treatment agents, with only three trials investigating taxane-containing treatments, with inconclusive results [69,70,78]. As taxanes are suggested for first-line chemotherapy by the current ESO-ESMO ABC4 guideline [59], the question remains if these recommendations are also applicable for these agents which are frequently used in clinical practice. A more recent trial by Park et al. showed that with a median duration of 12 versus 6 cycles of paclitaxel plus gemcitabine, median OS was prolonged with 8.7 months (HR 0.65; 95%CI 0.42-0.99) [67]. The Stop&Go trial randomized patients to an intermittent treatment strategy of 4 cycles of paclitaxel plus bevacizumab which were repeated at progression of disease, or to 8 successive cycles. [75]. When compared with 4 repeated cycles, 8 consecutive cycles resulted in a median OS gain of 3.4 months (HR 0.72; 95%CI 0.52-1.00).

Interestingly, although it is commonly thought that longer durations of chemotherapy might have a detrimental effect on QoL, Table 1 indicates that only one trial found a significant adverse impact of longer durations of chemotherapy [66].

Median chemotherapy durations observed in clinical practice were more comparable to the 'short' chemotherapy arms (≤6 months) than to the 'long' chemotherapy arms (≥7 months) (Fig. 1, Supplementary Table 4). Factors associated with significantly shorter median treatment durations in the listed observational studies were low performance status [79,80], lower hemoglobin at the start of treatment [79], multiple localizations of metastases [80]. and triple-negative (TN) tumors [81].

Furthermore, the median duration of chemotherapy decreased from first- to second- to third-line chemotherapy (Fig. 1). Three studies investigated the median line-specific treatment duration according to the type of regimen used, which indicated a large variation in treatment durations, especially for anthracyclines and taxanes.

The 2018 ASCO clinical practice guideline update on systemic therapy for patients with advanced HER2-positive breast cancer recommends to continue chemotherapy for 4-6 months or longer when combined with HER2-targeted therapy [82]. When given as separate treatment entity in HER2-negative disease, the ESO-ESMO ABC4 guideline recommends to continue chemotherapy as long as possible, where toxicity should be closely monitored and decisions on continuation should be made in agreement with the patient [59].

3.4. Multiple chemotherapy lines in clinical practice: number of lines, outcomes, and sequence of agents used

The majority of patients with ABC receive multiple lines of treatment over the course of their disease. Deciding whether or not to continue with a next-line of chemotherapy at disease progression can be challenging in clinical practice and is for obvious reasons not tested in RCTs.

In the identified observational studies, the applied follow-up period and the definitions of a new line of treatment, ORR and/or PFS varied considerably or were not described, complicating interpretation and comparison between studies. Despite this heterogeneity in definitions, results were quite similar (Table 2). The reported median number of chemotherapy lines varied from 1 to 3, with a large variation in range for all studies, up to 11 lines of chemotherapy. In the 3 studies specifically evaluating tumor subtypes [60,81,104], patients with HER2+ disease were treated with slightly more chemotherapy lines (medians 2 and 4), followed by the TN-subtype (medians 2 and 3). Patients with HR +/HER2- disease were treated with the least chemotherapy lines (medians 1, 1 and 3). The ESO-ESMO-ABC4 guideline does not specify any optimal number of regimens, but recommends to tailor the number of regimens to the individual patient [59].

In the 18 observational studies reporting on outcomes of specific chemotherapy lines for ABC identified in our search, the ORR seems to decline with each subsequent chemotherapy line (Fig. 2A), as do median PFS or TTP (Fig. 2B) (Supplementary Table 5).

Interestingly, 6 studies found that patients with a response and/or longer TTP or PFS of previous chemotherapy also had longer TTP or PFS on next-line chemotherapy [89,91,94,95,98,99,104]. Additionally, the median PFS of 11 months for second-line chemotherapy measured in the study by Brun et al. [89] is long compared with the other studies evaluating second-line chemotherapy (Fig. 2B). This might be explained by the fact that this study only selected patients who had a complete or partial response to first-line chemotherapy, supporting this notion of a possible prognostic role for response to previous-line chemotherapy for the length of next-line PFS.

The ESO-ESMO-ABC4 guideline does not include recommendations on the possible role of response to previous chemotherapy lines as a factor to take into account when prescribing a new line of chemotherapy [59]. However, the ASCO top 5 list of recommendations for practices that are not supported by high-level clinical evidence highlighted to not use cancer-directed therapies for patients with solid tumors that (amongst other characteristics) did not benefit from prior evidence-based interventions [105].

Another factor to take into account are the agents used. Possibly one sequence of agents is more beneficial than another. Our aim was to assess the sequence of agents applied in clinical practice, and if this sequence has changed according to expansion in availability (see also Supplementary Table 1). We therefore divided studies reporting on type of chemotherapy used into two groups: those evaluating patients treated up to 2004 and those evaluating patients treated from 2004 onwards (Fig. 3). Additionally, we classified the agents used according to the groups used by the ESMO [59] into anthracyclines (i.e. containing doxorubicin, epirubicin), taxanes (i.e. docetaxel, paclitaxel), capecitabine, vinorelbine, and others (i.e. gemcitabine, carboplatin, cyclophosphamide, cisplatin, 5-FU, etoposide, mitomycin C). If in a study the original classifications contained a group with agents from more than one of the ESMO-classified groups, the percentage of use was ascribed to both groups, leading to total percentages exceeding100%.

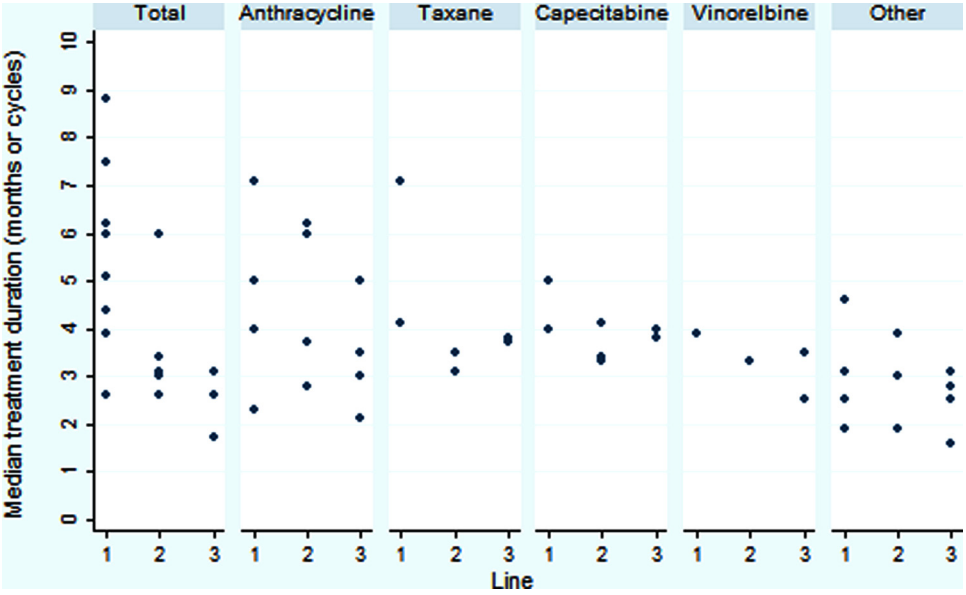

Fig. 1. Overview of median chemotherapy duration in observational studies in first- until third-line. Median chemotherapy duration per line without specification of agents used (overall) in 9 observational studies; and grouped per type of agent(s)* used (anthracyclines, taxanes, capecitabine, vinorelbine, others) in 3 observational studies. *Anthracylines included regimens containing either doxorubicin or epirubicin, taxanes included regimens containing either (liposomal) docetaxel or (nab-)paclitaxel. Other chemotherapy included regimens containing the following agents: bleomycin, carboplatin, cisplatin, cyclophosphamide, eribulin, (5-)fluorouracil, gemcitabine, ifosfamide, methotrexate, mitomycin C, mitozantrone, and vinblastine. NOTE: results shown here should be interpreted in relation with Fig. 2 which indicates that later-line chemotherapy is generally less effective; thereby limiting the treatment duration as a result of progression of disease. Additionally, comparison of treatment duration between different agents is biased by the imbalanced number of patients.

We found 15 observational studies reporting on the use of chemotherapy agents in first- until third chemotherapy line in the period between 1975 – 2015 (Supplementary Table 6). Older studies conducted before 2004 show that anthracycline-based and 'other' regimens were the most commonly used in the first-line (Fig. 3). The majority of the more recent studies with inclusion as of 2004 showed that taxane- and capecitabine-based therapy were most frequently used as first- and second-line chemotherapy followed by anthracyclines.

Additionally, Lin et al. conducted a physician survey about the preferred treatment sequence and prescribing patterns for post-menopausal patients with HR+/HER2- negative metastatic breast cancer [106]. The recommendations of 213 oncologist in the US were based on clinical experience, efficacy and toxicity. Capecitabine was the most frequently used in first- and second-line (35% and 26%, respectively), followed by paclitaxel (26% and 23%, respectively). Efficacy was mentioned as the main factor when prescribing first-line chemotherapy. For second-line chemotherapy, efficacy and tolerability were the most important considerations.

The ESO-ESMO-ABC4 guideline advises to take into account the toxicity profiles, previous exposure, patient preferences and availability of an agent when prescribing a new chemotherapy treatment [59]. The general recommendation is to choose anthracyclines or taxanes for first-line treatment of HER2 negative disease in patients who have not received these regimens as (neo)adjuvant treatments, to use taxane-based therapy for (further) treatment of patients with anthracycline-resistant disease, and to use capecitabine, vinorelbine or eribulin in patients who were previously treated with an anthracycline and a taxane (either in (neo)adjuvant and/or metastatic setting) [59].

3.5. Adding targeted therapy to a chemotherapy backbone vs. chemotherapy alone

With the shift of treatments for patients with ABC based on four major subtypes according to the HR- and HER2-receptors to treatments based on individual genetic profiles, the future implementation of new biological agents is expected. Our aim was to assess which regimens of a combination of targeted agents and chemotherapy are approved, and if the effects of chemotherapy are increased when targeted agents are added to a chemotherapy backbone. Up until the end of 2019, most targeted therapies are implemented for HER2-negative or HER2-positive disease, thus we divided our results accordingly (see also supplemental text).

3.5.1. HER2-negative disease

For HER2-negative disease, the combination of bevacizumab and paclitaxel was initially approved by the FDA in 2008 based on favorable PFS outcomes compared to paclitaxel alone [35]. However, none of the clinical trials on the addition of bevacizumab to chemotherapy showed a significant OS benefit (Table 3).

The ESO-ESMO-ABC4 guideline acknowledges these inconclusive results and furthermore states that there is a lack of predictive factors for efficacy of bevacizumab, thereby only recommending physicians to consider the addition of bevacizumab to first- or second-line chemotherapy in selected cases, and to not use this kind of combinations after first-/or second-line [59].

3.5.2. HER2-positive disease

About 15-20% of patients with ABC have an amplification of the HER2 receptor [5]. HER2-aimed therapy targets the extracellular domain of the HER2 receptor, resulting in inhibited tumor growth [31]. Trastuzumab was the first HER2-targeted therapy to be approved in combination with taxane chemotherapy in 2001 (Supplementary Table 1) [31]. Since then, new HER2-targeted therapy, such as lapatinib and pertuzumab have all been registered for use in combination with chemotherapy [13,14,33]. The latest combination to be approved by the FDA is fam-trastuzumab deruxtecan-nxki for patients with HER2 + ABC who have received two or more prior HER2-targeted therapies [22].

Table 3 shows the clinical trials for the combination of chemotherapy and HER2-targeted agents versus chemotherapy alone (see supplemental text for extensive evaluation). The majority of these trials showed that the addition of HER2-targeted therapy to chemotherapy significantly improved ORR and PFS, and generated a trend towards longer OS, compared with chemotherapy alone. As a result of these studies, the use of chemotherapy with HER2-targeted therapies is recommended by the ESO-ESMO-ABC4 guideline for patients with HER2+ disease [59].

4. Discussion

This review aimed to provide an overview of the optimal strategy to incorporate chemotherapy in the treatment of patients with ABC based on data from observational as well as randomized studies. Generally, chemotherapy-including regimens yielded a median OS of around 2 years in studies underlying approval. However, the older trials did not

Table 2
Observational studies on the number of chemotherapy lines given for advanced breast cancer.

Study	Data collection	Subtype	No. of patients per CT line	Agents	Median no. of total treatment lines (range)	Median no. of CT lines (range)
Gueth, 2009 [83] *Switzerland*	1990-1997 1998-2006	All	**1st**:26, **2nd**:31, **3rd**:14, **4th**:14, **5th**:7, **6th**:1, **7th**:3	A-based, LD, P, D, V, G, X, Trast., CMF, MC	4 (n.r.)	2 (n.r.)
Galy, 2011 [88] *France*	1994-1998 2003-2006	All	≥**1st**: 301	A-based, T-based, X, V, Trast.	n.r.	3 (1-11)
Planchat, 2011 [84] Updated from Tacca, 2009 [112] *France*	1994-2010	All	**1st**:529, **2nd**:401, **3rd**:304, **4th**:226, **5th**:149, **6th**:99, ≥**7th**:65	A-based, T-based, V, G, X, Trast., other	4	3 (n.r.)
Macalalad, 2014 [60] *USA*	2004-2010	HR+/HER2-	**1st**:144, **2nd**:119, **3rd**:85, **4th**:65, **5th**:42, **6th**:25	Single-agent X, P, A, D, G, combination regimens	**All**: 3 (1-12) **Recurrent:** 3(1-8) **De novo:** 4 (1-12)	**All**: 1 (0-9) **Recurrent:** 1(0-7) **De novo:** 2 (0-9)
Seah, 2014 [81] *USA*	2004-2007	All	**1st**:199, **2nd**:166, **3rd**:128, **4th**:95, **5th**:64, **6th**:46	X, V, P, other	n.r.	**All**: 3 (1-11) **HR+/HER2-**: 3 (1-11) **HER2+**: 4 (1-11) **TN**: 3 (1-8)
Bonotto, 2015 [91] Updated from Bonotto, 2014 [104] *Italy*	2004-2012	All	**1st**:367, **2nd**:234, **3rd**:160, **4th**:87	T-based, A-based, X, V, Epi, G, 5-FU, other	**All:** 3 (1-13) **HR+/HER2-**: 3 (1-12) **HER2+**: 2 (1-11) **TN**: 2 (1-6)	**All**: 1 (0-9) **HR+/HER2-**: 1 (0-7) **HER2+**: 2 (0-8) **TN**: 2 (1-6)
Mathew, 2016 [92] *USA*	2010-2014	All	**Last line**: 274	n.r.	n.r.	CT < 4 weeks of death: mean 4.3 (SD 2.4) No CT < 4 weeks of death: mean 2.8 (SD 2.3)
Aly, 2019 [62] *USA*	2004-2011	TN	**1st**: 317, **2nd**: 156, ≥**3rd**: 68	CT only	n.r.	1 (n.r.)

NOTE: Studies by *Galy* [88] and *Seah* [81] defined a new line of treatment as the start of a new treatment due to progression of disease. Studies by *Gueth* [83], *Planchat* [84] / *Tacca* [112], *Macalalad* [60] and *Aly* [62] defined a new line of treatment as the start of a new treatment irrespective of the reason. Studies by *Bonotto* [91] and *Mathew* [92] did not specify their definitions for a new treatment line. Studies by *Galy* [88], *Planchat* [84] / *Tacca* [112], *Seah* [81], *Bonotto* [91] and *Aly* [62] evaluated the number of treatment lines in a specific study period, without selections based on overall survival. Studies by *Gueth* [83], *Macalalad* [60] and *Mathew* [92] only evaluated the number of treatment lines in a selection of patients that were followed until death or definite stop of anti-tumor treatment, whichever came first.
Abbreviations: CT = chemotherapy; n.r. = not reported. A-based = anthracycline-based, T-containing = taxane-based, 5-FU = 5-fluorouracil; A = doxorubicin; C;= cyclophosphamide; CMF = cyclophosphamide plus methotrexate plus fluorouracil; D = docetaxel; Epi = epirubicin; G = gemcitabine; LD = liposomal doxorubicin; MC = mitomycin C; P = paclitaxel; Trast. = trastuzumab; V = vinorelbine; X = capecitabine.

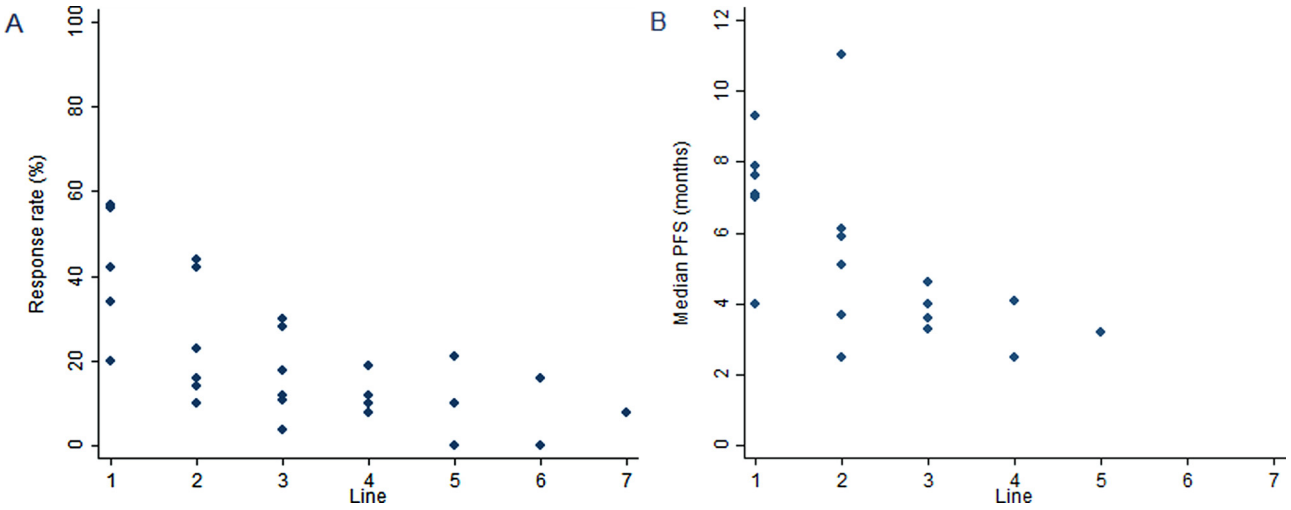

Fig. 2. Overview of outcomes in observational studies on multiple lines of chemotherapy for advanced breast cancer. A) Median line-specific overall response-rate of chemotherapy from 12 observational studies. B) Median line-specific progression-free survival of chemotherapy from 8 observational studies.

assess efficacy for different tumor-subtypes. Combining chemotherapy agents resulted in better ORR and PFS compared with single-agent chemotherapy, but without OS improvement and with greater toxicity. Therefore, sequential use of single agent chemotherapy is the preferred strategy. We noted that outcomes were fairly comparable between (single) cytostatic agents in registration studies. As to chemotherapy duration, longer treatment durations till 'unacceptable' toxicity in contrast to a predefined number of treatment cycles generated benefits in efficacy without detrimental impact on QoL in RCTs. Yet observational studies reported that chemotherapy was generally not given for more than 3-8 cycles. In addition, real-world studies indicated that after third-line chemotherapy, benefits of continuing next-line treatment were modest compared with those yielded by first- and second-line, but these clearly largely depend on individual patient factors. Although the ESO-ESMO-ABC4 guideline recommends the use of anthracyclines or taxanes as first-line chemotherapy [59], over time physicians more often prescribe capecitabine or taxanes, where tolerability in addition to efficacy seems to play an increasingly important role [106].

Although it is obvious that different cytotoxic agents generate different outcomes, the questions on the optimal agent for a specific treatment line and the optimal sequence of agents over multiple lines remains unanswered. Looking at Fig. 1, it seems as if anthracyclines and taxanes could be given longest, implying that these treatments would potentially be most efficient. However, results from Fig. 1 should be interpreted alongside Fig. 2, which shows a declining response rate and PFS over the course of the treatment lines. As we did not account for the number of patients receiving the different agents in Fig. 1, and we know from clinical practice that some agents are given more often in a specific treatment line than others, only relying on Fig. 1 to determine our choice of preferred agent would be insufficient. Capecitabine for example is, despite the increasing use in first-line over the years, still more often prescribed from second-line onwards (Fig. 3). We can see from

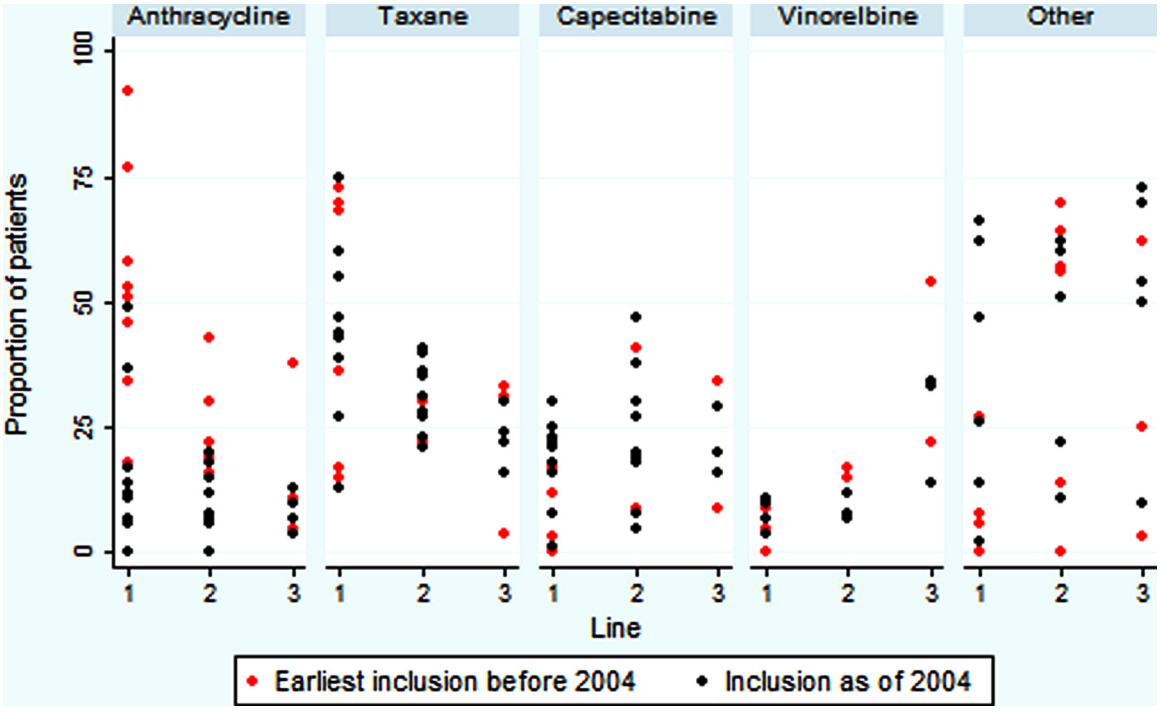

Fig. 3. Overview of the use of different groups of chemotherapy agents (proportion of patients) for first- until third-line in 16 observational studies.

Table 3
Randomized trials on chemotherapy in combination with targeted therapy vs. chemotherapy alone

Study	Subtype	CT line	Combi vs. CT (no. of patients)	ORR (%), *P*-value	Median PFS/TTP (mo)	PFS combi vs. CT HR (95% CI) or *P*-value	Median OS (mo)	OS combi vs. CT HR (95% CI) or *P*-value	Toxicity combi
Targeted therapy for HER2- disease + chemotherapy vs. chemotherapy alone									
Miller, 2005 [113]	All	≥ 2nd	X + Bev (232) vs. X (230)	*20 vs. 9, p = 0.001*	4.9 vs. 4.2, n.s.	0.98 (0.77-1.25)	15.1 vs. 14.5	n.s.	similar
Miller, 2007 [35]	All	1 st	P + Bev (347) vs. P (326)	*37 vs. 21, p < 0.001*	11.8 vs. 5.9	*0.60 (0.10-0.70)*	26.7 vs. 25.2	0.88, p = 0.16	worse
Miles, 2010 [114]	HER2-	1 st	D + Bev 7.5 mg/kg (247)/15 mg/kg (245) vs. D (238)	*55 / 64 vs. 46 p = 0.07/p < 0.001*	9.0 / 10.1 vs. 8.2	0.86 (0.72-1.04) / *0.77 (0.64-0.93)*	30.8/30.2 vs. 31.9	1.05 (0.81-1.36) / 1.03 (0.70-1.33)	similar
Robert, 2011 [115]	HER2-	1 st	X + Bev (409) vs. X (206)	*35 vs. 23, p = 0.0097*	8.6 vs. 5.7	*0.69 (0.56-0.84)*	n.r.	0.85 (0.63-1.14)	worse
Robert, 2011 [115]	HER2-	1 st	Tax/Anthra + BV (415) vs. Tax/Anthra (207)	*51 vs. 38, p = 0.0054*	9.2 vs. 8.0	*0.64 (0.52-0.80)*	n.r.	1.03 (0.77-1.38)	worse
Brufsky, 2011 [116]	HER2-	≥2nd	CT + Bev (459) vs. CT (225)	n.r.	7.2 vs. 5.1	*0.78 (0.64-0.93)*	18.0 vs. 16.4	0.90 (0.71-1.14)	worse
von Minckwitz, 2014 / Vrdoljak, 2016 [117,118]	HER2-	≥2nd	CT + Bev (247) vs. CT (247)	21 vs. 17, p = 0.35	6.3 vs. 4.2	*0.75 (0.61-0.93)*	19.7 vs. 18.7	0.96 (0.76-1.21)	worse
Targeted therapy for HER2+ disease + chemotherapy vs. chemotherapy alone									
Slamon, 2001 [31]	HER2+	1 st	Trast + CT (235) vs. CT (234)	*50 vs. 32, p < 0.001*	7.4 vs. 4.6	*0.51 (0.41-0.63)*	25.1 vs 20.3	0.80 (0.64-1.00)	worse
Marty, 2005 [32]	HER2+	1 st	Trast + D (92) vs. D (94)	*61 vs. 34, p = 0.0002*	11.7 vs. 6.1	n.r.	31.2 vs. 22.7	n.r.	similar
Gasparini, 2007 [119]	HER2+	1 st	Trast + P (63) vs. P (61)	*75 vs. 57, p = 0.037*	9.9 vs. 6.7	n.r.	n.r.	n.r.	similar
Di Leo, 2008 [120]	All	1 st	Lap + P (291) vs. P (288)	*35 vs. 25, p = 0.008*	7.3 vs. 5.8	0.87 (0.72-1.05)	24.8 vs. 21.8	0.86 (0.70-1.10)	worse
Cameron, 2010 [33]	HER2+	≥ 2nd	Lap + X (207) vs. X (201)	n.r.	6.5 vs. 4.5	*0.50 (0.34-0.74)*	17.2 vs. 14.8	0.87 (0.71-1.07)	similar
Von Minckwitz, 2009 [121]	HER2+	≥ 2nd	Trast + X (78) vs. X (78)	48 vs. 27, p = 0.0115	8.2 vs. 5.6	*0.69 (0.48-0.97)*	24.9 vs. 20.6	0.76 (0.48-1.21)	similar
Guan, 2013 [122]	HER2+	1 st	Lap + P (222) vs. P (222)	*69 vs. 50, p < 0.001*	9.7 vs. 6.5	*0.52 (0.42-0.64)*	27.8 vs. 20.5	*0.74 (0.58-0.94)*	worse

NOTE: *italic* HR's and/or P-values are statistically significant.
Abbreviations: CT = chemotherapy; ORR = overall response rate; PFS = progression-free survival; TTP = time to progression; HR = Hazard Ratio; 95%CI = 95% confidence interval; OS = overall survival; n.r. = not reported; n.s. = not significant; ; HR+ = hormone receptor positive; HR- = hormone receptor negative; HER2+ = HER2-neu receptor positive; HER2- = HER2-neu receptor negative; Tax = taxanes; Anthra = anthracyclines; AC = doxorubicin plus cyclophosphamide; Bev = Bevacizumab; CAF = cyclophosphamide plus doxorubicin plus fluorouracil; CMF = cyclophosphamide plus methotrexate plus fluorouracil; D = docetaxel; Lap = lapatinib; MAP = medroxyprogesterone; P = paclitaxel; X = capecitabine.

Fig. 1 that the treatment duration of capecitabine in second-line is relatively favorable to other agents used in second-line, whereas treatment duration of capecitabine in first-line seems shorter than for anthracyclines and taxanes. Considering the number of patients receiving first-line capecitabine is most likely notably smaller than the number of patients receiving these two other regimes, comparisons of treatment duration and the relation with efficacy should be made carefully. And noteworthy, the anthracycline-based studies were largely from a time including patients who had not received prior adjuvant chemotherapy. Future studies comparing different chemotherapy-agents head-to-head would contribute to the optimization of the optimal sequence.

As it is becoming a common practice to use single-agent chemotherapy and employ the less toxic agents like capecitabine and paclitaxel first, the optimization of treatment duration becomes more relevant again. From real-world studies it seemed that chemotherapy is frequently terminated because of unacceptable toxicity or because of a pre-defined treatment duration, as the reported treatment durations or TTF were generally shorter than the reported TTP or PFS. The real-world study by Kurosky specifically reported completion of the planned courses of treatment as a reason for stopping chemotherapy in 1/3 of patients within first-line and 14% of patients receiving second-line, while these numbers were only 1.8% and 0.95% for first- and second-line endocrine therapy [101]. Apparently, although RCTs indicated longer durations of chemotherapy did not adversely affect QoL, in clinical practice the more toxic treatments are often not continued for a prolonged period. Low-dose chronic regimens (metronomic chemotherapy with oral agents) could overcome the issues related to a limited implementation of prolonged chemotherapy durations in clinical practice.

Additionally, the optimal number of chemotherapy lines remains hard to define. The ASCO advises against the use of cancer-directed therapies for patients with solid tumors that did not benefit from prior evidence-based interventions [105]. Whether benefit from previous treatments is considered clinically relevant also depends on preferences of the treating physician and is susceptible to cultural beliefs. Both the ASCO and ESMO have developed decision aids (ESMO-MCBS, ASCO Value Framework) to help physicians assess the value of an oncologic treatment [107,108]. However, for the later lines of chemotherapy, very few evidence from RCTs is available to apply in these kinds of tools. When considering data from observational studies like those listed above, benefits of beyond third-line chemotherapy seem limited. One should be aware of the fact that these outcomes are not uniform in definition, and are the results of the alternation of chemotherapy and endocrine therapies during the disease course of the majority of patients (HR + population). No solid conclusions can be derived about the contribution of each agent to the benefits in OS and no information is available about the impact of subsequent lines of chemotherapy on the patients QoL.

A remarkable finding was the significant association between outcomes from previous chemotherapy regimens and outcomes of next-line chemotherapy described in 6 real-world studies [89,91,94,95,98,99,104]. Furthermore, response to previous chemotherapy [84,94,97,99,102] and longer PFS [88,90,104] was described to significantly increase OS in observational trials. The relationship between PFS and OS was also seen within approval studies of chemotherapy and previously described in a systematic review specifically focusing on first-line (mean ratio of median PFS: median OS of 1/3) [109]. These observations substantiate clinically relevant insights for the estimation of remaining median OS after progression on first-line chemotherapy. Notably, one should take into account that we did not investigate the ratio of PFS to OS within the different tumor subtypes, which might induce bias as the post-progression survival is considerable different within these subtypes.

Particularly, the development of new chemotherapy(including) regimens has slowed down compared with biological therapies after 2010. The latter have increased immensely in the last ten years, especially in combination with hormonal therapies. Due to the beneficial efficacy results obtained with these targeted therapies, we do not expect that new cytotoxic agents will be developed. The role of chemotherapy might even become limited to combination strategies. Several studies in ABC even suggest a possible synergistic effect of combining metronomic chemotherapy with endocrine-, immune-, or targeted therapies [110]. Future research regarding chemotherapy should thus focus on well-tolerated (metronomic) regimens as a backbone for targeted agents. Currently, there are numerous ongoing trials investigating combinations of a backbone of single-agent- or metronomic chemotherapy with hormonal therapy, targeted agents or immunotherapy (see ClinicalTrials.gov).

5. Conclusion

For HR-positive ABC, endocrine therapy is the preferred initial systemic treatment option. If chemotherapy is indicated, because of visceral distress, endocrine resistance and/or HR-negative disease, sequential use of single-agent chemotherapy rather than combinational chemotherapy is preferred. This chemotherapy may be continued until progression of disease or unacceptable toxicity. More than three lines of chemotherapy may be given only to a subset of patients with clear benefits from previous lines of chemotherapy and still with a good performance status. The optimal sequence of regimens preferably includes low toxic agents in early lines of treatment before employing less-tolerable agents. In patients with HER2-positive ABC, targeted therapy is generally included in addition to the chemotherapy-backbone.

Declaration of Competing Interest

SG has received research funding for her institution from Roche, Pfizer, E. Lilly and Novartis. MB has received Travel, accommodations and/or expenses from Roche, Novartis and Pfizer. FE has received honoraria from Roche and Novartis and has a consulting / advisory role for these companies. VTH has received honoraria from Pfizer, E. Lilly, Novartis and Roche, has a consulting or advisory role for Pfizer, E. Lilly, Novartis and Roche, has received research funding for her institution from Roche, Eisai, Pfizer, E. Lilly and Novartis, and has received Travel, accommodations and/or expenses from Pfizer, Novartis, and Roche. All remaining authors have declared no conflicts of interest.

CRediT authorship contribution statement

Anouk K.M. Claessens: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Visualization. **Khava I.E. Ibragimova:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Visualization. **Sandra M.E. Geurts:** Conceptualization, Formal analysis, Writing - review & editing, Visualization. **Monique E.M.M. Bos:** Conceptualization, Writing - review & editing. **Frans L.G. Erdkamp:** Conceptualization, Writing - review & editing. **Vivianne C.G. Tjan-Heijnen:** Conceptualization, Methodology, Writing - review & editing, Visualization, Supervision.

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Appendix A

Efficacy of systemic FDA/EMA approved regimens

Approval messages on FDA / EMA websites were searched for references to the underlying studies.

Single agent vs. combination chemotherapy

ESMO, ASCO and NCCN guidelines were searched for clinical trials underlying the recommendations on single vs. combination chemotherapy.

Duration of chemotherapy

- *General*

((((((chemotherapy) AND advanced) OR metastatic) AND breast cancer) AND duration) OR line*) OR schedule)

- *Specific for clinical trials*

((((((("Neoplasm Metastasis"[Mesh] OR (metasta*[tiab] OR advanced[tiab]))) AND ((((("Neoplasms"[Mesh] OR (Cancer*[tiab] OR cancer[sb] OR cancer*[tiab] OR carcinom*[tiab] OR malign*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab]) OR "Carcinoma"[Mesh])) AND (Breast[tiab] OR mammary[tiab]))) OR "Breast Neoplasms"[Mesh]))) AND ("Antineoplastic Agents"[Mesh] OR "Antineoplastic Combined Chemotherapy Protocols"[Mesh] OR "Drug Therapy"[Mesh:noexp] OR "Consolidation Chemotherapy"[Mesh] OR "Induction Chemotherapy"[Mesh] OR "Maintenance Chemotherapy"[Mesh] OR "Cytostatic Agents"[Mesh] OR chemotherap*[tiab] OR ((anti neoplast*[tiab] OR antineoplast*[tiab]) AND (drugs[tiab] OR agents[tiab])) OR cytostat*[tiab])) AND (Duration*[tiab] OR maintenance[tiab] OR cycle*[tiab] OR number* OR length[tiab] OR longer[tiab] OR shorter[tiab])) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized [tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) OR ("Prospective Studies"[Mesh] OR prospecti*[tiab]))

- *Specific for observational studies*

(((((((cohort study) OR real world study) OR observational study) AND chemotherapy) AND duration) AND metastatic) OR advanced) AND breast cancer

Multiple lines of chemotherapy in clinical practice

- *General*

((((((chemotherapy) AND advanced) OR metastatic) AND breast cancer) AND duration) OR line*) OR schedule)

- Specific for observational studies

(((((((cohort study) OR real world study) OR observational study) AND chemotherapy) AND duration) AND metastatic) OR advanced) AND breast cancer

Chemotherapy +/- targeted therapies

((((("Breast Neoplasms"[Mesh]) AND breast cancer)) AND (((survival) OR treatment outcome) OR mortality)) AND ((((((chemotherapy) OR trastuzumab) OR trastuzumab emtansine) OR lapatinib) OR pertuzumab) OR bevacizumab)

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2020.102988.

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