Published online: 2019-12-11

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

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

OPEN ACCESS

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

Key words
breast cancer, metastasis, hormone receptor-positive, HER2-negative, CDK4/6 inhibitor

Schlüsselwörter
Mammakarzinom, Metastasierung, hormonrezeptorpositiv, HER2-negativ, CDK4/6-Inhibitor

received 7.6.2019
revised 1.8.2019
accepted 29.10.2019

Bibliography
DOI https://doi.org/10.1055/a-1037-5205
Geburtsh Frauenheilk 2019; 79: 1328–1335 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0016-5751

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

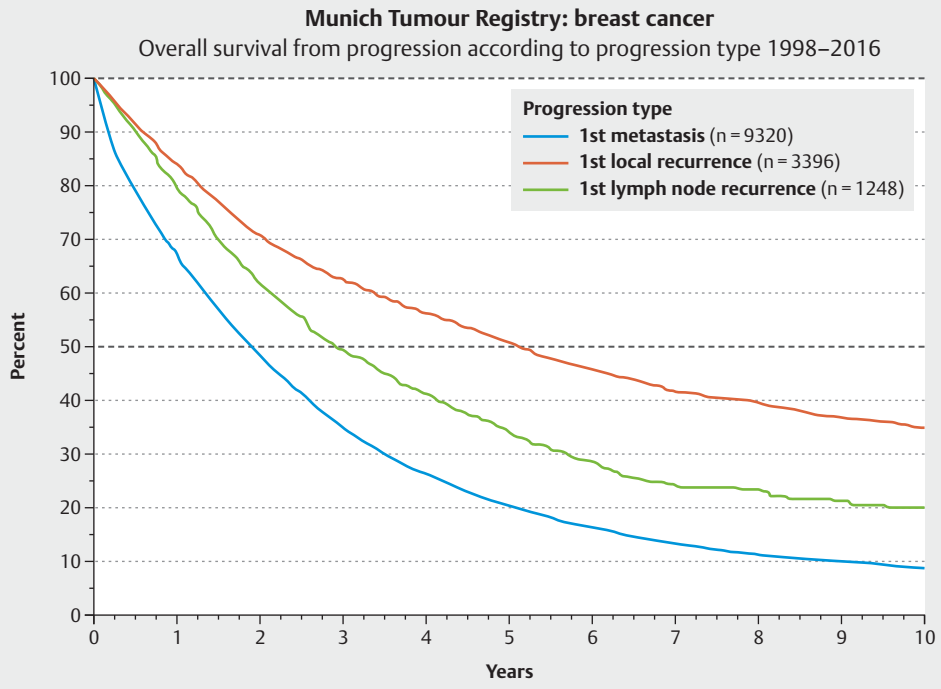
Deutsche Version unter:
https://doi.org/10.1055/a-1037-5205

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.



▶ **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 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).

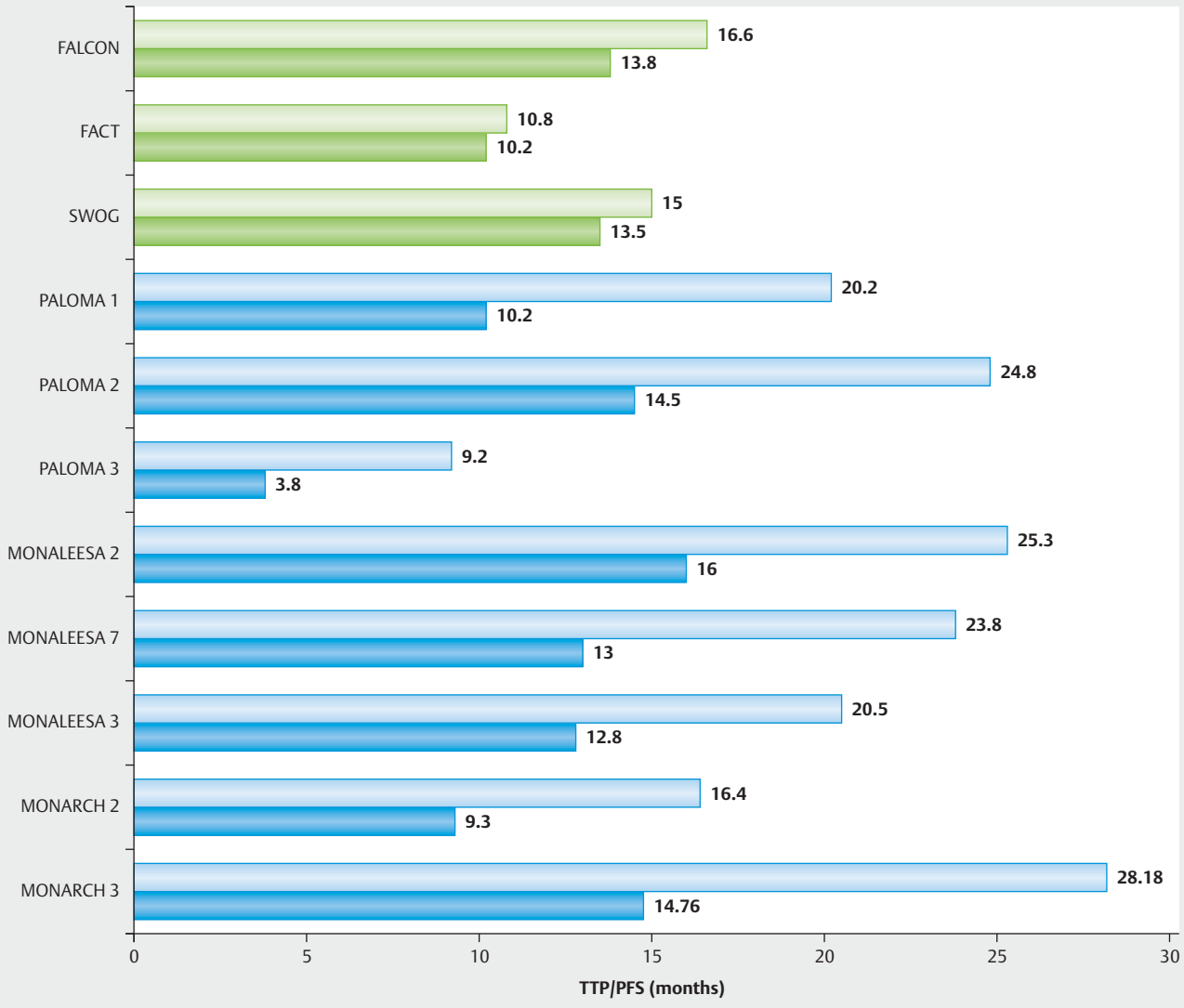
▶ **Table 1** Endocrine-based combined therapies.

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

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 inhibitor 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 antihormone 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.

Acknowledgements

We thank Dr. J. Engel and Ms S. Schrodi for providing the data and ▶ **Fig. 1** from Munich Tumour Registry.

Conflict of Interest

N. Ditsch: MSD, Roche, AstraZeneca, Teva. M. Schmidt: Amgen, AstraZeneca, Eisai, Lilly, Myelo Therapeutics, Novartis, Pantarhei Bioscience, Pfizer, Roche, BioNTech, Genentech, Pierre Fabre.

References

[1] Ervik E, Lam F, Ferlay J et al. Cancer Today. Lyon, France: International Agency for Research on Cancer; 2016. Online: http://gco.iarc.fr/today; last access: 28.08.2019

[2] Blows FM, Driver KE, Schmidt MK et al. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. PLoS Med 2010; 7: e1000279

[3] Ibrahim T, Farolfi A, Scarpi E et al. Hormonal receptor, human epeidermal growth factor-2, and Ki67 discordance between primary breast cancer and paired metastases: clinical impact. Oncology 2013; 84: 150–157

[4] Lindström LS, Karlsson E, Wilking UM et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol 2012; 30: 2601–2608

[5] Rugo HS, Rumble RB, Macrae E et al. Endocrine therapy for hormone-receptor-positive metastatic breast cancer. American Society of Clinical Oncology Guideline. J Clin Oncol 2016; 34: 3069–3103

[6] Harbeck N, Gnant M. Breast Cancer. Lancet 2017; 389: 1134–1150

[7] Bosseti C, Bertuccio P, Malvezzi M et al. Cancer mortality in Europe, 2005–2009, and an overview of trends since 1980. Ann Oncol 2013; 24: 2657–2671

[8] Jackisch C. Metastasiertes Mammakarzinom: Längeres und besseres Überleben. Dtsch Arztebl 2014; 111: 18

[9] Cardoso F, Senkus E, Costa A et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. Ann Oncol 2018; 29: 1634–1657

[10] Ettl J, Harbeck H. The safety and efficacy of palbociclib in the treatment of metastatic breast cancer. Expert Rev Anticancer Ther 2017; 17: 661–668

[11] Reinert T, Barrios CH. Overall survival and progression-free survival with endocrine therapy for hormone receptor-positive, HER2-negative advanced breast cancer: review. Ther Adv Med Oncol 2017; 9: 693–709

[12] Wöckel A, Festl J, Stüber T et al. Interdisciplinary Screening, Diagnosis, Therapy and Follow-up of Breast Cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017) – Part 1 with Recommendations for the Screening, Diagnosis and Therapy of Breast Cancer. Geburtsh Frauenheilk 2018; 78: 927–948. doi:10.1055/a-0646-4522

[13] Thill M, Liedtke C, Müller V et al.; AGO Breast Committee. AGO Recommendations for the Diagnosis and Treatment of Patients with Advanced and Metastatic Breast Cancer: Update 2018. Breast Care (Basel) 2018; 13: 209–215. doi:10.1159/000489331

[14] Sledge GW jr., Hu P, Falkson G et al. Comparison of chemotherapy with chemohormonal therapy as first-line therapy for metastatic, hormone-sensitive breast cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 2000; 18: 262–266

[15] Thill M, Schmidt M. Management of adverse events during cyclin-dependent kinase 4/6 (CDK4/6) inhibitor-based treatment in breast cancer. Ther Adv Med Oncol 2018; 10: 1758835918793326. doi:10.1177/1758835918793326

[16] Robertson JFR, Bondarenko IM, Trishkina E et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet 2016; 388: 2997–3005

[17] Echavarria I, Jerez Y, Martin M et al. Incorporating CDK4/6 Inhibitors in the Treatment of Advanced Luminal Breast Cancer. Breast Care (Basel) 2017; 12: 296–302

[18] VanArsdale T, Bischoff C, Arndt KT et al. Molecular pathways: targeting the cyclin D-CDK4/6 axis for cancer treatment. AACR Annual Meeting 2015. Clin Cancer Res 2015; 21: 2905–2910

[19] Finn RS, Crown JP, Lang I. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015; 16: 25–35

[20] Loibl S, Turner NC, Ro J et al. Palbociclib combined with fulvestrant in premenopausal women with advanced breast cancer and prior progression on endocrine therapy: PALOMA-3 results. Oncologist 2017; 22: 1028–1038

[21] Turner NC, Slamon DC, Ro J et al. Overall survival with Palbociclib and Fulvestrant in advanced breast cancer. N Engl J Med 2018. doi:10.1056/NEJMoa1810527

[22] Hortobagyi GN, Stemmer SM, Burris HA et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016; 375: 1738–1748

[23] Slamon DJ, Neven P, Cjia S et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. MONALEESA-3. J Clin Oncol 2018; 36: 2465–2472

[24] Goetz MP, Toi M, Campone M et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 2017; 35: 3638–3646

[25] Sledge GW jr., Toi M, Neven P et al. MONARCH2: Abemaciclib in combination with fulvestrant in women with HR+/HER2-advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017; 35: 2875–2884

[26] Robertson JFR, Di Leo A, Fazal M et al. Fulvestrant for hormone receptor-positive advanced breast cancer in patients with visceral versus non-visceral metastases: Findings from FALCON, FIRST and CONFIRM. San Antonio, TX: San Antonio Breast Cancer Symposium 2017: PD5-09

[27] Bergh J, Jönsson PE, Lidbrink EK et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol 2012; 30: 1919–1925. doi:10.1200/JCO.2011.38.1095

[28] Mehta RS, Barlow WE, Albain KS et al. Combination anastrozole and fulvestrant in metastatic breast cancer. N Engl J Med 2012; 367: 435–444. doi:10.1056/NEJMoa1201622

[29] Finn RS, Martin M, Rugo HS et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016; 375: 1925–1936

[30] Turner NC, Ro J, André F et al.; PALOMA3 Study Group. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med 2015; 373: 209–219. doi:10.1056/NEJMoa1505270

[31] Tripathy D, Im S, Colleoni M 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; 19: 904–915

[32] Klijn JG, Blamey R, Boccardo F et al. Combined hormone agents Trialists Group and the European Organization for Reasearch and Treatment of Cancer. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol 2001; 19: 343–353

[33] Hurvitz SA, Im SA, Lu YS et al. Phase III MONALEESA-7 trial of premenopausal patients with HR+/HER2− advanced breast cancer (ABC) treated with endocrine therapy ± ribociclib: overall survival (OS) results. J Clin Oncol 2019; 37 (Suppl.): Abstr. LBA1008. doi:10.1200/JCO.2019.37.18_suppl.LBA1008

[34] Lopez-Knowles E, O'Toole SA, McNeil CM et al. PI3K pathway activation in breast cancer is associated with the basal-like phenotype and cancer specific mortality. Int J Cancer 2010; 126: 1121–1131

[35] Bachelot T, Bourgier C, Cropet C et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. J Clin Oncol 2012; 30: 2718–2724

[36] Baselga J, Campone M, Piccart M et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012; 366: 520–529

[37] Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011; 378: 771–784

[38] Coleman RE, Bolten WW, Lansdown M et al. Aromatase inhibitor-induced arthralgia: clinical experience and treatment recommendations. Cancer Treat Rev 2008; 34: 275–282

[39] Dieras V, Rugo HS, Schnell P et al. Long-term pooled safety analysis of Palbociclib in combination with endocrine therapy for HR+/HER2- advanced breast cancer. J Natl Cancer Inst 2018. doi:10.1093/jnci/djy109

[40] Durairaj C, Ruir-Garcia A, Gauthier ER et al. Palbociclib has no clinically relevant effect on the QTc interval in patients with advanced breast cancer. Anticancer Drugs 2018; 29: 271–280

[41] Tolaney SM, Lin NU, Thornton D et al. Abemaciclib for the treatment of brain metastases (BM) secondary to hormone receptor positive (HR+), HER2 negative breast cancer. J Clin Oncol 2017; 35 (15 Suppl.): Abstr. 1019

[42] Park YH, Kim TY, Kim GM et al. A randomized phase II study of palbociclib plus exemestane with GnRH agonist versus capecitabine in premenopausal women with hormone receptor-positive metastatic breast cancer (KCSG-BR 15-10, NCT02592746). J Clin Oncol 2019; 37: Abstr. 1007

[43] Lobbezoo DJ, van Kampen RJ, Voogd AC et al. In real life, one-quarter of patients with hormone receptor-positive metastatic breast cancer receive chemotherapy as initial palliative therapy: a study of the Southeast Netherlands Breast Cancer Consortium. Ann Oncol 2016; 27: 256–262. doi:10.1093/annonc/mdv544

[44] Kolberg H-C, Schneeweiss A, Fehm TN et al. Update Breast Cancer 2019 Part 3 – Current Developments in Early Breast Cancer: Review and Critical Assessment by an International Expert Panel. Geburtsh Frauenheilk 2019; 79: 470–482

[45] Wöckel A, Festl J, Stüber T et al. Interdisciplinary Screening, Diagnosis, Therapy and Follow-up of Breast Cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017) – Part 1 with Recommendations for the Screening, Diagnosis and Therapy of Breast Cancer. Geburtsh Frauenheilk 2018; 78: 927–948