CDK4/6 inhibition in low burden and extensive metastatic breast cancer: summary of an ESMO Open-Cancer Horizons pro and con discussion

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ABSTRACT

In December 2017, *ESMO Open—Cancer Horizons* convened a round-table discussion on the background and latest data regarding cyclin-dependent kinase (CDK)4/6 inhibitors with endocrine therapy (ET) in the treatment of endocrine-sensitive breast cancer (BC). A review on this discussion was published in summer 2018 (https://esmoopen.bmj.com/content/3/5/e000368).

Several open questions were identified, which led to a second *ESMO Open* discussion on CDK4/6 inhibitors, taking place in December 2018 and covered in this article. The panel discussed two important clinical scenarios and the pro and cons of a treatment approach with CDK4/6 inhibitors for each scenario:

- Endocrine-sensitive BC with non-visceral disease and limited spread of the metastases.
- Endocrine-sensitive BC with non-life-threatening visceral involvement.

Regarding scenario 1, the panel agreed that CDK4/6 inhibitors should be recommended in first-line therapy for most patients if cost and practicality allow. However, the use of single-agent ET with an aromatase inhibitor in the first-line treatment of these patients is still a possibility for a small group of patients with very limited disease, such as one or two bone lesions or limited lymph node involvement.

Regarding scenario 2, chemotherapy is the first approach for patients with endocrine-sensitive metastatic BC with life-threatening visceral involvement because of the need for a faster response. The therapeutic approaches for patients with non-life-threatening visceral involvement are still under debate. Nevertheless, CDK4/6 inhibitors are currently the treatment of choice for most patients with a close follow-up of tumour response. A treatment algorithm has been suggested at the round table.

INTRODUCTION

Cyclin-dependent kinase (CDK)4/6 inhibitors with standard endocrine therapy (ET) have changed the treatment of patients with breast cancer (BC) with metastatic hormone receptor (HR)-positive/human epidermal growth factor 2 (HER2)-negative disease. The antitumour activity with a favourable toxicity profile has been demonstrated in several phase III trials and is now a standard of care.[1–3] Consistently, all three CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) have shown a significant and clinically meaningful prolongation of progression-free survival (PFS) over ET alone, thereby establishing a novel treatment standard not only in pretreated patients but also in the first-line setting of endocrine-sensitive metastatic breast cancer (MBC). Yet, most of the patients with HR-positive/HER2-negative tumours undergo many lines of treatment over several years during their disease. There is more and more evidence of an overall survival (OS) benefit with the addition of CDK4/6 inhibitors, and further positive studies for OS will be reported soon. However, the real value of CDK4/6 inhibitors cannot conclusively be judged yet, and the optimal strategy for deploying them in clinical practice is not yet completely known. It is expected that the presentation of additional studies concerning OS benefit will further clarify the role of CDK4/6 inhibitors in endocrine-sensitive MBC.

An *ESMO Open—Cancer Horizons* round-table discussion convened in December 2017 on the background and latest data regarding CDK4/6 inhibitors with ET in the treatment of endocrine-sensitive BC concluded that there are still many open questions regarding time points and patient populations for the best use of CDK4/6 inhibitors that need to be addressed.[4]

In December 2018, *ESMO Open—Cancer Horizons* convened a pro and con discussion looking at best management of two important clinical scenarios, that is, endocrine-sensitive BC with non-visceral disease and limited spread of the metastases and endocrine-sensitive BC with non-life-threatening visceral involvement. The panel discussed the data and clinical advantages and disadvantages of a treatment approach with CDK4/6 inhibitors and ET in first-line therapy versus second-line

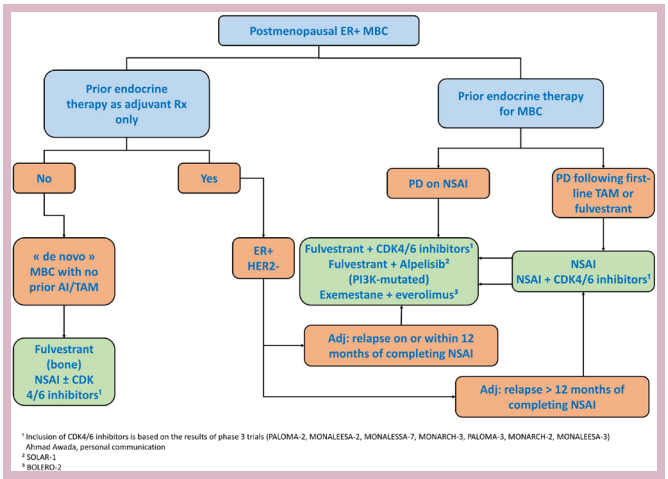

Figure 1 Proposed therapeutic algorithm for luminal subtype non-life-threatening MBC in 2019. AI, aromatase inhibition; CDK, cyclin-dependent kinase; ER+, oestrogen receptor positive; HER2–, human epidermal growth factor 2 negative; MBC, metastatic breast cancer; NSAI, non-steroidal aromatase inhibition; PD, progressive disease; Rx, treatment; TAM, tamoxifen.

(and beyond) therapy compared with aromatase inhibition (AI) only and chemotherapy, respectively. Figure 1 proposes a therapeutic algorithm for non-life-threatening MBC (but the bulk and the site of the disease in the treatment decision are worth considering).

SCENARIO 1: ENDOCRINE-SENSITIVE BC WITH NON-VISCERAL DISEASE AND LIMITED SPREAD OF THE METASTASES

Treatment approach: AI only

There is no question about the importance of CDK4/6 inhibitors in the treatment strategy of HR-positive/HER2-negative MBC, but a relevant question is whether CDK4/6 inhibitors also need to be used as first-line therapy—particularly in situations of limited disease activity—or whether AI is sufficient at this stage.

There is only indirect data to answer this question, so far, as there are no direct comparisons of strategies specifically in this subgroup yet. Phase III trials comparing upfront AI alone versus AI plus CDK4/6 inhibitors in HR-positive/HER2-negative MBC are the PALOMA-2, MONALEESA-2, MONARCH 3 and MONALEESA-7 trials.[1–3 5] Relevant subgroup analyses of these trials show that the addition of CDK4/6 inhibitors to AI increase PFS consistently in all clinical subgroups, but only MONALEESA-7 demonstrates OS benefit so far. The magnitude of the PFS benefit seems to be reduced in patients aged ≥65 years and patients with Eastern Cooperative Oncology Group (ECOG) status of ≥1 according to some studies.[6 7] However, a review on efficacy and safety in older patients with HR-positive, HER2-negative advanced BC found ET+CDK4/6 inhibitors likely to be safe and effective.[8]

Also, the addition of CDK4/6 inhibitors does not improve quality of life substantially compared with AI alone.[5 9]

PALOMA-3 is the first CDK4/6 inhibitor trial showing a statistically non-significant increase in OS, but which can be clinically meaningful in second-line treatment of endocrine-sensitive MBC. (Please see further discussion on the PALOMA-3 OS results in the section Is OS improved when adding a CDK4/6 inhibitor to standard ET alone?)

This OS benefit of CDK4/6 inhibitors, in combination with fulvestrant compared with fulvestrant alone, might also be an argument for a non-upfront strategy with CDK4/6 inhibitors.[10] Yet, the highest numerical advantage is seen in the endocrine-sensitive population of PALOMA-3. More recently and as presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2019 and published in the *New England Journal of Medicine*, the MONALEESA-7 trial showed survival advantage when ET plus luteinising hormone-releasing hormone (LHRH) agonist plus ribociclib were combined as first-line therapy in premenopausal patients. 60% of these patients were ET naive.[11] More upcoming data will clarify the survival benefit in the first-line setting and beyond.

Also the ASCO's Guideline on Endocrine Therapy for HR-positive/HER2-negative Metastatic Breast Cancer, the European School of Oncology's -European Society of Medical Oncology's (ESO-ESMO) International Consensus Guideline for Advanced Breast Cancer and the National Comprehensive Cancer Network's (NCCN) Clinical Practice Guideline in Oncology on Breast Cancer support the possibility to use single-agent ET with AI and to avoid CDK4/6 inhibitors in first-line treatment of patients with HR-positive/HER2-negative MBC.[12–14] So, the use of CDK4/6 inhibitors in second-line must be considered. Once valid OS data is available, a global strategy integrating CDK4/6 inhibitors in first- or second-line will need to be discussed again.

Treatment approach: ET plus CDK4/6 inhibition

The use of CDK4/6 inhibitors with standard ET has changed the treatment of patients with BC with metastatic HR-positive/HER2-negative disease. Relevant antitumour activity and a favourable toxicity profile have been shown in several phase III trials.[1–3] All three drugs (palbociclib, ribociclib, abemaciclib) have resulted in a significant and clinically meaningful prolongation of PFS over ET alone. From a medical point of view, there are no contraindications for the use of a CDK4/6 inhibitor-based therapy in all patients, including those with endocrine-sensitive BC with limited spread to the lymph nodes or bone-only disease.

Are there subgroups of patients who have a larger or reduced benefit from adding a CDK4/6 inhibitor to ET compared with ET alone as first-line therapy?

The PALOMA-2, MONALEESA-2, MONALEESA-7 and MONARCH 3 trials included only patient populations who had not yet received an ET-based approach in the advanced setting.[1–3 5] In addition, in the PALOMA-3,

MONALEESA-3 and MONARCH 2 trials, some subpopulations received the combination of CDK4/6 inhibitors and ET as first-line therapy in the advanced setting.[9 10 15 16] In all these trials, the magnitude of benefit was similar in terms of HRs in different subgroups (defined according to age, race, site of metastatic disease at baseline, prior hormonal therapy, disease-free interval (DFI), region, ECOG performance status, bone-only disease at baseline, measurable disease, prior chemotherapy (CT), most recent therapy, number of disease sites and histopathological classification). Subgroup analyses of the MONARCH 2 and 3 trials showed that patients with bad prognostic features, such as liver metastases, being progesterone receptor (PR) negative, high-grade disease and short treatment-free interval, also benefited from the addition of abemaciclib to ET.[17]

Unfortunately, biomarkers are currently also not available to select candidates for the treatment with CDK4/6 inhibitors. More research is needed to develop a more rational approach of treatment sequencing.

Is optimal-dose fulvestrant an option instead of using a CDK4/6 inhibitor?

The FALCON trial reported an increase in median PFS from 13.8 months in the anastrazole group to 16.6 months in the high-dose fulvestrant group.[18] No benefit was observed in patients presenting with visceral metastases. The major benefit reported in the small subgroup of patients without visceral disease suggests that optimal high-dose (500 mg) fulvestrant could be a treatment option for these patients. Nevertheless, it is important to have in mind that patients included in this trial have never undergone any ET before, neither in the adjuvant setting nor in the metastatic setting. Consequently, it is important to evaluate the benefit of a CDK4/6 inhibitor in a similar patient subgroup and particularly if adding a CDK4/6 inhibitor to high-dose fulvestrant is useful in this situation. Only the MONALEESA-3 trial gives some answers to this question.[15] Indeed, in the subgroup of 'treatment naive' patients, some present with de novo metastatic disease. Median PFS was not reached for those patients receiving ribociclib+fulvestrant compared with 18.3 months for patients in the fulvestrant+placebo group, corresponding to a 42% reduction in the risk of progression. Although optimal-dose fulvestrant is a good treatment option for patients never exposed to ET, these results indicate that outcome can be much better if a CDK4/6 inhibitor is added to high-dose fulvestrant.

Is AI plus fulvestrant combination an option instead of using a CDK4/6 inhibitor?

Three phase III trials have compared the combination of an AI plus fulvestrant to single-agent AI:

- Fulvestrant and Anastrozole Combination Therapy (FACT).[19]
- Study of Faslodex with or without Concomitant Arimidex versus Exemestane Following Progression on Nonsteroidal Aromatase Inhibitors (SoFEA) trial.[20]
- SWOG S0226 trial (anastrozole and fulvestrant versus anastrozole followed by fulvestrant in absence of visceral crisis at progression).[21]

In all these trials, fulvestrant was given with a loading dose schedule of a 500 mg on day 1, followed by 250 mg on days 15 and 29. Thereafter, 250 mg was given every 28 days until progression or toxicity. However, the population was different. FACT included both premenopausal and postmenopausal women, with locally advanced and/or metastatic disease. About 70% of them were pretreated with antiestrogen therapy and 30% were ET naive. There was no difference in PFS and OS between the two arms.[19] In the SoFEA trial, only patients with acquired resistance to non-steroidal AI were enrolled. This population is of worse prognosis, and median OS in the trial was less than 2 years with no difference between the three arms.[20] Patients enrolled in the SWOG S0226 trial were more similar to those in the FALCON trial previously mentioned. About 40% of the patients had de novo metastatic disease; time between diagnosis of primary and metastatic disease was at least 5 years for close to 50% of the population, and 40% of the patients received tamoxifen in the adjuvant setting. The population is more endocrine-sensitive. The final survival outcome report was recently published.[15] The median OS was 49.8 months in the combination arm and 42.0 months in the anastrozole-alone arm (HR 0.82, 95% CI 0.69 to 0.98, p=0.03). In a subgroup analysis, OS among women who had not received tamoxifen previously was 52.2 months in the combination arm compared with 40.3 months in the anastrozole-alone arm (HR 0.73, 95% CI 0.58 to 0.92). At a maximum of 12 years of follow-up, the combination of fulvestrant and anastrozole might also be considered as a valid option in an endocrine-sensitive population since direct comparison with CDK4/6 inhibitor plus fulvestrant does not exist. OS benefit with CDK4/6 inhibitors in combination with fulvestrant in this situation will be reported soon.

Is OS improved when adding a CDK4/6 inhibitor to standard ET alone?

Mature OS data have only been reported for two of the randomised phase III trials (PALOMA-3 and MONALEESA-7) evaluating this class of drugs.[5 8] Individual trials are overall less powered for OS. It will be important in the future to perform a meta-analysis including all phase III trials to evaluate the impact of CDK4/6 inhibitors on OS outcome.

From a statistical point of view, the OS results for the PALOMA-3 trial do not indicate an advantage when adding palbociclib to fulvestrant compared with placebo and fulvestrant.[22]

Nevertheless, for clinicians, the improvement of almost 7 months in OS is relevant.

We look forward to seeing additional data from other trials to better conclude if this is an effect of chance or if the statistically significant difference in PFS translates in a similar difference in OS as suggested by the PALOMA-3 trial.

Interestingly, when an analysis was performed restricted to more endocrine-sensitive tumours (relapse in the adjuvant setting of more than 2 years after starting ET or clinical benefit observed with ET administered for advanced disease), the absolute difference in terms of OS was even 10 months. Consequently, it is reasonable to hope that patients with more indolent disease, which is potentially more endocrine-sensitive, will benefit most from adding a CDK4/6 inhibitor to ET. Furthermore, the absolute difference was 2.9 months for patients with visceral disease (27.6 vs 24.7) compared with 11.5 months for patients without visceral disease (46.9 vs 35.4). Concerning DFI, a numerical advantage of 9.8 months (29.5 vs 39.3) was only observed if the DFI was longer than 2 years.[22]

How should the side-effect profile of CDK4/6 inhibitors influence the treatment choice?

Fortunately, most of the side effects of CDK4/6 inhibitors are laboratory test abnormalities and not clinical toxicities. Especially Grade 3–4 neutropenia is high but usually this is uncomplicated neutropenia. In general, low-grade nausea, fatigue or alopecia can be observed.

Abemaciclib is associated with less frequent neutropenia but with more frequent and higher-grade diarrhoea.

Thromboembolic events are also more frequent with this drug (4% of patients).

Ribociclib is associated with a risk of QT prolongation and more frequent liver test abnormalities compared with the other CDK4/6 inhibitors.[1–3 5 10 15 16] An extensive review of side effects and their management has been published recently.[23]

In summary, the side-effect profile is overall favourable for CDK4/6 inhibitors, but good results are mainly observed if the treatment schedule is respected, significant drug–drug interactions are avoided, side effects are managed early and appropriately, and dose reductions are performed in case of significant toxicities.

Should a CDK4/6 inhibitor be proposed to all patients in first-line therapy for advanced disease?

From a medical point of view, there are no contraindications for the use of a CDK4/6 inhibitor-based therapy in all patients. The benefit is consistent in all subgroups, and the absolute benefit is highest in the subgroups with the best prognosis. Nevertheless, other factors must be considered:

- One important factor is the cost of the treatment, and consequently, access may be different from one country to another.
- Patient preference is another important aspect. Although quality of life is at least maintained when adding a CDK4/6 inhibitor to standard ET alone, more side effects compared with ET alone are observed. This is particularly relevant for patients who are fully or almost asymptomatic.
- In addition, the monitoring procedures and visits are more frequent when administering a CDK4/6 inhibitor, especially for the first few months. For example, a blood analysis is indicated during the first two cycles on days 1 and 15 and thereafter monthly for 6 months. These more frequent visits may be a hurdle, especially for older patients and patients living far away from their hospital or oncological centre.
- Older patients with severe comorbidities or late relapses may also not be the best candidates for upfront use of CDK4/6 inhibitors as there is a high risk that their life expectancy is limited by other factors.

A Dutch group has launched a phase lll sequential trial with the primary endpoint after two lines of treatment (NCT03425838). Given the uncertain benefit in efficacy of adding CDK4/6 to first-line rather than second-line ET, the aim of the project is to evaluate whether the sequence of an AI plus CDK4/6 in first-line therapy followed by fulvestrant in second-line therapy is superior to the sequence of an AI in first-line therapy followed by fulvestrant plus CDK4/6 in second-line therapy.

SCENARIO 2: ENDOCRINE-SENSITIVE BC WITH NON-LIFE-THREATENING VISCERAL INVOLVEMENT

According to guidelines, chemotherapy (CT) is the first approach to life-threatening disease in patients with endocrine-sensitive MBC because the time to tumour response is shorter than that for ET. The therapeutic approaches for patients with non-life-threatening visceral involvement are still under debate. The recent development of biological agents with endocrine agents renews the debate. The arguments for ET plus CDK4/6 inhibitors versus CT as first-line therapy are discussed as follows.

Treatment approach: ET plus CDK4/6 inhibition

Let us start with a clinical case: a 66-year-old female patient was diagnosed 7 years ago with invasive ductal carcinoma (oestrogen receptor (ER) 6/8, PR 7/8, HER2-negative). Following local therapy, she received 2.5 years of adjuvant anastrozole followed by 2.5 years of tamoxifen. Two years after completing 5 years of adjuvant hormone therapy, she presented with bone, lung and liver metastases. It is important to note that a slight elevation of liver function tests was observed, the ECOG performance status was 1, and the patient was paucisymptomatic. Liver biopsy confirmed metastatic adenocarcinoma of the breast with the same biological features. Tumour sequencing of liver metastases reported PIK3CA mutation. Her visceral metastases were non-life-threatening.

According to available data from trials, the following therapeutic approaches might be considered in this scenario:

- Fulvestrant (500 mg).
- AI with or without CDK4/6 inhibitor.
- Fulvestrant plus CDK inhibitor.
- Chemotherapy.
- Exemestane plus everolimus.
- Fulvestrant plus PIK3CA inhibitor.

Table 1 CDK4/6 inhibitors in the first-line setting: ORR results[1–3 37]

Trial treatment	PALOMA-2 Palbociclib+letrozole versus placebo+letrozole	MONALEESA-2 Ribociclib+letrozole versus placebo+letrozole	MONARCH 3 Abemaciclib+NSAI versus placebo+NSAI
Patients (n)	444 vs 222	334 vs 334	328 vs 165
% of patients+visceral	48 vs 49	59 vs 59	52 vs 54
ORR (%) (all patients)*	55 vs 44	54.5 vs 38.8	61 vs 45.5
ORR (%) (visceral)	41.3 vs 37	45 vs 35	57.5 vs 20

*Measurable.
NA, not available; NSAI, non-steroidal aromatase inhibitor; ORR, objective response rate.

Data from studies supporting these therapeutic options can be summarised as follows.

As mentioned previously, the FALCON trial[18] compared fulvestrant (500 mg) to anastrozole in ET-naive luminal MBC only. The superiority of fulvestrant over anastrozole seemed to be restricted to patients with bone metastases in this patient group.

AI or fulvestrant in combination with CDK4/6 inhibitors offered the best therapeutic index.

The objective response rate (ORR) in the first-line setting ranged from 40% to 60% as illustrated in table 1. HR for PFS was around 0.55 (PALOMA-2, MONALEESA-2 and MONARCH 3) with a median PFS of about 25 months (PALOMA-2).[1–3] Despite the fact that the included populations are not directly comparable, there seems to be a longer PFS on patients receiving CDK4/6 inhibitors on the CDK4/6 inhibitors' trials, as compared with patients included on trials testing chemotherapy as illustrated in table 2.[24–27]

The therapeutic index of the combination exemestane plus everolimus is so narrow that it is proposed as a later approach.[28]

The combination of fulvestrant plus alpelisib in patients with phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations (SOLAR-1 study)[29] is of interest, but the true value of this combination needs more data and follow-up, compared with CDK4/6-based inhibitors and also compared with everolimus/exemestane.

In conclusion, for patients with non-life-threatening visceral involvement, a therapeutic algorithm is proposed in figure 2. This therapeutic algorithm is applicable when close follow-up of patients is possible.

Treatment approach: chemotherapy

When evaluating therapeutic strategies in patients with MBC with visceral involvement, it is important to weigh the benefits and risks of ET±biologicals versus systemic CT, particularly considering the necessity of rapid symptom control. While national and international guidelines consider ET to be the treatment of choice for most endocrine-sensitive patients with MBC,[12–14] patients with visceral crisis, heavy disease burden and patients with concern or proof of endocrine resistance are still candidates for systemic CT.

Late-stage metastatic endocrine-sensitive BC with visceral involvement and visceral crisis

The term 'late-stage or heavily MBC' is not well defined but implies multiple metastatic lesions usually present in

Table 2 Selected single-agent chemotherapy in the first-line setting: PFS results (all patients versus patients with visceral disease)[24–27]

Treatment	Paclitaxel (weekly) versus Nab–paclitaxel (weekly)[19]	Paclitaxel+bevacizumab (weekly) versus paclitaxel (weekly)[20]	Pegylated liposomal doxorubicin versus conventional doxorubicin[21]	Capecitabine versus eribulin mesylate[22]
Patients (n)	267 vs 275	347 vs 326	254 vs 255	548 vs 554
% of patients+visceral	77 vs 76	80 vs 87	59 vs 56	Lung 51 vs 50 Liver 50 vs 47
Median PFS (months)	11.0 vs 9.3	11.8 vs 5.9	6.9 vs 7.8	4.2 vs 4.1
PFS HR+CI (all patients)	1.20 (1.0 to 1.45)	0.60 (0.51 to 0.70)	1 (0.82 to 1.22)	1.08 (0.93 to 1.25)
PFS HR+CI (visceral)	1.46 (1.41 to 1.85)	0.59 (0.49 to 0.7)	Similar for all patients	NA

NA, not available; Nab, nanoparticle albumin-bound; PFS, progression-free survival.

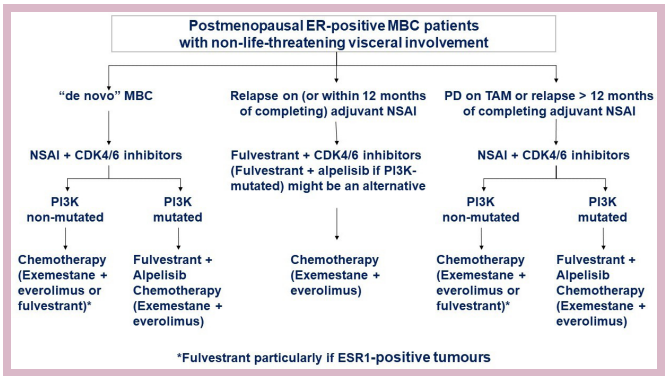

Figure 2 Proposed therapeutic algorithm for luminal subtype MBC with non-life-threatening visceral involvement with close follow-up of the patient. CDK, cyclin-dependent kinase; ER, oestrogen receptor; ESR1, oestrogen receptor 1; MBC, metastatic breast cancer; PD, progressive disease; NSAI, non-steroidal aromatase inhibition; TAM, tamoxifen.

several organs. While this condition is usually associated with symptomatic disease, it is not necessarily identical with visceral crisis, which is described by severe organ dysfunction and rapid disease progression. Visceral crisis is therefore not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a rapidly efficacious therapy, that is, CT, since other treatment options at progression are unlikely to be feasible.[13]

Even with the addition of CDK4/6 inhibitors, visceral crisis remains a contraindication for ET in the first-line and second-line metastatic settings, mainly for the lack of clinical data. Visceral crisis and heavy disease burden—as assessed by the investigator—were explicit exclusion criteria in the PALOMA-2, PALOMA-3, MONALEESA-3 and MONARCH 3 trials, and ECOG 0/I performance status was a prerequisite for inclusion into the MONALEESA-2 and MONALEESA-7 trial.[1–3 5 10 15 16]

So far, no trial has directly compared ET-CDK4/6 inhibitory treatment strategies with CT, but many clinicians would consider combination CT for HR-positive/HER2-negative patients with rapid clinical progression, life-threatening visceral metastases or need for rapid symptom or disease control. Single-arm phase II studies of weekly/monthly docetaxel and gemcitabine combinations have yielded ORRs of 64% and 79% in the first-line and second-line settings[30 31] but have also been associated with considerable side effects, thus making mono CT the preferred choice for cases of non-ET-treated advanced BC.[7] Nevertheless, the ORR achievable with combination CT appears to compare favourably to the 22% ORR achieved by palbociclib+fulvestrant combinations in patients with visceral metastases and ECOG performance status of 1/2 in the second-line setting, or the 54% ORR achieved by palbociclib+letrozole in patients with visceral metastases and ECOG 1/2 in the first-line setting.[32]

Bulky disease with high metastatic burden is also associated with an increase in tumour cell proliferation and a shift from a luminal A subtype in the primary tumour to a luminal B-dominant subtype in the metastatic lesions.[33 34]

Often this biological behaviour is characterised by the rapid development of endocrine resistance. While the addition of CDK4/6 inhibitors has improved PFS compared with ET alone, even in tumours that had progressed under prior ET, some CDK4/6 inhibitor studies conducted in the first-line setting (PALOMA-2, and PALOMA–3, MONALEESA-3, and MONARCH 2 and 3) enrolled women only if they had experienced disease progression no sooner than 12 months after completion of (neo-)adjuvant treatment.[1 3 10 15 16] The results of these trials therefore must be interpreted with caution, particularly when considering treatment in women with primary and secondary endocrine resistance (ie, in women whose disease had recurred during or within the first year after (neo-)adjuvant ET).

HR heterogeneity across metastatic lesions

While no biomarker has yet been identified to date that allows prediction of response to CDK4/6 inhibitors, the HR status is known to be both prognostic and predictive of response to ET in premenopausal and postmenopausal patients alike.[35] Since the HR status has been shown to change along tumour progression in few patients, it is important to confirm HR positivity in a setting where ET is considered together with CDK4/6 inhibition. A biopsy of a distant lesion should be attempted at least once metastatic disease is suspected. This is important in order to (1) confirm advanced BC and to (2) determine the ER and PR status of the metastatic lesion, which has been demonstrated can change between primary tumour and relapse up to 32% and 41%, respectively.[33]

HR assessment in patients with multiple (from two to six) consecutive relapses has further revealed that alterations in ER and PR status occur in 33.6% and 32.0%, respectively.[33] These receptor alterations translate to a statistically significant different OS, which is related to intraindividual ER and PR status in primary tumour and relapse. Particularly women with ER-positive primary tumours that change to ER-negative phenotype in the metastatic lesion have a 48% increased risk of death, compared with women with stable ER-positive tumours.[33]

The described longitudinal receptor dynamic impacts on treatment decisions and suggests that sequential tumour biopsies (or more easily liquid biopsies) will be necessary to optimise treatment decision making in the coming years.

The situation is further complicated by spatial HR heterogeneity: a recent study conducted in 91 patients with HR-positive/HER2-negative BC revealed a total of 1617 metastases in bone (78%), lymph node (15%), lung (4%) or liver (2%), which were identified by either CT scan (11.2%), 18Fluorestradiol (FES)-positron emission tomography (56.6%) or both (32.2%). In total, 86% of patients had at least one 18F-FES-positive lesion. Of these, 49% had 18F-FES-positive lesions exclusively, while 15% had only 18F-FES-negative lesions. Thirty-six per cent

had 18F-FES-positive and 18F-FES-negative lesions, thus suggesting considerable intraindividual heterogeneity of ER expression within different metastases at a given time point.[36] This observation could be one possible explanation for a radiographical 'mixed response' pattern that is often seen in response to ET. While there are no clinical data regarding the response to CDK4/6 inhibitors in patients with multiple, both HR-positive and HR-negative metastatic lesions, it is likely that the biological heterogeneity of metastatic lesions might also influence the efficacy of CDK4/6 inhibitors.

Nevertheless, more research is warranted to further investigate the clinical relevance of these findings. Evaluation of other targets (HER2 and PIK3CA) is also indicated on the biopsy of the metastatic lesion.

CONCLUSION

Figure 1 proposes a therapeutic algorithm for non-life-threatening MBC, but the bulk and the site of the disease in the treatment decision are worth considering.

Regarding scenario 1, it was the consensus of the round-table panel that CDK4/6 inhibitors should be recommended in first-line therapy for most patients with early-stage endocrine-sensitive MBC if cost and practicality allow. However, the use of single-agent ET with AI in first-line treatment is still a possibility for this group of patients. The most appropriate treatment options, including benefits and side effects, should be discussed with the patient before the final decision on treatment.

Regarding scenario 2, CT is the first approach for patients with endocrine-sensitive MBC with life-threatening visceral involvement, because of the shorter time to tumour response. Also, patients with concern or proof of endocrine resistance are still candidates for systemic CT.

The therapeutic approaches for patients with endocrine-sensitive MBC with non-life-threatening visceral involvement are still under debate, but CDK4/6 inhibitors are the treatment of choice for most patients. A treatment algorithm has been suggested at the round table (figure 2).

Ongoing and upcoming trials will provide more data on best (sequential) management of patients in both stages of endocrine-sensitive MBC.

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