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Prognostic impact of the choice of chemotherapy after first-line CDK4/6 inhibitor therapy in patients with metastatic hormone receptor-positive, HER2-negative breast cancer

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ABSTRACT

Introduction: Whereas CDK4/6 inhibitors (CDK4/6i) are the standard first-line therapy for patients with hormone receptor-positive (HRpos), HER2-negative (HER2neg) metastatic breast cancer, guidelines on treatment options after progression on CDK4/6i are more diverse. Chemotherapy is recommended if a patient develops endocrine resistance or experiences a visceral crisis. However, the impact of the choice of chemotherapy remains unknown.
Methods: HRpos/HER2neg patients who received first-line CDK4/6i, followed by second-line chemotherapy (N = 215) were selected from the prospective PRAEGNANT registry (NCT02338167). Cox regression analyses were used to evaluate the correlation between the choice of chemotherapy (capecitabine monotherapy, capecitabine + bevacizumab, taxane monotherapy, taxane + bevacizumab, anthracycline, other chemotherapeutics) and progression-free survival (PFS) and overall survival (OS).
Results: Patients who received second-line chemotherapy mostly had high-grade tumors (G2: 62.3 %, G3: 33.3 %), visceral metastases (62.3 %) and developed metastatic disease following a primary breast cancer diagnosis (73.8 %). Capecitabine was the most common regimen (25.1 %), followed by taxane + bevacizumab (17.2 %). When adjusting for other prognostic factors (age, BMI, grading, ECOG, metastasis group and time to metastases), the choice of chemotherapy did not influence PFS (p = 0.16) nor OS (p = 0.47). Adjusted hazard ratios for PFS were lowest in regimens with bevacizumab (capecitabine as reference; capecitabine + bevacizumab: 0.53 (95 %CI: 0.29, 0.97); taxane + bevacizumab: 0.64 (95 %CI 0.35, 1.15)).
Conclusion: Although the choice of chemotherapy post-CDK4/6i did not significantly affect PFS or OS, combinations with bevacizumab may have some benefit. Nevertheless, considering side effects may be most important when choosing the type of second-line chemotherapy.

1. Introduction

Over the past years, advances have been made regarding treatment options for patients with hormone receptor-positive (HRpos), HER2-negative (HER2neg) advanced or metastatic breast cancer. As such, cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) have become the standard first-line treatment for metastatic HRpos/HER2neg disease, which is recommended by both national and international guidelines [1–3].

Depending on the type of CDK4/6i, median progression-free survival (PFS) times between 23.8 months and 29.0 months [4–8] and overall survival (OS) times between 53.9 months and 67.1 months have been reported for patients receiving first-line CDK4/6i therapy [9–12]. After progression, several second-line therapies can be considered depending on the response to first-line therapy and molecular markers [1–3]. Molecular markers (*gBRCA*, *ESR1*, *AKT*, *PI3K*, *PTEN*) are required to determine optimal second-line treatment after progression on CDK4/6i-based first-line therapy, especially if second-line endocrine based therapy is aimed for. A such, poly (ADP-ribose) polymerase (PARP) inhibitors can be given to patients with a germline *BRCA1/2* mutation [13,14], elacestrant to patients with an estrogen receptor 1 (*ESR1)* mutation [15], alpelisib in combination with ET to patients with a somatic phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA)* mutation [16], and capivasertib in combination with fulvestrant to patients with alterations in the AKT-pathway (*PIK3CA*, *AKT1* or *PTEN*) [17]. For patients without specific genetic alterations who progress on CDK4/6i, serial ET (monotherapy or combinations with everolimus) is recommended until the patient develops endocrine resistance or experiences a visceral crisis, warranting chemotherapy [1–3]. In patients with a poor response to first-line CDK4/6i-based therapy, second-line endocrine-based systemic therapy is less promising and chemotherapy is therefore often the preferred choice for these patients. Nevertheless, chemotherapies are also recommended as a first-line treatment for patients with endocrine resistance or a visceral crisis. Based on the findings of the DESTINY-Breast06 trial, the FDA has recently approved trastuzumab deruxtecan for use in patients with HRpos/HER2-low breast cancer who have progressed after receiving one or more endocrine therapies in the metastatic setting [18]. This broadens the treatment options available to patients who progress on CDK4/6i.

The number of patients receiving chemotherapy as a second-line treatment varies greatly. The pivotal CDK4/6i randomized controlled trials in the first-line setting reported chemotherapy as a second-line therapy after disease progression in 12–71 % of patients [6,9,19–21]. Real-world data indicates that 16–73 % of patients received chemotherapy after progression on CDK4/6i therapy [22–25]. Moreover, the type of chemotherapy given after CDK4/6i treatment also varies. In PALOMA-2 (first-line palbociclib), paclitaxel was the most common second-line chemotherapy, followed by capecitabine, doxorubicin and cyclophosphamide [19]. Furthermore, in MONALEESA-2 (first-line ribociclib), post-CDK4/6i chemotherapies were mostly pyrimidine analogues, followed by taxane, anthracyclines and platinum compounds [20], whereas in MONARCH 3 (first-line abemaciclib), post-discontinuation chemotherapies commonly consisted of paclitaxel, capecitabine, cyclophosphamide and doxorubicin [6]. Notably, in the recent DESTINY-Breast06 trial, physician's choice chemotherapy options in the control arm consisted of capecitabine, nab-paclitaxel and paclitaxel, with the majority of patients receiving capecitabine (59.8 %) [18].

To date, the optimal choice of chemotherapy after first-line CDK4/6i therapy remains unclear. Therefore, we investigated how the choice of chemotherapy affects outcome following first-line CDK4/6i therapy in HRpos/HER2neg metastatic breast cancer patients using data from the prospective, real-world PRAEGNANT registry.

2. Methods

2.1. Patient population

Patients with advanced or metastatic breast cancer were enrolled in the prospective PRAEGNANT (Prospective Academic Translational Research Network for the Optimization of the Oncological Health Care Quality in the Adjuvant and Advanced/Metastatic Setting) registry (NCT02338167) at any time during their disease course. All patients provided written informed consent and the study was approved by the relevant ethics committees (ethical approval number: 234/2014BO1: first approval on June 17 2014, Ethics Committee of the Medical Faculty, University of Tübingen, Tübingen, Germany). The work was carried out in accordance with the Declaration of Helsinki. All procedures were performed in compliance with relevant laws and institutional guidelines.

Between July 2014 and January 2024, 5544 patients from 63 study sites were included into the PRAEGNANT registry. Patients with triple negative or HER2 positive disease, missing tumor/ treatment information or missing follow up were excluded from the current analysis (Fig. 1).

2.2. Data collection

Trained staff collected and documented data in an electronic case report form. On-site monitoring and automated plausibility checks were performed. Data that is usually not documented as part of routine clinical work was collected prospectively using structured paper questionnaires (epidemiological data such as family history, cancer risk factors, quality of life, nutrition and lifestyle items, and psychological health). Supplemental table 1 provides an overview of the data collected.

2.3. Definition of HR status, HER2 Status, and grading

The definition of HR status, HER2 status, and grading has been described previously [26]. Briefly, if a biomarker assessment of the metastatic site was available, this receptor status was used for the analysis. If there was no information for metastases, the latest biomarker results from the primary tumor were used. All patients who received endocrine therapy in the metastatic setting were assumed to be HR-positive (HRpos), and all patients who had ever received anti-HER2 therapy were assumed to be HER2pos. There was no central review of

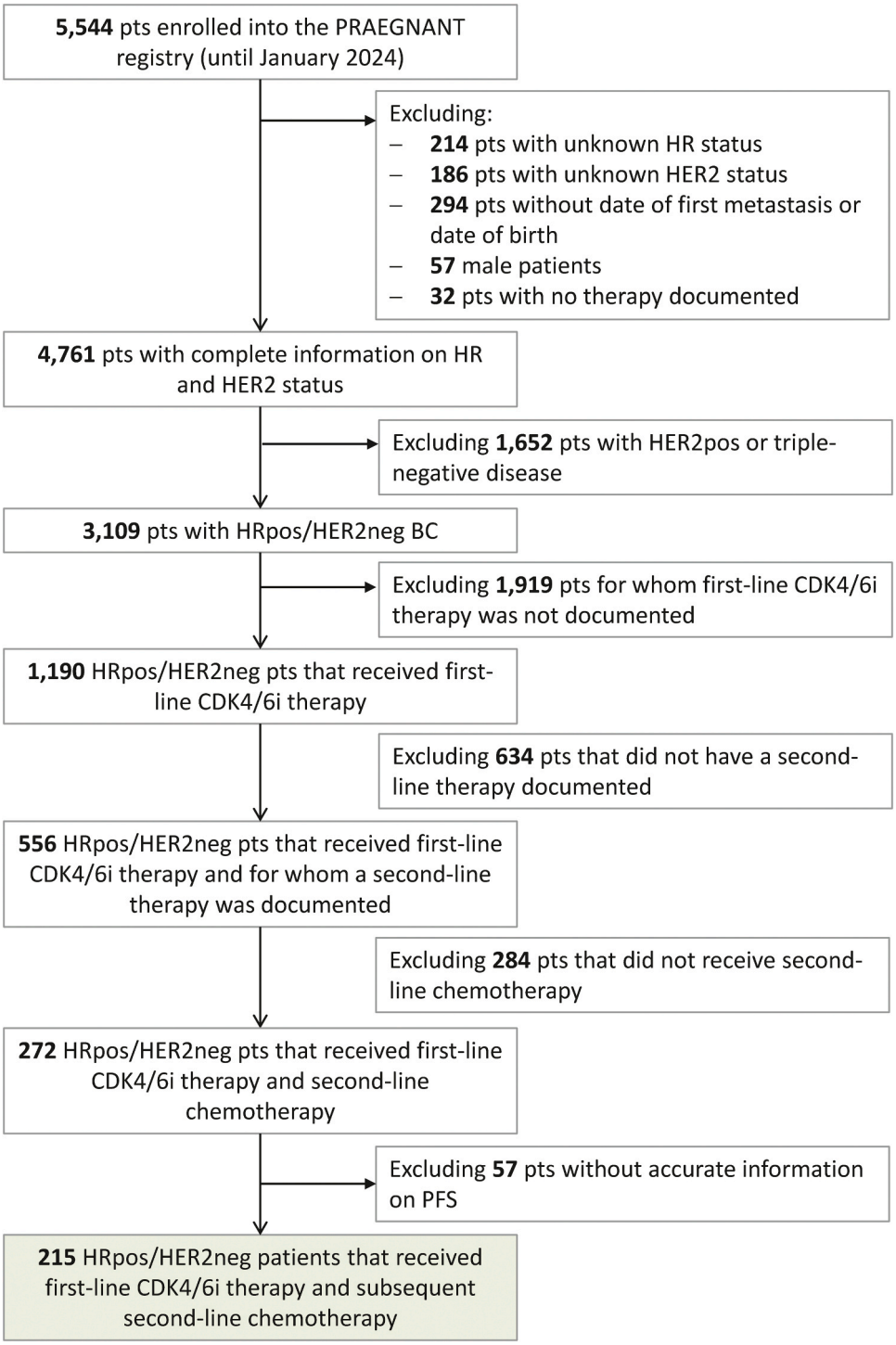

Fig. 1. CONSORT diagram. [pts: patients; HR: hormone receptor; HRpos: hormone receptor-positive; HER2pos: HER2-positive; HER2neg: HER2-negative; CDK4/6i; CDK4/6 inhibitor, PFS: progression-free survival; BC: breast cancer].

biomarkers. The study protocol recommended assessing estrogen receptor and progesterone receptor status as positive if ≥ 1 % was stained. A positive HER2 status required an immunohistochemistry score of 3 + or positive fluorescence in situ hybridization/chromogenic in situ hybridization.

2.4. Statistical analysis

PFS was defined as the time from the start of therapy to the earliest date of disease progression (distant-metastasis, local recurrence, or death from any cause) or the last date known to be progression-free. Therapies which started after or at most 90 days before date of study entry are considered. If therapy start was before date of study entry, observation time was left-truncated for time to enter the study. Overall survival (OS) was defined in a similar fashion.

The primary objective was to investigate whether the choice of chemotherapy had an impact on PFS when accounting for known prognostic factors. For this purpose, a multiple Cox regression model (*the basic model*) was fitted with PFS as the outcome and the following predictors: age at study entry (continuous), body mass index (BMI, continuous), grading (ordinal; G1, G2, G3), ECOG (ordinal; 0–4) and time from diagnosis to metastasis (TDTM) (categorical; *de novo* metastases/cM1, cM0 and TDTM < 60 months, cM0 and TDTM > 60 months), metastasis group (categorical; brain, visceral, bone only, others). Subsequently, an additional Cox regression model (*the full model*) was fitted containing the predictor chemotherapy (categorical; capecitabine monotherapy, capecitabine + bevacizumab, taxane monotherapy, taxane + bevacizumab, anthracycline, other chemotherapeutics) and the predictors of the previous basic model. Both models were compared using the likelihood ratio test. Adjusted hazard ratios for chemotherapy were estimated, using the full model. The proportional hazards assumptions were checked using the Grambsch-Therneau method. Missing values for other predictors were imputed as described previously [27].

OS was analyzed in accordance with the same approach. As sensitivity analysis, corresponding unadjusted HRs were estimated for PFS and OS, using a Cox regression model with chemotherapy as the only predictor. Unadjusted survival rates with 95 % confidence intervals (CIs) and median survival times were estimated using the Kaplan-Meier product limits method. The 95 % CI of median survival time was computed using the method of Brookmeyer and Crowley [28].

All of the tests were two-sided, and a P value < 0.05 was regarded as statistically significant. Calculations were carried out using the R system for statistical computing (version 4.3.0; R Development Core Team, Vienna, Austria, 2023).

3. Results

3.1. Patients

Second-line therapy was documented for 46.7 % (N = 556) who received first-line CDK4/6i therapy (N = 1190). Of those, chemotherapy was given in 48.9 % of cases (N = 272) (Fig. 1). Information on the duration of first-line CDK4/6i therapy for the final population of patients who received second-line chemotherapy (N = 215) is provided in Supplemental table 2. Patients receiving second-line chemotherapy were on average 59.6 years old. Most patients had high-grade tumors (G2: 62.3 %, N = 127; G3: 33.3 %, N = 68) and visceral metastases (62.3 %, N = 134). Metastatic disease occurred *de novo* in 26.2 % of patients (N = 49), while 73.8 % of patients (N = 138) developed metastatic disease following a primary breast cancer diagnosis. Half of these patients progressed to metastasis within 60 months (N = 69), while the other half progressed after 60 months after the initial diagnosis (N = 69). Further patient characteristics are presented in Table 1. The most common chemotherapeutic regimen was capecitabine (25.1 %, N = 54), followed by taxane + bevacizumab (17.2 %, N = 37), capecitabine + bevacizumab (15.3 %, N = 33), taxane (15.3 %, N = 33), anthracycline (13.5 %, N = 29), and other chemotherapeutic regimes (13.5 %, N = 29).

3.2. Chemotherapy and patient characteristics

Patient characteristics stratified by chemotherapeutic regimen are presented in Table 1. Patient who received capecitabine were older than those receiving other types of chemotherapy (62.5 years vs. 59.2 years

Table 1
Patient characteristics stratified by second line therapy, showing mean and standard deviation or count and percentage.

Characteristic		All patients (N = 215)	Capecitabine (N = 54)	Capecitabine + bevacizumab (N = 33)	Taxane (N = 33)	Taxane+ bevacizumab (N = 37)	Anthracycline (N = 29)	Other (N = 29)
Age (years)		59.6 (12.5)	62.5 (15.1)	59.2 (11.1)	59.2 (11.6)	57.8 (11.4)	58.1 (11.6)	58.9 (12.2)
Body mass index (kg/m^2)		26.3 (5.3)	26.1 (5.2)	25.3 (4.9)	26.6 (5.4)	25.5 (4.5)	29.4 (6.7)	25.5 (4.5)
Grading	G1	9 (4.4)	2 (3.8)	1 (3.2)	1 (3.0)	0 (0.0)	3 (10.7)	2 (7.4)
	G2	127 (62.3)	28 (53.8)	16 (51.6)	19 (57.6)	26 (78.8)	20 (71.4)	18 (66.7)
	G3	68 (33.3)	22 (42.3)	14 (45.2)	13 (39.4)	7 (21.2)	5 (17.9)	7 (25.9)
	Missing	11	2	2	0	4	1	2
ECOG at the start of chemotherapy	0	98 (50.8)	23 (47.9)	13 (44.8)	12 (40.0)	21 (61.8)	14 (51.9)	15 (60.0)
	1	74 (38.3)	22 (45.8)	16 (55.2)	9 (30.0)	10 (29.4)	10 (37.0)	7 (28.0)
	2	19 (9.8)	2 (4.2)	0 (0.0)	8 (26.7)	3 (8.8)	3 (11.1)	3 (12.0)
	3	2 (1.0)	1 (2.1)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	22	6	4	3	3	2	4
TDTM	*de novo* metastases	49 (26.2)	12 (25.5)	7 (23.3)	11 (40.7)	10 (33.3)	6 (23.1)	3 (11.1)
	TDTM ≤ 60 mo.	69 (36.9)	18 (38.3)	11 (36.7)	4 (14.8)	11 (36.7)	11 (42.3)	14 (51.9)
	TDTM > 60 mo.	69 (36.9)	17 (36.2)	12 (40.0)	12 (44.4)	9 (30.0)	9 (34.6)	10 (37.0)
	Missing	28	7	3	6	7	3	2
Metastasis group	Brain	15 (7.0)	5 (9.3)	2 (6.1)	2 (6.1)	2 (5.4)	3 (10.3)	1 (3.4)
	Visceral	134 (62.3)	37 (68.5)	25 (75.8)	16 (48.5)	22 (59.5)	17 (58.6)	17 (58.6)
	Bone only	26 (12.1)	3 (5.6)	3 (9.1)	6 (18.2)	8 (21.6)	1 (3.4)	5 (17.2)
	Others	40 (18.6)	9 (16.7)	3 (9.1)	9 (27.3)	5 (13.5)	8 (27.6)	6 (20.7)

TDTM time from diagnosis to metastasis, mo months.

for capecitabine + bevacizumab, 59.2 years for taxane monotherapy, 57.8 years for taxane + bevacizumab, 58.1 years for anthracycline, 58.9 years for other chemotherapeutics). BMI was similar across groups. G3 tumors were most frequent in patients who received capecitabine regimens (capecitabine monotherapy: 42.3 %, N = 22; capecitabine + bevacizumab: 45.2 %, N = 14), while G1 tumors were most frequently observed in the anthracycline subgroup (10.7 %, N = 3). The site of metastases varied across subgroups. Visceral disease was the most common form of metastatic disease in all subgroups, with highest rates in the capecitabin + bevacizumab subgroup (75.8 %, N = 25). Bone only metastatic disease was highest in the taxane + bevacizumab subgroup (21.6 %, N = 8). Relative to other chemotherapy regimens, taxane monotherapy was more frequently given to patients with *de novo* metastases (40.7 % of patients, N = 11) and the least frequent to patients with a disease-free interval of ≤ 60 months (14.8 %, N = 4).

3.3. Progression-free survival

Median observation time for PFS was 5.5 months (interquartile range (IQR): 2.9, 10.3). We were unable to demonstrate that the choice of chemotherapy impacted PFS, after accounting for other prognostic factors ($P = 0.16$, likelihood ratio test). Adjusted hazard ratios ranged from 0.53 (95 % CI, 0.29–0.97) for capecitabine + bevacizumab versus capecitabine monotherapy (reference) to 1.12 (95 % CI, 0.63–2.01) for other chemotherapy versus capecitabine monotherapy (Table 2). Median survival time was highest in patients receiving capecitabine + bevacizumab (8.6 months (95 % CI: 5.9, 14.1)) and lowest in patients receiving taxane monotherapy (3.7 months (95 % CI: 3.3, 7.7). Median progression-free survival times and 6-, 12- and 24- month progression-free survival rates are presented in Table 3. Kaplan-Meier curves are presented in Fig. 2. Patients that received bevacizumab (capecitabine + bevacizumab and taxane + bevacizumab) appeared to experience less frequent progression within the first months of therapy compared to those receiving chemotherapy without bevacizumab (6-month survival rates: capecitabine + bevacizumab: 0.62 (95 % CI, 0.47–0.82), taxane + bevacizumab: 0.65 (95 % CI, 0.51–0.82), taxane monotherapy: 0.29 (95 % CI, 0.17–0.50), capecitabine: 0.48 (95 % CI, 0.36–0.64), anthracycline: 0.35 (95 % CI, 0.21–0.58), other chemotherapy: 0.42 (95 % CI, 0.27–0.66)).

Table 2
Cox regression analyses, showing adjusted and unadjusted hazard ratios for chemotherapy.

Outcome	Chemotherapy	Adjusted[1] hazard ratio(95 % CI)	Unadjusted hazard ratio(95 % CI)
PFS	Capecitabine	Reference	Reference
	Capecitabine + bevacizumab	0.53 (0.29, 0.97)	0.63 (0.39, 1.02)
	Taxane	0.81 (0.44, 1.51)	1.10 (0.68, 1.77)
	Taxane + bevacizumab	0.64 (0.35, 1.15)	0.82 (0.53, 1.27)
	Anthracycline	1.03 (0.57, 1.84)	1.01 (0.63, 1.64)
	Other chemo	1.12 (0.62, 2.01)	0.87 (0.53, 1.43)
OS	Capecitabine	Reference	Reference
	Capecitabine + bevacizumab	0.94 (0.48, 1.84)	0.82 (0.47, 1.43)
	Taxane	1.09 (0.54, 2.22)	1.14 (0.63, 2.05)
	Taxane + bevacizumab	1.10 (0.55, 2.20)	1.21 (0.71, 2.04)
	Anthracycline	1.54 (0.79, 2.98)	1.29 (0.74, 2.26)
	Other chemo	1.73 (0.89, 3.37)	1.18 (0.66, 2.10)

CI confidence interval, PFS progression-free survival, OS overall survival. Hazard ratios were adjusted for age at study entry, body mass index, grading (ordinal; G1, G2, G3), ECOG (ordinal; 0–4), time from primary breast cancer diagnosis to metastasis and metastasis group.

3.4. Overall survival

Median observation time for OS was 11.6 months (IQR: 5.6, 22.3). We were unable to demonstrate that the choice of chemotherapy affects OS, after accounting for other prognostic factors ($P = 0.47$, likelihood ratio test). Here, the adjusted hazard ratios ranged from 0.94 (95 % CI, 0.48–1.84) for capecitabine + bevacizumab versus capecitabine monotherapy (reference) to 1.73 (95 % CI, 0.89–3.37) for other chemotherapies (Table 2). Median survival time was highest in patients receiving capecitabine + bevacizumab (20.7 months (95 % CI: 17.7, 34.5)) and lowest in patients receiving other chemotherapies (13.5 months (95 % CI: 10.5, NA)). Median progression-free survival times and 6-, 12- and 24- month progression-free survival rates are presented in Table 3. Kaplan-Meier curves are presented in Fig. 2.

4. Discussion

In this retrospective real-world analysis, the choice of chemotherapy after first-line CDK4/6i therapy for metastatic HRpos/HER2neg disease did not significantly affect outcome, neither PFS, nor OS. In exploratory analyses, patients receiving regimens with bevacizumab (either in combination with capecitabine or taxane) seemed to have the longest PFS. These results indicate that, while choosing the type of chemotherapy, focus should be placed on patients' preference, taking into account the different toxicity profiles.

The therapeutic landscape for patients with metastatic breast cancer is everchanging. Together with the approval of CDK4/6i therapy as the standard first-line therapy for HRpos/HER2neg metastatic breast cancer patients, chemotherapy applications have decreased, especially in the early therapeutic lines [29]. According to national and international guidelines, chemotherapy may be recommended as a second-line therapy after progression on CDK4/6i in patients with suspected endocrine resistance or a visceral crisis [1–3]. In clinical trials and real-world analyses, the percentage of patients receiving chemotherapy after progression on CDK4/6i varied between 12 % and 73 % [6,9,19–25,30]. In our real-world population, 49 % of patients for whom a second-line therapy was documented received chemotherapy. Furthermore, capecitabine monotherapy and capecitabin-containing regimens were the most commonly administered chemotherapy treatments in our patient population, which is also in line with recent real-world analyses and clinical trials [18,30,31]. Studies evaluating the efficacy of chemotherapy after first-line CDK4/6i therapy have reported median PFS times of 3.7–5.1 months [32,33]. A recent small retrospective study assessing capecitabine after first-line CDK4/6i reported a median PFS of 5.6 months [34], whereas a PFS of 6.89 months was reported with oral chemotherapy (mainly consisting of capecitabine) after first-line CDK4/6i therapy in a larger recent retrospective cohort study [30]. In our patient population, PFS was 5.1 months for capecitabine monotherapy and 8.6 months for capecitabine + bevacizumab. Notably, in the physician's choice chemotherapy comparator arm of the DESTINY-Breast06 trial, which predominantly consisted of capecitabine, median PFS was 8.1 months (95 % CI: 7.0, 9.0) [18]. There are conflicting results when comparing efficacy of different chemotherapeutic regimes. A study compared the time to therapy failure (TTF) of capecitabine, taxane-based regimens or other chemotherapies as a first chemotherapy after ET in the advanced setting. Here, capecitabine had the most favorable TTF with 6.1 months vs. 4.9 months for taxane-based regimens and 4.4 months for other chemotherapeutics [35]. This study did however not differentiate with regard to the number of previous ET lines, and included both CDK4/6i regimens and endocrine monotherapy. In a subgroup analysis of patients who received CDK4/6i therapy, taxane-based regimes appeared more beneficial than capecitabine therapy [35]. Another study showed a longer PFS with oral chemotherapy compared to intravenous chemotherapy (6.89 vs. 5.44 months) [30]. This study also indicated a lower risk of progression with oral chemotherapy than with intravenous chemotherapy, but no

Table 3
Median survival times and survival rates stratified by second-line chemotherapy.

Outcome	Chemotherapy	N	Events	Median survival time[1] (95 % CI)	6-month survival rate (95 % CI)	12-month survival rate (95 % CI)	24-month survival rate (95 % CI)
PFS	Capecitabine	54	45	5.1 (3.9, 7.3)	0.48 (0.36, 0.64)	0.21 (0.12, 0.37)	0.06 (0.02, 0.22)
	Capecitabine + bevacizumab	33	29	8.6 (5.9, 14.1)	0.62 (0.47, 0.82)	0.36 (0.22, 0.57)	0.14 (0.06, 0.35)
	Taxane	33	27	3.7 (3.3, 7.7)	0.29 (0.17, 0.50)	0.17 (0.07, 0.39)	0.13 (0.05, 0.35)
	Taxane + bevacizumab	37	36	7.8 (6.3, 10.6)	0.65 (0.51, 0.82)	0.22 (0.12, 0.40)	0.03 (0.00, 0.19)
	Anthracycline	29	27	5.0 (3.0, 10.6)	0.35 (0.21, 0.58)	0.21 (0.10, 0.43)	0.05 (0.01, 0.30)
	Other chemo	29	25	5.5 (2.9, 10.5)	0.42 (0.27, 0.66)	0.18 (0.07, 0.42)	0.13 (0.05, 0.37)
OS	Capecitabine	54	30	16.8 (13.8, 33.4)	0.81 (0.70, 0.92)	0.65 (0.52, 0.80)	0.48 (0.35, 0.66)
	Capecitabine + bevacizumab	33	22	20.7 (17.7, 34.5)	0.90 (0.80, 1.00)	0.73 (0.59, 0.91)	0.42 (0.27, 0.66)
	Taxane	33	18	14.3 (10.2, NA)	0.77 (0.63, 0.94)	0.61 (0.45, 0.82)	0.41 (0.25, 0.67)
	Taxane + bevacizumab	37	26	19.4 (12.3, 27.1)	0.86 (0.75, 0.98)	0.65 (0.51, 0.83)	0.33 (0.20, 0.55)
	Anthracycline	29	21	13.9 (7.3, 20.0)	0.74 (0.60, 0.93)	0.55 (0.39, 0.78)	0.22 (0.11, 0.47)
	Other chemo	29	19	13.5 (10.5, NA)	0.71 (0.56, 0.90)	0.51 (0.35, 0.74)	0.37 (0.22, 0.63)

difference in OS [30]. In the current study, we could not show a significant effect of chemotherapy choice on PFS or OS. Notably, patients who receive chemotherapy as a second-line therapy are likely to be highly endocrine resistant. This has a negative effect on outcome and may in part explain why no difference between groups was observed.

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF) that can be administered with chemotherapy. The Food and Drug Administration (FDA) withdrew its approval for metastatic breast cancer in 2011, as multiple studies failed to demonstrate improvement in overall survival for bevacizumab [36–39]. Bevacizumab is approved by the European Medicines Agency (EMA) for combination with either paclitaxel or capecitabine in the first-line treatment of metastatic breast cancer. Nevertheless, international guidelines only recommend the addition of bevacizumab in patients with rapid disease progression, high tumor burden or visceral crisis [1, 40]. In clinical studies, the addition of bevacizumab to chemotherapy moderately improved PFS, whereas no effect on OS was observed [37, 38]. Although we did not observe differences in treatment efficacy between different chemotherapeutic regimes, we detected a modest effect of the addition of bevacizumab on PFS, but not OS.

It is important to note that several studies are currently investigating further targeted treatment options for metastatic patients who have progressed on CKD4/6i. As such, the therapeutic landscape will continue to change in the next years and chemotherapy will be further shifted to later lines of therapy. New targeted treatments like Selective Estrogen Receptor Degrader (SERDs) and proteolytic targeting chimeras (PROTACs) as well as effective combination therapies like capivasertib for patients with an alteration in the PI3K/AKT/PTEN pathway can potentially help to overcome endocrine resistance after CDK4/6i and delay the use of chemotherapy. Both endocrine SERD monotherapies, elacestrant and vepdegestrant (not yet approved as of June 2025), have comparable median PFS times to the chemotherapies investigated in our study [15,41] and capivasertib has even longer median PFS times [17]. The EMBER-3 study showed that even longer median PFS times were achieved with the SERD imlunestrant in combination with abemaciclib after progression under a CDK4/6i. These more effective endocrine treatment options may lead to them being used more frequently than chemotherapy, the given median PFS times of 5–6 months shown in our study. In the past, the median PFS times of around 3–4 months [15,17, 41,42] with an endocrine monotherapy might not have been convincing enough to avoid chemotherapy for most patients.

Additionally, the two antibody-drug conjugates (ADCs) trastuzumab deruxtecan and sacituzumab govitecan have been approved for HER2-neg/HER2low patients that have received prior chemotherapy for metastatic disease. Both trastuzumab deruxtecan and sacituzumab govitecan have shown improved progression-free and overall survival compared to physician's choice chemotherapy in HRpos metastatic breast cancer patients who received at least one line of chemotherapy in the advanced setting [43–45]. The efficacy of these ADCs as second-line treatment is further evaluated in recent studies. Results from the DESTINY-Breast06 trial that investigated trastuzumab deruxtecan after endocrine therapy showed improved PFS in patients receiving trastuzumab deruxtecan versus patients receiving physician's choice chemotherapy [18]. Results for OS were not significant, although it has to be noted that the data was still immature. Importantly, 67.4 % of patients in the study received first-line CDK4/6i therapy in combination with endocrine therapy [18]. Based on these findings, trastuzumab deruxtecan has been approved for use in patients with HRpos/HER2-low breast cancer who have progressed after receiving one or more endocrine therapies in the metastatic setting. It should be noted that the FDA granted approval in January 2025, and at the time of writing the EMA had not yet approved trastuzumab deruxtecan as a second-line therapy after CDK4/6i. Therefore, the analyzed patient population did not include patients who had received an ADC as a second-line treatment after first-line CDK4/6i. Furthermore, the current prerequisite of receiving a chemotherapy line prior to ADC use in metastatic cases may have influenced the decision to use classical chemotherapy after CDK4/6i progression.

Our study has some limitations and strengths. Although this is a retrospective analysis, the PRAEGNANT registry collects real-world data prospectively, which limits the bias associated with classical retrospective analyses. Only half of the patients with a documented first-line CDK4/6i therapy had a documented second-line therapy, which could have introduced selection bias. Furthermore, the number of metastatic breast cancer patients that received chemotherapy after progression on CDK4/6i in our registry was low, resulting in a relatively small patient population (N = 215) and subgroups. The limited sample size influences the robustness of our analyses and limits the strength and generalizability. In addition, although Cox regression analyses used to assess outcome parameters included known predictors, bias in the survival analyses cannot be completely ruled out. Lastly, the toxicity profiles of the chemotherapies used were not fully documented within our registry, which prevented them from being included in the current analysis. Future analyses containing detailed information on the real-world side effects of different chemotherapies could therefore help to optimize the choice of chemotherapy after first-line CDK4/6i.

In summary, the choice of chemotherapy following first-line CDK4/6i therapy did not demonstrate a significant impact on outcome in a real-world cohort of patients with metastatic HR-positive/HER2-negative breast cancer. This highlights the importance of tailoring treatment decisions to individual patient characteristics, prior lines of therapy, and the specific toxicity profiles of available options to optimize outcomes and quality of live in this patient population.

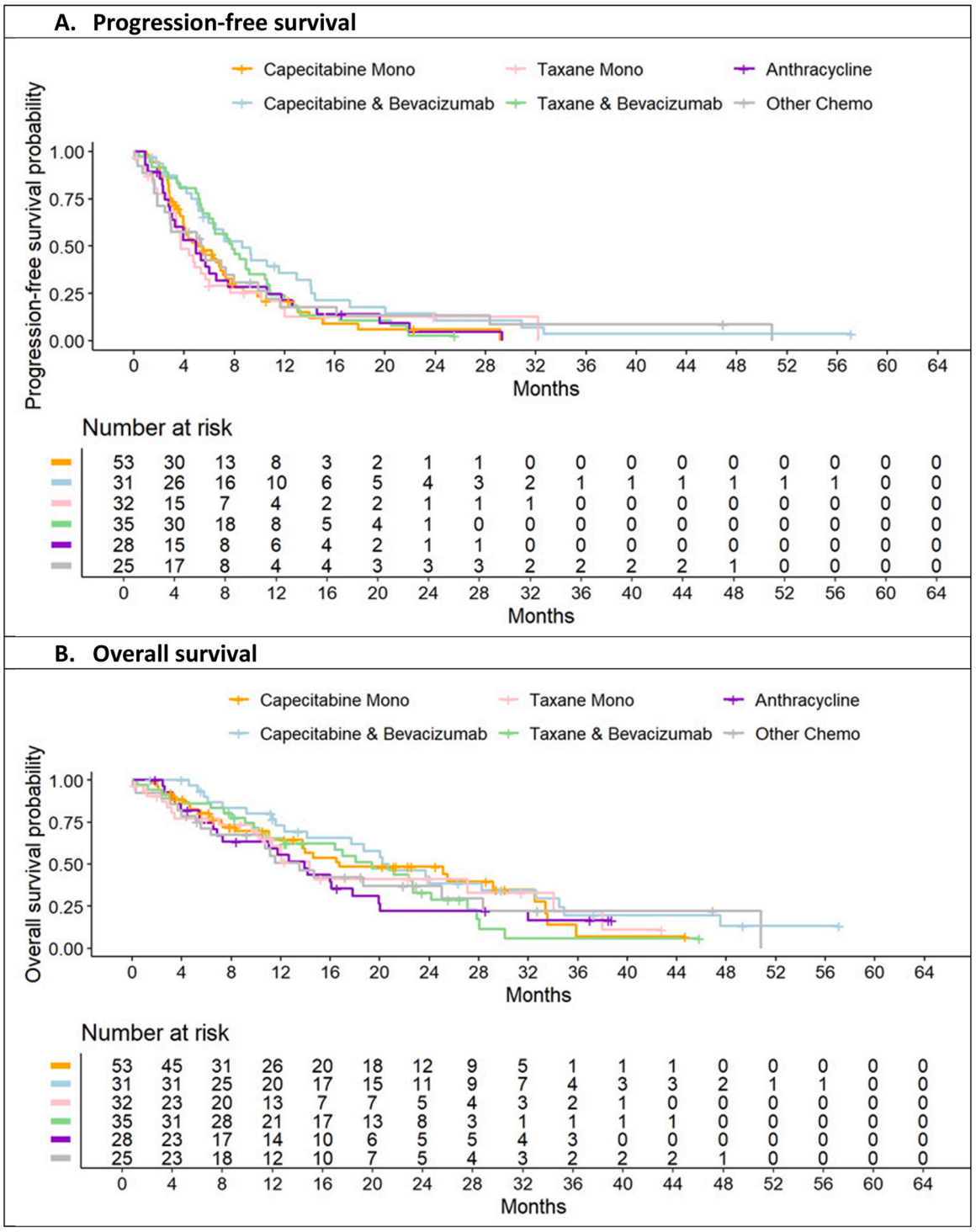

Fig. 2. Progression-free (A) and overall survival (B) according to second-line chemotherapy.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **LLM**: received honoraria from Amgen, AstraZeneca, Celgene, Gilead, Lilly, MSD, Novartis, Pfizer, Roche and Eisai for advisory boards, lectures and travel support. **ADH:** has received honoraria from Roche, Novartis, Lilly, MSD, AstraZeneca, Seagen, GSK, Exact Science, Riemser, Teva, Onkowissen, Gilead, Stemline Therapeutics, Pfizer, Amgen, Pierre Fabre and Eisai and travel support from Roche, Novartis, Lilly, AstraZeneca, GSK, Exact Science, Gilead, Stemline Therapeutics and Pfizer. **MW**: received speaker honoraria from AstraZeneca, Celgene, Roche, MSD and Novartis. **H-CK**: has received honoraria from Pfizer, Novartis, Roche, Genomic Health/Exact Sciences, Amgen, AstraZeneca, Riemser, Carl Zeiss Meditec, TEVA, Theraclion, Janssen-Cilag, GSK, LIV Pharma, Lilly, SurgVision, Onkowissen, Gilead, Daiichi Sankyo and MSD, travel support from Carl Zeiss Meditec, LIV Pharma, Novartis, Amgen, Pfizer, Daiichi Sankyo, Tesaro, Gilead, Stemline Therapeutics and AbbVie and owns stock of Theraclion SA. **PH:** has received honoraria from Amgen, Novartis, Hexal and Pfizer. **HT**: has received honoraria from Novartis, Roche, Celgene, Teva, and Pfizer, and travel support from Roche, Celgene and Pfizer. **JE**: has received honoraria/travel support from Roche, Celgene, Novartis, Pfizer, Lilly, Pierre Fabre, Teva, Tesaro, AstraZeneca, Daiichi Sankyo, Seagen, Gilead, Stemline Therapeutics, and ClinSol. **DL**: has received honoraria from Amgen, Loreal, Pfizer, Novartis, Eli Lilly, Samsung, Celgene, Astra Zeneca, Teva and GSK. **VM**: has received speaker honoraria from AstraZeneca, Daiichi Sankyo, Eisai, Pfizer, MSD, Medac, Novartis, Roche, Seagen, Onkowissen, high5 Oncology, Medscape, Gilead, Pierre Fabre, iMED Institut. 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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115689.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

References

[1] Gennari A, et al. ESMO clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32(12):1475–95.
[2] Al Sukhun S, et al. Systemic treatment of patients with metastatic breast cancer: ASCO resource-stratified guideline. JCO Glob Oncol 2024;(10):e2300285 (p).
[3] Thill M, et al. AGO recommendations for the diagnosis and treatment of patients with locally advanced and metastatic breast cancer: update 2023. Breast Care 2023;18(4):306–15.
[4] Rugo HS, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. Breast Cancer Res Treat 2019;174(3):719–29.
[5] Johnston S, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer 2019;5:5.
[6] Johnston S, et al. Abemaciclib as initial therapy for advanced breast cancer: MONARCH 3 updated results in prognostic subgroups. NPJ Breast Cancer 2021;7(1):80.
[7] Hortobagyi GN, et al. Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2L) advanced breast cancer (ABC) treated with endocrine therapy (ET) +/- ribociclib (RIB). Ann Oncol 2021;32:S1290–1.
[8] Tripathy D, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol 2018.
[9] Hortobagyi GN, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. N Engl J Med 2022;386(10):942–50.
[10] Lu YS, et al. Updated overall survival of ribociclib plus endocrine therapy versus endocrine therapy alone in Pre- and perimenopausal patients with HR(+)/HER2(-) advanced breast cancer in MONALEESA-7: a phase III randomized clinical trial. Clin Cancer Res 2021.
[11] Finn RS, et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2− ABC): analyses from PALOMA-2. J Clin Oncol 2022;40(17_):LBA1003. -LBA1003.
[12] Goetz, M., et al. MONARCH 3: Final overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as first-line therapy for HR+, HER2- advanced breast cancer (oral presentation GS01-12). in San Antonio Breast Cancer Symposium®. 2023. San Antonia, TX, USA.
[13] Robson M, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 2017;377(6):523–33.
[14] Litton JK, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 2018;379(8):753–63.
[15] Bidard FC, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen Receptor-Positive, human epidermal growth factor receptor 2-Negative advanced breast cancer: results from the randomized phase III EMERALD trial. J Clin Oncol 2022. JCO2200338.
[16] Andre F, et al. Alpelisib for PIK3CA-Mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019;380(20):1929–40.
[17] Turner NC, et al. Capivasertib in hormone receptor-positive advanced breast cancer. N Engl J Med 2023;388(22):2058–70.
[18] Bardia A, et al. Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. N Engl J Med 2024.
[19] Rugo HS, et al. Effect of palbociclib plus endocrine therapy on time to chemotherapy across subgroups of patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: post hoc analyses from PALOMA-2 and PALOMA-3. Breast 2022;66:324–31.
[20] Im SA, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. N Engl J Med 2019.
[21] Turner NC, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med 2018;379(20):1926–36.
[22] Choong GM, et al. Clinical management of metastatic hormone receptor-positive, HER2-negative breast cancer (MBC) after CDK 4/6 inhibitors: a retrospective single-institution study. Breast Cancer Res Treat 2022;196(1):229–37.
[23] Read SH, et al. Treatment patterns of patients with HR+/HER2- metastatic breast cancer receiving CDK4/6 inhibitor-based regimens: a cohort study in the French nationwide healthcare database. Breast Cancer Res Treat 2024.
[24] Sawaki M, et al. Real-world treatment patterns of subsequent therapy after palbociclib in patients with advanced breast cancer in Japan. Breast 2023;70:1–7.
[25] Princic N, et al. Predictors of systemic therapy sequences following a CDK 4/6 inhibitor-based regimen in post-menopausal women with hormone receptor positive, HEGFR-2 negative metastatic breast cancer. Curr Med Res Opin 2019;35(1):73–80.
[26] Hartkopf AD, et al. Treatment landscape of advanced breast cancer patients with hormone receptor positive HER2 negative tumors - data from the German PRAEGNANT breast cancer registry. Breast 2018;37:42–51.
[27] Salmen J, et al. Pooled analysis of the prognostic relevance of progesterone receptor status in five German cohort studies. Breast Cancer Res Treat 2014;148(1):143–51.
[28] Brookmeyer R, Crowley J. A Confidence-Interval for the median Survival-Time. Biometrics 1982;38(1):29–41.
[29] Engler T, et al. Implementation of CDK4/6 inhibitors and its influence on the treatment landscape of advanced breast cancer patients - data from the Real-World registry PRAEGNANT. Geburtshilfe Frau 2022;82(10):1055–67.
[30] Berton Giachetti PPM, et al. Survival following CDK4/6 inhibitor therapy for hormone Receptor-Positive, ERBB2-Negative metastatic breast cancer. JAMA Netw Open 2025;8(2):e2461067.
[31] Basile D, et al. First- and second-line treatment strategies for hormone-receptor (HR)-positive HER2-negative metastatic breast cancer: a real-world study. Breast 2021;57:104–12.
[32] Karacin C, et al. Efficacy of subsequent treatments in patients with hormone-positive advanced breast cancer who had disease progression under CDK 4/6 inhibitor therapy. BMC Cancer 2023;23(1):136.
[33] Martin JM, et al. Systemic therapies following progression on First-line CDK4/6-inhibitor treatment: analysis of Real-world data. Oncologist 2022;27(6):441–6.
[34] Bender L, et al. Capecitabine efficacy after cycline-dependent-kinase 4/6 inhibitor plus endocrine therapy in metastatic hormone receptor-positive breast cancer. Cancer Treat Res Commun 2023;36:100738.
[35] Chainitikun S, et al. The efficacy of first-line chemotherapy in endocrine-resistant hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer. Breast Cancer Res Treat 2020;183(3):729–39.
[36] Miller K, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357(26):2666–76.
[37] Miles DW, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2010;28(20):3239–47.
[38] Robert NJ, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol 2011;29(10):1252–60.
[39] Brufsky AM, et al. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2011;29(32):4286–93.
[40] Moy B, et al. Chemotherapy and targeted therapy for patients with human epidermal growth factor receptor 2-Negative metastatic breast cancer that is either Endocrine-Pretreated or hormone Receptor-Negative: ASCO guideline update. J Clin Oncol 2021;39(35):3938–58.
[41] Campone M, et al. Vepdegestrant, a PROTAC estrogen receptor degrader, in advanced breast cancer. N Engl J Med 2025.
[42] Jhaveri KL, et al. Imlunestrant with or without abemaciclib in advanced breast cancer. N Engl J Med 2025;392(12):1189–202.
[43] Modi S, et al. Trastuzumab deruxtecan in previously treated HER2-Low advanced breast cancer. N Engl J Med 2022.
[44] Rugo HS, et al. Sacituzumab govitecan in hormone Receptor-Positive/Human epidermal growth factor receptor 2-Negative metastatic breast cancer. J Clin Oncol 2022;40(29):3365–76.
[45] Rugo HS, et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. Lancet 2023.