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REVIEW

How I treat endocrine-dependent metastatic breast cancer

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Estrogen receptor-positive (ER+)/HER2-negative (HER2−), the so-called luminal-type breast cancer, is the most frequent subset, accounting for around 70% of all breast cancer cases. Endocrine therapy (ET) combined with cyclin-dependent kinases (CDK) 4/6 inhibitors is the standard first option in the management of advanced luminal breast cancer independently of disease extension. Classically, patients undergo multiple lines of ET ± targeted treatments until endocrine resistance occurs and palliative chemotherapy is proposed. Understanding endocrine resistance mechanisms and development of novel ET options is one of the main challenges in current clinical research. Another area of utmost interest is the improvement of post-endocrine therapeutic approaches. Among others, the development of antibody−drug conjugates (ADCs) is very promising, and some of these drugs will probably soon become a part of the therapeutic arsenal against this incurable disease. This review paper provides an overview of currently available treatment options in ER+/HER2− metastatic breast cancer and extensively discusses new approaches in late clinical development.

Key words: luminal breast cancer, CDK 4/6, PIK3CA, SERD, antibody−drug conjugate (ADC)

INTRODUCTION

Estrogen receptor-positive (ER+, defined as 1%-100% staining of tumor nuclei)/HER2-negative (HER2−) (immunohistochemistry [IHC] 0 to 2+, FISH negative), the so-called luminal breast cancer, is the most frequent subset, accounting for around 70% of all breast cancer cases.[1] Despite optimal adjuvant treatment, there is recurrence in 5%-25% of patients. The risk of relapse is mainly dependent on clinical, histological and biological factors and can occur late after the primary diagnosis.[2,3] In addition, a small percentage of patients are diagnosed with *de novo* metastatic breast cancer (MBC; stage IV). A growing number of these cases were included in recent phase III clinical trials, consisting around 30% of patients. MBC remains an incurable disease and the goals of treatment should not only be the improvement of patient's survival but also factors such as maintaining the quality of life (QOL), palliation of symptoms and taking into account patient's wish.[4] Endocrine therapy (ET) combined with cyclin-dependent kinases (CDK) 4/6 inhibitors is the standard first choice in the management of advanced luminal breast cancer independently of disease extension. Classically, patients undergo multiple lines of ET ± targeted treatments until endocrine resistance occurs and palliative chemotherapy is proposed.[4,5] Characterization of the genetic landscape by using next-generation sequencing (NGS) techniques on tumor tissue, or on circulating tumor DNA (ctDNA), can help guide treatment decisions.[5]

In this review, we describe available options in ER+/HER2 non-amplified metastatic breast with a focus on lately approved therapeutics and drugs in advanced clinical development.

CLINICAL CONSIDERATIONS WHEN USING CDK 4/6 INHIBITORS—DO ALL THREE AVAILABLE AGENTS BEHAVE SIMILARLY?

Based on the results of several phase III trials, CDK 4/6 inhibitors (palbociclib, abemaciclib and ribociclib) combined with endocrine treatment [non-steroidal aromatase inhibitors (NSAIs) or fulvestrant] not only became a standard treatment in ER+/HER2 non-amplified advanced breast cancer, but unarguably represents one of the major breakthrough in breast oncology in the past two decades.[6-15] The main results of these trials and patient population included are summarized in Table 1. Current guidelines recommend that every advanced luminal breast cancer patient be treated with CDK 4/6 inhibitors based on the clinically meaningful progression-free survival (PFS) benefit seen in

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Table 1. Available data on phase III trials assessing the efficacy of CDK 4/6 inhibitors in combination with endocrine treatments in metastatic breast cancer

Study design	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7	PALOMA-3	MONARCH-2	Monaleesa-3
	Phase III Placebo-controlled **First-line** ($n = 666$) Postmenopausal	Phase III Placebo-controlled **First-line** ($n = 668$) Postmenopausal	Phase III Placebo-controlled **First-line** ($n = 493$) Postmenopausal	Phase III Placebo-controlled **First-line** ($n = 672$) Premenopausal	Phase III Placebo-controlled **≥Second-line** ($n = 521$) Pre- and postmenopausal	Phase III Placebo-controlled **Second-line** ($n = 672$) Pre- and postmenopausal	Phase III Placebo-controlled **First and second-line** ($n = 726$) Postmenopausal
Endocrine therapy	Letrozole	Letrozole	NSAI	Tamoxifen NSAI/LHRHa	Fulvestrant	Fulvestrant	Fulvestrant
CDK 4/6 inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib	Abemaciclib	Ribociclib
Prior therapy	**No prior systemic therapy for ABC** **Prior (neo)adjuvant ET: 56%** Tam: 47% AI: 27.5% **DFI since adjuvant ET**: ≤12 months: 22% >12 months: 40% **Prior (neo) adjuvant chemo:** 48%	**No prior systemic therapy for ABC** **Prior (neo)adjuvant ET: 52.4%** **Tam: 42%** **AI: 30%** **DFI since adjuvant ET**: ≤12 months: 1.2% >12 months: 64.7% **Prior (neo) adjuvant chemo: 43.7%**	**No prior systemic therapy for ABC** **Prior (neo)adjuvant ET: 45.7%** **AI: 26%** **Other: 19.8%** **DFI since adjuvant ET**: ≤36 months: 28% >36 months: 62.7% **Prior (neo) adjuvant chemo: 38%**	**No prior ET** **Up to 1 CT for ABC** **Prior (neo)adjuvant ET: 38%** **DFI since adjuvant ET**: ≤12 months: 30% >12 months: 7% **Prior (neo) adjuvant chemo**: 41% **Prior chemo for ABC:** 14%	**Prior ET:** **-(neo)adjuvant: 77%** **-ABC: 22%** Prior AI: 85.3% **Prior chemo for ABC:** 30.8% **Prior lines of tt for ABC:** 0: 24.2% 1: 38% 2: 26% ≥3: 11.8%	**Prior ET:** **-(neo)adjuvant: 59%** **-ABC: 38.3%** **Prior AI: 71%** **Prior chemo for ABC: none.** **Prior lines of tt for ABC (only one line of ET permitted):** 38.3%	**Prior ET:** **-(neo)adjuvant: 59.7%** **-ABC: 22.7%** **Prior AI: NA** **Prior chemo for ABC: none.** **Prior lines of tt for ABC (only one line of ET permitted): 48.8%**
Patient population	*De novo*: 37% Bone only: 23% Visceral: 48%	*De novo*: 34% Bone only: 20.7% Visceral: 59%	*De novo*: 41.2% Bone only: 21.3% Visceral: 52.4%	*De novo*: 41% Bone only: 24% Visceral: 58% Premenopausal: 100%	Prior sensitivity to ET: -yes: 79% -no: 21% Bone only: 24% Visceral: 59.4% Premenopausal: 20.7%	Prior sensitivity to ET: -yes: 73% -no: 25% Bone only: 27.6% Visceral: 55% Premenopausal: 16%	Prior sensitivity to ET: NA *De novo*: 20% Bone only: 21.3% Visceral: 60.5% Premenopausal: none
HR PFS	0.58	0.56	0.54	0.55	0.46	0.55	0.59
Median PFS (months)	24.8 versus 14.5	25.3 versus 16.0	28 versus 14.7	23.8 versus 13.0	11.2 versus 4.6	16.4 versus 9.3	20.5 versus 12.8
HR OS	0.95 (NS)	0.76	NA	0.71	0.81 (NS)	0.75	0.73
Median OS	52.2 versus 53.9	63.9 versus 51.4	NA	NR versus 40.9	34.8 versus 28	46.7 versus 37.3	53.7 versus 41.5

ABC, advanced breast cancer; AI, aromatase inhibitor; DFI, disease-free interval; CDK 4/6, cyclin-dependent kinase 4 and 6; chemo, chemotherapy; ET, endocrine therapy; HR, hazard ratio; LHRHa, luteinizing hormone-releasing hormon agonist; NA, not available; NSAI, non-steroidal aromatase inhibitor; NS, non significal; OS, overall survival; PFS, progression-free survival; Tam, tamoxifen.

all trials [hazard ratio (HR) around 0.55], the improvement in overall survival (OS) seen in several trials (HR 0.72-0.75), the manageable toxicity profile and the maintenance or improvement of QOL.[4] Although some differences can be noticed in the inclusion criteria of pivotal trials mainly regarding prior anticancer treatment, results can be considered overall similar with the three different drugs. One exception might be noticed regarding efficacy data. In the first- and second-line trials using ribociclib (Monaleesa 2, 7 and 3) and in one second-line trial using abemaciclib (Monarch-2), a significant OS benefit was observed (HR 0.72-0.76). On the other hand, the two phase III trials using palbociclib (Paloma-2 and -3) did not report a significant OS benefit in the overall patient population, although both were clearly positive for the primary endpoint, which was PFS.[16] This might be due to a less rigorous selection of patients recruited, a weaker potency of this drug to inhibit CDK 4/6 or factors related to post-progression disease on palbociclib.

The optimal sequence of different endocrine backbone agents at this time is uncertain and it depends on which agents were previously used [in the (neo)adjuvant or advanced settings], duration of response to those agents, burden of the disease, patients' preference and availability. Regarding CDK 4/6 inhibitors, the absolute longest PFS was achieved in the first-line setting, although there is a small group of patients who can benefit long time from ET alone. Probably this category of patients can be characterized by a very limited number of metastatic lesions having a particularly endocrine-sensitive disease with indolent biology (e.g. late relapse after adjuvant ET), although currently no data support this hypothesis. The SONIA trial specifically addressing this strategic question is ongoing.[17]

In patients with ER-positive MBC harboring a germline *BRCA1* or *BRCA2* mutation, poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors such as olaparib or talazoparib should be considered (see section 'Role of PARP inhibitors in ER+ patients with germline BRCA mutations'). The optimal sequence of PARP inhibitors and ET with or without CDK 4/6 inhibitors is unknown. Given the OS benefit seen with CDK 4/6 inhibitors, these should be recommended before a PARP inhibitor.

Does treatment-free interval or prior endocrine sensitivity impact the benefit from CDK 4/6 inhibitors?

First-line trials (see Table 1) recruited NSAI-sensitive patients; 38%-56% of these had prior adjuvant ET and all of them relapsed >1 year after the end of an adjuvant aromatase inhibitor (AI) if received. In most of these trials a subpopulation treatment effect pattern plot (STEPP) analysis was conducted to assess the effect of treatment-free interval on PFS (HR). Treatment-free interval (TFI) was measured as the time elapsed between the end of adjuvant treatment and relapse.

STEPP analysis from Paloma-2 did not identify any interaction between PFS and baseline TFI in patients who had received adjuvant ET independently, regardless of whether they had visceral metastases or not.[18,19] Similarly, according to findings from Monaleesa-2, the PFS benefit with ribociclib was maintained irrespective of TFI duration. HR of ribociclib + letrozole benefit over placebo + letrozole was similar in patients with a TFI of ≤24 months versus >24 months, ≤36 months versus >36 months and ≤48 months versus >48 months.[11] In Monarch-3, a STEPP analysis of the 18-month PFS rate and the PFS HR was carried out for both the abemaciclib and placebo arms. Firstly, this analysis shows that TFI has a prognostic value in both arms, as the 18-month PFS increases in both arms with the increase in TFI. Secondly, HR of the abemaciclib effect on PFS was more pronounced with shorter TFI. When TFI is dichotomized at 36 months patients with a TFI <36 months had more benefit from the addition of abemaciclib to NSAI: median PFS 29.52 months with NSAI + abemaciclib versus 9 months with NSAI alone [HR 0.441, 95% confidence interval (CI) 0.241-0.805]. The difference in median PFS between both groups was only 7 months in patients who had a TFI of ≥36 months [HR 0.78, 95% confidence interval (CI) 0.469-1.296]. This unplanned subgroup analysis after a relatively short follow-up (17.8 months) in the context of a low number of events should be interpreted with caution.

A relative high number of patients diagnosed with *de novo* MBC was included in first-line trials (34%-41% of the whole patient population). The benefit of ribociclib with regard to PFS was of the same magnitude in these patients than in the whole trial population according to a subgroup analysis of Monaleesa 2.[11] In addition, according to the recently updated OS data of the same trial, benefit seems to be more pronounced in patients with *de novo* MBC (HR 0.52 versus 0.91 in the case of disease relapse). Of note, 34% of patients included in this trial had *de novo* metastatic disease.[13]

Roughly, one-third of patients treated with CDK 4/6 inhibitors and fulvestrant in the three pivotal trials (Paloma-3, Monaleesa-3 and Monarch-2) received previous endocrine treatment for advanced breast cancer and all of them were resistant to ET (e.g. relapsed within 12 months after adjuvant treatment or progressed during ET in the setting of advanced breast cancer) except a group of patients in Monaleesa-3 who were treatment naïve ($n = 367$). In patients with primary endocrine resistance as defined by ESMO guidelines,[4] a numerically stronger effect (HR) was seen with fulvestrant and abemaciclib for both PFS and OS (PFS: HR 0.454 in primary resistance, HR 0.591 in secondary resistance; OS: HR 0.686 in primary resistance, HR 0.787 in secondary resistance).[20,21] This is in contrast with OS data of Paloma-3, where only patients who showed prior sensitivity to ET derived significant benefit from combination therapy [median OS (mOS) 39.7 months with fulvestrant + palbociclib versus 29.7 months with fulvestrant + placebo, HR 0.72], whereas no significant difference in OS was observed in the intention-to treat population.[22]

These data are reassuring regarding the use of abemaciclib in an endocrine-resistant setting or in cases of early relapse after adjuvant treatment, but it should be interpreted in the light of a slightly different patient population

included in these trials. Paloma-3 patients were more heavily pre-treated (30.8% received chemotherapy and 37.8% had ≥2 lines of treatment in a metastatic setting), whereas Monarch-2 recruited a mixed population of first- and second-line patients without prior chemotherapy.[7,10]

Clinical considerations in special patient populations: premenopausal, elderly and men

Historically, premenopausal patients were largely underrepresented in trials exploring endocrine treatments. Regarding phase III trials using CDK 4/6 inhibitors, all included essentially postmenopausal patients with the exception of Monaleesa-7 which is focusing on an exclusively premenopausal population ($n = 672$).[6] Two of the three trials using fulvestrant (Paloma-3 and Monarch-2) accepted premenopausal patients as well (around 20% of the patients included). Premenopausal patients received parallel ovarian function suppression (OFS). Outcome with NSAI + ribociclib + OFS in Monaleesa-7 and with fulvestrant + OFS + palbociclib or abemaciclib within the small subgroup of premenopausal patients in Paloma-3 and Monarch-2 was comparable with the results obtained in postmenopausal patients (HR of PFS 0.45-0.55).[6,23,24] Because of the higher risk of QT prolongation when combining ribociclib with tamoxifen, this strategy is not recommended in clinical practice.

More aggressive disease biology in young patients might still influence the choice of some physicians towards a chemotherapy than endocrine-based regimen. A small phase II randomized trial (KCSG-BR15-10, $n = 189$) compared the activity of palbociclib + ET (exemestane + leuprolid) to a frequently used oral chemotherapy (capecitabine) in premenopausal patients who were previously exposed to tamoxifen. The median PFS in patients treated with palbociclib + ET was longer than in those receiving capecitabine (20 months versus 14.4 months, HR 0.659, $P = 0.0235$) with a better toxicity profile. These data are rather reassuring and endorse the recommendation that young patients should be treated identically to their postmenopausal counterparts.[25]

Similar to young patients, elderly patients are also underrepresented in clinical trials. A joint analysis of all Paloma trials identified 304 patients aged ≥65 years treated with ET + palbociclib (218 with letrozole and palbociclib, 86 with fulvestrant and palbociclib). Efficacy seems to be maintained in elderly patients [median PFS (mPFS) 27.5 months in patients between 65 and 74 years of age]. Dose intensity was similar to the general patient population and QOL was maintained.[26] Of note, data in patients older than 75 years and in those with frail geriatric status are still missing. Furthermore, these trials did not include comprehensive geriatric assessment tools at baseline. Special attention should be paid as well to drug—drug interactions in the elderly population when prescribing CDK 4/6 inhibitors. An ongoing single-arm trial (RIBOB) is currently recruiting frail geriatric patients aged ≥75 years with comorbidities and altered laboratory tests to assess the efficacy and tolerability of ribociclib and letrozole. Importantly, this trial will also evaluate aging biomarkers and their impact on efficacy and toxicity.[27]

Men were eligible in only one pivotal phase III trial (Monaleesa 3), but recruitment went fast and finally none of them was included. The phase IIIb Compleement-1 trial using the same CDK 4/6 inhibitor (ribociclib) recruited a more heterogeneous real-life patient population, including 1.2% men ($n = 39$). This number is still too low to make any conclusion. Despite the lack of data, men should be offered the same treatment options as women (NSAI or fulvestrant + CDK 4/6 inhibitor) in combination with an luteinizing hormone-releasing hormone agonist.[4]

Does tumor biology matter?

The most common molecular alterations in ER+ MBC are ESR1- and PIK3CA-activating mutations. ESR1 mutations are enriched after exposure to an AI (30%-40% of patients) and is typically associated with worse prognosis.[15,28,29] PIK3CA alteration occurs in around 40% of ER+/HER2− patients and it is relatively stable during disease evolution. In this particular subtype of breast cancer, it seems to be linked to worse OS and chemotherapy resistance.[30,31] The benefit from CDK 4/6 inhibitors + ET versus ET alone seems to be regardless of the presence or absence of these mutations.[15,32-34]

Unprecedented efforts have been made to identify biomarkers which could be related to sensitivity or resistance to CDK 4/6 inhibitors using NGS techniques and/or gene expression profiling.

In a recently reported pooled analysis of the Monaleesa trials, a targeted panel of 557 genes was used to analyze baseline ctDNA samples of 1503 patients to identify somatic alterations related to response or resistance to ribociclib. Treatment with ribociclib was associated with a trend towards a greater benefit compared to placebo in patients with alterations in *FRS2*, *PRKCA*, *MDM2*, *ERBB2*, *AKT1_E17K* and *BRCA1/2* (HR between 0.23 and 0.33). In contrast, patients with alterations in *CHD4*, *BCL11B*, *ATM* or *CDKN2A/2B/2C* genes were identified as potential biomarkers of resistance.[32] Although this is the largest available pooled dataset on baseline ctDNA samples, the number of patients in whom one of these particular mutations is identified remains low. Therefore, although provocative, these data remain hypothesis-generating and hardly applicable in clinical practice. The magnitude of benefit from adding ribociclib to ET in premenopausal patients (Monaleesa-7) was more important when *PIK3CA* mutation was detected in baseline plasma samples [HR 0.45, Δ PFS 12.48 months in wild-type (wt) and HR 0.57, Δ PFS 1.9 months in mutated (mut)]; however, this was not statistically significant.[34]

mRNA expression levels were assessed for genes including those relevant to the CDK 4/6 pathway, MAPK pathway, receptor tyrosine kinases, ER signaling and proliferation using baseline tumor samples collected from Monaleesa-3 ($n = 531$). For this purpose, the investigators used NanoString 800-gene nCounter® GX Customized Panel

(nanoString, Seattle, WA) and defined as endpoint the correlations between PFS and gene expression levels in the aforementioned pathways. PFS benefit for ribociclib versus placebo was similar across all gene expression subgroups.[35]

In a similar way, EdgeSeq Oncology BM Panel (HTG Molecular Diagnostics, Tucson, AZ) which assesses 2534 cancer-related genes was used for mRNA profiling of tumor samples of 302 patients included in the Paloma-3 trial (194 in the palbociclib arm, 108 treated with placebo). Of note, metastatic tissue was available in almost half of the patients ($n = 142$). Interestingly, investigators identified high cyclin E1 (CCNE1) mRNA expression as a potential biomarker of resistance to palbociclib. Median PFS with palbociclib in patients showing high expression was 7.6 months versus 14.1 months when expression is low. The outcome was relatively similar in both groups when patients received fulvestrant + placebo (4 months versus 4.8 months)—interaction $P = 0.00238$. The effect of CCNE1 mRNA expression was more evident in metastatic samples compared to archival primary biopsies, highlighting the need to collect contemporaneous tissue samples in studies aiming to realize clinical biomarker assessment. Another important finding of the same mRNA expression analysis is that palbociclib efficacy seems to be independent of breast cancer intrinsic subtypes.[36]

A recent pooled analysis of Monaleesa 2, 3 and 7 trials used PAM50 to determine whether ribociclib has the same efficacy in different intrinsic breast cancer subtypes using 1160 tumor samples (72% primary, 28% metastatic). These data confirm the independent prognostic value of intrinsic subtype in MBC in both patient groups, treated with ET alone or in combination with ribociclib. All subtypes exhibited a significant PFS improvement with ribociclib except basal-like, which represented only 2.6% of patient population. The HER2-enriched subtype seems to have the most important absolute benefit (HR 0.39 versus 0.63 in luminal A, 0.52 in luminal B and 0.46 in normal-like subtypes).[37] The currently ongoing HARMONIA trial is a face-to-face comparison of ET + ribociclib versus ET + palbociclib in patients with MBC with the HER2-enriched intrinsic subtype (NCT05207709).

Molecular profiling of tumor and ctDNA samples collected after progression on CDK 4/6 inhibitors shows a post-treatment enrichment of fimbroblast growth factor (FGFR) pathway alterations.[38,39] Furthermore, the FGFR1 amplification detected in baseline ctDNA samples of patients enrolled in Monaleesa-2 was related to worse PFS.[38] These data suggest that FGFR alterations could play a role in resistance to CDK 4/6 inhibitors. A phase Ib trial combining the FGFR inhibitor erdafitinib with fulvestrant and palbociclib in 23 patients diagnosed with ER+/HER2−/FGFR-amplified MBC, all of them previously exposed to CDK 4/6 inhibitors, was recently published. Despite the preclinical rationale, the preliminary efficacy of this combination was somewhat disappointing, showing a median PFS of only 3 months and a clinical benefit rate (CBR) of 28% at 6 months.[40]

Paired baseline and end-of-treatment ctDNA NGS from 195 patients in the Paloma-3 trial showed that *RB1* mutation (often subclonal) occurs in 5% of patients progressing on palbociclib and fulvestrant, while other driver mutations (such as *PIK3CA* and *ESR1*) are enriched after progression in both arms. These data suggest that RB1 somatic alteration can play a role in resistance to CDK 4/6 inhibitors.[39,41]

Sequential analysis of ctDNA samples during treatment and evaluation of early ctDNA dynamics could be a better surrogate of long-term outcome than the sole assessment of genetic alterations at baseline. Early PIK3CA ctDNA dynamics as assessed by circulating DNA ratio (CDR15, the ratio of mutated PIK3CA copies/ml on D15 relative to baseline) during treatment with fulvestrant and palbociclib was associated with PFS in a retrospective analysis of baseline and day 15 plasma samples collected in the Paloma-3 trial. Patients with PIK3CA CDR15 above the median value of 0.034 had inferior PFS compared with those below the median ($P = 0.0013$, HR 3.94, 95% CI 1.61-9.64). In contrast, ESR1 early ctDNA dynamics, which is commonly subclonal, was a much weaker predictor of outcome.[42]

The recently published PADA-1 trial ($n = 1017$) monitored ESR1 mutations in patients treated with first-line AI + palbociclib at baseline and 1 month after treatment initiation. PFS was significantly worse when ESR1 mutation was detectable in baseline plasma samples (11 months in $ESR1_{mut}$ versus 26.7 month in $ESR1_{wt}$). Moreover, clearance of the ESR1 mutations after 1 month was associated with improved prognosis. Median PFS was 24.1 months, compared to 7.4 months for patients who did not clear this particular mutation.[28] Additionally, they evaluated the benefit of switching treatment to fulvestrant + palbociclib when rising ESR1 mutation is detected without clinical progression in patients treated with first-line AI + palbociclib. The median PFS was 5.7 months when AI + palbociclib was continued upon raise in ESR1 mutation and 11.9 months when treatment was changed to fulvestrant + palbociclib early on.[43]

In conclusion, a huge effort was made in relation to biomarkers in patients treated by CDK 4/6 inhibitors but without any clinical value as the predictive tool so far. On the other hand, these biomarkers or their dynamics during treatment have a clearly prognostic value.

Re-challenge with CDK 4/6 inhibitors after previous exposure

Cross-resistance between CDK 4/6 inhibitors is unknown. Retrospective data suggest potential clinical activity with abemaciclib in patients who had prior exposure to palbociclib. Median PFS with abemaciclib alone (24% of patients) or combined with ET (76% of patients) was 5.8 months and 36% of patients had treatment duration exceeding 6 months. A second retrospective, multicenter analysis raising a similar question showed that treatment with a second CDK 4/6 inhibitor in patients who progressed on a first one can still lead to tumor shrinkage. Partial response rate occurred in 29% of patients and time to subsequent therapy

was 22 weeks.[44,45] The first prospective phase II randomized trial (MAINTAIN) exploring this hypothesis showed a significant PFS benefit using ribociclib + switching ET versus placebo + switching ET in patients progressing on ET + CDK 4/6 inhibitor (mPFS 5.29 months versus 2.76 months, HR 0.57, 95% CI 0.39-0.95, $P = 0.006$). The previous CDK 4/6 inhibitor was palbociclib in 87% of cases and the switching ET was mainly fulvestrant. Benefit seems to be limited to the ESR1wt group.[46]

The efficacy of pursuing CDK 4/6 inhibitors beyond progression is currently assessed in other phase II trials having as primary endpoint PFS or CBR at 24 months.[47]

Those patients who were exposed to CDK 4/6 inhibitors in the adjuvant setting can be probably re-challenged when relapse occurs later than 1 year after stopping adjuvant treatment. However, no data exist so far to confirm the efficacy of CDK 4/6 inhibitor re-challenge in this particular situation.

In summary, keeping pressure on CDK 4/6 pathway after exposure to CDK 4/6 inhibitors is an important question still under investigation.

OTHER TARGETED TREATMENTS AND HOW TO SEQUENCE THEM WITH CDK 4/6 INHIBITORS?

Besides CDK 4/6 inhibitors, numerous other targeted therapies such as phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) inhibitors in combination with ET have proven their effectiveness in the management of ER+ advanced breast cancer. However, as mentioned before, there is no currently available data to define how best sequence these treatment options. The unequivocal and consistent efficacy of CDK 4/6 inhibitors on various survival endpoint places these drugs as a standard first- (or second)-line treatment. There is no solid data to support the use of the majority of other ET+/− targeted therapy options after progression on CDK 4/6 inhibitors. Albeit, this strategy is the one encouraged by current guidelines.[47]

Data on treatment strategies used immediately after progression in both arms of Monarch-2 and Paloma-3 trials were collected. Almost half of the patients (41.7%) showing progression while taking abemaciclib and fulvestrant were considered for subsequent ET and 28.5% of them received targeted treatment. The median PFS on subsequent ET and/or targeted therapy was around 4 months in patients who progressed on palbociclib + fulvestrant.[20,22] These data support that a number of patients can still benefit from chemotherapy-free treatment after progression on CDK 4/6 inhibitors.

Phosphoinositide 3-kinase (PI3K) inhibitors

Alpelisib, an oral PI3K-α-specific inhibitor, showed efficacy in the SOLAR-1 phase III randomized trial in combination with fulvestrant in patients who were prospectively tested positive for PIK3CA mutation using a PCR-based assay evaluating 12 specific mutations in exons 7, 9 and 20 on an archival or fresh tumor tissue specimen. The PFS was 11.0 months in the combination arm versus 5.7 months with fulvestrant alone (HR 0.65, 95% CI 0.50-0.85, $P < 0.001$) in the PIK3CA-mutant cohort. There was no benefit in those patients who tested negative for this particular somatic mutation.[48] Although numerically higher OS was achieved with fulvestrant + alpelisib (39.3 months versus 31.4 months), this was not statistically significant (HR 0.86, $P = 0.15$, 95% CI 0.64 1.15).[49] Similar results were obtained when the PIK3CA mutational status was determined on baseline ctDNA samples using the same PCR-based assay as for the primary analysis: PFS 10.9 months with fulvestrant + alpelisib versus 3.7 months with fulvestrant alone (HR 0.55). To note, using the PCR-based assay on plasma samples, a relatively low sensitivity of PIK3CA mutation detection was observed: only 34% of the patients tested positive ($n = 186/549$), while 60% tested positive on tissue samples ($n = 341/572$).[50]

Although most of the PIK3CA mutations occur in exons 9 and 20, NGS techniques allow to identify rare mutations where PI3K inhibitors can be also effective or have more sensitivity to detect double or multiple mutations. The latter event occurred in 44 patients in Solar-1 and multiple PIK3CA mutations (the vast majority being double mutations) are found in 12%-15% of breast cancers.[51] Double PIK3CA mutations have been previously related to increased sensitivity to the β-sparing PI3K inhibitor, taselisib, according to a retrospective analysis of ctDNA samples in the Sandpiper trial. Multiple mutant patients on taselisib achieved an objective response rate of 30.2% versus 8.7% compared to placebo.[51] Patients with multiple mutations treated with alpelisib in Solar-1 ($n = 20$) had a PFS of 9.36 months compared to 7.29 months with placebo ($n = 24$) with wide CIs; therefore, data have to be interpreted with caution.[52] A retrospective exploratory analysis was done on tumor and ctDNA samples collected in Solar-1 using NGS techniques: the FoundationOne® CDx 324-gene assay was realized on tissue samples and FoundationOne® CDx 311-gene assay, on plasma samples. Valid tissue NGS results were available for 404 patients (71% of the whole trial population), 239 of them harboring a PIK3CA mutation, including a small group of 31 patients not identified by PCR. With regard to the clinical outcome, alpelisib demonstrated the same magnitude of benefit in patients whose tumors harbor PIK3CA alterations detected by NGS, including in those where alterations were not detectable by the PCR-based test: PFS 11 months with alpelisib versus 5.52 months with placebo (HR 0.59).[52] When carrying out the FoundationOne® CDx 311-gene assay on baseline plasma samples of the 188 patients who tested negative for PIK3CA alterations, 72 had a positive test when tumor tissue was analyzed by PCR or NGS. Regarding the clinical outcome, some benefit from alpelisib was observed in patients with not-detected PIK3CA alteration in ctDNA using NGS: PFS 10.9 months versus 5.5 months with placebo (HR 0.60), probably driven by tissue alterations (low shedding tumors) or the technical performance of the test in the case of low variant

allele frequency.[53] These data support in clinical practice the need for reflex tissue testing when PIK3CA alterations are not detected by ctDNA NGS techniques.

The above-described data undeniably confirm the oncogene addiction of PIK3CA-altered ER+ breast cancer. However, since the Solar-1 trial design and recruitment, CDK 4/6 inhibitors became the standard first-line treatment option and only a small number of patients ($n = 20$, 5.9%) treated with alpelisib + fulvestrant has been previously exposed to a CDK 4/6 inhibitor. BYLieve is the only prospective phase II trial evaluating the efficacy of a targeted treatment, alpelisib, in combination with ET (fulvestrant or letrozole) in patients with PIK3CA-mutated ER+/HER2− MBC previously treated with a CDK 4/6 inhibitor. The median PFS among patients treated with fulvestrant + alpelisib (cohort A, received as immediate prior treatment AI + CDK 4/6 inhibitor) was 7.3 months and among those treated with letrozole + alpelisib (cohort B, received as immediate prior treatment fulvestrant + CDK 4/6 inhibitor) was 5.7 months. To note, the majority of patients (82%) in cohort B previously progressed on an AI; thus these results can be considered clinically meaningful.[54,55] Although this a relatively small phase II, single-arm trial ($n = 224$ in both cohorts), it supports the use of alpelisib after CDK 4/6 inhibitors.

The safety profile of alpelisib is a source of concern and its management needs expertise. Seventy-five percent of patients experience grade 3 or 4 adverse events, most frequently hyperglycemia (32.7% grade 3, 4% grade 4), skin rash (10% grade 3) and diarrhea (6.7% grade 3).[48] Treatment discontinuation due to toxicity occurred in 25% of patients in Solar-1, in 14.3% in the lastly published cohort B of BYLieve, probably due to improved management of side effects with experience.[48,55] Alpelisib should not be administered in patients with uncontrolled diabetes (HbA1c >6.5%), and primary antihistaminic prophylaxis of skin rash is recommended. Early detection, appropriate monitoring of adverse events and patient education are crucial. Dose intensity seems to be important to ensure optimal treatment benefit, highlighting the need for prompt and efficient management of side effects.[56] QOL data indicate no impact on global health status but significant deterioration in social functioning and symptoms such as diarrhea, loss of appetite, nausea or vomiting and fatigue.[57]

Everolimus—is it still a viable treatment option?

Everolimus is a rapamycin derivate that inhibits mTOR by binding to mTORC1. The combination of everolimus and an endocrine agent has been studied in three randomized trials in patients with locally advanced breast cancer and MBC, all showing consistent improvement in PFS.[58-60]

The phase III BOLERO-2 registration trial ($n = 724$) was conducted in postmenopausal patients diagnosed with estrogen receptor (ER) positive (ER+/HER2− MBC whose disease progressed during or after treatment with NSAIs and showed a significantly improved PFS with exemestane + everolimus (10.6 months) versus exemestane alone (4.1 months) (HR 0.43; 95% CI 0.35-0.54, $P < 0.001$).[59]

Translational research efforts conducted so far on primary/metastatic tumor tissue or baseline ctDNA samples have failed to identify clinically useful biomarkers of benefit, except for p4EBP1. This, however, requires metastatic biopsies before starting treatment.[29,61-63]

The establishment of CDK 4/6 inhibitors as first-line treatment for ER+ MBC pushed everolimus-based combinations to second or later lines. Although data are largely missing in this situation, it can be recommended in patients whose tumor does not harbor PIK3CA mutation and therefore cannot benefit from alpelisib.

The PFS with everolimus when used as immediate subsequent treatment after palbociclib + fulvestrant in Paloma-3 is estimated to be 4.3 months, which is in line with the results described in a small retrospective dataset.[64]

Although the efficacy of everolimus seems to be more modest in the post-CDK 4/6 setting than in the pivotal BOLERO-2 trial, this option can be considered when a clinical trial is not available.

The combination of everolimus with fulvestrant or with a new oral selective estrogen receptor down-regulator (SERD) is probably a more adapted option in patients previously exposed to AIs. This latest approach is under clinical development (NCT03284957, NCT03616587, NCT04802759, NCT04188548). These currently ongoing phase I-II trials assess the safety and preliminary efficacy of the combination of oral SERDs (amcenestrant, camizestrant, giredestrant and LY3484356) with other targeted agents such as everolimus after progression on CDK 4/6 inhibitors.

Role of PARP inhibitors in ER+ patients with germline BRCA mutations

Approximately 5% of all types of breast cancers carry the germline breast cancer susceptibility gene *BRCA 1* or *2* mutations leading to a DNA double-strand break repair deficiency via homologous recombination. These cancers are particularly sensitive to PARP inhibitors. PARP is a central player in the repair of DNA single-strand breaks. Two pivotal trials (OlympiAD and EMBRACA) assessing the efficacy of olaparib or talazoparib compared to physician's choice single-agent chemotherapy in HER2− MBC patients showed a significantly longer PFS with both PARP inhibitors. Around half of the patients recruited in these trials had ER+/HER2− breast cancer. Among these patients, the PFS was 7 months and 8.6 months with olaparib and talazoparib, respectively.[65,66] These drugs should be part of the treatment sequence of ER+ breast cancer patients and be placed probably after CDK 4/6 inhibitors even if no data exist to determine the optimal position sequence of PARP inhibitors.

A proposed treatment decision algorithm of patients with luminal MBC is illustrated in Figure 1.

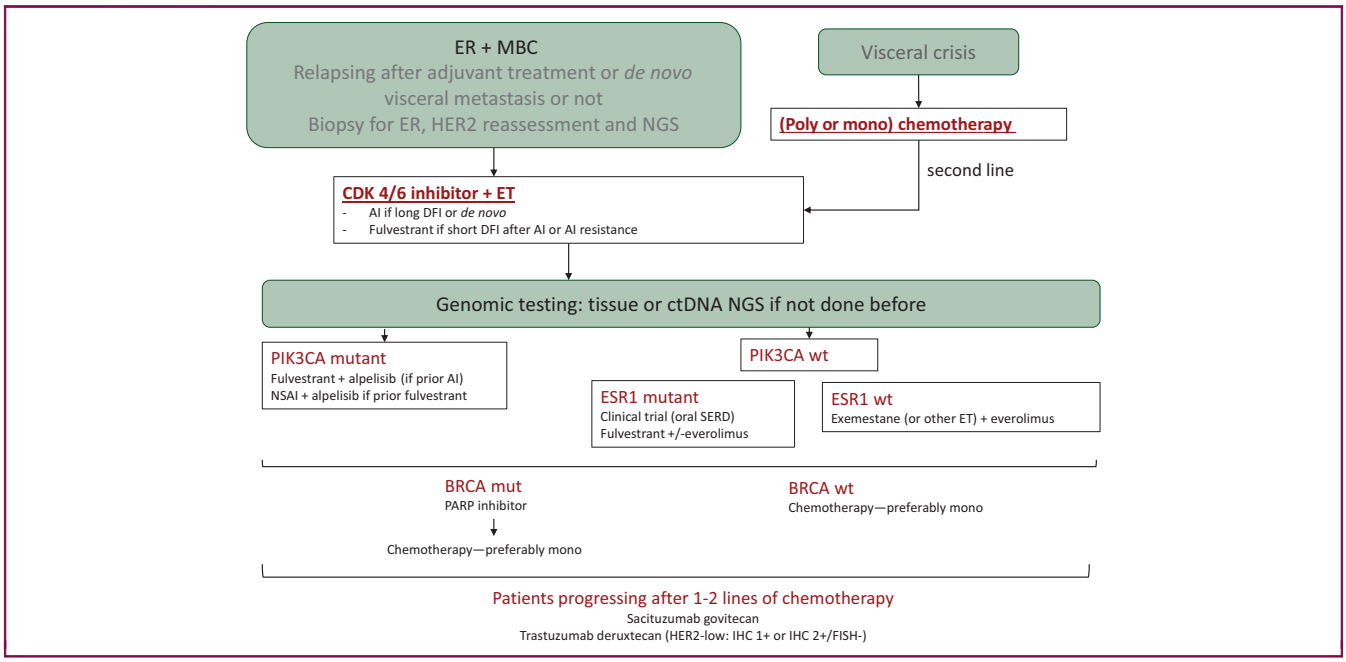

Figure 1. Treatment algorithm of estrogen receptor-positive/HER2-negative advanced breast cancer.
AI, aromatase inhibitor; ctDNA, circulating tumor DNA; DFI, disease-free interval; ER, estrogen receptor; ESR-1, gene encoding estrogen receptor-α; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; NGS, next-generation sequencing; NSAI, non-steroidal aromatase inhibitor; SERD, selective estrogen receptor degrader; BRCA, BReast CAncer gene; wt, wild-type; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; CDK 4/6, cyclin-dependent kinase 4 and 6.

THE NEW THERAPEUTIC PLAYERS

Antibody—drug conjugates

The basis of the development of antibody—drug conjugates (ADCs) is an attractive approach that combines the specificity of monoclonal antibodies to the cytotoxicity of potent chemotherapy agents (called the payload). The theoretical aim is to increase efficacy by delivering higher concentration of chemotherapy to the tumor and to decrease toxicity. Most of the new ADCs are engineered to encompass a high drug-to-antibody ratio (DAR) and to be able to release the chemotherapy component in the tumor microenvironment, thus acting also on cells which do not express the target of the monoclonal antibody (mAb; the so-called 'bystander' effect).

In ER+ breast cancer, this concept has recently been investigated by several early-phase trials using ADCs targeting HER2, Trop-2 and HER3 and showing very promising results.

Trastuzumab deruxtecan (DS-8201a,T-DXd) is an HER2-targeting mAb conjugated to the topoisomerase I inhibitor DXd, with a high DAR of eight molecules per HER2 antibody. Besides HER2-amplified breast cancer, it showed impressive efficacy in MBC with low HER2 expression in the phase III DESTINY-Breast04 trial.[66] HER2-low breast cancer is defined as an immunohistochemistry score of + or ++, without gene amplification identified by an *in situ* hybridization assay (ISH) and consists about 45%-55% of all breast cancers.[67]

The aforementioned phase III trial included 557 centrally confirmed HER2-low (88.7% of those ER+) MBC patients (57.6% HER2 1+, 42.4% HER2 2+) randomized 2 : 1 to receive trastuzumab deruxtecan or physician's choice chemotherapy. All patients received one or two lines of chemotherapy and 70% were previously exposed to a CDK 4/6 inhibitor. The median PFS was 10.1 months for the T-DXd-treated patients versus 5.4 months for those who received standard chemotherapy in the ER+ population (HR 0.51, 95% CI 0.40-0.64, $P < 0.001$). Importantly, this trial also showed an unprecedented OS benefit of 6.4 months in favor of trastuzumab deruxtecan (HR 0.64, 95% CI 0.48-0.86, $P = 0.003$). One of the side effects of concern is interstitial lung disease which occurred in 12.1% of patients treated in this trial, three of them (0.8%) being fatal.[68] Consequently, particular attention and early management are required for this toxicity.

A second phase III trial is currently assessing the efficacy of trastuzumab deruxtecan compared with investigator's choice chemotherapy in ER+/HER2-low advanced breast cancer resistant to ET ± targeted treatments who did not previously receive chemotherapy.[69]

Trophoblast cell-surface antigen-2 (Trop-2) is highly expressed in all breast cancer subtypes, and is associated with tumor growth and worse prognosis.[70] Sacituzumab govitecan (SG) is an anti-Trop-2 ADC with a high DAR, up to eight SN-38 molecules (active metabolite of the topoisomerase I inhibitor irinotecan) per Trop-2 mAb. After showing an impressive activity in heavily pre-treated triple-negative breast cancer (TNBC) patients, this drug has been granted accelerated Food and Drug Administration approval. A phase I/II basket trial including 54 ER+ MBC patients who progressed on prior ET and at least two prior chemotherapy (medium: five lines) demonstrated a confirmed partial response in 31.5% of patients and a median PFS of 5.5 months.[71] The results of a phase III trial which recruited the same type of heavily pre-treated patients (at least two previous lines of chemotherapy), who were randomized to

Table 2. Antibody–drug conjugates in the treatment of ER+ breast cancer

Drug	Target and payload	Current data	Ongoing phase III trials in ER + advanced breast cancer
Trastuzumab deruxtecan (DS-8201a,T-DXd Daiichi Sankyo, Astra Zeneca)	HER2/topoisomerase I inhibitor (DXd)	**Destiny-Breast 04** ($n = 373$) T-DXd versus TPC, 1-2 prior chemo, HER 2 1+/2+ ER+ cohort ($n = 331$) mPFS: 10.1 versus 5.4 months (HR 0.51; 95% CI: 0.40-0.64, $P < 0.001$) mOS: 23.9 versus 17.5 months (HR 0.64; 95% CI: 0.48-0.86, $P = 0.003$)	**Destiny-Breast 06** ($n = 850$) – NCT04494425: trastuzumab deruxtecan versus investigator's choice chemotherapy; no prior chemotherapy for MBC; HER2 + or ++ or >0<1
Datopotamab deruxtecan (Dato-DXd, Daiichi Sankyo, AstraZeneca)	Trop2/topoisomerase I inhibitor (DXd)	NA in ER+ MBC	Tropion-Breast01 ($n = 700$) – NCT 0510486: A phase III, open-label, randomized study of Dato-DXd versus investigator's choice of chemotherapy (ICC) in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy
Sacituzumab govitecan (SG, Trodelvy®, Immunomedics)	Trop-2/topoisomerase I inhibitor (SN-38)	**Tropics-2** ($n = 543$) SG versus TPC, 2-4 prior chemo mPFS: 5.5 versus 4.0 months (HR 0.66; 95% CI: 0.53-0.83, $P = 0.0001$) mOS: 24.4 versus 11.2 months (HR 0.79; 95% CI: 0.65-0.96, $P = 0.02$)	None
Patritumab deruxtecan (HER3-DXd, U3-1402, Daiichi Sankyo)	HER3 (patritumumab)/ topoisomerase I inhibitor (DXd)	HER3+/ER+/HER2– MBC $n = 113$ Prior regimens: 6 (2-13) RR: 30.1%, mPFS: 7.4 months 6 months PFS: 53.5%	None

CI, confidence interval; ER, estrogen receptor; HER2, Human epidermal growth factor 2; HR, hazard ratio; MBC, NA, not available; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

receive SG versus the investigator's choice of chemotherapy (Tropics-2, IMMU 132-09), were recently published. A statistically significant 34% reduction of disease progression or death was reported (mPFS 5.5 months with SG versus 4.0 months with treatment of physician's choice, HR 0.66, 95% CI 0.53-0.83).[72] Similarly, a statistically significant OS benefit was shown for SG: median OS 14.4 months versus 11.2 months, HR 0.79 (0.65-0.96), $P = 0.035$.[73] This trial demonstrates that the prognosis of this heavily pre-treated ER+/HER2– MBC population is poor. This is the first trial showing a meaningful benefit in a heavily pre-treated population; therefore, SG should be considered as a viable option in this setting.

A second Trop-2-directed ADC (datopotamab deruxtecan, Dato-DXd) englobing the same topoisomerase-1 inhibitor payload as T-DXd showed clinical activity in TNBC and a currently ongoing phase III trial investigates its efficacy in ER+/HER2– advanced breast cancer who have been treated with one or two prior lines of chemotherapy (NCT05104866, Tropion-Beast01).[74]

Patritumab deruxtecan (HER3-DXd, U3-1402) is a novel ADC directed against HER3 (expressed in 30%-50% of breast cancers and associated with poor prognosis) composed of a fully human IgG1 mAb (patritumab) covalently linked to a topoisomerase I inhibitor payload (deruxtecan, DXd). Two dose-expansion cohorts of a phase I trial recruited ER+/HER2– breast cancer patients with HER3-high (defined as >75% expression) and HER3-low (defined as expression between 25% and 75%) tumors, respectively, as determined by IHC on archival or pre-treatment samples. The ER+/HER2– cohort included 113 patients who received a median number of six lines (2-13) of anticancer regimens. Activity is encouraging and clinically meaningful: response rate of around 30% and a median PFS of 7.4 months. An important finding of this trial is that IHC expression of HER3 changes over time, between archival and pre-treatment biopsies, but this does not seem to influence clinical activity.[75] An academic window-of-opportunity trial evaluates the impact of HER3 mRNA expression status on the biological activity of U3-1402.[76] Therefore, the best method and adequate timing to assess HER3 expression status is yet to be determined.

The preliminary efficacy of ADCs in ER+/HER2– MBC is listed in Table 2.

New oral selective estrogen receptor down-regulators (SERDs)

Mutations of ESR-1 occur in the ligand-binding domain, are typically more frequent in advanced breast cancer (30%) and favor constitutive ER activation and resistance to AIs. Retrospective analysis using digital PCR to identify ESR-1 mutations in plasma sample collected from patients included in two phase III trials (SoFEA and EFECT) showed a significantly worse PFS and OS in patients treated with exemestane compared to fulvestrant when ESR-1 mutation was detected.[77]

Oral SERDs show promising activity even after CDK 4/6 inhibitors in early-phase trials. According to available data,

Table 3. New oral SERDs in clinical development

SERD	Development phase	Metastatic breast cancer		Early breast cancer	
		Compared to ET after CDK 4/6 inhibitors	Combination with CDK 4/6 inhibitors first line	Preoperative	Adjuvant
Elacestrant	III	NCT03778931 (EMERALD) results available		NCT04797728 (ELIPSE)	
Amcenestrant (SAR-439859)	III	NCT04059484 (AMEERA-3) results available	NCT04478266 (AMEERA-5)	NCT04191382 (AMEERA-4)	NCT05128773 (AMEERA-6)
Camizestrant (AZD-9833)	III	NCT04214288 (SERENA-2) results available	NCT047111252 (SERENA-4) NCT04964934 (SERENA-6)		
Giredestrant (GDC-9545)	III	NCT04576455 (acelERA) results available	NCT04546009 (persevERA)	NCT04436744 (coopERA) NCT03916744	NCT04961996 (lidERA)
Imlunestrant (LY-3484356)	III	NCT04975309 (EMBER-3)		NCT04647487 (EMBER-2)	
Rintodestrant (G1T48)	I				
LSZ 102	I				

CDK 4/6, cyclin-dependent kinase 4 and 6; ET, endocrine therapy; SERDs, selective estrogen receptors degraders.

response rate with new oral SERDs (elacestrant, AZD-9833, GDC-9545, LSZ102, LY3484356, G1T48, SAR439859) in patients progressing on previous ET ± CDK 4/5 inhibitors is around 13%-20% and the median PFS ranges between 4.5 and 7.8 months.[76,78-83] Combining these drugs with CDK 4/6 inhibitors seems feasible.[80,81,84,85]

The first phase III trial comparing elacestrant with ET alone ($n = 477$) in patients pre-treated with CDK 4/6 inhibitors showed a statistically significant albeit limited PFS benefit (HR 0.70 in all-comers and 0.55 in ESR-1mut patients). However, the activity of ET alone in this post-CDK 4/6 inhibitor setting seems to be very limited (mPFS 2.8 months with elacestrant and only 1.9 months with fulvestrant), highlighting the need to develop novel combinations and potent drugs.[86] Two other trials in the same setting investigating giredestrant and amcenestrant were recently reported as negatives.[87,88]

Further clinical trials are assessing the efficacy of new oral SERDs in metastatic and early luminal breast cancer. A non-exhaustive list of these trials is illustrated in Table 3.

CONCLUSIONS AND FUTURE DIRECTIONS

In the light of the data described in this paper, we can conclude that during the recent years the management of ER+ advanced breast cancer patients substantially improved due to a better understanding of disease biology and endocrine resistance and recently available targeted treatments such as CDK 4/6 and PIK3CA inhibitors which significantly improve outcome. NGS on tumor tissue and/or ctDNA is now part of procedures which can help to guide treatment decisions in MBC patients, and identify driver alterations which can make them eligible for clinical trials or standard treatment with PIK3CA inhibitors. The use of repeated biopsies, or sequential ctDNA assessment, will most likely gain interest as novel treatment options arise. These procedures might be important to unravel resistance mechanisms and adapt therapy in each individual patient.

Some of the new oral SERDs are probably more potent than the currently available endocrine therapies and in a good way to soon become one of the effective tools to defend this lethal disease. Most of the novel SERDs currently under active development showed acceptable toxicity profile and efficacy even after CDK 4/6 inhibitors and fulvestrant in both ESR1-mutant and wild-type tumors. They can be easily combined with CDK 4/6 and PIK3CA inhibitors due to the lack of overlapping toxicities. A high number of clinical trials are now recruiting patients aiming to define the place of oral SERDs in the sequence of treatment options of luminal breast cancer.

Other emerging therapies which revolutionize the way we deliver chemotherapy are the ADCs which use the attractive concept to combine mAbs and chemotherapy in a single molecule. After HER2-amplified and TNBC, these drugs make their way in ER+ breast cancer as well and will probably replace some of the classical single cytotoxic chemotherapies in the near future.

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REFERENCES

1. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst*. 2014;106(5):dju055.
2. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379(2):111-121.
3. Pan H, Gray R, Braybrooke J, et al. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med*. 2017;377(19):1836-1846.
4. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020;31(12):1623-1649.
5. Burstein HJ. Systemic therapy for estrogen receptor—positive, HER2-negative breast cancer. *N Engl J Med*. 2020;383(26):2557-2570.
6. Tripathy D, Im S-A, 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(7):904-915.
7. Turner NC, Ro J, André F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2015;373(3):209-219.
8. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol*. 2016;17(4):425-439.
9. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32):3638-3646.
10. Sledge GW, 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(25):2875-2884.
11. Hortobagyi GN. Ribociclib for the first-line treatment of advanced hormone receptor-positive breast cancer: a review of subgroup analyses from the MONALEESA-2 trial. *Breast Cancer Res*. 2018;20(1):123.
12. 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(24):2465-2472.
13. Hortobagyi GN, Stemmer SM, Burris HA III, et al. LBA17_PR-Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). *Ann Oncol*. 2021;32(suppl 5):S1283-S1346. Available at https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/overall-survival-os-results-from-the-phase-iii-monaleesa-2-ml-2-trial-of-post-menopausal-patients-pts-with-hormone-receptor-positive-human-epi.
14. Slamon DJ, Neven P, Chia SKL, et al. Updated overall survival (OS) results from the phase III MONALEESA-3 trial of postmenopausal patients (pts) with HR+/HER2- advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB). *JCO*. 2021;39(suppl 15):1001.
15. 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. *JCO*. 2021;39(suppl 15):1000.
16. 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. *JCO*. 2022;40(suppl 17):LBA1003.
17. Borstkanker Onderzoek Groep. BOOG 2017-03: Endocrine Therapy Plus CDK 4/6 Inhibition in First- or Second-line for Hormone Receptor Positive Advanced Breast Cancer - the SONIA Study [Internet]. clinicaltrials.gov 2020 Jan. Report No.: NCT03425838. Available at https://clinicaltrials.gov/ct2/show/NCT03425838. Accessed May 9, 2021.
18. Turner NC, Finn RS, Martin M, et al. Clinical considerations of the role of palbociclib in the management of advanced breast cancer patients with and without visceral metastases. *Ann Oncol*. 2018;29(3):669-680.
19. Finn RS, Cristofanilli M, Ettl J, et al. Treatment effect of palbociclib plus endocrine therapy by prognostic and intrinsic subtype and biomarker analysis in patients with bone-only disease: a joint analysis of PALOMA-2 and PALOMA-3 clinical trials. *Breast Cancer Res Treat*. 2020;184(1):23-35.
20. Sledge GW, 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(1):116-124.
21. Di Leo A, O'Shaughnessy J, Sledge GW, et al. Prognostic characteristics in hormone receptor-positive advanced breast cancer and characterization of abemaciclib efficacy. *NPJ Breast Cancer*. 2018;4:41.
22. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379(20):1926-1936.
23. Neven P, Rugo HS, Tolaney SM, et al. Abemaciclib for pre/perimenopausal women with HR+, HER2- advanced breast cancer. *JCO*. 2018;36(suppl 15):1002.
24. 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(9):1028-1038.
25. Park YH, Kim T-Y, Kim GM, et al. Palbociclib plus exemestane with gonadotropin-releasing hormone agonist versus capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer (KCSG-BR15-10): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2019;20(12):1750-1759.
26. Rugo HS, Turner NC, Finn RS, et al. Palbociclib plus endocrine therapy in older women with HR+/HER2- advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. *Eur J Cancer*. 2018;101:123-133.

27. Wildiers H. A Phase IV Study to Collect Data on the Efficacy and Safety of RIBociclib With Letrozole in Older Women (≥70 Years) With HR+ and HER2- Advanced Breast Cancer (aBC) With no Prior Systemic Therapy for Advanced Disease. [Internet]. clinicaltrials.gov 2019 May. Report No.: NCT03956654. Available at https://clinicaltrials.gov/ct2/show/NCT03956654. Accessed March 10, 2021.
28. Bidard FC, Callens C, Dalenc F, et al. Prognostic impact of ESR1 mutations in ER+ HER2- MBC patients prior treated with first line AI and palbociclib: an exploratory analysis of the PADA-1 trial. *JCO*. 2020;38(suppl 15):1010.
29. Chandarlapaty S, Chen D, He W, et al. Prevalence of ESR1 mutations in cell-free DNA and outcomes in metastatic breast cancer: a secondary analysis of the BOLERO-2 clinical trial. *JAMA Oncol*. 2016;2(10):1310-1315.
30. Koboldt DC, Fulton RS, McLellan MD, et al. Comprehensive molecular portraits of human breast tumours. *Nature*. 2012;490(7418):61-70.
31. Mosele F, Stefanovska B, Lusque A, et al. Outcome and molecular landscape of patients with PIK3CA-mutated metastatic breast cancer. *Ann Oncol*. 2020;31(3):377-386.
32. Andre F, Su F, Solovieff N, et al. Pooled ctDNA analysis of the MONALEESA (ML) phase III advanced breast cancer (ABC) trials. *JCO*. 2020;38(suppl 15):1009.
33. Tolaney SM, Toi M, Neven P, et al. Clinical significance of PIK3CA and ESR1 mutations in circulating tumor DNA: analysis from the MONARCH 2 study of abemaciclib plus fulvestrant. *Clin Cancer Res*. 2022;28(8):1500-1506.
34. Bardia A, Su F, Solovieff N, et al. Genomic profiling of premenopausal HR+ and HER2− metastatic breast cancer by circulating tumor DNA and association of genetic alterations with therapeutic response to endocrine therapy and ribociclib. *JCO Precis Oncol*. 2021;5:PO.20.00445.
35. Chia S, Su F, Neven P, et al. Abstract PD2-08: Gene expression analysis and association with treatment response in postmenopausal patients with hormone receptor-positive, HER2-negative advanced breast cancer in the MONALEESA-3 study. *Cancer Res*. 2020;80(suppl 4):PD2-PD2-08.
36. Turner NC, Liu Y, Zhu Z, et al. Cyclin E1 expression and palbociclib efficacy in previously treated hormone receptor−positive metastatic breast cancer. *J Clin Oncol*. 2019;37(14):1169-1178.
37. Prat A, Chaudhury A, Solovieff N, et al. Correlative biomarker analysis of intrinsic subtypes and efficacy across the MONALEESA phase III studies. *J Clin Oncol*. 2021;39(13):1458-1467.
38. Formisano L, Lu Y, Servetto A, et al. Aberrant FGFR signaling mediates resistance to CDK4/6 inhibitors in ER+ breast cancer. *Nat Commun*. 2019;10(1):1373.
39. Razavi P, dos Anjos CH, Brown DN, et al. Molecular profiling of ER+ metastatic breast cancers to reveal association of genomic alterations with acquired resistance to CDK4/6 inhibitors. *JCO*. 2019;37(suppl 15):1009.
40. Mayer IA, Haley BB, Abramson VG, et al. Abstract PD1-03: a phase Ib trial of fulvestrant + CDK4/6 inhibitor (CDK4/6i) palbociclib + pan-FGFR tyrosine kinase inhibitor (TKI) erdafitinib in FGFR-amplified/ER+/ HER2-negative metastatic breast cancer (MBC). *Cancer Res*. 2021;81(suppl 4):PD1-PD1-03.
41. O'Leary B, Cutts RJ, Liu Y, et al. The genetic landscape and clonal evolution of breast cancer resistance to palbociclib plus fulvestrant in the PALOMA-3 trial. *Cancer Discov*. 2018;8(11):1390-1403.
42. O'Leary B, Hrebien S, Morden JP, et al. Early circulating tumor DNA dynamics and clonal selection with palbociclib and fulvestrant for breast cancer. *Nat Commun*. 2018;9:896.
43. 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 [Internet]. Available at https://www.abstractsonline.com/pp8/#!/10462/presentation/652. Accessed July 28, 2022.
44. Wander SA, Zangardi M, Niemierko A, et al. A multicenter analysis of abemaciclib after progression on palbociclib in patients (pts) with hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC). *JCO*. 2019;37(suppl 15):1057.
45. dos Anjos CH, Razavi P, Herbert J, et al. A large retrospective analysis of CDK 4/6 inhibitor retreatment in ER+ metastatic breast cancer (MBC). *JCO*. 2019;37(suppl 15):1053.
46. Kalinsky K, Accordino MK, Chiuzan C, et al. A randomized, phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition (CDK 4/6i) in patients (pts) with unresectable or hormone receptor−positive (HR+), HER2-negative metastatic breast cancer (MBC): MAINTAIN trial. *J Clin Oncol*. 2022;40(suppl 17):LBA1004.
47. MedSIR. International, Multicenter, Randomized, Open-label, Phase II to Evaluate the Efficacy and Safety of Continuation of Palbociclib+2nd Line Endocrine Therapy in HR+/HER2- ABC Patients Who Had Clinical Benefit During 1st Line Palbociclib. [Internet]. clinicaltrials.gov 2020 Nov. Report No.: NCT03809988. Available at https://clinicaltrials.gov/ct2/show/NCT03809988. Accessed March 29, 2021.
48. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor−positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940.
49. André F, Ciruelos EM, Juric D, et al. LBA18 Overall survival (os) results from SOLAR-1, a phase III study of alpelisib (ALP) + fulvestrant (FUL) for hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC). *Ann Oncol*. 2020;31:S1150-S1151.
50. Juric D, Ciruelos E, Rubovszky G, et al. Abstract GS3-08: Alpelisib + fulvestrant for advanced breast cancer: subgroup analyses from the phase III SOLAR-1 trial. *Cancer Res*. 2019;79(suppl 4):GS3-GS3-08.
51. Vasan N, Razavi P, Johnson JL, et al. Abstract NG16: Double PIK3CA mutations in cis increase oncogenicity and sensitivity to PI3Kα inhibitors. *Cancer Res*. 2020;80(suppl 16):NG16.
52. Juric D, Andre F, Singer CF, et al. Abstract P4-10-04: Clinical outcomes of alpelisib in hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer by next-generation sequencing-detected PIK3CA alteration status and phosphatase and tensin homolog loss: Biomarker analysis from the SOLAR-1 study. *Cancer Res*. 2020;80(suppl 4):P4-P4-10-04.
53. Ciruelos EM, Loibl S, Mayer IA, et al. Abstract PD2-06: Clinical outcomes of alpelisib plus fulvestrant in hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer with PIK3CA alterations detected in plasma ctDNA by next-generation sequencing: Biomarker analysis from the SOLAR-1 study. *Cancer Res*. 2021;81(suppl 4):PD2-PD2-06.
54. Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib (ALP) + fulvestrant (FUL) in patients (pts) with PIK3CA-mutated (mut) hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC) previously treated with cyclin-dependent kinase 4/6 inhibitor (CDKi) + aromatase inhibitor (AI): BYLieve study results. *JCO*. 2020;38(suppl 15):1006.
55. Rugo HS, Lerebours F, Juric D, et al. Abstract PD2-07: Alpelisib + letrozole in patients with PIK3CA-mutated, hormone-receptor positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (ABC) previously treated with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) + fulvestrant: BYLieve study results. *Cancer Res*. 2021;81(suppl 4):PD2-PD2-07.
56. Rugo HS, André F, Yamashita T, et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. *Ann Oncol*. 2020;31(8):1001-1010.
57. Ciruelos EM, Rugo HS, Mayer IA, et al. Patient-reported outcomes in patients with PIK3CA-mutated hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer from SOLAR-1. *J Clin Oncol*. 2021;39:2005-2015.
58. Kornblum N, Zhao F, Manola J, et al. Randomized phase II trial of fulvestrant plus everolimus or placebo in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer resistant to aromatase inhibitor therapy: results of PrE0102. *J Clin Oncol*. 2018;36(16):1556-1563.

59. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520-529.
60. 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(22):2718-2724.
61. Bachelot TD, Treilleux I, Schiffler C, et al. mTORC1 activation assessed in metastatic sample to predict outcome in patients with metastatic breast cancer treated with everolimus-exemestan: results from the SAFIRTOR study. *JCO*. 2019;37(suppl 15):1024.
62. Hortobagyi GN, Chen D, Piccart M, et al. Correlative analysis of genetic alterations and everolimus benefit in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from BOLERO-2. *J Clin Oncol*. 2016;34(5):419-426.
63. Moynahan ME, Chen D, He W, et al. Correlation between PIK3CA mutations in cell-free DNA and everolimus efficacy in HR +, HER2 − advanced breast cancer: results from BOLERO-2. *Br J Cancer*. 2017;116(6):726-730.
64. Dhakal A, Antony Thomas R, Levine EG, et al. Outcome of everolimus-based therapy in hormone-receptor-positive metastatic breast cancer patients after progression on palbociclib. *Breast Cancer (Auckl)*. 2020;14:1178223420944864. https://doi.org/10.1177/1178223420944864.
65. Robson M, Im S-A, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377(6):523-533.
66. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med*. 2018;379(8):753-763.
67. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: pathological and clinical landscape. *J Clin Oncol*. 2020;38(17):1951-1962.
68. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387(1):9-20.
69. AstraZeneca. A phase 3, randomized, multi-center, open-label study of trastuzumab deruxtecan (T-DXd) versus investigator's choice chemotherapy in HER2-low, hormone receptor positive breast cancer patients whose disease has progressed on endocrine therapy in the metastatic setting (DESTINY-Breast06) [Internet]. clinicaltrials.gov 2022 Jul. Report No.: NCT04494425. Available at https://clinicaltrials.gov/ct2/show/NCT04494425. Accessed July 27, 2022.
70. Vidula N, Yau C, Rugo HS. Trop2 gene expression (Trop2e) in primary breast cancer (BC): Correlations with clinical and tumor characteristics. *JCO*. 2017;35(suppl 15):1075.
71. Kalinsky K, Diamond JR, Vahdat LT, et al. Sacituzumab govitecan in previously treated hormone receptor-positive/HER2-negative metastatic breast cancer: final results from a phase I/II, single-arm, basket trial. *Ann Oncol*. 2020;31(12):1709-1718.
72. 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. *JCO*. 2022;40(suppl 17):LBA1001.
73. Rugo HS, Bardia A, Marmé F, et al. LBA76 Overall survival (OS) results from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HR+/HER2- metastatic breast cancer (mBC). *Ann Oncol*. 2022;33:S1386.
74. AstraZeneca. A phase-3, open-label, randomized study of Dato-DXd versus investigator's choice of chemotherapy (ICC) in participants with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy (TROPION-Breast01) [Internet]. clinicaltrials.gov 2022 Jul. Report No.: NCT05104866. Available at https://clinicaltrials.gov/ct2/show/NCT05104866. Accessed July 27, 2022.
75. Krop IE, Masuda N, Mukohara T, et al. Results from the phase 1/2 study of patritumab deruxtecan, a HER3-directed antibody-drug conjugate (ADC), in patients with HER3-expressing metastatic breast cancer (MBC). *JCO*. 2022;40(suppl 16):1002.
76. SOLTI Breast Cancer Research Group. A window-of-opportunity study of U3-1402, a HER3-targeting antibody-drug conjugate in operable breast cancer according to ERBB3 expression [Internet]. clinicaltrials.gov 2021 Jan. Report No.: NCT04610528. Available at https://clinicaltrials.gov/ct2/show/NCT04610528. Accessed April 14, 2021.
77. Turner NC, Swift C, Kilburn L, et al. ESR1 Mutations and overall survival on fulvestrant versus exemestane in advanced hormone receptor-positive breast cancer: a combined analysis of the phase III SoFEA and EFECT trials. *Clin Cancer Res*. 2020;26(19):5172-5177.
78. Bardia A, Kabos P, Elledge R, et al. Evaluation of RAD1901, a novel investigational, selective estrogen receptor degrader (SERD), for the treatment of ER-positive (ER+) advanced breast cancer. *JCO*. 2017;35(suppl 15):1014.
79. Kaklamani V, Bardia A, Wilks S, et al. Abstract PD7-07: final analysis of phase 1 study of elacestrant (RAD1901), a novel selective estrogen receptor degrader (SERD), in estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer. *Cancer Res*. 2020;80(suppl 4):PD7-07.
80. Hamilton EP, Patel MR, Armstrong AC, et al. A first-in-human study of the new oral selective estrogen receptor degrader AZD9496 for ER+/HER2- advanced breast cancer. *Clin Cancer Res*. 2018;24(15):3510-3518.
81. Jhaveri K, Juric D, Cresta S, et al. Abstract PD7-09: A phase 1/1b study of LSZ102, an oral selective estrogen receptor degrader (SERD), in combination with ribociclib in patients with estrogen receptor-positive (ER+) advanced breast cancer (ABC) who had progressed after endocrine therapy (ET). *Cancer Res*. 2020;80(suppl 4):PD7-09.
82. Jhaveri KL, Lim E, Hamilton EP, et al. A first-in-human phase 1a/b trial of LY3484356, an oral selective estrogen receptor (ER) degrader (SERD) in ER+ advanced breast cancer (aBC) and endometrial endometrioid cancer (EEC): results from the EMBER study. *JCO*. 2021;39(suppl 15):1050.
83. Aftimos P, Neven P, Pegram M, et al. Abstract PS12-04: Rintodestrant (G1T48), an oral selective estrogen receptor degrader in ER+/HER2- locally advanced or metastatic breast cancer: updated phase 1 results and dose selection. *Cancer Res*. 2021;81(suppl 4):PS12-PS12-04.
84. Bouaboula M, Shomali M, Cheng J, et al. Abstract 943: SAR439859, an orally bioavailable selective estrogen receptor degrader (SERD) that demonstrates robust antitumor efficacy and limited cross-resistance in ER+ breast cancer. *Cancer Res*. 2018;78(suppl 13):943.
85. Lim E, Jhaveri KL, Perez-Fidalgo JA, et al. A phase Ib study to evaluate the oral selective estrogen receptor degrader GDC-9545 alone or combined with palbociclib in metastatic ER-positive HER2-negative breast cancer. *JCO*. 2020;38(suppl 15):1023.
86. Bidard F-C, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol*. 2022;40:3246-3256.
87. Jimenez MM, Lim E, Gregor MCM, et al. 211MO Giredestrant (GDC-9545) vs physician choice of endocrine monotherapy (PCET) in patients (pts) with ER+, HER2− locally advanced/metastatic breast cancer (LA/mBC): primary analysis of the phase II, randomised, open-label acelERA BC study. *Ann Oncol*. 2022;33:S633-S634.
88. Rosa K. Amcenestrant Provides Numerically Similar PFS to Endocrine Therapy in Endocrine-Resistant ER+ Advanced Breast Cancer [Internet]. OncLive. Available at https://www.onclive.com/view/amcenestrant-provides-numerically-similar-pfs-to-endocrine-therapy-in-endocrine-resistant-er-advanced-breast-cancer. Accessed September 29, 2022.