Thieme

Update Breast Cancer 2022 Part 4 – Advanced-Stage Breast Cancer

Update Mammakarzinom 2022 Teil 4 – Brustkrebs in fortgeschrittenen Krankheitsstadien

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ABSTRACT

For the treatment of patients with advanced HER2-negative hormone receptor-positive breast cancer, several substances have been introduced into practice in recent years. In addition, other drugs are under development. A number of studies have been published over the past year which have shown either an advantage for progression-free survival or for overall survival. This review summarizes the latest results, which have been published at current congresses or in specialist journals, and classifies them in the clinical treatment context. In particular, the importance of therapy with CDK4/6 inhibitors – trastuzumab deruxtecan, sacituzumab govitecan and capivasertib – is discussed. For trastuzumab deruxtecan, an overall survival benefit in HER2-negative breast cancer with low HER2 expression (HER2-low expression) was reported in the Destiny-Breast-04 study. Similarly, there was an overall survival benefit in the FAKTION study with capivasertib. The lack of overall survival benefit for palbociclib in the first line of therapy raises the question of clinical classification.

ZUSAMMENFASSUNG

Für die Behandlung von Patientinnen mit fortgeschrittenem HER2-negativem, hormonrezeptorpositivem Mammakarzinom sind in den letzten Jahren einige Substanzen in die Praxis eingeführt worden. Zusätzlich sind weitere Medikamente in der Entwicklung. Im letzten Jahr sind einige Studien veröffentlicht worden, die entweder einen Vorteil für das progressionsfreie Überleben oder aber auch für das Gesamtüberleben gezeigt haben. Diese Übersichtsarbeit fasst die neuesten Ergebnisse, welche auf aktuellen Kongressen oder in Fachzeitschriften veröffentlicht wurden, zusammen und ordnet sie in den klinischen Behandlungskontext ein. Insbesondere wird auf den Stellenwert einer Therapie mit CDK4/6 Inhibitoren, Trastuzumab-Deruxtecan, Sacituzumab-Govitecan und Capivasertib eingegangen. Für Trastuzumab-Deruxtecan wurde in der Destiny-Breast-04-Studie ein Gesamtüberlebensvorteil bei HER2-negativem Mammakarzinom mit einer niedrigen HER2-Expression (HER2-low expression) berichtet. Ebenso konnte ein Gesamtüberlebensvorteil in der FAKTION-Studie mit Capivasertib verzeichnet werden. Nach dem fehlenden Gesamtüberlebensvorteil für Palbociclib in der 1. Therapielinie stellt sich hier die Frage nach der klinischen Einordnung.

Introduction

The new developments for the treatment of patients in the metastatic treatment situation have produced some new standard therapies, such as the CDK4/6 inhibitors in the first advanced line of therapy in hormone-receptor-positive, HER2-negative breast cancer, the immune checkpoint inhibitors in triple-negative, PD-L1-positive breast cancer, and the PARP inhibitors in a *BRCA1/2* germ line mutation. Furthermore, the antibody-drug conjugates (ADCs) sacituzumab govitecan could become established in subsequent lines of therapy for patients with triple-negative breast cancer and trastuzumab-deruxtecan in patients with HER2-positive breast cancer. In particular, new patient groups have recently been identified for the ADC, in which these drugs were able to display a high effectiveness despite low expression of the target molecule.

HER2-low – Biomarker or New Subgroup

The anti-HER2 ADC trastuzumab deruxtecan (T-DXd) demonstrated high efficacy in patients with positive HER2 status (HER2 positive according to the criteria of the ASCO/CAP guidelines [1]) in both the single-arm Destiny-B01 study and the Destiny-B03 study. "Positive" in this context means that the patients either had to have a score of 3+ in immunohistochemistry or had to have an amplification of the *HER2* gene with a gene-to-centromer ratio of ≥ 2.0. This definition identifies patients who have an extremely poor prognosis without anti-HER2 treatment because of the activated HER2 pathway. However, the Destiny-B01 study also included patients who did not have overexpression or amplification of *HER2*, but had some expression of HER2 with an immunohistochemical score of 1+ or 2+ (without amplification). This population is called "HER2-low".

"Low Expression" as a therapy concept

The therapy concept that molecules on the cancer surface can be used to direct therapies there, even if they are not necessarily responsible for a poor prognosis, is not new. For example, in clinical studies, anti-HER2 CAR-T cells have already been used for a therapy with sarcomas [2] and anti-HER2 CAR-NK cells for therapy of glioblastomas [3]. In both cases, no overexpression or amplification was required for therapy. Another example is the Di-Sialo ganglioside GD2, which can be found in breast cancer and other carcinomas [4] and which is already relevant for antibody therapy in certain neuroblastomas [5]. Although GD2 can be found in about 50 % of all breast cancers, it has no influence on the prognosis and is certainly an interesting target [4]. A known, further example is Trop2, a target which can be addressed by means of ADC sacituzumab govitecan and is approved for the treatment of patients with previously treated, metastatic TNBC [6].

Thus, the use of therapies against targets that mark the cancer cell, but do not necessarily have to be responsible for the aggres-

siveness of a tumor, is not a new concept. With the new, highly effective ADCs, these patient groups now seem to be suitable for the establishment of new therapies. With regard to tumors with low HER2 expression (HER2-low), it was shown in a registry study that the degree of expression (score of 1+ or 2+) had no influence on PFS or OS in HER2-low patients. In the distribution to the molecular subgroups (▶ **Fig. 1**), it can be seen that approximately 40% of triple-negative tumors and 53% of HR-positive HER2-negative tumors have a low expression of HER2 and would thus be suitable for such a therapy.

It should be noted that, in the future, new standards will have to be established in the immunohistochemical assessment of HER2 expression. Until now, low expression values had no therapeutic relevance. For a therapy decision, there should be an agreement between pathologists and therapists.

Trastuzumab deruxtecan in HER2-negative tumors with low HER2 expression

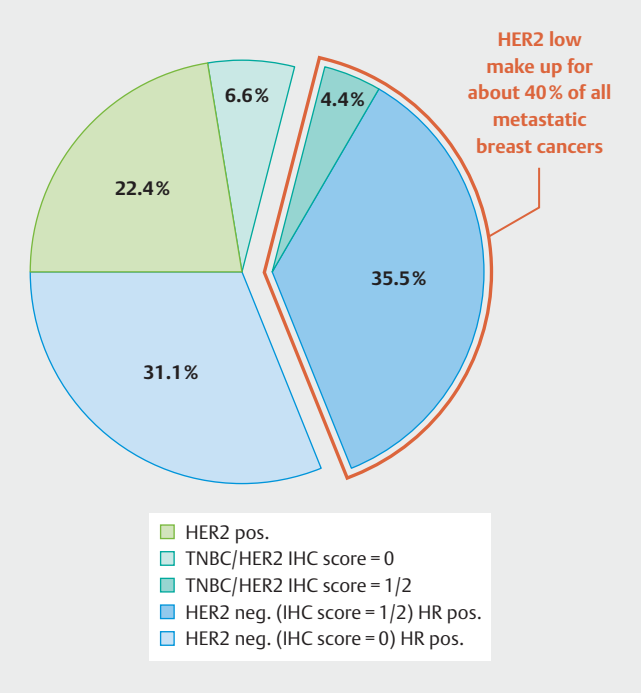
For patients with HER2-negative HR-positive advanced breast cancer, all endocrine therapy options should first be exhausted [7]. However, real-world data show that even after the introduction of CDK4/6 inhibitors, about 40–50% of patients in the second or third line of therapy are still treated with chemotherapy [8], while about 80% of patients are already treated with a CDK4/6 inhibitor [9] in the first line of therapy. An improvement in the therapy situation for these patients would mean a significant progress in therapy. Against this background, the Destiny-Breast-04 study compared chemotherapy of the physician's choice (capecitabine, eribulin, gemcitabine, paclitaxel or Nab-paclitaxel) with ADC trastuzumab deruxtecan [10]. Only patients who were considered to have endocrine resistance and who had already undergone one or two chemotherapies in the advanced treatment situation could be included.

In the Destiny-Breast-04 study, 65% of hormone receptor-positive patients had received preliminary therapy with a CDK4/6 inhibitor and around 60% had received chemotherapy in the metastatic situation. 58% had a HER2 IHC score of 1+ and 42% had a score of 2+ in the absence of amplification of the *HER2* gene [10].

Median progression-free survival was improved from 4.8 months to 9.9 months (HR = 0.50; 95% CI: 0.40–0.63; p < 0.0001). This was true for both hormone receptor-positive and hormone-receptor-negative patients (HR = 0.51; 95% CI 0.40–0.64 for HR-positive and HR = 0.46; 95% CI: 0.24–0.89 for TNBC).

Median overall survival was also improved. In the overall population, the HR was 0.64 (95% CI: 0.49–0.84). Again, the effect was significant in both the HR-positive population (HR = 0.64; 95% CI: 0.48–0.86; ▶ **Fig. 2**) and in the TNBC population (HR = 0.48; 95% CI: 0.24–0.95).

However, it should be noted that with 58 TNBC patients, the analysis was only of an exploratory nature. Also, with a median follow-up period of 18.4 months, it must be noted that no statement can be made about the overall survival during a longer follow-up period. Nevertheless, the statement that over a period of 1.5 years, approximately 35% fewer deaths occur if therapy with T-DXd is carried out instead of chemotherapy, has statistical significance and will most likely influence the therapy decisions.



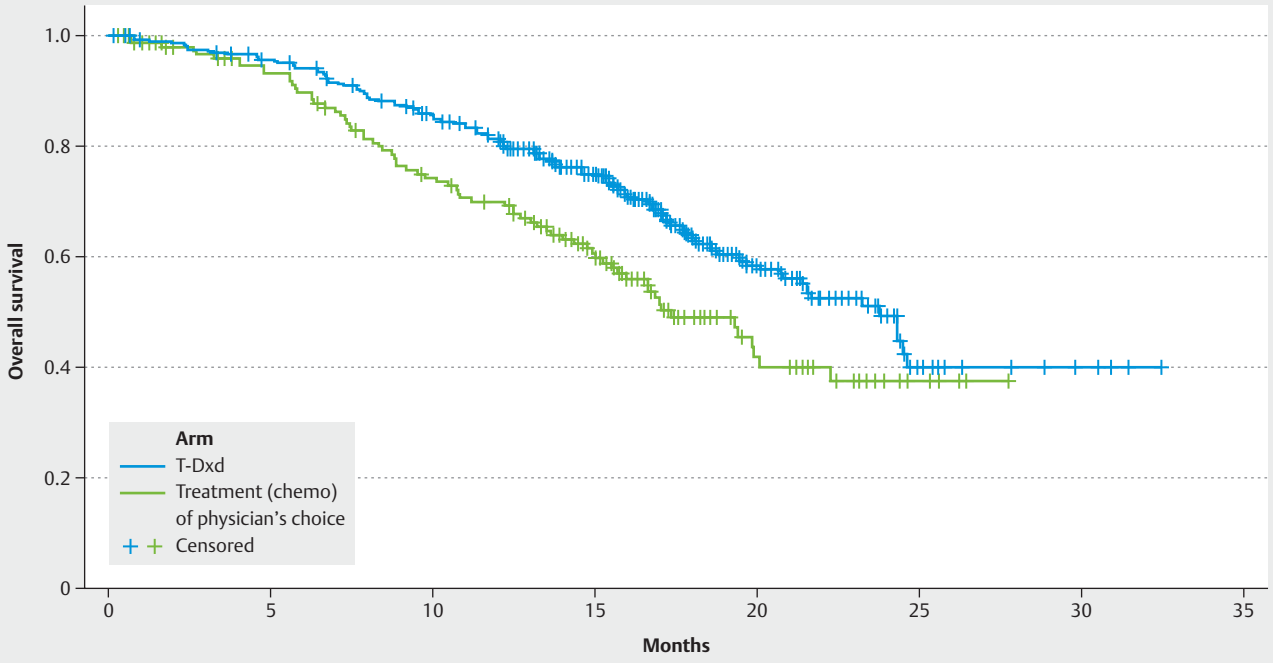
▶ **Fig. 1** Distribution of the "HER2-low-expressing" tumors in the molecular subtypes in the metastatic situation (Fig. based on data from [51]).

Unlike in the Destiny-B03 study, the Destiny-B04 study again reported 3 deaths associated with interstitial lung disease as a result of T-DXd therapy. The possibility of these rare but dangerous side effects should be known to the practitioner, and diagnostic (low dose, high resolution CT) and therapeutic (cortisone therapy) measures should always be initiated immediately in case of respiratory symptoms or suspicion of interstitial lung disease.

New Data on the Therapy of the PI3K/AKT/PTEN Signaling Pathway

The *PIK3CA* pathway as a central component of signal transduction

There are few therapies for which there are clear predictive biomarkers. The presence of hormone receptors predicts the effect of endocrine therapies and HER2 status predicts the effectiveness of anti-HER2 therapies. Another predictive factor is the presence of *PIK3CA* tumor mutations for the efficacy of PI3K inhibitors. This was demonstrated for both buparlisib in the BELLE-2 study and alpelisib in the SOLAR-1 study. In the BELLE-2 study, the hazard ratio in favor of fulvestrant + buparlisib therapy in a group with *PIK3CA* mutation was 0.58 (95% CI: 0.41–0.82) and 1.02 in the group without *PIK3CA* mutation (95% CI: 0.79–1.30) [11]. In the SOLAR-1 study, the HR in the *PIK3CA* mutated group was 0.65 (95% CI: 0.50–0.85) and 0.85 in the wild-type group (95% CI: 0.58–1.25) [12]. Thus, this principle could be confirmed in 2 studies. In fact,



▶ **Fig. 2** Overall survival in the Destiny-Breast-04 study. Data extracted from Modi et al. [10] using the method according to Guyot et al. [52]. With this method in a 2:1 randomization, the number of death events is estimated to be 123 patients in the T-Dxd arm and 72 in the TPC arm.

the PI3K/AKT signaling pathway is a central mechanism of signal transduction with an extraordinary significance for many physiological and pathophysiological processes [13, 14].

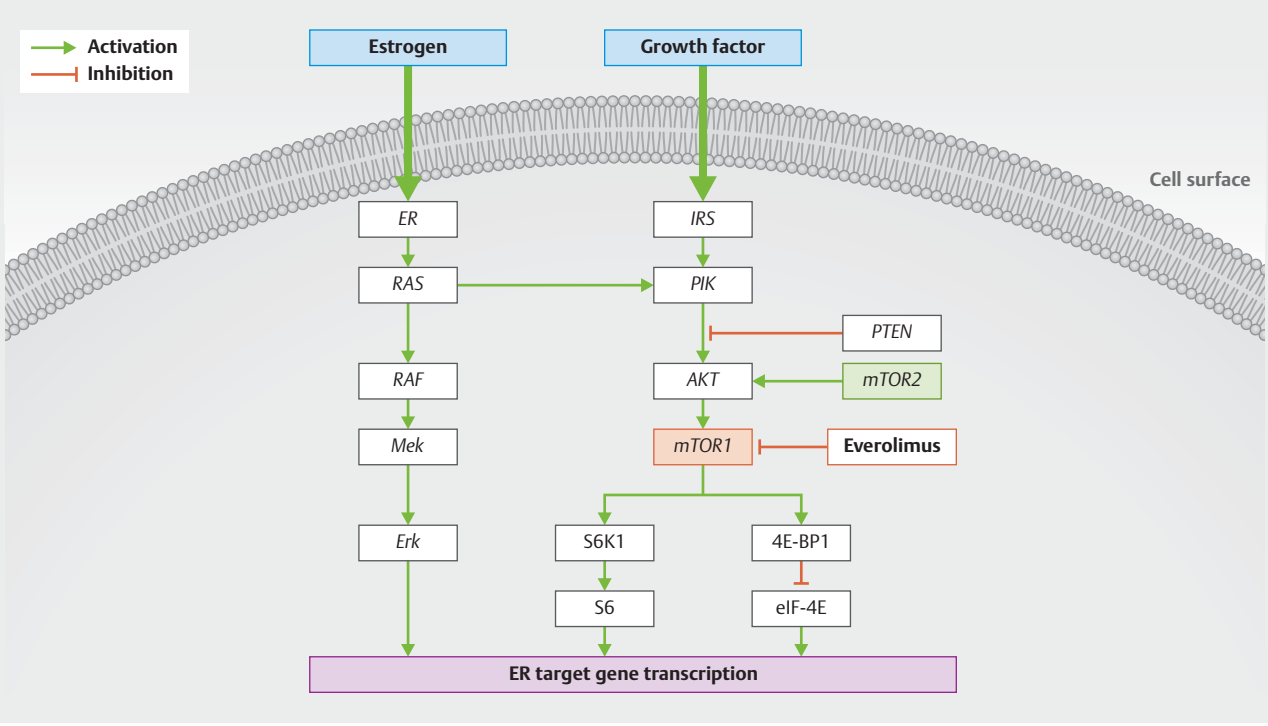
While the PI3 kinase interacts with the transmembrane receptors at the beginning of the signal cascade, the AKT kinase downstream of PIK3 and PTEN is responsible for the further signal transduction. Activation of this signaling pathway occurs in patients with hormone receptor-positive disease in approx. 55% of all cases [15]. A review of these signal transduction pathways is shown in ▶ **Fig. 3**.

The FAKTION study is one of the first studies to investigate the effects of the selective AKT inhibitor capivasertib [16]. The study, which had recruited patients from 2016 to 2018, included patients with resistance to an aromatase inhibitor. Furthermore, one chemotherapy line and up to 3 previous endocrine therapies were permitted as long as they did not contain fulvestrant or a PI3K/AKT/mTOR inhibitor. A total of 140 patients were randomized 1:1 to treatment with fulvestrant or fulvestrant + capivasertib. Data on significant improvement in progression-free survival have already been published [15]. Overall survival data, extended data on PFS and extensive biomarker data have now been presented. The PFS difference was consolidated with the longer follow-up and, with an HR of 0.56 (95% CI: 0.38–0.81), is consistent with the initial report. At 4.8 months and 10.3 months, the median PFS times were the same as in the initial report. This PFS benefit was also translated into a statistically significant overall survival benefit with an HR of 0.66 (95% CI: 0.45–0.97). Median overall survival improved from 23.4 months to 29.3 months [16].

The biomarker data are of particular interest for this study. For the recently presented analysis, new state-of-the-art analysis methods were used to divide the patients into two groups: "PI3K/AKT/PTEN signaling pathway activated" vs. "not activated". This was done by means of mutation tests for *PIK3CA, AKT1, PTEN* and immunohistochemical examinations for PTEN loss. Thus, 76 patients could be assigned to the group with altered signaling pathway and 64 to the group with non-altered signaling pathway. The results confirmed the efficacy of capivasertib therapy in patients whose signaling pathway was altered and the lack of efficacy in patients whose signaling pathway was not altered (▶ **Table 1**).

This underscores the principle that molecular testing can identify patients for whom therapy, in this case with capivasertib, makes sense. The adverse reaction profile showed a higher rate in capivasertib patients for the following side effects: Diarrhea, rash, hyperglycemia, vomiting, infections and oral mucositis.

Since the FAKTION study was conducted at a time when treatment with CDK4/6 inhibitor was not yet standard, this preliminary treatment is missing in this study. Against this background, the results of the CAPItello-291 study will provide insights into a population in which a CDK4/6 inhibitor was also approved as a preliminary therapy [17]. Combination therapy with CDK4/6 inhibition, as tested in the CAPItello-292 study [18], is also of interest.



▶ **Fig. 3** The PI3K/AKT/PTEN signaling pathway [53].

▶ **Table 1** Results of the analysis of the FAKTION study according to biomarker status for the PI3K/AKT/PTEN pathway.

	Total population	PIK3/AKT/PTEN altered	PIK3/AKT/PTEN altered
N	140	76	64
Median PFS fulvestrant	4.8 months	4.6 months	4.9 months
Median PFS fulvestrant + capivasertib	10.3 months	12.8 months	7.7 months
Hazard ratio PFS (fulvestrant + capivasertib vs. fulvestrant)	0.56 (95% CI: 0.38–0.81)	0.44 (95% CI: 0.26–0.72)	0.70 (95% CI: 0.40–1.25)
Median OS fulvestrant	23.4 months	20.0 months	25.2 months
Median OS fulvestrant + capivasertib	29.3 months	38.9 months	26.0 months
Hazard ratio OS (fulvestrant + capivasertib vs. fulvestrant)	0.66 (95% CI: 0.45–0.97)	0.46 (95% CI: 0.27–0.79)	0.86 (95% CI: 0.49–1.52)

Data from the Large, Randomized CDK4/6 Inhibitor Studies are Almost Complete

Data overview for the phase III CDK4/6 inhibitor studies is almost complete

For the three CDK4/6 inhibitors palbociclib, ribociclib and abemaciclib, a total of seven large randomized studies have been conducted (▶ **Table 2**). Because of the improved prognosis, the data from the studies in the first line of therapy in relation to overall survival have only recently been published.

Subgroup analysis of the MONALEESA-3 study reports median overall survival for the first line of therapy

The MONALEESA-3 study is the only study that included patients with both tumors sensitive to hormone therapy and resistant to hormone therapy, defined by the time between discontinuation of adjuvant anti-hormonal therapy (first line) or progression under antihormone therapy in first-line therapy. In this context, the evaluation of these subgroups is of particular interest. The subgroups evaluated independently were those with de novo metastases and those who had a therapy-free interval from the end of adjuvant therapy of more than 12 months. This population is called first-line population in MONALEESA-3. Patients with a treatment-free interval of less than 12 months (even if they had been treated in

▶ **Table 2** Overview of the large, randomized phase III CDK4/6 inhibitor studies.

	N	Therapy	Last patient in	PFS HR (95% CI)	Median PFS CDK4/6 | Placebo*	OS HR (95% CI)	Median OS CDK arm | Placebo*	Proportion of de novo metastatic patients	Proportion of patients with DFI < 12 months	References
MONALEESA-2	668	Ribociclib + letrozole	03/2015	0.56 (0.43–0.72)	25.3 | 16.0	0.76 (0.63–0.93)	63.9 | 51.4	34%	2.1%	[20, 34]
MONARCH 3	493	Abemaciclib + NSAI	11/2015	0.54 (0.41–0.72)	28.2 | 14.8	0.76 (0.58–0.97)	67.1 | 54.1	40%	**	[35, 36]
PALOMA-2	666	Palbociclib + letrozole	07/2014	0.58 (0.46–0.72)	24.8 | 14.5	0.96 (0.78–1.18)	53.9 | 51.2	37%	22%***	[21, 37]
MONALEESA-7	672	Ribociclib + ET	08/2016	0.55 (0.44–0.69)	23.8 | 13.0	0.71 (0.54–0.95)	58.7 | 48.0	19%	4.3%	[38 – 40]
MONALEESA-3	726	Ribociclib + fulvestrant	06/2016	0.59 (0.48–0.73)	20.5 | 12.8	0.72 (0.57–0.92)	53.7 | 41.5	40%	5.4%	[41 – 44]
MONARCH 2	669	Abemaciclib + fulvestrant	12/2015	0.55 (0.45–0.68)	16.9 | 9.3	0.76 (0.61–0.95)	46.7 | 37.3	NA	NA	[45, 46]
PALOMA-3	521	Palbociclib + fulvestrant	08/2014	0.46 (0.36–0.59)	9.5 | 4.6	0.81 (0.64–1.03)	34.8 | 28.0	NA	NA	[47 – 49]
DAWNA-1	361	Dalpiciclib* + fulvestrant	09/2020*	0.42 (0.31–0.58)	15.7 | 7.2	Not yet reported	Not yet reported	NA	NA	[50]

* Based on the respective publication with the longest follow-up.

** Presumably similar to MONALEESA-2 and MONALEESA-7, as the following inclusion criterion applied: "Endocrine therapy in the neoadjuvant or adjuvant setting was permitted if the patient had a disease-free interval. 12 months from the completion of endocrine therapy."

*** This study reported treatment-free interval (not DFI). Not comparable with other DFI percentages.

NA: Not applicable since preliminary therapies were a prerequisite for participation in the advanced setting; ET: endocrine therapy

the first line of therapy) and patients with endocrine preliminary therapy were treated as patients of the second-line therapy. In the patients sensitive to hormone therapy (MONALEESA-3 first-line population), a very clear difference between the treatment arms could be seen with a hazard ratio of 0.67 (95% CI: 00.50–0.90) [19]. The median overall survival in this population was 51.8 months for fulvestrant monotherapy and 67.6 months for ribociclib-fulvestrant therapy. In the hormone-resistant group (MONALEESA-3 second-line population), the difference was not so clear (HR = 0.80; 95% CI: 0.61–1.05) with median overall survival times of 33.7 and 39.7 months [19].

Negative overall survival data from the PALOMA-2 study is difficult to interpret

The MONALEESA-2 study was the first study in the first line of therapy in combination with aromatase inhibitors to report a statistically significant overall survival benefit [20] (▶ **Table 2**). The PALOMA-2 study had similar inclusion and exclusion criteria as the MONALEESA-2 study. In addition to the MONALEESA-2 population, patients who had a disease-free interval of less than 12 months from the end of adjuvant endocrine therapy were also included. This group accounted for 22% of the PALOMA-2 patients (▶ **Table 2**). In all, the analysis of the overall survival data from the PALOMA-2 study did not show that adding palbociclib to letrozole could improve overall survival [21]. The hazard ratio for the entire patient population was 0.96 (95% CI: 0.78–1.18). The median overall survival was 51.2 months for the letrozole arm and 53.9 months for the palbociclib + letrozole arm. Overall, however, the study is difficult to interpret due to a follow-up bias. In the palbociclib arm, 13% of patients were not censored for death by month 84, and 21% in the endocrine monotherapy arm. These differences were sometimes even greater in the subgroup analyses and more balanced in others, so that the interpretation of the subgroups is also rather difficult. However, these subgroups would have been of particular interest because a certain endocrine resistance had to be assumed in the PALOMA-2 study in a total of 22% of patients, since in these patients the interval from the end of adjuvant endocrine therapy to relapse had been less than 12 months. If we look at the population of patients in whom this interval had been more than 12 months, we find a hazard ratio (0.73; 95% CI: 0.53–1.01), which was very similar to that of MONALEESA-2 and MONARCH-3. However, the beneficial effect of palbociclib was not seen in the de novo metastatic group (HR = 1.19; 95%: 0.84–1.7), whereas a clear therapeutic effect was seen in this group in the MONALEESA-2 study. This subgroup of de novo metastatic patients again had a clear follow-up bias in the PALOMA-2 study. This example shows how difficult it is to interpret the data from the PALOMA-2 study.

There are still no direct comparisons between the CDK4/6 inhibitors, so that no statement can be made about varying clinical efficacy. In the clinical decision, however, the existing data situation must not be disregarded, because therapy alternatives are available for each choice of a substance.

The final overall survival analysis of the MONARCH-3 study is still pending. In an interim analysis, we find a hazard ratio of 0.76

(95% CI: 0.58–0.97), which had not yet achieved statistical significance due to the study design with interim analysis.

Should CDK4/6 inhibitor therapy be continued with progress?

After progress under a CDK4/6 inhibitor, the question arises as to how to proceed further. This treatment situation was investigated in the maintain study. Patients with progress under CDK4/6 inhibitor therapy were randomized 1 : 1 to either ribociclib + modified ET therapy (continuation of CDK4/6 inhibitor therapy under ribociclib or switch to ribociclib) and to therapy with a modified ET alone. In patients receiving an aromatase inhibitor, therapy with fulvestrant was initiated, and in patients receiving fulvestrant, a change to exemestane was permitted later in the course of the study. A total of 119 patients were randomized. The majority of patients enrolled (n = 103) were on palbociclib therapy at the time of enrollment in the study, 14 were on ribociclib therapy and 2 on abemaciclib therapy. It has been shown that discontinuation of CDK4/6 therapy and continuation of treatment with endocrine monotherapy has not been beneficial for patients. Prolonged median progression-free survival (5.3 months) was seen with continued CDK4/6 inhibitor therapy compared to the monotherapy arm (2.8 months). The corresponding hazard ratio was 0.57 (95% CI: 0.39–0.95). This effect appeared to be present both in the case of a switch from fulvestrant to exemestane (n = 20) and in the case of a switch from aromatase inhibitor to fulvestrant (n = 99), although it must be noted that the subgroup of exemestane patients was very small. The hypothesis that the switch to fulvestrant was most likely going to eventuate in a therapeutic benefit due to an accumulation of somatic *ESR1* mutations could not be confirmed. In a total of 78 patients there was a mutation status of *ESR1*. No treatment benefit for the continuation of CDK4/6 inhibitor therapy was observed in the group of patients with an *ESR1* mutation (HR = 1.22; 95% CI: 0.59–1.49), while the benefit in the group of patients without mutation recorded a hazard ratio of 0.30 (95% CI: 0.15–0.62).

This study underscores the importance of a better understanding of the progression mechanisms among CDK4/6 inhibitors. The PADA-1 study investigated another question in this context. In early detection of *ESR1* mutations in the blood without clinical progression, a benefit could be seen in the PADA-1 study in the switch from aromatase inhibitors to fulvestrant [22]. The change in clinical progression in the MAINTAIN study in the group of *ESR1*-mutated patients had shown no effect. The reasons can only be presumed, but can possibly be explained by high fulvestrant activity. This shows that progression mechanisms may be more complicated than previously assumed and further studies are necessary to enable better sequence planning. Studies such as MINERVA [23] and the CAPTOR-BC study [23], which are currently starting to recruit, address these questions.

Sacituzumab Govitecan in Patients with HER2-negative HR-positive Breast Cancer

Trop-2 is an antigen which is overexpressed in some cancers such as breast cancer, some thyroid carcinomas, pancreatic carcinoma, colon carcinoma, urothelial carcinoma and other tumors [24–26]. Even if participations in signaling pathways are postulated, which play a role in the development of cancer or progression, it has not yet been possible to prove that Trop-2 is a prognosis marker for patients with breast cancer [27]. However, as already described above, the activity of the addressed signaling pathway does not necessarily appear to be of great importance for an efficacy of some ADCs, but rather the pure presence of the target molecule, in the case of Trop-2. Already in the ASCENT study, it was shown that even with low Trop-2 expression, an effect of sacituzumab govitecan could still be demonstrated [28].

Against this background, the results of the TROPiCS-02 study have now been presented. The TROPiCS-02 study included hormone receptor-positive, HER2-negative patients who had to have completed some preliminary therapies. These included at least endocrine therapy, taxane therapy and therapy with a CDK4/6 inhibitor. At least 2 and no more than 4 chemotherapy lines for metastatic disease had to be completed. Thus, only HR-positive/HER2-negative patients who had clearly completed preliminary therapies were included in this study [29].

Patients were randomized 1 : 1 to treatment with sacituzumab govitecan or to chemotherapy at the physician's choice (capecitabine, vinorelin, gemcitabine, eribulin). The aim of such a study should be to improve the prognosis with a more favorable side effect profile.

The study was positive with regard to the primary study objective PFS. The median PFS was extended from 4.0 months to 5.5 months. The hazard ratio was 0.66 (95% CI: 0.53–0.83; p = 0.0003). With these results, the study was able to fairly accurately demonstrate the effect that had been planned and assumed in advance. Overall survival was not statistically significantly different in this interim analysis. Median overall survival was improved from 12.3 to 13.9 months. This corresponded to an HR of 0.84 (95% CI: 0.67–1.06; p = 0.14) [29].

It is questionable whether a difference in median PFS of 1.5 months is clinically relevant, in particular because the side effect profile in terms of hematological, gastrointestinal side effects and alopecia was less favorable in the sacituzumab-govitecan arm than in the chemotherapy arm [29]. However, this adverse reaction profile did not appear to affect the quality of life. The quality of life measured by the EORTC-QLQ-C30 questionnaire was maintained longer (time to deterioration) with sacituzumab govitecan than with chemotherapy [29].

It is known from real-world data that patients still receive a large proportion of chemotherapy in the second and third lines of therapy after CDK4/6 inhibitor therapy [8]. Against this background, the data from the TROPiCS-02 study are certainly promising and it is desirable that this drug is investigated in earlier lines of therapy with the intention of checking whether a larger, absolute improvement in the prognosis can also be achieved in a collective with a generally better prognosis.

Outlook

For patients with advanced, hormone receptor-positive, HER2-negative breast cancer, new findings have been published with the PALOMA-2 study, the Destiny-Breast-04 study and the

TROPiCS-02 study, which have a high relevance for clinical practice. With an overall survival benefit and an acceptable side effect profile, trastuzumab deruxtecan could establish itself after an approval extension for patients with an MBC and the property HER2-low. The Destiny-Breast-06 study [30], which examines the substance in patients with metastatic breast cancer and HER2-low expression in previous lines of therapy, is currently still recruiting.

The lack of evidence of an overall survival benefit presents both doctors and patients with the challenge of meaningfully interpreting the data. Experience from clinical practice will show whether the different data situation (▶ **Table 1**) will result in different prescribing behavior. With the CDK4/6 inhibitors as standard of care and the different study data, the need to better understand the mechanisms of action and resistance in order to better plan treatment sequencing or further combination therapies is growing. Clinical studies, for example, pursue the approach of switching the therapy to a SERD in the case of an *ESR1* mutation under therapy with a CDK4/6 inhibitor and aromatase inhibitor [31]. Furthermore, the CAPTOR-BC study [32] and the MINERVA study [23] mark the launch of two translational research programs in Germany, which also investigate the molecular mechanisms of resistance and mode of action of the CDK4/6 inhibitors ribociclib and abemaciclib.

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Conflict of Interest

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References

[1] Wolff AC, Hammond MEH, Allison KH et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018; 36: 2105–2122. doi:10.1200/JCO.2018.77.8738

[2] Ahmed N, Brawley VS, Hegde M et al. Human Epidermal Growth Factor Receptor 2 (HER2) -Specific Chimeric Antigen Receptor-Modified T Cells for the Immunotherapy of HER2-Positive Sarcoma. J Clin Oncol 2015; 33: 1688–1696. doi:10.1200/JCO.2014.58.0225

[3] Burger MC, Zhang C, Harter PN et al. CAR-Engineered NK Cells for the Treatment of Glioblastoma: Turning Innate Effectors Into Precision Tools for Cancer Immunotherapy. Front Immunol 2019; 10: 2683. doi:10.3389/fimmu.2019.02683

[4] Erber R, Kailayangiri S, Huebner H et al. Variable Expression of the Disialoganglioside GD2 in Breast Cancer Molecular Subtypes. Cancers (Basel) 2021; 13: 5577. doi:10.3390/cancers13215577

[5] Yu AL, Gilman AL, Ozkaynak MF et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med 2010; 363: 1324–1334. doi:10.1056/NEJMoa0911123

[6] Bardia A, Hurvitz SA, Tolaney SM et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med 2021; 384: 1529–1541. doi:10.1056/NEJMoa2028485

[7] Thill M, Friedrich M, Kolberg-Liedtke C et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Locally Advanced and Metastatic Breast Cancer: Update 2021. Breast Care (Basel) 2021; 16: 228–235. doi:10.1159/000516420

[8] Schneeweiss A, Ettl J, Luftner D et al. Initial experience with CDK4/6 inhibitor-based therapies compared to antihormone monotherapies in routine clinical use in patients with hormone receptor positive, HER2 negative breast cancer – Data from the PRAEGNANT research network for the first 2 years of drug availability in Germany. Breast 2020; 54: 88–95. doi:10.1016/j.breast.2020.08.011

[9] Engler T, Fasching PA, Lüftner D 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 Frauenheilkd 2022. doi:10.1055/a-1880-0087

[10] Modi S, Jacot W, Yamashita T et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med 2022. doi:10.1056/NEJMoa2203690

[11] Baselga J, Im SA, Iwata H et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017; 18: 904–916. doi:10.1016/S1470-2045(17)30376-5

[12] Andre F, Ciruelos E, Rubovszky G et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2019; 380: 1929–1940. doi:10.1056/NEJMoa1813904

[13] Vanhaesebroeck B, Perry MWD, Brown JR et al. PI3K inhibitors are finally coming of age. Nat Rev Drug Discov 2021; 20: 741–769. doi:10.1038/s41573-021-00209-1

[14] Vasan N, Cantley LC. At a crossroads: how to translate the roles of PI3K in oncogenic and metabolic signalling into improvements in cancer therapy. Nat Rev Clin Oncol 2022; 19: 471–485. doi:10.1038/s41571-022-00633-1

[15] Jones RH, Casbard A, Carucci M et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol 2020; 21: 345–357. doi:10.1016/S1470-2045(19)30817-4

[16] Jones RH, Casbard AC, Carucci M et al. Fulvestrant plus capivasertib versus fulvestrant plus placebo after relapse or progression on an aromatase inhibitor in metastatic, estrogen receptor–positive breast cancer (FAKTION): Overall survival and updated progression-free survival data with enhanced biomarker analysis. J Clin Oncol 2022; 40: 1005-1005. doi:10.1200/JCO.2022.40.16_suppl.1005

[17] clinicaltrials.gov. Capivasertib+Fulvestrant vs. Placebo+Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic HR+/HER2- Breast Cancer (CAPItello-291). 2022. Accessed June 27, 2022 at: https://clinicaltrials.gov/ct2/show/NCT04305496

[18] clinicaltrials.gov. Capivasertib + Palbociclib + Fulvestrant for HR+/HER2- Advanced Breast Cancer (CAPItello-292). (CAPItello-292). 2022. Accessed June 27, 2022 at: https://clinicaltrials.gov/ct2/show/NCT04862663

[19] Neven P, Fasching PA, Chia S et al. Updated overall survival (OS) results from the first-line (1 L) population in the Phase III MONALEESA-3 trial of postmenopausal patients (pts) with HR+/HER2? advanced breast cancer (ABC) treated with ribociclib (RIB) + fulvestrant (FUL). Ann Oncol 2022; 33 (suppl_3): S194–S223. doi:10.1016/annonc/annonc894

[20] Hortobagyi GN, Stemmer SM, Burris HA et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. N Engl J Med 2022; 386: 942–950. doi:10.1056/NEJMoa2114663

[21] Finn RS, Rugo HS, Dieras VC 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: LBA1003–LBA1003. doi:10.1200/JCO.2022.40.17_suppl.LBA1003

[22] Bidard F, Hardy-Bessard A, Bachelot T et al. Fulvestrant-palbociclib vs. continuing aromatase inhibitor-palbociclib upon detection of circulating ESR1 mutation in HR+ HER2- metastatic breast cancer patients: Results of PADA-1, a UCBG-GINECO randomized phase 3 trial. San Antonio Breast Cancer Symposium 2021; 2021: GS3-05

[23] clinicaltrials.gov. Combination of Abemaciclib and Endocrine Therapy in Hormone Receptor Positive HER2 Negative Locally Advanced or Metastatic Breast Cancer With Focus on Digital Side Effect Management (MINERVA). 2022. Accessed June 26, 2022 at: https://clinicaltrials.gov/ct2/show/NCT05362760

[24] Goldenberg DM, Stein R, Sharkey RM. The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target. Oncotarget 2018; 9: 28989–29006. doi:10.18632/oncotarget.25615

[25] Zaman S, Jadid H, Denson AC et al. Targeting Trop-2 in solid tumors: future prospects. Onco Targets Ther 2019; 12: 1781–1790. doi:10.2147/OTT.S162447

[26] Vranic S, Gatalica Z. Trop-2 protein as a therapeutic target: A focused review on Trop-2-based antibody-drug conjugates and their predictive biomarkers. Bosn J Basic Med Sci 2022; 22: 14–21. doi:10.17305/bjbms.2021.6100

[27] Liu X, Zhou T, Wang Y et al. TROP2 as Patient-Tailoring but Not Prognostic Biomarker for Breast Cancer. Onco Targets Ther 2022; 15: 509–520. doi:10.2147/OTT.S354048

[28] Hurvitz SA, Tolaney SM, Punie K et al. Biomarker evaluation in the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer. San Antonio Breast Cancer Symposium 2020; 2020: GS3-06

[29] Rugo HS, Bardia A, Marmé F et al. Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone receptor–positive/HER2-negative (HR+/HER2-) advanced breast cancer. J Clin Oncol 2022; 40: LBA1001–LBA1001. doi:10.1200/JCO.2022.40.17_suppl.LBA1001

[30] Clinicaltrials.gov. Study of Trastuzumab Deruxtecan (T-DXd) vs. Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive, Metastatic Breast Cancer (DB-06). 2022. Accessed June 26, 2022 at: https://clinicaltrials.gov/ct2/show/NCT04494425

[31] clinicaltrials.gov. Phase III Study to Assess AZD9833+ CDK4/6 Inhibitor in HR+/HER2-MBC With Detectable ESR1 m Before Progression (SERENA-6) (SERENA-6). 2021. Accessed October 24, 2021 at: https://clinicaltrials.gov/ct2/show/NCT04964934

[32] clinicaltrials.gov. Comprehensive Analysis of Spatial, Temporal and Molecular Patters of Ribociclib Efficacy and Resistance in Advanced Breast Cancer Patients (CAPTOR-BC). 2022. Accessed July 16, 2022 at: https://clinicaltrials.gov/ct2/show/NCT05452213

[33] Fasching PA. CAPTOR-BC: Gemeinsam Forschen für eine individualisierte Ribociclib-Therapie Senologiekongress 2022. 2022. Accessed June 26, 2022 at: https://www.senologiekongress.de/xconfig/upload/files/Programme/Seno2022_Programm.pdf

[34] 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. doi:10.1056/NEJMoa1609709

[35] European Medicines Agency. Verzenios Summary of product characteristics (SmPC). 2022. Accessed March 26, 2022 at: https://www.ema.europa.eu/en/documents/product-information/verzenios-epar-product-information_de.pdf

[36] 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. doi:10.1200/JCO.2017.75.6155

[37] Finn RS, Martin M, Rugo HS et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016; 375: 1925–1936. doi:10.1056/NEJMoa1607303

[38] Im SA, Lu YS, Bardia A et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. N Engl J Med 2019; 381: 307–316. doi:10.1056/NEJMoa1903765

[39] Tripathy D, Im S-A, Colleoni M et al. Abstract PD2-04: Updated overall survival (OS) results from the phase III MONALEESA-7 trial of pre- or perimenopausal patients with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. Cancer Res 2021; 81: PD2-04-PD02–04. doi:10.1158/1538-7445.Sabcs20-pd2-04

[40] Tripathy D, Im SA, 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. doi:10.1016/S1470-2045(18)30292-4

[41] Fasching PA, Esteva FJ, Pivot X et al. Patient-reported outcomes (PROs) in advanced breast cancer (ABC) treated with ribociclib plus fulvestrant: Results from MONALEESA-3. Ann Oncol 2018; 29: viii90–viii121. doi:10.1093/annonc/mdy272

[42] Slamon DJ, Neven P, Chia S et al. Overall Survival Results from the Phase 3 MONALEESA-3 Study of Fulvestrant ± Ribociclib in Postmenopausal Patients With HR+/HER2− Advanced Breast Cancer. Ann Oncol 2019; 30 (suppl_5): v851–v934. doi:810.1093/annonc/mdz1394

[43] Slamon DJ, Neven P, Chia S et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med 2020; 382: 514–524. doi:10.1056/NEJMoa1911149

[44] Slamon DJ, Neven P, Chia 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. doi:10.1200/JCO.2018.78.9909

[45] Sledge GW jr., Toi M, Neven P et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA Oncol 2020; 6: 116–124. doi:10.1001/jamaoncol.2019.4782

[46] Sledge GW jr., Toi M, Neven P et al. MONARCH 2: 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. doi:10.1200/JCO.2017.73.7585

[47] Cristofanilli M, Rugo HS, Im S-A et al. Overall survival (OS) with palbociclib (PAL) + fulvestrant (FUL) in women with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): Updated analyses from PALOMA-3. J Clin Oncol 2021; 39: 1000-1000. doi:10.1200/JCO.2021.39.15_suppl.1000

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

[49] Turner NC, Slamon DJ, Ro J et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. N Engl J Med 2018; 379: 1926–1936. doi:10.1056/NEJMoa1810527

[50] Xu B, Zhang Q, Zhang P et al. Dalpiciclib or placebo plus fulvestrant in hormone receptor-positive and HER2-negative advanced breast cancer: a randomized, phase 3 trial. Nat Med 2021; 27: 1904–1909. doi:10.1038/s41591-021-01562-9

[51] Hein A, Hartkopf AD, Emons J et al. Prognostic effect of low-level HER2 expression in patients with clinically negative HER2 status. Eur J Cancer 2021; 155: 1–12. doi:10.1016/j.ejca.2021.06.033

[52] Guyot P, Ades AE, Ouwens MJ et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012; 12: 9. doi:10.1186/1471-2288-12-9

[53] Yi Z, Ma F. Biomarkers of Everolimus Sensitivity in Hormone Receptor-Positive Breast Cancer. J Breast Cancer 2017; 20: 321–326. doi:10.4048/jbc.2017.20.4.321