Systemic treatment landscape and algorithm for hormone-receptor positive, HER2 negative advanced breast cancer

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SUMMARY

Hormone-receptor positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer accounts for 65% of all metastatic breast cancer (MBC) cases. With the advent of CDK4/6 inhibitors, single-agent endocrine therapy (ET) is no longer the only first-line systemic treatment option for the vast majority of patients presenting without visceral crisis. Other endocrine-based treatment options are emerging in further lines, with the goal to delay the administration of chemotherapy as long as possible. The optimal sequence of treatment is unknown. We here present a review of the available treatments and propose a treatment algorithm taking into account the latest therapeutic developments.

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Breast cancer remains the leading cause of cancer and cancer-related death among women in Europe.[1–3] Among patients with metastatic breast cancer (MBC), the luminal B subtype (hormone-receptor positive/ human epidermal growth factor receptor 2-negative (HR+/HER2-) and the HER2 positive subtype have the highest rate of primary metastatic disease. Secondary metastatic HR+/HER2- breast cancer is less frequent than in other subtypes (such as triple negative breast cancer), but the prognosis is poorer than in the primary metastatic setting.[4] Unfortunately, MBC is still an incurable disease. The goal of treatment is to improve disease-related symptoms but also to prolong survival while maintaining a good quality of life. Several promising treatments have emerged in recent years, improving the quality of life (QoL) and survival in our patients.

CDK4/6 INHIBITORS

The cyclin-dependant kinase (CDK) 4 and 6 pathway and the retinoblastoma protein (pRB, encoded by the *RB1* gene) play a central role in cell cycle progression and are often

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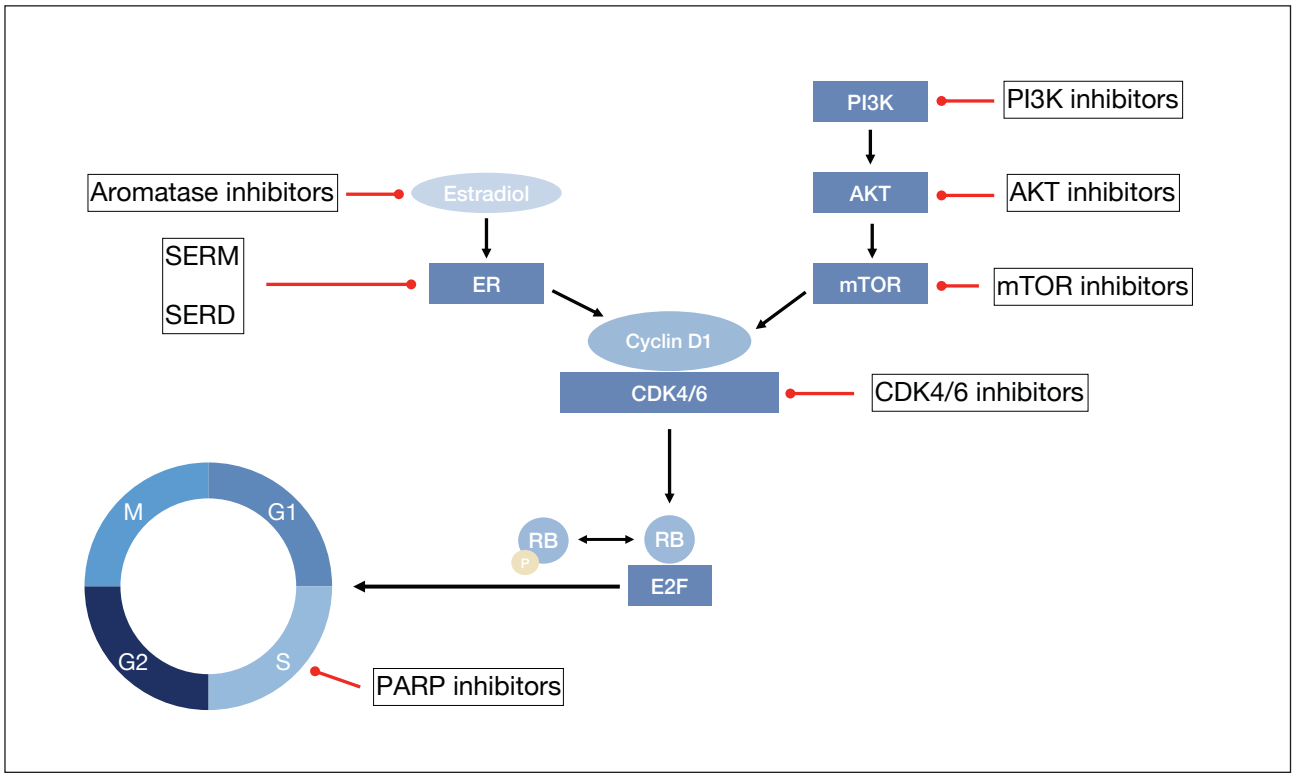

FIGURE 1. CDK4/6 and PI3K/AKT/mTOR pathways and their inhibitors.

AKT; protein kinase B, CDK4/6; cyclin-dependent kinase 4/6, E2F; E2 factor, ER; estradiol receptor, mTOR; mammalian target of rapamycin, PI3K; phosphatidylinositol 3-kinase, RB; retinoblastoma, SERM; selective oestrogen receptor modulators, SERD; selective oestrogen receptor degrader, SERM; selective oestrogen receptor modulator.

dysregulated in specific breast cancer subtypes, such as the HR+/HER2- subtype. Activation of the CDK4/6 complex leads to the phosphorylation of pRB and this in turn promotes the transition from the G1 to the S phase of the cell cycle. This pathway is mediated by oestrogen signalling, which contributes to the efficacy of ET in HR+ breast cancer. In HR+ breast cancer, dysregulation of the CDK4/6 activity is frequently observed due to overexpression and amplification of the *CCDN1* gene, which codes for the cyclin D1 protein. At the same time, in most luminal cases, pRB remains functional leading to cellular proliferation. These mechanisms explain the efficacy of CDK4/6 inhibitors on cell proliferation (*Figure 1*). Unfortunately, resistance to CDK4/6 inhibitors can appear, driven by multiple factors such as: upstream oncogenic alterations (*e.g. FGFR* amplification, *ERBB2* mutation, AKT hyperactivation, FAT1 loss) or cell cycle alterations (*e.g.* RB1 loss, cyclin E overexpression, aurora kinase 1 alteration).[5]

CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) are now approved in combination with aromatase inhibitors and fulvestrant for the treatment of advanced HR+/HER2- breast cancer, based on positive results observed in terms of progression-free survival (PFS) in all published phase III trials, while encouraging overall survival (OS) data is only reported in a subset (*Table 1*).

CDK4/6 INHIBITORS WITH NON-STEROIDAL AROMATASE INHIBITORS

All three CDK4/6 inhibitors were studied in combination with AIs as first-line therapy in the PALOMA-2 (palbociclib), MONALEESA-2 (ribociclib) and MONARCH 3 (abemaciclib) studies. Patients included were postmenopausal, had not received prior systemic therapy for advanced disease, and (neo) adjuvant endocrine therapy was permitted if there was a disease-free interval of more than twelve months. All three studies showed a significant improvement in PFS with the addition of CDK4/6 inhibitors. In the PALOMA-2 trial, median PFS was 27.6 months *vs.* 14.5 months (HR 0.58; p< 0.001) in the placebo group. MONALEESA-2 showed a median PFS of 25.3 months *vs.* 16.0 months (HR 0.57; p< 0.001), and MONARCH 3 showed a median PFS of 28.2 months *vs.* 14.8 months (HR 0.54; p< 0.001).[6–8] Patient populations in these three phase III trials were comparable, as were hazard ratios for PFS of the three combinations. Overall survival (OS) data have not yet been reported. In MONALEESA-7, premenopausal women were randomised to either tamoxifen or AI + ovarian function

TABLE 1. Phase III studies evaluating CDK4/6 inhibitors in advanced HR+/HER2- breast cancer in first-line and beyond.

Study	Investigational arm	Line	Menopausal status	N	Median PFS (months)	Median OS (months)
PALOMA-2 [6]	Palbociclib/letrozole	1st	Postmenopausal	666	27.6 *vs.* 14.5 (HR 0.56; 95% CI 0.46-0.71; p< 0.001)	not reported
MONALEESA-2 [7]	Ribociclib/letrozole	1st	Postmenopausal	668	25.3 *vs.* 16.0 (HR 0.57; 95% CI 0.45-0.70; p< 0.001)	not reported
MONARCH 3 [8]	Abemaciclib/NSAIs	1st	Postmenopausal	493	28.2 *vs.* 14.8 (HR 0.54; 95% CI 0.42-0.69; p< 0.001)	not reported
PALOMA-3 [12]	Palbociclib/fulvestrant	1st and beyond	Postmenopausal Premenopausal	521	9.5 vs. 4.6 (HR 0.46; 95% CI 0.36-0.59; p< 0.001)	39.7 *vs.* 29.7 (HR 0.72; 95% CI 0.55-0.94; p= 0.09)
MONALEESA-3 [13]	Ribociclib/fulvestrant	1st + 2nd	Postmenopausal + Men	726	20.5 *vs.* 12.8 (HR 0.60; 95% CI 0.48-0.73; p< 0.001)	Not reached *vs.* 40.0 (HR 0.72; p= 0.005)
MONARCH 2 [14]	Abemaciclib/fulvestrant	1st + 2nd	Postmenopausal Premenopausal	669	16.4 *vs.* 9.3 (HR 0.55; 95% CI 0.45-0.68; p< 0.001)	46.7 *vs.* 37.3 (HR 0.76; 95% CI 0.61-0.95; p= 0.014)
MONALEESA-7 [9]	Ribociclib/NSAIs or tam + OFS	1st	Pre and perimenopausal	672	23.8 *vs.* 13.0 (HR 0.55; 95% CI 0.44-0.69; p< 0.001)	Not reached *vs.* 40.9 (HR 0.71; p= 0.01)

CI; confidence interval, HR; hazard ratio, N; number of patients, NSAI; non-steroidal aromatase inhibitor, OS; overall survival, PFS; progression-free survival, tam; tamoxifen.

suppression (OFS) + ribociclib or placebo. The addition of ribociclib improved PFS and OS, compared with placebo, as shown in *Table 1*.[9] Ribociclib is not recommended to be used in combination with tamoxifen because a drug-drug interaction seemed to augment the risk of QT interval-prolongation.[10,11]

CDK4/6 INHIBITORS WITH FULVESTRANT

The combination with fulvestrant was studied for the three CDK4/6 inhibitors in both first- and second-line treatment in advanced HR+/HER2- breast cancer. The numbers of patients treated beyond first-line was the highest in PALOMA-3, which also allowed one prior chemotherapy line. The PALOMA-3, MONALEESA-3 and MONARCH 2 trials showed significant improvements in PFS with a median PFS of 9.5 months, 20.5 months and 16.4 months respectively, compared to the fulvestrant monotherapy arm, which had a median PFS of 4.6 months, 12.8 months and 9.3 months, respectively. While all three trials provided clinically relevant OS differences in different patient populations (6.9 months, HR 0.81, p= 0.09 in PALOMA-3; not reached, HR 0.72, p= 0.00456 in MONALEESA-3; 9.4 months, HR 0.757, p= 0.014 in MONARCH 2), the difference was statistically significant for ribociclib and abemaciclib, while for palbociclib the trend for OS missed the significance boundary.[12–14] Premenopausal women have been included in PALOMA-3 and MONARCH 2, with encouraging results in reported subgroup analyses.[15,16]

CDK4/6 INHIBITORS IN LATER LINES

In heavily pre-treated patients, only few data exist concerning the efficacy of CDK4/6 inhibitors. The MONARCH 1 trial, a phase II single-arm study, evaluated single agent abemaciclib in heavily pre-treated patients and showed en-

couraging results with a median PFS of six months and a median overall survival of seventeen months.[17] In Belgium, palbociclib has been evaluated in patients who had at least four lines of systemic treatment. Clinical benefit rate (CBR) at six months was 41.5% (95%CI: 0.477–0.686) and the safety profile was favourable.[18]

CDK4/6 INHIBITORS TOXICITY

CDK4/6 inhibitors are generally well tolerated, and adverse events can be easily managed with treatment interruptions, dose reductions and supportive care. Neutropenia was observed with the three molecules, but it was more frequently reported for palbociclib and ribociclib compared with abemaciclib. Besides neutropenia, each molecule has its own toxicity profile. Abemaciclib is more associated with diarrhoea, for which prompt and aggressive treatment is warranted, while venous thromboembolic events are possibly slightly increased. Abnormal liver function tests have been described with all three drugs, but seem slightly more frequent with ribociclib and abemaciclib than with palbociclib (increased ALT/ALT grade 3/4 of 4-9.3% in MONALEESA-2, -3, -7 *vs.* 2.3-7% in MONARCH 2, 3 *vs.* 0%-3.2% in PALOMA-2, -3, respectively).[19] Ribociclib has been associated with asymptomatic QT interval prolongation. An increase in serum creatinine is frequently observed with abemaciclib. However, this is a result of its inhibitory effect of renal efflux transporters of creatinine without effect on renal function. Interstitial lung disease can be a rare side effect of all three drugs. Drug-drug and drug-food interactions have to be taken into account in all available CDK4/6-inhibitors.[10,20]

DO ALL PATIENTS NEED CDK4/6 INHIBITORS IN FIRST-LINE?

At this time, there is no prospective data dictating the preferred treatment sequence. The SONIA trial, which is still under recruitment, compares two different sequences with, in one arm, the combination of AIs and CDK4/6 inhibitors in first-line followed by fulvestrant monotherapy in second-line, and in the other arm, AI monotherapy followed by the combination of fulvestrant and CDK4/6 inhibitors.[21]

In view of the available studies and their results, we recommend the use of CDK4/6 inhibitors in first-line in the vast majority of patients based on the following data. First, the efficacy results with absolute improvement in mPFS are largely in favour of CDK4/6 inhibitors when used as a first-line treatment. The objective response rate (ORR) and the median duration of response (DOR) of each molecule favour CDK4/6 inhibitors. In PALOMA-2, ORR was 55.3% *vs.* 44.4% in patients with measurable disease, and median DOR 20.3 months *vs.* 11.1 months. In MONALEESA-2, the ORR in the combination arm was 54.5% *vs.* 38.8% in the placebo arm, and the median DOR was 26.7 months *vs.* 18.6 months. The results of MONARCH 3 showed an ORR of 61% *vs.* 45.5% and a median DOR of 27.39 months *vs.* 17.46 months.[6,7,22] Second, QoL was assessed in the PALOMA-2 and MONALEESA-2 trials using Functional Assessment of Cancer Therapy (FACT) Breast, EuroQOL 5 dimensions (EQ-5D) questionnaires and Health related Quality of Life questionnaire (HRQoL) respectively, with the conclusion that the addition of palbociclib or ribociclib to letrozole maintained QoL.[23,24] Additionally, the PFS benefit of CDK4/6 inhibitors in the first-line setting has been consistent among subgroups for all three agents. It is also important to note that the benefit of CDK4/6 inhibitors was similar in the older population, although older adults have higher rates of toxicity and do need more frequent dose reductions compared to younger patients.[25]

Upfront combination therapy with CDK4/6 inhibitors and ET is therefore the preferred treatment approach for the majority of patients with HR+ HER2- MBC and has replaced ET monotherapy in the first-line setting in the majority of patients.[1,26,27] Nevertheless, the implications of this treatment option always need to be discussed with patients to assess their preferences. Endocrine monotherapy (as discussed below) can be a reasonable treatment option in selected cases, and the practical impact also has to be taken into account (with several hospital visits and the expected length of treatment duration and related exposure to adverse events).

There are no reported comparative trials between available CDK4/6 inhibitors. Taking into account the comparable hazard ratios for PFS benefit in comparable patient populations as in PALOMA-2, MONALEESA-2 and MONARCH 3, the overall activity of these drugs seems comparable.

Regarding subgroup analyses, the PFS and reported OS benefit of abemaciclib in MONARCH 2 and 3 seemed to be more pronounced in patients with visceral metastases and less pronounced in patients with bone-only disease, while the benefit from palbociclib and ribociclib was more consistent in both subgroups.

Despite reports of activity in brain metastases for all CDK4/6-inhibitors and despite the lack of evidence from a comparative clinical trial, there are more reported preclinical and clinical data for abemaciclib monotherapy in brain metastases. However, the dose of 200 mg abemaciclib twice daily which was used in this setting, is not approved by the EMA nor available or reimbursed in Belgium.[28]

In the majority of patients, the toxicity profile, baseline patient and disease characteristics and patient's and/or physician's preferences guide the choice between the different

TABLE 2. Studies evaluating aromatase inhibitors and fulvestrant in first-line, in metastatic HR+ HER2- breast cancer – adapted from *Ballinger et al.*[32]

Study	Design	N	ORR	PFS or TTP (months)	OS (months)
North American Trial	Anastrozole 1 mg *vs.* tamoxifen 20 mg	353	21 *vs.* 17%	11.1 *vs.* 5.6 (HR 1.44; 95% CI 1.16; p= 0.005)	40.4 *vs.* 38.5 (HR 1.02, 95% CI 0.81-NR)
ILBCG	Letrozole 2.5 mg *vs.* tamoxifen 20 mg	907	32 *vs.* 21%	9.4 *vs.* 6.0 (HR 0.70; 95% CI 0.60-0.82)	34 *vs.* 30 (HR : NA)
EORTC	Exemestane 25 mg *vs.* tamoxifen 20 mg	371	46 *vs.* 31%	9.9 *vs.* 5.8 (HR : NA)	37.2 *vs.* 43.3 (HR : NA)
FIRST (phase II)	Fulvestrant 500 mg *vs.* anastrozole 1 mg	205	31.4 *vs.* 31.1%	23.4 *vs.* 13.1 (HR 0.66; 95% CI 0.47-0.92)	54.1 *vs.* 48.4 (HR 0.70; 95% CI 0.50-0.98; p= 0.04)
FACT	Fulvestrant 250 mg + anastrozole 1 mg *vs.* anastrozole 1 mg	514	31.8 *vs.* 33.6%	10.8 *vs.* 10.2 (HR 0.99; 95% CI 0.81-1.20; p= 0.91)	37.8 vs. 38.2 (HR 1.0; 95% CI 0.76-1.32; p= 1.00)
FALCON	Fulvestrant 500 mg *vs.* anastrozole 1 mg	562	46 *vs.* 45%	16.6 *vs.* 13.8 (HR 0.80; 95% CI 0.64-1.00; p= 0.049)	Pending
S0226	Fulvestrant 250 mg + anastrozole 1 mg *vs.* anastrozole 1 mg	707	27 *vs.* 22%	15.0 *vs.* 13.5 (HR 0.80; 95% CI 0.68-0.94; p= 0.007)	47.7 vs. 41.3 (HR 0.81; 95% CI 0.69-0.98; p= 0.03)

CI; confidence interval, HR; hazard ratio, N; number of patients, NSAI; non-steroidal aromatase inhibitor, OS; overall survival, PFS; progression-free survival, tam; tamoxifen.

agents, while practical implications regarding monitoring or intake/schedule can play some role in selected situations.

SINGLE AGENT ENDOCRINE THERAPY

Since the advent of CDK4/6 inhibitors, ET monotherapy is no longer the recommended first-line treatment for both pre- and post-menopausal patients.[29] However, single agent ET should be considered in selected cases, such as in patients with high competing risk of non-breast cancer mortality in the short term. Single agent ET can also be a reasonable treatment option in asymptomatic patients with limited bone-only disease and long disease-free interval after prior adjuvant endocrine therapy. Additionally, in case of contra-indications or hypersensitivity to CDK4/6 inhibitors or if important toxicity occurs under CDK4/6 inhibitors. Life expectancy, comorbidities and patient's preference should also guide our decision.[30]

Even if ET monotherapy is not the preferred option in first-line in the vast majority of patients, it is still a valid option in second- and/or later lines, especially in endocrine-sensitive patients. The choice of ET depends on menopausal status, the use of previous ET in the adjuvant setting, endocrine resistance and comorbidities.[3]

SINGLE AGENT ENDOCRINE THERAPY IN FIRST-LINE

In premenopausal patients, OFS is one of the keystones of the treatment. Three options can be discussed with the patient: bilateral oophorectomy, the use of a luteinising hormone-releasing hormone (LHRH) agonist, or ovarian irradiation (which is seldom performed). Given the uncertainty about adequate OFS under LHRH agonists in some patients, bilateral oophorectomy is the preferred OFS modality in the advanced setting.[31] If OFS is accepted by the patients, the ET choice should be the same than in post-menopausal patients. If premenopausal patients refuse OFS, tamoxifen is the only endocrine option, but it is the least effective one.[1] In postmenopausal patients, AIs or fulvestrant should be preferred over tamoxifen as first-line ET monotherapy in advanced breast cancer.[32,33] Indeed, multiple studies have already shown a better ORR, time to progression (TTP) and disease control rate for AIs as compared to tamoxifen in first-line (*Table 2*). In a meta-analysis evaluating 25 studies, with a total of 8,504 patients, the use of AIs was associated with a significant improvement in overall survival in comparison with tamoxifen.[34] In the FALCON trial, fulvestrant was compared to anastrozole in endocrine the-

rapy-naïve patients and showed a longer median PFS in the fulvestrant arm than in the anastrozole arm. (16.6 months *vs.* 13.8 months). The ORR in the two groups was quite similar (46% *vs.* 45%), but the median DOR was longer in the fulvestrant arm (20 months *vs.* 13.2 months). These results were concordant with the FIRST trial (phase II) where the median PFS was also higher in the fulvestrant arm.[30,35] The combination of fulvestrant and non-steroidal AI has also been evaluated in the FACT and S0226 trials, in comparison to non-steroidal AI alone. In the FACT study, the combination was not superior to the single agent, and in the S0226 study PFS and OS were superior with the combination.[32]

SINGLE AGENT ENDOCRINE THERAPY IN SECOND- AND LATER LINES

In case of previous ET, the sequence in clinical practice is often guided by endocrine resistance. Primary endocrine resistance is defined as relapse within two years after the introduction of adjuvant ET or progression within six months after initiating ET for advanced breast cancer. Secondary endocrine resistance is defined as relapse after a minimum of two years on adjuvant ET, or within twelve months after the completion of adjuvant ET, or if progressive disease occurs more than six months after the onset of ET in MBC.[1,33] If primary endocrine resistance occurs in a patient previously treated with tamoxifen (in the adjuvant or metastatic setting), AIs or fulvestrant should be preferred. If secondary endocrine resistance occurs in patients previously treated with tamoxifen, AIs are the recommended option. In case of prior NSAI use, exemestane or fulvestrant may be options.[33] The ORR and median PFS of second-line fulvestrant alone or in combination with an AI are low, as shown in the SoFEA study (fulvestrant + anastrozole *vs.* fulvestrant + placebo *vs.* exemestane - ORR of 7 *vs.* 7 *vs.* 4% - median PFS of 4.4 *vs.* 4.8 *vs.* 3.4 months) and in the EFECT study (fulvestrant *vs.* exemestane – ORR of 7.4 *vs.* 6.7% - median PFS of 3.7 *vs.* 3.7 months).[32] Second-line ET monotherapy should also be considered after progression on CDK4/6 inhibitors and AIs since in the extended 38-months follow-up of PALOMA-2, the PFS benefit of palbociclib and letrozole was maintained in the next two subsequent lines, with a delay of the use of chemotherapy (40.4 months *vs.* 29.9 months for palbociclib-letrozole *vs.* placebo-letrozole), suggesting similar overall activity of single agent ET in this setting. ET was the most common second-line in both arms of the study (60.8% in the combination arm) with 30.8% of patients having fulvestrant and 21.6% exemestane.[6] Single agent ET is also a standard-of-care in the metastatic setting after induction chemotherapy when cumulative toxicity is reached, and in the absence of disease progression.[36,37]

PI3K/AKT/MTOR PATHWAY INHIBITORS

The phosphatidylinositol 3-kinase (PI3K)-protein kinase B (PKB/AKT) – mammalian target of rapamycin (mTOR) pathway regulates cell proliferation, survival and metabolism, and can be dysregulated in breast cancer. Alterations of the PI3K/AKT pathway are associated with endocrine resistance, worse outcomes and chemoresistance in advanced HR+ HER2- breast cancer. These alterations include: (i) activating *PIK3CA* mutations (most frequent hotspots in exons 9 and 20), inducing hyperactivation of the p110alpha isoform, (ii) loss of function mutations or deletions of the negative regulator *PTEN*, (iii) activating mutations in *AKT1*.[38]

In the first-line setting, most tumours are sensitive to endocrine therapies, but as treatment progresses, upregulation of the PI3K/AKT/mTOR pathway can be a mechanism involved in endocrine resistance, while the activating mutations in *PIK3CA* are expected to be truncal and thus present in the primary tumour in the majority of cases. Pathway inhibition at various levels could therefore overcome endocrine resistance (*Figure 1*).[39]

Outcome analysis from the SAFIR02 trial showed that *PIK3CA* mutations are associated with chemotherapy-resistance. Therefore, PIK3CA inhibitors combined with endocrine therapy could have an important potential in prolonging the chemotherapy free interval in PIK3CA-altered patients.[40]

EVEROLIMUS

Everolimus is an oral mTOR inhibitor which has been investigated to circumvent or delay endocrine resistance, both in first- and later lines.

The use of everolimus in combination with ET (AI, tamoxifen or fulvestrant) showed a significant PFS benefit, but no statistically significant improvement in OS in first- or later lines. The PFS benefit of everolimus is maintained regardless of the *PIK3CA* mutational status (*Table 4*).[41–43]

The BOLERO-2 trial results led to the approval of everolimus plus exemestane in postmenopausal patients with advanced HR+/HER2- breast cancer after failure of treatment with an AI.[49] The association of everolimus with tamoxifen was evaluated in the phase II TAMRAD trial, with a CBR of 61.1% for the combination *vs.* 42.1% for tamoxifen alone. The median time to progression (TTP) was also improved in this trial with 8.6 months in the everolimus arm *vs.* 4.5 months in the tamoxifen alone arm.[42] The combination of fulvestrant with everolimus was studied in the MANTA and PrECOG0102 studies, with an improvement in median PFS in the fulvestrant + everolimus arms, which was not statically significant.[46,47] Most common grade 3/4 adverse events reported in the everolimus plus exemestane arm were sto-

TABLE 3. Results of phase II / III studies evaluating everolimus, after prior use of AI.

Study	Design	Phase	Line	N	Median PFS (months)	Median OS (months)
BOLERO-2 [41]	Exemestane + everolimus *vs.* exemestane + placebo	III	1st 2nd and +	724	7.8 *vs.* 3.2 (HR 0.45; 95% CI: 0.38-0.54; p< 0.0001)	31.0 *vs.* 26.6 (HR 0.89; 95% CI: 0.73-1.1; p= 0.14)
BOLERO-6 [44]	Exemestane + everolimus *vs.* everolimus alone *vs.* capecitabine alone	II	2nd	309	8.4 (E+E) *vs.* 6.8 (E) (HR 0.74; 90% CI : 0.57-0.97) 8.4 (E+E) *vs.* 9.6 (C) (HR 1.15; 90% CI : 0.86-1.52)	23.1 (E+E) *vs.* 29.3 (E) (HR 1.27; 90% CI : 0.95-1.70) 23.1 (E+E) *vs.* 25.6 (C) (HR 1.27; 90% CI : 0.99-1.79)
BOLERO-4 [45]	Letrozole + everolimus in first line and exemestane + everolimus if progression - single arm	II	1st 2nd	202	1st line: 22.0 (95% CI: 18.1-25.1) 2nd line: 2.7 (95% CI: 1.9 – 7.4)	1st line: not reached at median follow-up
TAMRAD [42]	Tamoxifen + everolimus *vs.* tamoxifen	II	2nd	111	CBR at 6 months : 61% (95% CI: 47-74) *vs.* 42% (95% CI: 29-56) Median TTP : 8.6 *vs.* 4.5 (HR 0.54; 95% CI: 0.36-0.81; p= 0.0021)	Not reached for tam+everolimus arm Tamoxifen alone: 32.9 (HR 0.45; 95% CI: 0.24-0.81; p= 0.007)
MANTA [46]	Fulvestrant vs. fulvestrant + everolimus vs. vistusertib continuous + fulvestrant *vs.* vistusertib intermittent + fulvestrant	II	2nd and +	333	5.4 *vs.* 12.3 vs. 7.6 *vs.* 8 (F *vs.* V cont: HR 0.88; 95% CI: 0.63-1.24; p= 0.46) (F *vs.* V int : HR 0.79; 95% CI: 0.55-1.12; p= 0.16)	/
PrECOG0102 [47]	Fulvestrant + everolimus *vs.* fulvestrant + placebo	II	1st 2nd	131	10.3 *vs.* 5.1 (HR 0.61; 95% CI: 0.4-0.92, p = 0.02)	/
NCT02291913 [48]	Standard ET in progression + everolimus	II	1st 2nd and +	47	6.6	/

AI; aromatase inhibitor, C; capecitabine, CBR; clinical benefit rate, CI; confidence interval, E; exemestane, E + E; exemestane + everolimus, ET; endocrine therapy, EXE; exemestane, HR; hazard ratio, N; number of patients, OS; overall survival, PFS; progression-free survival, TTP; time to progression, V; vistusertib.

matitis, fatigue and dyspnoea. Stomatitis and pneumonitis were both AEs leading to the discontinuation of everolimus in this study. The incidence and severity of stomatitis can be significantly reduced with the prophylactic use of dexamethasone oral solution.[50] Given these results, a combination of everolimus with ET may be chosen in second- or later lines, both before or after the use of chemotherapy

PI3K INHIBITORS

Alpelisib, an oral PI3K inhibitor, selectively targets the alpha isoform, leading to a more favourable safety profile compared to unselective PI3K inhibitors.[51]

In the phase III SOLAR-1 trial, addition of alpelisib to fulvestrant demonstrated a significant improvement in PFS, leading to its approval by the Food and Drug Ad-

ministration (FDA) and a recommendation for use by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency.[51,52] The median PFS in the *PIK3CA*-mutant cohort was 11 months in the alpelisib arm *vs.* 5.7 months in the control arm (HR[95%CI]: 0.65[0.50-0.85]; p< 0.001). In the *PIK3CA* wild-type cohort, the addition of alpelisib to fulvestrant had no significant effect in terms of PFS (7.4 *versus* 5.6 months; HR[95%CI]: 0.85[0.58-1.25]).[51] However, given the advent of CDK4/6-inhibitors drastically changed the treatment landscape since initiation of the SOLAR-1 trial, the majority of patients in this trial were CDK4/6-inhibitor-naïve, initially raising doubts if the activity of alpelisib would be maintained in CDK4/6 inhibitors-pre-treated patients.[40] Recently presented results from the ongoing phase II BYLieve trial have now shed light on this question. This phase II study evaluates alpelisib with fulvestrant or letrozole after progression on/after CDK4/6 inhibitors in *PIK3CA* mutant patients.[53] The first results of cohort A (alpelisib + fulvestrant after CDK4/6 + AI use) were presented at the ASCO20 virtual meeting. The primary endpoint was met, with 50.4% of patients alive without disease progression at six months. The median PFS was 7.3 months. These data provide the first solid phase II evidence of an endocrine-based treatment combination in the post CDK4-6 setting, confirm the results of SOLAR-1 and support the use of alpelisib in combination with fulvestrant in the post-CDK4/6 setting in patients with *PIK3CA* activating mutations.[54] In the SOLAR-1 trial, the most common grade 3 or 4 adverse events were hyperglycaemia, rash and diarrhoea. Prophylaxis with antihistamines may reduce the onset of dermatological adverse events.[55] Monitoring for hyperglycaemia is important and a low threshold for dietary sugar restriction and metformin initiation should be adapted if hyperglycaemia occurs, given the fact that suppression of insulin feedback enhances the activity of PI3K inhibitors.[56]

MEGESTROL ACETATE

Known since 1960, megestrol acetate (MA) is a semi-synthetic progestin with a long history in the treatment of advanced breast cancer.[57] It has been studied in first-, second- and later lines in comparison with either tamoxifen or AIs. Its use has decreased since the advent of AIs and fulvestrant, despite its favourable toxicity profile.[58] Nevertheless, in later lines, MA has an approximate response rate of 25% and a median DOR of 15 months.[59–62] In 2014, a phase II trial evaluated MA in patients with progression on AIs. The CBR was 40% and the median duration of clinical benefit was 10.0 months. Median PFS was 3.9 months.[58] In this study, a low incidence of grade 3 adverse events was reported, without any grade 4 events. The most common side effects described are nausea, weight gain, deep venous thrombosis, vaginal bleeding and fluid retention. Based on this data, MA could be considered in later lines, especially in asymptomatic patients with low disease-burden, long endocrine treatment sensitivity in metastatic setting or in symptomatic patients unfit for chemotherapy, at the dose of 160 mg daily.

PARP INHIBITORS

BRCA1/2 mutations are found in 5% of all breast cancers, with a higher rate in the HER2- negative subtypes. *BRCA1* and *BRCA2* are tumour suppressor genes involved in the repair of DNA double-strand breaks by homologous recombination, and the poly-adenosine diphosponate-ribose polymerase (PARP) enzymes play a role in the repair of single-stranded DNA breaks. By inhibiting PARP, repair of single-strand breaks is no longer effective, resulting in double-strand breaks after replication, and in the case of *BRCA1/2* mutations (resulting in homologous recombination deficiency (HRD)), PARP inhibition leads to cell death. Therefore, PARP inhibitors now are an approved treatment option in HER2-negative MBC patients with germline *BRCA1/2* pathogenic variants, while there is increasing data on activity in other germline or somatic HRD alterations.[63,64]

The OlympiAD trial compared olaparib to a chemotherapy regimen of physician's choice (vinorelbine, eribulin or capecitabine) in patients who received less than two prior lines of chemotherapy or at least one prior ET in the luminal cases. The median PFS was significantly longer in the olaparib group, with 7 months *vs.* 3.2 months (HR[95%-CI] 0.58[0.43-0.80]; p< 0.001). Subsequent follow-ups did not show any statistically significant difference in OS, and the trial was not powered to assess these differences among treatment groups (mOS 19.4 months *vs.* 17.1 months, HR[95%CI]: 0.90[0.66-1.23]; p= 0.513). In HR+/HER2- patients, median OS was 21.8 months *vs.* 21.3 months (HR[95%CI]: 0.86[0.55-1.36]; p= not significant). However, results of OS in the subgroups suggest a greater benefit in patients who did not receive prior chemotherapy. Also, QoL was better in the olaparib arm.[65–67]

The EMBRACA trial had a similar design to the OlympiAD trial and compared talazoparib to chemotherapy regimen of physician's choice (vinorelbine, eribulin, capecitabine, gemcitabine). Patients included had received less than three prior lines of chemotherapy with at least one line including anthracyclines or taxanes. In HR+ cases, patients who had previously received ET were included. Patients with central nervous metastases were also included. The median PFS was longer in the talazoparib arm, with 8.6 months *vs.*

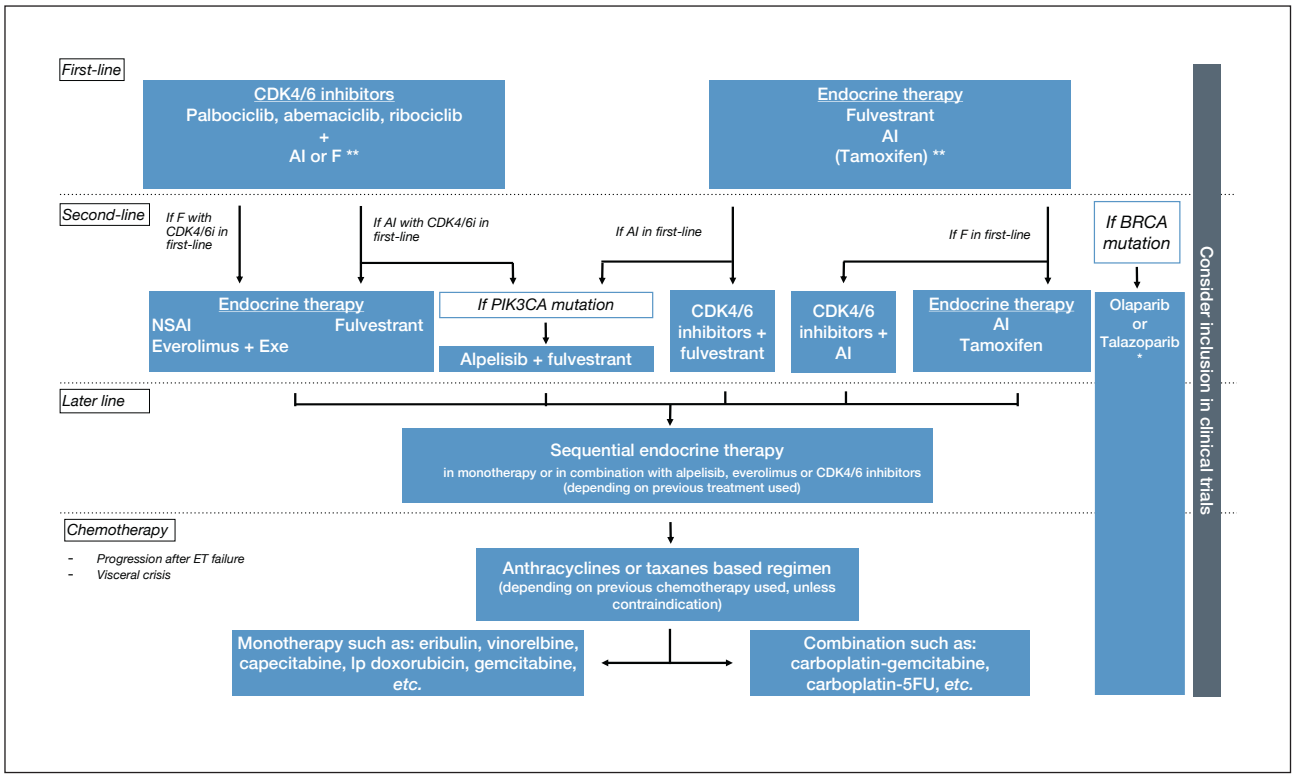

FIGURE 2. Proposed treatment algorithm for patients with hormone-receptor positive, human epidermal growth factor receptor 2-negative advanced breast cancer.

5FU; 5-fluorouracil, AC; doxorubicin and cyclophosphamide, AI; aromatase inhibitors, CDK4/6i; CDK4/6 inhibitors, EC; epirubicin and cyclophosphamide, ET; endocrine therapy, Exe; exemestane, F; fulvestrant, lp; liposomal, NSAI; non-steroidal aromatase inhibitors, OFS; ovarian function suppression.

* after ET, taxanes and/or anthracyclines (irrespective of setting).

** with OFS in premenopausal patients.

5.6 months (HR[95%CI]: 0.76[CI: 0.55-1.06]; p= 0.11). No difference was observed in OS in the final results disclosed at the AACR 2020 annual meeting, but quality of life was significantly better in the talazoparib group.[68]

In a subgroup analysis, HR+/HER2- patients in the talazoparib arm had a better objective response, median PFS and clinical benefit rate than in the chemotherapy arm (ORR 74% *vs.* 25%, mPFS 9.4 months *vs.* 6.7 months, CBR 74.5% *vs.* 46.4%). QoL evaluation and safety profile in this subgroup were also in favour of talazoparib use.[69] Considering these results, olaparib and talazoparib present new treatment options in *BRCA*-associated HER2-negative MBC, after progression on ET and after prior treatment with anthracyclines and/or taxanes (in the neo-adjuvant, adjuvant or metastatic setting).[1]

CHEMOTHERAPY

Chemotherapy as treatment for ER+/HER2- MBC is generally considered in patients with visceral crisis or in case of progression after multiple lines of ET or targeted therapies.[1]

The definition of visceral crisis is a severe organ dysfunction assessed by laboratory studies and rapid progression of the disease. In this condition, a chemotherapy regimen is recommended because a rapid response is needed due to the life-threatening situation. This presentation however is rare in first-line in advanced luminal breast cancer.[29]

There is no standard single agent or combination regimen for palliative chemotherapy in these patients. In MBC, quality of life is the aim of palliative chemotherapy. The benefit of chemotherapy has to be weighed against the risk of toxic effects. For this purpose, sequential therapies and monotherapy are the preferred choice in the absence of rapid clinical progression, even if combination therapies are known to have a better response rate, but without a clear impact on OS.[70]

In the event of visceral crisis, anthracycline or taxane-based regimens will be offered as first-line therapy to patients who have not received these regiments as (neo) adjuvant treatment. If patients are taxane-naïve and anthracycline-resistant or have received the maximum cumulative dose of

KEY MESSAGES FOR CLINICAL PRACTICE

1. Combination of CDK4/6 inhibitors and AI or fulvestrant has replaced ET monotherapy as preferred treatment option in the first-line setting for the vast majority of patients with advanced HR+/HER2-negative breast cancer.
2. Current reimbursement criteria tailor choice of endocrine partner.
3. *PIK3CA* activating mutation is predictive for the effect of adding alpelisib to fulvestrant. EMA approval is expected soon. Label and reimbursement criteria are still unclear.
4. In *BRCA*-mutated advanced HR+/HER2- breast cancer, PARP inhibitors can be proposed after ET based treatment.
5. Several AKT inhibitors and new SERDS are promising and currently under phase I-III evaluation.
6. Two new antibody drug conjugates recently approved in other breast cancer subtypes (trastuzumab deruxtecan, sacituzumab govitecan) have shown promising phase I-II results in advanced HR+/HER2- breast cancer, and are currently under phase III evaluation after prior chemotherapy.
7. Visceral crisis is rarely seen in early lines of metastatic breast cancer, therefore chemotherapy in first-line is rarely the right approach.

anthracycline or have had previous anthracycline toxicities, taxane-based treatment in monotherapy is indicated.
In pre-treated patients (with anthracyclines or/and taxanes), single agent regimens with capecitabine, vinorelbine or eribulin may be proposed, as well as platinum salts, gemcitabine and liposomal doxorubicin. Taxanes and anthracyclines may also be re-used in certain circumstances, while there is also data for pegylated liposomal doxorubicin, nab-paclitaxel, cyclophosphamide, methotrexate, 5-fluorouracil.[1,70–81]
In case of liver metastases resistant to chemotherapy or progressive under systemic treatment, intra-hepatic mitomycin C bolus infusion is able to give a good disease control with a favourable toxicity profile.[82,83] Other locoregional treatments may be considered in these situations.

FUTURE PERSPECTIVES

NEW SELECTIVE ESTROGEN RECEPTOR DEGRADERS (SERDS)

Fulvestrant is for now the only SERD approved, but several orally bioavailable non-steroidal SERDs are currently evaluated in phase III studies.[84] Elacestrant is currently studied in the phase III EMERALD trial. The trial is enrolling ER+/HER2- patients previously treated with endocrine therapies including CDK4/6 inhibitors, and no more than one chemotherapy regimen may have been administered in the metastatic setting. It will compare elacestrant to investigor's choice endocrine therapy (fulvestrant, anastrozole, letrozole, exemestane). The primary endpoint is PFS in *ESR1*-mutated patients and in all patients.[85]

AKT INHIBITORS

Capivasertib is an oral selective inhibitor of all three AKT isoforms. The recently published results of the FAKTION study are encouraging for the use of AKT inhibitors in pre-treated ER+/HER2- BC patients. This phase II trial evaluated the combination of fulvestrant + capivasertib/placebo after relapse or progression on AIs in metastatic HR+/HER2- patients and showed a significantly longer PFS in patients receiving capivasertib (mPFS of 10.3 months (95% CI: 5.0-13.2) *vs.* 4.8 months (95% CI: 3.1-7.7)). The PI3K alteration status did not change the effect of capivasertib, although subgroup analyses were underpowered.[38] FAKTION OS data are not yet mature.[38] Another phase III trial in combination with fulvestrant in this setting is ongoing in all-comers.[86]
In the phase II BEECH trial, the combination of capivasertib with paclitaxel was compared to paclitaxel alone in advanced HR+/HER2- breast cancer, with no effect on PFS in the overall population or in the *PIK3CA* mutated subgroup.[87]
Both ipatasertib and capivasertib have shown benefit in phase II trials in metastatic triple negative breast cancer (TNBC) but also here doubts remain on the predictive value of pathway alterations for activity of AKT-inhibitors.[88,89] Ipatasertib

is currently under investigation in combination with paclitaxel in phase III IPATunity130 in first-line metastatic ER+/HER2- and TNBC with PIK3CA/AKT1/PTEN-alterations.[90]

PEMBROLIZUMAB IN MSI-HIGH PATIENTS

The FDA has approved pembrolizumab for the treatment of patients with metastatic disease and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours. However, this agnostic indication was rejected by EMA. Pembrolizumab has demonstrated efficacy in heavily pre-treated patients with high tumour mutation burden, particularly in triple negative breast cancer. The phase IB KEYNOTE-28 trial evaluated pembrolizumab in patients with advanced PDL-1 positive (CBS ≥1) solid tumours that had not responded to current therapy. In this study, 25 HR+/HER2- patients were enrolled, but only 3 had a partial response (ORR 12%, 95%CI: 2.5%-31.2%) and 4 had stable disease (16%). Median DOR was 12 months (range, 7.4-15.9 months).[91]

ANTIBODY-DRUG CONJUGATES (ADC)

Recently, two new antibody-drug conjugates received FDA approval for metastatic breast cancer. Sacitizumab govitecanhziy was approved based on phase II data in pre-treated patients with advanced triple negative breast cancer.[92,93] There is however also encouraging activity reported in heavily pre-treated patients ER+/HER2- MBC with an overall response rate of 31%.[94] A phase III trial with sacituzumab govitecan *vs.* treatment of investigator's choice is ongoing after prior chemotherapy in advanced setting.[95]
Additionally, trastuzumab-deruxtecan (TDx-d) has been approved in third-line after trastuzumab-emtansine in HER2-positive MBC and is under evaluation in different treatment settings with, among others, an ongoing phase III in ER+ MBC without amplification for HER2 but with 1/2+ stainings for HER2 on immunohistochemistry.[96]

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