Thieme

Treatment of Advanced Hormone Receptor-Positive (HR+) HER2-negative Breast Cancer

Therapie des fortgeschrittenen hormonrezeptor-(HR-)positiven HER2-negativen Mammakarzinoms

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Authors
Nina Ditsch[1], Marcus Schmidt[2]

Affiliations
1   Universitätsklinikum Augsburg, Brustzentrum, Klinik für Gynäkologie und Geburtshilfe, Augsburg, Germany
2   Klinik und Poliklinik für Geburtshilfe und Frauengesundheit der Johannes-Gutenberg-Universität Mainz, Mainz, Germany

Correspondence
Prof. Dr. Nina Ditsch
Universitätsklinikum Augsburg, Brustzentrum,
Klinik für Gynäkologie und Geburtshilfe
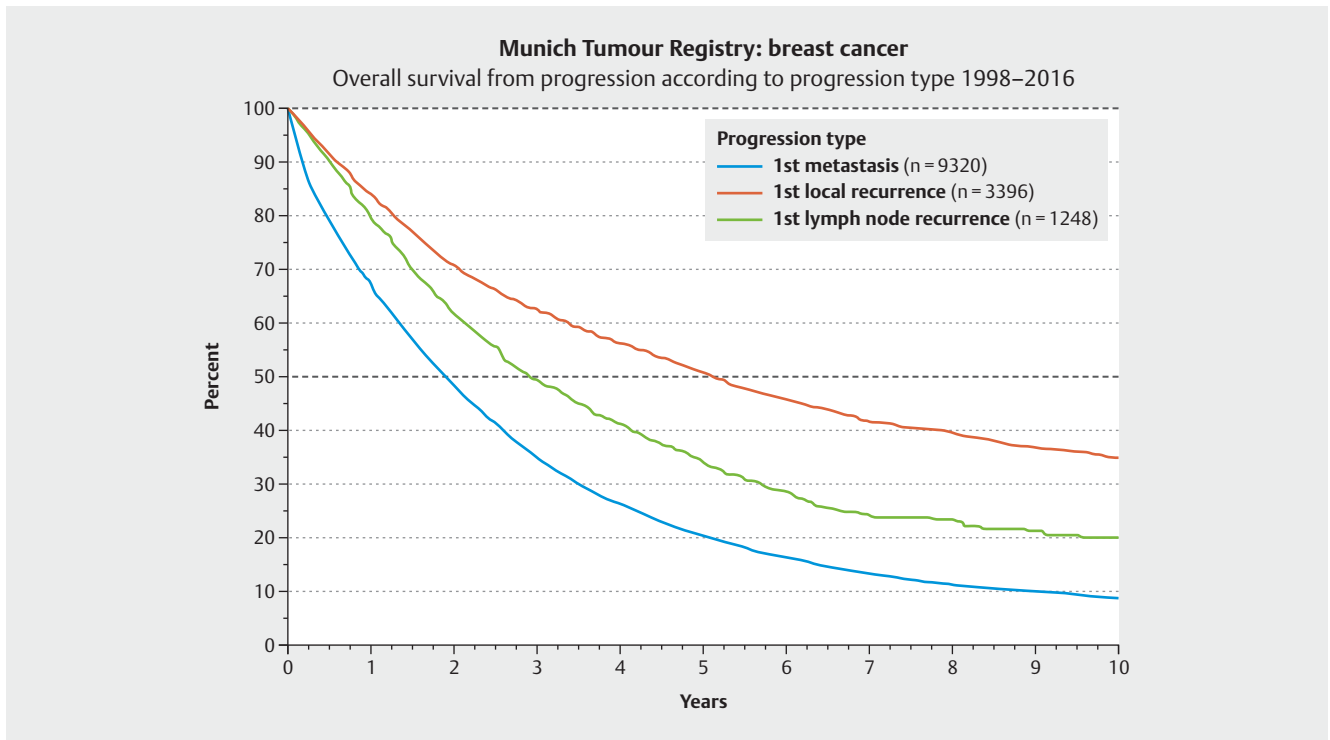Stenglinstraße 2, 86156 Augsburg, Germany
nina.ditsch@uk-augsburg.de

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ABSTRACT

The article gives an overview of current treatment options for metastatic hormone receptor-positive and HER2-negative breast cancer. The focus is on combined therapies, e.g., with CDK4/6 inhibition compared with purely endocrine-based therapies in the pre- and postmenopause, presenting the latest study results. The addition of a CDK4/6 inhibitor to endocrine-based therapy with an aromatase inhibitor or fulvestrant leads to a marked improvement in progression-free survival and is independently beneficial whether palbociclib, ribociclib or abemaciclib is involved. The particular clinical status of inhibition of cyclin-dependent kinases argues for its use in the first-line treatment of women with metastatic, hormone receptor-positive and HER2-negative breast cancer compared with the available purely endocrine-based therapies.

ZUSAMMENFASSUNG

Der Artikel gibt einen Überblick über die aktuellen Therapieoptionen des metastasierten hormonrezeptorpositiven und HER2-negativen Mammakarzinoms. Im Fokus stehen Kombinationstherapien z. B. mit CDK4/6-Inhibition im Vergleich zu rein endokrin basierten Therapien in Prä- und Postmenopause mit Darlegung der neuesten Studienergebnisse. Die Hinzunahme eines CDK4/6-Inhibitors zu einer endokrin basierten Therapie mit Aromataseinhibitor oder Fulvestrant führt zu einer deutlichen Verbesserung des progressionsfreien Überlebens und ist unabhängig vorteilig, ob es sich um Palbociclib, Ribociclib oder Abemaciclib handelt. Der damit besondere klinische Stellenwert der Inhibition Cyclin-abhängiger Kinasen spricht für den Einsatz in der Erstlinienbehandlung von Frauen mit metastasiertem, hormonrezeptorpositivem und HER2-negativem Mammakarzinom im Vergleich zu den verfügbaren rein endokrin basierten Therapien.

Munich Tumour Registry: breast cancer
Overall survival from progression according to progression type 1998–2016

▶ **Fig. 1** Survival from progression according to progression type (Fig. from Munich Tumour Registry analysis, 2017).

Introduction

Breast cancer is the commonest malignant tumour in women, with 1.67 million new cases annually worldwide, and over half a million women die of it annually [1]. Survival from progression depends on the type of progression. The relative 5-year survival is 20% with distant metastasis, 48% with local recurrence and 30% with lymph node recurrence (▶ **Fig. 1**).

Metastatic breast cancer is regarded as an incurable disease. The course of the disease is associated with the histopathological and intrinsic characteristics of the tumour. Over 70% of all cases are hormone receptor-positive (HR+), oestrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR+) and human epidermal growth factor-negative (HER2−) on immunohistochemistry [2]. Since hormone receptor and HER2 expression can change in the course of the disease, requiring a change in treatment, the advantages of targeted therapy should be used optimally according to reassessment of the pathology following metastasis [3,4]. Because it is regarded as an incurable but treatable disease, the focus is on systemic therapy. Endocrine therapy is the treatment of choice for HR+, HER2− advanced postmenopausal breast cancer [5]. With endocrine monotherapy, however, further disease progression occurs after 13–16 months on average. This is attributed to the development of endocrine resistance, among other things, which ultimately leads to failure of the effective and well tolerated treatment and requires the use of other therapies and the development of new treatment modalities. The main clinical aim in the metastatic situation is an improvement of symptoms and prolongation of survival with good quality of life

[6]. Targeted therapies can markedly improve the results of treatment in this chronic phase of the disease [7–9]. Significant improvements in response and progression-free survival are possible by combining several drugs of demonstrated effectiveness [10]. Overall, the demand made of treatment has changed markedly in recent years: longer survival with good quality of life even in the long term is pursued. In general, however, for nearly all forms of treatment, the aim of improving overall survival is only rarely achieved in the metastatic situation [11].

Review

The following questions are crucial for the choice of individual disease-adapted systemic therapy:
- Is the disease symptomatic?
- Can rapid or slow progression be expected?
- How great are the response rates, the progression-free interval and the overall survival with the selected therapy?
- What are the side effects?

Menopausal status, the type of previous treatment, the interval between the end of the primary therapy and the diagnosis of metastasis as well as the persistent long-term sequelae of previous treatments and symptoms of metastasis determine the choice of treatment. Endocrine therapies have low toxicity with a high range of effects and are therefore preferred, in a consensus of national and international guidelines, for hormone receptor-positive/HER2-negative forms, albeit with a slow response [9, 12, 13, 44, 45]. The response rates are comparable to those of chemo-

therapy. Given the markedly increased side effect profile, the latter is used as first-line therapy only when rapid symptom control is necessary and pressure to achieve remission is high due to rapid tumour progression with a life-threatening complication – acute visceral crisis (definition: ago-online.de). Moreover, recent data indicate that chemotherapy alone is inferior in the case of HR positivity and HER2 negativity [42, 43]. In addition, endocrine-based therapy and chemotherapy should not be given concurrently as this leads to increased toxicity without an increase in efficacy [14].

Endocrine-based therapy

The (anti-) endocrine drugs (GnRH analogues, tamoxifen, fulvestrant, aromatase inhibitors), on the one hand, and the targeted combination partners (everolimus, palbociclib, ribociclib, abemaciclib), on the other, are the available options for endocrine-based treatment of metastatic breast cancer (▶ Table 1).

Apart from tamoxifen, the aromatase inhibitors in particular have proved effective as first-line endocrine therapy in postmenopausal patients [15]. Fulvestrant (FALCON study) shows superior efficacy for hormone receptor-positive disease when given in a dosage of 500 mg [16].

There has been a paradigm change since the introduction of the CDK4/6 inhibitors. What is distinctive about the mechanism of action of the CDK4/6 inhibitors is that they intervene directly in the cell cycle and achieve synergistic effects in combination with endocrine therapy, which not only produces an increase in efficacy but also allows endocrine resistance to be overcome by restoring endocrine sensitivity [17]. CDK4/6 inhibitors block overactivated CDK4/6 kinases and achieve dephosphorylation. The tumour suppressor (retinoblastoma protein, which regulates the checkpoint, controls the transition from the G1 to the S phase and prevents the transition from taking place without a mitogenic signal) becomes active and prevents uncontrolled transition from the G1 to the S phase. The cell cycle is arrested, with inhibition of tumour cell proliferation [18].

With the approval of the first CDK4/6 inhibitor, the substance class became the new standard because of the consistent efficacy and safety data of the pivotal studies. Doubling of the response was obtained by the combined therapy compared with anti-hormonal therapy alone. Palbociclib is the first CDK4/6 inhibitor licensed in Germany. In the PALOMA 1 study, a PFS (progression-free survival) benefit of 20.2 months in postmenopausal patients was shown for first-line therapy with the combination of the aromatase inhibitor letrozole vs. 10.2 months with letrozole alone (HR: 0.488; 95% CI 0.32–0.75, p = 0.0004) [19]. These data were confirmed in the PALOMA 2 study (first-line) with a benefit in median PFS of 24.8 vs. 14.4 months. Furthermore, the health-related quality of life (QoL) was maintained. A deterioration in QoL was observed only in the case of progression. The PALOMA 3 study used fulvestrant instead of an aromatase inhibitor after prior treatment with an aromatase inhibitor (as second-line for advanced or metastatic hormone receptor-positive, HER2-negative breast cancer after failure of previous endocrine therapy). Here, too, the combined therapy showed a PFS benefit (9.2 vs. 3.8 months, HR: 0.42, 95% CI: 0.318–0.56; p < 0.000001; ORR (objective response rate): 19 vs. 9%; OR (odds ratio): 2.247; p = 0.0019). Overall, nearly two thirds of the patients in the combined arm

▶ Table 1 Endocrine-based combined therapies.

| Drug	Dosage
mTOR inhibitor	
▪ Everolimus (+ exemestane)	10 mg p. o. daily
CDK4/6 inhibitors (+ AI or fulvestrant)	
▪ Palbociclib	125 mg p. o. d1–21, q28
▪ Ribociclib	600 mg p. o. d1–21, q28

benefited (CBR [clinical benefit rate]: 67 vs. 40%; OR 3.05; p < 0.0001). 21% of the patients were premenopausal so goserelin was given in addition. The effect of treatment also applied to the premenopausal situation [20]. In the patient population overall, a non-significant trend to prolongation of overall survival was seen for the combination at 34.9 vs. 28 months (HR: 0.81, 95% CI: 0.64–1.03) [21]. In the subgroup of patients who showed endocrine sensitivity, the overall survival was prolonged statistically significantly in the combination with palbociclib: 39.7 vs. 29.7 months (HR: 0.72; 95% CI: 0.55–0.94). Quality of life analysis found no deterioration compared with endocrine therapy alone but even showed a significant improvement (p = 0.0011). Further deterioration in quality of life and the pain situation was significantly delayed (p < 0.025 and p < 0.001).

As the second CDK4/6 inhibitor, ribociclib as first-line therapy in the MONALEESA 2 study also produced a prolongation of PFS (HR: 0.56, 95% CI: 0.43–0.72; p < 0.0001); after 18 months, 63% of the patients were still progression-free vs. 42.2% in the control arm. The ORR was 52.7% for patients with clinically measurable disease vs. 37.1% on letrozole alone [22]. In the MONALEESA 3 study [23] the PFS was prolonged significantly from 12.8 to 20.5 months in 776 postmenopausal patients with ribociclib in combination with fulvestrant as first- or second-line therapy (HR: 0.593, 95% CI: 0.480–0.732, p < 0.001). In the case of measurable lesions, the response rate of the combined therapy was 40.9% compared with 28.7% with fulvestrant therapy alone (+ placebo).

The third CDK4/6 inhibitor, abemaciclib, likewise showed a marked benefit as first-line therapy in combination with a nonsteroidal aromatase inhibitor (HR: 0.54, 95% CI: 0.41–0.72, p = 0.00021) in the MONARCH 3 study [24] or with fulvestrant in the MONARCH 2 study as first- or second-line therapy with maximal endocrine therapy and no chemotherapy for the treatment of metastasis (relative risk reduction PFS of 44.7% at 16.4 vs. 9.3 months; HR: 0.553; p < 0.000001) after previously endocrine-treated metastasis in the pre- or postmenopausal situation [25].

In summary, 5 randomised studies, including 1 phase II and 4 phase III studies, of combined endocrine-based CDK4/6 therapies yielded evidence for prolonged PFS. The last interim analysis of the phase III studies demonstrated median PFS between 25.3 and 27.6 months for the combination (with aromatase inhibitor), which is markedly superior compared with endocrine monotherapy where PFS was 13.0 to 16.0 months (the median PFS in MONARCH 3 was not reached with a median follow-up of 17.8 months). The benefits were also apparent for the subgroups of elderly patients and were independent of the metastasis pattern (visceral
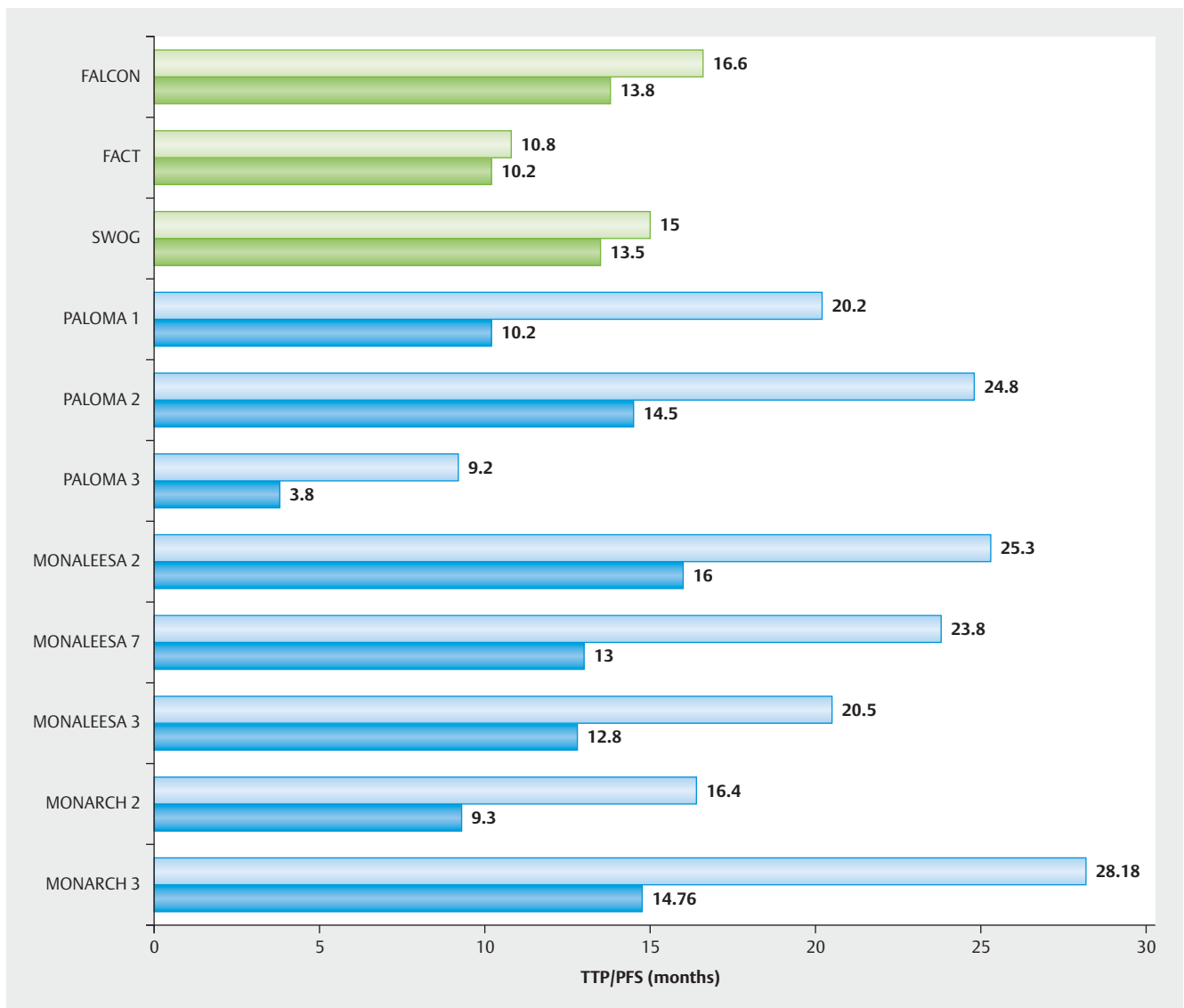
▶ **Fig. 2** Effectiveness of endocrine-based therapies in first- and second-line treatment of HR-positive/HER2-negative breast cancer. (Study groups are shown with light colours and control groups are shown with dark colours; purely endocrine-based studies are FALCON, FACT and SWOG, all others are combined therapies; study references are listed under ▶ **Table 2**.)

vs. osseous) and prior treatment. For non-visceral metastasis, preference may be given to the combination with fulvestrant by analogy with the FALCON study which found markedly longer median PFS of 22.3 months with fulvestrant compared with 13.8 months with anastrozole [26].

The Breast AGO (Gynaecologic Oncology Working Group) has therefore assessed combined endocrine-based CDK4/6 therapy as a treatment option for patients with metastatic HR+ HER2− breast cancer with a recommendation of "++" (LoE: 1b, GR: B). The following figure and table summarise the individual studies (▶ **Fig. 2** and **Table 2**).

Premenopause

Since most studies of metastatic disease where the tumour is endocrine-sensitive and HER2-negative at the same time refer to postmenopausal patients and have excluded premenopausal patients, very few statistically valid conclusions about the premenopausal situation are available.

The premenopausal situation involves sustained ovarian suppression (oophorectomy/GnRH analogues) in addition to tamoxifen, an aromatase inhibitor or fulvestrant. Meta-analyses comparing GnRH analogues alone vs. in combination with tamoxifen confirmed the benefits of the primary combination [32]. The observation times for combined therapy with GnRH and aromatase inhibitors are shorter but show good efficacy and tolerability after failure of tamoxifen-containing therapy. The choice of treatment is also decided depending on the adjuvant therapy, its duration and the time to progression.

Premenopausal patients were included for the first time in the PALOMA 3 study and treated with fulvestrant, GnRH analogues

▶ **Table 2** CDK4/6 inhibition: comparison of studies (first- and second-line therapy).

Study	Therapy	Case number	mPFS/TTP	p value
FALCON [16]	Fulvestrant	230	16.6	0.0486
	vs.			
	Anastrozole	232	13.8	
FACT [27]	Fulvestrant + anastrozole	256	10.8	0.91
	vs.			
	Fulvestrant	258	10.2	
SWOG [28]	Fulvestrant + anastrozole	349	15	0.007
	vs.			
	Anastrozole	345	13.5	
PALOMA 1 (1st line) [19]	Palbociclib + letrozole	84	20.2	0.0004
	vs.			
	Letrozole + placebo	81	10.2	
PALOMA 2 (1st line) [29]	Palbociclib + letrozole	444	24.8	< 0.000001
	vs.			
	Letrozole + placebo	222	14.5	
PALOMA 3 (2nd line) [30]	Palbociclib + fulvestrant	347	9.2	< 0.000001
	vs.			
	Fulvestrant + placebo	174	3.8	
MONALEESA 2 (1st line) [22]	Ribociclib + letrozole	334	25.3	9.63×10^{-8}
	vs.			
	Letrozole + placebo	334	16	
MONALEESA 7 (premenopausal, 1st line) [31]	Tamoxifen or NSAI + ribociclib + goserelin	335	23.8	0.0000000983
	vs.			
	Tamoxifen or NSAI + placebo + goserelin	337	13	
MONALEESA 3 (2nd line) [23]	Ribociclib + fulvestrant	440	20.5	0.0000041
	vs.			
	Fulvestrant + placebo	229	12.8	
MONARCH 2 (2nd line) [25]	Abemaciclib + fulvestrant	446	16.4	< 0.000001
	vs.			
	Fulvestrant	223	9.3	
MONARCH 3 (1st line) [24]	Abemaciclib + NSAI	328	median PFS not reached	0.00021
	vs.			
	NSAI	165	14.8	

and palbociclib. When there was previous endocrine treatment, an improvement in PFS was found for the combination vs. fulvestrant and GnRH analogue without CDK4/6 blockade (9.5 vs. 5.6 months; HR: 0.5; 95% CI: 0.29–0.87). Similarly good results were apparent with the combination of fulvestrant, GnRH analogue and the CDK4/6 inhibitor abemaciclib (16.4 vs. 9.3 months; HR: 0.553, 95% CI: 0.449–0.681). In another phase III study (MONALEESA 7 study) exclusively premenopausal patients received either tamoxifen or aromatase inhibitors in combination with GnRH analogues with or without ribociclib [31] as first line. Here, too, the advantages in PFS through combination with the CDK4/6 inhibitor were confirmed (23.8 vs. 13 months; HR: 0.55, 95% CI: 0.44–0.69). Moreover, the first positive survival data regarding a CDK4/6 in-

hibitor in the premenopausal situation were recently presented at the ASCO conference. After median follow-up of 34.6 months, combination with ribociclib was shown to be markedly superior in overall survival compared with endocrine therapy alone (HR: 0.712, 95% CI: 0.54–0.95; p = 0.00973) [33].

Other treatment options

Primary or acquired resistance often limits continuation of anti-hormone treatment in metastatic breast cancer and requires a switch to chemotherapy, which has markedly more side effects.

The "mammalian target of rapamycin" (mTOR) is an important key protein in the PI3K/AKT/mTOR signal transduction pathway. This signalling pathway is dysregulated in 70% of all breast can-

cers and makes mTOR inhibitors like everolimus and temserolimus an interesting approach against secondary resistance [34]. In endocrine-responsive metastatic breast cancer (HER2neu−) the effect and tolerability of the combination of tamoxifen and everolimus was evaluated in a phase II study and stratified according to primary and secondary resistance [35]. The combination of tamoxifen plus everolimus compared with tamoxifen alone led to an improvement of 19% in the rate of clinical benefit (61 vs. 42%), an increase of 4.1 months in the time to tumour progression (8.6 vs. 4.5 months; p = 0.0021) and a reduction in the mortality risk (p = 0.007). Interestingly, a subgroup analysis showed that only patients with secondary endocrine resistance benefited from everolimus. Patients with metastatic ER+/HER2neu− breast cancer after previous treatment with nonsteroidal aromatase inhibitors benefit from switching to the combination of an mTOR inhibitor (everolimus) with a steroidal aromatase inhibitor (exemestane), as the BOLERO 3 study found. PFS was prolonged from 4.1 months on exemestane alone to 10.6 months with the combination (p < 0.001) [36]. The combination is licensed for the treatment of hormone receptor-positive MBC after previous treatment with a nonsteroidal aromatase inhibitor, but is used only secondarily because of the more severe side effect profile. The side effect profile of everolimus comprises stomatitis, fatigue, non-infective pneumonitis and hyperglycaemia. Treatment should therefore be managed similarly to that with chemotherapy. This also includes close monitoring in the first 4–6 weeks.

Other endocrine-based combined therapies, e.g., with bevacizumab, did not achieve any clear benefits compared with endocrine monotherapy and are therefore not recommended.

The effect of PIK3 inhibitors must be evaluated further and they are therefore not yet included in routine recommendations.

When progression occurs on endocrine monotherapy or combined (CDK4/6) first-line therapy, a switch can be made to exemestane and everolimus, and to the combination with a CDK4/6 inhibitor after endocrine monotherapy. If further progression occurs or there is high remission pressure, switching to chemotherapeutic agents may be preferable.

Side effect profile

The side effect profile of tamoxifen is characterised by an increased risk of thromboembolic events and possible induction of endometrial carcinoma. However, these side effects do not produce an increase in mortality [37]. In the case of aromatase inhibitors, joint and bone pains and osteoporosis predominate in particular [38], and more rarely a deterioration in cognitive skills. Side effects such as nausea, weakness, reactions at injection sites and elevated liver enzyme levels are described for fulvestrant.

As regards the side effect profile, endocrine monotherapy is, as expected, superior to combined therapies.

The main side effects of combined therapy with the mTOR inhibitor everolimus, which occur significantly more frequently compared with endocrine therapy alone (BOLERO 2) are stomatitis, hyperglycaemia, fatigue, pneumonitides and lipid alterations. Close monitoring for side effects is therefore necessary to enable prompt dose reduction or interruption of treatment if necessary.

When the various combined therapies are compared, the CDK4/6 combinations come out best, ahead of the mTOR combinations and also ahead of chemotherapy.

The interference of the CDK4/6 inhibitors in the cell cycle explains their mechanism of action as well as their side effect profile. The side effect spectrum, which is similar for all CDK4/6 inhibitors, is focused on neutropenia with an overall incidence of all grades of up to 80% and on leucopenia through an inhibitory influence on the proliferation activity of the leucocytes. There is an increased incidence of grade 3 neutropenia (in up to about 50%, e.g., with ribociclib) and leucopenia (in over 10%), and up to grade 4 in rare cases (over 5 to about 10%). Unlike the neutropenia and leucopenia seen with chemotherapy, these are usually not associated with fever or clinically significant infections and are therefore hardly noticed by the patients, and they can be managed readily in clinical practice, e.g., by dose reductions. Because of this, a full blood count check every 2 weeks initially was introduced. In addition, fatigue may occur (but this is rarely severe). No clinically significant QT interval change or cumulative or delayed toxicity was found [39, 40]. The tolerability especially in elderly patients was also confirmed in a pooled analysis.

In the case of ribociclib, the side effects led to treatment discontinuation in 7.5 vs. 2.1% in the placebo arm [22]. As with palbociclib, the side effect profile was dominated by neutropenia (59.3%) and leucopenia (21%), diminishes in the course of treatment and is completely reversible. However, previously described hepatic (transaminase increase) and cardiac toxicity (prolongation of QT interval) require close follow-up and ECG monitoring.

For abemaciclib, which differs in molecular structure from palbo- and ribociclib and binds selectively to CDK4 and CDK6 and additionally to CDK9, the side effect spectrum therefore differs partially with lower myelotoxicity but more frequent gastrointestinal symptoms such as diarrhoea [25]. As a result of the low myelotoxicity, abemaciclib can be used continuously and without a break in treatment. In addition, it can cross the blood-brain barrier and might therefore have an effect on cerebral metastases [41].

For all CDH4/6 inhibitors, there is a consistent and sometimes even markedly positive influence on quality of life for the endocrine-based combined therapy, which remains good and unaffected by their respective toxicities.

Conclusions

The PALOMA 2, MONALEESA 2 and MONARCH 3 studies showed a marked prolongation of PFS with combined therapy consisting of a CDK4/6 inhibitor with an aromatase inhibitor. For fulvestrant the PALOMA 3, MONALEESA 3 und MONARCH 2 studies demonstrated a risk reduction of up to 50% for disease progression in both pre- and postmenopausal patients. The described efficacy benefits have led to licensing of the endocrine-based combinations and signify marked medical progress with their confirmed practical use and readily manageable adherence, with preserved quality of life and side effects that can be treated in routine clinical practice. The effect of the combined therapy has also been confirmed for premenopausal patients on ovarian suppression, so its use is the preferred endocrine-based first-line treatment

for the breast cancer patient in the metastatic hormone receptor-positive, HER2-negative situation.

If the first-line therapy fails, it is possible to switch to combined treatment with exemestane and everolimus. If a CDK4/6 inhibitor has not been used in first-line therapy, preference should be given to the CDK4/6 inhibitor in the second line because of the better side effect profile. When weighing the patient's general health status and pre-existing diseases, the effects and side effect profile must be considered, and endocrine monotherapy must therefore be preferred in individual cases. Direct comparative data between CDK4/6-based combinations and chemotherapy are lacking. CDK4/6 inhibitors consistently show a good and rapid range of effects and can therefore postpone chemotherapy indications to later treatment lines. In case of doubt, in the acute life-threatening situation and when it is important to shrink the tumour as fast as possible, chemotherapy should be favoured. This may also apply when clear endocrine resistance is highly suspected.

Since data on a suitable treatment sequence are still lacking, clear evidence-based recommendations are not possible and further controlled studies are required.

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Conflict of Interest

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